Children's Heart Issues in Marfan, Loeys-Dietz, and Vascular Ehlers-Danlos Syndromes

Ronald V. Lacro, M.D.
The Marfan Foundation
Virtual Medical Symposium Series
April 9, 2019

Boston Children's Hospital
Heart Center

HARVARD MEDICAL SCHOOL
TEACHING HOSPITAL

Ronald V. Lacro, M.D.

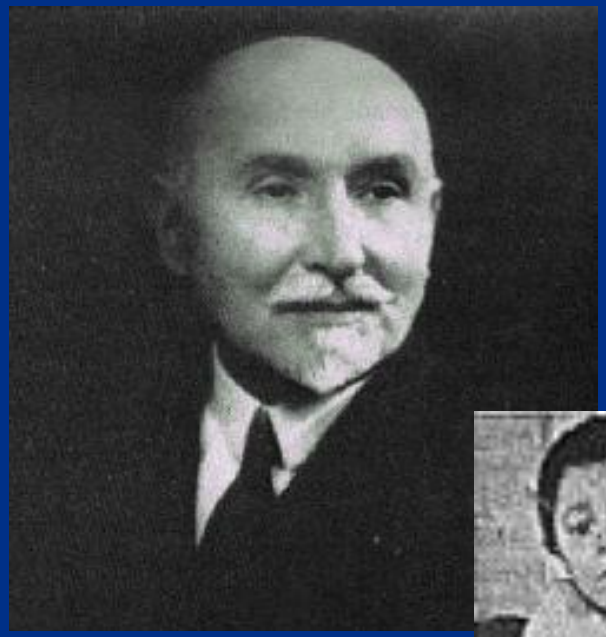
Financial Disclosures

- No relevant financial relationships with any commercial interests.

Learning Objectives

- Introduction of the syndromes
- Basic cardiovascular anatomy
- Common cardiovascular findings
- Imaging techniques
  - Deciphering z-scores
- Medical Therapy
- Surgical Therapy
- Physical Activity and Exercise
- FDA warning about fluoroquinolones
- Your Questions and Answers

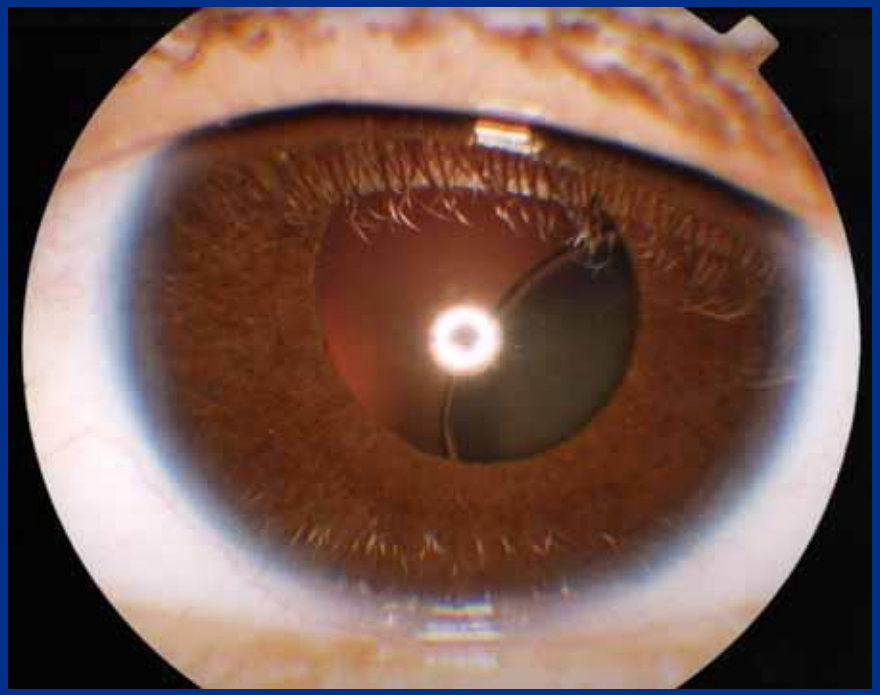
Marfan Syndrome (MFS) Skeletal Features



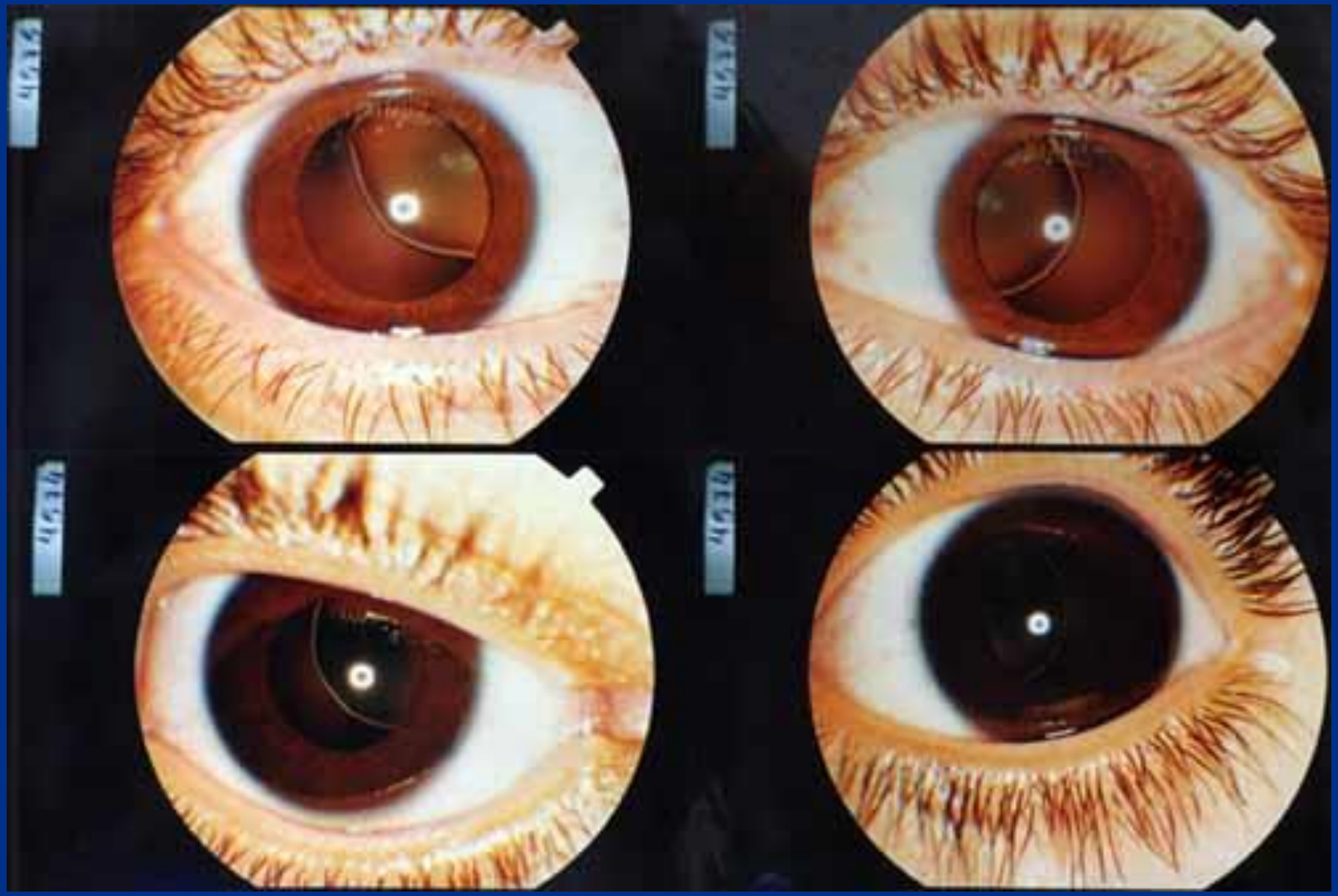
Gabrielle P.

- 1896
- Dr. Antoine Bernard-Jean Marfan
- Paris pediatrician describes skeletal abnormalities in a 5 year old girl
- Referred to the condition as dolichostenomelia
  - Long, thin limbs

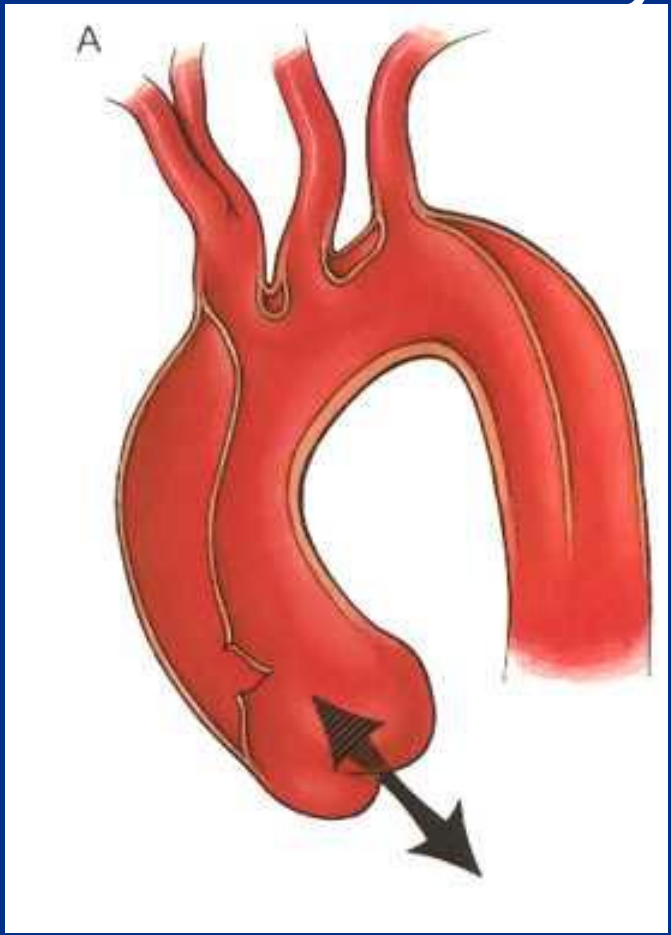
Marfan Syndrome: Dislocation of the Lens



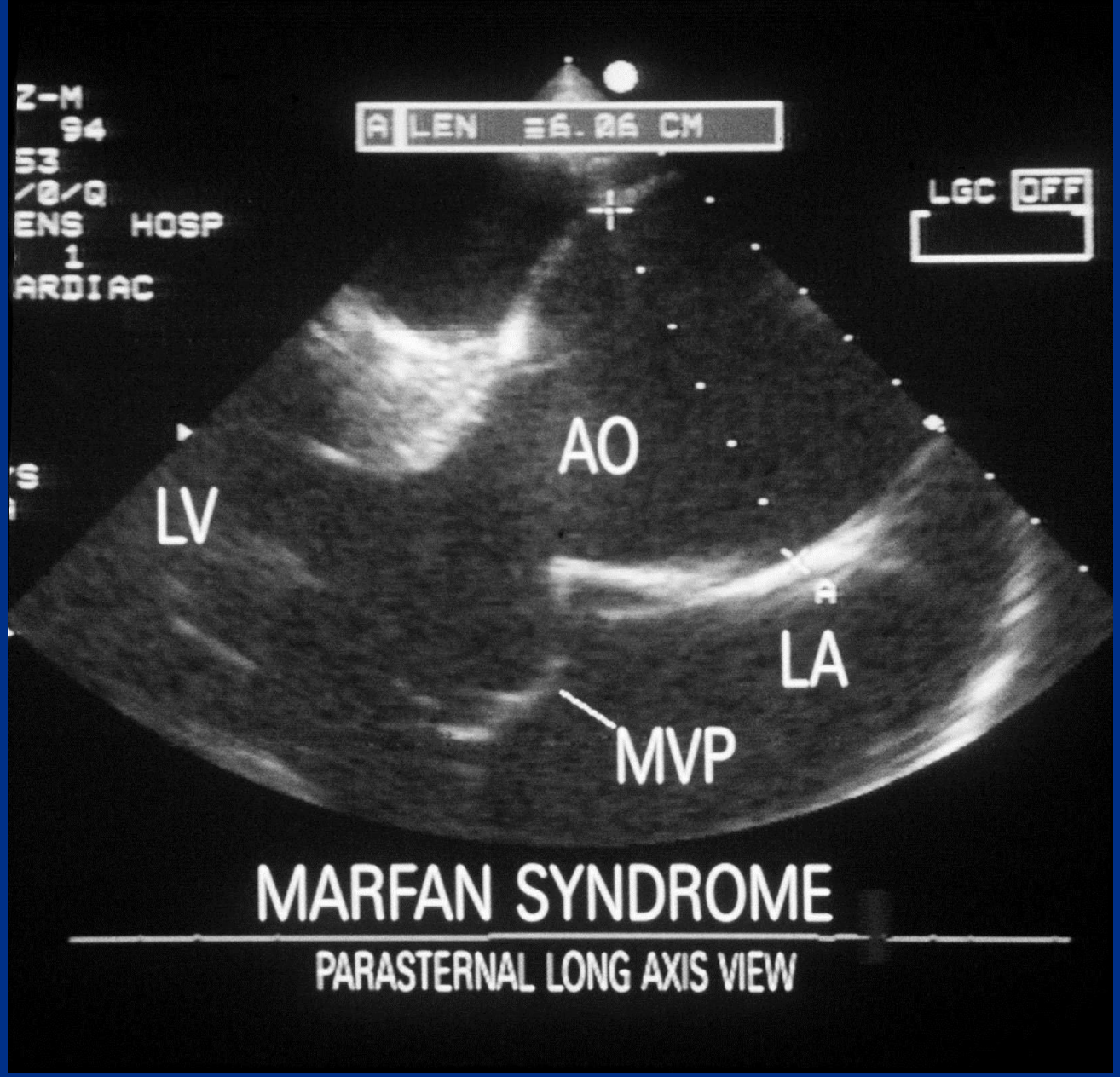
- 1914
- Boerger notes association of dislocated lenses in the eye with skeletal abnormalities



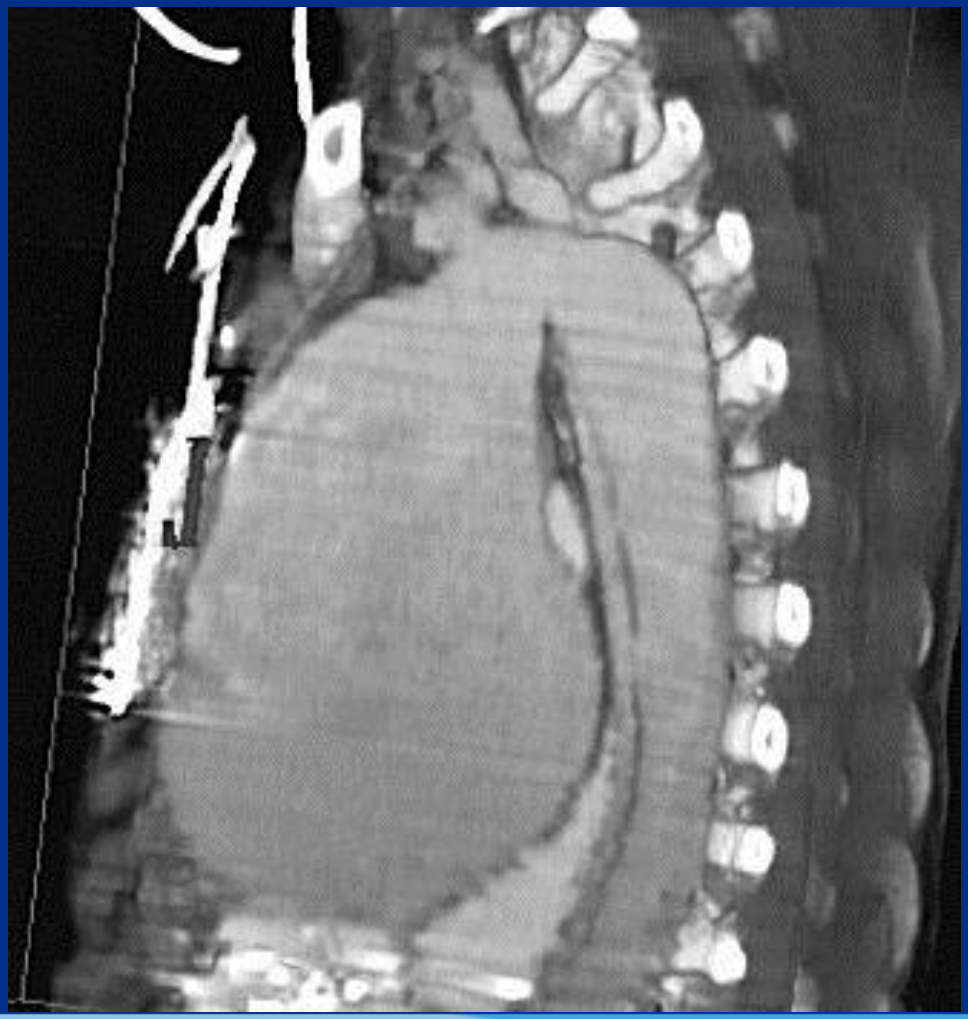
Marfan Syndrome
Aortic Aneurysm/Dissection



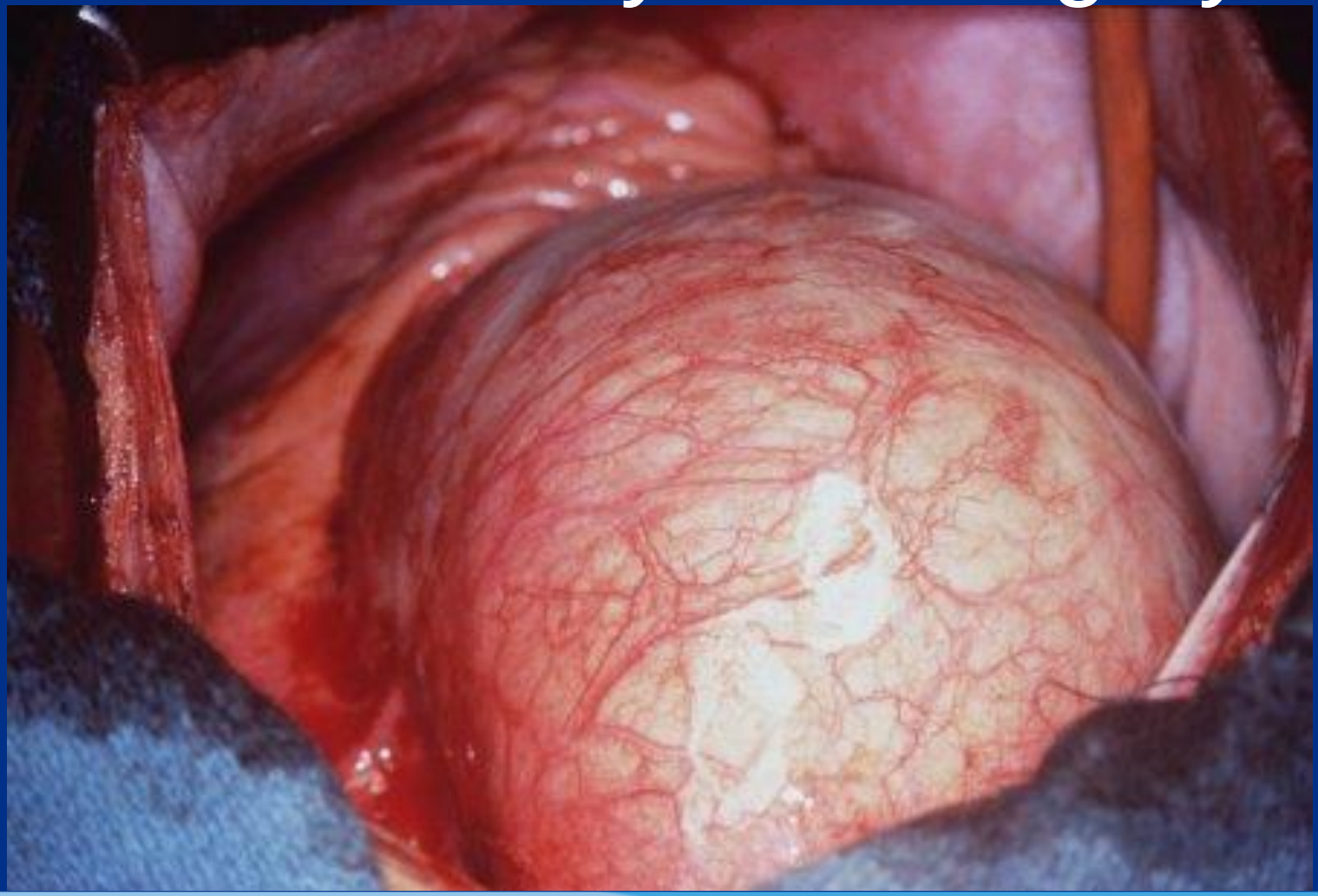
- 1943
- Aneurysm of the aorta and aortic dissection reported in single cases


Z-M
94
53
/0/Q
ENS HOSP
1
ARDI AC
A LEN =6.06 CM
LGC OFF
AO
LV
A
LA
MVP
MARFAN SYNDROME
PARASTERNAL LONG AXIS VIEW

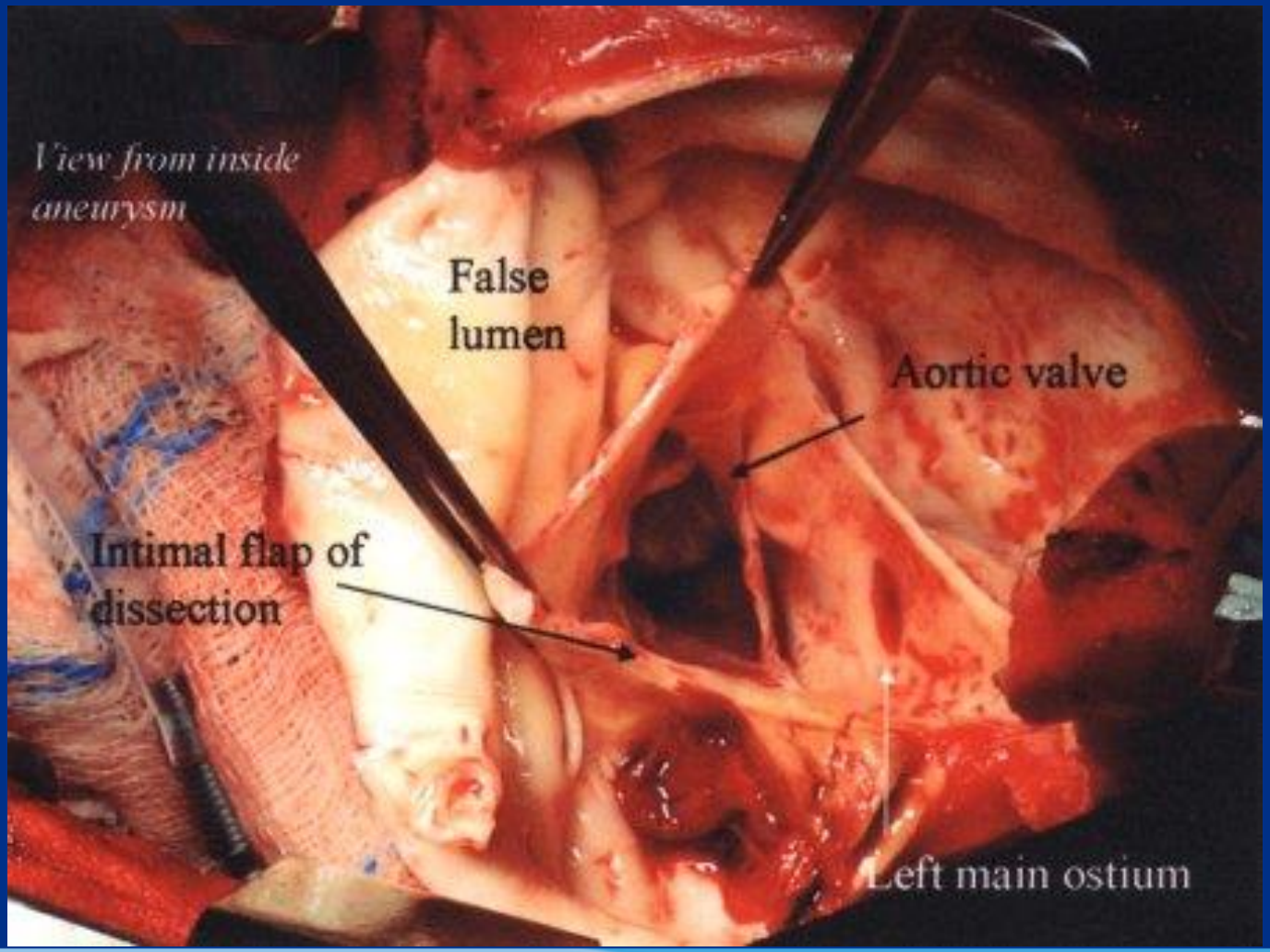
Aortic Aneurysm: CT scan



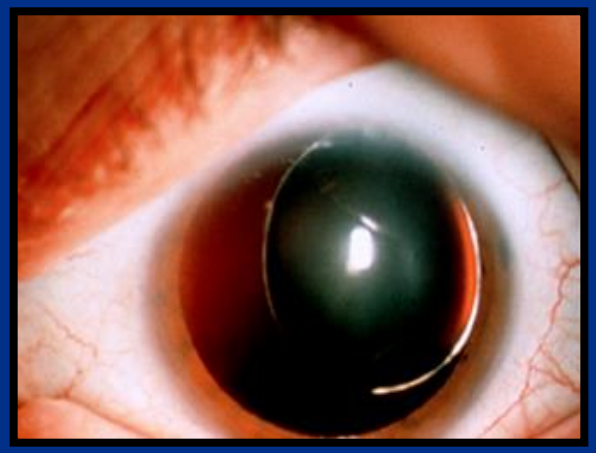
Aortic Aneurysm: Surgery

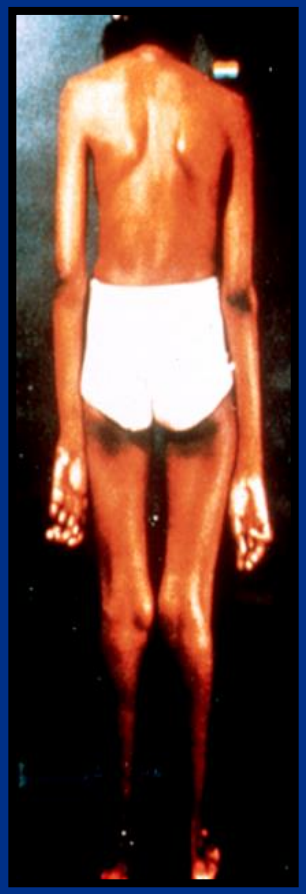


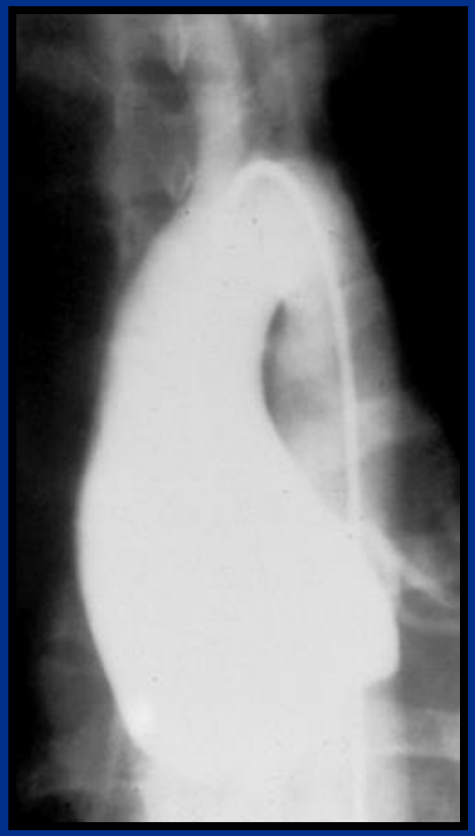
Aortic Aneurysm/Dissection



Marfan Syndrome (MFS)
FBN1



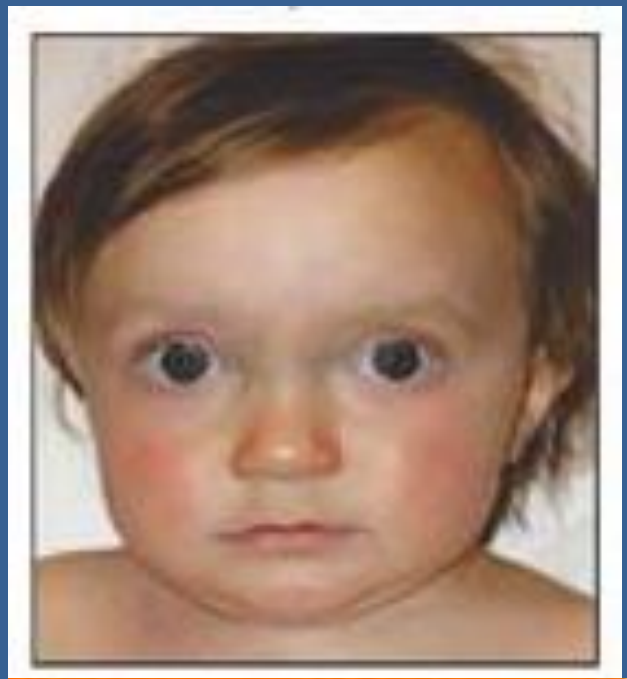




Loeys-Dietz Syndrome (LDS): General Clinical Features

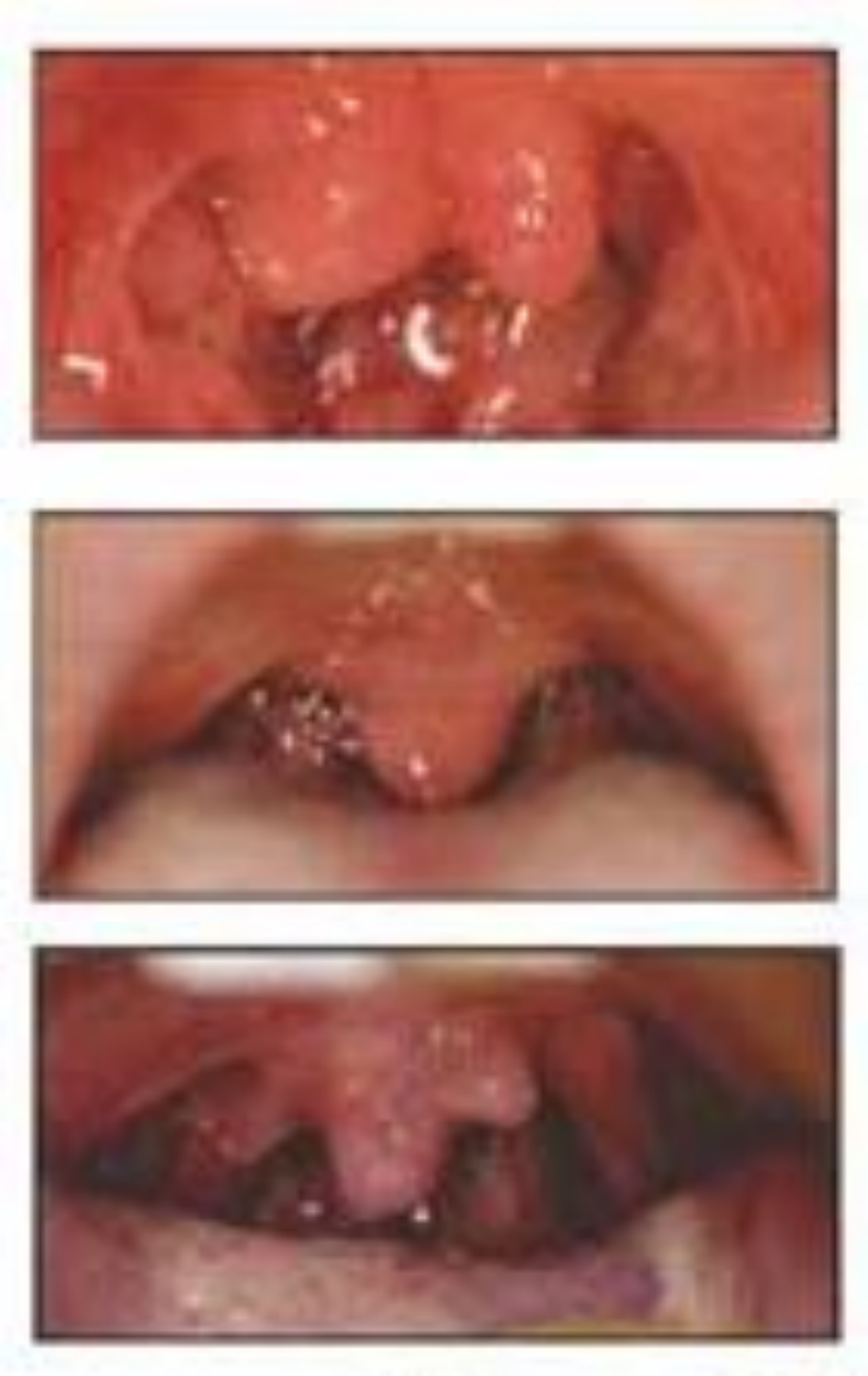
- First published in 2005: Loeys et al, Nature Genetics 2005;37(3):275-281
- Overlapping phenotype with MFS, often carrried diagnosis of “atypical MFS,” can meet Ghent criteria
- More aggressive and diffuse vascular disease
- Generalized arterial tortuosity
- Craniofacial findings, including craniosynostosis and cleft palate/bifid uvula
- Structural brain anomalies/developmental delay
- Congenital heart disease

Loeys-Dietz Syndrome: Facial Features



National Heart Lung and Blood Institute
People Science Health

Loeys et al. Nature Genetics 2005;37(3):275-281



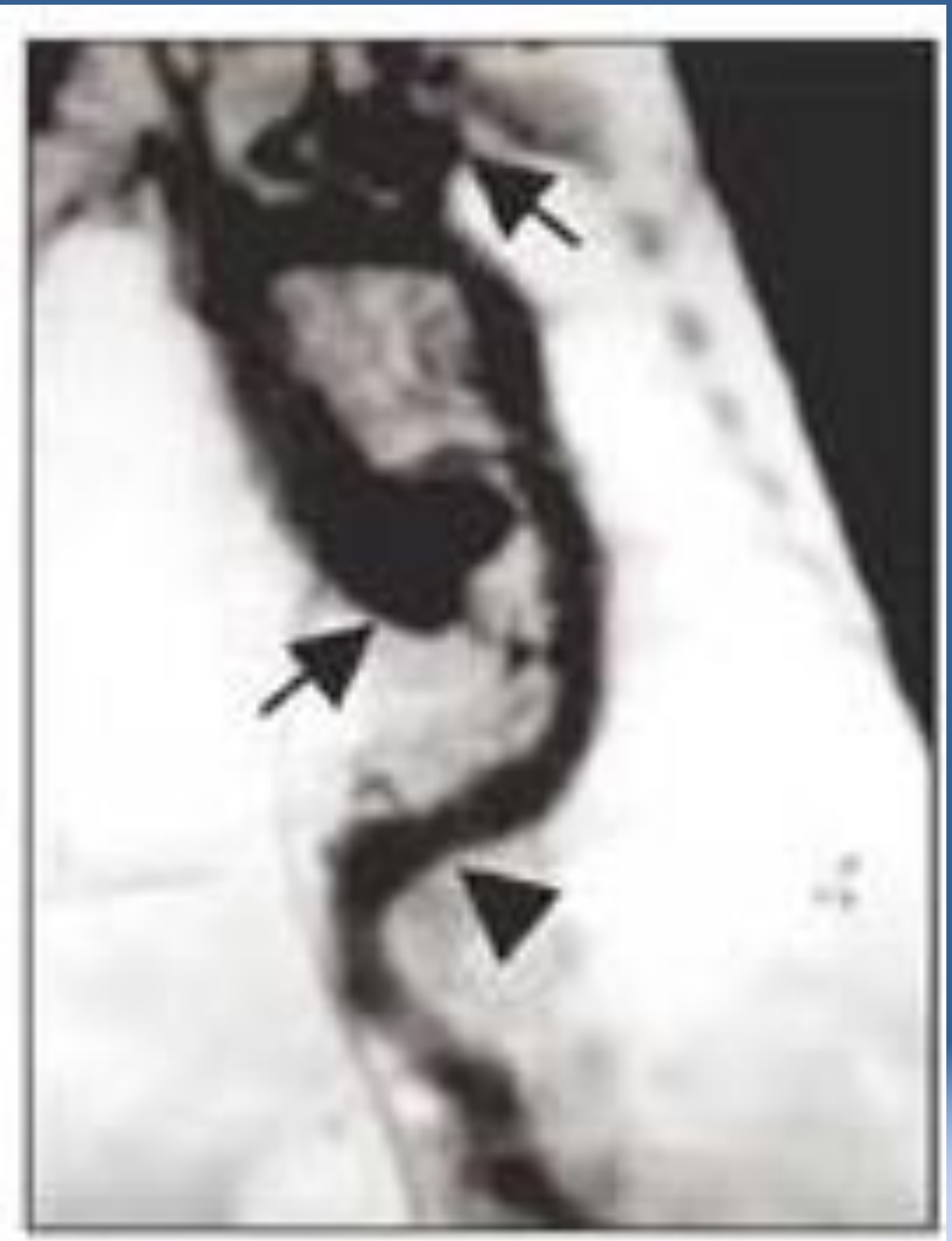
Loeys et al, Nature Genetics 2005;37(3):275-281

National Heart Lung and Blood Institute
People Science Health

PEDIATRIC HEART NETWORK

Loeys-Dietz Syndrome: Cardiovascular Features

- Aortic root aneurysm (16/16)
- Patent ductus arteriosus (7/13)
- Arterial tortuosity (11/11)
- Bicuspid aortic valve (2/12)
- Bicuspid pulmonary valve (1/9)
- MVP (4/14)
- Pulmonary artery aneurysm (9/13)
- Descending aortic aneurysm (3/9)
- Ductal aneurysm (3/12)
- Subclavian artery aneurysm (2/7)
- Superior mesenteric artery aneurysm (1/8)
- Cerebral aneurysm (2/9)
- Atrial septal defect (4/13)



Aortic root and subclavian artery aneurysm

Marked tortuosity of the aorta

Loeys et al, Nature Genetics 2005;37(3):275-281

PEDIATRIC HEART NETWORK

Pigtail loops of the carotid arteries

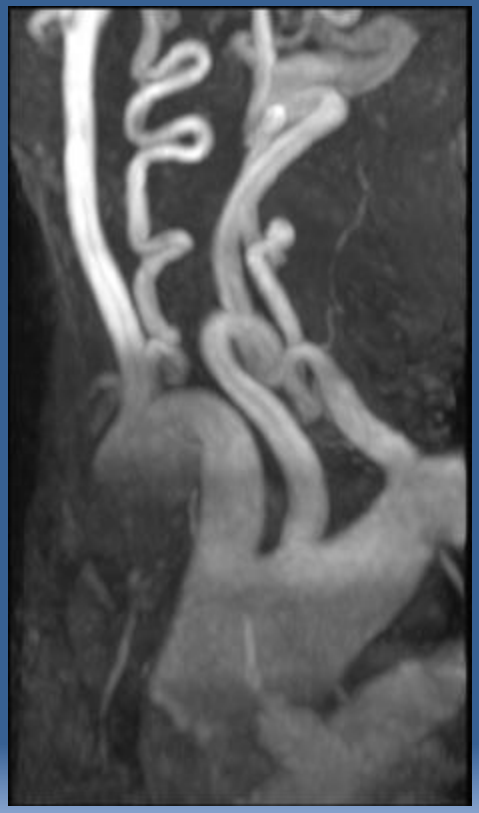
Proximal descending aorta makes a hairpin turn

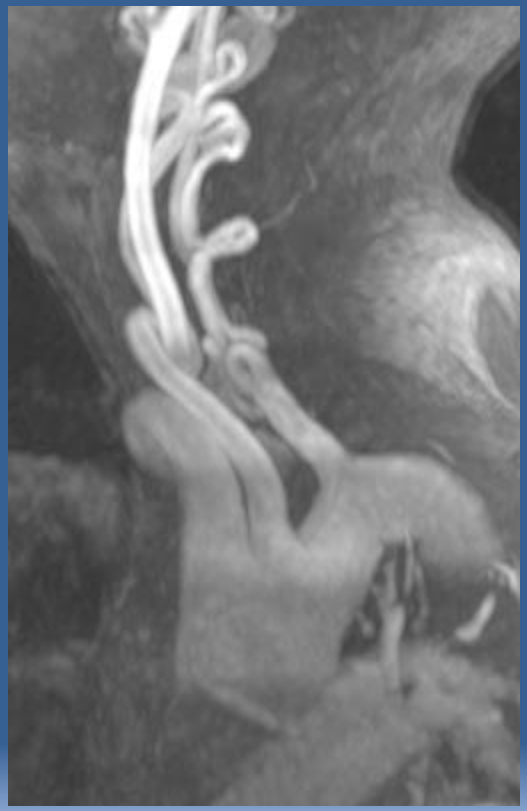
People Science Health

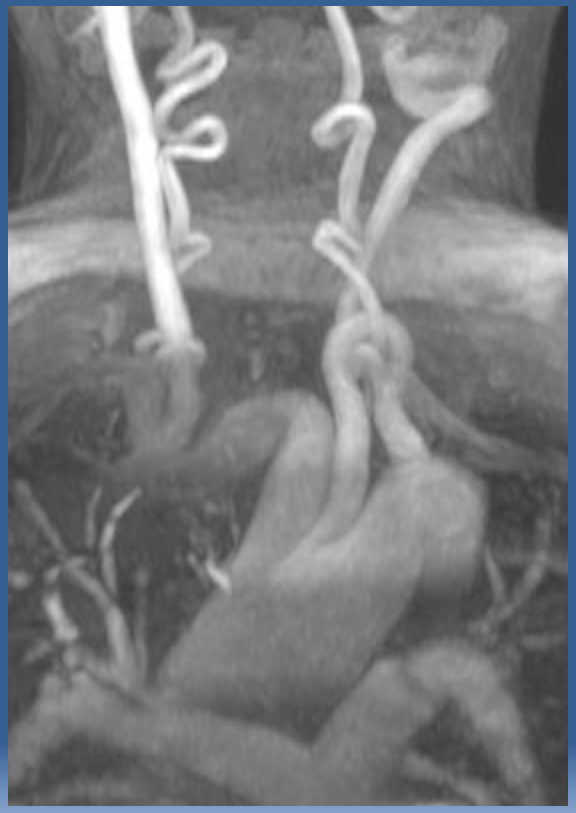
PEDIATRIC HEART NETWORK

Loeys et al. Nature Genetics 2005;37(3):275-281

LDS: Aortic Arch and Head and Neck Vessels by MRI







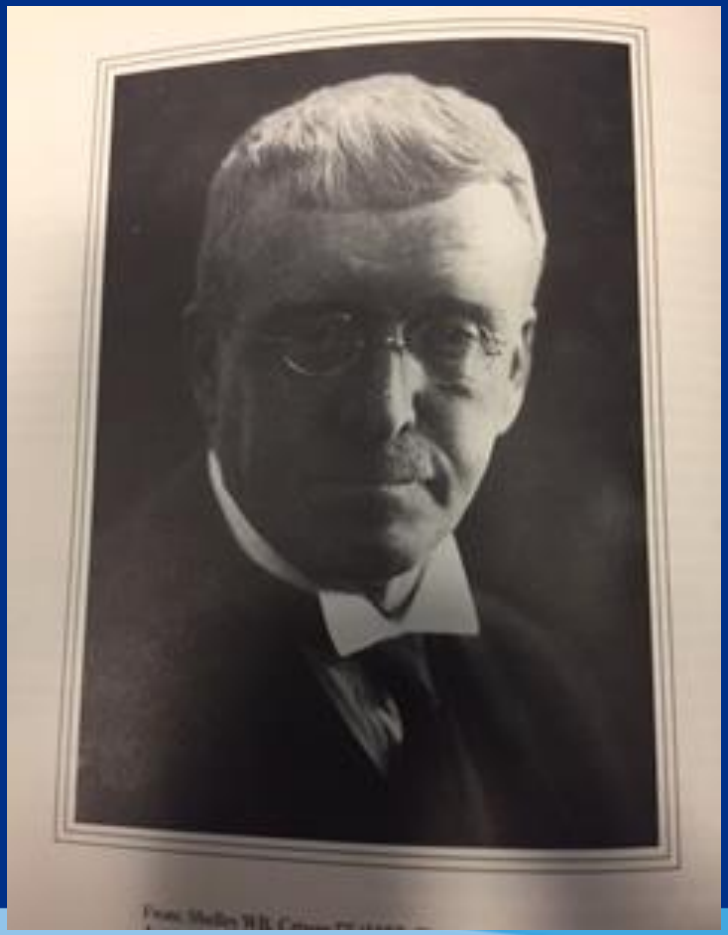
National Heart Lung and Blood Institute
People Science Health

PEDIATRIC HEART NETWORK

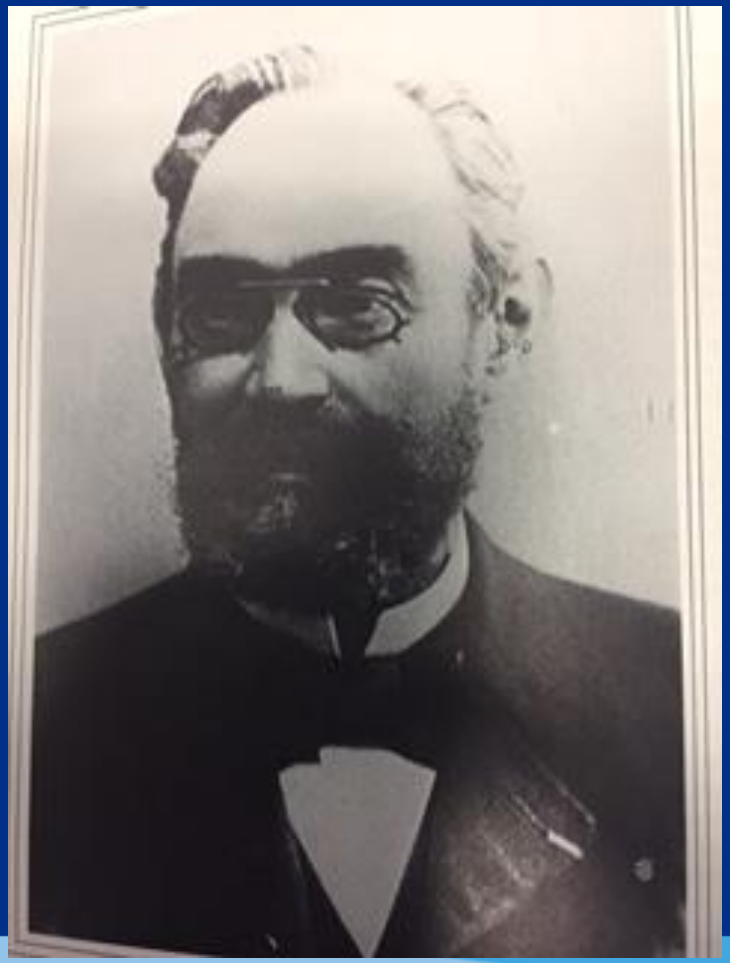
Loeys-Dietz Syndrome

- *TGFBR1*
- *TGFBR2*
- *TGFB2*
- *TGFB3*
- *SMAD3*
- *SMAD2*

Edvard Ehlers (1863-1937)



Henri-Alexandre Danlos (1844-1912)



Vascular Ehlers-Danlos Syndrome (vEDS)

- Mutations in *COL3A1*
- Major Diagnostic Criteria
  - Arterial aneurysms, dissection, or rupture
  - Intestinal rupture
  - Uterine rupture during pregnancy
  - Family history of vEDS

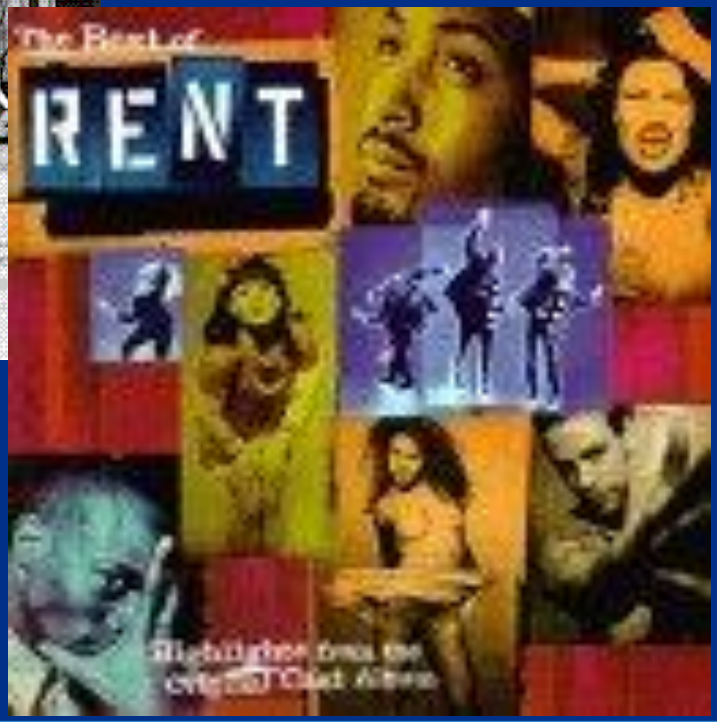
Vascular Ehlers-Danlos Syndrome

- Mutations in *COL3A1*
- Minor Diagnostic Criteria
  - Thin, translucent skin (especially noticeable on the chest/abdomen)
  - Characteristic facial appearance (thin vermilion of the lips, micrognathia, narrow nose, prominent eyes)
  - Acrogeria (an aged appearance to the extremities, particularly the hands)
  - Carotid-cavernous sinus arteriovenous fistula
  - Hypermobility of small joints
  - Tendon/muscle rupture
  - Early-onset varicose veins
  - Pneumothorax/hemopneumothorax
  - Easy bruising (spontaneous or with minimal trauma)
  - Chronic joint subluxations/dislocations
  - Congenital dislocation of the hips
  - Talipes equinovarus (clubfoot)

MFS, LDS, vEDS
General Characteristics

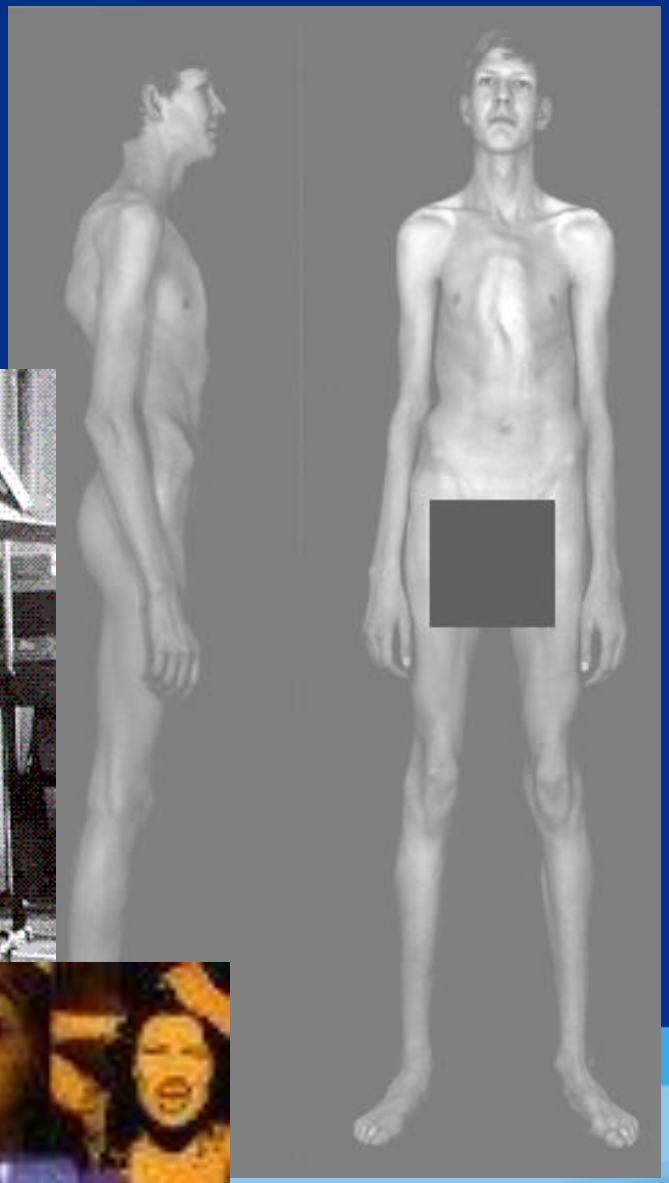
- **P**leiotropy
- **P**henotypic variation
- High **P**enetrance
- **P**rogression over time
- Early diagnosis allows **P**revention

Jonathan Larson



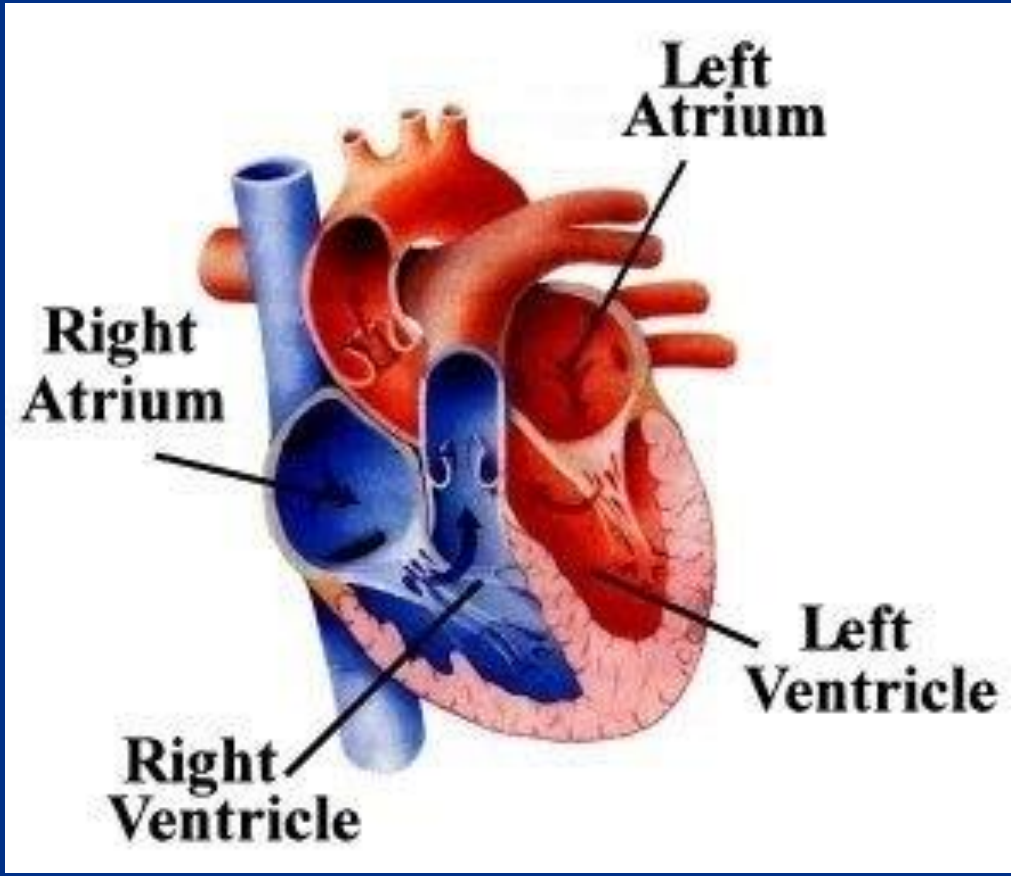
Died the day before his musical opened in 1996 of an aortic dissection after 2 days of chest pain and 2 visits to NYC ED

DIAGNOSIS ALLOWS PREVENTION

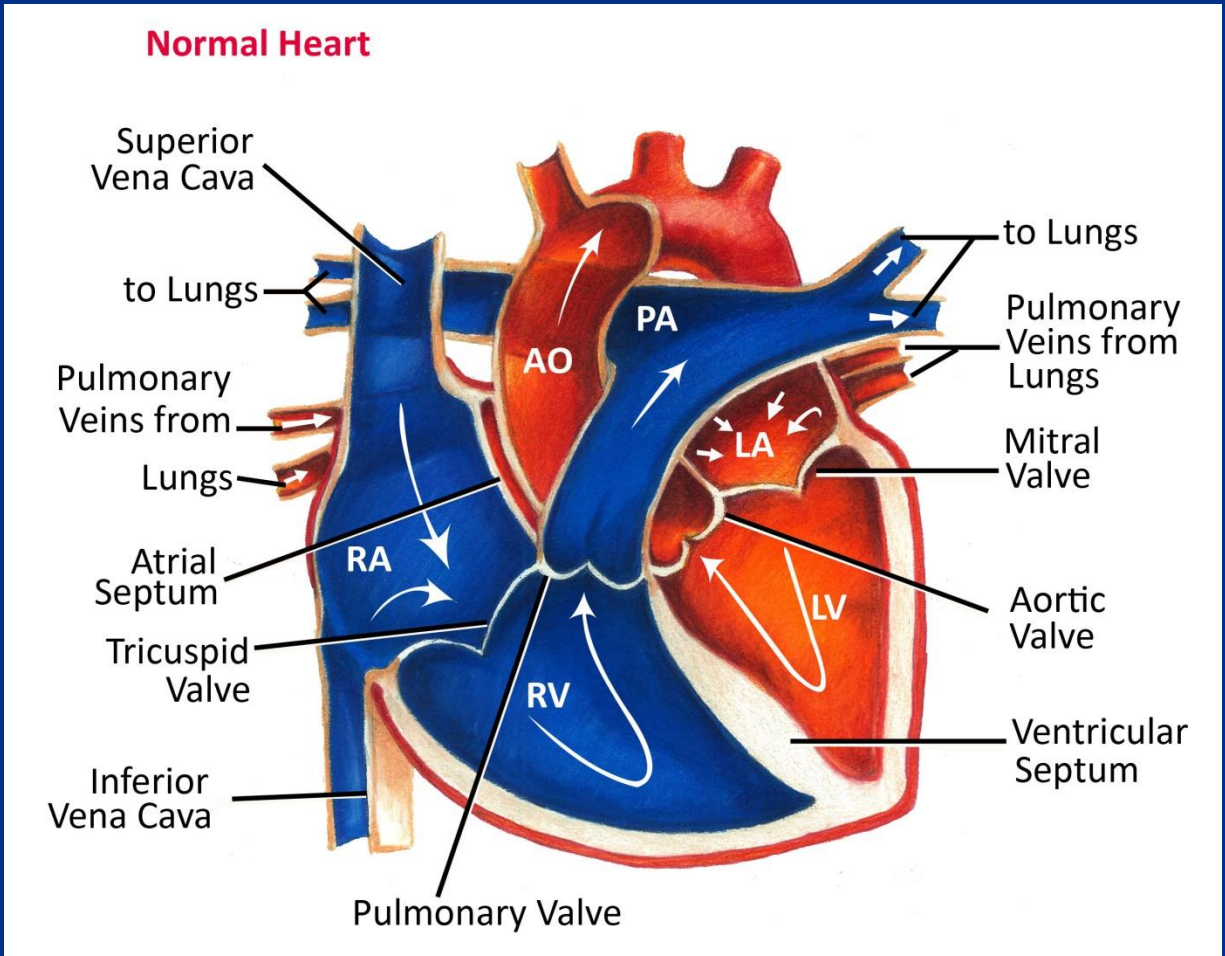


Basic Cardiac Anatomy

Basic Cardiac Anatomy



Basic Cardiac Anatomy

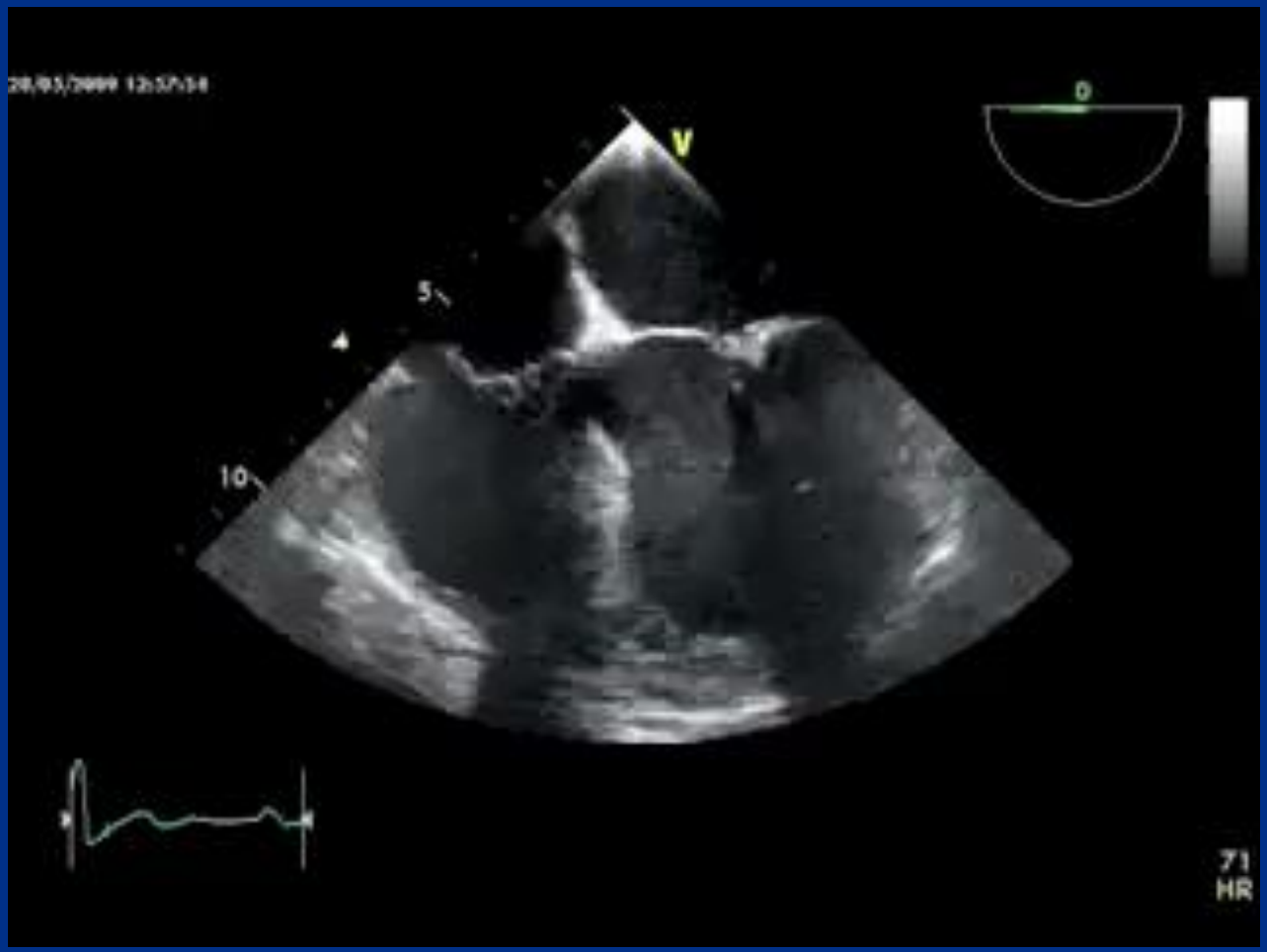


Common Cardiovascular Findings

Common Cardiovascular Findings

- Aortic enlargement/dilation, aneurysm, dissection; aortic regurgitation
- Mitral valve prolapse/mitral regurgitation
- Tricuspid valve prolapse/tricuspid regurgitation
- Left ventricular dilation, dysfunction
- Arterial Tortuosity
- Peripheral artery aneurysm, dissection
- Congenital heart disease (more common LDS)
  - Bicuspid aortic valve, Patent ductus arteriosus, others

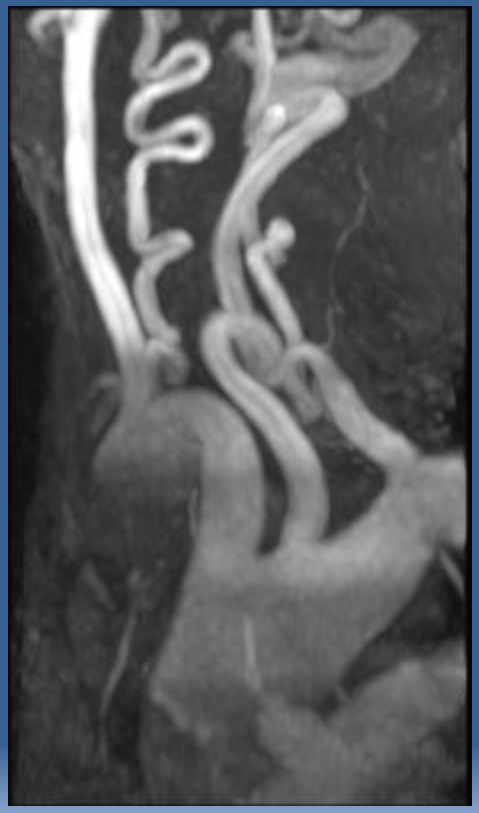
Mitral Valve Prolapse

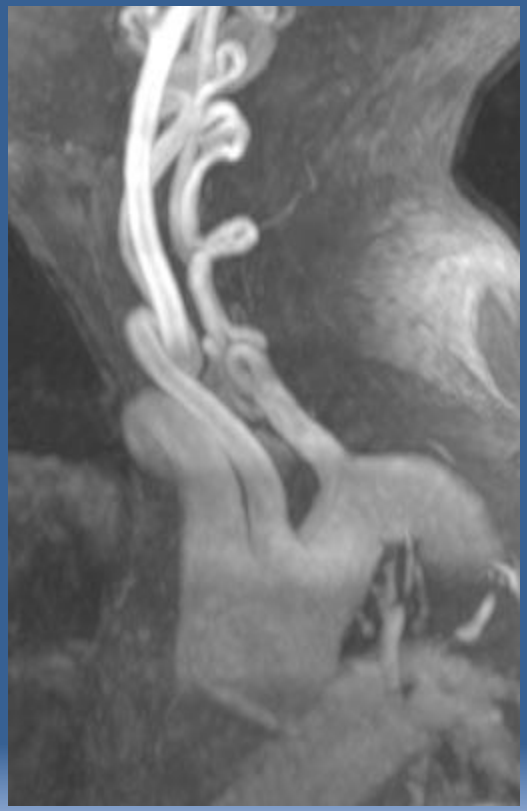


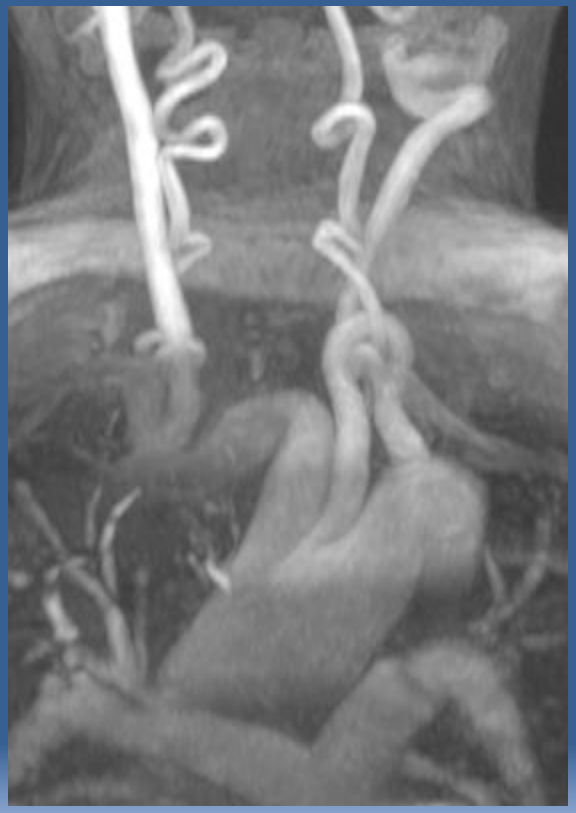
Common Cardiovascular Findings

- Aortic enlargement/dilation, aneurysm, dissection; aortic regurgitation
- Mitral valve prolapse/mitral regurgitation
- Tricuspid valve prolapse/tricuspid regurgitation
- Left ventricular dilation, dysfunction
- Arterial Tortuosity
- Peripheral artery aneurysm, dissection
- Congenital heart disease (more common LDS)
  - Bicuspid aortic valve, Patent ductus arteriosus, others

LDS: Aortic Arch and Head and Neck Vessels by MRI







National Heart Lung and Blood Institute
People Science Health

PEDIATRIC HEART NETWORK

Common Cardiovascular Findings

- Aortic enlargement/dilation, aneurysm, dissection; aortic regurgitation
- Mitral valve prolapse/mitral regurgitation
- Tricuspid valve prolapse/tricuspid regurgitation
- Left ventricular dilation, dysfunction
- Arterial Tortuosity
- Peripheral artery aneurysm, dissection
- Congenital heart disease (more common LDS)
  - Bicuspid aortic valve, Patent ductus arteriosus, others

Imaging Techniques

Imaging Techniques

- Echocardiography/Ultrasound
  - Echocardiogram/Sonogram
  - Good visualization of the heart, aortic root, blood vessels close to heart
  - Quality of imaging dependent on age, body size, skeletal issues, motion
  - Widely available, easy to perform, well tolerated
  - Best for initial diagnosis and ongoing management

Imaging Techniques

- Echocardiography/Ultrasound
  - Echocardiogram/Sonogram
  - Good visualization of the heart, aortic root, blood vessels close to heart
  - Quality of imaging dependent on age, body size, skeletal issues, motion
  - Widely available, easy to perform, well tolerated
  - Best for initial diagnosis and ongoing management
- CT (computerized tomography)
  - CT scan
  - Excellent visualization of all blood vessels, including tortuosity and dissection
  - Widely available, quick, well tolerated
  - Radiation exposure is less with modern scanners
  - Best in an emergency situation when dissection is the question

Imaging Techniques

- Echocardiography/Ultrasound
  - Echocardiogram/Sonogram
  - Good visualization of the heart, aortic root, blood vessels close to heart
  - Quality of imaging dependent on age, body size, skeletal issues, motion
  - Widely available, easy to perform, well tolerated
  - Best for initial diagnosis and ongoing management
- CT (computerized tomography)
  - CT scan
  - Excellent visualization of all blood vessels, including tortuosity
  - Widely available, quick, well tolerated
  - Radiation
  - Best in an emergency situation when dissection is the question

- MRI (magnetic resonance imaging)
  - MRI scan
  - Excellent visualization of heart and all blood vessels, including tortuosity and dissection
  - Less widely available, takes a lot longer than a CT scan
  - No radiation
  - Best for long-term follow-up, peripheral vessels, and when echo images not adequate

Imaging Techniques

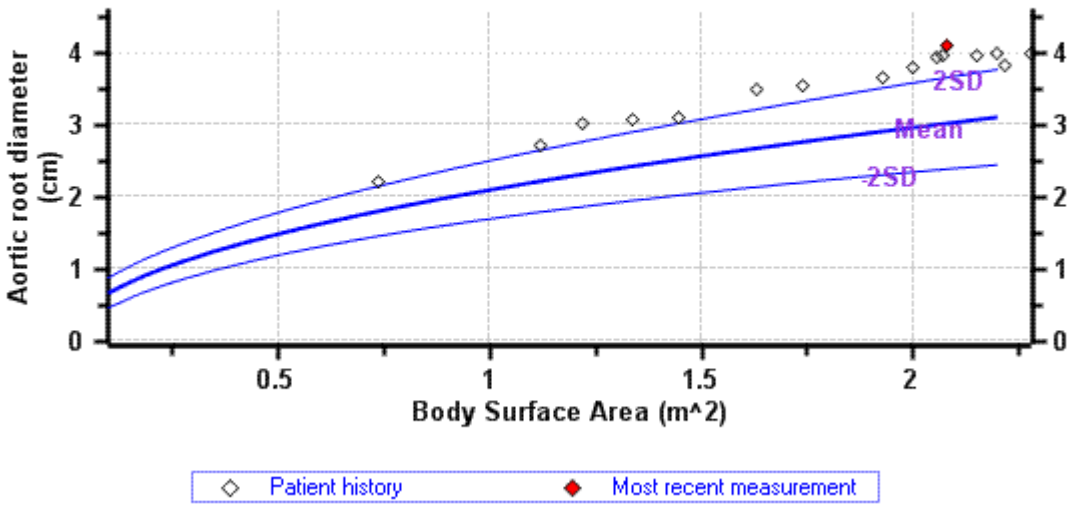
- Echocardiography/Ultrasound
- CT (computerized tomography)
- MRI (magnetic resonance imaging)

- Usually a combination of imaging modalities
- Important to have measurements done in a consistent fashion, ideally in a single center with lots of experience with patients with connective tissue conditions
- Important to compare to prior studies and follow trends over time

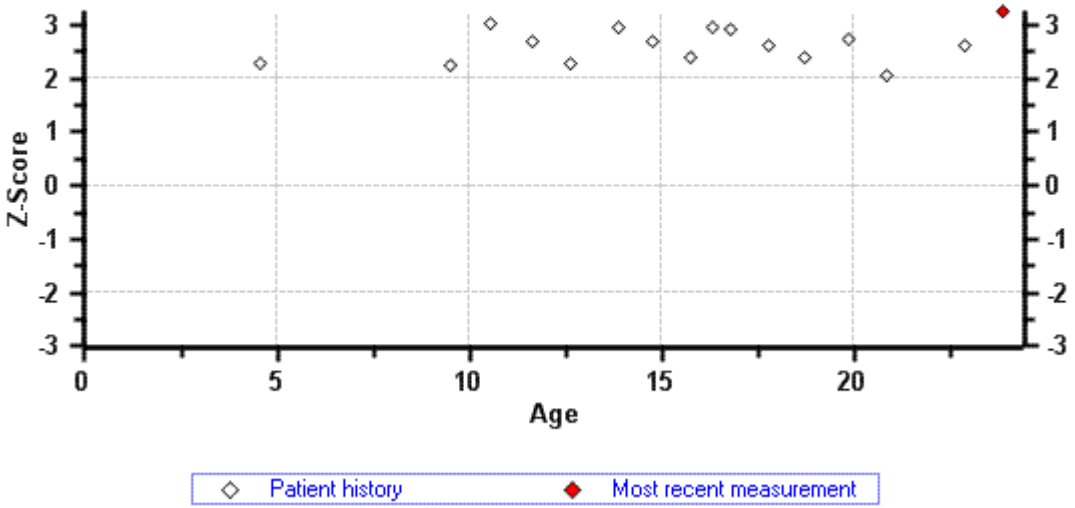
Following the Aorta in Connective Tissue Conditions

- In adults, medical and surgical decisions based on absolute dimension
- In growing children, there are limitations to using absolute dimension alone
- What should the aortic size be for any given body size?
- Using aortic-root diameter z-score (ARz), adjusted for BSA, allows us to assess severity and progression over time
- If the z-score stays the same, the aorta is growing in proportion to the rest of the body

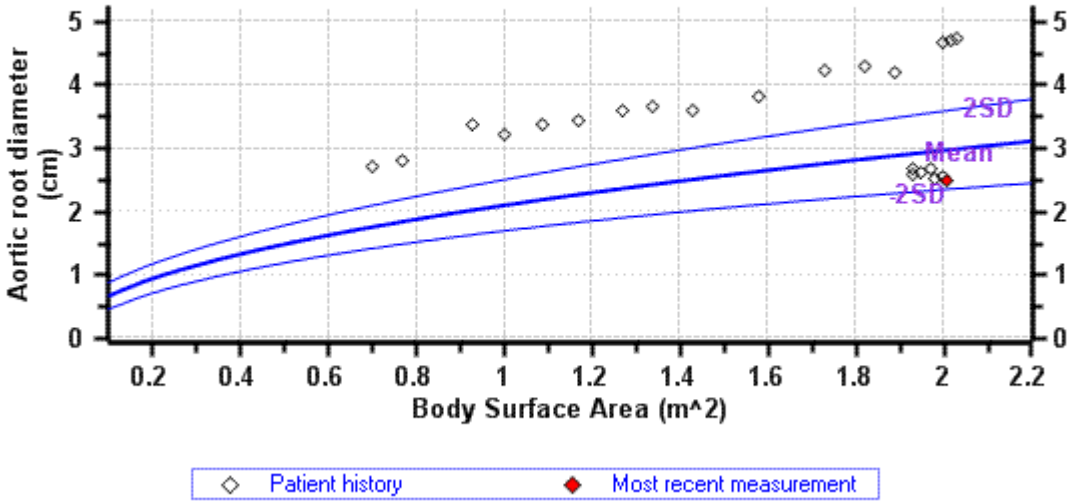
Aortic root diameter vs BSA



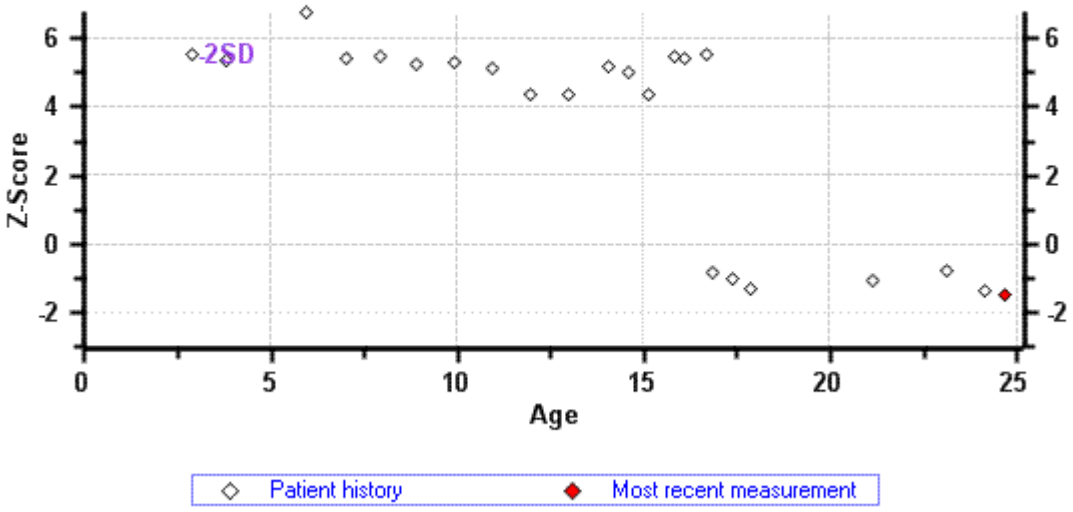
Z-Score vs Age



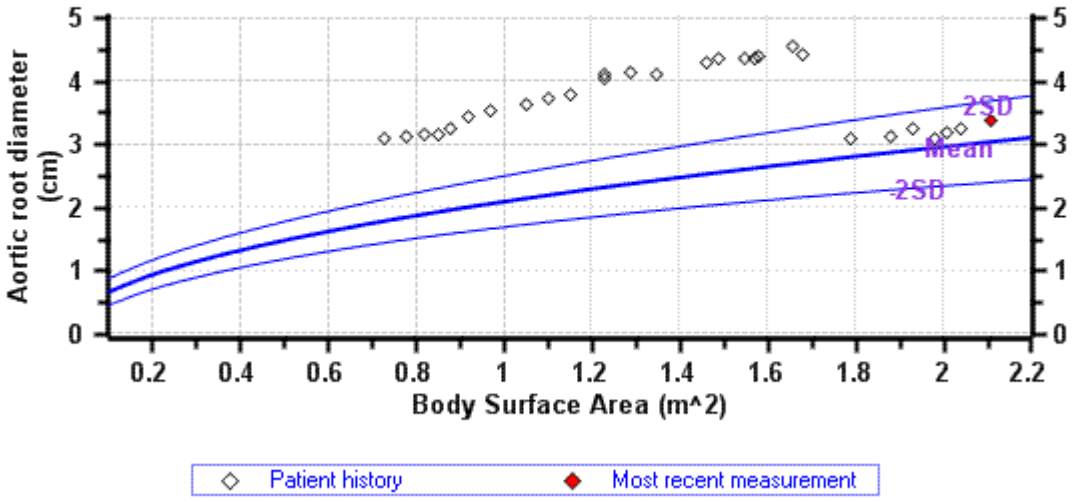
Aortic root diameter vs BSA



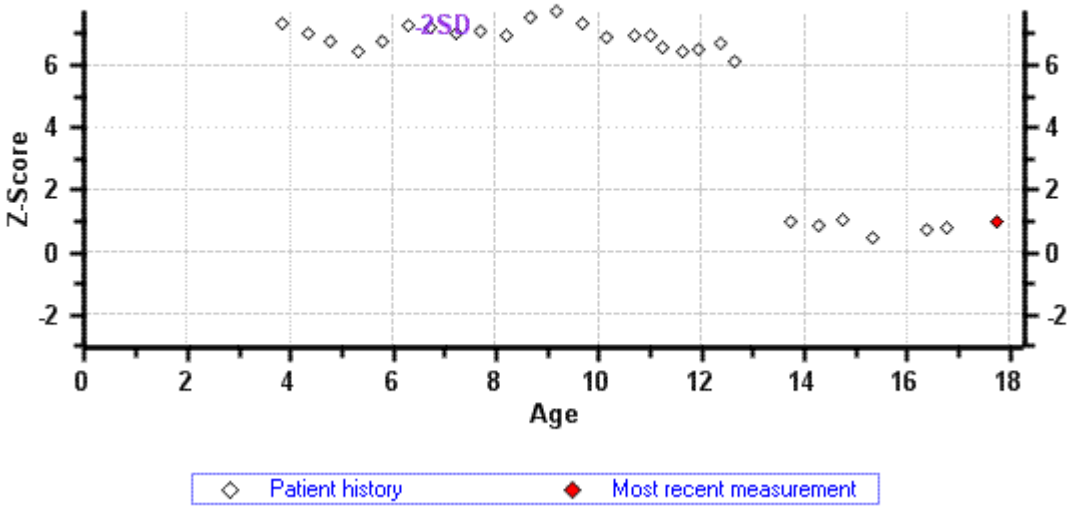
Z-Score vs Age

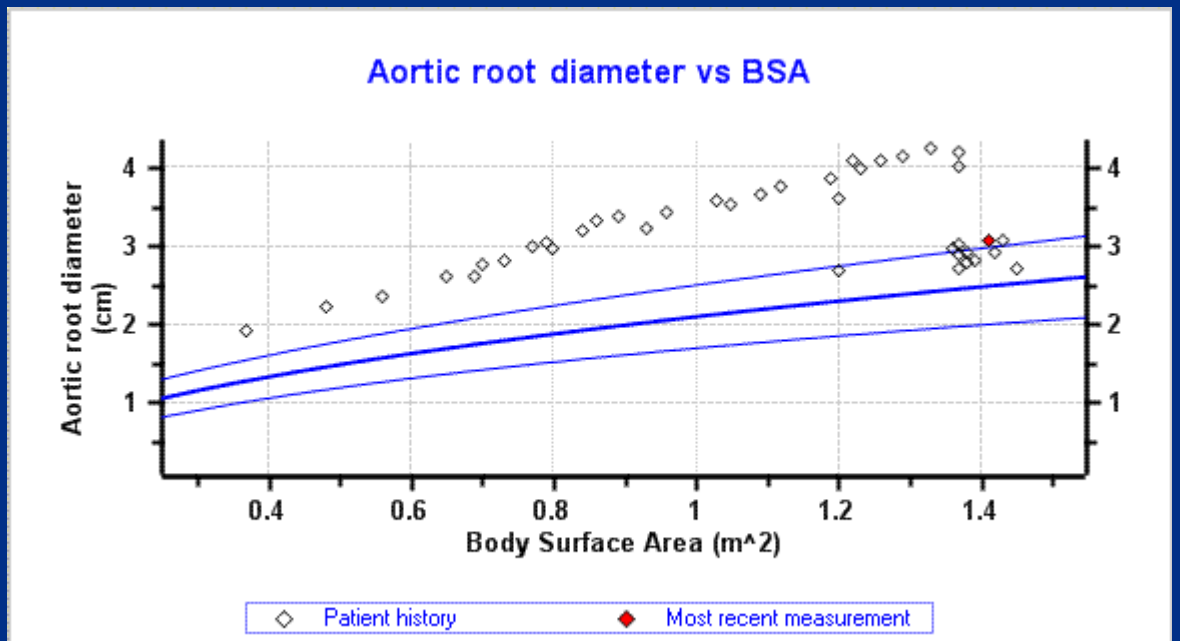


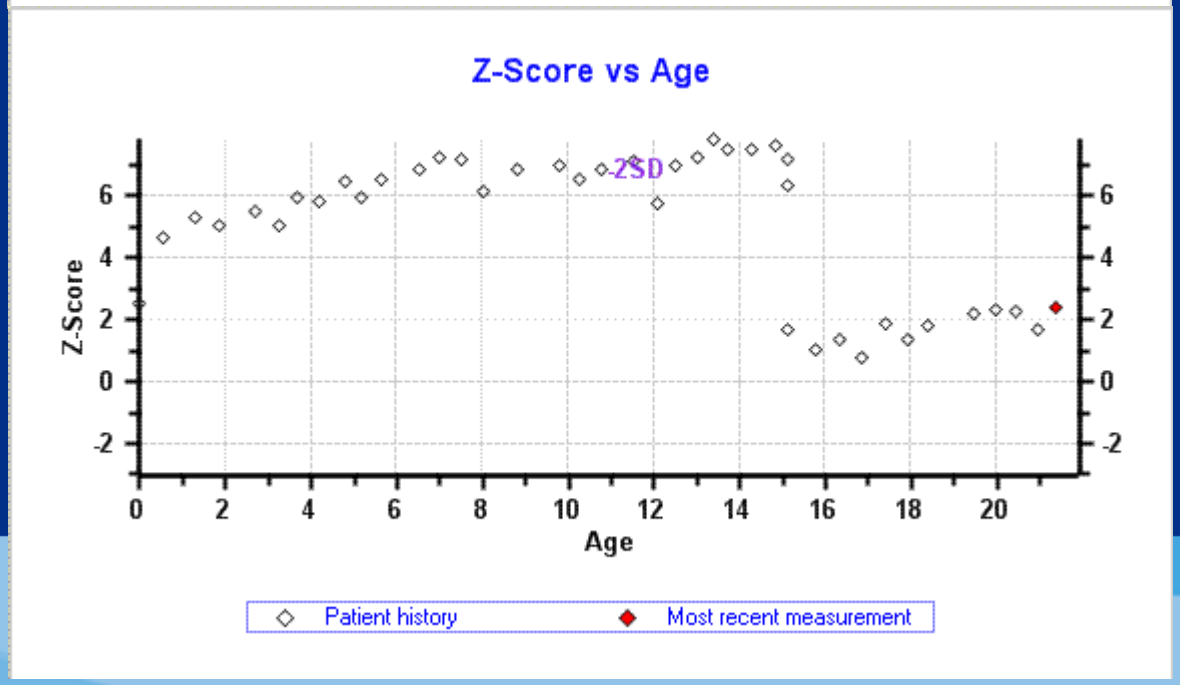
Aortic root diameter vs BSA

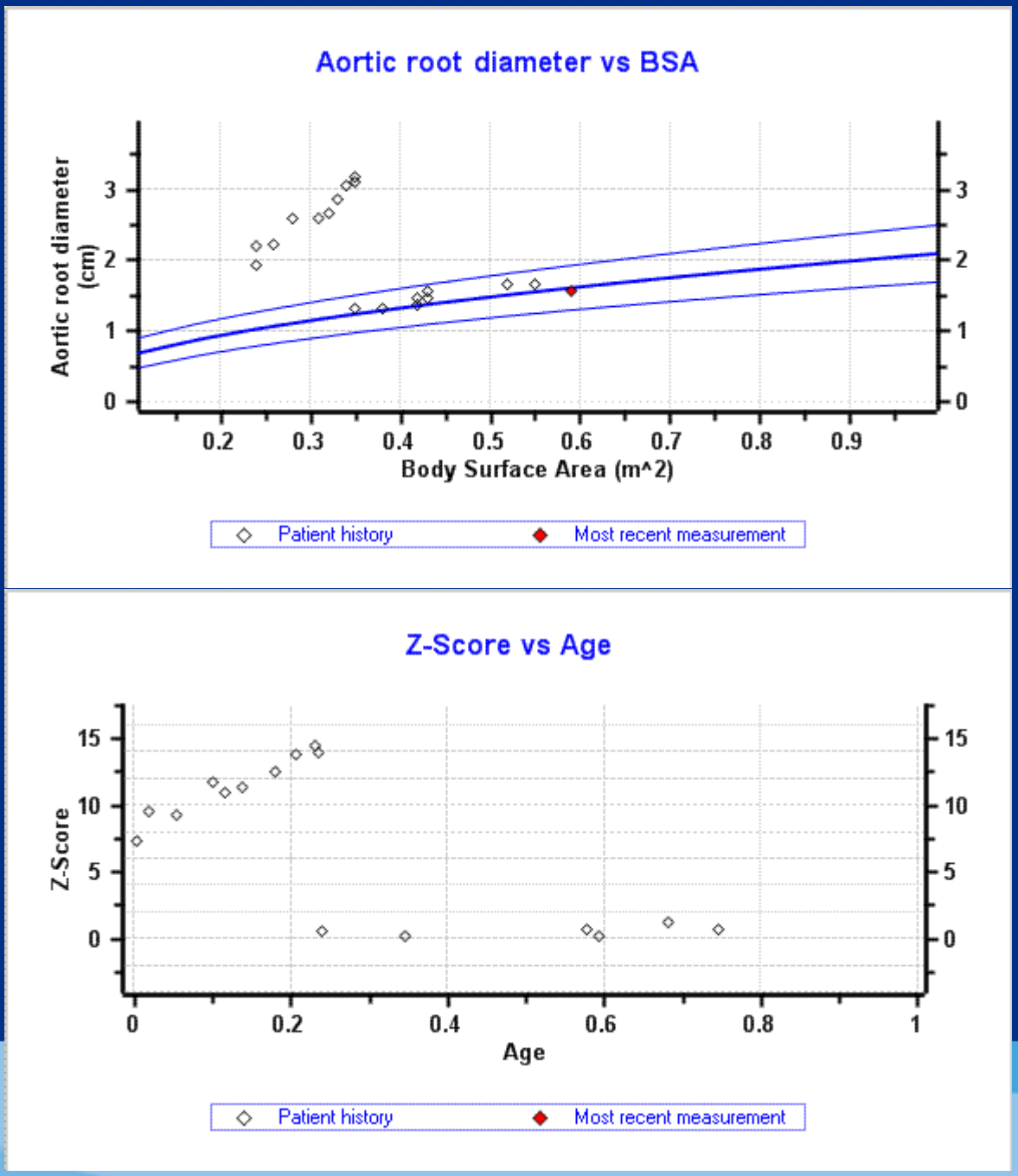


Z-Score vs Age




Aortic root diameter vs BSA
Aortic root diameter (cm)
4
3
2
1
0.4
0.6
0.8
1
1.2
1.4
Body Surface Area (m^2)
Patient history
Most recent measurement


Z-Score vs Age
Z-Score
6
4
2
0
-2
2SD
0
2
4
6
8
10
12
14
16
18
20
Age
Patient history
Most recent measurement


Aortic root diameter vs BSA
Aortic root diameter (cm)
0
1
2
3
0.2
0.3
0.4
0.5
0.6
0.7
0.8
0.9
Body Surface Area (m^2)
Patient history
Most recent measurement
Z-Score vs Age
Z-Score
0
5
10
15
0
0.2
0.4
0.6
0.8
1
Age
Patient history
Most recent measurement

Clinical Observations Related to Aortic Root z-score

- z-score ≥ 7 is uncommon
- z-scores are stable over time (or slowly increase) in vast majority
- For MFS and LDS syndromes, we expect the aortic root z-score to stay the same or slowly increase or many years
- In growing children, despite stable z-score, aorta continues to get bigger

Medical Therapy

Medical Therapy

- Beta-blockers (beta-adrenergic receptor blockers) ["–olol"]
  - atenolol, betaxolol, bisoprolol, celiprolol, esmolol, labetabol, metoprolol, nadolol, nebivolol, propranolol
  - blocks the effects of adrenalin or epinephrine
  - lowers heart rate and blood pressure
- Angiotensin II receptor blockers ["-sartan"]
  - azilsartan, candesartan, eprosartan, irbesartan, losartan, olmesartan, telmisartan, valsartan
  - blocks the action of angiotensin II
  - relaxes blood vessels and lowers blood pressure

Randomized Trial of Atenolol Versus Losartan in Children and Young Adults with Marfan Syndrome

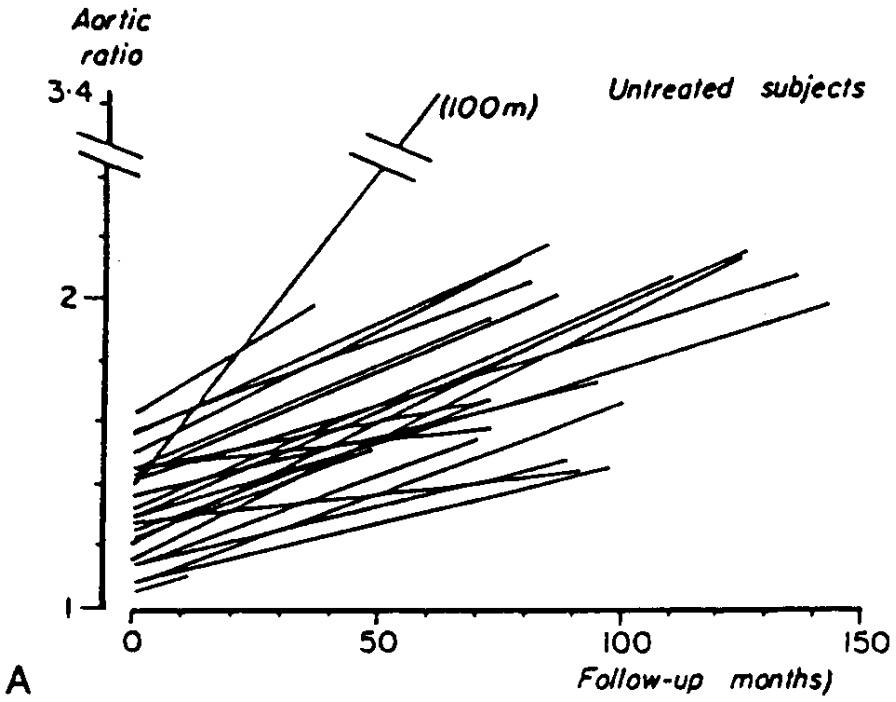
Ronald V. Lacro, Harry C. Dietz, Lynn A. Sleeper, Anji T. Yetman, Timothy J. Bradley, Steven D. Colan, Gail D. Pearson, Elif Seda Selamet Tierney, Jami C. Levine, Andrew M. Atz, D. Woodrow Benson, Alan C. Braverman, Shan Chen, Julie De Backer, Bruce D. Gelb, Paul D. Grossfeld, Gloria L. Klein, Wyman W. Lai, Aimee Liou, Bart L. Loeys, Larry W. Markham, Aaron K. Olson, Stephen M. Paridon, Victoria L. Pemberton, Mary Ella Pierpont, Reed E. Pyeritz, Elizabeth Radojewski, Mary J. Roman, Angela M. Sharkey, Mario P. Stylianou, Stephanie Burns Wechsler, Luciana T. Young, Lynn Mahony for the Pediatric Heart Network Investigators

NIH National Heart, Lung, and Blood Institute

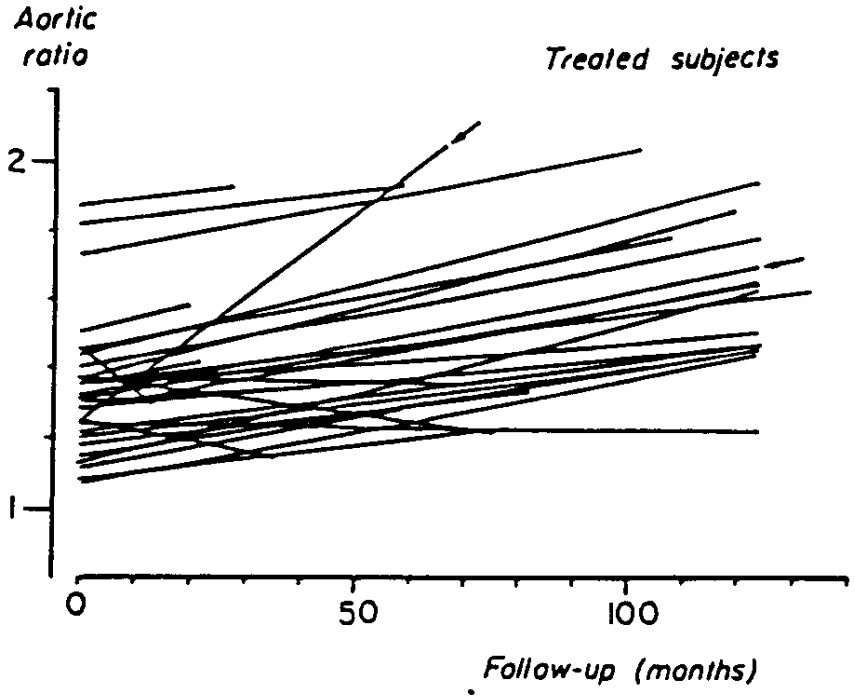
PEDIATRIC HEART NETWORK

Therapy for Marfan Syndrome

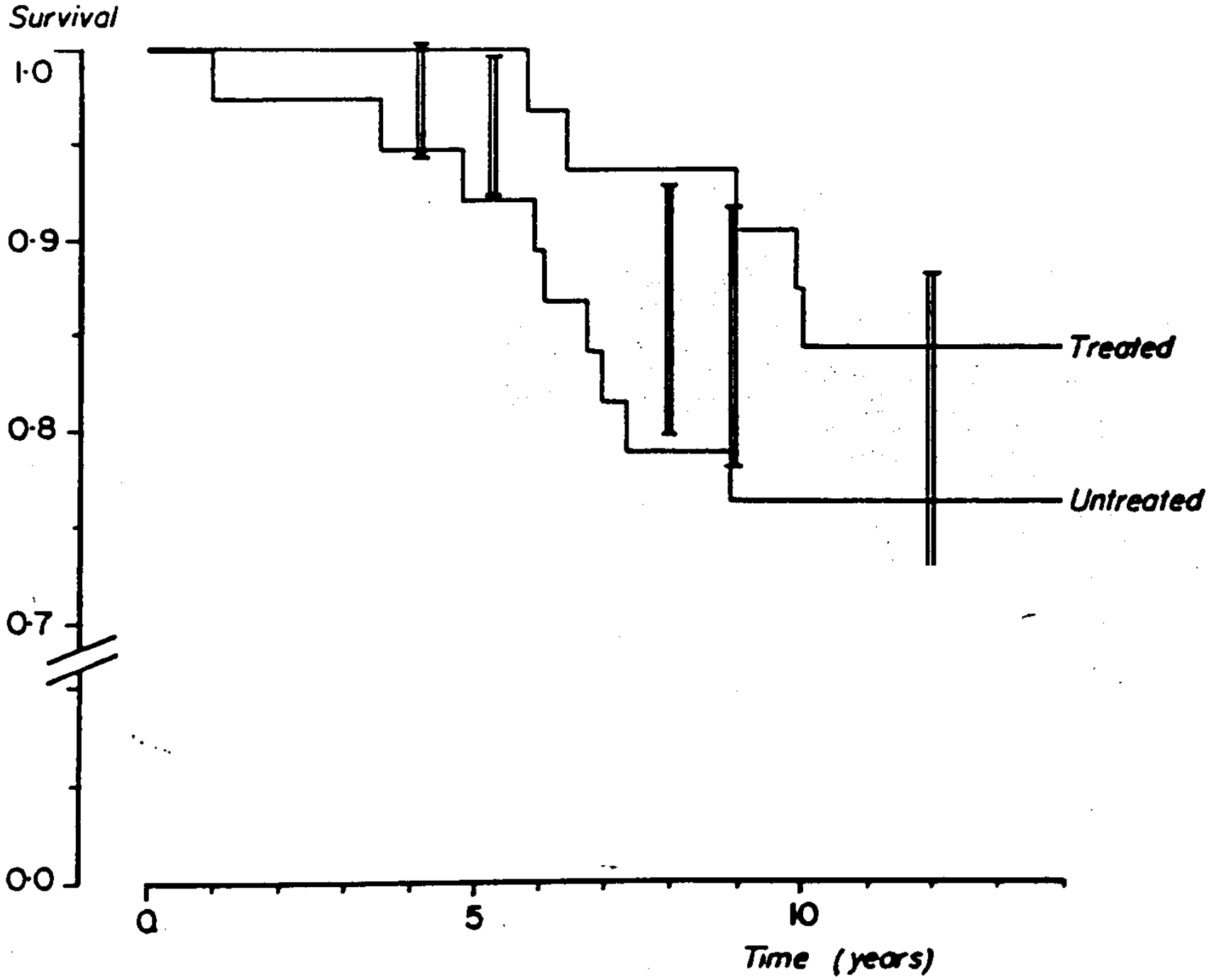
- β-blockers common medical management (Shores et al, NEJM 1994)
- Excessive TGF-β signaling thought to contribute to MFS manifestations
- Losartan may attenuate TGF-β signaling and may be more effective in slowing aortic-root enlargement than β-blockers.



A



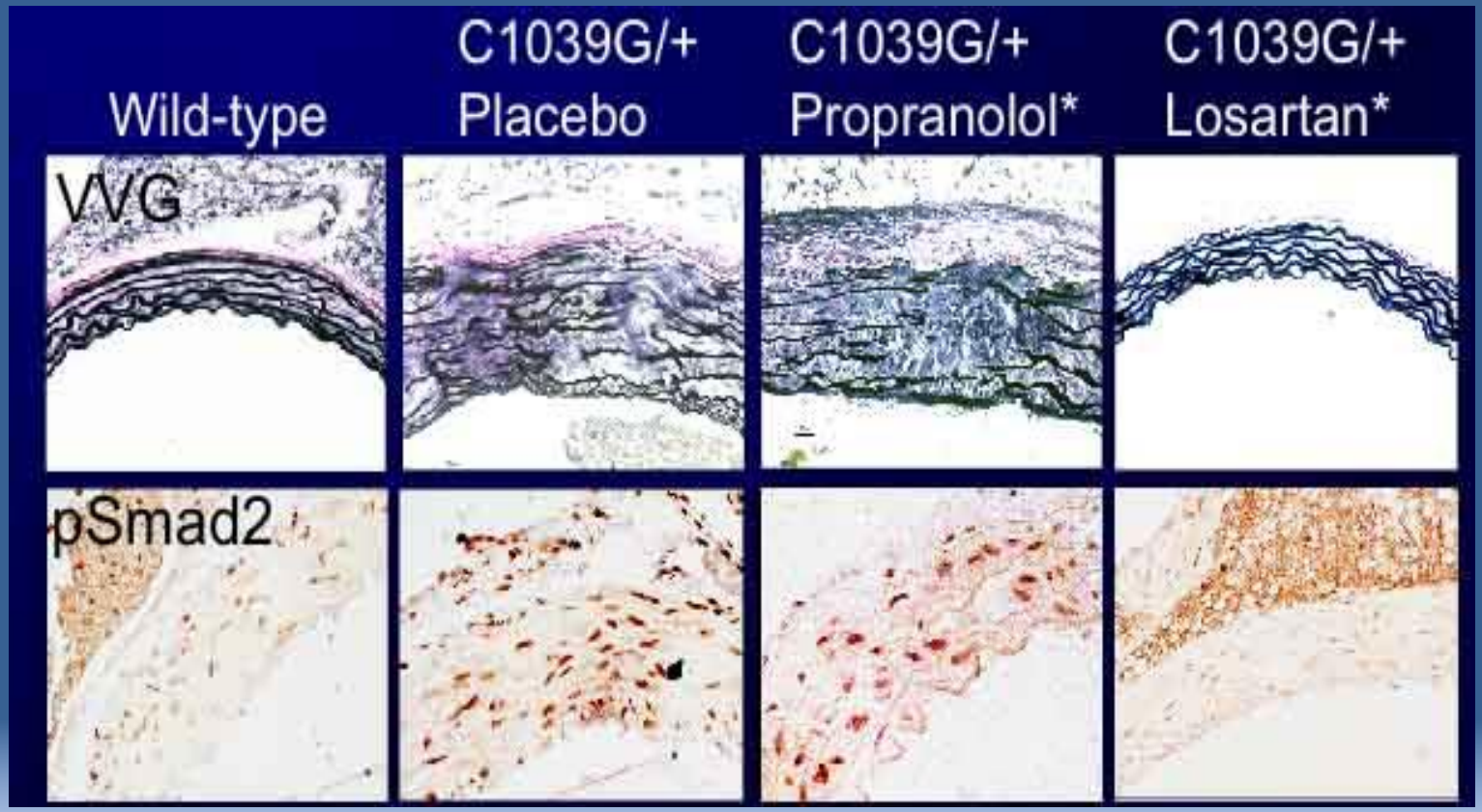
B


Survival
1·0
0·9
0·8
0·7
0·0
0
5
10
Time (years)
Treated
Untreated

Background

- After Shores et al (1994), beta-blockers became the mainstay of medical management at most centers.
- Excessive TGF-B activation and signaling are now thought to contribute to the pleiotropic MFS manifestations, including aortic root dilation and dissection.
- Recent studies suggest that losartan may be more effective in slowing aortic root enlargement than B-blockers

Losartan rescues aortic wall architecture



Habashi et al. Science 312:117-21, 2006.

National Heart Lung and Blood Institute
People Science Health

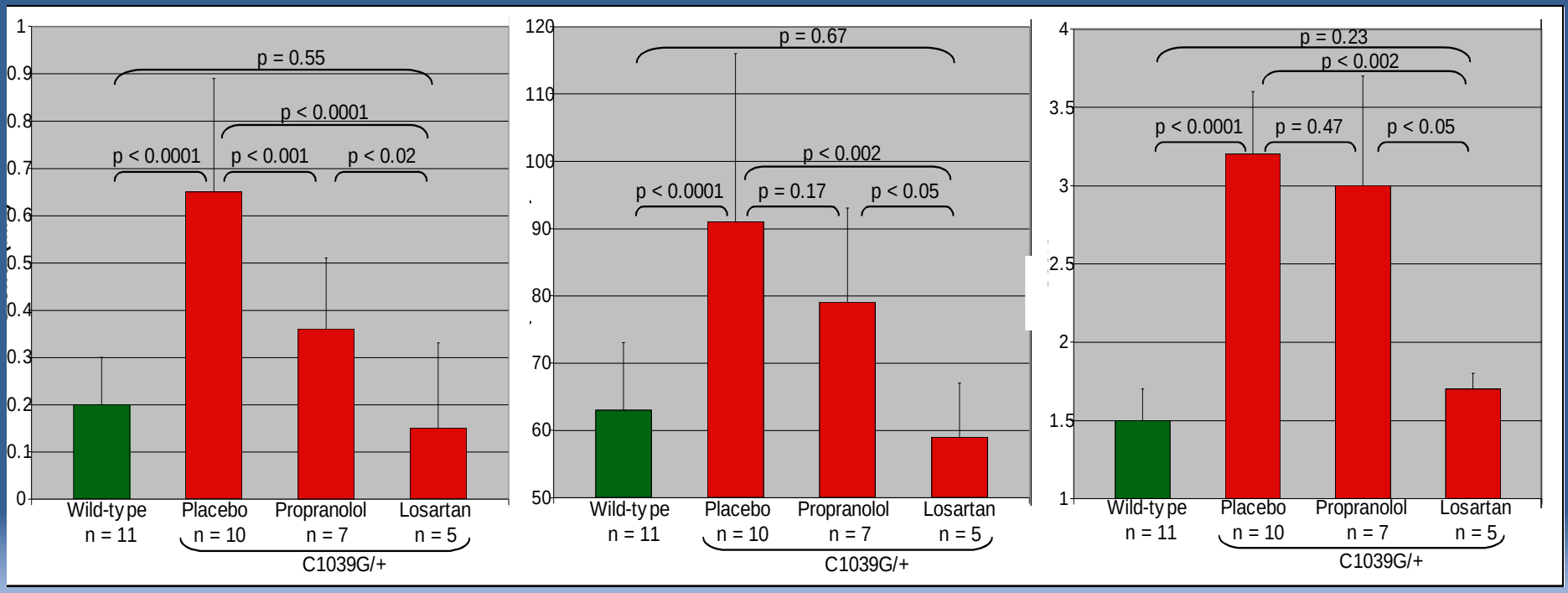
PEDIATRIC HEART NETWORK

Losartan rescues aortic root performance

Aortic root growth (mm/6 months)

Aortic wall thickness (micrometers)

Aortic wall architecture (score 1-4)



National Heart Lung and Blood Institute
People Science Health

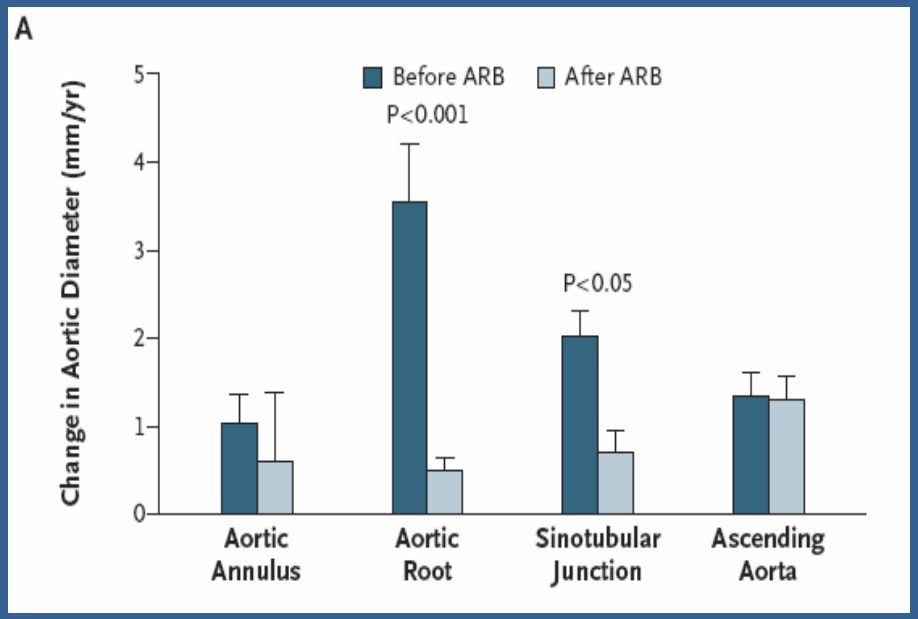
Habashi et al. Science 312:117-21, 2006.

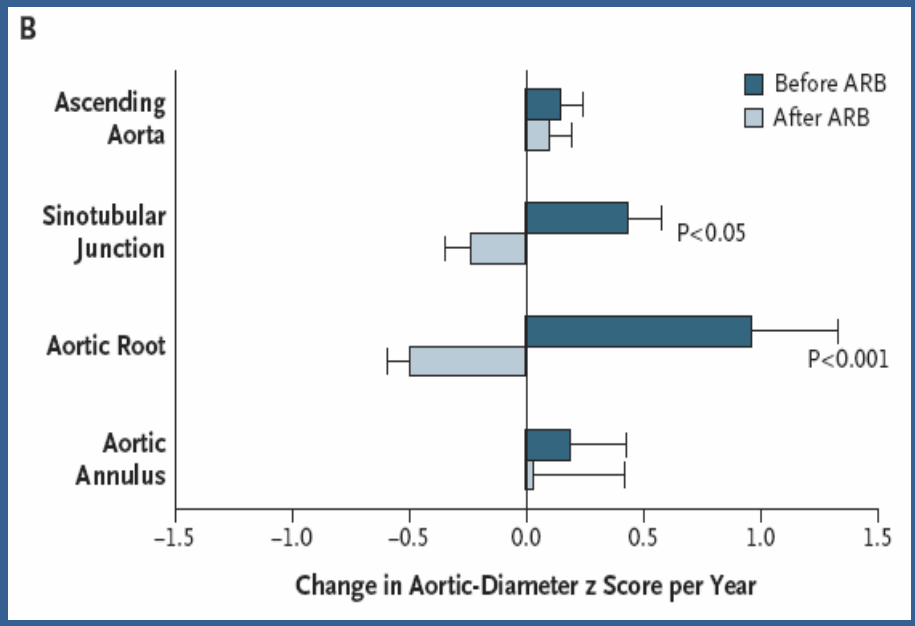
PEDIATRIC HEART NETWORK

ARB in Children with Severe MFS Brooke et al, NEJM 2008

- Non-randomized, open label
- Aortic root growth rate (Change in Z-score) before and after ARB
- N=18; losartan 17, irbesartan 1
- All failed other therapy
- Median age 6.5 yr (range 1 – 16 yr)
- Follow-up 12 – 47 months
- Dramatic reduction in aortic root growth rate

Losartan in children with severe MFS





Angiotensin II Blockade and Aortic-Root Dilation in Marfan's Syndrome

Benjamin S. Brooke, M.D., Jennifer P. Habashi, M.D., Daniel P. Judge, M.D., Nishant Patel, B.A., Bart Loeys, M.D., Ph.D., and Harry C. Dietz III, M.D.

N Engl J Med 2008;358:2787-95.

National Heart Lung and Blood Institute
People Science Health

PEDIATRIC HEART NETWORK

Specific Aim/Primary End Point

- **Purpose: To compare effect of atenolol to that of losartan on aortic-root growth in MFS over 3 years**
- **Hypothesis: Rate of aortic growth will be lower in those receiving losartan than in those receiving atenolol**
- **Primary end point: Rate of change in BSA-adjusted maximum aortic-root diameter z-score (ARz)**

Secondary Endpoints

- Rate of change in aortic-root absolute diameter
- Adverse clinical outcomes:
  - Aortic dissection
  - Aortic-root surgery
  - Death
  - Composite end point
- Adverse events and subject-reported symptoms

Inclusion Criteria

- Age 6 months to 25 years
- Diagnosis of MFS by original Ghent criteria
- ARz > 3.0

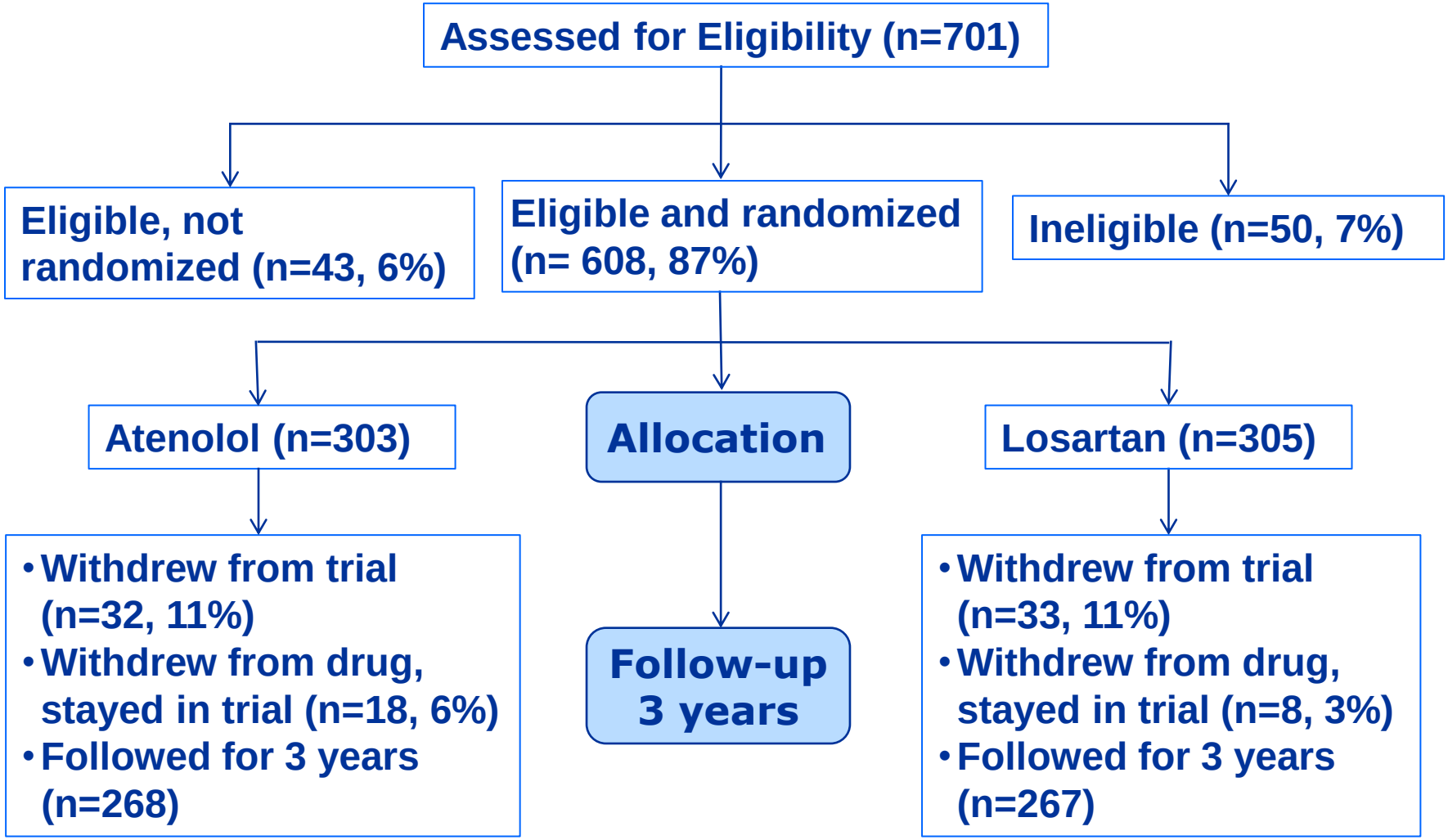
Exclusion Criteria

- Prior or impending aortic surgery
- Aortic-root diameter > 5 cm
- Aortic dissection
- Loeys-Dietz or Sphrintzen-Goldberg syndromes
- Therapeutic use of ACE-I, BB, or ARB
- Intolerance or contraindication to BB or ARB

Study Design

- Randomization to atenolol or losartan stratified
  - Growing children vs. adult (♂≥16 yr, ♀≥15 yr)
  - Baseline ARz <4.5 vs. ≥4.5
- Dynamic allocation within each of 21 centers
- Atenolol
  - Maximum dose of 4 mg/kg/day (max 250 mg)
  - Goal of ≥20% decrease in mean heart rate by 24-hr recording
- Losartan
  - Maximum dose of 1.4 mg/kg/day (max 100 mg), as recommended by FDA

Screening, Randomization, and Follow-up



Baseline Characteristics

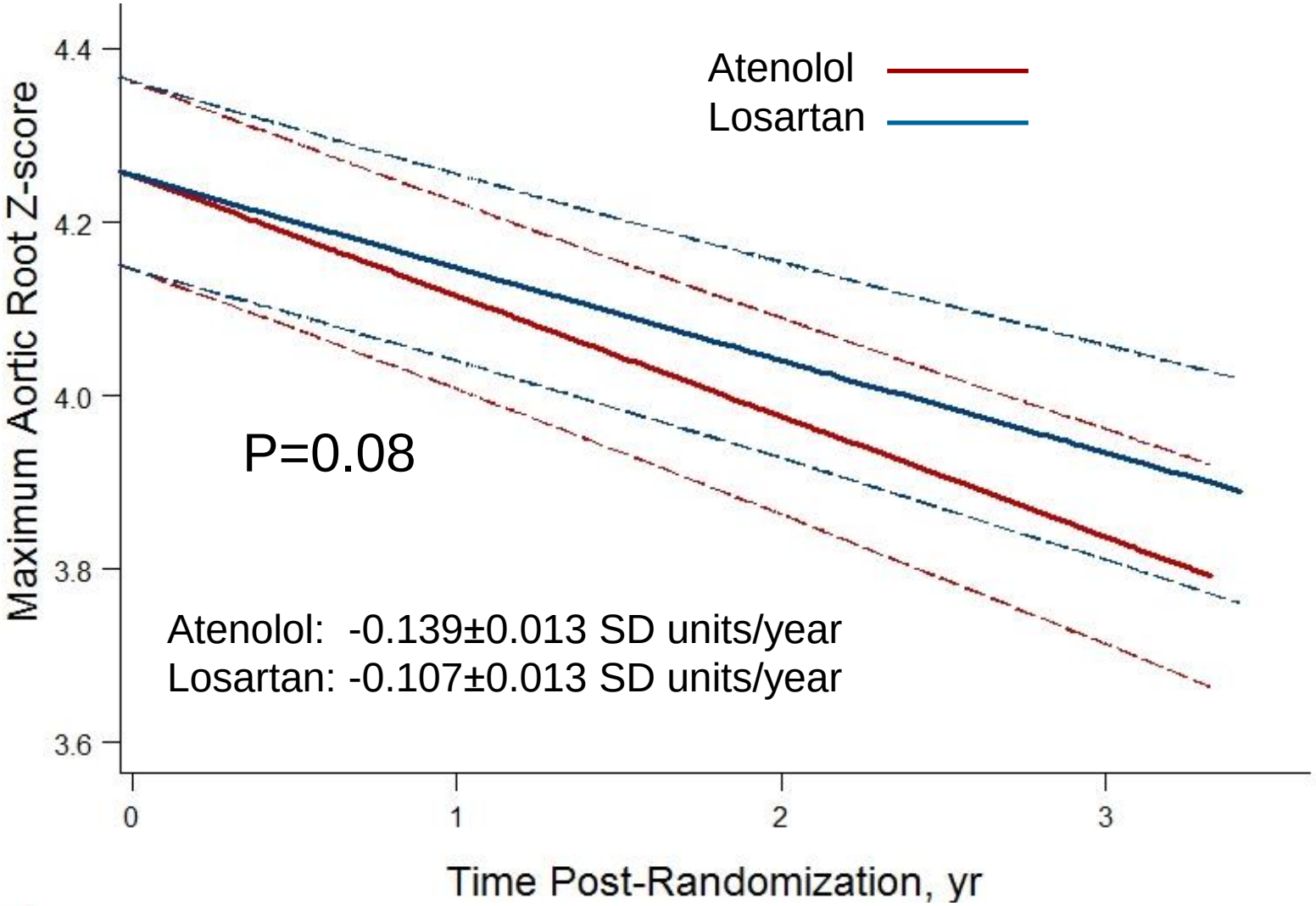
Characteristic	Atenolol (n=303)	Losartan (n=305)
Age at randomization, yr	11.5±6.5	11.0±6.2
Adult (♂≥16 yr, ♀≥15 yr)	76 (25%)	75 (25%)
Male	180 (59%)	186 (61%)
Max. aortic-root diameter, cm	3.4±0.7	3.4±0.7
Max. aortic-root diameter z-score	4.0 (3.5, 4.8)	4.0 (3.3, 5.0)
Prior use of beta-blocker	173 (57%)	171 (56%)

Prescribed Doses of Study Medications

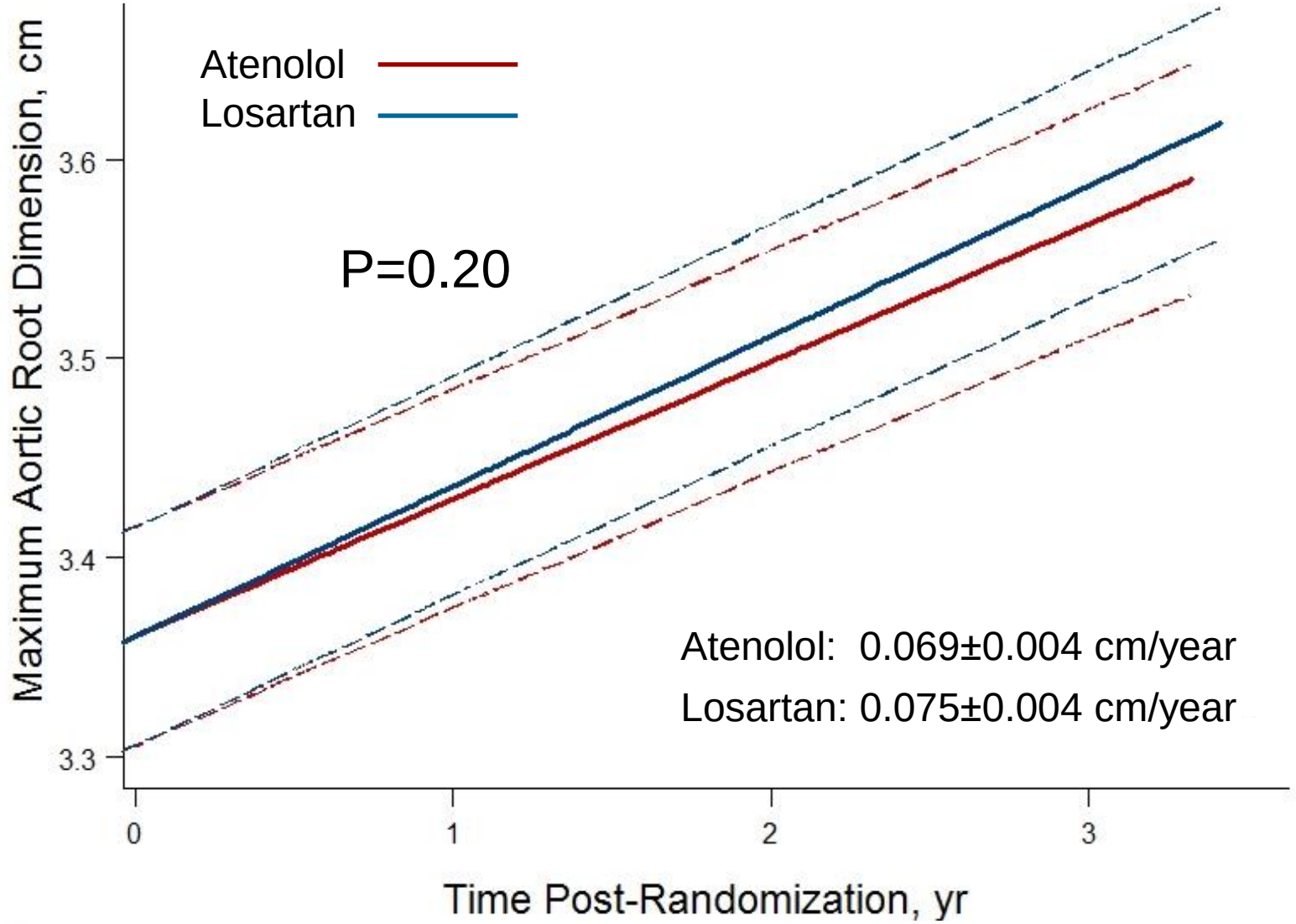
	Atenolol (mg/kg/d)	Losartan (mg/kg/d)
All	2.7±1.1	1.3±0.2
Children	2.8±1.0	1.3±0.2
Adults	2.3±1.2	1.2±0.2

Absolute doses for adults (mg/d):
Atenolol 151±75 mg
Losartan 85±14 mg

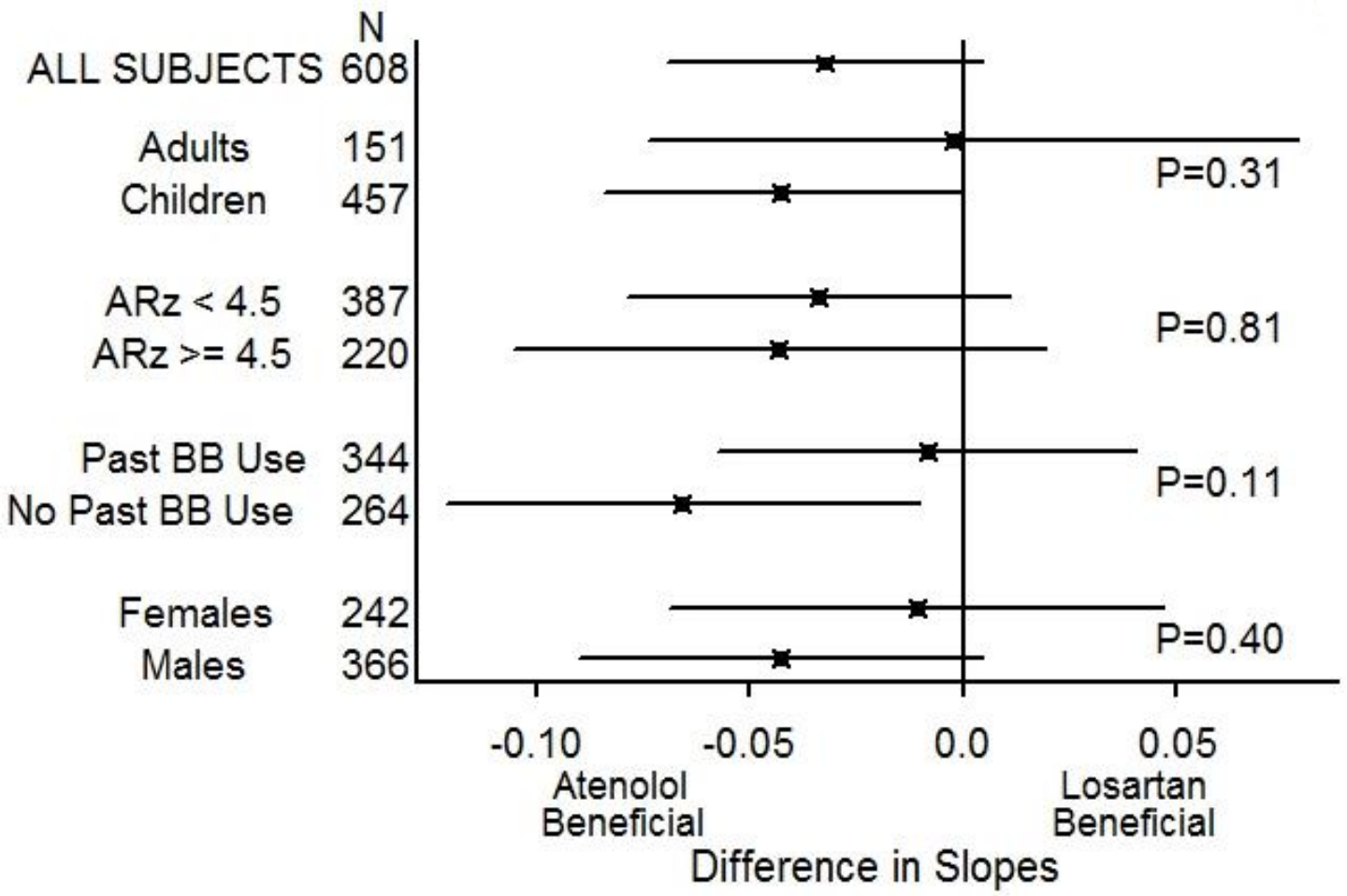
Estimated Rate of Change in ARz



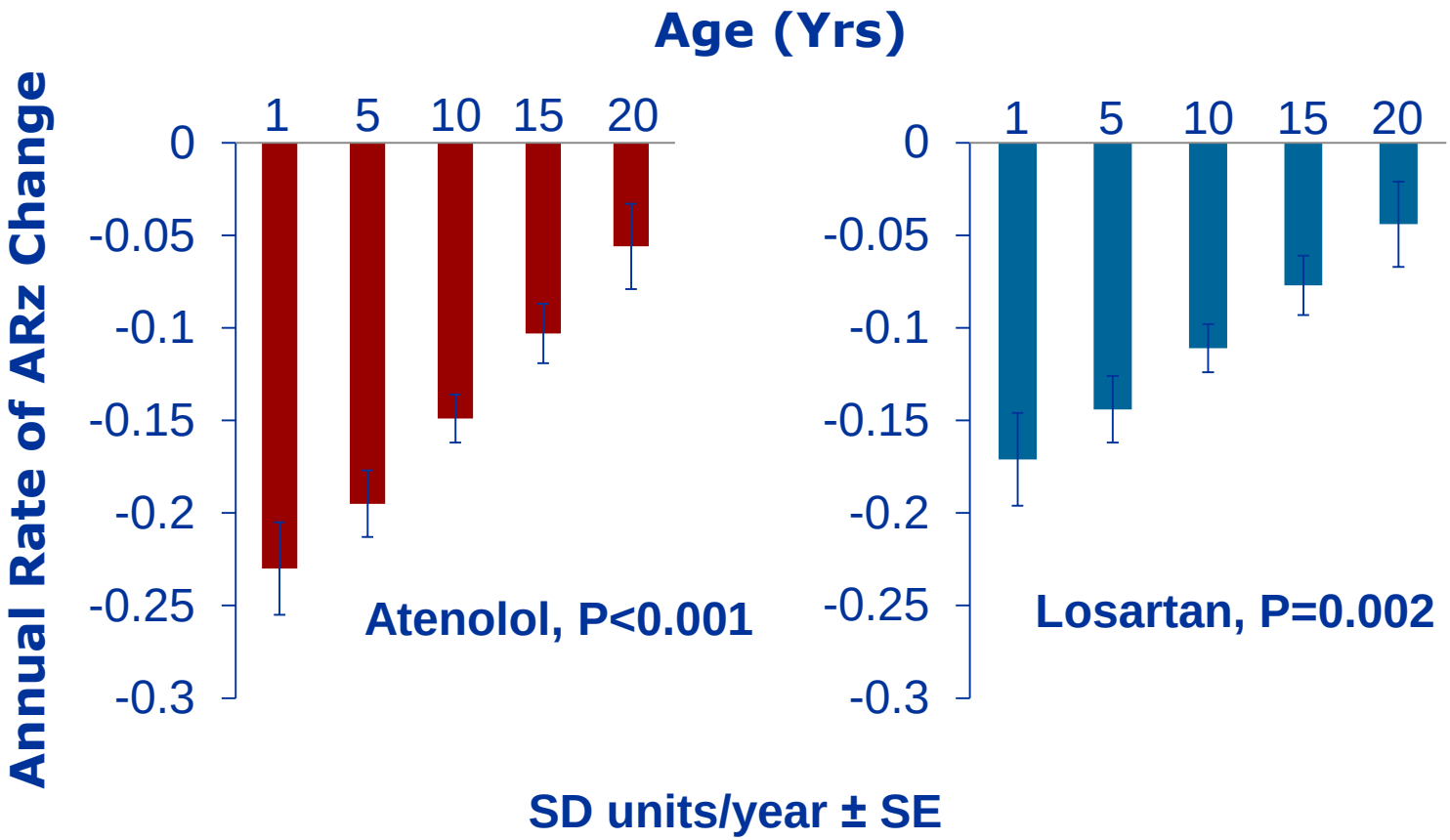
Estimated Rate of Change in Aortic-Root Absolute Diameter



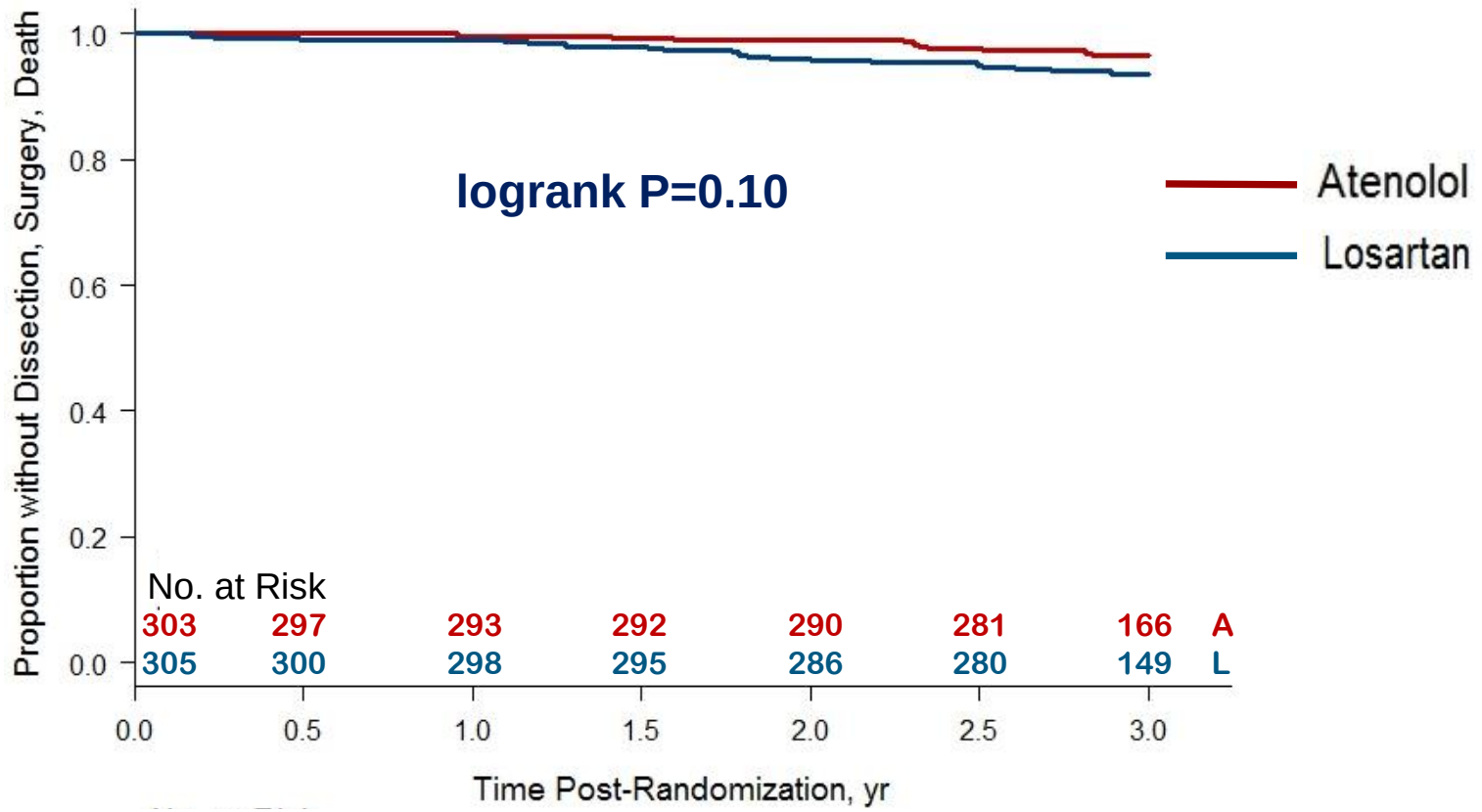
Subgroup Analysis



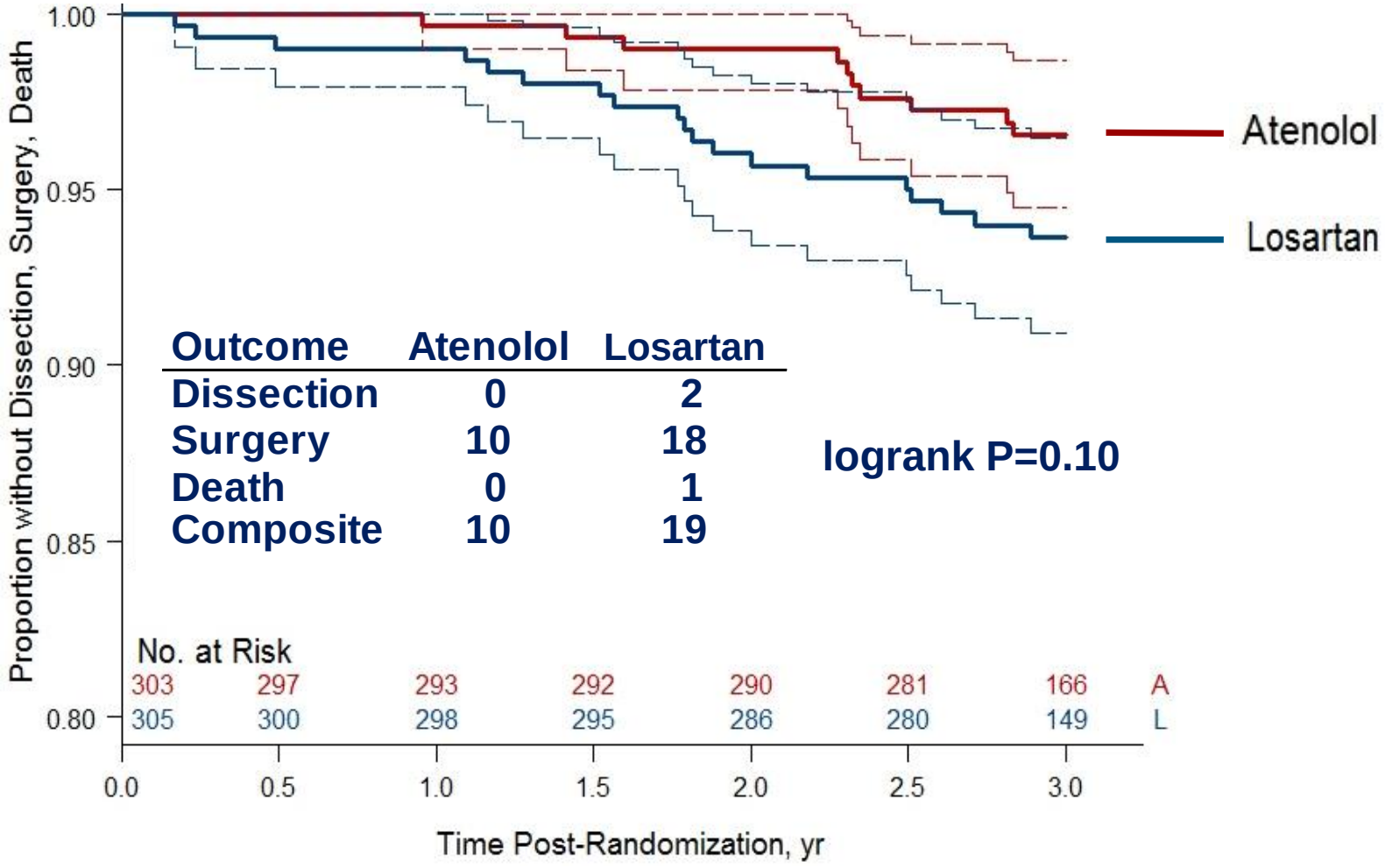
Estimated Change in ARz by Baseline Age



Freedom from Dissection, Surgery, Death



Freedom from Dissection, Surgery, Death



Outcome	Atenolol	Losartan
Dissection	0	2
Surgery	10	18
Death	0	1
Composite	10	19

logrank P=0.10

Adverse Events and Reported Symptoms

	Atenolol	Losartan	P value*
All:			
AE	408	365	0.10
SAE	40	50	0.31
Possibly/probably related:			
AE	204	163	0.03
SAE	5	2	0.25

Subject-reported symptoms: Bothersome symptoms were rare at baseline and during maintenance.

*Poisson regression

Conclusions

- We found no significant difference in the rate of aortic-root dilation between the two treatment groups over 3 years.
- The treatment effect did not differ according to pre-specified subgroups.
- The dose of atenolol used in this study was higher than that in many other studies.
- Both drugs were well-tolerated.
- Losartan and atenolol may be more effective at reducing ARz in younger subjects.

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

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*

Thank You

- Patients and families
- Study coordinators
- Referring physicians
- The Marfan Foundation
- NHLBI
- FDA Office of Orphan Products Development
- Merck & Co, Inc.
- Teva Canada Limited

Other Trials (other than NIH/PHN)

- Is combination therapy (losartan + BB) better than beta-blocker alone?
  - Results from several trials are mixed.
- Is irbesartan + BB better than beta-blocker alone?
  - United Kingdom trial results say yes.
- Meta-Analysis
  - Can we learn from combining results from all the trials?

Medical Therapy for Marfan Syndrome

No Aortic-Root Dilation, z score < 2.5

- Consider patient factors:
  - -Family history of aneurysm
  - -Family history of dissection
  - -Vertebral artery tortuosity
  - -Increased aortic stiffness

Aortic-Root Dilation, z score > 2.5

- Beta Blocker titrated to HR OR Angiotensin Receptor Blocker

Severe or Progressive Aortic-Root Dilation z score > 5 or Increasing z score

- Consider combination therapy with Beta Blocker AND Angiotensin Receptor Blocker

Celiprolol vs. No treatment in Vascular EDS

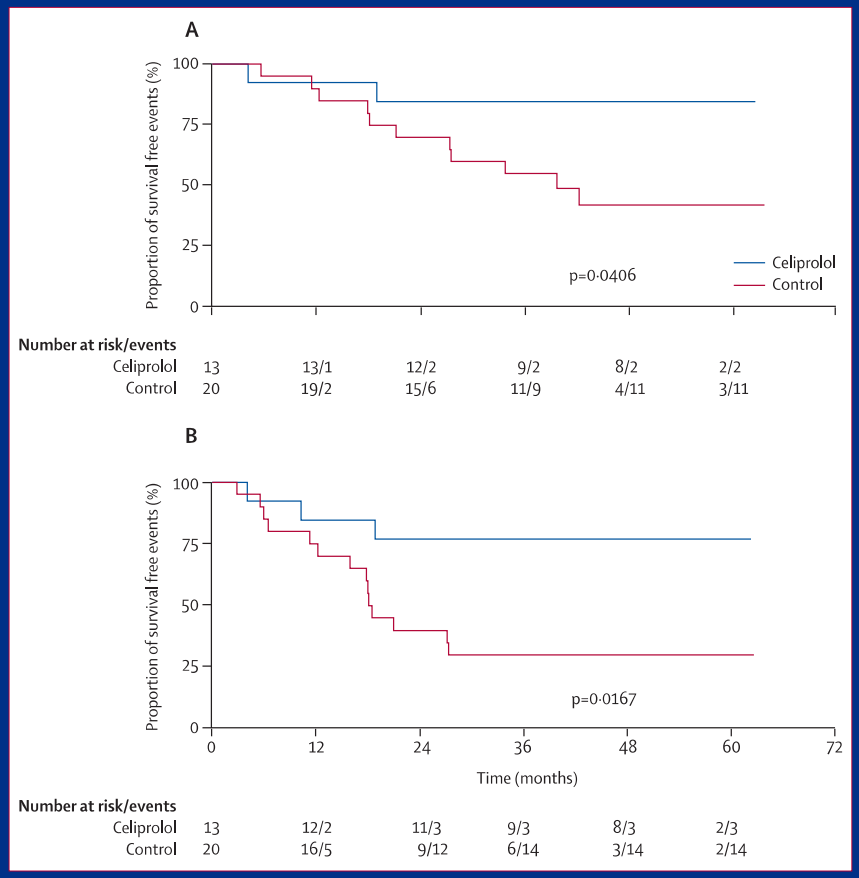


Figure 3: **Kaplan-Meier curves of event-free survival in 33 patients with positive *COL3A1* mutation**
Primary endpoint (A). Primary and secondary endpoints (B).

Surgical Therapy

Personalized Treatment for Aortic Dilation/Aneurysm

- Size
- Family History
- Gene
- Genetic mutation
- Tortuosity
- Stiffness

Physical Activity and Exercise

Exercise and Physical Activity in Connective Tissue Conditions

The Marfan Foundation
Virtual Medical Symposium Series
April 9, 2019

Ronald V. Lacro, MD

Department of Cardiology
Boston Children's Hospital
Harvard Medical School

Benefits of Routine Exercise: Health and Well-Being

Cardiovascular

- Lower HR, BP
- Lower cholesterol
- Less coronary disease
- Lower risk of heart attack and stroke

Musculoskeletal

- less osteoporosis
- less back pain
- balance

Lower blood sugar

Longer life

Social aspects

Weight loss

Lower risk of colon and breast cancer

Mental health

- Less depression
- Less anxiety
- Improved mood
- Improved memory

How do we counsel individuals with hereditary aortic disease (Marfan, Loeys-Dietz, vEDS, FTAA) regarding exercise, both for the athlete and non-athlete?

What type of exercise is safe?

How much exercise is safe?

Do we always have the **right** answer?

We typically err on the side of safety…

We do not have any outcomes data in this area to guide us.

Physical Activity Recommendations Should Be Individualized Modifications Based on Multiple System Involvement

Ocular

retinal detachment, lens dislocation

Musculoskeletal

back, feet, hips

Pulmonary

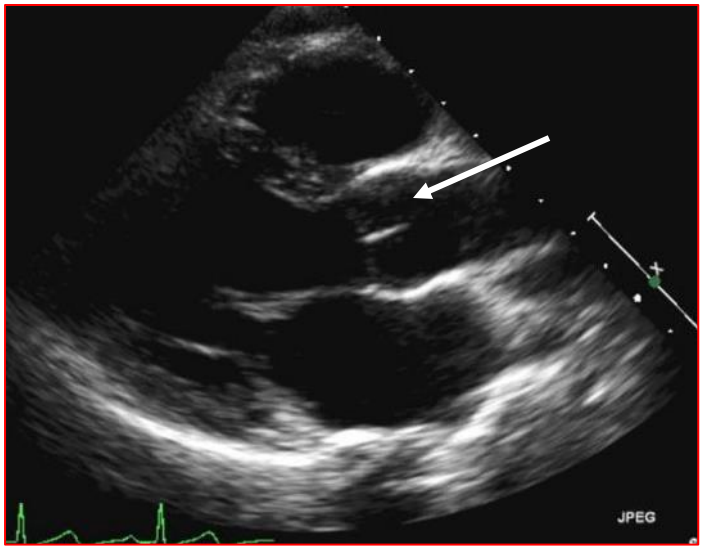
pneumothorax, restrictive lung disease

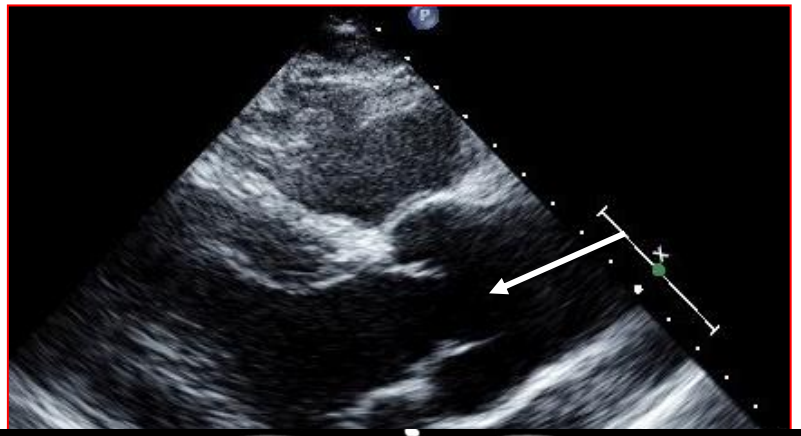
Cardiovascular

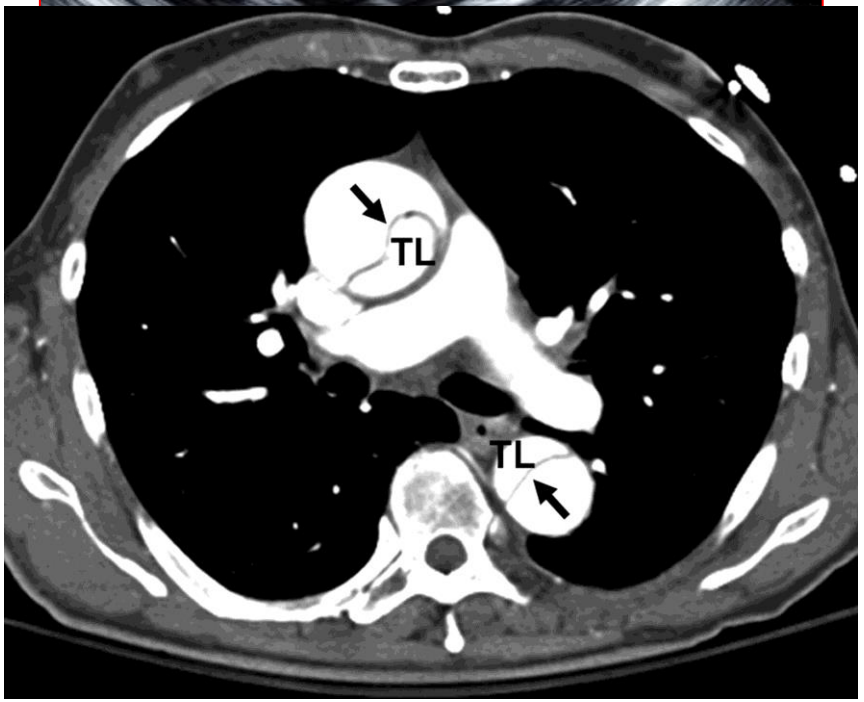
cardiomyopathy
valvular disease
arrhythmias
mechanical valve/anticoagulation

Physical Activity Concerns in Marfan Syndrome and Related Conditions

Aortic size





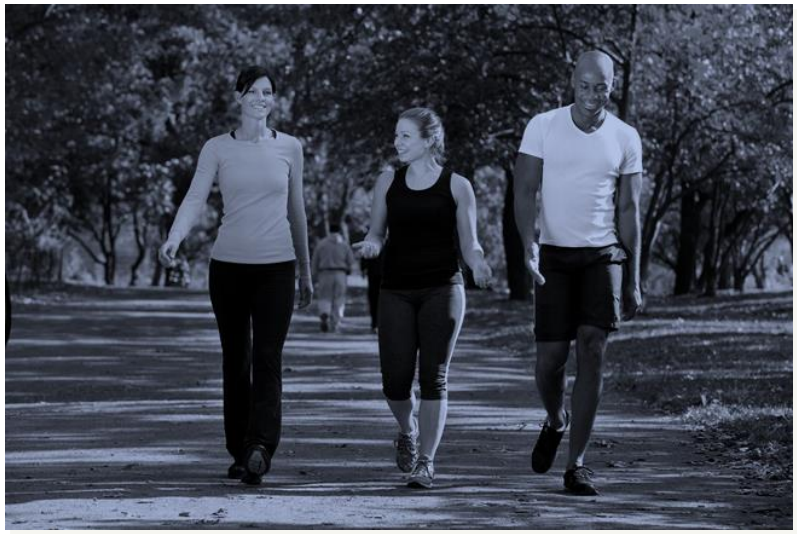


The demands on the cardiovascular system differ among various types of exercise and physical activity.

Dynamic (isotonic) exercise

- refers to shortening or lengthening of muscle fibers during contraction
- results in muscle movement
- blood vessels dilate
- modest increase in mean BP

Physiologic response to exercise: Not all types of physical activity are the same



Dynamic (isotonic) exercise

- refers to shortening or lengthening of muscle fibers during contraction
- results in muscle **movement**
- blood vessels dilate
- modest increase in mean BP

Static (isometric) exercise

- refers to muscle contraction without movement
- vasoconstriction to non-contracting muscles
- ↑ flow to contracting muscles
- associated with increases in BP

Competitive Athletics

- Systematic training
- Primary pursuit is athletic excellence and achievement
- Typically push to highest natural physical limits

Recreational Athletics

- Non-competitive
- Light-to-moderate exercise
- Fitness and fun

Competitive Athletics

- Systematic training
- Primary pursuit is athletic excellence and achievement
- Typically push to highest natural physical limits

Recreational Athletics

- Non-competitive
- Light-to-moderate exercise
- Fitness and fun

Exercise and the Aorta: Lessons from the Medical Literature

- **Can exercise lead to progressive enlargement of the aorta?**
- Can exercise cause aortic dissection?
- How common is sudden cardiac death in competitive athletes?
- How common is aortic dissection or rupture in Marfan syndrome among competitive athletes?
- Is there any evidence that lower levels of exercise are helpful or harmful to the aorta?

Exercise and the Aorta: Lessons from the Medical Literature

- Can exercise lead to progressive enlargement of the aorta?
- **Can exercise cause aortic dissection?**
- How common is sudden cardiac death in competitive athletes?
- How common is aortic dissection or rupture in Marfan syndrome among competitive athletes?
- Is there any evidence that lower levels of exercise are helpful or harmful to the aorta?

Exercise and the Aorta: Lessons from the Medical Literature

- Can exercise lead to progressive enlargement of the aorta?
- Can exercise cause aortic dissection?
- **How common is sudden cardiac death among competitive athletes?**
- **How common is aortic dissection or rupture in Marfan syndrome among competitive athletes?**
- Is there any evidence that lower levels of exercise are helpful or harmful to the aorta?

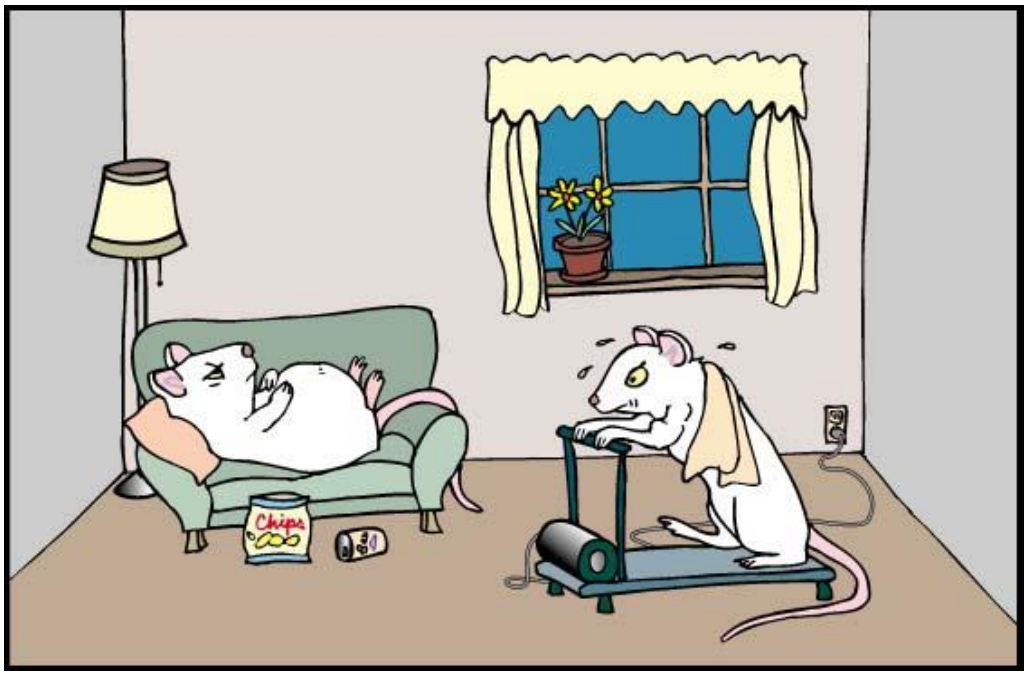
Exercise and the Aorta: Lessons from the Medical Literature

- Can exercise lead to progressive enlargement of the aorta?
- Can exercise cause aortic dissection?
- How common is sudden cardiac death in competitive athletes?
- How common is aortic dissection or rupture in Marfan syndrome among competitive athletes?
- **Is there any evidence that lower levels of exercise are helpful or harmful to the aorta?**

Mild aerobic exercise protects aortic structure and function in a mouse model of Marfan syndrome.

Gibson C, et al. J Appl Physiol 2017 doi:10.1152/japplphysiol.00132.2017

4-week old Marfan and wild-type mice were subjected to voluntary and forced exercise regimens, or a sedentary lifestyle for 5 months.



Mild aerobic exercise protects aortic structure and function in a mouse model of Marfan syndrome.

Gibson C, et al. J Appl Physiol 2017 doi:10.1152/japplphysiol.00132.2017

Marfan mice that exercised had improved aortic wall structure and function, with beneficial effect optimum at low intensity exercise (~60% of $V0_2$ max) and tapering off at higher intensity of exercise (85% of $V0_2$ max).

There was decreased MMP-2 and MMP-9 expression within the aortic wall of Marfan mice that exercised.

Society	Recommendations
COMPETITIVE ATHLETES	
ACC/AHA Guidelines* (2015)	Athletes with Marfan syndrome, familial TAA syndrome, Loeys-Dietz syndrome, unexplained aortic aneurysm, vascular Ehlers-Danlos syndrome, or a related aortic aneurysm condition should not participate in any competitive sports that involve **intense physical exertion** or the potential for **bodily collision**

*Braverman AC et al. J Am Coll Cardiol 2015;66:2398-2405

Approaching Exercise and Physical Activity in a Safe and Practical Manner

What advice is recommended regarding ***recreational* (*non-competitive*)** exercise and physical activity in individuals with Marfan syndrome and related conditions?

Guidelines for Recreational (Non-Competitive) Sports and Exercise

Society/Organization	Recommendations for those with Marfan Syndrome and Related Conditions
Recreational (Non-Competitive) Exercise	
ACC/AHA, ESC	• Avoid collision sports and strenuous activities involving lifting, pushing or straining that require Valsalva • Avoid intense isometric activities
Marfan Foundation	• Favor non-competitive, dynamic exercises such as walking, jogging, leisurely bicycling or slow-paced tennis • Avoid isometric activities (push-ups, sit-ups, weightlifting) • Avoid intense contact sports
Loeys-Dietz Foundation	• Remain active with aerobic activities performed in moderation (hiking, biking, jogging, swimming) • Avoid competitive sports, esp. contact sports, or muscle straining activities performed to the level of exhaustion • Avoid straining activities (push-ups, chin-ups, sit-ups)

Modified from: Cheng A, Owens D. Br J Sports Med 2016;50:100.

Recreational (non-competitive) Sports and Exercise Recommendations in Marfan Syndrome and Related Conditions (in the absence of significant aortic dilatation)

Permitted	Intermediate*	Strongly Discouraged
Bowling	Singles tennis	Body building
Golf	Baseball/Softball	Ice hockey
Brisk walking	Hiking	Rock climbing
Modest hiking	Swimming (lap)	Windsurfing
Doubles tennis	Horseback riding	Surfing
Treadmill	Biking	Scuba Diving
Stationery bike	Ice skating	Weightlifting
Archery	Racquetball	Football
Table tennis	Dancing	
Light weightlifting with repetitions	Jogging	
Yoga, Pilates	Badminton	

*intermediate activities should be assessed clinically with recommendations based on individual circumstances

Modified from: Cheng A, Owens D. Br J Sports Med 2016;50:100.

Recommendations for Physical Activity and Exercise in Marfan Syndrome and Related Conditions

Stay at an aerobic level of exercise wherein one can talk in a conversational voice during the activity, or using a perceived activity scale:

RPE Scale	Rate of Perceived Exertion
10	**Max Effort Activity** Feels almost impossible to keep going. Completely out of breath, unable to talk. Cannot maintain for more than a very short time.
9	**Very Hard Activity** Very difficult to maintain exercise intensity. Can barely breath and speak only a few words
7-8	**Vigorous Activity** Borderline uncomfortable. Short of breath, can speak a sentence.
4-6	**Moderate Activity** Breathing heavily, can hold short conversation. Still somewhat comfortable, but becoming noticeably more challenging.
2-3	**Light Activity** Feels like you can maintain for hours. Easy to breathe and carry a conversation
1	**Very Light Activity** Hardly any exertion, but more than sleeping, watching TV, etc

www.thefittutor.com

Physical Activity Recommendations Should Be Individualized Modifications Based on Multiple System Involvement

Ocular

retinal detachment, lens dislocation

Musculoskeletal

back, feet, hips

Pulmonary

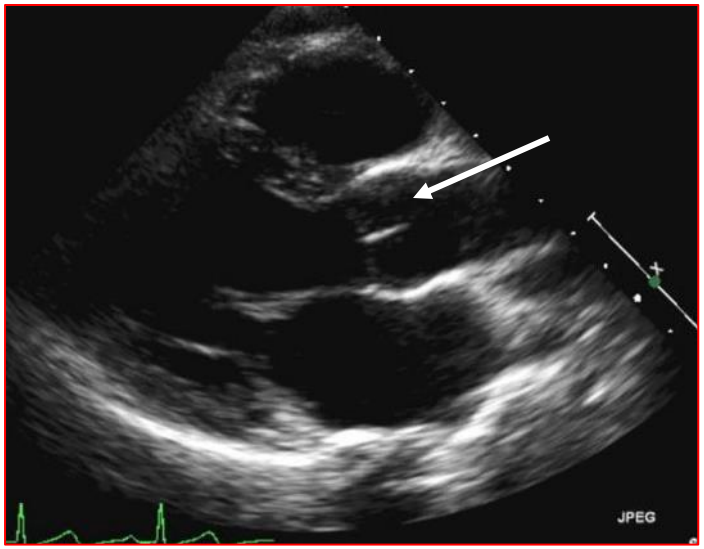
pneumothorax, restrictive lung disease

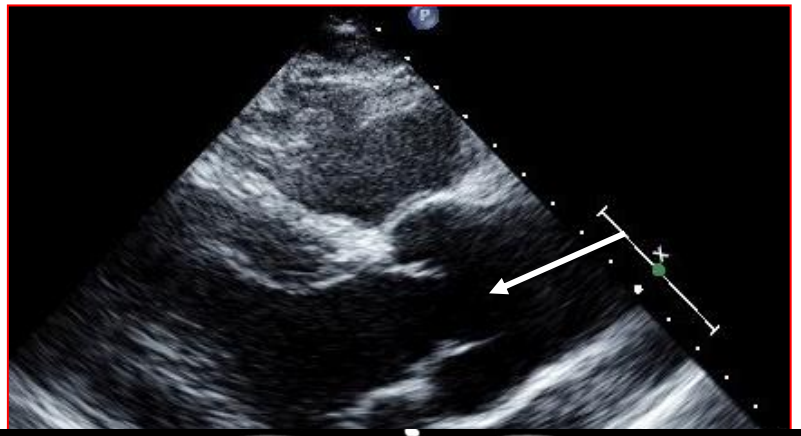
Cardiovascular

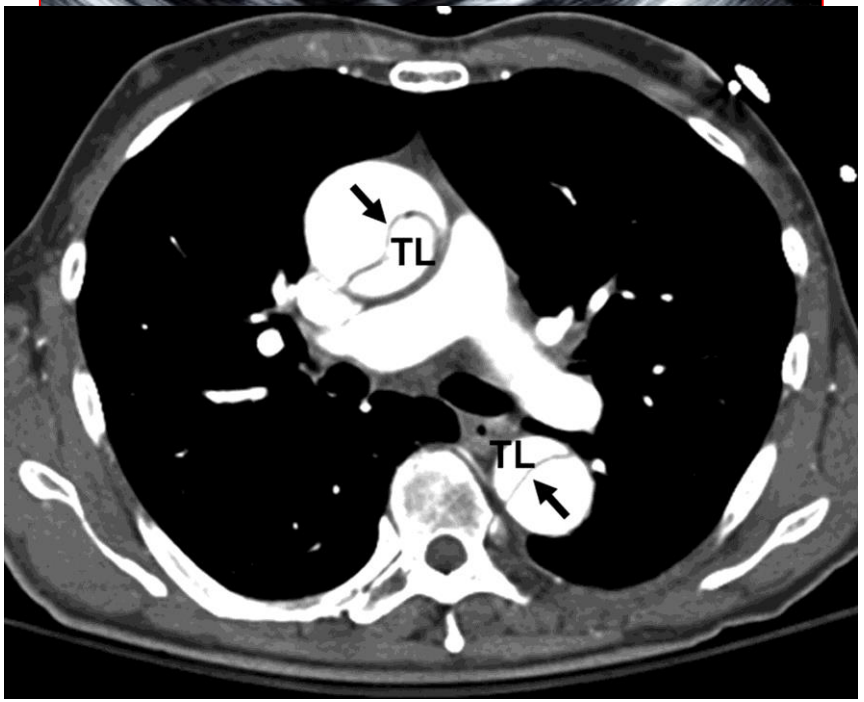
cardiomyopathy
valvular disease
arrhythmias
mechanical valve/anticoagulation

Physical Activity Concerns in Marfan Syndrome and Related Conditions

Aortic size





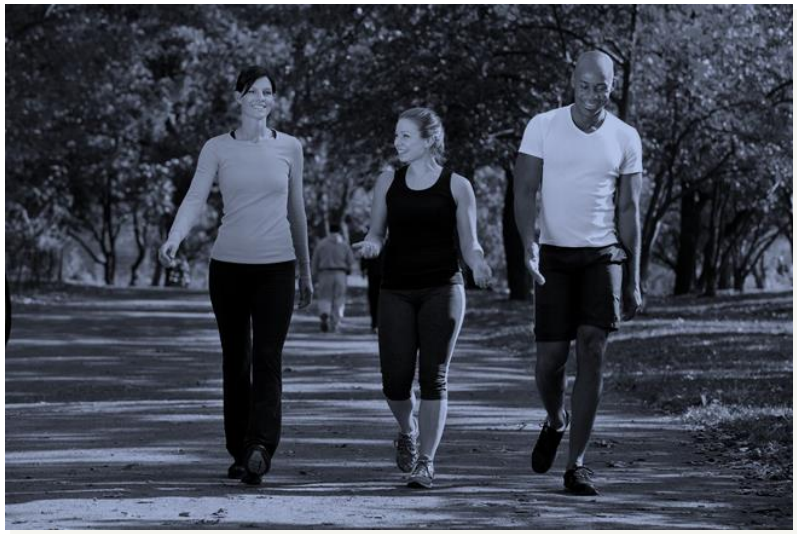


The demands on the cardiovascular system differ among various types of exercise and physical activity.

Dynamic (isotonic) exercise

- refers to shortening or lengthening of muscle fibers during contraction
- results in muscle movement
- blood vessels dilate
- modest increase in mean BP

Physiologic response to exercise: Not all types of physical activity are the same



Dynamic (isotonic) exercise

- refers to shortening or lengthening of muscle fibers during contraction
- results in muscle **movement**
- blood vessels dilate
- modest increase in mean BP

Static (isometric) exercise

- refers to muscle contraction without movement
- vasoconstriction to non-contracting muscles
- ↑ flow to contracting muscles
- associated with increases in BP

Competitive Athletics

- Systematic training
- Primary pursuit is athletic excellence and achievement
- Typically push to highest natural physical limits

Recreational Athletics

- Non-competitive
- Light-to-moderate exercise
- Fitness and fun

Competitive Athletics

- Systematic training
- Primary pursuit is athletic excellence and achievement
- Typically push to highest natural physical limits

Recreational Athletics

- Non-competitive
- Light-to-moderate exercise
- Fitness and fun

FDA warning about fluoroquinolones

Recent FDA Warning concerning Fluoroquinolones (-floxacin)

- December 2018: FDA warning against the use of fluoroquinolones in people with genetic aortic conditions associated with aortic aneurysms and dissections, such as Marfan, Loeys-Dietz, and vascular Ehlers-Danlos syndromes
- Commonly prescribed class of antibiotics: Avelox (moxifloxacin), Cipro (ciprofloxacin), Levaquin (levofloxacin), Ocuflox (ofloxacin)
- A review of several recent studies shows that people who have taken a fluoroquinolone are twice as likely to experience an aortic aneurysm or dissection than those who have not taken one of these drugs.

Recent FDA Warning concerning Fluoroquinolones (-floxacin)

- FDA requires that a new warning about this risk be added to the labelling of these medications
- Physicians should not prescribe fluoroquinolones to people with these genetic conditions unless no other treatment options are available.
- If you have been prescribed a fluoroquinolone to treat an infection, do not stop taking the medication without first talking with your provider
- If you experience symptoms of a dissection such as a sudden, severe pain in the chest, back, or abdomen, it is critical to call 911 and/or go to an emergency room immediately.

Questions and Answers

Ronald V. Lacro, M.D.
The Marfan Foundation
Virtual Medical Symposium Series
April 9, 2019

Boston Children's Hospital
Heart Center

HARVARD MEDICAL SCHOOL
TEACHING HOSPITAL