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AATS Consensus Guidelines on Bicuspid Aortic Valve-Related Aortopathy: Full Online Only Version

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Abstract

Bicuspid aortic valve (BAV) disease is the most common congenital cardiac disorder, being present in 1-2% of the general population. Associated aortopathy is a common finding in patients with BAV disease, with thoracic aortic dilation noted in approximately 40% of patients in referral centers. Several previous consensus statements and guidelines have addressed the management of BAV-associated aortopathy, but none focused entirely on this disease process. The current guidelines cover all major aspects of BAV-aortopathy including natural history, phenotypic expression, histology and molecular pathomechanisms, imaging, indications for surgery, surveillance and follow up, and recommendations for future research. It is intended to provide clinicians with a current and comprehensive review of BAV-aortopathy and to guide the daily management of these complex patients.

1 **Outline:**

2

3   1. Introduction

4   2. Epidemiology and Natural History

5   3. Patient Phenotypes

6   4. Histopathology and Molecular Mechanisms of BAV Aortopathy

7   5. Diagnostic Modalities

8   6. Indications for Surgery

9   7. Surgical Follow-up, Medical Management / Watchful Waiting, Family Screening

10   8. Knowledge Gaps and Future Research

11

12

13

1   **1. Introduction**

2   Bicuspid aortic valve (BAV) disease is the most common congenital cardiac

3   disorder, being present in 1-2% of the general population. [1] Associated aortopathy is a

4   common finding in patients with BAV disease, with thoracic aortic dilation noted in

5   approximately 40% of patients in referral centers. [2] The risk of acute aortic emergencies,

6   most commonly aortic dissection, is higher in BAV patients than in the general

7   population. [3] Optimal timing of surgical intervention – in order to avoid aortic

8   emergencies – is defined as that time point when the risk of conservative management

9   exceeds the risk of surgery. Precise determination of this time point is difficult, however,

10   and depends on several factors including patient age, risk factors, comorbidities, family

11   history, and presence or absence of significant aortic valvular disease.

12   Historically, aortopathy observed in patients with BAV disease was thought to be

13   no different than that associated with tricuspid aortic valve (TAV) disease. That is, aortic

14   dilation was thought to be due to turbulent blood flow downstream from a stenotic aortic

15   valve. In the 1990s and 2000s, however, several observations and studies led

16   investigators to think that a strong genetic role contributed to BAV-associated aortopathy

17   and that the risk of acute aortic complications was substantially increased in this patient

18   population. [4] Such hypotheses led to recommendations for a more aggressive surgical

19   approach to this disease, with some suggesting that BAV-aortopathy was roughly

20   equivalent to Marfan syndrome. [5] Subsequent studies and observations have led to a

21   middle ground, however, suggesting that hemodynamic and genetic components play

22   varying roles in different subgroups of BAV patients [6] and that the risk of aortic

23   emergencies is not as high as previously thought in this patient population. [7, 8]

1   Determination of the cause of BAV-aortopathy is important because of the therapeutic

2   implications for patients with isolated aneurysmal dilation of the aorta and in those

3   undergoing aortic valve surgery for BAV disease.

4   Several previous documents have addressed the management of BAV-associated

5   aortopathy, with the first being a set of multi-societal guidelines published in 2010.[5] This

6   document made aggressive recommendations for the management of BAV-aortopathy,

7   grouping such patients in with Marfan and other connective tissue disorders. However,

8   multiple studies reported since that time have provided new insights into the

9   pathophysiology and mechanistic aspects of BAV-aortopathy. As such, a more

10   conservative set of recommendations was made in the more recently published valvular

11   heart disease guidelines by the American Heart Association and the American College of

12   Cardiology.[9] The marked difference in the positions of these two sets of guidelines

13   resulted in recent publication of a clarification statement.[10] The European Society of

14   Cardiology also published guidelines on the management of valvular heart disease in

15   2012[11] and aortic disease specifically in 2014.[12] Both of these documents contained

16   more conservative recommendations for BAV-aortopathy, in line with the 2014

17   ACC/AHA guidelines.

18   Of the above mentioned publications, none focused entirely on patients with

19   BAV-aortopathy. The current consensus statement therefore differs in that it covers all

20   major aspects of BAV-aortopathy including its natural history, phenotypic expression,

21   histology and molecular pathomechanisms, imaging, indications for surgery, surveillance

22   and follow up, and recommendations for future research. Such research will hopefully

1   lead to new insights into this common disease and the need for an update to the current

2   consensus statement in a few years.

3   BAV-aortopathy is a markedly heterogeneous entity. Dilation may occur in the

4   aortic root, the tubular ascending aorta, the proximal aortic arch, or any contiguous

5   combination of these three. [13] The current document uses the term "aortic root" to refer

6   to the proximal aorta extending from the nadir of the aortic annulus to the sinotubular

7   junction including the coronary ostia. For purposes of consistency, the term "tubular

8   aorta" (also known as supracoronary aorta) is used to describe the area between the

9   sinotubular junction and the takeoff of the brachiocephalic artery. The "aortic arch" refers

10 to the area extending from the brachiocephalic to the left subclavian artery. In addition,

11 the Sievers' classification[14] is used to describe BAV morphology (see. Figure 1).

12 Although several different classification systems have been used to describe BAV

13 morphology, the Sievers' system is the one that is used most commonly within the

14 cardiac surgery literature. It is clear, however, that a more comprehensive classification

15 system that takes into consideration BAV morphology, BAV pathology (i.e. stenosis,

16 insufficiency, or mixed), and location and extent of associated BAV-aortopathy is

17 required.
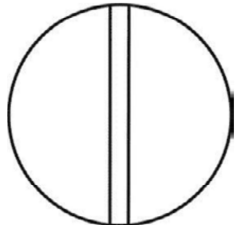
18   Because BAV-aortopathy is a relatively common disorder, decisions regarding its

19 therapeutic management must be made by cardiovascular clinicians on a regular basis.

20 Despite this, there is significant confusion within the cardiovascular community

21 regarding appropriate decision making in this patient population. [15] The confusion is not

22 surprising, however, given the above-described differences in recommendations made by

23 various societies and the shifting discussion on the etiology and pathophysiology of

1   BAV-aortopathy. The purpose of this consensus statement is to therefore provide

2   clinicians with a current and comprehensive review of all major aspects of BAV-

3   aortopathy and to serve as a guide in the daily management of these complex patients.

4

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main category: number of raphes	0 raphe - **Type 0**		1 raphe - **Type 1**			2 raphes - **Type 2**
	21 (7)		269 (88)			14 (5)
1. subcategory: spatial position of cusps in Type 0 and raphes in Types 1 and 2	lat 13 (4)	ap 7 (2)	L – R 216 (71)	R – N 45 (15)	N – L 8 (3)	L – R / R – N 14 (5)
2. subcategory: V A L V U L A R / F U N C T I O N — I	6 (2)	1 (0.3)	79 (26)	22 (7)	3 (1)	6 (2)
S	7 (2)	5 (2)	119 (39)	15 (5)	3 (1)	6 (2)
B (I + S)		1 (0.3)	15 (5)	7 (2)	2 (1)	2 (1)
No			3 (1)	1 (0.3)		

Figure 1. Sievers' classification system for BAV as viewed from the surgeon's side with the left coronary at left. The number of specimens is given as well as the percentage in parenthesis. The blackened lines represent raphe. The main category is based on the number of raphes, the first subcategory is based on spatial position, and second subcategory reflects valve function. Ap=anterior-posterior, lat=lateral, L=left coronary sinus, R=right coronary sinus, N=non-coronary sinus, I=insufficiency, S=stenosis, B=balanced valvular lesion, No=normal function. Used with permission from Sievers et al [14].

9

1

2. Epidemiology and Natural History

A. Epidemiology

Aortic enlargement and aneurysm formation, especially in the ascending aorta, are part and parcel of BAV disease—the so-called "bicuspid aortopathy."

I. Prevalence

The prevalence of BAV in the general population is known to be 1-2%.[1, 16-20] Hoffman reports prevalence in this range based on "unselected consecutive necropsies," which he considers the "standard" for detection.[1] This makes BAV the most common congenital anomaly affecting the human heart (if one excludes tiny muscular VSDs which close spontaneously by one year of age). It is said that BAV accounts for more morbidity and mortality than all other congenital heart lesions combined.[18, 21] This mortality may be incurred via multiple disease mechanisms: aortic stenosis, aortic insufficiency, or ascending aortic aneurysm and dissection. Males are thought to predominate, by a margin of about 2 to 1.[22] It has been shown in a single-center experience that 50% of all aortic valve operations performed on patients over 50 years are done for bicuspid aortic valve disease.[23] Likewise 50% of all valve operations performed in patients with coarctation of the aorta can be attributed to bicuspid aortic valve disease.[24]

Although these statistics are staggering, the true burden of BAV disease may yet be grossly underestimated, because bicuspid valve disease may remain asymptomatic in childhood and even into adulthood, so that no imaging studies are indicated or performed.[25]

1 *II. Likelihood of Aneurysm Development in Bicuspid Patients*

2   Multiple studies have quantified the risk over time of development of dilatation of

3 the ascending aorta (to a size of 4.0 to 4.5 cm) in patients with BAV. These studies

4 indicate that 20 to 30% of bicuspid patients develop aneurysmal enlargement during

5 follow-up of 9 to 25 years.[26-28] A recent review paper suggests that up to 84% of

6 bicuspid patients may ultimately develop an aneurysm (based on eight individual

7 studies). The risk of aneurysm development was found to be 80-fold higher than for the

8 general population.[28]

9 *III. Aneurysm Location*

10   Heterogeneity is the rule in terms of the segment of the ascending aorta involved

11 by bicuspid aneurysm.[26] The tubular ascending aorta is most commonly involved (60-

12 70% of bicuspid aneurysms), although all segments, including the aortic root and the

13 aortic arch, can be involved (see Figure 2.) There is evidence that the "root phenotype" of

14 BAV-aortopathy -- in which the predominant dilatation is at the level of the sinuses of

15 Valsalva -- represents a more malignant and rapidly progressive aortopathy (see Section

16 3.C).[29 30 31, 32]

17   The marked heterogeneity of BAV-associated aneurysm location is distinctly

18 different from other common types of ascending aortic aneurysms. Degenerative

19 aneurysms tend to start in the mid-ascending aorta and then progress distally and

20 proximally, while those associated with connective tissue disease are usually confined to

21 the aortic root. BAV morphology and pathology seem to play a role in determining where

22 the BAV-associated aneurysm is located (see Section 3).

23 *IV. Major Role in Causation of Aortic Dissection*

1   An important point to note is the large number of aortic dissections associated

2   with BAV-aortopathy. While only 5% or fewer of bicuspid patients will dissect their

3   aortas over a lifetime,[21] bicuspid valve disease affects 1 in every 50 to 100 human beings.

4   Thus, not only the better appreciated Marfan syndrome, but also BAV are important

5   causes of aortic dissection.[3] However, some recent studies have found substantially lower

6   rates of aortic dissection in bicuspid patients than previously determined, especially in

7   younger patients.[27, 33] For instance in a recent study by Itagaki et al. the rate of aortic

8   dissection in BAV patients 15 years after AVR was 0.55% and not significantly different

9   from tricuspid patients (0.41%).[7] However patients with Marfan syndrome had a

10   substantially higher rate of aortic dissection (5.5%) that was significantly greater than

11   BAV or TAV patients (p<0.001).

12   *V. Genetics*

13   Although there is a definite genetic component to bicuspid valve disease, the

14   precise patterns of inheritance have been elusive. Approximately 9-15% of first-order

15   family members also have bicuspid valve disease, with males and females equally

16   affected within those families.[34-36] These percentages are much higher than in the general

17   population (1-2%), demonstrating the influence of genetics in this disease. Missense

18   mutations in the NOTCH1 gene have been implicated in some bicuspid patients.[37-39] The

19   vital NOTCH signaling pathway, involved in differentiation of multiple organs (including

20   skeletal muscle, CNS, pancreas, and blood vessels) is highly evolutionarily conserved

21   (i.e. in humans, mice, and zebrafish).[40] High evolutionary conservation indicates critical

22   pathways whose aberration is likely to lead to significant or life-threatening disease.

23   NOTCH genes play an important role in familial bicuspid valve disease, but they are

1 found in only 4% of spontaneous cases.[41] The variety and complexity of inheritance of

2 BAV is under intense investigation but remains to be fully clarified.

3 *VI. Associated Lesions*

4   Many other lesions and syndromes are strongly associated with BAV (see Table

5 1). Associated anatomic lesions include aortic coarctation and patent ductus arteriosus.

6 Coarctation-mediated hypertension greatly increases the risk of aortic dissection.[42] In the

7 pre-surgical era, death from aortic dissection occurred in 19% of patients with BAV, but

8 in 50% of patients with concomitant BAV disease and coarctation.[43, 44] Aortic coarctation

9 accompanies BAV much more commonly in males (4:1) than in females.[42] Syndromes

10 associated with bicuspid valve disease include Turner's syndrome (monosomy X,

11 characterized by short stature, lymphedema of the hands and feet, and amenorrhea) and

12 William's syndrome (abnormal facial appearance, low nasal bridge, unusually cheerful

13 demeanor). In addition to those lesions described in Table 1, BAV patients are also

14 known to have an increased prevalence anterior mitral valve leaflet elongation and

15 prolapse. [45 46]

16

17 *B. Natural History*

18   BAV disease can cause morbidity and mortality either through the valve disease

19 (stenosis or insufficiency) or by ascending aortic aneurysm (leading to aortic dissection

20 or rarely, rupture). However, recent studies have demonstrated, in the modern era of

21 diagnosis and care, an overall survival for bicuspid patients identical to that of the normal

22 population.[26] As long as patients are followed regularly and surgery is offered in a timely

1 fashion, then the risk of catastrophic aortic events is low. However, some important

2 observations should be kept in mind when following BAV patients.

3 *I. Aortic Valve Dysfunction is not needed for Aortic Dissection to Occur*

4 It is important to recognize that neither aortic stenosis nor aortic insufficiency

5 needs to be present for aortic dissection to occur.[47] In BAV disease, valvular

6 complications—aortic stenosis or regurgitation—progress at their own independent rates,

7 different from the rate of progression of the bicuspid aneurysm. Thus, the lack of aortic

8 stenosis does not preclude aortic dissection from occurring. However, bicuspid patients

9 suffering concurrently from valvular disease (stenosis or insufficiency) are at increased

10 risk of rupture and dissection of the aorta.[48] Increasingly, evidence demonstrates

11 regurgitant BAVs having a more malignant phenotype than stenotic BAVs, with a much

12 higher risk of aortic dissection. [49] This topic will be discussed in more detail in Sections

13 3 and 6.

14 *II. More Malignant Behavior of Bicuspid Aorta*?

15 Many have thought of BAV-aortopathy as "Marfan syndrome light"—that is to

16 say, more severe than ordinary aortic aneurysm disease, but not quite as virulent as the

17 Marfanoid aorta. Despite the clinical impression that BAV-aortopathy is a malignant

18 actor, supportive concrete evidence has been elusive.

19 A study by Davies and colleagues looked for disparities in behavior between

20 ascending aortic aneurysm patients with and without BAV.[50] Patients with BAV

21 presented at a smaller aortic diameter (4.6 cm vs 4.9 cm for non-BAV patients). Also,

22 their aortas grew more rapidly than those of TAV patients: 1.9 mm/yr compared to 1.3

23 mm/yr.[50] A higher proportion of bicuspid patients required operative treatment of their

1 aortas (72.8% vs. 44.8%) at a significantly younger age (48.9 vs. 63.1 years).[50] However,

2 among unoperated patients, there was no detriment in survival for the bicuspid group who

3 actually did better than TAV patients (8.6% vs. 25.7% rate of rupture, dissection, or death

4 at 5 years of follow-up).[50] This likely reflects the substantially younger age at

5 presentation of the bicuspid group (49 vs. 64 years).[50] However, among the BAV group,

6 those patients with aortic stenosis in addition to the aneurysm had an increased risk of

7 aortic rupture, dissection, or death prior to operative repair when compared to patients

8 with a normally functioning bicuspid valve.[50] One possible limitation of the above data is

9 the fact that it comes from a thoracic aortic referral center, and therefore may not

10 accurately reflect the natural history of BAV aneurysms in the general population.

11   Other studies have also reported "mild" behavior with near normal long-term

12 survival and low overall growth rates for the bicuspid aorta, on the order of 0.4 to 0.6

13 mm/year, with no differences noted according to specific pattern of leaflet fusion.[29, 51]

14 These studies did not find a relationship between growth rate and original aortic size. The

15 discrepancies between these studies and the above study from Davies et al. have several

16 possible explanations. Firstly, these were studies derived from echocardiographic

17 databases and not from a thoracic aortic referral center, which may have implications on

18 patient selection bias. Secondly, the investigators may not have adequately imaged the

19 uppermost portion of the ascending aorta in some patients, since this is a known

20 limitation of echocardiography. Finally, the patients from the echocardiographic-based

21 studies initially presented with smaller aortic diameters (4.1 cm and 3.8 cm) than those in

22 the study from Davies et al (4.6 cm).

23 *III. Medical Therapy for Bicuspid Aortopathy*?

1 It is unclear whether any medical therapy is effective in preventing adverse events in

2 aortic aneurysms of any kind, even in the most thoroughly studied Marfan population.

3 Although B-blockers and angiotensin receptor blocking drugs are commonly applied to

4 "protect" the BAV aorta, supportive evidence is lacking.[52-54] Such agents should be

5 given, however, in patients with documented hypertension. Statins have recently been

6 shown to be ineffective, while other studies show a possible protective effect.[55]

7 *IV. Contemporary Clinical Outcomes*

8   Contemporary clinical outcomes for patients with BAV have been summarized in

9 a comprehensive table by Michelena and colleagues from the International BAV

10 Consortium (see Table 2).[28] Age at presentation, survival, and likelihood of heart failure,

11 aortic valve surgery, endocarditis, aneurysm formation, aneurysm surgery, and aortic

12 dissection are described for eight contemporary clinical studies. This Table demonstrates

13 excellent overall survival of bicuspid patients in community, population-based studies,

14 while outcomes are much poorer in referral center patients who have required aortic

15 valve replacement (AVR). Heart failure is particularly uncommon in BAV patients, and

16 aortic stenosis is a more common indication for surgery than aortic insufficiency. As

17 well, aneurysm formation (aortic diameter > 45 mm) occurs in 25 to 45% of patients over

18 prolonged periods of follow up, but aortic dissection is a rare event (~1%) outside of

19 tertiary referral center populations, where it is much more common (~10%).[28]

1
2 **Table 1.** Cardiovascular conditions associated with BAV disease.
3

Condition	Incidence of BAV
Coarctation of the aorta	50%
Turner syndrome	30%
Supravalvular aortic stenosis	30%
Sinus of Valsalva aneurysm	15-20%
Ventricular septal defect	30%
Shone complex	60-85%
Ascending aortic aneurysm	Common
Loeys-Dietz syndrome	2.5-17%
ACTA mutation familial thoracic aneurysm syndrome	3%
Anterior mitral leaflet prolongation/prolapse	Common[45, 46]

4 Modification of Braverman A. "BAV and Associated Conditions". Up-to-Date. 2016.

5 Graphic 83657 Version 1.0. www.uptodate.com .Wolters Kluwer.

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1
2 **Table 2.** Contemporary clinical outcomes in BAV patients.
3

Contemporary Clinical Outcomes BAV Studies*

Study Features, Clinical Outcomes	Michelena et al [26]	Tzemos et al [27]	Michelena et al [33]	Davies et al [50]†	Russo et [56]	Borger et al [57]‡	McKellar et al [58]	Girdauskas et al [30]§
Publication year	2008	2008	2011	2007	2002	2004	2010	2012
Clinical setting	Community, population-based	Tertiary referral center	Community, population-based	Tertiary referral center	Tertiary referral center	Tertiary referral center	Tertiary referral center	Tertiary referral center
Inclusion characteristics	Minimal BAV dysfunction	Any BAV dysfunction	Any BAV dysfunction	Any BAV dysfunction with aortic aneurysm (mean baseline diameter 4.6 mm)	Status post AVR	Status post AVR	Status post AVR	Status post isolated AVR with aortic aneurysm (mean baseline diameter 4.6 mm)
N	212	642	416	70	50	201	1286	153
Baseline age, y, mean±SD	32±20	35±16	35±21	49	51±12	56±15	58±14	54±11
Follow-up years, mean±SD	15±6	9±5	16±7	5	20±2	10±4	12±7	12±3
Survival	90% at 20 y	96% at 10 y	80% at 25 y	91% at 5 y	≈40% at 15 y	67% at 15 y	52% at 15 y	78% at 15 y
Heart failure	7% at 20 y	2%	–	–	–	–	–	–
Aortic valve surgery	24% at 20 y	21%	53% at 25 y	68%	–	–	–	–
Reason for aortic valve surgery	AS 67% AR 15%	AS 61% AR 27%	AS 61% AR 29%	–	–	–	–	–
Endocarditis	2%	2%	2%	–	4%	2%	–	–
Aneurysm formation (definition, mm)	39% (>40 mm)	45% (>35 mm)	26% at 25 y (≥45 mm)	–	–	9% (≥50 mm)	10% (≥50 mm)	3% (≥50 mm)
Aortic surgery (for aneurysm)	5% at 20 y	7%	9%	73%	6%	9%	1%	3%
Aortic dissection	0% at 20 y	1%	0.5% at 25 y	9%	10% at 20 y	0.5%	1% at 15 y	0%

4
5 AR indicates aortic regurgitation; AS, aortic stenosis; AVR, aortic valve replacement; BAV, bicuspid
6 aortic valve; and SD, standard deviation.
7 ↵* Outcomes reported as percentage only were not reported within Kaplan-Meier survival
8 analyses. Survival in the first 3 studies [26, 27, 33] was not different than that of the general population.
9 Survival in the McKellar study [58] was inferior to that of the general population, and the rest of the
10 studies were not compared with the general population.

1 ↵† This study compared BAV patients with aneurysms versus tricuspid aortic

2 valve patients with aneurysms. The incidence of aortic dissection was the same for both groups

3 with superior survival in BAV patients and both groups dissecting at similar aortic diameters.

4 ↵‡ This study suggested that patients with aortic dimension ≥45 mm at the time of AVR should have
5 the aorta concomitantly repaired; the basis of the current recommendations.
6 ↵§ This study included consecutive patients with isolated AVR performed for aortic stenosis only.
7 However, 21 patients with predominant dilatation of the root (mean diameter, 44 mm) and severe
8 aortic regurgitation who underwent AVR were followed in parallel for a mean of 10 years and 2 acute
9 dissections occurred.
10 (Reproduced with permission from Michelena et al [28])
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BAV and Ascending Aortic Aneurysms

Overall distribution (*n* = 224)

Normal	Supracoronary aneurysm	Marfanoid-type aneurysm	Tubular-type aneurysm
	63.8% (n = 143)	11.2% (n = 25)	25.0% (n = 56)
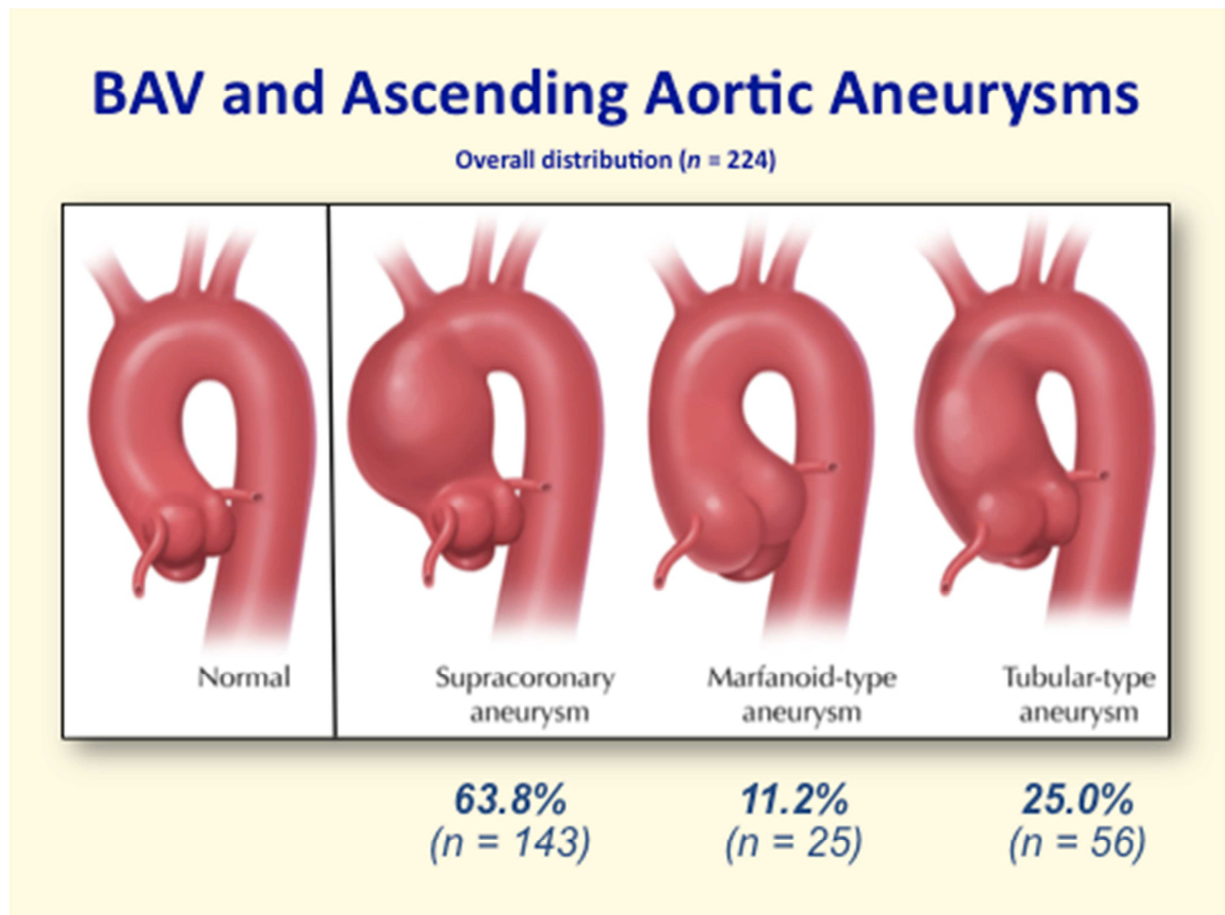
4
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6 **Figure 2.** Anatomic distribution of aortic aneurysms in patients with bicuspid aortic

7 valves. (Unpublished data, Aortic Institute at Yale-New Haven.) This data is similar to

8 that reported by Michelena et al.[26]

9

10

1   **3. Patient Phenotypes**

2   *A. Introduction*

3   Evidence of phenotypic heterogeneity of BAV-aortopathy has emerged in the

4   last decade from several observational studies and stimulated a critical re-appraisal of

5   literature and treatment recommendations. The hypothesis has been proposed that

6   different types of BAV-aortopathy (i.e., so-called aortic phenotypes) may be caused by

7   distinct pathogenetic mechanisms and therefore require individualized surgical

8   approaches.[59, 60] In particular, the two long-debated theories on BAV-aortopathy

9   pathogenesis, namely the genetic and the hemodynamic one, could both be plausible

10   inasmuch as different phenotypic forms might be subtended by different contributions of

11   both causative factors. Phenotypic heterogeneity of BAV-aortopathy may also explain to

12   some extent the inconsistencies in published natural history and follow-up studies,

13   especially regarding the risk of aortic events in BAV disease. Previous data from mixed

14   BAV cohorts resulted in a broad-spectrum of surgical treatment methods being

15   suggested, ranging from very conservative approaches to very aggressive

16   recommendations, usually extrapolated from guidelines for management of patients with

17   connective tissue disorders (e.g., Marfan syndrome).[5]

18   Although the evidence of BAV-aortopathy heterogeneity has gained increasing

19   recognition in the last decade, data on individual aortic phenotypes are still scarce. The

20   majority of published natural history / follow-up studies contain mixed BAV cohorts and

21   include different stages of BAV disease. A better understanding of the interaction

22   between morphologic features, functional characteristics of the aortic root, and

23   transvalvular hemodynamics is required.

1   Scientific efforts to address the phenotypic heterogeneity in BAV-aortopathy

2   were mainly based on valve-related factors including BAV morphology (i.e. number and

3   location of fused cusps), functional lesion (i.e. stenosis, insufficiency or mixed lesions)

4   and shape / configuration of the proximal aorta which are addressed in detail below.

5

6   *B. BAV Morphology*

7   As mentioned in the Introduction, BAV morphology is described throughout this

8   manuscript according to the Sievers classification (see Fig. 1). [14] BAV morphology with

9   fusion of the right-left coronary cusps (i.e. Sievers type I, R/L) and right-non-coronary

10   cusp (Sievers type I, R/N) represent the two most common BAV morphologies,

11   accounting for approximately 75% and 20% of clinical cases, respectively.[14] Sievers type

12   I L/N and patients without a raphe (i.e. Sievers type 0) are very uncommon. The low

13   prevalence of these specific fusion morphologies resulted in exclusion of these patients in

14   most case series.

15   An embryogenetic study by Fernandez at al. demonstrated that the two most

16   common BAV morphologies (i.e., R/L and R/N) develop at different embryonic stages

17   through distinct mechanisms and therefore should be interpreted as separate etiological

18   entities.[61] The authors further suggested that the etiological factors giving rise to the

19   specific BAV morphologies might be involved in the occurrence of distinct forms of

20   BAV-aortopathy as well.[61] However, it is known that both morphologies can frequently

21   appear within the same pedigree.[62]

22   Recent 4-D flow MRI studies demonstrated that distinct aortic cusp fusion

23   patterns result in specific orientations of eccentric flow jets (Figure 3),[63-65] which in turn

may lead to differential distributions of aortic wall shear stress[63, 65] and subsequent focal flow-induced vascular remodelling.[64] Eccentric transvalvular flow results in elevated regional wall shear stress at the right-anterior wall of the proximal aorta for R/L BAV and right-posterior walls for R/N BAV.[65] Bissell et al. demonstrated more severe flow abnormalities (complex flow, higher in-plane wall shear stress) and larger aortas in the R/N BAV vs. R/L BAV.[63] However, propagation patterns of transvalvular flow are still not uniform in BAV patients with the same cusp fusion morphology[63-66] and thus the impact of additional functional parameters (e.g., subvalvular components, geometric orientation of residual aortic valve orifice) have been postulated.[66]

The R/L morphology has been associated with younger patient age and absence of significant aortic stenosis or regurgitation,[67] whereas a greater prevalence of female patients is observed in R/N patients.[68, 69] Regarding the associated aortopathy, BAV R/L fusion morphology has been linked with increased diameters of the sinuses of Valsalva.[51, 68-71] In contrast, R/N fusion morphology is associated with smaller dimension of the aortic root and larger aortic arch diameters.[68-71] However, some authors found no significant correlation between aortic dimensions and BAV morphology.[72, 73] In addition, the published data on progression of BAV-aortopathy in R/L vs. R/N fusion morphologies are inconsistent. Some authors found that BAV patients with R/L fusion are at increased risk of rapid aortic dilatation,[71, 74] while others reported the same findings in patients with R/N fusion.[75] Different statistical approaches and different age ranges of the study populations may explain the differences between studies, since the two types of BAV morphology seem to progress in an age-dependent manner.[69, 76] Other studies have found no correlation between ascending aortic dilatation rates and BAV morphology.[29, 51]

1   The data on proximal aortopathy in unicuspid aortic valve (UAV) disease is very

2   limited. Sievers et al. reported on more extensive aortopathy, including aortic root and

3   ascending aorta, at very young age in UAV patients.[77] Moreover, UAV patients are more

4   likely to require ascending aortic repair during their valvular procedure.[78] Furthermore,

5   significantly higher expression of GATA5 and endothelial nitric oxide synthase in the

6   ascending aortas of patients with UAV disease vs. BAV and TAV disease has been

7   recently reported.[79] Another recent study[80] demonstrated decreased long-term survival in

8   UAV patients undergoing isolated AVR when compared to UAV patients who underwent

9   simultaneous aortic surgery.

10

11   *C. Valve Function*

12   The most common clinical presentation of BAV disease is calcific aortic

13   stenosis (BAV-AS), usually presenting between the 5th and 7th decades of life in both

14   male and female patients. In contrast, pure/predominant BAV insufficiency (BAV-AI)

15   tends to occur in younger, male patients and accounts for only 10-15% cases of BAV

16   lesions in autopsy series.[81] Distinct patterns of associated aortopathy have also been

17   observed in BAV-AS vs. BAV-AI.[47, 67, 82] Moreover, differences in histological and

18   extracellular matrix protein changes,[83-85] consistent with the clinical evidence from post-

19   AVR follow-up studies,[86] have also led investigators to suggest different pathobiological

20   mechanisms of BAV-aortopathy for these two groups of patients. BAV-AS is strongly

21   associated with an asymmetric dilatation of the tubular ascending aorta, which represents

22   the most common aortic phenotype.[47, 78, 82, 87] In contrast, BAV-AI is mainly accompanied

23   by aortic root dilatation (i.e., so-called "root phenotype").[78, 82, 86] However, these

1 associations are not absolute and heterogeneity within subgroups of valve function have

2 been observed.[48, 82] As stated previously, BAV-aortopathy is a very heterogeneous

3 disease.

4   Aortic dilation observed in patients with normally functioning BAVs has been

5 previously used as an argument for a genetic origin of BAV-aortopathy.[48] However,

6 recent experimental *in vitro* models[88] and *in vivo* 4-D flow MRI studies[89] demonstrate

7 that even clinically normally functioning BAVs (i.e., without transvalvular pressure

8 gradient or significant insufficiency) are associated with eccentric transvalvular flow and

9 asymmetrically increased wall shear stress in the proximal aorta. Aortic dilatation in

10 normally functioning BAVs occurs most frequently in the tubular ascending aorta[90] and

11 has a natural history that is comparable to their TAV counterparts in terms of rate of

12 dilatation and occurrence of aortic events.[90]

13

14 *D. Shape of the Proximal Aorta*

15   Della Corte and co-authors were the first to introduce a phenotypic classification

16 of the proximal aorta based on the aortic segment involved and suggested the terms "root

17 phenotype" and "ascending phenotype"[82] (Figure 4). This classification system separated

18 BAV patients with a possible greater expression of genetically-triggered aortopathy (i.e.,

19 root phenotype) from those with a presumed hemodynamic cause of aortopathy (i.e.,

20 ascending phenotype). Other classification systems for the pattern of dimensions of the

21 different aortic segments have been proposed: each of them has merits and flaws and

22 none can completely cover the entire spectrum of forms of dilatation.

1   Four distinct patterns of aortic dilatation in BAV patients have been suggested

2   by Fazel and coauthors from Stanford using a model of hierarchical clustering and

3   integrating non-echocardiographic imaging (i.e. CT scan and MRI).[13] They identified 4

4   "clusters": aortic root dilatation alone (cluster I), tubular ascending aorta dilatation alone

5   (cluster II), simultaneous involvement of tubular portion and aortic arch (cluster III) and

6   more diffuse dilatation involving aortic root, tubular portion and aortic arch (cluster

7   IV).[13] Cluster IV was the most frequent pattern of aortopathy, however, no risk factor

8   analysis or longitudinal data were included. A slightly modified CT-scan based

9   classification system of proximal aortic shape has been used by Kang and co-authors,[91]

10   confirming the previously reported association of the atypical morphologies (mainly R/N)

11   with arch involvement.[68]

12   From an echocardiographic analysis, Schaefer et al. defined three shapes of the

13   proximal aorta based on the relative dimensions of sinuses of Valsalva, sinotubular

14   junction (STJ) and tubular segment: *type N*, with dilation of the sinuses with preservation

15   of the STJ; *type A*, dilation of the tubular aorta with preserved STJ; and *type E,* dilation of

16   the STJ with preserved sinus of Valsalva, regardless of the diameter of tubular aorta.[68]

17   Finally, Park and associates proposed a classification scheme of BAV aortic

18   phenotypes in a surgical study based on the segment involved (root vs tubular aorta) in

19   the aneurysmal disease.[92] These authors classified "type I" dilatation as that involving the

20   tubular ascending aorta only, "type II" involving both the tubular ascending aorta and the

21   root, and "type III" confined to the aortic root.[92]

22   In a recent longitudinal study that sought to validate the three different

23   echocardiography-based BAV phenotypic classifications of the proximal aorta,[68, 82, 92]

1 only the classification system distinguishing between ascending phenotype and root

2 phenotype showed a potential prognostic value in predicting growth rate of the aorta over

3 time.[93] Consistent with these findings, a prior longitudinal study demonstrated that the

4 root phenotype is associated with a significantly greater risk of aortic events following

5 isolated AVR.[30] This classification system also has practical value, since the root

6 phenotype frequently requires a Bentall or valve-sparing procedure, whereas replacement

7 of the tubular aorta is usually sufficient to treat the ascending phenotype (Figure 5). Of

8 note, two aortic dissection series revealed that BAV patients received a Bentall operation

9 significantly more often (85-94%) than TAV patients (20-30%), due to the presence of a

10 pre-existing root aneurysm or the involvement of the sinuses by the dissecting process.[31,

11 32] It should be stressed that while valve morphology is a congenital feature of a BAV

12 patient, the aortic phenotype can change during life. That is, a proportion of root

13 phenotype patients can progress to an ascending phenotype over time.[29] Further research

14 in this area will undoubtedly lead to further insights into BAV-aortopathy patterns.

15 Hopefully a single classification system will emerge that encompasses BAV morphology,

16 BAV lesion, and location and extent of associated aortopathy in a clinically meaningful

17 manner.

18

19 *E. Symmetry vs. Asymmetry of Aortic Dilatation*

20   Symmetry versus asymmetry of aortic dilatation may also provide an important

21 clue regarding the predominant pathogenesis of BAV-aortopathy inasmuch as

22 asymmetrical aortic involvement might be an indicator of rheological factors involved,

23 whereas symmetrical involvement might be more predictive of genetically-triggered

1   vessel wall weakness. By "asymmetric dilatation", predominant enlargement of the

2   greater, outer curvature (usually referred to by the misnomer "convexity" as opposite to

3   the lesser, inner curvature or "concavity") of the tubular aorta is meant. Preoperative

4   imaging methods can be used to identify asymmetric aneurysms.[94, 95] Several studies

5   found significant correlation between functional BAV lesion (i.e., BAV-AS) and

6   asymmetric dilatation of the tubular aorta.[95, 96] Asymmetric patterns of histological

7   lesions and extracellular matrix protein expression have also been demonstrated between

8   the concavity (where less severe changes are observed) and the convexity (more severe

9   structural changes) in such patients.[66, 85] A recent study looked at the expression of

10 transforming growth factor beta-1 and matrix metalloproteinases in BAV-aortopathy, and

11 found that wall areas which had been mapped as regions of increased wall shear stress by

12 preoperative 4D-flow MRI exhibited greater expression of these markers of vascular

13 remodelling.[64] No similar study has thus far been performed in patients with BAV-AI.

14

15

Normal Aortic Valve   **Bicuspid Aortic Valve**
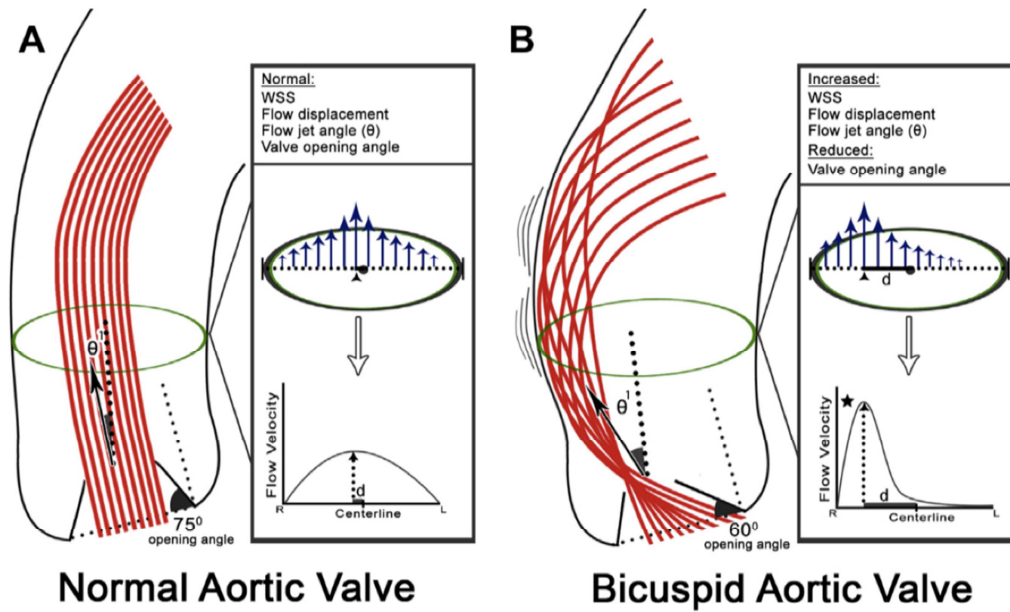
1

2   **Figure 3. A)** Normal aortic valve anatomy with an opening angle of 75 degrees, flow jet

3   angle (θ^1, which measures displacement of peak systolic flow (arrow) from vessel

4   midline).   B) BAV showing restricted valve opening (opening angle of 60 degrees),

5   displaced flow jet with associated θ^1, displaced high flow velocities near the vessel wall

6   leading to asymmetrically increased wall shear stress (WSS) at the aortic convexity

7   (reproduced with permission from Burris and Hope). [97]

8

1
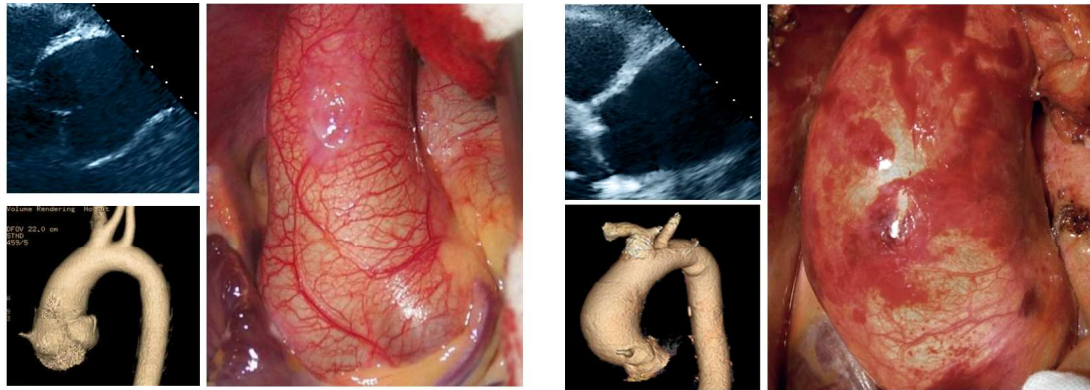
Root Phenotype   Ascending Phenotype

2

Figure 4. Root phenotype vs. ascending phenotype of BAV aortopathy. Echocardiographic imaging is shown in the upper left corner, 3D reconstruction shown in lower left corner, and intraoperative findings shown at right. In the root phenotype the diameter of the aorta at the level of the sinuses of Valsalva is greater than that of the tubular ascending aorta, whereas in the ascending phenotype the diameter of the tubular ascending aorta is greater than that of the sinuses.

9

10

Areas of Possible Involvement in BAV Aortopathy
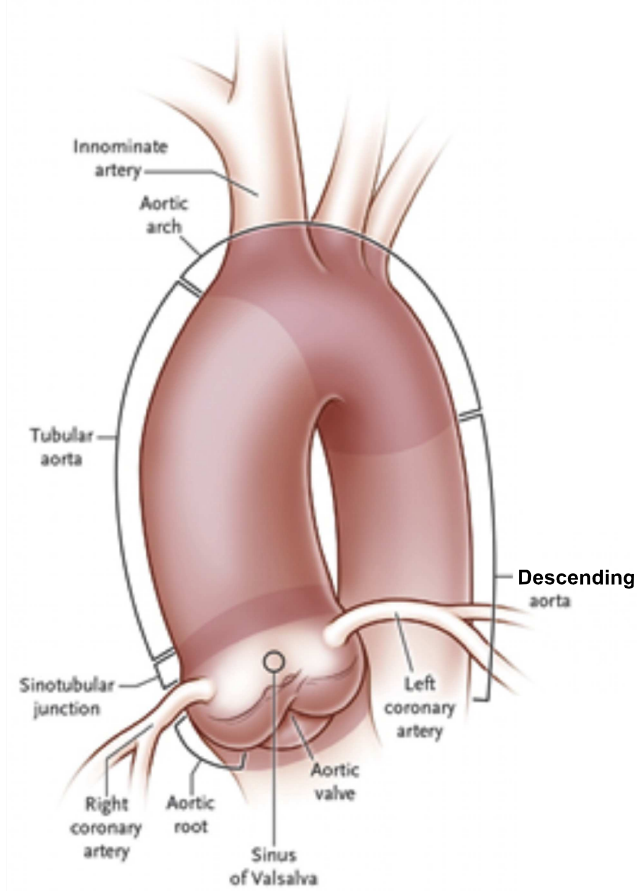
1
2
3 **Figure 5.** Subdivision of proximal aortic involvement in BAV aortopathy. Reproduced

4 with permission from Verma and Siu. [18]

5

1

2 **4. Histopathological and Biomechanical Findings of BAV-Aortopathy**

3 *A.* *Histopathologic Studies*

4   BAV-aortopathy consists of premature cystic medial degeneration in approximately

5 one half of surgically excised BAV aortas.[98] Histopathologic changes in the media have

6 been well documented and specifically delineated for the BAV-associated aneurysms[85, 99-

7 102]. It is also well established that the aortic extracellular matrix (ECM) plays an important

8 role in maintaining the aorta through both the binding/storing secreted proteins and

9 maintaining the structural integrity of the vascular wall.[100] The presence of thin, fragmented

10 elastin fibers, reduced fibrillin-1 content[99] and decreased types I and III collagen have

11 suggested elevated proteolytic activity.[85, 100] The degradation of ECM is under the balanced

12 control of matrix metalloproteinases (MMPs) and their specific tissue inhibitors (TIMPs),

13 which are secreted by vascular smooth muscle cells (SMCs), fibroblasts and endothelial

14 cells.[103] Various studies have shown a disturbance in the ECM of surgically resected BAV

15 aortas with increased activity of MMPs, with MMP-1, MMP-2, MMP-9, MMP-12 and

16 MMP-14 (MT1-MMP) being most often implicated.[104-108] The critical role of MMP-2 as a

17 key molecular mediator was supported by a recent meta-analysis.[109] Wang and colleagues

18 further showed MMP-2 as a circulating biomarker of aortic dilatation in BAV patients.[110]

19 Like MMPs, the expression of TIMPs is controlled during tissue remodeling and

20 physiological conditions to maintain a balance in the metabolism of the ECM. Studies have

21 demonstrated increased TIMP-1, TIMP-2 and TIMP-4 levels associated with BAV-

22 aortopathy.[107] Altered MMP/TIMP stoichiometry leads to apoptosis and degeneration of the

23 aortic wall (i.e. loss of elastic tissue and smooth muscle cells) and the eventual progression

1   of aneurysms. Importantly, histologic grading has revealed more extensive degradation of

2   the ascending aortic wall in patient with Sievers 1 R/L fusion.[101] This has further been

3   supported with data showing elevated proteolytic indices (i.e MMP abundance corrected for

4   TIMP abundance) for MMP-1, MMP-2, MMP-9, and MMP-12.[111] Consistent with findings

5   in patients with Marfan syndrome,[112] early data points to involvement of transforming

6   growth factor (TGF)-β signaling contributing to the progression of BAV-aortopathy,

7   although this remains somewhat controversial.[113-115]

8   Phillippi and co-workers further characterized the medial matrix remodeling of the

9   BAV aorta and found unique patterns as compared to TAV patients.[116] Grewal and co-

10   workers compared the histopathology of BAV, TAV, and Marfan aortic tissue and found

11   both similarities and differences between all three groups with respect to parameters of

12   matrix remodeling and vascular smooth muscle markers.[117] The complexity of the

13   histopathologic findings is substantial and it is not clear what molecular pathways are unique

14   to the BAV aorta. The complexity is further confounded by the findings of Heng and

15   colleagues. In this recent study, tissue pathology was compared between TAV and BAV

16   patients at matched aortic diameters.[118] At odds with conventional wisdom, more severe

17   histologic abnormalities were found in TAV as compared with BAV aortas, especially when

18   stratified by diameter.

19   In addition to ECM degradation, SMC loss is a prominent feature of BAV-

20   aortopathy. SMC phenotype, oxidative stress patterns and SMC responsiveness to oxidative

21   stress appear altered in the BAV-aortic wall.[115, 119-124] Metallothionein, a free radical

22   scavenger, expression is dysregulated, and consequent SMC cell viability is reduced in

23   response to oxidative stress in the BAV-aorta. Regional differences in apoptotic activity

1   also appear to be present comparing the concave and convex portions of the bicuspid

2   aorta.[125] Given the mounting evidence of regional differences in both the biology and the

3   biomechanics of BAV-aortopathy, it is very likely that they correlate with one another.

4   Aims to leverage these collective insights toward better diagnostics and risk adjudication are

5   approaching.

6

7   ***B. Biomechanical Studies***

8   Biomechanical functional testing of aortic tissues may provide further insights into

9   BAV-aortopathy. Ascending aortic wall properties are biomechanically anisotropic.

10 Despite total collagen and elastin content and histopathologic findings that are similar,

11 microarchitectural and biomechanical differences are apparent when comparing aortic wall

12 characteristics from BAV patients to TAV patients. The tensile strength, particularly in the

13 circumferential and longitudinal directions, is higher in surgically resected ascending aortas

14 in BAV compared to TAV patients,[126, 127] while the delamination strength of the aortic wall

15 of BAV-aorta is lower than TAV-aorta.[128] Aortic wall remodeling characteristics in BAV

16 patients also appear distinct with more highly aligned collagen fibers, more undulating and

17 less aligned elastin fibers, thinner elastic lamellae, and greater distances between elastic

18 lamellae.[100, 116, 127, 129, 130] Aortic stiffness is associated with progressive aortic dilatation and

19 aneurysm formation, which is characteristic of BAV-aortopathy.[131] Indeed, a recent study of

20 abdominal aortic aneurysms found that segmental stiffening of the aorta preceded aneurysm

21 growth and introduced the concept that stiffening may act as an early mechanism triggering

22 elastin breakdown and aneurysm growth.[132] Nonetheless, the evidence regarding cellular and

1 molecular mechanisms for BAV-aortopathy remain complex and contradictory, with a need

2 for larger cohort, well-controlled studies.

3   Although stimuli for BAV-aortopathy are likely multifactorial, results from recent

4 studies provide strong evidence that a hemodynamic (i.e. rheologic) stimulus, known as

5 wall shear stress (WSS), may change local matrix homeostasis and, in turn, ascending

6 aortic structure and associated functional properties. [64, 133-138] Indeed, WSS is known to

7 impact MMP2 levels[139] and has been implicated in the development of aortopathy.[89, 140]

8 Aortic WSS calculations demonstrate differences in regional and radial wall stresses[141,

9 [142] but how these differences correspond to aortic wall remodeling, biology, and clinical

10 outcome is not yet known. Proof-of-concept data was recently obtained using a novel *ex*

11 *vivo* tissue model. Atkins and co-workers modeled regional WSS from a TAV- as

12 compared to a BAV-aorta in an ex vivo procine tissue model,[143] and the impact of BAV-

13 mediated WSS was determined on aortic wall remodeling. The investigators found

14 cellular, molecular (i.e. increased MMP-2 activity), and structural changes that are

15 characertistic of human BAV-aortopathy. As highlighted by the investgators, the study

16 indictates that altered WSS resulting from a BAV can focally mediate aortic medial

17 degradation. These unique experimental findings provide compelling support for an

18 important role of hemodynamics in mediating BAV-aortopathy.

19   Recent advances in MRI have permitted unobstructed in-vivo assessment of time-

20 resolved 3D blood velocity, using a volumetric technique referred to as 4D flow MRI. 4D

21 flow MRI provides the unique ability to quantify complex 3D blood flow patterns in-vivo

22 and has facilitated new insights and discovery with respect to complex cardiovascular

23 hemodynamics.[65, 144-148] Multi-dimensional 4D flow MRI data (3 spatial dimensions

1   describing 3D velocity over time) enables aortic blood flow visualization, quantification

2   of regional flow and velocity,[145, 149-151] and WSS quantification.[134-136, 138, 152, 153] Recent

3   MRI studies provide strong evidence that valve-mediated local flow dynamics[144] and

4   regional differences in WSS[65] are associated with changes in regional aortic wall

5   histology and proteolytic events,[64] which are known to drive adverse aortic remodeling.

6   Early studies employed less-sophisticated MRI techniques (2D PC-MRI) to demonstrate

7   BAV-mediated changes in flow and WSS[153] and their association with aortic

8   enlargement.[154] Subsequent 4D flow MRI studies have conclusively documented that

9   aortic WSS is increased in BAV subjects independent of stenosis severity when

10 compared to age- and aortic size-matched controls.[144] Moreover, regional variation of

11 WSS within the aorta is dependent on aortic valve fusion phenotype [65, 144, 155] and is

12 associated with aortic diameter.[63] A recent study with 30 BAV patients and 30 age-

13 appropriate TAV controls provided evidence that altered aortic hemodynamics may be a

14 pathophysiologic mechanism by which R/L or R/N BAV fusion patterns influence the

15 expression of aortopathy.[65]

16   Similar to the findings of Atkins and Sucosky in the porcine model, aortic

17 hemodynamic alterations were found to be related to medial wall degeneration.[64] In a

18 recent study that included both in-vivo 4D flow MRI and aortic tissue resection in 20

19 BAV patients, elastin content and structure was severely disrupted in regions of high

20 WSS with a shift in the expression of specific MMPs and TGF-beta. Girdauskas and

21 colleagues found a similar correlation between systolic transvalvular flow patterns and

22 proximal aortic wall changes in the setting of BAV-AS.[66] With more extensive

23 investigation it is conceivable that quantitative metrics of valve-mediated hemodynamics

1   could be used to guide more precise and individualized surgical resection strategies

2   beyond contemporary empirical size thresholds.

1 **5. Diagnostic Modalities**

2 *A. General Vascular Imaging Concepts*

3   Transthoracic echocardiography (TTE) is the recommended imaging modality for

4 the initial assessment of the aortic valve and thoracic aorta, including the assessment of

5 hemodynamic valve function (see Table 3, as well as Figures 6 and 7).[156] If any part of the

6 examination is not possible by TTE, computed tomography (CT) or magnetic resonance

7 imaging (MRI) is recommended to assess the presence and extent of aortopathy (Figures 8

8 and 9). Hemodynamic valve assessment can also be performed by MRI,[157] although TTE

9 remains the gold standard. TTE assessment of aortic valve function is usually sufficient,

10 but transesophageal echocardiography (TEE) should be performed in patients with AI that

11 is difficult to quantify with TTE. BAV-AI may result in an eccentric jet that can be better

12 visualized with TEE, particularly if patients have less-than-severe AI by TTE and

13 unexplained LV dilation or dysfunction. In addition, TEE may best determine the

14 mechanism of AI when aortic valve repair is being considered.

15   When evaluating the BAV aorta with echocardiography, the entire thoracic aorta

16 should be assessed: aortic root (aortic annulus, sinuses of Valsalva and sinotubular

17 junction), tubular ascending (proximal, mid and distal), aortic arch, and descending

18 thoracic aorta including diameter measurement and Doppler assessment for the presence of

19 coarctation (see Table 3 and Figure 10). It is important to recognize that the term "aortic

20 root" has been loosely used in the past to include the ascending aorta, and it is critical that

21 both the components of the aortic root and tubular ascending aorta are measured separately

22 and reported as such. The abdominal and pelvic aorta need not be assessed in isolated

23 BAV disease, unless a family history of abdominal or iliac aneurysms is present, or

1 suspicion of coarctation exists. In addition, although intracranial arterial aneurysms have

2 been found in 10% of BAV patients versus 1% of control patients,[158] these are small (i.e.,

3 <10 mm in diameter) and no increased prevalence of BAV has been found in patients with

4 intracranial aneurysm-related subarachnoid hemorrhages.[159] Therefore, routine brain

5 angiography is not recommended in BAV patients unless coarctation of the aorta is present

6 (see Table 3).[42] Intracranial hemorrhage is a complication of coarctation of the aorta,

7 independent of the presence of BAV.

8

9 *B. Image Acquisition and Analysis: Echocardiography, MRI and CT*

10   There is no consensus regarding a standard method to measure and compare aortic

11 measurements across echocardiography, MRI, and CT,[160] and different methods are

12 frequently used within the same institution. Although it is clear that end-diastolic leading

13 edge-to-leading edge is the method of choice for TTE in adults,[160] no such consensus

14 exists for CT/MR. Some advocate end-diastolic outer wall-to-outer wall measurements,[5]

15 while others advocate inner wall-to-inner wall dimensions.[160] [161] Recent data suggest no

16 systematic measurement bias when comparing the current echocardiographic method to the

17 CT/MR inner wall-to-inner wall method for measuring the ascending aorta in the absence

18 of root asymmetry.[161]

19   Care must be taken when interpreting results across modalities. The maximum

20 diameter observed in the aorta, regardless of the position in which it is measured, should be

21 reported in addition to the measurements obtained at predefined anatomic locations (see

22 Table 3). Herein we recommend best practices for each modality.

1   Measurements of the adult thoracic aorta by TTE and TEE should be obtained in

2   diastole (i.e. at the QRS complex) with the leading-edge to leading-edge technique (Figure

3   11).[160] For TTE, measurements of root and tubular ascending aorta are made in the left

4   parasternal long axis view (Figures 6 and 7), but other views such as left "high" parasternal

5   and right parasternal are complimentary and recommended. For TEE, the mid-esophageal

6   long axis view and high-esophageal mid-ascending aorta view are utilized (Figure 12).

7   Both TTE and TEE modalities have the disadvantage of potentially measuring obliquely

8   and not perpendicular to the long axis of the tubular ascending aorta, which could render

9   inaccurate aortic diameter measurements.

10   MRI and CT acquire 3D fields of view, and thus, the aorta diameter should be

11   measured with multi-planar reconstruction to obtain double-oblique cross-sectional views

12   of the vessel (perpendicular to the longitudinal axis of the aorta). The double oblique view

13   corrects for measurement errors caused by projecting the 3D aorta on a 2D screen. For the

14   same reason, it is recommended that ascending aortic diameters ≥45 mm obtained by

15   echocardiography be further investigated by ECG-gated MRI or CT angiography during

16   diastole. CT or MRI may also be performed in patients with aortic dilation (i.e. 40-44 mm)

17   and poor quality echocardiographic images. Recommended CT and MRI measurement

18   locations are displayed in Figure 11. If measurements are comparable and reproducible

19   between techniques, then future interval measurements can be obtained by TTE alone, with

20   repeat CT or MRI examination every 3 years to re-verify reproducibility and agreement.

21   If initial measurements are discrepant, then CT or MRI should be the techniques of choice

22   for interval aortic diameter measurements.

1   Regarding the aortic root, TTE measurements are consistently lower than those

2   measured by ECG-gated CT angiography.[162] [161] This is particularly true for the asymmetric

3   dilated BAV root whose dimensions are frequently underestimated by single 2-

4   dimensional parasternal long-axis and standard short axis TTE views. When root dilatation

5   is visually suspected by TTE or the root is significantly asymmetric, we recommend

6   measuring diastolic leading-edge-to-leading edge sinus-to-sinus diameters in parasternal

7   short axis TTE view or alternatively, go straight to CT/MR ECG-gated root assessment.

8   Because of the highly reproducible nature of ECG-gated CT and MRI, these

9   techniques should be used for accurate assessment of aortic root measurements. However,

10   it is important to note that clinical cut-offs for intervention have largely been derived from

11   echocardiography,[28] a difficult conundrum to reconcile.[156] Nevertheless, akin to the tubular

12   aorta, echocardiography-derived aortic root diameters ≥45 mm should be verified by

13   ECG-gated CT or MRI (see Table 3). Given that the sinuses can dilate asymmetrically, all

14   three sinus-to-commissure (or sinus-to-sinus) dimensions should be measured.[163] The CT

15   measurements that correlate best with echocardiographic-derived values are inner wall-to-

16   inner wall dimensions, which require the administration of contrast medium (Figure 11).

17   [164]

18   The choice between CT and MRI is dependent on their availability, institutional

19   expertise and age of the patient. Younger patients (i.e., < 50 years-old) would benefit from

20   MRI in order to avoid CT-associated radiation exposure, but ECG-gated MRI is not

21   commonly performed in most institutions. Ideally, interval measurements should be

22   performed with the same imaging modality, same technique (i.e. ECG-gated), and

23   compared side-by-side by an experienced reader.[156]

1   It should be noted that radiologists occasionally recognize signs of BAV aortopathy

2   in a patient with no previous diagnosis of BAV. Suggestive signs are aortic leaflet

3   calcification at a young age (i.e. < 60) and an asymmetric shape to the ascending aorta,

4   with bulging of the outer curvature.[165] Such patients should undergo TTE in order to

5   confirm the diagnosis.

6

7   *C. Aortic Imaging Surveillance*

8   After the first echocardiographic evaluation, the thoracic aorta should be re-

9   assessed entirely on a yearly basis if greater than 45 mm (see Table 4). A first interval

10   repeat measurement could be considered at 6 months prior to proceeding to yearly

11   assessments, especially if other risk factors such as aortic coarctation or family history of

12   dissection are present.   As opposed to Marfan syndrome where the aortic root is

13   predominantly involved,[51] the most common segment involved in BAV patients is the

14   tubular ascending aorta (i.e. 60-70% of BAV dilated aortas).[28] It is vitally important that

15   images of any type not be compared to the last prior image, but rather to the oldest prior

16   image, which can be harder to access. Otherwise, gradual growth can go undetected. [166]

17   Aortic growth rates for the tubular ascending segment in BAV adults have recently

18   been reported to range from 0.4 to 0.6 mm/year,[29, 51] while earlier studies demonstrated

19   maximal dilatation rates of 1 to 2 mm/year. Very few patients are observed to dilate at > 2

20   mm/year.[29, 51] Although these represent "artificially-annualized" rates, it remains very

21   unlikely that BAV patients will dilate at ≥ 3 mm/year. It is also important to note that an

22   interval diameter change of 1 or 2 mm by current imaging modalities is within the realm of

23   error. Therefore, an interval dilatation of ≥ 3 mm should be considered clinically

1 significant.[12] Absolute echocardiographic aortic diameters at baseline are not reliable

2 predictors of the rate of dilatation during follow up,[29, 51] thus regular interval imaging

3 (according to Table 3) is recommended regardless of baseline diameter. Previous AVR is

4 more common in BAV patients presenting with aortic dissection, compared to TAV

5 patients with dissection.[167] BAV patients with previous AVR have the highest reported risk

6 of aortic dissection after 15 years of follow-up (i.e. 1%),[58] particularly if the original

7 operation was performed for BAV with aortic regurgitation.[49] Therefore, continued

8 interval monitoring of the unrepaired aorta post-AVR is suggested.

9

10 ***D. Abnormal Aortic Diameter Values and Indexing***

11 The sinuses of Valsalva are normally larger than the STJ and tubular ascending

12 aorta, and the latter is larger than the arch and descending thoracic aorta. Normal values in

13 adults by age, body-size and gender have been reported for the aortic root[160, 168] and tubular

14 ascending aorta.[160, 169, 170] An aneurysm is defined as a permanent focal dilatation of an

15 artery having at least 50% increase in diameter compared to expected.[5, 171] In clinical

16 practice, however, it is generally considered that a tubular ascending aorta > 37 mm or

17 aortic root > 40 mm represents aortic dilation (but not aneurysm formation) in adult

18 patients.[172]

19 It is important to recognize that the aforementioned cutoffs are not absolute, such

20 that 50 mm could represent moderate dilatation in a large male but may be severe

21 dilatation in a small female. Thus, correction for body size parameters has been proposed

22 (see Table 3). Surgical repair has been suggested for patients with Turner syndrome who

23 have an indexed aortic diameter of 2.75 cm/m^2 or greater.[173] The ratio of aortic cross

1   sectional area divided by height [Ratio= $r^2 \pi (cm^2)$/height (m)] has also been proposed as a

2   method to correct for dissimilarities in body size.[174] A ratio greater than 10 cm^2/m has been

3   recommended as cutoff for elective aorta repair in both Marfan syndrome and BAV

4   disease,[5] and a recent study involving 380 BAV patients with dilated aortas found that a

5   cut-off of 13 cm^2/m for the tubular ascending aorta and 10 cm^2/m for the root exhibited

6   superior predictive accuracy for the occurrence of dissection than absolute cutoffs.[175]

7   Another indexed measure of the aorta, the "aortic size index" in which the maximum aortic

8   size in centimeters divided by the body surface area has been validated in a large database

9   of aneurysm patients and was found to be more predictive of adverse events than

10   maximum aortic dimension alone. [176] Similarly, a large database of tricuspid valve patients

11   with aortic aneurysms found that indexed aortic size improved the ability to predict long-

12   term events.[177] However, more research needs to be done in order to confirm these

13   findings.

14

15   ***E. Emerging Imaging Technology and Imaging Biomarkers***

16   Imaging research for risk factors associated with BAV-aortopathy has primarily

17   focused on degree of co-existing aortic valve stenosis or regurgitation. These functional

18   metrics alone do not reflect the rheologic burden on the aortic wall due to BAV. With this

19   in mind, a number of techniques have shown promising initial results in the search for

20   imaging biomarkers predictive of rheology-associated aortopathy development. For

21   example, Della Corte et al. investigated the valve opening angle obtained via 2D bSSFP

22   (steady state free precession) cine images to compute a proxy measurement for

23   understanding the impact of flow eccentricity on aortic growth.[154] In this 36 subject

1   cohort, they found the fused leaflet opening angle predicted ascending aorta diameters

2   and growth rates. Using a similar hypothesis, Burris et al. computed the barycenter of the

3   of the velocity field from 2D phase contrast MRI to obtain 'flow displacement', a

4   parameter representative of the eccentricity of vessel cross section velocity field.[178] The

5   baseline displacement measurement was found to be predictive of ascending aorta growth

6   in small cohort of subjects.

7   Using insight from 2D phase contrast MRI studies,[153] a number of investigators

8   have assessed the rheologic forces at the aorta wall using 4D flow MRI and the

9   computation of WSS. [89, 179, 180] These studies have directly measured the impact of

10 eccentric flow and their forces on the aortic wall (Figures 13 and 14) and found

11 correlations to the aorta phenotype [65] and regional tissue aortopathy.[64, 180] While further

12 study is needed, these preliminary findings indicate that rheologically-mediated aorta

13 remodeling is an important factor to consider in the design of future studies.

14

1 **Table 3:** Recommendations for initial imaging of the aorta in BAV patients.
2

Recommendation	Class / LOE
Transthoracic echocardiogram (TTE) is the initial imaging modality of choice for assessment of the aortic valve and thoracic aorta in patients with BAV.	I / C[5, 160]
The entire thoracic aorta should be measured by TTE, reporting each aortic segment separately in millimeters: Root (sinuses of Valsalva), sino-tubular junction, tubular ascending aorta (proximal, mid and distal), arch and descending thoracic aorta (see Figure 11). Maximum diameter, regardless of location, should be reported. Aortic coarctation should be ruled out with Doppler evaluation of the descending thoracic aorta and abdominal aorta.	I / C [5, 160, 181]
If TTE cannot visualize any aortic segment and/or any segment measures $\geq$ 45 mm and/or aortic coarctation cannot be ruled out, recommend assessment of the entire thoracic aorta with ECG-gated cardiac magnetic resonance angiography (MRA) or computed tomography angiography (CTA).	I / C [33, 57]
If a patient is undergoing cardiac surgery and root and/or tubular ascending aorta measure 40 – 44 mm by TTE, recommend assessment of the thoracic aorta with MRA or CTA prior to surgery.	I / C[33, 57, 167]
If aortic coarctation is present, screening for cerebral aneurysms is recommended.	I/ B[181]

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1 **Table 4:** Recommendations for interval monitoring imaging of the aorta in BAV patients
2

Recommendation	Class / LOE
Interval imaging should be performed with the same imaging technique and measurement method, and compared side-by-side with previous study by an expert in that imaging technique.	I/ C [12, 156, 160]
Interval aorta imaging recommendations apply to patients with native BAV and also those who have undergone aortic valve replacement, given that aorta complications may occur in BAV patients post-surgery.	I/B [58, 167]
In patients with normal initial aortic diameters by TTE, the thoracic aorta should be re-imaged every 3 to 5 years.	I / C [51, 156]
In patients with initial aortic dilatation (root and/or tubular ascending aorta measure 40 - 49 mm), the thoracic aorta should be re-imaged at 12 months. If stability is confirmed, then re-imaging can be performed every 2 or 3 years.	I / C [12, 29, 51, 156]
In patients with more advanced initial aortic dilatation (root and/or tubular ascending aorta measure 50 – 54 mm), the thoracic aorta should be re-imaged at least every 12 months (yearly).	I/ C [12, 51, 156]
If thoracic aortic dilation (≥ 45 mm) noted by TEE is not reproducible with CTA or MRA (i.e. > 2 mm difference between modalities), then interval imaging follow-up should be performed with MRA or CTA.	I / C [156, 160]

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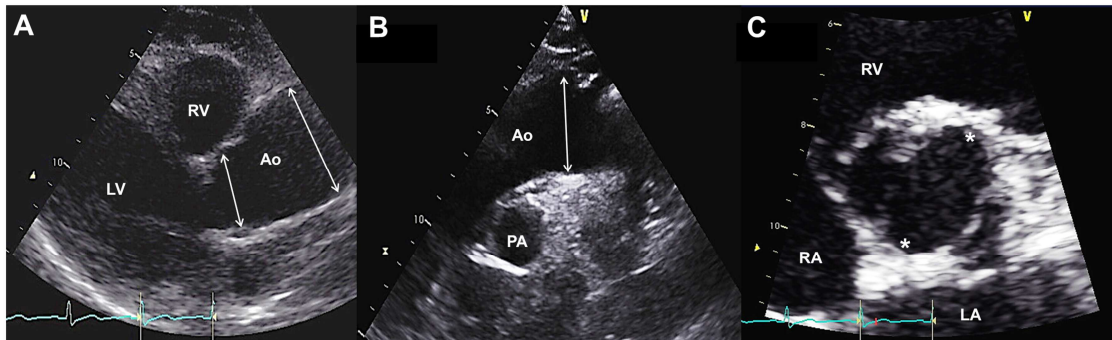
Figure 6. Typical echocardiographic findings in a BAV patient with tubular ascending

aorta dilatation phenotype. A.) Echocardiogram of a 60 year-old woman with R/N BAV,

no aortic valve regurgitation and a fusiform ascending tubular aortic aneurysm. Left

parasternal long axis view in diastole shows root measurement of 36 mm (first arrow

left), and mid tubular ascending aorta measurement of 47 mm (second arrow from left).

LV=left ventricle, RV=right ventricle, Ao=Aorta. B.) Suprasternal diastolic view shows

the mildly dilated proximal arch (36 mm, arrow) and normal upper descending aorta.

PA=pulmonary artery. C.) Parasternal short axis en-face view of the aortic valve in

systole shows 2 commissures (asterisks) at 1 and 7 o'clock with right-non fusion.

RA=right atrium, LA=left atrium.

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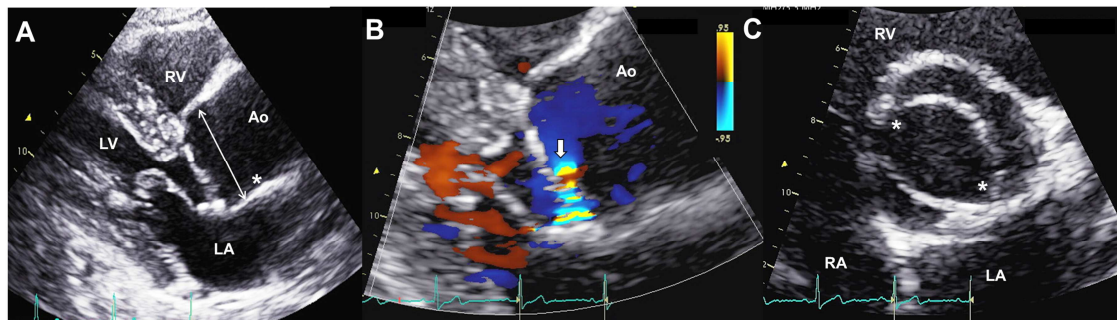
Figure 7. BAV patient with root phenotype aortic dilation. A.) Echocardiogram of a 53-

year old man with R/L BAV, severe aortic valve regurgitation and root-proximal

ascending aortic aneurysm. Left parasternal long axis view in diastole shows root

measurement of 46 mm (arrow), sinotubular junction effacement (asterisk) and proximal

tubular ascending aorta dilatation (Ao). RV=right ventricle, LV=left ventricle, LA=left

atrium, Ao=Aorta B.) Left parasternal long axis zoomed color-Doppler view in diastole

shows the flow convergence (arrow) of a posteriorly directed jet that quantified to 78 cc

per beat of regurgitant volume. C.) Parasternal short axis en-face view of the aortic valve

in systole shows 2 commissures (asterisks) at 4 and 10 o'clock with right-left fusion.

RA=right atrium.

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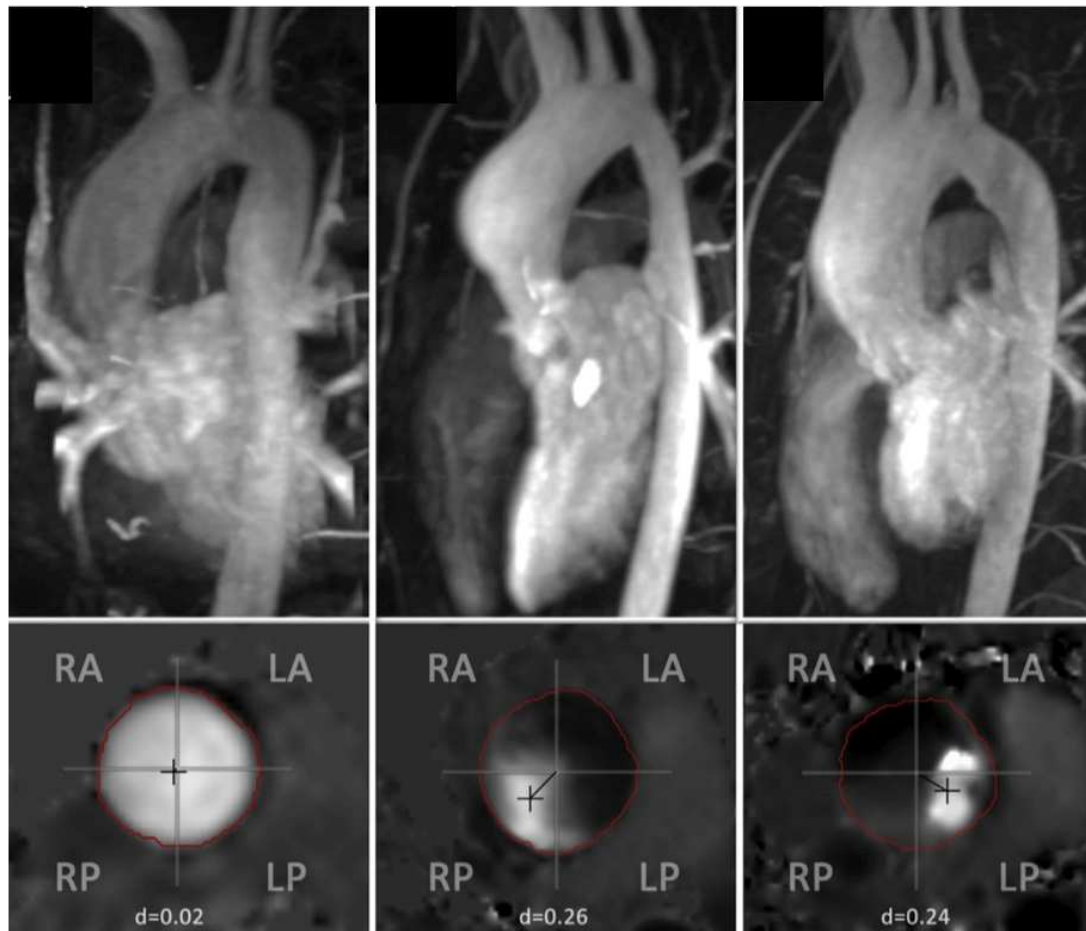
2
3 **Figure 8.** MRI assessment of BAV patients showing normal aortas (left panel) and

4 different types of BAV aortopathy (middle and right panel). Each of the three upper

5 panels shows maximum intensity projection of magnetic resonance angiography with the

6 corresponding inferior panel demonstrating the planar analysis of systolic flow. The left

7 panel demonstrates imaging from a normal patient, the middle panel demonstrates

8 aneurysmal dilation at the level of the sinuses with flow directed rightward and

9 posteriorly in a patient with a left-right cusp fusion. The right panel shows more diffuse

10 aneurysmal dilation in a patient with right-noncoronary cusp fusion and flow directed

11 leftward and posteriorly. Adapted from Burris and Hope[182]

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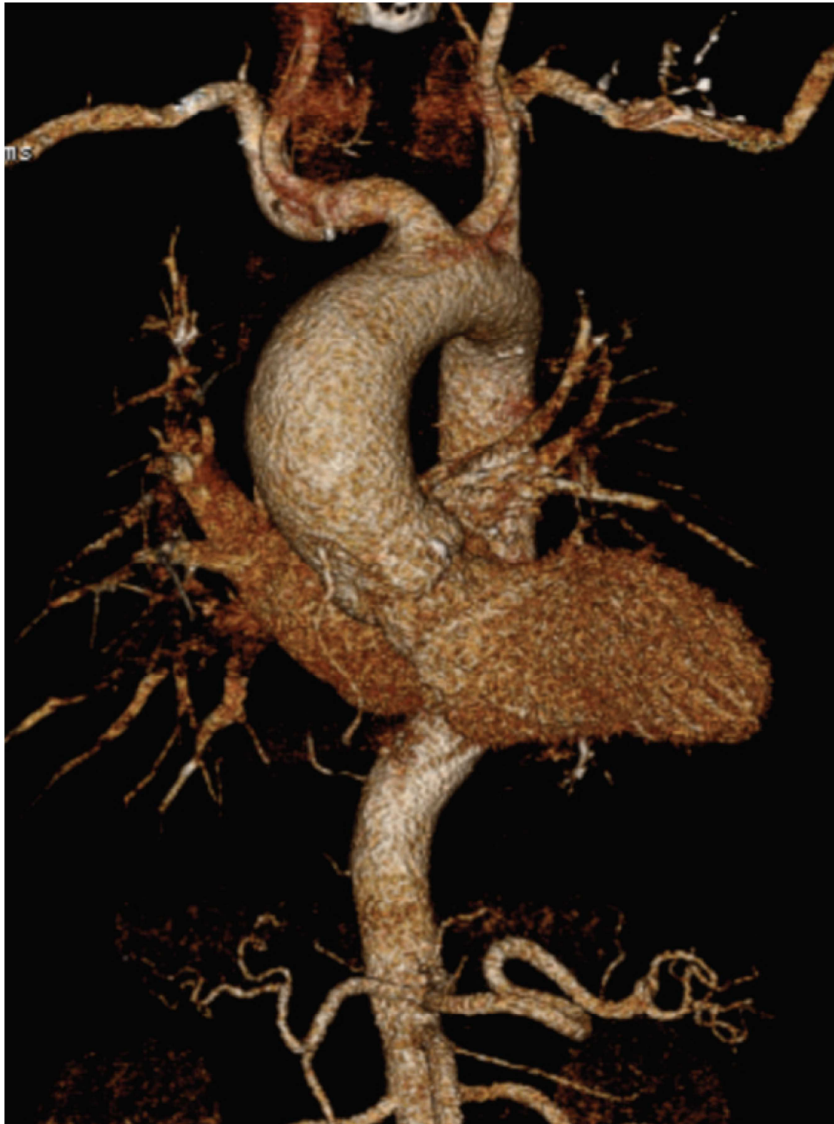
Figure 9. CT imaging with 3 dimensional reconstruction of BAV patient with associated

aortopathy.

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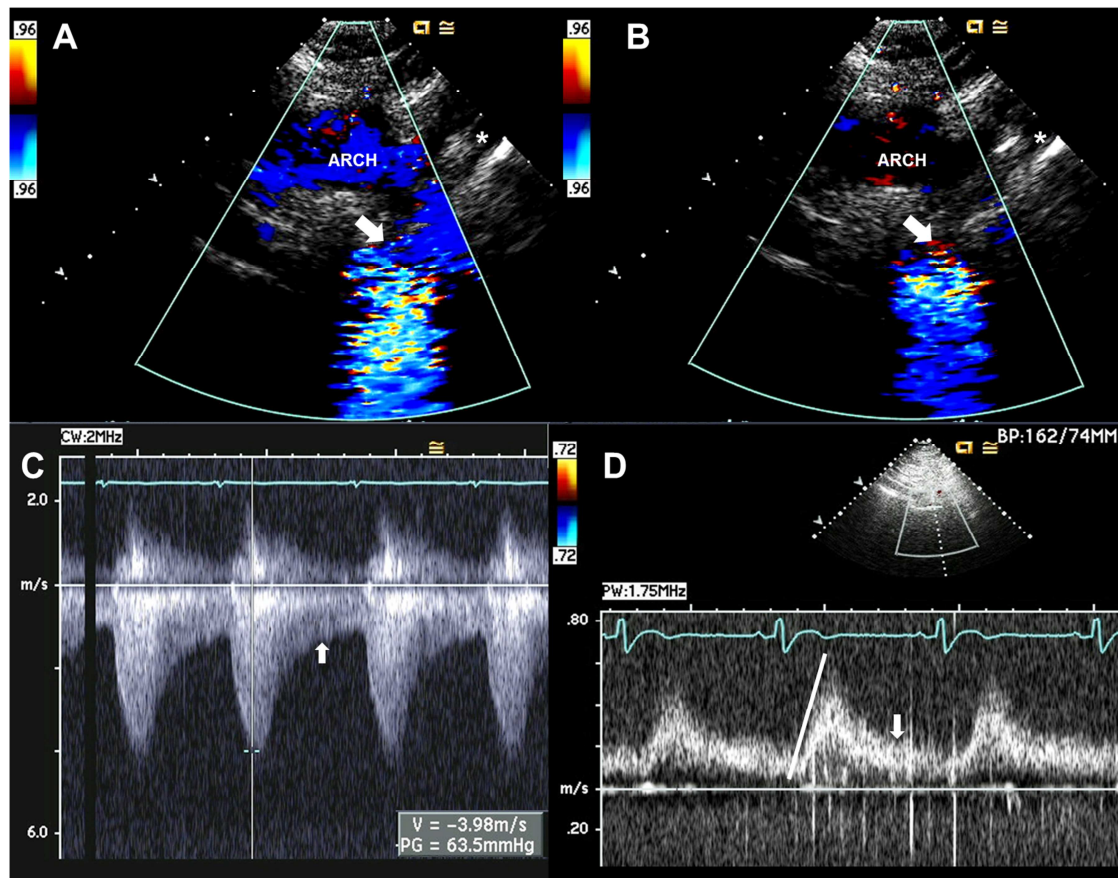
Figure 10. Transthoracic assessment for aortic coarctation. A.) Echocardiogram of a 31-

year old woman with BAV and severe aortic coarctation. Suprasternal systolic still frame

shows laminar Doppler flow through the proximal portion of the arch ("ARCH") before

becoming turbulent flow across a tight coarctation (arrow) just distal to the left

subclavian (asterisk). B.) Suprasternal diastolic still frame shows no Doppler flow

through the proximal portion of the arch but persistent diastolic turbulent flow across the

coarctation (arrow) just distal to the left subclavian (asterisk). C.) Continuous-wave

Doppler signal across the coarctation shows a systolic (measurement) peak gradient of

64 mmHg through the coarctation, with persistent flow in diastole (arrow). D.) Pulsed-

wave Doppler signal of the abdominal aorta shows a delayed peaking of the systolic

1   signal (line) with prominent persistent flow in diastole (arrow), pathognomonic of

2   coarctation.

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A. Echocardiography*

B. Sinus measurement

sinus to sinus

LCA

RCA

sinus to commissure

* leading edge to leading edge

C. MRI and CT**

proximal arch

mid ascending aorta

proximal DAo/ distal arch

sinotubular junction

root

mid descending aorta

** inner to inner wall (or self-consistent)

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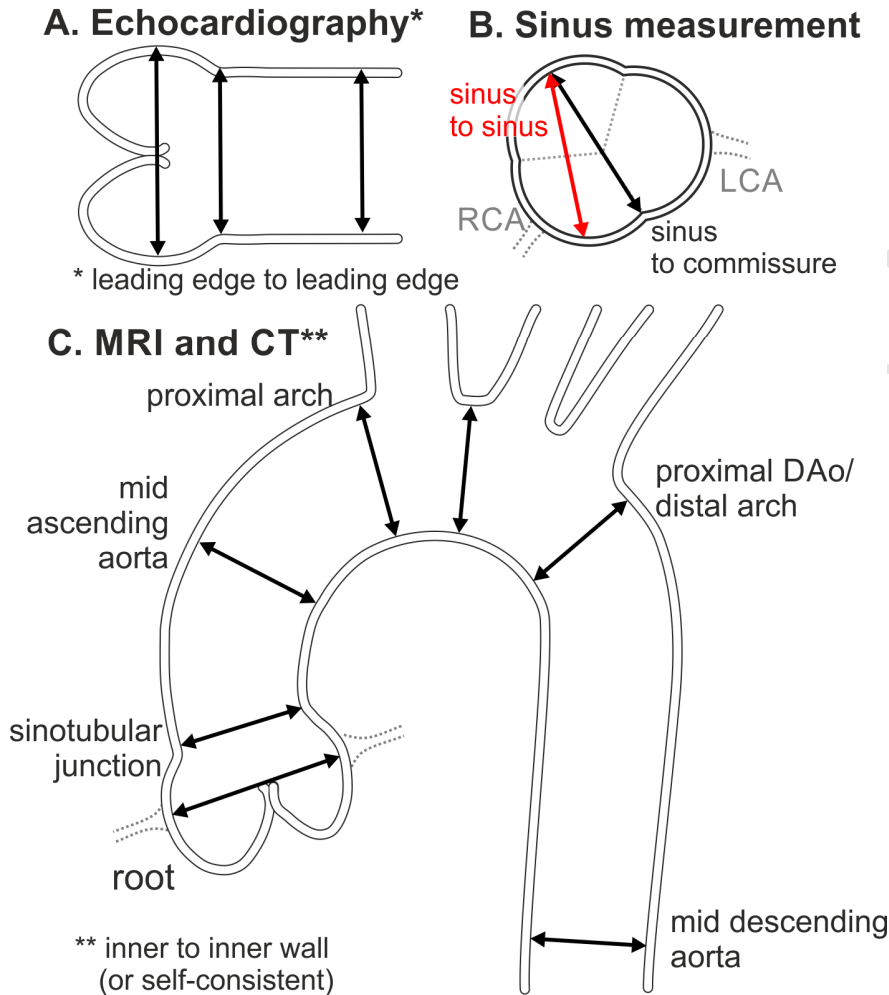
Figure 11. A.) Schematic shows the leading-edge to leading-edge measurement

technique used in echocardiography, from left-to-right; measurement of the sinuses of

Valsalva, sinotubular junction and proximal tubular ascending aorta. B.) Inner-to-inner

measurements used in MRI and CT. In addition, a consistent approach to measuring all

three sinuses with MRI and CT is necessary. The sinus-to-commissure and sinus-to-

sinus measurements can both be used, but consistency is necessary for interval

1   surveillance. C.) Standard measurement locations for MRI and CT with the inner wall to

2   inner wall technique.

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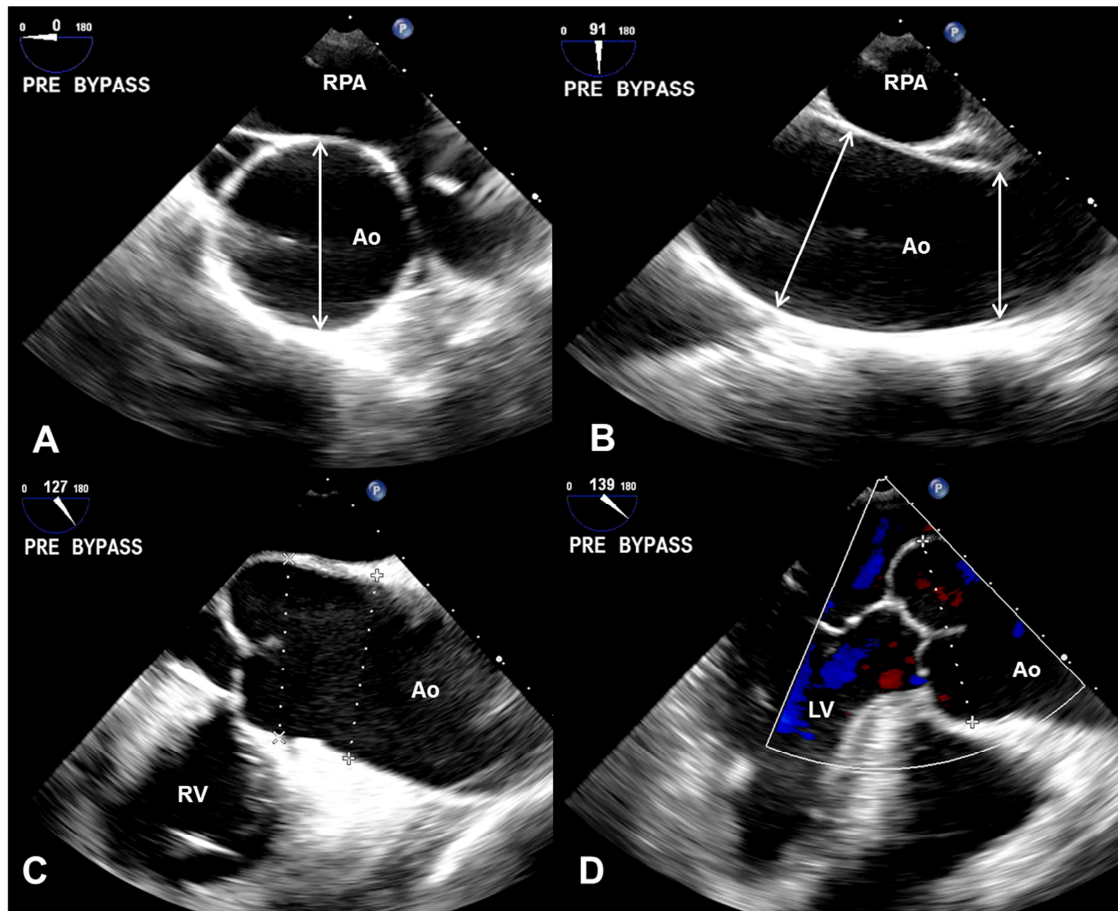
Figure 12. Transesophageal echocardiography aorta assessment. A.) Pre-bypass

echocardiogram of a 79 year-old man with typical BAV (right-left cusp fusion), mild

aortic stenosis and severe generalized aorta dilatation. High-esophageal mid-ascending

aorta short axis measurement (arrow) at 0°. RPA=right pulmonary artery, Ao=aorta. B.)

Same imaging position as A, now at 91° reveals the mid-ascending aorta at 52 mm (long

arrow) and the distal aorta (short arrow) at 49 mm. C.) Mid-esophageal long axis at 127°

allows measurements of the proximal ascending aorta and root (dotted lines). RV=right

ventricle. D.) Mid-esophageal long axis at 139° allows improved visualization of the

1   root, which measured 49 mm (dotted line). The patient underwent a Bentall procedure.

2   LV=left ventricle.

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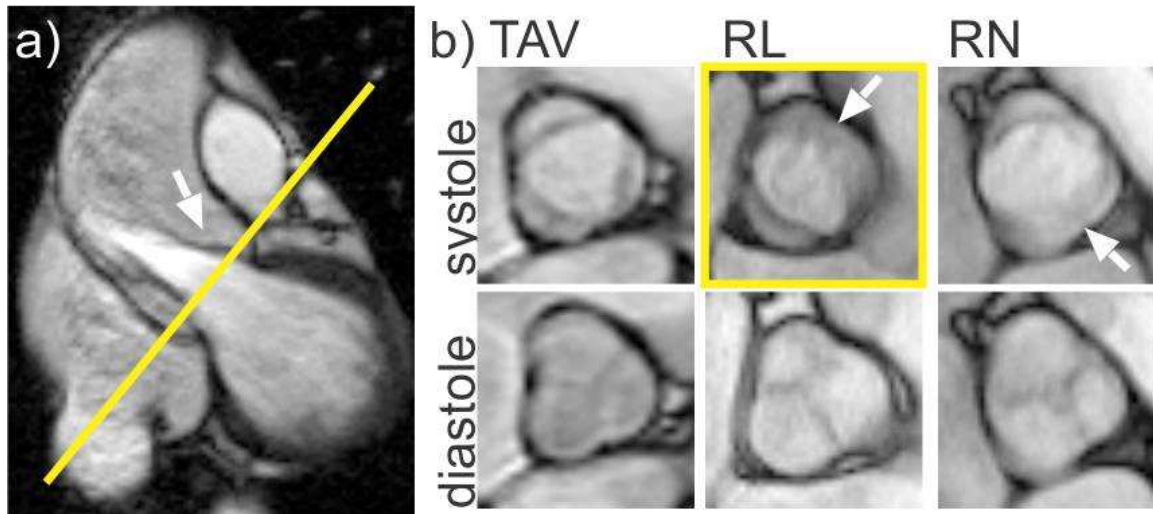
Figure 13. A.) 2D SSFP (steady state free precession) cine MRI showing the left ventricular outflow tract and the position of the aortic valve imaging plane shown in yellow. B.) TAV and the two most common BAV phenotypes, i.e. R/L and R/N cusp fusion. Arrows show the location of the raphe (if present) between the conjoined cusps. The conjoined R/L cusp (yellow box, arrow) is also seen to be doming in the corresponding left ventricular outflow tract view (see A, arrow). Bicuspidality of the aortic valve should be assessed in systole rather than diastole, since the valves often appear tricuspid when closed. Adapted from Entezari et al. [183]

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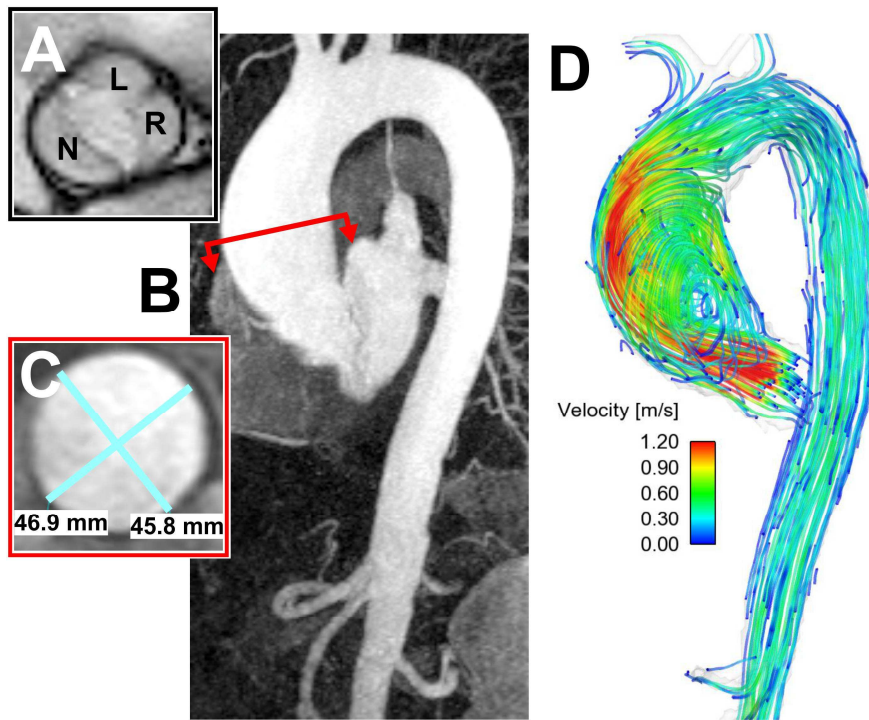
Figure 14. MRI of a 73 year-old male showing the (A) bSSFP (steady state free

precession) valve cines of a BAV patient with R/L fusion and no stenosis. B.) Contrast

enhanced MRA showed mild dilation of the sinus of Valsalva with a maximal dimension

of 40 mm and (C) a 47 mm dilation of the mid-ascending aorta. D.) An eccentric jet is

observed downstream from the non-stenotic bicuspid valve that impacts along the

anterior portion of the tubular aorta.

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6. Indications for Surgery

The most important clinical decision for patients with BAV-associated aortopathy is the appropriate timing of surgical intervention. Optimally, surgery should be recommended as soon as the risk of watchful waiting exceeds the risk of surgical intervention. Unfortunately, the precise time point when this occurs is patient- and surgeon-/center-specific and therefore oftentimes difficult to identify. Prophylactic aortic repair is recommended in order to prevent catastrophic aortic complications, particularly aortic dissection and rupture. When examining data obtained from retrospective and natural history studies, it is important to include patients suffering sudden, unexplained cardiac death as presumed (or at least possible) aortic complications.

Factors that need to be considered when recommending aortic repair include maximum aortic diameter, presence of aortic risk factors (i.e. rate of aortic growth, BAV phenotype, systemic hypertension, family history of aortic complications, or other aortic conditions such as coarctation or connective tissue disorders), presence of surgical risk factors (eg. advanced age, decreased left ventricular function, redo surgery), concomitant indications for cardiac surgery (most commonly aortic valvular stenosis or insufficiency), and surgeon / team experience and level of expertise. Although many different factors need to be considered when making this clinical decision, it is worthwhile noting that operative risk usually plays a lesser role for experienced aortic surgeons since the majority of BAV patients are relatively young with few surgical risk factors.

Despite the multitude of factors that need to be simultaneously assessed, we herein describe our general recommendations for surgical repair in BAV patients with aortopathy. For the purposes of clarity, indications have been divided into patients with

1 and without concomitant indications for AV surgery. In addition, recommendations for

2 management of the aortic arch are listed at the end of this section.

3

4 *A. Risk-Benefit Assessment of Additional Aortic Repair: General Considerations*

5 As in all surgical decision-making, the decision to repair the aortic root and/or

6 ascending aorta must be based upon the risk-benefit for a given patient in a given

7 institution or surgeon's hands. In this clinical scenario the risk of any complications

8 related to aortic surgery must be weighed against the potential benefit from preventing

9 aneurysm-related complications. According to recent STS data, isolated ascending aorta

10 replacement surgery is associated with a 3.4% risk of mortality and 3.2% risk of

11 stroke,[184] while aortic arch surgery is associated with a 5.1% risk of in-hospital mortality

12 and 5.3% risk of stroke.[184] In contrast, the corresponding risks for isolated AVR are 2.5%

13 and 1.5%.[185] While the addition of an aortic procedure to AVR is associated with no

14 demonstrable increase in morbidity or mortality at some large volume centers,[186-188] this

15 is not the case for most cardiac surgery institutions. Center- and surgeon-specific

16 volumes have consistently been shown to have an influence on outcomes in a wide

17 variety of technically complex operations, and aortic surgery is no exception. For

18 instance, Hughes et al examined patients undergoing aortic root or AVR plus ascending

19 aortic replacement surgery and found that operative mortality was 58% lower in high-

20 volume centers compared to low-volume centers.[189]

21

22

1 ***B. Indications for Aortic Repair in BAV Patients with Significant AV Dysfunction***

2   For those BAV patients with valve dysfunction significant enough to meet

3 indications for AV surgery, the recommended cut-off for concomitant ascending aortic

4 replacement is 4.5 cm (Class IIa, level of evidence C in AHA/ACC 2014 guidelines,[9]

5 ESC 2014 aortic guidelines,[12] ESC valvular guidelines[11]) (see Table 5). This

6 recommendation is primarily based on a retrospective study by Borger et al that showed a

7 higher incidence of subsequent aortic events in BAV patients undergoing AVR with an

8 aortic diameter of 4.5 cm or more.[57] It should be noted, however, that the vast majority of

9 follow up events were simple replacement of the ascending aorta during elective

10 reoperative AVR surgery. Another study supporting this cut-off showed that the majority

11 of BAV patients status post AVR who developed aortic dissection had aortic dilation

12 ≥4.5,[167] and a second study demonstrated an increased risk of dissection among BAV

13 patients with aortic dilation ≥4.5cm.[33] The incidence of aortic dissection and other aortic

14 catastrophes post-AVR is low, particularly in BAV patients with aortic stenosis.[49,57]

15   One argument supporting concomitant replacement of the aorta during AV

16 surgery, regardless of future risk of aortic complications, is the fact that the aortic wall

17 tends to be quite thin when the diameter exceeds 4.5 cm. Surgeons may therefore elect to

18 replace the aorta in such patients, rather than risk experiencing catastrophic tears in the

19 suture line of an effaced aorta at the end of the procedure. In contrast, avoidance of

20 prophylactic aortic repair in patients with moderate aortic dilation (i.e. 4.5 – 5.0 cm) is

21 prudent when extension of the myocardial ischemic time should be avoided (eg. patients

22 with poor left ventricular function).

23

1 *C. Specific Surgical Considerations for BAV Patients Undergoing AV Surgery*

2   Most BAV patients undergoing AVR do not require aortic root replacement

3 surgery. Indeed, the incidence of significant aortic root dilation post-AVR in BAV

4 patients is low, similar to patients with TAV disease [92, 190, 191] Root replacement is

5 recommended, however, in BAV patients with an aortic root diameter exceeding 4.5 cm.

6 [26, 57, 156, 192] Root replacement is oftentimes required is in BAV patients presenting with

7 acute aortic dissection, since the proximal root is frequently involved in the dissection

8 process.[32]   However, performing ascending aortic replacement alone and leaving a

9 modestly dilated root if the valve is intact may be prudent in patients in extremis in whom

10 an expedient operation may decrease operative mortality.[188]   Leaving the root "for

11 another day" should not be considered a failure in surgery for acute aortic dissection.

12   BAV patients may present with aneurysmal dilation and effacement of the

13 ascending aorta that extends preferentially into the non-coronary sinus. Such patients may

14 be effectively treated with a modified remodeling operation with a tongue of graft

15 extending into the non-coronary sinus. Such an approach spares the patient from the

16 added complexity and increased risk associated with a complete root replacement

17 operation, and is associated with a very low rate of subsequent aortic events. Studies

18 have shown excellent mid-term results using this technique.[193]

19   Type of implanted valve at the time of AVR may also influence the extent of

20 aortic repair in BAV patients. In patients with moderate aortic root dilation (i.e. 4.5 – 5.0

21 cm) who have opted for a mechanical valve, complete root replacement is reasonable.

22 Isolated AVR is preferable, however, in young patients who have opted for a biological

1   valve because of the low risk of subsequent aortic root rupture / dissection [92, 191] and the

2   increased technical difficulty associated with repeat aortic root replacement surgery.[194]

3   AVR surgery in BAV patients may be complicated by coronary anomalies, which

4   are far more common than in TAV patients.[195] The most common BAV-associated

5   coronary anomaly is a non-dominant right coronary artery, which can have implications

6   for myocardial protection during AV surgery. The position of the coronary ostia is also

7   more variable in BAV patients, with ostia frequently positioned directly adjacent to an

8   AV commissure. Such anomalies are important to note preoperatively and may cause the

9   surgeon to take a less aggressive approach to aortic root repair in such patients.

10

11 *D. Role of Valve-Sparing Aortic Root Replacement and AV Repair*

12   Patients with bicuspid aortopathy and relatively normal aortic cusps with good

13 mobility can be considered for valve-sparing aortic root replacement surgery (i.e. David

14 operation) in select centers. However, the indications for aortic repair should be the same

15 as for patients undergoing more conventional forms of surgery (see Table 5). With

16 careful patient selection, studies from high volume centers have shown that valve

17 sparing-aortic root replacement can be performed in BAV patients without increasing the

18 risk of reoperation or recurrent aortic regurgitation when compared to TAV patients.[196-

19 198] However, long-term results remain pending and some have expressed concerns of

20 increased long-term risk of aortic stenosis or recurrent insufficiency.[199-201] Further

21 research insights into the different BAV patient phenotypes will possibly shed more light

22 on the actual risk of these complications following repair/sparing procedures. Given that

23 valve-sparing aortic root replacement is more technically challenging in BAV patients,

1   such operations should be performed in referral centers by surgeons with substantial

2   clinical experience with the David operation.

3   Isolated AV repair has also been applied in select BAV patients. Based upon the

4   pathophysiologic classification of aortic regurgitation developed by El Khoury et al.,[202]

5   various approaches to AV repair have been developed.[203, 204] While good mid-term

6   results in BAV patients have been demonstrated in expert hands,[205, 206] debate continues

7   regarding the optimal method and even necessity of annular stabilization in such

8   patients.[207-210] Another topic of debate is the optimal commissural geometry for AV

9   repair in BAV patients.[211-213] The lack of consensus regarding these issues, the lack of

10   long-term follow up data, and the increased technical complexity of AV repair in BAV

11   patients has resulted in a lack of widespread adoption of these techniques by the general

12   cardiac surgery community.

13

14   *E. Indications for Aortic Repair in BAV Patients without Significant AV Dysfunction*

15   Current guidelines recommend intervention on the aorta in BAV patients without

16   significant aortic valvular dysfunction (i.e., valvular dysfunction does not meet criteria

17   for surgical valve repair/replacement) if the maximal aortic diameter exceeds 5.5 cm and

18   patients are lacking any high risk characteristics (see Table 5) (Class I, level B in

19   AHA/ACC guidelines[9, 10] and Class I, level C in ESC 2014 guidelines[12]). Such

20   recommendations are based on the observation that 6.0 cm represents a definite inflection

21   point in the risk of aortic complications in all patients regardless of AV morphology,[214]

22   and that natural history studies demonstrating a definitively increased risk of such

23   complications in BAV (in comparison to TAV) patients are debatable. Although

1   Michelena et al. demonstrated that BAV patients have a higher risk of aortic dissection

2   than the general population[33] it is unknown at what aortic diameter these dissections tend

3   to occur. In addition, the observation that many patients with aortic dissection present

4   with an aortic diameter of less than 5.5 cm (i.e. "aortic size paradox")[215, 216] is difficult to

5   interpret given that the denominator size for this group of patients is very large.[214] Indeed,

6   some studies of patients presenting with acute aortic dissection have demonstrated larger

7   ascending aortic diameters in BAV patients,[32, 167] refuting the notion that the BAV aorta

8   is less stable than the TAV aorta. The larger aortic diameters in BAV patients may be a

9   result of longer periods of exposure to increased aortic shear stress in patients born with a

10   congenital anomaly, as opposed to acquired disorders such as hypertension or

11   atherosclerosis. Such an explanation would be consistent with the increasing amount of

12   data supporting the hemodynamic theory of BAV-aortopathy, as opposed to the genetic

13   theory (see Section 3.A).   It would also underscore the importance of ongoing

14   surveillance of the aorta in BAV patients, with surgical intervention being recommended

15   only when appropriate thresholds have been reached. The above observations and the

16   definite -- albeit low -- risk of surgical intervention argue against routine replacement of

17   the aorta in BAV patients with smaller aortic diameters at the current time.

18   Certain factors may increase the risk of aortic complications in BAV patients and

19   therefore lead to earlier intervention.   Current guidelines recommend surgical

20   intervention at an aortic diameter of 5.0 cm in patients with any of the following risk

21   factors: aortic coarctation, systemic hypertension, a family history of aortic dissection, or

22   rapid aortic growth (> 3 - 5 mm/year) in experienced hands. In the AHA/ACC guidelines

23   this is a Class IIa, level of evidence C recommendation[9, 10] and in the ESC 2014 aortic

1   guidelines this is a Class I, level C recommendation.[12] Intervention at lower dimensions

2   can also be considered in patients with small BSA or stature, particularly if they have

3   Turner syndrome. Surgical repair is reasonable in Turner syndrome patients with an

4   indexed aortic diameter of 2.75 cm/m^2 or greater.[173] A similar indexed aortic diameter

5   cutoff[176] or an aortic cross-sectional area to height ratio of > 10 cm^2 / m[175] may also be

6   used to guide earlier surgical intervention in small stature patients. A lower threshold for

7   aortic repair (i.e. diameter of 5.0 cm) may also be considered in females planning

8   pregnancy, because of an increased risk of aortic complications in such patients. [217]

9   Finally, earlier intervention may also be occasionally justified in patients with a strong

10   preference for early surgery, particularly if their condition causes undue emotional stress.

11   A statement of clarification on management of aortopathy in BAV -- released by

12   the AHA/ACC in 2016 -- also recommended surgery if the aortic diameter is ≥ 5.0 cm,

13   the patient is at low operative risk, and the operation is performed by an experienced

14   aortic surgical team in a center with established expertise (class IIa, level of evidence B).

15   [10] Masri et al found that surgical intervention in BAV patients restored them to a normal

16   population survival curve and that patients with an aortic diameter > 5.0 cm who did not

17   undergo operative repair had a modestly increased risk of death or aortic dissection

18   during follow up.[2] However, the perioperative mortality in this study was only 0.4%.

19   Wojnarski et al from the same center also demonstrated a modestly increased risk of

20   aortic dissection starting at 5.0 cm in BAV patients, with a more pronounced increase in

21   risk starting at 5.5 cm.[175] Based on these findings, the current document makes a class

22   IIb, level of evidence C recommendation for surgical repair of low risk patients in

23   experienced aortic centers if the aortic diameter is > 5.0 cm (Table 5).

1   The above recommendations reflect a general change towards a more

2   conservative approach for BAV-associated aortopathy when compared to previous

3   guidelines, which stated that such patients should be managed as aggressively as those

4   with connective tissue disorders.[5] Studies published subsequent to these earlier guidelines

5   have demonstrated that BAV patients have a markedly lower risk of aortic complications

6   and aortic dilation than those with Marfan syndrome.[7, 33, 51] A recent joint statement of

7   clarification was published in order address these issues. [10]

8   Recent evidence suggests a marked difference in the natural history of BAV

9   patients with aortic regurgitation compared to stenosis. Girdauskas et al. found that the

10   ten-year freedom from adverse aortic events (dissection/rupture, death, and need for

11   proximal aortic surgery) was 78% in BAV with aortic regurgitation vs. 93% in BAV

12   stenosis patients.[86] Wang et al recently confirmed these results in a retrospective study.

13   [218] Other studies have demonstrated more rapid progression of BAV aortopathy in

14   patients with aortic root phenotype (i.e. dilation with greater diameter at the sinuses of

15   Valsalva than the tubular ascending aorta, typically associated with aortic regurgitation,

16   see Section 3.C).[29, 51, 82] In addition, a meta-analysis found BAV patients with aortic

17   regurgitation to be ten-times more likely to experience aortic dissection than those with

18   aortic stenosis.[219] It is therefore reasonable to consider aortic repair in BAV patients with

19   aortic regurgitation and root phenotype of aortic dilation at an aortic diameter of 5.0 cm.

20   Such patients may particularly benefit from a valve-sparing aortic root replacement

21   (David) operation, if done in an experienced center with known outcomes.

22

23

1 *F. Management of Aortic Arch*

2   In contrast to the ascending aortopathy, the natural history of the aortic arch in

3 patients with BAV is not well established. While there is correlation between BAV

4 morphology (e.g. Sievers type 1, R/L) and proximal aortic aneurysm, the association with

5 regards to aortic arch pathology is less clear.[220] Although some investigators have found a

6 correlation between Sievers type 1, R/N and aortic arch dilation[13, 68] this association is not

7 consistent. The relative lack of natural history studies is further confounded with the

8 denominator neglect phenomenon: while a few studies report the complications of aortic

9 arch aneurysm (e.g. numerator),[13, 220, 221] there is lack of data on risk of development of

10 aortic arch pathologies with BAV (e.g. denominator). Furthermore, the gap in knowledge

11 also applies to non-size criteria for intervention such as risk factors, genetic clusters,

12 aortic wall thickness and strain measurements for patients with BAV.

13   BAV aortopathy has been briefly addressed in multiple guidelines and consensus

14 statements, but most do not address the aortic arch specifically. Neither the 2010

15 ACC/AHA guidelines[5] nor the European Society of Cardiology Guidelines[12] discuss

16 indications for aortic arch repair in BAV patients. The 2014 Canadian Cardiovascular

17 Society Position statement was the first to recommend a threshold of 5.5 cm for

18 replacement of aortic arch aneurysm associated with BAV.[222]

19

20 *I. Aortic arch dissection*

21   Based on the IRAD registry, the risk that the aortic arch is involved during acute

22 type A aortic dissection is lower in BAV than TAV and Marfan syndrome patients.[223]

23 Furthermore, a Mayo clinic study reported that among patients with known aortic

1 dilatation prior to dissection, the mean diameter was lower for those with TAV compared

2 to BAV.[167] One can conclude from these observations that patients presenting with acute

3 aortic syndromes (acute dissection, IMH, or PAU) of the aortic arch should be treated

4 following the recommended guidelines for these pathologies, regardless of the aortic

5 valve morphology.

6

7 *II. Aortic arch aneurysm*

8 There is controversy regarding the indication for surgical therapy in aneurysmal

9 aortic arch disease in patients with BAV. While experts agree that symptomatic

10 aneurysmal aortic arch disease should be treated regardless of size, there is disagreement

11 in regard to the asymptomatic patient and the extent of the distal aortic repair.

12 Park and co-authors reported on a series of 422 BAV patients undergoing

13 replacement of the ascending aorta without intervention on the aortic arch.[221] These

14 patients were followed up for a median of 4 years with no reoperations for arch

15 dilatation.[221] They concluded that subsequent enlargement of the aortic arch after

16 ascending aortic replacement is rare.[221] They therefore recommended tailoring the extent

17 of distal aortic operation in BAV patients and avoiding arch repair if the transverse arch

18 is not significantly enlarged (i.e. ≥ 4.5 cm).[221]

19 A contrarian view has been expressed from investigators at Stanford University.[13,]

20 [220] Based partly on embryological studies showing migration of cells of neural crest

21 origin into the aortic arch, Fazel and co-authors performed hierarchical cluster analysis

22 and found five distinct patterns of aortic involvement in 127 patients with BAV. In

23 cluster III and IV, they found more frequent involvement of the aortic arch and therefore

70

1 recommended aggressive hemiarch or total arch replacement in experienced centers.

2 However, this study did not provide longitudinal information about the fate of the various

3 clusters. Furthermore, the amount of arch dilation found in such patients (median of 3.5

4 cm in cluster III) was well below the recommended thresholds for aortic arch repair.

5 Malaisrie et al. recently advocated extending resection into the arch when the

6 distal ascending or proximal arch was larger than 4.0 cm.[224] They compared 177 patients

7 who underwent hemiarch replacement to 207 patients who received isolated ascending

8 aortic replacement. The mortality rate increased from 1.5% to 3.0% in the hemiarch

9 patients, although the difference did not reach statistical significance in this small series.

10 There was, however, a statistically significant 54% increase in cardiopulmonary bypass

11 times and 35% increase in cross-clamp times in hemiarch patients.

12 The above information suggests that indications for repair of the aortic arch

13 should be no different in the setting of BAV compared to TAV. If a BAV patient presents

14 for AVR and has an ascending aortic aneurysm with a normal aortic diameter below the

15 takeoff of the innominate artery, ascending aortic repair without arch intervention is

16 recommended. If the aortic arch has a diameter of > 4.5 cm at the innominate artery

17 takeoff, hemiarch replacement is reasonable in experienced centers, with the

18 understanding that operative mortality and risk of stroke may be mildly increased. A total

19 arch replacement is reasonable in BAV patients undergoing AVR with a mid-aortic arch

20 diameter of ≥ 4.5 cm at the level of left carotid artery as measured by 3D aortic centerline

21 reconstructions. Such pathology is rare, however, and is usually found in BAV patients

22 with other causes of aortic arch dilation (eg. previous aortic coarctation repair,

23 concomitant connective tissue disorder or Turner syndrome, chronic aortic dissection).

1   Given the complexity of the latter operations, a referral to experienced aortic centers is

2   recommended. In emergency situations (eg. aortic dissection), even experienced aortic

3   surgeons may wisely opt to avoid compete resection of the diseased aorta and deal only

4   with the most critical aspects of the procedure. Complete resection of all affected aorta,

5   if necessary, can then be considered electively at a later time.

6

7   *III. Operative Volume and Outcome*

8   Situations in which an operation should be extended to a more aggressive

9   approach should take into consideration the expertise and comfort level of the surgeon

10   and the experience of the center. One set of previously published guidelines attempted to

11   define an experienced aortic center, but the recommended benchmark mortality rates (i.e.

12   < 1% for elective repair of ascending aorta and aortic root aneurysm repair) is far below

13   most reported series. [222]

14   A Japanese cooperative study examined 2,875 patients undergoing thoracic aortic

15   surgery in 36 centers between 2003 and 2005[225] and found an important impact of

16   hospital and surgeon volume on operative mortality. They found in young patients (<65

17   years of age), outcomes improved with increased hospital volume.[225] Risk-adjusted

18   mortality was 10% for centers performing less than 20 thoracic aortic operations during a

19   3-year period compared to 4% for centers performing more than 20 operations.[225] In

20   addition, observed outcomes in high-risk patients (i.e. Japan Adult Cardiovascular

21   Surgery Database predicted risk of mortality ≥6%) improved with increased hospital

22   volume.[225] Risk-adjusted mortality in these high-risk patients was 20% for centers

23   performing less than 20 thoracic aortic operations, compared to 12% for centers

1 performing more than 20 operations.[225] Gazoni et al.[226] also compared low volume

2 centers (less than 40 cases in 3 years) to high volume centers (greater than 80 cases in 3

3 years) in the Virginia Cardiac Surgery Quality Initiative. They found no difference in

4 mortality for ascending aneurysm with valve procedure (3.4% high vs. 5.2% low,

5 p=0.40), but increased mortality in low volume centers for isolated ascending aneurysms

6 (17% versus 3%, p = 0.01) and arch aneurysms (25% versus 5%, p = 0.01).[226] Thus,

7 ascending aortic replacement with or without aortic arch repair may be associated with a

8 higher complication rate than previously identified in centers with limited experience.

9 Taking into account the above findings, patients requiring more extensive aortic repair

10 involving the aortic arch should be referred to a center of expertise for non-emergent

11 surgery.

12

13 **Table 5:** Recommendations for aortic repair in patients with BAV aortopathy.

14

Recommendation	Class / LOE
Repair of the ascending aorta / root is recommended when the aortic diameter is 55 mm or greater in patients without risk factors	I / B [26, 27, 33, 156, 227]
Repair of the ascending aorta / root should be performed when the aortic diameter is 50 mm or greater in patients with risk factors (i.e. root phenotype and/or predominant aortic insufficiency, uncontrolled hypertension, family history of aortic dissection / sudden death, coarctation, aortic growth > 3 mm / year)	IIa / B [26, 27, 33, 156, 227]
Repair of the ascending aorta / root may be performed in patients with an aortic diameter of 50 mm or greater when the patients are at low surgical	IIb / C [2, 175]

risk and operated on by an experienced aortic team in a center with established surgical results.	
Concomitant repair of the ascending aorta / root should be performed when the aortic diameter is 45 mm or greater in patients undergoing cardiac surgery.	IIa / B [26, 33, 57, 156, 167, 192]
Repair of the aortic arch is recommended in patients with an aortic arch diameter of 55 mm or greater.	I / B [222, 228]
Concomitant repair of the aortic arch should be performed in patients undergoing cardiac surgery with an aortic arch diameter of 50 mm or greater.	IIa / C [229]
Concomitant repair of the aortic arch may be performed in patients undergoing cardiac surgery with an aortic arch diameter of 45 mm or greater, provided the patients are at low surgical risk and operated on by an experienced aortic team with established surgical results.	IIb / C [221]
It is recommended that patients undergoing elective aortic arch repair be referred to an experienced aortic team with established surgical results.	I / B [225, 226]

1   Legend: LOE = level of evidence

2

1

2 **8. Surgical Follow-up, Medical Management / Watchful Waiting, Family Screening**

3   The current section provides information regarding management and radiological

4 follow-up of BAV patients undergoing watchful waiting, as well as BAV patients who

5 have undergone aortic repair surgery. Recently published guidelines and review articles

6 on the subject may also be instructive. [18, 222]

7

8 *A.   Imaging post-surgery*

9   Imaging of the aorta soon after initial surgical repair is aimed at detecting

10 anastomotic leaks and pseudoaneurysms, as well as establishing a baseline for future

11 comparisons. For this purpose, an EKG-gated cardiac CT is preferred to TTE as

12 echocardiography is often limited by the presence of prosthetic aortic valves and provides

13 incomplete aortic imaging. In younger individuals (<50 years of age), however, MRI

14 may be preferable to repeat CT examinations in order to avoid the risk of radiation-

15 induced malignancy. Furthermore, in the setting of acute aortic syndromes, MRI is

16 particularly helpful in distinguishing mural thrombus from intramural blood.[230, 231]

17   The interval at which repeat imaging is performed following aortic surgery is

18 often dictated by the extent of the initial operation, and whether areas of aortic dilatation

19 were not addressed during the initial surgery. For example, if a supracoronary graft

20 replacement was performed in the setting of a moderate root dilatation that was not

21 addressed, then the imaging surveillance interval may be shorter. A similar situation may

22 arise if a moderately dilated aortic arch was left untreated during replacement of the

23 ascending aorta or if limited resection was performed in the setting of a type A dissection.

24 In patients who underwent complex hybrid reconstructions of the aorta (i.e. debranching

1 combined with endovascular repair), more frequent imaging is also advisable. In the

2 absence of residual aortic dilation / pathology, it is reasonable to suggest that the entire

3 aorta be imaged by CT or MR once every 3-5 years following aortic repair (see Table 6).

4 When possible, these studies should be performed at the same institution using similar

5 imaging techniques and protocols in order to minimize variation.

6

7 ***B.*** ***Medical management and watchful waiting***

8 The medical management of patients with BAV aortopathy who are subject to

9 ongoing watchful waiting is usually focussed on blood pressure control and overall

10 cardiovascular risk reduction via pharmacological and non-pharmacological measures.

11 The rationale for antihypertensive therapy is based on mechanistic and animal studies,[232,]

12 [233] as well as observational reports linking aortic dissection with hypertension. [234, 235] In

13 patients with BAV aortopathy, there are no randomized trials or observational studies to

14 help guide decision making. Treating hypertension with beta-blockers and/or inhibitors

15 of the renin-angiotensin system has been suggested, based largely on extrapolation of

16 data from Marfan patients. [18, 222] At the present time there are no data to support lower

17 BP thresholds for patients with dilated aortas in the setting of BAV, and therefore,

18 country- and region-specific guidelines for treatment of hypertension should be followed.

19 Target blood pressure thresholds in individuals without diabetes, over the age of 60, and

20 with multiple risk factors are likely going to change following the results of the SPRINT

21 trial, which demonstrated a reduction in overall cardiovascular mortality with an

22 intensive BP target of 120/80 in such individuals. [236] Although clinical data is lacking, it

23 may be reasonable to achieve these targets in subjects who do not meet the SPRINT

1   criteria who have specific factors including prior patient or family history of acute aortic

2   syndrome or sudden death, or aortic aneurysm growth despite medical therapy.

3   In patients with chronic aortic dissection, observational reports suggest lower risk

4   for operative repair with beta-blocker therapy. [237] In patients with type A and type B

5   aortic dissections, beta-blockers are associated with improved survival. [238] Use of

6   calcium-channel blockers has also been associated with improved survival in type B

7   aortic dissections, [238] as well as decreased rate of aortic expansion.[239] One study

8   identified an association between ACE inhibitor and better survival in patients with type

9   B aortic dissection, [240] although this was not confirmed in a more recent study. [238]

10   General counseling on non-pharmacological approaches to risk reduction should

11   be part of watchful waiting in BAV aortopathy patients. Such recommendations include

12   limiting salt intake (to reduce hypertension), a diet low in saturated fats, exercise (with

13   caveats, see below), and smoking cessation. Management of dyslipidemia should follow

14   regional and/or national guidelines based on primary or secondary prevention thresholds

15   and targets, where applicable.

16   There are no specific recommendations regarding automobile driving within the

17   2010 ACC/AHA guidelines.[5]   However, the Canadian Medical Association has

18   recommended that patients with abdominal aortic aneurysm be precluded from driving

19   when the rupture risk exceeds 10% per year. Based on the best observational data

20   available, these thresholds of risk occur for thoracic aortic aneurysms greater than 6.0 cm

21   in the ascending aorta or arch, and greater than 6.5 cm in the descending aorta.[176] A lower

22   threshold for rupture risk is reasonable for commercial driving. [222, 241]

1   Exercise prescription and/or restrictions should be individualized in patients with

2   aortic aneurysms. Patients with previously repaired aortic dissection should avoid

3   strenuous lifting, pushing, or straining that would require a Valsalva maneuver.[5, 222, 242,

4   243] *S*trenuous strength training may be dangerous for patients with BAV aortopathy, as

5   aortic dissection has been linked with weight lifting. [243] The proposed mechanism is

6   transiently elevated blood pressure associated with isometric exercise or Valsalva

7   maneuver. [242] Heavy weight lifting or competitive athletics involving isometric exercise

8   may trigger aortic dissection and therefore such activities should be avoided in patients

9   with moderately dilated aortas (i.e. > 4.5 cm), or where there has been a significant

10   interval increase in aortic size. However, individuals with bicuspid aortopathy can and

11   should undergo aerobic or endurance exercise, as these exercises are beneficial for blood

12   pressure lowering.[244] If patients wish to engage in vigorous aerobic exercise, such as

13   running or basketball, one might consider performing a symptom-limited stress test to

14   ensure that the patient does not have a hypertensive response to exercise. In patients with

15   a normal bicuspid valve and no associated dilated aorta, no restrictions of activity are

16   required.

17   The management of pregnancy in the setting of BAV is not well studied, and this

18   area has been recently summarized in a review.[18] In general, women with BAV should

19   undergo imaging of the entire aorta prior to pregnancy,[245] and pre-pregnancy evaluation

20   in women with known BAV aortopathy should be performed by practitioners with

21   expertise in the management of pregnant women with heart disease. The exact threshold

22   to recommend against pregnancy is not known, but it would reasonable to suggest that if

23   the ascending aortic diameter is either close to the threshold of surgical intervention, then

1   the risks and benefits be weighed and individualized decisions be made. Some studies

2   have suggested that women with ascending aorta and/or root dimension > 4.5 cm should

3   be advised against pregnancy, although this is controversial.[181, 222] A thorough

4   interdisciplinary, team-based approach is recommended in order to discuss case-by-case

5   scenarios.

6   Pregnant women with a dilated aorta, including BAV aortopathy, should have

7   strict blood pressure control and repeated echocardiographic imaging every 4–12 weeks

8   during pregnancy. [245] MRI (without gadolinium) is recommended if there is an indication

9   for imaging of distal ascending aorta, aortic arch or descending aorta during pregnancy.

10   TEE is an alternative to MRI for imaging of aorta during pregnancy.

11   Beta adrenergic blockers, to reduce shear stress on the aorta, may be considered

12   during pregnancy in women with a dilated aorta. Women with bicuspid aortopathy or

13   history of aortic dissection should deliver in a center where cardiothoracic surgery is

14   available.[245] The type of delivery (eg. cesarean section) and peripartum anesthetic

15   requirements should be determined in advance by the obstetrics and anesthesia teams.

16

17   *C. Family Screening*

18   Most cases of BAV disease are sporadic, but familial clustering has been a long

19   recognized phenomenon.[246] Genetic studies have suggested an autosomal dominant

20   pattern with incomplete penetrance and variable expressivity as the likely mode of

21   inheritance.[247] However, the preponderance of male patients with BAV and the

22   association with Turner syndrome has also suggested an X-linked pattern.[248] Several

23   different gene mutations have been linked to BAV disease including NOTCH1, TGF-ß2,

1 ACTA2, FNB1, KCNJ2, GATA5, Nkx2-5, and SMAD6.[249] The degree of genetic

2 heterogeneity is not surprising, given the marked heterogeneity of clinical findings in

3 BAV patients.

4   The heritability of BAV disease is over 80% and approximately 9-15% of first-

5 degree relatives have the disorder.[250] It is therefore recommended that first-degree

6 relatives of patients with BAV are screened with echocardiography.

7

8

9 **Table 6.** Recommendations for post-surgical repair, medical management and watchful

10 waiting.

Recommendation	Class / LOE
Radiological imaging (with either CTA or MRA) may be performed following aortic surgery to establish a post-repair baseline.	IIb / C
Ongoing postoperative surveillance intervals should be individualized based on the clinical, anatomical and surgical features. In the presence of residual aortic dilation / pathology, it is reasonable to image the entire aorta every 3-5 years by CT or MRI after repair.	IIa / B[12, 29, 51, 58, 156, 167]
MR should be considered for repeat examinations in an adolescent or in the adult population below the age of 50.	IIa / B[160]
Treatment of hypertension is recommended according to country- and region-specific guidelines.	I / C[52-54, 156, 251, 252]
Beta-blockers and inhibitors of the renin-angiotensin system should be considered for blood pressure control based on evidence extrapolated from	IIa / C[52-54, 156251, 252]

connective tissue disease populations. Non-pharmacological approaches (salt reduction, weight reduction) should also be advocated as part of blood pressure control strategies.	
Patients with aortic aneurysms that are at or near surgical thresholds for correction should avoid strenuous lifting, pushing, or straining that would require a Valsalva maneuver.	IIa / C[5, 222, 242, 243, 253]
It is recommended to avoid heavy weight lifting or competitive athletics involving isometric exercise when the ascending aortic diameter is greater than 45 mm.	I / B[5, 222, 242, 243, 253]
Patients with BAV and dilated aorta should be precluded from private driving if the ascending aorta diameter is greater than 6.0, and restricted from commercial driving if the ascending thoracic aorta diameter is greater than 5.5 cm.	IIa / C[222, 241]
It is recommended that pre-pregnancy evaluation and post-pregnancy management of women with BAV with or without associated aortopathy be performed by practitioners with expertise in the management of pregnant women with heart disease.	I / C[254]
First-degree relatives of patients with BAV should undergo screening echocardiography.	IIa / B[250]

1

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4

1 9. **Knowledge Gaps and Future Research**

2   Key questions remain unanswered with respect to BAV-associated aortopathy.

3 First, specific genetic and developmental causes of the congenital bicuspid valve

4 malformation itself remain unclear. A thorough genetic understanding has been

5 especially elusive, likely reflecting multifactorial genetic mechanisms. This critical gap in

6 knowledge influences the understanding of the wider spectrum of manifestations of

7 BAV-related diseases, including the heterogeneous expression of different phenotypes of

8 BAV aortopathy. It is reasonable to assume that the underlying pathogenesis of the

9 bicuspid valve itself may also play a role in the propensity, development, and progression

10 of BAV aortopathy. Further investigations of these root causes are necessary for a more

11 complete understanding of bicuspid aortopathy. Second, the causes of valve dysfunction

12 in the majority of BAV patients over time are unclear. Similarly, the causes of BAV

13 aortopathy in many – but a smaller proportion of -- BAV patients remain elusive. Third,

14 the marked clinical heterogeneity of BAV disease and the specific risk factors that

15 predispose individual BAV patients to valve dysfunction and/or to aortic

16 dilatation/dissection remain mysterious. Further research to clarify the pathophysiology

17 of BAV disease progression and to more precisely identify risk profiles for individual

18 patients with BAV is needed. Addressing these knowledge-gaps could dramatically

19 change our clinical and surgical approach to BAV aortopathy.[255]

20   Advances in knowledge may have been hampered thus far by a circuitous debate

21 about the pathogenesis of BAV aortopathy as "genetic" versus "hemodynamic". In light

22 of the increasing recognition of the heterogeneity of BAV aortopathy, this dichotomy has

23 begun to be questioned.[82, 256] In a recent study, aortic dilatation progressed at a yearly

1 rate that varied within a very wide range in a cohort of BAV patients followed for 3

2 years, and did not progress at all in 43% of them.[51] This marked heterogeneity suggests a

3 more complex pathogenesis than just "genetically determined" or "hemodynamically

4 driven". Both genetic variants and rheological abnormalities may coexist resulting in

5 diverse clinical phenotypes with distinct natural histories.

6   Most studies on BAV aortopathy generally disregarded the abovementioned

7 heterogeneous nature of BAV disease in terms of clinical features (age of onset, velocity

8 of progression, risk of acute events, etc.), valve morphology, and phenotypes. Future

9 studies on BAV aortopathy should be adequately designed to differentiate among distinct

10 forms of the disease.

11   Another common limitation of previous research in this field is the observational

12 nature of the majority of previous studies. Such retrospective studies report the

13 association of clinical factors, flow features, histopathology or molecular findings with

14 aortic dilatation in BAV patients and consequently infer their role in the underlying

15 pathogenesis. However, it is unclear whether the associated findings are a consequence of

16 the dilatation itself rather than a determinant or risk factor.[257] Future research must

17 advance beyond associative studies toward more informative mechanistic investigations,

18 functional studies, and experimental validations. Clinical randomized trials, particularly

19 of pharmacological treatments to either slow the progression of aortic dilatation or

20 prevent acute events, are particularly warranted. However, conducting these studies will

21 be challenging due to the slow progression of BAV disease and the need for large cohorts

22 to account for the different phenotypes. Nevertheless, multi-site longitudinal studies that

1   link clinical, genetic, and/or hemodynamic risk factors to patient outcome are urgently

2   needed.

3   Clinical studies may also be confounded by patient referral patterns and/or

4   selection criteria for enrolment. These issues may explain contradictory studies, which

5   are common in the field of BAV research. Clinical features of BAV aortopathy can vary

6   according to whether they are analyzed in population studies or with specific hospital

7   referral patterns, as well as between surgical and non-surgical studies. Failure to account

8   for these confounding factors and sources of bias can lead to misleading conclusions.

9   Another limitation of past research on BAV aortopathy has been the use of

10   inconsistent or ambiguous terminology, making it difficult to compare results between

11   studies.[93, 258] In addition, many clinical series were obtained from single center

12   experiences with a limited number of patients observed. Future collaborative multicenter

13   efforts with clearly defined terminology are warranted. Such studies may be spearheaded

14   by international organizations such as the recently established Bicuspid Aortic Valve

15   Consortium (BAVCON) research group.[28] Previous studies, especially those on

16   molecular and cellular aspects, tended to address novel pathways and pathogenetic

17   hypotheses rather than verify and expand previously acquired knowledge. Thus various

18   findings from different research efforts cannot converge into the establishment of a

19   definite pathogenetic sequence, i.e. all the subsequent mechanistic steps from the first

20   cause to the ultimate effect. It may be necessary to merge large amounts of patient data

21   and different investigators' expertise to ensure adequately powered study populations and

22   correct study designs.

1   At the present time, the greatest unmet clinical research need need is the

2   identification of optimal criteria for risk stratification. Prognostic stratification of BAV

3   aortopathy suffers from two important issues: the gaps in knowledge on the pathogenesis

4   of bicuspid aortopathy and the unknown mechanisms of acute aortic complications,

5   namely aortic dissection. It has been demonstrated that dissection occurs in the majority

6   of cases at aortic sizes well below the threshold recommending prophylactic aortic

7   resection,[259] although this observation can be explained by the "size paradox". [214] Some

8   investigators have advocated non-dimensional criteria for risk stratification.[260] These

9   should be derived from the validation of novel methods detect aortopathy in its early

10   stages and predict aortic disease development via pre-clinical aortic wall dysfunction or

11   aortic tissue disarray. Circulating biomarkers that are associated with aortopathy may be

12   particularly helpful in this regard, although preliminary studies in this area have not been

13   fruitful. A greater prognostic armamentarium would support a patient-specific approach

14   to BAV aortopathy,[59, 69, 255] especially in terms of criteria informing surveillance, surgical

15   indications and follow-up. Future advances may be best achieved using emerging

16   diagnostic imaging modalities, such as 4D-flow MRI and computation fluid dynamics,[144]

17   possibly combined with novel molecular biomarkers.[260]

18   In conclusion, research on BAV aortopathy is challenging for many reasons.

19   There remain significant gaps in our current knowledge that limit best practices and

20   adherence to clinical guidelines. Future investigations should account for epidemiologic

21   and phenotypic heterogeneity of the disease. Multicenter and multidisciplinary teams

22   should be leveraged to perform robust hypothesis driven analyses.[28] Basic and

23   translational approaches may help inform clinical studies.

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16

A L R N

B

C 46.9 mm 45.8 mm

D

Velocity [m/s]
1.20
0.90
0.60
0.30
0.00