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Prognostic significance of paravalvular regurgitation in patients with severe low-flow, low-gradient aortic stenosis undergoing TAVR: a report from the LOW-TAVR registry

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ABSTRACT

Background: Paravalvular regurgitation (PVR) remains a frequent complication after transcatheter aortic valve replacement (TAVR) and may impact clinical outcomes in patients with high-gradient aortic stenosis (AS). However, the prognostic role of PVR patients with low-flow, low-gradient aortic stenosis (LFLG-AS) undergoing TAVR has not yet been established.

Aims: To evaluate the prognostic significance of PVR severity using a five-class grading scheme in patients with LFLG-AS undergoing TAVR with current-generation prostheses.

Methods: This registry-based, multicenter, cohort study included consecutive patients with LFLG-AS undergoing TAVR from January 2019 to December 2024 at seventeen high-volume Italian centers. The primary outcome was the composite of all-cause death and hospitalization for heart failure (HF) up to two years.

Results: The study included 1358 patients. Kaplan-Meier curves showed a significant reduction in the survival free from the primary outcome for patients with mild-moderate or worse (≥2+) PVR at discharge. Therefore, the study population was divided into patients with PVR ≥2+ (10.7%) and those with none/trace or mild PVR (<2+, 89.3%). The propensity score weighted Cox analysis confirmed the significantly higher risk of the composite outcome (adjusted HR: 4.71; 95%CI: 3.61-6.13), all-cause death, cardiovascular death, and HF hospitalization in patients with PVR ≥2+ compared with those with PVR <2+ up to two years. These results were consistently significant in patients stratified by classical or paradoxical LFLG-AS form.

Conclusions: In this real-world study on TAVR treatment of patients with LFLG-AS, PVR ≥2+ was significantly associated with an increased risk of adverse events after discharge, regardless of LFLG-AS form.

Keywords: transcatheter aortic valve implantation; paravalvular leak; outcome; heart failure.

INTRODUCTION

Low-flow, low-gradient aortic stenosis (LFLG-AS) represents approximately 10–20% of severe aortic stenosis (AS) cases. [1] [2]

Patients with LFLG-AS have more comorbidities and more advanced cardiac damage compared to those with the high-gradient form, making them a particularly high-risk subset of AS. [3] [4] [5] Transcatheter aortic valve replacement (TAVR) is an effective treatment option, less invasive than surgery, which offers a favourable risk-benefit profile in high-risk patients with AS, including those with LFLG-AS. [6] [7] [8]

The "low-flow state" refers to a reduced forward output from the left ventricle secondary to afterload mismatch, impaired myocardial contractility, and restrictive physiology. [9] This condition leads to worsening haemodynamics after TAVR, particularly in individuals with forward overload due to a high transvalvular gradient, and has been associated with increased mortality in LFLG-AS. [10] [11]

Paravalvular regurgitation (PVR) is a common complication after TAVR [12] [13], leading to retrograde left ventricular overload, increased end-diastolic pressures, unfavourable remodeling, and pulmonary congestion, resulting in patients' clinical deterioration. [14] [15] Mild-moderate or worse PVR is reported in about 10-15% of patients with high-gradient AS after TAVR and has been associated with an increased risk of adverse events during follow-up. [14] [16] [17] However, the prognostic significance of PVR has never been investigated in patients with LFLG-AS undergoing TAVR.

Large, multicenter registries provide the opportunity to evaluate the characteristics and clinical outcomes of specific TAVR populations, such as LFLG-AS patients. Against this background, this registry-based, multicenter cohort study aims to investigate the prognostic significance of PVR severity in patients with LFLG-AS undergoing TAVR with current-generation prostheses

METHODS

Study population

This registry-based, multicenter cohort study included patients with LFLG-AS undergoing TAVR from January 2019 to December 2024 at seventeen high-volume Italian centers and enrolled in the Transcatheter Aortic Valve Replacement in Severe Low Flow, Low Gradient Aortic Stenosis (LOW-TAVR) registry.

Patients were accepted as candidates for TAVR after the Heart Team's decision-making process based on comprehensive surgical risk, clinical, echocardiographic, and computed tomography assessments. For this study, the registry population was divided into groups based on PVR severity assessed by transthoracic echocardiography (TTE) after TAVR, prior to discharge. Patients who died during the hospitalization, underwent open surgery during/after TAVR procedure, or required surgical/percutaneous closure of PVR during the index hospitalization were excluded.

LOW-TAVR Registry

LOW-TAVR is a real-world, retrospective, and prospective multicenter Italian registry designed to evaluate the characteristics and clinical outcomes of patients with severe LFLG-AS undergoing TAVR (NCT06589063). The registry included all-comers patients with a confirmed diagnosis of LFLG-AS undergoing TAVR with implantation of current-generation prostheses from January 2019. LFLG-AS was defined by aortic valve area (AVA) <1 cm^2 or an indexed AVA ≤0.6 cm^2/m^2, mean transaortic gradient <40 mmHg, and stroke volume index (SVi) <36 mL/m^2 according to current guidelines. [1] LFLG-AS was classified according to left ventricular ejection fraction (LVEF) values in classical (<50%) and paradoxical (≥50%) forms. Dobutamine stress echocardiography was systematically performed in patients with LVEF <50% to exclude pseudo-severe AS. Calcium

volume assessment by computed tomography was also performed in patients with paradoxical LFLG-AS to confirm the severity of AS.

All patients underwent TTE at hospital admission and before discharge. Patients were followed by clinical visits or phone contact at one and twelve months, and yearly thereafter. In-hospital and follow-up outcome measures were defined according to the Valve Academic Research Consortium (VARC) 3 statement. [18]

Study data were collected and managed using the REDCap electronic data capture tools hosted at the Department of Medicine, Surgery, and Dentistry of the University of Salerno. Remote electronic data monitoring was systematically conducted to identify and actively correct missing and/or inconsistent information.

The registry adheres to the principles outlined in the Declaration of Helsinki. The institutional review boards approved the protocol. All patients were informed about their participation in the registry and provided written informed consent.

TAVR planning, procedure, and pre-discharge assessments

A systematic preoperative work-up was performed in patients with severe LFLG-AS who were eligible for TAVR, including contrast-enhanced computed tomography of the chest, abdomen, and ilio-femoral axes, utilizing 64-row or higher scans with cardiac cycle synchronization.

The procedural planning, including arterial access approach, device type and size, pre-dilation, and post-dilation, was at the operator's discretion. Non-femoral access was restricted to patients with complex ilio-femoral anatomy and peripheral arterial disease that were not amenable to conventional arterial access.

Technical success was defined as freedom from mortality, successful arterial access, delivery of the device and retrieval of the delivery system, correct positioning of a single prosthetic heart valve into the proper anatomical location, and freedom from surgery or intervention related to the device or major vascular, access-related, or cardiac structural complications. [18]

After TAVR, the presence and severity of PVR were systematically assessed by TTE before hospital discharge. PVR was graded as no/trace (0), mild (1+), mild-moderate (2+), moderate (3+), moderate-severe (4+), and severe (5+) using an integrative multiparametric approach including qualitative, semiquantitative, and quantitative measures according to the VARC-3 statement. [18]

Study outcome measures

The primary outcome of this study was the composite of all-cause death and hospitalization for worsening heart failure (HF) up to two years. The secondary outcomes of interest were the single components of the composite outcome, cardiovascular death and stroke. Other outcomes of interest included in-hospital and one-year adverse events as defined by the VARC-3. (16)

Statistical analysis

Survival free from the composite outcome was displayed using Kaplan–Meier curves stratified by PVR grade. The comparison over strata and the pairwise comparisons between groups were conducted using the log-rank test. Based on the net separation of Kaplan-Meier curves between patients with mild (1+) and mild-moderate or worse (≥2+) PVR, the study population was divided into two groups based on PVR severity after TAVR: <2+ (none/trace and mild degree PVR) and ≥2+ (mild-moderate or worse).

The normality of the continuous parameters was tested using the Kolmogorov-Smirnov test. Normally distributed variables were expressed as mean ± standard deviation and compared using the Student t-test. Variables with a skewed distribution were reported as median and interquartile range and compared with the Mann-Whitney U test. Categorical variables were compared with the chi-squared test, or Fisher's exact test, as appropriate. Ordinal variables were compared with the Kendall's Tau-c test.

The unadjusted and adjusted hazard ratios (HR) for the outcomes of interest were calculated using Cox proportional hazards regression and reported with 95% confidence intervals (CI).

We used the propensity score weighting (PSW) technique to account for potential selection bias between patients with PVR <2+ and those with PVR ≥2+. The PSW model was developed using a parsimonious approach, incorporating all baseline covariates significantly associated with the exposure and/or the primary outcome at univariable Cox analysis. [19] Differences between groups before and after weighting were assessed using standardized mean differences (SMDs), a statistical measure that evaluates the magnitude of differences between two groups independently of the sample size. An SMD below 0.10, indicating an optimal balance for all covariates included in the propensity score models, was achieved.

The consistency of the study results was assessed in prespecified patient subgroups with classical or paradoxical LFLG-AS forms, and the estimated interaction effect was expressed as $P_{interaction}$.

Missing data were handled using multiple imputation with the chained equations method. Twenty imputed data sets were generated and combined using Rubin's rules. [20]

For all tests, a p-value <0.05 was considered statistically significant. Statistical analysis was performed using R version 4.3.3 (R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

The study included 1358 patients, with a median age of 83 years (IQR, 79-86), and 50.4% were female. The distribution of PVR degree at discharge in the study population is shown in Figure 1A: 733 patients had no/trace PVR, 479 mild (1+), 114 mild-moderate (2+), and 32 moderate or worse PVR (≥3+).

Kaplan-Meier curves for survival free from the primary outcome stratified by PVR degree are shown in Figure 1B. Overall, there was a significant difference between groups ($p<0.001$) with net curve separation between groups with PVR < 2+ and those with mild-moderate or worse PVR (≥2+; 0 vs 2+, $p<0.001$; 1 vs 2+, $p<0.001$).

The baseline characteristics of the study population overall and stratified by PVR <2+ and PVR ≥2+ are reported in Table 1. At baseline, patients with PVR ≥2+ showed a higher percentage of atrial fibrillation ($p=0.005$) and a higher surgical risk according to the EuroSCORE II ($p<0.001$) compared with patients with PVR<2+. No statistical difference was observed in the other comorbidities or in the NYHA class between the groups.

Before TAVR, patients with PVR≥2+ had a higher percentage of moderate-severe mitral regurgitation ($p<0.001$) and higher systolic pulmonary artery pressure ($p<0.001$) than patients with PVR<2+.

There was no difference between groups in terms of procedural TAVR features. The percentage of VARC-3 technical success was high (98.7%) and comparable between groups. Myocardial infarction occurred in 5 (0.4%) patients, transient ischemic attack/stroke in 19 (1.5%), and major vascular complication in 24 (1.8%), with no significant differences between groups.

There was no significant difference in the percentage of mild-moderate or worse PVR between the BEV and SEV groups. However, a higher percentage of mild PVR was reported in the SEV group.

Up to two years, the primary outcome was reported in 281 (20.7%) patients (median FU 305 [103-632 IQR] days); all-cause death was reported in 193 (14.2%) patients, and was related to

cardiovascular causes in the majority of cases (78.7%); HF hospitalization was reported in 159 (11.7%) patients. Patients with PVR ≥2+ showed a significantly higher percentage of the composite outcome (p<0.001), all-cause death (p<0.001), cardiovascular death (p<0.001), HF hospitalization (p<0.001), and stroke (p=0.040).

The PSW-adjusted Cox analysis confirmed a significantly higher risk for the composite outcome (adjusted HR: 4.71; 95%CI: 3.61-6.13), all-cause death (adjusted HR: 4.87; 95%CI: 3.59-6.63), cardiovascular death (adjusted HR: 5.28; 95%CI: 3.75-7.42), and HF hospitalization (adjusted HR: 5.05; 95%CI: 3.58-7.12) in patients with PVR ≥ 2+ compared with those with PVR < 2+ up to two years (Figure 2). No difference in the risk of stroke was observed between groups.

The estimates for the risk of the primary and secondary outcomes were consistently significant in patients with classical and paradoxical LFLG-AS forms, with no significant subgroup interaction (Figure 3).

DISCUSSION

This is the largest study to date focused on assessing the prognostic role of PVR severity following TAVR with current-generation prostheses in patients with LFLG-AS.

The main findings of this study can be summarized as follows:

i) In this LFLG-AS population, mild-moderate or worse PVR was reported in approximately 11% of cases. These patients had a higher incidence of mortality or HF hospitalization within two years of discharge than those without;

ii) After adjustment for potential confounders, mild-moderate or worse PVR confirmed an independent association with the risk of developing adverse events during follow-up;

iii) The negative impact of PVR on clinical outcomes was confirmed both in patients with classical and paradoxical LFLG-AS forms, with no significant interaction between subgroups.

In this large, multicenter, registry-based population of patients with LFLG-AS treated with current-generation TAVR prostheses, PVR ≥ 2+ was observed in 11% of cases. This percentage is consistent with previous studies on high-gradient AS, indicating that residual PVR after TAVR remains a frequent complication despite advancements in prosthesis design and implantation techniques. [21] [16]

Although PVR is not uncommon after TAVR, there is limited evidence about its prognostic significance in patients with LFLG-AS. In this study, we used the five-class grading scheme for PVR classification recommended in the VARC-3 statement, as it provides a more granular stratification of PVR severity compared to the three-class scheme and discriminates between mild and mild-moderate forms, which may have different prognostic impacts. [22] [18] Using Kaplan–Meier curves, in fact, we observed a net separation between patients with mild PVR vs those with mild-moderate PVR, which confirms the importance of discriminating mild-moderate from the mild form of PVR also in the LFLG-AS setting. This result is consistent with a previous study on 1,128 patients with high-gradient AS undergoing TAVR from 2007 to 2015, which showed that mild-moderate PVR conferred a significantly higher risk of adverse events than mild PVR. (10)

In our study, for the first time in a large, multicenter LFLG-AS population, we found that mild-moderate or worse PVR on TTE strongly stratifies clinical outcomes, including all-cause death, cardiovascular death, and HF hospitalization. These results align with previous research on high-gradient AS. [23] [21] For instance, a recent study from the France-TAVI registry, including 20,878 patients with high-gradient AS undergoing TAVR with old-generation prostheses, found that mild-

moderate or worse PVR was associated with a significantly higher risk of mortality during follow-up.[24]

In the high-risk context of LFLG-AS, we observed that mild-moderate or worse PVR increased the risk of death or HF rehospitalization by four to five times. These risk estimates are much higher than those reported in previous studies, indicating a strong hemodynamic and clinical impact of PVR in these AS patients. PVR causes retrograde volume overload of the left ventricle and increases left ventricular end-diastolic pressures. [14] [25] We can hypothesize that pre-existing cardiac damage and myocardial dysfunction make LFLG-AS patients particularly susceptible to the hemodynamic deterioration secondary to the retrograde left ventricular overload of PVR. This increased vulnerability significantly increases the risk of adverse events after TAVR. (9) (17)

We also conducted a prespecified subgroup analysis to investigate whether LFLG-AS classical or paradoxical forms may influence the effect of PVR on patients' clinical outcomes. We found that estimates of the risk of the primary outcome, all-cause mortality, cardiovascular mortality, and HF hospitalization were consistent and, of note, statistically significant in both patients with classical and paradoxical LFLG-AS forms. This result suggests that the prognostic impact of PVR was independent of LVEF.

In classical LFLG-AS, the volume overload secondary to residual PVR leads to left ventricular dilation, increases myocardial wall stress, and limits the recovery of left ventricular function and reverse remodeling. In paradoxical LFLG-AS, PVR-related retrograde volume overload markedly increases diastolic filling pressures in a small, stiff left ventricles, leading to pulmonary congestion and worsening HF status and clinical outcomes. (9)

Ultimately, this study emphasizes the importance of optimizing procedural planning in patients with LFLG-AS to minimize residual PVR. Patients with residual mild-moderate or worse PVR at

discharge need close clinical monitoring and careful guideline-directed HF medical therapy. (1) In these patients with worsening HF status despite optimal clinical management, percutaneous closure of PVR should be considered on a case-by-case basis, independently of LFLG-AS form. [26]

However, the therapeutic management of PVR in LFLG-AS was not the focus of this study and requires further investigation.

STUDY LIMITATION

Our results should be interpreted in light of certain limitations. Although we employed the PSW technique to account for baseline patient-related characteristics, we cannot exclude a residual selection bias secondary to concealed confounders.

The LOW-TAVR protocol does not include the systematic verification of echocardiographic measures in a core laboratory. However, this study evaluated parameters commonly used in clinical practice, particularly in high-volume TAVR centers, and our TTE findings are consistent with previous studies on LFLG-AS. [6] [27]

This study does not provide information on echocardiographic follow-up, as this information is not mandatory in the LOW-TAVR registry and was not systematically collected. Indeed, this study was not designed to assess echocardiographic changes after TAVR, but to investigate clinical outcomes in patients treated with TAVR who had echocardiographic evidence of residual PVR before discharge.

Eventually, since aortic valve calcium volume is not a mandatory field in the LOW-TAVR, it was not evaluated in this analysis. However, the aim of this study was not to investigate the mechanism of PVR, which has already been extensively investigated, but to evaluate the prognostic significance of PVR in the high-risk TAVR population of LFLG-AS.

CONCLUSION

PVR is still a matter of concern in patients with AS. In this large, real-world, multicentre study, including patients with LFLG-AS who underwent TAVR with current-generation prostheses, mild-moderate or worse PVR significantly increased the risk of adverse events after discharge. These results were confirmed in both classical and paradoxical LFLG-AS forms.

It is crucial to optimize procedural planning for patients with LFLG-AS to minimize residual PVR. Patients with residual mild-moderate or worse PVR at discharge require close monitoring and tailored medical therapy, as they face an increased risk of mortality and hospitalization for worsening heart failure.

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Disclosures

The authors declare that they have no commercial or financial relationships that could be construed as a potential conflict of interest.

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TABLES

Table 1. Clinical, echocardiographic and procedural characteristics of the study population

	All (N = 1358)	**PVR≥2+ (N = 146)**	**PVR<2+ (N = 1212)**	***P***
Age, years	83 (79-86)	83 (80-87)	83 (79-86)	0.314
Sex female, N (%)	684 (50.4)	68 (46.6)	616 (50.8)	0.332
BSA, m^2	1.8±0.3	1.8±0.2	1.8±0.3	0.841
Diabetes, N (%)	444 (32.8)	53 (36.3)	391 (32.3)	0.336
Hypertension, N (%)	1207 (88.9)	129 (88.4)	1078 (88.9)	0.831
Hypercholesterolemia, N (%)	932 (69.0)	95 (65.1)	837 (69.5)	0.272
Smoking, N (%)	248 (18.9)	34 (23.6)	214 (18.3)	0.122
COPD, N (%)	317 (23.9)	37 (25.5)	280 (23.6)	0.618
eGFR, mL/min	56 (53-60)	56 (52-59)	57 (53-60)	0.375
CCS, N (%)	577 (42.5)	71 (48.6)	506 (41.8)	0.114
Prior MI, N (%)	294 (21.7)	40 (27.4)	254 (21.0)	0.079
Prior PCI, N (%)	349 (25.7)	46 (31.5)	303 (25.0)	0.090
Prior CABG, N (%)	143 (10.6)	18 (12.4)	125 (10.3)	0.440
Atrial fibrillation/flutter, N (%)	543 (40.0)	74 (50.7)	469 (38.7)	0.005
Prior stroke/TIA, N (%)	109 (8.0)	14 (9.6)	95 (7.9)	0.468
Peripheral arteriopathy, N (%)	268 (19.7)	33 (22.8)	235 (19.4)	0.336
Pacemaker, N (%)	175 (12.9)	21 (14.4)	154 (12.7)	0.575
ICD/CRT-D, N (%)	53 (4.0)	5 (3.4)	48 (4.0)	0.740
EuroSCORE II, %	4.2 (2.5-7.3)	5.0 (3.1-9.7)	4.0 (2.4-7.1)	<0.001
NYHA				
NYHA I, N (%)	60 (4.4)	13 (8.9)	47 (3.9)	
NYHA II, N (%)	595 (43.8)	52 (35.6)	543 (44.8)	0.271
NYHA III, N (%)	628 (46.2)	62 (42.5)	566 (46.7)	
NYHA IV, N (%)	75 (5.5)	19 (13.0)	56 (4.6)	
Baseline echocardiography				
LVEF, %,	50 (37-60)	50 (38-60)	50 (36-60)	0.735
Mean AVG, mmHg	30±6	29±6	30±6	0.486
Aortic valve area, cm^2	0.7±0.2	0.7±0.2	0.7±0.1	0.564
Paradoxical LFLG, N (%)	741 (54.6)	77 (52.7)	664 (54.8)	0.639
Classical LFLG, N (%)	617 (45.4)	69 (47.3)	548 (45.2)	0.639
Moderate-to-severe AR, N (%)	67 (5.0)	11 (7.6)	56 (4.6)	0.123
Moderate-to-severe MR, N (%)	181 (13.4)	44 (30.3)	137 (11.4)	<0.001
BAV, N (%)	27 (2.1)	2 (1.4)	25 (2.2)	0.557
sPAP, mmHg	40 (33-48)	45 (35-55)	38 (32-47)	<0.001

Procedural features				
Transfemoral approach, N (%)	1306 (96.2)	139 (95.2)	1167 (96.3)	0.520
Subclavian/axillary approach, N (%)	34 (2.5)	5 (3.4)	29 (2.4)	0.451
Transapical approach, N (%)	10 (0.7)	2 (1.4)	8 (0.7)	0.343
Pacing, N (%)	1134 (84.0)	121 (82.9)	1013 (84.1)	0.695
Pre-dilation, N (%)	415 (31.1)	40 (27.6)	375 (31.5)	0.338
BEV, N (%)	586 (43.2)	63 (43.2)	523 (43.2)	1.000
SEV, N (%)	772 (56.8)	83 (56.8)	689 (56.8)	1.000
Prosthesis size ≤23 mm, N (%)	278 (20.5)	34 (23.3)	244 (20.1)	0.372
Post-dilation, N (%)	219 (16.3)	30 (20.8)	189 (15.8)	0.121
VARC-3 Technical success, N (%)	1340 (98.7)	143 (97.9)	1197 (98.8)	0.415

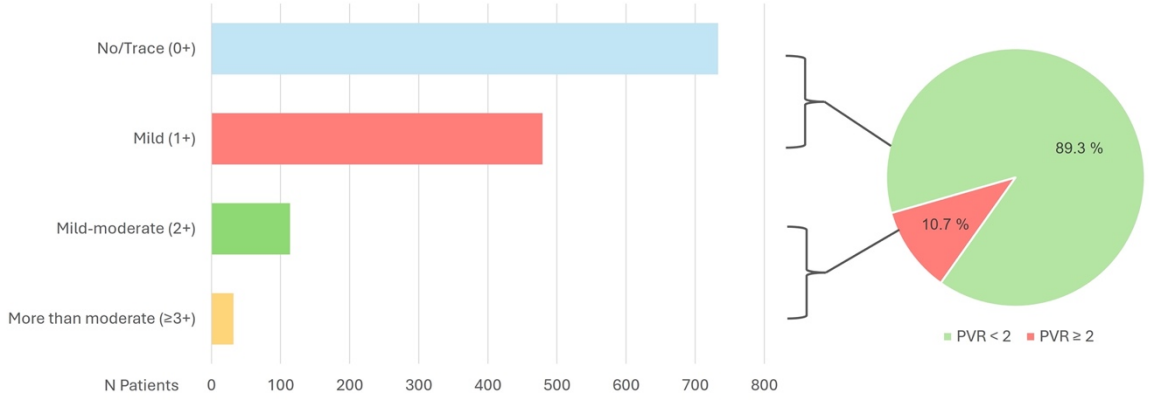
Continuous normally distributed variables are expressed as mean ± SD. Categorical variables are expressed as N (%). Continuous non-normally distributed variables are expressed as median (interquartile range).

AVG, aortic valve gradient; AR, aortic regurgitation; BAV, bicuspid aortic valve; BSA, body surface area; CABG, coronary artery bypass graft surgery; CCS, chronic coronary syndrome; COPD, chronic obstructive pulmonary disease; CRT-D, cardiac resynchronization therapy-defibrillator; eGFR, estimated glomerular filtration rate; EuroSCORE II, European system for cardiac operative risk evaluation; ICD, implantable cardioverter-defibrillator; LVEF, left ventricular ejection fraction; MI, myocardial infarction; MR, mitral regurgitation; NYHA, New York Heart Association functional class; PVR, paravalvular regurgitation; sPAP, systolic pulmonary artery pressure; TIA, transient ischemic attack.

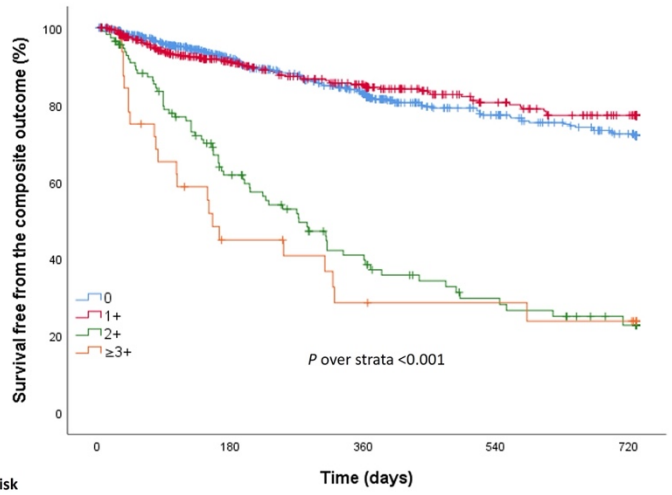
FIGURE LEGENDS

Figure 1. (A) Presence and severity of PVR at discharge in the study population; (B) Kaplan–Meier curves for survival free from the composite outcome according to PVR severity.

A



B

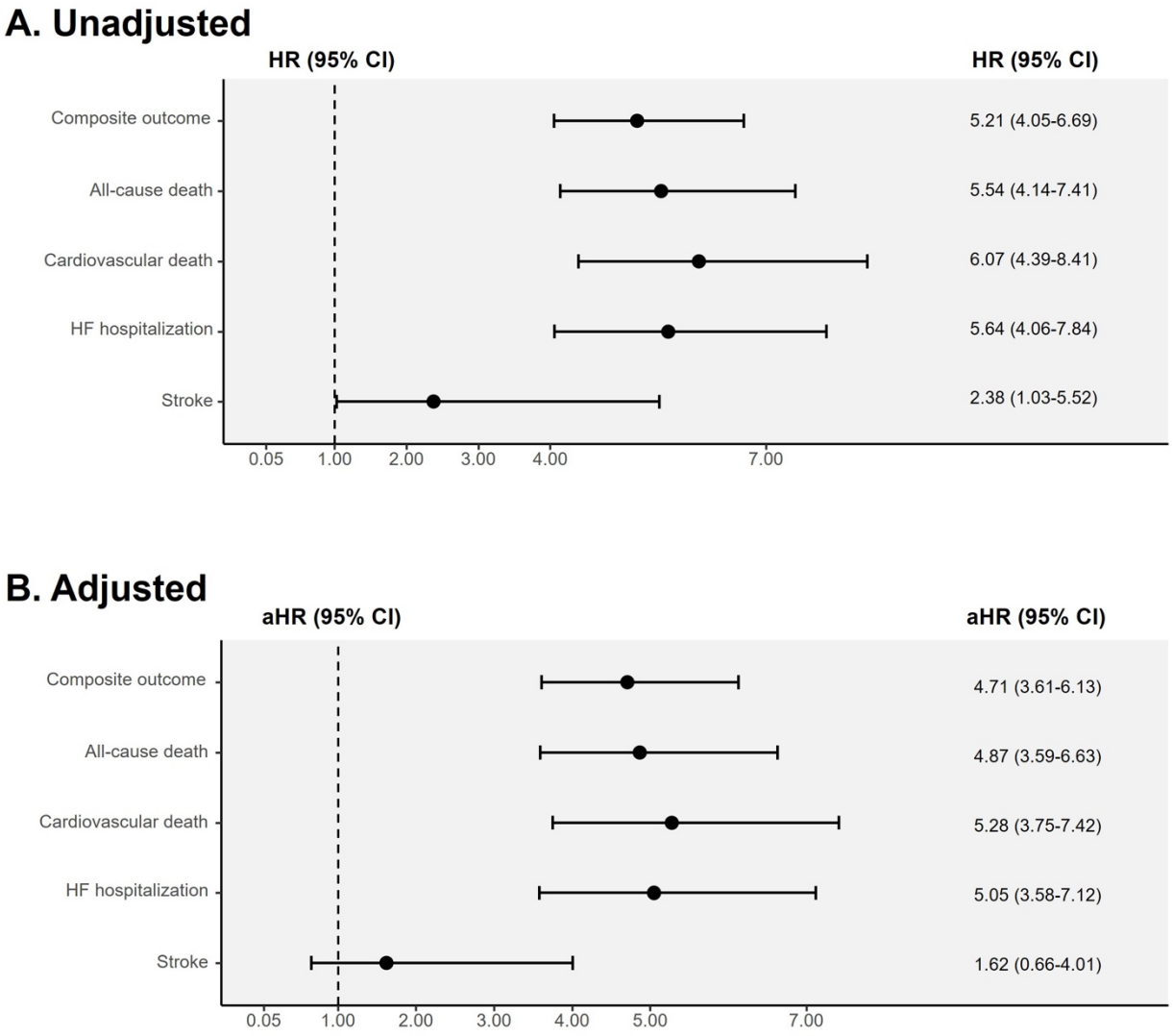


N at risk					
PVR 0	735	452	339	207	163
PVR=1+	477	293	231	151	121
PVR=2+	114	59	32	19	10
PVR≥3+	32	12	7	6	5

Pairwise comparisons	
	Log-Rank
0 vs 1+	0.373
0 vs 2+	<0.001
0 vs ≥3+	<0.001
1+ vs 2+	<0.001
1+ vs ≥3+	<0.001
2+ vs ≥3+	0.327

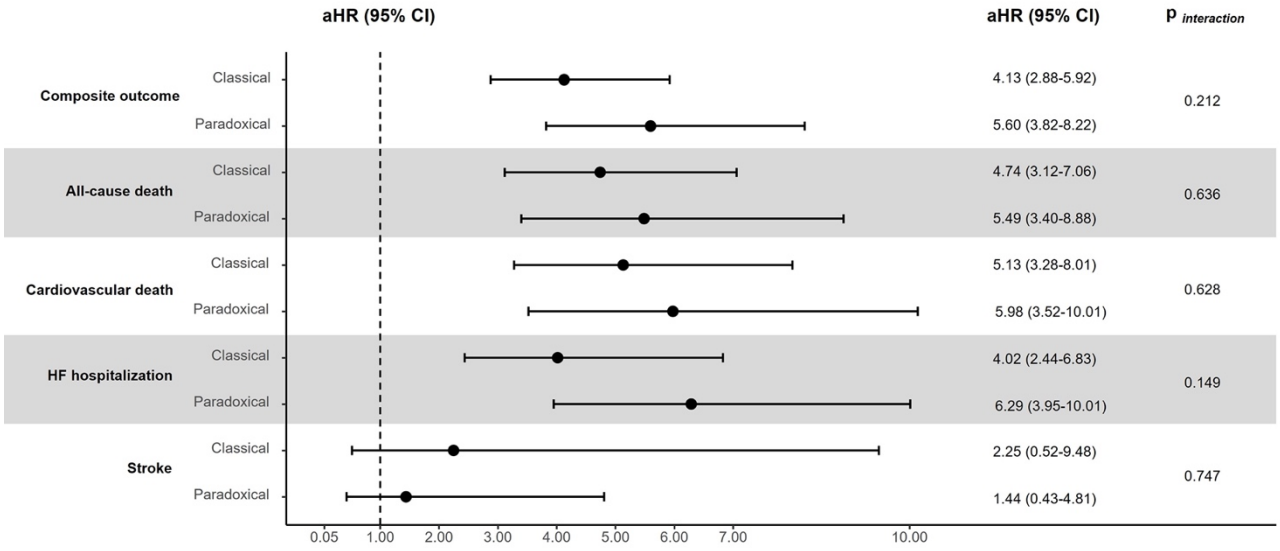
PVR, paravalvular regurgitation.

Figure 2. Risk of adverse events up to two years according to PVR < or ≥2+.



aHR, adjusted hazard ratio; CI, confidence interval; HF, heart failure; HR, hazard ratio; PVR, paravalvular regurgitation.

Figure 3. Subgroup analysis for the risk of adverse events up to two years according to PVR < or ≥2+ in classical and paradoxical LFLG-AS forms.



aHR, adjusted hazard ratio; CI, confidence interval; HF, heart failure; LFLG-AS, low-flow low-gradient aortic stenosis; PVR, paravalvular regurgitation.