EuroValve
January 26-27, 2017

Ascending aorta dilation and aortic valve disease : mechanism and progression

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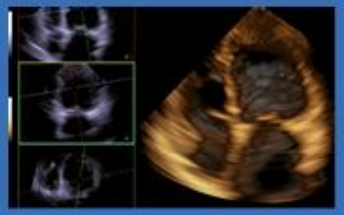

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Faculty disclosure

Agnes Pasquet

I have **no financial relationships** to disclose.

But the hospital where I'm working receive research grant from:
Daichi Sankyo
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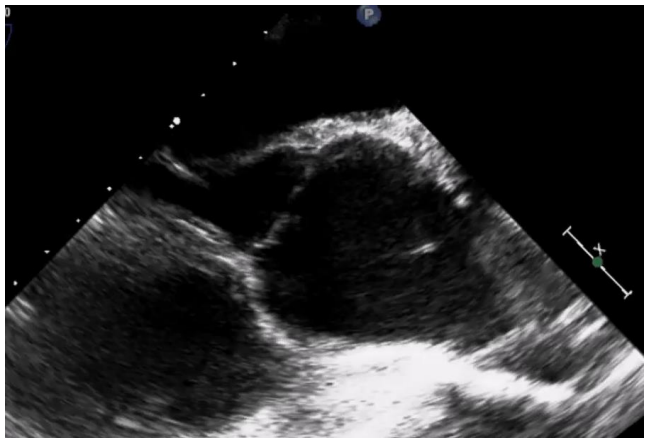

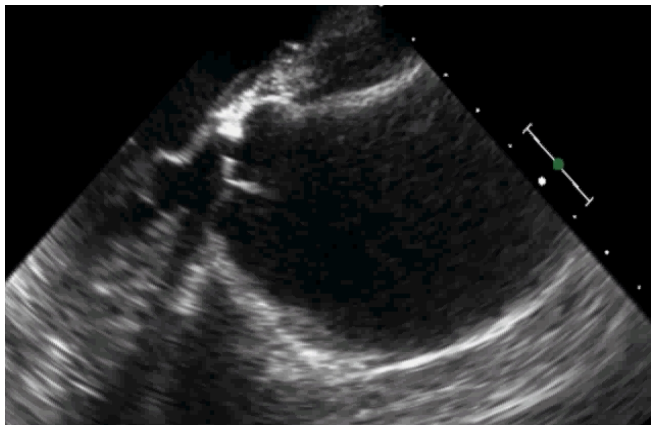

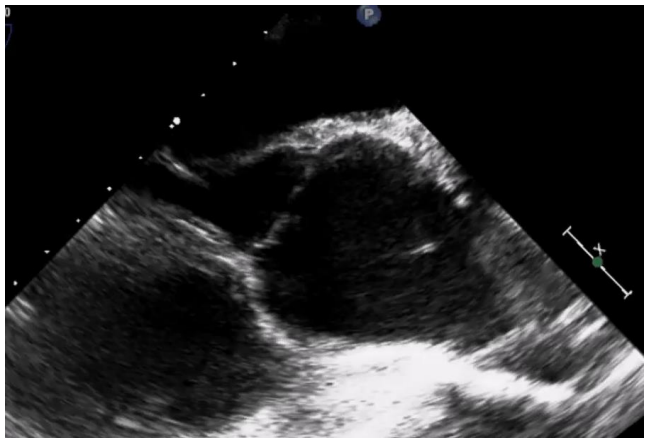

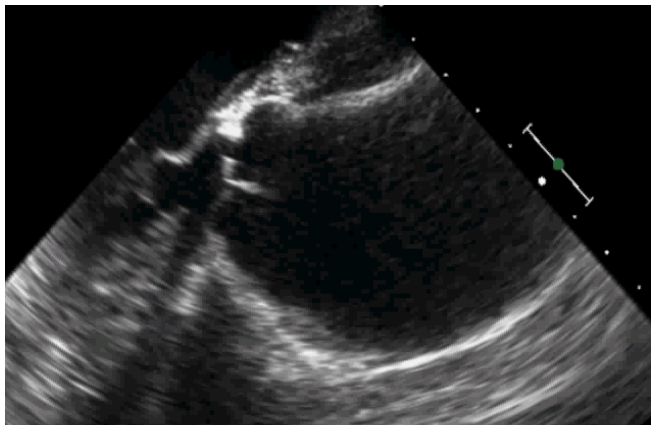

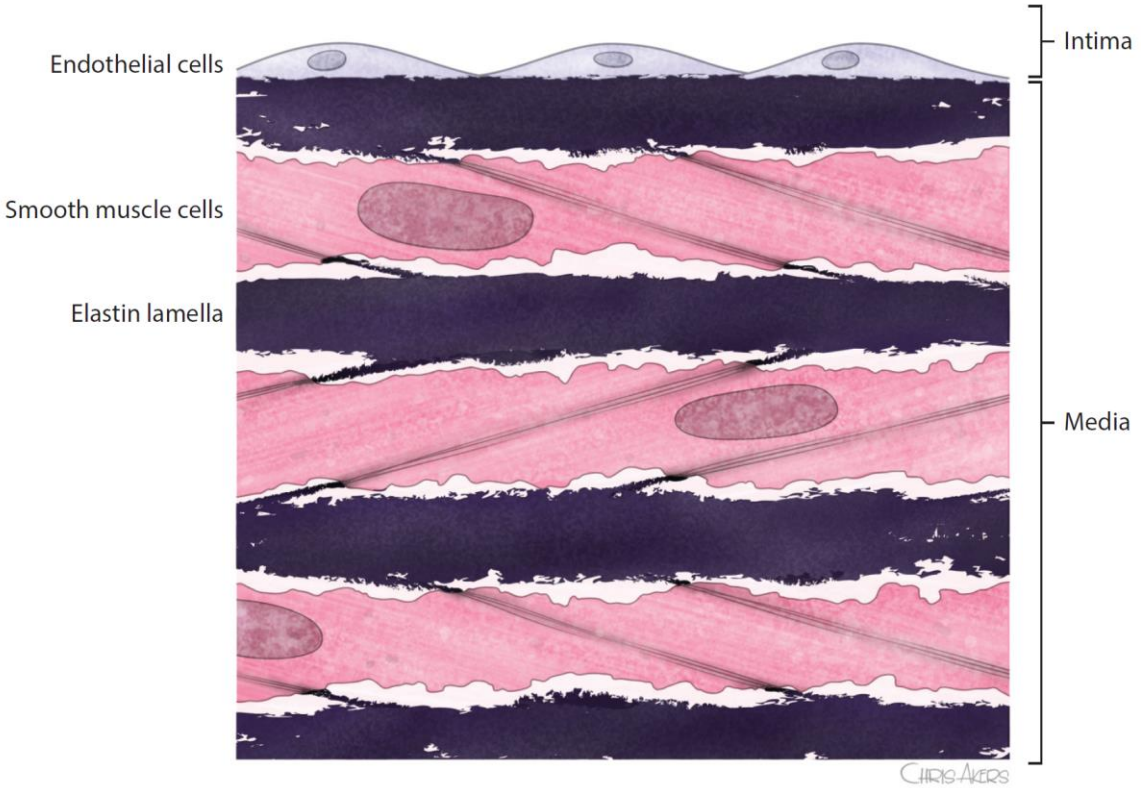

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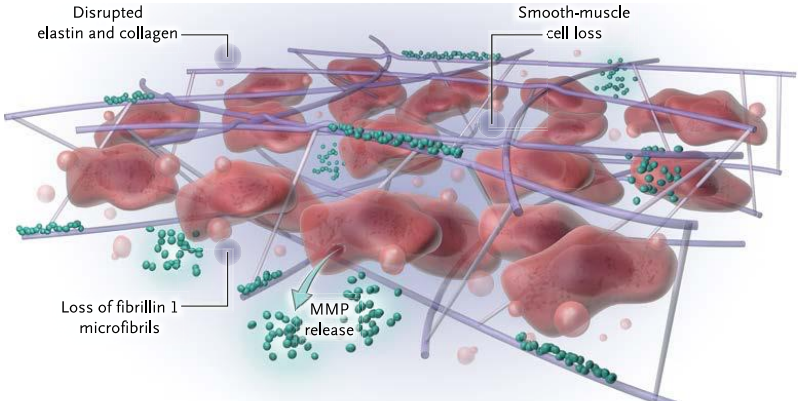
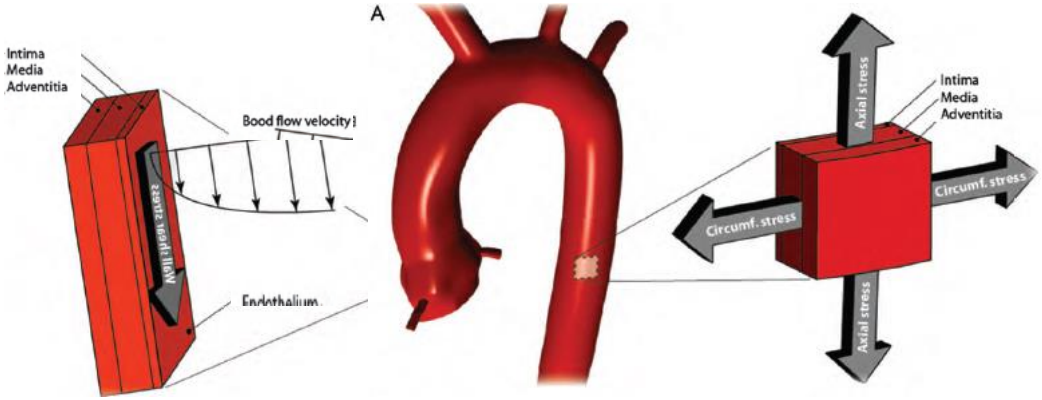
« *media disease* »



Collagen disease:

- Marfan,
- Ehlers Danlos IV,
- Loeyz –Dietz……

Increase in wall stress



HYPERTENSION

Smoking

Age

Atheroma

History of cardiac surgery (15%)

…..

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Crowne Plaza Barcelona Fira Center, SPAIN

TAAD: Thoracic Aortic Aneuvrysm and Dissection ?

Syndromic TAAD

"involvement of tissue and other organ than aorta

- Marfan
- Loeys-Dietz Syndrome
- Turner
- Ehlers Danlos IV
- Arterial tortuosity
- Aneurysm arthritis syndrome

Non syndromic TAAD

"only" aorta is involved

- Famillial TAAD
  - *Bicuspid aortic valve*
  - *Sporadic form*

Up to 20% have a first degree relative with TAAD !

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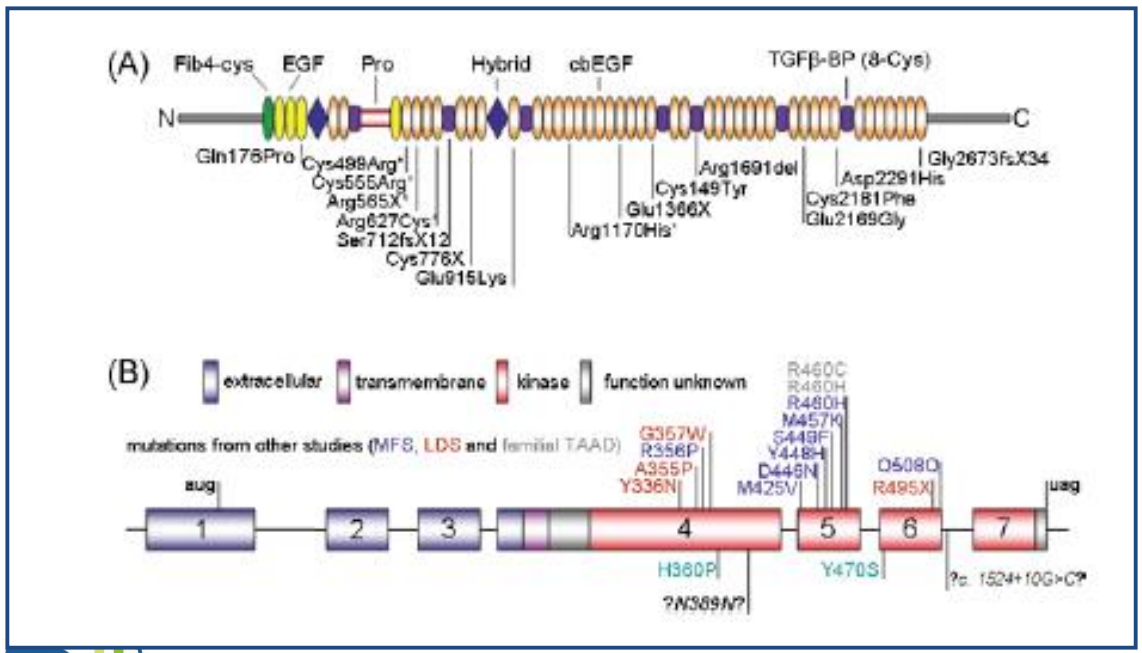
Marfan disease:

- Most frequent collagen disease (1/5000 people),
- Autosomic dominant , very variable expression! 25% neomutations !,



FBN1 (fibrillin) Chr 15

Elastic and support tissue

> 600 FBN1 mutations identified !

TGFBR2 (Overlap avec Loets Dietz)

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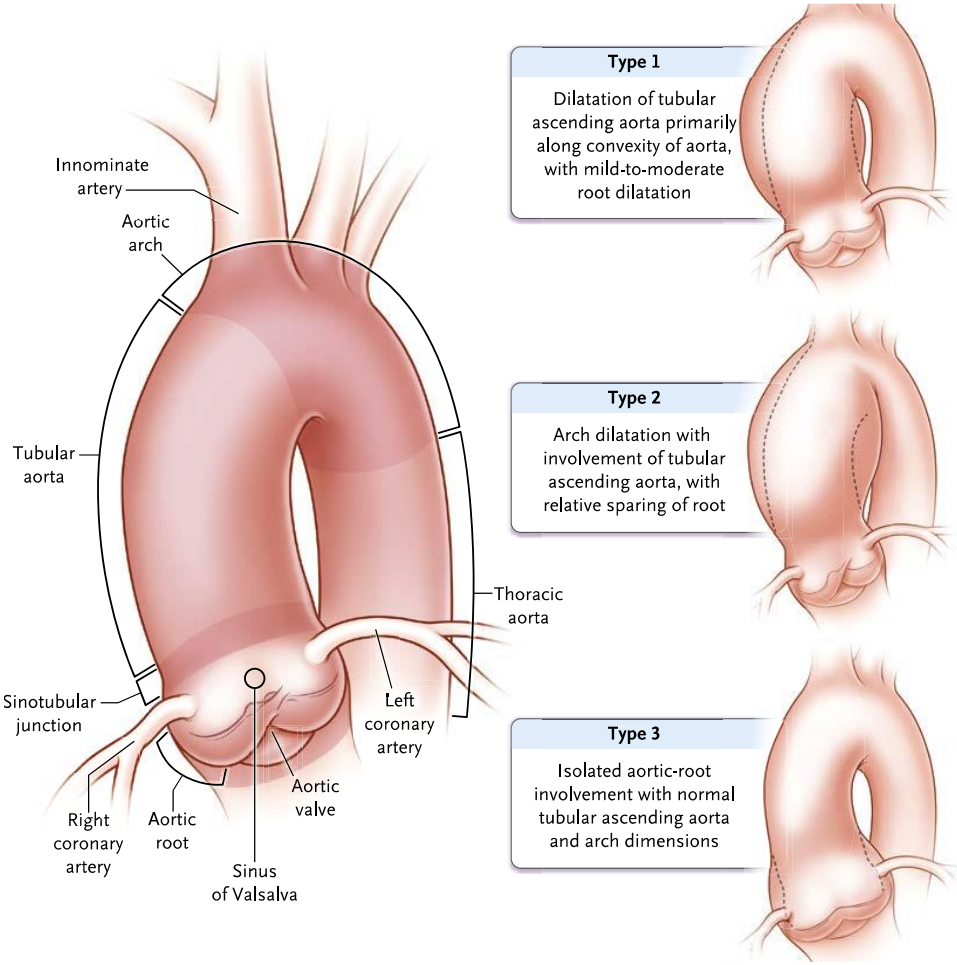
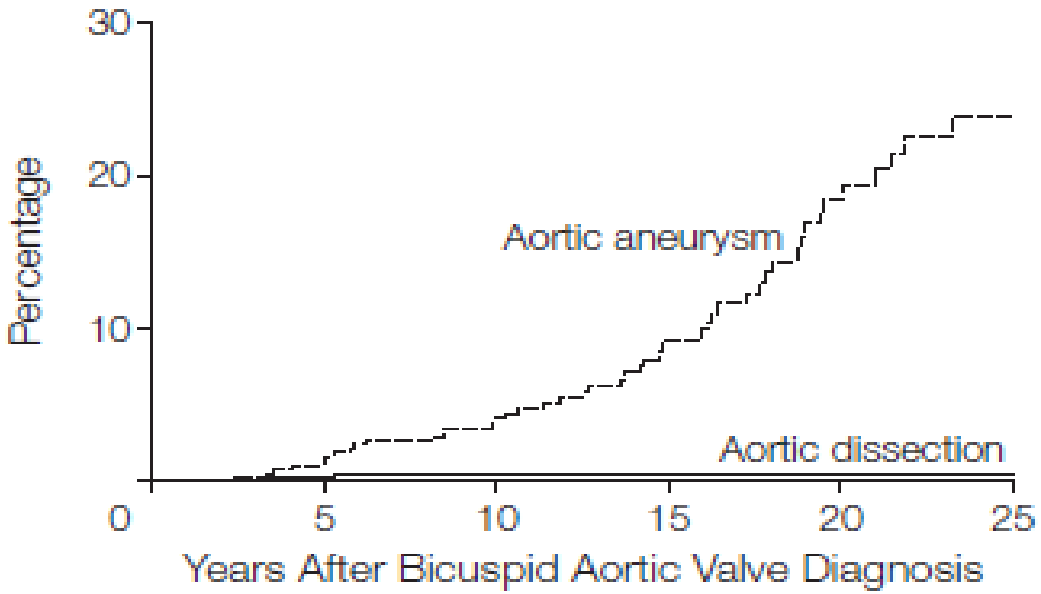
Bicuspid aortic valve:

- Aortic root dilatation in 20-84 % of BAV pts
- Start in young adult or teenagers and slowly continue
- 22 % of pts with aortic dissection < 40 years old have bicuspid aortic valve



Verma and Siu *NEJM* 2014: 370: 1920-9

BAV: Natural history or aortopathy:



No. at risk

Aortic aneurysm	384	352	309	186	88	39
Aortic dissection	416	387	348	209	110	53

At 25y: 26% will develop aneuvrysm

84.9/10 000 pts year BAV

1.04/10 000 pts year all population

RR:84 x !

Risk of aneurysm formation in pt without aneurysm at diagnosis

Michelena et al JAMA. 2011;306(10):1104-1113

BAV a genetic disease ?:

- Prevalence rise up to 24% if one relative is affected
- Inheritance is found > 50% families mainly if associated lesion (coarctation….)
- *Syndromic Form*:

TABLE 1 Human Genetic Syndromes That Include Bicuspid Aortic Valve

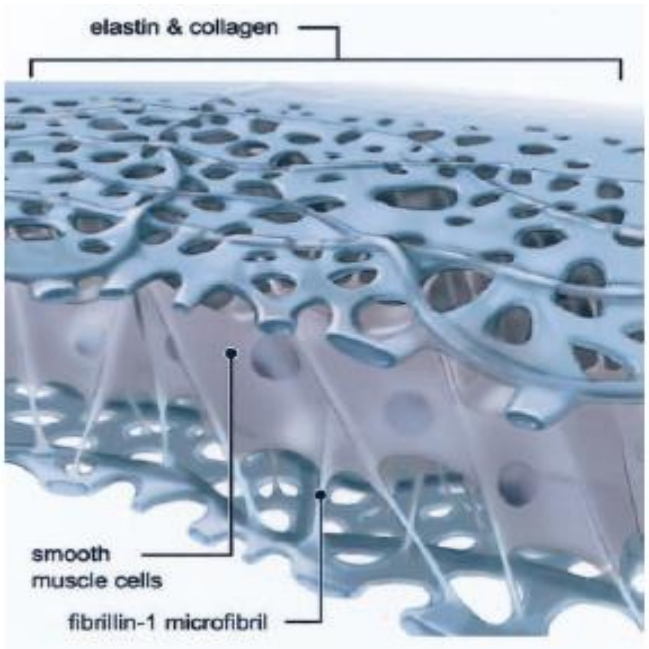
Syndrome	Genetic Defect	Clinical Features	OMIM No.
Turner	Monosomy X	Short stature, infertility, coarctation	–
Loeys-Dietz	*TGFBR1*, *TGFBR2* mutations	TAAD, craniosynostosis, bifid uvula, skeletal defects	609192, 608967 (type 1) 610168, 610380 (type 2)
DiGeorge	22q11.2 deletion	Truncus arteriosus, tetralogy of Fallot, craniofacial defects	188400 (DiGeorge) 192430 (VCF)
Andersen-Tawil	*KCNJ2* mutations (60%)	Dysmorphic features, cardiac arrhythmias, periodic paralysis	170390 (LQTS 7)
Larsen	*FLNB* mutations	Craniofacial and skeletal defects	150250
Kabuki	*KMT2D*, *KDM6A* mutations (70%)	Mental retardation, hearing loss, coarctation	147920 (type 1) 300867 (type 2)

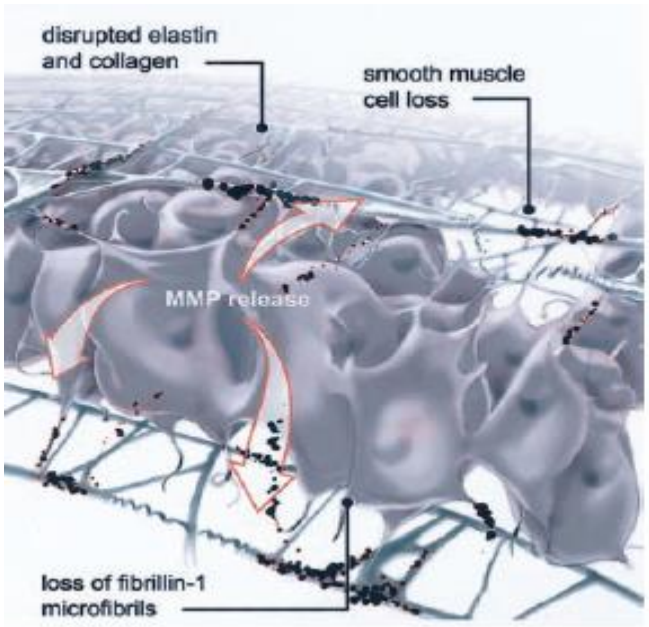
AAT = aortic aneurysm, familial thoracic; LDS = Loeys-Dietz syndrome; LQTS = long-QT syndrome; OMIM = Online Mendelian Inheritance in Man; TAAD = thoracic aortic aneurysms and dissections; VCF = velocardiofacial syndrome.

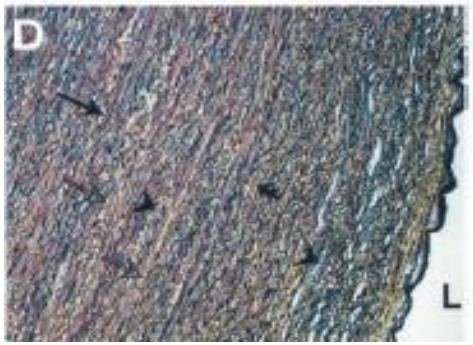
- *non syndromic form*: TAAD: 30%

  Numerous gene associated: TGFBR2, TGFBR1, ACTA2, KCNJ2, NOTCH1

Aortic Root dilatation in BAV a structural problem ?:







- Loss smooth muscle
- Disarray elastic fibers

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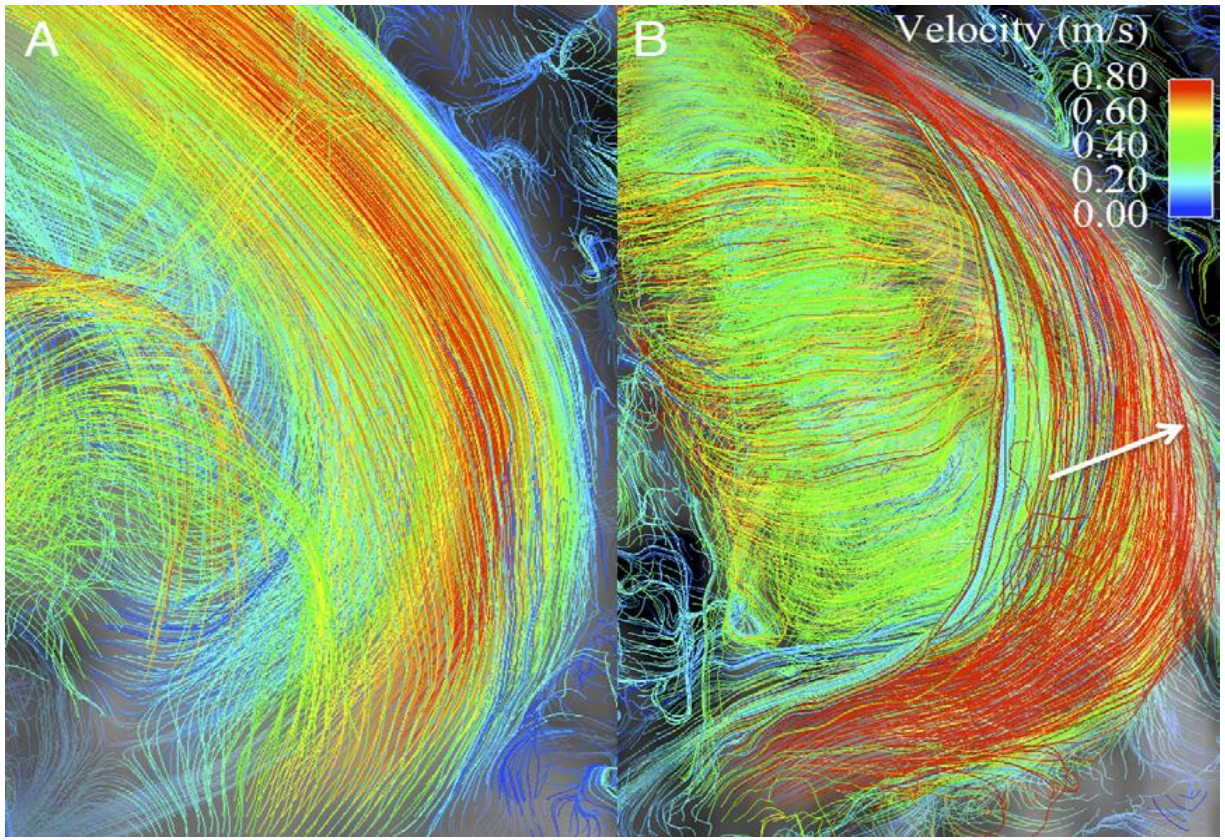
Fedak et al , Circ 2002, 106: 900-4

Aortic Root dilatation in BAV an hemodynamic problem ?



Growth
Maximal shear stress

BAV nl root

BAV with rapid dilatation

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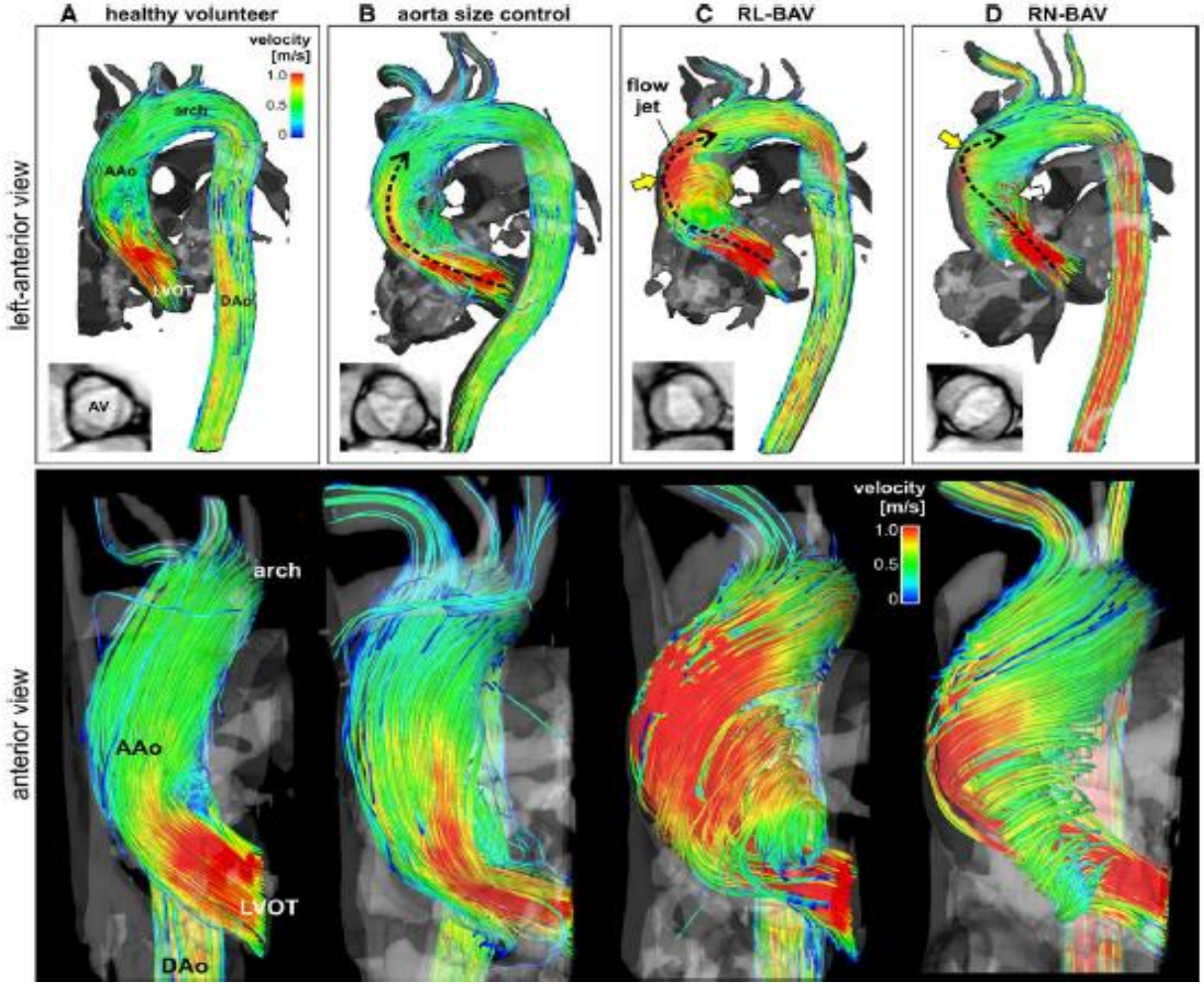
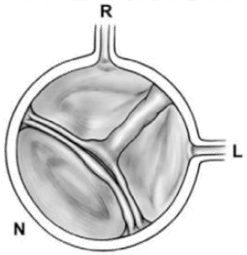
Hope et al , JACC 2012, 60: 356-7

Aortic Root dilatation in BAV an hemodynamic problem ?

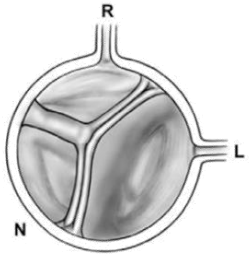


R-L fusion



± 70 %

R-N fusion



± 30 %

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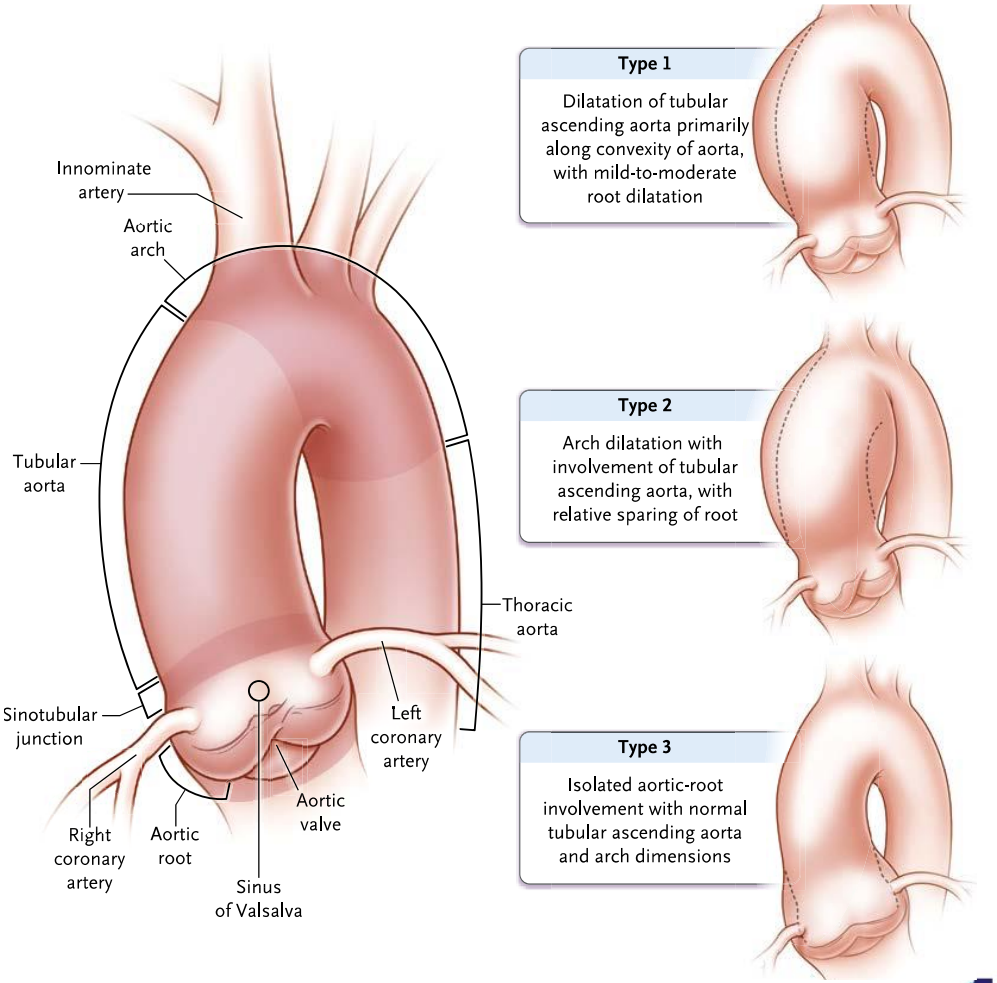
Mahadevia et al , Clirc 2014, 129: 673-82

Pattern of aortic dilatation:

EDITORIAL COMMENT

Bicuspid Aortic Valve and Aortopathy: See the First, Then Look at the Second*

Rosario V. Freeman, MD, MS, Catherine M. Otto, MD
Seattle, Washington



Age > 50
RL fusion
AS

Type 1 RN fusion

Male, < 40 y
True BAV
AR
Genetic

Verma and Siu *NEJM* 2014: 370: 1920-9

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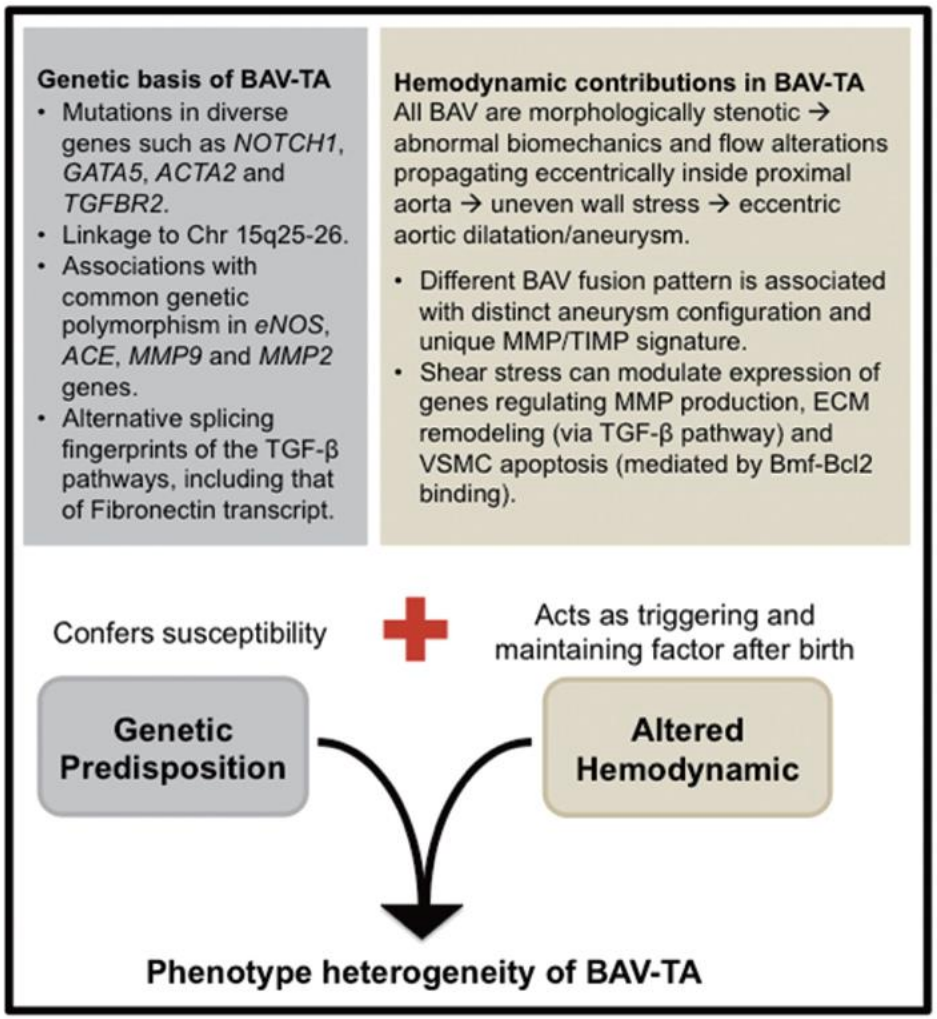
Aortic dilatation in BAV:



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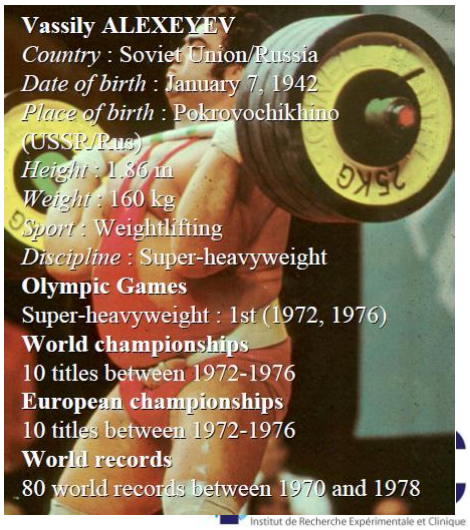
Padang et al, Annal of thor surg , 2013 2:83-91

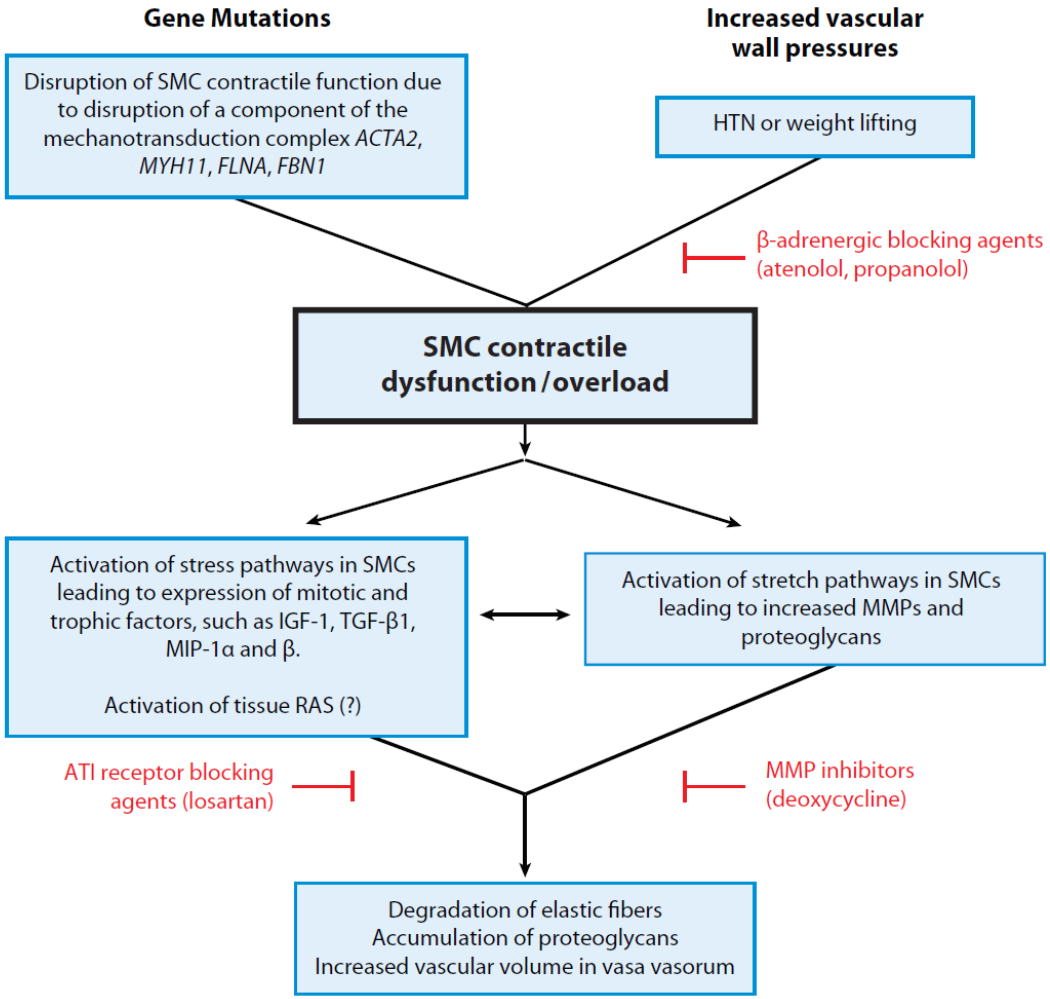
« Environnemental factors »:

- *Hypertension*: increased mechanical stresses on the vascular wall and mechanical strain is a mitogenic stimulus for smooth muscle cells (SMC), increasing the production of IGF-1 and TGF-β1 and increasing stretch-induced pathways

- Smoking
- Intense isometric exercise (weightlifting)
- Age
- Atheroma
- …



Mechanism of dilatation ?



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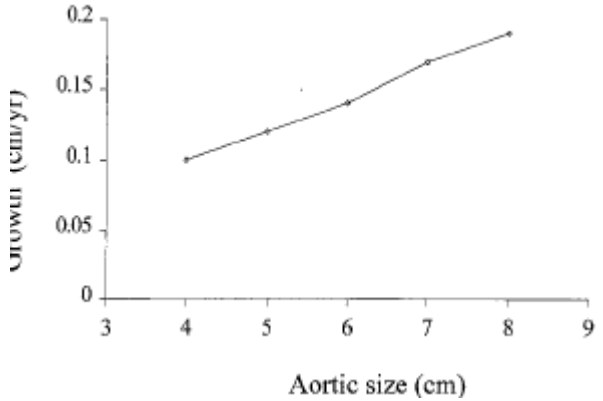
Milewicz et al, Annu. Rev. Genomics Hum. Genet. 2008.9:283–302

What about progression ?



Patient category	Annual growth rate according to initial aneurysm size*					
	4.0 cm	*5.0 cm*	*6.0 cm*	*7.0 cm*	*8.0 cm*	*5.2 cm (sample mean)*
All (n = 79)	0.10 cm/yr (0.05-0.14)	0.12 cm/yr (0.06-0.18)	0.14 cm/yr (0.07-0.21)	0.17 cm/yr (0.09-0.25)	0.19 cm/yr (0.10-0.28)	0.12 cm/yr (0.06-0.18)
Dissection status						
Chronic dissection (n = 16)	0.28 cm/yr (0.10-0.47)	0.35 cm/yr (0.13-0.59)	0.42 cm/yr (0.15-0.70)	0.49 cm/yr (0.18-0.82)	0.56 cm/yr (0.20-0.94)	0.37 cm/yr (0.13-0.61)
No dissection (n = 63)	0.07 cm/yr (0.02-0.11)	0.08 cm/yr (0.03-0.14)	0.10 cm/yr (0.03-0.17)	0.12 cm/yr (0.04-0.20)	0.14 cm/yr (0.04-0.23)	0.09 cm/yr (0.03-0.15)
Location of aneurysm						
Ascending or arch (n = 54)	0.08 cm/yr (0.03-0.12)	0.10 cm/yr (0.04-0.15)	0.11 cm/yr (0.05-0.18)	0.13 cm/yr (0.06-0.21)	0.15 cm/yr (0.06-024)	0.10 cm/yr (0.04-0.16)
Descending or thoracic aorta (n = 25)	0.23 cm/yr (0.07-0.39)	0.28 cm/yr (0.08-0.49)	0.34 cm/yr (0.10-0.59)	0.40 cm/yr (0.12-0.69)	0.45 cm/yr (0.13-0.79)	0.29 cm/yr (0.09-0.51)

*95% Confidence interval is given in parentheses.

Coady et all, J CV thor Surg 1997,113, 476-491

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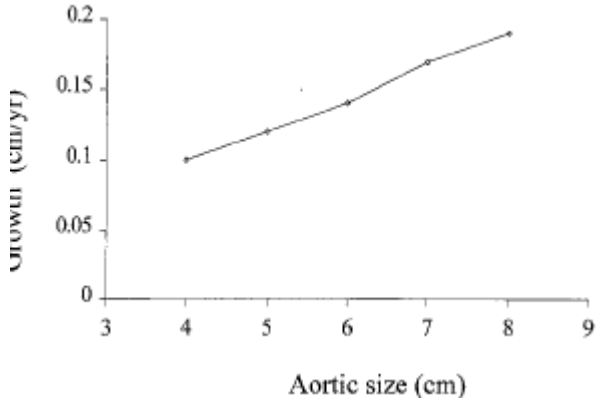
What about progression ?



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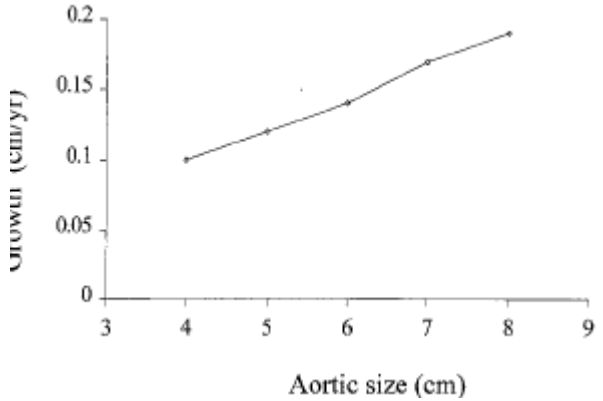

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What about progression ?:

Table 2. Growth rates of thoracic aortic aneurysms (TAA).

Study	Aneurysm measurement technique (location measured)	Mean ± SD or mean (range) baseline TAA diameter (mm)	Mean ± SD or mean (range) growth rates (mm/y)	Growth rate estimation method
Detaint et al. (2014)[16]	NR (maximally dilated segment)	BAV: 37.9 ± 6.0 DA: 44.5 ± 4.0 MFS: 32.4 ± 5	BAV: 0.42 ± 0.6 DA: 0.20 ± 0.3 MFS: 0.49 ± 0.5	Linear: (D2−D1/T)
Geibusch et al. (2014)[17]	Volume measurements (ascending aorta)	Volume: 132.8 ± 39.4 mL/y	Volume: 0.95 ± 4.5 mL/y	Linear: (D2−D1/T)
Shang et al. (2013)[21]	3D reconstruction + aneurysm outline tracing (maximally dilated segment)	47.8 ± 8.0	2.9 ± 2.4	NR
Davies et al. (2002)[5]	NR (NR)	5.0 (3.5−11.0)	1.0	Exponential: multivariable regression
Bonser et al. (2000)[13]	Calliper method (aortic outer diameter of maximally dilated segment)	NR	1.43 (−6.9 to −40.7)	Linear: (D2−D1/T)
Lobato et al. (1998)[22]	NR (AP and transverse diameter of maximally dilated segment)	Transverse: 44 AP: 41	Transverse: 3.4 AP: 2.8	Linear: (D2−D1/T)
Juvonen et al. (1997)[19]	3D reconstruction + aneurysm outline tracing (maximally dilated segment)	4.9 (2.5−8.2)	2.7	NR
Cambria et al. (1995)[14]	NR (maximal transverse diameter)	NR	2.0 (0−14)	NR
Dapunt et al. (1994)[15]	3D reconstruction + aneurysm outline tracing (maximally dilated segment)	NR	Descending TAA: 3.2 (—) Volume change: 53 mL/y	Exponential: regression analysis
Masuda et al. (1992)[20]	AP and transverse diameter (largest chosen)	50 ± 9	1.3 ± 1.2	NR
Hirose et al. (1992)[18]	Calliper method: (aortic outer diameter of maximally dilated segment)	Ascending: 50.5 ± 5.0 Arch: 48.5 ± 9.3 Descending: 44.8 ± 8.5	4.2 ± 4.5	Linear: (D2−D1/T)

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Oladukum D et al, Eur J Vasc Endovasc Surg (2016) 51, 674e681

What about progression ?

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Shang et al. (2013)[21]	3D reconstruction + aneury outline traci dila			
Davies et al. (2002)[5]	NR			
Bonser et al. (2000)[13]	Callip diame segme			
Lobato et al. (1998)[22]	NR (AP diamete segment			
Juvonen et al. (1997)[19]	3D recon outline tr dilated se			
Cambria et al. (1995)[14]	NR (maxim diameter)			
Dapunt et al. (1994)[15]	3D reconstr outline traci dilated segm		AA: 3.2 (—) Volume change: 53 mL/y	Exponential: regression analysis
Masuda et al. (1992)[20]	AP and transv (largest chosen)	50 ± 9	1.3 ± 1.2	NR
Hirose et al. (1992)[18]	Calliper method: (aortic outer diameter of maximally dilated segment)	Ascending: 50.5 ± 5.0 Arch: 48.5 ± 9.3 Descending: 44.8 ± 8.5	4.2 ± 4.5	Linear: (D2—D1/T)

Reported mean growth rates for all TAAs ranged from 0.2 to 4.2 mm/year

Mean growth rates for ascending and aortic arch TAAs ranged from 0.2 to 2.8mm/year,

while those for descending and thoracoabdominal aneurysms ranged from 1.9 to 3.4 mm/year

Mixed population : Marfan and BAV greater growth rates

Oladukum D et al, Eur J Vasc Endovasc Surg (2016) 51, 674e681

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What about progression?

- Wide variation :
- Marfan disease : 0,1 to 0,4 cm/year (Loetz Diets: up to 1 cm/year)

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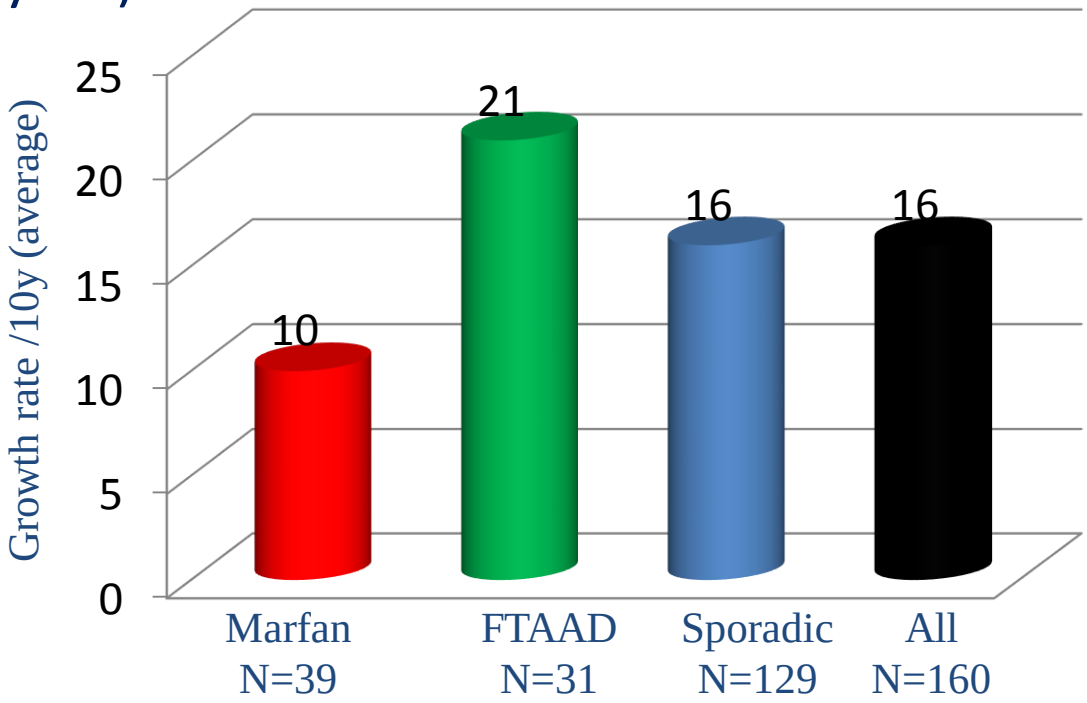
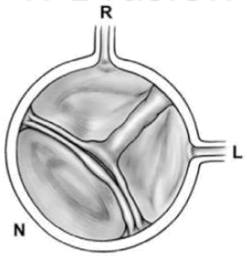


Albornoz et al , annals of thor surg 2006,82, 1400-1406

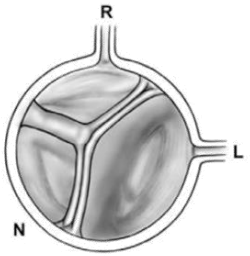
Predictors of fact growth in BAV:

R-L fusion



± 70 %

R-N fusion



± 30 %

Table 4. Multivariate Predictors of Fast Growth of the Aortic Diameter

	Predictor	OR	95% CI	p Value
Dependent variable: ascending tract growth rate >0.9 mm/year				
All patients	Root phenotype	14.0	3.2–62	*0.001*
RL type	Root phenotype	7.0	2.0–24	*0.002*
RN type	Aortic regurgitation (any degree)	20.0	1.3–76	*0.03*
Dependent variable: root growth rate >0.5 mm/year				
All patients	RN type	3.7	1.1–12	*0.03*
RL type	Small aortic root*	28.0	2.2–39	*0.011*
RN type	Fast progression of the ascending diameter	6.2	1.0–37	*0.04*

For each segment of the aorta (ascending and root), 3 separate logistic regression models were developed: 1 for the entire cohort and 1 for each of the 2 subgroups of BAV morphotype. In each model, among all the study variables (listed in Table 1), only those showing significant univariate association with the outcome variable (see Results) were entered as covariates. Italicized p values are statistically significant. *Small aortic root = diameter at the sinuses >2 SD smaller than the mean expected normal value (see Methods), irrespective of the diameter at the ascending tract (a feature possibly associated with either the normal or ascending phenotypes).
CI = confidence interval; OR = odds ratio; other abbreviations as in Table 1.

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Della Corte A et al J Am Coll Cardiol Img 2013;6:1301–10

Relative growth in aortopathy ?

Table 1 Baseline aortic diameters and yearly aortic dilatation rates in patients with BAV, DA, and MFS

	BAV N=353	DA N=51	MFS N=50	p Value
Age, year	48±15	71±11	35±11	<0.0001
Gender, male n (%)	254 (72%)	40 (78%)	36 (72%)	0.60
Systolic BP mm Hg (baseline)	124±17	124±16	128±19	0.59
Ejection fraction,%	59±8	55±11	63±9	<0.0001
AR ≥2, n (%)	123 (35%)	9 (18%)	1 (2%)	<0.0001
Aorta diameter at baseline				
Aortic annulus, mm	25.0±3	24.6±3	24.6±2	0.49
Sinuses of Valsalva, mm	37.1±6	41.5±6	41.8±6	<0.0001*†
Sinotubular junction, mm	31.5±5	37.5±5	33.3±5	<0.0001*†‡
Ascending aorta, mm	37.9±6	44.5±4	32.4±5	<0.0001*†‡
Dilatation rate, mm/year				
Aortic annulus	0.05±0.2§	0.005±0.2	0.04±0.7	0.51
Sinuses of Valsalva	0.21±0.4§	0.09±0.2§	0.49±0.5§	<0.0001*†‡
Sino-tubular junction	0.18±0.5§	0.10±0.2§	0.10±1.2	0.50
Ascending aorta	0.42±0.6§	0.20±0.3§	0.12±1.0§	0.0005*†
Maximal dilatation rate	0.42±0.6	0.20±0.3	0.49±0.5	0.02*‡

*Indicates significant differences between BAV and DA.
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§Indicates significant differences between baseline and follow-up diameters.
Larger baseline aortic diameters in DA patients reflect the inclusion criteria of 40 mm for these patients versus 37 mm for BAV and MFS.
AR, aortic regurgitation; BAV, bicuspid aortic valve; BP, blood pressure; DA, degenerative aortopathy; MFS, Marfan syndrome.

Detaint Sarano, heart 2014, 100: 126-134

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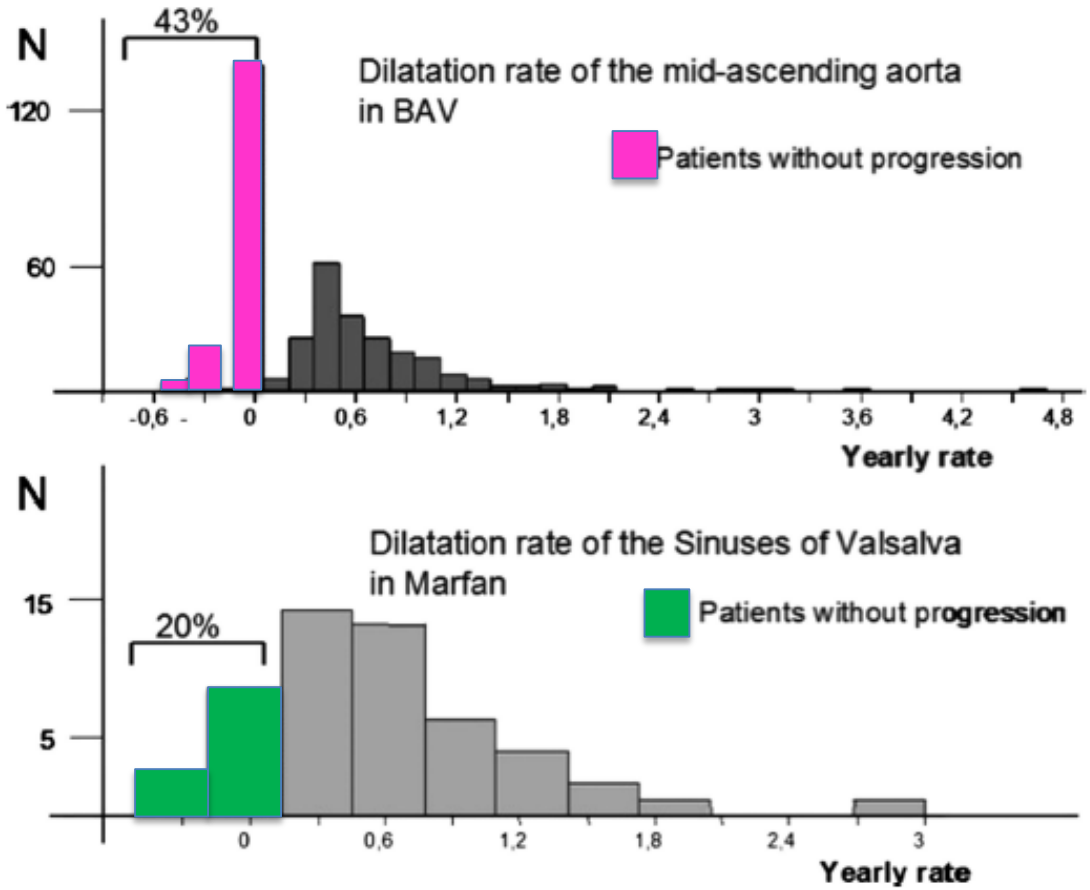
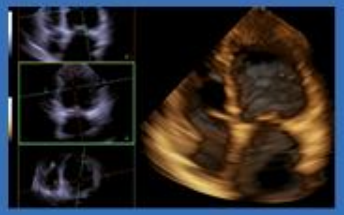


Greater proportion of patient without change in Ao dimension in the BAV group !

Detaint Sarano, heart 2014, 100: 126-134

Conclusion:

- We are improving our knowledge of mechanism leading to aortic dilatation.
- Beside genetic aspect there is obviously a role for « environmental » factors.
- Growth rate vary widely according to underlying pathology.
- Some patient with BAV will develop some form of aortic root dilatation. The challenge for the upcoming year will be to identify such patients.



EuroValve

January 26-27, 2017

Thank you for your attention

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