

An Interventional Echocardiographic Screening Program for First-Degree Relatives of Patients with Bicuspid Aortic Valve: Is It Practical?

Kan CS^{1*}, Zailani NH¹, Zuki R², Bujang MA³, Soon SY¹, Jong YH¹

¹Department of Cardiothoracic Surgery, Sarawak Heart Center, Kota Samarahan, Sarawak, Malaysia

²Department of Cardiology, Sarawak Heart Center, Kota Samarahan, Sarawak, Malaysia

³Clinical Research Center, Sarawak General Hospital, Sarawak, Malaysia

*Corresponding author:

Chan Siang Kan,
Department of Cardiothoracic Surgery, Sarawak
Heart Center, Kota Samarahan, Sarawak,
Malaysia, E-mail:kanchansiang@gmail.com

Received: 26 Mar 2022

Accepted: 08 Apr 2022

Published: 14 Apr 2022

J Short Name: JCMI

Copyright:

©2022 Kan CS, This is an open access article distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution, and build upon your work non-commercially.

Citation:

Kan CS, An Interventional Echocardiographic Screening Program for First-Degree Relatives of Patients with Bicuspid Aortic Valve: Is It Practical?. J Clin Med Img. 2022; V6(6): 1-12

1. Abstract

1.1. Introduction

Bicuspid Aortic Valve (BAV) represents one of the most common congenital cardiac anomalies with a prevalence of 0.5-2% in the general population. Literature demonstrated that the prevalence of BAV among First-Degree Relatives (FDR) of those with diagnosed BAV ranges from 7.3% to 9.1%. BAV has diverse genetic etiologies that vary from complex inheritance in families to sporadic cases without any evidence of inheritance. This interventional study aims to identify potential subjects with BAV by screening the FDRs of patients with BAV, which allows early detection of aortic valvular dysfunction and aortic complications associated with BAV. In addition, we hope to explore the practicality of running a routine ECHO screening program for FDR of patients with BAV in a tertiary hospital setting by analyzing the outcomes. We identified a total of 51 patients who had undergone aortic valve surgery performed at Sarawak Heart Centre (previously Sarawak General Hospital) in the context of BAV disease from p 2002 to 2018. This study only recruited the FDR of patients with true bicuspid aortic valves. Interviews with BAV patients and their family members were conducted to obtain a detailed minimum three-generation family history. Standardized, complete two-dimensional and Doppler transthoracic echocardiograms (ECHO) were performed on all participants by a single expert echocardiographer with more than 20 years of experience.

1.2. Results

Fifty-one subjects with a mean age of 37.4 (± 14.9) years were recruited. Majority were females [27 (52.9%)], Chinese [35 (68%)] and non-smokers [44 (86.3%)]. The prevalence of newly diagnosed BAV in our cohort of FDR was 7.8% (4 out of 51 FDR). The average AV Max Velocity in the BAV group was higher than the TAV group by a mere 0.04 m/sec, and the difference was statistically significant [1.66 (± 0.97) m/sec vs. 1.26 (± 0.30) m/sec respectively, $p=0.05$]. Only 1 out of the four patients diagnosed with BAV in this screening program demonstrated mild aortic stenosis (AV Max Velocity = 3.1 m/sec and AV mean PG = 10 mmHg). Two out of the four patients with newly diagnosed BAV came from a family of the same proband or indexed patient. 2 out of 51 patients (without BAV) screened had demonstrated aortic root dilatation (aortic root diameter of more than 4.0 cm).

1.3. Conclusion

The prevalence of BAV is higher in FDR of BAV patients than in the general population. Therefore, echocardiographic screening of FDR is a practical, low-cost approach for identifying asymptomatic cases to allow intervention before complications arise. A routine ECHO screening program should be considered at the institutional level or even better at the national level. Future research on this screening program's long-term practicality and cost-effectiveness is needed to produce a well-structured and systematic ECHO screening program and validate the long-term benefit.

2. Introduction

2.1. Prevalence

A standard aortic valve possesses three leaflets - left, right, and non-coronary cusps. Bicuspid aortic valve (BAV) is a condition where, instead of typical three leaflets aortic valve in the normal heart, only two unequal-sized leaflets are present and indirectly create flow disturbance. A small percentage of malfunctioning congenitally abnormal aortic valves are unicuspid or possess a single commissure [1]. BAV is one of the most common congenital cardiac anomalies, with a prevalence of 0.5-2% in the general population [2]. In the general population, BAV is more prevalent in Men (1-2%) than women (0.5%) at a ratio of ~3:1 [3,4]. Approximately 3:1 suggesting the loss of genes on the X chromosome may predispose to BAV syndrome [5]. BAV is one of the most common congenital cardiac anomalies, prevalence 0.5-2% in general population [2]. In general population, BAV is more prevalent in Men (1-2%) than women (0.5%) at a ratio of ~3:1 suggesting the loss of genes on the X chromosome may predispose to BAV syndrome [3-5]. Carro A et al. demonstrated that the prevalence of BAV among the FDR screened was 7.3%, significantly higher than that reported in the general populations (0.5-1.0%) [6]. Generally, the prevalence of BAV among first-degree relatives (FDRs) of affected individuals is 9% to 21% [7,8]. Whereas Siu SC et al. found out that the prevalence of BAV stands nearly 10-fold higher in primary relatives of patients with BAV than in the general population [5]. FDR's chances of getting BAV in a family with 2 or more affected members was reported to be even higher at 28-37%. In contrast to families with inherited BAV disease, more than 80% of patients with BAV have no known affected relatives and are regarded as sporadic cases [9].

2.2. Anatomy & Pathology

In the early pathology studies, there were three crucial characteristics of BAV: inequality of cusp size, presence of central raphe or ridge in the center of the larger of the two cusps, and smooth cusp margins even in the diseased valves [10]. When a tricuspid aortic valve (TAV) has two cusps become fused due to rheumatic or other inflammatory processes, this is also called pseudobicuspid [11]. Post-inflammatory valves, cusp margins tend to be severely distorted and fused, resulting in the valve often having a central tri-radiate orifice. Some confusion may still be present. When doubt exists, histopathological examination (HPE) can help to distinguish between acquired or congenital BAV. The latter shows no valve tissue in the raphe, whereas post-inflammatory valves show evidence of previous valvitis [11,12]. Stenosis usually develops in BAV containing no redundant cusp tissue, and incompetence often in valves in which redundancy and prolapse are prominent [13]. In cases of BAV, the ordinarily thin aortic valve cusps often prematurely calcify, leading to valvular thickening and stenosis [14].

2.3. Genetic

BAV has highly variable phenotypic characteristics and diverse genetic etiologies ranging from complex inheritance in families to sporadic cases with no evidence of inheritance. Some subjects who transmit BAV to their offspring who are assumed to harbor causative genetic mutations may not manifest BAV clinically themselves or have other cardiovascular abnormalities. Linda Cripe et al. demonstrated high heritability in 50 probands with BAV, suggesting that the BAV determination is almost entirely genetic (Heritability (h²) of BAV and BAV +/- cardiovascular malformation were 89% and 75%, respectively) [15]. Growing evidence supports its familial predisposition with an autosomal dominant pattern of inheritance that occurs without syndromic features [2,16,17]. The inheritance pattern of BAV may also be autosomal dominant with incomplete penetrance or a Mendelian inheritance pattern [5,7,18]. By genome-wide scan of the available family members with polymorphic microsatellite markers and linkage analysis, BAV-susceptibility loci have been mapped on chromosomes 9q34-35, [19,20] 18q, 5q15-21 and 13q33-qter, and NOTCH1 (which is involved in the initial stages of valve formation involve multiple signaling molecules) [21]. Of these, the mutation in NOTCH1, a single-pass transmembrane receptor that functions in a highly-conserved pathway, plays critical roles in cell fate determination during organogenesis, were associated strongly with non-syndromic BAV in humans [19,22,23]. However, genetic testing for NOTCH1 mutations remains unclear for non-familial cases.

2.4. Classification of BAV

There are different variants of BAV morphology. Morphology determines the natural history, clinical presentation, and long-term prognosis. The "purely" BAV is composed of two cusps, morphologically and functionally [24]. Classification of BAV according to Schaefer: Type I Fusion between RCC and LCC (R-L) occurs most frequently (70%), followed by type II fusion of RCC and NCC (R-NC) (28%). LCC and NCC (Type III fusion) were rarely fused (1.4-2%) [25,26]. Type I (R-L) fusion is associated with additional congenital heart disease/cardiac malformation, for example, coarctation of the aorta (CoA), interrupted aortic arch, and hypoplastic left heart syndrome [5,25]. Type II (R-NC) cusp fusion is associated with atrioventricular valve (AV) dysfunction/ cuspal pathology [aortic regurgitation (AR) or aortic stenosis (AS)] and minor association with aortic root dilatation [25,27].

Sievers et al. also classified BAV into three significant types were identified: type 0 (no raphe), type 1 (one raphe), and type 2 (two raphes). [Figure 1] shows the schematic illustration of the valve phenotype according to Sievers' classification based on the raphes number and configuration. Type 0 has a 6% prevalence; type 1 is the most common phenotype with a prevalence of 89%, whereas type II has a prevalence of 5%. Type 0 can further be classified into

0-AP (anteroposterior) or 0-lat (Lateral) based on the configuration of cusps. In addition, type 1 is further categorized into subtypes: 1-LR for the fusion of the right and left coronary cusps (71%),

1-RN for the fusion of the right, and noncoronary cusps (15%) and 1-NL for the fusion of the noncoronary and left coronary cusps [24].

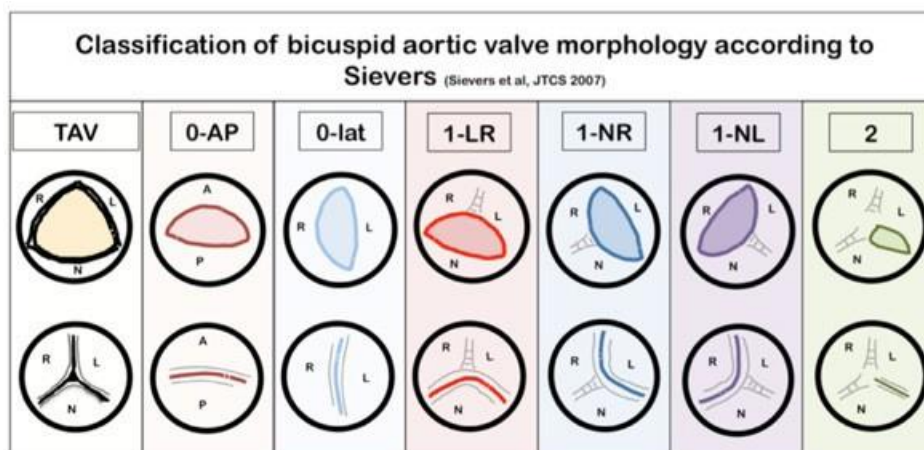


Figure 1: Schematic illustration of the valve phenotype of bicuspid aortic (BAV) according to sievers' classification based on the raphe number and configuration. (Sievers et al., JTCS 2007)²⁴

2.5. Association of BAV to Valvular dysfunction & Vascular Anomalies

BAV is a clinically heterogeneous disease with a high incidence (up to 35%) of surgery-related complications of the aortic valve and ascending aorta. The morbidity of BAV is extremely high already in younger adulthood, and 25% of affected people experience in the course of their life would develop severe aortic valvular dysfunction, ascending aortic aneurysm, cardiac mortality, hospital admission for heart failure, and aortic dissection or rupture [28]. A BAV occurs in 20-85% of cases of CoA [29-32]. The presence of an untreated, inadequately treated, or recurrent coarctation increases the likelihood of developing aortic stenosis, aortic regurgitation, or dissection of the aorta. BAV has also been reported in 27% of 52 cases of interrupted aortic arch suggesting a common developmental pathogenesis [33]. BAV accounts for 70-85% of pediatric patients' aortic stenosis (AS) and at least 50% of the stenotic aortic valve in adults [7,31]. Severe AS (1.5-71%) in BAV are very rigid because of fibrosis and heavy calcification but are not narrowed [12,34,35]. Aortic regurgitation (AR) (1.5-40%) is more complex than AS. The etiology of AR in patients with BAV usually results from prolapse of larger unequally sized cusps [13], an association of aortic dilatation [36], coarctation of the aorta, or infective endocarditis [10]. Disruption or dissolution of elastic tissue within the upper aortic ring (STJ) secondary to root dilatation leads to AR (50%), as this structure provides the main support for the valve cusps [36,37]. An autopsy study in adults suggested that about 30% of congenitally bicuspid aortic valves become stenotic, 40% become regurgitant, and the remainder function normally [34]. A large pathological review by Sabet and colleagues revealed that BAV disease results in a stenotic lesion in three-quarters of patients, insufficiency in 15%, and a mixed lesion in 10% [38].

Calcification and fibrosis are age-related BAV cusps that often prematurely calcify, leading to valvular thickening and stenosis [35]. Stenosis is rapid if the aortic cusps are asymmetrical or in the anteroposterior position [13]. Sclerosis of valve begins in the second decade whereas calcification is increasingly prominent from fourth decade onwards. Calcification in BAV is progressive and more diffuse than degenerative aortic valve disease [39]. In addition, patients with poor lipid profiles and those who smoke are also at an elevated risk of developing hemodynamically significant bicuspid aortic stenosis [40]. These are potentially modifiable risk factors amenable to treatment. Approximately half of the young adults with a BAV have aortic root dilatation [5,41]. Thus, potential candidates for resultant aortic regurgitation. Aortic root dilatation, a precursor of dissection, occurs in 50-60% of patients with a normally functioning BAV [41,42]. When the aortic root reaches 6cm, the aortic dissection risk increases 9-fold [43]. Average annual changes in ascending aorta in patients with BAV vary between 0.2 to 1.2 mm/year [44-48]. Several authors have suggested that ascending aortic dilatation is one component of the bicuspid syndrome inherited together with BAV. However, both conditions do not necessarily appear together in the same individual.

BAV is present in 1-13% of unselected cases of aortic dissection [13]. The presence of a BAV increases the risk of dissection 9-fold; this rises to 18-fold if there is a unicommissural aortic valve [43]. The actual incidence of aortic dissection is debated. Although the prevalence varies depending on the cohort studied, a pooled estimate of cases of dissection associated with BAV was 4% [49,50]. The reason for the high incidence of aortic dissection in BAV is unclear. The life-threatening complication of aortic dissection in the setting of BAV is rare in childhood or adolescence. Several authors have proposed ascending aortic dilatation is one component of

the bicuspid syndrome inherited together with BAV. The Tricuspid aortic valve usually has right coronary artery (RCA) dominance, and the left main stem averages 10 mm in length. With a BAV, left dominance is more common (29.0-56.8%), and in 90% of cases, the left main stem is less than 5mm in length [51]. It is vital to recognize that these associations may result in inadequate myocardial perfusion.

2.6. Diagnosis

In childhood, BAV disease is commonly asymptomatic. It is estimated that only 1 in 50 children have clinically significant valve disease by adolescence [52]. During clinical examination, the presence of an ejection clicks with or without an ejection systolic murmur over the aortic area lacks predictive accuracy as it may be present in tricuspid aortic stenosis [13]. Auscultatory findings include an ejection sound best heard at the apex. There may be associated murmurs of aortic stenosis, incompetence, or coarctation of the aorta when these lesions are present [5]. A single transthoracic echocardiogram (TTE) can reliably identify BAV and dilated aorta in most cases, with cardiac magnetic resonance imaging (MRI) able to define the anatomy when TTE imaging is suboptimal. In the current era, transthoracic echocardiograms usually confirm the diagnosis with sensitivities and specificities of 92% and 96% are reported for detecting BAV anatomy [5]. The positive predictive value (PPV) of a cross-sectional and Doppler echocardiography was found to be 93%.¹³ It can be difficult in patients with heavily calcified valves [53]. A meta-analysis by Hillebrand M et al. identified that TTE has a pooled sensitivity of 87.8% and a pooled specificity of 88.3% for BAV. This study showed that TTE yields almost ideal diagnostic accuracy when ideal investigators examine ideal patients [54].

Echocardiographic diagnosis demonstrates two cusps and two commissures during short-axis view. Other supportive features include cusp redundancy, eccentric valve closure, single coaptation line between cusps during diastole (closure of the aortic valve). The predictors of an inaccurate diagnosis of BAV include TTE in non-tertiary care settings, concomitant aortic aneurysm, and presence of severe aortic valve calcification [54]. A prominent raphe that can give the appearance of a third coaptation line produces a false-negative result. In contrast, a false-positive may be produced when one coaptation line of a TAV is unclear. Differentiating severe bicuspid aortic stenosis from severe unicuspid unicommissural aortic stenosis can also be difficult, but this is particularly vital when considering aortic valvuloplasty. To establish the diagnosis, the valve must be visualized in systole in the short-axis view. During diastole, the raphe can make the valve appear trileaflet [5]. Patient-related factors such as patients with obesity, chest wall deformities, narrow intercostal spaces, and the presence of pulmonary emphysema can produce suboptimal imaging quality during TTE [54]. Suboptimal imaging quality may also result from preventable investigator-related factors. These include suboptimal positioning

of patients, suboptimal angulation of ultrasound probe, incomplete assessment of all aortic valve cusp structures, incomplete use of all available views, imaging modalities, and software options [54].

2.7. Importance of Family Screening

As BAV and TAA are asymptomatic and exhibit only a few signs (if any) until either hemodynamical changes or aortic dissection occurs, earlier detection must be of vital importance. Eventually, a significant percentage of patients with BAV require cardiac intervention during their lifetimes, up to 40% during the fifth decade [55]. By definition, a screening Program is worth when the disease screened is asymptomatic and not readily identified during routine care, a screening test is available that can reliably identify the disease, an effective treatment is available for the disease, and lastly, early intervention can alter the outcome of the disease [56]. Because of familial clustering and aggregation of isolated BAV or BAV with vascular anomalies [17]. It might be appropriate to screen FDR. FDRs of BAV patients should be screened for the presence of BAV and dilation of the ascending aorta due to its significant association as FDR are also at risk of developing aortic complications without BAV [57]. Because many of these BAV-related complications can be predicted or prevented, the identification of BAV heritability supports the previous recommendation that echocardiographic screening of first-degree relatives of patients with BAV is warranted in order to identify persons with structural cardiac abnormalities [17]. (Table 1) summarizes the guidelines on family screening recommendations and surgical intervention for bicuspid aortic valve patients/bicuspid aortic-related aortopathy published for the last decade [58-65]. Despite well-established clinical guidelines for screening BAV and defining the timing of operative interventions to prevent complications outlined by WHO, family screening is still not widely practiced worldwide.

2.8. Objective

This study aims to explore the practicalities of running a routine echocardiographic screening program for FDR of patients with surgically diagnosed BAV. With a simple TTE, we sought to determine the prevalence of BAV in FDRs of patients with isolated BAV and the occurrence of aortic dilatation/familial BAV. This screening program will permit an early diagnosis of the valve and aortic anomaly in family members of BAV patients. Early detection of the problem allows intervention to occur before complications arise.

2.9. Study Design & Method

We identified a total of 55 patients with surgically confirmed BAV who had undergone aortic valve surgery performed at Sarawak Heart Center (previously Sarawak General Hospital until the year 2010) from the year 2002 to 2018. In all cases, the aortic valve morphology and the etiology of aortic stenosis/regurgitation were determined by surgical inspection of the valve intra-operatively. Therefore, this study only considers the true bicuspid aortic val-

ves diagnosed during surgery rather than an echocardiogram. We excluded patients with an aortic valve that exhibited two cusps but three sinuses with three interleaflet triangles indicating an acquired rather than the congenital bicuspid structure of the aortic valve (pseudobicuspid aortic valve). Out of the 55 patients identified, 15 of them died at the time of recruitment. In the remaining 40 patients, 19 were uncontactable for various reasons. Interviews with the patients were conducted by telephone. Finally, nine patients and their family members were agreeable to being recruited into this interventional project. Among the nine families, the member recruited for each family ranged from one to fifteen family members per family. The total number of first-degree relatives screened was 51 subjects (Table 2,3 and 5).

We obtained a detailed minimum three-generation family history via interviews with BAV patients and their family members. Of which, patient or their families expressing interest in the study were contacted by phone or during outpatient visits to request participation. Each proband's FDR willing to participate were enrolled into the study. For every newly affected individual identified, all of that individual's FDR was subsequently evaluated (Sequential Sampling). Sampling was extended to Second-degree relatives when medical history or study echocardiography identified additional affected individuals. Detailed physical examinations were performed on each subject. Anthropometric measurements (height

and weight) were taken, and body mass index was calculated in all subjects. Vital signs during the assessment were recorded and analysed. In addition, thorough cardiovascular examinations were carried out to identify the presence of systolic murmur and other signs that may suggest valvular dysfunction and related aortopathy.

Standardized, complete two-dimensional, and Doppler transthoracic echocardiograms were obtained on all participants. A single expert echocardiographer of more than 20 years' experience was allocated to perform and interpret all echocardiograms. It was then followed by detailed validation by a second expert echocardiographer. ECHO assessment includes aortic valve leaflets and morphology (assessed in both systole and diastole), other valves structures, AV Max Velocity, AV Mean PG, EF, and BAV Phenotypes (AP Configuration, Right-Left Configuration). Other supportive structures of BAV include cusp redundancy, valve thickening, and eccentric valve leaflet closure. Individuals who had aortic valves with two clearly defined cusps or with the characteristic systolic fish mouth appearance of the aortic valve cusps and 2 of 3 supportive features of BAV, including systolic doming or diastolic prolapse of the aortic valve cusps and eccentric valve leaflet closure, were considered to have a BAV. The diameter of the aortic root dimension was measured at end-diastolic in the parasternal long-axis view, leading edge to leading edge. Sinus of Valsalva and tubular ascending aorta was dilated if the diameter exceeded 40 mm.

Table 1: Guidelines on Family Screening Recommendations and Surgical Intervention for Bicuspid Aortic Valve Patients/Bicuspid Aortic-related Aortopathy

Guideline	Family Screening Recommendations	Ascending Aorta Threshold for Surgery
ACC/AHA Thoracic Aortic Disease, 2010 ⁵⁸	First-degree relatives of patients with a bicuspid aortic valve, premature onset of thoracic aortic disease with minimal risk factors, and/or a familial form of thoracic aortic aneurysm and dissection	>55 mm
European Society of Cardiology Valvular Heart Disease Guidelines, 2012 ⁵⁹	Screening of first-degree relatives of patients with bicuspid aortic valve with aortic root disease should be considered	55 mm (without aortic valve dysfunction) 45 mm (with aortic valve dysfunction)
Society of Thoracic Surgeons Clinical Practice Guidelines, 2013 ⁶⁰	First-degree relatives of patients with bicuspid aortic valve should undergo imaging of the aorta	> 50 mm
AHA/ACC Valvular Heart Disease Guidelines, 2014 ⁶¹	NA	>55 mm >50 mm in patients with BAV and family history of aortic dissection or progressive aortic expansion of > 5 mm per year >45 mm (with aortic valve dysfunction)
European Society of Cardiology Aortic Disease Guidelines, 2014 ⁶²	Screening of first-degree relatives of patients with bicuspid aortic valve may be considered	> 50 mm with risk factors
Canadian Cardiovascular Society Guidelines, 2014 ⁶³	Clinical screening and imaging screening are recommended	50-55 mm

ACC/AHA Surgery for Aortic Dilatation in Patients with BAV, 2016 ⁶⁴	NA	>55 mm >50 mm in patients with BAV and family history of aortic dissection or progressive aortic expansion of > 5 mm per year
The American Association for Thoracic Surgery (AATS) Consensus Guidelines, 2018 ⁶⁵	First-degree relatives of patients with BAV should undergo screening echocardiography	≥55 mm (without risk factors) ≥50 mm (with risk factors*) ≥45 mm (inpatients requiring concomitant cardiac surgery)

ACC, American College of Cardiology; AHA, American Heart Association; NA, not available

*root phenotype or predominant aortic insufficiency, uncontrolled hypertension, family history of aortic dissection/sudden death, or aortic growth >3 mm per year

Table 2: Demographic Characteristics of FDR of patients with BAV screened

Characteristics, n = 51	Number (°/0)	Mean (±SD)
Age (years)	Range 7 - 66	37.4
Gender		
Male	24 (47.1%)	
Female	27 (52.9%)	
Race		
Chinese	35 (68.6%)	
Malay	9 (17.6%)	
Iban	7 (13.7%)	
Body Mass Index (Kg/m ²)		25.2 (±6.9)
Smoking History		
Active Smoker	6 (11.7%)	
Ex-Smoker	1 (2.0%)	
Non-Smoker	44 (86.3%)	

BAV, bicuspid aortic valve. FDR, first-degree relative.

Table 3: Medical history and clinical presentation of FDR of patients with BAV screened

Parameters, n = 51	Incidence (°/0)	Mean (±SD)
Comorbid		
Hypertension	11 (21.6%)	
Diabetes melitus	2 (3.9%)	
Ischaemic heart disease	2 (3.9%)	
Obstructive sleep apnea	1 (2.0%)	
Bronchial asthma	1 (2.0%)	
Symptoms		
Syncope	0 (0.0%)	
Pre-syncope	5 (9.8%)	
Angina	1 (2.0%)	
Reduced effort tolerance	5 (9.8%)	
Orthopnea	0 (0.0%)	
Paroxysmal nocturnal dyspnea	0 (0.0%)	
Vital signs (at assessment)	Range	
Systolic blood pressure (mmHg)	81 - 170	133 (±23)
Diastolic blood pressure (mmHg)	52 - 108	81 (±12)
Pulse rate (beats/min)	50 - 95	74 (±12)
Respiratory rate (breaths/min)	12-20	15 (±3)
CVS Examination		
Systolic murmur	2 (3.9%)	

BAV, bicuspid aortic valve.; FDR, first-degree relative; CVS, cardiovascular system

Table 4: Incidence of BAV & its associated complications in FDR screened

Condition	Number of affected FDR/ total FDR screened	Incidence (%/0)
Bicuspid aortic valve	4/51	7.8
Abnormal aortic valve morphology	7/51	13.7
Aortic stenosis*	1/51	2
Aortic regurgitation)	2/51	3.9
Aortic dilatation (>4 cm)	2/51	3.9
Aortic dissection	0/51	0
Incidental findings		
Mitral regurgitation	7/51	13.7
Tricuspid regurgitation	2/51	3.9

BAV, bicuspid aortic valve; FDR, first-degree relative. #Abnormal aortic valve morphology includes BAV, quadricuspid aortic valve, thickened RCC and NCC. *BAV, mild aortic stenosis. ³TAV, moderate aortic regurgitation.

Table 5: Relevant Transthoracic Echocardiographic (TTE) Parameters

Parameters	Bicuspid Aortic Valve mean (SD)	Tricuspid Aortic Valve (N=47) mean (SD)	P value*
LV EF (%/0)	63.3 (5.92)	64.3 (5.73)	0.732
AV Max Velocity (m/sec)	1.66 (0.97)	1.26 (0.30)	0.05
AV mean PG (mmHg)	5.00 (3.34)	3.67 (1.35)	0.107
AVA (cm ²)	2.23 (0.84)	2.41 (0.62)	0.571
Aortic Root Diameter (mm)	2.60 (6.10)	26.7 (3.65)	0.770

N, number of persons examined with TTE. *One-way ANOVA test for quantitative data. TTE, transthoracic echocardiography. LV EF, left ventricular ejection fraction. AV, aortic valve. AVA, aortic valve area. PG, pressure gradient.

2.10. Statistical Analysis

Descriptive statistics were used to summarize the demographic characteristics of the participants according to the group. Data were reported as mean \pm standard deviation and median (minimum-maximum range) for ordinal or continuous variables and as numbers and percentages for categorical variables. The mean of continuous and categorical variables was compared using the One-way ANOVA test analysis. P values < 0.05 were considered statistically significant. All analyses were performed using Statistical Package for the Social Sciences (SPSS) version 23.

3. Results

Fifty-five patients with surgically diagnosed BAV underwent surgical aortic valve replacement (AVR), or AVR with concomitant Aortic surgery were identified from an institutional database. After a thorough screening of the patients, excluding those who had passed away, lost to follow-up, uncontactable by phone, and those who refused to participate in the screening program, only nine patients and their family members, were agreeable to be recruited into this interventional project. Among the nine families, the member recruited for each family ranged from one to fifteen individuals per family. The total number of first-degree relatives recruited and screened was 51 subjects. (Average 5 FDR per indexed patient). The age of the subjects screened ranges from 7 to 66 years old with a mean age of 37.4 (\pm 14.9) years, and an almost equal number of males and females [24 (47.1%) and 27 (52.9%)

respectively]. Sixty-eight percent (n=35) of the subjects were Chinese, followed by 17.6% of Malay (n=9) and, lastly, 13.7% of local Sarawak ethnic known as Iban (n=13.7%). The subjects had an average body mass index of 25.2 (\pm 6.9) Kg/m², and the majority of them were non-smokers (n=44, 86.3%). As many as 17 of them (33.3%) had some concurrent medical illnesses such as hypertension (n=11, 21.6%), type 2 diabetes mellitus (n=2, 3.9%), ischaemic heart disease (n=2, 3.9%), obstructive sleep apnea (n=1, 2%) as well as bronchial asthma (n=1, 2%). The common cardiovascular presentations BAV and its related complication in this population were consists of presyncope attack (n=5, 9.8%), angina pectoris (n=1, 2%) and reduction in effort tolerance (n=5, 9.8%). Most of the clinical symptoms above were present in patients later diagnosed with at least one valvular pathology.

During the screening, an assessment of vital signs was performed after the patient went through an interview session. Eighteen subjects had a systolic pressure of more than 140 mmHg during the assessment; the range of systolic and diastolic blood pressure was between 81 to 170 mmHg [Mean of 133 (\pm 23) mmHg] and 52 to 108 mmHg [Mean of 81 (\pm 12) mmHg] respectively. All subjects who participated in this screening program had regular pulse rate [range 50 to 95 beats per minute, mean 74 (\pm 12)] and respiratory rate during the assessment. Two patients were found to have systolic murmur during the cardiovascular examination.

The prevalence of newly diagnosed BAV in our cohort of FDR was

7.8% (4 out of 51 FDR). Two out of the four patients with newly diagnosed BAV were coming from a family of the same proband or indexed patient. Including the BAV, the screening program had identified seven subjects (13.7%) with abnormal aortic valve morphology such as BAV, quadricuspid aortic valve, thickened RCC, and NCC. One of the four patients with true BAV had started to show a significant degree of aortic stenosis. Two patients with tricuspid aortic valves also presented significant aortic regurgitation during the echocardiographic screening. Regarding aortic pathology, 2 out of 51 patients screened had demonstrated aortic root dilatation (aortic root diameter of more than 4.0 cm). On top of the aortic pathology and aortic valvular abnormality detected, this echocardiographic screening program also incidentally picked up seven subjects (13.7%) with at least moderate mitral regurgitation and two subjects (3.9%) with significant tricuspid regurgitation.

(Table 4) compares echocardiographic parameters between the subjects with BAV and TAV. The mean left ventricular ejection fraction (LV EF) of both groups appears to have no significant difference and was both normal - higher than 55% [63.3 (\pm 5.92) % vs. 64.3 (\pm 5.73) % respectively, $p=0.732$]. Three important parameters to assess the severity of aortic stenosis, particularly in the presence of BAV; aortic valve maximal velocity [AV Max Velocity (measured in meters/seconds or m/sec)], aortic valve mean pressure gradient [AV mean PG (measured in mmHg)] and aortic valve area [AVA (measured in cm^2)]. The average AV Max Velocity in the BAV group was higher than the TAV group by a mere 0.04 m/sec, and the difference was statistically significant [1.66 (\pm 0.97) m/sec vs. 1.26 (\pm 0.30) m/sec respectively, $p=0.05$]. This result appears to be similar for AV mean PG, where the mean PG across aortic valve in the BAV group was higher than that of the TAV group; however, the difference was not significant. [5.00 (\pm 3.34) vs 3.67 (\pm 1.35) respectively, $p=0.107$]. Only 1 out of the four patients diagnosed with BAV in this screening program demonstrated mild aortic stenosis (AV Max Velocity = 3.1 m/sec and AV mean PG = 10 mmHg). Both groups' mean aortic valve area showed little difference, although BAV had slightly smaller AVA than TAV. [BAV, 2.23 (\pm 0.84) cm^2 vs TAV, 2.41 (\pm 0.62) cm^2 , $p=0.571$]. The average aortic root diameter for the subjects was 26 (\pm 6.10) mm for BAV and 26.7 (\pm 3.65) mm for TAV groups, and there was no difference ($p=0.770$). This study identified two patients (2/51, 3.9%) with an aortic root diameter of > 40 mm without BAV.

4. Discussion

The prevalence of newly diagnosed BAV through family screening programs in our cohort was comparable to that of other studies (7.8% in our study compared to 9% to 21%) [7,8]. Aortic dilation prevalence in FDR with TAV was relatively lower than the figures found in the literature (3.9%). Those aortic dilations were mild and more frequently observed in patients with hypertension. BAV is associated with several long-term health risks such as progressive valvular dysfunction and associated aortopathy if not identi-

fied early and managed appropriately. Therefore, it is paramount to identify at-risk family members and facilitate family screening to reduce long-term morbidity and mortality. Over the last decade, various guidelines have been published and revised on the recommendation of family screening and surgical intervention for bicuspid aortic valve patients/bicuspid aortic-related aortopathy [58-65] (Table 1).

Nishimura et al. suggested that young patients (<30-year-old) with AVmeanPG > 30 mmHg should have annual ECHO, and those < 30 mmHg should have every other year ECHO. Those with Ascending aortic diameter > 40 mm regardless of age, should have baseline CT or MRI for adequate visualization and annual ECHO surveillance [61]. According to the AHA/ACC Guideline for the Management of Patients with Valvular Heart Disease published in 2016, surgical Intervention is advised for asymptomatic Ascending Aortic diameter >55mm. In contrast, the cut-off for Intervention was reduced to a diameter of 45 mm with severe AV stenosis and severe aortic insufficiency or positive family history of aortic dissection or aneurysmal rupture. Progressive aortic root dilatation > 5mm per year was also an indication for surgery. Additionally, women of childbearing age with BAV and aortic diameter > 45 mm should be advised against pregnancy, and athletes with aortic diameters > 45 mm should refrain from high-intensity sports [64]. Two years later, Borger MA et al. published an executive summary of the American Association for Thoracic Surgery consensus guidelines, the latest guideline on bicuspid aortic valve-related aortopathy.

Alice et al. conducted a study to examine the utility and cost of echocardiography screening of siblings of patients with BAV in clinical practice. They concluded that echo screening among siblings of those with BAV is effective and inexpensive. Therefore, it should be incorporated into clinical care [66]. Screening of FDR followed by serial regular surveillance imaging of individuals with identified BAV from the screening will help to prepare them for the complication that may arise in the future. In addition, the family members screened can also receive interventions to reduce cardiovascular risk factors and perhaps, emerging therapies targeted to prevent these complications.

All patients should be advised to quit smoking and have well-controlled blood pressure. A beta-blocker is suitable as first-line anti-hypertensive because of its noted wall shear-stress reduction effect. Be careful in cases of severe aortic stenosis, which may reduce coronary perfusion if diastolic blood pressure is too low. Angiotensin-converting enzyme inhibitors (ACEi) and angiotensin II receptor blockers (ARB) are suitable for afterload reduction [67]. No additional medical treatment was needed to be initiated in any of the subjects screened. Although both the 2010 ACC/AHA guideline and 2014 ESC Guideline on Aortic Diseases recommended the prescription of beta-blockade, stringent control of hypertension, with an angiotensin receptor blocker or an angioten-

sin-converting enzyme inhibitor as an alternative, this remains debatable [58,62].

Given the prevalence of BAV in the general population, the recommendations for health supervision and family screening should not fall only under the purview and responsibility of the cardiologist or cardiac surgeons. Primary care and family medicine physicians should have a working knowledge of the health risks associated with BAV and its complications and the relevant screening recommendations for affected individuals and at-risk family members. However, when should cardiac screening for BAV and aortic dilatation start and at what intervals after the initial assessment repeat echocardiographic screening should occur remains unknown. Therefore, two subjects with aortic root dilatation (aortic root diameter of more than 4 cm) will undergo yearly CT surveillance. In addition, seven patients with significant MR and two patients with TR will undergo annual ECHO surveillance to monitor disease progression.

The impact of this study may not be substantial, but family screening could be worthwhile. Most individuals screened are asymptomatic and will otherwise not visit a physician until the first symptoms of valvular dysfunction or aortic disease develop. Relatively inexpensive echocardiography could reliably identify the disease and prepare the individuals at risk for early detection, early diagnosis, and early intervention. However, there is uncertainty about the outcome in preventing aortic dissections. Not to forget the negative impact on patients' quality of life, stress, and cost of personal health insurance, which will be affected.

Because BAV formation and disease involve many genes, developing clinical genetic tests to identify patients at risk for BAV-related complications, such as aortic stenosis or TAAD, will require considerable time and research [9]. Therefore, early identification and careful surveillance of at-risk family members will likely remain primary clinical strategies until then.

5. Limitations

Limitation from this study includes small sample size. Sarawak, a state located in East-Malaysia Borneo island, is a huge state with less accessibility to the rural area. This has becoming a challenge for the participants to come for screening due to the travelling time and cost. The rise of COVID-19 pandemic also influenced the participation rate of this study. 2 positive results represent 5% incidence from the 41 participants. At least 232 subjects are required to achieve 95% confidence interval thus reflecting a larger population.

6. Conclusion

Both local and international data suggest a high prevalence and incidence of BAV among FDR patients with this common congenital cardiac abnormality. Based on these data, the authors strongly agree with the recommendation for an echocardiographic evaluation of all FDR of patients with BAV as class IIa in search of aortic

dilatation and BAV. The ultimate Endpoint – reduce the potential morbidity and mortality associated with BAV and its related aortopathy. A routine ECHO screening program should be considered at the institutional level or even better at the national level. In addition, all patients with BAV should be made aware of its familial pattern of inheritance. Finally, future research on this screening program's long-term practicality and cost-effectiveness is needed to produce a well-structured and systematic ECHO screening program and validate the long-term benefit.

7. Ethic Approval

This study complied with the ethical principles outlined in the Declaration of Helsinki and the Malaysian Good Clinical Practice Guideline. This research was registered under the National Institute of Health, Ministry of Health, Malaysia via the National Medical Research Registry (NMRR Number: NMRR-19-2429-46869).

8. Consent

Written informed consent and a complete medical history were obtained from all participants during the first interview session.

9. Authors' Contributions

C.S.K. was the principal investigator who did the literature search and wrote the report. N.H.Z. conducted the interviews and assessments. R.Z. performed all the screening echocardiography. B.M.A. assisted in data analysis. S.Y.S. and Y.H.J. both supervised the project.

10. Conflict of Interest

The authors declare that they have no financial conflict of interest concerning the content of this report.

11. Funding Sources

None

References

1. Roberts WC. The congenitally bicuspid aortic valve: a study of 85 autopsy cases. *The American journal of cardiology*. 1970; 26(1): 72-83.
2. Panayotova R, Hosmane S, Macnab A, Waterworth P. 136 Should familial screening be routinely offered to patients with bicuspid aortic valve disease? *Heart*. 2011; 97(Suppl 1): A76-77.
3. Brenner JI, Kuehl K. Hypoplastic left heart syndrome and other left heart disease: evolution of understanding from population-based analysis to molecular biology and back again—a brief overview. *Cardiology in the Young*. 2011; 21(S2): 23-27.
4. Tutar E, Ekici F, Atalay S, Nacar N. The prevalence of bicuspid aortic valve in newborns by echocardiographic screening. *American heart journal*. 2005; 150(3): 513-515.
5. Siu SC, Silversides CK. Bicuspid aortic valve disease. *Journal of the American College of Cardiology*. 2010; 55(25): 2789-2800.
6. Carro A, Teixeira G, Sanz M, Galuppo V, Galian L, Huget F, et al. Bicuspid aortic valve and aortic disease. The role of family screening. *European Heart Journal*. 2013; 1: 34(suppl_1).

7. Cripe L, Andelfinger G, Martin LJ, Shooner K, Benson DW. Bicuspid aortic valve is heritable. *Journal of the American College of Cardiology*. 2004; 44(1): 138-143.
8. Glick BN, Roberts WC. Congenitally bicuspid aortic valve in multiple family members. *The American journal of cardiology*. 1994; 73(5): 400-404.
9. Prakash SK, Bossé Y, Muehlschlegel JD, Michelena HI, Limongelli G, Della Corte A, et al. A roadmap to investigate the genetic basis of bicuspid aortic valve and its complications: insights from the International BAVCon (Bicuspid Aortic Valve Consortium). *Journal of the American College of Cardiology*. 2014; 64(8): 832-839.
10. Osler W. The bicuspid condition of the aortic valves. *Transactions of the Association of American Physicians*. 1886; 1: 185-192.
11. Lewis T. Observation relating to subacute infective endocarditis. *Heart*. 1923; 10: 21-29.
12. Pomerance A. Pathogenesis of aortic stenosis and its relation to age. *British heart journal*. 1972; 34(6): 569.
13. Ward C. Clinical significance of the bicuspid aortic valve. *Heart*. 2000; 83(1): 81-85.
14. Otto CM. Calcification of bicuspid aortic valves. *Heart*. 2002; 88(4): 321-322.
15. Cripe L, Andelfinger G, Martin LJ, Shooner K, Benson DW. Bicuspid aortic valve is heritable. *J Am Coll Cardiol*. 2004; 44: 138-143.
16. Calloway TJ, Martin LJ, Zhang X, Tandon A, Benson DW, Hinton RB, et al. Risk factors for aortic valve disease in bicuspid aortic valve: A family-based study. *American journal of medical genetics Part A*. 2011; 155(5): 1015-1020.
17. Huntington K, Hunter AG, Chan KL. A prospective study to assess the frequency of familial clustering of congenital bicuspid aortic valve. *Journal of the American College of Cardiology*. 1997; 30(7): 1809-1812.
18. Clementi M, Notari L, Borghi A, Tenconi R. Familial congenital bicuspid aortic valve: a disorder of uncertain inheritance. *American journal of medical genetics*. 1996; 62(4): 336-338.
19. Garg V, Muth AN, Ransom JF, Schluterman MK, Barnes R, King IN, et al. Mutations in NOTCH1 cause aortic valve disease. *Nature*. 2005; 437(7056): 270-274.
20. Martin LJ, Ramachandran V, Cripe LH, Hinton RB, Andelfinger G, Tabangin M, et al. Evidence in favor of linkage to human chromosomal regions 18q, 5q and 13q for bicuspid aortic valve and associated cardiovascular malformations. *Human genetics*. 2007; 121(2): 275-284.
21. Markwald RR, Norris RA, Moreno-Rodriguez R, Levine RA. Developmental basis of adult cardiovascular diseases: valvular heart diseases. *Annals of the New York Academy of Sciences*. 2010; 1188(1): 177-183.
22. McBride KL, Riley MF, Zender GA, Fitzgerald-Butt SM, Towbin JA, Belmont JW, et al. NOTCH1 mutations in individuals with left ventricular outflow tract malformations reduce ligand-induced signaling. *Human molecular genetics*. 2008; 17(18): 2886-2993.
23. Mohamed SA, Aherrahrou Z, Liptau H, Erasmi AW, Hagemann C, Wrobel S, et al. Novel missense mutations (p. T596M and p. P1797H) in NOTCH1 in patients with bicuspid aortic valve. *Biochemical and biophysical research communications*. 2006; 345(4): 1460-1465.
24. Sievers HH, Schmidtke C. A classification system for the bicuspid aortic valve from 304 surgical specimens. *The Journal of thoracic and cardiovascular surgery*. 2007; 133(5): 1226-1233.
25. Fernandes SM, Sanders SP, Khairy P, Jenkins KJ, Gauvreau K, Lang P, et al. Morphology of bicuspid aortic valve in children and adolescents. *Journal of the American College of Cardiology*. 2004; 44(8): 1648-1651.
26. Buchner S, Hulsmann M, Poschenrieder F, Hamer OW, Fellner C, Kobuch R, et al. Variable phenotypes of bicuspid aortic valve disease: classification by cardiovascular magnetic resonance. *Heart*. 2010; 96(15): 1233-1240.
27. Bonachea EM, Chang SW, Zender G, LaHaye S, Fitzgerald-Butt S, McBride KL, et al. Rare GATA5 sequence variants identified in individuals with bicuspid aortic valve. *Pediatric research*. 2014; 76(2): 211-216.
28. Vallely MP, Semsarian C, Bannon PG. Management of the ascending aorta in patients with bicuspid aortic valve disease. *Heart, Lung and Circulation*. 2008; 17(5): 357-363.
29. Stewart AB, Ahmed R, Travill CM, Newman CG. Coarctation of the aorta life and health 20-44 years after surgical repair. *Heart*. 1993; 69(1) :65-70.
30. Presbitero P, Demarie D, Villani M, Perinotto EA, Riva G, Orzan F, et al. Long term results (15-30 years) of surgical repair of aortic coarctation. *Heart*. 1987; 57(5): 462-467.
31. Mack G, Silberbach M. Aortic and pulmonary stenosis. *Pediatr Rev*. 2000; 21: 79-85.
32. Duran AC, Frescura C, Sans-Coma V, Angelini A, Basso C, Thiene G, et al. Bicuspid aortic valves in hearts with other congenital heart disease. *The Journal of heart valve disease*. 1995; 4(6): 581-590.
33. Roberts WC, Morrow AG, Braunwald E. Complete interruption of the aortic arch. *Circulation*. 1962; 26(1): 39-59.
34. Fenoglio Jr JJ, McAllister Jr HA, DeCastro CM, Davia JE, Cheitlin MD. Congenital bicuspid aortic valve after age 20. *The American journal of cardiology*. 1977; 39(2): 164-169.
35. Subramanian R, Olson LJ, Edwards WD. Surgical pathology of pure aortic stenosis: a study of 374 cases. In *Mayo Clinic Proceedings*. 1984; 59(10): 683-690.
36. Guiney TE, Davies MJ, Parker DJ, Leech GJ, Leatham AU. The aetiology and course of isolated severe aortic regurgitation: a clinical, pathological, and echocardiographic study. *Heart*. 1987; 58(4): 358-368.
37. American College of Cardiology Foundation, American Heart Association Task Force on Practice Guidelines, American Association for Thoracic Surgery, American College of Radiology, American Stroke Association, Society of Cardiovascular Anesthesiologists, Society for Cardiovascular Angiography and Interventions, Society of Interventional Radiology, Society of Thoracic Surgeons, Society for Vascular Medicine, North American Society for Cardiovascular

- Imaging. 2010 ACCF/AHA/AATS/ACR/ASA/SCA/SCAI/SIR/STS/SVM guidelines for the diagnosis and management of patients with thoracic aortic disease. *Journal of the American College of Cardiology*. 2010; 55(14): e127-129.
38. Sabet HY, Edwards WD, Tazelaar HD, Daly RC. Congenitally bicuspid aortic valves: a surgical pathology study of 542 cases (1991 through 1996) and a literature review of 2,715 additional cases. *In-Mayo Clinic Proceedings*. 1999; 74(1): 14-26.
 39. Mautner GC, Mautner SL, Cannon III RO, Hunsberger SA, Roberts WC. Clinical factors useful in predicting aortic valve structure in patients > 40 years of age with isolated valvular aortic stenosis. *The American journal of cardiology*. 1993; 72(2): 194-198.
 40. Chan KL, Ghani M, Woodend K, Burwash IG. Case-controlled study to assess risk factors for aortic stenosis in congenitally bicuspid aortic valve. *American Journal of Cardiology*. 2001; 88(6): 690-693.
 41. Nistri S, Sorbo MD, Marin M, Palisi M, Scognamiglio R, Thiene G, et al. Aortic root dilatation in young men with normally functioning bicuspid aortic valves. *Heart*. 1999; 82(1): 19-22.
 42. Pachulski RT, Weinberg AL, Chan KL. Aortic aneurysm in patients with functionally normal or minimally stenotic bicuspid aortic valve. *The American journal of cardiology*. 1991; 67(8): 781-782.
 43. Larson EW, Edwards WD. Risk factors for aortic dissection: a necropsy study of 161 cases. *The American journal of cardiology*. 1984; 53(6): 849-855.
 44. Beroukhi RS, Kruzick TL, Taylor AL, Gao D, Yetman AT. Progression of aortic dilation in children with a functionally normal bicuspid aortic valve. *The American journal of cardiology*. 2006; 98(6): 828-830.
 45. Thanassoulis G, Yip JW, Filion K, Jamorski M, Webb G, Siu SC, et al. Retrospective study to identify predictors of the presence and rapid progression of aortic dilatation in patients with bicuspid aortic valves. *Nature clinical practice Cardiovascular medicine*. 2008; 5(12): 821-828.
 46. Novaro GM, Griffin BP. Congenital bicuspid aortic valve and rate of ascending aortic dilatation. *The American journal of cardiology*. 2004; 4(93): 525-526.
 47. Ferencik M, Pape LA. Changes in size of ascending aorta and aortic valve function with time in patients with congenitally bicuspid aortic valves. *The American journal of cardiology*. 2003; 92(1): 43-46.
 48. La Canna G, Ficarra E, Tsagalau E, Nardi M, Morandini A, Chieffo A, et al. Progression rate of ascending aortic dilation in patients with normally functioning bicuspid and tricuspid aortic valves. *The American journal of cardiology*. 2006; 98(2): 249-253.
 49. Roberts CS, Roberts WC. Dissection of the aorta associated with congenital malformation of the aortic valve. *Journal of the American College of Cardiology*. 1991; 17(3): 712-716.
 50. Guntheroth WG. A critical review of the American College of Cardiology/American Heart Association practice guidelines on bicuspid aortic valve with dilated ascending aorta. *The American journal of cardiology*. 2008; 102(1): 107-110.
 51. Murphy ES, Rosch J, Rahimtoola SH. Frequency and significance of coronary arterial dominance in isolated aortic stenosis. *The American journal of cardiology*. 1977; 39(4): 505-509.
 52. Bonow RO, Carabello BA, Chatterjee K, De Leon AC, Faxon DP, Freed MD, et al. ACC/AHA 2006 guidelines for the management of patients with valvular heart disease: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (writing Committee to Revise the 1998 guidelines for the management of patients with valvular heart disease) developed in collaboration with the Society of Cardiovascular Anesthesiologists endorsed by the Society for Cardiovascular Angiography and Interventions and the Society of Thoracic Surgeons. *Journal of the American College of Cardiology*. 2006; 114(5): e84-231.
 53. Chan KL, Stinson WA, Veinot JP. Reliability of transthoracic echocardiography in the assessment of aortic valve morphology: pathological correlation in 178 patients. *The Canadian journal of cardiology*. 1999; 15(1): 48-52.
 54. Hillebrand M, Koschyk D, Ter Hark P, Schüler H, Rybczynski M, Berger J, et al. Diagnostic accuracy study of routine echocardiography for bicuspid aortic valve: a retrospective study and meta-analysis. *Cardiovascular diagnosis and therapy*. 2017; 7(4): 367-379.
 55. Baibars M, Darmoch F, Kabach A, Fanari Z, Alraies MC. Bicuspid Aortic Valve—Family Screening and Indications for Intervention. *Ochsner Journal*. 2018; 18(1): 9.
 56. InformedHealth.org [Internet]. Cologne, Germany: Institute for Quality and Efficiency in Health Care (IQWiG); 2006-. Benefits and risks of screening tests. 2013.
 57. Biner S, Rafique AM, Ray I, Cuk O, Siegel RJ, Tolstrup K, et al. Aortopathy is prevalent in relatives of bicuspid aortic valve patients. *Journal of the American College of Cardiology*. 2009; 53(24): 2288-2295.
 58. Hiratzka LF, Bakris GL, Beckman JA. American College of Cardiology Foundation, American Heart Association Task Force on Practice Guidelines, American Association for Thoracic Surgery, American College of Radiology, American Stroke Association, Society of Cardiovascular Anesthesiologists, Society for Cardiovascular Angiography and Interventions, Society of Interventional Radiology, Society of Thoracic Surgeons, Society for Vascular Medicine, North American Society for Cardiovascular Imaging. 2010 ACCF/AHA/AATS/ACR/ASA/SCA/SCAI/SIR/STS/SVM guidelines for the diagnosis and management of patients with thoracic aortic disease. *Journal of the American College of Cardiology*. 2010; 121(13): e266-369.
 59. Vahanian A, Alfieri O, Andreotti F. Guidelines on the management of valvular heart disease (version 2012). *Eur Heart J*. 2012; 33(19): 2451-2496.
 60. Svenson LG, Adams DH, Bonow RO, Kouchoukos NT, Miller DC, O'Gara PT, et al. Aortic valve and ascending aorta guidelines for management and quality measures: executive summary. *Ann Thorac Surg*. 2013; 95: 1491-1505.
 61. Nishimura RA, Otto CM, Bonow RO, Carabello BA, Erwin JP, Guyton RA, et al. 2014 AHA/ACC guideline for the management of patients with valvular heart disease: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *Journal of the American College of Cardiology*. 2014; 129(23): 2440-2492.

62. Erbel R, Aboyans V, Boileau C, Bossone E, Bartolomeo RD, Eggebrecht H, et al. 2014 ESC Guidelines on the diagnosis and treatment of aortic diseases: document covering acute and chronic aortic diseases of the thoracic and abdominal aorta of the adult The Task Force for the Diagnosis and Treatment of Aortic Diseases of the European Society of Cardiology (ESC). *European heart journal*. 2014; 35(41): 2873-2926.
63. Boodhwani M, Andelfinger G, Leipsic J, Lindsay T, McMurtry MS, Therrien J, et al. Canadian Cardiovascular Society position statement on the management of thoracic aortic disease. *Canadian Journal of Cardiology*. 2014; 30(6): 577-589.
64. 2010 ACCF/AHA/AATS/ACR/ASA/SCA/SCAI/SIR/STS/SVM GUIDELINES FOR THE DIAGNOSIS AND MANAGEMENT OF PATIENTS WITH THORACIC AORTIC DISEASE REPRESENTATIVE MEMBERS*, Hiratzka LF, Creager MA, Isselbacher EM, Svensson LG, 2014 AHA/ACC Guideline for the Management of Patients With Valvular Heart Disease Representative Members*, Nishimura RA, Bonow RO, Guyton RA, Sundt III TM, ACC/AHA Task Force Members. Surgery for aortic dilatation in patients with bicuspid aortic valves: a statement of clarification from the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *Circulation*. 2016; 133(7): 680-686.
65. Borger MA, Fedak PW, Stephens EH, Gleason TG, Girdauskas E, Ikonomidis JS, et al. The American Association for Thoracic Surgery consensus guidelines on bicuspid aortic valve–related aortopathy: executive summary. *The Journal of thoracic and cardiovascular surgery*. 2018; 156(2): 473-480.
66. Hales AR, Mahle WT. Echocardiography screening of siblings of children with bicuspid aortic valve. *Pediatrics*. 2014; 133(5): e1212-1217.
67. Verma S, Siu SC. Aortic dilatation in patients with bicuspid aortic valve. *N Engl J Med*. 2014; 370(20): 1920-1929.