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NEW RESEARCH PAPERS

FOCUS ON TRANSCATHETER AORTIC VALVE REPLACEMENT

Effect of Transcatheter Aortic Valve Replacement on Concomitant Mitral Regurgitation and Its Impact on Mortality

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ABSTRACT

OBJECTIVES The purpose of this study was to examine the impact of residual mitral regurgitation (MR) on mortality in patients undergoing transcatheter aortic valve replacement (TAVR).

BACKGROUND MR is common in patients undergoing TAVR. Data on optimal management of patients with significant MR after TAVR are limited.

METHODS The registry consisted of 16 TAVR centers (n = 7,303). Outcomes of patients with ≥ moderate versus lesser grade MR after TAVR were compared.

RESULTS In 1,983 (27.2%) patients, baseline MR grade was ≥ moderate. MR regressed in 874 (44.1%) patients and persisted in 1,109 (55.9%) after TAVR. Four-year mortality was higher for those with MR persistence, but not for those with MR regression after TAVR, compared with nonsignificant baseline MR (43.8% vs. 35.1% vs. 32.4%; hazard ratio [HR]: 1.38; p = 0.008; HR: 1.02; p = 0.383, respectively). New York Heart Association functional class III to IV after TAVR was more common in those with MR persistence vs. regression (14.4% vs. 3.9%; p < 0.001). In a propensity score–matched cohort (91 patients' pairs), with significant residual MR after TAVR who did or did not undergo staged mitral intervention, staged intervention was associated with a better functional class through 1 year of follow-up (82.4% vs. 33.3% New York Heart Association functional class I or II; p < 0.001), and a numerically lower 4-year mortality, which was not statistically significant (64.6% vs. 37.5%; HR: 1.66; p = 0.097).

CONCLUSIONS Risk stratification based on improvement in MR and symptoms after TAVR can identify patients at increased mortality risk after TAVR. These patients may benefit from a staged transcatheter mitral intervention, but this requires further proof from future studies. (Transcatheter Treatment for Combined Aortic and Mitral Valve Disease. The Aortic+Mitral TRAnsCatheter [AMTRAC] Valve Registry [AMTRAC]; NCT04031274).
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ABBREVIATIONS AND ACRONYMS

AS = aortic stenosis

CI = confidence interval

HR = hazard ratio

IQR = interquartile range

MR = mitral regurgitation

NYHA = New York Heart Association

PMVR = percutaneous edge-to-edge mitral valve repair

PSM = propensity score matched/propensity score matching

SAVR = surgical aortic valve replacement

TAVR = transcatheter aortic valve replacement

TMVR/r = transcatheter mitral valve replacement or repair

Among patients suffering from valvular heart disease, 25% show involvement of both the aortic and mitral valves (1). The prevalence of significant (≥ moderate) mitral regurgitation (MR) in patients undergoing transcatheter aortic valve replacement (TAVR) is around 25% (2,3), and its presence confers increased mortality following TAVR (2,4). These patients present a unique challenge in terms of both diagnosis as well as treatment: the hemodynamic interplay between aortic stenosis (AS) and MR can cause an overestimation of MR grade due to the increase in end systolic pressure in the presence of AS, and the reduced forward ejection fraction in the presence of MR can result in underestimation of AS severity, or misclassification of classic severe AS to low-gradient AS. This diagnostic ambiguity obviously affects treatment decisions. When the main modality for treatment of valvular heart disease was surgery, combined AS + MR was amenable for treatment during the same procedure, although with increased operative mortality (5). However, as TAVR is becoming the dominant treatment modality in elderly patients, and those not at low surgical risk (6), data on the optimal management of these patients are limited. These challenges are compounded by the fact that MR grade will improve following TAVR in around 50% of cases (2,4,7–10), and hence the more relevant and clinically meaningful question is not the prognostic effect of baseline, but rather that of residual MR post-TAVR. Data on this issue are limited and inconsistent, with some (9,10), but not all (8), studies finding improvement in MR grade to be associated with improved survival. Considering all the previous, a treatment strategy of isolated TAVR followed by a consideration of staged transcatheter mitral valve replacement or repair (TMVR/r) for patients whose MR did not regress following TAVR seems attractive for this patient population (11). The rapid increase in TMVR/r volume and the availability of more techniques or devices (12,13) makes this approach even more feasible.

A recent multicenter registry of such cases (N = 106) found that although TMVR/r following TAVR is infrequent, it can be performed with a high procedural success rate, and is associated with a significant improvement in MR grade and New York Heart Association (NYHA) functional class up to 1 year of follow-up (14).

The aim of this study was to assess the prognostic effect of residual MR following TAVR, identify predictors of MR response to TAVR, and explore the possible benefits of a staged TAVR + TMVR/r over medical management in a large international cohort of patients with significant residual MR after TAVR.

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METHODS

The AMTRAC (Aortic+Mitral TRAnsCatheter) valve registry is an investigator-initiated, international multicenter registry that initially collected data on patients undergoing TAVR + TMVR/r in 23 centers from Europe, North America, Israel, and Japan (14).

For this study, 13 of the initial 23 centers, and 3 additional centers shared data on all consecutive TAVR cases treated between January 1, 2007, to December 31, 2019. Patients' data were collected at each center using a uniform electronic case report form, and following anonymization, the data were sent to the coordinating center (Rabin Medical Center, Petach Tikva, Israel), where the unified database was compiled and analyzed.

PATIENT POPULATION. Patients were eligible to be included in the registry if they underwent TAVR and had available assessment of MR grade both at

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The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the Author Center.

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TABLE 1 Baseline Characteristics

	Nonsignificant Baseline MR (n = 5,320)	Baseline MR Significant (Regressed) (n = 874)	Baseline MR Significant (Persisted) (n = 1,109)	p Value: Baseline MR Significant vs. Nonsignificant	p Value: Baseline MR Significant Regressed vs. Persisted
Age, yrs	81.0 ± 6.7	81.9 ± 6.4	81.8 ± 6.6	0.457	0.915
Female	2,644 (49.7)	464 (53.1)	600 (54.1)	<0.01	0.241
BMI, kg/m^2	26.4 ± 5.8	25.8 ± 4.7	25.6 ± 4.5	0.516	0.652
eGFR, ml/min	61.2 ± 26.8	54.9 ± 26.6	51.7 ± 24.2	<0.01	0.110
Hemoglobin, g/l	11.0 ± 2.7	11.8 ± 2.5	11.7 ± 2.3	0.387	0.359
STS score	5.3 ± 2.7	6.4 ± 2.6	7.1 ± 3.0	<0.01	0.350
AV peak, mm Hg	76.4 ± 27.1	75.1 ± 26.2	76.8 ± 29.1	0.866	0.692
AV mean, mm Hg	46.8 ± 14.0	46.3 ± 16.3	46.2 ± 15.2	0.921	0.994
EF, %	55.7 ± 10.8	51.0 ± 13.2	50.1 ± 13.5	<0.01	0.532
AVA, cm^2	0.79 ± 0.19	0.66 ± 0.23	0.68 ± 0.28	0.469	0.482
Degenerative MR etiology	3,942 (74.1)	420 (48.1)	724 (65.3)	<0.001	0.004
Previous PCI	1,410 (26.5)	229 (26.2)	312 (28.1)	0.544	0.204
Previous MI	782 (14.7)	134 (15.3)	192 (17.3)	0.065	0.110
Previous cardiac surgery	1,021 (19.2)	185 (21.2)	255 (23.0)	0.288	0.426
Frailty	1,410 (26.5)	303 (34.7)	430 (38.8)	<0.01	0.467
AF	1,282 (24.1)	291 (33.3)	450 (40.6)	<0.01	0.003
PPM	527 (9.9)	118 (13.5)	164 (14.8)	<0.01	0.723
COPD	990 (18.6)	171 (19.6)	197 (17.8)	0.986	0.961
DM	1,724 (32.4)	256 (29.3)	298 (26.9)	<0.01	0.081
Hypertension	4,442 (83.5)	724 (82.8)	919 (82.9)	0.502	0.721
Bicuspid valve	207 (3.9)	21 (2.4)	35 (3.2)	0.108	0.674
Femoral access	5,017 (94.3)	809 (92.6)	1,003 (90.4)	0.203	0.452
Balloon expandable valve	1,814 (34.1)	295 (33.8)	321 (28.9)	0.321	0.208
NYHA functional class III–IV	3,756 (70.6)	697 (79.7)	887 (80.0)	<0.01	0.998
Years				0.471	0.236
2007–2010	354 (6.7)	46 (5.3)	73 (6.6)		
2011–2014	1,440 (27.1)	225 (25.8)	299 (27.0)		
2015–2019	3,526 (66.3)	603 (69.0)	737 (66.5)		

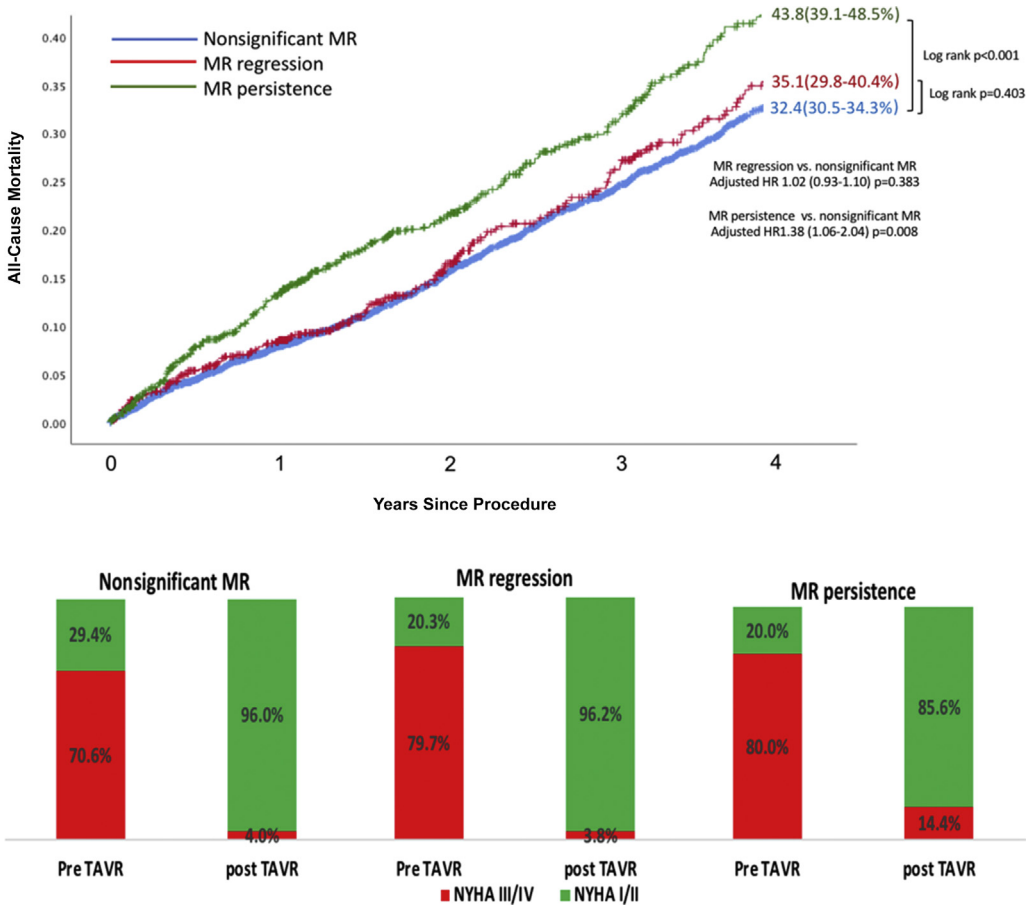
Values are mean ± SD or n (%).

AF = atrial fibrillation; AV = aortic valve; AVA = aortic valve area; BMI = body mass index; COPD = chronic obstructive pulmonary disease; DM = diabetes mellitus; EF = ejection fraction; eGFR = estimated glomerular filtration rate; MI = myocardial infarction; MR = mitral regurgitation; NYHA = New York Heart Association; PCI = percutaneous coronary intervention; PPM = prosthesis-patient mismatch; PSM = propensity score matching; PMVR = percutaneous edge-to-edge mitral valve repair; STS = Society of Thoracic Surgeons.

baseline (prior to TAVR) and at 30 days after TAVR. Patients with previous mitral valves surgery were excluded.

STATISTICAL METHODS. Patients were divided into 3 groups according to baseline MR grade and its response to TAVR: 1) baseline MR < moderate (nonsignificant MR); 2) baseline MR ≥ moderate and after TAVR MR < moderate (MR regression); and 3) baseline and post-TAVR MR ≥ moderate (MR persistence). Baseline characteristics, presented as mean ± SD or median (interquartile range [IQR]) as appropriate for continuous variables and count and percentage for categorical variables, were compared between the nonsignificant MR and all patients with baseline significant MR and separately between the MR regression and persistence groups using the independent sample Student's *t*-test, Mann-Whitney *U* test, and the chi-square test, as appropriate. Cumulative all-cause mortality is presented using Kaplan-Meier curves and compared between the groups using the log-rank test. Adjusted hazard ratios (HRs) for mortality for MR regression or persistence as compared with the nonsignificant MR group as reference were calculated using a multivariate adjusted Cox proportional hazards model. Patients who underwent TMVR/r following TAVR (n = 131) were excluded from this analysis. Baseline or procedural characteristics associated with the regression or persistence of MR grade (< or ≥ moderate) and symptoms (NYHA functional class III to IV) after

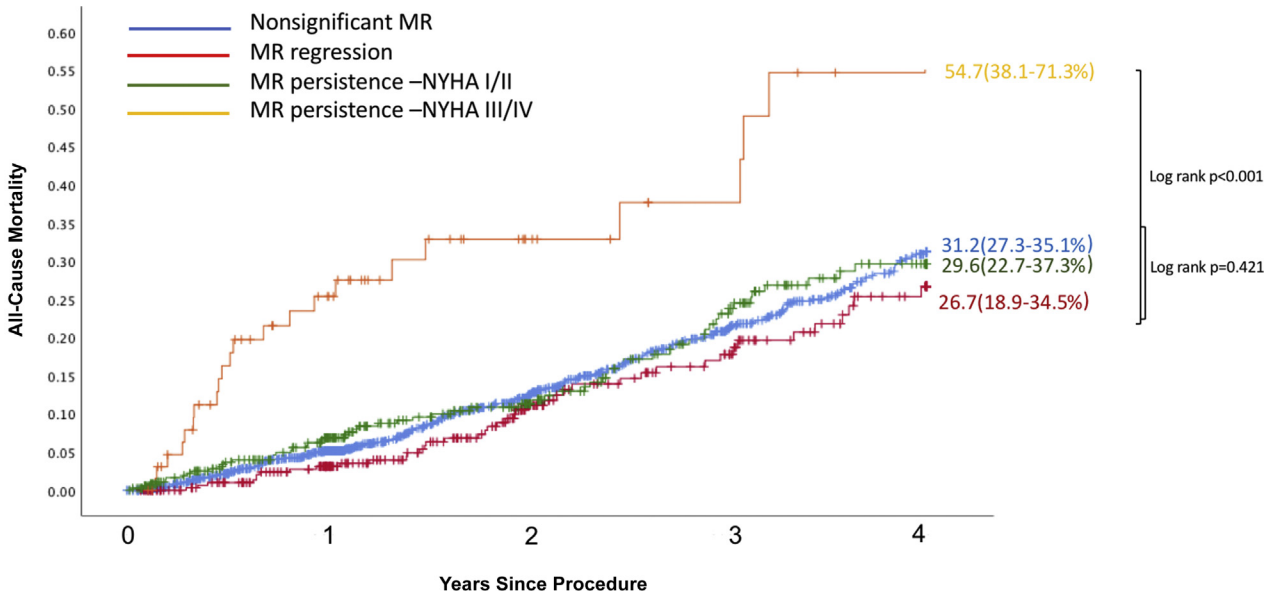
FIGURE 1 Mortality and NYHA Functional Class Following TAVR



Kaplan-Meier curves for all-cause mortality according to mitral regurgitation (MR) status **(top)** and change in New York Heart Association (NYHA) functional classification following transcatheter aortic valve replacement (TAVR) according to MR status **(bottom)**. Adjusted for age, sex, frailty, NYHA functional class, atrial fibrillation, estimated glomerular filtration rate, Society of Thoracic Surgeons score, and ejection fraction. HR = hazard ratio.

TAVR were identified using a univariate logistic regression model (using a 0.1 significance level), and multivariate models to predict the likelihood of MR grade and symptoms regression or persistence following TAVR were constructed using the individual factors with significant univariate association. The discrimination ability of the models to predict MR grade and symptomatic response to TAVR was assessed using a receiver-operating characteristic curve and the C-statistic. To examine the potential benefits of a staged TAVR + TMVR/r versus no intervention, we assembled a propensity score-matched (PSM) cohort of patients with significant MR persistence following TAVR who did or did not undergo TMVR/r and compared functional class at 6 and 12 months, and all-cause mortality. The PS was calculated by fitting a logistic regression model that used mitral intervention as the outcome and major demographic and clinical baseline characteristics as well as MR grade after TAVR as covariates. Matched pairs of patients who did or did not undergo TMVR/r following TAVR on a 1:1 ratio were created according to the propensity score using the nearest-neighbor method. To avoid immortal time bias, each TAVR + TMVR/r patient was matched to a patient treated medically after TAVR, who was alive at the same interval from TAVR when the TMVR/r was performed, and survival was compared from this time point onward. Because percutaneous edge-to-edge mitral valve repair (PMVR) is by far the most frequent mitral intervention after TAVR (14) as well as in the overall MR population (12), only patients who underwent staged PMVR were included in this analysis.

FIGURE 2 Kaplan-Meier Curves for All-Cause Mortality According to MR Status and NYHA Response



Abbreviations as in Figure 1.

ETHICAL APPROVAL AND STUDY REGISTRATION. The registry protocol was approved by the local institutional review board as required at each participating center. The registry is listed in ClinicalTrials.gov (NCT04031274).

RESULTS

In total, our registry included 12,472 consecutive patients who underwent TAVR at 16 centers. Baseline MR grade was available in 11,512 (92.3%) patients, of whom 3,180 (27.6%) had significant MR. Baseline and 1-month post-TAVR MR grade was available in 7,303 (58.6%) patients, who were included in the analysis. Overall, 1,983 (27.2%) had significant baseline MR. Baseline characteristics of patients with or without matched baseline and post-TAVR MR data available were similar (Supplemental Table 1).

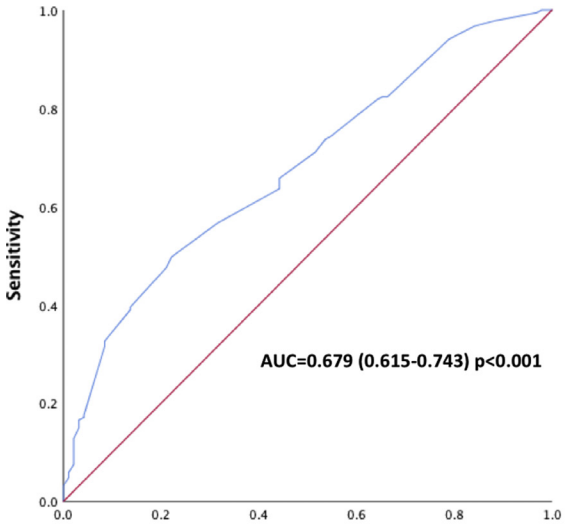
Out of the 1,983 patients with significant MR at baseline, the MR regressed following TAVR in 874 (44.1%) and persisted in 1,109 (55.9%) patients (Supplemental Figure 1). Baseline characteristics of patients according to baseline MR and the MR response to TAVR are presented in **Table 1**.

Compared with the nonsignificant baseline MR group, patients with significant baseline MR were more often female, were frail, had higher prevalence of atrial fibrillation, had permanent pacemaker, had degenerative etiology, and had baseline NYHA functional class III to IV but had lower prevalence of diabetes mellitus. These patients had higher mean Society of Thoracic Surgeons score, lower estimated glomerular filtration rate, and lower ejection fraction. When comparing patients with significant baseline MR that regressed or persisted after TAVR, those with persistent MR had a higher prevalence of degenerative etiology and atrial fibrillation.

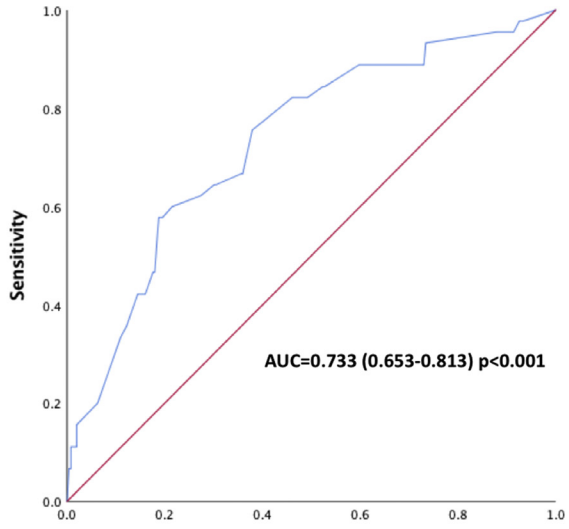
EFFECT OF BASELINE MR AND ITS RESPONSE TO TAVR ON MORTALITY. After a median follow-up of 3.3 years (IQR: 2.5 years-4.3 years), the Kaplan-Meier estimate for 4-year cumulative all-cause mortality was 32.4% (IQR: 30.5% to 34.3%) in the nonsignificant baseline MR group, 35.1% (IQR: 29.8%-40.4%) in the significant MR regressed group, and 43.8% (IQR: 39.1%-48.5%) in the MR persistence group. The difference between the MR regressed and nonsignificant baseline MR groups was not statistically significant (log-rank $p = 0.403$), while the difference between the MR persistence group and both other groups was significant ($p < 0.01$ for both) (**Figure 1**).

The multivariate adjusted HR for mortality was 1.38 (95% confidence interval [CI]: 1.06-2.04; $p = 0.008$) in the MR persistence versus nonsignificant baseline MR group and 1.02 (95% CI: 0.93-1.10; $p = 0.383$) for the MR regressed versus nonsignificant baseline MR group (**Figure 1**). Within the MR

FIGURE 3 Predictors of MR and Symptomatic Response to TAVR



	OR	95% CI	P value
AF	1.37	1.14-1.65	0.001
Baseline severe MR	4.07	2.46-6.72	<0.001
Annulus calcifications ≥ moderate	1.41	1.02-1.96	0.039
Leaflet calcifications ≥ moderate	1.67	1.15-2.51	0.008
SPAP>45mmHg	1.47	1.02-1.97	0.044
Self expandable valve	1.25	1.03-1.52	0.021
Degenerative MR	1.49	1.17-1.91	0.001



	OR	95% CI	P value
Baseline NYHA III/IV	1.97	0.94-4.13	0.071
Age>80	2.56	1.53-4.31	<0.001
Male	1.71	1.02-2.85	0.041
AF	1.68	0.99-2.84	0.051
Degenerative MR	1.92	0.96-3.82	0.064

Receiver-operating characteristic curves for prediction of MR **(left)** and NYHA regression **(right)** for a multivariate model based on the individual characteristics listed below each curve. AF = atrial fibrillation; AUC = area under the curve; OR = odds ratio; SPAP = systolic pulmonary artery pressure; other abbreviations as in Figure 1.

persistence group, mortality was similar regardless of MR etiology (Supplemental Figure 2).

INTERACTION BETWEEN CHANGE IN NYHA FUNCTIONAL CLASS AND PROGNOSTIC EFFECT OF MR RESPONSE. Data on NYHA functional class at 1 month after TAVR were available in 2,425 (33.2%) of 7,303 patients. NYHA functional class III to IV 1 month post-TAVR was more prevalent in the MR persistence group compared with nonsignificant baseline MR and MR regression (14.4% vs. 4.0% vs. 3.8%; $p < 0.001$) (Figure 1). Within the MR persistence group, those achieving NYHA functional class I or II showed similar 4-year mortality as the nonsignificant MR and MR regression groups (29.6% vs. 31.2% and 26.7%, respectively; log-rank $p = 0.421$), while those at NYHA functional class III to IV had significantly increased mortality risk of 54.7% (95% CI: 38.1% to 71.3%; log-rank $p < 0.001$) (Figure 2).

PREDICTORS OF MR RESPONSE TO TAVR. Using a univariate logistic regression with MR regression as the dependent variable, 7 baseline characteristics (baseline severe MR grade, atrial fibrillation, mitral annulus calcifications ≥ moderate, mitral leaflets calcifications ≥ moderate, systolic pulmonary artery pressure >45 mm Hg, degenerative MR etiology, and the use of self-expandable valve) were associated with a lower likelihood of MR regression after TAVR. When stratifying patients according to MR etiology, baseline severe MR grade was associated with MR persistence regardless of etiology (and was the strongest predictor of MR persistence); for patients with functional MR, the only other predictor of MR persistence was ejection fraction; and for those with degenerative MR atrial fibrillation, annulus and leaflet calcification and the use of self-expandable valve were also associated with MR persistence. Prediction models based on these characteristics had a poor discrimination for predicting MR regression after TAVR, more so for degenerative MR than for functional MR (Figure 3, Supplemental Figure 3).

PREDICTORS OF NYHA FUNCTIONAL CLASS RESPONSE TO TAVR. In patients with MR persistence after TAVR, 5 baseline characteristics showed a univariate association with the odds for remaining in

NYHA functional class III to IV following TAVR: baseline NYHA functional class III to IV, >80 years of age, male sex, atrial fibrillation, and degenerative MR etiology. These characteristics had a moderate discrimination for predicting the NYHA response after TAVR in patients with MR persistence (Figure 3).

BENEFITS OF STAGED PMVR AFTER TAVR. Stratified by treatment strategy post-TAVR, patients with persistent MR who underwent staged PMVR (n = 131) showed lower 3-year mortality compared with those who did not (n = 1,852): 29.9% versus 43.1% (log-rank p = 0.041) (unadjusted HR: 1.36; p = 0.042) (Supplemental Figure 4).

PSM yielded 91 matched pairs of patients who remained with significant MR following TAVR and did or did not undergo staged PMVR. Baseline characteristics were similar between the 2 groups (Table 2). Of note, almost 70% of patients in both groups remained at NYHA functional class III to IV following TAVR. Median time from TAVR to PMVR was 61 days.

While the prevalence of NYHA functional class III to IV functional class was similar between patients who did or did not undergo staged PMVR at baseline (67.1% vs. 68.2%; p = 0.893), at 6- and 12-month follow-up, NYHA functional class improved significantly in the staged PMVR group (19.1% and 17.6% at NYHA functional class III to IV, respectively) but remained unchanged in the no PMVR group (68.0% and 66.7%, NYHA functional class III to IV, respectively) (Figure 4).

Four-year cumulative mortality was higher in the no PMVR group compared with those undergoing staged PMVR, 64.6% (IQR: 51.3%-77.9%) versus 37.5% (IQR: 22.9% to 52.1%), but this was not statistically significant (log-rank p = 0.092) (univariate HR: 1.66 (95% CI: 0.94-2.86; p = 0.097) (Figure 4).

TABLE 2 Baseline Characteristics in the PSM Cohort

	Conservative (n = 91)	Staged PMVR (n = 91)	p Value
Age, yrs	78.8 ± 6.5	77.5 ± 7.4	0.429
Female	42 (46.2)	43 (47.3)	0.996
BMI, kg/m^2	25.9 ± 6.1	26.12 ± 5.9	0.666
eGFR, ml/min	50.4 ± 20.8	51.6 ± 18.1	0.441
Hemoglobin, g/l	11.6 ± 2.6	11.4 ± 2.1	0.615
STS score	6.8 ± 2.5	6.6 ± 2.7	0.575
AV peak, mm Hg	69.7 ± 21.8	66.5 ± 20.4	0.655
AV mean, mm Hg	45.9 ± 15.7	44.6 ± 15.5	0.647
EF, %	48.5 ± 13.4	49.6 ± 13.6	0.506
AVA, cm^2	0.68 ± 0.21	0.69 ± 0.19	0.724
Degenerative MR etiology	62 (68.1)	63 (69.2)	0.846
Previous PCI	32 (35.2)	32 (35.2)	0.994
Previous MI	18 (20.2)	22 (24.2)	0.517
Previous cardiac surgery	31 (34.1)	33 (36.3)	0.582
Frailty	31 (34.1)	31 (34.1)	1.000
AF	26 (29.0)	29 (31.8)	0.516
PPM	12 (13.6)	13 (14.3)	0.862
COPD	20 (22.0)	17 (18.7)	0.556
DM	35 (39.0)	33 (35.8)	0.362
Hypertension	73 (80.2)	71 (78.9)	0.764
Bicuspid valve	4 (4.4)	3 (3.3)	0.137
Femoral access	82 (90.1)	81 (89.0)	0.621
Balloon expandable valve	25 (27.4)	27 (29.5)	0.732
NYHA functional class III-IV	62 (68.6)	61 (67.1)	0.835
Years			0.453
2007-2010	8 (8.8)	5 (5.5)	
2011-2014	20 (22.0)	20 (22.0)	
2015-2019	63 (69.2)	66 (72.5)	

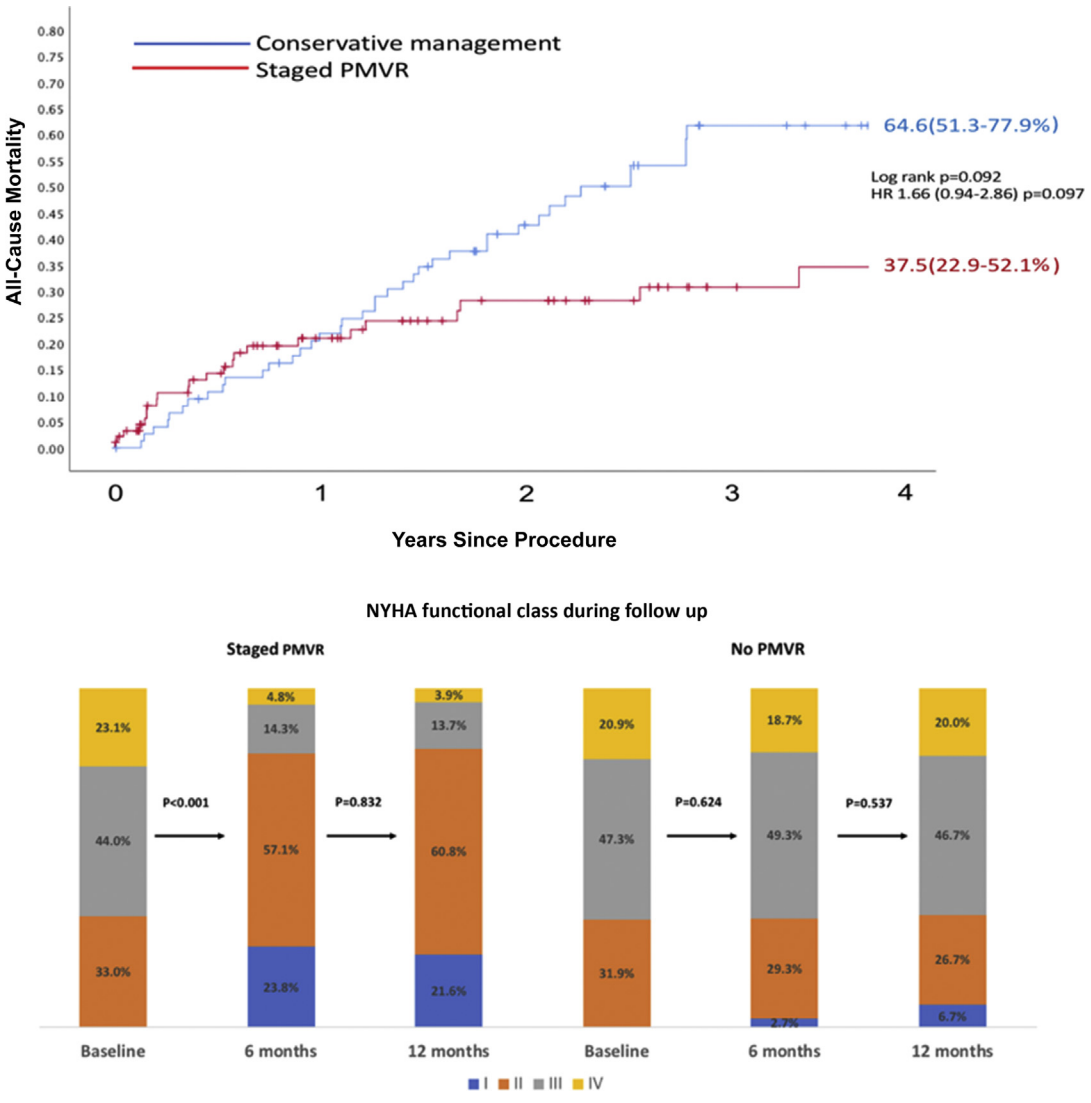
Values are mean ± SD or n (%).
PSM = propensity score matching; other abbreviations as in Table 1.

DISCUSSION

We performed a retrospective cohort study based on individual patient data from a large multicenter registry to assess the impact of MR on mortality following TAVR. The major findings are the following. First, MR response to TAVR, and more importantly, symptomatic improvement following TAVR, not baseline MR grade, affects the long-term prognosis following TAVR (Central Illustration). Second, MR persistence post-TAVR occurs in 55% of patients with significant baseline MR, and symptoms persist in just under 15% of these patients. Third, the likelihood of MR regression is associated with several clinical, echocardiographic, and procedural characteristics; NYHA functional class improvement after TAVR is associated mainly with demographic and clinical characteristics. The ability to predict MR response to TAVR is poor, more so in patients with degenerative MR. Last, when MR persists post-TAVR, the use of staged PMVR to treat the MR is rare (<10% of cases), but when this is feasible, a staged PMVR strategy results in improved clinical outcomes (although this was statistically significant only for functional class only, not for overall mortality after propensity score matching).

The rapid increase in the use of TAVR over surgical aortic valve replacement (SAVR), which is expected to expand into low-surgical-risk patients as well (15), requires a reassessment of the management strategy for patients with AS + MR. Currently, the common practice is to perform TAVR, which in many cases will result in regression of MR as well. The main dilemma

FIGURE 4 Survival Analysis in the PSM Cohort

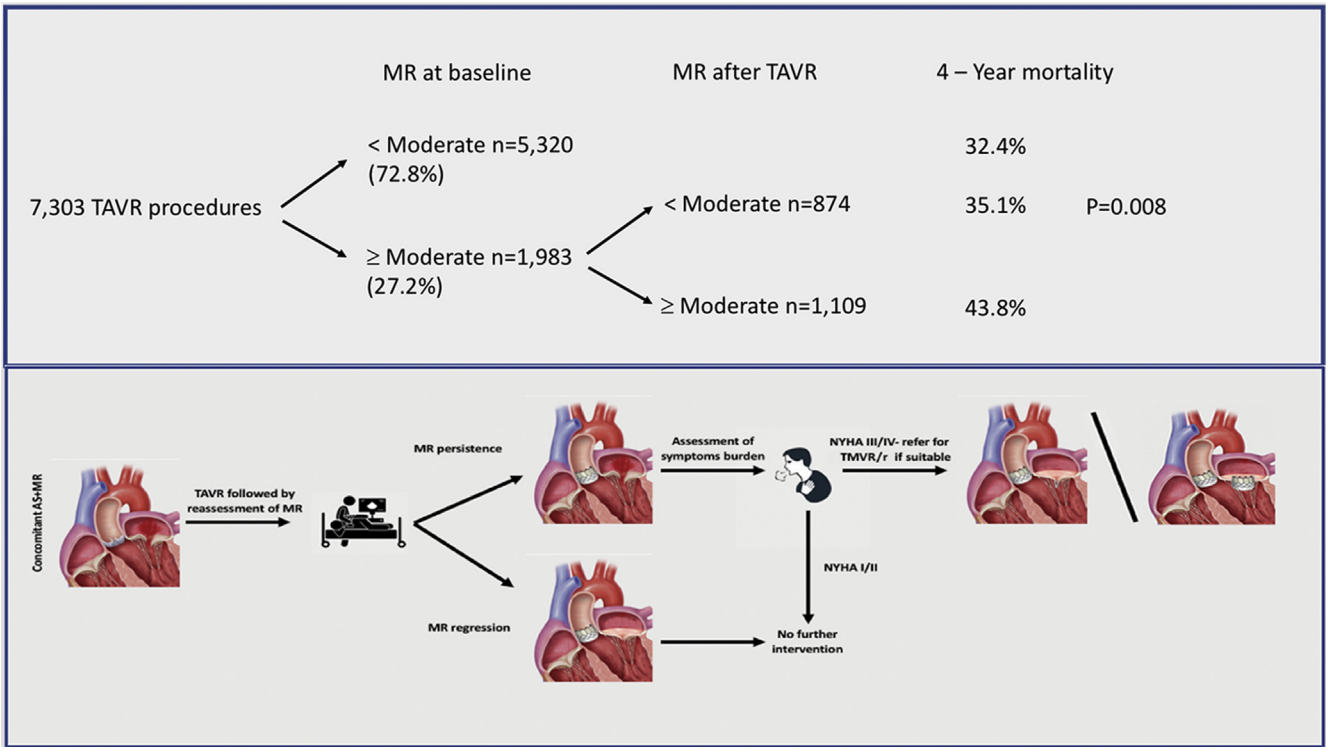


Kaplan-Meier curves for all-cause mortality according to management strategy after TAVR in the propensity score–matched (PSM) cohort **(top)** and distribution of NYHA functional class through 12-month follow-up in patients undergoing staged percutaneous mitral edge-to-edge repair (PMVR) **(bottom left)** or no PMVR in the PSM cohort **(bottom right)**. HR = hazard ratio; other abbreviations as in Figure 1.

is how to manage those patients with persistent MR following isolated TAVR. The major evidence gaps on this issue are: 1) what are the predictors of prognosis following TAVR in patients with significant baseline MR pre TAVR? 2) can the likelihood of MR regression following TAVR be estimated prior to TAVR? 3) what is the applicability of PMVR in patients with MR persistence following TAVR? and 4) which patients are likely to benefit from transcatheter mitral interventions following TAVR? We believe that our results have several important findings that address these evidence gaps. We show that it is not baseline, but rather post-TAVR MR grade that is associated with midterm mortality. Data on this issue have been inconsistent thus far: Cortes et al. (8) showed no difference in overall or cardiovascular mortality between patients whose MR regressed or persisted following TAVR, while Mauri et al. (9) and Mavromatis et al. (10) reported better survival for those with MR regression following TAVR.

Although there are several differences between the studies mentioned previously as well as ours, such as

CENTRAL ILLUSTRATION **Outcomes of 7,303 Patients With Matched Baseline and Post-TAVR MR in 16 European Centers Between 2007 and 2019**



Witberg, G. et al. J Am Coll Cardiol Intv. 2021;14(11):1181–92.

(Top) Distribution of MR grade at baseline, post-transcatheter aortic valve replacement (TAVR), and corresponding rates of 4-year mortality in the study cohort. **(Bottom)** Proposed scheme for assessment and management of patients with concomitant significant aortic stenosis (AS) + mitral regurgitation (MR). NYHA = New York Heart Association; TMVR/r = transcatheter mitral valve replacement or repair.

design (single or multicenter) follow-up period (ranging from 1 to 3 years), definition of significant MR (> or ≥ moderate), MR regression (improvement by 1 grade or to below the threshold used to define significant MR) and timing of assessment for MR regression (at discharge from TAVR or 1-month follow-up), and sample size, taken together, the currently available evidence suggests that the key factor for risk stratification in the AS + MR population is the MR response to TAVR, not the MR severity pre-TAVR (which was used as the stratification variable in most previous studies that examined the interaction between AS and MR in patients undergoing TAVR) (2-4).

Our results extend the current evidence on the management of patients with AS + MR in 2 major issues: 1) refining the risk stratification following TAVR; and 2) examining the benefit of staged PMVR after TAVR. Our study is the first to examine the significance of NYHA change after TAVR in those with significant baseline MR. Our results show that persistence of NYHA functional class III to IV is much more likely when MR persists following TAVR, and it seems that this patient group is responsible for the increased mortality in the MR persistence group. This has important implications on patient management, as although MR persistence after TAVR is seen in 55.9% of patients with baseline significant MR, our results show that only 14.4% of this group remained highly symptomatic 1 month following TAVR, while the vast majority showed symptomatic improvement that was associated with similar mortality to those with nonsignificant MR at baseline or MR regression. Symptoms resolution after TAVR despite MR persistence probably identifies a subgroup of patients whose MR plays a smaller role in the overall morbidity burden compared with AS, and is therefore less likely to have an impact on prognosis post-TAVR. It seems that such patients can be conservatively managed in a similar fashion to current

recommendations for patients with asymptomatic MR (5), while those with persistent symptoms despite successful treatment of the AS are those whose MR bears more clinical and subsequently prognostic significance. Our findings highlight the need for early (probably within 1 to 3 months) post-TAVR reassessment of MR grade and NYHA functional class in order to determine the optimal management of patients with significant baseline MR undergoing TAVR.

The importance of appropriate risk stratification after TAVR is emphasized by our comparison of patients with persistent MR post-TAVR who underwent staged PMVR with those who did not undergo further interventions: both unadjusted and PSM analyses showed that staged PMVR is associated with improved prognosis and that persistent significant MR post-TAVR results in dismal prognosis (55% three-year mortality). Although the mortality advantage of PMVR did not reach statistical significance in the PSM analysis, this was likely due to the small sample size. However, the benefit of staged PMVR in terms of functional class through 1 year of follow-up was dramatic and statistically significant. These findings, though still only hypothesis generating, confirm previous results from our registry (14), with the main difference being that the current analysis used a more comprehensive and representative control group for PSM.

The 2 main remaining evidence gaps that require addressing in order to improve the triage of patients with AS + MR are the ability to predict the MR response to isolated TAVR and assessing the applicability of complete transcatheter treatment for AS + MR in this patient population. As our data show, the ability to predict the MR (as well as symptomatic response) to TAVR is very limited. This is probably the result of the complex and heterogeneous nature of the pathophysiologic mechanisms of MR. Cortes et al. (8) reported somewhat better prediction ability (that was still only moderate) using mitral valve annulus diameter and a binary variable (which was not available in our database) (see Study Limitations). One other reason for the poor ability to predict MR response in our database is the lack of uniform core lab analysis of echocardiographic data, which undoubtedly introduced some heterogeneity to this data assessment (see Study Limitations).

The importance of predicting MR response to TAVR lies in its potential to impact the treatment strategy in cases of AS + MR. Ideally, if the likelihood of MR regression post-TAVR is low, the option of double-valve surgery should be seriously considered, especially in patients who are viable surgical candidates (in our cohort, a third of those with persistent MR were in the low surgical risk category according to their Society of Thoracic Surgeons score). In such cases, the ability to treat both valves in a single procedure may be a "tie breaker," swaying the heart team choice between TAVR or SAVR toward the surgical option. However, given the challenges in predicting MR response to TAVR, it seems that at least for those not at low surgical risk for SAVR, a strategy of TAVR first would seems to be the more attractive option, allowing the benefit of a less invasive procedure for treatment of the aortic disease, which also offers a reasonable chance for satisfactory MR regression and symptomatic improvement (which would render further interventions to the mitral valve unnecessary), while maintaining the option for future transcatheter mitral intervention pending anatomic suitability for those with unsatisfactory MR and symptoms response.

The other remaining piece of the jigsaw in determining the optimal treatment strategy for AS + MR is the applicability of staged PMVR following TAVR. The use of staged PMVR in cases when significant MR persists post-TAVR is infrequent (just under 10% in our cohort). This is likely to be the result of 2 factors: 1) many patients with persistent MR still show significant symptomatic improvement post-TAVR, so there is no clinical indication for further valvular intervention; and 2) as previously described by Cortes et al. (8), in many cases, PMVR is not anatomically feasible. Data on this issue are scarce and represent a less evolved and mature era of transcatheter mitral valve interventions (the data published by Cortes et al. date back to 2007 to 2015). The annual volume and geographic availability of PMVR in particular and TMVR/r in general is growing rapidly, and in addition, more devices and techniques to treat MR are being developed and put into clinical practice (12,13). This may make complete transcatheter treatment of AS + MR applicable for a much larger fraction of those with persistent MR post-TAVR

Our study has several strengths. It is the first to present data representing current clinical practice from an international cohort of patients; our follow-up period is longer compared with previous studies that examined this issue before; it is the first to examine the interaction between MR response, symptoms response, and prognosis following TAVR; and it includes a comparison assessing the prognostic benefit of staged TAVR + PMVR strategy for patients left with significant residual MR following TAVR, a management option that is infrequently used these days (14) but may be relevant to a growing number of TAVR patients in the coming years.

STUDY LIMITATIONS. Echocardiographic data were analyzed at each center and not in a centralized core

lab, and we could not examine one of the remining knowledge gaps in this field—estimating the fraction of patients with significant residual MR following TAVR who would be anatomically suitable for TMVR/r using currently available devices (see previously). Also, our database did not include several factors previously reported to be associated with MR regression in some studies, such as mitral annulus diameter (8,9), left ventricle diameter (16), implantation depth (17), and left bundle branch block (8), so these were not included in the MR response prediction analysis. Our cohort included only 58.6% of the total registry patients due to missing data on post-TAVR MR (although our analysis did not show any signs of selection bias given the similar baseline characteristics of patients with or without MR data available following TAVR). Our examination of the clinical benefit of PMVR post-TAVR should be interpreted cautiously, and can only be considered hypothesis generating given the limited sample size, the exclusion of other interventions except staged PMVR, and not having data on the reasons for not performing PMVR, so these data require validation by further studies.

Remaining evidence gaps such as optimal timing of the intervention (concomitant or staged, optimal interval in the case of a staged intervention), and benefit from using MVR/r techniques other than PMVR, should ideally be answered by a properly designed prospective trial that would randomize patients with significant residual MR and symptoms following TAVR, who are suitable for TMVR/r (according to core lab assessment), to medical management versus TMVR/r.

CONCLUSIONS

Significant baseline MR is frequent in patients undergoing TAVR. In about one-half of these patients, significant MR persists after TAVR. These patients, especially those who remain symptomatic, are at an increased risk for mortality. A staged PMVR strategy is associated with improved functional class and a numerically but not statistically significantly lower mortality compared with medical management.

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Dr. Barbanti has received consultant fees from Edwards Lifesciences. Dr. Grasso has served as a proctor for Abbott Vascular. Dr. De Backer has received research grants and consultant fees from Abbott and Boston Scientific. Dr. Andreas has served as a proctor for Abbott and Edwards Lifesciences; and has received advisory board fees from Medtronic. Dr. Estévez-Loureiro has served as a consultant for Abbott Vascular and Boston Scientific. Dr. Amat-Santos has served as a proctor for Boston Scientific. Dr. Nombela-Franco has received consultant fees from Edwards Lifesciences; and has served as a proctor for Abbott. Dr. Søndergaard has received consultant fees and institutional research from Abbott, Boston Scientific, Edwards Lifesciences, and Medtronic. Dr. Van Mieghem has received research grant support from Abbott, Boston Scientific, Edwards Lifesciences, Medtronic, PulseCath BV, and Daiichi-Sankyo; and has received advisory fees from Abbott, Boston Scientific, Ancora, Medtronic, PulseCath BV, and Daiichi-Sankyo. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.

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PERSPECTIVES

WHAT IS KNOWN? MR is common in patients suffering from severe AS undergoing TAVR. Data regarding the optimal management of residual MR post-AVR is scarce.

WHAT IS NEW? Risk stratification based on the response of MR grade and NYHA functional class to TAVR can identify those patients who are at increased risk for mortality and should be assessed for further interventions, from those whose residual MR should be treated conservatively. For symptomatic patients, a staged PMVR strategy seems to be associated with improved mortality.

WHAT IS NEXT? Additional studies are necessary to examine the optimal selection of patient and timing for mitral interventions after TAVR, and a larger scale examination of its effect on mortality, ideally through a randomized clinical trial.

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KEY WORDS aortic stenosis, mitral regurgitation, TAVR, TMVR/r

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