Research Square

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Impact of Mild Aortic Valve Disease on Late Outcomes after Replacement of the Ascending Aorta Case-control Study

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Abstract

Background: The time course of mild aortic valve disease after replacement of the ascending aorta is unclear. We sought to clarify it.

Methods: Between January 2011 and December 2016, 26 patients (9 bicuspid and 17 tricuspid aortic valve disease) underwent replacement of the enlarged ascending aorta alone. We compared the postoperative disease course between bicuspid and tricuspid aortic valve by transthoracic echocardiography and computed tomography performed at 73 ± 23 and 60 ± 23 months post-surgery, respectively.

Results: The bicuspid group was younger than the tricuspid group (62.1 ± 4.8 vs 73.3 ± 4.8 years). Pathophysiology predominantly involved aortic valve stenosis and regurgitation in the bicuspid and tricuspid group, respectively. The peak and mean pressure gradient increased (P = .16, and P = .46) and the aortic valve area decreased significantly in the bicuspid group (P = .005). Two patients in the bicuspid group who required re-operation had an aortic valve area of 1.2 cm^2 at initial operation. Seventy percent of patients in the tricuspid group had less than mild aortic valve regurgitation preoperatively, which improved up to 82% at follow-up. Freedom from re-operation was 66.7% and 100% at 8 years for the bicuspid and tricuspid group, respectively.

Conclusions: Aortic valve replacement may be considered for patients with bicuspid aortic valve stenosis if the aortic valve area is less than 1.2 cm^2, even if the general diagnosis is mild aortic valve stenosis at initial surgery. Even mild aortic valve regurgitation may be improved by surgical intervention in the ascending aorta.

Background

According to the 2020 guidelines**,** the Japanese Circulation Society has revised the indication for ascending aortic surgery in patients with bicuspid aortic valves (BAVs) as being ≥ 55 mm in diameter.[1] One of the reasons for this change is that there is now sufficient evidence to indicate that BAV has a low incidence of aortopathy compared to other hereditary aortic diseases.[2-6] Nevertheless, this criterion is based on data from Western countries. Kinoshita et al. reported that the presence of aortic regurgitation (AR) and an ascending aorta of >40 mm in diameter at the time of initial surgery were predictors of late dilatation of the aorta after aortic valve replacement (AVR) for BAV but BAV phenotype was not[7].

However, there are no clear criteria for surgical interventions on mild aortic valve stenosis (AS) in BAV patients with ascending aortic enlargement, because there has been no evidence of the fate of mild AS after surgical intervention in the ascending aorta alone. In addition, it has been reported that AR caused by enlargement of the sinotubular junction (STJ) alone, so-called type I lesion[8], can well been controlled by STJ remodeling with or without aortic cusp repair in patients with tricuspid aortic valves (TAVs) [9,10]. Nonetheless, it has been unclear whether STJ remodeling alone is enough in this setting and to what extent STJ should be reduced.

This study compared the long-term course of mild aortic valve disease in patients with BAVs and TAVs after surgical intervention in the ascending aorta alone.

Methods

Subjects

This study was approved by the institutional review board at the Saitama Cardiovascular and Respiratory Center (No. 2020014). Written informed consent was obtained from all patients for using the data for academic publication purposes. The study was registered with the University Hospital Medical Information Network (study ID: UMIN000040843).

Between January 2011 and December 2016, 129 patients underwent ascending aorta replacement with or without AVR at our center. Of these, 26 patients with mild aortic valve disease who underwent replacement of the enlarged ascending aorta alone were included in the study. Nine of these patients had a BAV and 17 were TAV patients. The clinical profiles of the patients are shown in Table 1.

Pre-operative Evaluation

To acquire hemodynamic and geometric data before the operation, transesophageal echocardiography (TEE) and transthoracic echocardiography (TTE) were performed by two experienced echocardiographers, using a Philips EPIQ CVx machine (Phillips HealthCare, Hamburg, Germany). Conventional echocardiographic data, including left ventricular (LV) end-diastolic and end-systolic dimensions (LVEDd and LVEDs, respectively), LV ejection fraction (EF), the grade of aortic valve disease (AS or AR), aortic valve annulus diameter, Valsalva sinus diameter, and STJ diameter, were collected. The mean and peak aortic valve pressure gradient (MPG and PPG, respectively) were also collected, particularly for patients with AS. According to cusp fusion pattern, BAV patients were further categorized as the right-left coronary cusp fusion (RL) type or non-RL (nRL) fusion type. The assessment of the ascending aorta was performed by computed tomography (CT) scan. The pre-operative CT and echocardiographic assessment variables are shown in Table 2.

Initial Surgery

Ascending aortic replacement was performed by open hemi-arch replacement (n=2) or with a clamped ascending aorta (n=24) during the initial surgery. No surgical intervention on the aortic valve was performed in all patients.

Data Collection and Study Endpoint

Baseline data were collected from medical records or the echocardiography database. Follow-up data on survival and symptoms were collected through annual outpatient visits, and/or from referring physicians, by mail or telephone. The primary outcome was all-cause death and re-operation on the aortic valve. The secondary endpoint was diagnosis of severe aortic valvular diseases.

Statistical Analysis

All data were analyzed using IBM SPSS Statistics for Windows (version 26.0; IBM Corp., Armonk, NY, USA). Continuous variables are presented as means ± standard deviations. Normality of all variables was assessed using the Shapiro-Wilk test. The paired t-test was used for comparison before and after surgery, and the unpaired t-test was used for comparison between the two groups. Categorical variables were analyzed by the chi-square test or Fisher's exact test. Survival was assessed using the Kaplan–Meier method, and differences between groups were assessed with the log-rank test. A probability value of $< .05$ was considered to indicate statistical significance.

Results

The BAV group had a significantly younger mean age than the TAV group (P < .001). The mean body surface area was significantly smaller in the TAV group than in the BAV group (P = .005). Hypertension was significantly more common in the TAV group (P = .015), but there were no obvious differences between the groups in other variables. The clinical profiles of the patients in each group are shown in **Table 1**.

Table 1

The clinical profiles of the patients in each group

Characteristic	TAV	BAV	P-value
No of patients	17	9	
Male	9	6	.79
Age (year)	73.3 ± 4.8	62.1 ± 4.8	< .001
BSA (m^2)	1.52 ± 0.15	1.73 ± 0.18	.005
NYHA class			
□–□	16 (94)	9 (100)	
□–□	1 (6)	0 (0)	
Smoke	7 (41)	5 (56)	.67
Hypertension	17 (100)	5 (56)	.015
COPD	3 (17.6)	1 (11)	.56
Atrial fibrillation	1 (5.8)	3 (33)	.086
Diabetes mellitus	2 (11.7)	1 (11)	.55
chronic kidney disease	1 (5.8)	0 (0)	.74
peripheral arterial disease	3 (17.6)	1 (11)	.89
cerebrovascular disease	1 (5.8)	0 (0)	.74
Values are mean ± SD or n (%). NYHA, New York Heart Association COPD, chronic obstructive pulmonary disease;			

The pre-operative CT and echocardiographic assessment variables are shown in **Table 2**. The diameters of the ascending aorta, Valsalva sinus, and STJ were similar in both groups (P = .95, .24, and .54). In the BAV group, the RL phenotype was present in about half of patients. Three patients had mild AS in BAV group and five patients had moderate AR in TAV group preoperatively. The peri-operative data are shown in **Table 3**. The mean size of the vascular grafts was 28 mm in diameter in both groups. Two patients in the BAV group underwent coronary artery bypass grafting surgery concomitantly, and two patients in the TAV group underwent arch vessel reconstruction. The operative time and cardiopulmonary bypass (CPB) time were comparable between the two groups (P = .41 and

P = .42, respectively). However, the length of stay in the intensive care unit and in the hospital was significantly shorter in the BAV group (P = .046 and P = .047, respectively). The blood transfusion rate was significantly lower in the BAV group (P = .039).

Table 2

Pre-operative computed tomographic and echocardiographic assessment variables

	TAV	BAV	P-value
Ascending aorta (mm)	52.1 ± 5.8	52.0 ± 5.0	.95
Valsalva sinus (mm)	38.2 ± 5.1	35.3 ± 6.8	.24
STJ (mm)	32.6 ± 3.8	31.4 ± 5.6	.54
LVEF (%)	63.1 ± 8.8	59.5 ± 8.7	.33
LVESd (mm)	31.4 ± 5.5	30.6 ± 3.8	.73
LVEDd (mm)	48.4 ± 6.3	46.0 ± 5.1	.33
BAV phenotype (fusion)		RL: 5 (55.5%)	
		nRL: 4 (44.4%)	
ASR degree			
None	05		
Trivial	AR (4)	ASr (1), Ar (3)	
Mild	AR (8)	AS (3), AR (1)	
Moderate	AR (5)		
PPG (mmHg)		17.8 ± 10.5	
MPG (mmHg)		9.9 ± 7.0	
AVA (cm^2)		2.09 ± 0.94	
Avd (cm)		22.3 ± 2.0	

Values are mean ± SD or n (%). STJ, sinotubular junction; AR: aortic valve regurgitation; AS: Aortic valve stenosis; ASR: aortic valve stenosis and regurgitation; LVEDd, left ventricular end-diastolic diameter; LVEDs, left ventricular end-systolic diameter; LVEF, left ventricular ejection fraction; MPG: mean aortic valve pressure gradient; PPG: peak aortic valve pressure gradient; AVA, aortic valve area; Avd, aortic valve annulus diameter; RL, right-left coronary cusp fusion type; nRL, non-right-left coronary cusp fusion type; TAV, tricuspid aortic valve; BAV, bicuspid aortic valve

Table 3

The baseline characteristics of the two groups peri-operatively

	TAV (n = 17)	BAV (n = 9)	P-value
Vascular graft size (mm)	28.5 ± 1.5	28.2 ± 2.3	.74
Operative time (min)	345 ± 98	320 ± 54	.41
CPB time (min)	160 ± 52	147 ± 26	.42
AXC time (min)	122 ± 40	104 ± 13	.09
Blood transfusion (%)	11 (64)	2 (25)	.039
ICU stay (days)	7.3 ± 7.0	3.4 ± 0.9	.046
Hospital stay (days)	32 ± 19	21 ± 2.6	.047
β-blocker (%)	9 (53)	4 (44)	.68
Concomitant operation	CABG (2)	PAR (2)	

Values are mean ± SD or n (%). TAV, tricuspid aortic valve; BAV, bicuspid aortic valve; OR, odds ratio; CABG, coronary artery bypass grafting; CPB, cardiopulmonary bypass time; AXC, aorta clamping time; PAR, partial arch replacement

Routine follow-up evaluations with TTE and CT were performed at 73 ± 23 months and 60 ± 23 months postoperatively in the BAV and TAV groups, respectively (P = .18). The follow-up echocardiographic data for the two groups are shown in **Table 4**.

Table 4

Comparison of the two techniques through post-operative echocardiographic data

	TAV (n = 17)	BAV (n = 9)	P value
LVEF (%)	59.9 ± 8.8	56.7 ± 6.8	.36
LVEDd (mm)	47.0 ± 6.3	46.4 ± 6.7	.83
LVESd (mm)	31.1 ± 5.8	32.2 ± 6.1	.63
ASR degree			
None	2	3	
Trivial	AR (4)	ASR (1)	
Mild	AR (8)	ASR (2)	
Moderate	AR (3)	ASR (1)	
Severe	AS (2)		
PPG (mmHg)		33.7 ± 35.9	
MPG (mmHg)		20.1 ± 26.2	
AVA (cm^2)		1.55 ± 0.87	

Values are mean ± SD. MPG: mean aortic valve pressure gradient; PPG: peak aortic valve pressure gradient; AVA, aortic valve area; ASR: aortic valve stenosis and regurgitation; LVEDd, left ventricular end-diastolic diameter; LVEDs, left ventricular end-systolic diameter; LVEF, left ventricular ejection fraction; TAV, tricuspid aortic valve; BAV, bicuspid aortic valve

There were no statistically significant differences in LVEF (P = .36), or LVEDd (P = .83) or LVEDs (P = .63) between the two groups.

BAV cases more commonly had AS than AR. Two patients who had mild AS pre-operatively required re-operation 96 month and 100month after initial surgery in each. However, the diagnosis of severe AS was made after 61 and 31 months later, respectively.

In BAV patients with AS, there was an increase in PPG (17.8 ± 10.5 to 33.7 ± 35.9 mmHg) and MPG (9.9 ± 7.0 to 20.1 ± 26.2 mmHg) from pre-operation to follow-up, which was not significantly different (P = .16 and P = .46), respectively. The aortic valve area (AVA) was decreased from 2.09 ± 0.94 to 1.55 ± 0.87 cm^2 at follow-up, which was statistically significant (P = .002). In particular, the mean AVA of the three patients with a pre-operative mild AS decreased from 1.30 ± 0.17 to 0.79 ± 0.49 cm^2 at follow-up (P= .153). Changes at follow-up in all BAV cases are shown in Table 4 and Figure 1. The details of the nine BAV patients are shown in **Table 5**.

Table 5.

characteristics of all bicuspid aortic valve-type patients

No	Sex	Age	Phenotype	AS degree	Follow-up Years	NYHA	PPG (mmHg)	MPG (mmHg)	AVA (cm^2)	B-Blocker
1	F	57	nRL	Severe (mild)	8		118 (24)	85 (15)	0.25 (1.2)	+
2	M	62	RL	Trivial (none)	7		19 (14)	8 (7)	1.74 (3.0)	
3	F	65	nRL	Severe (mild)	8		66 (35)	37 (20)	0.91 (1.2)	
4	M	60	RL	None (none)	8		11 (9)	6 (5)	3.30(3.9)	
5	M	53	nRL	None (none)	7		15 (2)	7 (1)	2.10 (2.7)	+
6	M	66	nRL	Moderate (trivial)	7		18 (16)	10 (9)	0.96 (1.2)	+
7	M	62	RL	None (none)	3		18 (19)	10 (9)	1.92 (2.1)	
8	M	66	RL	Mild (none)	4		10 (11)	5 (7)	1.56 (2.05)	+
9	F	68	RL	Mild (mild)	4		29 (30)	13 (15)	1.23 (1.50)	

( ):before operation

M, male; F, female; AS, aortic stenosis; MPG: mean aortic valve pressure gradient; PPG: peak aortic valve pressure gradient; AVA, aortic valve area; RL, right-left coronary cusp fusion type; nRL, non-right-left coronary cusp fusion type

TAV patients predominantly had AR, even before surgery. Pre-operatively, 70% of patients had less than mild AR and 23% had less than trivial AR. Postoperatively, 88% of patients had less than mild AR and 35% had less than trivial AR, which represented an improvement **(Figure 2**). The freedom from re-operation was 66.7% for BAV and 100% for TAV patients over an 8-year follow-up period. The freedom from diagnosis of severe valvular degeneration were 71.1% for BAV and 100% for TAV patients. The overall survival rates were 83.3% for BAV and 100% for TAV patients **(Figure 3, 4, and 5).** It was not possible to analyze a Cox proportional hazard model due to the small sample size and large number of covariates.

Discussion

This study compared the time course of aortic valve disease in patients with BAVs with that in patients with TAVs, after surgical intervention in the ascending aorta. We found that the pathophysiology of aortic valve disease predominantly involved AS in BAV and AR in the TAV groups.

A BAV is the most common type of congenital heart disease; individuals with BAVs account for 2% of the total population.[11] BAV disease carries an approximately 6% lifetime risk of aortic dissection, which is nine-fold higher than that of the age- and sex-matched general population.[12] BAV patients account for 15% of aortic dissections. In addition, it is estimated that 5% of BAV patients suffer from aortic dissection.[13] In a study comparing BAVs and

Marfan syndrome, the incidence of aortic dissection was lower in BAVs and the mortality at 10 years was 3.5% in BAVs and 8.7% in Marfan syndrome.[3]

The Japanese Society of Cardiology guidelines had recommended the replacement of the ascending aorta in patients with a BAV when the ascending aortic diameter measures ≥ 45 mm, but this was changed to ≥ 55 mm in 2020 (Class I). However, this criterion is based on the evidence of low incidence of bicuspid valve aortopathy compared to other hereditary aortic diseases[2-6] and the progression of aortic valvular disease is not taken into account in this criterion. [1-6] On the other hand, there has been no evidence of the fate of mild aortic valve disease after replacement of the ascending aorta alone. The aim of this study is to follow the long-term prognosis of patients with mild bicuspid or tricuspid aortic valvular disease who underwent aortic intervention only (ascending aortic replacement or partial arch replacement).

Tzemos et al.[5] found no significant difference in ascending aortic diameter between patients with TAV and those with BAV, but the age of surgical intervention in the ascending aorta was younger in the BAV patients, similar to our findings. Thus, when considering the timing of future surgery for the aortic valve, it is useful to examine the durability of unoperated BAVs and TAVs.

In the present study, AS was the most common underlying disease of BAVs, while TAVs were predominantly affected by AR, but there was a clear difference in the degree of progression between the two groups. This may be because BAVs are prone to pathological degenerative changes and pathophysiological progression due to hemodynamical and genetic reasons.[14] The degree of progression can become problematic. In this study, two patients in the BAV group developed severe valvular disease within 5 years, and one developed moderate disease; the two severe patients required re-operation. This raises the question at what level of AS should undergo simultaneous surgical intervention.

The three mild AS cases in the present study were all NYHA I pre-operatively, and the comprehensive pre-operative diagnosis by the cardiology department indicated that surgical intervention was not necessary. However, two of them were diagnosed with severe AS at 31 month and 61 months after initial surgery and became symptomatic and needed to undergo AVR at 3 and 6 years after diagnosis of severe AS.

When only AVA was considered, AVA of the three cases was within the moderate range according to the guideline (1.0–1.5 cm^2)[15]. Considering that case #6 also had a pre-operative AVA of 1.2 cm^2 but initial diagnosis was trivial AS by the cardiology department and had AS progression post-operatively, the AVA may play an important role to predict candidates for simultaneous AVR at initial surgery (Table 5).

If severe AS is diagnosed, the timing of re-operation is controversial. Miyake et al. reported that, in a comparison of asymptomatic severe AS in the surgery group and in cases that eventually became operable after conservative observation, survival rate was better in the initial surgery group with a peak aortic jet velocity of 4.5 m/s or higher.[16] It has been reported that RL fusion cases are more likely to be severely affected.[17] In contradiction, in our study, both of the two cases who underwent re-operation had the nRL type. Furthermore, Russo et al. concluded that there was no difference in AS progression in the fusion pattern, confirming our finding.[7,17]

Beppu et al. reported that PPG in BAV patients increased by approximately 20 mmHg over 10 years, which was faster than that in TAV patients.[18]

In this study, the two re-operated cases had vascular graft sizes of 24 mm and 26 mm, and it was very difficult to replace the aortic valve at the time of re-operation, because of the limited working space. If there was a possibility of re-operation for the remaining aortic valve, it would have been better to consider to use a larger vascular graft to facilitate AVR in case with severe adhesion in the aortic root.

AR in the 17 TAV cases showed some improvement after ascending aortic replacement without aortic cusp repair. The mechanism underlying this phenomenon may be related to morphological factors involving changes caused by the dilatation of the STJ.[19]

One of the causes of AR is enlargement of the STJ, so-called type I lesion[8], for which STJ remodeling is suggested to control AR.

Asano et al. reported that STJ remodeling with or without aortic cusp repair was able to control AR caused by ascending aortic aneurysm, but emphasized that aortoventricular junction of 28 mm or more was a risk factor for reoperation.[9] Our patients had small aortic annulus diameter (22.3 ± 2.0 mm), so STJ remodeling alone was enough to control AR.

David et al. performed the same strategy to treat type I AR and reported that the freedom from severe AR and AVR at 10 years was 98% ± 1% and 97% ± 1%, respectively, which seems similar to our findings (both 100% at 8 years).[10]

The results of our study suggest that there may be time to consider the optimal timing of reoperation, even when the valve disease is graded as severe at echocardiography. An increasing number of reports recommend b-blockers as a means of preventing the progression of valvular disease, but this may also be a means of delaying surgical intervention.[20,21]

Limitations

This study utilized a retrospective, single-institution analysis, which may limit its generalizability. The sample size was relatively small; therefore, the results might be biased. It was not possible to perform a Cox proportional hazard analysis due to the small sample size and large number of covariates. Since there were only two cases of re-operation in this study, most of the categorical variables presented in either of the two cases. Therefore, in order to perform multivariable analysis, a larger patient group and longer follow-up period may be necessary. Nevertheless, we could speculate that the extent of valvular area at the time of initial surgery might play an important role in predicting late AS progression. However, further follow-up and larger studies are needed to corroborate our speculation.

Conclusion

This study showed that AVR may be considered for bicuspid AS if the AVA is moderate range according to the guideline or less than 1.2 cm^2, even if the general diagnosis of AS is mild level at the initial surgery. However, even if severe AS is diagnosed after initial surgery, the optimal timing of reoperation should be considered. Type I AR may be improved by surgical intervention in the ascending aorta alone, even if it is moderate at the time of the initial surgery. Additionally, at the initial surgery, if the possibility of future AVR is considered, it may be better to use a larger vascular graft.

List Of Abbreviations

AR: Aortic valve regurgitation

AS: Aortic valve stenosis

ASR: Aortic valve stenosis and regurgitation

AVR: aortic valve replacement

BAV: Bicuspid aortic valve

CT: Computed tomography

EDd: End-diastolic dimension

EDs: End-systolic dimension

EF: Ejection fraction

LV: Left ventricular

MPG: Mean aortic valve pressure gradient

PPG: Peak aortic valve pressure gradient

STJ: Sinotublar junction

TAV: Tricuspid aortic valve

TEE: Transesophageal echocardiography

TTE: Transthoracic echocardiography

Declarations

IRB

the institutional review board at the Saitama Cardiovascular and Respiratory Center (No. 2020014)

Conflict of interest:

The authors declare that there are no conflicts of interest.

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Ethics approval and consent to participate*:*

The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. This study conformed to the provisions of the Declaration of Helsinki (as revised in 2013). This study was approved by the institutional review board at the Saitama Cardiovascular and Respiratory Center (No. 2020014).

Consent for publication:

Written informed consent was obtained from the patients for using the data for academic publication purposes.

Availability of data and materials:

The datasets generated and/or analysed during the current study are not publicly available due to possibility that individuals may be identified but are available from the corresponding author on reasonable request.

The datasets used and analyzed during the current study are available from the corresponding author on reasonable request.

Competing interests:

All authors have completed the Journal of BMC Surgery uniform disclosure form. The authors have no conflicts of interest to declare.

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(I) Conception and design: K Nakamura, T Kunihara, K Hashimoto
(II) Administrative support: T Kondo, M Nakao, M Wakatabe
(III) Provision of study materials or patients: K Nakamura, K Orii
(IV) Collection and assembly of data: K Nakamura
(V) Data analysis and interpretation: K Nakamura, T Kunuhara
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(VII) Final approval of manuscript: All authors

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Figures

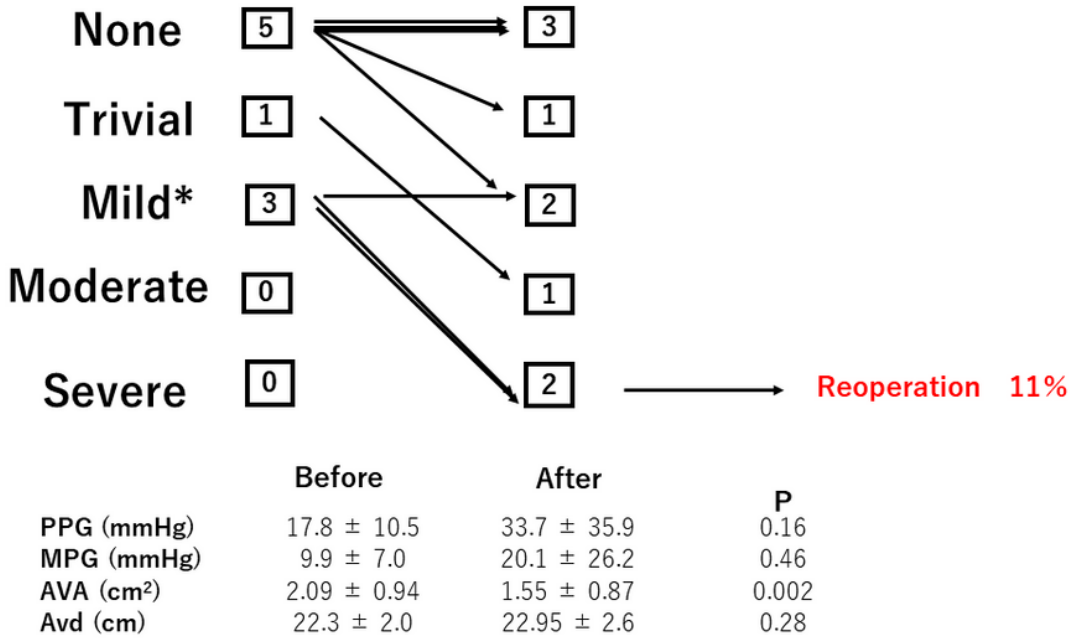

Figure 1

Figure 1

Aortic stenosis (AS) assessment after operation in patients with bicuspid aortic valve disease (BAV) Two patients who had mild AS pre-operatively developed severe AS and required re-operation.

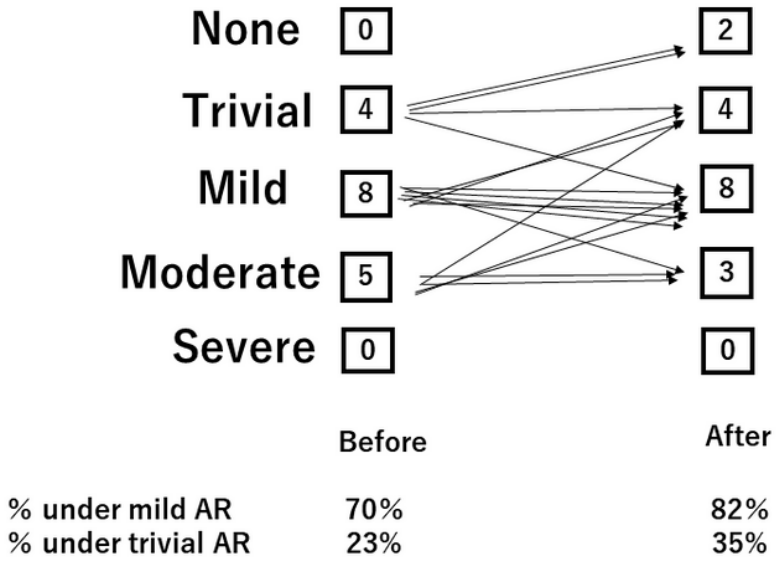

Figure 2

Figure 2

Aortic regurgitation (AR) assessment after operation in patients with tricuspid aortic valve disease (TAV) Pre-operatively, 70% of patients had sub-mild AR and 23% had sub-trivial AR. Postoperatively, 82% of patients had sub-mild AR and 35% had sub-trivial AR, showing improvement.

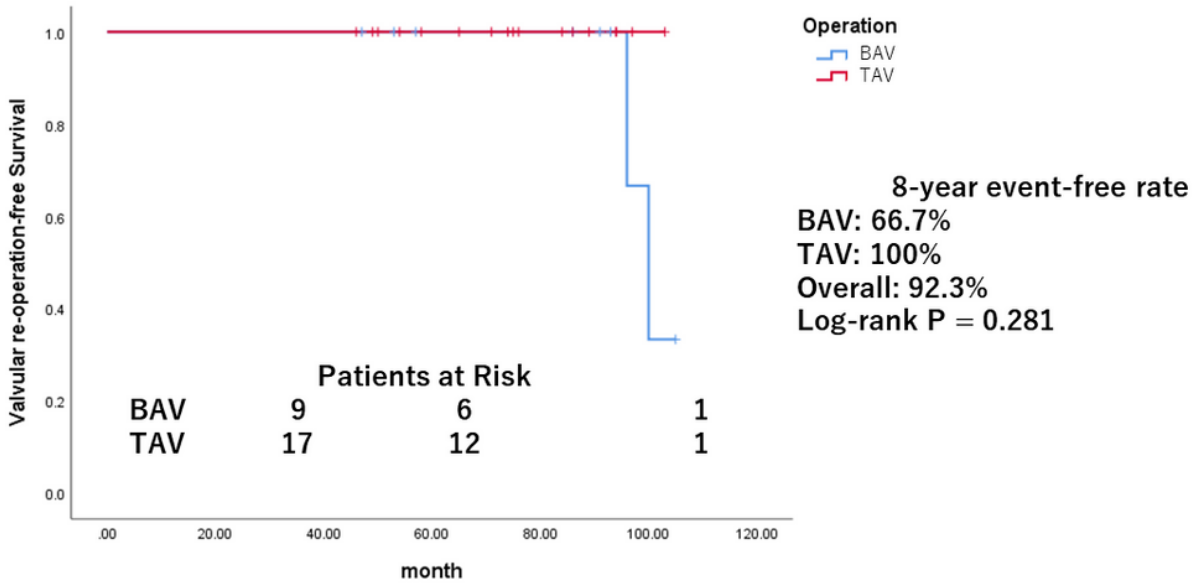

Figure 3

Figure 3

Survival after valvular re-operation

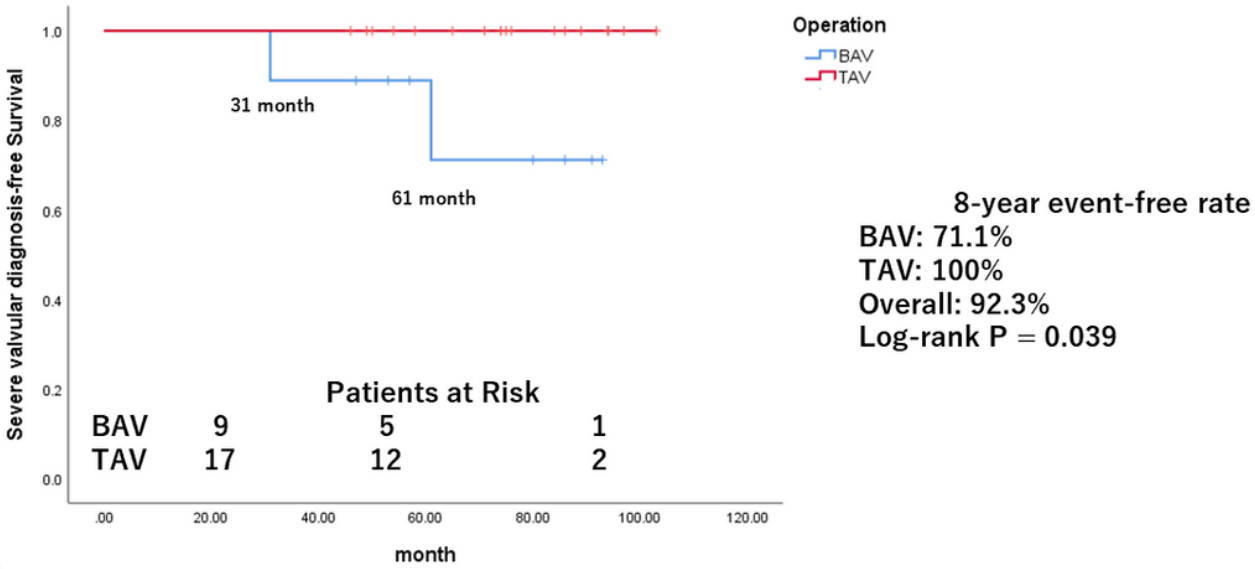

Figure 4

Figure 4

Survival after diagnosis of severe valvular stenosis

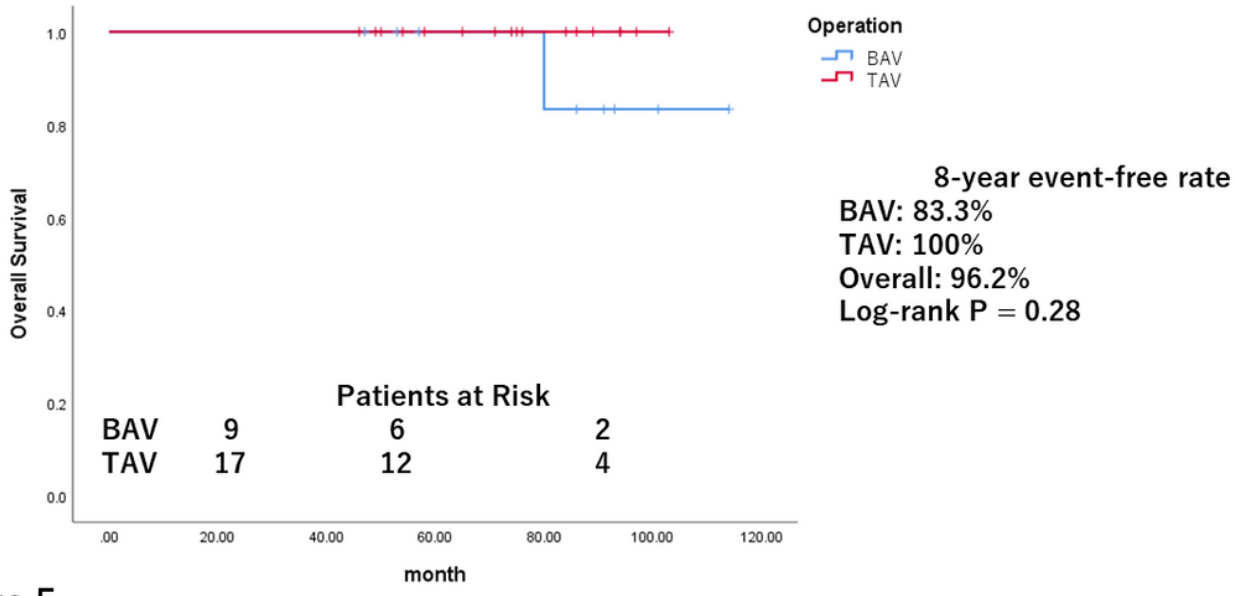

Figure 5

Figure 5

Overall survival