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Outcomes of Transcatheter Aortic Valve Replacement in Mixed Aortic Valve Disease

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ABSTRACT

OBJECTIVES The aim of this study was to compare outcomes after transcatheter aortic valve replacement (TAVR) in patients with pure aortic stenosis (AS) (i.e., no or trivial associated aortic regurgitation [AR]) with those in patients with AS and mild or more severe AR (i.e., mixed aortic valve disease [MAVD]).

BACKGROUND TAVR is indicated in treating patients with severe AS. Limited data exist regarding the outcomes of TAVR in patients with MAVD.

METHODS A total of 1,133 patients who underwent TAVR between January 2014 and December 2017 were included. The primary outcome was all-cause mortality. The comparison was adjusted to account for post-TAVR AR development in both groups. The secondary outcomes included composite endpoints of early safety and clinical efficacy as specified in the Valve Academic Research Consortium-2 criteria. Variables were compared using Mann-Whitney, chi-square, and Fisher exact tests, while Kaplan-Meier analyses were used to compare survival.

RESULTS A total of 688 patients (61%) had MAVD (median age 83, 43% women). Among these, 17% developed mild, 2% moderate, and <1% severe post-TAVR AR. Overall, patients with MAVD had better survival compared with patients with pure AS ($p = 0.03$). Among patients who developed post-TAVR AR, those in the MAVD group had better survival ($p = 0.04$). In contrast, in patients who did not develop post-TAVR AR, pre-TAVR AR did not improve survival ($p = 0.11$).

CONCLUSIONS Patients with MAVD who underwent TAVR had better survival compared with patients with pure AS. This is explained by the better survival of patients with MAVD who developed post-TAVR AR, likely due to left ventricular adaptation to AR. (J Am Coll Cardiol Intv 2019;■:■–■) © 2019 Published by Elsevier on behalf of the American College of Cardiology Foundation.

Transcatheter aortic valve replacement (TAVR) technology has revolutionized the management of aortic valve (AV) disease and has become the mainstay of treatment in patients with symptomatic severe calcific aortic stenosis (AS) with high or prohibitive surgical risk (1,2). The indications have been expanded to include patients with intermediate surgical risk as well (3,4). It can also be useful in the management of patients with pure aortic regurgitation (AR) as well as younger, lower-risk patients with AS when appropriately selected (5–7).

Given the wide acceptance of TAVR technology and its overall safety and efficacy, it has become an option for those with severe AS and associated pre-existing AR (i.e., mixed AV disease [MAVD]) as well. Major society guidelines recommend making clinical

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ABBREVIATIONS AND ACRONYMS

AR = aortic regurgitation

AS = aortic stenosis

AV = aortic valve

LVOT = left ventricular outflow tract

MAVD = mixed aortic valve disease

PVR = paravalvular regurgitation

SAVR = surgical aortic valve replacement

TAVR = transcatheter aortic valve replacement

decisions on the basis of the predominant native lesion (8,9). There is, however, a lack of robust data regarding the overall safety and efficacy of TAVR in patients with MAVD, making evidence-based recommendations in this group of patients challenging. It is suggested that the natural history of MAVD is more aggressive than isolated AS, highlighting the need for effective treatment strategies to address it (10). We sought to compare the outcomes of patients with MVAD undergoing TAVR with those of patients with pure AS and to determine the impact of pre-existing AR.

METHODS

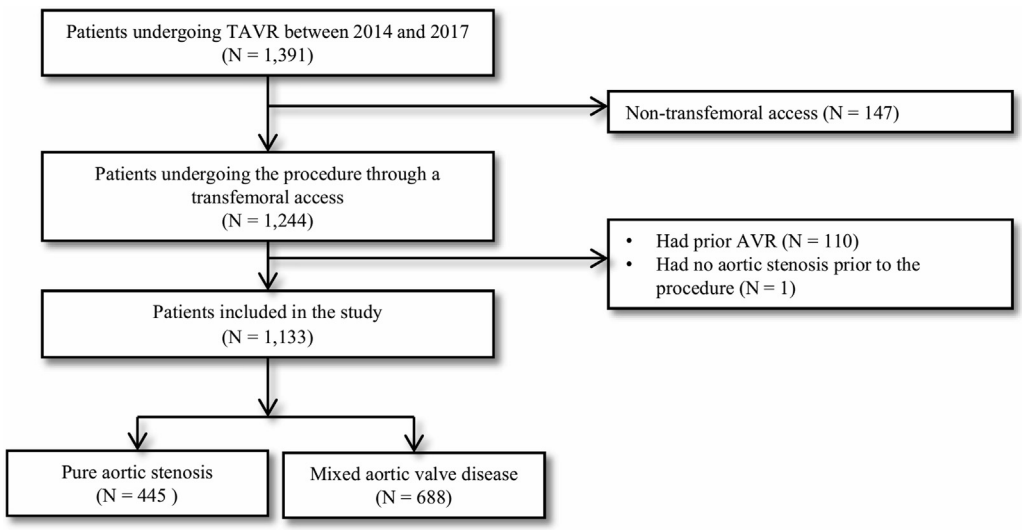
This was a single-center, retrospective, observational study that was approved by the Cleveland Clinic Institutional Review Board. The requirement to obtain informed consent was waived, and data were deidentified. All patients who underwent TAVR between January 2014 and December 2017 were included. Patients with histories of surgical or AV replacement, patients with no AS (who underwent TAVR for other indications), and those who underwent TAVR via nontransfemoral access were excluded. Patients were further divided into 2 groups on the basis of the presence of pre-TAVR AR into pure AS (no or trivial AR) and MVAD (AS with associated mild, moderate, or severe AR).

All patients underwent echocardiography before TAVR, and the vast majority underwent repeat echocardiography after the procedure. To assess left ventricular ejection fraction and end-diastolic and end-systolic volumes, the biplane method of disks was used. AS and AR before and after the procedure were graded as mild, moderate, or severe according to guidelines (11,12).

The primary endpoint was all-cause mortality. Secondary clinical endpoints were determined on the basis of the Valve Academic Research Consortium-2 criteria (13) and included bleeding and vascular complications, stroke, kidney injury, valve dysfunction, and composite endpoints of early safety (within 30 days of TAVR) and clinical efficacy (after 30 days).

Patient characteristics were collected using electronic medical records, including age, sex, race, body mass index, comorbidities (history of diabetes mellitus, hypertension, hyperlipidemia, end-stage renal disease, peripheral vascular disease, stroke or transient ischemic attack, previous coronary artery bypass graft, previous percutaneous coronary intervention, and prior pacing devices), as well as echocardiographic variables (AR severity, left ventricular ejection fraction, AV mean gradient, AV peak gradient, left ventricular outflow tract [LVOT] mean velocity, AV mean velocity, AV velocity-time integral,

FIGURE 1 Study Flowchart



Flowchart showing the selection process of the study population. AVR = aortic valve replacement; TAVR = transcatheter aortic valve replacement.

area, AV index, LVOT diameter, LVOT stroke volume, and LVOT stroke volume index). Also, post-TAVR echocardiography reports within 30 days of the procedure were reviewed to assess development of or residual post-TAVR AR. Furthermore, information related to primary and secondary outcomes was collected. Date of death was obtained from electronic medical records. When that information was missing, the patient's online obituary was searched using legacy.com.

Continuous variables are expressed as median (interquartile range), and categorical variables are expressed as percentages. The Mann-Whitney *U* test was used to compare continuous variables, while chi-square and Fisher exact tests were used to compare categorical variables. Kaplan-Meier analysis and log-rank tests were used to compare survival. Propensity score matching was used to exclude possible confounding factors such as diabetes and body mass index, which were significantly different between the groups. Patients were matched 1:1 to the nearest neighbor with a propensity caliper of 0.1. To further confirm the outcome, we used multivariate logistic regression analysis to evaluate the association between patient characteristics (including pre-TAVR AR) and mortality. Associations are expressed as hazard ratios for mortality. Statistical analyses were performed using SPSS version 25.0 (IBM, Armonk, New York).

RESULTS

A total of 1,391 consecutive patients underwent TAVR between January 1, 2014, and December 31, 2017. After excluding patients with histories of AV replacement (n = 110), patients with no AS (n = 1), and patients with nontransfemoral access (n = 147), a total of 1,133 patients were included in the final analysis (**Figure 1**). Median follow-up duration was 27 months (interquartile range: 18 to 38 months).

Among these, 688 patients (61%) had MAVD. The median age was 83 years (interquartile range: 76 to 87 years), and 43% of the cohort were women. The MAVD group had slightly lower body mass index (27 vs. 29 kg/m^2; $p < 0.01$), less prevalence of diabetes mellitus (36% vs. 44%; $p < 0.01$) and atrial fibrillation (41% vs. 47%; $p = 0.04$), but higher prevalence of prior stroke or transient ischemic attack (22% vs. 17%; $p = 0.03$) (**Table 1**). Most of these patients (81%) did not develop post-TAVR AR, while 17% had mild, 2% had moderate, and <1% had severe post-TAVR total AR (**Figure 2**). The MAVD group had a higher prevalence of post-TAVR AR (22.1% vs. 14.4%; $p = 0.001$).

TABLE 1 Baseline Characteristics

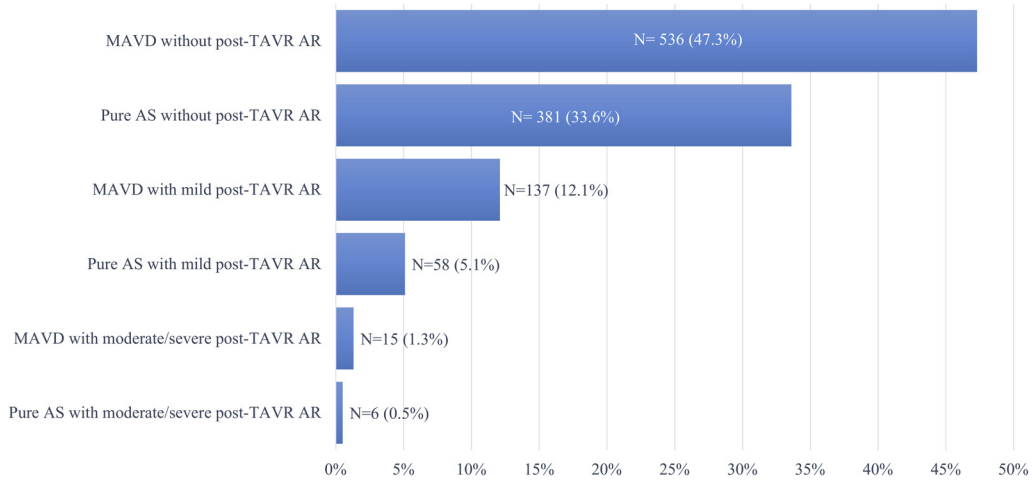
	Total (N = 1,133)	Mixed Aortic Valve Disease (n = 688)	Pure Aortic Stenosis (n = 445)	p Value
Age, yrs	83 (76–87)	83 (76.2–87)	82 (75–87)	0.60
Female	486 (42.9)	306 (44.5)	180 (40.4)	0.18
Caucasian	1066 (94.1)	638 (92.7)	428 (96.2)	0.10
BMI, kg/m^2	27.7 (24.5–32.5)	27.4 (24.4–31.6)	28.8 (25.1–33.4)	0.01
DM	441 (38.9)	248 (35.9)	194 (43.6)	0.01
HLD	857 (75.6)	523 (76)	334 (75.1)	0.71
HTN	1043 (92.1)	633 (92)	410 (92.1)	0.93
ESRD	45 (4)	23 (3.3)	22 (4.9)	0.21
PVD	390 (34.4)	233 (33.9)	157 (35.3)	0.62
Stroke or TIA	225 (19.9)	151 (21.9)	74 (16.6)	0.02
Atrial fibrillation	492 (43.4)	282 (41)	210 (47.2)	0.04
Previous CABG	313 (27.6)	179 (26)	134 (30.1)	0.13
Previous PCI	417 (36.8)	248 (36)	169 (38)	0.51
Prior pacing devices	138 (12.2)	78 (11.3)	13.5)	0.28
Aortic stenosis				0.64
Moderate	35 (3.1)	16 (2.3)	19 (4.3)	
Severe	1098 (96.9)	672 (97.7)	426 (95.7)	
LVEF, %	57.8 (50–63.2)	57.1 (49.3–62.9)	58.7 (50.7–63.8)	0.14
Aortic valve peak gradient, mm Hg	70.8 (57.3–86.4)	72.5 (57.8–89.5)	68.1 (55.5–81.9)	0.01
Aortic valve mean gradient, mm Hg	41.7 (33–52)	42.9 (34–54.3)	40 (31.5–49.5)	0.01
LVOT mean velocity, cm/s	0.62 (0.53–0.73)	0.63 (0.53–0.73)	0.61 (0.51–0.73)	0.25
LVOT diameter, cm	2 (1.9–2.1)	2 (1.9–2.1)	2 (1.9–2.1)	0.25
Aortic valve mean velocity, cm/s	3 (2.6–3.3)	3 (2.7–3.4)	2.9 (2.6–3.3)	0.002
Aortic valve VTI, cm	1 (0.8–1.1)	1 (0.8–1.1)	0.9 (0.8–1.1)	0.03
Aortic valve area, cm^2	0.6 (0.5–0.8)	0.6 (0.5–0.8)	0.6 (0.5–0.8)	0.71
Aortic valve area index	0.3 (0.2–0.4)	0.3 (0.2–0.4)	0.3 (0.2–0.4)	0.01
LVOT stroke volume, ml	68.3 (56.2–81)	69.1 (56.3–82.2)	66.9 (56.2–79.8)	0.16
LVOT stroke volume index, ml/m^2	35.3 (29–42.3)	36.7 (30–43.2)	33.6 (27.7–40.8)	<0.001

Values are median (interquartile range) or n (%).

AR = aortic regurgitation; AS = aortic stenosis; BMI = body mass index; CABG = coronary artery bypass graft; DM = diabetes mellitus; ESRD = end-stage renal disease; HLD = hyperlipidemia; HTN = hypertension; LVEF = left ventricular ejection fraction; LVOT = left ventricular outflow tract; PCI = percutaneous coronary intervention; PVD = peripheral vascular disease; TIA = transient ischemic attack; VTI = velocity-time integral.

On Kaplan-Meier curves, patients in the MAVD group had better overall survival compared with patients in the pure AS group ($p = 0.03$) (**Central Illustration**). The survival benefit was sustained after propensity score matching (Online Figure 1), as well as multivariate logistic regression (Online Table 1). Furthermore, among patients who developed post-TAVR AR, those in the MAVD group had better survival ($p = 0.04$). In contrast, among patients who did not develop post-TAVR AR, pre-TAVR AR did not improve survival ($p = 0.11$) (**Central Illustration**). Patients with MAVD were also found to have a decreased 3-year mortality

FIGURE 2 Frequency of Different Degrees of Post-Transcatheter Aortic Valve Replacement Aortic Regurgitation



Clustered bar chart depicting the frequency of different degrees of post-transcatheter aortic valve replacement (TAVR) aortic regurgitation (AR) in patients with pure aortic stenosis (AS) and mixed aortic valve disease (MAVD).

rate overall ($p = 0.02$) and when post-TAVR AR occurred ($p = 0.03$) (**Central Illustration**).

There was no statistically significant difference in secondary outcomes between the 2 groups (**Table 2**). Readmission for congestive heart failure or valve-related symptoms 30 days after the procedure was slightly higher in the pure AS group but did not reach significance (10.3% vs. 14.2%; $p = 0.051$). Major or life-threatening bleeding was found in 17.9% of the total cohort, but there was no significant statistical difference between the groups (17.4% in the MAVD group vs. 18.7% in the pure AS group; $p = 0.6$). The composite endpoints (early safety endpoint within 30 days of TAVR and clinical efficacy endpoint 30 days after TAVR) were not different among the groups ($p = 0.12$ and $p = 0.21$, respectively).

DISCUSSION

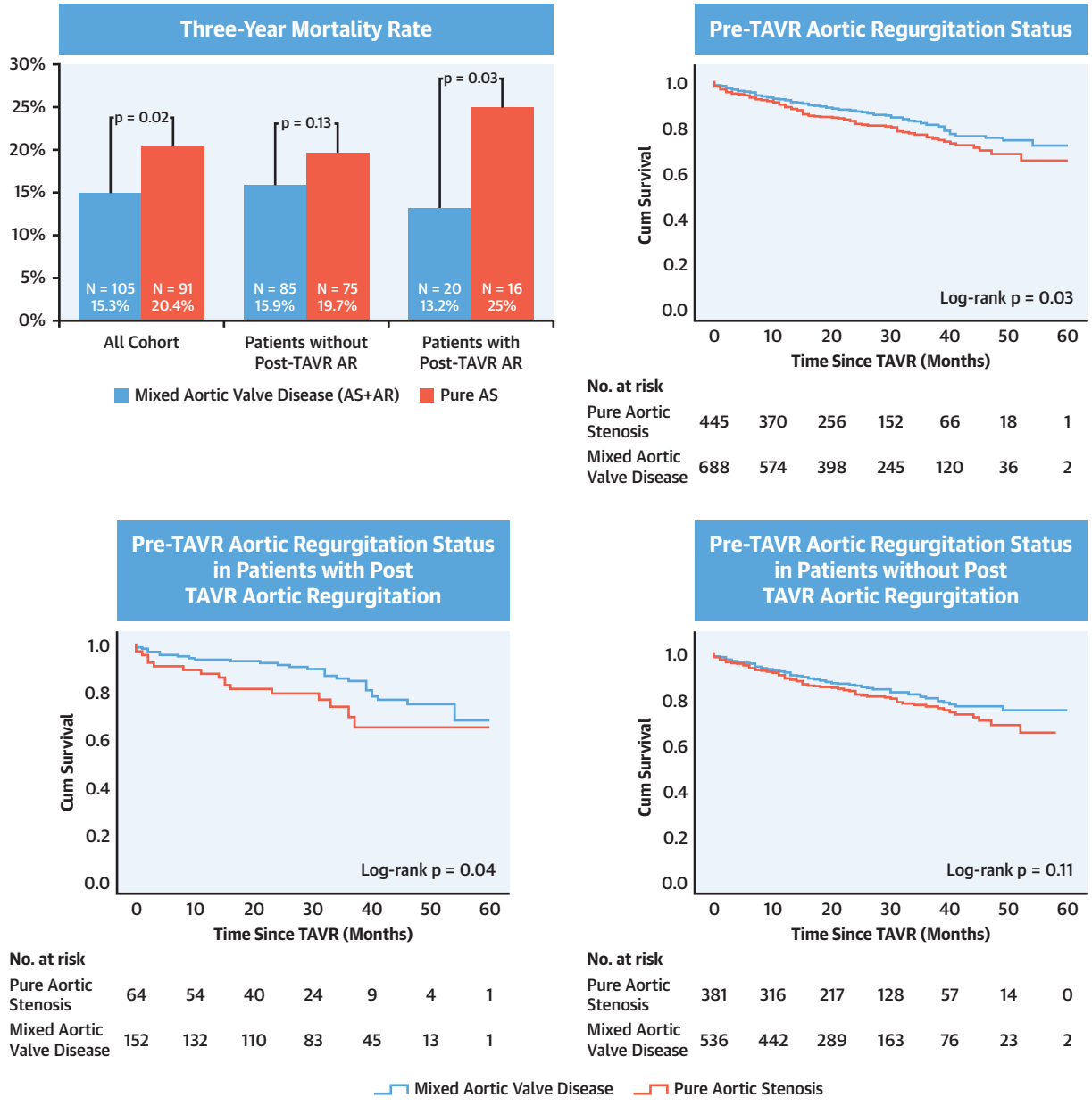
The main purpose of our study involving 1,133 subjects was to determine outcomes after TAVR in patients with MAVD and to compare these outcomes with those in patients who underwent TAVR for pure AS.

Our main findings include the following: 1) Patients in the MAVD group had better cumulative long-term survival compared with those in the pure AS group. 2) Among patients who developed post-TAVR AR, those in the MAVD group had better survival. On the contrary, there was no difference in mortality between the groups among patients who did not develop post-TAVR AR. 3) The secondary outcomes (within 30 days and 30 days after TAVR) were statistically comparable between the groups.

Many of the landmark trials that studied the role of TAVR in patients with severe AS with high or intermediate surgical risk did not include subjects with MAVD, and hence it has been challenging to extrapolate the excellent outcomes of TAVR to this particular group (3,4,14). Moreover, the incidence of MAVD is also expected to increase because of an overall aging population and an associated increase in the incidence of degenerative heart valve conditions. The natural course of these patients is considered to be worse than those with either pure AS or AR (10,15-17).

Prior studies looking at the utility of TAVR in treating MAVD have had mixed results. Stathogiannis et al. (18) noted in a study of 176 patients that at multivariate analysis, severe AR pre-TAVR was an independent predictor of long-term mortality (odds ratio: 9; 95% confidence interval: 1.922 to 42; $p < 0.005$). Abdelghani et al. (19) noted in a study of 793 patients who underwent TAVR that clinical outcomes in patients with MAVD are comparable with those in patients with pure AS in the acute and mid-term phases despite a higher risk at baseline in MAVD. Similarly, in a study of 734 patients by Seeger et al. (20), the primary endpoint of all-cause mortality or stroke was comparable between MAVD and pure AS (19.9% vs. 18.3%; $p = 0.87$). Our study, which included a much larger cohort (total, $n = 1,133$; pure AS, $n = 445$; MAVD, $n = 688$), interestingly indicates improved survival in patients with MAVD over the

CENTRAL ILLUSTRATION **Post-Transcatheter Aortic Valve Replacement 3-Year Mortality and Survival Curves of the 2 Study Groups**



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Clustered column chart showing increased 3-year mortality in patients with pre-transcatheter aortic valve replacement (TAVR) pure aortic stenosis (AS) ($p = 0.02$) compared with those with pre-TAVR mixed aortic valve disease (MAVD). When accounting for post-TAVR aortic regurgitation (AR) development in both groups, patients with pure AS exhibited higher mortality only if they developed post-TAVR AR ($p = 0.03$ vs. $p = 0.13$) **(top left)**. Kaplan-Meier survival curves showing improved survival in patients with MAVD, compared with those with pure AS ($p = 0.03$) **(top right)**. Among patients who developed post-TAVR AR, those in the MAVD group had better survival as well ($p = 0.04$) **(bottom left)**. There was no difference in survival between the groups if post-TAVR AR did not occur ($p = 0.11$) **(bottom right)**.

TABLE 2 Outcomes Based on the Valve Academic Research Consortium-2 Criteria

	Total (N = 1,133)	Mixed Aortic Valve Disease (n = 688)	Pure Aortic Stenosis (n = 445)	p Value
Bleeding (all)	18.6	18.3	19.1	0.74
Minor	8.2	8	8.5	0.74
Major	14.7	14.8	14.6	0.91
Life-threatening or disabling	4.9	4.2	6.1	0.16
Major or life-threatening	17.9	17.4	18.7	0.60
Major vascular complications	4.7	4.7	4.7	1
Minor vascular complications	10.4	11.3	9	0.2
Need for PCI or CABG within 30 days	1.2	1.3	1.1	1
Need for pacing devices	16.6	15.6	18.2	0.24
Conversion to open surgery	1	1	0.9	1
Early valve dysfunction requiring procedure	0.6	0.4	0.9	0.44
Late valve dysfunction	4	4.1	3.8	0.87
Successful valve implantation	99.6	99.9	99.1	0.08
Stroke or TIA within 30 days	2.3	2.2	2.5	0.84
Stroke or TIA after 30 days	3	2.9	3.1	0.85
Acute renal failure in the first week	9.9	9.6	10.3	0.68
Last NYHA functional class				0.71
I or II	88.3	88	88.8	
III or IV	11.7	12	11.2	
Hospitalization for CHF or valve-related	11.8	10.3	14.2	0.05
Time to hospitalization (days)	228 (62–476)	230 (81–513)	225 (50–469)	1
Hospitalization for CHF or valve-related symptoms within 30 days	1.4	0.9	2.2	0.07
Hospitalization for CHF or valve-related symptoms after 30 days	10.4	9.4	11.9	0.19
30-day mortality	1.9	1.6	2.2	0.5
Early safety endpoint	19.8	18.3	22	0.12
Clinical efficacy endpoint	33.5	32.1	35.7	0.21

Values are % or median (interquartile range).
CHF = congestive heart failure; NYHA = New York Heart Association; other abbreviations as in Table 1.

longer term, which has not been shown in any other prior studies.

It is also worthwhile to note that mixed results have also been seen when studying survival in patients with MAVD after surgical AV replacement (SAVR). In a retrospective review by Philip et al. (21) of 1,011 patients who underwent SAVR, patients with pre-existing AS and mild AR had comparable survival with those with AS and accompanying moderate or greater AR (p = 0.19). However, in patients with predominant AR, those with associated severe AS had reduced survival after SAVR (p = 0.02). In another study involving 110 subjects by Catovic et al. (22), patients with AS without AR or with mild AR had similar survival probabilities as well as left ventricular function recovery compared with patients with AS and moderate to severe AR. Our study differs in that it indicates better overall survival for patients with MAVD after TAVR intervention compared with AS alone.

The anatomy of the AV and left ventricle in patients with MAVD differs from that in patients with pure AS. Although the latter causes pressure-induced hypertrophy of the left ventricle with subsequent diastolic dysfunction, pre-existing AR results in volume overload leading to left ventricular dilatation and eccentric hypertrophy (23). One of the main causes of TAVR-related adverse outcomes is the development of post-TAVR paravalvular regurgitation (PVR) (24). Although PVR develops in patients with MAVD and pure AS pre-TAVR, it would seem that patients with pure AS have worse survival. The rates of moderate to severe post-procedural PVR after TAVR for pure AS range from 6% to 21% depending on the type of valve system used (balloon expandable vs. self-expandable), imaging modalities used (transthoracic echocardiography, transesophageal echocardiography, angiography), timing of assessment (immediately after implantation, before discharge, at 30 days), and adjudication of events (25). The presence of PVR has been shown to be an independent predictor of short- and long-term mortality as well as nonresponse to therapy (26). The incidence of PVR after TAVR in pure AS in our study was about 6% (mild AR 5%, moderate or severe AR 0.5%), consistent with prior reports. Although the overall rate of AR post-TAVR was higher in the MAVD group (22.1% vs. 14%; p = 0.001), this did not translate to worse outcomes.

We hypothesize that in patients with MAVD with pre-existing AR, the left ventricle has already been accustomed and has likely remodeled because of volume overload, making it easier for these patients to tolerate post-TAVR AR. On the contrary, in patients with pure AS, the ventricle is hypertrophied with reduced compliance, making it less likely to tolerate post-TAVR AR. This could explain the better outcomes observed in patients with MAVD who developed post-TAVR AR, which was not seen in patients with MAVD who did not develop post-TAVR AR.

STUDY LIMITATIONS. Our study included the largest cohort of patients with MAVD reported to date. However, it was a single-center retrospective observational study that suffers the known related limitations. Also, mortality data may be underestimated because we relied on our electronic medical record as well as a commercial obituary service. Whether our results can be applied to SAVR or AV repair for MAVD is yet to be investigated. Large prospective,

randomized controlled, multicenter trials are needed to validate our findings.

CONCLUSIONS

Patients with MAVD who underwent TAVR had better survival compared with those with pure AS yet with comparable secondary outcomes. This is explained by better survival of patients with MAVD who developed post-TAVR AR, likely because of left ventricular adaptation to AR.

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PERSPECTIVES

WHAT IS KNOWN? TAVR is indicated in treating patients with severe AS. In the presence of mixed valvular disease, major society guidelines recommend making clinical decisions on the basis of the predominant native lesion.

WHAT IS NEW? Patients with MAVD have better survival overall, particularly in those who develop residual AR after the procedure.

WHAT IS NEXT? Further large prospective, randomized controlled, multicenter trials are needed to validate our findings and investigate whether a similar relationship exists in SAVR and AV repair for mixed AV disease.

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