BAV Aortopathy
When to Operate?

Ismail El-Hamamsy, MD PhD

"There is no disease more conducive to clinical humility than aneurysms of the aorta"

- Sir William Osler (1849-1919)

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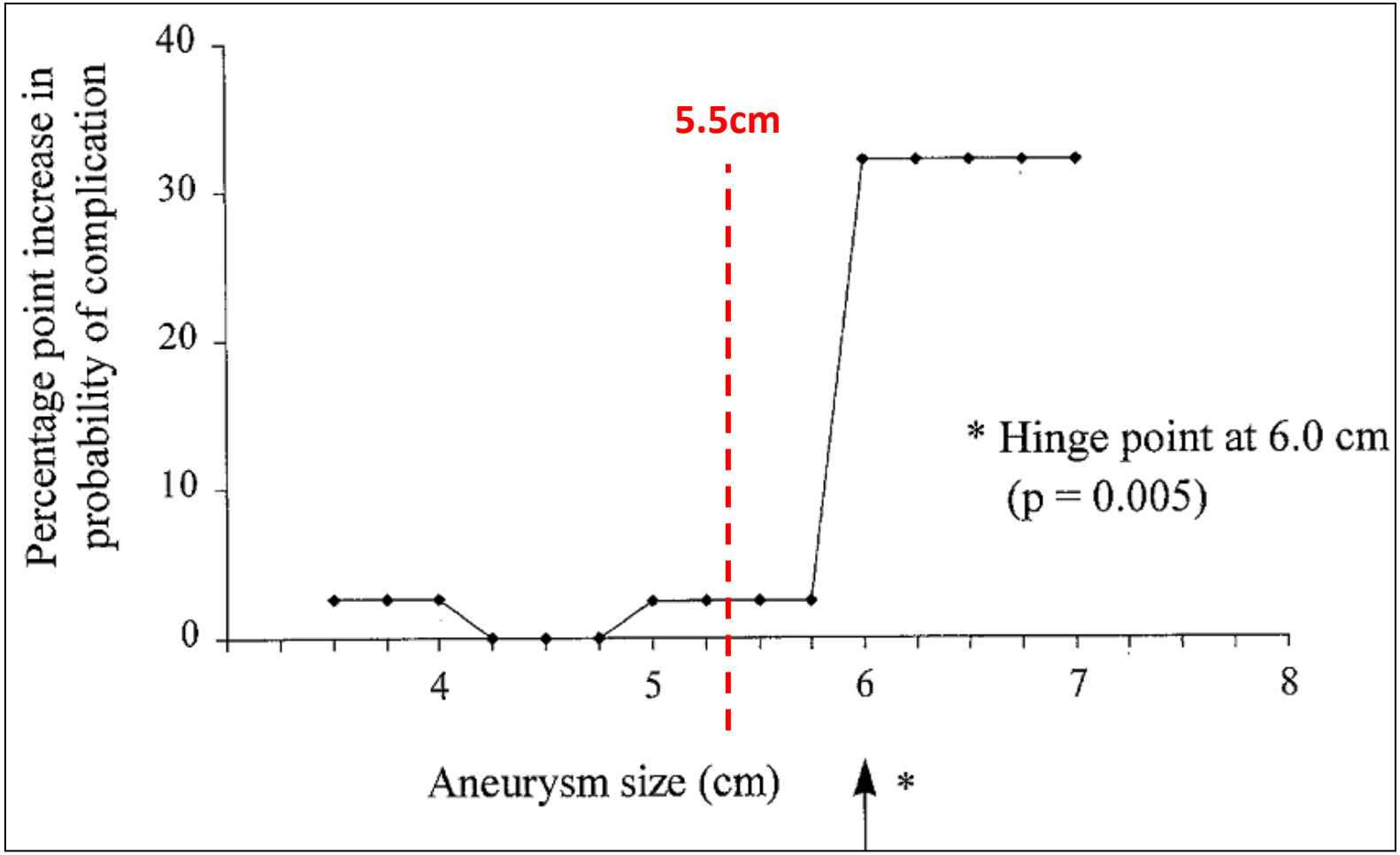
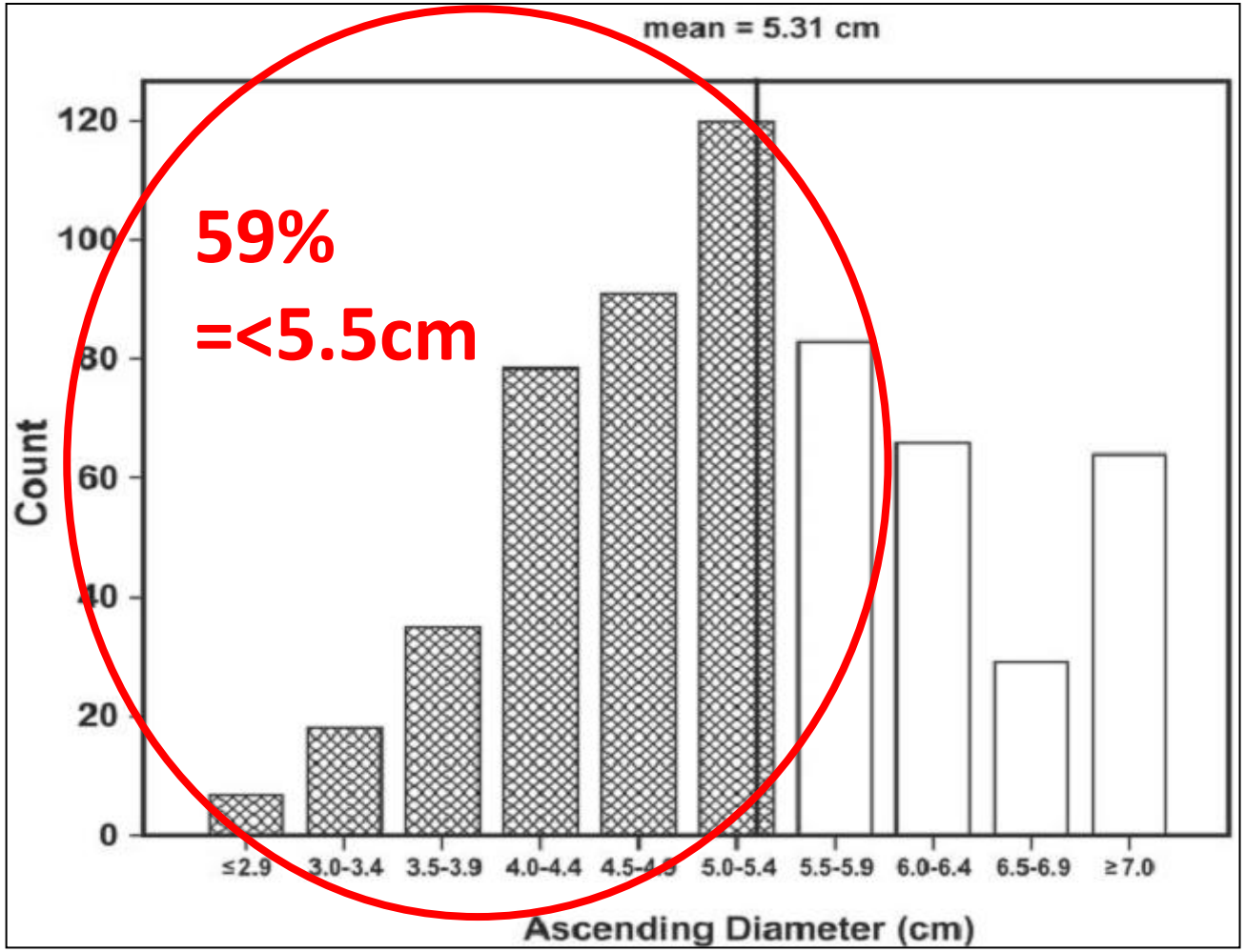
Surgical Indications



Coady et al. J Thorac Cardiovasc Surg 1997;113:476-91

Surgical Indications



Pape et al. Circulation 2007;116:1120-7

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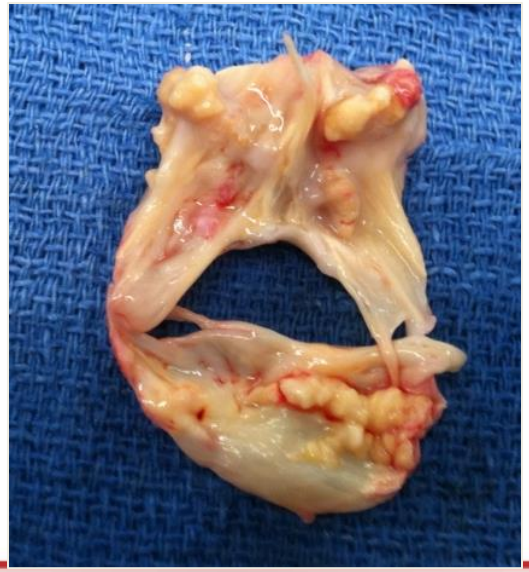
Surgical Indications

~~***One Size Fits All***~~

Bicuspid Aortic Valves

- 1-2% of the population

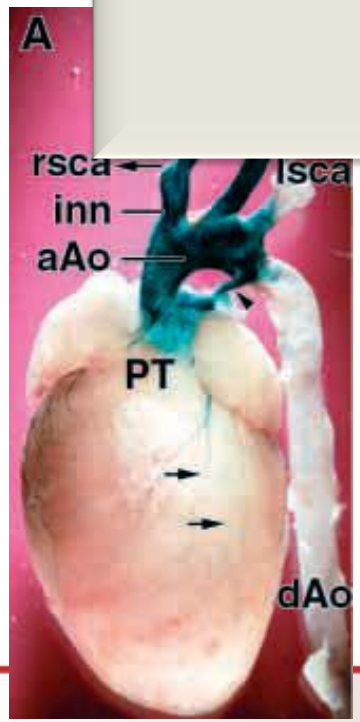
- The most common cardiac congenital malformation



Bicuspid Aortic Valves

Common Cell Lineage – Neural crest cells

40% = Dilatation of the Ascending Aorta



However...

- BAV is **NOT** a single disease entity
- BAV is a common phenotypic manifestation of different “entities”
- Can vary in phenotype, genetics, molecular and clinical behaviour

BAV Heterogeneity

- Phenotype
- Genotype
- Associated Features
- Natural History

Etiology of Aortic Disease

Aortic Aneurysms

- SYNDROMIC (5%)
- NON-SYNDROMIC (95%)
  - FAMILIAL (20%)
  - SPORADIC (80%)

Thoracic Aortic Aneurysms

Table 1 | Summary of the known syndromic and nonsyndromic familial forms of TAAs

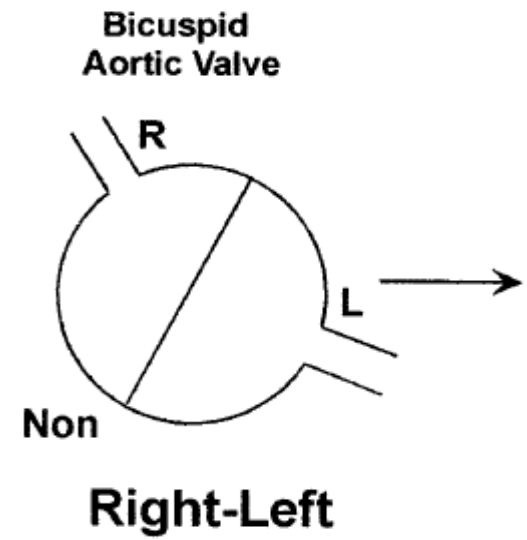
TAA classification	Chromosome	Gene	Protein	Location	References
Syndromic					
Marfan syndrome	15q21.1	*FBN1*	Fibrillin 1	ECM	2, 49, 99, 144, 148, 160–162
Marfan-like syndrome	3p24-25	*TGFBR2*	TGF-βR2	Cell surface	107, 108
Loeys–Dietz syndrome	3p24-25 9q33-34	*TGFBR2*, *TGFBR1*	TGF-βR2, TGF-βR1	Cell surface	80, 81 81
Ehlers–Danlos syndrome	2q24.3-31	*COL3A1*	Type III collagen	ECM	109, 111
BAV–TAA syndrome	9q34-35, others	*NOTCH1* Unidentified	Notch 1 Unidentified	Intracellular	57, 112, 116 114, 115, 163
Arterial tortuosity syndrome	20q13.1	*SLC2A10*	GLUT10	Intracellular	120, 121
Turner syndrome	45,X0	Unidentified	Unidentified	Unidentified	118
Noonan syndrome	12q24.1 2p21-22 12p12.1	*PTPN11* *SOS1* *KRAS*	PTPN11 (SHP2) SOS1 GTPase K-Ras Unidentified Unidentified	Intracellular Cell membrane Cell membrane	122
Polycystic kidney disease	16p13.3 4q21-22	*PKD1* *PKD2*	Polycystin 1 Polycystin 2	Cell membrane	123

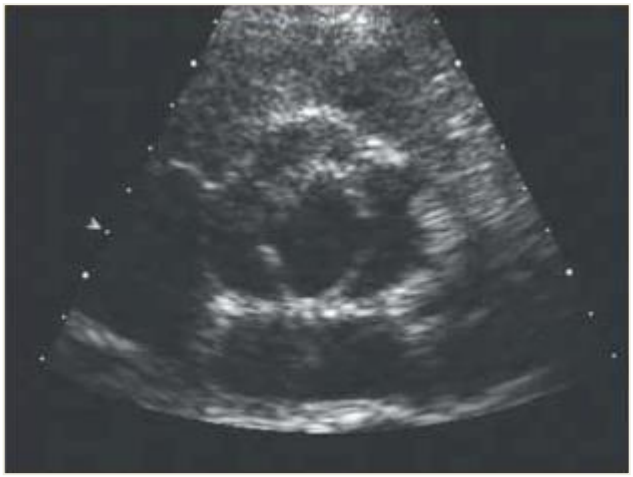
El-Hamamsy and Yacoub. Nature Reviews Cardiology 2009

BAV Heterogeneity

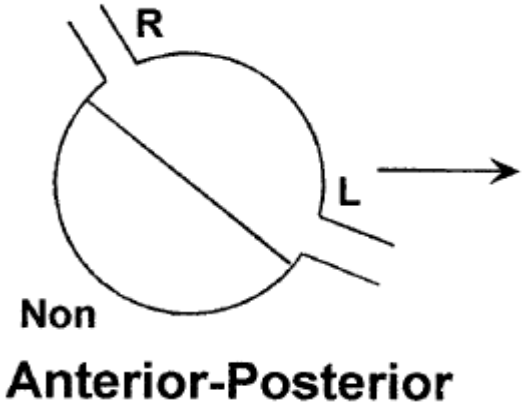
Condition	Incidence of BAV
Coarctation of the aorta	50%
Turner syndrome	30%
Supravalvular AS	30%
Sinus of Valsalva aneurysm	15%-20%
Ventricular septal defect	30%
Shone complex	60%-85%
Ascending aortic aneurysm	Common
Loeys–Dietz syndrome	2.5%-17%
ACTA2 mutation familial thoracic aneurysm syndrome	3%
Anterior mitral leaflet prolongation/prolapse	Common[45,46]

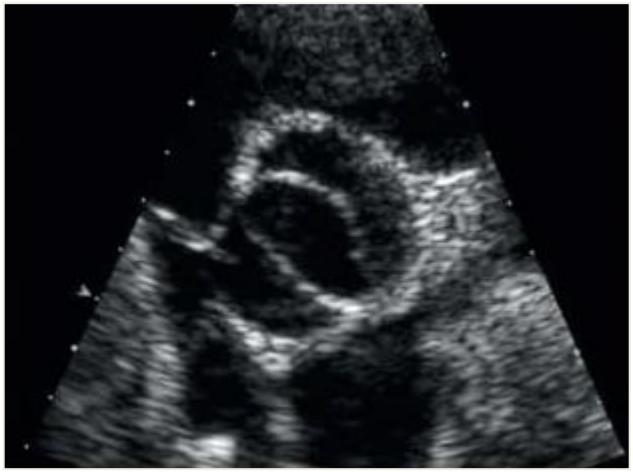
Phenotypic Heterogeneity





10-25% of BAVs

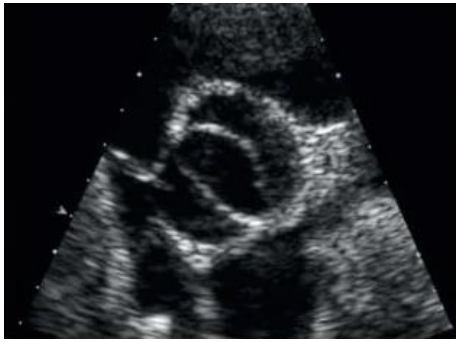


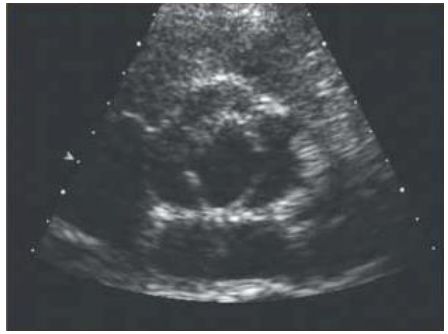


75-90% of BAVs

Tzemos et al. JAMA 2008

BAV Phenotype and Co-Features

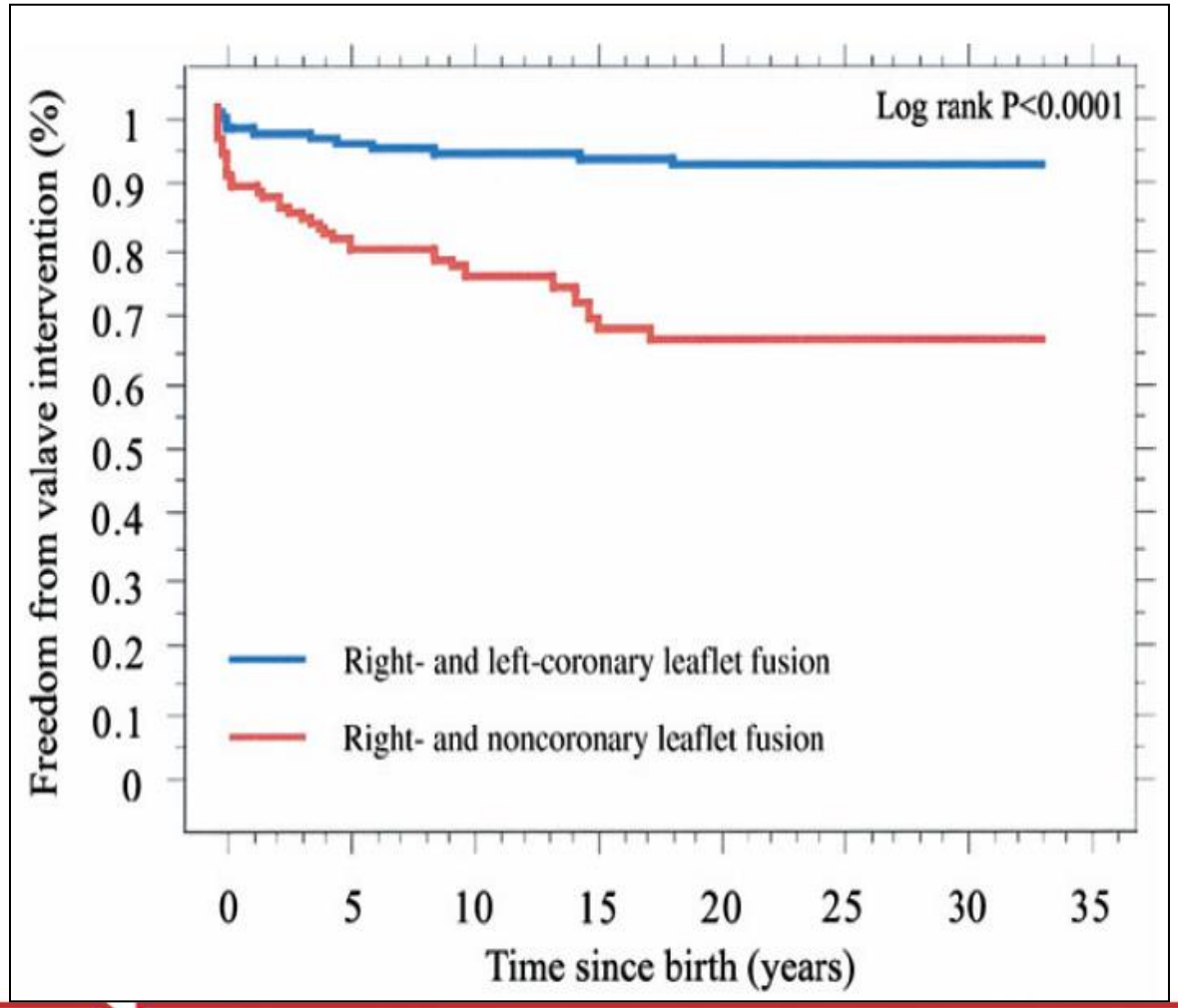


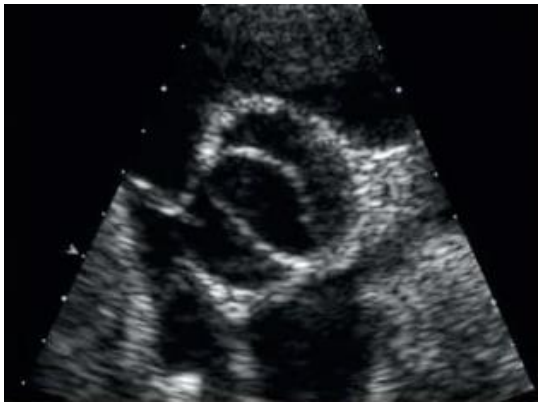


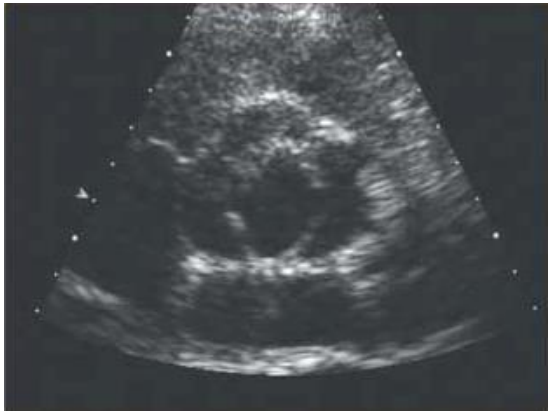
	Total Patients	Valve Morphology, N (%)	
		R-L	R-N
Isolated BAV	569	335 (58.9)	225 (39.5)
Aortic coarctation	295	262 (88.8)	31 (10.5)
Left heart defects*	155	123 (79.4)	28 (18.1)
Non-left heart defects†	116	79 (68.1)	36 (31.0)
All patients	1,135	799 (70.4)	320 (28.2)

Fernandes et al. JACC 2004

BAV Phenotype and Interventions







Fernandes et al. JACC 2004

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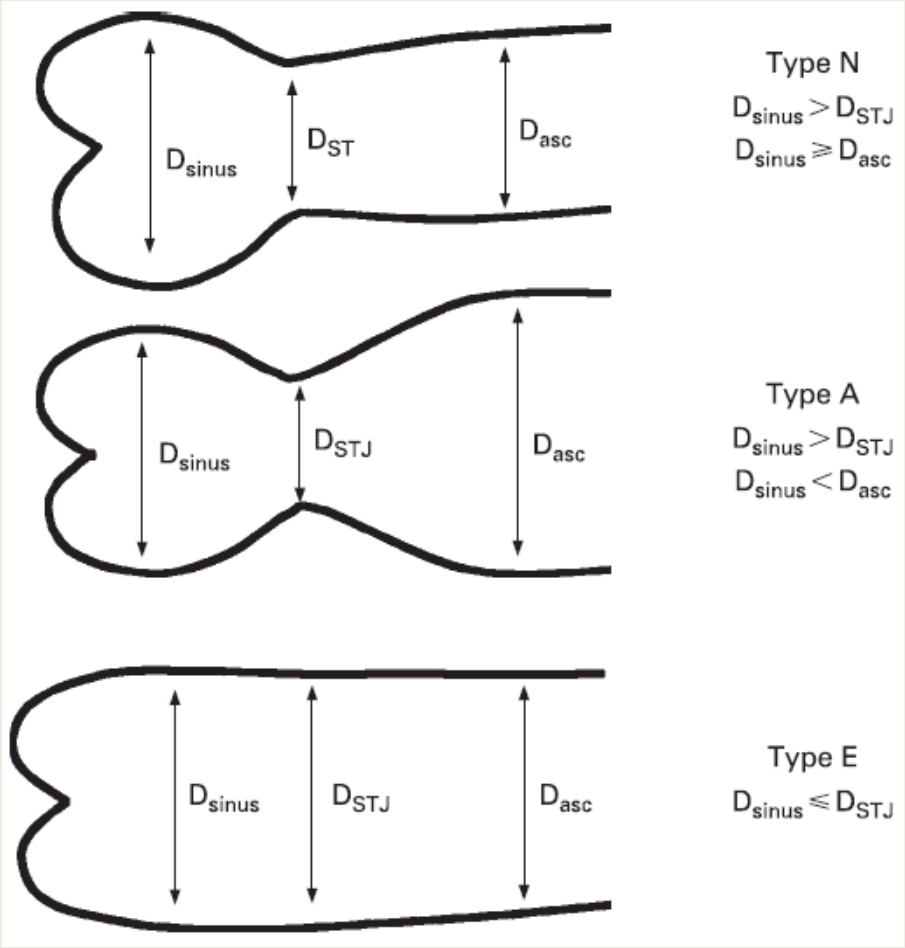
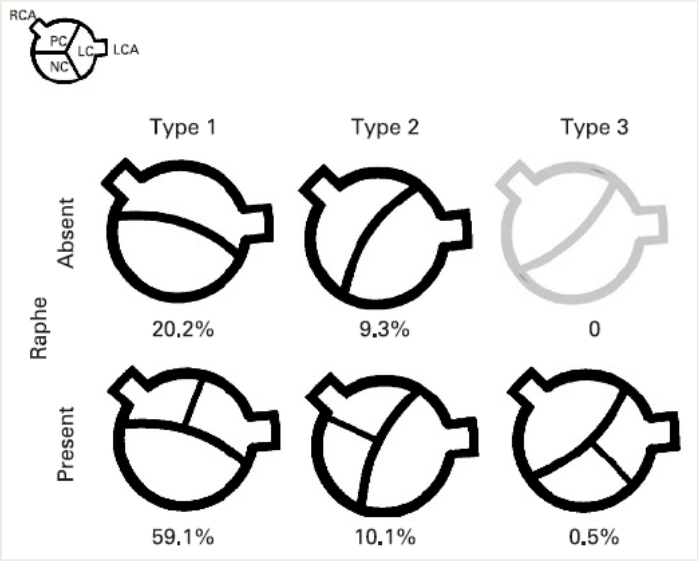
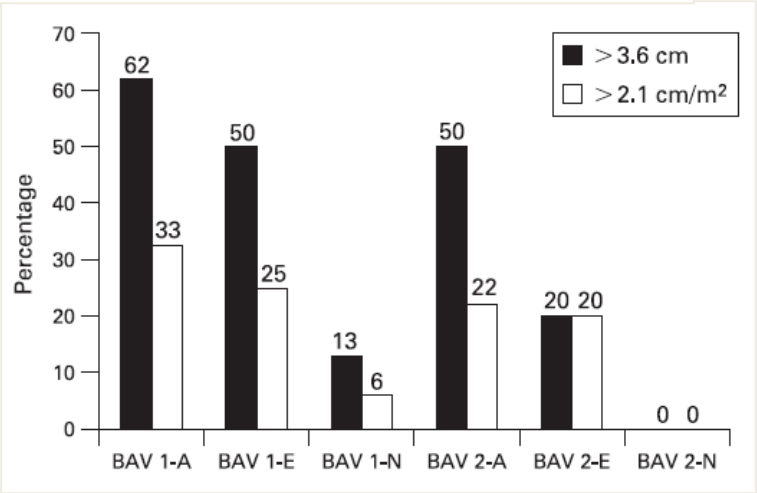
Phenotype and Aortic Morphology







Schaefer et al. Heart 2008

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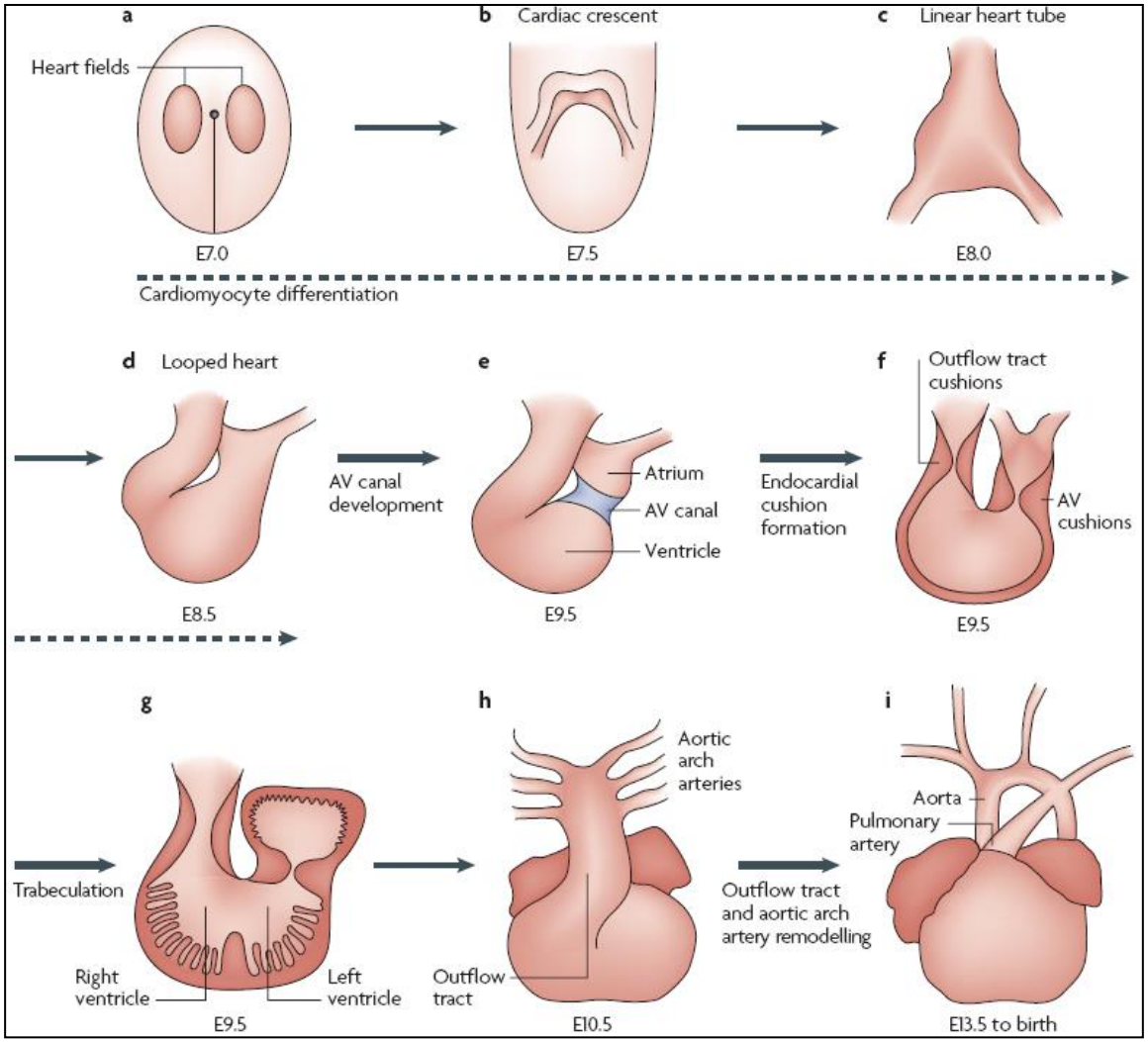
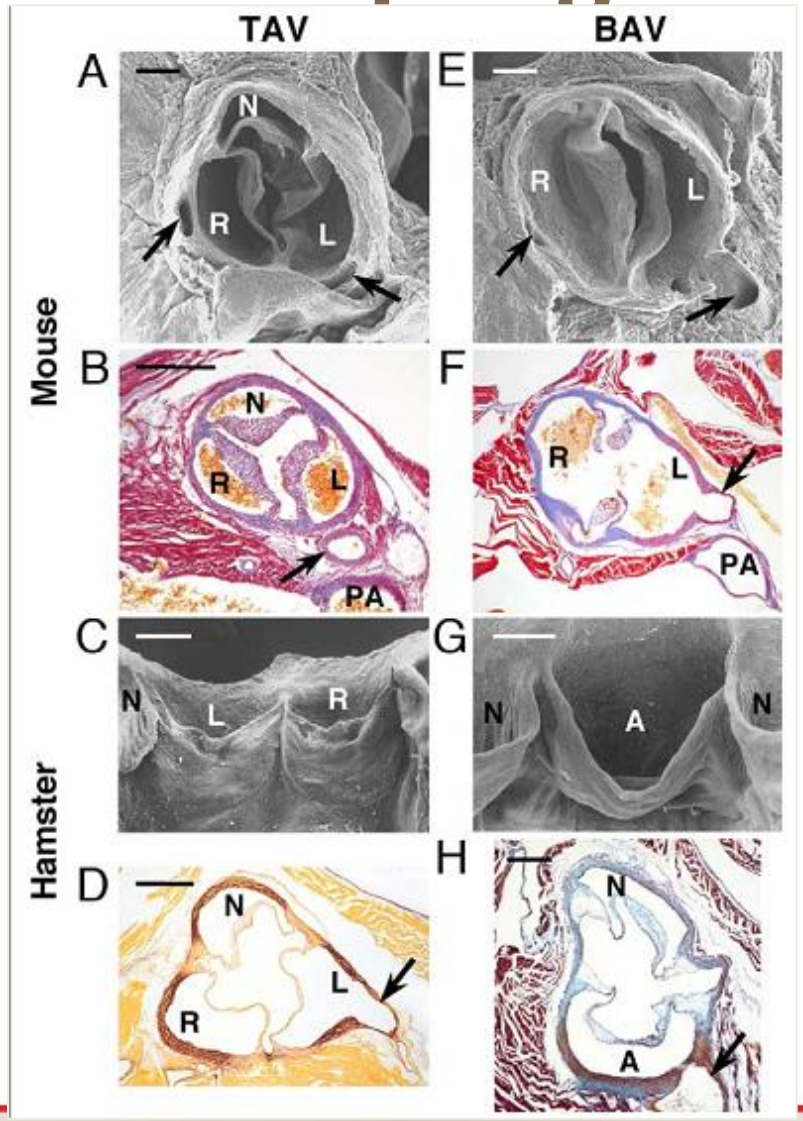
Developmental Biology



Valve Morphogenesis



eNOS -/-
(R-N BAV)

Spontaneous
(R-L BAV)

Fernandez et al. JACC 2009

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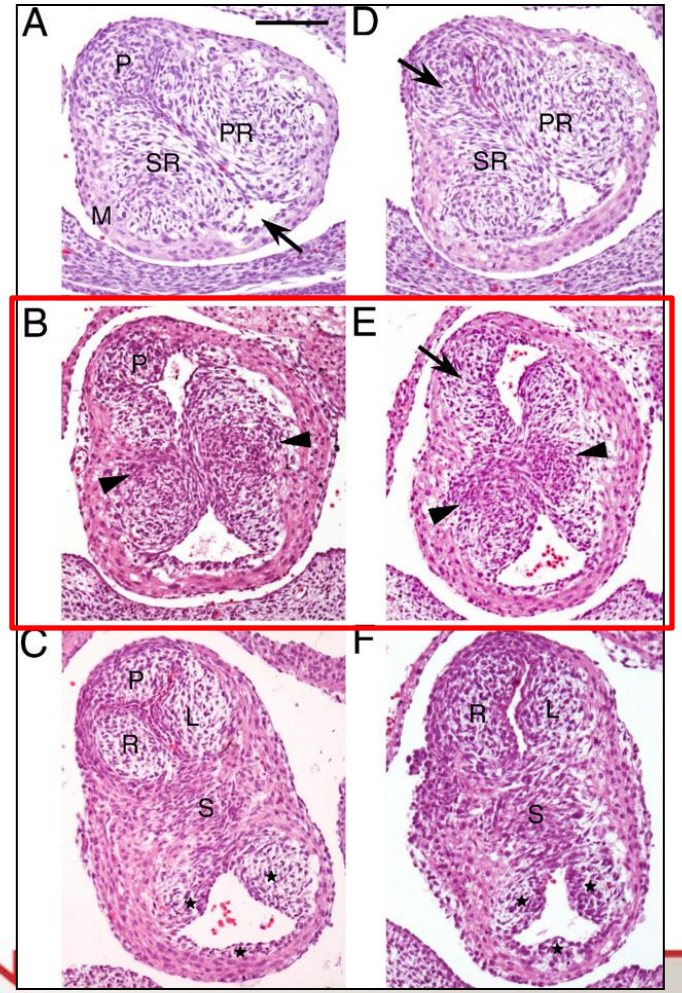
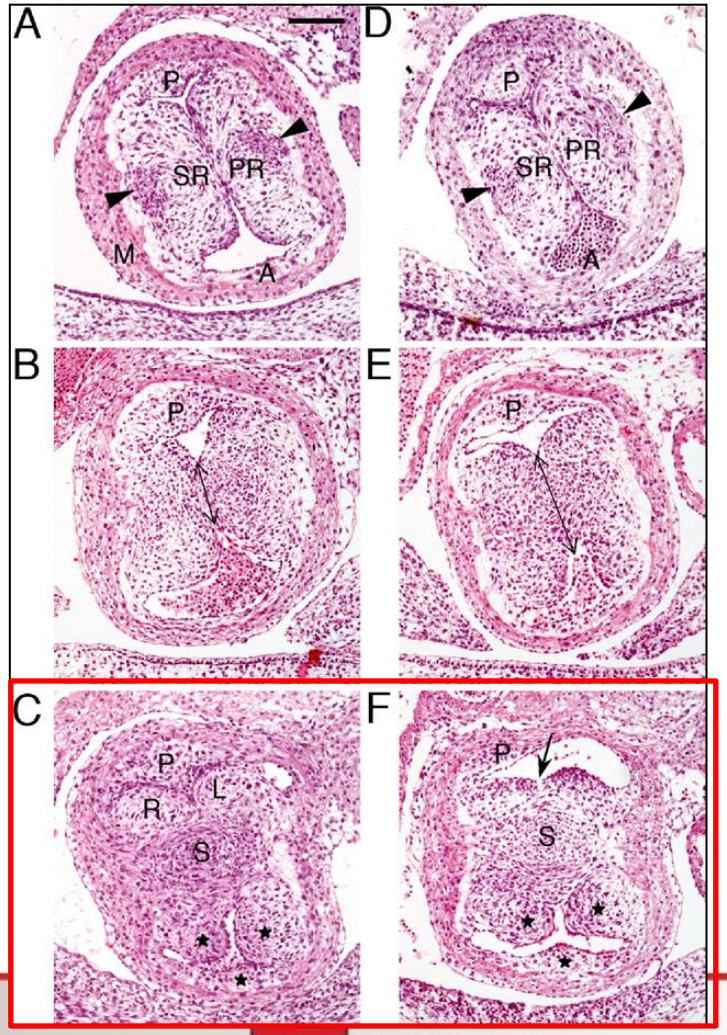
Valve Morphogenesis

Mouse (R-N)



Hamster (R-L)



Fernandez et al. JACC 2009

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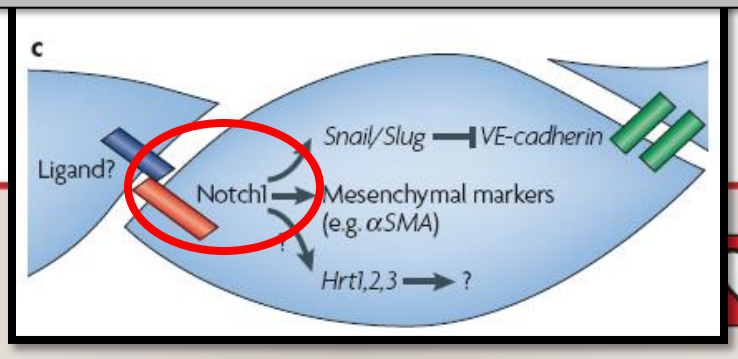
Genetic Heterogeneity

- Several genes implicated on different chromosomes
  - KCNJ2 *(Andelfinger G, Am J Hum Genet 2002)*
  - NOTCH-1 *(Garg, Nature 2005)*
  - ACTA-2
  - 18q, 5q and 13q *(Martin LJ, Hum Genet 2007)*

NOTCH-1 and BAV

NOTCH-1 Signalling

- Valve development
- Outflow tract remodelling
- Boundary formation in the AV canal
- Ventricular trabeculation
- Cardiomyocyte differentiation



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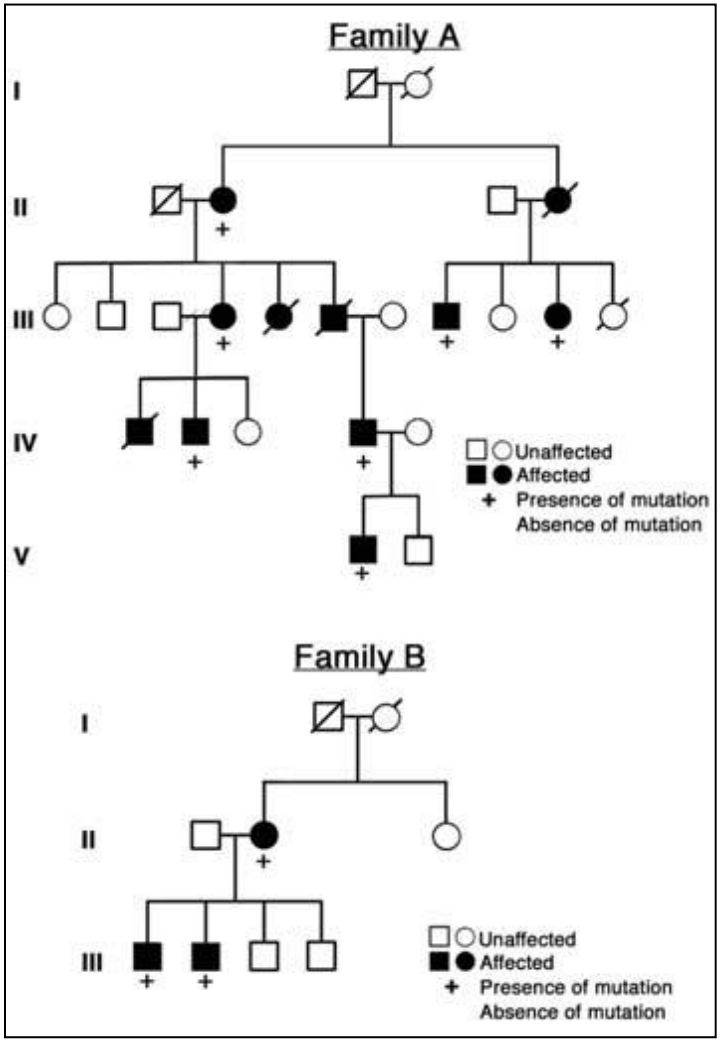
NOTCH-1 and BAV



II-1	AS	+	
II-2	AS	+	+
III-3	Dysmorphic AV	+	
III-4	VSD		
III-5	Severe AS	+	+
III-6	Severe AI	+	+
III-8	Mild AI		+
IV-1	TOF		
IV-2	Mild AS	+	
IV-4	MS, VSD		+
V-1	Mild AS	+	+
II-1	Severe AS	+	+
III-1	MA, HLV, DORV		+
III-2	Severe AS	+	+

Garg et al. Nature 2005

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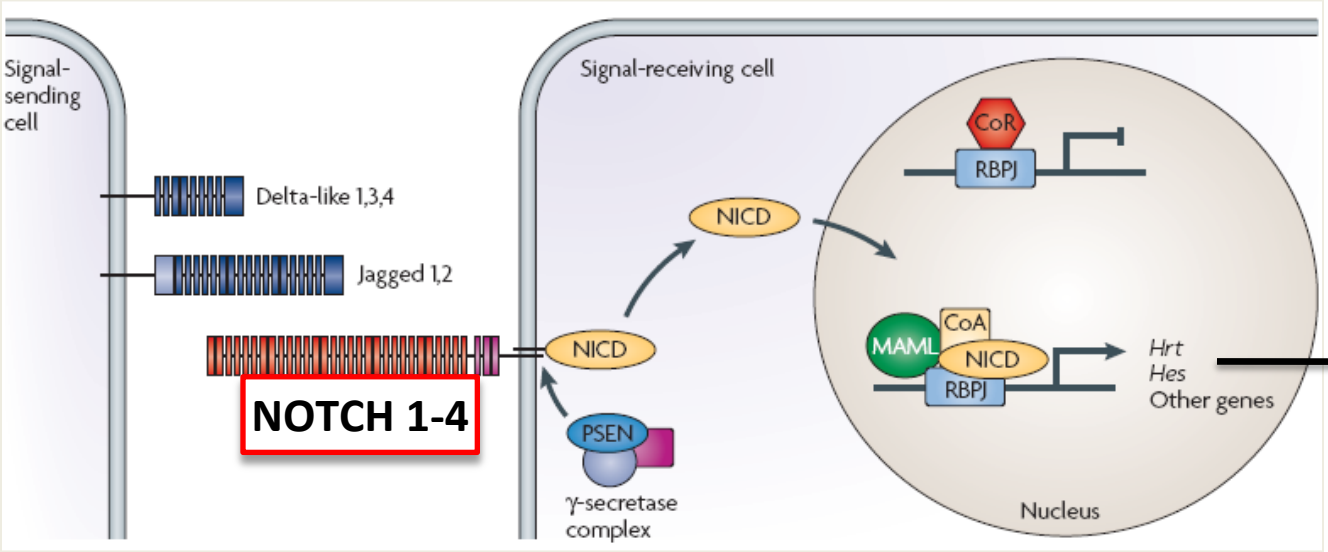
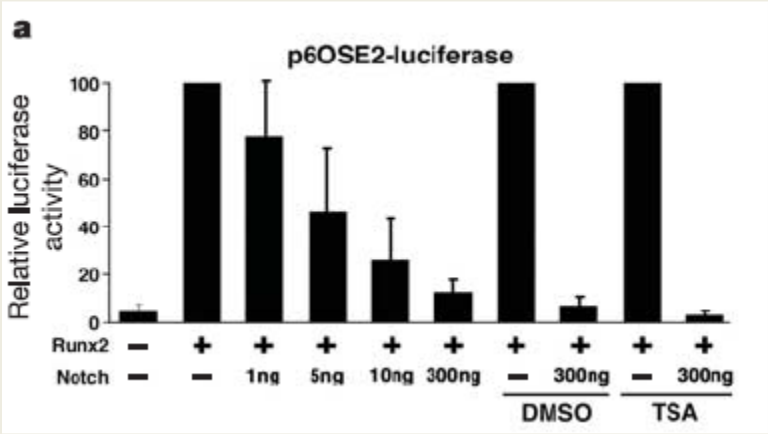
NOTCH-1



Runx2 (cbfa1)

Ostoecalcin
Osteopontin

Calcification



Garg et al. Nature 2005

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Genetic Heterogeneity

- NOTCH-1 Mutations < 10% of BAVs

  Mohamed et al. Biovhem BiophysRes Comm 2006

  McKellar et al. JTCVS 2008

BAV and Associated Aortopathy

BAV and Aortic Dilatation

Aortic dilatation

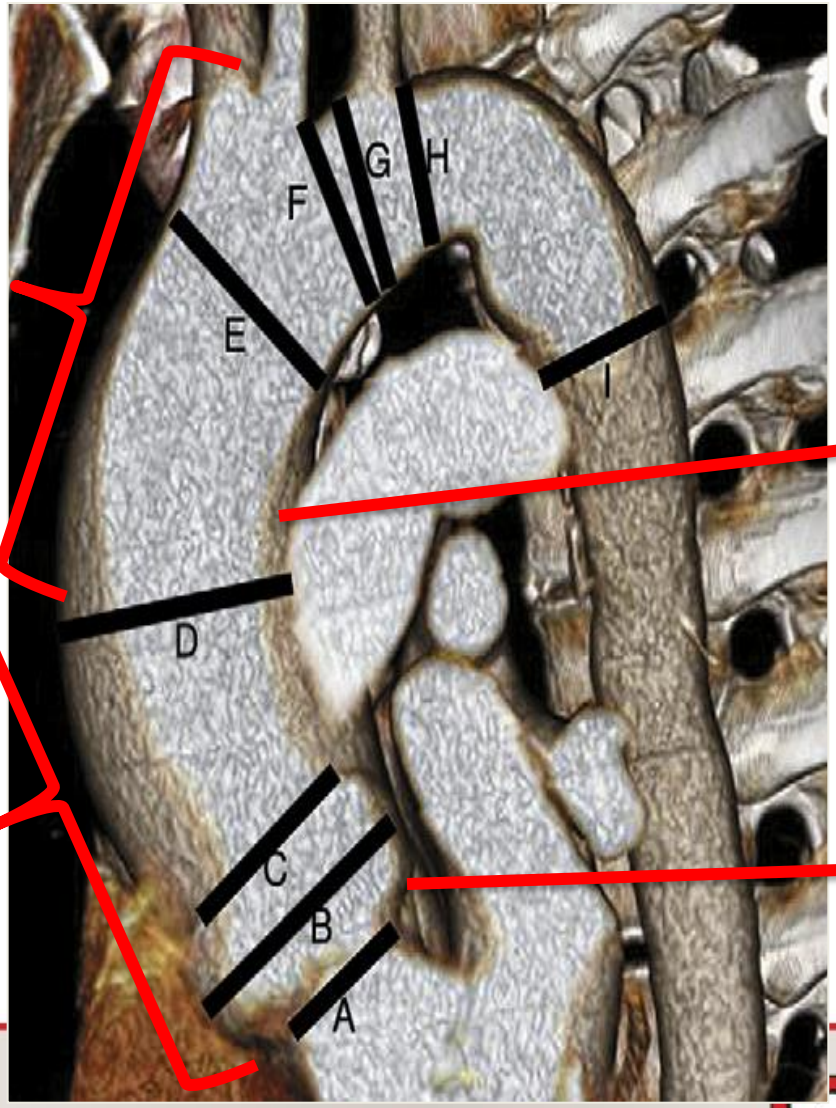
=

30-50% of BAVs

Patterns of Aortic Dilatation

III- Asc Aorta + Arch - 28%

IV- Root + Asc Aorta - 45%

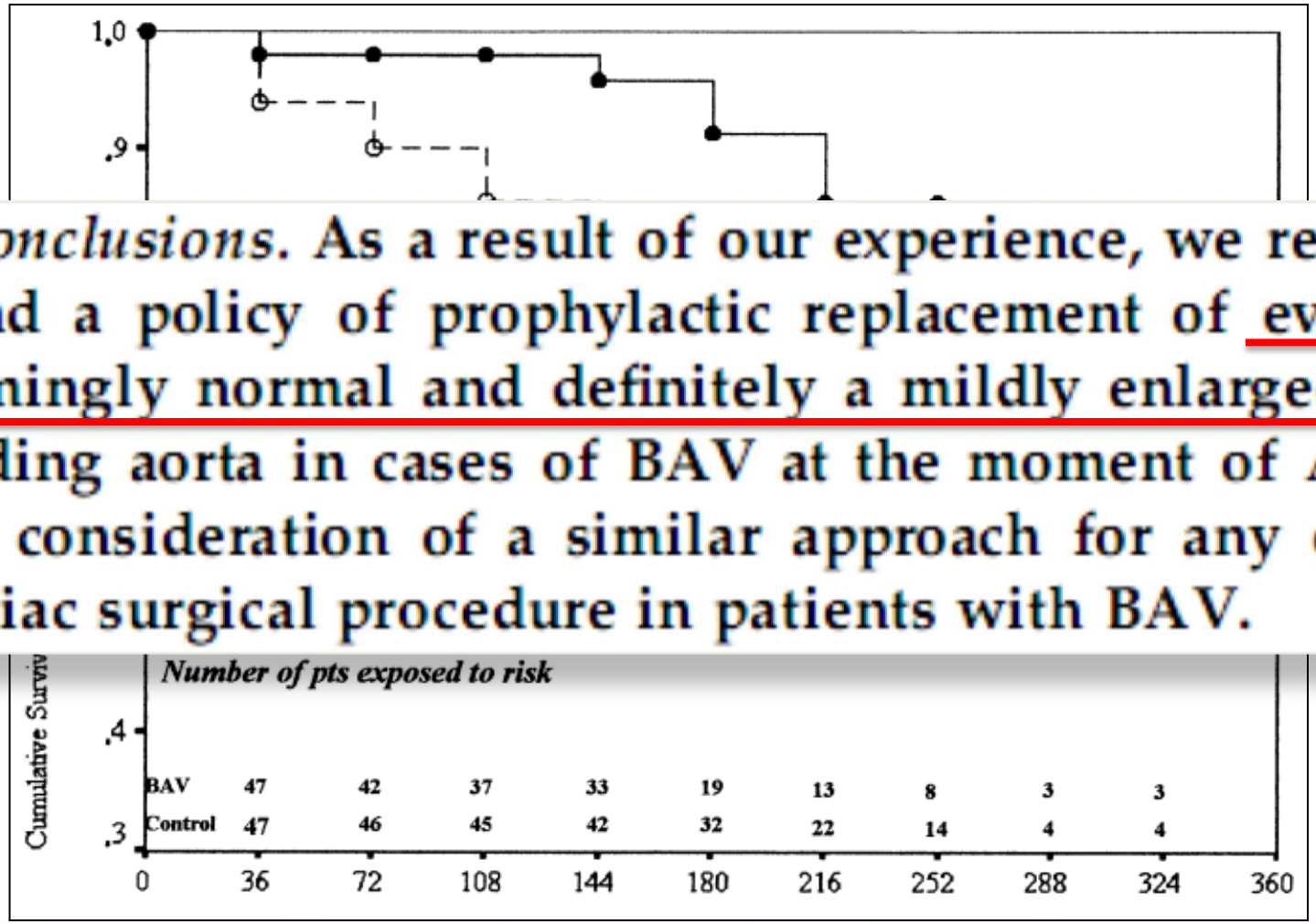


II- Asc Aorta alone - 14%

I- Root alone 13%

Fazel et al. JTCVS 2008

Natural History of Aorta in BAV



Conclusions. As a result of our experience, we recommend a policy of prophylactic replacement of even a seemingly normal and definitely a mildly enlarged ascending aorta in cases of BAV at the moment of AVR, and consideration of a similar approach for any other cardiac surgical procedure in patients with BAV.

Russo et al. ATS 2002

Bicuspid Aortic Valves

3.3. Bicuspid Aortic Valve With Dilated Ascending Aorta

Class I

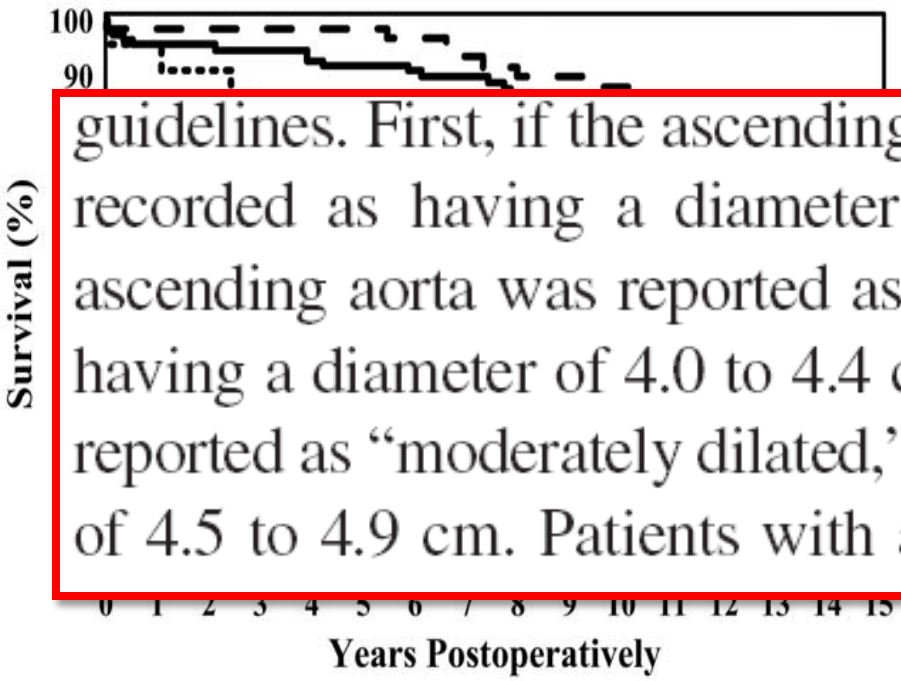
4. Surgery to repair the aortic root or replace the ascending aorta is indicated in patients with bicuspid aortic valves if the diameter of the aortic root or ascending aorta is greater than 5.0 cm* or if the rate of increase in diameter is 0.5 cm per year or more. *(Level of Evidence: C)*
5. In patients with bicuspid valves undergoing AVR because of severe AS or AR (see Sections 3.1.7 and

3.2.3.8), repair of the aortic root or replacement of the ascending aorta is indicated if the diameter of the aortic root or ascending aorta is greater than 4.5 cm.*

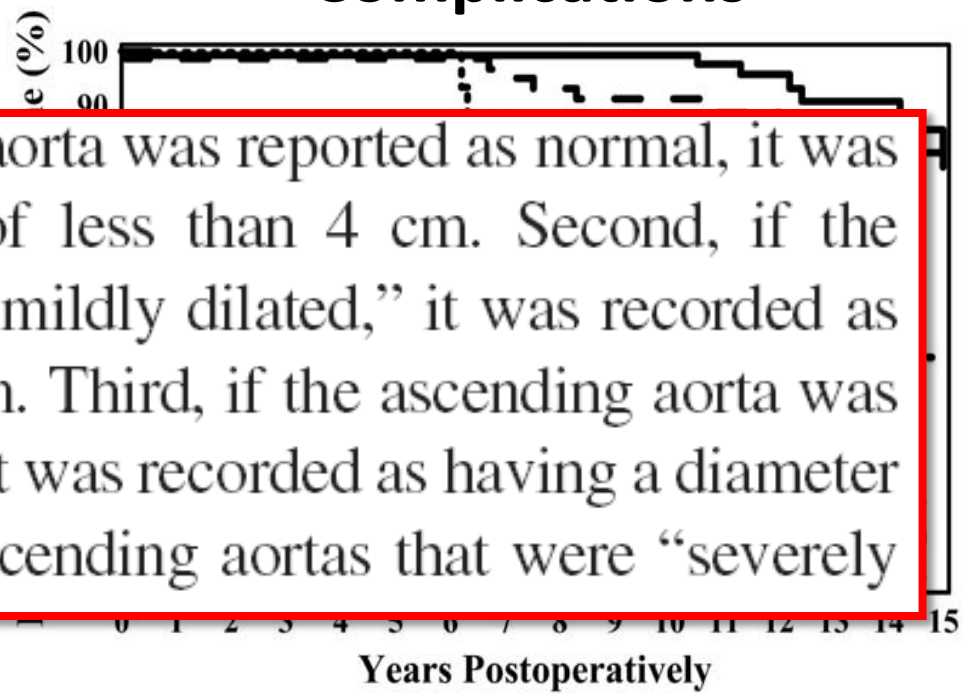
ACC/AHA Valve Guidelines, Circulation 2006

Bicuspid Aortic Valves

Survival



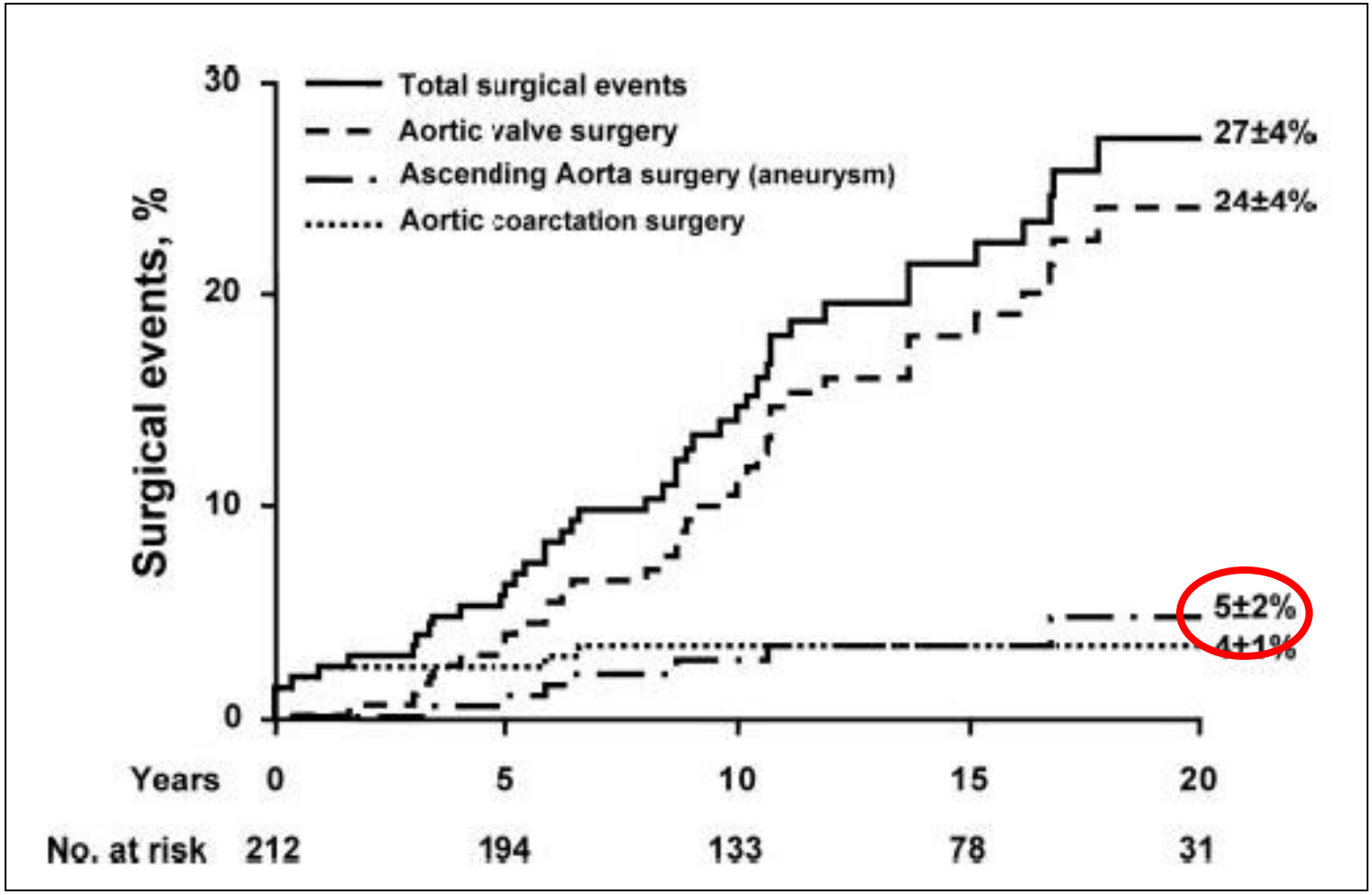
Complications



guidelines. First, if the ascending aorta was reported as normal, it was recorded as having a diameter of less than 4 cm. Second, if the ascending aorta was reported as "mildly dilated," it was recorded as having a diameter of 4.0 to 4.4 cm. Third, if the ascending aorta was reported as "moderately dilated," it was recorded as having a diameter of 4.5 to 4.9 cm. Patients with ascending aortas that were "severely

Borger et al., JTCVS 2004

Natural History of Aorta and BAV



Michelena et al. Circulation 2008

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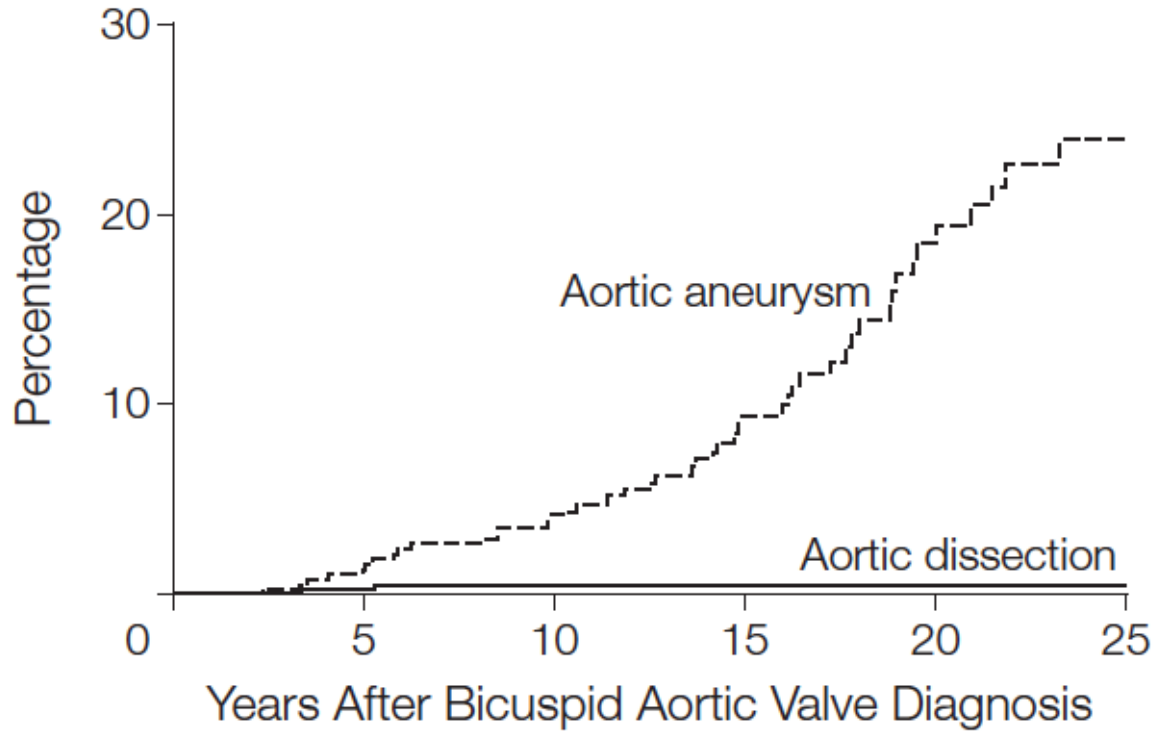
Study features, clinical outcomes	Contemporary clinical outcomes of BAV studies*							
	Michelena and colleagues[26]	Tzemos and colleagues[27]	Michelena and colleagues[33]	Davies and colleagues[50,†]	Russo and colleagues[56]	Borger and colleagues[57,‡]	McKellar and colleagues[58]	Girdauskas and colleagues[30,§]
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 postisolated 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 y, 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%

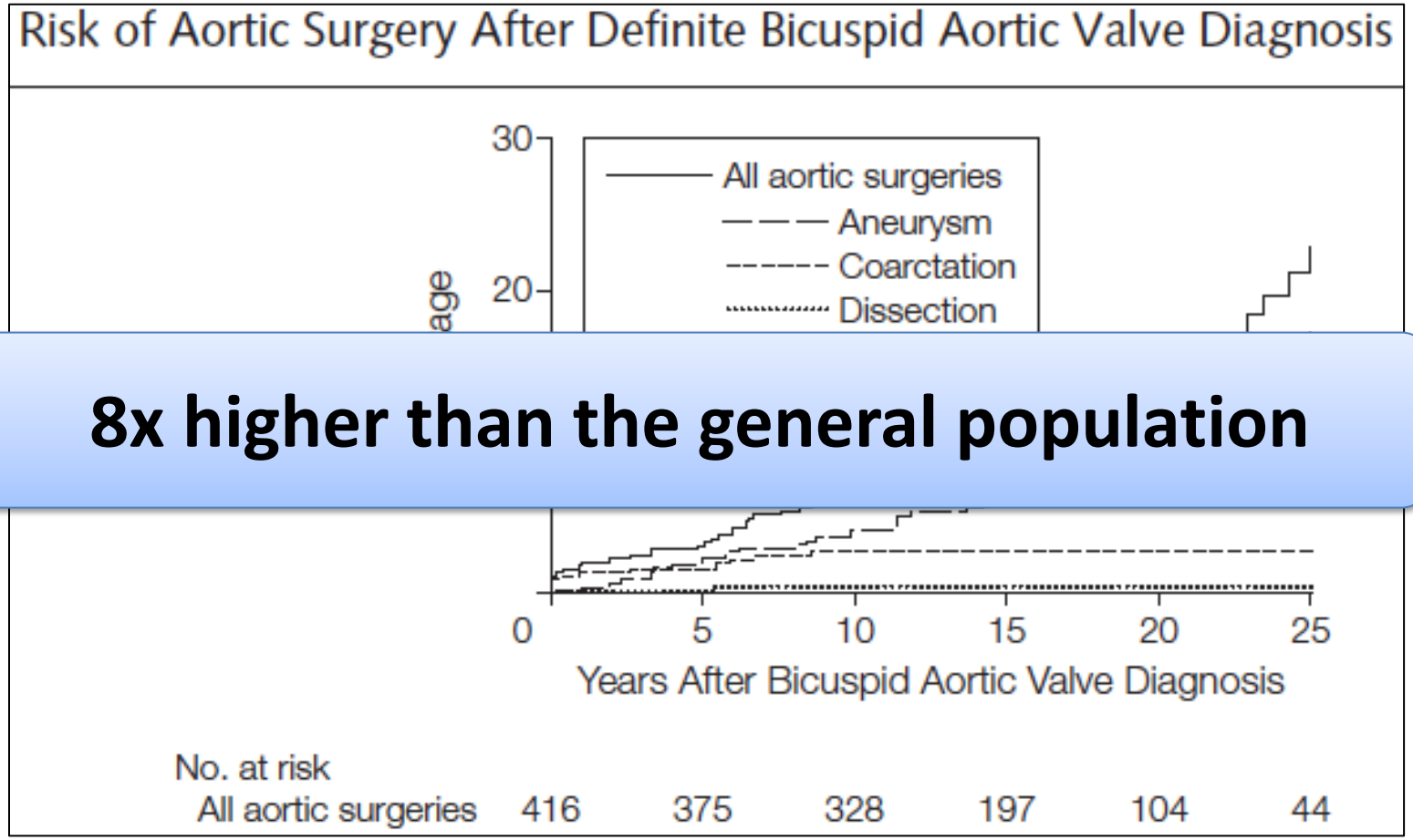
Incidence of Aortic Complications in Patients With Bicuspid Aortic Valves



No. at risk						
Aortic aneurysm	384	352	309	186	88	39
Aortic dissection	416	387	348	209	110	53

Michelena et al. JAMA 2011

Incidence of Aortic Complications in Patients With Bicuspid Aortic Valves



8x higher than the general population

Michelena et al. JAMA 2011

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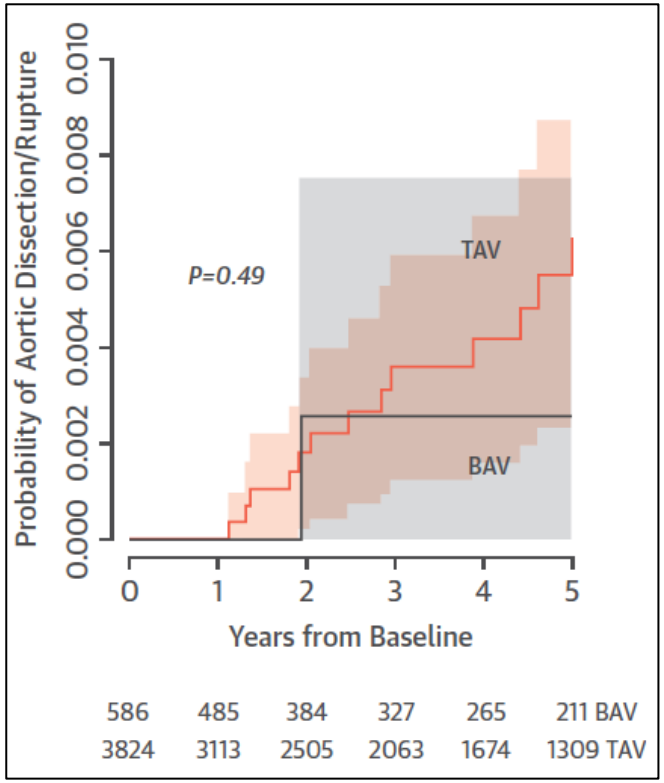
Risk of Aortic Dissection in the Moderately Dilated Ascending Aorta

Joon Bum Kim, MD, PHD,[a] Matthew Spotnitz, MD,[b,f] Mark E. Lindsay, MD, PHD,[c,d,e] Thomas E. MacGillivray, MD,[b,e] Eric M. Isselbacher, MD,[c,e] Thoralf M. Sundt III, MD[b,e]

TABLE 2 Outcomes of Patients

	Total (N = 4,654)	BAV (n = 586)	TAV (n = 4,068)	p Value
Ascending aortic event	14 (0.3)	1 (0.2)	13 (0.3)	>0.99
Ascending aorta surgery	176 (3.8)	108 (18.4)	68 (1.7)	<0.001
Death of other causes	738 (15.9)	31 (5.3)	698 (17.2)	<0.001



Kim et al. JACC 2016

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Aortic Dissection in BAV

- **YES**
  - The risk of acute aortic event is not as high

- **BUT…**
  - The risk is significantly higher than the general population (~8x)

WHO ARE THOSE 1-5% OF PATIENTS?

Bicuspid Aortic Valves

Table 1. Clinical markers of poor prognosis for ascending aortas in patients with bicuspid aortic valve disease

Family history of acute aortic events
Family history of thoracic aortic aneurysms
Associated coarctation of the aorta
Size > 50 mm
Rapid progression in the aorta's size (> 0.5 mm/y)
Age < 40 years
Aortic regurgitation*
Shape of the dilatation (obliteration of the sinotubular junction)

El-Hamamsy and Yacoub. Curr Cardiol Rep 2009

Bicuspid Aortic Valves

Class I

1. **Operative intervention to repair the aortic sinuses or replace the ascending aorta is indicated in patients with a bicuspid aortic valve if the diameter of the aortic sinuses or ascending aorta is greater than 5.5 cm (106-108).** ***(Level of Evidence: B)***

Class IIa

1. **Operative intervention to repair the aortic sinuses or replace the ascending aorta is reasonable in patients with bicuspid aortic valves if the diameter of the aortic sinuses or ascending aorta is greater than 5.0 cm and a risk factor for dissection is present (family history of aortic dissection or if the rate of increase in diameter is ≥0.5 cm per year).** ***(Level of Evidence: C)***
2. **Replacement of the ascending aorta is reasonable in patients with a bicuspid aortic valve who are undergoing aortic valve surgery because of severe AS or AR (Sections 3.4 and 4.4) if the diameter of the ascending aorta is greater than 4.5 cm.** ***(Level of Evidence: C)***

ACC/AHA Valve Guidelines, Circulation 2014

B. Aortic root or tubular ascending aortic aneurysm[d] (irrespective of the severity of aortic regurgitation)		
Aortic valve repair, using the reimplantation or remodelling with aortic annuloplasty technique, is recommended in young patients with aortic root dilation and tricuspid aortic valves, when performed by experienced surgeons.	I	C
Surgery is indicated in patients with Marfan syndrome who have aortic root disease with a maximal ascending aortic diameter ≥50 mm.	I	C
• ≥55 mm for all other patients.	IIa	C
When surgery is primarily indicated for the aortic valve, replacement of the aortic root or tubular ascending aorta should be considered when ≥45 mm, particularly in the presence of a bicuspid valve.[g]	IIa	C

[e]Family history of aortic dissection (or personal history of spontaneous vascular dissection), severe aortic regurgitation or mitral regurgitation, desire for pregnancy, systemic hypertension and/or aortic size increase >3 mm/year (on repeated measurements using the same ECG-gated imaging technique measured at the same level of the aorta with side-by-side comparison and confirmed by another technique).

ESC Valve Guidelines, Circulation 2014

The American Association for Thoracic Surgery consensus guidelines on bicuspid aortic valve–related aortopathy: Full online-only version

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Borger et al. JTCVS 2018

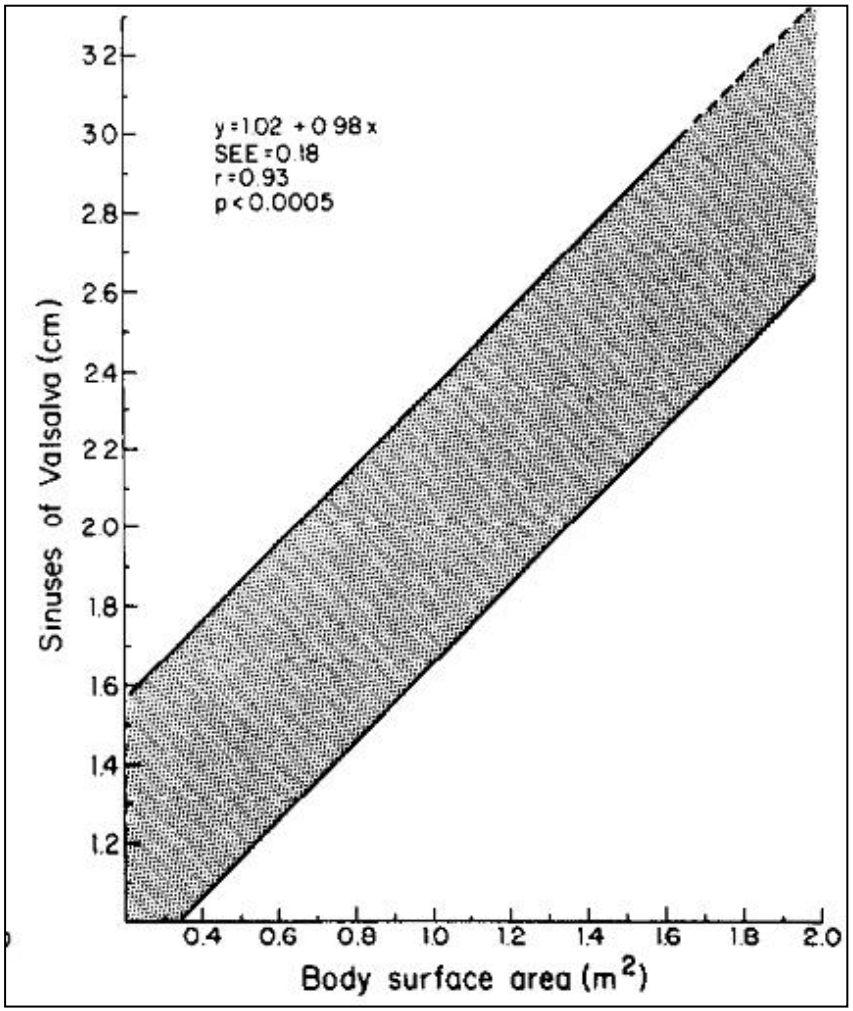
Recommendation	Class/LOE
Repair of the ascending aorta/root is recommended when the aortic diameter is ≥55 mm in patients without risk factors	I/B[26,27,33,155,226]
Repair of the ascending aorta/root should be performed when the aortic diameter is ≥50 mm in patients with risk factors (ie, root phenotype or predominant AI, uncontrolled hypertension, family history of aortic dissection/sudden death, coarctation, aortic growth >3 mm/y)	IIa/B[26,27,33,155,226]
Repair of the ascending aorta/root may be performed in patients with an aortic diameter of ≥50 mm when the patients are at low surgical risk and operated on by an experienced aortic team in a center with established surgical results.	IIb/C[2,174]
Concomitant repair of the ascending aorta/root should be performed when the aortic diameter is ≥45 mm in patients undergoing cardiac surgery.	IIa/B[26,33,57,155,166,191]

Borger et al. JTCVS 2018

SPECIAL CONSIDERATIONS

Surgical Indications

Importance of indexing, especially in patients <18 years of age



Roman et al. Am J Cardiol 1989

Indexed diameters

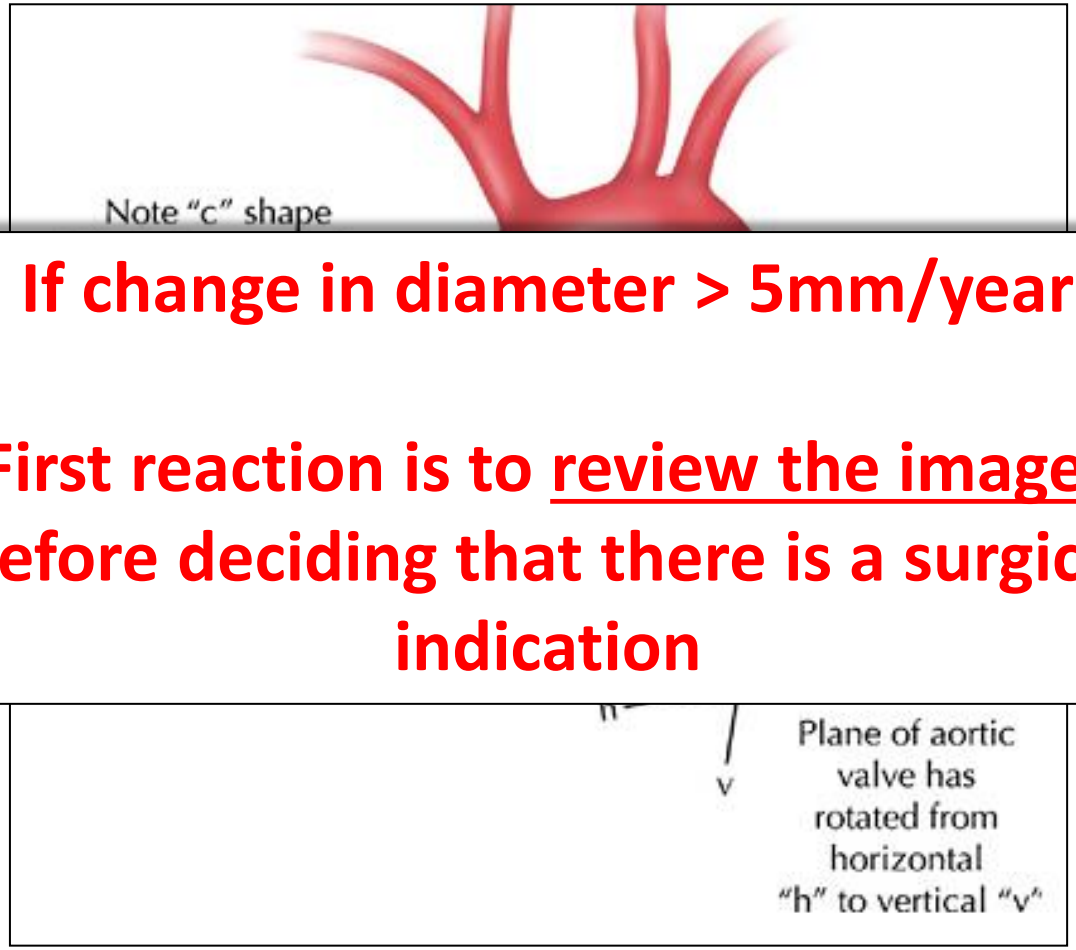
BSA	3.5	4.0	7.0	7.5	8.0
1.30	2.69	3.08	5.38	5.77	6.15
1.40	2.50	2.86	5.00	[illegible]	[illegible]
1.50	2.33	2.67	4.67	[illegible]	[illegible]
1.60	2.19	2.50	4.38	4.69	5.00
1.70	2.05	2.35	4.12	4.41	4.71
1.80	1.94	2.22	3.89	4.17	4.44
1.90	1.84	2.11	3.68	3.95	4.22
2.00	1.75	2.00	3.50	3.75	4.00
2.10	1.67	1.90	3.33	3.57	3.80
2.20	[illegible]	[illegible].82	3.18	3.41	2.64
2.30	[illegible]	[illegible].74	3.04	3.26	3.48
2.40	1.46	1.67	2.92	3.13	3.33
2.50	1.40	1.60	2.80	3.00	3.20

4%/year

20%/year

Elefteriades et al. Ann Thorac Surg 2006;81:169-77

Special Situations
5. Aortic Measurements



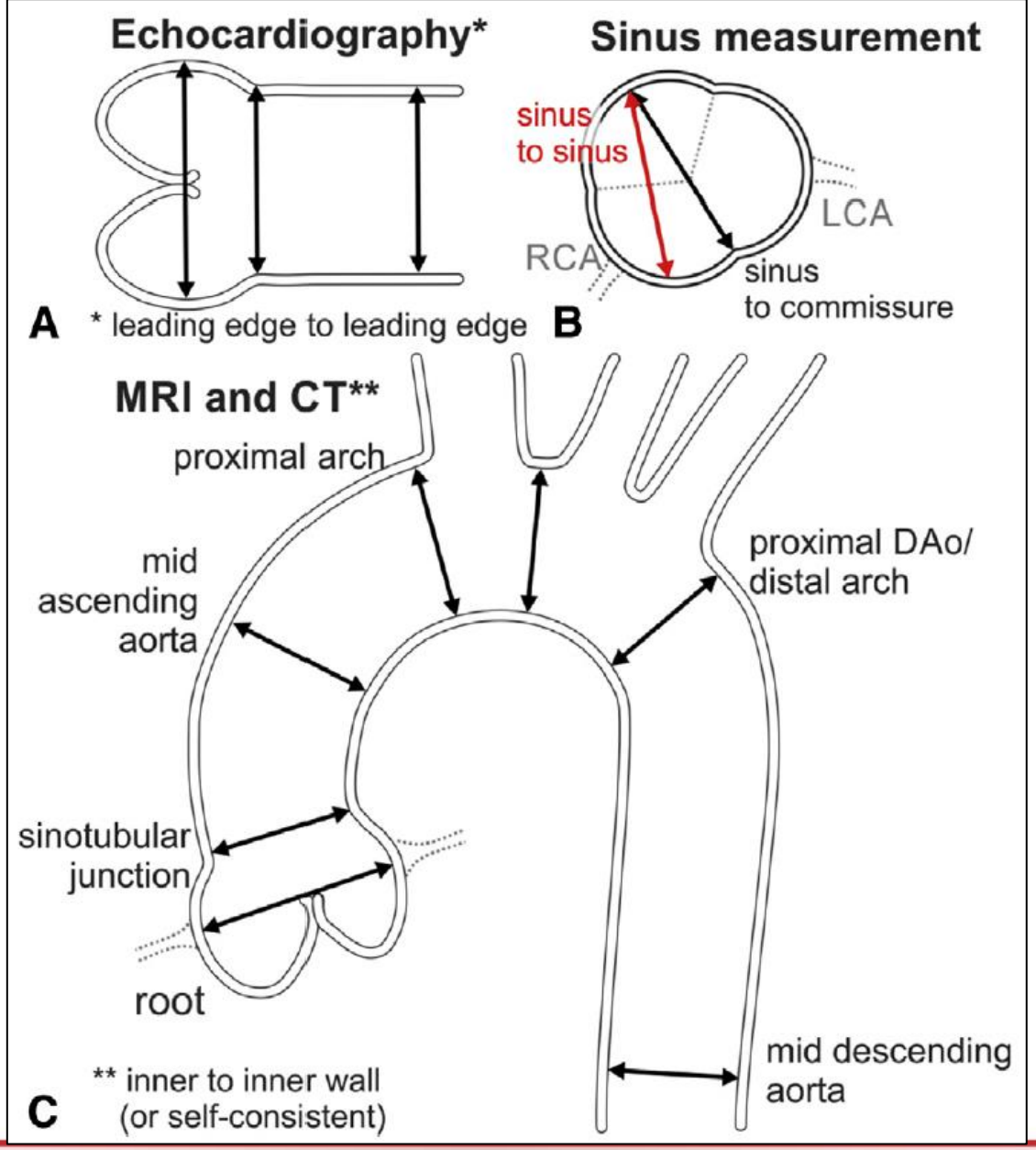
If change in diameter > 5mm/year

First reaction is to <u>review the images</u> before deciding that there is a surgical indication

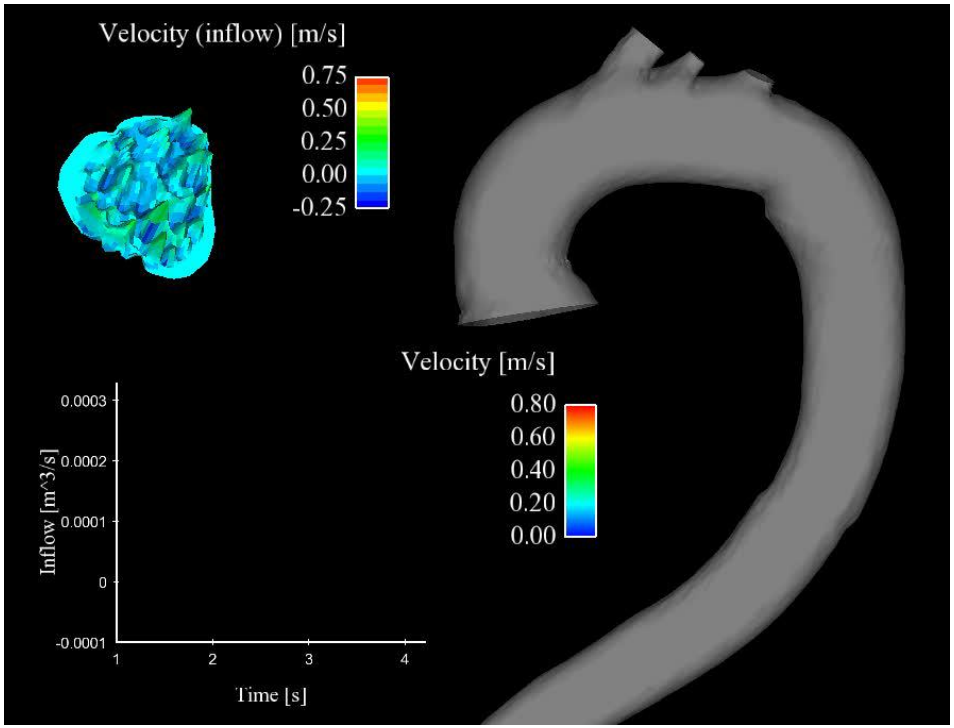
Elefteriades et al. JACC 2010;55:841-57

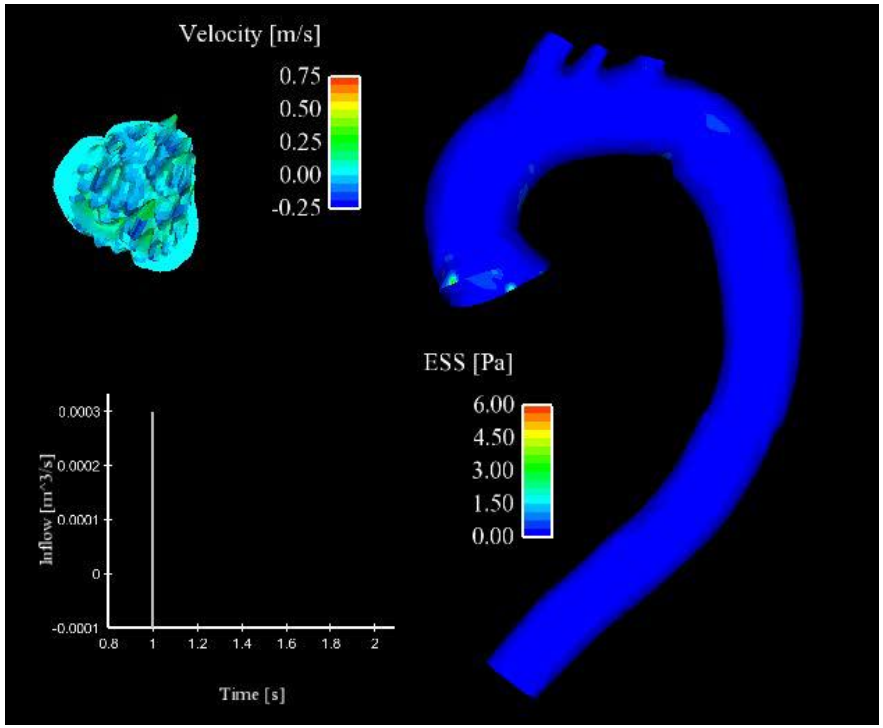
INSTITUT DE CARDIOLOGIE DE MONTRÉAL

AFFILIÉ À Université de Montréal

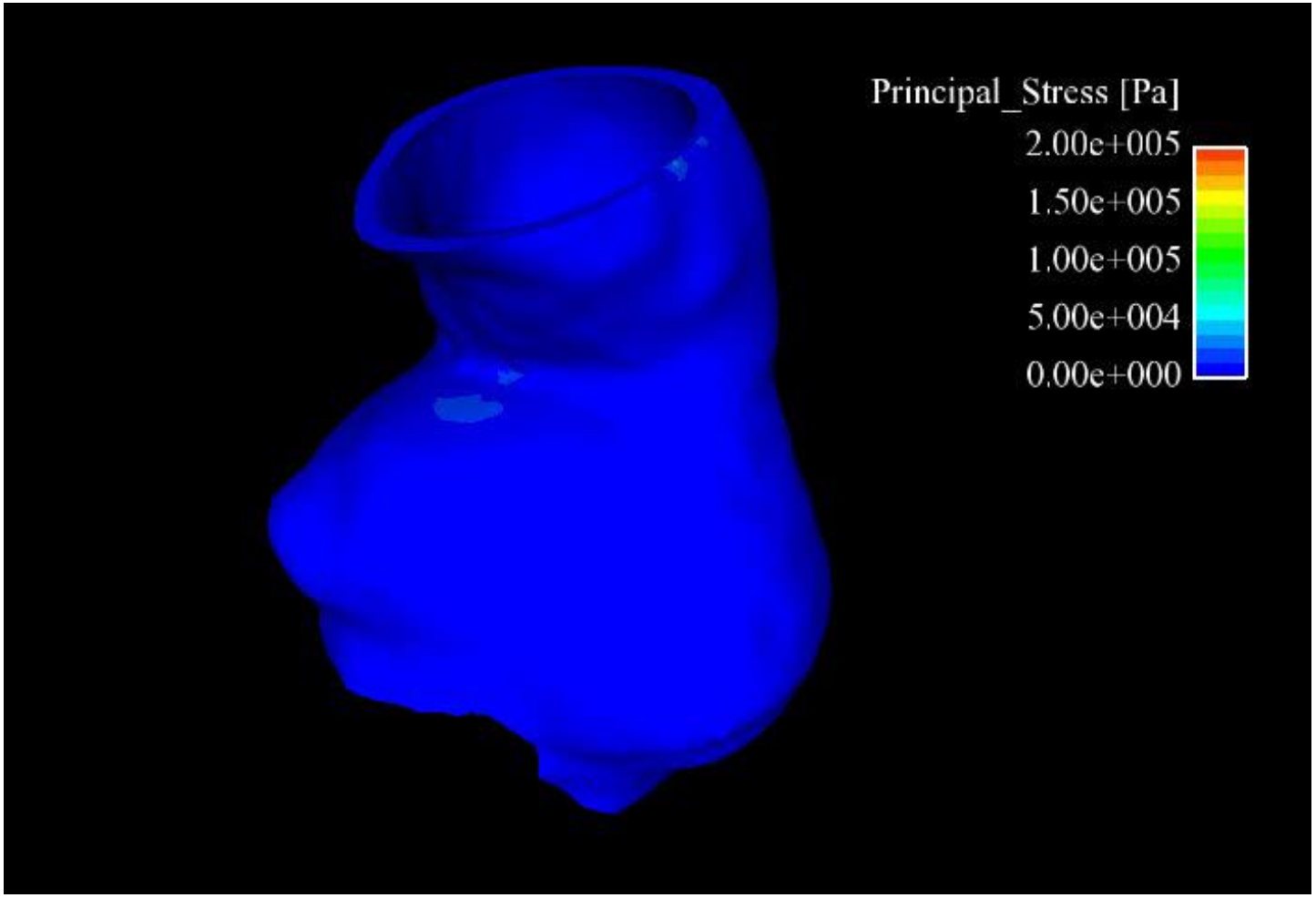

Echocardiography*
Sinus measurement
sinus
to sinus
LCA
RCA
sinus
to commissure
A
* leading edge to leading edge
B
MRI and CT**
proximal arch
mid
ascending
aorta
proximal DAo/
distal arch
sinotubular
junction
root
mid descending
aorta
** inner to inner wall
(or self-consistent)
C

Functional Biomechanics





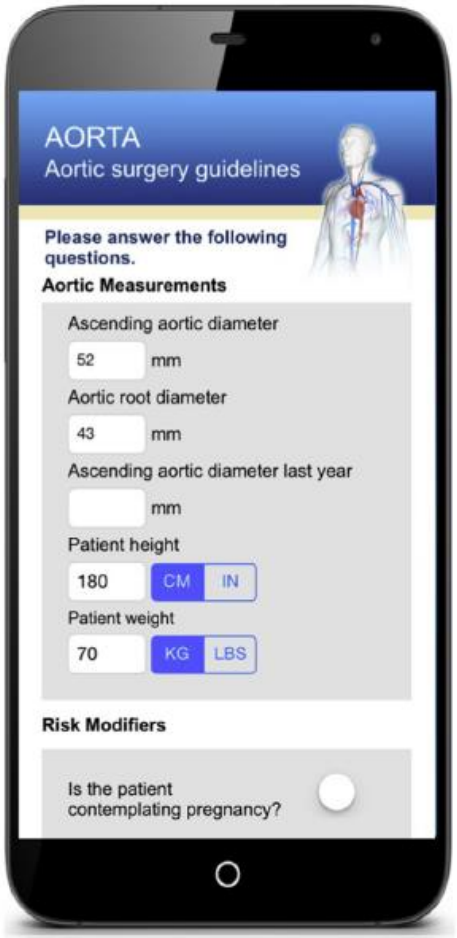
Functional Biomechanics

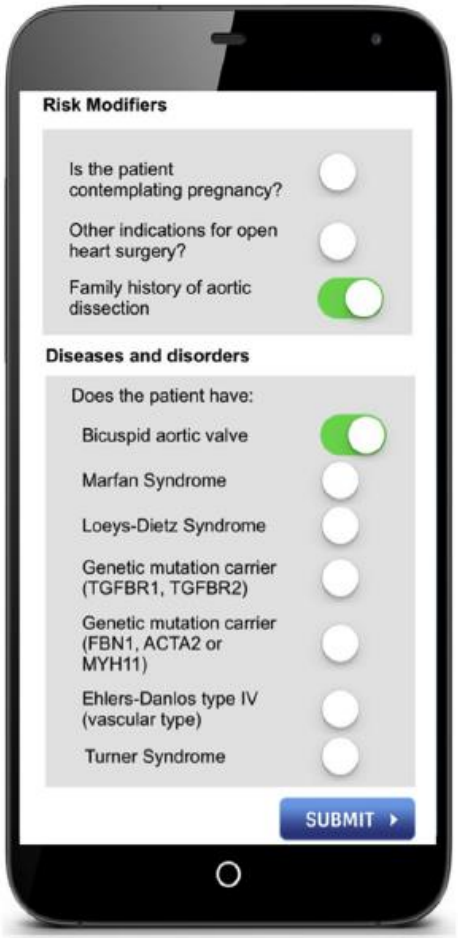


SUMMARY

- **BAV is not a single disease entity**
- **Heterogeneity in etiology = Heterogeneity in natural history**
- **Risk of acute aortic events is low, but still higher than the general population**
- **Need for further refinement of clinical decision-making (functional MRI, biomechanics, biomarkers…)**

FREE APP - AORTA





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