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Mitral Regurgitation in Low-Flow, Low-Gradient Aortic Stenosis Patients Undergoing TAVR

Insights From the TOPAS-TAVI Registry

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ABSTRACT

OBJECTIVES This study sought to determine the incidence, clinical impact, and changes over time of mitral regurgitation (MR) in patients with low-flow, low-gradient aortic stenosis (LFLG-AS) undergoing transcatheter aortic valve replacement (TAVR).

BACKGROUND Few data exist on the clinical impact and changes in severity over time of MR in patients with LFLG-AS undergoing TAVR.

METHODS A total of 308 TAVR candidates with LFLG-AS were included. Patients were categorized according to MR severity at baseline, and presence of MR improvement at 12-month follow-up. Clinical outcomes were assessed at 1 and 12 months (+ echocardiography), and yearly thereafter.

RESULTS Baseline mild and moderate-to-severe MR were present in 118 (38.3%) and 115 (37.3%) patients, respectively. MR was of functional and mixed etiology in 77.2% and 22.7% of patients, respectively. A total of 131 patients (42.5%) died after a median follow-up of 2 (1 to 3) years. Baseline moderate-or-greater MR had no impact on mortality (hazard ratio [HR]: 1.34; 95% confidence interval [CI]: 0.72 to 2.48) or heart failure hospitalization (HR: 1.02; 95% CI: 0.49 to 2.10). At 1-year follow-up, MR improved in 44.3% of patients and remained unchanged/worsened in 55.7%. The lack of MR improvement was associated with a higher risk of all-cause and cardiac mortality (HR: 2.02; 95% CI: 1.29 to 3.17; HR: 3.03; 95% CI: 1.27 to 7.23, respectively), rehospitalization for cardiac causes (HR: 1.50; 95% CI: 1.04 to 2.15), and an increased overall-mortality/heart failure rehospitalization (HR: 1.94; 95% CI: 1.25 to 3.02). A higher baseline left ventricular end-diastolic diameter and a higher increase in left ventricular ejection fraction were found to be independent predictors of MR improvement at 1-year follow-up (odds ratio: 0.69; 95% CI: 0.51 to 0.94; and odds ratio: 0.81; 95% CI: 0.67 to 0.96, respectively).

CONCLUSIONS Most TAVR candidates with LFLG-AS had some degree of MR, of functional origin in most cases. MR improved in about one-half of patients, with larger left ventricular size and a higher increase in left ventricular ejection fraction post-TAVR determining MR improvement over time. The lack of MR improvement at 1 year was associated with poorer outcomes. (J Am Coll Cardiol Intv 2020;13:567–79)
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ABBREVIATIONS AND ACRONYMS

AS = aortic stenosis

CI = confidence interval

HF = heart failure

HR = hazard ratio

LFLG-AS = low-flow, low-gradient aortic stenosis

LV = left ventricular

LVEDD = left ventricular end-diastolic diameter

LVEF = left ventricular ejection fraction

MR = mitral regurgitation

TAVR = transcatheter aortic valve replacement

Patients with classical low-flow, low-gradient (LFLG) aortic stenosis (AS) represent around 5% to 10% of the population with severe AS (1). This entity is associated with a higher perioperative mortality and worse long-term outcomes (survival rates <50% at 3-year follow-up) when compared with patients with high-gradient AS and/or preserved left ventricular ejection fraction (LVEF) (1). Additionally, an important proportion of these patients have functional mitral regurgitation (MR), in part caused by enlarged left ventricular (LV) cavities and associated ischemic cardiomyopathy. The presence of significant MR at baseline and its persistence following aortic valve replacement (either surgical aortic valve replacement or transcatheter aortic valve replacement [TAVR]) has also been associated with a worse survival (2–5).

Surgery has been shown to improve mid- and long-term survival in patients with LFLG-AS but is linked with a high perioperative risk (6–11). On the other hand, some studies including the TOPAS-TAVI (True or Pseudo-Severe Aortic Stenosis-Transcatheter Aortic Valve Implantation) registry showed that TAVR seems to be a safe alternative to surgery, with satisfactory early and late outcomes (12,13). However, information regarding the impact of MR in patients with classical LFLG-AS is scarce. The objectives of our study were to determine in TAVR candidates with LFLG-AS: 1) the incidence, severity, and type of MR; 2) the clinical impact of significant MR at baseline (pre-TAVR); and 3) the changes in MR severity over time and its impact on clinical outcomes.

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METHODS

STUDY POPULATION. This is a substudy of the ongoing TOPAS-TAVI multicenter registry (NCT01835028), including consecutive patients with classical LFLG-AS undergoing TAVR. Classical LFLG-AS was defined as an aortic valve area <1 cm^2 or an indexed aortic valve area ≤0.6 cm^2/m^2, a mean transvalvular gradient <35 mm Hg, and a LVEF ≤40%. Patient recruitment started in January 2013, and all data were prospectively entered into a dedicated database. Additionally, data were retrospectively collected in 9 out of the 14 participating sites from 2007 to 2013, leading to a final study population of 308 patients.

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TABLE 1 Clinical, Echocardiographic, Procedural Characteristics, and 30-Day Outcomes of the Study Population, Overall and According to the Severity of MR (N = 308)

	All Patients (N = 308)	Patients With MR ≤ Mild (n = 193)	Patients With MR ≥ Moderate (n = 115)	p Value
Clinical variables				
Age, yrs	80.5 ± 7.2	80.5 ± 7.1	80.5 ± 7.5	0.945
Female	83 (27.0)	48 (24.9)	35 (30.4)	0.292
BMI, kg/m^2	26.7 ± 5.5	27.0 ± 5.7	26.3 ± 5.1	0.253
Diabetes mellitus	128 (41.6)	74 (38.3)	54 (47.0)	0.150
Hypertension	257 (83.4)	160 (82.9)	97 (84.3)	0.874
Active smokers	12 (3.9)	8 (4.2)	4 (3.5)	1.000
Peripheral artery disease	88 (28.6)	57 (29.5)	31 (27.0)	0.794
Coronary artery disease	227 (73.7)	141 (73.1)	86 (74.8)	0.688
Prior myocardial infarction	110 (35.7)	75 (38.9)	35 (30.4)	0.141
Prior CABG	123 (39.9)	73 (37.8)	50 (43.5)	0.335
Atrial fibrillation	142 (46.1)	91 (47.2)	51 (44.4)	0.636
NYHA functional class III-IV	253 (82.1)	155 (80.3)	98 (85.2)	0.276
COPD	104 (33.8)	67 (34.7)	37 (32.2)	0.709
Hemoglobin, g/dl	12.0 ± 1.7	12.1 ± 1.8	11.8 ± 1.6	0.150
CKD (eGFR 60 ml/min/m^2)	157 (51.0)	97 (50.3)	60 (52.2)	0.814
LBBB	66 (21.4)	44 (22.8)	22 (19.1)	0.474
STS-PROM, %	7.7 (5.3–11.9)	8.0 (5.0–12.0)	8.0 (5.4–11.2)	0.954
Echocardiographic variables				
LVEF, %	30.7 ± 9.4	32.3 ± 9.1	28.0 ± 9.4	<0.001
Mean aortic gradient, mm Hg	26 ± 7	26 ± 7	25 ± 7	0.044
Aortic valve area, cm^2	0.8 ± 0.2	0.7 ± 0.2	0.8 ± 0.2	0.614
Type of MR etiology*				0.029
MR functional	180/233 (77.2)	98/118 (83.0)	82/115 (71.3)	
MR mixed	53/233 (22.7)	20/118 (16.9)	33/115 (28.7)	
LAD, mm	45.6 ± 9.8	45.4 ± 9.2	45.8 ± 10.8	0.801
LVESD	44.7 ± 9.3	43.9 ± 9.8	46.2 ± 8.4	0.047
LVEDD	53.9 ± 8.8	53.5 ± 9.3	54.7 ± 7.8	0.290
Moderate-to-severe AR	42 (13.6)	22 (11.4)	20 (17.4)	0.166
Aortic annulus, mm	21.5 ± 2.2	21.5 ± 2.1	21.7 ± 2.2	0.530
Stroke-volume indexed, ml/min/m^2	29.3 ± 8.1	29.4 ± 8.1	29.2 ± 8.1	0.786
Pulmonary systolic artery pressure, mm Hg	46.9 ± 14.4	44.2 ± 13.5	50.9 ± 14.9	0.001
Dobutamine contractile reserve	79/241 (32.8)	49/138 (35.5)	30/103 (29.1)	0.894
Procedural variables				
Prosthesis type				
Balloon expandable	249 (80.8)	148 (76.7)	101 (87.8)	0.017
Valve generation				
Old generation	274 (89.0)	170 (88.0)	104 (90.4)	0.577
New generation	34 (11.0)	23 (11.9)	11 (9.6)	
Prosthesis size, mm				
≤23	62 (20.1)	33 (17.1)	29 (25.2)	0.106
Approach				
TF	220 (71.4)	138 (71.5)	82 (71.3)	1.000
Post-dilatation	52 (16.9)	32 (16.6)	20 (17.4)	1.000
Post-procedure echocardiography				
Aortic mean gradient, mm Hg	8.8 ± 3.8	8.8 ± 3.8	8.8 ± 3.7	0.989
Aortic valve area, cm^2	1.69 ± 0.56	1.68 ± 0.53	1.72 ± 0.60	0.560
Residual moderate-to-severe AR	23 (7.5)	10 (5.2)	13 (11.3)	0.040
30-day outcomes				
Death	11 (3.6)	6 (3.1)	5 (4.3)	0.767
All stroke	7 (2.3)	6 (3.1)	1 (0.9)	0.257
Disabling	3 (1.0)	2 (1.0)	1 (0.9)	–
Nondisabling	4 (1.3)	4 (2.1)	0 (0.0)	–
Myocardial infarction	4 (1.3)	2 (1.0)	2 (1.7)	0.641
Major/life-threatening bleeding	18 (5.8)	14 (7.3)	4 (3.5)	0.210
Need for hemodynamic support	18 (5.8)	11 (5.7)	7 (6.1)	1.000

Values are mean ± SD or n (%). *Patients with none/trace MR excluded.

AR = aortic regurgitation; BMI = body mass index; CABG = coronary artery bypass grafting; CKD = chronic kidney disease; COPD = chronic obstructive pulmonary disease; eGFR = estimated glomerular filtration rate; LAD = left atrium diameter; LBBB = left bundle branch block; LVEDD = left ventricular end-diastolic diameter; LVEF = left ventricular ejection fraction; LVESD = left ventricular end-systolic diameter; MR = mitral regurgitation; NYHA = New York Heart Association; STS-PROM = Society of Thoracic Surgeons-Predicted Risk of Mortality; TF = transfemoral.

TABLE 2 Long-Term Clinical Outcomes According to Baseline MR Severity

	Overall (N = 308)	Patients With MR < Moderate (n = 193)	Patients With MR ≥ Moderate (n = 115)	HR* (95% CI)	p Value
Cumulative mortality	131 (42.5)	82 (42.5)	49 (42.6)	1.34 (0.72–2.48)	0.355
Cumulative cardiac mortality	62 (20.1)	43 (22.3)	19 (16.5)	0.91 (0.43–1.94)	0.808
Rehospitalization global	137 (44.5)	90 (46.6)	47 (40.9)	0.77 (0.53–1.12)	0.174
Rehospitalization for HF	68 (22.1)	45 (23.3)	23 (20.0)	1.02 (0.49–2.10)	0.962
Rehospitalization for cardiac causes	103 (33.4)	68 (35.2)	35 (30.4)	0.91 (0.48–1.70)	0.766
Cumulative mortality and/or rehospitalization for HF	165 (53.6)	104 (53.9)	61 (53.0)	1.22 (0.74–2.00)	0.430

Values are n (%), unless otherwise indicated. *Adjusted for baseline characteristics.
CI = confidence interval; HF = heart failure; HR = hazard ratio; other abbreviation as in Table 1.

Indications for TAVR, device type, and approach were left at the discretion of the heart team at each participating center. The registry used a web-based case report form and remote electronic data monitoring was performed in all cases to actively search and correct missing and/or inconsistent information. Patients were followed by clinical visits or telephone contact at 1 and 12 months, and yearly thereafter. Clinical events were recorded and defined according to the VARC-2 (Valve Academic Consortium) criteria (14). The local institutional review board of each center approved the study and written informed consent was obtained from all patients recruited prospectively. For those patients recruited retrospectively, written informed consent was waived by the institutional review board, which approved the study.

ECHOCARDIOGRAPHIC EVALUATION. Transthoracic echocardiography was performed before TAVR, at hospital discharge, and at 1-year follow-up according to the recommendations of the American Society of Echocardiography (15). MR was graded as none/trace, mild, moderate, and severe using a multiparametric integrative approach in accordance with current guidelines at each participating center (15). Additionally, MR was further classified as predominantly functional (secondary), organic (primary), or mixed etiology (organic and functional). After excluding patients with baseline none/trace MR, any decrease of at least 1 degree was considered an improvement in MR severity.

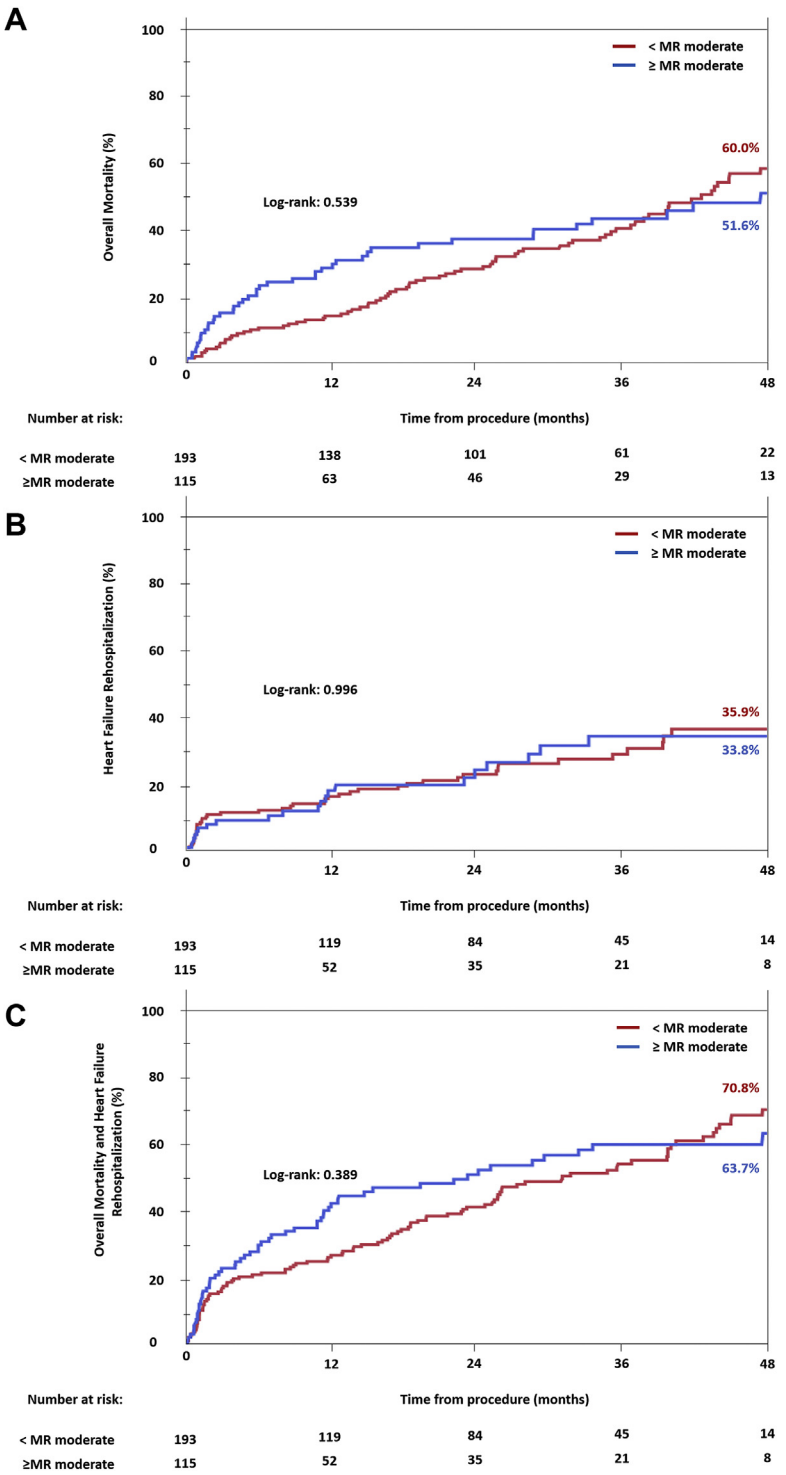
A dobutamine stress echocardiography was performed at baseline in 241 patients (78.2%) according to standard protocols (16,17). Contractile reserve was defined as an increment of at least 20% in stroke volume during dobutamine infusion.

STATISTICAL ANALYSIS. Categorical variables were expressed as a number (percentage) and continuous variables as mean ± SD or median (interquartile range: 25th to 75th percentile). Assessment of normality was performed using the Shapiro-Wilk test. Comparison of qualitative variables was performed with the chi-square or Fisher exact test. Quantitative variables were analyzed with a 2-sided Student's *t*-test or median test. A linear-mixed model analysis with repeated measurements analysis was used to evaluate changes in LVEF and left ventricular end-diastolic diameter (LVEDD) over the period between baseline and 1-year follow-up. A logistic regression model was performed to determine independent predictors of MR improvement at 1-year follow-up. Those variables from the univariable analysis with a p value < 0.10 were entered into a multivariable regression analysis. Clinical outcomes (all-cause death, cardiovascular death, heart failure [HF] hospitalization) according to baseline MR (moderate or severe) and MR improvement were determined and adjusted by baseline differences between groups using a proportional hazard model. Clinical events over time were also calculated with the Kaplan-Meier method, and the log-rank test was applied for comparison between groups. A p value < 0.05 was considered significant. Analyses were performed using the statistical packages SAS version 9.4 (SAS Institute, Cary, North Carolina).

RESULTS

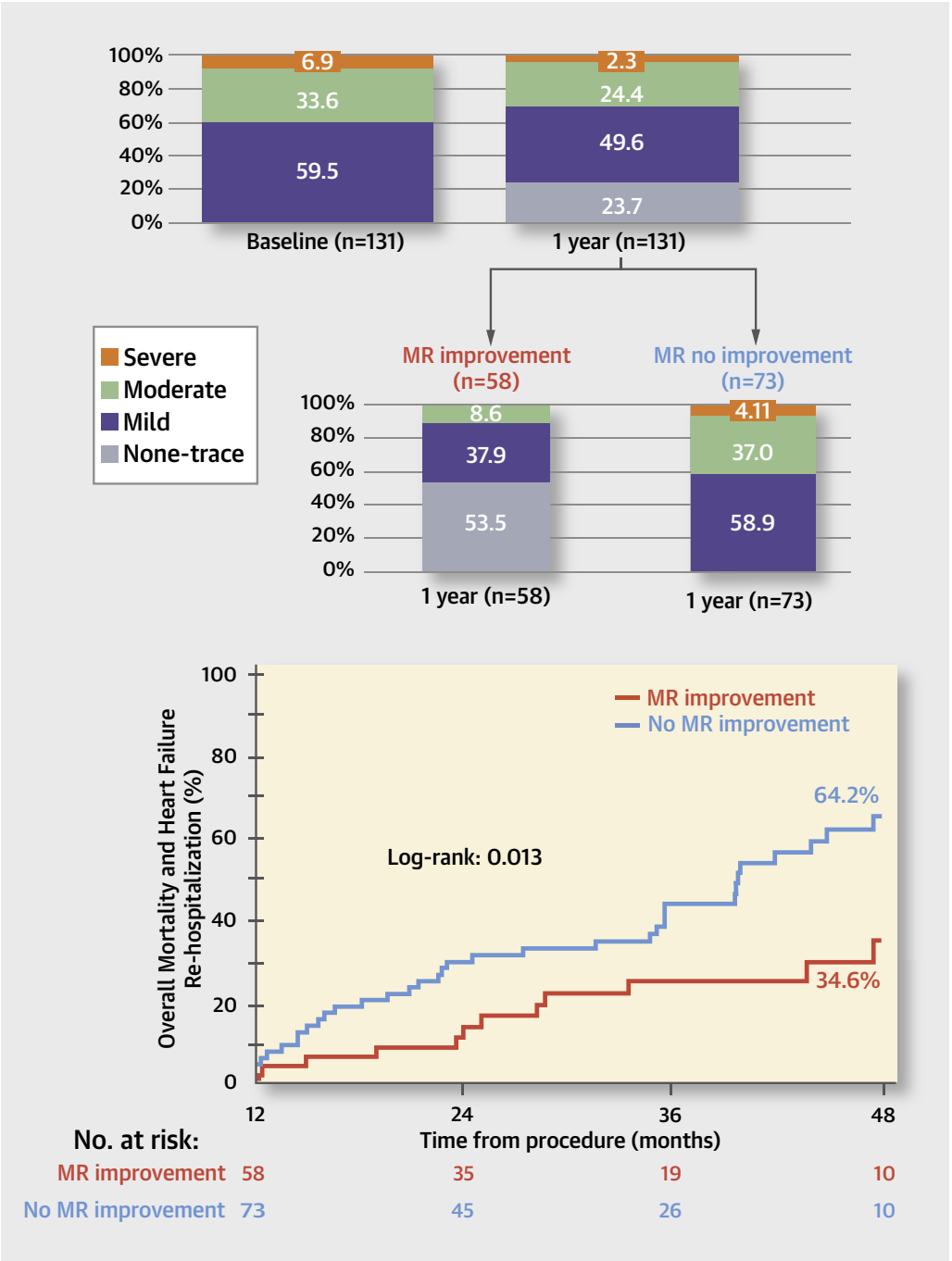
The clinical, echocardiographic, and procedural characteristics of the study population, overall (n = 308) and according to the degree of MR (mild or less, n = 193 [62.7%]; moderate or severe, n = 115 [37.3%]), are summarized in Table 1. The mean age of

FIGURE 1 Kaplan-Meier Curves for Overall Mortality and Heart Failure Rehospitalization According to Baseline MR



Kaplan-Meier curves for **(A)** overall mortality, **(B)** heart failure rehospitalization, and **(C)** the combined endpoint of overall mortality and heart failure rehospitalization according to baseline mitral regurgitation. MR = mitral regurgitation.

CENTRAL ILLUSTRATION **Evolution of MR and Long-Term Outcomes in Patients With Low-Flow, Low-Gradient Aortic Stenosis**



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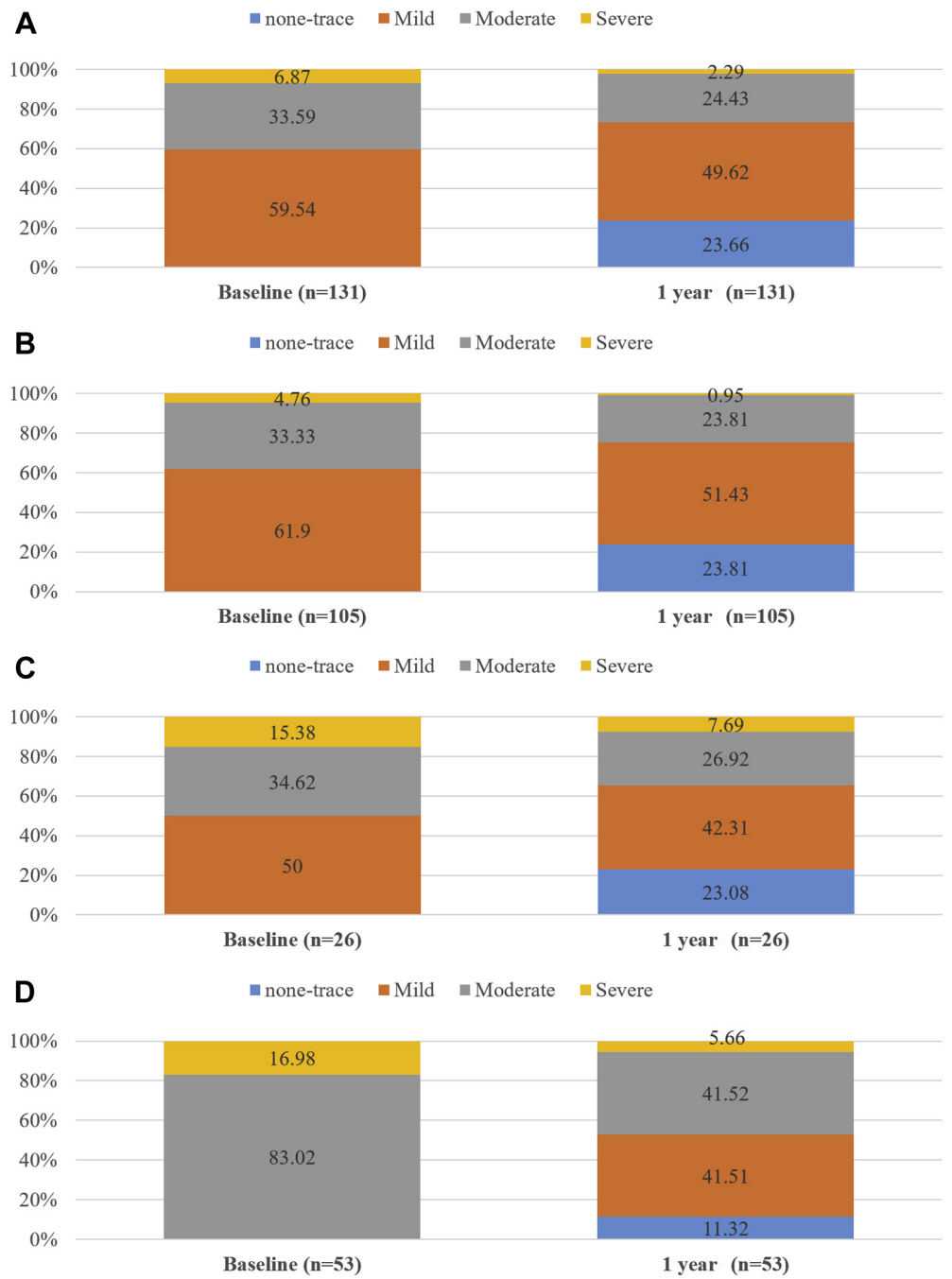
(Top) Changes in MR severity following transcatheter aortic valve replacement from baseline to 1-year follow-up in the overall cohort and according to MR improvement. **(Bottom)** Kaplan-Meier curves for the combined endpoint of all-cause death and heart failure hospitalization according to MR improvement at 1-year follow-up (landmark analysis). MR = mitral regurgitation.

FIGURE 2 Evolution of MR



Evolution of MR over time in patients with echocardiographic examination at baseline and 1-year follow-up in the overall cohort **(A)**, patients with functional MR **(B)**, patients with MR of mixed etiology **(C)**, and the subgroup of patients with baseline moderate-or-greater MR **(D)**. MR = mitral regurgitation.

TABLE 3 Factors Associated With MR Improvement Over Time

	Overall* (N = 131)	MR No Improvement (n = 73)	MR Improvement (n = 58)	Univariate Model		Multivariate Model	
				OR (95% CI)	p Value	OR (95% CI)	p Value
Clinical variables							
Age, yrs	79.7 ± 7.4	80.2 ± 6.7	79.0 ± 8.2	1.02 (0.97-1.07)	0.379	–	–
Female	40 (30.5)	20 (27.4)	20 (34.5)	0.72 (0.34-1.51)	0.383	–	–
BMI, kg/m^2	26.8 ± 5.6	27.0 ± 6.0	26.5 ± 5.1	1.01 (0.95-1.08)	0.638	–	–
Diabetes mellitus	61 (46.6)	32 (43.8)	29 (50.0)	0.78 (0.39-1.56)	0.483	–	–
Hypertension	115 (87.8)	68 (93.2)	47 (81.0)	3.18 (1.04-9.76)	0.043	3.15 (0.66-14.96)	0.148
Active smokers	4 (3.1)	3 (4.1)	1 (1.7)	2.44 (0.25-24.12)	0.445	–	–
Peripheral artery disease	44 (33.6)	25 (34.2)	19 (32.8)	1.07 (0.51-2.22)	0.858	–	–
Coronary artery disease	97 (74.0)	55 (75.3)	42 (72.4)	1.16 (0.53-2.55)	0.704	–	–
Prior myocardial infarction	52 (39.7)	32 (43.8)	20 (34.5)	1.44 (0.71-2.95)	0.313	–	–
Prior CABG	52 (39.7)	29 (39.7)	23 (39.7)	1.00 (0.50-2.03)	0.993	–	–
Atrial fibrilation	54 (41.2)	29 (39.7)	25 (43.1)	0.89 (0.44-1.79)	0.745	–	–
NYHA functional class III-IV	104 (79.4)	60 (82.2)	44 (75.9)	1.47 (0.63-3.43)	0.375	–	–
COPD	37 (28.2)	24 (32.9)	13 (22.4)	1.69 (0.77-3.72)	0.189	–	–
Hemoglobin, g/dl	12.01 ± 1.67	11.94 ± 1.81	12.10 ± 1.48	0.95 (0.76-1.17)	0.611	–	–
CKD (eGFR <60 ml/min/m^2)	67 (51.1)	42 (57.5)	25 (43.1)	1.79 (0.89-3.59)	0.102	–	–
LBBB	32 (24.4)	18 (24.7)	14 (24.1)	1.06 (0.47-2.38)	0.882	–	–
STS-PROM, %	7.0 (5.0-10.7)	7.0 (5.5-10.9)	6.9 (4.0-10.7)	1.03 (0.96-1.11)	0.363	–	–
Echocardiographic variables							
LVEF, %	28.9 ± 8.8	29.8 ± 7.7	27.6 ± 9.9	1.03 (0.99-1.07)	0.157	–	–
Mean aortic gradient, mm Hg	25.0 ± 6.6	25.0 ± 6.7	25.0 ± 6.5	1.000 (0.95-1.05)	0.991	–	–
Aortic valve area, cm^2	0.76 ± 0.19	0.76 ± 0.18	0.77 ± 0.21	0.95 (0.15-6.02)	0.953	–	–
MR type				1.10 (0.46-2.60)	0.829	–	–
MR functional etiology	105/131 (80.1)	59/73 (80.8)	46/58 (79.3)	–	–	–	–
MR mixed etiology	26/131 (19.8)	14/73 (19.2)	12/58 (20.7)	–	–	–	–
LAD, mm	45.0 ± 9.5	44.9 ± 8.7	45.2 ± 11.6	0.10 (0.96-1.04)	0.902	–	–
LVESD, mm	44.9 ± 9.5	43.9 ± 8.3	45.0 ± 10.7	0.98 (0.94-1.02)	0.262	–	–
LVEDD, mm†	54.4 ± 7.9	53.0 ± 8.0	56.1 ± 7.5	0.76 (0.59- 0.98)	0.039	0.69 (0.51-0.94)	0.019
Moderate to severe AR	36 (27.5)	16 (21.9)	20 (34.5)	0.52 (0.24-1.13)	0.100	–	–
Aortic annulus, mm	21.5 ± 2.2	21.3 ± 2.1	21.6 ± 2.2	0.95 (0.80-1.13)	0.586	–	–
Stroke volume indexed, ml/min/m^2	27.7 ± 6.9	28.3 ± 6.5	27.1 ± 7.5	1.03 (0.97-1.08)	0.375	–	–
Pulmonary systolic artery pressure, mm Hg	44.4 ± 14.0	44.0 ± 14.0	44.8 ± 14.3	1.00 (0.97-1.03)	0.777	–	–
Dobutamine contractile reserve	35/110 (31.8)	23/61 (37.7)	12/49 (24.5)	1.76 (0.79-3.94)	0.167	–	–
Procedural variables							
Balloon expandable prosthesis	102 (77.9)	50 (68.5)	52 (89.7)	0.28 (0.10-0.74)	0.011	0.33 (0.10-1.13)	0.077
Prosthesis size ≤23 mm	27 (20.6)	16 (21.9)	11 (19.0)	1.20 (0.51-2.83)	0.678	–	–
Approach TF	96 (73.3)	53 (72.6)	43 (74.1)	0.92 (0.42-2.02)	0.844	–	–
Postdilatation	25 (19.1)	14 (19.2)	11 (19.0)	1.06 (0.44-2.56)	0.903	–	–
Post-procedure echocardiography							
Delta LVEF, %‡	8.1 ± 13.0	5.8 ± 12.0	11.1 ± 13.8	0.85 (0.73-0.98)	0.023	0.81 (0.67-0.96)	0.017
Delta LVEDD, mm§	2.3 ± 0.9	0.3 ± 1.2	4.6 ± 1.1	1.1 (1.02-1.16)	0.014	–	–
Aortic mean gradient, mm Hg	8.2 ± 3.1	7.7 ± 2.9	8.8 ± 3.3	0.89 (0.79- 1.00)	0.051	0.90 (0.78-1.05)	0.177
Aortic valve area, cm^2	1.70 ± 0.58	1.69 ± 0.57	1.71 ± 0.59	0.93 (0.47-1.83)	0.838	–	–
Residual moderate to severe AR	9 (6.9)	5 (6.8)	4 (6.9)	0.88 (0.22-3.49)	0.860	–	–

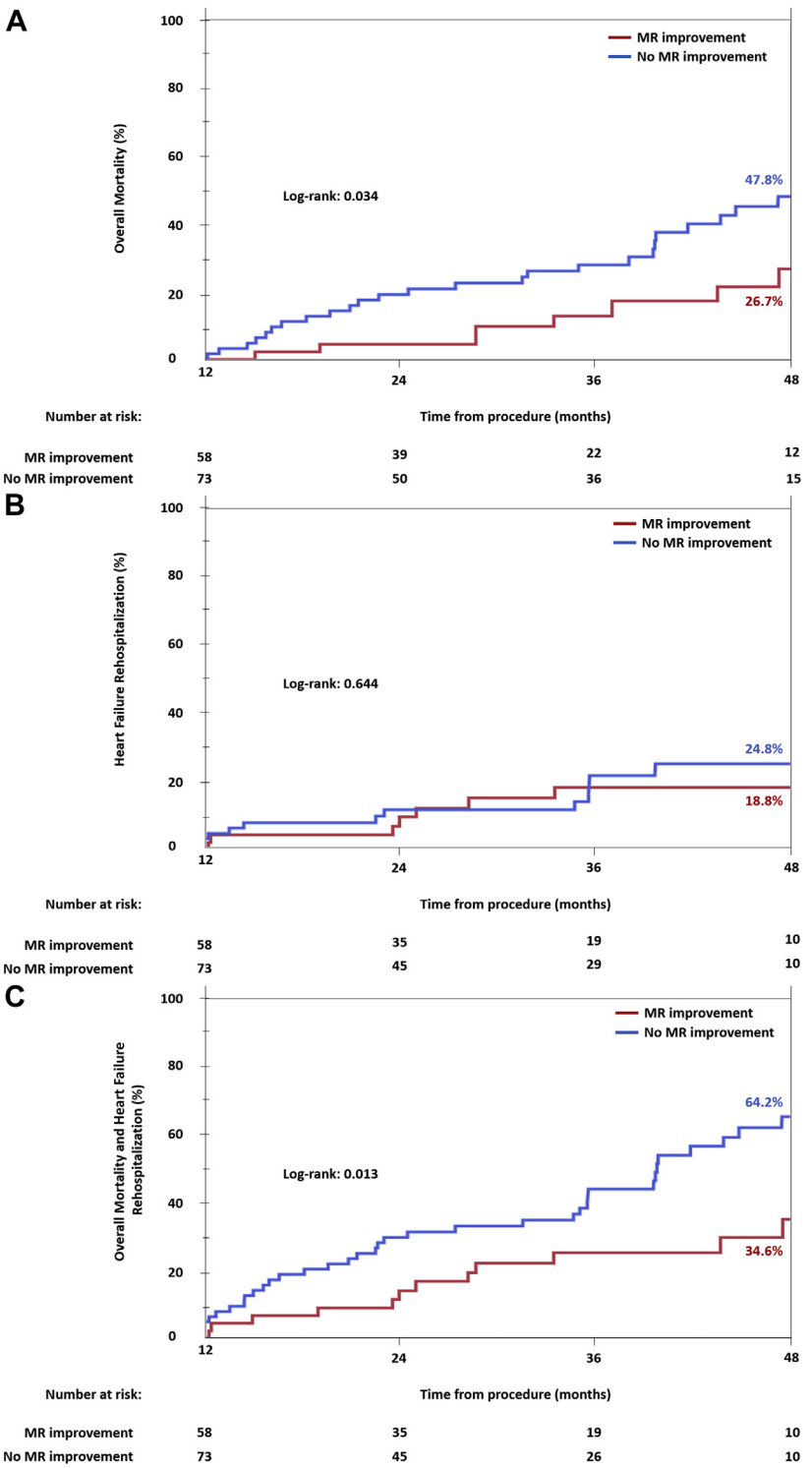
Values are mean ± SD, n (%), or n/N (%), unless otherwise indicated. *Patients with none/trace MR excluded. †For each increase of 5 mm of LVEDD. ‡For each increase of 5% of delta LVEF. §Delta LVEDD not included in the multivariate analysis because of collinearity with baseline LVEDD.

OR = odds ratio; other abbreviations as in Tables 1 and 2.

the overall cohort was 80.5 ± 7.2 years, 27% of patients were women, mean LVEF was 30.7 ± 9.4%, and patients exhibited a high-risk profile (mean Society of Thoracic Surgeons score: 7.7% [5.3 to 11.9]). The etiology of MR in those patients with some degree of MR (mild, moderate, severe) was functional and mixed (functional + organic) in 180 (77.2%) and 53 (22.7%) patients, respectively. In the mild MR group, MR etiology was functional and mixed in 98 (83.0%) and 20 (16.9%) patients, respectively. In the moderate-or-greater MR group, MR origin was functional and mixed in 82 (71.3%) and 33 (28.7%) patients, respectively (p = 0.029 vs. patients with mild MR).

Patients with moderate-or-greater MR exhibited a lower LVEF (28.0 ± 9.4% vs. 32.3 ± 9.1%; p < 0.001), a lower mean aortic gradient (25 ± 7 mm Hg vs. 26 ± 7 mm Hg; p = 0.044), more dilated ventricles (LV end-systolic diameter: 46.2 ± 8.4 mm vs. 43.9 ± 9.8 mm; p = 0.047) and higher pulmonary artery pressure (50.9 ± 14.9 vs. 42.2 ± 13.5 mm Hg; p = 0.001). Moderate-or-severe MR patients were also more frequently treated with balloon-expandable valves

FIGURE 3 **Kaplan-Meier Curves for Combined Endpoint of Overall Mortality and Heart Failure Rehospitalization According to MR Improvement at 1 Year (Landmark Analysis)**



Kaplan-Meier curves for **(A)** overall mortality, **(B)** heart failure rehospitalization, and **(C)** the combined endpoint of overall mortality and heart failure rehospitalization according to mitral regurgitation improvement at 1 year (landmark analysis). MR = mitral regurgitation.

TABLE 4 Long-Term Clinical Outcomes According to MR Improvement

	Overall (N = 131)	MR No Improvement (n = 73)	MR Improvement (n = 58)	HR* (95% CI)	p Value
Cumulative mortality	39 (29.8)	28 (38.4)	11 (19.0)	2.02 (1.29–3.17)	0.002
Cumulative cardiac mortality	19 (14.5)	15 (20.5)	4 (6.9)	3.03 (1.27–7.23)	0.012
Rehospitalization (global)	81 (61.8)	49 (67.1)	32 (55.2)	1.50 (1.01–2.22)	0.044
Rehospitalization for HF	42 (32.1)	27 (37.0)	15 (25.9)	1.56 (0.87–2.80)	0.134
Rehospitalization for cardiac causes	64 (48.9)	39 (53.4)	25 (43.1)	1.50 (1.04–2.15)	0.030
Cumulative mortality and/or rehospitalization for HF	62 (47.3)	43 (58.9)	19 (32.8)	1.94 (1.25–3.02)	0.003

Values are n (%), unless otherwise indicated. *Adjusted for baseline differences between group.
Abbreviations as in Tables 1 and 2.

(87.8% vs. 76.7%; p = 0.017) and displayed a higher percentage of residual moderate-to-severe aortic regurgitation (AR) (11.3% vs. 5.2%; p = 0.040) at discharge. The 30-day outcomes did not differ between the 2 groups. Only 3 out of 115 patients with moderate-or-greater MR (2.6%) underwent mitral valve repair following TAVR. In 2 out of these 3 patients MR did not improve at 1-year follow-up.

A total of 131 (42.5%) patients died after a median follow-up of 2 (1 to 3) years, 62 (20.1%) from cardiovascular causes, and 68 (22.1%) had at least 1 episode of hospitalization because of HF decompensation. The main clinical long-term outcomes according to the presence of baseline moderate-or-greater MR are shown in **Table 2**. There were no differences in all-cause mortality (adjusted hazard ratio [HR]: 1.34; 95% confidence interval [CI]: 0.72 to 2.48; p = 0.355), cardiovascular mortality (adjusted HR: 0.91; 95% CI: 0.43 to 1.94; p = 0.808), and HF hospitalization (adjusted HR: 1.02; 95% CI: 0.49 to 2.10; p = 0.962) between groups. The Kaplan-Meier curves, according to the presence of baseline moderate-or-greater MR, for the main clinical events up to 4-year follow-up are depicted in **Figure 1**.

CHANGES IN MR SEVERITY OVER TIME. A total of 131 patients with baseline MR (≥mild) had a control echocardiography at 1-year follow-up (70.1% of patients at risk). The changes in MR severity over time (between baseline and 1-year follow-up) are detailed in the **Central Illustration** (top) and **Figure 2**. In the overall MR cohort, MR improved by at least 1 degree in 58 (44.3%) patients. In those patients with functional MR (n = 105), MR improved in 46 (43.8%) patients versus 12 (46.2%) in those patients with mixed MR (n = 26). In the subgroup of patients with baseline moderate-to-severe MR (n = 53), 62.3% (33 of 53) showed an improvement in the degree of MR at 1-year follow-up and, in the remaining 37.7% (20 of 53), MR did not improve or worsened.

The main clinical, procedural, and imaging factors associated with an improvement on the degree of MR at 1 year are summarized in **Table 3**. Changes in LVEF and LVEDD over time are depicted in Online Figures 1 and 2, respectively. In the multivariable model, the factors independently associated with MR improvement were a larger baseline LVEDD (odds ratio for each increase in 5 mm: 0.69; 95% CI: 0.51 to 0.94), and a higher increase in LVEF post-TAVR (odds ratio for each increase in 5%: 0.81; 95% CI: 0.67 to 0.96). The main clinical events (from 1 year onward) according to MR improvement are shown in **Table 4**. The lack of MR improvement from baseline to 1 year following TAVR was associated with a significantly higher overall mortality (HR: 2.02; 95% CI: 1.29 to 3.17), cardiac mortality (HR: 3.03; 95% CI: 1.27 to 7.23), overall rehospitalization (HR: 1.50; 95% CI: 1.01 to 2.22), cardiac rehospitalization (HR: 1.50; 95% CI: 1.04 to 2.15), and combined endpoint of overall mortality/HF hospitalization (HR: 1.94; 95% CI: 1.25 to 3.02) beyond 1 year. The Kaplan-Meier curves (landmark analysis at 1 year) according to MR improvement at 1-year follow-up are shown in **Central Illustration** (bottom) and **Figure 3**. Evidenced-based HF medication, devices (implantable defibrillator and cardiac resynchronization therapy), and the rates of coronary revascularization did not significantly differ between groups (Online Table 1).

DISCUSSION

To the best of our knowledge, this is the largest study to date evaluating the impact and changes in MR severity in patients with LFLG-AS undergoing TAVR. Some degree of MR was present in most patients (moderate or severe in about one-third), and was of functional or mixed origin in all cases. MR improved in about 44% of patients, and a larger LV dimension

and a greater improvement in ventricular function post-TAVR determined a higher likelihood of MR improvement. The lack of MR improvement (but not moderate-or-greater MR pre-TAVR) was associated with poorer outcomes, including an increased overall and cardiac mortality and a higher combined HF rehospitalization/all-cause mortality.

Concomitant moderate-to-severe MR is present in about 15% to 20% of patients undergoing TAVR (3,18), but the prevalence may increase to up to 55% in the subset of patients with classical LFLG-AS (3,19). Unlike the general TAVR population, where a primary MR etiology is present in approximately one-half of cases (3), the etiology of MR in LFLG-AS patients is most commonly functional and results from the complex interplay of systolic leaflet tethering as a result of global and/or regional distortion of LV geometry and papillary muscle displacement, reduced closing forces attributable to impaired LVEF and an enlarged orifice secondary to annular dilatation (20). Nonetheless, in patients with severe degenerative AS, the mitral valvular apparatus is often calcified and the criteria for pure secondary MR are seldom met (21). Another factor that may contribute or worsen functional MR in these patients is the presence of residual AR. In the herein study, those with moderate or greater MR had also a greater prevalence of moderate or severe AR. The volume overload caused by the persistence of AR after TAVR has been shown to impair reverse cardiac remodeling (22), leading to subsequently higher LV diastolic volumes that may contribute to functional MR.

In our cohort, baseline MR was not associated with worse 30-day and late clinical outcomes. There are limited data on whether coexisting moderate-or-severe MR in patients with classical LFLG-AS independently affects outcomes in patients undergoing TAVR. Although some studies did observe an adjusted higher mortality rate at 1-year follow-up in patients with significant baseline MR and persistent low-flow after TAVR (19,23), the TOPAS-TAVI (True or Pseudo-Severe Aortic Stenosis-Transcatheter Aortic Valve Implantation) registry did not find an association between baseline moderate-or-greater MR and poorer outcomes (12). Similarly, a recent study evaluating the prognostic impact of patients with secondary MR and reduced LVEF reported an independent association between moderate/severe MR with HF hospitalizations but not with mortality in the multivariable analysis (24). In this population, it still remains unclear if prognosis is more related to the underlying cardiomyopathic process or to the presence of MR per se. The dynamic changes in LVEF and MR severity, with significant improvement over time in a high proportion of patients, may partially explain the lack of impact of significant baseline MR in TAVR recipients with LFLG-AS.

Several meta-analyses have shown that concomitant MR improves in approximately 50% to 60% of patients after TAVR, especially in the presence of functional MR (2,3,25). Similarly, in our study, close to two-thirds of the patients with moderate or greater MR exhibited a significant improvement in MR at 1-year follow-up. A number of physiological changes that occur following valve implantation may contribute to reducing MR severity. In the short term, acute improvement after the procedure may be explained by a decrease in LV afterload and improved mitral leaflet tethering (26). In the long term, TAVR is associated with reverse cardiac remodeling, which may also lead to an improvement in MR. This process encompasses several morphological and hemodynamic changes, such as regression of LV hypertrophy and diffuse fibrosis, reduction in LVED volumes and mitral tethering forces, LVEF improvement, and normalization of diastolic function (18,27,28). In the univariate analysis, a larger baseline LVEDD, a greater increase in LVEF (LVEF at baseline - LVEF at 1 year), a greater decrease in LVEDD (LVEDD at baseline - LVEDD at 1 year) and the use of a balloon-expandable prosthesis, were associated with MR improvement. Similar factors have been found in other studies but also include MR etiology (functional vs. organic), a lower baseline LVEF, a higher baseline transaortic mean gradient, the absence of pulmonary hypertension and atrial fibrillation, absence of mitral annular calcification, and a deeper valve implantation (18). After multivariate analysis, only a higher baseline LVEDD and an increase in LVEF remained as independent predictors of MR improvement. A post hoc analysis of the PARTNER II trial where patients were dichotomized according to the degree of preprocedural MR (moderate/severe MR vs. less than moderate), found a lower preoperative LVEF and larger LVEDD to be independent predictors of MR improvement (29). The authors suggested that resolution of AS in patients with failing ventricles may lead to reverse remodeling with subsequent MR reduction. LV dilation and dysfunction are a maladaptive response to pressure overload that may be implicated in the mechanism of functional MR and may reverse after stenosis release. In fact, some studies have found that a lower baseline LVEF and indexed stroke-volume are associated with greater post-procedural recovery of LVEF after TAVR (30,31). Also, the absence of improvement in indexed stroke-volume following TAVR is associated with reduced

survival (23). The greater increase in delta LVEF and reduction of LVEDD seen in the cohort of patients experiencing MR improvement is likely caused by LV pressure reduction and positive cardiac remodeling, and the absence of MR reduction, with the resulting volume overload, may impair these physiological changes. In fact, it has been described that early reversal of functional MR in patients with reduced LVEF undergoing cardiac resynchronization therapy is associated with reverse cardiac remodeling and improved outcomes (32).

Even though baseline moderate/severe MR was not linked to worse outcomes, patients who did not experience a reduction of at least 1 degree in MR severity at 1 year had a significantly higher adjusted risk of overall and cardiac mortality, rehospitalization for any cause, rehospitalization for cardiac causes, and as for the combined endpoint of overall-mortality/rehospitalization for HF. Aggressive evidence-based HF medical therapy is the cornerstone of functional MR management, followed by cardiac resynchronization therapy and revascularization when appropriate (33). However, in patients who do not respond to those therapies, transcatheter mitral valve repair may play a role in reducing the risk of hospitalizations and potentially death by interrupting the vicious cycle whereby ventricular dilatation potentiates MR and MR potentiates LV dilatation. The recently published COAPT trial demonstrated that, in patients with reduced LVEF, optimal HF treatment, and secondary MR, transcatheter mitral valve repair had a survival benefit and was associated with a lower risk of hospitalization (34). Our results highlight the importance of a close follow-up in patients who do not exhibit positive remodeling and MR persists after TAVR, and suggests that transcatheter interventions that target the mitral valve should be considered in selected cases to potentially improve outcomes.

STUDY LIMITATIONS. First, whereas most patients were included in this registry prospectively, data were retrospectively collected in approximately one-third of the patients. Second, the echocardiographic data were site-reported, and no centralized analysis in an echocardiography core laboratory was performed. Third, the study had no onsite monitoring or event adjudication committee. Fourth, because the study protocol did not foresee an echocardiographic examination during the first months after the procedure, we were unable to analyze if earlier changes in MR might have had an impact on 1-year outcomes. Finally, the relatively low number of patients limits the strengths of our results. Still, this is the largest study to date focusing on this particular subset of patients.

CONCLUSIONS

This study showed that in LFLG-AS patients undergoing TAVR, the presence of MR was frequent and improved in a significant proportion of patients following TAVR. The absence of MR improvement at 1 year, but not baseline MR, was associated with worse clinical outcomes, most likely representing those patients who failed to exhibit positive cardiac remodeling after aortic valve stenosis release. These results suggest that the presence of MR should not be considered as a factor determining treatment futility in LFLG-AS patients referred for TAVR. Also, our study seems to indicate that patients with MR should be closely followed after TAVR, and an intervention targeting the mitral valve should be considered if significant MR persists after 1 year to reduce MR severity and improve outcomes. Future studies should evaluate if an earlier diagnosis and treatment of residual MR (<1 year) might also have an impact on outcomes.

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PERSPECTIVES

WHAT IS KNOWN? Concomitant MR is commonly observed in patients with LFLG-AS, but data regarding its evolution and clinical impact following TAVR are scarce.

WHAT IS NEW? In most cases, MR is caused by functional etiology and improves in a high proportion of patients following the procedure. The absence of MR reduction at 1 year, but not baseline MR, was associated with worse clinical outcomes. These patients may benefit from a closer follow-up after TAVR, especially during the first year, and a strategy to reduce MR should be considered if MR persists.

WHAT IS NEXT? Further studies are needed to better predict in which patients MR is less likely to improve and identify those more likely to benefit from transcatheter interventions that target the mitral valve.

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KEY WORDS low-flow low-gradient aortic stenosis, mitral regurgitation, reduced left ventricular ejection fraction, transcatheter aortic valve replacement

APPENDIX For supplemental figures and a table, please see the online version of this paper.