Journal of the American Heart Association

ORIGINAL RESEARCH

Impact of Transcatheter Aortic Valve Replacement on Cardiac Reverse Remodeling and Prognosis in Mixed Aortic Valve Disease

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BACKGROUND: The management of mixed aortic valve disease (MAVD), defined as the concomitant presence of aortic stenosis (AS) and aortic regurgitation, remains a clinical challenging. The present study assessed the impact of transcatheter aortic valve replacement (TAVR) on cardiac geometry and prognosis in patients with MAVD.

METHODS AND RESULTS: A retrospective multicenter TAVR registry was conducted, including patients who underwent TAVR for severe symptomatic AS between January 2015 and March 2019. Patients were subdivided into 2 groups according to concomitant presence of moderate or more severe aortic regurgitation as the MAVD group, and with mild or less severe aortic regurgitation as the isolated AS group. The primary outcome was a composite of cardiovascular death and rehospitalization due to cardiovascular causes. A total of 1742 patients (isolated AS, 1522 patients; MAVD, 220 patients) were included (84.0±5.2 years). Although MAVD exhibited significantly larger left ventricular volumes and higher left ventricular mass index at the TAVR procedure than isolated AS (respectively, $P<0.001$), MAVD showed a greater improvement of left ventricular volumes and left ventricular mass index after TAVR (respectively, $P\leq0.001$). During a median follow-up of 747 days, 301 patients achieved the primary event. The prognosis post-TAVR was comparable between the 2 groups (log-rank $P=0.65$). Even after adjustment using propensity score matching to reduce the potential bias between the 2 groups, similar results were obtained for the entire cohort.

CONCLUSIONS: Despite more advanced cardiac remodeling in MAVD at the time of TAVR compared with isolated AS, a greater improvement of cardiac reverse remodeling was found in MAVD, and the prognosis following TAVR was comparable between the 2 groups.

Key Words: aortic regurgitation ■ aortic stenosis ■ mixed aortic valve disease ■ reverse remodeling ■ transcatheter aortic valve replacement

Transcatheter aortic valve replacement (TAVR) technology has dramatically revolutionized therapeutic strategy of patients with aortic stenosis (AS), offering comparable survival improvement to surgical aortic valve replacement even in patients with high surgical risk.[1,2] The indications for TAVR have been expanded to aortic valve (AV) disease including aortic regurgitation (AR) in younger patients with lower surgical risk.[3,4] However, the management of mixed aortic valve disease (MAVD), defined as the concomitant

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This manuscript was sent to Erik B. Schelbert, MD, MS, Associate Editor, for review by expert referees, editorial decision, and final disposition.

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Supplemental Material is available at https://www.ahajournals.org/doi/suppl/10.1161/JAHA.123.033289

For Sources of Funding and Disclosures, see page 10.

JAHA is available at: www.ahajournals.org/journal/jaha

CLINICAL PERSPECTIVE

What Is New?

- The prognosis after transcatheter aortic valve replacement (TAVR) was comparable between mixed aortic valve stenosis (MAVD; defined as the concomitant presence of severe aortic stenosis and moderate or more severe aortic regurgitation) and isolated severe aortic stenosis.
- Although patients with MAVD had more advanced cardiac remodeling at the time of the TAVR procedure, patients with MAVD had a greater improvement of cardiac remodeling following TAVR than those with pure severe aortic stenosis.

What Are the Clinical Implications?

- TAVR is an effective treatment for patients with MAVD and similarly with patients with isolated severe aortic stenosis.
- The present study provides additional evidence for the efficacy of TAVR in patients with MAVD, and we should consider the TAVR procedure as a therapeutic option in patients with MAVD.

Nonstandard Abbreviations and Acronyms

AR	aortic regurgitation
AS	aortic stenosis
AV	aortic valve
MAVD	mixed aortic valve disease
PARTNER	Placement of Aortic Transcatheter Valve Trial
PS	propensity score
TAVR	transcatheter aortic valve replacement

presence of AS and AR, remains a clinical challenge.[5] MAVD is clinically different from isolated AS or AR in patients with advanced left ventricular (LV) remodeling and a worse prognosis compared with patients with the same degree of isolated AV lesion.[6–8] Despite this, the decision to perform TAVR in patients with MAVD is typically based on the criteria for isolated AS, as there is no specific guideline recommendation for any therapeutic strategy in MAVD.[9,10] The previous studies have yielded equivocal results regarding the efficacy of TAVR in patients with MAVD; furthermore, the impact of TAVR on cardiac remodeling remains poorly understood. Consequently, the aims of the present study are to assess the utility of TAVR on prognosis and to evaluate the changes of cardiac geometry following TAVR in patients with MAVD.

METHODS

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

Study Design and Patients

We analyzed data from the multicenter registry. The design of the present study has been previously published.[11] In brief, this study was conducted as a retrospective multicenter TAVR registry that included 17 cardiovascular centers in Japan. All patients who underwent TAVR for severe symptomatic AS between January 1, 2015, and March 31, 2019, with preprocedural echocardiographic evaluation and follow-up after TAVR were enrolled. Patients without comprehensive baseline echocardiographic evaluation and follow-up after TAVR were excluded.

The study protocol was approved by the Ethical Review Committee of the University of Tsukuba Hospital (reference number: H30-363) and followed the guidelines of the Declaration of Helsinki. Data were deidentified, so the requirement for informed consent was waived.

Data Collection and Outcome

Clinical and demographic data were obtained via manual extraction from the patients' electronic medical records. Patients were followed up by chart review with the date of the last follow-up or death recorded (last queried December 31, 2019). Additionally, all-cause death, cardiovascular death, and rehospitalization due to cardiovascular events (congestive heart failure, arrhythmia, coronary artery disease, stroke, prosthetic valve–related issues, and permanent pacemaker implantation) were obtained from patients' medical records or available electronic databases. We used a composite of cardiovascular death and rehospitalization due to cardiovascular causes as the primary outcome.

Echocardiographic Assessment

All patients underwent comprehensive echocardiographic assessment using commercially available ultrasound systems. All echocardiographic measurements were reviewed and measured by experienced readers according to current guidelines.[12,13] Echocardiographic parameters included the following variables: peak AV velocity, peak and mean transvalvular gradient, aortic jet velocity–time integral, left ventricular outflow tract (LVOT) diameter, mean LVOT flow velocity, LVOT velocity–time integral, AV area, LV ejection fraction, LV end-diastolic volume, LV end-systolic volume, and stroke volume. The AV area was calculated using the continuity equation. Stroke volume was calculated from the

cross-sectional area of the LVOT and the velocity–time integral of the LVOT flow. Patients were subdivided into 2 groups according to the concomitant presence of moderate or more severe AR as the MAVD group, or with mild or less severe AR as the isolated AS group. Valvular disease was evaluated through echocardiographic imaging and graded according to the current guidelines.[14] The severity of AR was derived using a multiparametric approach that included jet width in the LVOT with color Doppler, jet deceleration rate with continuous-wave Doppler, presence of diastolic flow reversal in the descending aorta, vena contracta width, jet width/LVOT ratio, and regurgitant volume and fraction, as necessary.

Representative cases are shown in Figure 1, including an 87-year-old man with isolated severe AS and an 80-year-old man with MAVD. The patient with isolated severe AS (Figure 1A) had severe AS (peak AV velocity, 5.3 m/s; mean AV pressure gradient, 50 mm Hg) and trivial AR, with normal range of LV mass index and LV volume. The patient with MAVD (Figure 1B) had a similar degree of severe AS (peak AV velocity, 5.3 m/s; mean AV pressure gradient, 53 mm Hg) and severe AR. This case represented a high LV mass index and enlargement of LV.

Follow-Up Echocardiography

Follow-up echocardiography data obtained within 30 days after TAVR were defined as the early follow-up. One-year follow-up data were treated as the late follow-up. We evaluated echocardiographic changes of LV geometry and functional parameters such as LV end-diastolic volume, LV end-systolic volume, LV ejection fraction, and LV mass index.

Statistical Analysis

Continuous variables were presented as mean±SD for normal distribution or median and interquartile ranges for skewed distribution. Normality was assessed using the Kolmogorov–Smirnov test. Categorical data are presented as absolute number and percentage. We used the unpaired *t*-test, Mann–Whitney test, and χ^2 test to compare the data between the 2 groups as appropriate. Survival rate was estimated using the Kaplan–Meier method, and differences between survival curves were tested with a log-rank test. All-cause death was treated as the competition risk factor for the primary outcome. Because the primary end point (cardiac death and hospitalization due to cardiac events) and death due to other causes were considered competing risks, we also performed the Fine–Gray regression model to calculate the subdistribution hazard ratio. To assess for potential impact of differences between the isolated AS and MAVD groups after controlling for potential confounding factors (age, sex, chronic heart failure, coronary artery disease, diabetes, hypertension, chronic lung disease, prior cardiac surgery, smoking, and Society of Thoracic Surgeons risk score), we calculated a propensity score (PS). The PS was estimated with the use of a multivariable logistic-regression model, with the presence of MAVD as the dependent variable and the clinical characteristics as covariates. We performed PS matching to obtain 2 groups (isolated

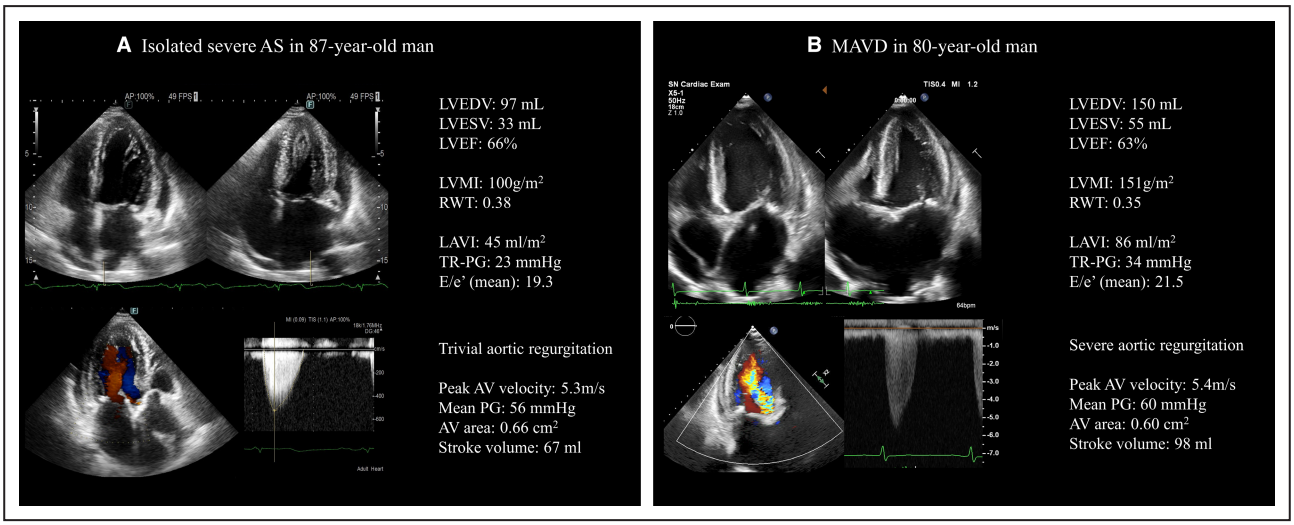

Figure 1. Representative cases of isolated AS and MAVD.
A, An 87-year-old man with isolated severe AS with normal range of LV mass index and LV end-diastolic volume. **B**, An 80-year-old man with MAVD with high LV mass index and enlargement of LV. AS indicates aortic stenosis; AV, aortic valve; LV, left ventricular; LVEDV, left ventricular end-diastolic volume; LVEF, left ventricular ejection fraction; LVESV, left ventricular end-systolic volume; LVMI, left ventricular mass index; MAVD, mixed aortic valve disease; PG, pressure gradient; RWT, relative wall thickness; and TR-PG, tricuspid regurgitation pressure gradient.

AS group and MAVD group) of identical size, which were well balanced in baseline characteristics, with the use of a 1:1 nearest neighbor matching protocol without replacement and a caliper width equal to 0.2 of the SD of the PS. To assess differences in changes of echocardiographic parameters following TAVR between the 2 groups classified according to the concomitant presence of moderate or more severe AR, we applied a linear mixed-effects model with unstructured covariance for random effects. We used LV end-diastolic volume, LV end-systolic volume, LV ejection fraction, and LV mass index as a factor; time after initial echocardiographic assessment as a covariate; and their first-degree interactions (time × group). Statistical analysis was performed using SPSS version 25 (SPSS Inc., Chicago, IL) and R software version 4.2.1 (R Foundation for Statistical Computing, Vienna, Austria). A *P* value of <0.05 was considered significant. Participants with missing data were excluded from analysis of each variable.

RESULTS

Study Population and Characteristics

A total of 1742 patients who satisfied the inclusion criteria were included in the study. We excluded 8 patients with no sufficient baseline evaluation and 19 patients with no follow-up data as shown in study flowchart of Figure S1. Baseline clinical characteristics are shown in Table 1. The average age was 84.0±5.2 years, and 594 patients were men (34%). There were 220 patients in the MAVD group, while 1522 patients had mild or less severe AR as the isolated AS group. Patients with MAVD were younger (83.4±5.9 years versus 84.2±5.0 years; *P*=0.037) and there were more male patients (45% versus 32%; *P*<0.001) and more coronary artery disease (38% versus 30%; *P*=0.024) than those in the isolated AS group. Furthermore, the MAVD group represented more symptomatic status represented by the New York Heart Association functional class (III–IV, 44.6% versus 32.4%; *P*=0.003) at the time of the TAVR procedure, when compared with isolated AS group. Probabilities of other comorbidities and Society of Thoracic Surgeons risk score were comparable between the 2 groups.

Procedural features are shown in Table 2. TAVR was performed via a transfemoral approach in four fifths of all procedures, using Sapient3 in nearly half of patients. There were no statistically significant differences in the approach of TAVR and prosthetic valve type between the 2 groups. There was a statistically significant difference in prosthetic valve size between the 2 groups, with patients with MAVD having a higher probability of

Table 1. Clinical Characteristics

Variables	Entire cohort					Matched cohort			
	No.	Isolated AS (n=1522)	MAVD (n=220)	*P* value	SD	Isolated AS (n=216)	MAVD (n=216)	*P* value	SD
Age, y	1742	84.2±5.0	83.4±5.9	0.037*	0.34	83.5±5.0	83.7±5.4	0.70	0.09
Male sex	1742	491 (32)	99 (45)	<0.001*	0.27	94 (43)	97 (45)	0.77	0.04
Chronic heart failure	1738	905 (60)	127 (58)	0.66	0.04	129 (59)	125 (58)	0.85	0.02
Coronary artery disease	1741	459 (30)	83 (38)	0.024*	0.17	75 (35)	79 (37)	0.69	0.04
Diabetes	1742	428 (28)	56 (26)	0.41	0.05	59 (27)	55 (26)	0.74	0.03
Hypertension	1742	1231 (81)	168 (76)	0.12	0.12	160 (74)	166 (77)	0.44	0.07
Chronic lung disease	1742	246 (16)	40 (18)	0.45	0.05	41 (19)	38 (18)	0.80	0.03
Prior cardiac surgery	1740	108 (7)	20 (9)	0.29	0.07	21 (9.7)	19 (8.8)	0.87	0.03
Smoking quit/current	1735	375 (25)	70 (32)	0.025*	0.16	69 (32)	68 (32)	1.0	0
STS score, points	1721	6.9±5.2	7.6±6.7	0.13	0.29	6.9±6.2	7.7±6.8	0.22	0.31
NYHA functional class	1742			0.003*				0.032*	
I		108 (7.1)	12 (5.5)			15 (6.9)	10 (4.7)		
II		921 (60.5)	110 (50)			132 (61.1)	107 (49.8)		
III		421 (27.7)	80 (36.4)			58 (26.9)	80 (37.2)		
IV		72 (4.7)	18 (8.2)			11 (5.1)	18 (8.4)		
BNP, pg/mL	1266	222 (102–494)	309 (137–722)	<0.001*		195 (84–469)	312 (141–768)	<0.001*	
NT-proBNP, pg/mL	655	1112 (506–2970)	2459 (983–6452)	<0.001*		1132 (391–3284)	2459 (983–6452)	<0.001*	

Values are mean±SD, n (%), or median (interquartile range). AS indicates aortic stenosis; MAVD, mixed aortic valve disease; NT-proBNP, N-terminal pro–brain natriuretic peptide; NYHA, New York Heart Association; and STS, Society of Thoracic Surgeons.

*$P<0.05$.

Table 2. TAVR Procedure and Prosthetic Valve Profiles

Variables	Entire cohort				Matched cohort		
	No.	Isolated AS (n=1522)	MAVD (n=220)	*P* value	Isolated AS (n=216)	MAVD (n=216)	*P* value
Approach	1742			0.97			0.87
Transfemoral		1276 (84)	183 (83)		172 (80)	179 (83)	
Transapical		182 (12)	28 (13)		30 (14)	28 (13)	
Transaorta		40 (2.6)	5 (2.3)		8 (3.7)	5 (2.3)	
Others		24 (1.6)	4 (1.8)		6 (2.8)	4 (1.8)	
Valve type	1742			0.13			0.75
Sapient3		763 (50)	118 (54)		107 (50)	115 (53)	
Sapient XT		397 (26)	60 (27)		67 (31)	60 (28)	
EvoluteR		211 (14)	23 (11)		27 (13)	22 (10)	
Corevalve		96 (6.3)	7 (3.2)		8 (3.8)	7 (3.2)	
EvolutePRO		55 (3.6)	12 (5.5)		7 (3.2)	12 (5.6)	
Valve size	1742			0.007*			0.033*
20 mm		70 (4.6)	16 (7.3)		8 (3.7)	16 (7.4)	
23 mm		677 (44.5)	74 (33.6)		97 (44.9)	73 (34.0)	
26 mm		554 (36.4)	86 (39.1)		81 (37.5)	83 (38.1)	
29 mm		221 (14.5)	44 (20.0)		30 (13.9)	44 (20.5)	

Values are n (%). AS indicates aortic stenosis; MAVD, mixed aortic valve disease; and TAVR, transcatheter aortic valve replacement.
*$P<0.05$.

prosthetic valve size of 26 and 29 mm, when compared with patients with isolated AS ($P=0.007$).

Echocardiographic Variables at Baseline

Baseline echocardiographic variables are described in Table 3. Patients with MAVD had statistically significant larger LV end-diastolic volume (99.7±41.0 mL versus 83.8±30.1 mL; $P<0.001$), higher LV mass index (140.4±41.5 g/m^2 versus 121.9±37.8 g/m^2; $P<0.001$), and lower LV ejection fraction (59.1±12.7% versus 61.8±10.9%; $P=0.001$) than patients with isolated AS. Patients with MAVD had worse LV diastolic dysfunction with higher E/A ratio (0.87±0.54 versus 0.78±0.48; $P=0.030$) and tricuspid regurgitation pressure gradient (30±12 mm Hg versus 28±10 mm Hg; $P=0.008$) and larger LA volume index (63.8±26.4 mL/m^2 versus 55.7±23.0 mL/m^2; $P<0.001$). More than moderate mitral regurgitation and tricuspid regurgitation at baseline were more frequent in the MAVD group, compared with the isolated AS group (mitral regurgitation, 26.8% versus 9.5%; $P<0.001$; tricuspid regurgitation, 18.7% versus 8.8%; $P<0.001$).

Outcome of Patients With MAVD After TAVR

During a median follow-up period of 747 days (interquartile range, 389–1115 days), 301 patients exhibited primary events (86 cardiovascular deaths and 254 rehospitalizations for cardiovascular causes). In the MAVD group, 46 patients (20.9%) achieved the primary end point, while 255 (16.8%) patients with isolated AS did so. Of note, 39 patients who were rehospitalized due to cardiovascular events eventually died of cardiovascular disease. All-cause death was observed in 248 patients (16.3%) in the isolated AS group and 42 patients (19.1%) in the MAVD group.

Kaplan–Meier analysis shows that prognosis after TAVR were comparable between the isolated AS and MAVD groups during the follow-up period (log-rank $P=0.17$; Figure 2A). After PS matching, 1310 patients were not matched due to exceeding the defined caliper width of the standard deviation of the PS, and the remaining 532 patients (216 patients with isolated AS and 216 patients with MAVD) were included in the matched cohort. Even adjusted by potential confounding factors using PS matching, the survival rate after TAVR was comparable between the isolated AS and MAVD groups (log-rank $P=0.65$; Figure 2B). Furthermore, during the follow-up period, there was no significant difference in all-cause death following TAVR between the isolated AS and MAVD groups in the entire cohort (log-rank $P=0.42$) and matched cohorts (log-rank $P=0.69$), as presented in Figure 3. Even after the Fine–Gray regression analysis was performed to consider the competing risk factor between the primary end point and other causes of death, there were no significant differences in probability of the primary end point between the isolated AS and MAVD groups in the entire cohort (hazard ratio [HR], 1.24 [95% CI,

Table 3. Echocardiographic Characteristics

Variables	Entire cohort				Matched cohort		
	No.	Isolated AS (n=1522)	MAVD (n=220)	*P* value	Isolated AS (n=216)	MAVD (n=216)	*P* value
LV end-diastolic volume, mL	1742	83.8±30.1	99.7±41.0	<0.001*	83.7±28.3	99.7±40.7	<0.001*
LV end-diastolic volume index, mL/m^2	1742	57.9±19.9	67.9±25.3	<0.001*	58.1±18.8	67.9±25.0	<0.001*
LV ejection fraction %	1742	61.8±10.9	59.1±12.7	0.001*	61.9±11.3	59.0±12.8	0.012*
LV mass index, g/m^2	1742	121.9±37.8	140.4±41.5	<0.001*	121.1±41.3	141.0±41.4	<0.001*
LA volume index, mL/m^2	1587	55.7±23.0	63.8±26.4	<0.001*	52.6±22.4	64.2±26.4	<0.001*
E/A ratio	1676	0.78±0.48	0.87±0.54	0.030*	0.74±0.39	0.87±0.54	0.013*
E/e′ ratio	1401	19.1±8.9	19.9±9.0	0.23	18.3±8.8	20.0±9.1	0.075
AV peak velocity, m/s	1742	4.52±0.79	4.61±0.87	0.14	4.49±0.83	4.60±0.85	0.17
Mean AV pressure gradient, mmHg	1742	50 19	52±20	0.18	49.4±19.4	52.1±20.4	0.17
AV area, cm^2	1742	0.63±0.18	0.64±0.19	0.90	0.64±0.18	0.63±0.19	0.85
AV area index, cm^2/m^2	1742	0.44±0.13	0.44±0.13	0.82	0.44±0.13	0.44±0.13	0.53
Stroke volume, mL	1742	66.8±19.2	69.0±20.1	0.14	66.2±18.9	68.6±20.8	0.20
Stroke volume index, mL/m^2	1742	46.4±13.4	47.4±13.3	0.30	46.3±14.0	47.1±13.2	0.53
TR pressure gradient, mmHg	1513	28±10	30±12	0.008*	27±19	30±12	0.007*
Moderate or more severe mitral regurgitation	1742	144 (9.5)	59 (26.8)	<0.001*	21 (9.7)	59 (27.4)	<0.001*
Moderate or more severe TR	1742	132 (8.8)	41 (18.7)	<0.001*	21 (9.8)	40 (18.7)	0.009*

Values are mean±standard deviation or n (%). AS indicates aortic stenosis; AV, aortic valve; LA, left atrial; LV, left ventricular; MAVD, mixed aortic valve disease; and TR, tricuspid regurgitation.
*P<0.05.

0.90–1.71]; P=0.18) and the matched cohort (HR, 1.11 [95% CI, 0.73–1.69]; P=0.64). Similar elevation in risk in the isolated AS and MAVD groups were observed in cardiovascular death, rehospitalization due to cardiovascular events, and permanent pacemaker implantation as shown in Table S1.

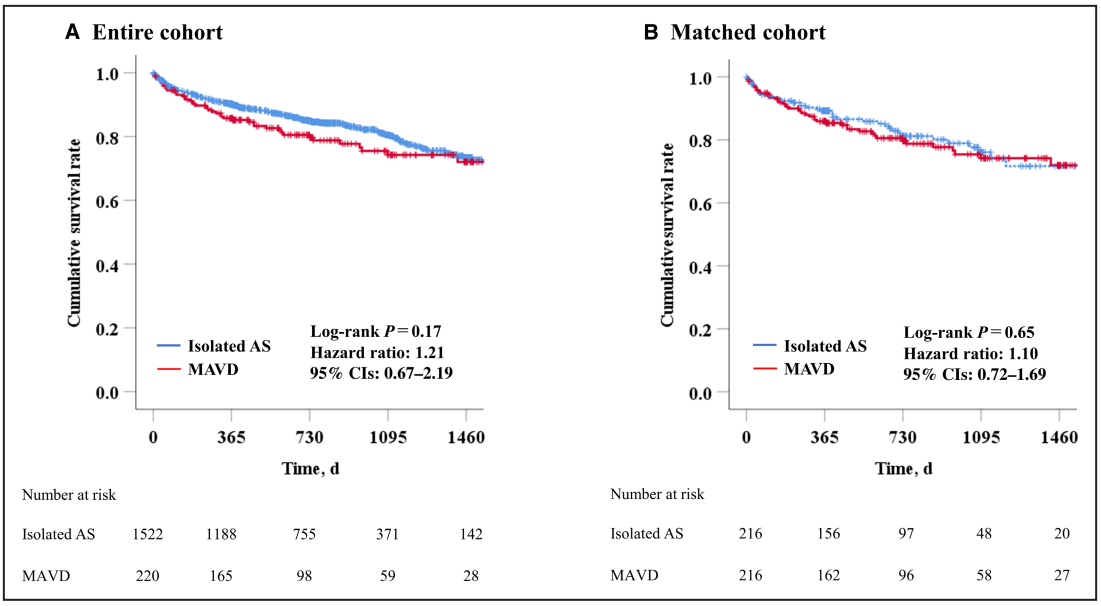

Figure 2. Survival curves for cumulative cardiovascular death and hospitalization due to cardiovascular events in isolated AS and MAVD groups.
Survival curves for cumulative cardiovascular death and hospitalization due to cardiovascular events of the isolated AS and MAVD groups in the entire cohort (**A**) or adjusted cohort by propensity score matching (**B**). AS indicates aortic stenosis; and MAVD, mixed aortic valve disease.

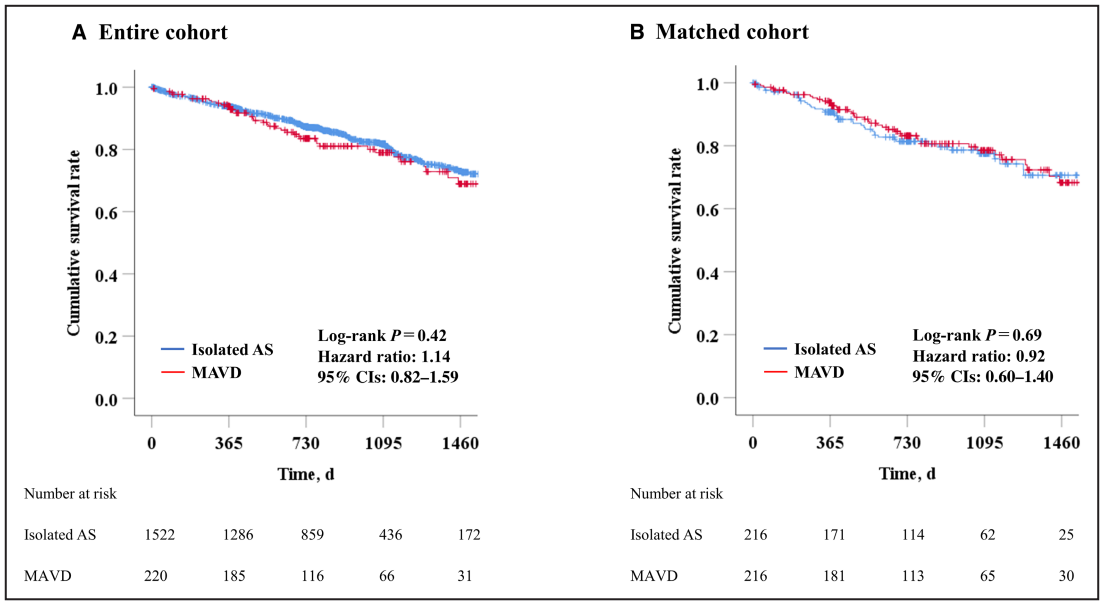

Figure 3. Survival curves for all-cause death due to cardiovascular events in isolated AS and MAVD. Survival curves for all-cause death of the isolated AS and MAVD groups in the entire cohort (**A**) or adjusted cohort by propensity score matching (**B**). AS indicates aortic stenosis; and MAVD, mixed aortic valve disease.

Cardiac Reverse Remodeling Following TAVR

A total of 1306 patients underwent early follow-up echocardiography (within 30 days after TAVR), and 1239 patients underwent late follow-up (at 1 year after TAVR). There were no significant differences between the isolated AS and MAVD groups in days from TAVR to early follow-up (isolated AS: median, 5 days; 25th–75th quartile range, 4–7 days versus MAVD: median, 6 days, 25th–75th quartile range; 5–8 days; P=0.091) and to late follow-up (isolated AS: median, 365 days; 25th–75th quartile range, 355–374 days versus MAVD: median, 366 days; 25th–75th quartile range, 354–377 days; P=0.43).

Changes in echocardiographic parameters after TAVR in the entire cohort are shown in Figure 4 and Table S2. As expected on the basis of parameter estimates obtained by the mixed-effects model, LV end-diastolic volume, LV end-systolic volume, and LV mass index in MAVD and isolated AS groups significantly decreased (respectively, P≤0.01), while LV ejection fraction increased (P≤0.01). Especially in the MAVD group, LV end-diastolic and end-systolic volumes and LV mass index showed significant decrease (respectively, P≤0.01). Consequently, LV end-diastolic volume at the late follow-up was comparable between the 2 groups. However, during follow-up, there was no difference in increasing rate of LV ejection fraction between the 2 groups (P=0.49). Even after the PS matching using confounding variables between the isolated AS and MAVD groups, similar results for the entire cohort were obtained, as shown in Figure S2 and Table S2.

At the early follow-up, while 59 patients with isolated AS had moderate or more severe paravalvular leakage, 13 patients with MAVD had moderate or more severe paravalvular leakage (isolated AS, 5.2% [59/1140] versus MAVD, 7.8% [13/166]; P=0.34). At late follow-up, moderate or more severe paravalvular leakage were present in 70 patients with isolated AS and 20 patients with MAVD (isolated AS, 6.5% [70/1076] versus MAVD, 12.3% [20/163]; P=0.003).

DISCUSSION

The main findings from the present study were as follows: (1) Prognoses after TAVR were comparable between the MAVD and isolated severe AS groups in both the entire cohort and the matched cohort; (2) patients with MAVD exhibited more advanced cardiac remodeling at the time of the TAVR procedure, with larger LV volume, higher LV mass index, and more frequent in at least moderate mitral regurgitation or tricuspid regurgitation; (3) patients with MAVD demonstrated a greater improvement in cardiac remodeling following TAVR compared with patients with isolated severe AS, resulting in no significant differences in LV geometry at the 1-year follow-up.

Utility of TAVR in Patients With MAVD

The natural history of moderate MAVD behaves similarly to that of isolated severe AS with similar mortality risk.[7] Recent studies show that surgical aortic valve replacement improves the prognosis in patients with

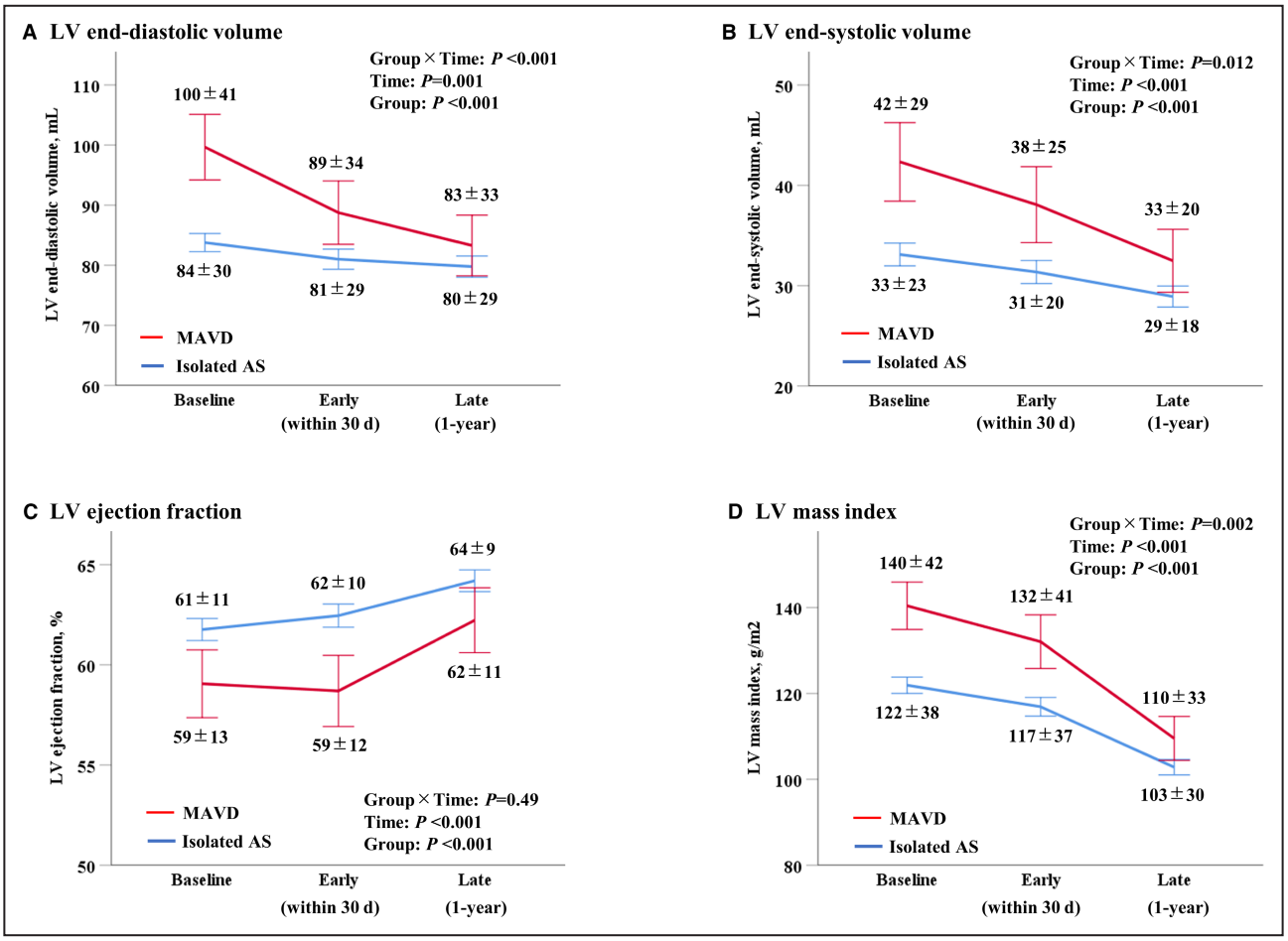

Figure 4. Consequence changes of cardiac geometry following TAVR in the entire cohort.
Consequence changes of cardiac geometry following TAVR in LV end-diastolic volume (**A**), LV end-systolic volume (**B**), LV ejection fraction (**C**), and LV mass index (**D**). Bars indicate 95% CIs. AS indicates aortic stenosis; LV, left ventricular; MAVD, mixed aortic valve disease; and TAVR, transcatheter aortic valve replacement.

moderate or more severe MAVD.[15] However, the appropriate indication of TAVR for patients with MAVD is undermined in the latest guidelines.[10,16] Real-world TAVR practice has expanded to groups of patients who were excluded from the pivotal clinical trials. In the large randomized PARTNER (Placement of Aortic Transcatheter Valve Trial) trials, patients with MAVD with severe AR have been excluded.[17] Prior studies have yielded equivocal results for the utility of TAVR for patients with MAVD; where some studies have reported higher cardiovascular and all-cause death in patients with MAVD after TAVR compared with patients with isolated severe AS, others have found similar or better survival rates in patients with MAVD. Indeed, Ugwu et al note in a meta-analysis study of 9505 patients that death within 1 year after TAVR is lower in MAVD than in AS.[18] On the other hand, a meta-analysis of 58 879 patients reported by Guddeti et al note that there are no significant differences in 30-days and 1-year all-cause mortality rates between the 2 groups.[19] The heterogeneity in the definition of MAVD, which in some studies included patients with mild AR, may contribute to the variability in prognosis among patients with MAVD. Since the presence of mild AR is known to have no additional significant hemodynamic prognosis beyond that caused by isolated AS,[20] we defined the coexistence of moderate and more severe AR as MAVD in the present study. Furthermore, the results from the present study using a PS matched cohort presents the utility of TAVR in patients with MAVD. All-cause death after TAVR, in addition to cardiac death and rehospitalization due to cardiac events, was also comparable between the 2 groups. Furthermore, permanent pacemaker implantation after TAVR, which was associated with poor outcomes, was found to have similar risk between the MAVD and isolated severe AS groups.[21]

Effect of Concomitant Presence of AS and AR on Cardiac Remodeling

The presence of AV disease affects LV function and geometry.[22,23] AS is known to be associated with

concentric hypertrophy, while the increase of stroke volume in AR leads to an eccentric hypertrophy. Recently, the impact of a concomitant presence of AS and AR on LV remodeling has been reported; patients with MAVD have more advanced LV remodeling, caused by the combination of pressure and volume overload, compared with those with isolated AV disease.[24,25] The findings from the present study are in line with the previous study, which showed that patients with MAVD had more advanced LV remodeling characterized by a combination of LV dilation and hypertrophy at the time of TAVR, compared with isolated AS patients. Furthermore, the presence of at least moderate mitral regurgitation and tricuspid regurgitation was more frequent in patients with MAVD, indicating more advanced cardiac remodeling in patients with MAVD compared with those with isolated AS.

Impact of TAVR on Cardiac Reverse Remodeling

As Sato et al reported, patients with AS have cardiac reverse remodeling following TAVR.[26] This is in line with the present study in cardiac reverse remodeling following TAVAR in patients with isolated AS, where cardiac revere remodeling was observed around 1 year after TAVR.[26] The unique point of the present study was assessing the reverse remodeling following TAVR in patients with MAVD. Despite the differences in LV geometry at the time of the TAVR procedure, patients with MAVD exhibited more dynamic improvements in cardiac remodeling, resulting from the relief of pressure and volume overload. Surprisingly, these changes led to no significant differences in LV geometry between the isolated AS and MAVD groups at 1-year follow-up after TAVR. Of note, we observed the differences of reverse remodeling following TAVR of LV enlargement and LV hypertrophy, where LV enlargement improved rapidly after TAVR, while improvement in LV hypertrophy was relatively slow. Further studies with imaging and pathological evaluation for damaged myocardium and fibrosis are warranted to clarify the reason for the differences in cardiac reverse remodeling between patients with isolated AS and patients with MAVD.

Paravalvular Leakage in MAVD

Patients with MAVD had a greater propensity to develop paravalvular leakage, which is a known predictor of worse outcome in patients with isolated AS undergoing TAVR.[27,28]

As reported for the large cohort with severe AS reported by Sá et al, patients with paravalvular leakage, even if just mild, experience higher risk of all-cause death, rehospitalization, and cardiovascular death following TAVR.[29] However, paravalvular leakage does not emerge as a significant predictor of prognosis in patients with MAVD.[30] The present study shows that the frequency of paravalvular leakage increased at 1-year follow-up after TAVR in patients with MAVD. This may be attributed to the differences in AV morphology and the extent of calcification involvement between patients with isolated AS and patients with MAVD, which can impede the complete adherence of the TAVR valve. The clinical impact of increasing frequency of the paravalvular leakage at 1-year follow-up in MAVD is unclear, due to the small number of patients with MAVD with significant paravalvular leakage. However, paravalvular leakage after TAVR sometimes indicates prosthetic valve dysfunction, and we should pay attention to the presence of paravalvular leakage during follow-up in patients with MAVD undergoing TAVR.

Clinical Implications

Given the increasing incidence of AV diseases and the expanding indications for TAVR in more complex anatomic and clinical scenarios, the number of patients with MAVD referred to TAVR is expected to rise. The present study using a large number of cohorts supports the utility of TAVR for patients with MAVD. To the best of our knowledge, this is the first study to assess changes in geometry following TAVR in patients with MAVD. Patients with MAVD with conservative therapy have a worse prognosis compared with patients with isolated AS.[7] However, there was no significant difference in prognosis after TAVR between patients with MAVD and patients with isolated AS, despite patients with MAVD having more symptomatic status and more advanced cardiac remodeling at the TAVR procedure. Furthermore, a greater improvement of cardiac remodeling following TAVR was found in patients with MAVD. Therefore, TAVR is an effective treatment for patients with MAVD as well as patients with isolated severe AS. The present study provides additional evidence for the efficacy of TAVR in patients with MAVD, and we should consider the TAVR procedure as a therapeutic option in patients with MAVD.

Limitations

First, an accurate assessment of AR could be challenging in the presence of severe AS. Stratifying patients with MAVD using echocardiographic grading of AR severity, despite limitations inherent to the grading process, is clinically relevant. Independent confirmation by other imaging modalities such as cardiovascular magnetic resonance is needed to elucidate this issue. Second, the pathologic anatomy of AR was not accurately characterized. We have not assessed the effect of the presence of bicuspid aortic valves and valve-in-valve procedures on prognosis after TAVR. Furthermore, we have not collected information about LVOT calcification. Third, we have a lot of follow-up

echocardiographic data, but data may be affected by selection bias because these patients have no follow-up echocardiographic studies. Fourth, we have not assessed the impact of prosthesis–patient mismatch after TAVR in patients with MAVD, although a previous meta-analysis study represents that severe prosthesis–patient mismatch after TAVR is associated with poor outcomes.[31] Fifth, real-world TAVR practices include a diverse set of patients. While the present study used PS matching to adjust for confounders, unmeasured confounders may still exist. Although having an older population, the present study did not assess the impact of frailty on prognosis. Sixth, data validity and accuracy may not be maximal due to no echocardiographic core laboratory in the present study.

CONCLUSIONS

The present study shows that prognosis after TAVR was comparable between the MAVD and isolated severe AS groups, although patients with MAVD had more advanced cardiac remodeling at the TAVR procedure. Patients with MAVD had a greater improvement of cardiac remodeling following TAVR than those with isolated AS, resulting in no significant differences in LV geometry at 1-year follow-up after TAVR.

APPENDIX

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Received November 24, 2023; accepted January 23, 2024.

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Sources of Funding

This study was approved as an academic project of the Japanese Society of Echocardiography and was supported by a grant from the Japanese Society of Echocardiography. This work was partially supported by JSPS Kakenhi Grants (23K07509 to K. Kusunose) and a grant from the Japan Agency for Medical Research and Development (AMED, JP22uk1024007 to K. Kusunose).

Disclosures

Dr Sato belongs to an endowed department funded by Medtronic and DVX. Dr Ishizu received speaker fees from Edwards Lifesciences. The remaining authors have no disclosures to report.

Supplemental Material

Tables S1–S2.
Figures S1–S2.

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