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ORIGINAL PAPER

Interplay of aortic stenosis flow groups and mitral regurgitation aetiology in patients undergoing transcatheter aortic valve replacement

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See the editorial comment for this article 'When mitral regurgitation persists after transcatheter aortic valve replacement: prognostic driver or stage marker?', by E. Donal *et al.*, https://doi.org/10.1093/ehjci/jeaf256.

Aims Management of transcatheter aortic valve replacement (TAVR) in aortic stenosis (AS) flow groups—high-gradient (HG-AS), classical low-flow low-gradient (cLFLG-AS), and paradoxical low-flow low-gradient (pLFLG-AS)—is debated. Concomitant mitral regurgitation (MR) worsens outcomes, but the influence of MR aetiology on AS subtypes is unclear. This study aims to evaluate the impact of MR aetiology and severity on outcomes across AS flow groups in TAVR patients.

Methods and results A retrospective analysis was performed on 2658 patients undergoing TAVR (2013–21). MR was categorized as atrial functional (aFMR), ventricular functional (vFMR), or primary MR (PMR). Outcomes included 3-year mortality, MR improvement, and symptomatic benefit. Out of 2658 TAVR patients, 531 (20.0%) showed at least moderate MR (MR ≥ 2+) (50.1% male, median age 83.1 years). The fraction of patients with MR ≥ 2+ was highest among cLFLG-AS patients (34.2%). MR aetiology varied among AS subtypes, with mostly vFMR in cLFLG-AS (83.0%) and highest rates of aFMR (43%) and PMR (45%) in pLFLG-AS patients. Three-year mortality was significantly affected by MR severity [hazard ratio (HR) for MR2+ vs. MR < 2 1.62 (1.38–1.90)]. Differences in 3-year mortality were found in high-gradient (HG)-AS [HR 1.52 (1.16–1.98)] and pLFLG-AS patients [HR 1.73 (1.24–2.40)], but not in cLFLG-AS patients [HR 1.21 (0.93–1.56)]. MR improvement after TAVR was commonly found in HG-AS (67.2%) and least often among pLFLG-AS (48.7%, $P = 0.03$ compared with HG-AS). While MR improvement was associated with a lower mortality in HG-AS [HR 0.21 (0.10–0.43)] and cLFLG-AS patients [HR 0.48 (0.29–0.79)], this was not the case in pLFLG-AS patients [1.32 (0.67–2.59)].

Conclusion MR aetiology and severity influence outcomes after TAVR depending on AS flow groups.

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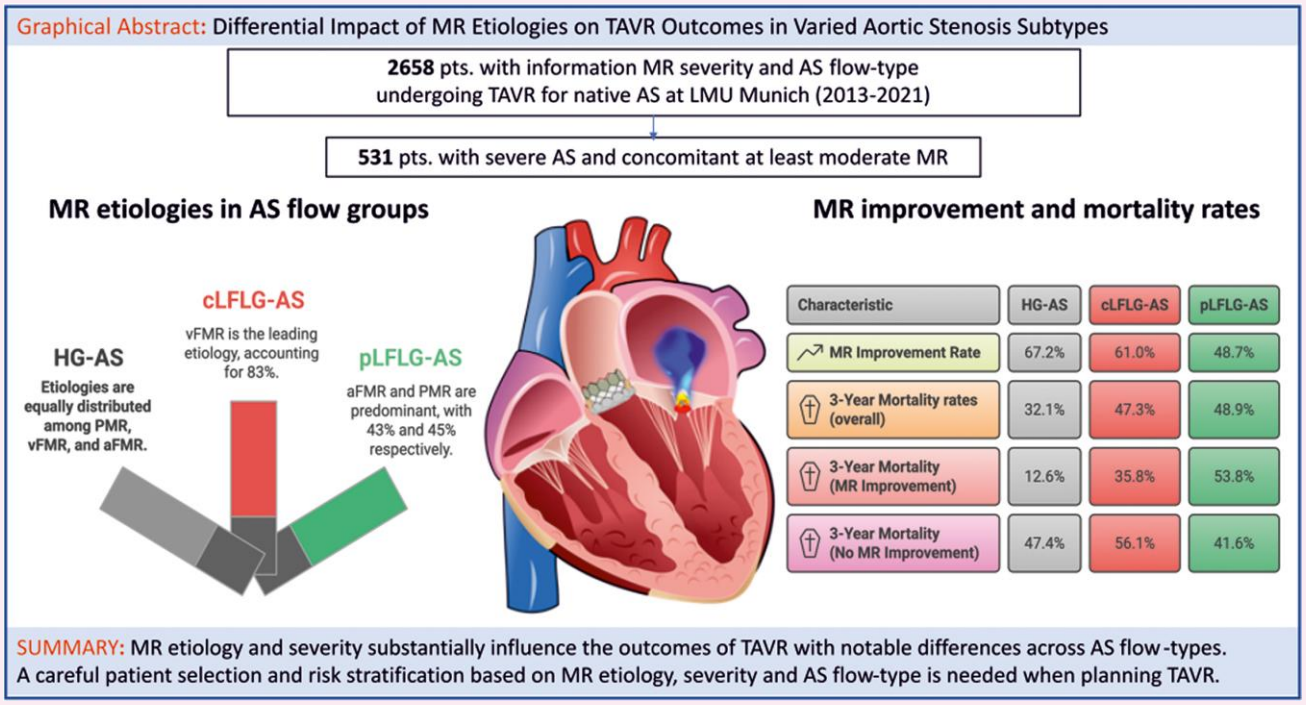
Graphical Abstract



Keywords TAVR • mitral regurgitation • atrial functional MR • primary MR • aortic stenosis • paradoxical low-flow low-gradient • multivalvular heart disease

Introduction

Aortic stenosis (AS) is the most common valvular heart disease in the western world. AS is subdivided into different flow groups according to transvalvular gradient, left ventricular ejection fraction (LVEF), and stroke volume: high-gradient AS (HG-AS), classical low-flow low-gradient (cLFLG-AS), and paradoxical low-flow low-gradient (pLFLG-AS).[1] Recently, transcatheter aortic valve replacement (TAVR) has emerged as a less invasive alternative to surgical aortic valve replacement in patients with intermediate or high surgical risk[2,3] and is increasingly used in patients with lower surgical risk.[4–6] However, data comparing flow groups are scarce, and management of patients with LFLG-AS remains a matter of debate.[7–11] European and American guidelines fail to guide physicians with clear recommendations.[12,13]

Mitral regurgitation (MR) is a common concomitant valvular pathology in patients with severe AS and is observed in 17–35% of patients undergoing TAVR.[2,14–17] Concomitant MR was shown to be associated with worse outcomes following TAVR.[17–19] MR severity decreases in 50–60% of patients with functional (FMR) and primary MR (PMR) after TAVR, possibly due to the elimination of outflow obstruction.[15,16,20] Due to diverse pathophysiological mechanisms, FMR is further subdivided into ventricular FMR and atrial FMR, the latter of which has recently come into the centre of scientific interest.[21,22] The interplay of different MR aetiologies with different AS flow groups has not yet been investigated, and the pathophysiological mechanisms are poorly understood. We therefore aimed to characterize a large cohort of patients with multivalvular heart disease who were treated for severe AS and investigating outcomes accordingly.

Methods

Study population

All consecutive patients undergoing transfemoral TAVR for native AS between 2013 and 2021 at LMU Munich University Hospital (Munich, Germany) with available baseline information on MR and AS subtypes were included in the analysis. Patients with normal-flow low-gradient AS were not included, as current guidelines regard severe aortic stenosis as 'unlikely' in these patients.[12] For completion however, most analyses have also been performed for normal-flow low-gradient patients and are shown in the Supplementary data (Supplementary data online, *Figure S1*). Additionally, patients with prior biological aortic valve replacement and prior mitral valve intervention or surgery and patients with TAVR for severe aortic regurgitation were excluded. All patients showing at least moderate MR (≥2) were individually categorized into aFMR, vFMR, and PMR as described below.

Before TAVR, a multidisciplinary heart team consensus by interventional cardiologists and cardiac surgeons was obligatory to evaluate the best treatment option in every individual patient. Patient data were collected in a database according to the local requirements for quality control and in accordance with the Declaration of Helsinki. Ethical approval was obtained from the institutional ethics board (EVERY-Valve registry, ethical code number 19-840). Clinical and echocardiographic follow-up information was obtained either by phone, during hospital admissions, or at outpatient clinic visits as described before.[23]

Echocardiography

Transthoracic echocardiographic images were obtained prior to the TAVR procedure in accordance with the guidelines.[24,25] The severity of AS was

assessed using the continuity equation method and according to mean valvular gradients as recommended by the current guidelines. Baseline MR severity and mitral stenosis were assessed according to the current recommendations.[26]

Pre-procedural echocardiography was individually assessed by an experienced physician to ensure a precise characterization of aetiology. In the case of mixed aetiologies, the leading aetiology was respected. Patients were considered to have aFMR, when showing preserved LVEF (≥50%) with normal LV (left ventricular) body surface area indexed dimensions, dilated left atria, and structurally normal mitral leaflets with absence of leaflet calcifications and without any regional LV wall motion abnormalities, as previously suggested.[27] Patients with reduced LVEF, presence of regional wall motion abnormalities, or increased LV dimensions were considered to have vFMR. Patients showing predominantly preserved LV function and dimensions with mitral valvular calcifications leading to restricted leaflet coaptation or damages or prolapse/flail were considered to have PMR. An overview on the echocardiographic characteristics is shown in *Table 1*.

Patients were stratified into three different AS flow groups according to mean transvalvular pressure gradient (dPmean), LVEF, and stroke volume index (SVi)[28]: patients with a dPmean ≥40 mmHg were classified as HG-AS, and patients with a dPmean < 40 mmHg were split into cLFLG-AS (LVEF < 50%) and pLFLG-AS (LVEF ≥ 50% and SVi ≤ 35 mL/m^2). Patient characteristics according to the ESC definition of LFLG are shown in Supplementary data online, *Table S7*. Before discharge, valve function including paravalvular leaks was evaluated as suggested by the Valve Academic Research Consortium 3-criteria guidelines (VARC-3).[29]

For echocardiographic follow-up information regarding MR severity, images were retrospectively analysed. In case of missing images, written reports were used.

TAVR procedure

Transfemoral access with local anaesthesia was used in all analysed patients. Peri-procedural anticoagulation was achieved with unfractionated heparin (50–70 IU/kg body weight). The decision to perform pre- and/or post-dilation was left to the operator's discretion. For access-site haemostasis, suture-mediated and plug-based closure devices were used. In patients with indication for oral anticoagulation, therapy was continued after the TAVR procedure. In patients undergoing percutaneous coronary intervention, antiplatelet and anticoagulation regimens were conducted according to current guidelines.[30]

Table 1 MR aetiology definition

MR type	Echocardiographic criteria
Atrial functional (aFMR)	• Preserved LVEF (≥50%) without any regional LV wall motion abnormalities • Normal LV body surface area indexed dimensions • Dilated left atrium • Structurally normal mitral leaflets, no calcifications
Ventricular functional (vFMR)	• Reduced LVEF • Regional wall motion abnormalities • Increased LV dimensions
Primary (PMR)	• Predominantly preserved LV function and dimensions • Damages, prolapse, or flail • Mitral valvular calcifications with restricted leaflet coaptation

MR, mitral regurgitation; LV, left ventricular; LVEF, left ventricular ejection fraction.

Trial endpoints and follow-up

In this analysis, we assessed all-cause mortality at 3 years and compared changes in MR severity and heart failure symptoms defined by New York Heart Association (NYHA) functional class at baseline and at last available follow-up. MR persistence was defined as no change or worsening of MR severity at latest available follow-up. In case of a mitral valve intervention or surgery during follow-up, the last echocardiographic MR grading before intervention was used, and patients were considered to have persistent MR. Additionally, we assessed procedural endpoints according to VARC-3 criteria.[29]

Statistical analysis

For descriptive statistics, categorical data are presented as numbers and proportions. Continuous data are presented as median [and interquartile

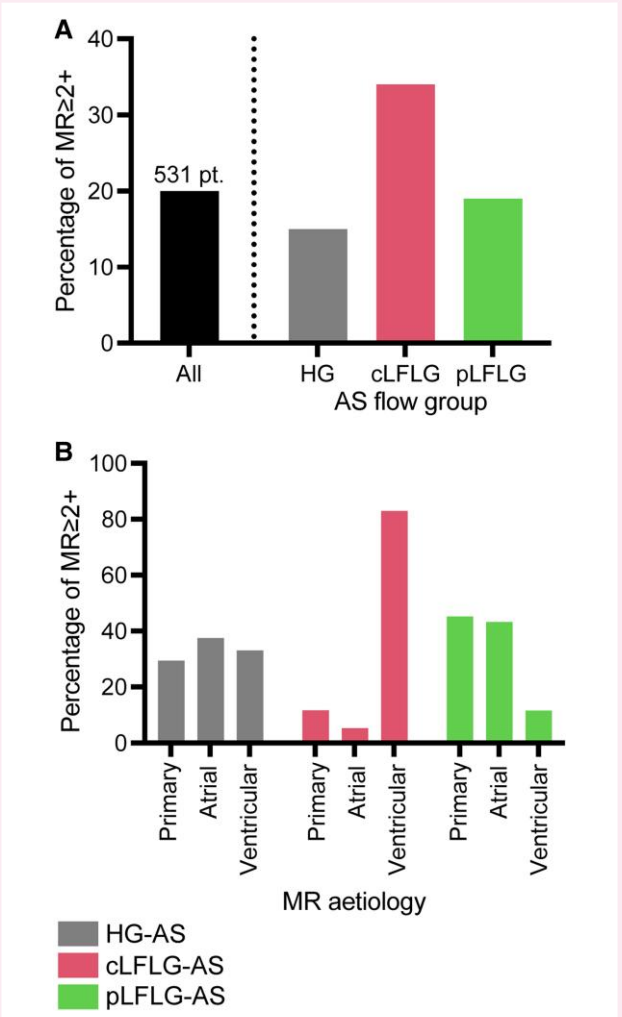


Figure 1 Fraction of at least moderate MR by groups. (*A*) Fraction of at least moderate MR (≥2) was not comparable between AS flow groups: all patients, 20.0%; HG-AS, 14.8%; cLFLG-AS, 34.2%; pLFLG-AS, 18.5% ($P < 0.01$). (*B*) When evaluating the rates of at least moderate MR by MR aetiology groups (primary vs. atrial functional vs. ventricular functional), strong differences appeared. See *Table 2* for details. AS, aortic stenosis; cLFLG, classical low-flow low-gradient AS; HG, high-gradient AS; MR, mitral regurgitation; pLFLG, paradoxical low-flow low-gradient AS.

Table 2 Patient baseline characteristics

	HG (*N* = 221)	cLFLG (*N* = 206)	pLFLG (*N* = 104)	Total (*N* = 531)	*P* value
Male sex	89 (40.3%)	134 (65.0%)	43 (41.3%)	266 (50.1%)	**<0.01**
Age (years)	83.8 [79.8–87.4]	82.5 [78.5–86.8]	82.9 [79.2–86.1]	83.1 [79.0–87.0]	0.37
Body mass index (kg/m^2)	24.6 [22.7–27.7]	24.5 [22.1–27.4]	24.6 [22.7–28.2]	24.6 [22.4–27.7]	0.59
Body surface area (m^2)	1.77 (±0.20)	1.82 (±0.19)	1.80 (±0.21)	1.77 (±0.20)	**0.01**
STS score	4.00 [2.72–6.70]	5.00 [3.01–7.15]	4.17 [2.61–6.74]	4.28 [2.92–7.00]	0.27
Diabetes mellitus	52 (23.5%)	63 (30.7%)	33 (31.7%)	148 (27.9%)	0.16
Hypertension	192 (86.9%)	190 (92.2%)	95 (91.3%)	477 (89.8%)	0.16
Smoker (active or past)	41 (18.6%)	48 (23.3%)	24 (23.1%)	113 (21.3%)	0.43
COPD	26 (13.7%)	22 (12.4%)	15 (18.8%)	63 (14.1%)	0.39
Hypercholesterolaemia	97 (43.9%)	100 (48.8%)	56 (53.8%)	253 (47.7%)	0.23
Positive family history[a]	18 (8.1%)	26 (12.6%)	11 (10.6%)	55 (10.4%)	0.32
Chronic kidney disease	101 (45.7%)	134 (65.0%)	49 (47.1%)	284 (53.5%)	**<0.01**
Atrial fibrillation	107 (48.4%)	103 (50.0%)	84 (80.8%)	294 (55.4%)	**<0.01**
Prior pacemaker	17 (7.7%)	36 (17.5%)	14 (13.5%)	67 (12.6%)	<0.01
Coronary artery disease	124 (56.1%)	146 (70.9%)	73 (70.2%)	343 (64.6%)	**<0.01**
Prior MI	23 (10.4%)	46 (22.3%)	15 (14.4%)	84 (15.8%)	**<0.01**
Prior PCI	55 (26.7%)	80 (40.0%)	40 (40.4%)	175 (34.7%)	**<0.01**

Bold values highlight statistical significance.
cLFLG, classical low-flow low-gradient aortic stenosis; COPD, chronic obstructive pulmonary disease; HG, high-gradient aortic stenosis; MI, myocardial infarction; PCI, percutaneous coronary intervention; pLFLG, paradoxical low-flow low-gradient aortic stenosis; STS score, Society of Thoracic Surgeons score.
[a]For cardiovascular disease according to the European definition.

range (IQR)] or, in case of normal distribution, as mean (± standard deviation). Normality of data distribution was assessed using the Shapiro–Wilk test. Comparisons between groups were performed using Pearson's χ^2 test or Fisher's exact test for categorical variables and Mann–Whitney *U* test or Kruskal–Wallis test for continuous variables. Bonferroni method was applied to correct for multiple testing.

Mortality was graphically displayed using Kaplan–Meier estimates and compared using log-rank test. The association of MR subtypes and AS flow groups within the group of patients with at least moderate MR was assessed by Cox proportional hazards regression. Hazard ratios (HRs) for 3-year mortality and the composite endpoint of 3-year mortality and mitral valve intervention were compared within each AS flow group and adjusted for Society of Thoracic Surgeons (STS) scores.

A $P < 0.05$ was considered statistically significant. Data analyses were performed with R (version 1.4.1717, The R Foundation for Statistical Computing, Vienna, Austria), and data visualization was performed with GraphPad Prism (version 10.2.1, GraphPad Software, San Diego, CA, USA).

Results

Study sample and clinical characteristics of MR subtypes

A total of 3815 patients undergoing TAVR for native AS at our centre between 2013 and 2021 were screened. Of the patients, 2658 fulfilled inclusion criteria and were further analysed for MR severity and AS flow group and, in case of at least moderate MR, split into MR aetiological subgroups (see Supplementary data online, *Figure S2*). A comparison of baseline characteristics of patients with or without at least moderate MR is presented in Supplementary data online, *Table S1*.

At least moderate MR was found in 531 patients (20.0%). Patients with at least moderate MR (50.1% male, median age 83.1 years) were grouped by AS flow group (HG-AS in 221, cLFLG-AS in 206, and pLFLG-AS in 104 patients) and further analysed for MR aetiology (PMR in 136, vFMR in 256, and aFMR in 136 patients). The rate of at least moderate MR differed significantly between AS flow groups, with the highest rate among cLFLG-AS patients (34.2%) and the lowest rate in HG-AS patients (14.8%; *Figure 1A*). Baseline clinical and echocardiographic data are shown in *Tables 2* and *3*. Overall, patients with cLFLG-AS or pLFLG-AS had more comorbidities than HG-AS patients.

Distribution of MR aetiologies differed considerably between different AS flow types ($P < 0.01$). Among HG-AS patients, PMR, vFMR, and aFMR aetiology were equally distributed, and among cLFLG-AS patients, vFMR was the leading aetiology of concomitant MR, and patients with pLFLG had predominantly aFMR and PMR (*Table 3* and *Figure 1B*).

Procedural results

Procedural details are presented in *Table 4*. Most patients were treated with balloon-expandable valves (73%), with the highest rate in cLFLG. In this group, aortic annuli were the largest, and the rate of post-dilatation was lowest. The two VARC-3 combination endpoints technical failure (at procedure end) and device failure (at 30 days) were comparable between groups. Also, when comparing MR subtypes, rates of the VARC-3 endpoints were comparable. Detailed VARC-3 endpoint data are displayed in Supplementary data online, *Table S2*.

Mortality

Follow-up rates were 99%, 93%, and 87% at 1, 2, and 3 years after study procedure. MR classified as at least moderate (MR ≥ 2) was associated with a significantly increased 3-year all-cause mortality compared with patients with no/mild MR {HR 1.62 [95% confidence interval (CI) 1.38–1.90], $P < 0.01$ by log rank test; *Figure 2A*}. This difference in 3-year all-cause mortality rates was predominantly seen in patients with HG-AS

Table 3 Echocardiography at baseline

	HG (*N* = 221)	cLFLG (*N* = 206)	pLFLG (*N* = 104)	Total (*N* = 531)	*P* value
Ejection fraction (%)	55.0 [45.0–58.0]	39.0 [32.0–44.0]	55.0 [51.8–55.0]	49.0 [39.5–55.0]	**<0.01**
LA area (cm^2)	27.0 [22.8–32.0]	28.1 [22.4–32.1]	29.9 [23.8–34.3]	28.0 [23.0–32.2]	**0.03**
LA volume indexed (mL/m^2)	45.1 [27.4–63.8]	48.6 [23.2–64.3]	46.9 [20.2–67.8]	46.3 [22.6–64.8]	0.93
RA area (cm^2)	20.0 [16.3–27.0]	23.1 [19.2–28.0]	23.6 [19.2–30.0]	22.4 [18.0–28.0]	**<0.01**
RA volume indexed (mL/m^2)	36.0 [26.9–53.6]	43.0 [32.7–56.1]	42.2 [32.4–60.9]	40.3 [29.9–55.7]	**<0.01**
Mitral annulus (mm)	31.0 [28.0–35.0]	32.0 [29.0–36.0]	30.0 [27.0–36.0]	31.0 [28.0–36.0]	0.06
LVIDd (mm)	4.80 [4.30–5.40]	5.30 [4.70–5.70]	4.70 [4.17–5.20]	5.00 [4.44–5.50]	**<0.01**
LVIDd indexed (mm/m^2)	2.7 (2.5, 3.0)	2.9 (2.6, 3.2)	2.5 (2.3, 2.9)	2.7 (2.5, 3.0)	<0.01
IVSd (mm)	1.30 [1.20–1.50]	1.20 [1.05–1.40]	1.30 [1.10–1.40]	1.30 [1.10–1.50]	**<0.01**
LVPWd (mm)	1.20 [1.00–1.40]	1.20 [0.99–1.32]	1.14 [1.00–1.36]	1.20 [1.00–1.40]	0.35
AVA (cm^2)	0.60 [0.49–0.72]	0.70 [0.60–0.84]	0.65 [0.58–0.80]	0.65 [0.52–0.80]	**<0.01**
AVA indexed (cm^2/m^2)	0.3 (0.3, 0.4)	0.4 (0.3, 0.5)	0.4 (0.3, 0.4)	0.4 (0.3, 0.4)	<0.01
dPmax (mmHg)	76.0 [68.0–90.0]	42.0 [32.0–52.0]	44.5 [35.8–52.0]	56.0 [40.0–73.0]	**<0.01**
dPmean (mmHg)	48.0 [43.0–56.0]	26.0 [19.2–31.0]	26.0 [21.0–33.0]	35.0 [24.0–45.5]	**<0.01**
SVi (mL/m^2)	34.8 [29.3–43.5]	26.3 [21.5–32.6]	28.2 [23.6–31.8]	30.3 [24.0–35.3]	**<0.01**
AR 1+	45 (20.4%)	38 (18.4%)	14 (13.6%)	97 (18.3%)	0.34
TR 1+	75 (36.2%)	73 (38.4%)	51 (49.5%)	199 (39.8%)	0.07
TAPSE (mm)	20.0 [17.0–24.0]	17.0 [14.0–20.0]	18.0 [15.0–21.0]	18.0 [15.0–21.0]	**< 0.01**
RV/RA gradient (mmHg)	42.0 [33.0–52.0]	40.0 [34.0–49.5]	40.0 [29.5–51.0]	40.0 [33.0–51.0]	0.20
RV/PA coupling (mm/mmHg)	0.4 [0.3–0.6]	0.3 [0.2–0.5]	0.4 [0.3–0.5]	0.4 [0.3–0.6]	0.50
MS grade					**<0.01**
0	149 (72.7%)	167 (87.9%)	76 (74.5%)	392 (78.9%)	
1	40 (19.5%)	20 (10.5%)	17 (16.7%)	77 (15.5%)	
2	14 (6.8%)	3 (1.6%)	6 (5.9%)	23 (4.6%)	
3	2 (1.0%)	0 (0.0%)	3 (2.9%)	5 (1.0%)	
MR grade					
2	169 (76.5%)	150 (72.8%)	81 (77.9%)	400 (75.3%)	
3	41 (18.6%)	51 (24.8%)	15 (14.4%)	107 (20.2%)	
4	11 (5.0%)	5 (2.4%)	8 (7.7%)	24 (4.5%)	
MR aetiology type					**<0.01**
Primary	65 (29.4%)	24 (11.7%)	47 (45.2%)	136 (25.6%)	
Atrial functional	83 (37.6%)	11 (5.3%)	45 (43.3%)	139 (26.2%)	
Ventricular functional	73 (33.0%)	171 (83.0%)	12 (11.5%)	256 (48.2%)	

Bold values highlight statistical significance.
AR, aortic regurgitation; AVA, aortic valve area; cLFLG, classical low-flow low-gradient aortic stenosis; dPmax, maximum transvalvular pressure gradient; dPmean, mean transvalvular pressure gradient; HG, high-gradient aortic stenosis; IVSd, diastolic interventricular septum diameter; LVEDd, left ventricular end-diastolic diameter; LVPWd, left ventricular posterior wall diastolic diameter; LA, left atrium; MR, mitral regurgitation; MS, mitral stenosis; pLFLG, paradoxical low-flow low-gradient aortic stenosis; RA, right atrium; RV, right ventricle; SVi, stroke volume index; TAPSE, tricuspid annular plane systolic excursion; TR, tricuspid regurgitation.

and pLFLG-AS but not in patients with cLFLG-AS (HG-AS: $P < 0.01$; pLFLG: $P < 0.01$; cLFLG: $P = 0.15$; *Figure 2B* and *C*). See Supplementary data online, *Tables S3–S5* for clinical and echocardiographic details compared by MR severity within AS flow groups.

Among the 531 patients with at least moderate MR, 3-year mortality rates in cLFLG und pLFLG patients were comparable [cLFLG-AS 47.3% (39.7–53.9%) and 48.9% (37.8–58.1%)], albeit being substantially higher than of HG patients [32.1% (25.4–38.2%), overall $P < 0.01$; Supplementary data online, *Figure S3*].

Among patients with at least moderate MR, mortality differences were found between AS flow groups but not between MR subtypes (*Figure 3*). Within the subgroups of cLFLG-AS and pLFLG-AS patients, functional MR types were not associated with an increased mortality compared with primary MR. However, vFMR was associated with an increased mortality in HG-AS patients ($P = 0.02$). Mortality differences in AS flow groups prevailed after adjustment for STS score.

MR severity development after TAVR

Echocardiographic follow-up could be obtained in 70% of patients. Median follow-up time was 295 (68–916) days (mean 611 ± 738 days). Overall, MR improved in 61.1% of these patients, but improvement rates differed significantly depending on aetiology of MR at baseline (PMR: 41.1%, vFMR: 48.3%, aFMR: 71.7%, $P < 0.01$; *Figure 4A*). In

Table 4 Procedural characteristics

	HG (*N* = 221)	cLFLG (*N* = 206)	pLFLG (*N* = 104)	Total (*N* = 531)	*P* value
Annulus area (mm^2)	4.42 [3.96–5.01]	5.04 [4.47–5.64]	4.20 [3.71–4.93]	4.72 [4.07–5.34]	**<0.01**
Annulus perimeter (mm)	76.8 [72.7–82.0]	82.2 [76.8–87.3]	75.3 [69.4–80.7]	79.0 [73.5–84.2]	**<0.01**
Balloon-expandable valve	153 (69.2%)	171 (83.0%)	66 (63.5%)	390 (73.4%)	**<0.01**
Prosthesis size (mm)	26.0 [23.0–27.0]	26.0 [26.0–29.0]	26.0 [23.0–27.0]	26.0 [25.0–29.0]	**<0.01**
Pre-dilatation	177 (80.1%)	129 (62.6%)	65 (62.5%)	371 (69.9%)	**<0.01**
Post-dilatation	18 (8.1%)	9 (4.4%)	9 (8.7%)	36 (6.8%)	0.21
PCI during TAVR	19 (8.6%)	32 (15.5%)	16 (15.4%)	67 (12.6%)	0.06
VARC-3 endpoint technical failure	8 (3.6%)	7 (3.4%)	8 (7.7%)	23 (4.3%)	0.17
VARC-3 endpoint device failure	26 (11.8%)	27 (13.1%)	17 (16.3%)	70 (13.2%)	0.52

Bold values highlight statistical significance.
cLFLG, classical low-flow low-gradient aortic stenosis; HG, high-gradient aortic stenosis; PCI, percutaneous coronary intervention; pLFLG, paradoxical low-flow low-gradient aortic stenosis; TAVR, transcatheter aortic valve replacement; VARC-3, Valve Academic Research Consortium.

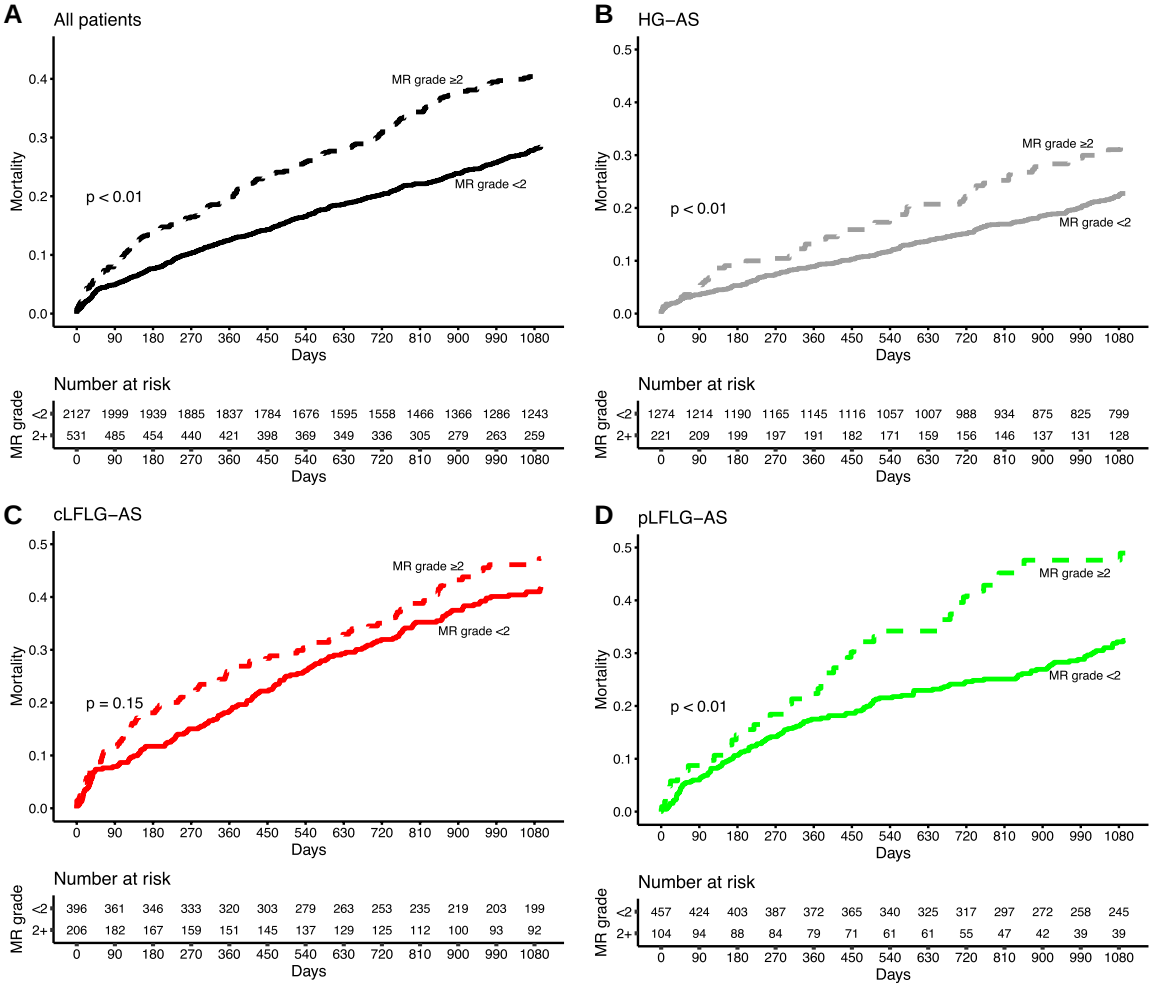


Figure 2 Kaplan–Meier curves for 3-year all-cause mortality stratified for MR grade by AS flow group. Kaplan–Meier estimates for 3-year all-cause mortality after TAVI, stratified by baseline MR. (*A*) At least moderate MR was associated with a significantly increased 3-year mortality [MR ≥ 2, 41.3 (95% CI, 36.8–45.5%), MR < 2, 28.4 (95% CI, 26.4–30.4%; HR 0.47 (0.33–0.67)]. Subgroup analyses were performed for AS flow groups (*B* and *C*). Differences in 3-year mortality between at least moderate MR and MR < 2 could be found in HG-AS und pLFLG-AS but not cLFLG-AS patients. Mortality rates were as follows: (*B*) HG: MR ≥ 2, 32.1 (95% CI, 25.4–38.2%); MR < 2, 22.7 (95% CI, 20.3–25.1%). (*C*) cLFLG: MR ≥ 2, 47.3 (95% CI, 30.7–53.9%); MR < 2, 41.9 (95% CI, 36.7–46.7%). (*D*) pLFLG: MR ≥ 2, 48.9 (95% CI, 37.8–58.1%); MR < 2, 32.4 (95% CI, 27.8–36.8%).

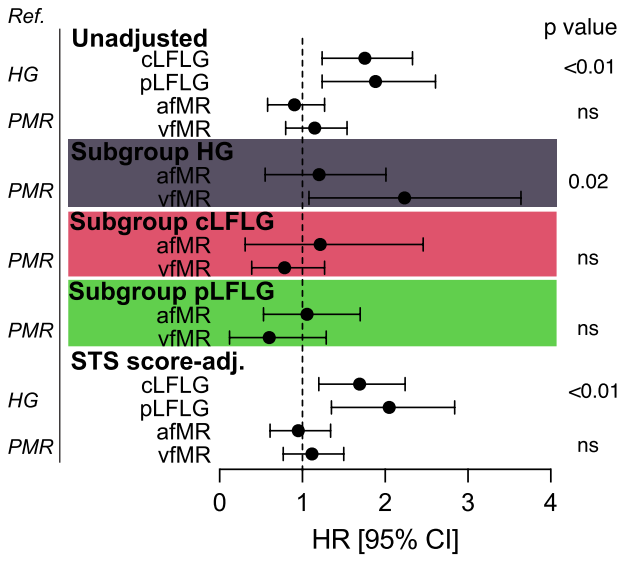


Figure 3 Cox proportional hazards model for 3-year all-cause mortality. This figure demonstrates the results of the Cox proportional hazard analysis depicted in a forest plot. Shown is the individual impact of flow group and MR aetiology on outcome. Above, we demonstrate the unadjusted regression analysis, in the middle the subgroups, and on the bottom the STS score adjusted results. aFMR, atrial functional mitral regurgitation; cLFLG, classical low-flow low-gradient aortic stenosis; HG, high-gradient aortic stenosis; HR, hazard ratio; pLFLG, paradoxical low-flow low-gradient aortic stenosis; pMR, primary mitral regurgitation; STS score, Society of Thoracic Surgeons score; vFMR, ventricular functional mitral regurgitation; 95% CI, 95% confidence interval.

addition, improvement of MR was different between AS flow groups. Rates of improvement were highest in HG-AS (67.2%) and cLFLG patients (61.0%). Patients with pLFLG AS showed significantly lower rates of MR improvement following TAVR (48.7%, $P = 0.03$ compared with HG-AS; *Figure 4B*). In all three AS flow groups, aFMR had the highest chance of improvement after TAVR (*Figure 4C*).

Overall, improvement of MR after TAVR was associated with a decreased overall 3-year mortality [HR 0.47 (95% CI, 0.33–0.67); *Figure 5A*]. This effect was found in HG-AS and cLFLG-AS patients but not in pLFLG-AS patients (*Figure 5B–D*). An additional Kaplan–Meier curve showing mortality curves from the time of echo follow-up is shown in Supplementary data online, *Figure S4*. A timeline with an overview on the outcomes of AS flow groups is demonstrated in Supplementary data online, *Figure S5*. Clinical and echocardiographic characteristics comparing patients with or without improvement of MR are shown in Supplementary data online, *Table S6*. Patients lacking an improvement had slightly higher STS scores (4.9 vs. 4.0), lower mean transvalvular gradients prior to TAVR (29 vs. 36 mmHg), and slightly worse RV function (TAPSE 17.0 vs. 18.0 mm). MR improvement was an independent predictor for 3-year mortality in a multivariate Cox regression analysis (HR 0.51, 95% CI: 0.33–0.79, $P = 0.003$; Supplementary data online, *Table S8*).

During echocardiography follow-up, worsened MR or mitral valve intervention for MR was observed in 39 patients in total (11.0%), with a significant difference between groups: HG-AS, 10 patients (7.3%); cLFLG-AS, 14 patients (9.9%); and pLFLG-AS, 15 patients (19.7%) ($P = 0.02$).

Symptomatic improvement

TAVR patients with concomitant MR showed significant overall symptomatic improvement at follow-up (see Supplementary data online, *Figure S6*). Symptomatic improvement following TAVR was generally comparable between MR subtypes and AS flow groups without significant differences. However, there was a lower symptomatic benefit in patients with pLFLG-AS (only 75.0% compared with 86.0% in cLFLG-AS, $P = 0.017$). Improvement of MR after TAVI corresponded to a more pronounced improvement of NYHA functional class (83.8% vs. 71.2%, $P = 0.03$).

Discussion

In our retrospective study, we performed a detailed pathophysiological and anatomical workup of patients suffering from high-gradient and low-flow low-gradient aortic stenosis and concomitant MR. We explored the relationship between different flow groups seen in AS patients undergoing TAVR in the context of different aetiologies of concomitant MR. We found (i) that at least moderate MR is most often found in classical LFLG patients and (ii) is associated with increased mortality in HG and paradoxical LFLG patients but less in classical LFLG patients and (iii) that MR persistence after TAVR is most often seen in paradoxical LFLG patients.

Previous studies have underlined the prognostic significance of concomitant MR in TAVR patients.[14,15,17,18] To our knowledge, this is the first detailed analysis of a large TAVR patient cohort with multivalvular heart disease that categorizes the aetiology of concurrent MR considering different flow groups of AS.

Managing multivalvular heart disease is a complex clinical endeavour, with limited treatment recommendations in the guidelines.[12] Faced with two valve defects with specific pathophysiologies, heart team specialists must engage in a sophisticated decision-making process. The lack of scientific data on this relevant multivalvular heart disease cohort further complicates these decisions, making a detailed pathophysiological evaluation of these patients critical for assessing the procedural and long-term benefits of TAVR.

MR often co-occurs in patients with severe AS and is linked to poorer outcomes post-TAVR. Recent studies have emphasized the

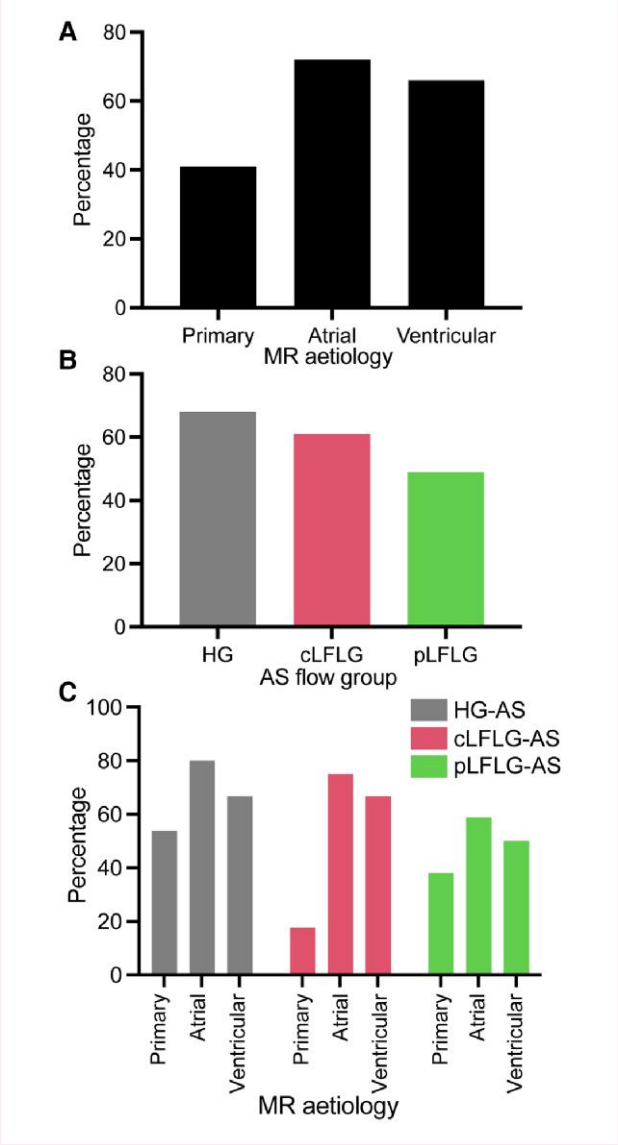


Figure 4 Improvement of MR after TAVR. Follow-up echocardiography was available for 70% of the patients. Among patients with at least moderate MR, improvement of MR was dependent on its aetiology (*A*) and AS flow group, with the lowest improvement rate in pLFLG-AS (*B*). (*C*) Differences between MR aetiology within AS flow groups were mainly found in cLFLG-AS patients ($P < 0.01$) but not in HG-AS ($P = 0.06$) or pLFLG-AS patients ($P = 0.21$).

importance of detailed categorization of MR aetiology into three groups: degenerative/primary, ventricular functional, and atrial functional. Post-TAVR reduction in afterload has been shown to effectively lessen the severity and symptoms of MR, particularly in cases of aFMR and vFMR.[21] This seems logical considering that the reduction in afterload reduces LV and LA filling pressures. Thus, a thorough multifactorial echocardiographic assessment of MR aetiology prior to TAVR could be advantageous to identify patients needing a closer follow-up for their concomitant mitral valve disease.

Patients with AS are very heterogeneous, with various flow patterns impacting post-TAVR outcomes differently. While TAVR seems beneficial for symptomatic relief and quality of life regardless of the flow groups, survival rates post-procedure vary notably among different AS flow groups.[11,23,31–33] Accordingly, differences were observed in the present study: the distribution of MR aetiologies and prognostic impact of severity significantly differ between AS flow groups. These observations reinforce the notion that AS patients of different flow groups need tailored treatment approaches.

Pathophysiologic explanations for this are difficult. MR can arise from the afterload-induced rise in LV pressure (e.g. in cLFLG-AS patients), but additional pathologies appear to exacerbate the severity of concurrent MR. Particularly, the presence of pLFLG-AS and concomitant significant MR may signal a separate underlying cardiac pathology affecting post-TAVR outcomes. This fact is certainly underlined by two observations: firstly, low MR improvement rates in pLFLG patients and, secondly, improvement of MR in pLFLG patients had no impact on 3-year mortality (in contrast to the other flow groups). Our findings in patients with pLFLG-AS warrant additional consideration. This subgroup often presents with pronounced concentric left ventricular hypertrophy and smaller cavity sizes, which, despite a preserved ejection fraction, can lead to impaired stroke volume and a blunted response to afterload reduction following TAVR. The co-existence of significant MR in these pLFLG-AS patients may further complicate the haemodynamic assessment and outcomes, potentially by influencing the true transmitral and transaortic gradients or by contributing to persistent symptoms if the MR itself is not adequately addressed or does not improve sufficiently post-TAVR.

Generally, mortality in pLFLG-AS patients is lower compared with cLFLG-AS patients. Nevertheless, while the presence of at least moderate MR showed no significant impact on mortality in cLFLG-AS patients, it appears to be of high relevance in pLFLG-AS patients undergoing TAVR, lifting mortality rates to the level of cLFLG-AS patients. Whether MR is the cause for low-flow conditions in pLFLG-AS patients remains subject of investigation. Nevertheless, our data demonstrate that pLFLG patients are very similar to HFpEF patients (sustained LVEF, higher rates of aFMR and PMR) which supports the fact that an additional underlying pathology, not sufficiently addressed by TAVR remains and causes higher mortality rates.

More research is required to elucidate the connections between MR aetiology and TAVR outcomes in the context of multivalvular heart disease, especially in the context of pLFLG AS. Future studies should consider both, the severity and the cause of MR when evaluating their impact on TAVR outcomes. Furthermore, these studies should consider different underlying cardiac pathologies associated with both, AS and MR. Especially the pathophysiological question of paradoxical low-flow conditions as a potential consequence of MR remains unanswered.

Our study's findings bear significant implications for the management of severe AS patients with concomitant MR. Meticulous patient selection and risk stratification, considering MR aetiology, severity, and AS flow type, could identify patients with a higher need for a closer follow-up regarding their concomitant mitral valve disease. Additionally, as recently proposed, multi-modality imaging should form an integral part of the multi-disciplinary heart team discussion on the choice of treatment in these complex patients.[34] For instance, patients with HG- and cLFLG-AS and concomitant MR may have a higher beneficial potential and thus be more apt candidates for TAVR. Conversely, patients with concomitant primary MR or pLFLG may necessitate additional treatment to tackle the underlying cardiac pathology and optimize cardiac function before/after TAVR.[21,35]

Additionally, our study accentuates the necessity for further research to grasp the impact of concomitant atrioventricular valve pathologies on TAVR outcomes. Future investigations should probe the advantages of different treatment strategies for severe AS patients with different MR aetiologies. For example, adjunctive mitral valve procedures in patients with primary MR could bolster TAVR outcomes. Especially patients with pLFLG-AS did not benefit sufficiently from TAVR alone and might represent patients who can benefit from a dual valve intervention combining TAVR with M-TEER, which needs to be evaluated in future research. Unfortunately, our retrospective analysis cannot test this hypothesis.

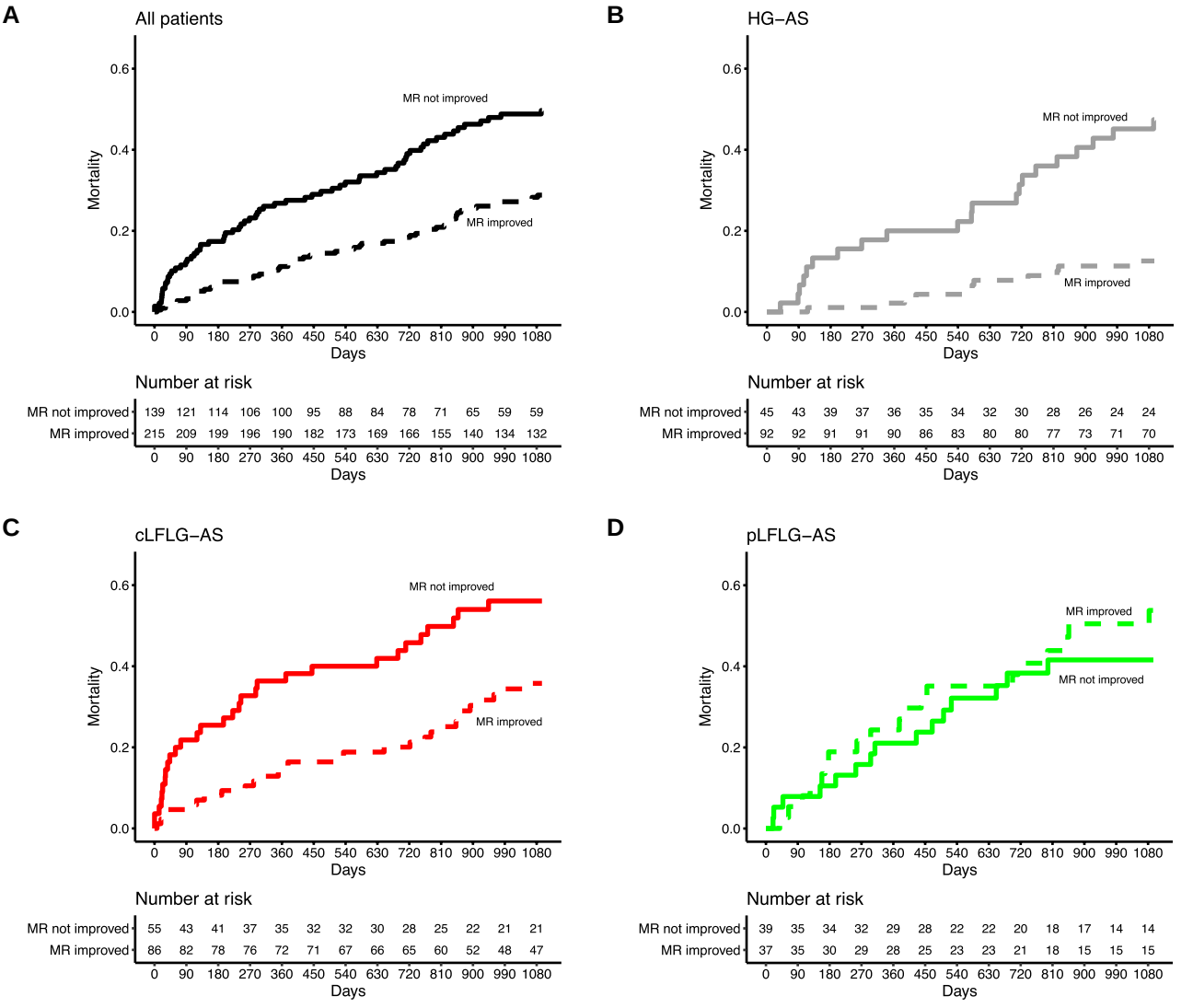


Figure 5 Kaplan–Meier curves for 3-year all-cause mortality stratified by improvement of MR after TAVR. Patients from the main cohort (at least moderate MR) were assessed for improvement of MR after TAVR. Echocardiographic follow-up was available in 70% of patients. (*A*) In the study cohort, MR improvement was associated with a significantly lower incidence of the combined endpoint [improvement, 28.8 (95% CI, 22.3–34.8%), vs. no improvement, 49.7 (95% CI, 40.3–57.6%), $P < 0.01$]. Analyses for the three AS flow groups are shown in (*B*) and (*C*). Incidences were as follows: (*B*) HG: improvement, 12.6 (95% CI, 5.3–19.3%), vs. no improvement, 47.4 (95% CI, 30.4–60.3%), HR 0.21 (0.10–0.43), $P < 0.01$. (*C*) cLFLG: improvement, 35.8 (95% CI, 24.3–45.5%), vs. no improvement, 56.1 (95% CI, 40.3–67.7%), HR 0.48 (0.29–0.79), $P < 0.01$. (*D*) pLFLG: improvement, 53.8 (95% CI, 33.6–67.9%), vs. no improvement, 41.6 (95% CI, 22.8–57.6%), HR 1.32 (0.67–2.59), $P = 0.43$.

Moreover, research should investigate the potential benefits of early antiarrhythmic therapy in TAVR patients with concurrent aFMR and/or pLFLG-AS, considering a majority of these patients in our cohort has atrial fibrillation.

Study limitations

Several limitations have to be acknowledged and mostly derive from the retrospective nature of the study. Despite the detailed classification of atrial functional MR, the retrospective adjudication of MR aetiology is prone to possible overlap between aFMR and vFMR and possible inter-observer variability. Additionally, our retrospective study design meant that patients who underwent subsequent mitral valve interventions were categorized as having 'persistent MR' based on their last available echocardiogram prior to the intervention. This approach may not fully capture the prognostic implications of a later 'MR correction' and represents a limitation of our current analysis, which is constrained by the small number of such events. Assumptions regarding the benefit from TAVR compared with optimal medical therapy cannot be made. Also, missing echocardiographic follow-up information in about 30% of patients and non-uniform timing of echocardiographic follow-up have to be acknowledged as a relevant selection bias. Moreover, distribution of patients into AS flow groups and further into MR severity or aetiology subgroups led to small group sizes and limits statistical power. Additionally, it has to be acknowledged that dobutamine stress echocardiography in classical LFLG-AS patients has not been performed

routinely to exclude pseudo-severe AS. Therefore, according to the current guidelines, moderate AS may have been present in some of these patients.

Conclusions

Our study offers real-world insights into the complex interplay of MR aetiologies and different AS flow groups. The data suggest that relief of aortic stenosis might not be the only therapy necessary and early mitral valve treatment should be considered in selected patients, too. Particularly, TAVR patients with more than mild MR at baseline or patients with low-flow low-gradient flow state may profit from a more frequent follow-up.

Impact on daily practice

This study highlights the importance of tailoring post-TAVR management based on AS flow types and MR aetiology. In general, our data support the approach to primarily perform TAVR in patients with multivalvular disease knowing, that MR is likely to improve after the procedure. Additionally, understanding that MR severity and improvement have distinct prognostic implications across AS subgroups emphasizes the need for a closer follow-up for the first years, particularly in low-flow low-gradient AS patients. In these patients, a scheduled follow-up visit for the MR evaluation might be recommendable, because identifying patients with persistent or severe MR despite TAVR may prompt consideration of adjunctive MR interventions such as M-TEER to optimize outcomes. This approach can help refine individualized care strategies and improve long-term survival in these complex patient populations.

Supplementary data

Supplementary data are available at *European Heart Journal - Cardiovascular Imaging* online.

Author contributions

Philipp M. Doldi (Conceptualization [lead], Formal analysis [equal], Investigation [lead], Project administration [lead], Software [lead], Validation [equal], Visualization [equal], Writing—original draft [lead], Writing—review & editing [equal]), Julius Steffen (Conceptualization [lead], Data curation [lead], Formal analysis [lead], Investigation [equal], Methodology [equal], Project administration [lead], Software [equal], Visualization [equal], Writing—original draft [supporting], Writing—review & editing [equal]), Antonia Gehlich (Data curation [supporting], Investigation [equal]), Maximilian Tischmacher (Data curation [supporting], Writing—review & editing [supporting]), Carolin Fröhlich (Data curation [supporting], Writing—review & editing [supporting]), Konstantin Stark (Data curation [supporting], Methodology [supporting], Writing—review & editing [supporting]), Magda Haum (Data curation [supporting], Writing—review & editing [supporting]), Julius Fischer (Data curation [supporting]), Lukas Stolz (Data curation [supporting], Methodology [supporting], Writing—review & editing [supporting]), Kornelia Loew (Data curation [supporting]), Hans Theiss (Methodology [supporting]), Konstantinos Rizas (Data curation [supporting], Methodology [supporting]), Sven Peterß (Methodology [supporting]), Jörg Hausleiter (Writing—review & editing [supporting]), Steffen Massberg (Data curation [supporting], Methodology [supporting], Supervision [supporting], Validation [supporting]), and Simon Deseive (Conceptualization [lead], Data curation [lead], Methodology [lead], Supervision [lead], Validation [equal], Writing—review & editing [lead])

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Data availability

The data underlying this article will be shared on reasonable request to the corresponding author.

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