XVII CONGRESSO NAZIONALE SIEC

PATOGENESI E STRATIFICAZIONE DEL RISCHIO DELL'AORTOPATIA BICUSPIDE

Stefano NISTRI

CMSR Veneto Medica

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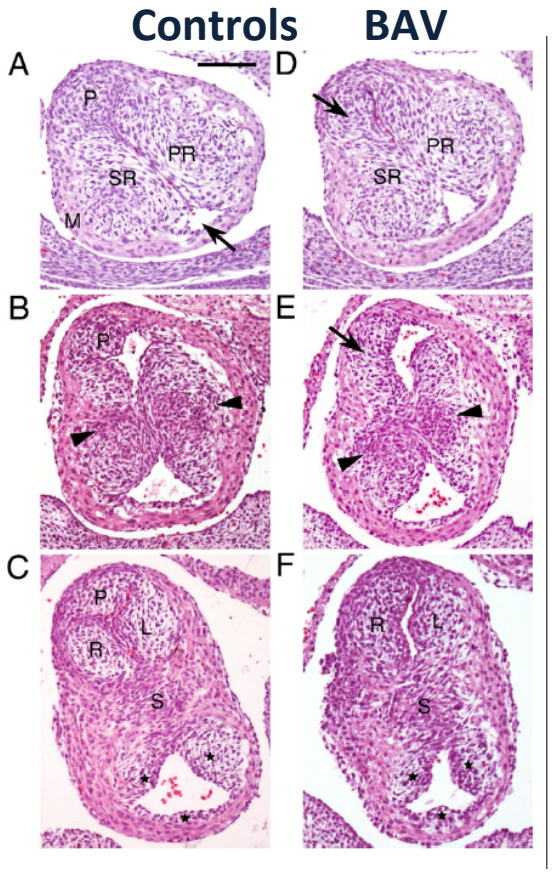
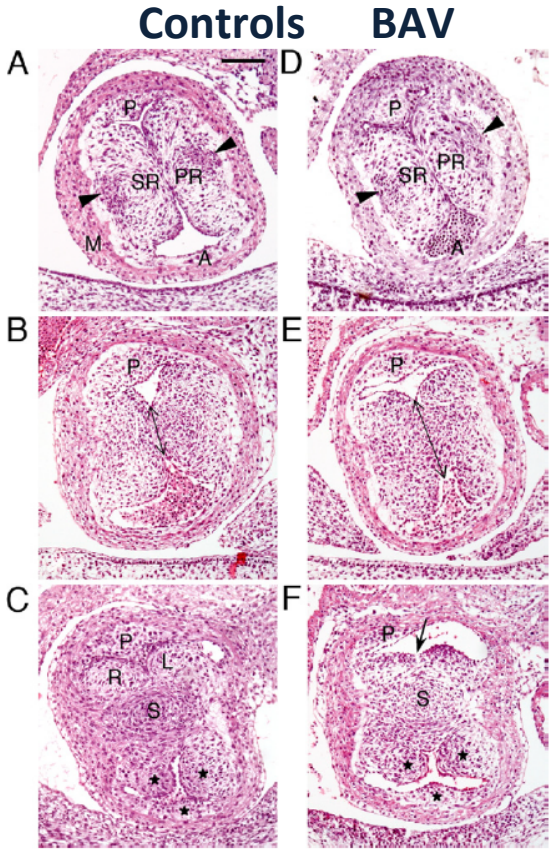
Embryology and etiology



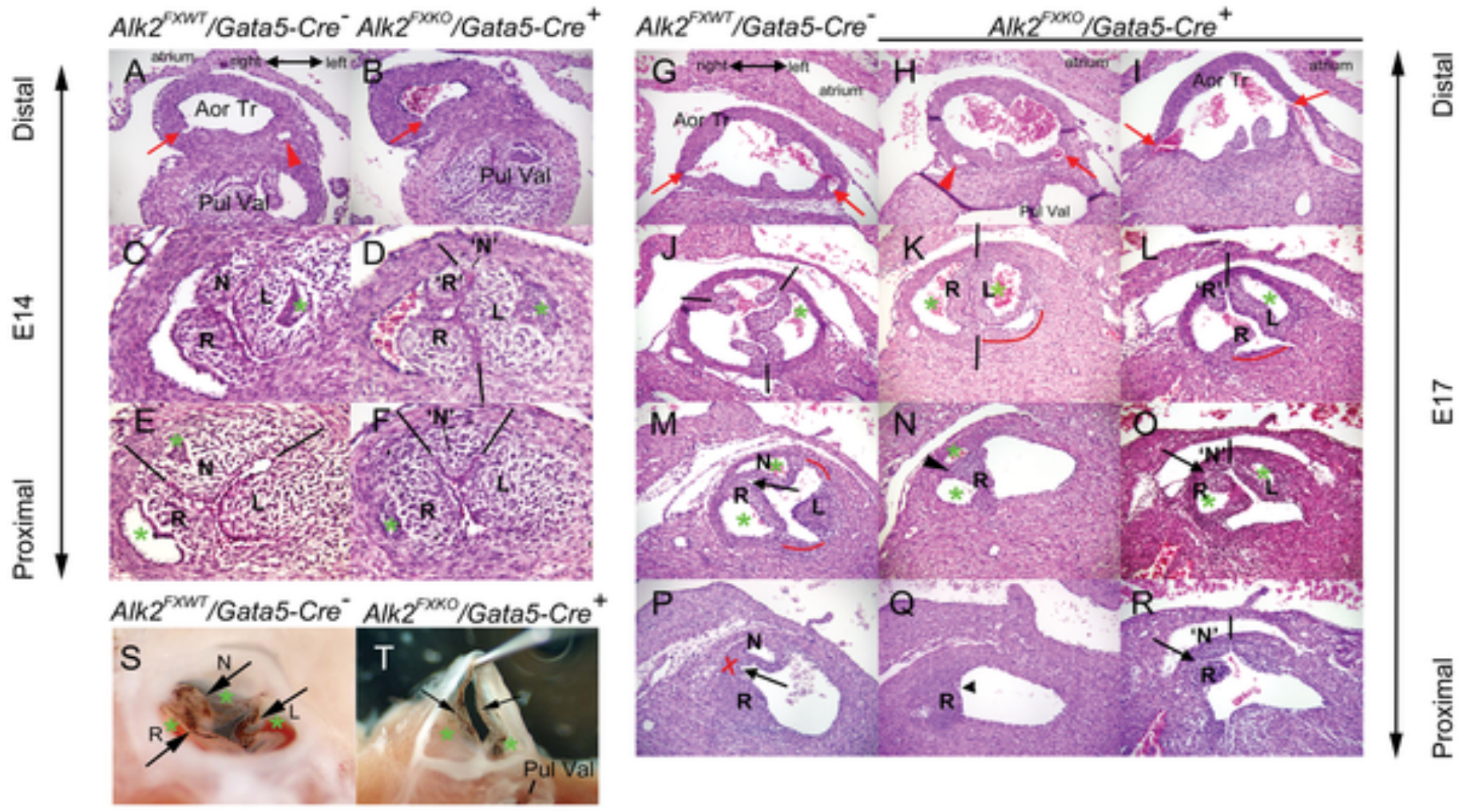
eNOS -/- mice
R-N BAV type



Syrian Hamster
R-L BAV type

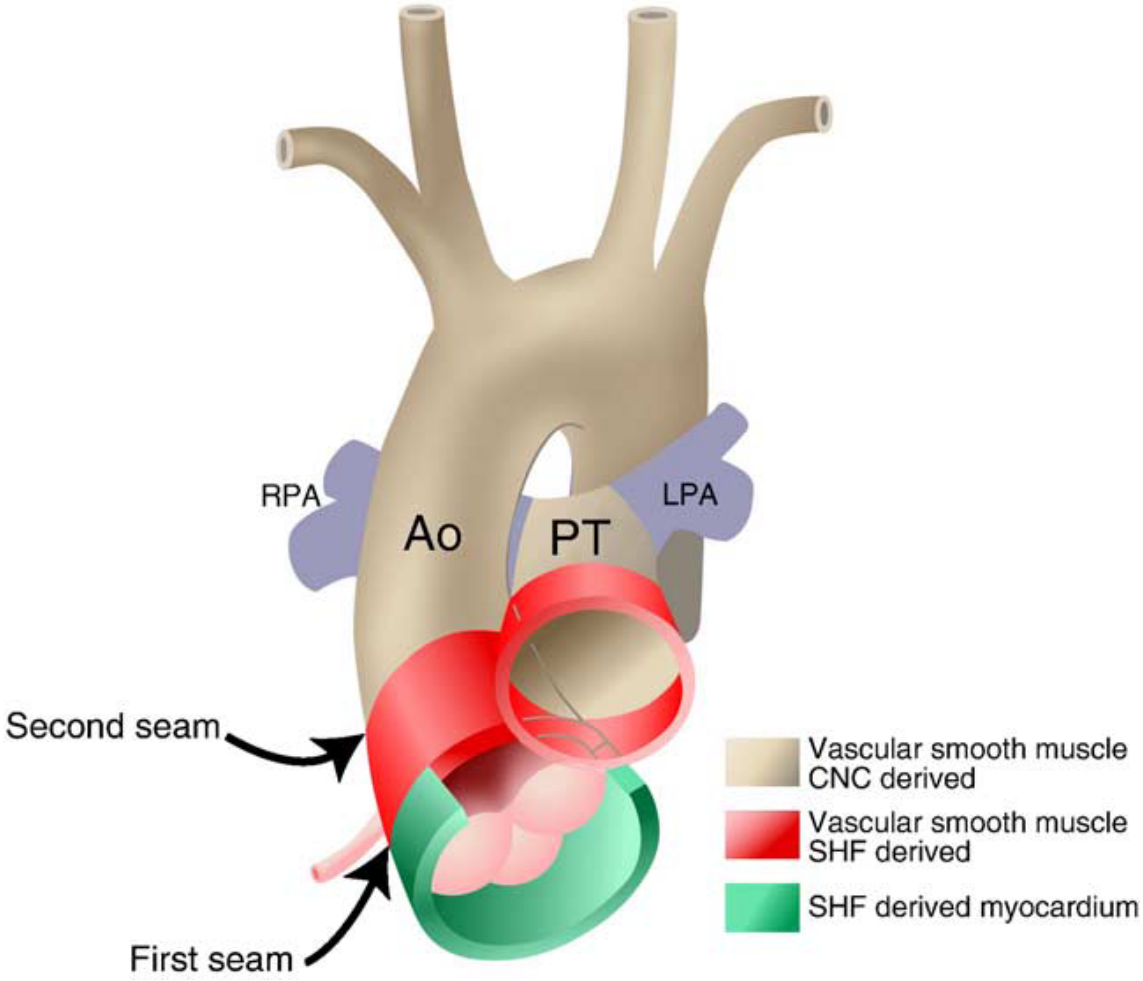
Fernandez B et al JACC 2009

Figure 3. Gata5-Cre-induced deletion of Alk2 function leads to defective development of aortic valves.



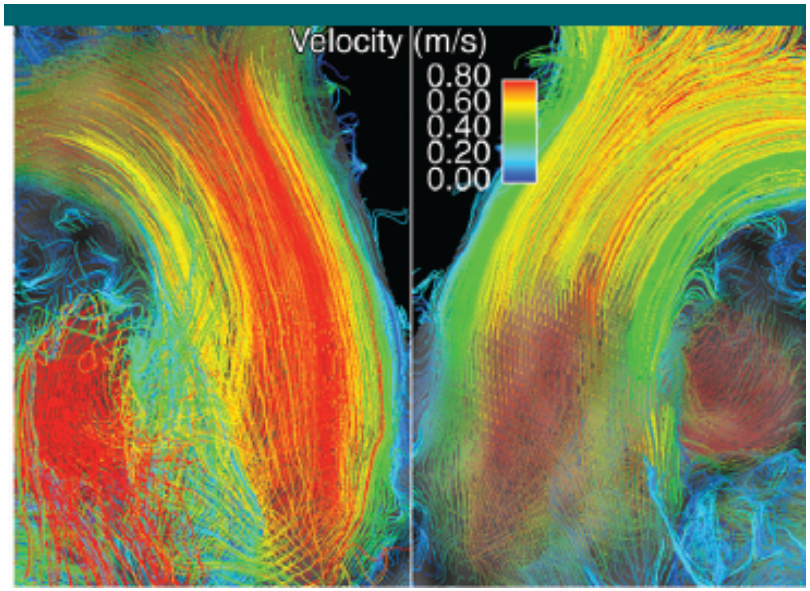
Thomas PS, Sridurongrit S, Ruiz-Lozano P, Kaartinen V (2012) Deficient Signaling via Alk2 (Acvr1) Leads to Bicuspid Aortic Valve Development. PLoS ONE 7(4): e35539. doi:10.1371/journal.pone.0035539
http://127.0.0.1:8081/plosone/article?id=info:doi/10.1371/journal.pone.0035539

Back to embryology: the second heart field

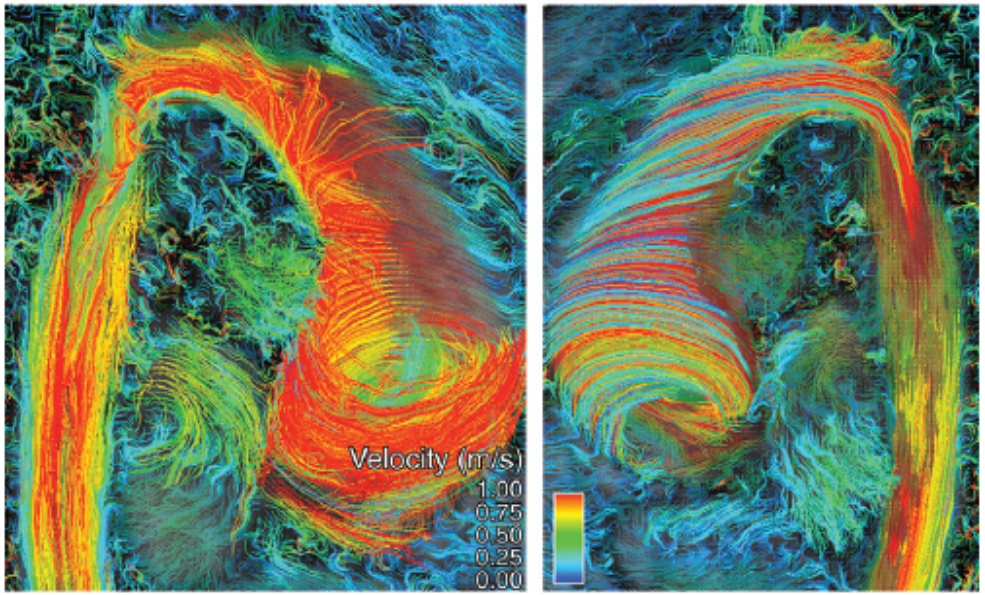


K.L. Waldo et al. Developmental Biology ,2005

Hemodynamic contribution to aortic dilatation/aneurysm



VAT

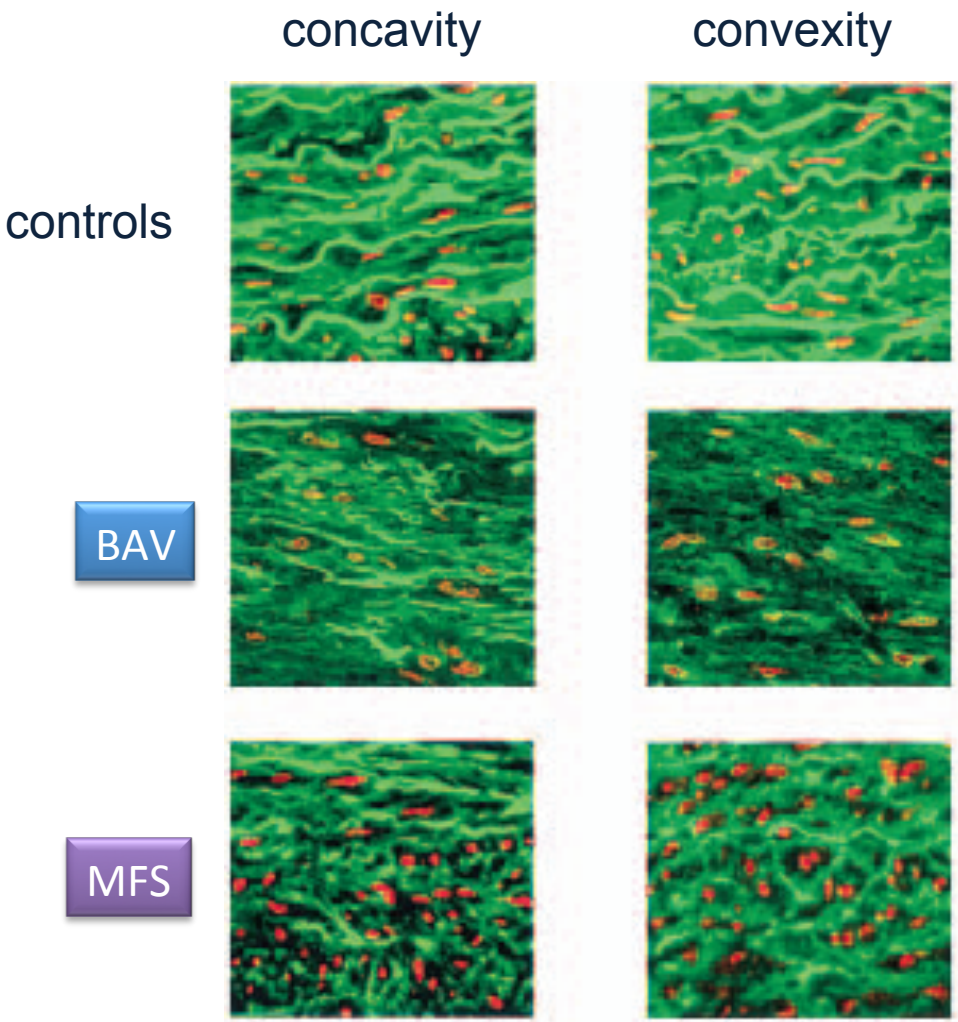


VAB

Hope D et al Radiology 2010

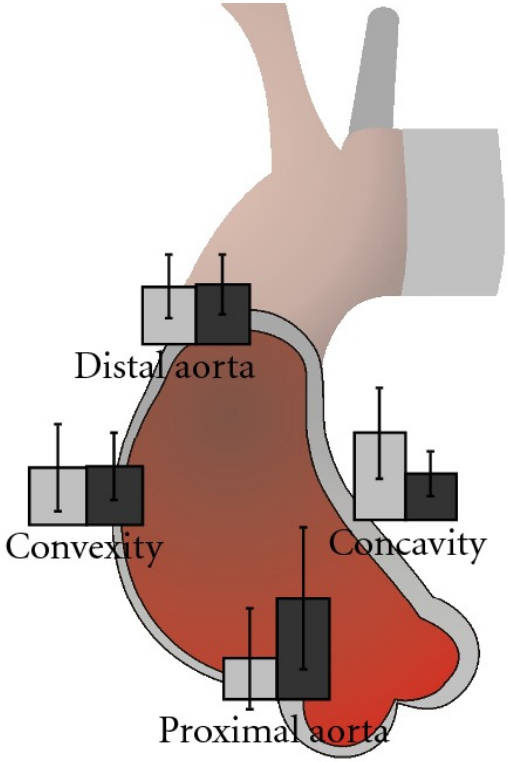
Spatial heterogeneity

type I collagen; SMC

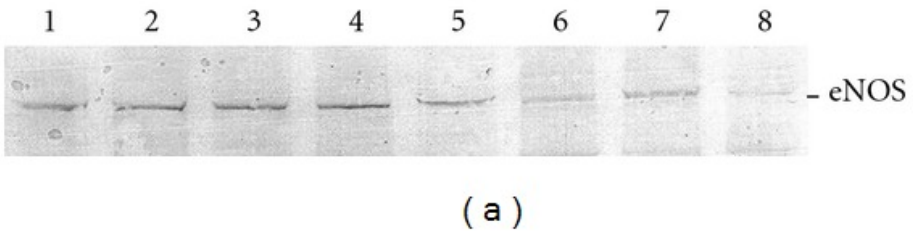


Research Article

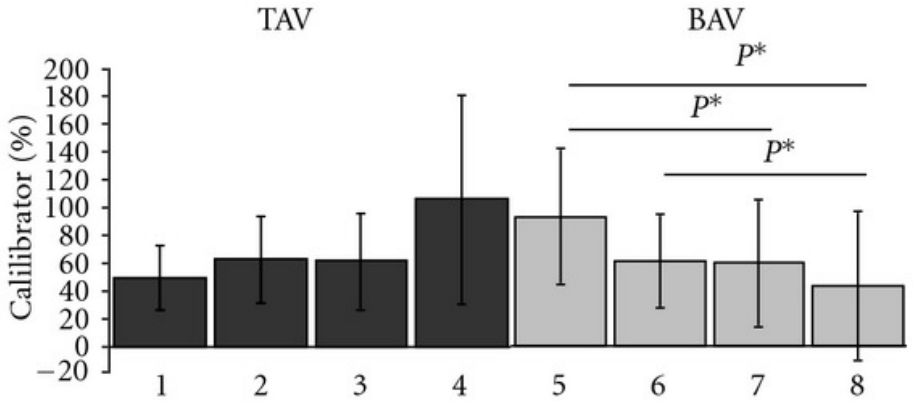
Locally Different Endothelial Nitric Oxide Synthase Protein Levels in Ascending Aortic Aneurysms of Bicuspid and Tricuspid Aortic Valve



(c)



(a)



Aortic elasticity and size in bicuspid aortic valve syndrome

Stefano Nistri[1]*, Jane Grande-Allen[2], Marianna Noale[3], Cristina Basso[4], Paola Siviero[3], Stefania Maggi[3], Gaetano Crepaldi[3], and Gaetano Thiene[4]

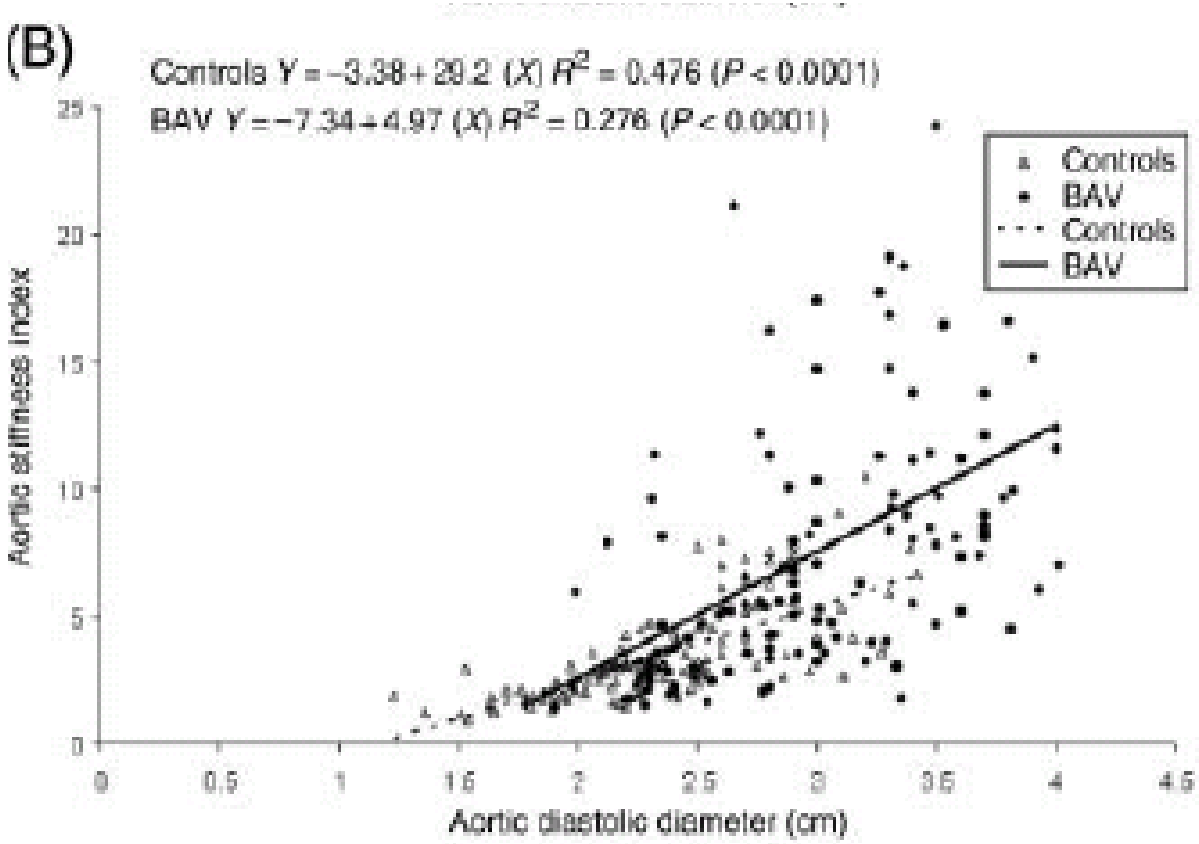
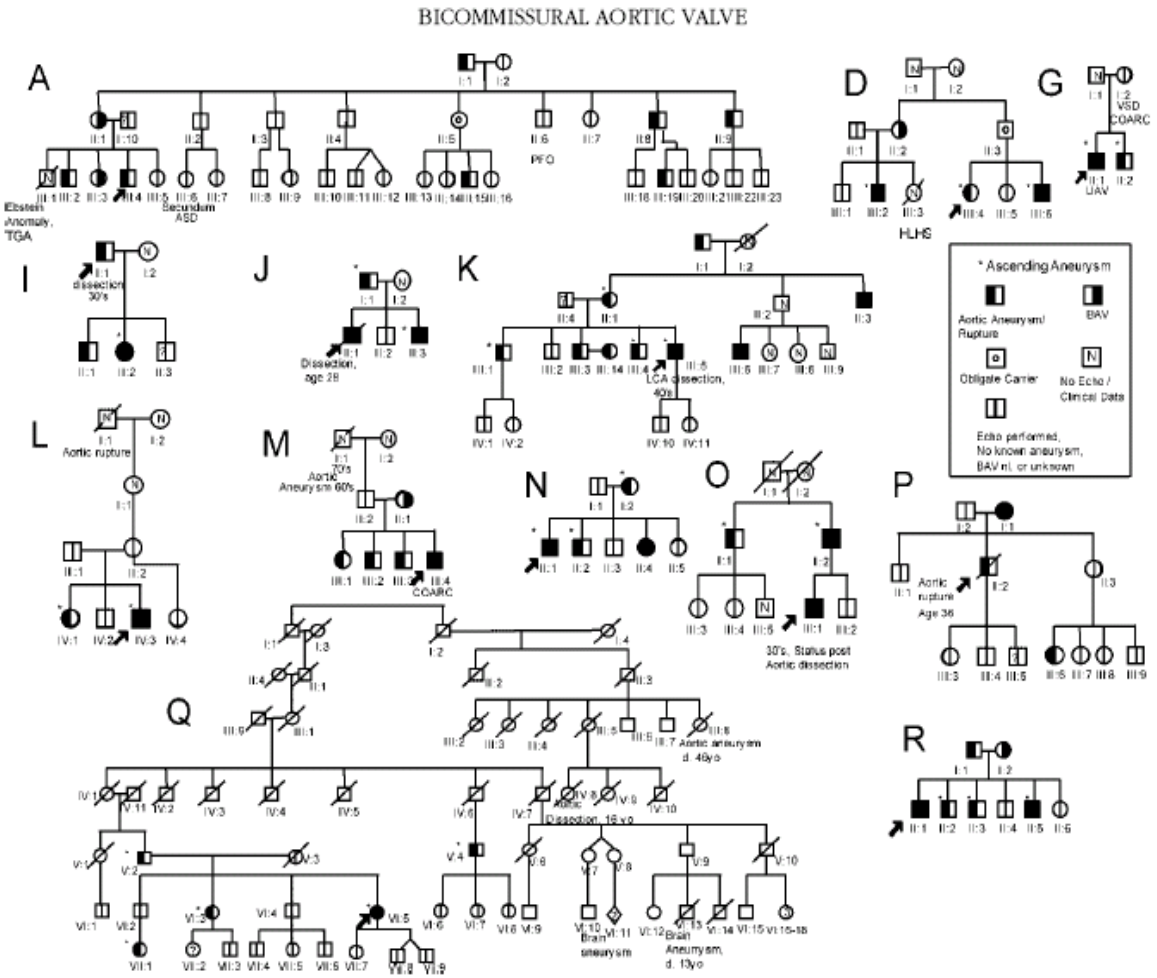


Table 3 Predictors of BAV subjects (vs. control), logistic regression model

	Odds ratio	95% confidence interval	*P*-value
Peak velocity (≥1.45 m/s)	20.529	7.265–58.009	<0.0001
AoS (cm)	6.172	2.323–16.400	0.0003
Aortic stiffness index	1.256	1.104–1.429	0.0006

Predictors considered in the model: AoS, AoD, AoS − AoD, SBP, DBP, PP, peak velocity, and SI. Stepwise selection method (see manuscript for abbreviations).

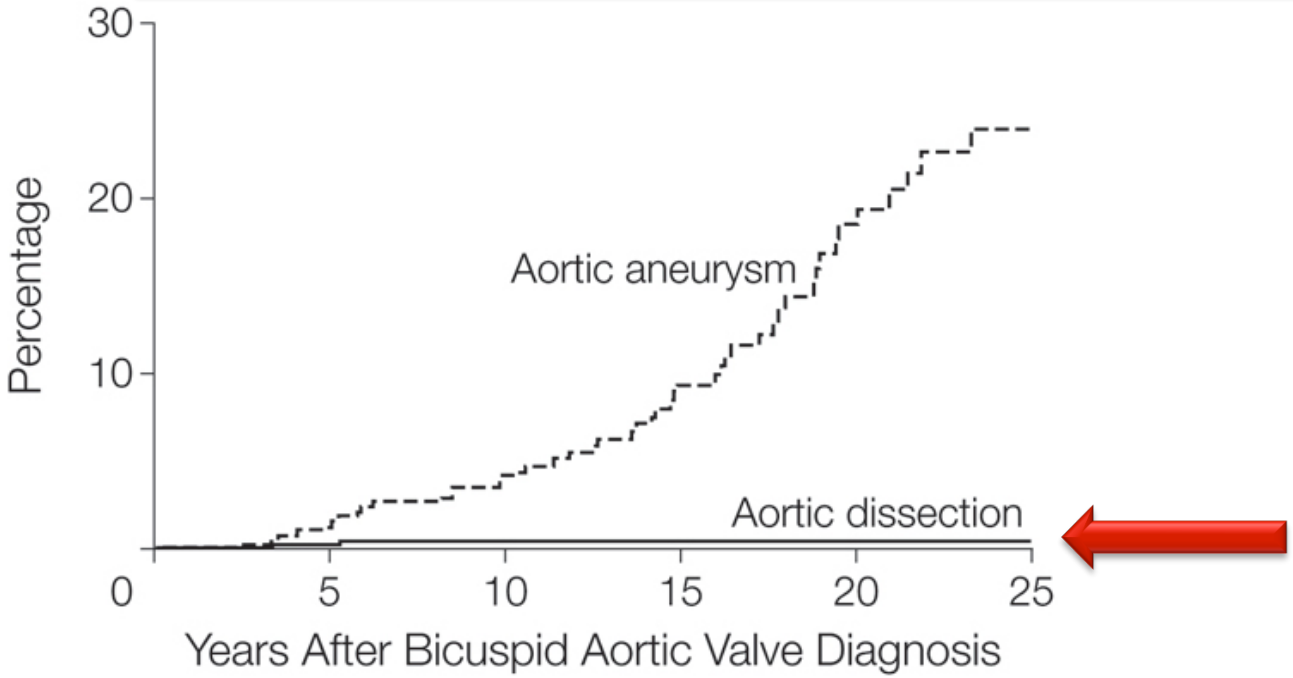
BAV is familial….



LoScalzo M et al 2007

TAA≥45 mm: 25-year risk of aneurysm formation was 26% (95% CI, 18.2%-33.8%;); incidence of 84.9 (95% CI, 63.3-110.9) per 10 000 patient-years.

TAA≥50 mm: the relative risk would remain high at 26.4 (95% CI, 16.6-41.9,) the cohort incidence of aneurysm would be 28.8 (95% CI, 17.5-44.2) per 10 000 patient-years



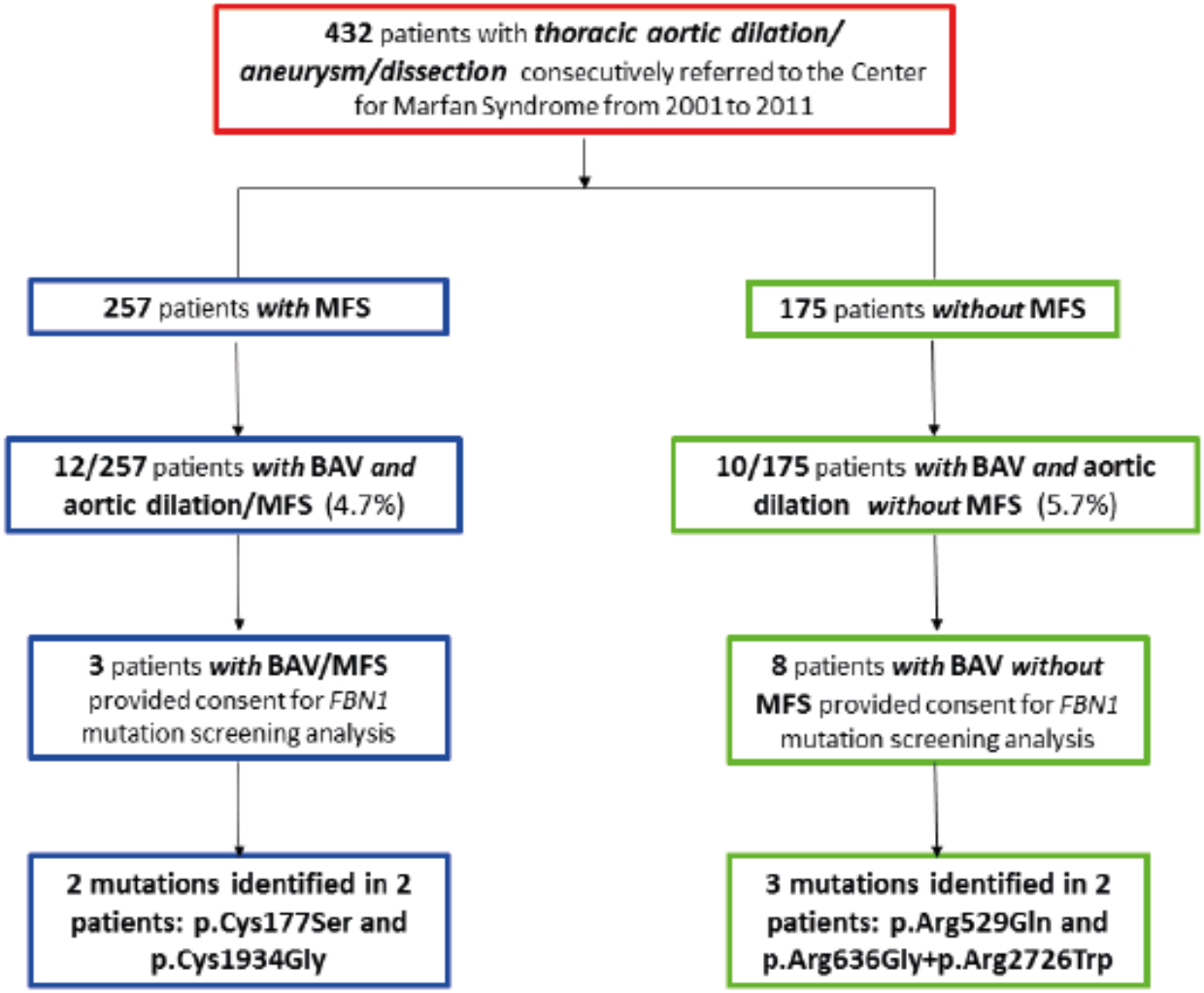
No. at risk						
Aortic aneurysm	384	352	309	186	88	39
Aortic dissection	416	387	348	209	110	53

Michelena, H. I. et al. JAMA 2011;306:1104-1112

Overall Natural History

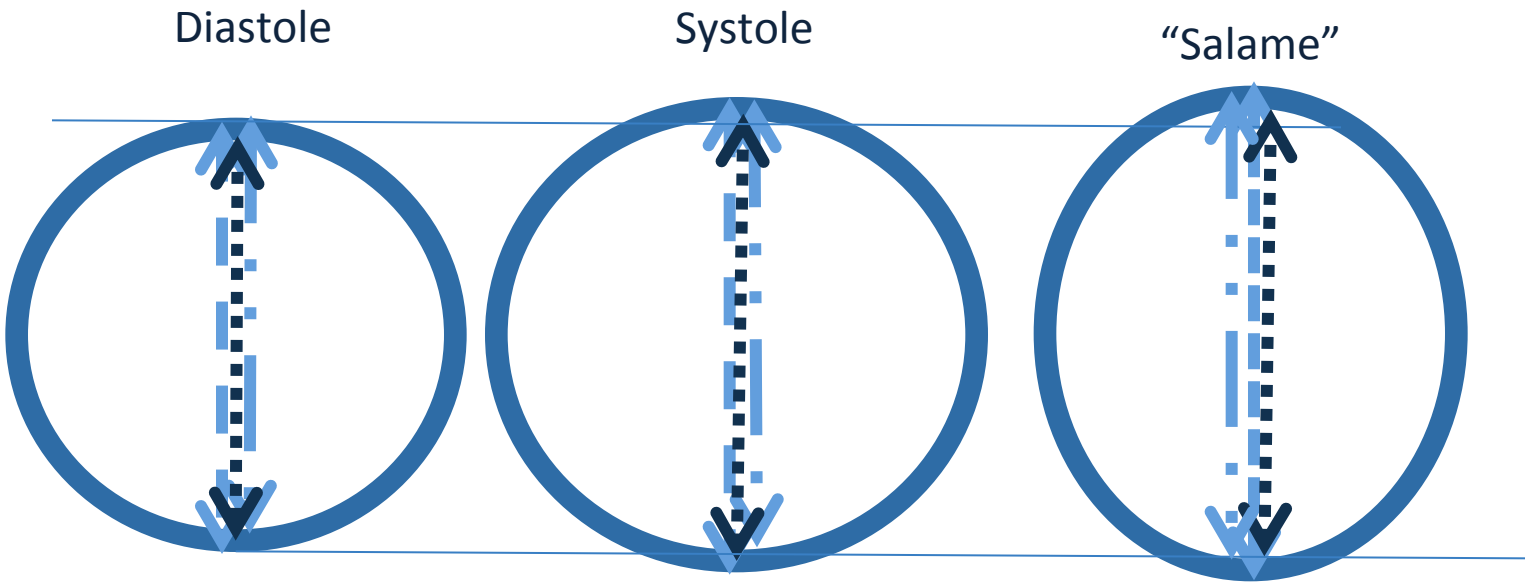
Cardiac Outcomes	No. (%) of Patients (N = 642)
Primary[a]	
Intervention on aortic valve or ascending aorta	142 (22)
Bioprosthetic aortic valve replacement	47
Ascending aortic graft and aortic valve replacement	38
Pulmonary autograft (Ross procedure)	34
Mechanical aortic valve replacement	14
Valve sparing aortic root replacement	5
Aortic valve repair	3
Percutaneous aortic valvotomy	1
Cardiac death	17 (3)
Heart failure	12
Aortic dissection	2
Postoperative after cardiac surgery	3
Hospital admission for heart failure	16 (2)
Aortic complication	11 (2)
Aortic dissection	5
Descending thoracic or abdominal aortic aneurysm	6

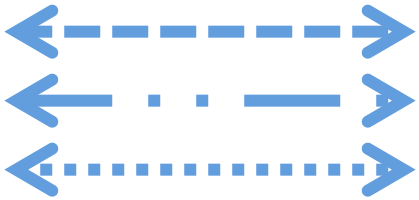
Tzemos N et al 2008


432 patients with ***thoracic aortic dilation/ aneurysm/dissection*** consecutively referred to the Center for Marfan Syndrome from 2001 to 2011
257 patients ***with*** **MFS**
175 patients ***without*** **MFS**
12/257 patients ***with*** **BAV *and* aortic dilation/MFS** (4.7%)
10/175 patients ***with*** **BAV *and* aortic dilation *without* MFS** (5.7%)
3 patients ***with*** **BAV/MFS** provided consent for *FBN1* mutation screening analysis
8 patients ***with*** **BAV *without* MFS** provided consent for *FBN1* mutation screening analysis
2 mutations identified in 2 patients: p.Cys177Ser and p.Cys1934Gly
3 mutations identified in 2 patients: p.Arg529Gln and p.Arg636Gly+p.Arg2726Trp

Dealing with discrepancies

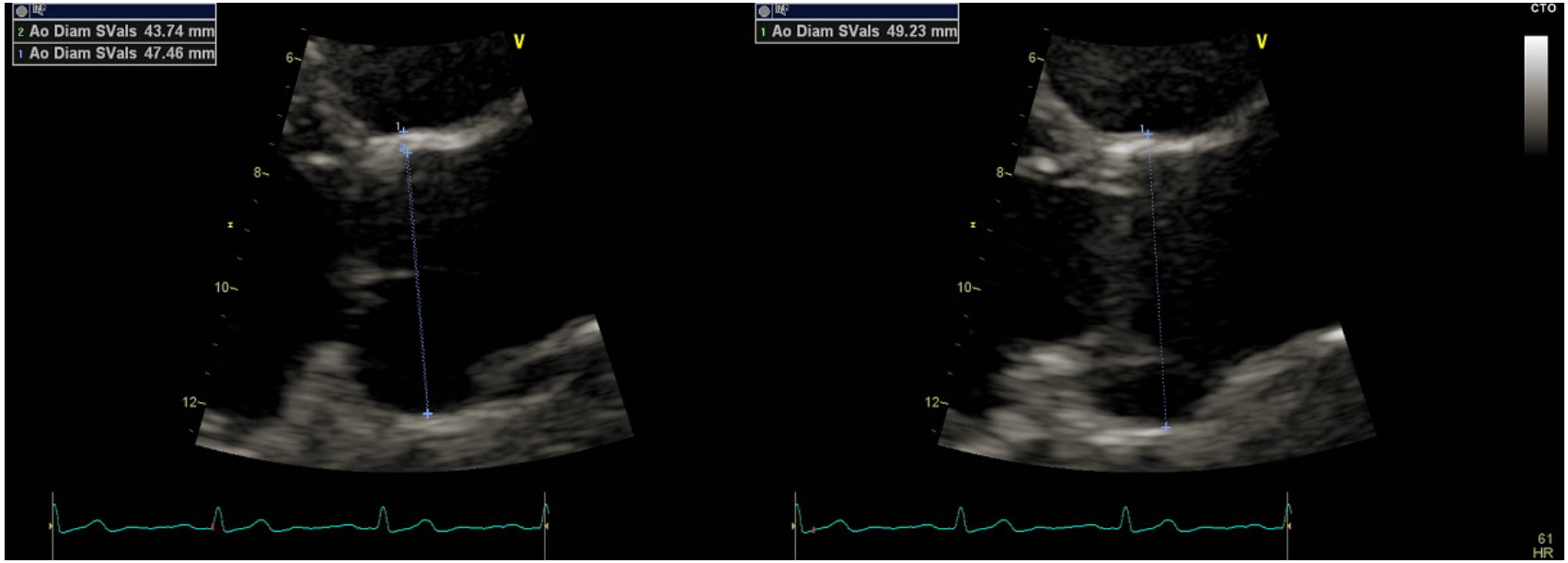
Angiographic sequences are somewhere here
Always inner-to-inner





External-external: 2 wall thickness included
Leading-to-leading: 1 wall thickness included
Inner-to-inner: no wall thickness included
[average wall thinckness≈ 2-3 mm]

Let's see it practically…by echo: 48 y.o. male, familial BAV + TAA



End-diastole

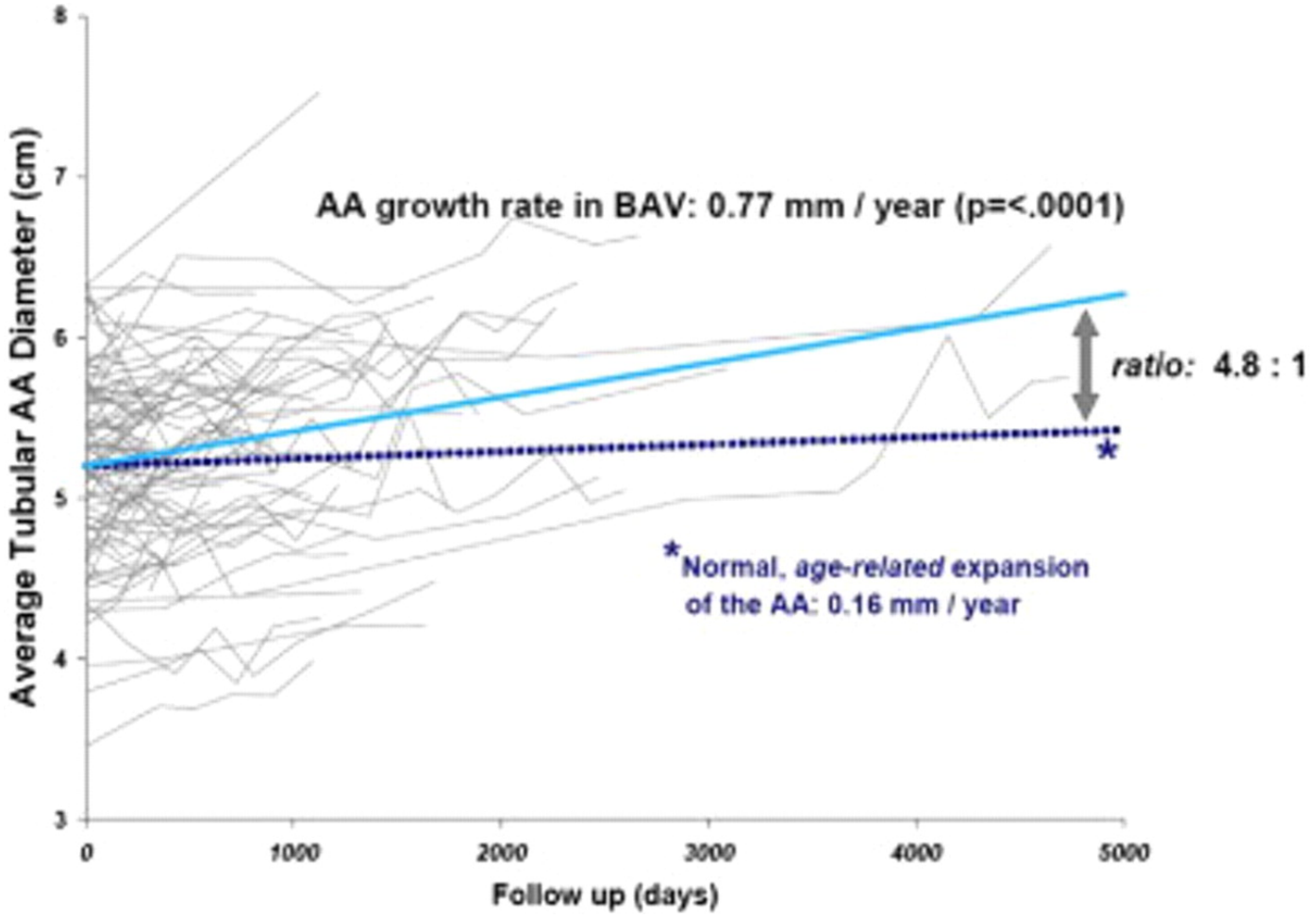
Mid-systole

49.2 → 47.4 → 43.7

49.2 →43.7 →47.4

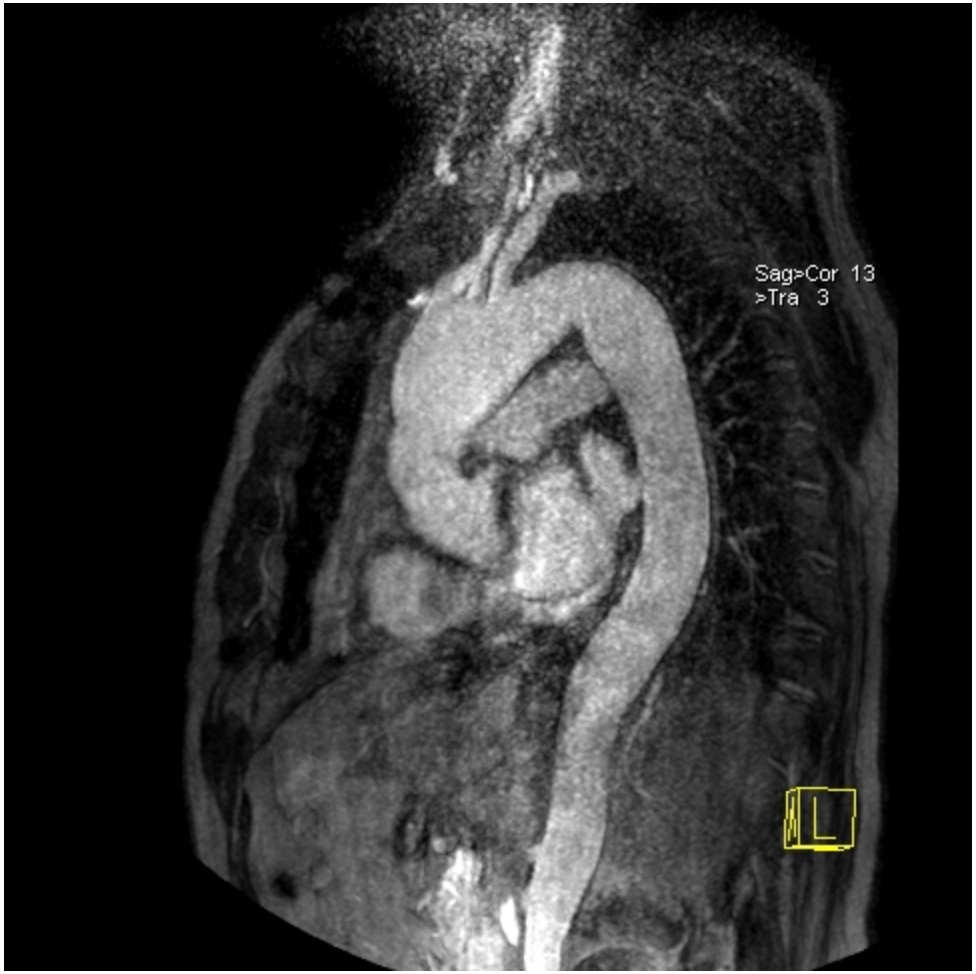
43.7 → 47.4 → 49.2

Variability in measurements and follow-up strategies



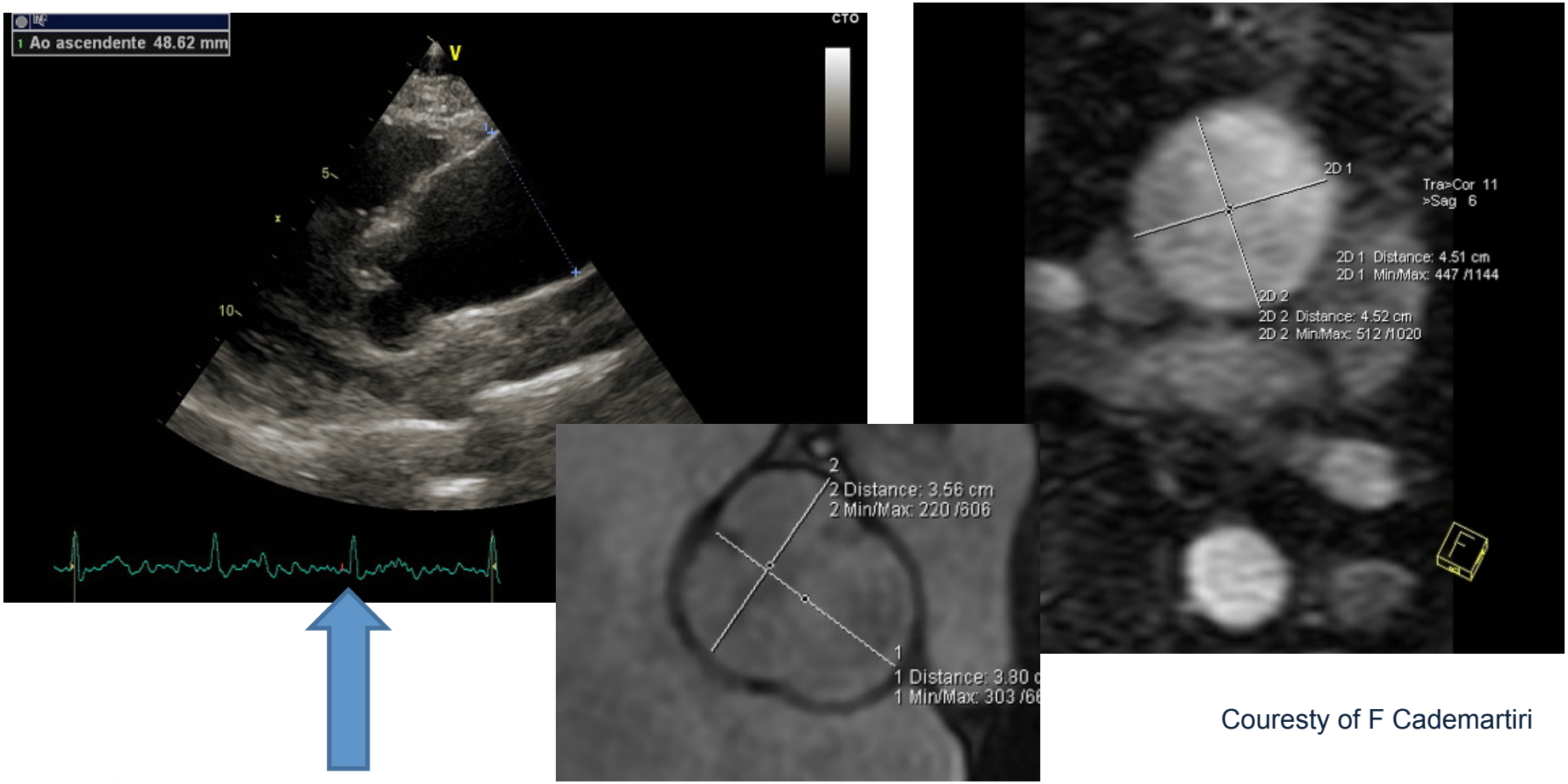
Etz C. D. et al.; Ann Thorac Surg 2010;90:1884-1892

The father….3 years after surgery



Let's see it practically…echo vs. MR

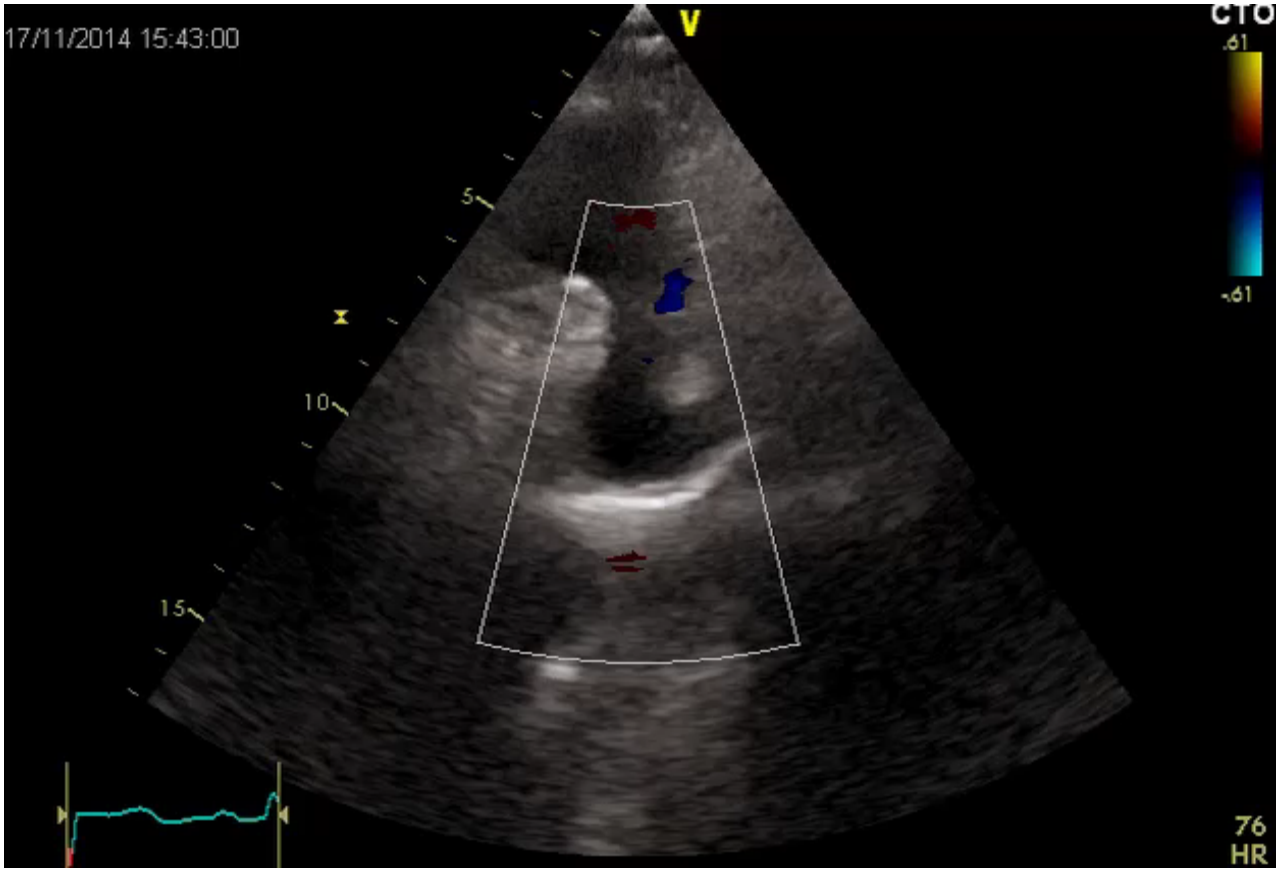
43 y.o. male, BAV + TAA



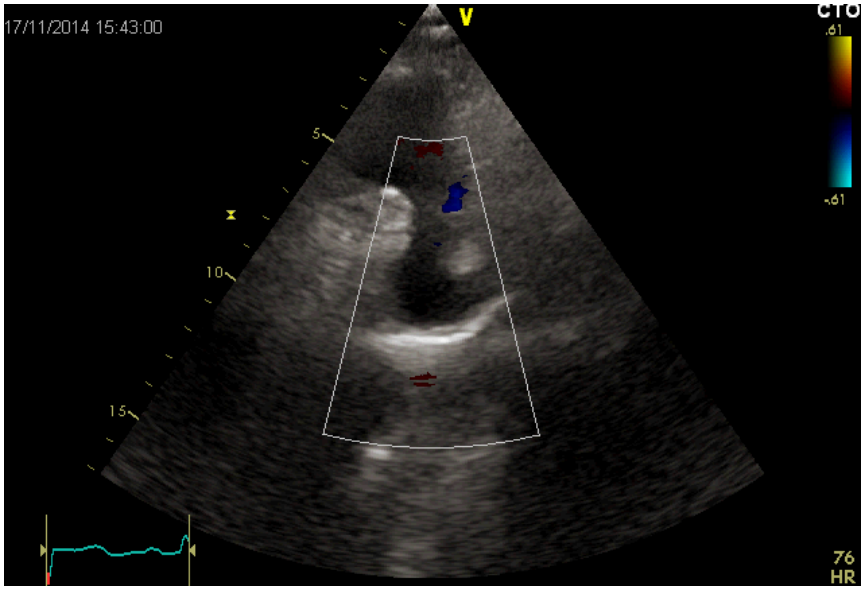
Couresty of F Cademartiri

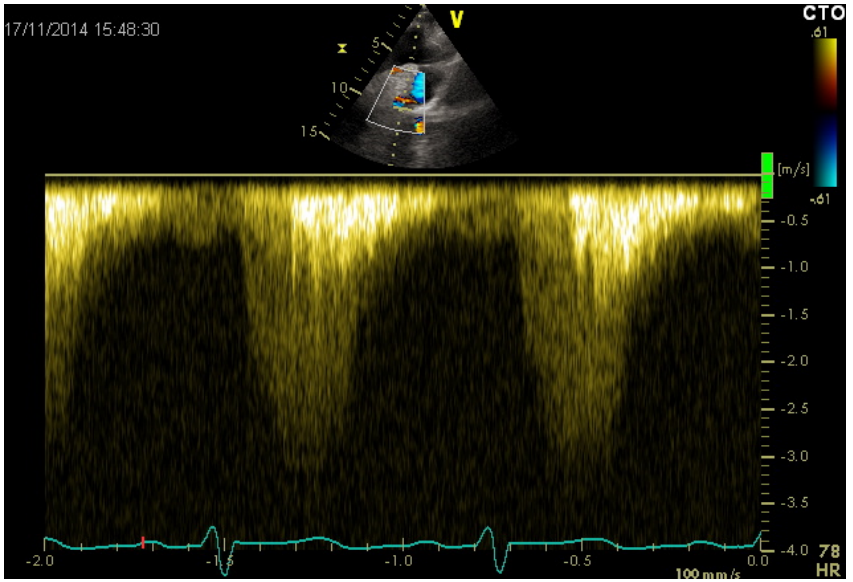
54 y.o. male athletes

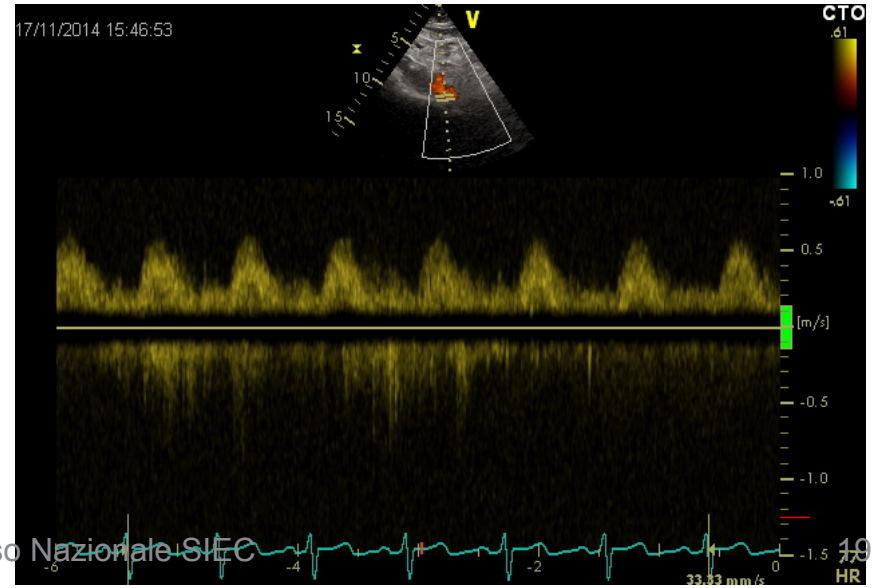
BAV, 46 mm Asc Aorta



Aortic coarctation



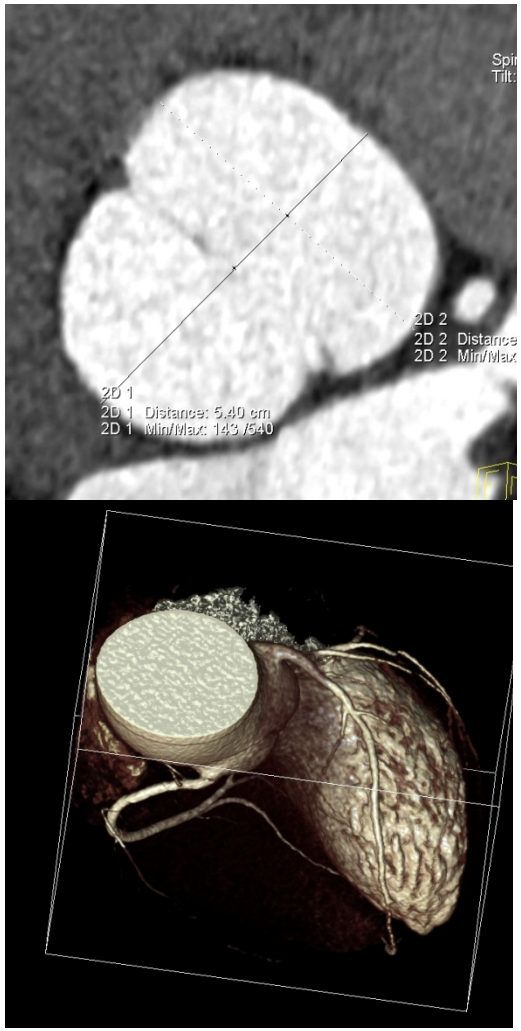


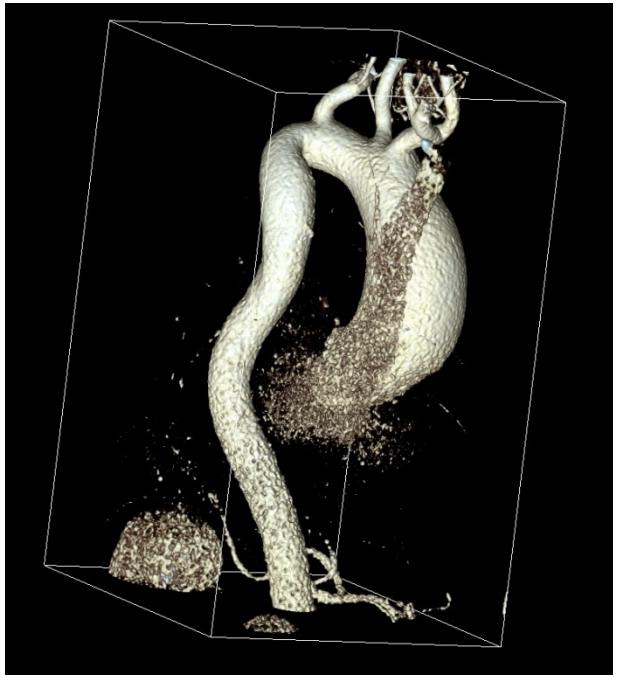


Aortic coarctation

Couresty of F Cademartiri

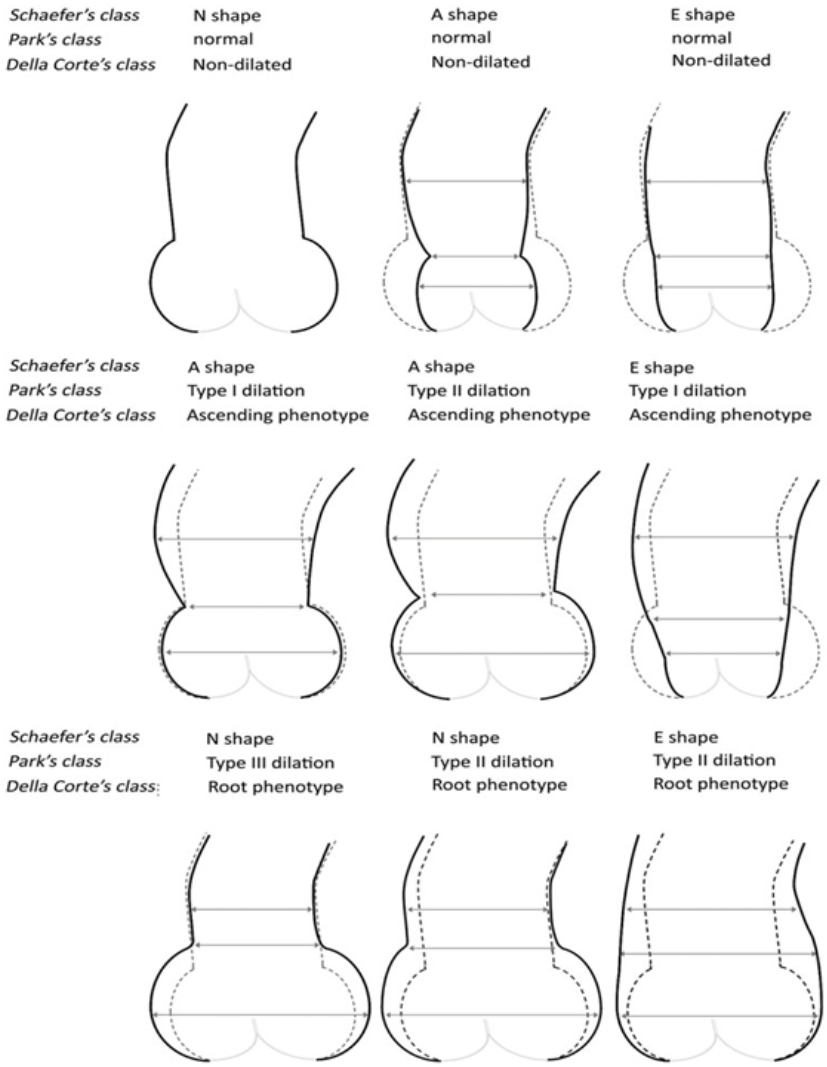
First diagnosis-familial BAV+TAA “one-stop-shop”



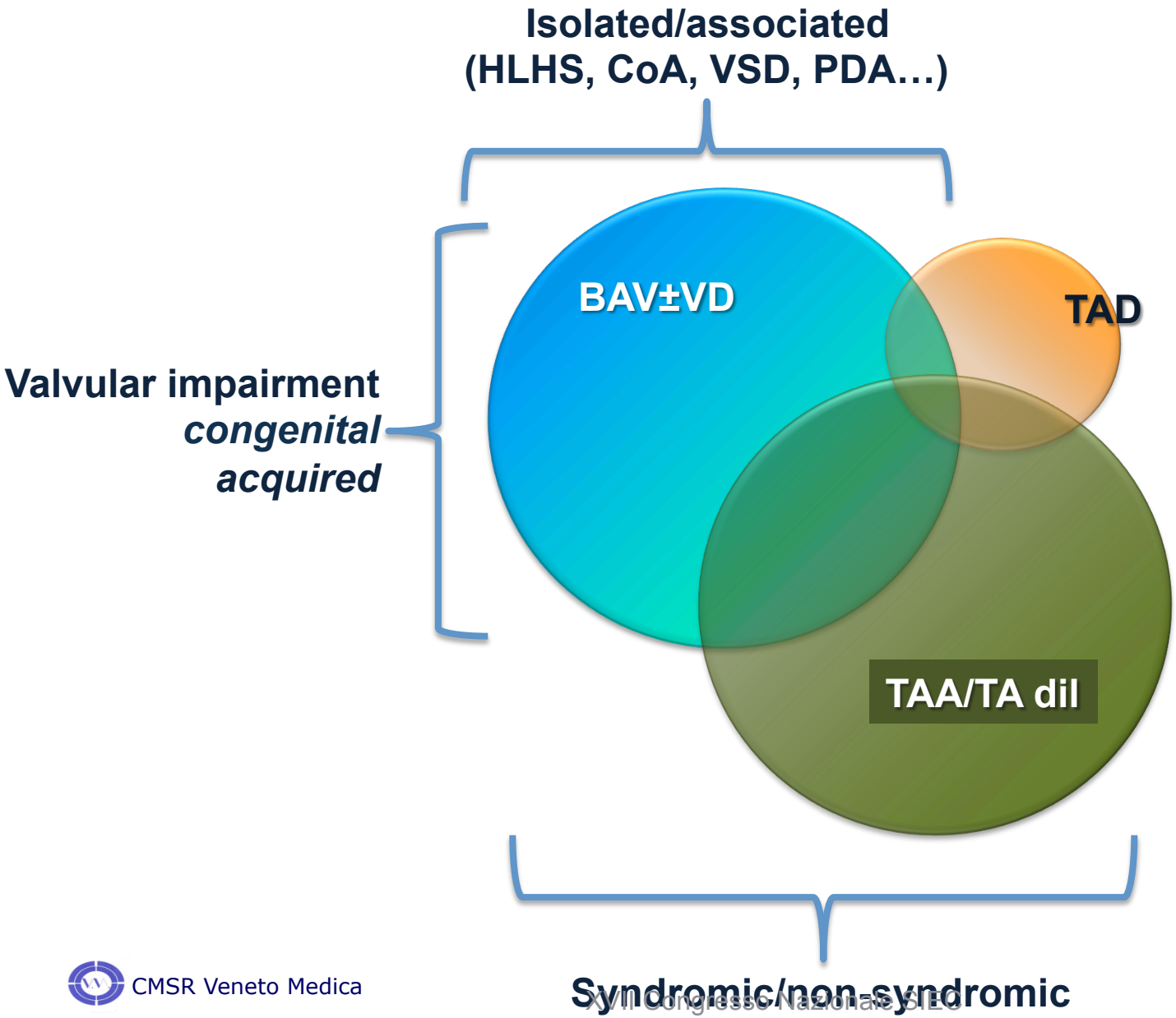


Couresty of F Cademartiri

Phenotyping the aorta



Della Corte A et al 2014


Isolated/associated
(HLHS, CoA, VSD, PDA…)
Valvular impairment
congenital
acquired
BAV±VD
TAD
TAA/TA dil
Syndromic/non-syndromic

Conclusive Remarks

- **<u>Heterogeneous syndrome</u>**
- Multimodality : for diagnosing & phenotyping
- BAV & Aortopathy:
  - BAV is a primarily heritable valvular disorder with aortopathy as an associated secondary phenomenon [BAV as a “clinical marker” for an underlying primary heritable vascular disorder]
  - BAV and its associated aortopathy have an oligogenic inheritance pattern, where at least 2 co-segregated genetic mutations are required for disease development
- Increased risk of Ao dissection→still small numbers!!

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