

15th Asian-Pacific Congress on Doppler Echocardiography

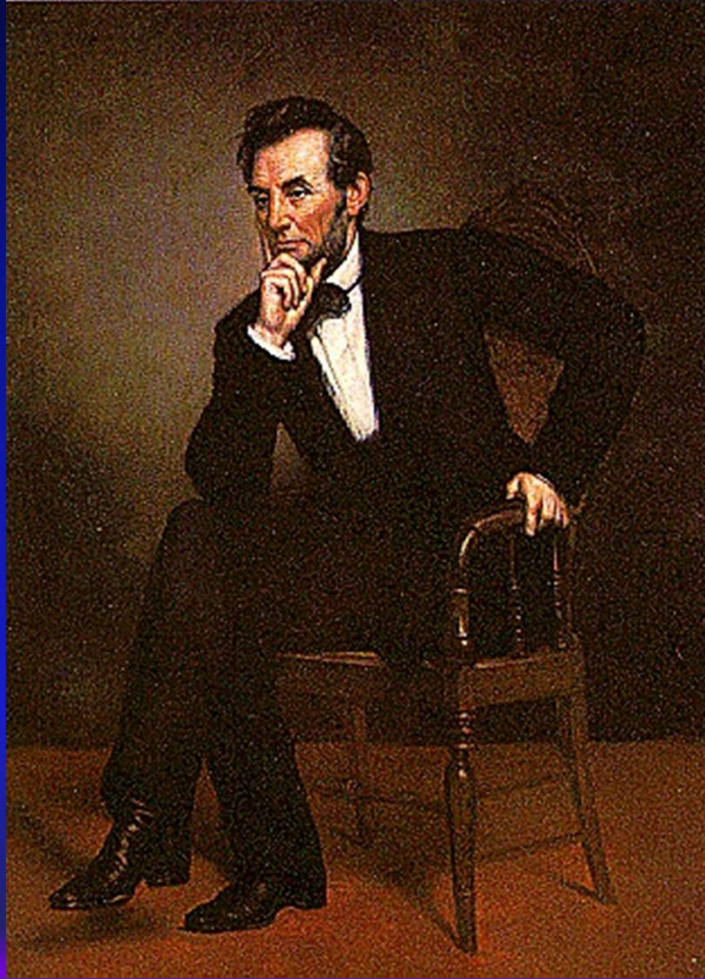
Aortic Root Disease in Marfan; From genetics to management

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Abraham Lincoln



6 ft 3.75 in

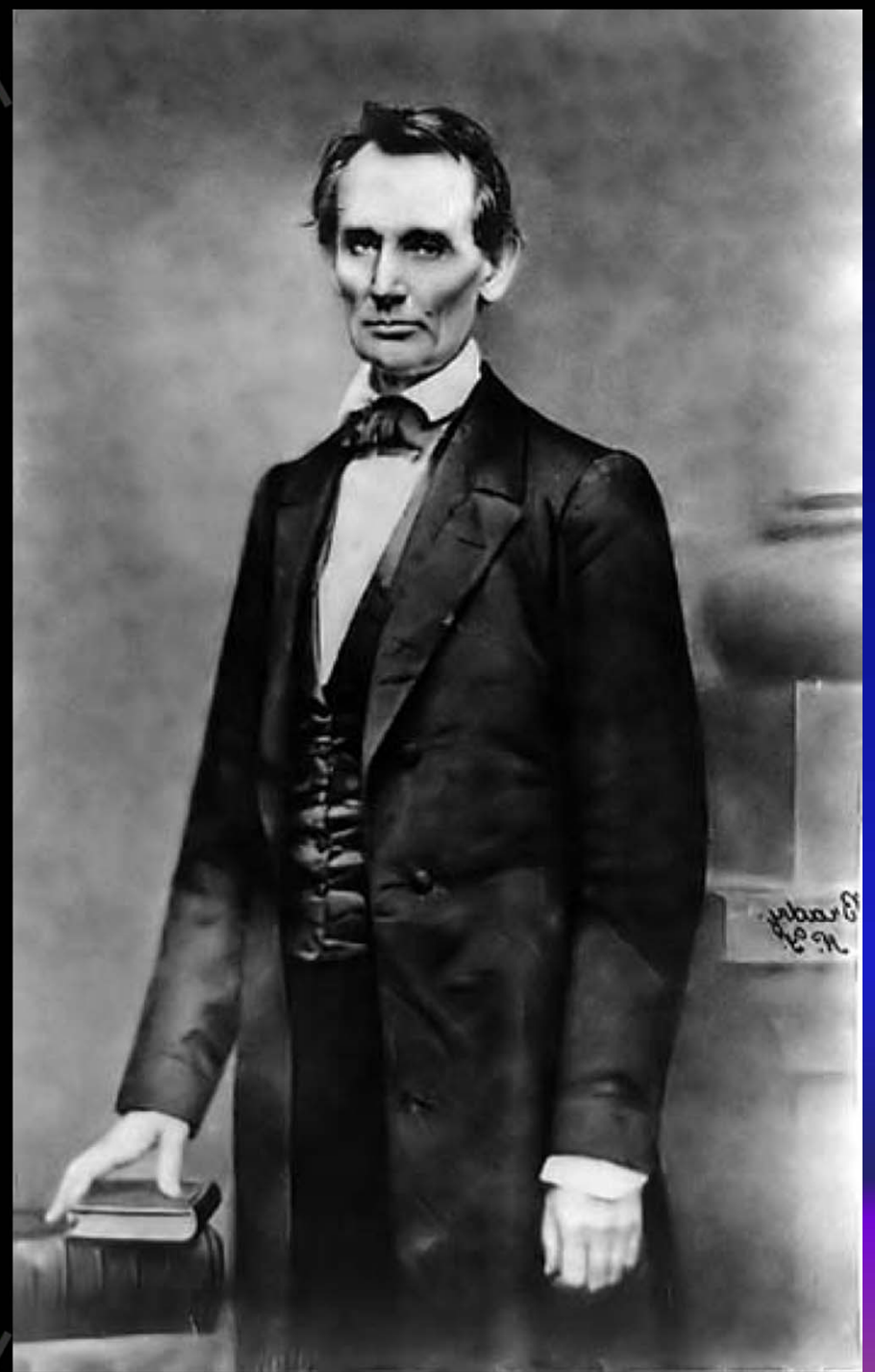
Elongated, gaunt face and neck

Pectus excavatum

Disproportionate long arms

Long, thin fingers

Disproportionate long legs & feet

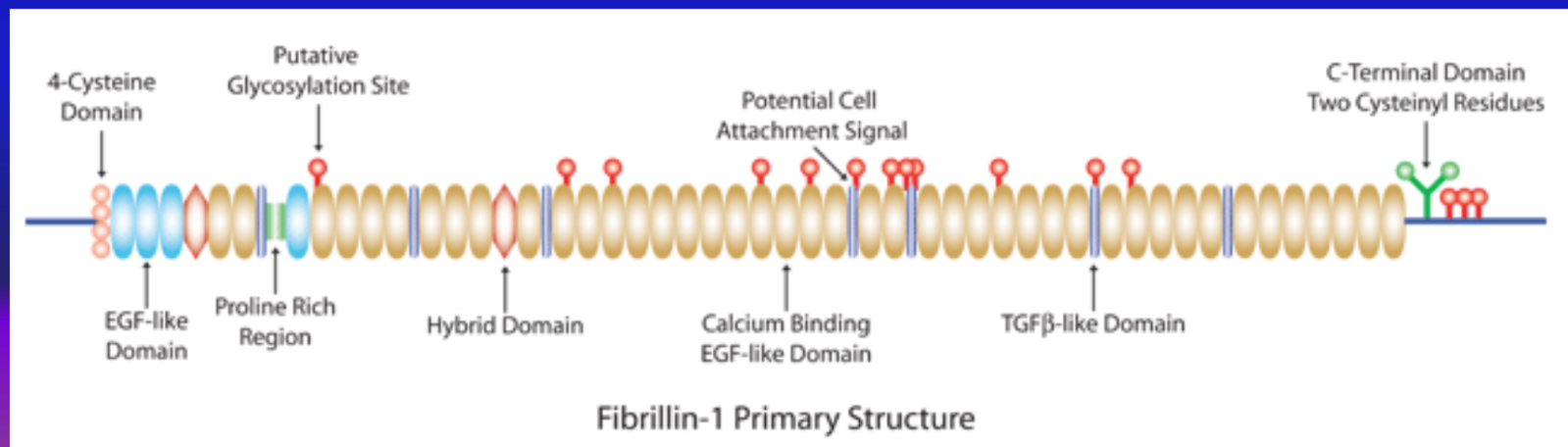


Epidemiology

- Common inherited connective tissue disorder of autosomal dominant inheritance
- First described in 1896; named in 1902.
 - Antoine Bernard-Jean Marfan, case report of a young girl with unusual musculoskeletal features
- Incidence: 1 in 5,000 to 10,000 individuals
- M = F; men with shorter life expectancy
- Races affected equally
- Wide range of clinical severity

What is Marfan's Syndrome(MFS)

- Fibrillin 1 → formation of extracellular matrix
 - Main component of microfibrils that together with elastin form elastic fiber
 - Abundant in the aorta, ligaments, ciliary body of the eye
- Classic MFS: mutation in the fibrillin-1 gene (*FBN1*)
 - Chromosome 15q21



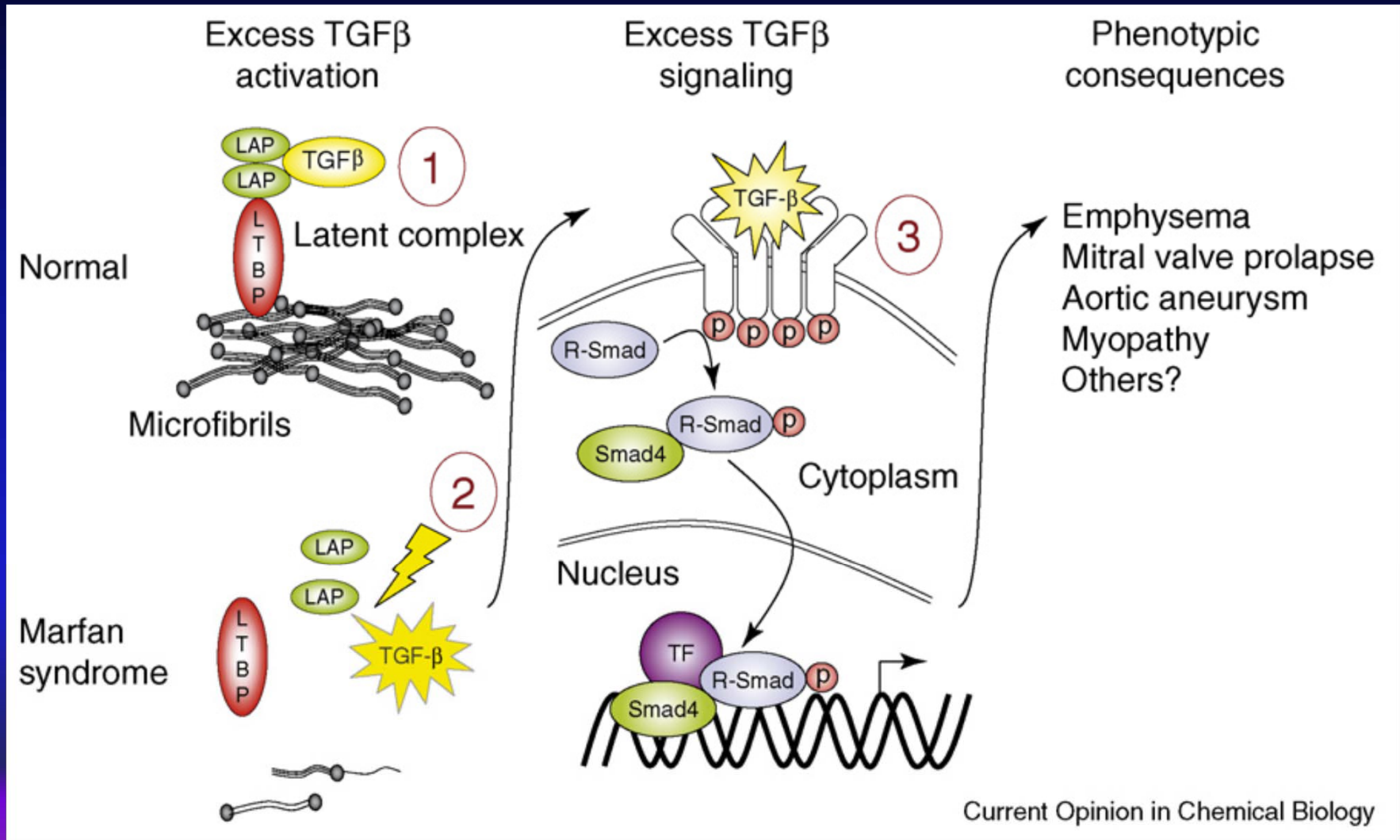
Genetics(1)

- Most cases involve one of various mutations of the fibrillin 1 gene (FBN1)
 - > 1,000 FBN1 Mutations (missense)
 - 60% are amino acid changes (EGF-like domain, cysteine residue)
 - 40% produce abnormally small Fibrillin-1
 - All reduce, alter structure, or impair transport
 - Result: Amount of available Fibrillin-1, which form microfibrils, reduced → weakens elastic fibers and over activates TGF-beta.
- More than 25% of Marfan cases represent probable new (*de novo*) mutations.

Genetics(2)

- Genes involved in Marfan-like Syndrome (MFS type II)
 - Type II subunit of membrane receptor of Transforming growth factor β (TGFB2)
 - Located on the short arm of Chromosome 3
 - TGF- β is a cytokine that works through apoptosis and cell cycle regulation; prevents proper incorporation of fibrillin into tissue & inflammatory reaction releasing proteases
 - degrade elastin fibers & other components of the ECM
- Other gene mutations may lead to similar phenotypes (Loeys-Dietz aneurysm syndrome, Familial thoracic aortic aneurysm syndrome)

Fibrillin & TGF β



Marfan's Syndrome Diagnosis

Diagnostic Criteria – Ghent Criteria

Major and Minor Manifestations of the Marfan Phenotype

Skeletal findings

Major manifestations – need four of eight

- Reduced upper to lower segment ratio (0.85 versus 0.93 in normals)
- Arm span exceeding height (ratio >1.05)
- Arachnodactyly of fingers and toes; positive wrist and thumb signs[†]
- Scoliosis >20° or kyphosis
- Pectus carinatum or pectus excavatum requiring surgery
- Reduced extension of elbows (<170°)
- Medial displacement of medial malleolus causing pes planus
- Protrusio acetabulae

Cardiovascular findings

Major manifestations – need one of two

- Dilatation of the aorta involving the sinuses of Valsalva
- Dissecting aortic aneurysm

Ocular findings

Major manifestations

- Ectopia lentis
- Secondary myopia, retinal detachment, glaucoma, and iritis

Other findings

Major manifestations

- Dural ectasia affecting the lumbosacral spinal canal

Minor manifestations

- Dolichostenomelia (limbs disproportionately large for trunk size)
- Dolichocephaly
- Tall stature (>95th percentile)
- Generalized joint hypermobility
- Osteopenia or osteoporosis

Minor manifestations

- Mitral valve prolapse
- Mitral regurgitation
- Left ventricular dilatation
- Dilatation of the pulmonary artery <age 40
- Calcification of mitral annulus <age 40
- Dilatation or dissection of descending aorta <age 50
- Tricuspid valve prolapse

Minor manifestations

- Myopia
- Flat cornea
- Increased axial globe length

Minor manifestations

- Spontaneous pneumothorax
- Apical blebs
- Cutaneous striae distensae
- Recurrent or incisional hernias

[†]Thumb sign – distal phalanx protrudes beyond border of clenched fist; wrist sign – thumb and fifth digit overlap circling the wrist

MFS ; Diagnostic Criteria

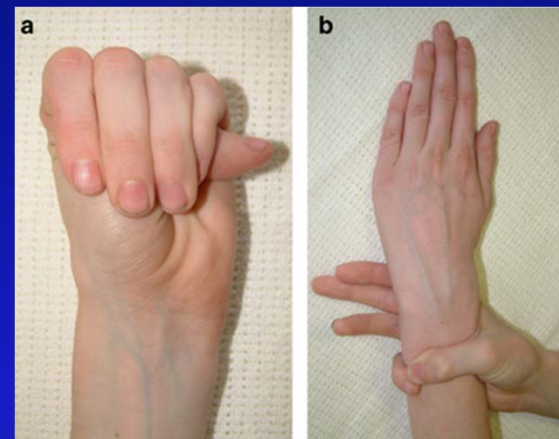
- 1. Skeletal system: Major criteria:
 - Four of the following 8 skeletal system features:
 - Reduced upper to lower body segment ratio (0.85 vs normal ratio of 0.93) or arm span exceeding height (ratio >1.05).
 - Arachnodactyly of fingers and toes with positive thumb & wrist signs
 - Scoliosis >20 degrees or spondylolisthesis
 - Pes planus
 - Reduced extension at the elbows (<170 degrees)
 - Pectus carinatum
 - Pectus excavatum requiring surgery
 - Protrusio acetabuli of any degree

MFS ; Diagnostic Criteria

- 1. Skeletal system: Minor criteria:
 - Pectus excavatum of moderate severity
 - Joint hypermobility
 - High arched palate with dental crowding
 - Dolichocephaly
 - Malar hypoplasia
 - Endophthalmos
 - Retrognathia
 - Down-slanting palpebral fissures

Skeletal

- Sternal deformity
 - Pectus excavatum (funnel chest)
 - Pectus carinatum (pigeon's chest)
- Joint hypermobility
 - Thumb sign
 - Wrist sign
- Arm span $>$ Height
 - ratio >1.05



MFS ; Diagnostic Criteria

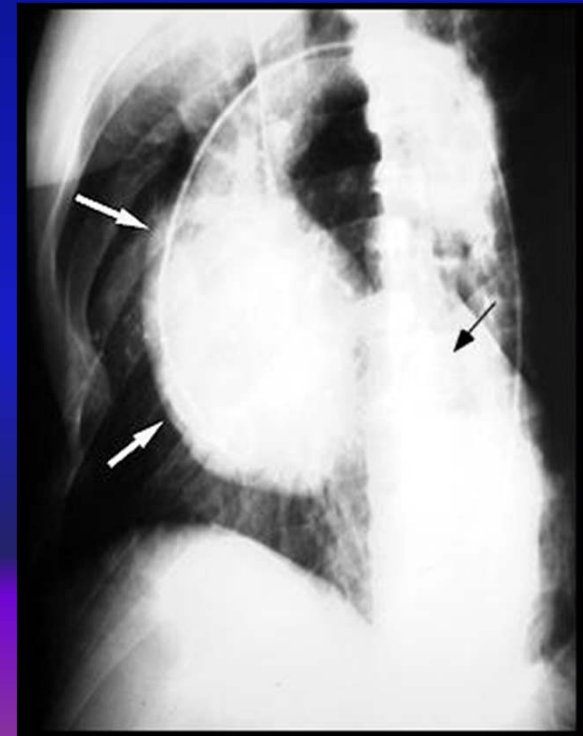
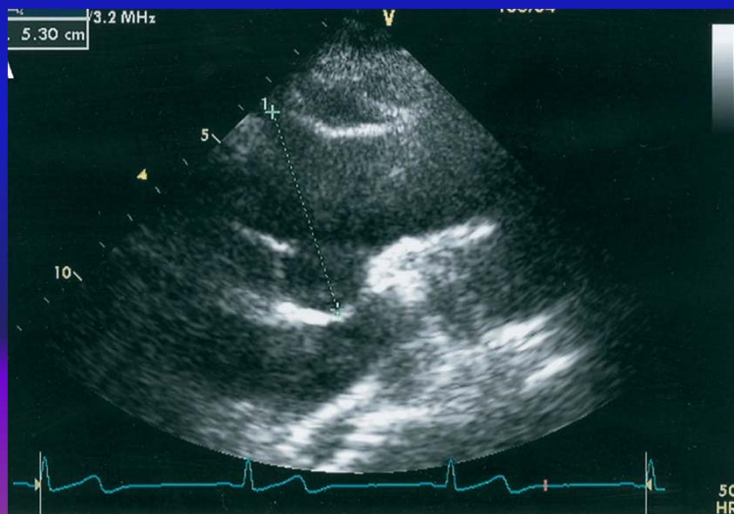
- 2. Cardiovascular system

- –Major criteria:

- Dilatation of the aorta involving the sinuses of Valsalva with or without aortic regurgitation

OR

- Ascending aortic dissection



MFS ; Diagnostic Criteria

- 2. Cardiovascular system

- Minor criteria:

- Mitral valve prolapse
 - Mitral regurgitation
 - Dilatation of the pulmonary artery (in the absence of pulmonic stenosis, under age 40)
 - Calcification of mitral annulus (before age 40)
 - Dilatation or dissection of descending thoracic/abdominal aorta (below age 50)

MFS ; Diagnostic Criteria

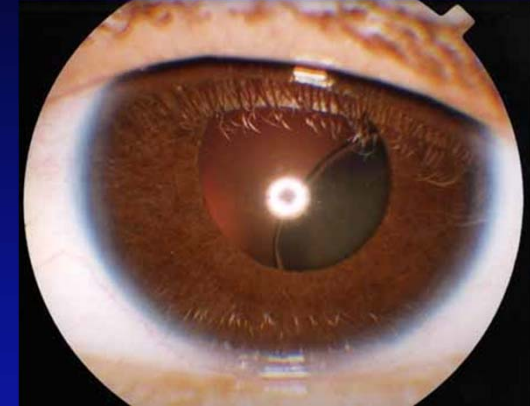
- 3. Ocular findings:

- Major criteria:

- Ectopia lentis (slit lamp exam)(60%)

- Minor criteria:

- Flat cornea
- Increased axial globe length
- Hypoplastic iris or hypoplastic ciliary muscle causing decreased miosis
- Myopia
- Retinal detachment



MFS ; Diagnostic Criteria

- 4. Other systems:
 - Major criteria:
 - Dural ectasia affecting the lumbosacral spinal canal (CT or MRI)
 - Minor criteria:
 - Spontaneous pneumothorax
 - Apical blebs
 - Cutaneous striae distensae
 - Recurrent or incisional hernias



MFS ; Diagnostic Criteria

- 5. Family / Genetic History:
 - Major criteria (needs one of the following):
 - A parent, child or sibling who meets criteria for Marfan independently
 - Presence of a mutation in FBN1 (in the patient) known to cause Marfan Syndrome
 - Presence of a haplotype around FBN1 (in the patient) inherited by descent, known to be associated with unequivocally diagnosed Marfan Syndrome in the family.

Diagnosis

- Clinical diagnosis: the Ghent criteria
 - physical exam: 6 organ systems involved
 - family history : most useful determination
 - genetic testing
- If (+) family history, additionally you need:
 - One major criterion with involvement of a second organ system (major or minor)
- If (–) family history, additionally you need:
 - Major criterion from 2 different systems and involvement of a 3rd system

Genetic Testing

- Detection of the mutation of the *FBN1* gene
 - 90-95% of patients who clinical criteria of MFS
- Limitation
 - Cost
 - Limited availability
 - 25-30% of MFS : new mutation
 - Mutation in *FBN1* can cause conditions other than MFS
 - None of the current method find all mutation in *FBN1*
- ***FBN1* mutation are not specific to MFS, and that the absence of a known mutation in this gene does not rule out MFS**

Clinical and genetic analysis of Korean patients with Marfan syndrome: possible ethnic differences in clinical manifestation

Yoo E-H, Woo H, Ki C-S, Lee HJ, Kim D-K, Kang I-S, Park P, Sung K, Lee CS, Chung T-Y, Moon JR, Han H, Lee S-T, Kim J-W. Clinical and genetic analysis of Korean patients with Marfan syndrome: possible ethnic differences in clinical manifestation.

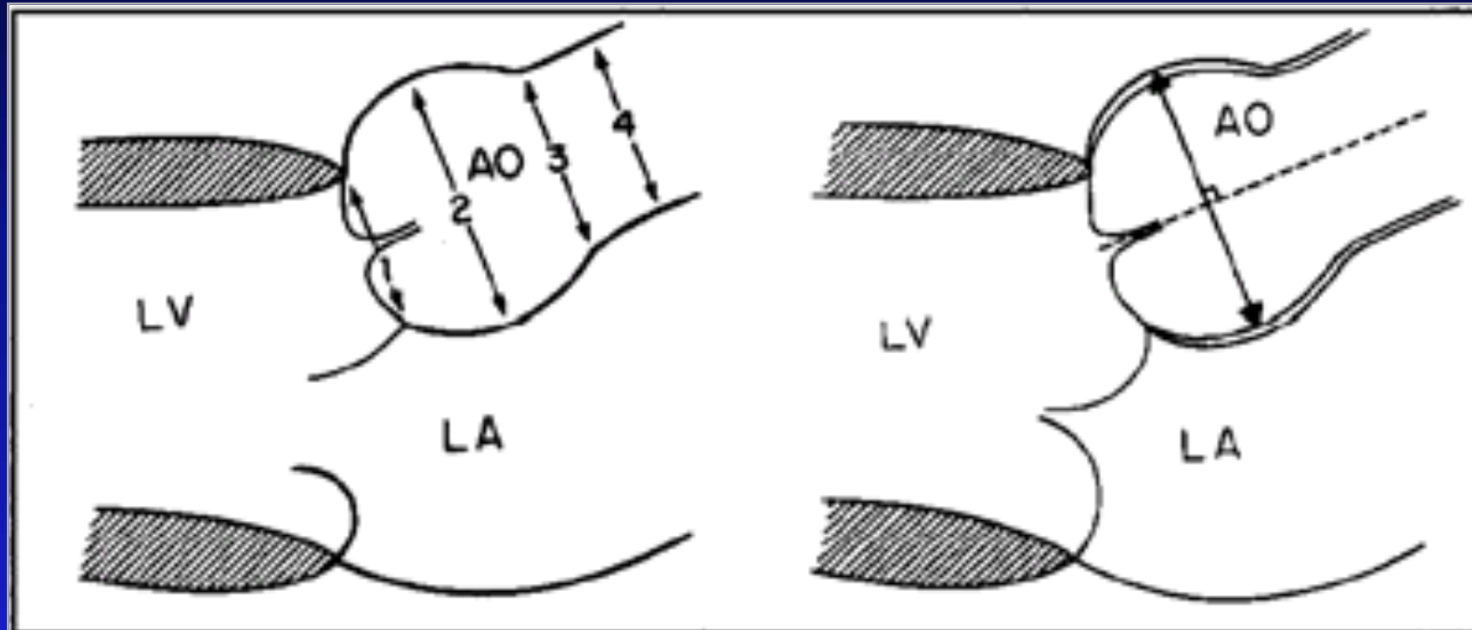
Clin Genet 2010; 77: 177–182. © John Wiley & Sons A/S, 2009

Marfan syndrome (MFS) is an autosomal dominant disorder of the fibrous connective tissue caused by mutations in the fibrillin-1 (*FBNI*) gene. Although clinical and genetic analyses have been performed in various populations, there have been few studies in Korea. The aim of this study was to investigate the clinical characteristics and genetic background of Korean patients with MFS. In 39 Korean patients with MFS who met the Ghent criteria, the most common clinical finding was aortic dilatation and/or dissection (94.9%), whereas only 35.9% of patients had ectopia lentis. The majority of MFS patients had fewer than four of the skeletal findings required to fulfill the major skeletal Ghent criterion for MFS. Only 21% of Korean patients had major skeletal abnormalities and most cases showed only minor skeletal involvement. *FBNI* gene mutations were detected in 35 out of 39 patients (89.7%), which is similar to rates presented in the previous reports. These results suggest that some clinical features in Korean patients with MFS differed from those reported in Western MFS patients.

Cardiovascular Abnormalities

- Most common cause of morbidity & mortality (~80%)
- Dilatation of the Aortic root & Asc. aorta with or without AR
 - In 50% children
 - In up to 70% of adults
- Aortic dissection (AD)
 - Predominantly type A AD
 - Prominent cause of AD in patients < 40 yrs
 - In IRAD, 50% among acute AD patients < 40 yrs
- Minor criterion
 - Mitral valve prolapse (60-80%)
 - Dilatation of the main pul. Artery
 - Calcification of the mitral annulus < 40 yrs
 - Dilatation or dissection of the des. or Abd. Aorta < 50 yrs

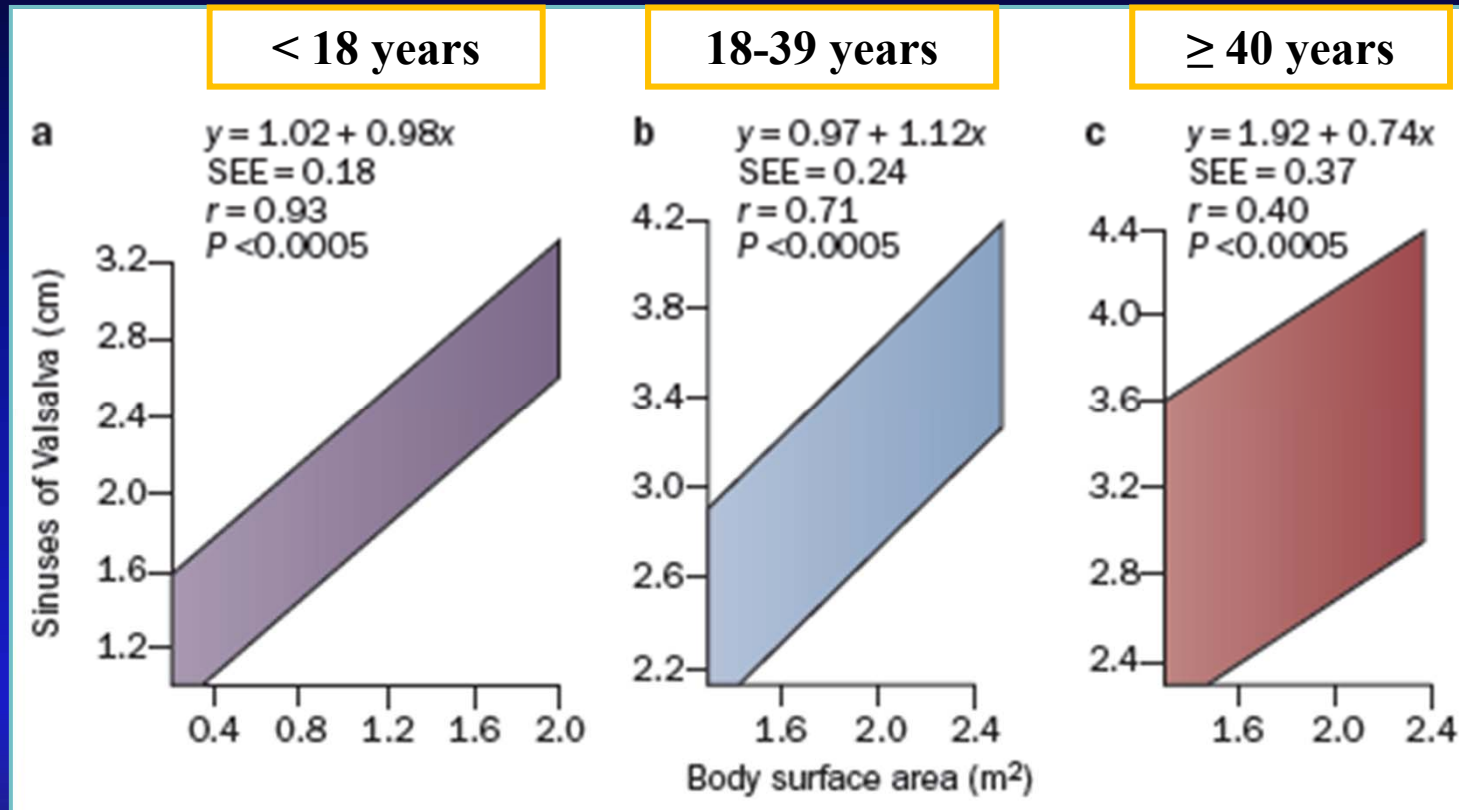
Aortic Root Measurement



Diameter should be compared with indexed nomograms that take into account the patient's age and BSA

Roman MJ, Devereux et al, Am J Cardiol; 1989(64):507-512

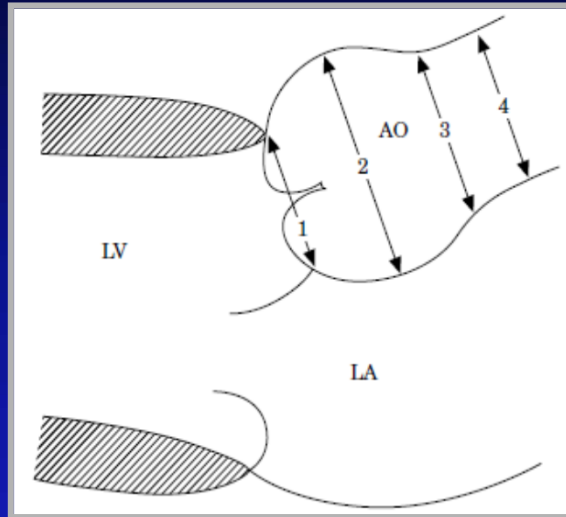
Aortic Root Measurements



- Aortic dilation ; $> \text{mean} + 2\text{SD}$ (Z-score > 2)

Roman MJ, Devereux et al, Am J Cardiol; 1989(64):507-512

Normal Aortic Dimension in Adult



| Diameter | | |
|--------------------------|------------------------------|-----------------------|
| Aortic annulus | | |
| Male | 2.6 ± 0.3 cm | TTE ^[33] |
| Female | 2.3 ± 0.2 cm | TTE ^[33] |
| Sinus of Valsalva | | |
| Male | 3.4 ± 0.3 cm | TTE ^[33] |
| Female | 3.0 ± 0.3 cm | TTE ^[33] |
| Aortic root | | |
| | <3.7 cm | TTE ^[33] |
| Proximal ascending aorta | | |
| Male | 2.9 ± 0.3 cm | TTE ^[33] |
| Female | 2.6 ± 0.3 cm | TTE ^[33] |
| Ascending aorta | | |
| | 1.4–2.1 cm . m ⁻² | TEE ^[45] |
| | <3.8 cm (2.5–3.8) | CT ^[2] |
| | <3.7 cm | TTE ^[46] |
| Descending aorta | | |
| | 1.0–1.6 cm . m ⁻² | TEE ^[45] |
| | <2.8 cm (1.7–2.8) | CT ^[2] |
| Wall thickness | | |
| Aortic wall | | |
| | <4 mm | CT ^[47] |
| | <3 mm | Angio ^[48] |
| | <4 mm | TEE ^[49] |

Change of Aortic Root according to Age & Gender

- Mean annual increased in aortic diameter
 - *Lazarevic AM et al. Int J Cardiol 2006;106(2):177-82*
 - At annulus : 0.4 ± 0.3 mm
 - At the sinuses of Valsalva ; 1.5 ± 1.3 mm
 - At supraaortic ridge ; 0.7 ± 0.6 mm
- Gender difference in the progression of aortic dilatation
 - *Meijboom LJ et al, Am J Cardiol 2005;96(10):1441-4.*
 - Women had on average a 5mm smaller aortic root diameter than men
 - Average aortic root growth
 - Men) 0.42 mm/y, Women) 0.38 mm/y

Management: Screening/Counseling

- **Echocardiogram**

- **Children**

- Perform in newborn period or before 1 year of age, then annually starting at 3 years of age
 - Every 6 months if abnormal

- **Adults**

- Yearly, as long as aortic root diameter is $< 45\text{mm}$
 - Every 6 months if diameter is $> 45\text{mm}$

- Annual ophtho. exam and orthopedic involvement as needed
- Counseling regarding physical activities
- Genetic counseling

Medical Management of Marfan's Aortic Disease

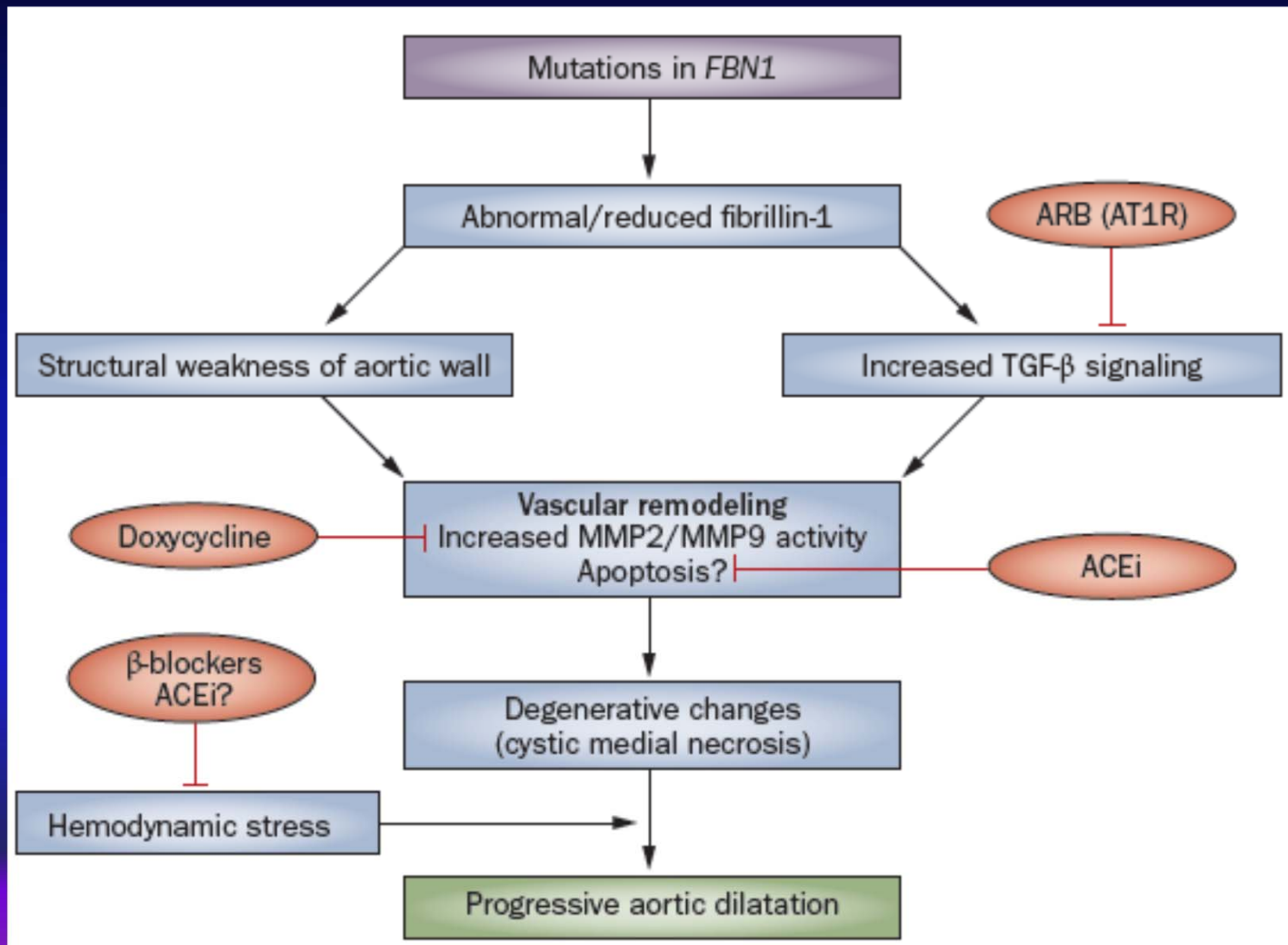
- Beta-blocker: standard of care
 - ACEi (?)
 - ARB (?)
- } possible alternatives to β -blocker

Beta Blockers

- **Properties:**
 - Decrease myocardial contractility & pulse Pressure
 - Reduction in aortic wall stress ($dP/dt \downarrow$)
 - May also improve the elastic properties of the aorta
- **Standard of care in adolescent & adults**
 - open-label, randomized trial of 70 Pts with classic MFS assigned to propranolol vs. no specific Tx ... 10yr data
 - Shores J et al, NEJM 1994;330:1335-41
 - Propranolol group had a significantly slower rate of aortic dilatation
 - Survival for the propranolol group was higher
- **More effective in patient with less aortic dilatation(<4cm)**
- Overall event-free survival was not significant

Current recommendation advise the early use of beta-blocker in all patient with MFS

Possible Pathogenic Target for Medical Treatment of Pts with MFS



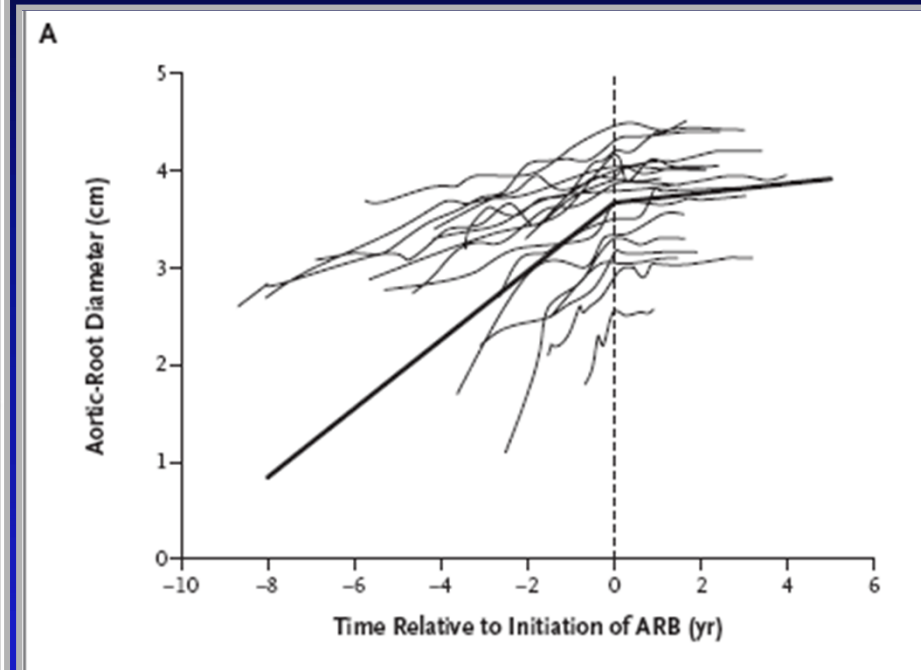
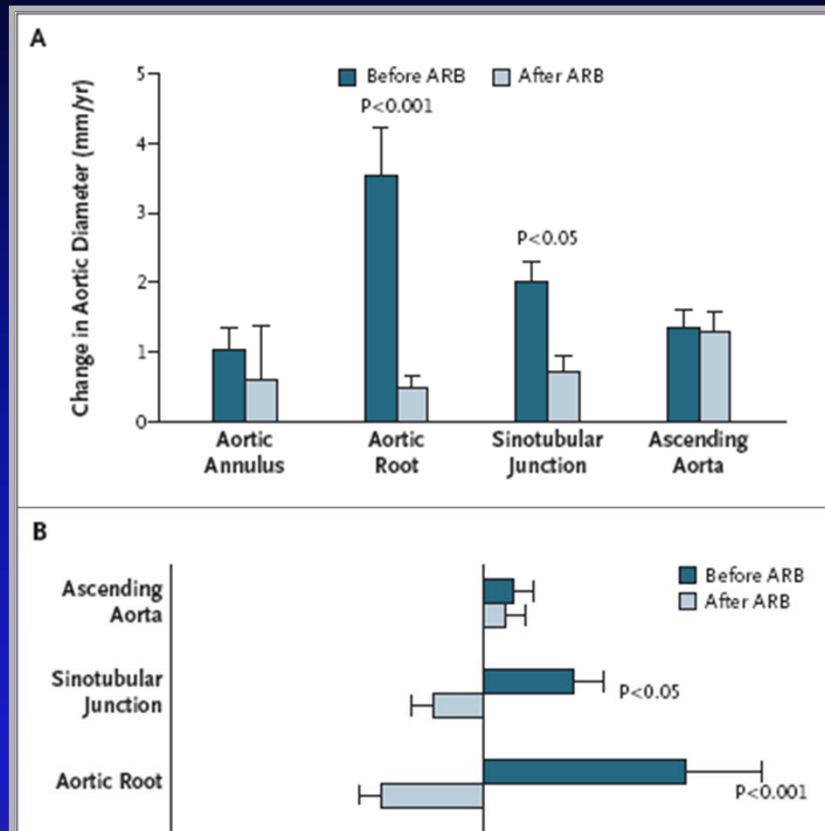
ACE Inhibitor

- Very randomized small study
- Enalapril vs Propranolol or atenolol
 - *Yetman AT et al. Am J Cardiol 2005;95:1125*
- Perindopril
 - *Ahimastos AA et al. JAMA 2007;298:1539*
- Conclusion
 - ACEi reduced both aortic stiffness & aortic root diameter in Pts with taking β -blocker
 - Large clinical trial are need

TGF β and ARB

- MFS: low levels of fibrillin-1 & rise TGF- β levels
 - degrade elastin fibers & other components of the ECM
 - progressive dilatation of aortic root
- Activation of TGF- β
 - Binding of AT II to AT1R
 - Expression of thrombospondin 1
 - \uparrow Activation of TGF- β & signaling
- ARB (losartan)
 - Inhibits the activation of TGF- β

ARB & Aortic Root Dilatation in MFS



CONCLUSIONS

In a small cohort study, the use of ARB therapy in patients with Marfan's syndrome significantly slowed the rate of progressive aortic-root dilation. These findings require confirmation in a randomized trial.

Surgical Management of Marfan's Aortic Disease

- Better survival with elective repair
- Valve sparing with reimplantation technique is better

Indications for Prophylactic Aortic Surgery

- **Greatest impact on the survival of MFS pt**
- Risk of dissection correlates positively with diameter of the aortic root & ascending aorta
- Limitation: based on absolute aortic root diameters
 - predicted aortic root diameter varies with body size
 - may be smaller in women
 - Aortic root diameter for surgery in pediatric is unclear

Indication for Prophylactic Replacement

2006 AHA/ACC, 2007 ESC, 2008 ACC/AHA

| | |
|---|---|
| Ascending aortic Diameter >4.0 cm | Search for connective tissue disorder, initiate β -blocker therapy, maintain strict blood pressure control, moderately restrict physical activity, provide prepregnancy counseling, perform yearly follow-up by TTE and/or CT / MRI |
| Diameter >4.5 cm and aortic valve surgery | Provide operative treatment |
| Diameter >4.5 cm in cases of connective tissue disorder | Consider operative treatment in cases of desired pregnancy, family history of aortic dissection, LDS, or TGFBR1/TGFBR2 mutation or progressive aortic growth >0.5 cm/y |
| Diameter >5.0 cm in cases of connective tissue disorder | Provide operative treatment |
| Diameter >5.5 cm in other cases | Provide operative treatment |

Conclusions

- Prognosis on Marfan syndrome is mainly determined by aortic complication
- Echocardiography is the gold standard tool for the assessment of early aortic root dilatation & demonstrating dissection and also serial follow-up of this patients
- Prophylactic aortic surgery has dramatically changed the prognosis of MFS in the past few decades

Thanks for your attention

Effect of Beta-blocker in children

- Previous study) more limited, controversy
- Ladouceur M et al. Am J Cardiol 2007;99:406
 - Randomized trial of 155 Pts < 12 yrs with classic MFS
 - Beta blockade significantly decreased the rate of aortic dilatation at the level of the sinuses of Valsalva by a mean of 0.16 mm/year