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AORTOPATHIES

What Do We Know and What Do We Need to Learn?

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Underlying Etiology
Thoracic Aortic Aneurysm

Inherited/Genetic 20%

Syndromic

Marfan
Loeys Dietz
Ehlers Danlos (EDS)
- Vascular
- Kyphoscoliosis

Turner Syndrome

**NOT hypermobility EDS

Non-syndromic/CHD

Bicuspid aortic valve
Familial Thoracic Aneurysm/Dissection

Sporadic 80%

Lifestyle/
CV risk factors
- HYPERTENSION

Vasculitis
Infectious Disease
-Syphilis
-TB

Iatrogenic
Trauma
-Deceleration injuries

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Preventing Aortic Dissection

- Medication → indirect by slowing aortic growth
- Surgical → direct by replacement of the aneurysmal aorta

SLOWING AORTIC GROWTH
MEDICAL THERAPY

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. J.C. Levine, A.M. Atz, D.W. Benson, A.C. Braverman, S. Chen, J. De B W.W. Lai, A. Liou, B.L. Loeys, L.W. Markham, A.K. Olson, S.M. Parido E. Radojewski, M.J. Roman, A.M. Sharkey, M.P. Stylianou, S. Bur for the Pediatric Heart Network Inv

Irbesartan in Marfan syndrome (AIMS): a double-blind, placebo-controlled randomised trial

Graham Stuart, Matthew Dodd, José Antonio Aragon-Martin, David Gaze, Anatoli Kiotsekoglou, in Dyck, Rosemary Knight, Tim Clayton, Lorna Swan, John D R Thomson, Guliz Erdem, David Crossman, stigators†

Effect is independent of blood pressure

Angiotensin receptor blockers and β Marfan syndrome: an individual patient data meta-analysis of randomised trials

Alex Pitcher, Enti Spata, Jonathan Emberson, Kelly Davies, Heather Halls, Lisa Holland, Kate Wilson, Christina Reith, Anne H Child, Tim Clayton, Matthew Dodd, Marcus Flather, Xu Yu Jin, George Sandor, Maarten Groenink, Barbara Mulder, Julie De Backer, Arturo Evangelista, Alberto Forteza, Gisela Teixido-Turà, Catherine Boileau, Guillaume Jondeau, Olivier Milleron, Ronald V Lacro, Lynn A Sleeper, Hsin-Hui Chiu, Mei-Hwan Wu, Stefan Neubauer, Hugh Watkins, Hal Dietz, Colin Baigent, on behalf of The Marfan Treatment Trialists' Collaboration

Effect of Losartan or Atenolol on Children and Young Adults With Bicuspid Aortic Valve and Dilated Aorta

Jonathan N. Flyer, MD[a], Lynn A. Sleeper, ScD[b,c], Steven D. Colan, MD[b,c], Michael N. Singh, MD[b,c], and Ronald V. Lacro, MD[b,c,*]

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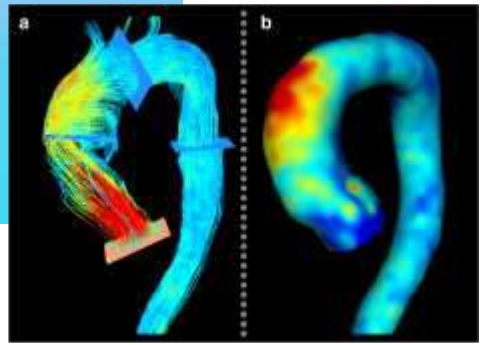
DOSING IS IMPORTANT



Losartan-

2.0 mg/kg/d; max 100mg (higher than PHN Trial)

Hepatic metabolism to active metabolite

Irbesartan-

8-10 mg/kg/d; max 300 mg

Metabolism not required

- **Atenolol-** <u>achieve beta blockade</u>
  - Dose typically 2-4mg/kg/d
  - Max 200 mg/d

- Medications to AVOID
  - Calcium Channel Blockers
  - Fluoroquinolone antibiotics
    - Topical ophthalmic and otic drops excluded

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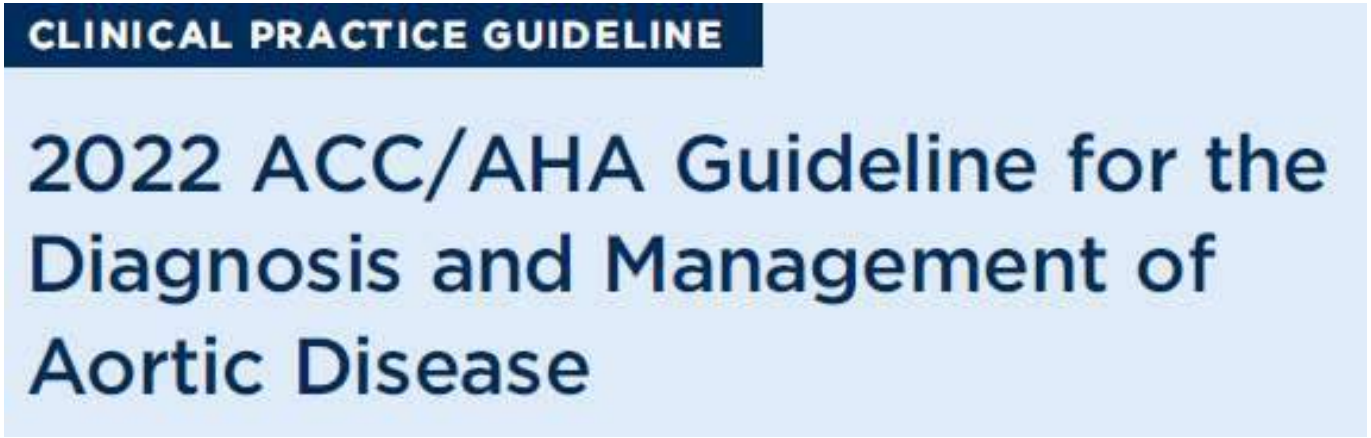
Surgical Intervention

No pediatric specific guidelines: loosely follow adult guidelines



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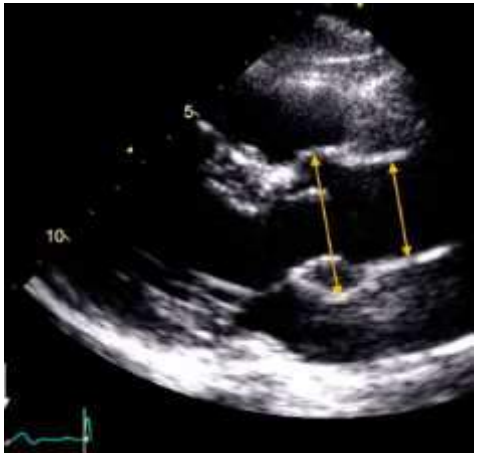
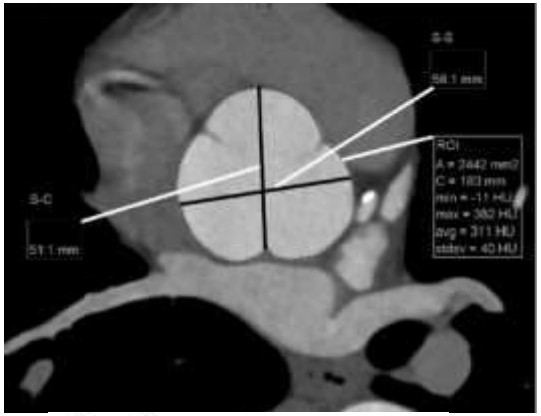
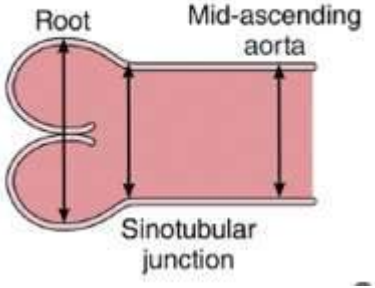
Aortic Diameter

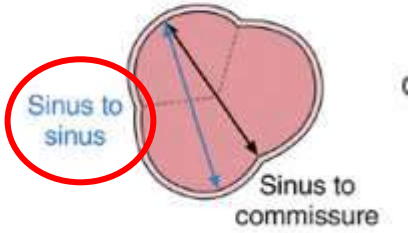




B Sinus measurement

Echocardiography*





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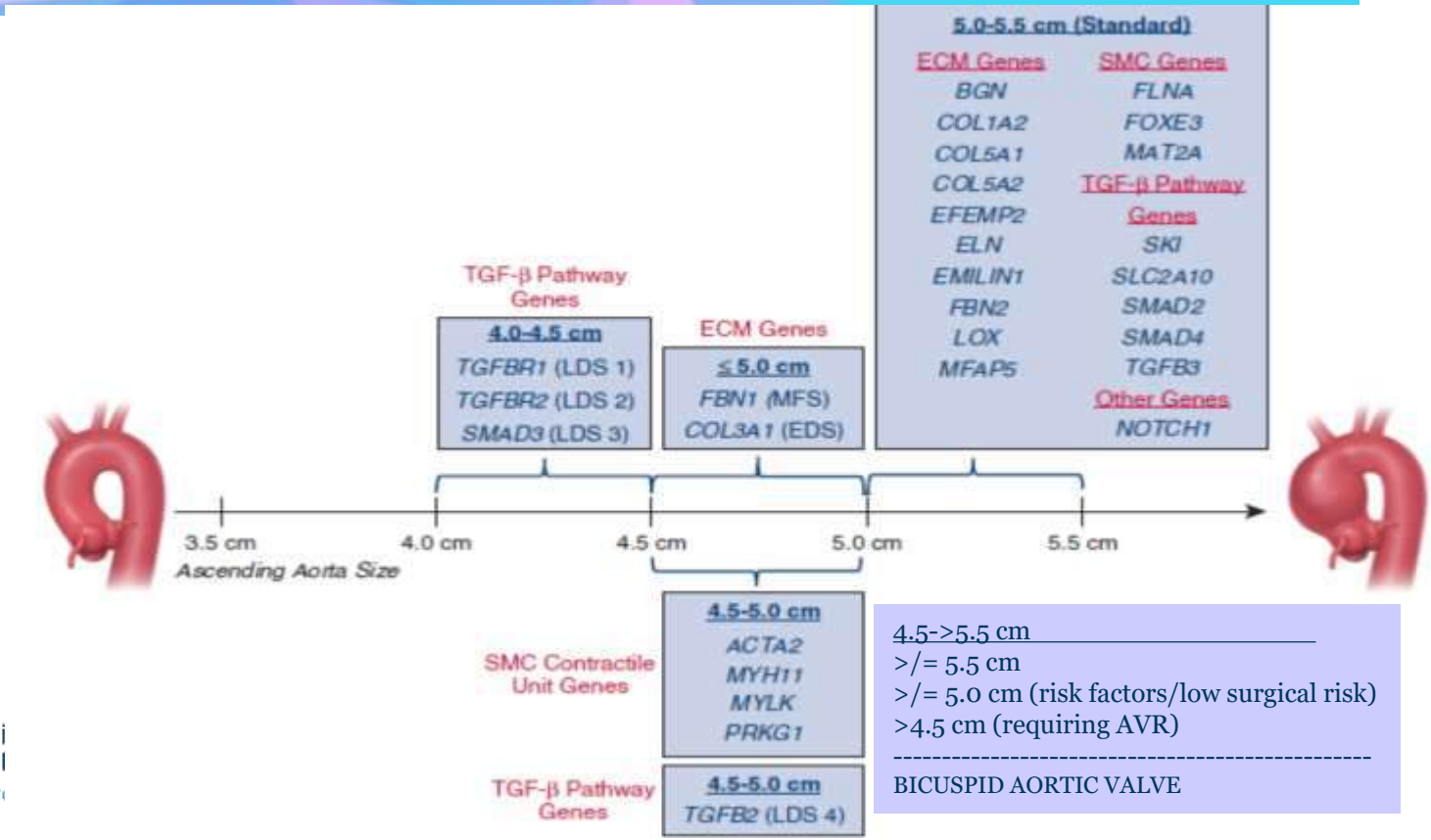
SURGICAL THRESHOLDS

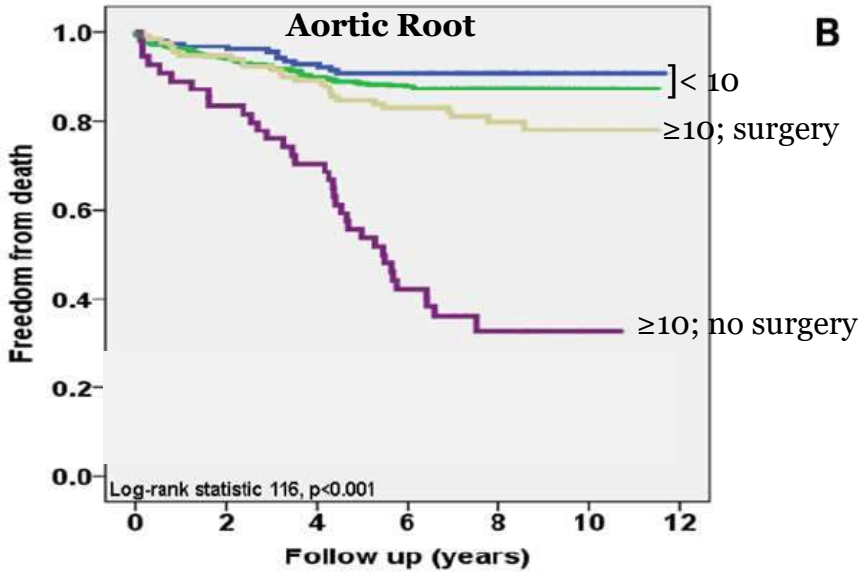


4.5->5.5 cm
>/= 5.5 cm
>/= 5.0 cm (risk factors/low surgical risk)
>4.5 cm (requiring AVR)

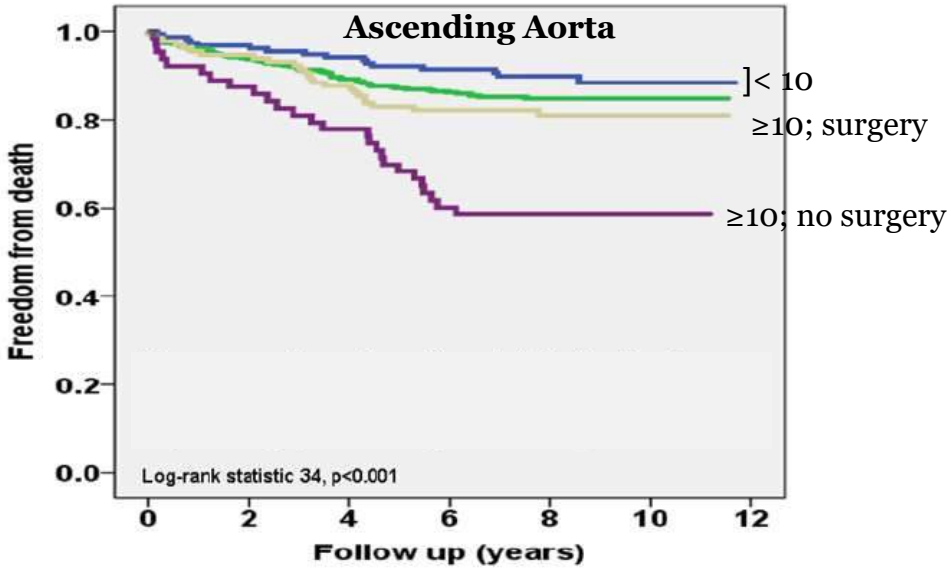
BICUSPID AORTIC VALVE

Aortic Cross Sectional Area:Height Ratio

CSA:Height ≥ 10 (cm2/m)



B



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Masri A, Kalahasti V, Svensson LG, et al. Aortic cross-sectional area/height ratio and outcomes in patients with a trileaflet aortic valve and a dilated aorta. Circulation. 2016;134:1724–1737.

Masri A, Kalahasti V, Svensson LG, et al. Aortic cross-sectional area/height ratio and outcomes in patients with bicuspid aortic valve and a dilated ascending aorta. Circ Cardiovasc Imaging. 2017;10

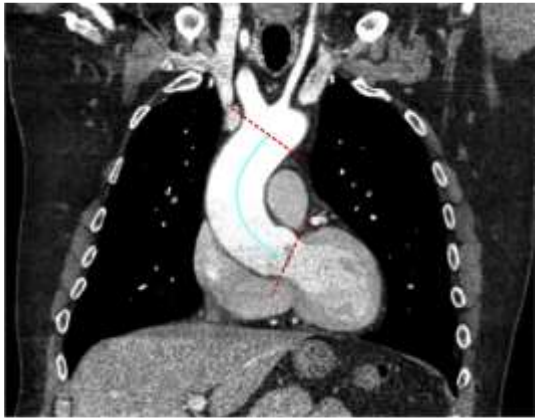
Where are we going?

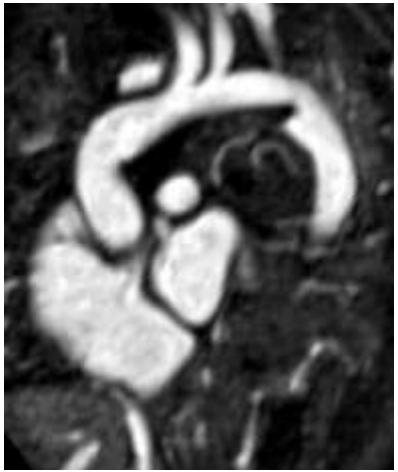
- Assessing risk
- Phenotypic variability

Understanding Who is At Risk for More Severe Aortic Disease

Length Ascending Aorta

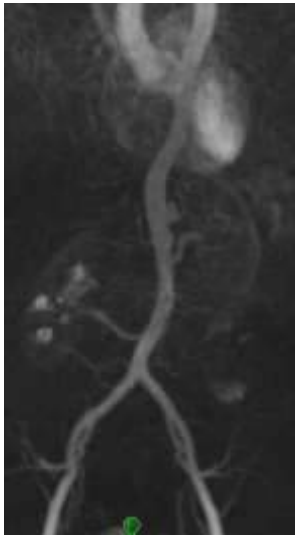
Aortic annulus → Innominate Artery

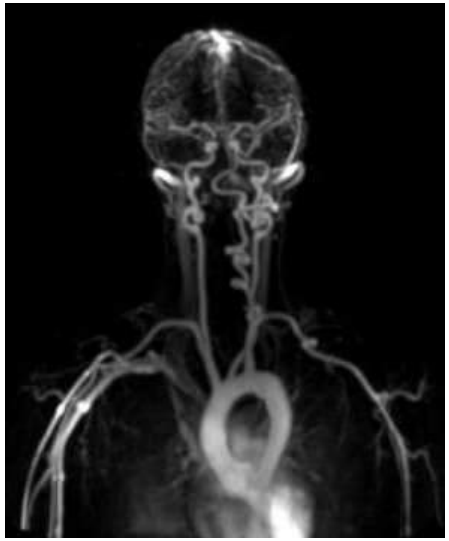




Arterial Tortuosity

Vertebral tortuosity index (VTI)





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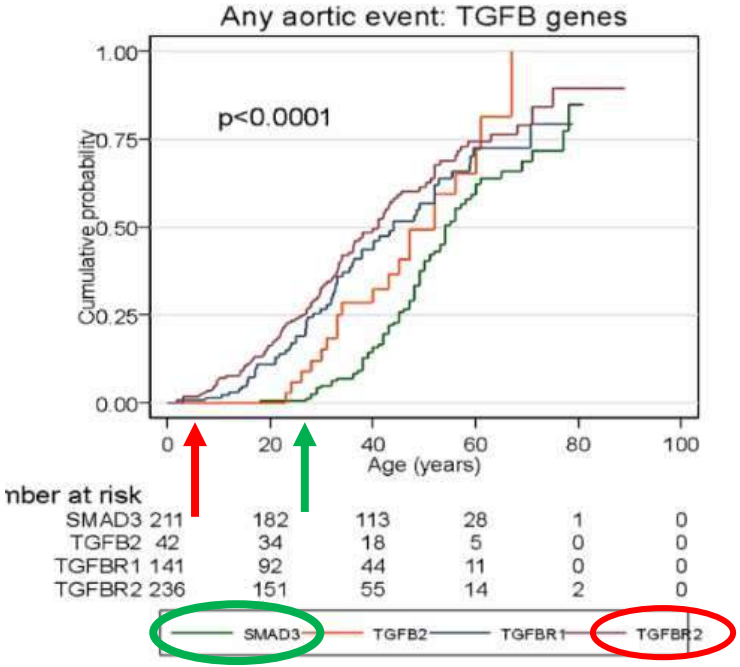
Wu J, Zafar MA, Li Y, et al. Ascending aortic length and risk of aortic adverse events: the neglected dimension. J Am Coll Cardiol. 2019;74:1883–1894.
Morris SA, Orbach DB, Geva T et al. Increased vertebral artery tortuosity index is associated with adverse outcomes in children and young adults with connective tissue disease. *Circulation*. 2011;124:388-396.)

Genotype

Specific Gene Involved

Loeys Dietz Syndrome



Affect on Protein Produced

Marfan Syndrome

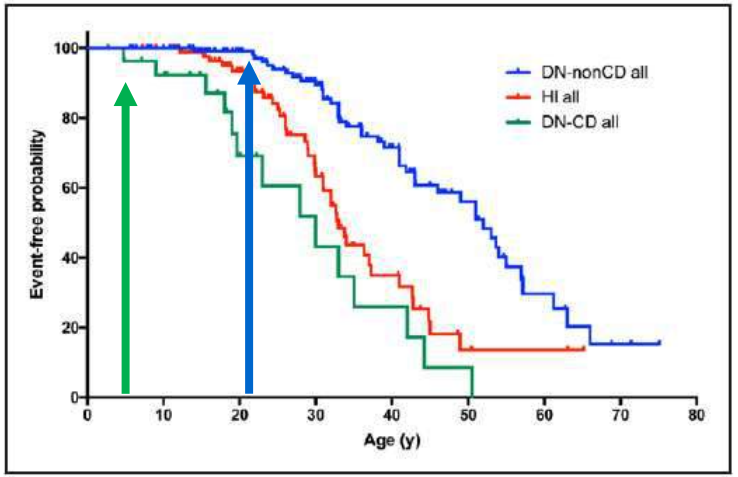
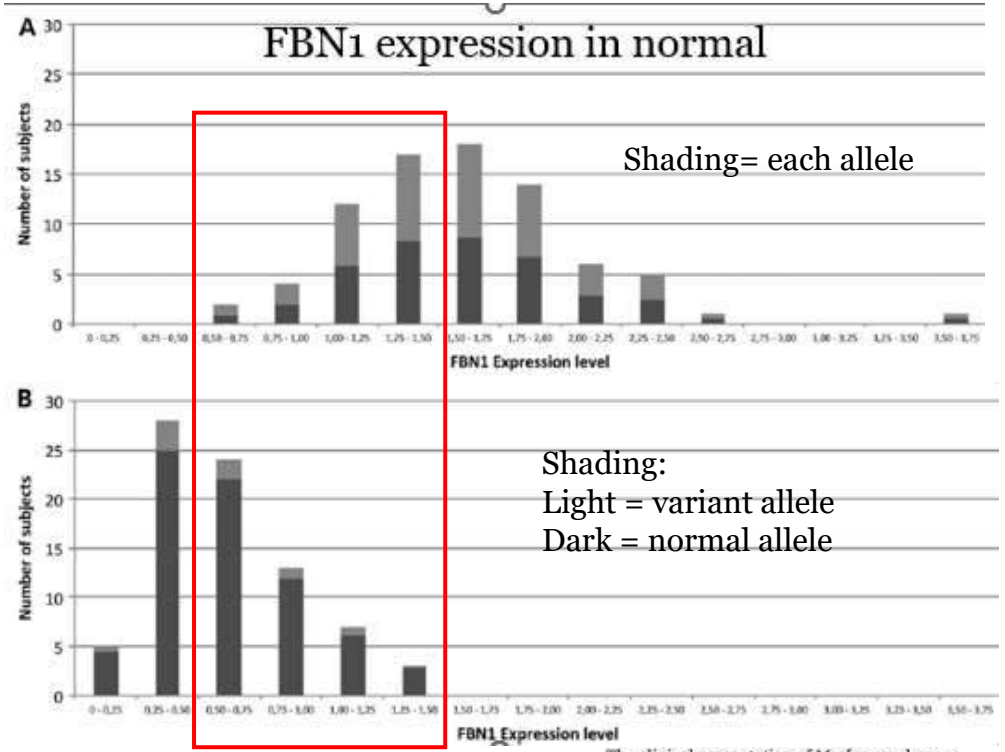


Figure 4. Kaplan–Meier estimates comparing the probability of the first severe aortic event between genotypes.
Cumulative aortic event-free probability of 28 dominant-negative (DN)-CD patients (green), 93 haploinsufficient type (HI) patients (red), and 127 DN-nonCD patients (blue).

Your Genes Are Not Your Destiny

Gene Expression Can Be Altered

- Modifier Genes
  - Genome wide association studies (GWAS)
    - Identified loci outside of FBN1 associated with
      - Baseline aortic diameters
      - Rate of aortic growth
      - Clinical events
  - Influence response to medication
- Epigenetic modification
  - Regulates gene expression
  - Both variant and normal alleles



The clinical presentation of Marfan syndrome is modulated by expression of wild-type FBN1 allele

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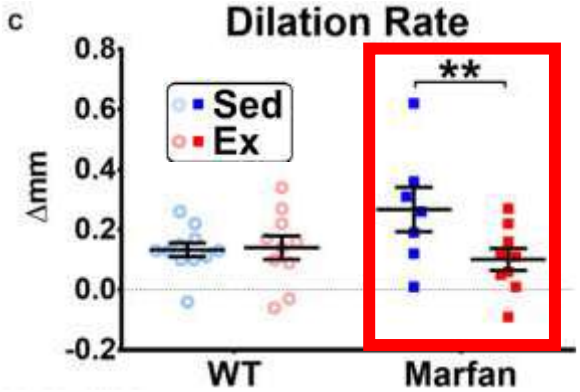
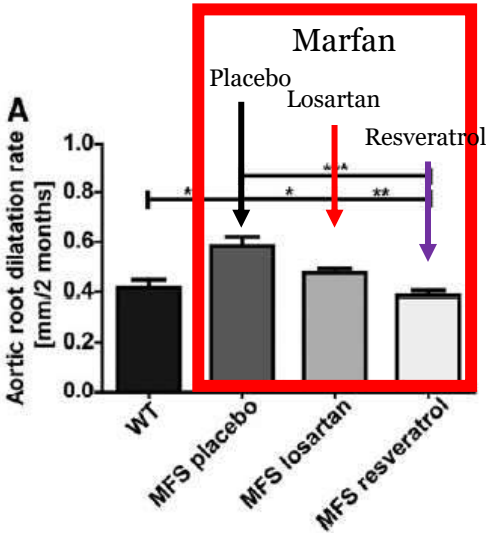
Epigenetics: Influences Gene Expression

- Lifestyle alters gene expression via epigenetic modification
  - DNA methylation, histone modification, microRNA
- Influence of Lifestyle- mouse studies

Moderate Exercise



Resveratrol



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KEY TAKEAWAYS

- ARBs and Atenolol are effective in slowing the rate of aortic growth **when used at therapeutic dosing**
- CSA:height should be considered in surgical decision making
- Risk for early aortic complications is multifactorial and often predictable
- Modifying gene expression may prove to be a useful tool to delay and prevent aortic dissection.

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THANK YOU!

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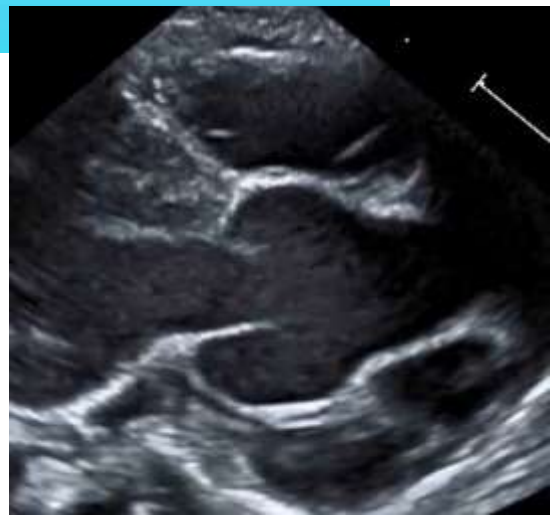
Case Presentation: Aortopathy

- Prenatal-
  - Club foot and thumb deformity
- Post natal-
  - Aortic root dilation on screening echo
- Genetics evaluation (10 y.o.)
  - Pectus carinatum
  - Hypertelorism
  - Bifid uvula
  - Micrognathia
  - Hypermobility



Loeys Dietz Syndrome

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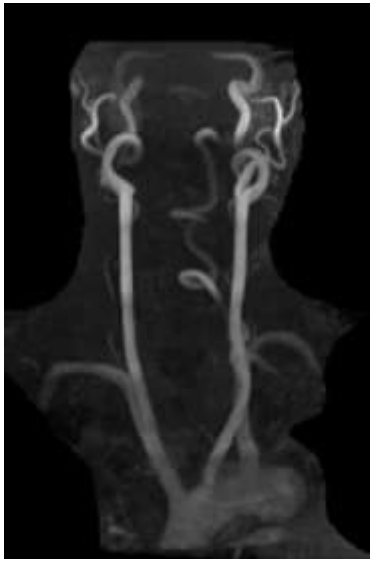
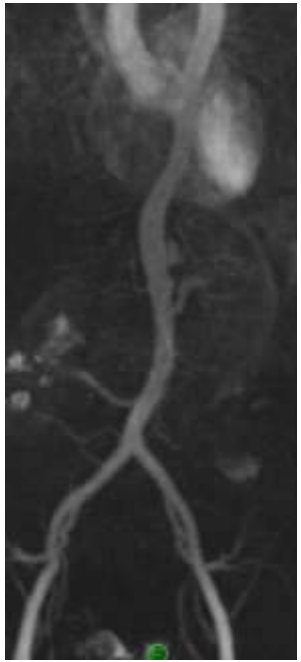
Risk Factors

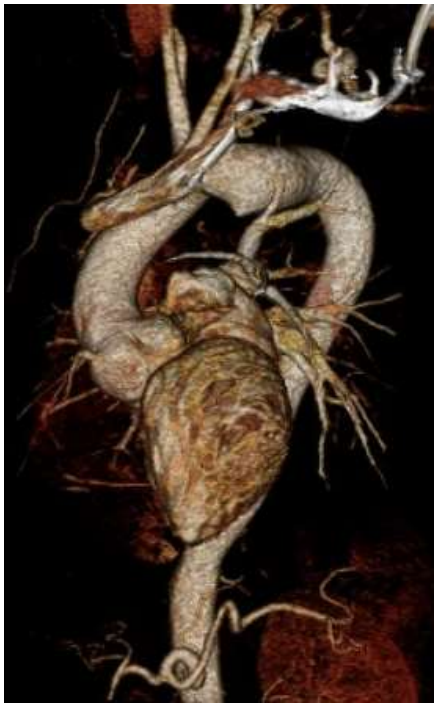
Gene involved- TGFBR2

MRA





CTA



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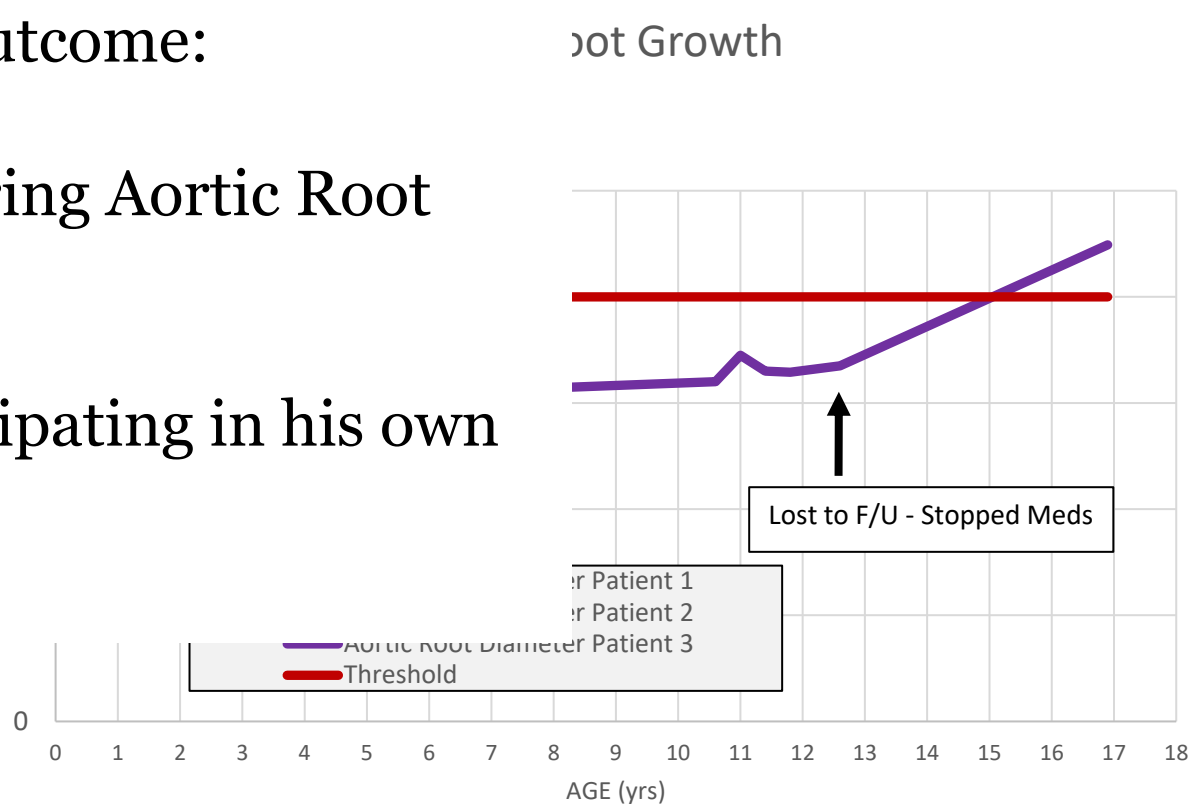
Aortic Diameter

Outcome:

s/p Valve Sparing Aortic Root Replacement

Actively participating in his own medical care



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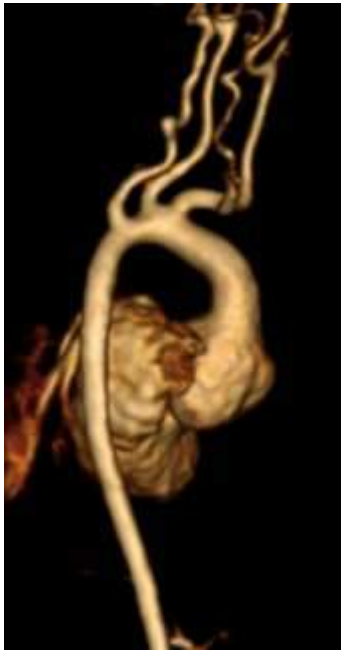
Collaborative for Longitudinal Aortic Research In The Young (CLARITY)

- International aortopathy registry for children and young adults with connective tissue disorders



Header

Subhead

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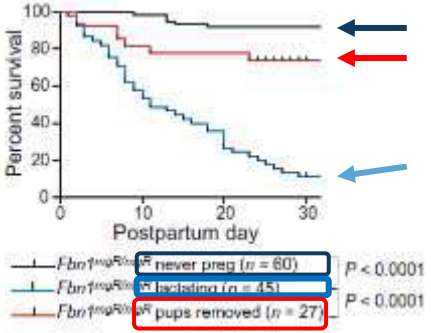
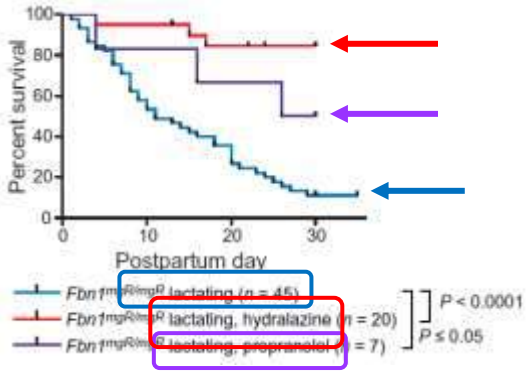
PREGNANCY ASSOCIATED AORTIC DISSECTION

- **Women with aortopathy at ↑ risk dissection**
  - Risk 10% when aortic diameter >4.0 cm
  - Recommend B blocker therapy during/after pregnancy
  - Late 3rd trimester-several months postpartum
  - Coincides with increased levels of oxytocin
  - Mouse model- blocking oxytocin using 2 clinically available medications prevented dissection
    - Hydralazine
    - Oxytocin inhibitor





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Oxytocin antagonism prevents pregnancy-associated aortic dissection in a mouse model of Marfan syndrome

Jennifer Pardo Habashi[1*], Elena Gallo MacFarlane[2*], Rustam Bagirzadeh[2], Caitlin Bowen[2], Nicholas Huso[2], Yichun Chen[2], Djahida Bedja[3], Tyler J. Creamer[4], Graham Rykiel[2], Maurice Manning[5], David Huso[3†], Harry C. Dietz[2,6†]

OVERVIEW

- What do we know?
  - Preventive medical therapy
  - Surgical guidelines
- Where are we going?

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