

Assess the Outcomes of Transcatheter Aortic Valve Replacement in Bicuspid Valve with Mixed Disease versus Predominant Aortic Stenosis

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Purpose: In mixed aortic valve disease (MAVD), the results of transcatheter aortic valve replacement (TAVR) are conflicting. There is limited data on the outcomes of TAVR in patients with bicuspid aortic valve (BAV) and MAVD. The objective of this study is to compare outcomes after TAVR in BAV patients with MAVD and predominant aortic stenosis (PAS).

Patients and Methods: Patients with BAV who underwent TAVR between January 2016 and April 2023 were included. The primary outcome was device success. The secondary endpoints were periprocedural mortality and other complications as defined by the Valve Academic Research Consortium-3 (VARC-3). Propensity score matching was used to minimize potential confounding.

Results: A total of 262 patients were included in this study, 83 of whom had MAVD. The median age was 72 years, and 55.7% were male. The baseline comorbidity risk files were comparable between the two groups. Patients with MAVD had more mitral regurgitation, tricuspid regurgitation and pulmonary hypertension, larger annular and left ventricular outflow tract dimensions, and more severe calcification than PAS. In the unmatched population, MAVD patients had similar device success rate (69.9% vs 79.9%, $P=0.075$) and 30-day mortality (3.6% vs 3.4%, $P=1$) compared to PAS. Propensity score matching resulted in 66 patient pairs. Device success rate were still comparable in the matched population. Other clinical outcomes, including stroke, bleeding (type 2–4), major vascular complications, acute kidney injury (stage 2–4) and permanent pacemaker implantation, were comparable between the two groups. Multivariable logistic regression analysis did not show MAVD to be an independent negative predictor of device success. At one year, survival was similar between patients with MAVD and those with PAS.

Conclusion: For the bicuspid valve, patients with MAVD had a more challenging anatomy. MAVD patients associated with comparable 30-day clinical outcomes after TAVR compared to PAS patients in patients with BAV.

Keywords: transcatheter aortic valve replacement, mixed aortic valve disease, bicuspid aortic valve, device success, propensity score match

Introduction

The indications for transcatheter aortic valve replacement (TAVR) have been expanded from a high surgical risk to a low surgical risk.^{1–3} The trend towards TAVR in younger and lower-risk patients has led to an increase in the number of BAV patients encountered by cardiac teams.⁴ In previous studies, the outcome of TAVR in patients with BAV was comparable to that in patients with tricuspid valve.^{5,6}

Mixed aortic valve disease (MAVD), a combination of AS and moderate or severe aortic regurgitation (AR), was not uncommon in practice.⁷ Moderate to severe AR was observed in 3% to 15% of patients with BAV treated with TAVR.^{5,8}

Due to pressure and volume overload, MAVD is more aggressive than isolated aortic valve lesions and is associated with worse clinical outcomes.^{9,10} MAVD is currently managed according to the predominant lesion and the underlying surgical risk.^{11,12} However, in patients with MAVD, the results of TAVR were mixed.^{13–16} In a retrospective study analysing 1133 patients (MAVD, $n=688$), patients with MAVD who underwent TAVR had a lower 3-year mortality rate compared with patients with AS alone (15.3% vs 20.4%), but similar early safety.¹⁵ A meta-analysis of six studies involving 58,879 patients showed that MAVD patients had lower odds of device success, while 30-day and 1-year mortality and other complications were similar between MAVD and severe AS.¹⁷ Demirel et al showed in their study that MAVD patients had worse long-term survival compared to isolated AS, with a HR of 1.412.¹⁸

There is a lack of data on the outcome of TAVR in patients with severe AS accompanied by moderate or severe AR in the BAV. The aim of this study was to evaluate the outcomes of TAVR for BAV with MAVD compared to PAS.

Materials and Methods

This is a retrospective study that was approved by the Research Ethics Committee of Guangdong Provincial People's Hospital (No. GDREC2019384H). Consecutive patients undergoing TAVR at Guangdong provincial people's hospital were enrolled into a prospective institutional registry database. Written informed consent was obtained from all participants for this registry. Our study complied the Declaration of Helsinki. All patients with BAV underwent TAVR between January 2016 and April 2023 were included. Patients with a history of aortic valve surgery, pure aortic regurgitation and missing baseline data were excluded. The database was retrospectively reviewed to obtain patient's age, sex, New York Heart Association (NYHA) heart failure, hypertension, diabetes mellitus, prior myocardial infarction, prior percutaneous coronary intervention, prior coronary artery bypass grafting, prior stroke, and peripheral arterial disease, echocardiographic variables. MAVD was defined as severe AS with associated moderate or severe AR. Patients were divided into two groups according to the presence of pre-operative AR: Predominant AS (PAS) and MAVD.

All patients underwent transthoracic echocardiography (TTE) prior to TAVR and repeat echocardiography at discharge. Mean aortic pressure gradients were calculated using the simplified Bernoulli equation. Left ventricular ejection fraction (LVEF) was calculated using Simpson's biplane method. According to guidelines,^{19,20} we defined moderate AS (pVel: 3.0–3.9 m/s and AVA 1.0–1.5 cm²); severe AS (pVel: ≥ 4.0 m/s and AVA ≤ 1.0 cm²), AR was graded as mild, moderate or severe. To avoid bias, two cardiologists assessed the valve disease together. Multidetector computed tomography (MDCT) was performed on all study patients prior to the procedure to determine the type of native aortic valve, annulus, left ventricular outflow tract (LVOT) variables, and aortic root angles. MDCT was also used to determine the size of the prosthetic valve and the vascular access. Severe calcification was defined as the sum of calcification volumes of each native aortic valve greater than 500 mm³. The details of multidetector computed tomography (MDCT) analysis were described in our previous study.²¹

According to the center expertise and device availability, self-expanding valve such as VenusA, VenusA-Pro, VenusA-Plus valve (Venus Medtech), Taurusone valve (Peijia Medical), ScienCrown valve (Lepu medical), Vitaflow (Microport), balloon-expanding valve such as Edwards Sapien (Edwards Lifesciences) and MuguetaTM (Xinchang medical) were implanted. Decisions about TAVI, device type and size were made by consensus by a dedicated heart team consisting of cardiac surgeons, interventional cardiologists and cardiac imaging specialists.

All outcomes were defined according to VARC-3 definitions. Technical success was defined as 1) freedom from mortality; 2) successful access, delivery of the device, and retrieval of the delivery system; 3) correct positioning of a single prosthetic heart valve into the proper anatomical location; and 4) freedom from surgery or intervention related to the device or to a major vascular or access-related, or cardiac structural complication at exit from the procedure room. The primary endpoint was device success, defined as 1) technical success; 2) 30-day freedom from mortality; 3) 30-day freedom from surgery or intervention related to the device or to a major vascular, or access related, or cardiac structural complication; and 4) less than moderate aortic regurgitation. Secondary endpoints included periprocedural mortality, stroke, major vascular complications, type 2–4 bleeding, permanent pacemaker implantation and acute kidney injury (AKI, stage 2–4) (within 30 days of TAVR).

Continuous variables were expressed as mean \pm standard deviation for normal distribution and median and interquartile range for skewed variables. Categorical variables were presented as number and percent. To compare baseline variables and outcomes between PAS and MAVD groups, we used Student's *t*-test for normally distributed continuous variables and Mann–Whitney *U*-test for non-normally distributed continuous variables. Categorical variables were compared using χ^2 or

Fisher's exact test as appropriate. Logistic regression analysis was performed to determine the association between MAVD and rate of device success. Unadjusted Kaplan-Meier analysis was used to evaluate the incidence of clinical outcomes at maximal follow-up and the log rank test was used for group comparisons.

A propensity score was estimated using a logistic regression model with MAVD as the dependent variable and baseline characteristics with statistically significant difference or clinically relevant as independent variables. The variables included in the propensity analysis were age, sex, coronary artery disease, diabetes mellitus, peripheral artery disease, mean gradient, LVEF, mitral regurgitation, tricuspid regurgitation, pulmonary hypertension, severe calcification, annulus areas, LVOT areas. Patients with MAVD were matched to a PAS patient based on the nearest propensity score using the one-to-one nearest neighbor method. Calliper was 0.2 of the logit of the propensity score and there was no replacement.

We evaluated association between patient's characteristic and device success and mortality in our study population using multivariable logistic analysis. Univariable logistic regression was performed to identify predictors for device success. Variables with P-values<0.05 in the univariable analysis were included in the multivariable analysis.

Result

A total of 274 patients with BAV underwent TAVR. 4 pure AR, 3 missing baseline data and 5 missing post-TAVR echocardiographic variables were excluded. Finally, 262 patients were included in the analysis. Of these, 83 (31.6%) were in the MAVD group and 179 (68.4%) in the PAS group. Baseline characteristics of the study population were presented in the Table 1. The median age was 72 years, and 44.3% of the total study population was female. Hypertension was the most

Table 1 Demographic and Computed Tomography Characteristics of the Study Populations

Variables	Total(N=262)	MAVD(N=83)	PAS(N=179)	P value
Age	72(67,75)	71(67,75)	72(67,75)	0.876
Male	146(55.7)	51(61.4)	95(53.1)	0.204
Hypertension	115(43.9)	34(41.0)	81(45.3)	0.515
Diabetes mellitus	58(22.1)	14(16.9)	44(24.6)	0.162
CAD	71(27.1)	20(24.1)	51(28.5)	0.456
Prior PCI	40(15.3)	9(10.8)	31(17.3)	0.175
Prior CABG	0	0	0	—
Prior AF	29(11.1)	7(8.4)	22(12.3)	0.355
Prior Stroke	14(5.3)	6(7.2)	8(4.5)	0.383
PAD	23(8.8)	6(7.2)	17(9.5)	0.564
CKD	71(27.1)	20(24.1)	51(28.5)	0.456
History of malignancy	20(7.6)	4(4.8)	16(8.9)	0.243
NYHA>II	146(55.7)	49(59.0)	97(54.2)	0.463
STS score, %	2.03(1.38,3.27)	2.04(1.44,3.16)	1.97(1.31,3.92)	0.909
Pre-procedure CT				
LVOT calcification	50(19.1)	16(19.3)	34(19.0)	0.957
Severe calcification	100(38.2)	40(48.2)	60(33.5)	0.023
Annulus Area, mm ²	381(89,484)	430(191,550)	371(79,463)	0.008
LVOT area, mm ²	320(22,468)	368(24,561)	307(22,433)	0.001
Aortic Root Angle, °	42(16,55)	42(15,56)	41(16,55)	0.909
NC calcification, mm ³	344(121,672)	371(168,734)	313(113,668)	0.258
RC calcification, mm ³	199(69,377)	255(100,419)	188(53,343.5)	0.101
LC calcification, mm ³	158(57,360)	156(74,365)	161(50,359)	0.559

Note: Data are presented as mean ± standard deviation, median (interquartile range), or n (%).

Abbreviations: CAD, Coronary artery disease; PCI, percutaneous coronary intervention; AF, Atrial fibrillation; PAD, peripheral artery disease; CKD, Chronic kidney disease; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association Functional classification; STS score, the Society of Thoracic Surgery risk score; LVOT, left ventricular outflow tract; NC, non-coronary cusp; RC, right coronary cusp; LC, left coronary cusp.

common comorbidity in the cohort and did not differ between the study groups. Other comorbidities were comparable between MAVD and PAS.

The MDCT characteristics were shown in [Table 1](#). Patients with MAVD generally had larger annulus and LVOT dimensions and more severe calcification. The echocardiographic characteristics were shown in [Table 2](#). In the study, pre-procedure and discharge echocardiography was performed by the same cardiac ultrasound team, but not by the same doctor. Prior to TAVR, concomitant mitral regurgitation, tricuspid regurgitation and pulmonary hypertension greater than mild were more common in patients with MAVD but lower LVEF ($P<0.001$). After the procedure, the rate of mitral regurgitation, tricuspid regurgitation and pulmonary hypertension greater than mild was not significantly different between the two groups. However, patients with MAVD still had a lower LVEF ($P<0.001$). The incidence of paravalvular leak (PVL) was similar between the two groups ($P=0.286$).

The details of procedure were summarized in [Table 3](#). Nearly all patients (95%) in the study underwent TAVR via a transfemoral approach. Patients with MAVD were more likely to implant a larger size prosthesis ($P<0.001$) and a second prostheses, although there was no statistical difference ($P=0.054$). Clinical outcomes compared between the two groups are shown in [Table 4](#). Technical success rates were similar between MAVD and PAS (83.1% vs 86.0%, $P=0.539$). Although patients with MAVD had a slightly lower device success rate than those with PAS, there was no significant statistical difference (69.9% vs 79.9%, $P=0.075$). There was no statistically significant difference in secondary outcomes between the two groups. 9 patients died within 30 days of TAVR, but there was no significant difference between the groups (3.6% in the MAVD group vs 3.4% in the PAS group, $P=1.00$). AKI was slightly higher in the MAVD group but did not reach significance (7.2% vs 2.2%, $P=0.078$). On multivariable analysis, only annular area, but not MAVD, was associated with lower device success, as shown in [Supplementary Table 1](#).

A total of 66 patient pairs were obtained using propensity score matching. Clinical outcomes after matching are shown in [Table 5](#). Clinical outcomes did not differ between MAVD and PAS patients: mortality (0% vs 4.5%, $P=0.244$), stroke (4.5% vs 1.5%, $P=0.619$), major vascular complication (1.5% vs 7.6%, $P=0.208$), acute kidney injury (9.1% vs 3.0%, $P=0.274$), pacemaker implantation (7.6% vs 3.0%, $P=0.44$), device success (78.8% vs 72.7%, $P=0.417$). MAVD patients had a slightly lower rate of bleeding (3.0% vs 12.1%, $P=0.048$).

During a median follow-up of 14 months, 19 patients (7.2%) died in the entire cohort. Kaplan-Meier analysis showed that there was no significant difference in survival between MAVD and PAS in unmatched patients (Log rank $P=0.53$). In matched patients, the cumulative survival rate was comparable between the two groups (Log rank $P=0.52$) ([Figure 1](#)).

Table 2 Echocardiographic Characteristics of the Populations

	MAVD(N=83)	PAS(N=179)	P value
Pre-procedure			
Mean aortic valve gradient, mm Hg	58(43,72)	61(52,76)	0.067
Peak velocity, m/s	5(4.4,5.6)	5(4.6,5.5)	0.354
Tricuspid regurgitation > mild, n (%)	27(32.5)	36(20.1)	0.029
Mitral regurgitation > mild, n (%)	44(53.0)	52(29.1)	<0.001
Pulmonary hypertension > mild, n (%)	27(32.5)	32(17.9)	0.008
LVEF, %	48(35,62)	62(49,68)	<0.001
Post-procedure			
Tricuspid regurgitation > mild, n (%)	11(13.3)	33(18.4)	0.296
Mitral regurgitation > mild, n (%)	18(21.7)	36(20.1)	0.769
Pulmonary hypertension > mild, n (%)	5(6.0)	11(6.1)	0.97
LVEF, %	56(42,62)	64(56,67)	<0.001
PVL, n (%)	58(69.9)	113(63.1)	0.286

Note: Data are presented as mean \pm standard deviation, median (interquartile range), or n (%).

Abbreviations: LVEF, left ventricular ejection fraction; PVL, Paravalvular leak.

Table 3 Procedure Details of Transcatheter Aortic Valve Replacement

	MAVD(N=83)	PAS(N=179)	P value
Combined with PCI, n (%)	4(4.8)	12(6.7)	0.553
Transfemoral access, n (%)	79(95.2)	167(93.3)	0.553
Pre-dilatation, n (%)	82(98.8)	178(99.4)	0.534
Post-dilatation, n (%)	48(57.8)	91(50.8)	0.291
Valve type			0.442
SE	82(98.8)	172(96.1)	
BE	1(1.2)	7(3.9)	
Valve size			<0.001
20–24mm	18(21.7)	75(41.9)	
25–27mm	32(38.6)	83(46.4)	
29–32mm	33(39.8)	21(11.7)	
TAV-in-TAV, n (%)	11(13.3)	11(6.1)	0.054

Note: Data are presented as mean \pm standard deviation, median (interquartile range), or n (%).

Abbreviations: SE, self-expandable prosthesis; BE, balloon-expandable prosthesis.

Table 4 Clinical Outcomes According to MAVD and PAS in Unmatched Population

	Total(N=262)	MAVD(N=83)	PAS(N=179)	P value
Device success	201(76.7)	58(69.9)	143(79.9)	0.075
Technical success	223(85.1)	69(83.1)	154(86.0)	0.539
In-hospital mortality	5(1.9)	1(1.2)	4(2.2)	1
Stroke	5(1.9)	3(3.6)	2(1.1)	0.33
Bleeding (type2-4)	19(7.3)	5(6.0)	14(7.8)	0.602
Major vascular complication	18(6.9)	3(3.6)	15(8.4)	0.156
Acute kidney injury (stage 2-4)	10(3.8)	6(7.2)	4(2.2)	0.078
Pacemaker implantation	11(4.2)	6(7.2)	5(2.8)	0.108
Periprocedural mortality	9(3.4)	3(3.6)	6(3.4)	1

Note: Data are presented as n (%).

Table 5 Clinical Outcomes According to MAVD and PAS in Matched Population

	Total(N=132)	MAVD(N=66)	PAS(N=66)	P value
Device success	100(75.8)	52(78.8)	48(72.7)	0.417
Technical success	112(84.8)	59(89.4)	53(80.3)	0.145
In-hospital mortality	3(2.3)	0	3(4.5)	0.244
Stroke	4(3.0)	3(4.5)	1(1.5)	0.619
Bleeding (type 2-4)	10(7.6)	2(3.0)	8(12.1)	0.048
Major vascular complication	6(4.5)	1(1.5)	5(7.6)	0.208
Acute kidney injury (stage 2-4)	8(6.1)	6(9.1)	2(3.0)	0.274
Pacemaker implantation	7(5.3)	5(7.6)	2(3.0)	0.44
Periprocedural mortality	7(5.3)	2(3.0)	5(7.6)	0.44

Note: Data are presented as n (%).

Discussion

This is the first study to compare anatomical characteristics and clinical outcomes after TAVR for mixed aortic valve disease with predominant AS in patients with BAV. Our main findings include the following: 1) Patients in the MAVD group had more calcification, larger dimensions of the ascending aorta, annulus and LVOT compared with those in the

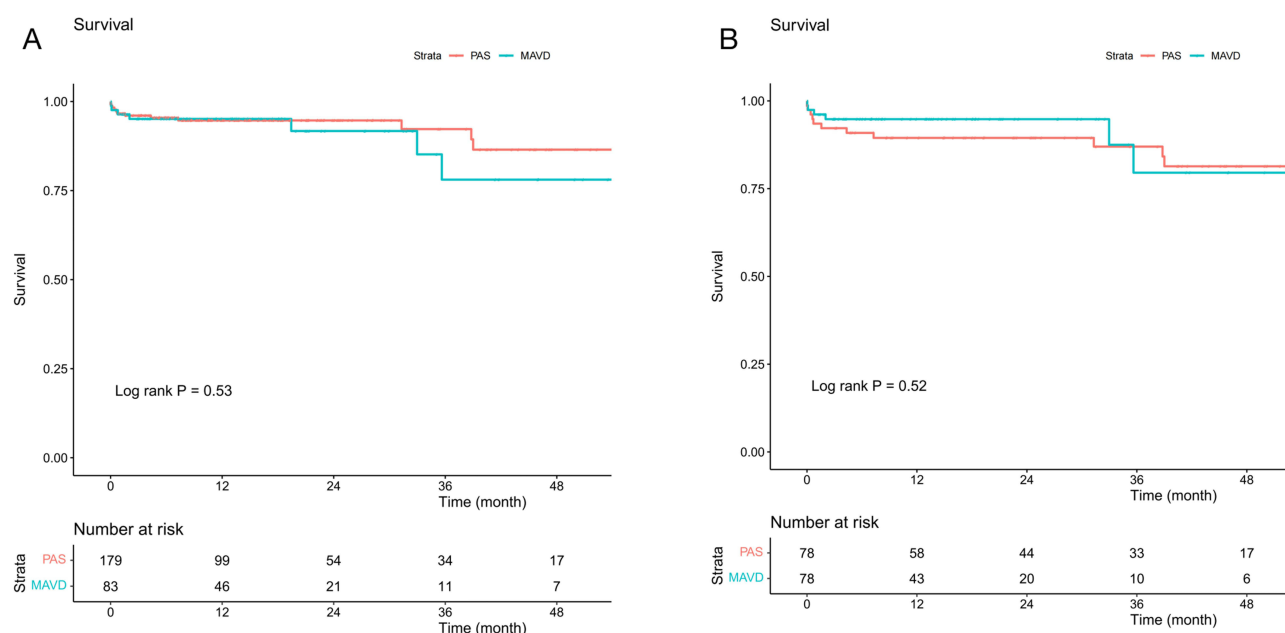


Figure 1 48 months survival in MAVD and PAS patients. (A) 48 months survival in the whole cohort; (B) 48 months survival in the propensity score matches cohort.

PAS group. 2) Annular area but not MAVD was associated with lower device success rate. 3) MAVD did not affect 30-day clinical outcomes or 1-year survival after TAVR.

Patients with MAVD are thought to have a worse natural history and prognosis than those with PAS.^{7,10} Clinical outcomes after TAVR in patients with MAVD are inconsistent in previous studies.^{17,22} Current guidelines recommend treatment for MAVD according to the predominant lesion. When the severity of both lesions is balanced, the indication for intervention should be based on symptoms and objective consequences. However, the timing and modalities of treatment are unclear.^{11,12} Patients with mixed aortic valve disease have been excluded from large randomized trials focusing on transcatheter aortic valve replacement.^{23,24} In a meta-analysis of six studies involving 58,879 patients, Guddeti et al found that the 30-day mortality rate after TAVR in patients with MAVD was 5.1%, with no significant difference between the MAVD and PAS groups.¹⁷ A study of 1133 patients found that the incidence of 30-day mortality in patients with MAVD undergoing TAVR was 1.6% and was not significant compared with patients with PAS.¹⁵ However, the above studies included both tricuspid and bicuspid aortic valves, and the majority of patients had a tricuspid valve. In the present study, which included 262 BAV (MAVD, n=83; PAS, n=179), 9(3.4%) patients died within 30 days after TAVR. 30-day mortality was similar between MAVD and PAS (3.6% vs 3.4%, $P=1.00$). Even in a propensity-matched analysis, the mortality rate in MAVD and PAS patients remains similar. The 30-day mortality rate in our study was consistent with previous studies.^{17,25} The present study was the first study to compare clinical outcomes after TAVR between MAVD and PAS in patients with BAV. The present results may provide clinical data to guide intervention for patients with BAV and MAVD.

Chieffo et al showed in their retrospective study that patients with MAVD had a lower device success rate compared to PAS, but this did not affect prognosis.¹³ However, the definition of MAVD in their study is severe aortic stenosis with \geq mild aortic regurgitation, which differs from the definition in our study. It is therefore difficult to fully compare the results of our analysis with their study. In several other analyses, MAVD was defined as severe aortic stenosis plus \geq moderate aortic regurgitation.^{14,16,26} Contrary to our study, previous studies have found that patients with MAVD have a significantly lower device success rate than those with PAS. In addition, the device success rate in our study was lower than in previous studies. Although there is a slightly lower device success rate in patients with MAVD, there is no significant difference. There is also no significant difference in peri-operative mortality, need for a second valve, moderate or severe post-procedural aortic regurgitation or major vascular complications between MAVD and PAS. Several potential factors may contribute to this. In our study, device success was defined according to the VARC-3 definition, which is stricter than the VARC-2 definition used in previous studies. BAV is a significant challenge for TAVR, with previous studies showing low rates of BAV. Therefore, the device success rate was

lower than in previous studies. Guddeti et al pointed out that annulus dilation and increased valve stress caused by aortic regurgitation may affect the success of the procedure.¹⁷ Vianello et al demonstrated that patients with MAVD had a predominant fibrotic pattern in the valve leaflets which may play a role in implant success.²⁷ In our study, patients with MAVD had a larger dimension of LOVT and annular and more severe calcification, which may have an impact on device success. Multivariable regression analysis indicated that annulus size was associated with lower rate of device success. After propensity score matching, there was no difference in device success between the two groups. Larroche et al showed that aortic valve calcification was significantly associated with less device success, but not with major adverse cardiac events.²⁸

PVL is common after TAVR and has been reported to be associated with worse short- and long-term clinical outcomes.^{29,30} However, there are analyses suggesting that post-TAVR aortic regurgitation is more common in the MAVD group than in the PAS group and is positive for survival in patients with MAVD.^{15,17} Pre-existing AR causes the left ventricle to adapt to volume overload and myocardial remodeling. As a result, patients with PAS who experienced PVL had a worse prognosis due to inadaptation. In the present study, the prevalence of aortic regurgitation after TAVR was higher than that reported in previous studies.^{13,15} In the present study, no significant difference in the incidence of post-TAVR aortic regurgitation \geq moderate between patients with MAVD and PAS. Data from several observational studies and registries have shown that patients with BAV are more likely to develop PVL after TAVR compared to TAV due to the more complicated anatomy of the aortic root: greater aortic root calcification, larger annulus and ascending aortic dimensions.³¹ A higher prevalence of post-procedural aortic regurgitation is associated with inter-operator echocardiographic variability and patient selection. Extensive calcification played a role in the under-expansion of the transcatheter valve and consequently in PVL.

In the present study, the anatomy of patients with MAVD was more challenging than that of patients with PAS. The geometry of the annular, LVOT and ascending aorta was larger in MAVD compared to PAS. In Chahine's study of 1133 patients (MAVD, n=668), the size of the LVOT was similar between MAVD and pure aortic stenosis. However, the tricuspid aortic valve was also included and the proportion of BAV in each group was unclear in their study.¹⁵ There was a lack of data to compare the anatomy of the aortic valve complex. Further cohort studies are needed to confirm our findings.

Our study had several limitations. It was a single-centre, retrospective, observational study with several known limitations. The number of advertising events was relatively low. Large prospective multicenter trials are needed to validate our findings. Data on cardiac remodeling after TAVR were not available in our study. The majority of patients in our study underwent TAVR with older-generation devices, which may overestimate the device failure rate. In addition, there may be measurement errors for the same ultrasound parameter when different examiners are involved. Although echocardiography is not performed by a single doctor, and there can be measurement errors between different operators, it is performed by the same ultrasound team and all team members have extensive experience in echocardiography.

Conclusion

For the bicuspid valve, patients with MAVD had a more challenging anatomy. MAVD patients associated with comparable 30-day clinical outcomes after TAVR compared to PAS patients in patients with BAV.

Abbreviations

AKI, acute kidney injury; AR, aortic regurgitation; AS, aortic stenosis; BAV, bicuspid aortic valve; LVOT, left ventricular outflow tract; LVEDD, left ventricular end diastolic diameter; LVEF, left ventricular ejection fraction; MAVD, mixed aortic valve disease; MDCT, Multidetector computed tomography; NYHA, New York Heart Association; PAS, predominant aortic stenosis; PVL, paravalvular leak; TAVR, transcatheter aortic valve replacement; TTE, transthoracic echocardiography; VARC3, Valve Academic Research Consortium-3.

Ethics Approval and Informed Consent

This is a retrospective study that was approved by the Research Ethics Committee of Guangdong Provincial People's Hospital (No. GDREC2019384H). Written informed consent was obtained from all participants for the study.

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Disclosure

The authors declare that there is no conflict of interest in this work.

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