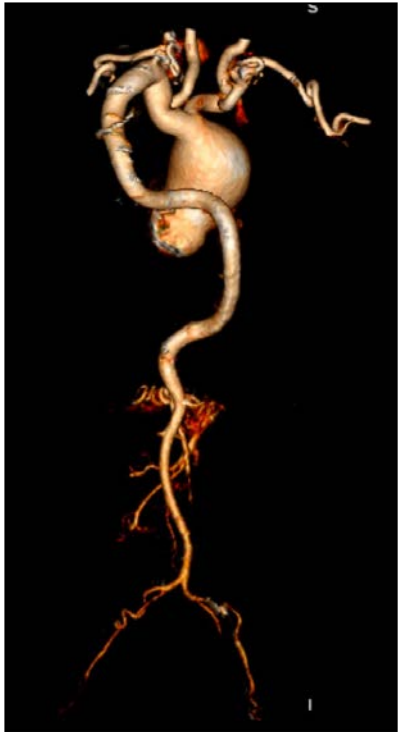
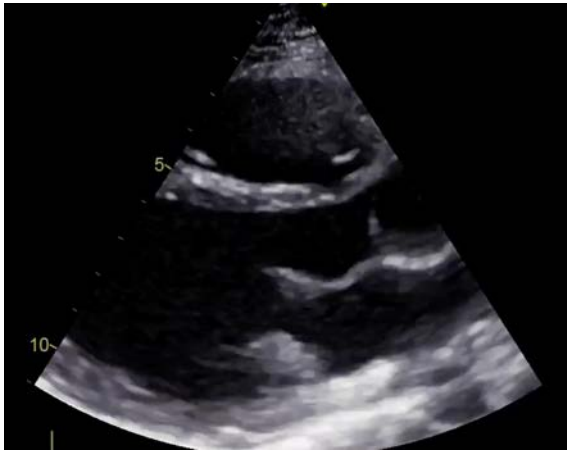
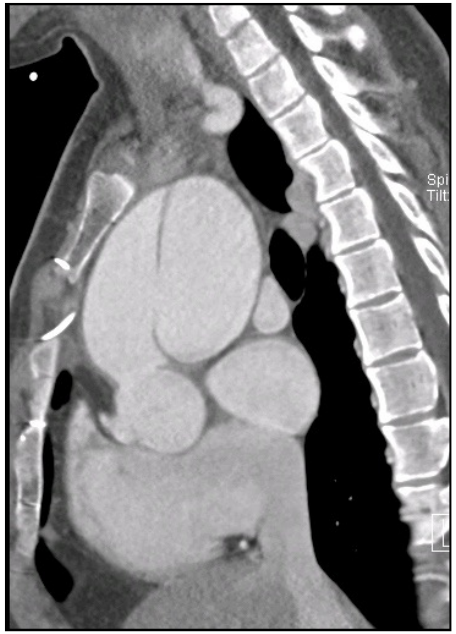
The Aortopathies: How They Manifest in the Young and Progress with Time



Shaine A. Morris, MD, MPH
Associate Professor of Pediatrics
Medical Director, Cardiovascular Genetics
Medical Director, Fetal Cardiology

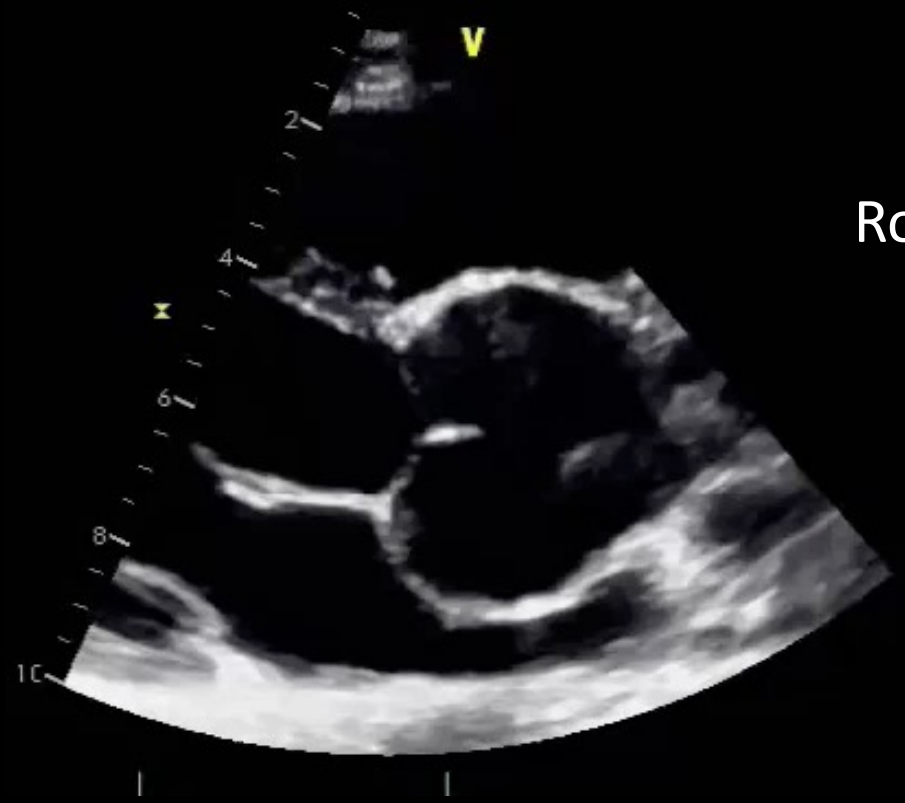




Objectives

- Highlight the major changes in management of aortopathy (aka Hereditary Thoracic Aortic Disease, HTAD) in the last 5 years
- Use these management updates to advance and standardize care of children with HTAD

Case: 13 year-old patient referred to cardiology clinic found to have aortic dilation

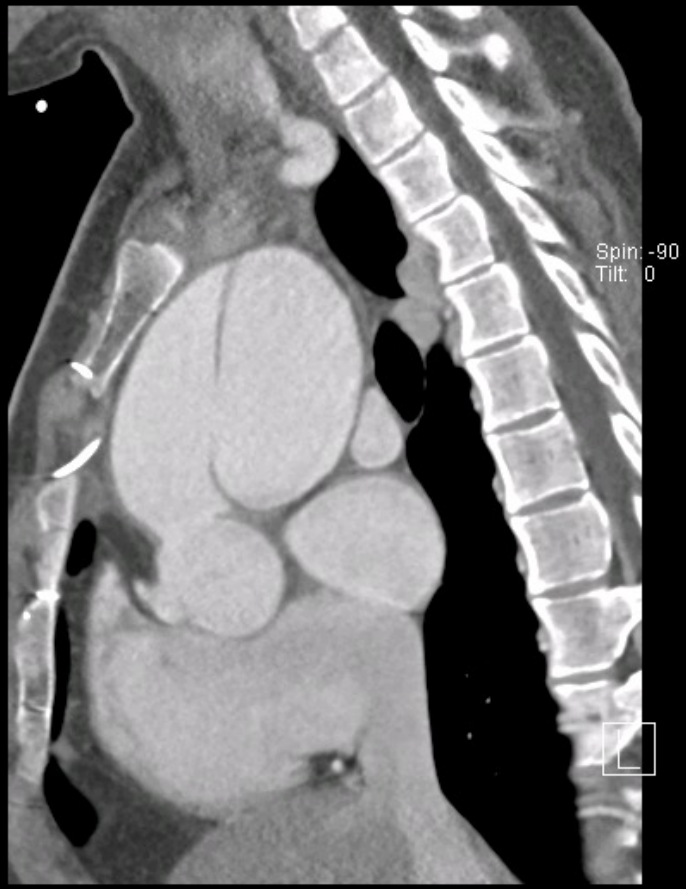


Root: 4.3 cm

Clinical questions

- What is this patient's risk of aortic or arterial dissection?
- What about non-aortic cardiovascular disease?
- Could there be extra-cardiac disease?
- Is medical therapy indicated?
- Is surgery indicated? If so, when?

Goal: prevent aortic dissection



Treatment decisions

- Prior era
  - Assess a patient clinically, Marfan syndrome yes or no?
  - Possible genetic testing, but costly
  - Medical treatment if at least moderate dilation
  - If treat, monotherapy with beta-blocker or ARB
  - No ones goes to surgery before 5.0 cm

Hereditary Thoracic Aortic Disease (HTAD) Update #1

- Aortopathy is often non-syndromic (isolated aortic dilation/dissection)
- No longer can you rely on physical examination to rule out genetic disease

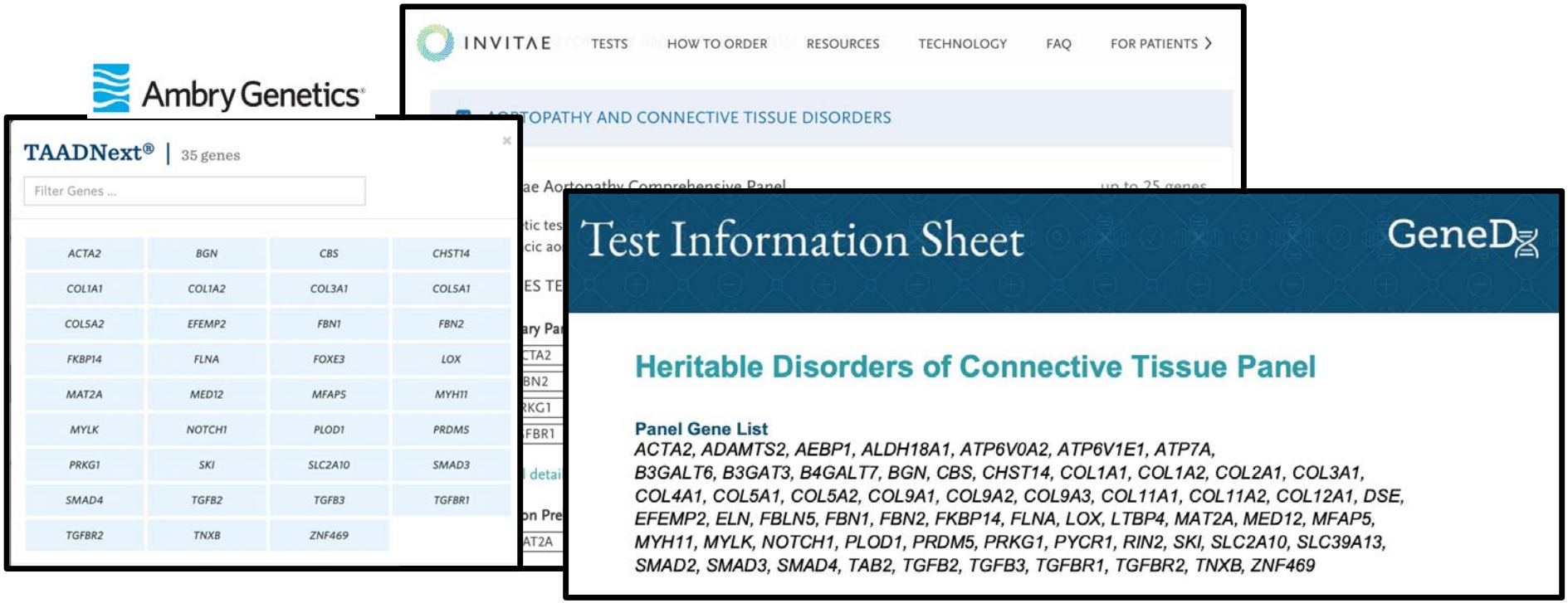
Syndromic
Marfan syndrome (*FBN1*)
Loeys-Dietz 1-6 (*TGFBR1, TGFBR2, SMAD3, TGFB2, TGFB3, SMAD2*)
Arterial Tortuosity syndrome (*SLC2A10*)
Vascular Ehlers-Danlos syndrome (*COL3A1*)
Turner syndrome (XO)

Non-Syndromic
FBN1 variants
TGFBR1, TGFBR2, SMAD3, TGFB2, TGFB3, SMAD2 variants
ACTA2
PRKG1
FLNA
NOTCH1
MYLK
MYH11

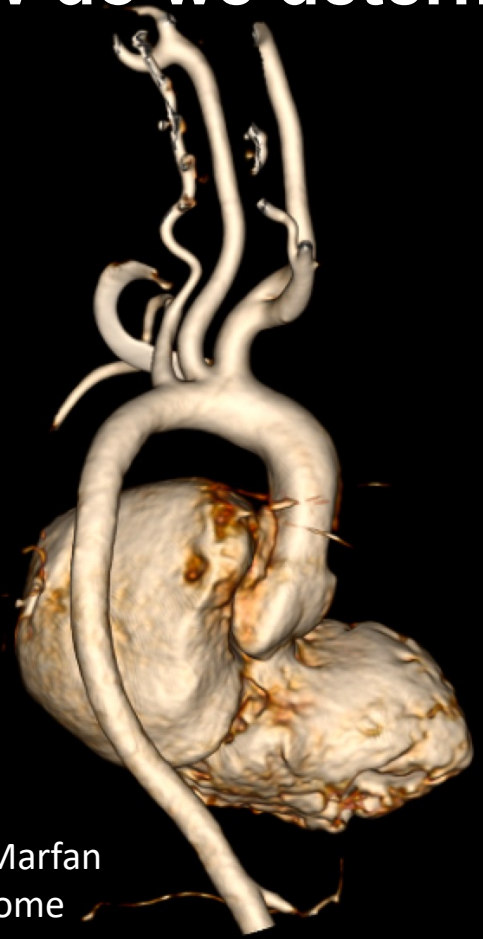
- **Consider genetic testing for any significant aortic dilation without explanation**

Hereditary Thoracic Aortic Disease (HTAD) Update #2

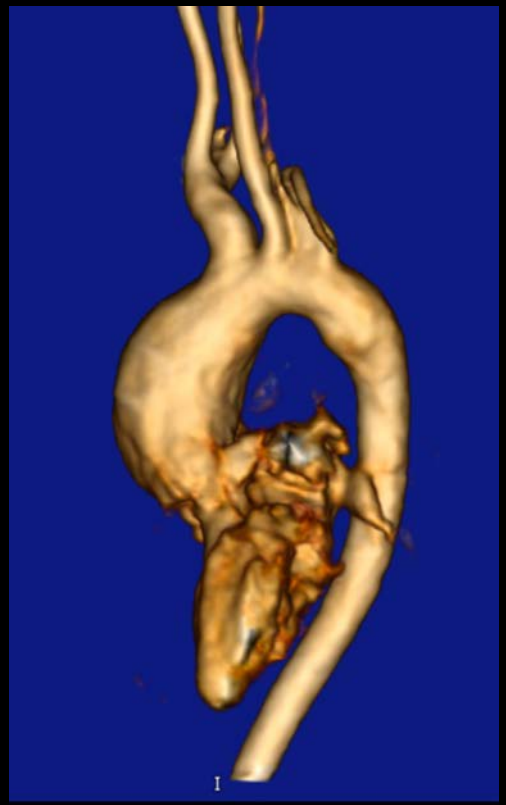
- HTAD genetic testing (sequencing) in the US is currently less expensive than a single echocardiogram



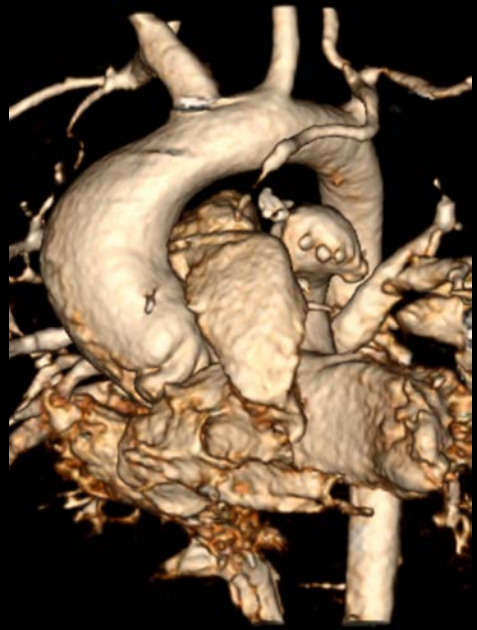
How do we determine risk - Phenotypic overlap



FBN1 - Marfan syndrome

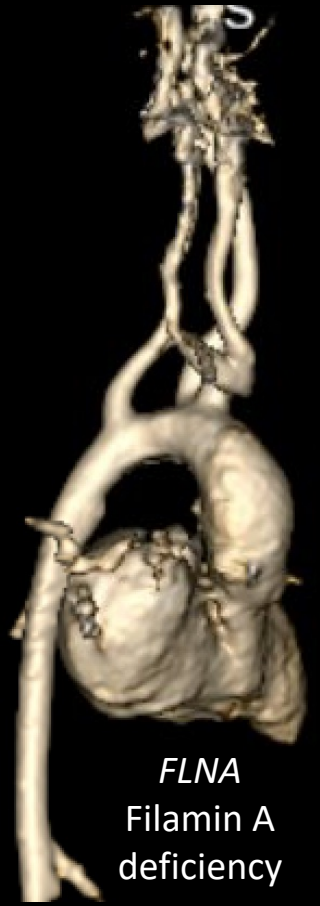


NOTCH1 with BAV



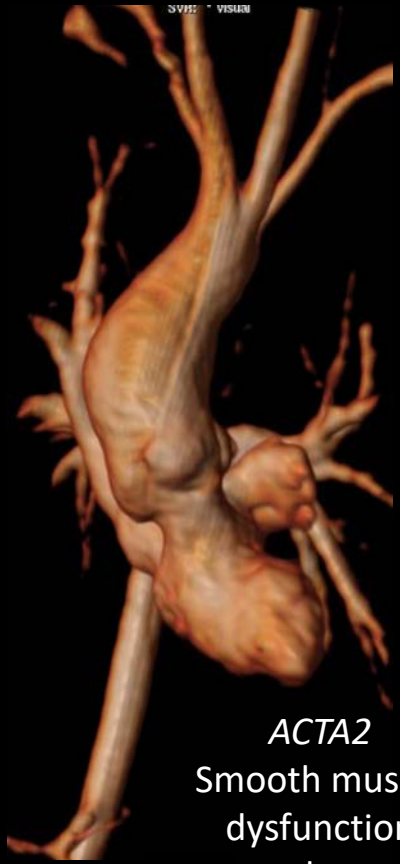
22q11.2 with TOF-Pulmonary atresia

Phenotypic overlap

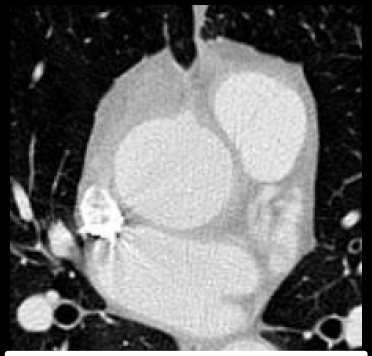


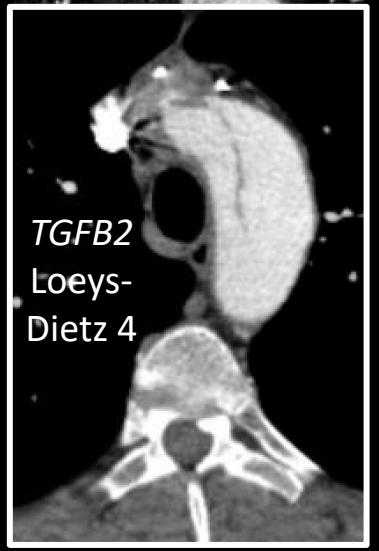
FLNA
Filamin A
deficiency

SLC2A10 BAV
in Arterial
tortuosity
syndrome



ACTA2
Smooth muscle
dysfunction
syndrome





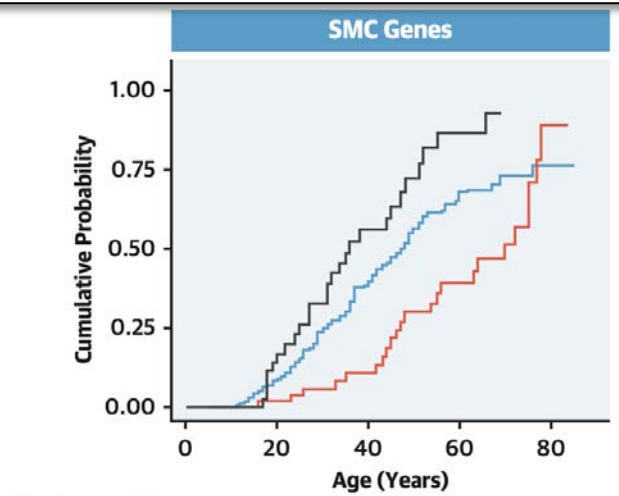
TGFB2
Loeys-
Dietz 4

Diagnosis informs risk→ management

Condition	Risk of aortic dissection/rupture
Vascular Ehlers-Danlos (*COL3A1*)	+++
Loeys-Dietz 1/2 (*TGFBR1/TGFBR2*)	+++
ACTA2 disease	+++
Marfan (*FBN1*)	++
Loeys-Dietz 3-5 (*SMAD3/TGFB2/TGFB3*)	++
Turner syndrome (monosomy X)	+
Isolated BAV	+
Periventricular nodular heterotopia (*FLNA*)	Unknown, rare, 2 cases
Congenital heart disease	Rare reported cases
22q11.2 deletion syndrome	2 reported cases
Arterial tortuosity syndrome (*SLC2A10*)	No reported cases

Comparative Risks of Initial Aortic Events Associated With Genetic Thoracic Aortic Disease

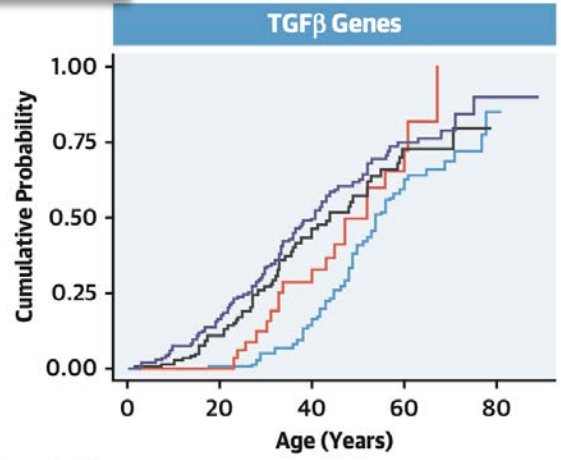
Ellen S. Regalado, PhD,[a] Shaine A. Morris, MD, MPH,[b] Alan C. Braverman, MD,[c] Ellen M. Hostetler, BA,[a] Julie De Backer, MD, PhD,[d,e] Ruosha Li, PhD,[f] Reed E. Pyeritz, MD, PhD,[g] Anji T. Yetman, MD,[h] Elena Cervi, MD,[i] Sherene Shalhub, MD,[j] Richmond Jeremy, MB, BS, PhD,[k] Scott LeMaire, MD,[l] Maral Ouzounian, MD, PhD,[m] Arturo Evangelista, MD,[e,n] Catherine Boileau, PhD,[e,o] Guillaume Jondeau, MD, PhD,[e,o] Dianna M. Milewicz, MD, PhD[a]



Number at risk

ACTA2	306	231	127	31	4
MYLK	55	51	34	17	1
PRKG1	37	30	12	2	0

ACTA2 *MYLK* *PRKG1*



Number at risk

SMAD3	211	182	113	28	1
TGFB2	42	34	18	5	0
TGFBR1	141	92	44	11	0
TGFBR2	236	151	55	14	2

SMAD3 *TGFB2* *TGFBR1* *TGFBR2*

Comparative Risks of Initial Aortic Events Associated With Genetic Thoracic Aortic Disease

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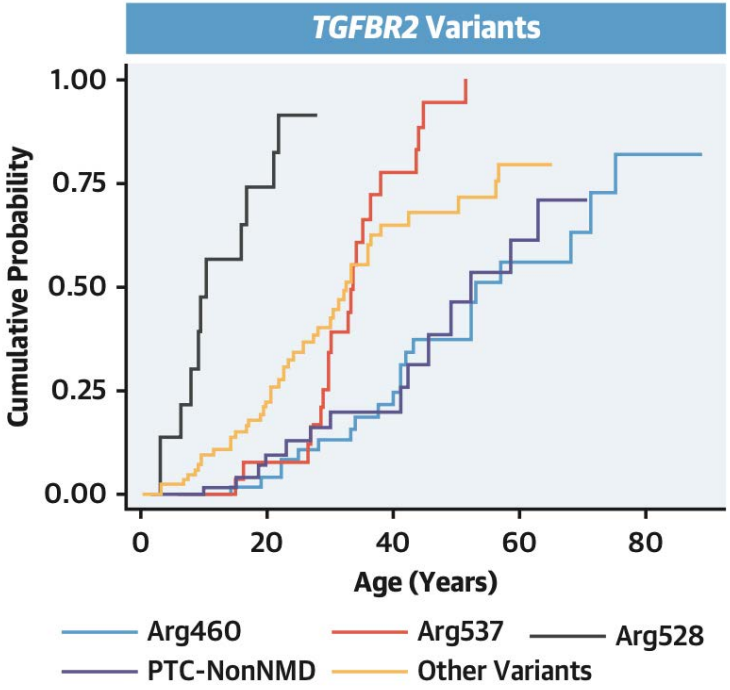
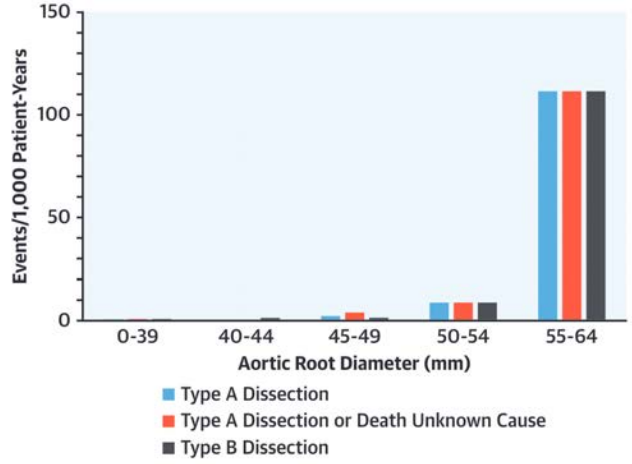


Risk factor: Aortic size

Marfan syndrome

CENTRAL ILLUSTRATION Risk as a Function of Aortic Root Diameter

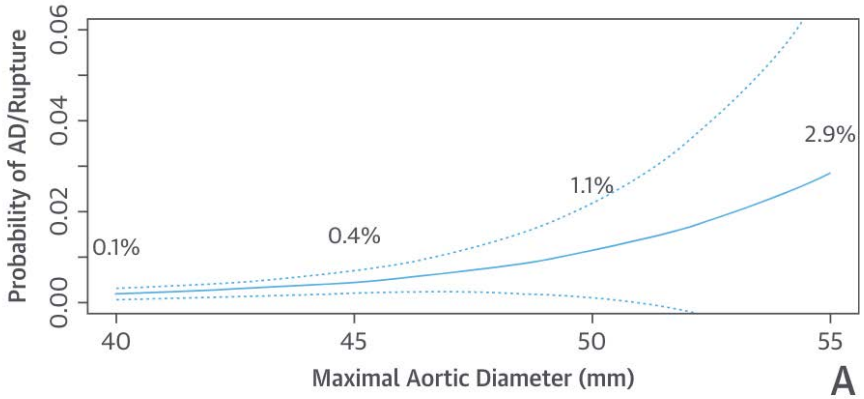


Milleron, O. et al. J Am Coll Cardiol. 2020;75(8):843-53.

Risk for aortic dissection (type A and type B), all deaths, and combined risk of aortic dissection and death of unknown cause in the total population, as a function of aortic root diameter measured in diastole using echocardiography.

Non-Syndromic HTAD

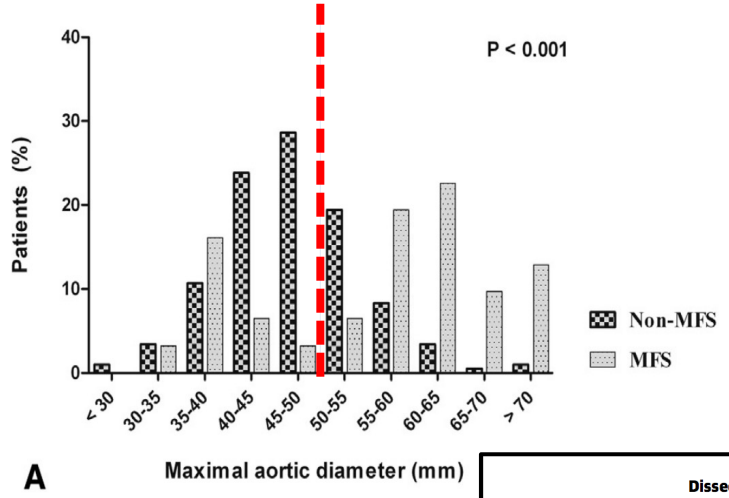
FIGURE 3 Probability of Aortic Dissection and/or Rupture, and Composite of Event and Surgery Within 5 Years

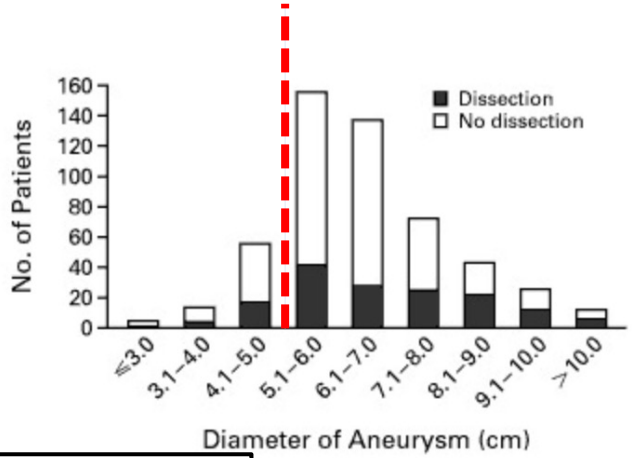


Joon Bum Kim, MD, PhD,[a] Matthew Spotnitz, MD,[b,f] Mark E. Lindsay, MD, PhD,[c,d,e] Thomas E. MacGillivray, MD,[b,e] Eric M. Isselbacher, MD,[c,e] Thoralf M. Sundt III, MD[b,e]

Aortic size as a risk factor

- A proportion of patients with Marfan syndrome and Loeys-Dietz syndrome have type A aortic dissection at a dimension <5.0 cm





Subject #	Diagnosis	Dissection Type	Dissection Origin	Pre-Dissection Aortic Size (cm)§
1	MFS	A	Root	4.6
2	MFS	A	Ascending	3.5
3	MFS	A	Ascending	3.3
4	MFS	A	Ascending	4.2

Kim et al. JCTVS 2013, Weinsaft et al, JACC 2016 et al. JCTVS 2013, Gott et al. NEJM 1999

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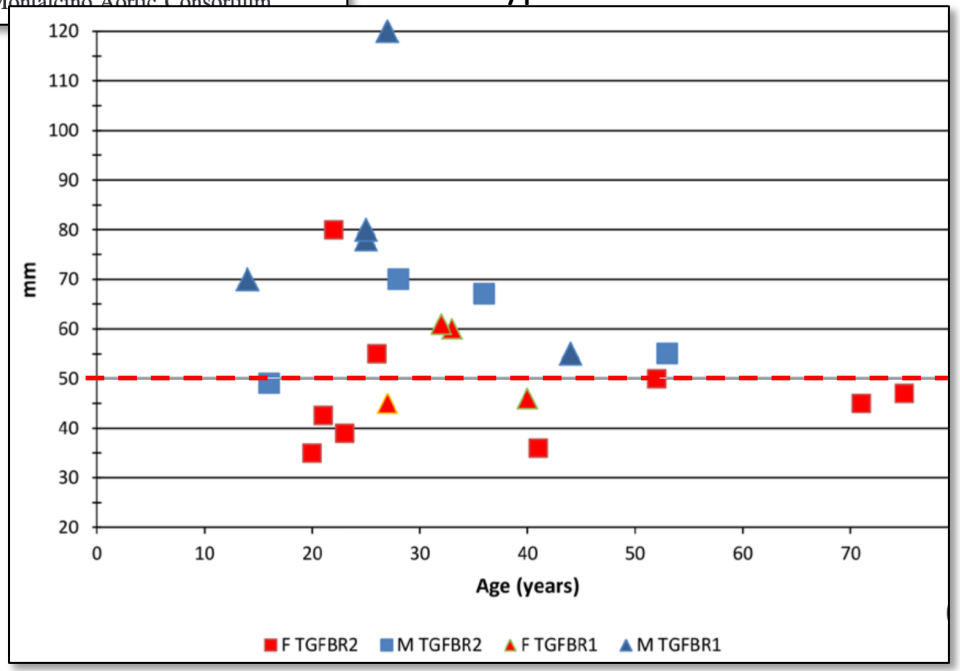
International Registry of Patients Carrying *TGFBR1* or *TGFBR2* Mutations

Results of the MAC (Montalcino Aortic Consortium)

Guillaume Jondeau, MD, PhD; Jacques Ropers, PharmD; Ellen Regalado, MS; Alan Braverman, MD; Arturo Evangelista, MD; Guisela Teixedo, MD; Julie De Backer, MD, PhD; Laura Muiño-Mosquera, MD; Sophie Naudion, MD; Cecile Zordan, BSc; Takayuki Morisaki, MD, PhD; Hiroto Morisaki, MD; Yskert Von Kodolitsch, MD; Sophie Dupuis-Girod, MD; Shaine A. Morris, MD; Richmond Jeremy, MD, PhD; Sylvie Odent, MD; Leslie C. Adès, MD; Madhura Bakshi, MD; Katherine Holman, BSci; Scott LeMaire, MD; Olivier Milleron, MD; Maud Langeois, BSc; Myrtille Spentchian, BSci; Melodie Aubart, MD; Catherine Boileau, PhD; Reed Pyeritz, MD; Dianna M. Milewicz, MD; for the Montalcino Aortic Consortium

Size at type A aortic dissection



Hereditary Thoracic Aortic Disease (HTAD) Update #3

- **Surgical thresholds depend on the gene**

ACC/AHA CLINICAL PRACTICE GUIDELINE

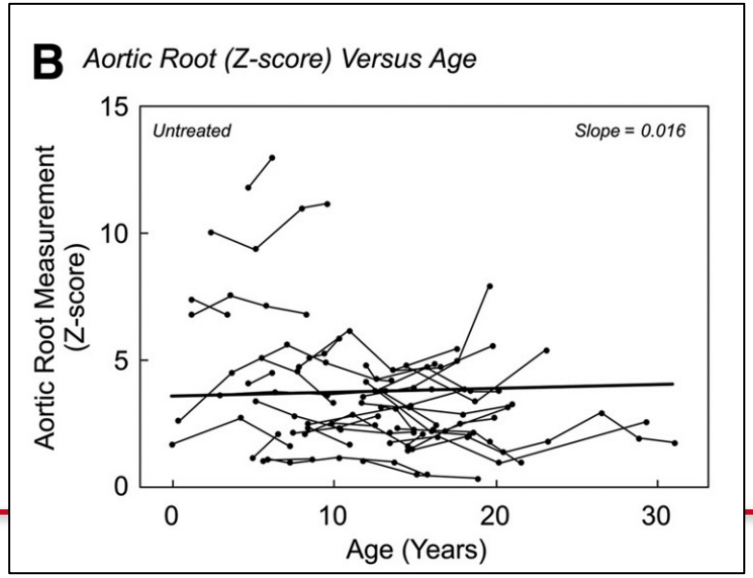
2022 ACC/AHA Guideline for the Diagnosis and Management of Aortic Disease: A Report of the American Heart Association/American College of Cardiology Joint Committee on Clinical Practice Guidelines

Table 11. Surgical Thresholds for Prophylactic Aortic Root and Ascending Aortic Replacement in Loeys-Dietz Syndrome Based on Genetic Variant

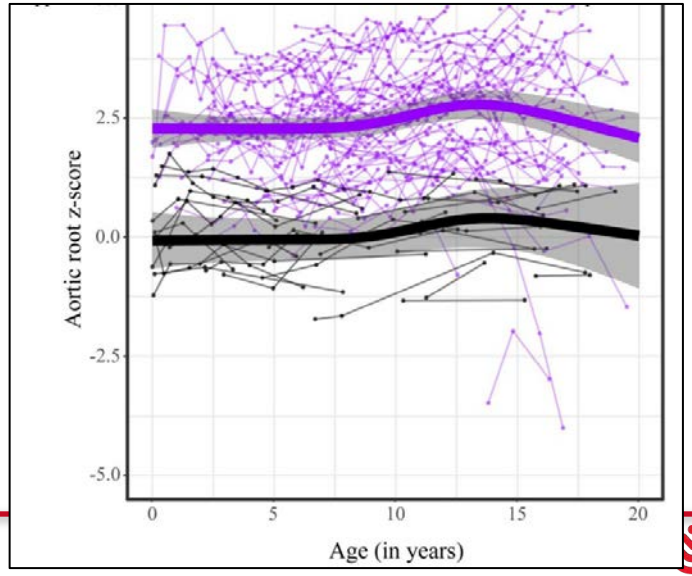
COR	LOE (references)	Genetic Variant	Presence of High-Risk Features*	Aortic Diameter (cm)
1	C-LD[2]	*TGFBR1*	No	≥4.5
1	C-LD[2]	*TGFBR2*	No	≥4.5
2b	C-EO[2]	*TGFBR1*	Yes	≥4.0
2a	C-LD[1,2]	*TGFBR2*	Yes	≥4.0
2a	C-EO[13,16]	*SMAD3*	–	≥4.5†
2b	C-EO[5-7]	*TGFB2*‡	–	≥4.5†
2b	C-EO[9,23]	*TGFB3*	–	≥5.0†

What about before surgery? Longitudinal changes and medical therapy

- Natural history is for aortic root z-scores to stay the same
- Goal of medication is to decrease the z-scores over time



Tierney et al 2007



van Elsäcker et al, 2022

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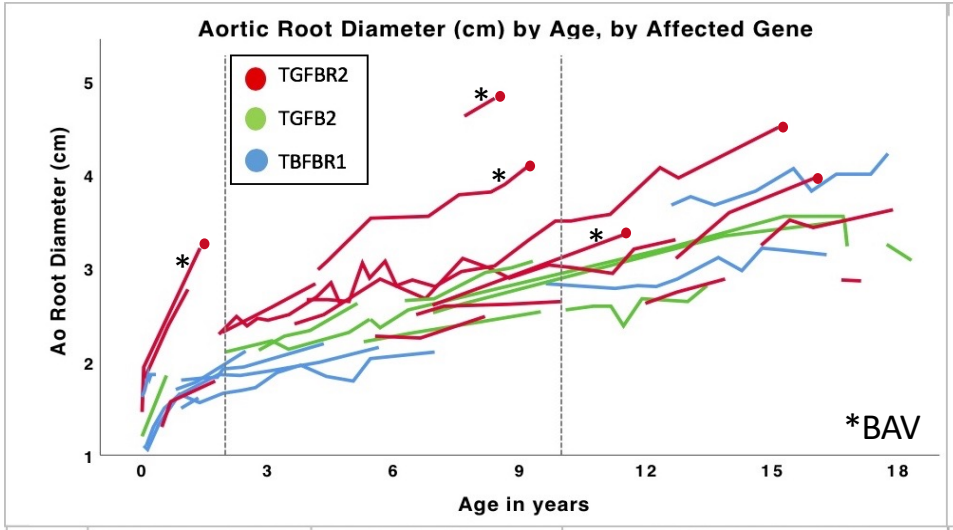
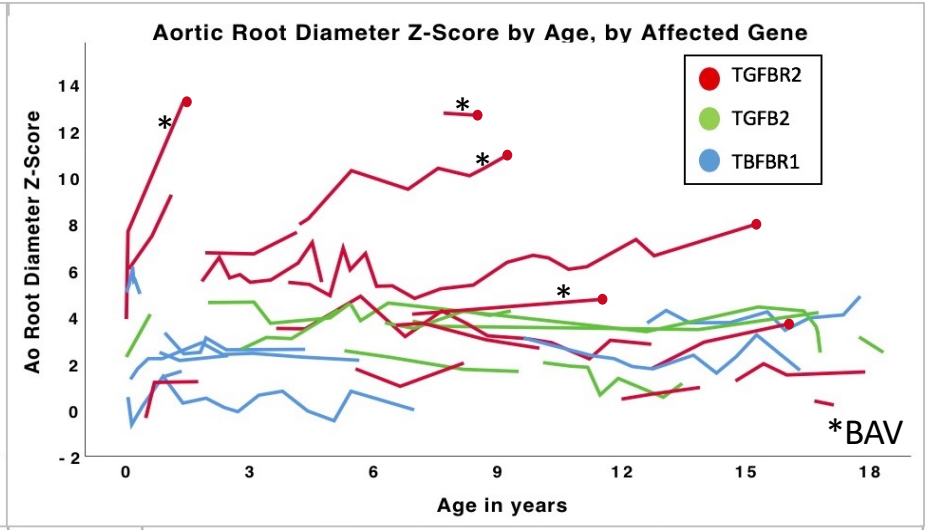
Aortic growth in children with *TGFBR1*, *TGFBR2*, and *TGFB2* mutations





	Age 0-1y mean root size and mean annual change	Age 2-10y mean root size and mean annual change	Age 11-18y mean root size and mean annual change
TGFBR2	2.08 ± 0.58 cm 0.76 ± 0.10 cm/y	2.97 ± 0.56 cm 0.12 ± 0.01 cm/y	3.37 ± 0.49 0.19 ± 0.03
TGFB2	1.72 ± 0.46 cm 0.57 ± 0.16 cm/y	2.50 ± 0.26 cm 0.12 ± 0.02 cm/y	3.12 ± 0.40 0.07 ± 0.02
TGFBR1	1.63 ± 0.25 cm 0.32 ± 0.04 cm/y	2.00 ± 0.27 cm 0.09 ± 0.02 cm/y	3.44 ± 0.50 0.09 ± 0.01

	Mean root z-score and mean annual change
TGFBR2	5.13 ± 3.07 cm, 0.09 ± 0.06 z-score/y (compared to rate of 0, p=0.10)
TGFB2	3.16 ± 1.16 cm,-0.05 ± 0.03 z-score/y (compared to rate of 0, p=0.10)
TGFBR1	2.49 ± 1.72 cm, 0.00 ± 0.03 z-score/y (compared to rate of 0, p=0.92)

Lovin et al., unpublished

Texas Children's Hospital

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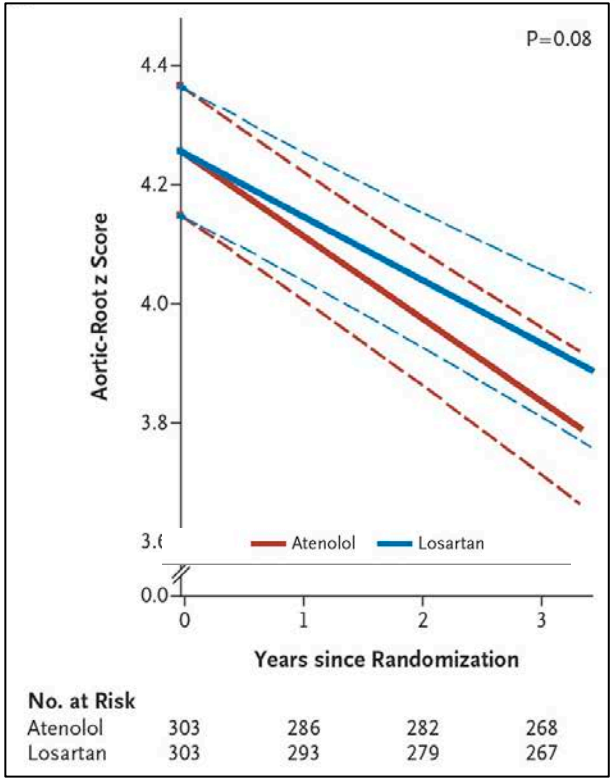
Atenolol versus Losartan in Children and Young Adults with Marfan's Syndrome

Ronald V. Lacro, M.D., Harry C. Dietz, M.D., Lynn A. Sleeper, Sc.D., Anji T. Yetman, M.D., Timothy J. Bradley, M.B., Ch.B., Steven D. Colan, M.D., Gail D. Pearson, M.D., Sc.D., E. Seda Selamet Tierney, M.D., Jami C. Levine, M.D., Andrew M. Atz, M.D., D. Woodrow Benson, M.D., Ph.D., Alan C. Braverman, M.D., et al., for the Pediatric Heart Network Investigators*

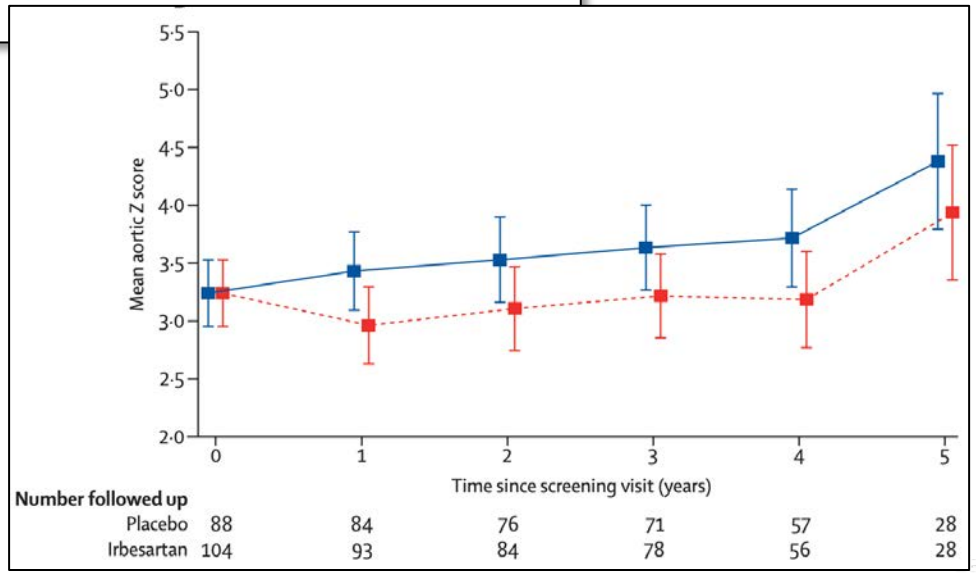


Hereditary Thoracic Aortic Disease (HTAD) Update #4

- **There is good evidence for dual therapy (BB + ARB)**

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

Michael Mullen, Xu Yu Jin*, Anne Child, A Graham Stuart, Matthew Dodd, José Antonio Aragon-Martin, David Gaze, Anatoli Kiotsekoglou, Li Yuan, Jiangting Hu, Claire Foley, Laura Van Dyck, Rosemary Knight, Tim Clayton, Lorna Swan, John D R Thomson, Guliz Erdem, David Crossman, Marcus Flather, on behalf of the AIMS Investigators†*



Hereditary Thoracic Aortic Disease (HTAD) Update #4

- **There is good evidence for dual therapy (BB + ARB)**

Angiotensin receptor blockers and β blockers in 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

	ARB		Control		Difference, mean (95% CI or 99% CI)
	n	Mean (SE)	n	Mean (SE)	
β blocker (χ^2_1=0·4; p=0·54)					
Yes	247	0·06 (0·02)	225	0·13 (0·02)	−0·07 (−0·15 to 0·01)
No	79	0·10 (0·03)	75	0·13 (0·03)	−0·04 (−0·15 to 0·07)

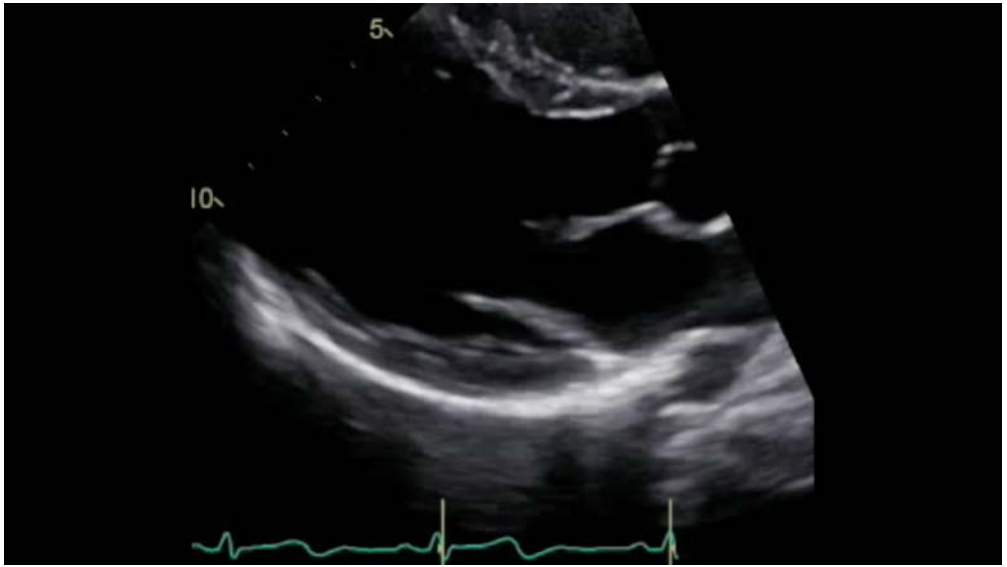
Hereditary Thoracic Aortic Disease (HTAD) Update #5

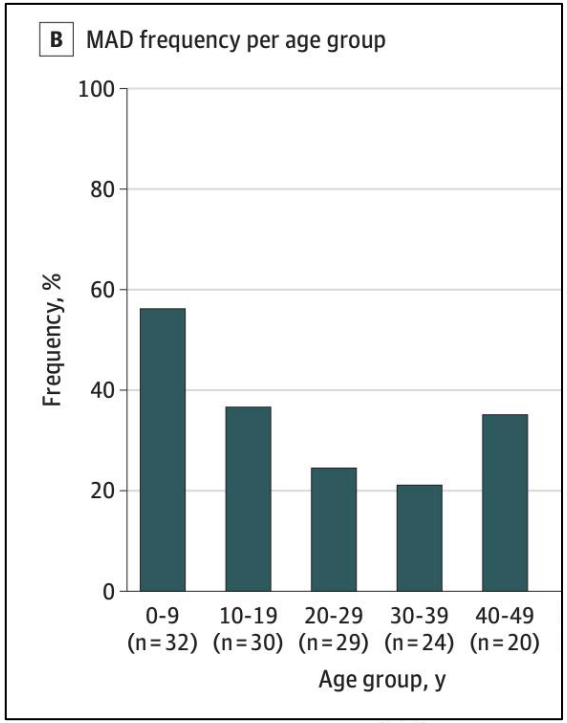
- **Be on the lookout for mitral annular disjunction (MAD)**

JAMA Cardiology | Original Investigation

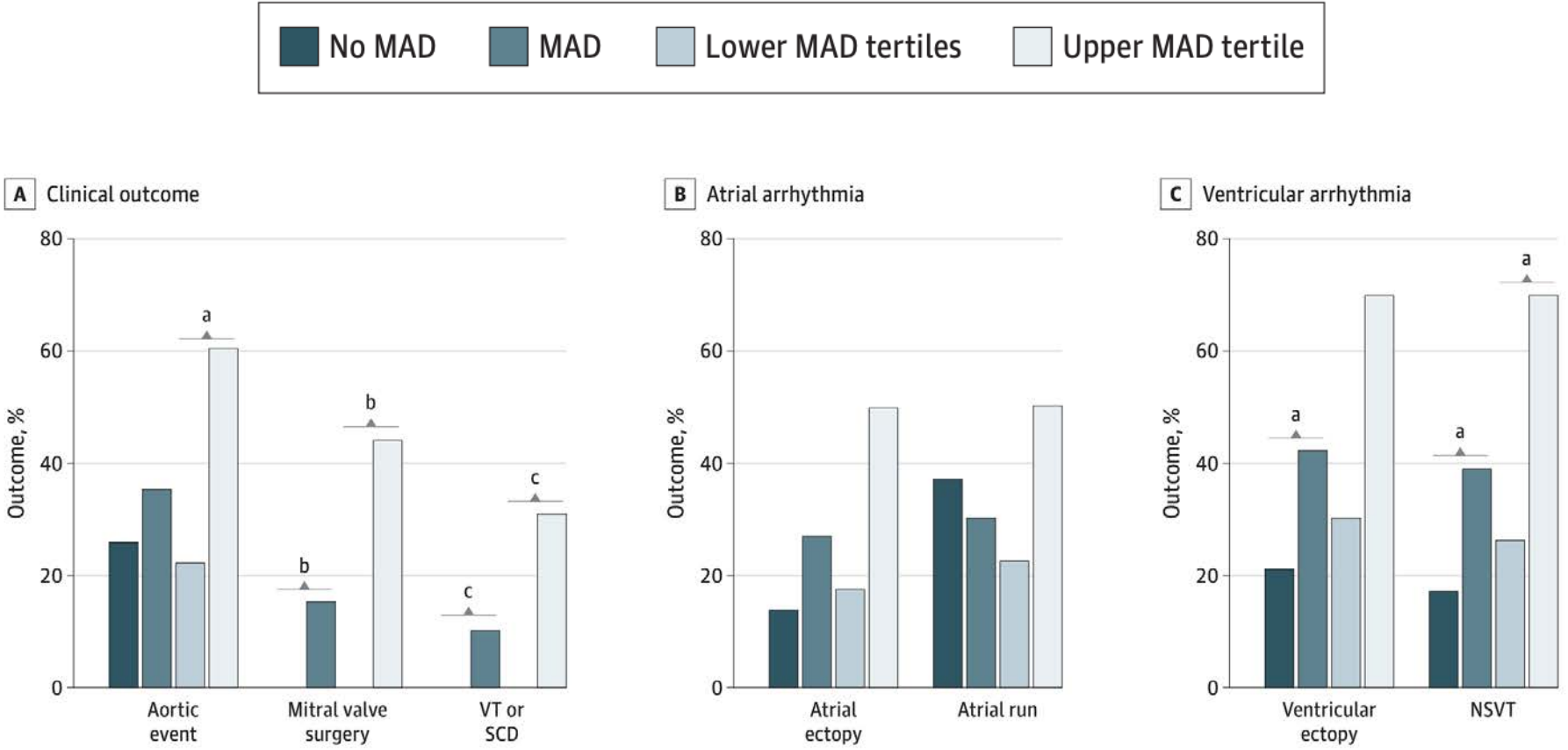
Association of Mitral Annular Disjunction With Cardiovascular Outcomes Among Patients With Marfan Syndrome

Anthony Demolder, MD; Frank Timmermans, MD, PhD; Mattias Duytschaever, MD, PhD; Laura Muiño-Mosquera, MD, PhD; Julie De Backer, MD, PhD





Mitral annular disjunction



Summary: What has changed in pediatric HTAD?

- Many aortopathies have no extracardiac features (non-syndromic)
- Genetic testing is less expensive than a single echocardiogram
- Outcomes and surgical management are gene/mutation-based
- Finally evidence for dual therapy with ARB and BB in Marfan syndrome
- Mitral annular disjunction (MAD) is highly prevalenet in pediatric HTAD and likely associated with increased arrhythmias

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COMMENTS/QUESTIONS?