Aortic Stenosis in bicuspid and tricuspid aortic valves are two different scenarios

Maria Celeste Carrero[1], Gerardo Masson[1], Ivan Constantin[1], Martin Ruano[1], Maria Mezzadra[1], Carla Pessio[1], Matias Lopez Rosetti[1], Gonzalo Diaz Babio[1], Facundo Veron[1], Sandra Diaz[1], Gustavo Stampone[1], and Pablo Stutzbach[1]

[1]Sanatorio Las Lomas SA

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Abstract

Patients with bicuspid aortic valve (BAV) represent a significant proportion of adults with severe aortic stenosis (AS) requiring aortic valve intervention (AVI). Evidence is discordant concerning progression of AS in BAV. The aim of this study was to compare baseline characteristics and the impact of the aortic valve phenotype on major cardiovascular outcomes. Methods: Retrospective observational study (consecutive AS in database, 2014-2016, third-level institution). Baseline characteristics were compared between BAV (n = 43) and tricuspid (TAV) (n = 159) patients. Primary end point was a composite of mortality and AVI. Survival analysis and logistic regression analysis was used to identify predictors of primary end-point. Results: 202 patients (72.2 ± 13.4 years, 63% men) were included. Patients with TAV were older, had more comorbidities and less aorta dilation. No significant differences were observed in the primary end point between the two valve phenotypes (34.8 vs. 40.8%; p=0.47, follow-up of 3.2 ± 1.6 years). In BAV group most of the events were at the expense of AVI (32.5 vs. 13.8%; p=0.001). The incidence of CV death was similar between both groups (4.8% vs. 12%, p=0.25). Non-CV mortality was higher in TAV group (16.8% vs 0%, p=0.001). Vmax and dimensionless index were independently associated with primary end point (p<0.001). Conclusions: Patients with AS have a high incidence of all-cause mortality and aortic valve intervention, regardless of valve phenotype. In particular, patients with BAV present different clinical characteristics with lower overall mortality and a more advanced AS when requiring aortic valve intervention.

Aortic Stenosis in bicuspid and tricuspid aortic valves are two different scenarios

María C. Carrero[a] Gerardo Masson[a,b], Iván Constantin[a] Martin Ruano[a,c], María D.C. Mezzadra[a,b], Carla Pessio [a], Matias Lopez Rosetti[a], Gonzalo Diaz Babio [a], Facundo Veron[a] , Sandra Díaz [a], Gustavo Stampone [a] y Pablo G Stutzbach[a].

*These authors contributed equally to the manuscript

a. Instituto Cardiovascular San Isidro (ICSI). Sanatorio Las Lomas, Buenos Aires, Argentina

b Servicio de Cardiología. Centro Médico Nordelta, Buenos Aires, Argentina

c. Servicio de Cardiología. Centro Médico Pilar, Buenos Aires, Argentina

Corresponding autor:

María Celeste Carrero*dra.celestecarrero@gmail.com*, von Wernicke 3031 - B1609JRA - San Isidro, Buenos Aires, Argentina. ICSI, Sanatorio Las Lomas. +54-11- 4129-5500.

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Abstract

Patients with bicuspid aortic valve (BAV) represent a significant proportion of adults with severe aortic stenosis (AS) requiring aortic valve intervention (AVI). Evidence is discordant concerning progression of AS in BAV. The aim of this study was to compare baseline characteristics and the impact of the aortic valve phenotype on major cardiovascular outcomes.

Methods: Retrospective observational study (consecutive AS in database, 2014-2016, third-level institution). Baseline characteristics were compared between BAV (n = 43) and tricuspid (TAV) (n = 159) patients. Primary end point was a composite of mortality and AVI. Survival analysis and logistic regression analysis was used to identify predictors of primary end-point.

Results: 202 patients (72.2 ± 13.4 years, 63% men) were included. Patients with TAV were older, had more comorbidities and less aorta dilation. No significant differences were observed in the primary end point between the two valve phenotypes (34.8 vs. 40.8%; p=0.47, follow-up of 3.2 ± 1.6 years). In BAV group most of the events were at the expense of AVI (32.5 vs. 13.8%; p=0.001). The incidence of CV death was similar between both groups (4.8% vs. 12%, p=0.25). Non-CV mortality was higher in TAV group (16.8% vs 0%, p=0.001). Vmax and dimensionless index were independently associated with primary end point (p<0.001).

Conclusions: Patients with AS have a high incidence of all-cause mortality and aortic valve intervention, regardless of valve phenotype. In particular, patients with BAV present different clinical and echocardiographic characteristics, with lower overall mortality and a more advanced AS when requiring aortic valve intervention.

Key Words: Bicuspid aortic valve, aortic stenosis, degenerative aortic stenosis.

Abbreviations

AS aortic stenosis

AVA aortic valve area

AVR aortic valve replacement

BAV bicuspid aortic valve

BSA body surface area

IQR interquartile range

TAV tricuspid aortic valve

TAVR transcatheter aortic valve replacement

Vmax maximum Doppler velocity

Introduction

Bicuspid aortic valve (BAV) is the most common congenital heart defect, affecting 1-2% of the population worldwide. Aortic valve dysfunction due to calcific aortic valve stenosis (AS) is the most common complication. Patients with BAV represent a significant proportion of adults with severe aortic stenosis (AS) requiring aortic valve replacement.[1]

Even though BAV is a frequent disease, few longitudinal data are available on asymptomatic patients with AS compared to patients with tricuspid aortic valve (TAV). [2,3] The progression of AS in both phenotypes shares a common disease process of inflammation, calcium deposition, and ossification, however, patient charachteristics and evolution have differences that should be evaluated.[4–7] Previous studies have shown that AS severity progress slowly over time in patients with BAV, but they have included young adults with BAV, most of them without significant aortic valve dysfunction.[8–10] But according to recent evidence, it seems possible that when calcification proccess begins, patients with BAV will show a higher rate of progression

and of aortic valve intervention requirement. [2,3,11] This discordance reflects the need of further research on this topic.

To answer these uncertainties, we conducted a retrospective cohort study comparing patients with AS according valve phenotype (BAV vs. TAV). We assessed baseline clinical and echocardiographic charachteristics. We aimed to study the impact of the aortic valve phenotype (i.e. BAV vs. TAV) on major cardiovascular outcomes.

Methods

Study population

A retrospective observational study was conducted at a tertiary academic centre in Buenos Aires, Argentina. We included all consecutive cases of AS identified on our echocardiography database from August 2014 to January 2016. We included all patients that were at least 18 years old, had AS defined by a peak aortic jet velocity (Vpeak) >2m/s and were followed-up by the Structural Heart Disease Group. Patients with a previous intervention on the aortic or mitral valve or pregnant were excluded.

We collected clinical data including age, sex, height, weight, body surface area (BSA), systolic and diastolic blood pressures, heart rate, hypertension, dyslipidaemia, diabetes, coronary artery disease, medications, and history of smoking, metabolic syndrome,vascular disease and abdominal aortic aneurysm.

Doppler echocardiography data

All Doppler echocardiography exams were performed with a Vivid S5 (GE® Vingmed Ultrasound, Israel) and a Vivid T8 (GE® Medical Systems, China) ultrasound system. Echocardiographic data was collected and analysed according to the American Society of Echocardiography and European Association for Cardiovascular Imaging guidelines by 5 experienced certified cardiologists (cardiac imaging specialists, Level III). Anonymous electronic recordings were analysed according to current echocardiographic recommendations. [12–14]

Aortic valve phenotype was assessed in the parasternal short-axis view. BAV was classified according to Schaefer et al as: I, fusion of coronary leaflets, II, fusion of right coronary and non-coronary leaflets and III: fusion of non-coronary and left coronary leaflets.[15]

Left ventricular outflow tract (LVOT) diameter was measured at the insertion of the leaflets in a zoom of the parasternal long-axis view and used to calculate the LVOT area. Stroke volume was obtained by multiplying the LVOT area by the velocity time integral measured by pulsed wave Doppler in the LVOT. Stroke volumen was indexed to BSA to obtain stroke volume index. The transvalvular flow rate was calculated by dividing the stroke volume by the left ventricular ejection time. LVEF was calculated with Simpson's biplane method.

AS haemodynamic severity was assessed with the following parameters: dimensionless index (ratio of the VTI of the LVOT flow on the VTI of the aortic valve flow), mean gradient (modified Bernoulli equation), maximum Doppler velocity (Vmax, with continuous wave Doppler) and aortic valve area (AVA, calculated with continuity equation). AS severity was categorised based on fulfilment of at least 2 criteria. into mild AS (AVA >1.5cm^2, Vmax <3.0m/s, mean gradient <20mmHg), moderate AS (AVA 1-1.5cm^2, Vmax 3.0-3.9m/s, mean gradient 20-39mmHg) and severe AS (AVA <1cm^2, Vmax [?]4.0m/s, mean gradient [?]40mmHg, dimensionless index [?] 0,25).[14]

All patients underwent baseline TTE and follow-up imaging studies according medical advise. Outcomes including aortic valve replacement (AVR), transcatheter aortic valve replacement (TAVR) all-cause mortality and cardiovascular mortality were collected until 20 March 2020.

AVR was defined as the need for mechanical (surgical or transcatheter replacement) treatment due to severe symptomatic AVS according current guidelines, including an estimated aortic valve area <0.9 cm^2. The standard of practice at our institution is to intervene on severe AS primarily on the basis of cardiovascular symptoms or ventricular dysfunction, based on current recommendations. In asymptomatic patients, referral

for surgery was made according to international guidelines: dilated aortic sinus or ascending aorta >50 mm in BAV or left ventricle ejection fraction <50%. [14]

All procedures followed the principles of the Declaration of Helsinki and good clinical practice regulations.

Study endpoints

The primary endpoint was the occurrence of the composite of aortic valve intervention (including AVR or TAVR) or all-cause mortality between baseline and last follow-up. The secondary endpoints were the occurrence of cardiovascular mortality and AVR/TAVR between baseline and last follow-up.

Statistical Analysis

Continuous variables were expressed as mean +- standard deviation or as median interquartile range (IQR), as appropriate and categorical variables were expressed as n (%). Continuous variables were tested for normality of distribution with a Shapiro–Wilk test and comparisons between BAV and TAV patients were done with two-tailed Student's t test or a Fisher's exact test, as appropriate.

Univariate analysis of all parameters obtained during patient recruitment was carried out to predict the primary and secondary endpoints. Then a multivariate analysis was performed and the criteria for introducing variables were their clinical relevance and statistical significance in the univariate analysis. Survival was computed using the Kaplan–Meier method and was compared between groups using the two-sample logrank test.

Statistical analysis was performed with STATA. A P-value <0.05 was considered significant.

Results

Baseline characteristics

The baseline clinical characteristics of the 202 patients included (72.3 +- 13.4 years, 63% men) and Doppler echocardiography according to valve morphology are presented in Table 1. Of the 202 patients, 43 (21%) had BAV and 159 (79%) has TAV.

As expected, patients with TAV compared to those with BAV were older (76 +- 9 vs. 55 +- 11 year old, p <0.0001), had a higher prevalence of comorbidities, such as hypertension (83% vs. 47%, p <0.0001), obstructive peripheral vascular disease (19% vs. 2%, p = 0.01) and a history of coronary heart disease (29% vs. 7%, p = 0.01).

At baseline patients with BAV had higher Vmax (3.1 +- 0.9 vs 2.9 +- 0.7 m/s, p=0.03) and higher transvalvular mean gradients (27.1 +- 15.1 vs 21.5 +- 12.3 mmHg, p=0.05) than TAV patients, but with similar AVA (1.2 +- 0.3 vs. 1.2 +- 0.3, p=0.8), indexed AVA (0.66 +- 0.22 vs. 0.65 +- 0.21 cm^2, p=0.8) and similar AS severity grade. Among the 43 patients with BAV, 33 (77%) had a raphe.

Patients with BAV had larger absolut and height-indexed ascending aorta diameteres (3.78 +-0.52 vs. 3.47 +-0.55, p<0.001 and 2.18 +- 0.3 cm/m vs 2.06 +- 0.2 cm/m, p=0.05) than those with TAV. No differences in left ventricular geometry were observed between both groups.

Cardiovascular Events

The median follow-up duration was 3.2 years (IQR 2.2-4.8) and similar in both groups. During follow-up there were 80 (39.6%) primary events (all-cause mortality, n=41; AVR, n= 24, TAVR, n=11, Ross procedure=1 and Bentall and De Bono procedure= 3) with no significant differences in terms of occurrence of the composite primary end-point between both groups (34.8 vs. 40.8%; p=0.2). Overall estimated all-cause mortality and intervention-free survival was 59+-4% in TAV patients vs. 65+- 7% in BAV patients at 5 years (log rank test p = 0.24), Figure 1. However, in patients with BAV, most of the events were at the expense of aortic valve intervention (39% of BAV group required aortic valve intervention during follow-up vs 13.8% in TAV group, p = 0.0004), as seen in Figure 2. Patients with BAV were younger (58.2 +- 8.8 vs 78.7 +- 7.4, p<0.0001) and had higher maximum aortic transvalvular velocity (4.4+- 0.4 vs 3.6 +- 0.5,

p=0.03) and higher mean gradient (47.8 +- 8.8 vs 33.1 +- 6.1, p=0.05) at the time of developing symptoms and requiring valve intervention.

The incidence of CV death did not present significant differences between both groups (4.8% vs. 12%, p=0.25). Although the TAV group had a trend towards higher CV mortality, 5 of these deaths occurred in patients with an indication for an intervention that was not carried out (due to high frailty, dementia or patient refusal). Lastly, 16.3% of the TAV group died of non-CV causes vs none in the VAB group, which translates into higher overall mortality (p = 0.001).

Type of aortic valve intervention is shown in Figure 3. TAVR was more frequent in TAV group (p=0.01) and correction of valve and ascending aortic disease (Bentall and De Bono and Ross procedures) were more frequent in BAV patients (p=0.03).

Vmax and dimensionless index were independently associated with primary end point occurrence during follow-up in both groups. Age and coronary heart disease were significantly associated with a higher incidence of the primary end-point at follow-up (p <0.001) in TAV group, whereas in BAV group mean gradient was significantly associated with a higher incidence of the primary end-point (p <0.001).

Discussion

The current study assessed the association of valve morphology to patient comorbidities, clinical profile and outcomes in a retrospective cohort of patients with different degrees of AS. As expected, there were relevant clinical differences between BAV and TAV patients with AS. On one side, cardiovascular risk factors, coronary heart disease and perypheral vascular disease were more frequent in the TAV group, On the other side, aortic dilatation at the ascending aorta was more frequent in patients with BAV. There were no significant differences in terms of occurrence of the composite primary end-point between both groups, but with significative differences in the composition of this end point. While in the bicuspid group the majority of events were aortic valve interventions, in TAV group the most frequent event was non-cardiovascular death, indicating different clinical evolution.

Previous studies have reflected similar finding regarding comorbidities in TAV patients. It shows that our cohort is consistent with previous findings. We also found that associated aortopathy is more prevalent in BAV group and it is related to treatment management, as reflected in Figure 3. So, these two groups of patients differ not only in terms of cardiac, valvular, and aortic parameters on imaging but also in terms of therapeutic decision-making. Also, BAV group developed symtpoms and/or left ventricle dysfunction in more advanced stages of AS, which could be related to differences in coronary heart disease prevalence between both groups.

There are some studies that have reported that AS severity progress slowly over time, but they have included younger patients with BAV and AS. [8] [9] Yap et al found less progression in younger BAV patients with mild disease than in older TAV patients. [8] Indeed, our group has showed that the majority of patients with BAV (mean age 43+-14.9 years) without significant baseline aortic valve dysfunction did not progress during follow-up of 4 years. [16] Nevertheless, when we analyse evolution of patients with AS over 50 years, aortic valve intervention rate is high. In fact, Shen et al have recently reported that after adjusting for age and comorbidities, BAV was independently associated with faster AS progression and higher risk of AVR or death tan TAV.[3] The mean age of the patients with BAV included in their study was similar to our study (49 +- 12 years). So, congenital AS should not be conceived as a benign disease. As Namasivayam recenty stated, latest findings support the need to pay careful attention to these patients, no matter how young or otherwise healthy they may seem, as they are not only at risk of accelerated disease progression but also adverse outcomes, even over a relatively short follow-up period.[17]

Lastly, in relation to aortic valve intervention requirement during evolution, it should be emphasized that BAV patients required more complex and combined procedures on aortic valve and ascending aorta, such as Bentall and de Bono or Ross procedures more frequently tan TAV patients. Conversely, TAVR was the procedure performed in 45% of patients of the TAV group that had symptoms/left ventricle dysfunction,

reflecting contemporary management of patients with AS.

Limitations

This study is subject to the inherent bias of retrospective studies. Its size is also moderate and the number of BAV patients compared to TAV patients in our cohort is relatively low and thus, may have restricted the power of our study.

Conclusions

In conclusion, TAV and BAV asymptomatic patients with AS exhibit many differences. Patients with AS have a high incidence of all-cause mortality and aortic valve intervention, regardless of valve type. In particular, patients with BAV present different clinical and echocardiographic characteristics, with lower overall mortality and a more advanced AS when requiring aortic valve intervention. On the other side, patients with TAV have more frequently association with coronary artery disease and are symptomatic with earlier stages of AS. Besides, type of intervention is different between these two groups. In our cohort, we identified Vmax and dimensionless index as independent predictors of primary end-point in both groups, which led to identification of group with a higher risk of major events.

These findings support that cardiologists should pay careful attention to adult patients with BAV and AS who are not only at risk of accelerated disease progression, but also adverse outcomes, and that underlying valve morphology should be considered when managing patients with AS.

Author Contribution

Maria C. Carrero Concept/design, Data analysis/interpretation, Drafting article, Critical revision of article, Statistics.

Gerardo Masson Concept/design, Data analysis/interpretation, Drafting article, Critical revision of article, Statistics.

Ivan Constantin Concept/design, Data analysis/interpretation, Drafting article, Critical revision of article, Statistics.

Martin Ruano Concept/design and Data collection

Maria D.C. Mezzadra Concept/design and Data collection

Carla Pessio Concept/design and Data collection

Matias Lopez Rosetti Concept/design and Data collection

Facundo Veron Concept/design and Data collection

Sandra Diaz Concept/design and Data collection

Gonzalo Diaz Babio Concept/design and Data collection

Gustavo Stampone Concept/design and Data collection

Pablo G Stutzbach Concept/design, Approval of article, Statistics

Data availability Statement

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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Table 1 - Baseline characteristics of the patients with aortic stenosis according to valve phenotype (bicuspid aortic valve or tricuspid aortic valve).

	Total	**BAV**	**TAV**	**p-value**
	(n= 202)	**(n=43)**	**(n=159)**	
Age, y	72.2 ± 13.4	55.4 ± 11.7	76.8 ± 9.7	**<0.0001**
Male, n (%)	127 (62%)	31 (72%)	96 (62%)	0.15
Hypertension, n (%)	153 (75%)	20 (47%)	133 (83%)	**<0.0001**
Diabetes mellitus, n (%)	35 (17%)	3 (7%)	32 (20%)	0.16
Smoking, n (%)	21 (10%)	7 (16%)	14 (8.8%)	0.43
Dyslipidemia (%)	121 (60%)	20 (47%)	101 (63%)	0.13
Chronic Kidney disease (%)	11 (5%)	1 (2%)	10 (6%)	0.5
Statin therapy (%)	116 (57%)	18 (42%)	98 (62%)	**0.05**
Obstructive Perypheral vascular disease (%)	31 (15%)	1 (2%)	30 (19%)	**0.01**
Abdominal aortic aneurysm (%)	7 (3%)	1 (2%)	6 (4%)	0.5
CAD (%)	49 (24%)	3 (7%)	46 (29%)	**0.01**
Body Surface Area - Dubois (m^2)	1.91 ± 0.25	1.97 ± 0.24	1.89 ± 0.25	0.06
SBP (mmHg)	126.6 ± 13.9	125.4 ± 11.7	126.7 ± 14.4	0.60
DBP (mmHg)	77.7 ± 7.8	78.1 ± 8.4	77.3 ± 7.7	0.59

	Total	**BAV**	**TAV**	**p-value**
Doppler echocardiography data				
Baseline LVEF, %	61.3 ± 9.0	65.0 ± 7.5	60.4 ± 9.3	**0.003**
Baseline end diastolic left ventricle diameter (cm)	4.8 ± 0.6	5.0 ± 0.7	4.8 ± 0.6	0.11
Baseline end systolic left ventricle diameter (cm)	2.9 ± 0.6	3.0 ± 0.7	2.9 ± 0.6	0.64
Baseline Vmax (m/s)	2.9 ± 0.8	3.1 ± 0.9	2.9 ± 0.7	**0.03**
Baseline Maximum gradient (mmHg)	36.9 ± 21.2	42.7 ± 24.9	35.4 ± 20.7	**0.02**
Baseline MG (mmHg)	22.8 ± 13.4	27.0 ± 16.5	21.7 ± 12.3	**0.05**
Baseline AVA (cm^2)	1.2 ± 0.3	1.2 ± 0.3	1.2 ± 0.3	0.80
Baseline AVAi (cm^2/m^2)	0.6 ± 0.2	0.6 ± 0.2	0.6 ± 0.2	0.64
Baseline Dimensionless index	0.3 ± 0.1	0.3 ± 0.1	0.3 ± 0.1	0.31
Baseline AS haemodynamic severity				
Mild AS n (%)	90 (44%)	18 (42%)	72 (45%)	0.68
Moderate AS n (%)	52 (26%)	11 (26%)	41 (26%)	0.97
Severe AS n (%)	60 (30%)	14 (32%)	46 (29%)	0.86

Statistically significant P values are highlighted in bold.

AS, aortic stenosis; AVA, aortic valve area; AVAi, aortic valve area indexed by body surface area; BAV, bicuspid aortic valve; CAD, coronary artery disease; DBP, diastolic blood pressure; LVEF, left ventricular ejection fraction; MG, mean transvalvular gradient; SBP, systolic blood pressure; TAV, tricuspid aortic valve; Vmax, peak aortic jet velocity.

Figures Legends

Figure 1. Adjusted Kaplan–Meier curves censored at time of aortic valve intervention or all-cause death according to aortic valve phenotype (BAV vs. TAV).

Abbreviations: BAV bicuspid aortic valve, TAV tricuspid aortic valve.

Figure 2. Adjusted Kaplan–Meier curves censored at time of aortic valve intervention according to aortic valve phenotype (BAV vs. TAV).

Abbreviations: BAV bicuspid aortic valve, TAV tricuspid aortic valve.

Figure 3. Type of aortic valve intervention according to aortic valve phenotype (BAV vs. TAV)

Abbreviations: BAV bicuspid aortic valve, TAV tricuspid aortic valve.