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
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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

• 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
Aortic Aneurysm: CT scan
Aortic Aneurysm: Surgery
Aortic Aneurysm/Dissection

View from inside aneurysm
False lumen
Aortic valve
Intimal flap of dissection
Left main ostium
Marfan Syndrome (MFS)  
FBN1
Loeys-Dietz Syndrome (LDS): General Clinical Features

- Overlapping phenotype with MFS, often carried 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
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

Pigtail loops of the carotid arteries

Proximal descending aorta makes a hairpin turn

LDS: Aortic Arch and Head and Neck Vessels by MRI
Loeys-Dietz Syndrome

- TGFBR1
- TGFBR2
- TGFBR3
- 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 \textit{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)
  - \textit{Carotid-cavernous sinus arteriovenous fistula}
  - Hypermobility of small joints
  - Tendon/muscle rupture
  - \textit{Early-onset varicose veins}
  - Pneumothorax/hemopneumothorax
  - \textit{Easy bruising (spontaneous or with minimal trauma)}
  - Chronic joint subluxations/dislocations
  - Congenital dislocation of the hips
  - Talipes equinovarus (clubfoot)
MFS, LDS, vEDS
General Characteristics

• Pleiotropy
• Phenotypic variation
• High Penetrance
• Progression over time
• Early diagnosis allows Prevention
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
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
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LDS: Aortic Arch and Head and Neck Vessels by MRI
Common Cardiovascular Findings

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- 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

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  • Good visualization of the heart, aortic root, blood vessels close to heart
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  • 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.
Clinical Observations Related to Aortic Root z-score

- z-score $\geq 7$ 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, labetalol, 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

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.
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

<table>
<thead>
<tr>
<th>Wild-type</th>
<th>C1039G/+ Placebo</th>
<th>C1039G/+ Propranolol*</th>
<th>C1039G/+ Losartan*</th>
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</table>

Losartan rescues aortic root performance

Aortic root growth (mm/6 months)

Aortic wall thickness (micrometers)

Aortic wall architecture (score 1-4)

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.

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

Assessed for Eligibility (n=701)

Eligible, not randomized (n=43, 6%)
  - Atenolol (n=303)
    - Withdrew from trial (n=32, 11%)
    - Withdrew from drug, stayed in trial (n=18, 6%)
    - Followed for 3 years (n=268)

Eligible and randomized (n= 608, 87%)
  - Allocation
    - Follow-up 3 years
      - Losartan (n=305)
        - Withdrew from trial (n=33, 11%)
        - Withdrew from drug, stayed in trial (n=8, 3%)
        - Followed for 3 years (n=267)

Ineligible (n=50, 7%)

Atenolol (n=303)

Follow-up 3 years

Losartan (n=305)

Follow-up 3 years
# Baseline Characteristics

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

<table>
<thead>
<tr>
<th></th>
<th>Atenolol (mg/kg/d)</th>
<th>Losartan (mg/kg/d)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All</td>
<td>2.7±1.1</td>
<td>1.3±0.2</td>
</tr>
<tr>
<td>Children</td>
<td>2.8±1.0</td>
<td>1.3±0.2</td>
</tr>
<tr>
<td>Adults</td>
<td>2.3±1.2</td>
<td>1.2±0.2</td>
</tr>
</tbody>
</table>

Absolute doses for adults (mg/d):  
Atenolol 151±75 mg  
Losartan 85±14 mg
Estimated Rate of Change in ARz

Atenolol: \(-0.139 \pm 0.013\) SD units/year
Losartan: \(-0.107 \pm 0.013\) SD units/year

\(P=0.08\)
Estimated Rate of Change in Aortic-Root Absolute Diameter

Atenolol: 0.069±0.004 cm/year
Losartan: 0.075±0.004 cm/year

P=0.20
Subgroup Analysis

- All Subjects: 608
  - Adults: 151
  - Children: 457
  - ARz < 4.5: 387
  - ARz >= 4.5: 220
  - Past BB Use: 344
  - No Past BB Use: 264
  - Females: 242
  - Males: 366

Difference in Slopes:
- Atenolol Beneficial: P=0.31
- Losartan Beneficial: P=0.81 (not significant for ARz < 4.5), P=0.11 (not significant for Past BB Use), P=0.40 (not significant for Males)
Estimated Change in ARz by Baseline Age

**Atenolol, P<0.001**

**Losartan, P=0.002**

Annual Rate of ARz Change

Age (Yrs)

SD units/year ± SE
Freedom from Dissection, Surgery, Death

![Graph showing freedom from dissection, surgery, and death for two groups, Atenolol and Losartan, with logrank P=0.10.](image)

- **Dissection**: 0, 2
- **Surgery**: 10, 18
- **Death**: 0, 1
- **Composite**: 10, 19

No. at Risk:
- Atenolol: 303, 297, 293, 292, 290, 281, 166
- Losartan: 305, 300, 298, 295, 286, 280, 149

Time Post-Randomization, yr: 0.00, 0.50, 1.00, 1.50, 2.00, 2.50, 3.00
Freedom from Dissection, Surgery, Death

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Atenolol</th>
<th>Losartan</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dissection</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>Surgery</td>
<td>10</td>
<td>18</td>
</tr>
<tr>
<td>Death</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Composite</td>
<td>10</td>
<td>19</td>
</tr>
</tbody>
</table>

logrank P=0.10
Adverse Events and Reported Symptoms

<table>
<thead>
<tr>
<th></th>
<th>Atenolol</th>
<th>Losartan</th>
<th>P value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>All:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AE</td>
<td>408</td>
<td>365</td>
<td>0.10</td>
</tr>
<tr>
<td>SAE</td>
<td>40</td>
<td>50</td>
<td>0.31</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Possibly/probably related:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AE</td>
<td>204</td>
<td>163</td>
<td>0.03</td>
</tr>
<tr>
<td>SAE</td>
<td>5</td>
<td>2</td>
<td>0.25</td>
</tr>
</tbody>
</table>

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

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

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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

### Social aspects

### Weight loss

### Lower risk of colon and breast cancer

### Mental health
- Less depression
- Less anxiety
- Improved mood
- Improved memory

---

Table 4: Health and Wellness Benefits of Physical Activity and Fitness

<table>
<thead>
<tr>
<th>Improved Cardiovascular Health</th>
<th>Enhanced Mental Health and Function</th>
<th>Opportunity for Successful Experience and Social Interactions</th>
<th>Improved Appearance</th>
<th>Greater Lean Body Mass and Less Body Fat</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Stronger heart muscle fitness and health</td>
<td>• Relief of depression</td>
<td>• Improved self-concept</td>
<td>• Better figure/physique</td>
<td>• Greater work efficiency</td>
</tr>
<tr>
<td>• Lower heart rate</td>
<td>• Improved sleep habits</td>
<td>• Opportunity to recognize and accept personal limitations</td>
<td>• Better posture</td>
<td>• Less susceptibility to disease</td>
</tr>
<tr>
<td>• Better electric stability of heart</td>
<td>• Fewer stress symptoms</td>
<td>• Improved sense of well-being</td>
<td>• Fat control</td>
<td>• Improved appearance</td>
</tr>
<tr>
<td>• Decreased sympathetic control of heart</td>
<td>• Ability to enjoy leisure and work</td>
<td>• Enjoyment of life and fun</td>
<td>• Less incidence of self-concept problems related to obesity</td>
<td>• Improved quality of life</td>
</tr>
<tr>
<td>• Increased O2 to brain</td>
<td>• Improved brain function</td>
<td>• Improved quality of life</td>
<td>• Improved flexibility</td>
<td>• Greater peak bone density</td>
</tr>
<tr>
<td>• Reduced blood fat, including low-density lipoproteins (LDLs)</td>
<td>• Reduced risk for heart attack</td>
<td></td>
<td>• Less chance of muscle injury</td>
<td>• Less chance of developing osteoporosis</td>
</tr>
<tr>
<td>• Increased protective high-density lipoproteins (HDLs)</td>
<td>• Reduced risk for stroke</td>
<td></td>
<td>• Increased work capacity</td>
<td>• Reduced risk for colon and breast cancer</td>
</tr>
<tr>
<td>• Delayed development of atherosclerosis</td>
<td>• Reduced risk for hypertension</td>
<td></td>
<td>• Improved bone health</td>
<td>• Possible reduced risk for rectal and prostate cancers</td>
</tr>
<tr>
<td>• Increased work capacity</td>
<td>• Greater chance of surviving a heart attack</td>
<td></td>
<td>• Improved ability to meet some stressors</td>
<td>• Reduced cancer risk</td>
</tr>
<tr>
<td>• Improved peripheral circulation</td>
<td>• Increased oxygen-carrying capacity of the blood</td>
<td></td>
<td>• Improved quality of life</td>
<td>• Reduced risk for colon and breast cancer</td>
</tr>
<tr>
<td>• Improved coronary circulation</td>
<td></td>
<td></td>
<td></td>
<td>• Possible reduced risk for rectal and prostate cancers</td>
</tr>
<tr>
<td>• Resistance to “emotional storm”</td>
<td></td>
<td></td>
<td></td>
<td>• Improved reduced effect of acquired aging</td>
</tr>
<tr>
<td>• Reduced risk for heart attack</td>
<td></td>
<td></td>
<td></td>
<td>• Improved ability to function in daily life</td>
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<tr>
<td>• Reduced risk for hypertension</td>
<td></td>
<td></td>
<td></td>
<td>• Better short-term memory</td>
</tr>
<tr>
<td>• Greater chance of surviving a heart attack</td>
<td></td>
<td></td>
<td></td>
<td>• Fewer illnesses</td>
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<tr>
<td>• Increased oxygen-carrying capacity of the blood</td>
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<td>Greater mobility</td>
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<td>Greater independence</td>
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<td>Greater ability to operate an automobile</td>
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<td></td>
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<td></td>
<td></td>
<td>Lower risk for dementia</td>
</tr>
</tbody>
</table>

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Other Health Benefits
- Decreased diabetes risk
- Quality of life for diabetics
- Improved metabolic fitness
- Extended life
- Decrease in dysfunctional years
- Aids for some people who have arthritis, PMS, asthma, chronic pain, fibromyalgia, or impotence
- Improved immune system

Improved Wellness
- Improved quality of life
- Leisure-time enjoyment
- Improved work capacity
- Ability to meet emergencies
- Improved creative capacity

www.cwcboe.org
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
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- Systematic training
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- Non-competitive
- Light-to-moderate exercise
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Mild aerobic exercise protects aortic structure and function in a mouse model of Marfan syndrome.


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.


Marfan mice that exercised had improved aortic wall structure and function, with beneficial effect optimum at low intensity exercise (~60% of VO₂ max) and tapering off at higher intensity of exercise (85% of VO₂ max).

There was decreased MMP-2 and MMP-9 expression within the aortic wall of Marfan mice that exercised.
<table>
<thead>
<tr>
<th>Society</th>
<th>Recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td>COMPETITIVE ATHLETES</td>
<td>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</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Society/Organization</th>
<th>Recommendations for those with Marfan Syndrome and Related Conditions</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Recreational (Non-Competitive) Exercise</strong></td>
<td></td>
</tr>
</tbody>
</table>
| 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) |

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

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

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

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:

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

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

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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.