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ORIGINAL ARTICLE

Impact of aortic valve replacement for severe aortic stenosis on organic and functional mitral regurgitation

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Abstract

Aims Concurrent mitral regurgitation (MR) influences treatment considerations in patients with severe aortic stenosis (sAS). Limited information exists regarding haemodynamic effects of sAS on MR severity and outcome of these patients. We assessed the impact of aortic valve replacement (AVR) on MR according to mechanism in patients with sAS and MR.

Methods and results In patients with sAS who received surgical or transcatheter AVR from 2008 to 2017, those with effective mitral regurgitant orifice area (ERO) $\geq$ 10 mm^2 prior to AVR were evaluated. The change in MR after AVR was considered significant when there was at least one grade difference. We compared the all-cause mortality of patients with and without improvement in MR. Of 234 patients with sAS and MR (age 80 ± 9 years, 52% male, ERO 19 ± 7 mm^2), organic and functional MR were present in 166 (71%) and 68 (29%), respectively. MR improved in 136 (58%); improvement occurred with similar frequency in organic versus functional MR (59% and 57%, P = 0.88). Associated determinants were absence of atrial fibrillation in organic MR [odds ratio (OR) 2.09, 95% confidence interval (CI) 1.00–4.37; P = 0.049] and indexed aortic valve area (iAVA) $\leq$ 0.40 cm^2 in functional MR (OR 3.28, 95% CI 1.13–9.47; P = 0.028). In the overall cohort, mitral annulus diameter $<$ 3 cm (OR 1.74, 95% CI 1.02–2.97; P = 0.041) and QRS duration $<$ 115 ms (OR 1.73, 95% CI 1.00–2.98; P = 0.049) were independently associated with improvement in MR. During median follow-up of 3.5 years, lack of improvement in MR was not associated with higher mortality in the overall cohort of patients with ERO $\geq$ 20 mm^2 [adjusted hazard ratio (HR) 1.71, 95% CI 0.90–3.27; P = 0.10, adjusted for age, New York Heart Association III or IV, diabetes, and creatinine $\geq$ 2.0 mg/dL]. Lack of improvement in organic MR was associated with higher mortality (adjusted HR 3.36, 95% CI 1.40–8.05; $P < 0.01$). In patients with functional MR, change in MR was not associated with mortality (HR 1.24, 95% CI 0.44–3.47; P = 0.68).

Conclusions In nearly 60% of patients with sAS and MR, MR improved after AVR, even in the majority of patients with organic MR. Absence of atrial fibrillation in organic MR, iAVA $\leq$ 0.40 cm^2 in functional MR, and mitral annulus diameter $<$ 3 cm and QRS duration $<$ 115 ms in the overall population were associated with MR improvement. Post-operative improvement in organic MR was associated with better survival.

Keywords Mitral regurgitation; Aortic stenosis; Valve disease; Echocardiography

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Introduction

Mitral regurgitation (MR) is common, and ≥moderate MR is observed in about 20% of patients with severe aortic stenosis (sAS).[1,2] Current guidelines do not provide specific recommendations for treatment for sAS and ≥moderate MR.[3,4] Transcatheter aortic valve replacement (TAVR) is increasingly used as a standard therapy for sAS and an alternative to surgical aortic valve replacement (SAVR).[5] In addition, transcatheter mitral repair and replacement are increasingly utilized for treatment of MR in select groups of patients at high surgical risk.[6] Optimal therapy for sAS and concurrent MR must

be considered at the time of surgical and transcatheter interventions. To determine the timing and type of intervention for concomitant MR, the impact of aortic valve replacement (AVR) on MR has received increased attention.

Previous studies evaluating the impact of AVR on MR have yielded conflicting results; MR improved after AVR in 40–80%.[2,7,8] In a previous small study using the proximal isovelocity surface area (PISA) method, the mean decreases in effective regurgitant orifice area (ERO) and regurgitant volume after AVR were ~5 mm^2 and ~10 mL, respectively.[9] Because most patients with sAS have degenerative change in mitral valve (MV) due to calcification rather than purely functional MR,[10,11] the impact of AVR and determinants for change in MR may vary according to MR mechanism. Moreover, the post-operative change in MR may affect the clinical outcomes. Thus, this study aimed to (i) assess the impact of AVR on MR severity according to MR mechanism, (ii) examine the determinants of changes in MR after AVR, and (iii) compare the all-cause mortality in patients with and without MR improvement.

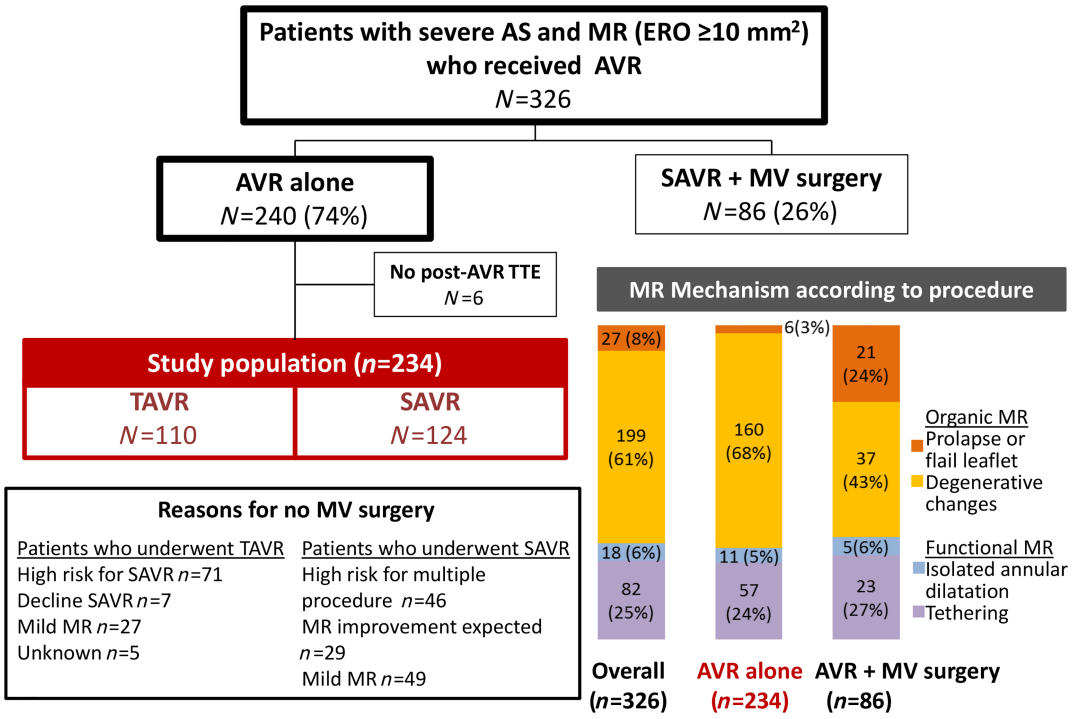
Methods

The Mayo Clinic Institutional Review Board approved the study, and patients who provided research authorization were included. We investigated patients who underwent SAVR or TAVR for sAS from January 2008 to December 2017. Of patients with MR, defined as ERO $\geq$ 10 mm^2 by PISA method with transthoracic echocardiography (TTE), those who did not receive MV intervention at the time of AVR were included. Patient flow chart is summarized in *Figure 1*. Patients with any prior surgical procedure on the aortic valve or MV surgery (repair or replacement) and hypertrophic obstructive cardiomyopathy were excluded. Baseline demographic, surgical, and outcome data were extracted from the electronic medical record. All included patients had post-operative TTE performed at the time of hospital dismissal according to usual clinical practice. Atrial fibrillation was considered present if observed at TTE. Atrial fibrillation was further classified as paroxysmal if typical episodes were self-terminating in <7 days and chronic if a decision had been made to stop attempts to restore and/or maintain sinus rhythm.[12]

Transthoracic echocardiography

Transthoracic echocardiography was performed using commercially available state-of-the-art ultrasound systems. Comprehensive TTE was performed according to current guidelines.[13–15] sAS was defined as aortic valve area (AVA) $\leq$ 1.0 cm^2, indexed AVA $\leq$ 0.6 cm^2, peak velocity $\geq$ 4.0 m/s, or mean systolic gradient $\geq$ 40 mmHg[14]

Figure 1 Patient flow chart and MR mechanism. AVR, aortic valve replacement; ERO, effective regurgitant orifice; MR, mitral regurgitation; MV, mitral valve; sAS, severe aortic stenosis; SAVR, surgical AVR; TAVR, transcatheter AVR.



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as well as typical appearance of the valve. Low-flow low-gradient sAS included the subset of peak velocity < 4.0 m/s or mean gradient < 40 mmHg with reduced ejection fraction (EF) ($<$50%). Paradoxical low-flow low-gradient sAS included the subset with stroke volume index < 35 mL/m^2 and normal EF. Aortic (AR) and tricuspid regurgitation was considered present if the severity was moderate or greater.[16] Mitral stenosis was defined as MV area ≤ 1.5 cm^2.[3] Patient-prosthesis mismatch was defined as indexed AVA ≤ 0.85 cm^2 at post-AVR TTE.[17]

Assessment of mitral regurgitation

Mitral regurgitation severity was evaluated based on the PISA method combined with a multi-parametric integrative approach.[16] Specifically, mild, moderate, and severe MR corresponded to a regurgitant volume of $<$30, 30 to 59, and $\geq$60 mL per beat, respectively, and an ERO of $<$20, 20 to 39, and $\geq$40 mm^2, respectively, for both organic and functional MR. Colour Doppler jet size was not used because it is affected by the increased left ventricular (LV) pressure in patients with sAS.[10] If quantification or semi-quantification of MR indicated different grades, MR grade was considered as mild to moderate or moderate to severe. The change in MR after AVR was considered significant when there was at least one grade difference between pre-operative and post-operative TTE.

The MR mechanism was determined on pre-operative (pre-AVR) TTE and categorized into two groups based on valve abnormality.[16] Organic MR was defined as MV prolapse, flail leaflet, or degenerative changes including calcification, thickening, or rheumatic change.[16] Functional MR was defined as isolated annulus dilation or systolic tethering of the leaflets due to a dilated left ventricle with global or regional wall motion abnormalities even in the presence of focal MV calcification not affecting leaflet motion.[16] Mitral annulus calcification (MAC) was defined as the presence of dense calcium deposits at the base of the mitral leaflets between the left atrium and ventricle.[18] We measured mitral annulus diameter, tenting area, and coaptation height of MV to assess these determinants of post-operative changes in MR. Mitral annulus diameter was measured in parasternal long-axis view at end-diastole.[19] Tenting area was measured as the area enclosed by the annular plane and two leaflets in parasternal long-axis view at the time of maximal MV closure in mid-systole as previously reported[19]; coaptation height was measured as the minimum distance between mitral leaflet coaptation and the mitral annular plane as well. Comprehensive TTE was performed by multiple credentialed sonographers according to usual clinical practice. All data pertaining to MR severity and MV dimensions were systematically reassessed by an investigator blinded to clinical outcome.

Follow-up and outcome

Post-AVR TTE, available in all patients, was used to assess the impact of AVR on MR. Results of follow-up TTE, available in a subset of patients, were also described to assess the longer-term impact of AVR on MR. Follow-up TTE was performed according to clinical judgment; for patients with multiple follow-up TTEs, the latest TTE before any MV intervention was used. LV and MV dimensions, including mitral annulus diameter, tenting area, and coaptation height, were assessed and compared at post-AVR and follow-up TTE.

Besides changes in MR, all-cause mortality during follow-up was assessed. Mortality was determined from medical records, Social Security Death Index (SSDI), and the Department of Cardiovascular Surgery surveys, which were sent to all surgical patients at 1, 3, 5, 10, and 15 years after operation. Patients were censored at the last time known to be alive, or date of death. Of patients with ERO ≥ 20 mm^2 pre-AVR, mortality was compared in patients with and without MR improvement at post-AVR TTE.

Statistics

Continuous data are expressed as mean ± standard deviation or median [interquartile range] and categorical data as frequency or percentage. Continuous variables were compared between organic and functional MR using the Student's *t*-test or Wilcoxon rank sum test where appropriate. Categorical variables were compared by means of the χ^2 test. Measurements at pre-AVR and post-AVR TTE, and post-AVR and follow-up TTE were compared using paired *t*-test or McNemar's test. The available data at both TTEs were compared. Logistic regression analysis was used to assess variables associated with MR improvement; variables with $P < 0.1$ (pre-AVR) or $<$0.2 (post-AVR) in univariate analysis were included as candidate variables for the multivariable model. The final multivariable model was then created using backward elimination. Some nominal variables were determined using the mean of the continuous variables. Odds ratios (ORs) and 95% confidence limits are summarized from the logistic regression analyses. Survival analysis was performed by the Kaplan–Meier method and log-rank test. In these analyses, patients with MV intervention were censored at the time of intervention. Cox proportional hazards modelling was used to identify independent predictors for all-cause mortality: the final models were created in the same way as the logistic regression analysis. To test whether associations between variables of interest and outcomes were different by type of MR, interactions were fit within the regression models. Two-sided $P < 0.05$ was considered statistically significant. All statistical analysis was performed using JMP pro 14 (SAS Institute, Cary, North Carolina).

Results

Patient characteristics

We identified 326 patients with sAS and MR who underwent AVR. Of these, 86 (26%) received concomitant MV surgery at the time of AVR and 6 were excluded because post-operative TTE was not performed, leaving a final cohort of 234 patients (*Figure 1*). Of patients with MR due to prolapse or flail leaflet, 78% received concomitant MV surgery, while 80% of patients with degenerative MR did not. In the final cohort, organic MR was observed in 166 (71%) including degenerative changes in 160 (68%) and prolapse or flail leaflet in 6 (3%). Functional MR was observed in 68 (29%) including 11 (5%) with isolated annular dilatation and 57 (24%) with tethering. Clinical and echocardiographic characteristics were compared according to MR mechanism in *Table 1*. The median age was 80 ± 9 years, and 121 (52%) were men. Atrial fibrillation was observed at pre-AVR TTE in 62 (26%) and was chronic in all. Additionally, 35 (15%) had paroxysmal atrial fibrillation. Moderate or greater AR coexisted with sAS in 26 (11%). TAVR was performed in 110 (47%): 75 (45%) with organic MR and 35 (51%) with functional MR (P = 0.38). Concomitant coronary artery bypass was performed in 65 (28%): 50 (30%) with organic MR and 15 (22%) with functional MR (P = 0.21).

Mitral annulus calcification was observed in 172 (74%): 127 (77%) with organic MR and 45 (66%) with functional MR (P = 0.13). The left ventricular ejection fraction (LVEF)

Table 1 Clinical and echocardiographic characteristics

	Overall n = 234	Organic MR n = 166	Functional MR n = 68	P*
Age, years	80 ± 9	80 ± 9	79 ± 9	0.83
Male	121 (52)	80 (48)	41 (60)	0.093
NYHA III or IV	185 (79)	128 (77)	57 (84)	0.25
Atrial fibrillation at pre-AVR TTE	62 (26)	39 (23)	23 (34)	0.10
QRS duration, ms	115 ± 31	113 ± 30	121 ± 34	0.81
QRS duration < 115 ms	146 (62)	109 (66)	37 (54)	0.11
Creatinine ≥ 2.0 mg/dL	23 (10)	15 (9)	8 (12)	0.52
NTproBNP, 10^2 pg/mL [n = 133]	35 [14–86]	28 [14–63]	67 [24–168]	<0.01
Diabetes	49 (21)	34 (20)	15 (22)	0.79
Dyslipidaemia	161 (69)	119 (72)	42 (62)	0.14
Hypertension	186 (79)	137 (84)	49 (72)	0.072
Coronary artery disease	99 (42)	64 (39)	35 (51)	0.069
Cerebral vascular disease	58 (25)	44 (27)	14 (21)	0.34
Chronic lung diseases	38 (16)	24 (14)	14 (21)	0.25
Echocardiography				
Left ventricle				
Ejection fraction, %	50 ± 15	55 ± 13	38 ± 13	<0.01
End-diastolic diameter, mm	53 ± 7	51 ± 6	57 ± 8	<0.01
End-systolic diameter, mm	38 ± 10	35 ± 8	46 ± 9	<0.01
Mass index, g/m^2	132 ± 37	127 ± 33	144 ± 42	<0.01
S$\prime$ septal, cm/s [n = 219]	4.6 ± 1.5	4.8 ± 1.5	4.0 ± 1.2	<0.01
S$\prime$ lateral, cm/s [n = 209]	5.7 ± 1.8	5.9 ± 1.7	4.9 ± 1.7	<0.01
Left atrium volume index, mL/m^2 [n = 133]	55 ± 18	53 ± 17	61 ± 19	<0.01
Aortic valve				
Peak velocity, m/s	4.3 ± 0.6	4.4 ± 0.6	4.1 ± 0.6	<0.01
Transaortic gradient, mmHg	46 ± 14	48 ± 15	43 ± 13	0.016
AVA, cm^2	0.77 ± 0.18	0.78 ± 0.19	0.76 ± 0.17	0.37
Indexed AVA, cm^2/m^2	0.42 ± 0.10	0.43 ± 0.10	0.40 ± 0.08	0.10
Aortic regurgitation	26 (11)	23 (14)	3 (4)	0.037
Mitral valve				
ERO, mm^2	19 ± 7	18 ± 7	20 ± 6	0.15
RV, mL	35 ± 12	35 ± 13	35 ± 10	0.71
E velocity, m/s	1.17 ± 0.31	1.19 ± 0.31	1.13 ± 0.30	0.16
Mitral stenosis	4 (2)	4 (10)	0 (0)	0.20
Mitral annulus calcification	172 (74)	127 (77)	45 (66)	0.13
Mitral annulus diameter, mm	30 ± 5	29 ± 5	32 ± 4	<0.01
Tenting area, cm^2	1.3 ± 0.5	1.2 ± 0.4	1.5 ± 0.5	<0.01
Coaptation height, mm	8.1 ± 2.1	7.7 ± 1.8	9.0 ± 2.3	<0.01
Tricuspid regurgitation	103 (45)	65 (40)	38 (57)	0.018
Right ventricular systolic pressure, mmHg	48 ± 15	47 ± 16	50 ± 13	0.11

AVA, aortic valve area; ERO, effective regurgitant orifice area; MR, mitral regurgitation; NTproBNP, N-terminal pro-brain natriuretic peptide; NYHA, New York Heart Association; RV, regurgitant volume.
Mean ± standard deviations, median [interquartile range], or numbers (%). The number of available data is expressed for those variables in which some data were missing.
*indicates $P < 0.05$ organic versus functional MR.

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was lower (38 ± 13% vs. 55 ± 13%, $P < 0.01$) and LV end-diastolic diameter was larger (57 ± 8 vs. 51 ± 6 mm, $P < 0.01$) in patients with functional MR compared with organic MR.

Impact of aortic valve replacement on mitral regurgitation

Transthoracic echocardiography was performed a median of 28 [8–56] days before AVR and 4 [3–6] days after AVR. The distribution of MR severity pre-operatively and post-operatively is shown in *Figure 2*. In the overall cohort, MR improved in 136 (58%) and worsened in 30 (13%). Improvement in MR grade was similar between patients with organic and functional MR (59% vs. 57%, $P = 0.88$). Of 6 with organic MR due to prolapse or flail leaflet, MR improved in 2 (33%) and worsened in 1 (17%). Of 11 with functional MR due to isolated annular dilatation, MR improved in 5 (45%) and worsened in 4 (36%). Of 51 patients with low-flow low-gradient AS, MR improved in 30 (59%) and worsened in 9 (18%). Of 20 with paradoxical low-flow low-gradient AS, MR improved in 10 (50%) and worsened in 3 (15%). There was no difference in improvement in MR grade in patients undergoing SAVR versus TAVR (60% vs. 56%, $P = 0.61$). Echocardiographic features of the two groups after AVR are compared on *Table 2*.

Pre-operative determinants of improvement in mitral regurgitation

Univariate logistic regression analyses to identify pre-operative variables associated with improvement in MR are listed in *Table 3*. In multivariable analysis, absence of atrial fibrillation at the index TTE (OR 2.09, 95% confidence interval [CI] 1.00–4.37; $P = 0.049$) in patients with organic MR (AUC = 0.61), and indexed AVA ≤ 0.40 cm^2 (OR 3.18, 95% CI 1.11–9.06; $P = 0.031$) in those with functional MR (AUC = 0.72), were the independent determinants of improvement in MR. Indexed AVA showed a significant interaction between organic and functional MR. In the overall cohort, mitral annulus diameter < 3 cm (the mean value, OR 1.74, 95% CI 1.02–2.97; $P = 0.041$) and QRS duration < 115 ms (the mean value, OR 1.73, 95% CI 1.00–2.98; $P = 0.049$) were independently associated with improvement in MR (AUC = 0.60). AR was not associated with improvement in MR. The prevalence and determinants of

Figure 2 Distribution of MR severity and change in MR after aortic valve replacement. Distribution of MR severity at pre-AVR and post-AVR (A). MR improved in 58% of the overall cohort (B). MR improvement occurred with similar frequency in organic versus functional MR (59% vs. 57%, $P = 0.88$). Abbreviations as in *Figure 1*.

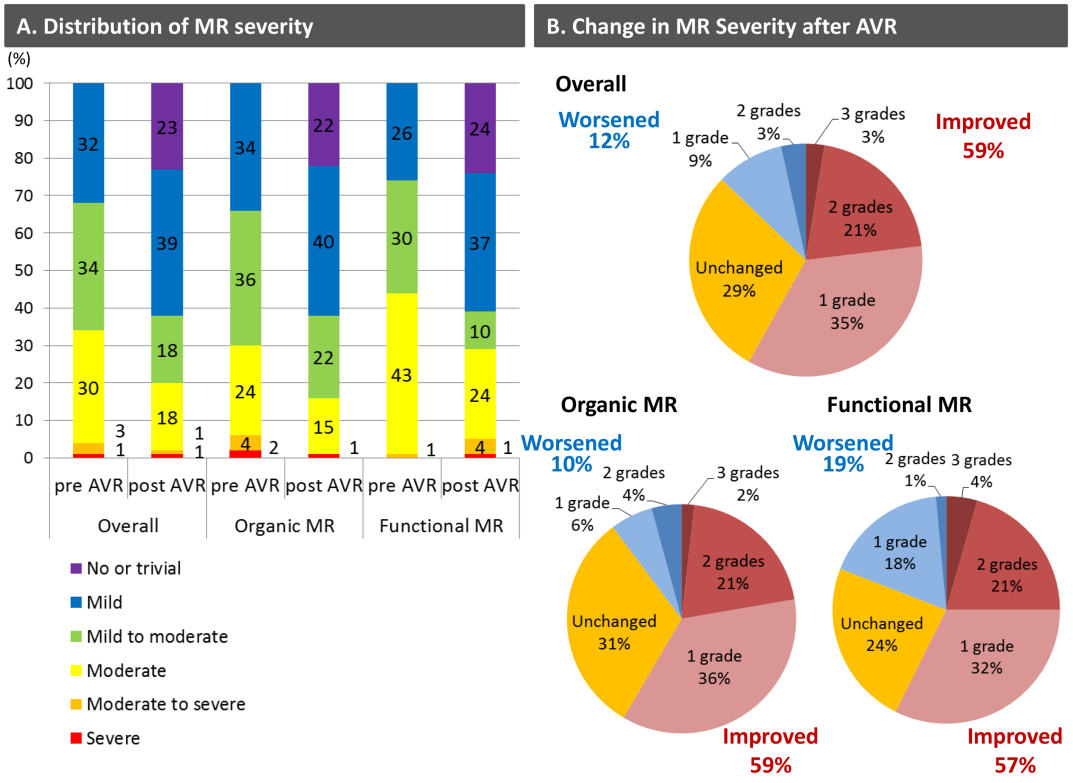


Table 2 Echocardiographic features after aortic valve replacement

	Organic MR $n = 166$	Functional MR $n = 68$	P
Left ventricle			
Ejection fraction, %	56 ± 12*	42 ± 13†	<0.01
End-diastolic diameter, mm	49 ± 8*	56 ± 8	<0.01
End-systolic diameter, mm	34 ± 8*	43 ± 10†	<0.01
Mass index, g/m^2	118 ± 32*	142 ± 37	<0.01
S$\prime$ septal, cm/s [$n = 196$]	4.8 ± 1.5	4.5 ± 1.6†	0.15
S$\prime$ lateral, cm/s [$n = 161$]	6.3 ± 2.0	5.5 ± 1.7†	0.022
Left atrium volume index, mL/m^2 [$n = 133$]	53 ± 16	58 ± 18	
Aortic valve			
Peak velocity, m/s	2.4 ± 0.5*	2.3 ± 0.4†	0.18
Transaortic gradient, mmHg	13 ± 5*	12 ± 5†	0.13
AVA, cm^2	2.08 ± 0.68*	2.07 ± 0.62†	0.91
Indexed AVA, cm^2/m^2	1.14 ± 0.36*	1.12 ± 0.34†	0.79
Para valvular regurgitation	11 (7)*	2 (3)	0.26
Mitral valve			
E velocity, m/s [$n = 209$]	1.15 ± 0.31	1.09 ± 0.30	0.16
Mitral annulus diameter, mm [$n = 223$]	28 ± 4*	31 ± 4	<0.01
Tenting area, cm^2 [$n = 218$]	1.1 ± 0.4*	1.4 ± 0.5	<0.01
Coaptation height, mm [$n = 218$]	7.1 ± 1.6*	8.4 ± 1.9	<0.01
Tricuspid regurgitation	75 (45)	25 (37)†	0.24
Right ventricular systolic pressure, mmHg	41 ± 13*	43 ± 12†	0.44

Other abbreviations as in *Table 1*.
Mean ± standard deviations, or numbers (%). The number of available data is expressed for those variables in which some data were missing.
*indicates $P < 0.05$ versus pre-AVR in organic MR.
†indicates $P < 0.05$ versus pre-AVR in functional MR.

improvement in MR were similar when those with AR were excluded.

The pre-operative determinant for worsened MR in the multivariable model was transaortic gradient in the overall cohort (OR 0.97 per 1 mmHg, 95% CI 0.94–0.99; $P = 0.033$) and in patients with organic MR (OR 0.95 per 1 mmHg, 95% CI 0.91–0.99; $P = 0.024$) when the same variables as in *Table 3* were assessed in the univariate model.

Association between improvement in mitral regurgitation and post-operative variables

Among post-operative variables as listed in Supporting Information, *Table S1*, decrease in LV end-systolic diameter was an independent determinant of improvement in functional MR in the multivariable analyses (adjusted OR 1.13, 95% CI 1.01–1.27; $P = 0.021$). There was no significant association of any post-operative variable with improvement in MR in the overall population or in organic MR. After AVR, QRS duration < 115 ms was present in 94 (40%) after AVR: 67 (40%) in organic MR and 27 (40%) in functional MR. New onset of QRS duration ≥ 115 ms was observed in 55 (23%); this was not associated with improvement in MR. At post-AVR TTE, atrial fibrillation was observed in 78 (33%) including 62 with chronic atrial fibrillation. At the time of AVR, 5 received pulmonary vein isolation or maze procedure and antiarrhythmic drugs were used in 36 after AVR. Atrial fibrillation at post-AVR TTE was not associated with changes in MR. Patient-prosthesis mismatch was observed in 46 (20%); this was not associated with improvement in MR.

Follow-up and clinical outcomes

Of 234 patients, 181 had their vital status recorded in the year prior to data collection. To ensure complete mortality follow-up, SSDI linkage was done in the remaining 53 patients. During median follow-up of 3.5 [2.3–5.9] years, 135 died: 99 with organic MR and 36 with functional MR. Intervention for MR, including MV replacement or MitraClip, was performed in 7: 6 with organic MR (3 within 6 months and 1 each at 1, 3, and 6 years after AVR) and 1 with functional MR at 5 years after AVR.

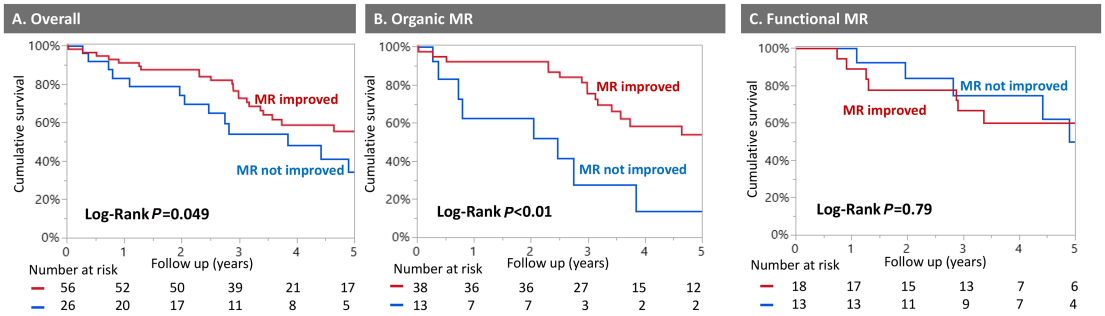
Of pre-operative variables, ERO tended to be associated with higher all-cause mortality in the overall cohort [adjusted hazard ratio (HR) 1.24 per 10 mm^2, 95% CI 0.95–1.58; $P = 0.093$, adjusted for age, New York Heart Association (NYHA) III or IV, diabetes, and creatinine ≥ 2.0 mg/dL; Supporting Information, *Table S2*]. All-cause mortality was compared among patients with ERO ≥ 20 mm^2 at pre-AVR TTE (*Figure 3*). Adjusted for age, NYHA III or IV, diabetes, and creatinine ≥ 2.0 mg/dL, lack of improvement in MR was not associated with higher mortality in the overall cohort (adjusted HR 1.71, 95% CI 0.90–3.27; $P = 0.10$). Lack of improvement in organic MR was associated with higher mortality (adjusted HR 3.36, 95% CI 1.40–8.05; $P < 0.01$). Change in

Table 3 Univariate association of pre-operative variables with improvement in mitral regurgitation

	Overall (n = 234)			Organic MR (n = 166)			Functional MR (n = 68)			Interaction[a]
	OR	95% CI	P	OR	95% CI	P	OR	95% CI	P	P
Clinical variables										
Age, per 1 year	1.00	0.97–1.03	1.00	0.99	0.96–1.03	0.71	1.01	0.96–1.07	0.56	0.49
Male	0.98	0.58–1.64	0.93	1.03	0.55–1.90	0.94	0.88	0.33–2.35	0.80	0.79
NYHA III or IV	0.76	0.40–1.46	0.41	0.77	0.37–1.63	0.50	0.73	0.19–2.78	0.65	0.94
Absence of atrial fibrillation at TTE	1.57	0.87–2.82	0.13	**2.20**	**1.06–4.56**	**0.034**	0.80	0.29–2.34	0.68	0.12
QRS duration < 115 ms	1.70	1.00–2.91	0.052	1.79	0.93–3.42	0.080	1.54	0.58–4.06	0.38	0.80
Creatinine, per 1 mg/dL	0.92	0.76–1.11	0.35	1.09	0.79–1.52	0.58	0.70	0.37–1.35	0.081	0.23
NTproBNP, per 1000 pg/mL	0.98	0.95–1.01	0.26	0.97	0.92–1.02	0.17	1.00	0.95–1.05	0.96	0.35
Coronary artery disease	0.96	0.57–1.63	0.88	1.18	0.63–2.24	0.60	0.61	0.23–1.60	0.31	0.26
TAVR	0.87	0.33–2.28	0.77	1.02	0.55–1.89	0.96	0.61	0.23–1.60	0.31	0.38
Echocardiographic variables										
Left ventricle										
Ejection fraction, per 1%	1.00	0.98–1.02	0.90	1.00	0.97–1.02	0.88	1.01	0.97–1.05	0.72	0.70
End-diastolic diameter, per 1 mm	1.00	0.97–1.04	0.87	1.01	0.96–1.06	0.69	1.00	0.94–1.06	0.90	0.73
End-systolic diameter, per 1 mm	1.00	0.97–1.03	0.94	1.01	0.97–1.05	0.67	0.99	0.94–1.05	0.78	0.63
Mass index, per 1 g/m^2	1.00	0.99–1.01	0.99	1.00	0.98–1.02	0.94	1.00	0.99–1.01	0.86	0.86
Left atrial volume index, per 1 mL/m^2	1.00	0.98–1.01	0.83	1.00	0.98–1.02	0.86	1.00	0.97–1.02	0.81	0.92
S$\prime$ septal, per 1 cm/s	0.94	0.78–1.21	0.48	0.92	0.75–1.14	0.45	0.96	0.64–1.44	0.84	0.87
S$\prime$ lateral, per 1 cm/s	0.91	0.78–1.06	0.22	0.93	0.77–1.13	0.46	0.82	0.60–1.12	0.20	0.50
Aortic valve										
Transaortic gradient, per 1 mmHg	1.01	0.99–1.03	0.20	1.01	0.99–1.03	0.39	1.02	0.98–1.06	0.29	0.62
AVA, per 0.10 cm^2	1.02	0.89–1.18	0.76	1.09	0.92–1.29	0.30	0.83	0.61–1.12	0.21	0.12
Indexed AVA, per 0.10 cm^2/m^2	1.05	0.79–1.39	0.75	1.23	0.88–1.72	0.21	0.52	0.26–1.05	0.059	**0.039**
Indexed AVA ≤ 0.40 cm^2/m^2	1.21	0.71–2.05	0.48	0.85	0.46–1.60	0.62	**2.91**	**1.07–7.96**	**0.037**	**0.042**
Aortic regurgitation	0.98	0.43–2.24	0.96	0.74	0.31–1.80	0.51	n/a	n/a	n/a	0.99
Mitral valve										
Mitral annulus calcification	0.76	0.42–1.39	0.54	0.55	0.25–1.17	0.12	1.38	0.50–3.78	0.54	0.15
Mitral annulus diameter < 3 cm	**1.70**	**1.00–2.88**	**0.048**	1.54	0.81–2.92	0.19	2.67	0.89–8.03	0.081	0.40
Tenting area, per 0.1 cm^2	0.97	0.92–1.03	0.30	1.01	0.94–1.09	0.80	0.91	0.83–1.00	0.051	0.10
Coaptation length, per 1 mm	1.03	0.91–1.18	0.60	1.10	0.92–1.31	0.31	0.97	0.79–1.19	0.77	0.38

CI, confidence interval; n/a, not applicable; OR, odds ratio; TAVR, transcatheter aortic valve replacement; TTE, transthoracic echocardiography; other abbreviations as in *Table 1*.
Bold: $P < 0.05$.
[a]Interaction between MR mechanism and each variable for improvement in MR.

Figure 3 Cumulative survival according to MR improvement. Improvement in MR tended to be associated with lower mortality in the overall cohort (A) and was significantly associated with lower mortality in patients with organic MR (B). Abbreviations as in *Figure 1*.



functional MR was not associated with mortality (HR 1.24, 95% CI 0.44–3.47; P = 0.68).

Follow-up TTE was performed at median 1.3 [0.5–2.9] years in 161 (69%). The timeline is described in Supporting Information, *Figure S1*. Of 115 with organic MR, MR improved in 18 (11%) and worsened in 56 (49%) compared with post-AVR TTE (*Table 4*). Of 46 with functional MR, MR improved in 16 (35%) and worsened in 16 (35%). LV dimensions did not significantly change in patients with organic MR, while these significantly decreased in those with functional MR compared with post-AVR TTE.

Outcomes in patients who received aortic valve replacement with and without mitral valve surgery

The outcomes were compared in patients who received AVR with and without MV surgery. Of 63 patients with ERO $\geq$ 20 mm^2 (age 74 ± 11 years, 54% male) who had MV surgery, replacement was performed in 27 (43%) and repair in 36 (57%). AVR and MV surgery were associated with better outcomes compared with the subgroup in whom MR did not improve after AVR in the overall cohort and patients with organic MR in the univariate analyses (Supporting Information, *Figure S2*) (HR 0.49, 95% CI 0.26–0.92; P = 0.027 and HR 0.28, 95% CI 0.12–0.64; $P < 0.01$, respectively). Adjusted for age, NYHA III or IV, diabetes, and creatinine $\geq$ 2.0 mg/dL, AVR and MV surgery were not associated with outcomes compared with the subgroup in whom MR did not improve after AVR in the overall cohort and patients with organic MR (adjusted HR 0.61, 95% CI 0.31–1.18; P = 0.14 and adjusted HR 0.48, 95% CI 0.20–1.18; P = 0.11, respectively).

Discussion

To our knowledge, the present study is the first to assess the impact of AVR on MR and the determinants for improvement in MR according to MR mechanism. MR improved after AVR in nearly 60% of patients with sAS and MR regardless of MR mechanism. Absence of atrial fibrillation at TTE in patients with organic MR, indexed AVA $\leq$ 0.40 cm^2 in those with functional MR, and QRS duration $<$ 115 ms and mitral annulus diameter $<$ 3 cm in the overall cohort were independent determinants of improvement in MR. Post-operative improvement was associated with reduced mortality during follow-up, notably in organic MR.

Although concomitant MR may have contributed to increased mortality in this study as previously reported by others,[20] MV surgery was not performed in many cases. Degenerative changes were the most frequently observed aetiology of MR in patients with sAS and less frequently corrected. Moreover, advanced age or high comorbid-burden comorbidities could be reasons to avoid multiple cardiac procedures.[21] In fact, patient selection for concomitant MV intervention has been poorly understood. Our data might provide the rationale to consider MV interventions for concomitant MR. The haemodynamic impact of AVR affected both functional MR and organic MR. However, sustained improvement in MR during follow-up was more often observed in patients with functional MR.

Organic MR improved as frequently as functional MR after AVR. However, these determinants should be considered according to MR mechanism because geometry and haemodynamics were quite different in patients with organic and functional MR. The absence of atrial fibrillation was a determinant of improvement in organic MR, concordant with the previous study in patients who received TAVR.[22] Atrial fibrillation has been associated with diminished mitral annulus contraction.[23] Diminished mitral annulus contraction in addition to MV leaflet abnormality would impair coaptation in MV leaflets.[23] In patients with functional MR, who had reduced LV function and mitral annulus enlargement, increased systolic LV pressure caused by critical AS might play a major role in improvement in functional MR after AVR.[19] Because functional MR severity is easily impacted by haemodynamic status, its improvement has been expected after AVR.[20,22] Mitral annulus enlargement would cause reduced mitral

Table 4 Left ventricle and mitral valve dimensions during follow-up

	Organic MR $N = 115$	Functional MR $N = 46$
Mitral regurgitation		
Mild	49 (43)	22 (48)
Mild to moderate	27 (23)	9 (20)
Moderate	17 (15)	5 (11)
Moderate to severe	10 (9)	4 (9)
Severe	4 (3)	1 (2)
Change after post-AVR TTE		
Improved	18 (16)	16 (35)
Unchanged	41 (35)	14 (30)
Worsened	56 (49)	16 (35)
Left ventricle		
Ejection fraction, %	56 ± 11	46 ± 14
End-diastolic diameter, mm	49 ± 7	54 ± 9*
End-systolic diameter, mm	34 ± 9	40 ± 10*
Mass index, g/m^2	113 ± 34	126 ± 31*
S′ septal, cm/s [$n = 131$]	4.8 ± 1.5	4.8 ± 1.9
S′ lateral, cm/s [$n = 123$]	6.4 ± 2.2	5.8 ± 1.8
Mitral valve		
Mitral annulus diameter, mm [$n = 158$]	29 ± 4.7*	30 ± 4.6
Tenting area, cm^2	1.2 ± 0.5*	1.4 ± 0.5
Coaptation height, mm [$n = 139$]	7.2 ± 1.7	7.7 ± 2.3

AVR, aortic valve replacement; other abbreviations as in *Tables 1 and 3*.
The number of available data is expressed for those variables in which some data were missing.
*indicates $P < 0.05$ versus at post-AVR in *Table 2*.

annulus contraction and coaptation area of MV, affecting the presence of MR.[24,25] Narrow QRS duration was a factor associated with improvement in MR after AVR in the overall group. Interestingly, enlarged mitral annulus diameter and LV dyssynchrony, which were frequently observed in most patients with wide QRS duration, have been associated with exercise-induced changes in functional MR.[26] QRS duration may also cause reduced MV closing force. Although mitral annulus diameter and QRS duration were not predictors in the subgroups, likely because of small sample size, these were important predictors of improvement in MR in the overall population. These results should be confirmed in a larger study.

Mitral regurgitation severity assessment is challenging in patients with sAS, and regurgitant volume is affected by the increased LV pressure. Thus, we included patients with ERO $\geq$ 10 mm^2. The pre-operative quantitative assessment of MR severity would best be performed by measurement of the ERO.[9] As higher ERO tended to be associated with higher all-cause mortality in our study, the outcomes were compared in patients with ERO $\geq$ 20 mm^2, who had an increased risk of death from any cause.[27] Early post-operative improvement in organic MR was associated with lower all-cause mortality, while improvement in functional MR did not directly impact survival. These outcomes might reflect that LV dimensions were not associated with change in organic MR; LV size had become smaller after release of LV systolic pressure during follow-up of functional MR. MV intervention for MR due to degenerative changes might be challenging because of low repairability or the presence of MAC. When organic MR is expected to improve after AVR, concomitant organic MR may be able to be left untreated at the time of AVR and carefully observed for the progression of MR. When organic MR is not expected to improve, concomitant MV surgery might be preferable. However, in the multivariable analyses, AVR and MV surgery did not show better outcomes than AVR alone. Double valve surgery might have increased the operative risk, notably in older patients.[21] In patients at substantial risk for double valve surgery, various treatment options, such as the simultaneous surgical and open atrial transcatheter MV replacement and early cardiac resynchronization therapy, can be considered.[28]

Limitations

We acknowledge the limitations of this retrospective study, including selection bias. Most patients had advanced age or multiple comorbidities, likely contributing to the decision not to repair or replace the MV. Patients who received AVR and MV surgery were younger and considered at lower risk for surgery. Although information regarding multiple comorbidities was included and considered in the analyses, a score of comorbidity burden was not available. Subgroup analysis was limited by small sample size. In our clinical practice, MR is generally not quantified if it is trivial or mild. Thus, MR was not quantitatively measured after AVR in all patients. MR severity, in particular, the regurgitant volume, might be affected by the increased LV pressure in patients with sAS, and thus, we included patients with ERO $\geq$ 10 mm^2. Consequently, some patients with mild MR were included. Change in mitral regurgitant volume following AVR has previously

been noted to be small (~10 mL). Therefore, we used five grades to express the change in MR severity. However, lack of quantitative data for all patients is a methodologic limitation of this retrospective study. Most post-AVR TTE were performed at discharge. Follow-up TTE was performed in only 70% of the cohort. Data regarding the long-term effect of AVR on MR were insufficient. Only all-cause mortality is reported here.[29]

Conclusions

Mitral regurgitation improved after AVR in 60% of patients with sAS and MR regardless of MR mechanism. Absence of atrial fibrillation in organic MR, indexed AVA $\leq$ 0.40 cm^2 in functional MR, and QRS duration $<$ 115 ms and mitral annulus diameter $<$ 3 cm regardless of MR mechanism were associated with improvement in MR. In patients without these features, the simultaneous or early intervention for concomitant MR should be considered.

Conflict of interest

All authors have reported that they have no relationships relevant to the contents of this paper to disclose.

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Supporting information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Table S1. Univariate Association of Postoperative Variables with Improvement in MR.
Table S2. Variables associated with all-cause mortality.
Figure S1. Timeline of Follow-up TTE
S: aortic stenosis, MR: mitral regurgitation, MV: mitral valve, TTE: transthoracic echocardiography, y: years.
Figure S2. All-cause Mortality for AVR + MV surgery vs. AVR alone
AVR and MV surgery were associated with better outcomes compared with the subgroup in whom MR did not improve after AVR in the overall cohort and patients with organic MR in the univariate analyses. AVR: aortic valve replacement, MR: mitral regurgitation, MVS: mitral valve surgery.

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