















ORIGINAL RESEARCH

Impact on Outcome of Different Mechanisms, Baseline Degree and Changes of Mitral Regurgitation in Patients With Aortic Stenosis Who Underwent Transcatheter Aortic Valve Replacement

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BACKGROUND: Mitral regurgitation (MR) is frequent in patients with aortic stenosis (AS). Although primary MR is an established negative prognostic factor, whether different mechanisms of MR have different effects on outcome is currently unknown. The aim of this study was to evaluate the impact of the MR mechanism in patients undergoing transcatheter aortic valve replacement (TAVR).

METHODS AND RESULTS: This is a retrospective observational study of patients who underwent TAVR for severe aortic stenosis in a high-volume tertiary care center. Echocardiographic comprehensive MR assessment was performed at baseline and within 3 months post TAVR. The study population was divided into 4 groups according to MR mechanism: Group I: fibro-calcific leaflet degeneration; Group II: prolapse/flail; Group III: ventricular secondary MR (functional MR); and Group IV: atrial functional MR. The study end point was a combination of death from cardiovascular cause and heart failure–related hospitalization.

The study population included 427 patients (mean age 81.7±6.5 years; 71% primary MR; 62% ≥moderate MR). At 3-year follow-up, survival free from the composite end point significantly differs according to MR mechanism: it was higher in group IV (atrial functional MR, 96.6%) compared with group I (80.4%, $P=0.002$) and group II patients (60.7%, $P=0.001$), and group III (84.8%, $P=0.037$); patients with MR due to leaflet prolapse showed poorer prognosis compared with patients with functional MR (group III, $P=0.023$ and group IV, $P=0.001$) and with group I ($P=0.040$). Overall, severe MR after TAVR identified patients with poorer prognosis and was significantly more frequent in group II (46.4%, $P=0.001$).

CONCLUSIONS: In patients undergoing TAVR, preprocedural identification of MR mechanism and mechanism provides prognostic insights.

Key Words: aortic stenosis ■ mitral regurgitation ■ transcatheter aortic valve implantation

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CLINICAL PERSPECTIVE

What Is New?

- Concomitant mitral regurgitation (MR) is common in patients with aortic stenosis, and identification of the MR mechanism beyond primary/secondary mechanism provides prognostic implications in patients undergoing transcatheter aortic valve replacement.
- Patients with atrial secondary MR have better survival and lowest rate of severe MR post-transcatheter aortic valve replacement compared with those with degenerative leaflet prolapse who experience the worst prognosis and highest rate of residual severe MR after transcatheter aortic valve replacement.

What Are the Clinical Implications?

- The study highlights the need for detailed MR assessment with identification of the mechanism of regurgitation in patients with severe aortic stenosis, because it may have additional weight in the decision making between transcatheter aortic valve replacement/surgical aortic valve replacement with the shift of percutaneous treatment towards younger patients.

Nonstandard Abbreviations and Acronyms

AS	aortic stenosis
FMR	functional mitral regurgitation
HF	heart failure
TAVR	transcatheter aortic valve replacement
TEE	transesophageal echocardiography

Concomitant mitral regurgitation (MR) is common in patients with aortic stenosis (AS). Surgery allows combined treatment of AS and MR at the cost of increased surgical risk.¹ Moderate or severe MR is present in up to one third of patients undergoing transcatheter aortic valve replacement (TAVR) and is a negative prognostic factor.² With expanding indication of TAVR towards lower-risk patients, the issue of concomitant significant MR and AS becomes increasingly relevant. Although MR improvement has also been described after TAVR,³ residual significant MR after the procedure portends a poor outcome.⁴ It is known that the majority of patients (up to 70%) are affected by primary MR and these are at increased risk of adverse clinical outcome as compared with those with secondary MR.⁵ However, most of the studies did not report the mechanism and mechanism of MR as well

as quantitative or semiquantitative parameters for MR grading in patients who underwent TAVR.

Interesting initial data on a staged transcatheter MR treatment with leaflet approach in patients with persistent significant MR after TAVR are now available, showing improved functional class and a trend towards lower mortality compared with medical therapy.⁶ This showed the importance of comprehensive evaluation of MR at the time of TAVR procedure in order to optimize treatment. In this setting, the mechanism of concomitant MR over the dichotomous classification between primary and secondary MR requires specific attention and should be carefully evaluated, but its prognostic significance is currently unknown.

The aim of the study was to evaluate the impact of different mechanisms and mechanisms of MR in patients who underwent TAVR for severe AS.

METHODS

The data that support the findings of this study may be available from the corresponding author upon reasonable request.

Study Population

We performed a retrospective observational study on a cohort of patients who underwent TAVR for severe AS between January 2015 and December 2019 at a single tertiary care center (San Raffaele Hospital, Milan). To be included in the study, patients had to be successfully discharged at home and at least 1-year follow-up after the procedure had to be available. Exclusion criteria were the following: previous mitral valve repair or replacement, aortic bioprosthetic degeneration, at least moderate mitral stenosis, and lack of comprehensive preprocedural echocardiographic evaluation performed by a trained cardiologist of the Cardiovascular Imaging Unit.

The study complies with the Declaration of Helsinki and was conducted as part of the research project approved by the Ethical Committee of San Raffaele Hospital with registration number 192/Int/2021. All patients provided informed consent for both the procedure and subsequent data collection and analysis by signing TAVR consent.

Preprocedural Evaluation

The preprocedural planning included multislice computed tomography transthoracic echocardiography, and when clinically indicated transesophageal echocardiography (TEE).

The echocardiographic examinations were performed with Vivid E9 and E95 (GE Healthcare, Illinois, USA) equipped with transthoracic MS5 and transesophageal 6VT probes, iE33 (Philips, Best, The Netherlands)

using X5-1 transthoracic and X7-2T transesophageal probes, and Epiq 7 (Phillips, Best, The Netherlands) equipped with X5-1 transthoracic probe and X7-2T or X8-2T TEE probes. All examinations were performed according to current guidelines with continuous ECG monitoring: left ventricle (LV) volumes and ejection fraction were measured using a biplane Simpson’s method. The aortic valve area was calculated by the continuity equation using the parasternal long-axis view to measure the LV outflow tract dimension.

In case of discordant transthoracic echocardiography findings, 3D TEE was performed to measure 3D LV outflow tract area as previously described.⁷ During TEE, 3D mitral valve volume was acquired in the zoom mode with the sector width adjusted to focus on the mitral valve only using single-beat or multibeats acquisition modes (2 to 4 consecutive beats, especially with 3D color-Doppler). Beyond 2D evaluation, 3D analysis was used to identify the MR mechanism.⁸

In patients with atrial fibrillation, we used a 5-beat average for measurements that included aortic gradient and LV outflow pulsed wave Doppler analysis for aortic valve area measurement. MR evaluation is further complicated by this arrhythmia that confers a typical pattern with multiple regurgitation jets over

the beat-to-beat variability. Because quantitative and semiquantitative measurement such as the proximal isovelocity surface area method or vena contracta are not applicable in case of multiple jets, we performed a multiparametric MR evaluation. This evaluation including a combination of different qualitative and quantitative parameters: continuous wave Doppler signal intensity, pulmonary flow pattern (acknowledging that could be blunted in atrial fibrillation), E wave mitral inflow velocity, and when possible (especially in patients undergoing TEE) regurgitant fraction calculation and 3D-vena contracta area.

MR severity was assessed on a 4-grade scale using an integrative approach based on qualitative and quantitative data according to current guidelines.⁹ According to the mechanisms and mechanisms of MR, the study population was divided into 4 groups: Group I: type IIIa due to fibro-calcific degeneration of the leaflets; Group II: type II (prolapse or flail); Group III, type IIIb: secondary MR (functional MR) due to leaflets tethering (ventricular functional MR); and Group IV: functional MR due to annular dysfunction or dilatation (atrial functional MR), type I. Primary MR and secondary MR gathered Groups I and II, and Groups III and IV, respectively.

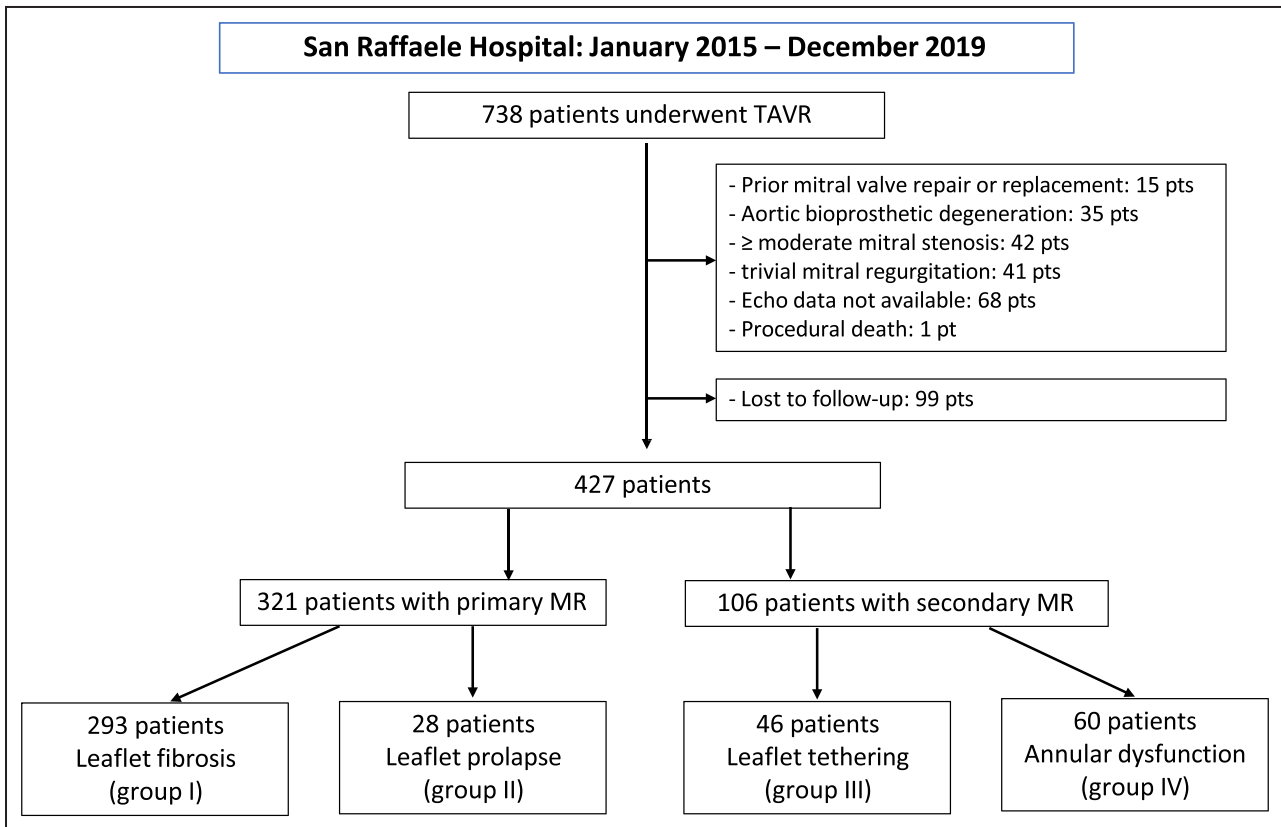


Figure 1. Study flow chart. MR indicates mitral regurgitation; and TAVR, transcatheter aortic valve replacement.

Procedure and Follow-Up

All procedures were performed with patients under conscious sedation with intraprocedural transthoracic echocardiographic monitoring and back-up TEE.¹⁰

All patients underwent both clinical and transthoracic echocardiographic follow-up within 3 months from the procedure, including MR evaluation with grading re-assessment.

MR improvement was defined as reduction of MR of at least 1 grade.

Further clinical follow-up was obtained by direct visit or telephone interview and was censored at the date of the last follow-up or at 3 years, whichever came first, to balance for different follow-up times.

Study End Points

Study end point was a combined end point of death from cardiovascular event and heart failure (HF)–related hospitalization, defined as hospital admission for acute HF symptoms requiring intravenous diuretic administration.

Statistical Analysis

Results are expressed as mean±SD for continuous variables and as percentages for categorical ones. Differences between groups were analyzed with the unpaired or paired *t* test for continuous variables. Cohen's kappa test was used to assess inter-rater variability of MR assessment before and after TAVR by 2 blinded readers (A.T and V.R.). The correlation between outcome and time elapsed from the beginning of the observational period and the event was assessed by LogRank test and represented by Kaplan–Meier curves. Cox regression analysis was used to identify predictors of the study end point among baseline clinical and echocardiographic characteristics. Multivariate Cox regression analysis was performed including only covariates that were significantly associated with the study end point at univariate analysis and the convention of limiting the number of independent variables to 1 for ≈10 events was followed. A probability value of <0.05 was considered statistically significant. SPSS 23.0 software was used for statistical analysis (SPSS Inc, Chicago, IL).

RESULTS

Study Population

During the index period, 738 patients underwent TAVR for AS in our tertiary care high-volume center. After excluding 211 patients who met exclusion criteria and 99 patients lost to follow-up, the final study population included 427 patients (Figure 1).

Baseline clinical and echocardiographic characteristics of the study population are summarized in Table 1. Mean age was 81.7±6.5 years (mean Society of Thoracic Surgeons score 25.4±10.9) and 48.7% of patients were male. TEE was performed in 224

Table 1. Baseline Clinical and Echocardiographic Characteristics of the Study Population

	Overall (n=427)	OMR (n=321)	FMR (n=106)
Clinical			
Age, y ±SD	81.7±6.5	81.7±6.7	81.7±5.7
Male, n (%)	208 (48.7)	144 (44.8)	64 (60.3)
BSA, m ² ±SD	1.7±0.2	1.7±0.1	1.7±0.1
BMI, ±SD	25.6±4.8	25.6±4.7	25.5±3.2
STS score, ±SD	5.3±3.5	5.5±3.9	4.6±2.3
STS MM score, ±SD	25.4±10.9	25.8±11.9	23.1±7.4
Euroscore II, ±SD	8.8±3.2	8.9±3.4	8.9±2.8
Log Euroscore, ±SD	16.2±11.2	16.3±11.7	16.5±11.4
CAD, n (%)	167 (39.1)	120 (37.3)	47 (44.3)
Prior MI, n (%)	68 (15.9)	48 (14.9)	20 (18.8)
Prior PCI, n (%)	124 (29.1)	89 (27.7)	35 (33)
Prior CABG, n (%)	15 (17.7)	30 (9.3)	12 (11.3)
Atrial fibrillation, n (%)	136 (31.9)	79 (24.6)	57 (53.7)
Prior stroke or TIA, n (%)	24 (5.6)	16 (4.9)	8 (7.5)
NYHA class			
≥3, n (%)	203 (47.5)	147 (45.7)	56 (52.8)
Echocardiographics			
IVS, mm±SD	14.5±6.6	13.4±2	12.8±2
EDD, mm±SD	45.4±11.2	45.9±6.9	49.3±9.5
EDV, mL±SD	115.2±46.6	109.1±40.2	133.4±61.3
ESV, mL±SD	59±40.4	49.2±28.9	79.3±57.2
EF, %±SD	47.2±15.9	56.6±9.4	47.4±12.9
E/E', ±SD	13.7±6.5	13±6	14.2±6.3
V _{max} , m/s±SD	4.4±2.3	4.5±2.6	4.1±0.6
Gm, mmHg ±SD	47.2±15.1	48.7±14.9	42.3±15.1
sPAP, mmHg ±SD	38.3±14.3	37.7±14.6	40.5±13.1
MR grade			
Mild, n (%)	161 (37.7)	131 (40.6)	30 (28.5)
Moderate, n (%)	218 (51)	154 (47.8)	64 (60.9)
Moderate to severe, n (%)	27 (6.3)	21 (6.5)	6 (5.7)
Severe, n (%)	21 (4.9)	15 (4.6)	6 (5.7)
AR, n (%)	260 (60.8)	202 (62.9)	58 (54.7)

AR indicates aortic regurgitation; BMI, body mass index; BSA, body surface area; CAD, coronary artery disease; CABG, coronary artery bypass grafting; EDV, end-diastolic volume; EDD, end-diastolic diameter; E/E', E-wave to E' wave ratio; EF, ejection fraction; ESV, end systolic volume; FMR, functional mitral regurgitation; Gm, transaortic mean gradient; IVS, interventricular septum; MI, myocardial infarction; MR, mitral regurgitation; NYHA, New York Heart Association; OMR, organic mitral regurgitation; PCI, percutaneous coronary intervention; sPAP, systolic pulmonary artery pressure; STS, Society of Thoracic Surgeons; TIA, transient ischemic attack; and V_{max}, transaortic maximum velocity.

patients (52.5%). A total of 321 patients (75.1%) had primary MR while secondary MR was present in 106 patients (24.8%); according to MR mechanism 293 (68.6%), 28 (6.5%), 46 (10.8%), and 60 (14.1%) patients were in group I, group II, group III, and group IV, respectively (Table 2). Overall, more than moderate MR (>2+) at baseline was present in 62.2% of patients, and the degree of regurgitation was mild in 37.7% of patients, moderate in 51%, moderate-to-severe in 6.3%, and severe in 4.9%. Mean LV ejection fraction was $47.2\pm 15.9\%$ and mean LV end-diastolic volume was 115.2 ± 46.6 mL. A total of 167 patients had coronary artery disease and 29.1% had a history of prior myocardial infarction. Atrial fibrillation was present in

31.9% of patients and was more frequent in group IV (73%). At baseline 49.8%, 42.8%, and 2.8% of patients were in New York Heart Association class II, class III, and ambulatory New York Heart Association class IV, respectively. Cumulative daily diuretic dose expressed as furosemide equivalents for each group are reported in Table S1 and Figure S1.

Post-TAVR Echocardiographic Evaluation

All included patients underwent transthoracic evaluation within 3 months post-TAVR as reported in Table 3. Mean aortic valve gradient was 10.3 ± 6.6 mmHg. MR improvement was observed

Table 2. Clinical and Echocardiographic Data According to MR Mechanism

	OMR		FMR	
	Group I (n = 293)	Group II (n = 28)	Group III (n = 46)	Group IV (n = 60)
Clinical				
Age, y, \pm SD	81.5 \pm 6.8	84.2 \pm 4.7	80.1 \pm 6.1	82.8 \pm 5.1
Male, n (%)	131 (44.7)	13 (46.2)	33 (71.3)	27 (45)
BMI, \pm SD	25.6 \pm 4.9	24.7 \pm 4.3	24.6 \pm 4.2	26.1 \pm 5.1
BSA, m ² \pm SD	1.7 \pm 0.2	1.8 \pm 0.2	1.7 \pm 0.2	1.7 \pm 0.7
STS mm score, \pm SD	25.5 \pm 11.8	29.8 \pm 12	25.6 \pm 8.8	23.1 \pm 6.7
Euroscore II, \pm SD	8.9 \pm 3.5	8.5 \pm 2.3	9.1 \pm 2.7	8.5 \pm 2.4
CAD, n (%)	112 (38.2)	6 (21.4)	28 (60.8)	16 (26.6)
Prior MI, n (%)	44 (15)	3 (10.7)	14 (30.4)	8 (13.3)
Prior PCI, n (%)	82 (27.9)	6 (21.4)	22 (47.8)	10 (16.6)
Prior CABG, n (%)	28 (9.5)	1 (3.5)	12 (26)	2 (3.3)
Atrial fibrillation, n (%)	67 (22.8)	14 (50)	13 (28.3)	44 (73.3)
Prior stroke or TIA, n (%)	10 (3.4)	1 (3.5)	2 (4.3)	5 (8.3)
NYHA class \geq 3, n (%)	137 (46.7)	15 (53.5)	22 (47.8)	29 (48.3)
Echocardiographic				
IVS, mm \pm SD	13.4 \pm 2.01	13.9 \pm 1.9	12.3 \pm 1.5	13.2 \pm 2.2
EDD, mm \pm SD	45.9 \pm 7.06	46.6 \pm 6.9	54.2 \pm 9.5	45.4 \pm 7.6
EDV, mL \pm SD	110.3 \pm 40.8	95.3 \pm 29.1	168.5 \pm 66.7	108.7 \pm 42.4
ESV, mL \pm SD	50.1 \pm 29.3	38.4 \pm 19.7	110.7 \pm 68.1	56.7 \pm 33.3
EF, % \pm SD	56.3 \pm 9.4	60.6 \pm 8.1	39.1 \pm 11.7	54.1 \pm 9.6
E/E', \pm SD	14.1 \pm 6.3	14.5 \pm 5.1	13.7 \pm 5.6	14.3 \pm 6.8
V _{max} , m/s \pm SD	4.5 \pm 2.7	4.09 \pm 0.6	3.8 \pm 0.6	4.3 \pm 0.6
Gm, mmHg \pm SD	49.3 \pm 14.7	41.6 \pm 11.1	36.5 \pm 13.2	46.3 \pm 14.9
sPAP, mmHg \pm SD	37.3 \pm 14.6	41.5 \pm 13.8	40.5 \pm 13.2	40.1 \pm 12.9
MR grade				
Mild, n (%)	127 (43.3)	5 (17.8)	12 (26)	16 (26)
Moderate, n (%)	146 (49.8)	7 (25)	29 (63)	36 (60)
Moderate to severe, n (%)	15 (5.1)	6 (21.4)	1 (2.1)	6 (10)
Severe, n (%)	5 (1.7)	10 (35.7)	4 (8.6)	2 (3.3)
AR, n (%)	231 (78.8)	18 (64.2)	36 (78.2)	48 (80)

AR indicates aortic regurgitation; BMI, body mass index; BSA, body surface area; CAD, coronary artery disease; CABG, coronary artery by-pass grafting; EDV, end-diastolic volume; EDD, end-diastolic diameter; E/E', E-wave to E' wave ratio; EF, ejection fraction; ESV, end systolic volume; FMR, functional mitral regurgitation; Gm, transaortic mean gradient; IVS, interventricular septum; MI, myocardial infarction; MR, mitral regurgitation; NYHA, New York Heart Association; OMR, organic mitral regurgitation; PCI, percutaneous coronary intervention; sPAP, systolic pulmonary artery pressure; STS, Society of Thoracic Surgeons; TIA, transient ischemic attack; and V_{max}, transaortic maximum velocity.

Table 3. Post-TAVR Transthoracic Evaluation

	OMR		FMR		
	Group I (n = 293)	Group II (n = 28)	Group III (n = 46)	Group IV (n = 60)	P value
EF, % ±SD	56±8.7	60±5	41±11.9	54±8.7	<0.001
E/E', ±SD	11.5±5.9	11.1±5.6	15±7.8	13.1±7.1	0.04
V _{max} , m/s ±SD	2.1±0.5	1.9±0.5	2.0±0.6	2.0±0.5	0.85
Gm, mmHg ±SD	10.1±5.3	8.3±4.6	9.3±6.9	11.4±10.2	0.07
sPAP, mmHg ±SD	36.0±10.6	41±13.0	39±13.2	38.0±10.0	0.76
MR grade					0.001
Mild, n (%)	170 (58.2)	6 (21.4)	23 (50.0)	37 (61.6)	
Moderate, n (%)	97 (33.1)	7 (25)	12 (26.1)	17 (28.3)	
Severe, n (%)	16 (5.4)	13 (46.4)	4 (8.7)	2 (3.3)	
AR grade					
Mild, n (%)	246 (83.9)	24 (85.7)	40 (86.9)	47 (78.3)	
Moderate, n (%)	46 (15.6)	4 (14.2)	5 (10.8)	13 (21.6)	/
Severe, n (%)	1 (0.3)	0 (0)	1 (2.1)	0 (0)	

AR indicates aortic regurgitation; E/E', E-wave to E' wave ratio; EF, ejection fraction; FMR, functional mitral regurgitation; Gm, transaortic mean gradient; MR, mitral regurgitation; OMR, organic mitral regurgitation; sPAP, systolic pulmonary artery pressure; TAVR, transcatheter aortic valve replacement; and V_{max}, transaortic maximum velocity.

in 99 (23.3%) patients and was significantly more frequent in patients with functional MR compared with organic mitral regurgitation (37.1% versus 18.8%, *P* <0.001) (Figure 2).

Overall, severe MR was present in 35 patients (8.2%) and was significantly more frequent in Group II (46.4%) than in Group I (5.3%), Group III (8.7%) and in Group IV (3.3%) (*P*=0.001, overall), respectively.

An inter-rater variability analysis was made by 2 readers (A.T and V.R.) blinded to the results of MR grading assessment on either pre-TAVR or post-TAVR

evaluation and showed excellent level of agreement on a sample of 116 patients (Table S2).

Clinical Outcome

The median follow-up was 1090 days. At 3-year follow-up, 79 patients (18.5%) met the composite end point of cardiovascular death or HF-related hospitalization. Overall mortality and cardiovascular mortality were 25.3% and 11.9%, respectively.

Patients with organic mitral regurgitation had a higher rate of the composite end point compared

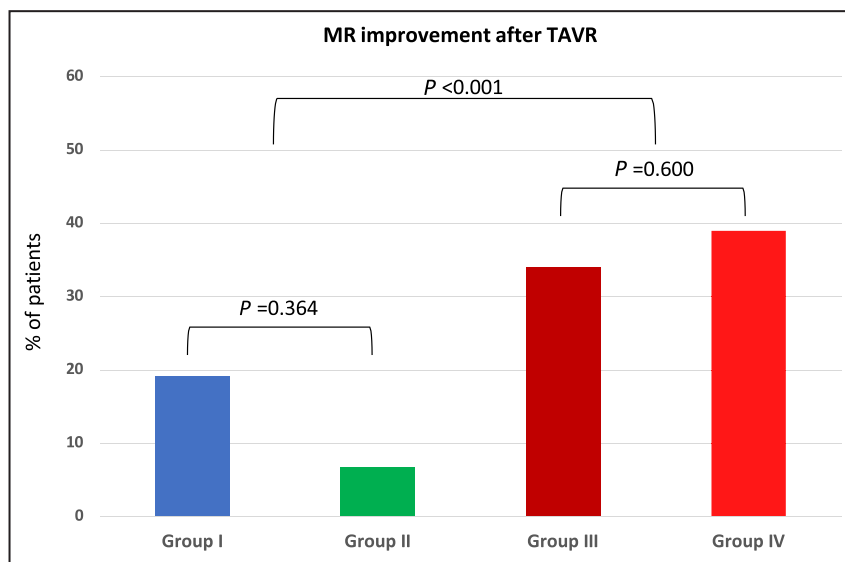


Figure 2. Rate of MR improvement after the procedure according to MR mechanism.

MR indicates mitral regurgitation; and TAVR, transcatheter aortic valve replacement.

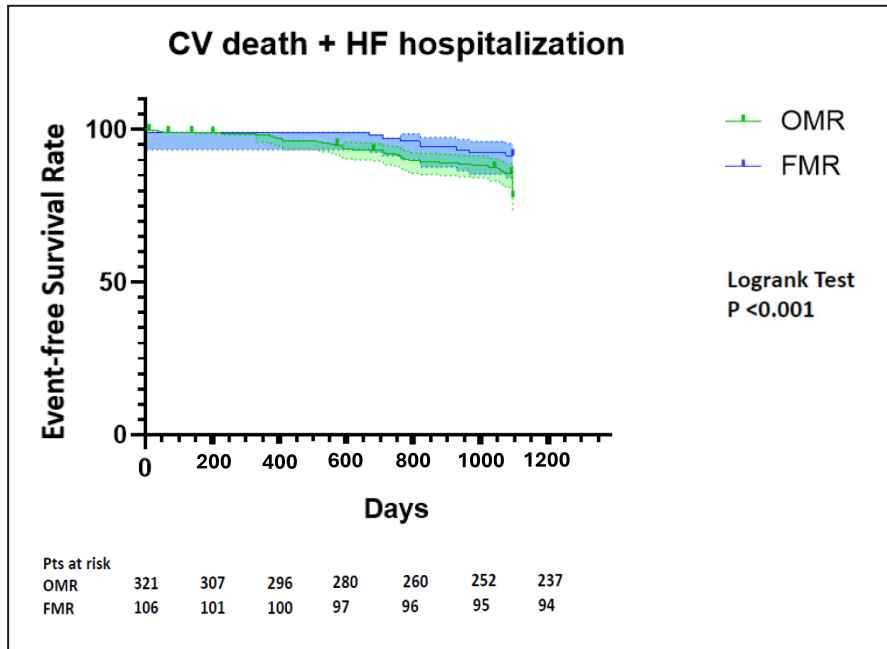


Figure 3. Kaplan–Meier curve for study end point according to primary or secondary MR mechanism.

CV indicates cardiovascular; FMR, functional mitral regurgitation; HF, heart failure; MR, mitral regurgitation; and OMR, organic mitral regurgitation.

with patients with functional MR (21.5% versus 8.5%, $P=0.001$) (Figure 3). According to MR mechanism, Group IV showed higher survival free from the composite end point (96.6%) compared with Group I (80.4%, $P=0.002$) and Group II patients (60.7%, $P=0.001$), and Group III (84.8%, $P=0.037$). Group II showed a poorer prognosis compared with other groups (Figure 4).

Overall, the rate of combined end points was similar in patients with \geq moderate MR at baseline compared with patients with $<$ moderate MR (log rank $P=0.068$).

However, when patients were stratified according to MR mechanism, in patients with organic mitral regurgitation the presence of \geq moderate MR at baseline was associated with higher rate of the composite end point at follow-up (52.8% versus 17.5%, $P=0.047$) (Figure S2).

Among baseline characteristics, univariate predictors of the study end point were age (hazard ratio [HR], 1.07 [95% CI, 1.02–1.11]; P value=0.001), New York Heart Association class (HR, 1.06 [95% CI, 1.07–2.20]; P value=0.019), MR mechanism (Group II HR, 2.07

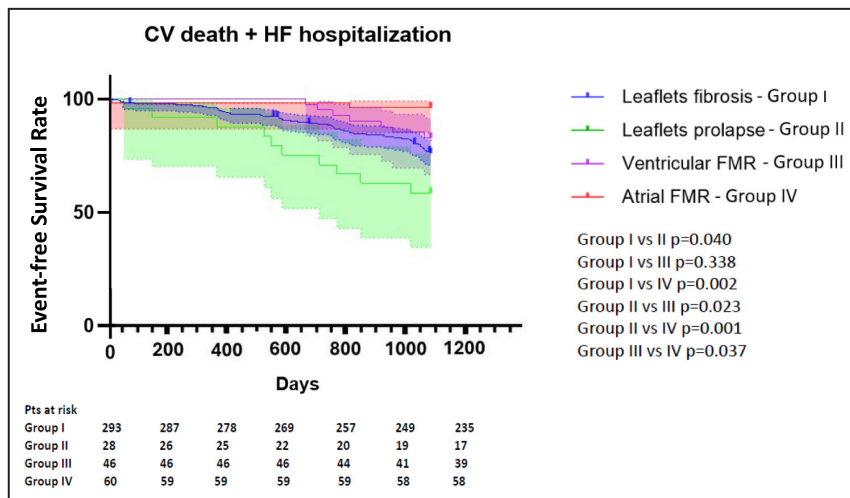


Figure 4. Kaplan–Meier curve for study end point according to MR mechanism.

CV indicates cardiovascular; FMR, functional mitral regurgitation; HF, heart failure; and MR, mitral regurgitation.

Table 4. Predictors of Cardiovascular Death and Heart Failure Hospitalizations at 3 Years of Follow-Up

	Univariate analysis			Multivariate analysis		
	HR	95% CI	P value	HR	95% CI	P value
Age	1.07	1.02–1.11	0.001	1.05	1.02–1.10	0.003
Female sex	0.87	0.56–1.35	0.544			
NYHA class	1.53	1.07–2.20	0.019	1.46	1.06–2.02	0.020
AF	0.97	0.61–1.55	0.198			
CAD	0.86	0.55–1.35	0.511			
Prior AMI	0.91	0.51–1.64	0.775			
EF	0.99	0.97–1.01	0.504			
Mean AV gradient	0.99	0.97–1.00	0.258			
MR mechanism			0.001			
Group 1	Ref			Ref		
Group 2	2.07	1.13–3.87	0.018	2.10	1.11–4.01	0.023
Group 3	0.76	0.27–1.29	0.188	0.63	0.29–1.38	0.254
Group 4	0.19	0.06–0.61	0.005	0.17	0.05–0.56	0.003
Baseline severe MR	1.51	0.81–2.79	0.186			
TAPSE	1.03	0.96–1.11	0.289			
sPAP	1.01	0.99–1.03	0.094			
Baseline TR >2+	1.81	0.98–3.36	0.057			
MR improvement after TAVR	0.90	0.52–1.54	0.709			

AF indicates atrial fibrillation; AMI, acute myocardial infarct; AV, aortic valve; CAD, coronary artery disease; EF, ejection fraction; HR, hazard ratio; MR, mitral regurgitation; NYHA, New York Heart Association; TAPSE, tricuspid annular plane systolic excursion; sPAP, systolic pulmonary artery pressure; TAVR, transcatheter aortic valve replacement; and TR, tricuspid regurgitation.

[95% CI, 1.13–3.87]; $P=0.018$ and Group IV HR, 0.19 [95% CI, 0.06–0.61]; $P=0.005$). At multivariate analysis, age, New York Heart Association class, MR mechanism (Group II HR, 2.10 [95% CI, 1.11–4.01]; $P=0.023$

and Group IV HR, 0.17 [95% CI, 0.05–0.56]; $P=0.003$) were independent predictors (Table 4).

Considering post-TAVR echocardiography evaluation, MR improvement of at least 1 grade was not

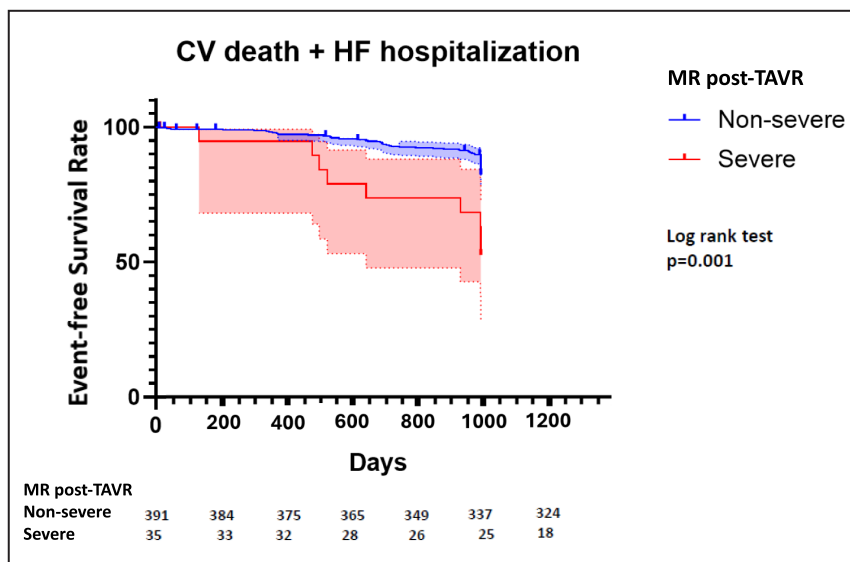


Figure 5. Kaplan–Meier curve for study end point according to MR grade post-TAVR (severe versus less degree of regurgitation).

CV indicates cardiovascular; HF, heart failure; MR, mitral regurgitation; and TAVR, transcatheter aortic valve replacement.

associated with improved prognosis (log rank $P=0.690$). However, patients with severe MR post-TAVR had an increased rate of the study end points compared with those with lesser degree of regurgitation (48.6% versus 15.8%, $P < 0.001$, Figure 5).

Three patients underwent successful percutaneous mitral transcatheter edge-to-edge repair at follow-up, at 3, 15, and 23 months, respectively following TAVR procedure (see Table S3 for patients' descriptions and Video S1).

DISCUSSION

This contemporary large-scale study firstly evaluated the impact on outcome of different mechanisms and specific mechanism of MR in patients who underwent TAVR for severe AS. We confirmed that patients with secondary MR had a better prognosis compared with those with primary MR; we firstly showed that (1) patients with secondary atrial MR had lower rates of cardiovascular mortality and HF-related hospitalization compared with both patients with primary MR and those with ventricular secondary MR; (2) patients with primary MR with prolapse had poorer prognosis compared with

both patients with secondary MR and primary MR with leaflet fibrosis; (3) both secondary atrial MR and primary MR with prolapse were independently associated with respectively lower and higher rate of cardiovascular events at 3-year follow-up; and (4) severe MR post-TAVR identified patients with poorer prognosis and was more common in patients with leaflet prolapse.

Concomitant MR is an issue in patients with severe AS. Fibro-calcific degeneration or prolapse due to fibroelastic deficiency may be present in elderly patients with degenerative AS; on the other hand, secondary MR may result from concomitant LV dysfunction/dilation leading to leaflet tethering (ventricular secondary MR) in the setting of concomitant coronary artery disease, chronic pressure overload, or annular dysfunction due to atrial fibrillation (present in nearly 75% of patients of group IV) or annulus calcification (atrial secondary MR). Increased afterload due to AS, leading to high transmitral systolic gradient (LV to left atrium), is associated to an increase of the regurgitant volume for any regurgitant orifice area. Furthermore, chronic pressure overload remodels the LV with mitral annular deformation increasing the tethering forces. On this basis, the relief of afterload after treating AS may

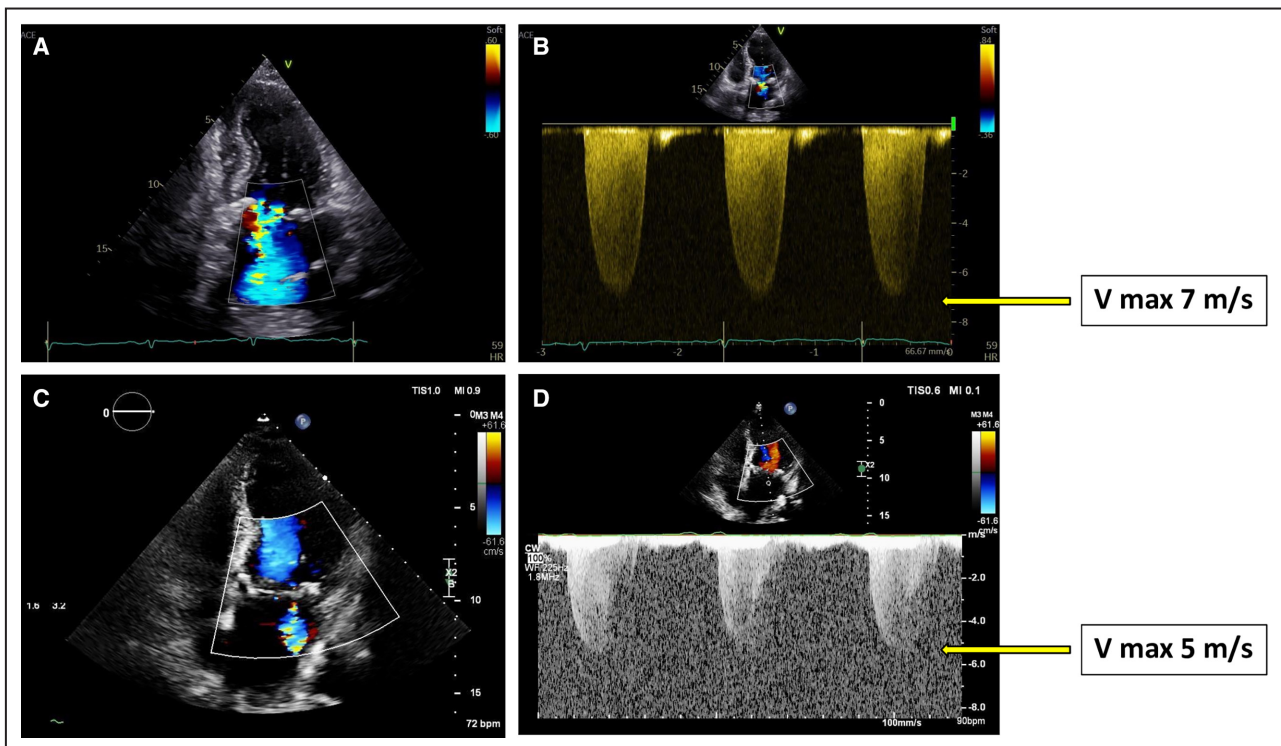


Figure 6. Transthoracic echocardiography images before and after TAVI intervention of a patient with concomitant severe aortic stenosis and primary mitral regurgitation (MR) secondary to degenerative disease.

A and **B**, Show apical 2-chamber view and CW of MR before TAVI intervention. The presence of a double, holosystolic jet with a large convergence area is representative of a severe regurgitation. **C** and **D**, Show apical 4-chamber view and CW of MR after TAVI intervention. The reduction of the regurgitation degree is noticeable by the presence of a single, proto-systolic jet. Note the reduction of the peak velocity of MR regurgitant jet on CWD due to reduced LV to LA systolic gradient. CW indicates continuous wave; CWD, continuous wave Doppler; LA, left atrial; LV, left ventricle; MR, mitral regurgitation; TAVI, transcatheter aortic valve implantation; and V_{max} , transaortic maximum velocity.

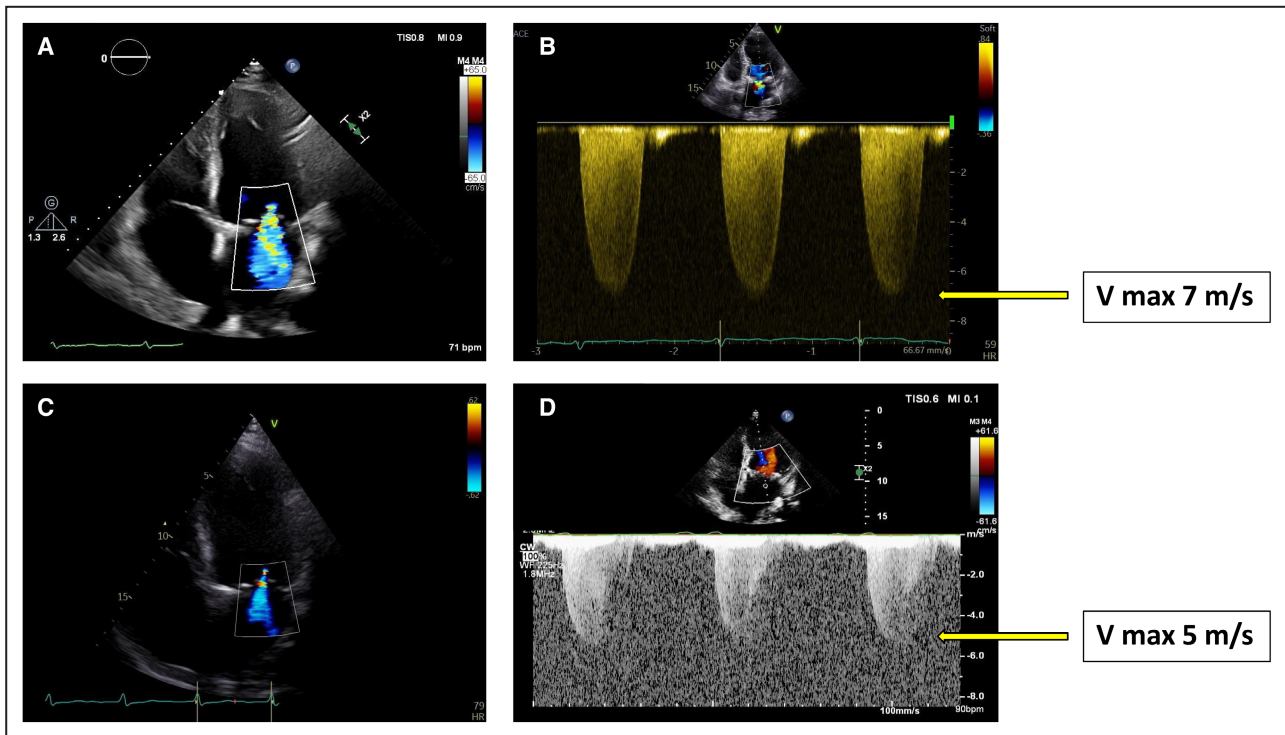


Figure 7. Transthoracic echocardiography images before and after TAVI intervention of a patient with concomitant severe aortic stenosis and secondary mitral regurgitation (MR) due to ischemic cardiomyopathy that underwent TAVI.

A and **B**, Show apical 4-chamber view and CW of MR before TAVI intervention. The jet severity was moderate–severe (holosystolic jet, vena contracta diameter 0.5mm, effective regurgitant orifice area (EROA)-PISA 0.33 cmq, regurgitant fraction 41%). **C** and **D**, Show apical 4-chamber view and CW of MR after TAVI intervention. The degree of MR has been reduced to mild (proto-systolic jet, vena contracta diameter 0.2mm, EROA-PISA 0.17 cmq, regurgitant fraction 27%). Note reduction of peak velocity of regurgitant MR jet on CWD as a consequence of reduced ventricular pressure after relief of afterload. CW indicates continuous wave; CWD, continuous wave Doppler; EROA-PISA, -proximal isovelocity surface area; MR, mitral regurgitation; TAVI, transcatheter aortic valve implantation; and V_{max} , transaortic maximum velocity.

result in MR improvement due to reduced ventricular pressures in the acute phase (Figures 6 and 7) and to reverse LV remodeling in the late phase. However, in a non-negligible proportion of patients, significant MR persists after aortic valve intervention.^{3,11,12}

Untreated significant MR at the time of aortic valve intervention is associated with worse outcomes in patients undergoing either surgical aortic valve replacement¹³ or TAVR.³

Until recently the only option for concomitant severe AS and MR was double valve surgery with a detrimental increase of the surgical risk, so that indication for double operation remains debatable in case of moderate MR. Indeed, in the Euro Heart Survey, double valve intervention was associated with a double-fold operative risk over single surgical aortic valve replacement, with limited mitral valve repair options and mitral valve replacement challenged by the presence of mitral annular calcification.¹⁴

Despite the variable degree of MR reduction observed after TAVR, residual MR is an established negative prognostic factor, and can be a relevant issue in the current TAVR population, which is shifting towards lower-risk patients. Recently, the opportunity

of transcatheter edge-to-edge repair after TAVR has been explored with promising results.⁶ The broadening of therapeutic options in the transcatheter field for MR increases the need for correct estimation of disease burden and identification of potential candidates to optimize treatment and improve long-term prognosis.

Echocardiography plays a central role for this purpose, but evaluation of concomitant AS and MR is challenging: ultrasound attenuation by calcification may lead to underestimation; color-Doppler jet area, being related to jet momentum that is itself dependent on jet velocity, may result increased with the same effective regurgitant orifice area due to high LV to LA pressure gradient; on the other hand, MR may contribute to reduced stroke volume and hence to low flow status. Taken together, these points highlight the need for careful and critical evaluation of both lesions, considering their interplay when present together. However, few studies reported the mechanism of MR in patients who underwent TAVR and the majority used qualitative, subjective grading of MR severity. In our study we used a multiparametric, guideline-recommended approach and detailed the mechanisms and mechanisms of MR.

In a contemporary cohort of patients undergoing TAVR, we confirmed that organic mitral regurgitation was more common than secondary functional MR and that degenerative disease was associated with poorer prognosis compared with secondary MR. MR improvement after the procedure was not sufficient to contribute to prognosis in the complex scenario of TAVR patients, but severe MR at discharge identified patients with significantly poorer prognosis and was definitely more common in those with mitral leaflet prolapse.

Accordingly, the most relevant finding of the study was that a more precise definition of MR mechanism and mechanism further stratified patients according to cardiovascular events. A recent study evaluating patients with more than moderate MR undergoing TAVR and stratifying according to atrial functional MR, ventricular functional MR, or primary MR, confirmed that MR persistence at follow-up was associated with increased mortality, but did not show survival difference between groups.¹⁵ In our study, patients with atrial secondary functional MR had a lower event rate of the composite end point of cardiovascular mortality and HF-related hospitalization compared with all remaining groups and patients with primary organic mitral regurgitation due to leaflet prolapse had the worse prognosis. Indeed, Group II showed the higher proportion of patients presenting with persistence of severe MR post-TAVR while Group IV showed the lowest. Consistently with the MR mechanism, patients with Group III had higher LV volumes and lower ejection fraction compared with patients with Group IV, thus probably accounting for the difference in event rate, despite having a similar proportion of significant MR after TAVR between the 2 groups. Finally, a higher proportion of patients with leaflet prolapse/flail had significant MR at baseline and post-TAVR compared with those with leaflet fibrosis, suggesting more extensive leaflet pathology.

Overall, more than moderate MR at baseline was not associated with increased cardiovascular events at follow-up in functional pathology, but in degenerative disease did, probably reflecting the higher rate of severe MR at discharge in patients with leaflet prolapse. In this light, conflicting results from previous studies on the impact of significant MR on mortality¹⁶ may be reconciled by their lack of stratifying patients according to MR mechanism, similarly to findings from another registry focusing on impact on MR mechanism on outcome.⁵

These results may impact the future direction of clinical practice in the challenging dilemma of patients with concomitant severe AS and MR, which may become even more relevant with the shifting of percutaneous treatment towards younger patients: the presence of concomitant atrial MR may contribute to tip the balance between surgery and percutaneous treatment of AS towards the latter, considering the good prognosis of this subgroup. Conversely, the presence of

significant MR due to leaflet prolapse/flail should raise suspicion towards the need to address the mitral valve pathology, either surgically or by transcatheter options.

Limitations

This is an observational single-center retrospective study with inherent limitations due to the study design. A quota of patients was excluded due to inadequate echocardiography imaging or lost to follow-up, and we acknowledge that the number of patients included in different groups might be relatively small, but this was necessary to allow precise evaluation of different MR mechanisms. Follow-up echocardiography included a comprehensive examination performed within 3 months after the procedure. Although it is sufficient to detect variation in MR grading after TAVR, we cannot confirm that the result would be maintained at long-term follow-up. We acknowledge the lack of blood pressure data collection as a limitation, given the impact of blood pressure on LV mechanics. Moreover, the evolution of MR after the procedure, especially functional MR, might have been influenced by changes in medical therapy that is not standardized and relies on medical choice. Finally, the results of the study represent the experience of a high-volume tertiary care center with excellent TAVR procedural outcomes and expert echocardiographic MR assessment. Thus, the results may not apply to other experiences. A prospective and multicenter study would be appropriate to strengthen the findings of the present study.

CONCLUSIONS

The presence of concomitant severe AS and MR represents a challenging situation. We demonstrated that in patients undergoing TAVR, the identification of MR mechanism and mechanism may provide prognostic insights. Patients with atrial functional MR seem to have better survival and lowest rate of severe MR at discharge compared with those with degenerative leaflet prolapse who experience a worse prognosis and highest rate of severe residual MR after TAVR.

ARTICLE INFORMATION

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Disclosures

None.

Supplemental Material

Tables S1–S3

Figures S1–S2

Video S1

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