ORIGINAL ARTICLE

Bicuspid and Unicuspid Aortic Valve: Fate of Moderate/Severe Mixed Aortic Valve Disease

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ABSTRACT

Objectives. There is a paucity of data about mixed aortic valve disease (MAVD) in patients with bicuspid/unicuspid aortic valve (BAV). This study sought to describe the outcomes of patients with moderate/severe MAVD.

Methods. We queried our database for patients with BAV and moderate/severe MAVD seen between 1994 and 2013. We excluded patients with baseline New York Heart Association (NYHA) III/IV symptoms, left ventricular ejection fraction <50%, aortic dimension >50 mm, and significant disease of other valves. The purpose of the study was to determine the freedom from NYHA III/IV symptoms and aortic valve replacement (AVR).

Results. We identified 138 patients with moderate/severe MAVD; mean age was 51 ± 12 years; 112 (81%) were males; and follow-up was 8.5 ± 4 years. Ninety-two patients (67%) underwent AVR within 3.7 ± 2.5 years. Mechanical prostheses were implanted in 73 patients (79%); 22 patients (26%) and 36 patients (39%) had concomitant coronary artery bypass graft and aorta replacement during AVR respectively. There were no surgical deaths. Freedom from AVR was 84%, 51%, and 20% at 1, 5 and 10 years respectively. Predictors of AVR were age at presentation (hazard ratio [HR] 5.22; confidence interval [CI] 3.10 to 6.64) for every decade increase in age; and having severe stenosis or regurgitation at the time of presentation (HR 1.32; CI 1.05 to 3.16).

Conclusions. Age and disease severity should be incorporated in the risk assessment of BAV patients with MAVD, and patients with both risk factors should be monitored closely.

Key Words. Bicuspid Valve; Aortic Stenosis; Aortic Regurgitation; Aortic Valve Replacement

Introduction

Bicuspid aortic valve (BAV) is the most common congenital heart defect and demonstrates significant male predominance.[1,2] It is associated with cardiovascular morbidities such as valvulopathy, aortic dilation, and coarctation of aorta.[3,4] BAV is currently one of the most common causes of aortic stenosis in patients <70 years of age.[5] The mechanism of stenosis in patients with BAV is usually due to excessive calcification and fibrosis while the mechanism of regurgitation may be due to cusp prolapse, aortic root dilation or prior infective endocarditis with associated cusp perforation.[2–4,6]

The natural history data of BAV are derived from population-based studies of patients, the majority of whom have trivial or mild aortic valve dysfunction.[7,8] As a result, the cardiovascular adverse event rates derived from these studies represent the risk of adverse events in patients with mild BAV disease and likely underestimate the risk expected in the typical BAV patient with valve dysfunction. Isolated aortic stenosis (AS) or aortic regurgitation (AR) in the BAV population is managed based on the same guidelines as senile degenerative aortic valve disease (SDAVD).[9,10] There are limited data to guide the management of BAV patients with combined AS and AR which we will refer to as mixed aortic valve disease (MAVD).

Two recently published series of MAVD were derived from both BAV and SDAVD patients.[11,12] BAVs generally undergo early calcification and degeneration resulting in a natural history that differs from SDAVD.[2–4] We believe that natural history of moderate-severe MAVD in BAV carries a

different prognosis than SDAVD and requires independent assessment.

Methods

Patient Selection

The study protocol was reviewed and approved by the Mayo Clinic Institutional Review Board. We retrospectively identified all asymptomatic adult patients (≥18 years of age) with BAV and a combination of at least moderate AS and moderate AR seen at our institution between January 1994 and December 2013. The diagnosis of BAV was confirmed by pathology in those patients that underwent surgical aortic valve replacement (AVR). We identified 856 consecutive patients using our search criteria (≥ moderate AS AND ≥ moderate AR, asymptomatic, New York Heart Association [NYHA] I/II, ejection fraction >50%). We then excluded patients with the following conditions: history of chest radiotherapy, prior cardiac surgery, inadequate follow-up or loss of follow-up, or ≥ moderate stenosis or regurgitation of the mitral, tricuspid or pulmonary valves. We also excluded patients with an aortic root or ascending aorta dimension > 50 mm. Based on echocardiographic criteria described below, we identified 351 patients with combined ≥ moderate AS and moderate AR. From this population, we excluded 213 patients with trileaflet aortic valve. Our final cohort comprised 138 patients with the diagnosis of bicuspid (n = 126) and unicuspid (n = 12) aortic valve (Figure 1).

The purpose of the study was to determine the freedom from the development of NYHA class III/IV symptoms (angina, exertional dyspnea, exertional syncope, or presyncope) and AVR. The baseline echocardiogram was used for the analysis of predictors of freedom from AVR.

Data Collection

Clinical and echocardiographic data were abstracted from the medical record of the 138 included patients from the time of initial presentation to their last follow-up (Table 1). The clinical data collected include age, gender, NYHA class, surgical indications, and associated comorbid conditions such as hypertension, hyperlipidemia, atrial fibrillation, renal failure, diabetes, and coronary artery disease. We defined hyperlipidemia as total cholesterol >200 mg/dl or being on lipid-lowering therapy; hypertension as blood pressure >140/90 mm Hg or systolic blood pressure >140 mm Hg for patients with severe AR; and renal failure as creatinine clearance <60 mL/min. Coronary artery disease was defined as a history of myocardial infarction, angioplasty, coronary artery bypass grafting, or angiographically documented coronary artery stenosis.

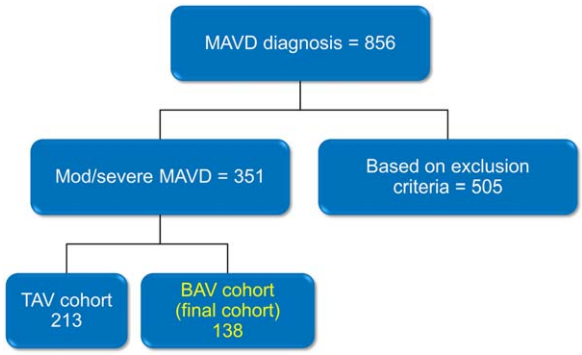

Figure 1. Patient selection. The final BAV cohort comprised of 138 patients (bicuspid, n = 126 and unicuspid, n = 12). MAVD, mixed aortic valve disease; TAV, trileaflet aortic valve; BAV, bicuspid aortic valve; Mod, moderate.

Echocardiographic data collected include aortic valve hemodynamics (peak aortic velocity, mean aortic valve gradient, aortic valve area, pressure half time, aortic regurgitant volume, vena contracta, presence of holodiastolic flow reversal in the descending aorta), left ventricular dimensions (left ventricular end-diastolic dimension, left ventricular end-systolic dimension, left ventricular ejection fraction, left ventricular mass index, relative wall thickness), left atrial volume, and right ventricular systolic pressure. We also reviewed the surgical database and collected the following data: surgical indications, year of AVR, prosthesis type, concomitant surgical procedures such as coronary artery bypass graft and aorta replacement, surgical complications, and early surgical mortality.

Study Classification

We divided our cohort into 4 aortic valve disease study groups based on severity of stenosis and regurgitation: Group 1—moderate AS and moderate AR; Group 2—severe AS and moderate AR; Group 3—moderate AS and severe AR; Group 4—severe AS and severe AR.

Definition of Echocardiographic Parameters

According to published guidelines,[13–15] we defined moderate AS (peak aortic velocity: 3.0–3.9 m/s and aortic valve area 1.1–1.5 cm^2); severe AS (peak aortic velocity: ≥4.0 m/s and aortic valve area

Table 1. Baseline Patient Characteristics

	Entire Cohort	AVR	No AVR	*P* Value
n	138	92	46	
Male	112 (81%)	76 (83%)	36 (78%)	.51
Age at diagnosis, years	51 ± 12	54 ± 13	47 ± 8	<.0001
Follow-up, years	8.5 ± 4	8.7 ± 4	7.1 ± 4	.02
Study groups				
Group 1	97 (70%)	68 (74%)	29 (63%)	
Group 2	16 (12%)	13 (14%)	3 (7%)	
Group 3	25 (18%)	11 (12%)	14 (30%)	
Group 4	0	0	0	
Echo data				
Aortic peak velocity, m/s	4.5 ± 0.6	4.5 ± 0.5	4.5 ± 0.6	.66
Aortic mean gradient, mm Hg	48 ± 11	48 ± 11	47 ± 11	.53
Aortic valve area, cm^2	1.21 (IQR: 1.01–1.40)	1.16 (IQR: 1.01–1.41)	1.20 (IQR:1.04–1.33)	.46
Aortic valve area index, cm^2/m^2	0.52 (IQR:0.46–0.67)	0.50 (IQR:0.49–0.68)	0.51 (IQR:0.46–0.60)	.17
Pressure half time, ms	279 ± 148	274 ± 128	281 ± 139	.83
LV ejection fraction,%	61 ± 4	60 ± 4	59 ± 3	.37
LV end diastolic dimension, mm	58 ± 7	58 ± 6	57 ± 7	.71
LV end systolic dimension, mm	33 ± 8	33 ± 9	33 ± 4	.59
LV mass index, g/m^2	141 ± 56	145 ± 46	135 ± 53	.08
LV diastolic dysfunction*	33 (32%)	31 (48%)	2 (5%)	.01
Left atrial volume, mm^3	36 (IQR: 31–48)	37 (IQR:31–46)	36 (IQR: 33–44)	.07
RV systolic pressure, mm Hg	31 ± 14	36 ± 11	29 ± 17	.41
Clinical				
Atrial fibrillation	14 (10%)	10 (12%)	3 (6%)	.06
Hypertension	60 (43%)	44 (48%)	16 (35%)	.04
Hyperlipidemia	53 (38%)	31 (34%)	22 (48%)	.77
Coronary artery disease	30 (15%)	26 (28%)	4 (9%)	.01
Endocarditis	4 (3%)	4 (4%)	0	
Stroke	1 (0.7%)	1 (1%)	0	
Aortic aneurysm†	61 (44%)	47 (51%)	14 (30%)	.01

AVR, aortic valve replacement; LV, left ventricle; RV, right ventricle.
*LV diastolic dysfunction: Only 102 had diastolic assessment. We defined diastolic dysfunction as grade 3&4.
†Aortic aneurysm, aortic root/ascending aorta >45 mm.

≤1.0 cm^2); moderate AR (at least 2 of the following: vena contracta 0.3–0.6 cm, regurgitant volume by proximal isovelocity surface area 30–60 mL, and pressure half time 200–500 ms); severe AR (at least 2 of the following: vena contracta >0.6 cm, regurgitant volume by proximal isovelocity surface area >60 mL, pressure half time <200 ms, and presence of holodiastolic flow reversal in the abdominal aorta). The severity of diastolic dysfunction was graded from grade 1 to 4. For the purpose of this study, significant diastolic dysfunction was defined as presence of grade 3 and 4 diastolic dysfunction; and aortic aneurysm as ascending aorta or aortic root dimension of >45 mm.

Statistical Analysis

All statistical calculations were performed with the JMP version 10.0 software (SAS Institute Inc., Cary, NC, USA). Categorical variables were expressed as percentages while continuous variables were expressed as mean ± SD or median (interquartile range, IQR) for skewed data. Comparison of categorical variables was performed using chi-square test or Fisher's exact test, while comparison of continuous variables was performed with two-sided unpaired Student *t*-test or Wilcoxon rank-sum test as appropriate. Cox proportional-hazard model was used to identify risk factors for AVR and expressed as hazard ratio (HR) and 95% confidence interval (CI). Only the variables that were significant on univariable analysis were included on the multivariable model. Event-free survival rate curves were generated with Kaplan-Meier method, and compared with log-rank test. All p values were two sided, and P values $< .05$ were considered significant.

Results

Baseline Characteristics

We identified138 patients with BAV and moderate/severe MAVD followed at Mayo Clinic between 1994 and 2013. The mean age at initial assessment was 51 ± 12 years, 112 patients (81%) were males, and mean follow-up duration was 8.5 ± 4 years, Table 1.

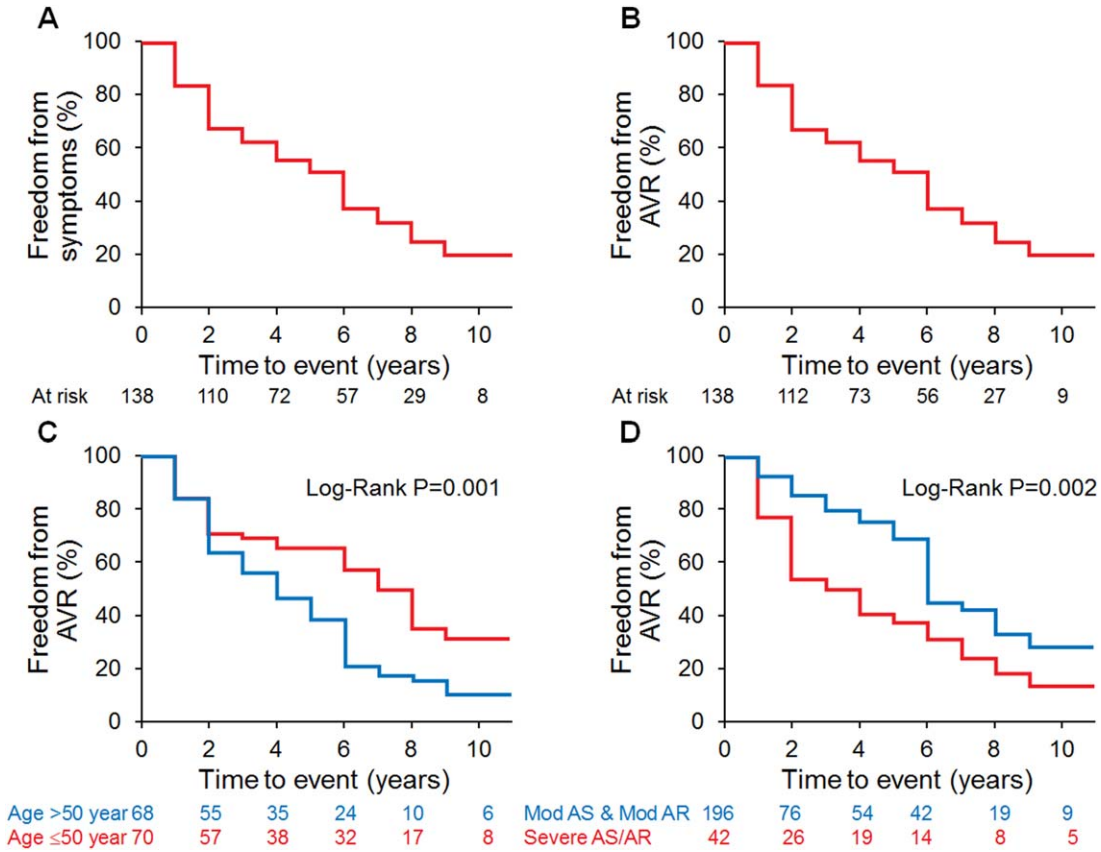

Figure 2. Freedom from symptoms and AVR. (A) Freedom from symptoms for the entire cohort; (B) Freedom from AVR for the entire cohort; (C) Freedom from AVR analyzed by age group, patients ≤ 50 years old (red) and patients >50 years old (blue); (D) Freedom from AVR analyzed by disease severity at presentation. AVR, aortic valve replacement

Freedom from NYHA III/IV Symptoms

A total of 86 patients developed NYHA III/IV symptoms (angina, exertional dyspnea, exertional syncope, or presyncope) during follow-up; 84 of them underwent AVR.

Two patients did not undergo AVR despite symptoms, for unknown reasons. They were five patients with documented nonsustained ventricular arrhythmia on Holter monitor but there was no history of sudden death or resuscitated cardiac arrest. Freedom from symptoms was 84%, 61%, 49%, and 21% at 1, 3, 5, and 10 years respectively, Figure 2.

Progression of Aortic Valve Disease

There were 67 patients with progression of aortic valve disease during the study period based on the severity criteria outlined in the methods section. Among these patients, 39 patients progressed from Group 1 (moderate AS and moderate AR) to Group 2 (severe AS and moderate AR) while 28 patients progressed from Group 1 to Group 3 (severe AS and moderate AR). Fifty-five of the patients with progression of valve disease severity subsequently underwent AVR.

Surgical Cohort

Ninety-two patients underwent AVR. The mean time from initial visit to AVR was 3.7 ± 2.5 years; and the time to AVR varied by age and disease severity at presentation, $P < .0001$ (Figure 3). The indication for surgery was the development of symptoms in 84 patients (91%). Eight patients (9%) had no documented symptoms prior to AVR; 6 of them had abnormal stress test, and 2 had an ascending aorta dimension > 50 mm (53 mm and 55 mm) at the time of AVR. A total of 65 patients had an abnormal stress test as one of the indications for AVR. These abnormal stress test findings were ischemic changes on electrocardiogram (n = 38.), hypotensive blood pressure response (n = 12) and

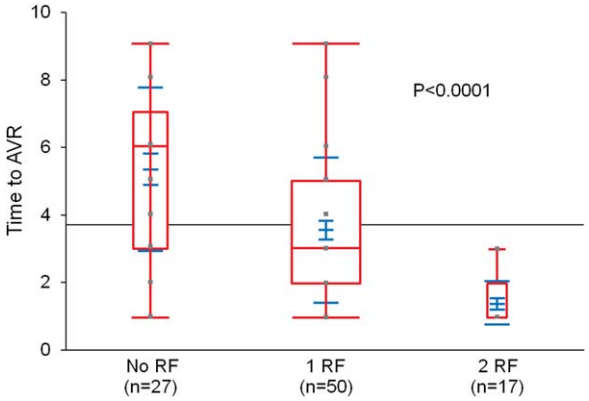

Figure 3. Comparison of time to AVR stratified by number of risk factors for patients that underwent aortic valve replacement (n = 92). Mean time to adverse event: 5.2 ± 2.3 years (no risk factor); 3.6 ± 2.1 years (1 risk factor); 1.4 ± 0.6 years (2 risk factor). RF, risk factor.

Table 2. Surgical Cohort

n	92
Age at AVR, years	53 ± 6
Male	76 (83%)
FU duration to AVR, years	3.7 ± 2.5
Mechanical prosthesis	73(79%)
Bioprosthesis	19(21%)
Additional procedure	48(52%)
CABG	22(26%)
Aortic replacement	36(39%)
Early surgical mortality	0
All-cause mortality	3(3%)
Postoperative EF <50%	14(15%)
Indication for AVR	
NYHA III/IV symptoms	84(91%)
Progression of AS or AR	55(60%)
Abnormal stress test	65(71%)
Aortic aneurysm/dissection	1(1%)

AR, aortic regurgitation; AS, aortic stenosis; AVR, aortic valve replacement; CABG, coronary artery bypass graft; EF, ejection fraction; FU, follow-up; NYHA, New York Heart Association.

limiting chest pain and dyspnea during stage I Bruce protocol (n = 15).

Seventy-three patients (79%) received a mechanical prosthesis while 19 patients (21%) received a bioprosthesis. Twenty-two patients (26%) and 36 patients (39%) underwent concomitant coronary artery bypass graft and aorta replacement respectively, Table 2. One patient had type A dissection with an ascending aorta dimension of 51 mm; he underwent emergent surgical AVR and aorta replacement and survived to hospital dismissal. There were no perioperative deaths.

Death

There were 3 deaths reported during the study period (1-cardiac, 1-noncardiac, and 1-unknown cause). One death occurred in a 68-year old man who underwent AVR and ascending aorta replacement with composite graft who had endocarditis and died of overwhelming sepsis and multi-organ failure at 4 months post-operatively. The second death involved a 76-year old man with bioprosthetic AVR who died of metastatic lymphoma 6 years postoperatively. The third death occurred in a 59-year old man who underwent AVR with mechanical prosthesis and died 2 years post-operatively of unknown cause; his autopsy report was not available for review.

The 10-year survival rate in our study was 97 ± 1%. The freedom from AVR was 84%, 63%, 51%, and 20% at 1, 3, 5, and 10 years respectively. The freedom from AVR varied by age at presentation ($P = .001$) and study group at the time of presentation ($P = .002$), Figure 2.

Multivariable analysis showed that older age (HR 5.22; CI 3.10 to 6.64, for every decade increase in age) and the presence of severe stenosis and/or regurgitation at the time of presentation (HR 1.32; CI 1.05 to 3.16) were risk factors for AVR, Table 3. Importantly, the mean time to AVR varied by the number of risk factors. Patients who have both risk factors (Age >50 years and severe stenosis and/or regurgitation) underwent AVR at 1.4 ± 0.6 years versus 5.3 ± 2.4 years in those without risk factors, $P < .0001$ (Figure 3).

Discussion

Aortic valve disease is present in approximately 2% of patients between 65 and 75 years of age; BAV accounts for a significant proportion of the patients requiring surgery.[5,16,17] There is a paucity of data describing the natural history of MAVD, and available data are derived from populations of BAV and SDAVD.[11,12,18] BAV is often associated with early calcification resulting in rapid progression of disease and as a result, its natural history differs significantly from that of SDAVD.[3,19] The natural history data on MAVD in the BAV population is needed to help make evidence-based recommendations.

The freedom from AVR in our cohort was 84%, 63%, and 38% at 1, 3, and 6 years respectively. A recently published prospective study of MAVD patients reported an event-free survival of 82%, 49%, and 19% at 1, 3, and 6 years, respectively.[11] Their event-free survival rate was slightly lower than noted in our series. Baseline characteristics of

Table 3. Predictors of Adverse Events

	Univariable Analysis		Multivariable Analysis	
	HR (95% CI)	*P* Value	HR (95% CI)	*P* Value
Age (per 10 year increase)	6.71 (2.61–8.33)	<.0001	5.22 (3.10–6.64)	<.0001
Study group ≥2*	3.61 (2.41–5.82)	.001	1.32 (1.05–3.16)	.04
Peak aortic velocity (per 1 m/s increase)	1.34 (1.07–3.51)	.01	1.29(0.68–1.78)	.25
Aortic valve area <1.0 cm^2	1.85(0.46–3.91)	.16		
Pressure half time (per 50 ms increase)	1.33 (0.86–2.32)	.42		
LVEDD (per 10 mm increase)	1.52 (0.66–3.89)	.42		
LVESD (per 10 mm increase)	1.53(1.26–2.21)	.003	1.31(0.72–1.98)	.15
LV mass index (per 10 g/m^2 increase)	1.63 (0.46–3.89)	.02	1.75 (0.53–4.74)	.41
Atrial fibrillation	1.55 (0.82–2.14)	.09	1.01(0.22–4.12)	.71
Diabetes	0.86 (0.46–1.19)	.092		
Hypertension	2.12 (1.53–3.94)	.03	2.06 (0.3–5.63)	.29
LV ejection fraction <55%	1.51 (0.63–2.44)	.26		
LA volume >35 mL/m^2	0.61(0.32–1.09)	.081		
Active smoking	1.55 (0.82–2.14)	.093		
Creatinine clearance <60 mL/min	1.38 (0.48–2.17)	.091		
Rheumatic heart disease	1.05 (0.32–2.14)	.24		
Coronary artery disease	0.41(0.11–0.83)	.007	0.81(0.33–1.73)	.37

CI, confidence interval; FU, follow up; HR, hazard ratio; LVEDD, left ventricular end-diastolic dimension; LVESD, left ventricular end-systolic dimension; LV, left ventricular.
Study group ≥2: Presence of severe aortic stenosis and/or regurgitation.
*Study group ≥2 vs. study group 1.
Note: separate multivariable models were used for peak aortic velocity and severity categories (study groups).

their cohort were similar to ours. However, they included patients with both BAV and SDAVD in their cohort. There was no subgroup analysis based on valve morphology. We believe that patients with BAV have a different pathologic entity and should be separately analyzed.

Rashedi and colleagues[12] reviewed a 524 asymptomatic patients with MAVD and reported that 349 (67%) of their patients underwent AVR during a mean follow-up period of 4 years. Their results were similar to ours but importantly they included patients with mild stenosis and mild regurgitation while our study analyzed only patients with more severe degrees of MAVD (≥ moderate AS and AR). Additional differences between the studies include their patients were older (mean age 66 years) and their study also combined patients with both BAV and SDAVD.

A cohort study examining cardiac outcomes in 642 BAV patients reported that 22% of their population underwent AVR over a mean duration of 9 years.[7] Our event rate seems higher in comparison with 67% of our cohort having AVR during a mean follow up period of 8.5 years. They studied a younger population (mean age 38 years) and 63% of the patients had trivial/mild AS or AR. Our patients were older and all had moderate or more valve disease at baseline.

Current practice guidelines recommend using symptoms, left ventricular function and dimensions as determinants for timing of AVR in patients with isolated AR, and symptoms and ventricular dysfunction to determine timing of AVR in patients with isolated AS.[9,10] In addition, peak aortic velocity has been shown to be a prognostic indicator for adverse outcomes in patients with isolated severe AS; patients with a peak velocity > 4.0 meters per second.[20–23] However, neither peak aortic velocity, nor ventricular function/dimension were associated with freedom from AVR in our study. We identified age at initial assessment and severe stenosis or severe regurgitation as risk factors for AVR. Older age at presentation was the strongest risk factor for AVR; freedom from AVR at 5 years was 38% in patients older than 50 years versus 66% in patients younger than 50 years. Calcification and degeneration begin as early as the third decade in patients with BAV, whereas in patients with trileaflet aortic valve it occurs around age 60 years.[2,3,19] This might explain why older age is a strong risk factor for AVR in our study and other studies of BAV patients.[7,8] In support of our findings, Tzemos and colleagues[7] reviewed 642 patients with BAV, and identified age and presence of moderate-to-severe AS or AR as predictors of adverse cardiovascular events. Age >50 years and the presence of valve degeneration were also identified as multivariable predictors of surgical intervention in another study of BAV patients.[8] The 10-year survival rate in our study was 97 ± 1%, which is comparable to survival in other BAV series and in the general population.[7]

Sixty-one patients (44%) had aortic aneurysm (ascending aorta diameter > 45 mm) at the time of presentation and 36 (39%) of them underwent

ascending aorta replacement at the time of AVR. Tzemos and colleagues identified aortic aneurysm in 28% of their cohort.[7] This apparent difference in prevalence of aortic aneurysm is mostly likely due to difference in the definition of aortic aneurysm in both studies. We defined aortic aneurysm as aortic dimension >45 mm while Tzemos[7] defined it as aortic dimension >50 mm. Both studies had similar incidence of dissection. A study by Davis et al reported 5.7% incidence of aortic dissection in a population of 70 patients with unoperated BAV and no significant valve disease. More than one third of their patients had an aortic dimension >55 mm; we excluded patients with aortic size >50 mm at initial presentation. Additionally, duration of follow up was significantly shorter in our study because most of our patients with aortic aneurysm underwent aorta replacement during time of AVR. We believe that these factors account for the difference in the incidence of aortic dissection.

Our study is unique from prior studies of MAVD[11,12] because we studied only patients with BAV instead of mixed cohort of congenital and SDAVD. Our study also differs from other studies of BAV patients because only patients with significant MAVD were included in our cohort.[7,8]

Study Limitations

First, our study is a retrospective chart review of patients followed at a single tertiary referral center. Nearly half of our population had aortic aneurysm and about a third underwent aorta replacement at the time of AVR. Although most of the patients that underwent AVR because of symptoms, it is possible that the presence of aortic aneurysm and need for aorta replacement might have influenced the timing of AVR. We excluded patients with incomplete follow-up (n = 14) and thus may have selected a group of patients with a more or less favorable profile. Lastly, our all-cause mortality rate may be underestimated because we relied of mortality data reported to our institution rather than social security indexing. We did try to control for this by excluding patients who have not followed up in our institution for more than 5 years.

Conclusions and Recommendations

We reviewed a large cohort of BAV with moderate/severe MAVD and identified older age and the presence of severe stenosis or regurgitation as risk factors for development NYHA III/IV symptoms and AVR. We recommend that age and disease severity should be incorporated in the risk assessment of BAV with MAVD. The patients with both risk factors should be followed every 6 months because almost half of them will require AVR within 1 year.

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Authors' Contributions

ACE: Study design, data collection, data analysis, initial drafting, critical review, final revision
HMC: data analysis, initial drafting, critical review, final revision
JTP: data collection, initial drafting, critical review, final revision
CAW: data analysis, initial drafting, critical review, final revision

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