Management of Marfan Syndrome

XXVIII GIORNATE CARDIOLOGICHE TORINES
October 13-15, 2016, Turin

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Practice Chair, Cardiovascular division
Mayo Clinic, Rochester, MN

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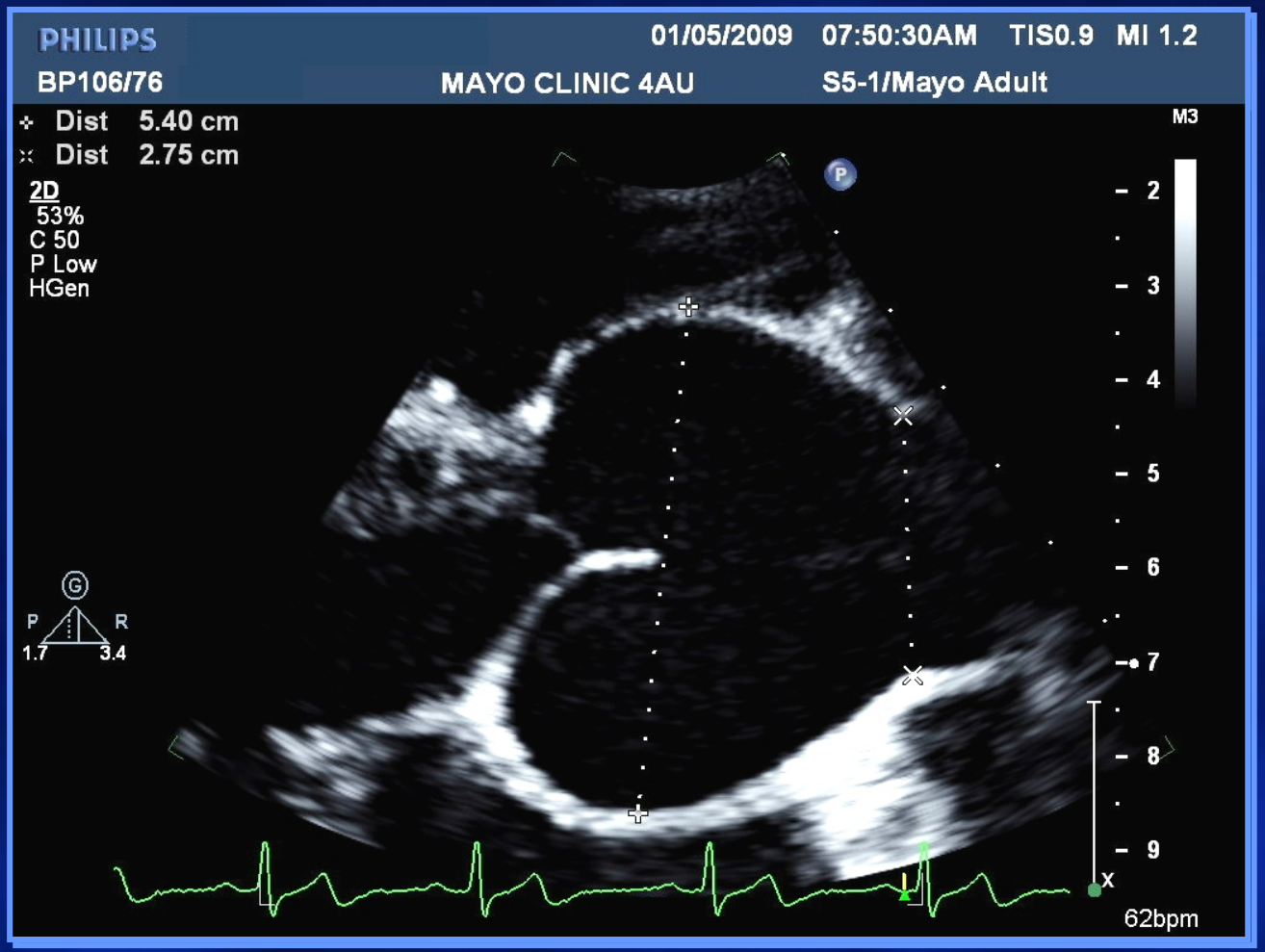
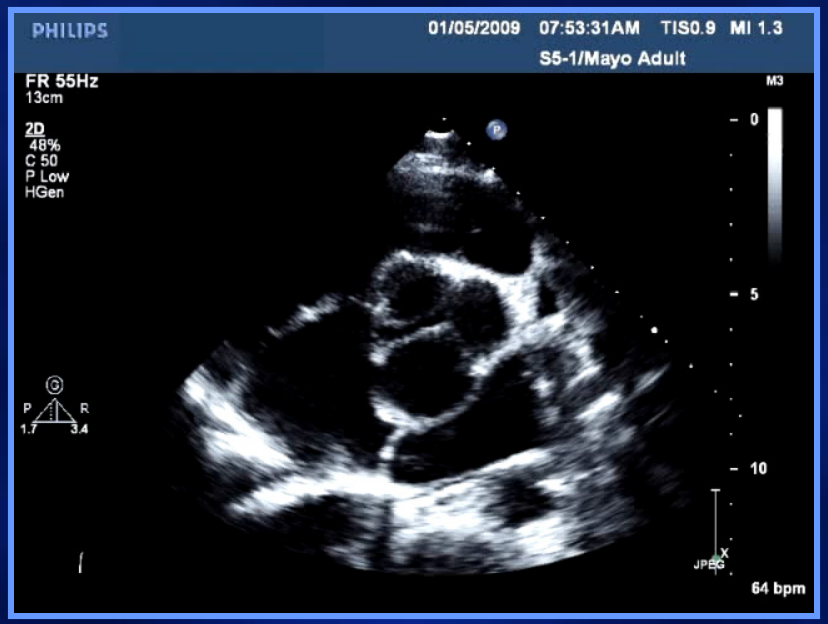
mayo

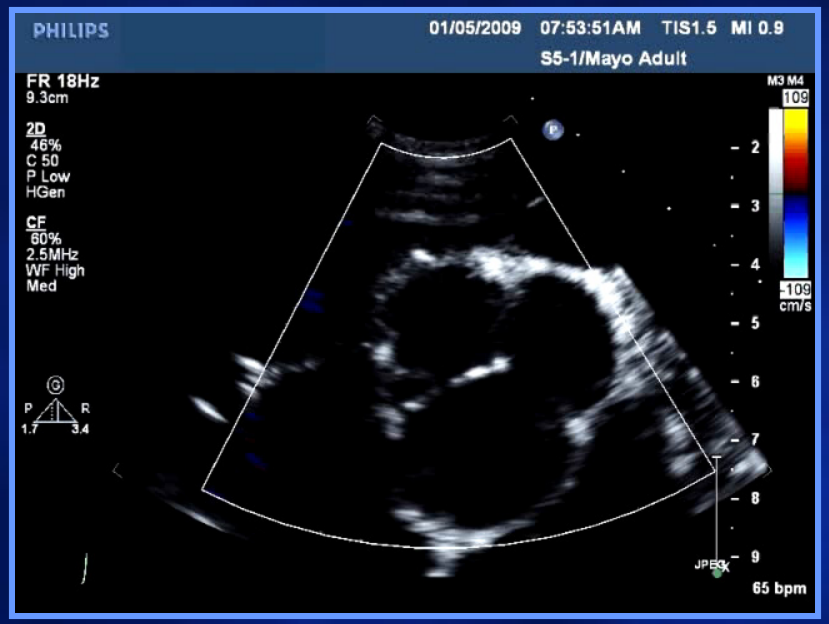
17 YO with Heart Murmur

54 mm



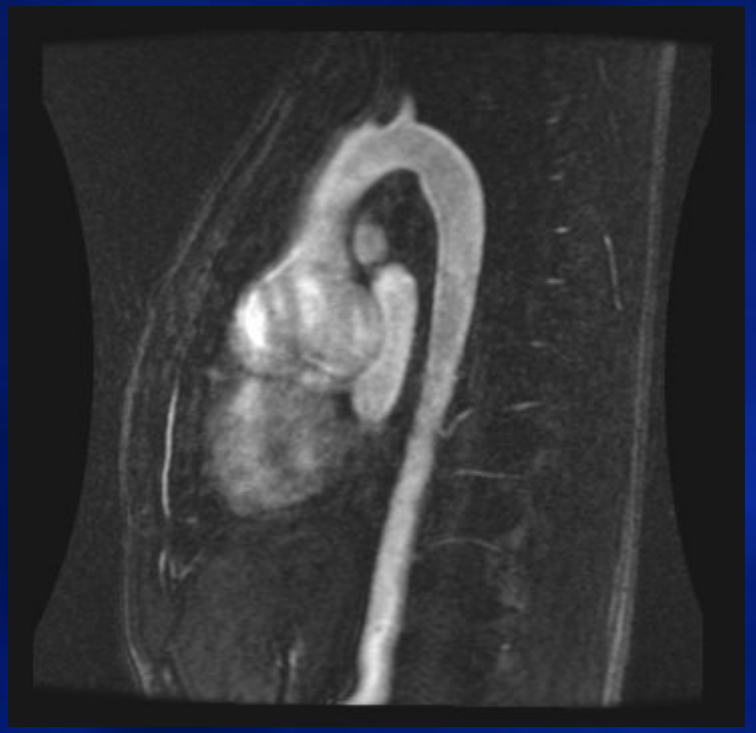
17 YO with Aortic Root Aneurysm





Is it Marfan syndrome?

17 YO with Aortic Root Aneurysm
Imaging of whole aorta



In absence of family history, the diagnosis of MFS is made in presence:

1. TAA (Z-score ≥2) and Ectopia Lentis
2. TAA (Z-score ≥2) and FBN1
3. Ectopia Lentis and FBN1(known aortopathy)
4. TAA (Z-score ≥2) and Systemic score (≥7pts)

Loeys et al: J M genetics, 2010

Z score measurement

Height (cm):	187
Weight (kg):	62
Gender:	male
BSA formula:	1.84 M^2

Site	Measured (mm)	Mean	ULN	Z-Score
Aortic Annulus:		21.47	26.06	
Sinuses:	54	29.93	36.33	5.90
ST Junction:	26	24.21	29.69	0.72
Ascending Aorta:	26	24.06	30.10	0.71

http://www.marfan.org/

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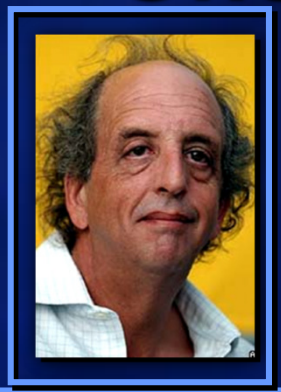
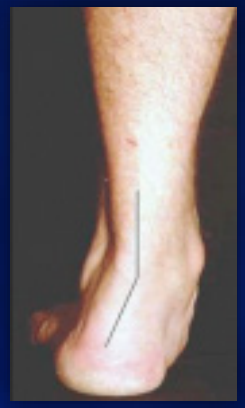
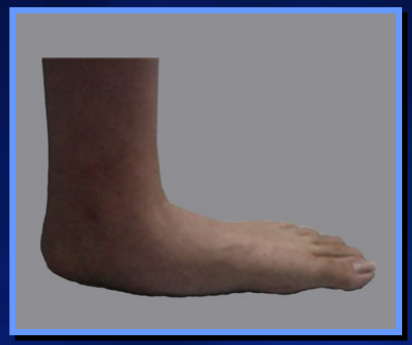
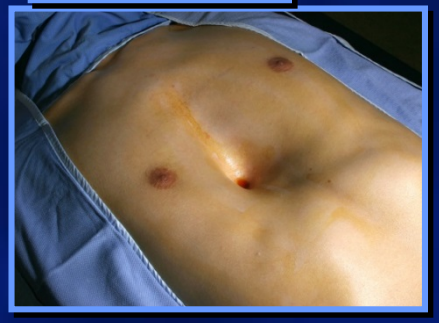
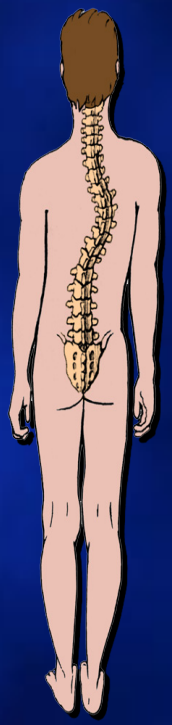
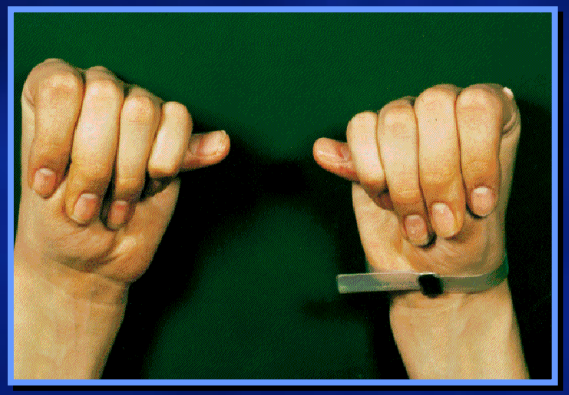
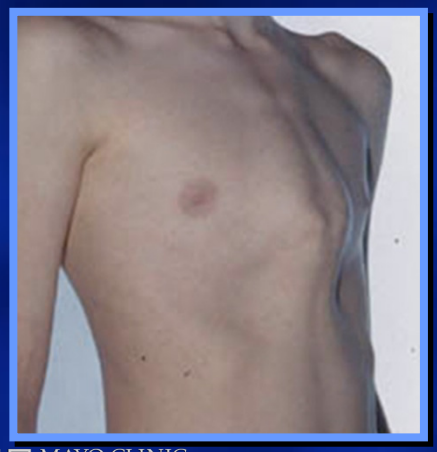
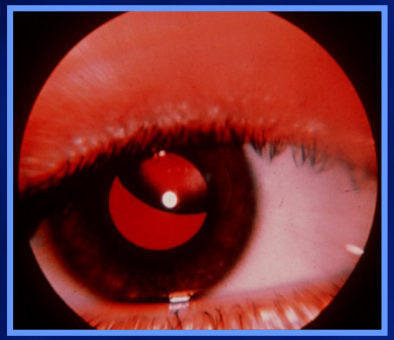
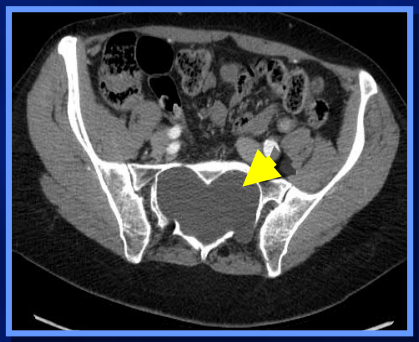
2. TAA (Z-score ≥2) and Systemic score (≥7pts)

Loeys et al: J M genetics, 2010

Ghent Criteria – Systemic Score



Systemic Features of MFS

	Points
Wrist AND thumb sign	3
Wrist OR thumb sign	1
Pectus carinatum deformity	2
Excavatum or chest asymmetry	1
Hindfoot deformity	2
plain pes planus	1
Pneumothorax	2
Dural ectasia	2
Protrusio acetabuli	2

	Points
Reduced US/LS + increased arm/height	1
Scoliosis or thoracolumbar kyphosis	1
Reduced elbow extension	1
Facial features (3/5)	1
dolichocephaly/ enophthalmos/ down slanting palpebral fissures malar hypoplasia/ retrognathia	
Skin striae	1
Myopia > 3 diopters	1
Mitral valve prolapse (all types)	1

Loeys et al: J M genetics, 2010

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Mitral valve prolapse (all types)	1

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Systemic Score = 10 Points

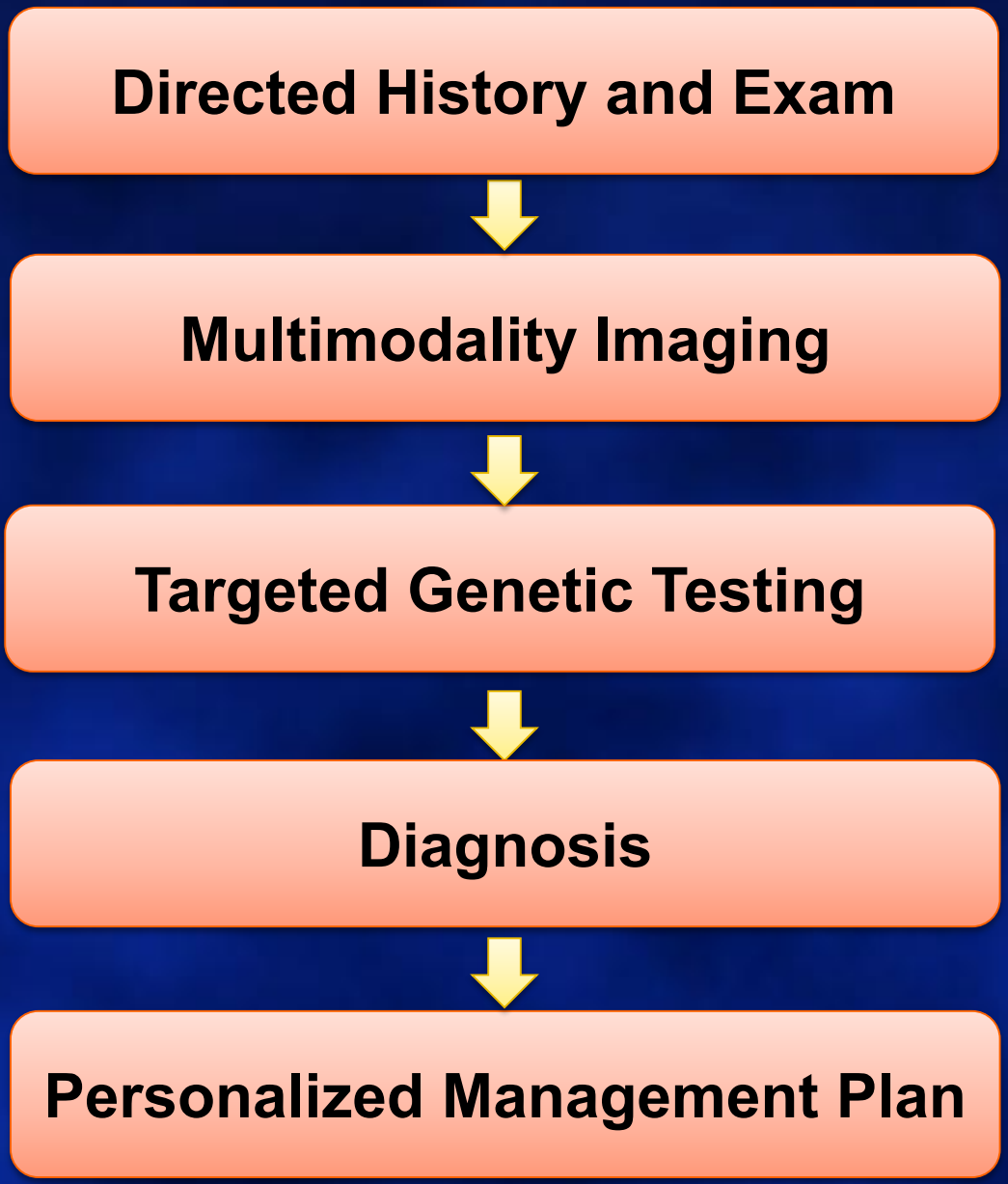
In absence of family history, the diagnosis of MFS is made in presence:

1. TAA (Z-score ≥2) and FBN1

2. TAA (Z-score ≥2) and Systemic score (≥7pts)

Loeys et al: J M genetics, 2010

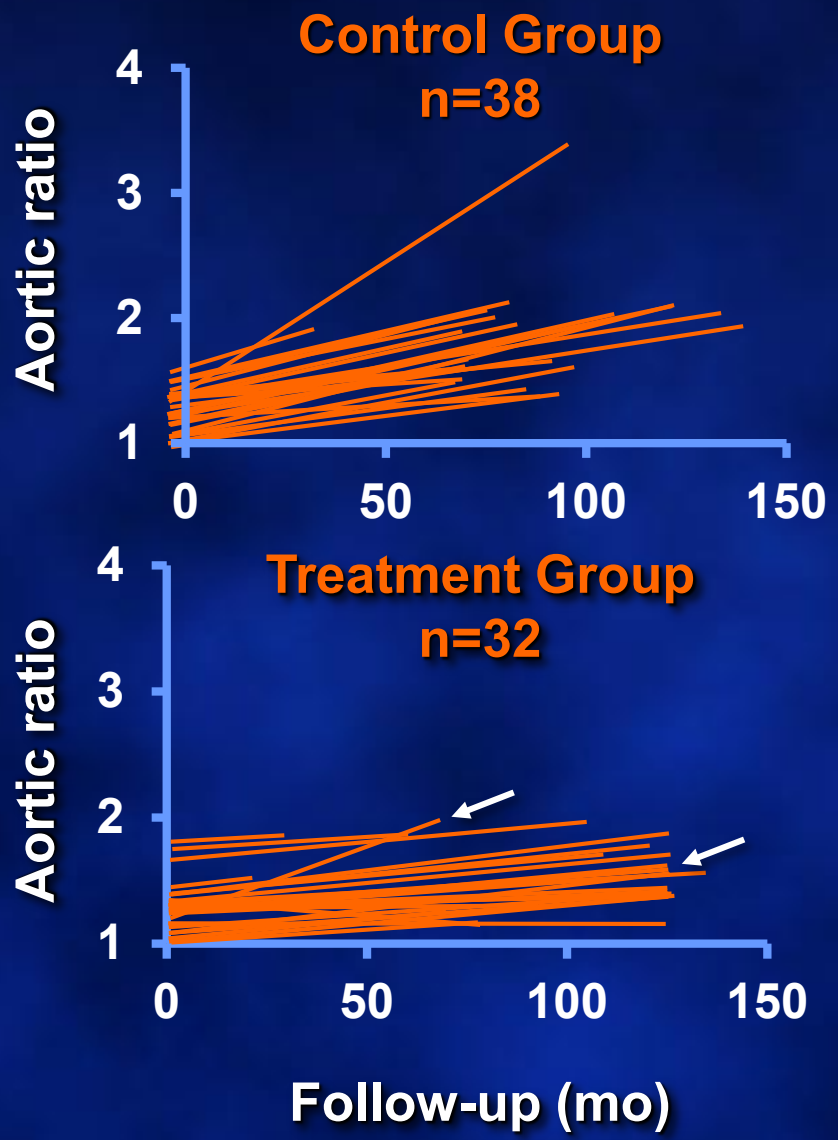
Clinical Approach to Dilated Aorta



Medical Management For MFS

Shores: NEJM, 1994

- Propranolol in MFS
- β blockers
  - ↓ HR and LV ejection
  - ↓ aortic root dilation
  - ↓ CV complications



Medical Management For MFS

Brooke B, Dietz H et al: NEJM 2008

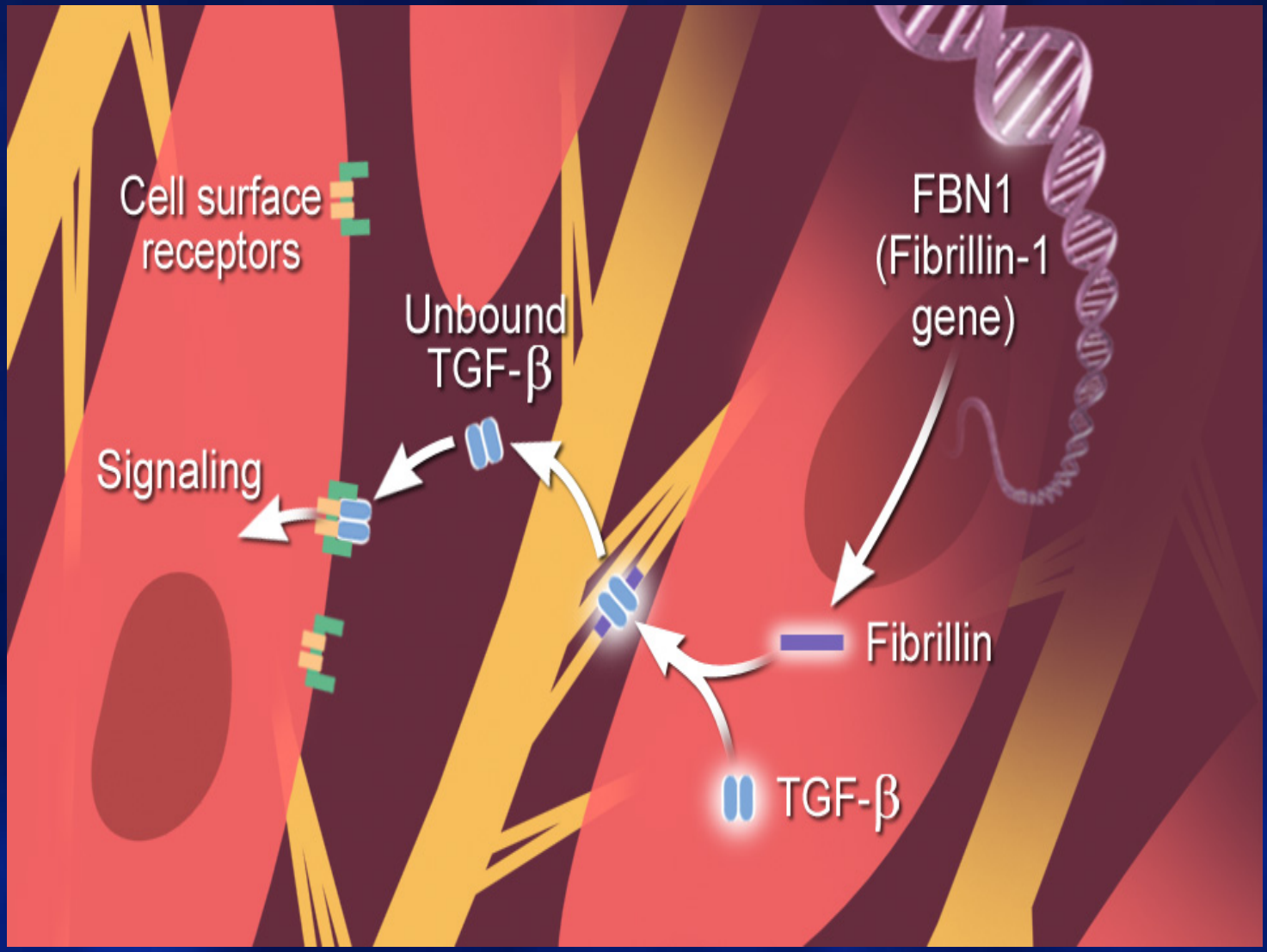
- 18 pediatric MFS pt - age 14 mo to 16 yr

  Treated with ARB 12 to 47 mo

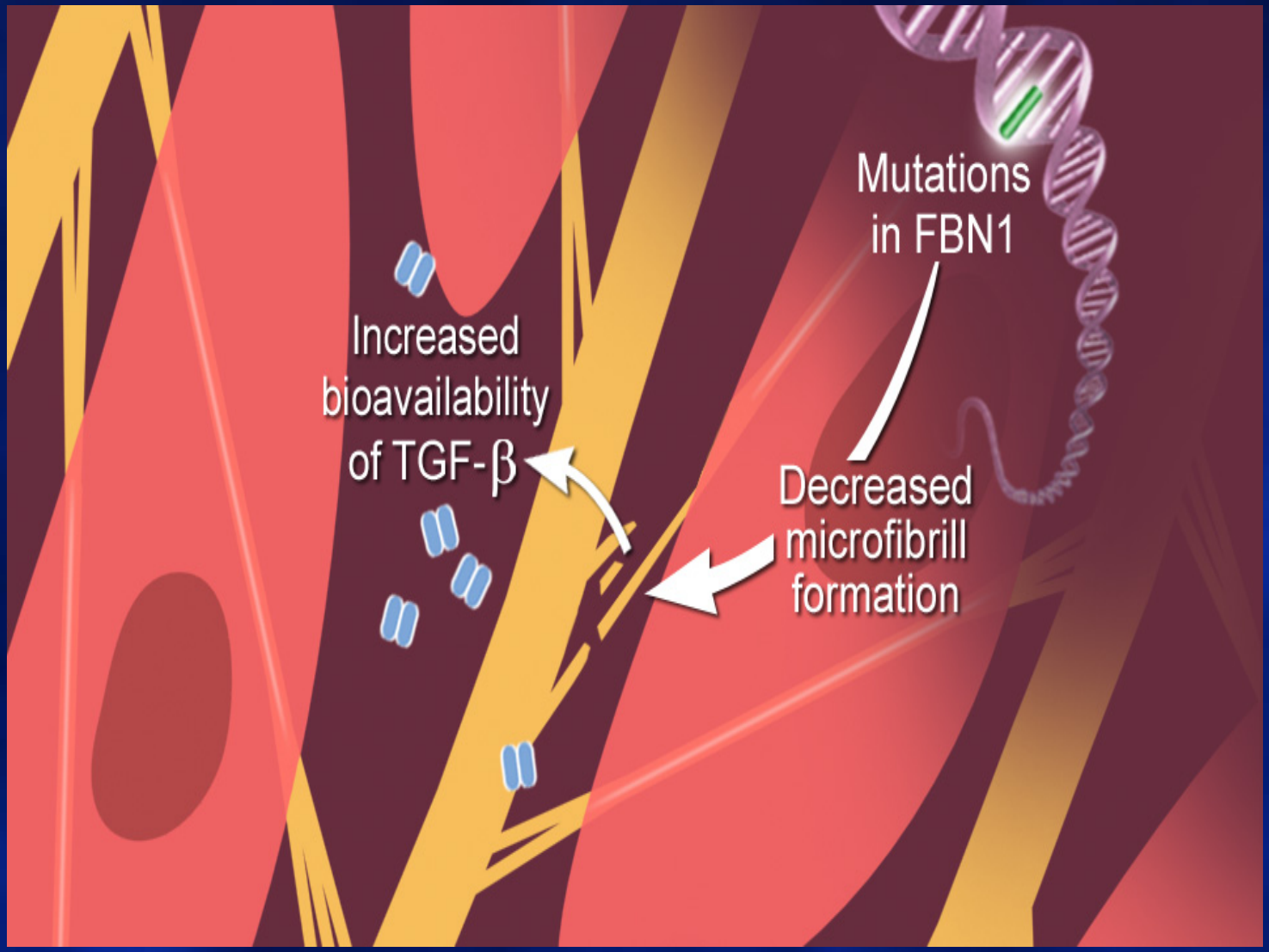
- Significant ↓ in rate of aortic root dilatation

  3.5 mm/yr → 0.5 mm/yr

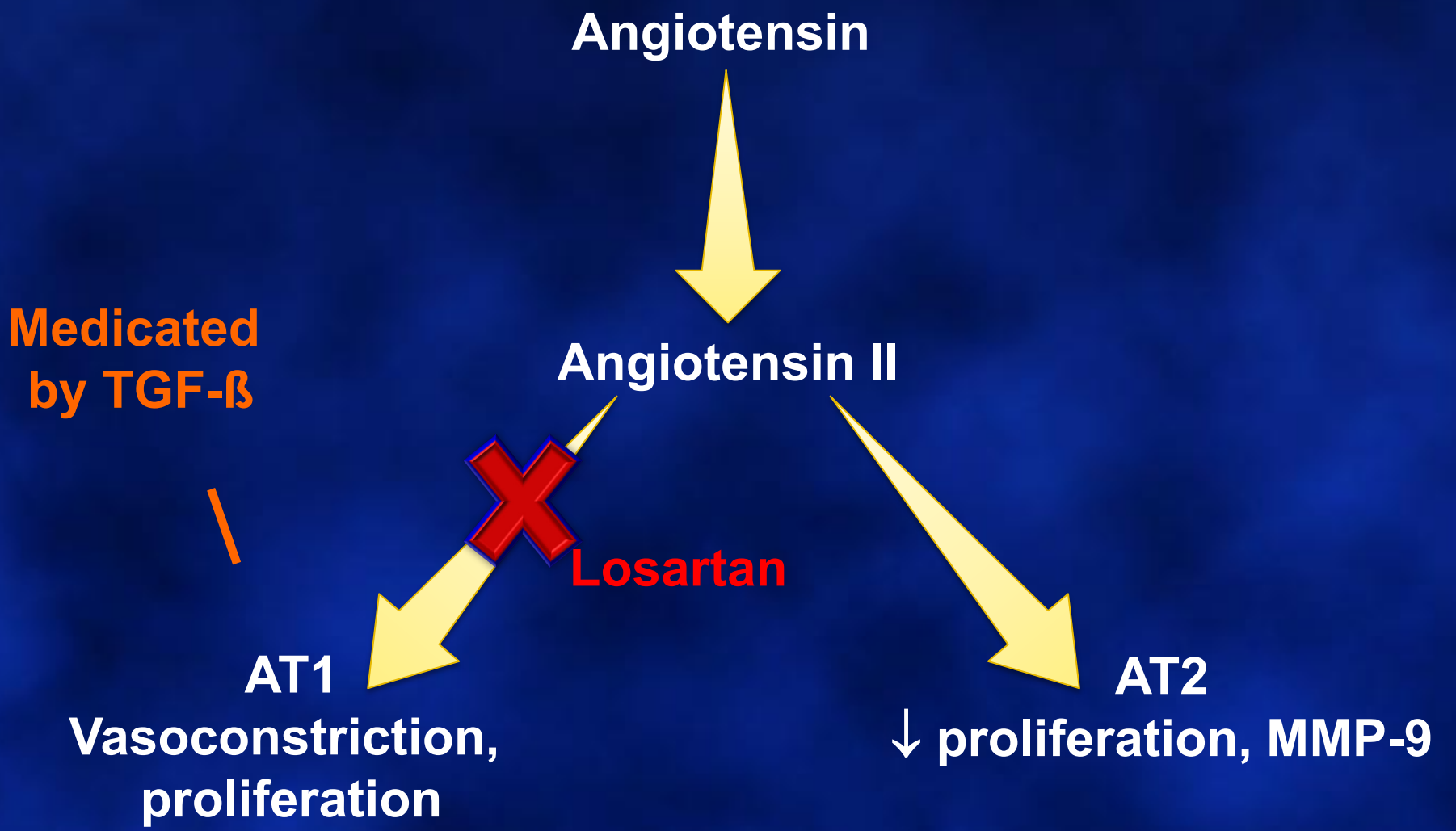
Molecular Biology of Thoracic Aorta



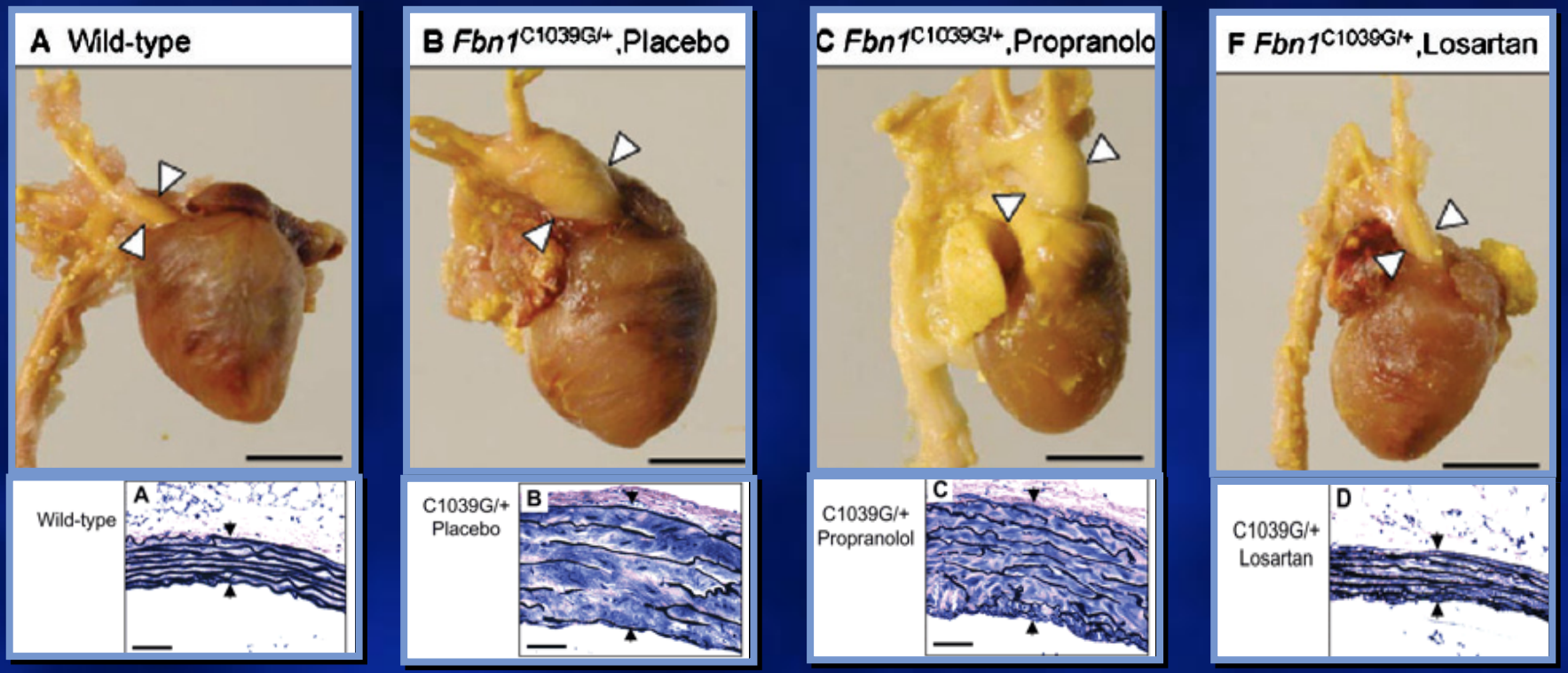
Molecular Biology in Marfan Syndrome



Role for ARB in treatment of MFS



Losartan in Marfan syndrome



Losartan lowers TGFB signaling is increased in MFS

MFS mice - no progression of aneurysm, some reversal aortic pathology, normal aortic growth, size, thickness and architecture

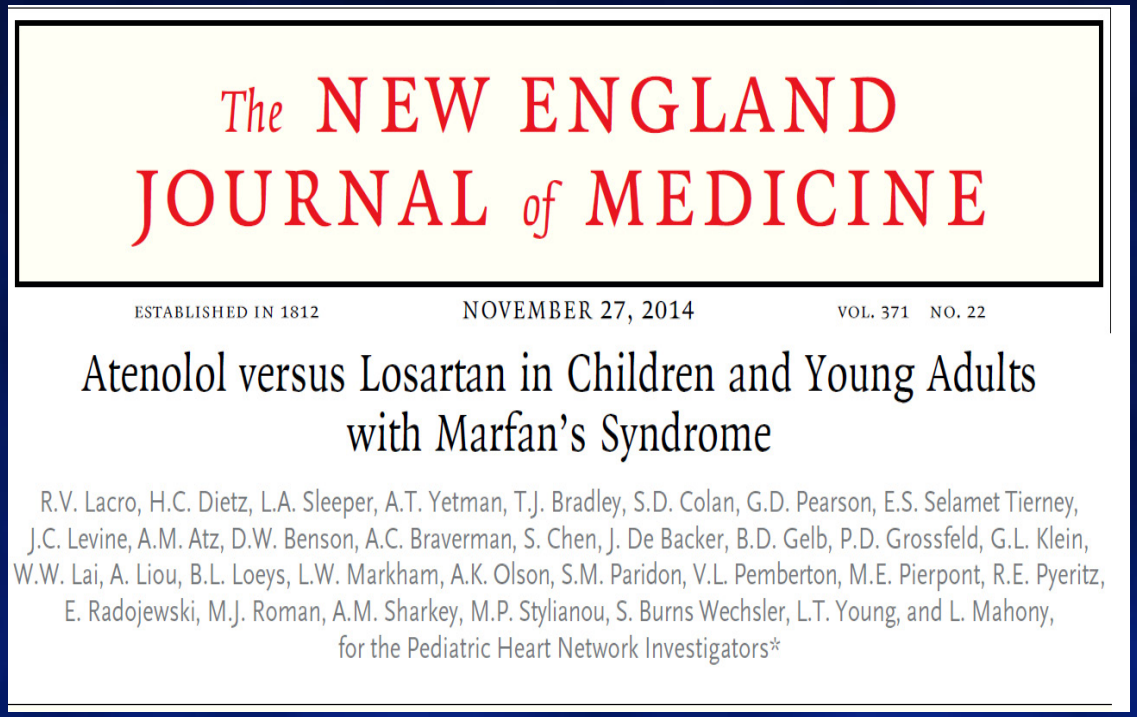
Habashi et al: Science 2006

European Heart Journal (2013) **34**, 3491–3500
doi:10.1093/eurheartj/eht334

Losartan reduces aortic dilatation rate in adults with Marfan syndrome: a randomized controlled trial

Maarten Groenink[1,2,3]*, Alexander W. den Hartog[1,2†], Romy Franken[1,2†], Teodora Radonic[4], Vivian de Waard[5], Janneke Timmermans[6], Arthur J. Scholte[7], Maarten P. van den Berg[8], Anje M. Spijkerboer[3], Henk A. Marquering[3,9]

In adult Marfan pt, losartan treatment reduces aortic root dilatation rate. After aortic root replacement, losartan treatment reduces dilatation rate of the aortic arch. EHJ 2013



The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 NOVEMBER 27, 2014 VOL. 371 NO. 22

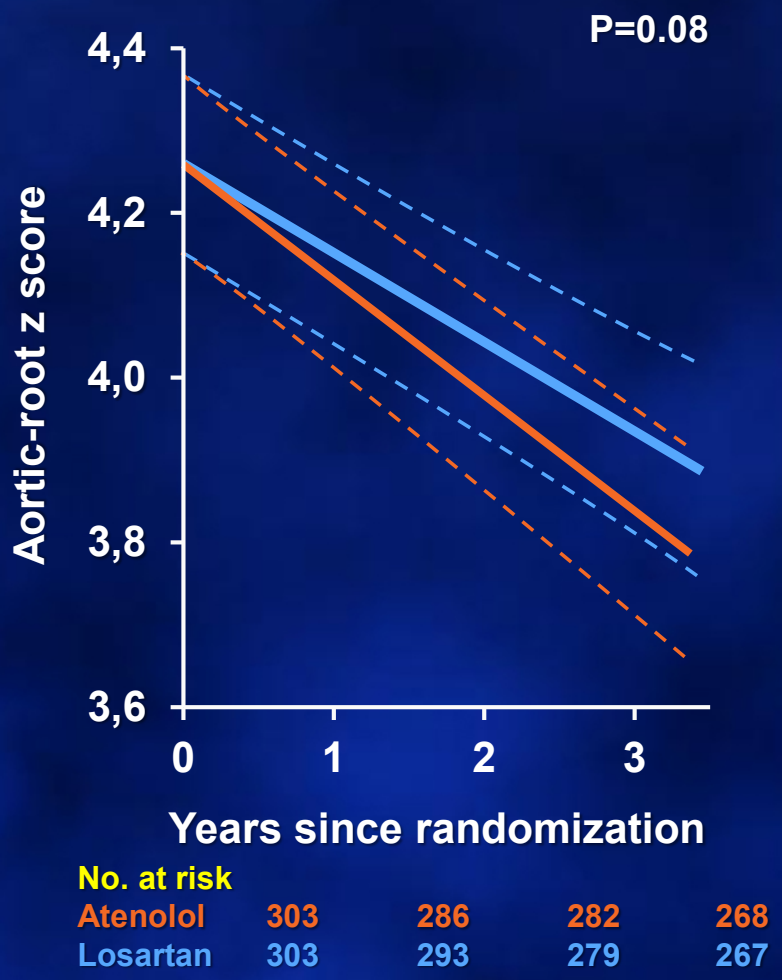
Atenolol versus Losartan in Children and Young Adults with Marfan's Syndrome

R.V. Lacro, H.C. Dietz, L.A. Sleeper, A.T. Yetman, T.J. Bradley, S.D. Colan, G.D. Pearson, E.S. Selamet Tierney, J.C. Levine, A.M. Atz, D.W. Benson, A.C. Braverman, S. Chen, J. De Backer, B.D. Gelb, P.D. Grossfeld, G.L. Klein, W.W. Lai, A. Liou, B.L. Loeys, L.W. Markham, A.K. Olson, S.M. Paridon, V.L. Pemberton, M.E. Pierpont, R.E. Pyeritz, E. Radojewski, M.J. Roman, A.M. Sharkey, M.P. Stylianou, S. Burns Wechsler, L.T. Young, and L. Mahony, for the Pediatric Heart Network Investigators*

- 608 participants: Age-6 months to 25 years
- Aortic root z score greater than 3.0
- Primary outcome: rate of aortic root enlargement

  Z score over a 3-year period

Atenolol vs. Losartan in Children and Young adults with MFS



- Z score too high at baseline?
- Aorta resistant as we get older?
- Med dose: Atenolol (151±75)
  Losartan (100)
- Was Losartan dose optimal?
- 1:1 compare sturdy, ? Synergism

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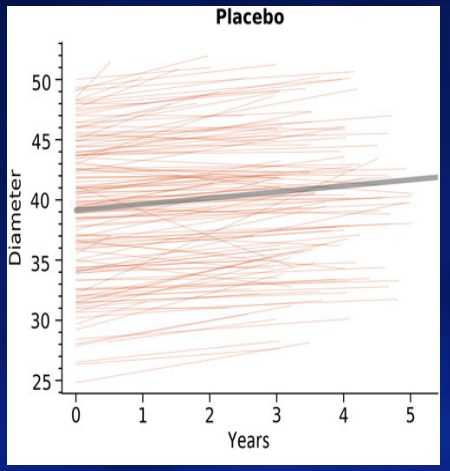
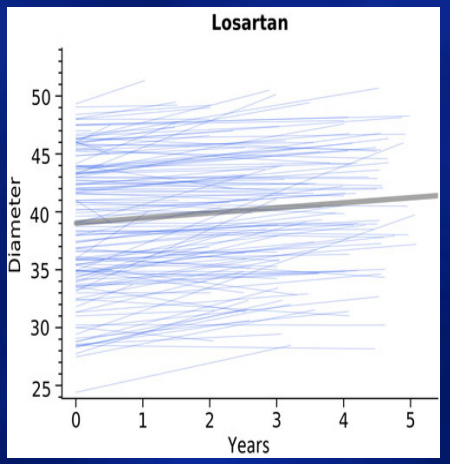
Lacro et al: N Engl J Med 2014

Marfan Sartan: Randomized, double-blind, placebo-controlled trial

- 303 MFS older than 10 years (mean 29.9)
  - 86% on ß blockers
  - median FU 3.5 years
- Mean/individual slopes dilatation at SOV
  - mean ↑ in diameter at SOV
    - 0.44 mm/year with Losartan
    - 0.51 mm/year with placebo





Milleron et al; EHJ, 2015

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Eligibility and Disqualification Recommendations for Competitive Athletes

Marfan syndrome

- Avoid contact sports, isometric exercise, smoking
- Avoid strenuous exercise
- Low to moderate static/ low dynamic exercise in absence of *(Class IIa; LOEC)*

  a. Aortic root dilatation (ie, *z* score > 2)

  b. Moderate to severe mitral regurgitation

  c. Left ventricular dysfunction (EF <40%)

  d. Family history of aortic dissection at aorta <50 mm

Braverman, ***Circulation*. 2015**

Management Strategies in Pregnant Women With Marfan sndrome

Pregnancy not advised

- Marfan syndrome >45 mm
- Rapid growth of aortic diameter
- Personal or family history of premature aortic dissection

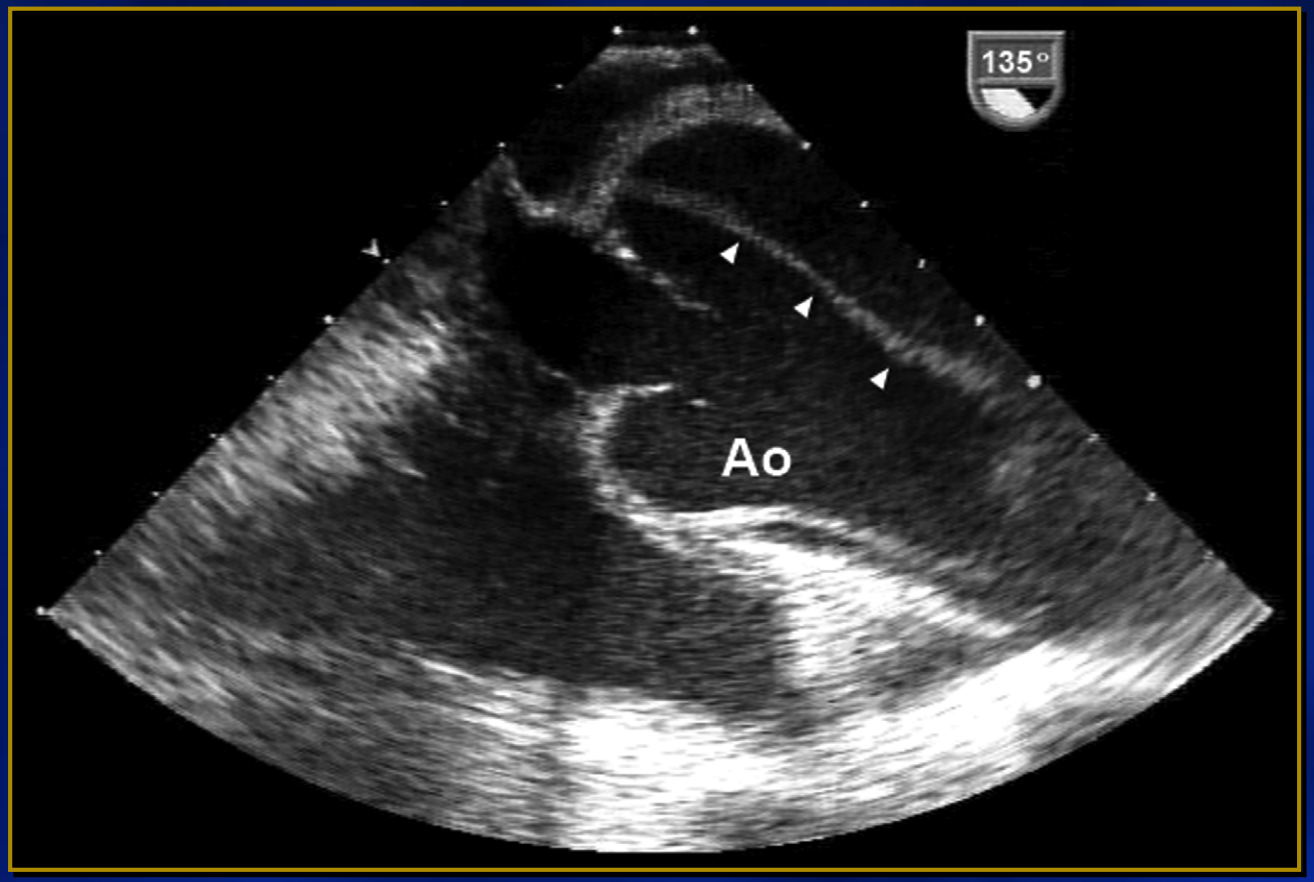
Pregnancy management

- STOP ACE Inh and ARB
- Beta-blockers to keep normal BP and heart rate, possible hydralazine
- Frequent echo assessment

Normal-sized aorta	Follow-up each trimester	Vaginal delivery
Dilated aorta <40 mm	Follow-up 4-6 weeks	Vaginal delivery
Dilated aorta 40-45 mm	Follow-up monthly	Cesarean section
Aorta >45 mm	Prophylactic surgery pre-pregnancy or during pregnancy in women with rapid growth of the aorta	

Elkayam, U. et al: J Am Coll Cardiol 68(5):502, 2016

Aortic Dissection Prevention in MFS



MFS accounts for 50% of AD if <40 yr

Indications for Operation MFS

Asc Ao size
45-50 mm

Rapid ↑
>3 mm/yr

Predictors of dissection

Family history of aortic complications

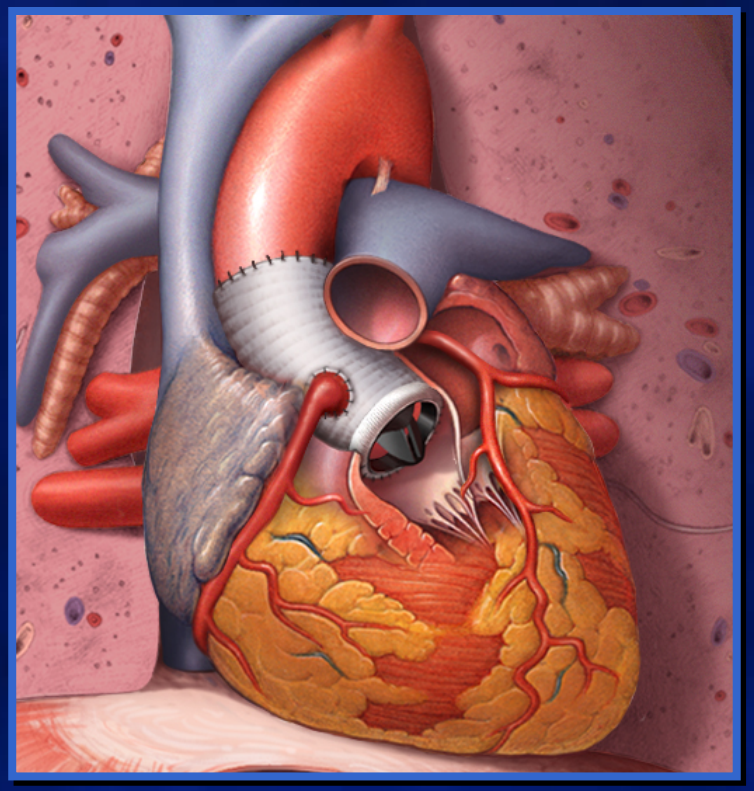
Small pt - indexed diameter adjusted for BSA of 2.5 cm/m2 **

Early Operation in MFS

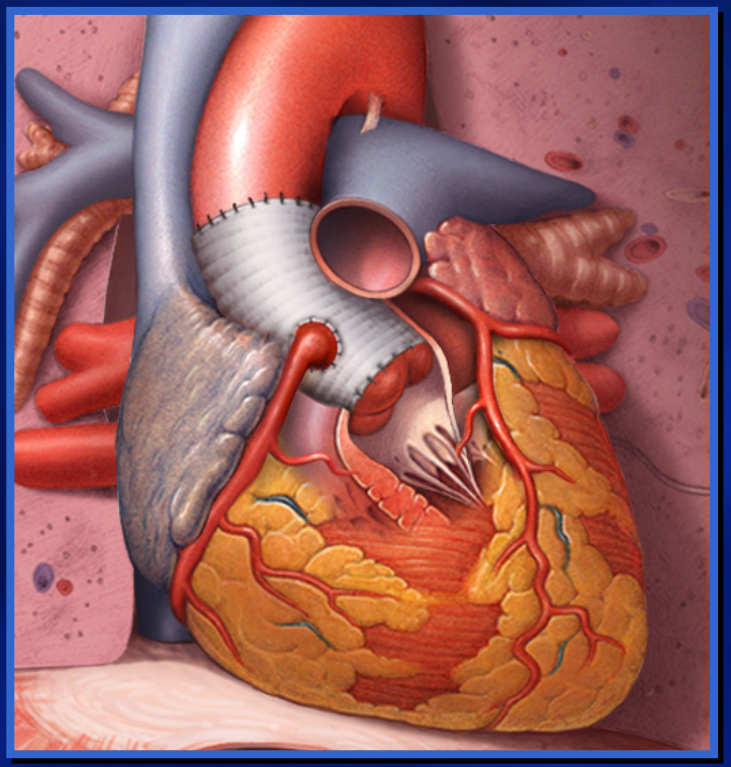
1. Aortic aneurysm beyond the Sinus of Valsalva
2. Personal history of aortic dissection
3. Progressive aortic regurgitation
4. Labile hypertension
5. Associated MV disease or LV dysfunction
6. Desire for VS root replacement
7. Pregnancy consideration

Thoracic Aortic Aneurysm

Bentall operation

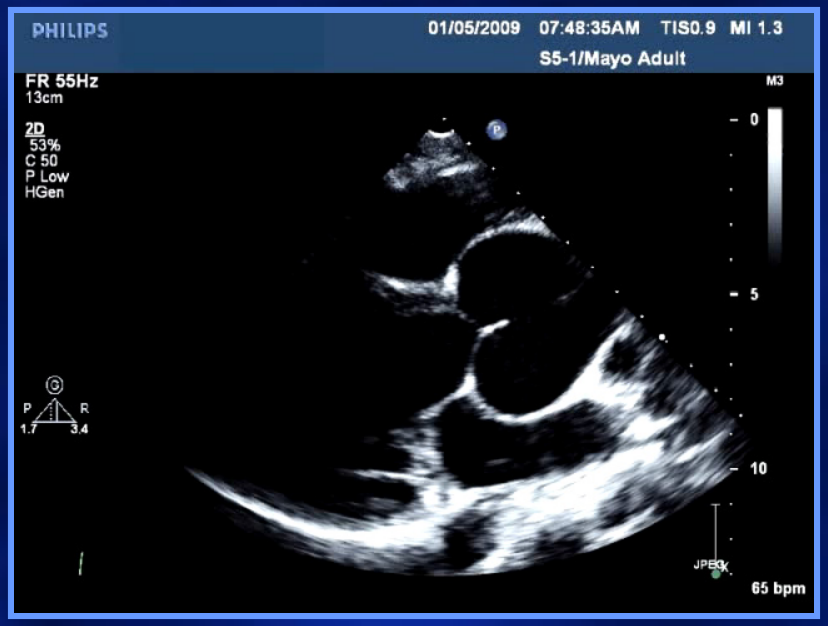


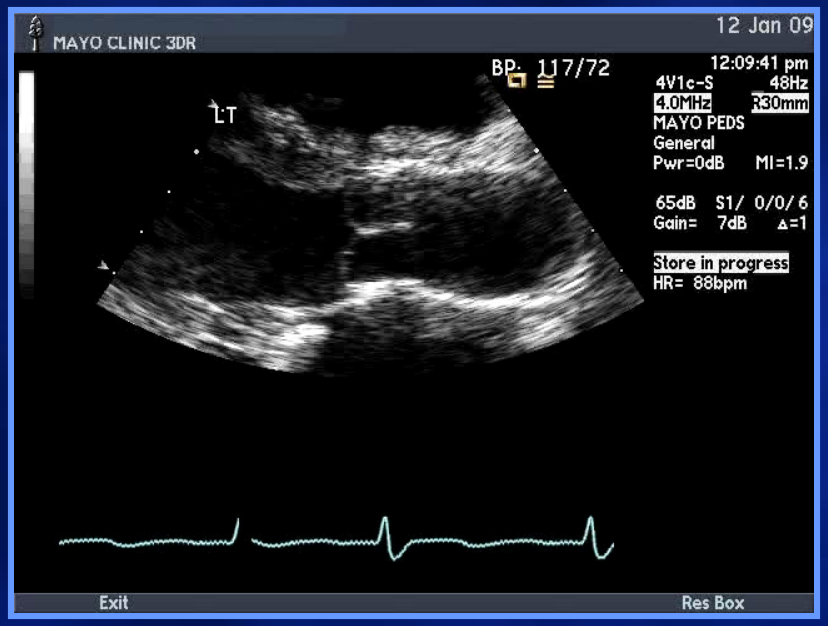
Valve-sparing operation



Continue medical treatment indefinitely

17 YO with Marfan syndrome





Pre-op

Post-op

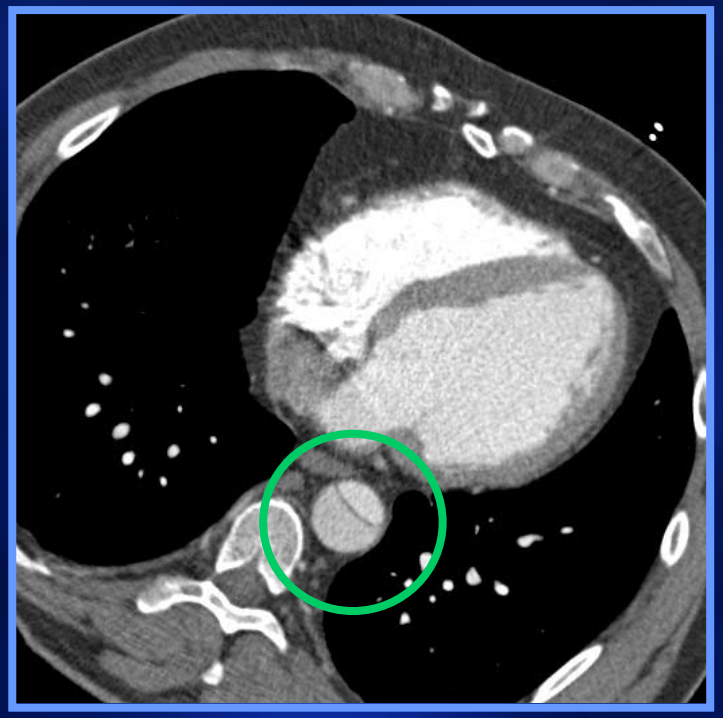
AV Sparing Root Replacement in MFS

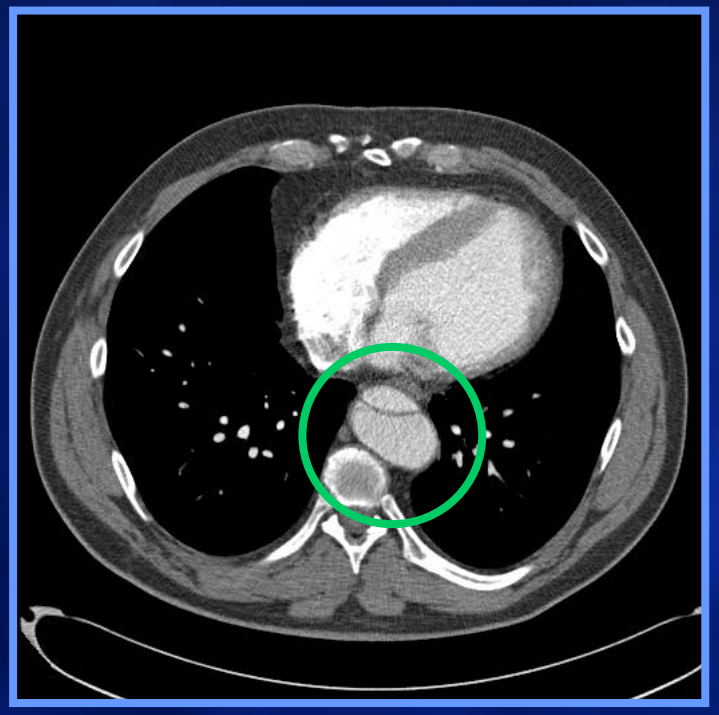
- Long term outcome in all 146 VSRR (median FU10 yrs)
  - Dissection in 14: 9 acute, 5 chronic (2 A, 3 B)
- Mortality: 1 early and 6 late deaths
  - Mortality rate at 15 years was 6.8 ± 2.9%
- AV reoperation in 5 (2/endocarditis and 3/AR)
  - Rate of AR at 15 years was 7.9 ± 3.3%
- New distal dissection in 9
  - Rate of dissection at 15 years was 16.5 ± 3.4%

Surveillance imaging continues postoperatively

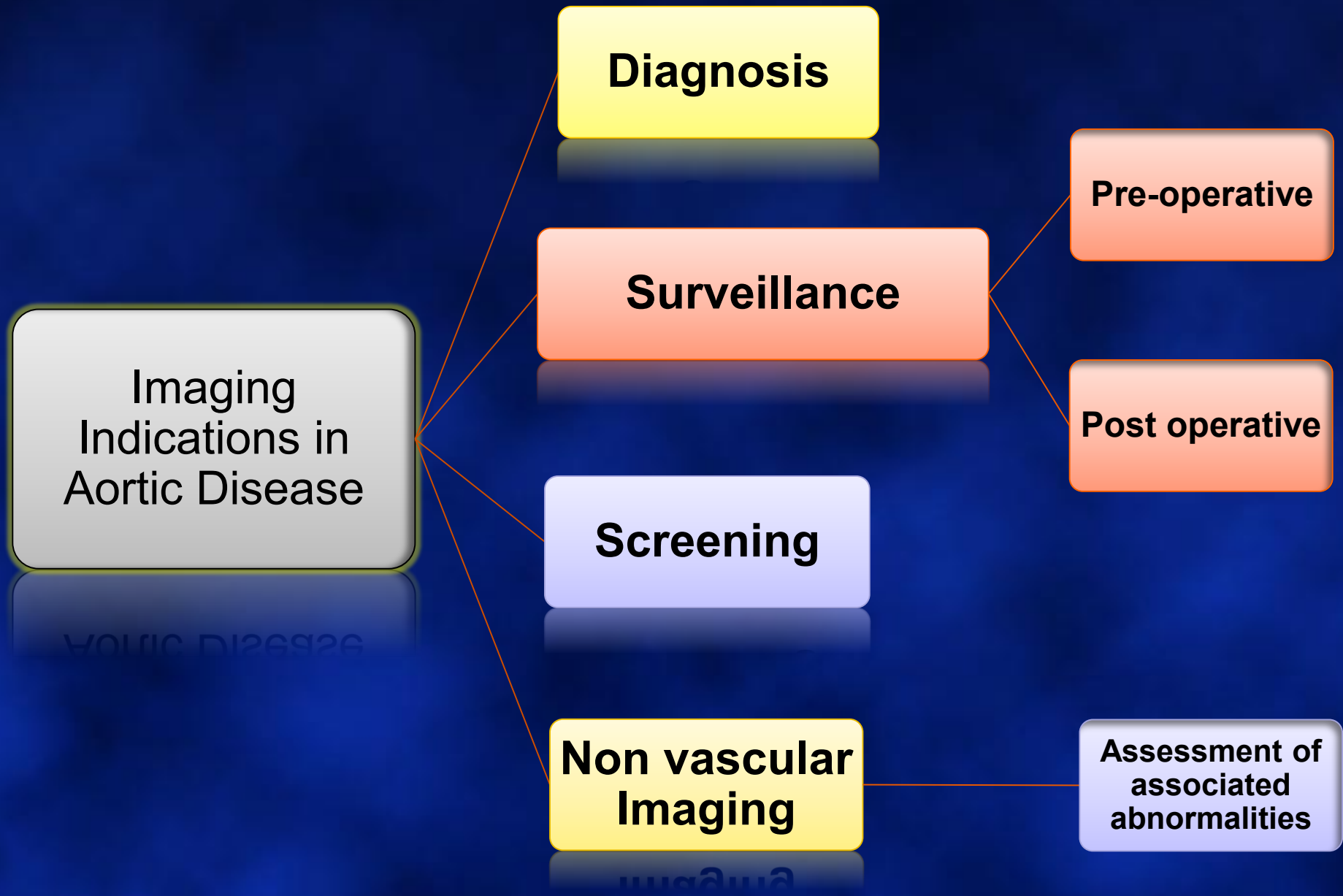
David, J Am Coll Cardiol 2015

37 YO with Marfan syndrome S/P VSRR

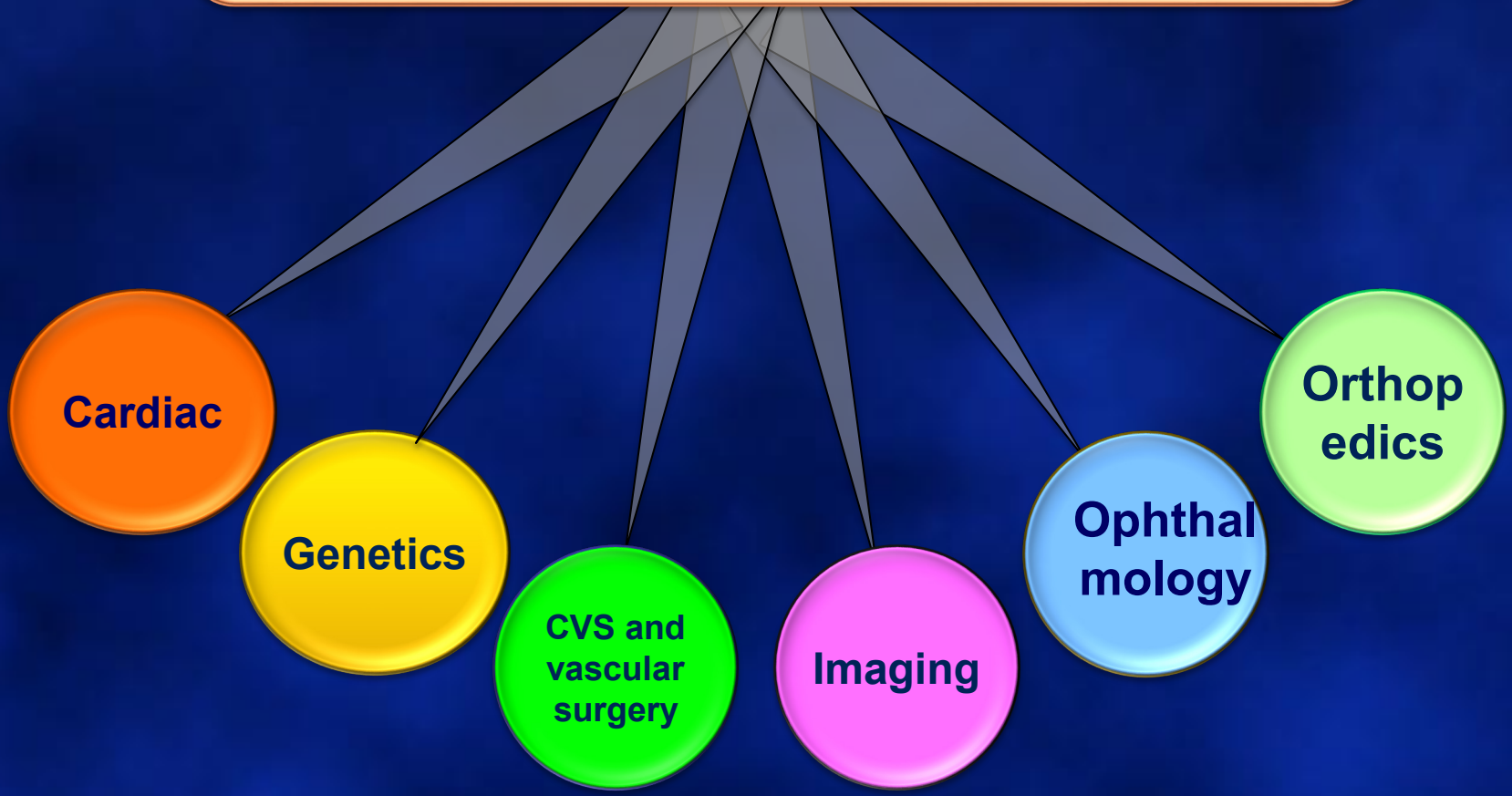




Surgery when descending aorta reaches 55 mm


Imaging Indications in Aortic Disease
Diagnosis
Surveillance
Pre-operative
Post operative
Screening
Non vascular Imaging
Assessment of associated abnormalities

Management of Marfan syndrome: Personalized and Multidisciplinary



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