

*la pratica dev' essere edificata sopra la buona teorica  
(Practice must always be founded on sound theory)  
Leonardo Da Vinci*

# **Bicuspid Aortopathy- to replace or not to?**

Dr. Fabian A. Kari

Heart Center Freiburg University

Cardiovascular Surgery

**I.**

**I have received (a) research grant(s) / in kind support**

**A**

**... from current sponsor(s)**

**YES**

**NO**

**B**

**... from any institution**

**YES**

**NO**

**II.**

**I have been a speaker or participant in accredited CME/CPD ...**

**A**

**... from current sponsor(s)**

**YES**

**NO**

**B**

**... from any institution**

**YES**

**NO**

**III.**

**I have been a consultant / strategic advisor etc. ...**

**A**

**... for current sponsor(s)**

**YES**

**NO**

**B**

**... for any institution**

**YES**

**NO**

**IV.**

**I am a holder of (a) patent / shares / stocks or ownership...**

**A**

**... related to presentation**

**YES**

**NO**

**B**

**... not related to presentation**

**YES**

**NO**

**SCORE: 1234**

# Agenda

- I. Status quo (5')
- II. Evidence (10')
- III. Guidelines (5')
- IV. New risk markers (10')

# I. Status quo

## - Case Scenario



# I. Clinical Scenario

- 62 y/o male, NYHA II, FH: positive for BAV, one unclear sudden death, CVRF: arterial hypertension
- Bicuspid combined valvular dysfunction with leading stenotic component (4 m/sec)
- Valve Type: one Raphe, fused left-right coronary cusps
- Root Geometry: unbalanced (150 degrees)
- Sinotubular definition
- Aortic annulus: elliptical, max. **29mm** – Aortic root: **42mm**, Ascending Aorta: **45mm**, rate last 2 years: **1mm/year**

**What to do with the ascending aorta?**

Fictional patient – real attendings

# I. Clinical Scenario

## Attending Surgeon 1

- Thickness of ascending aortic tissue?
- Reduction Plasty

## Attending Surgeon 3

- Leave aorta alone, no indication

## Attending Surgeon 2

- Modified Bentall / CVG

## Attending Surgeon 4

- Leave root alone
- Wheat procedure

- Surgeon preference
- Tissue „quality“ characteristics?

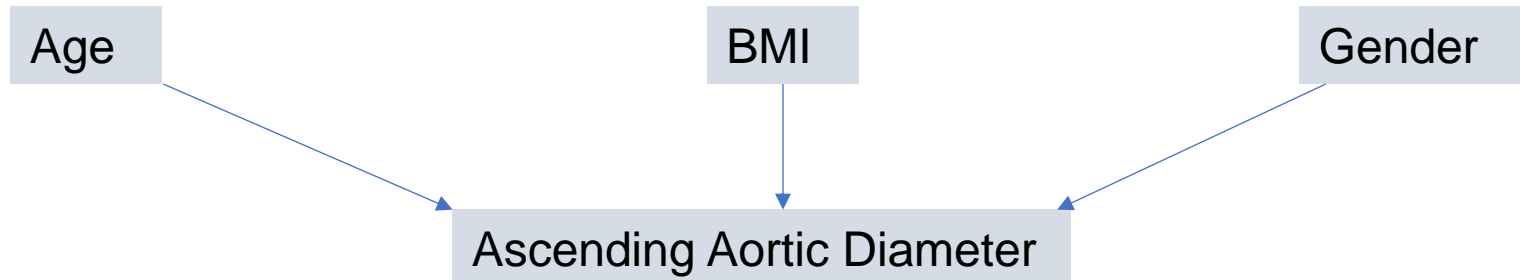
# II. Evidence

- Bicuspid Aortopathy
- Aortopathy Clusters





# Ascending Aorta – dilated or not?



Upper normal diameter based on patient age:  
 $D \text{ (mm)} = 31 + 0,16 \times \text{age (years)}$

For extreme BMI:  
 $D \text{ (mm)} = 21 + 0,14 \times \text{age (years)} + (0,41 \times \text{BMI})$

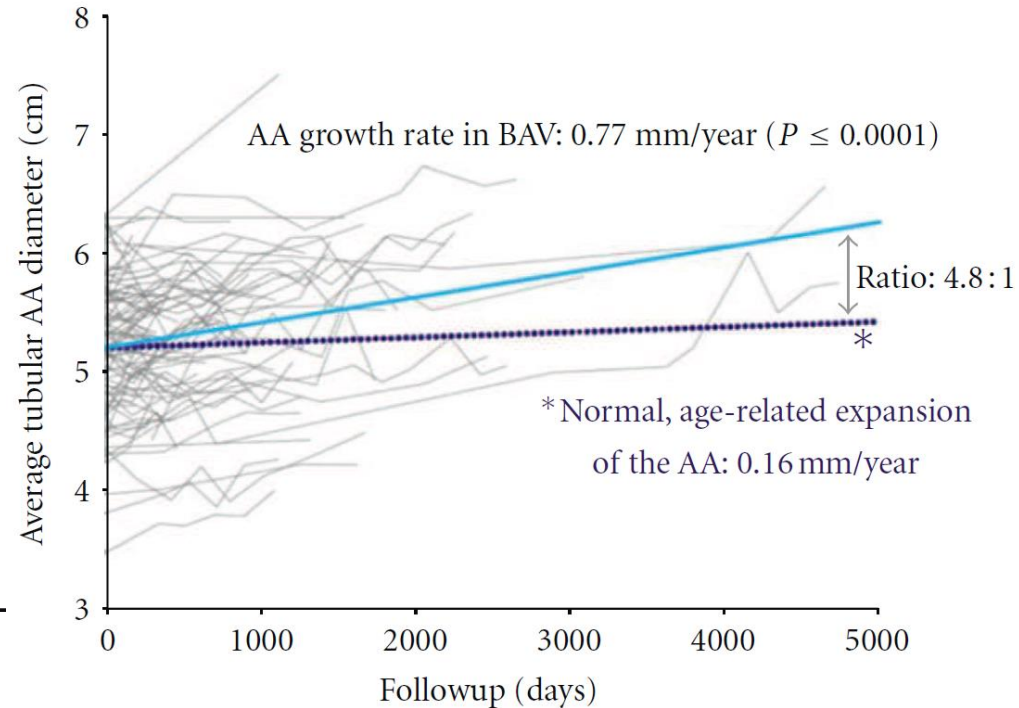
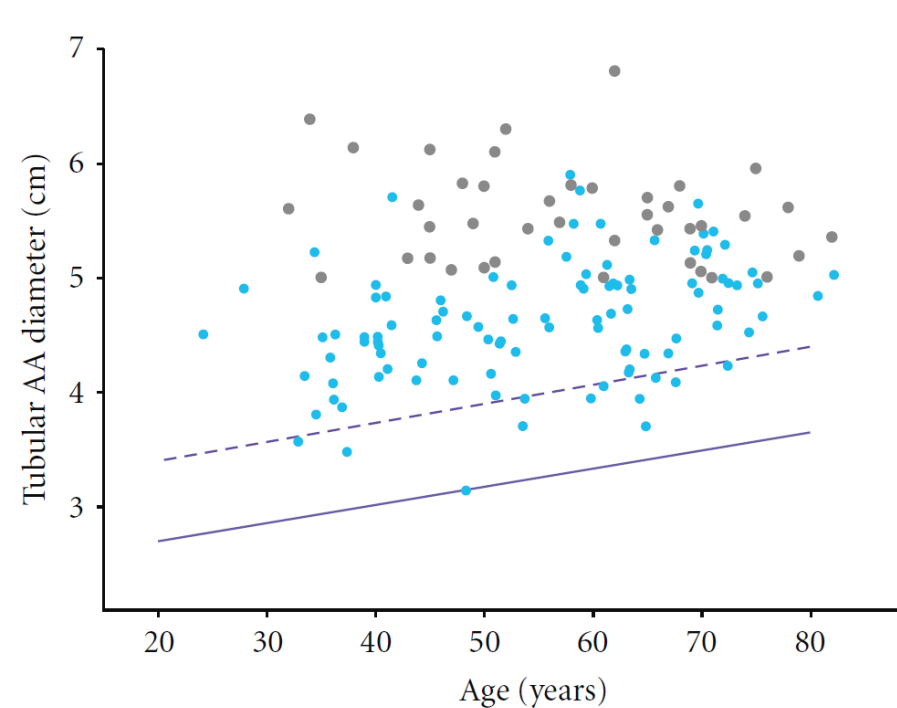
20 y/o average 27mm, 34 still “normal”  
80 y/o average 37mm, 44 still “normal”

50% increase in Diameter  
Ectasia-Aneurysm  
**BUT**  
20 y/o – 40mm  
40 y/o – 45mm  
60 y/o – 50mm  
80 y/o – 55mm

Hannuksela M, Lundqvist S and Carlberg B. Thoracic aorta--dilated or not?  
Scand Cardiovasc J. 2006;40:175-8.



# Ascending Aorta – growth, but how fast ?

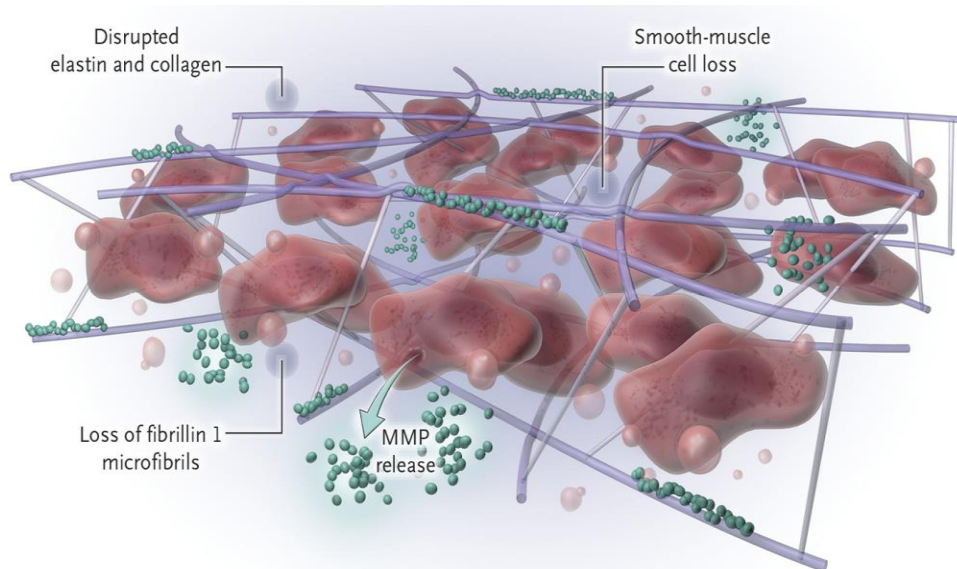
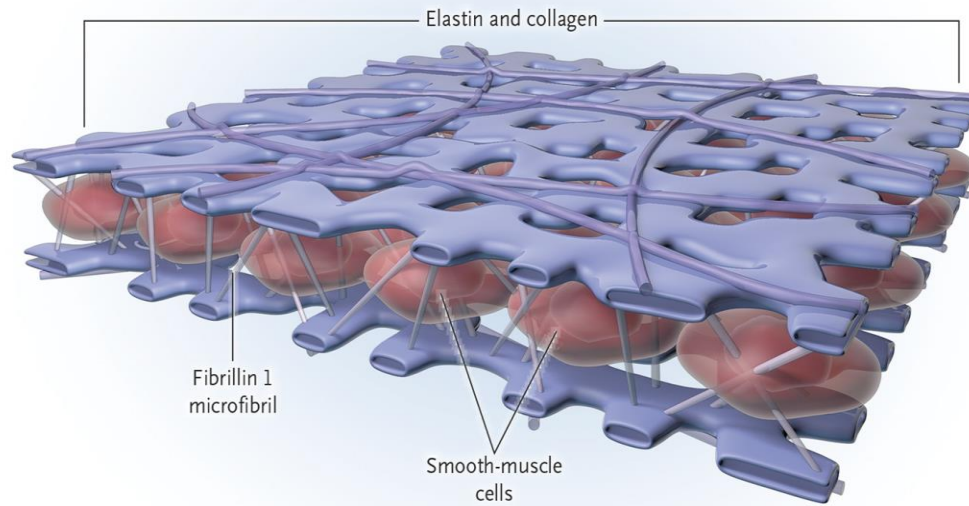


- Normal ascending aorta\*
- - - Normal ascending aorta: upper limit\*
- Immediate surgery (N = 42)
- Surveillance (N = 116)

Hannuksela M, Lundqvist S and Carlberg B. Thoracic aorta--dilated or not? Scand Cardiovasc J. 2006;40:175-8.

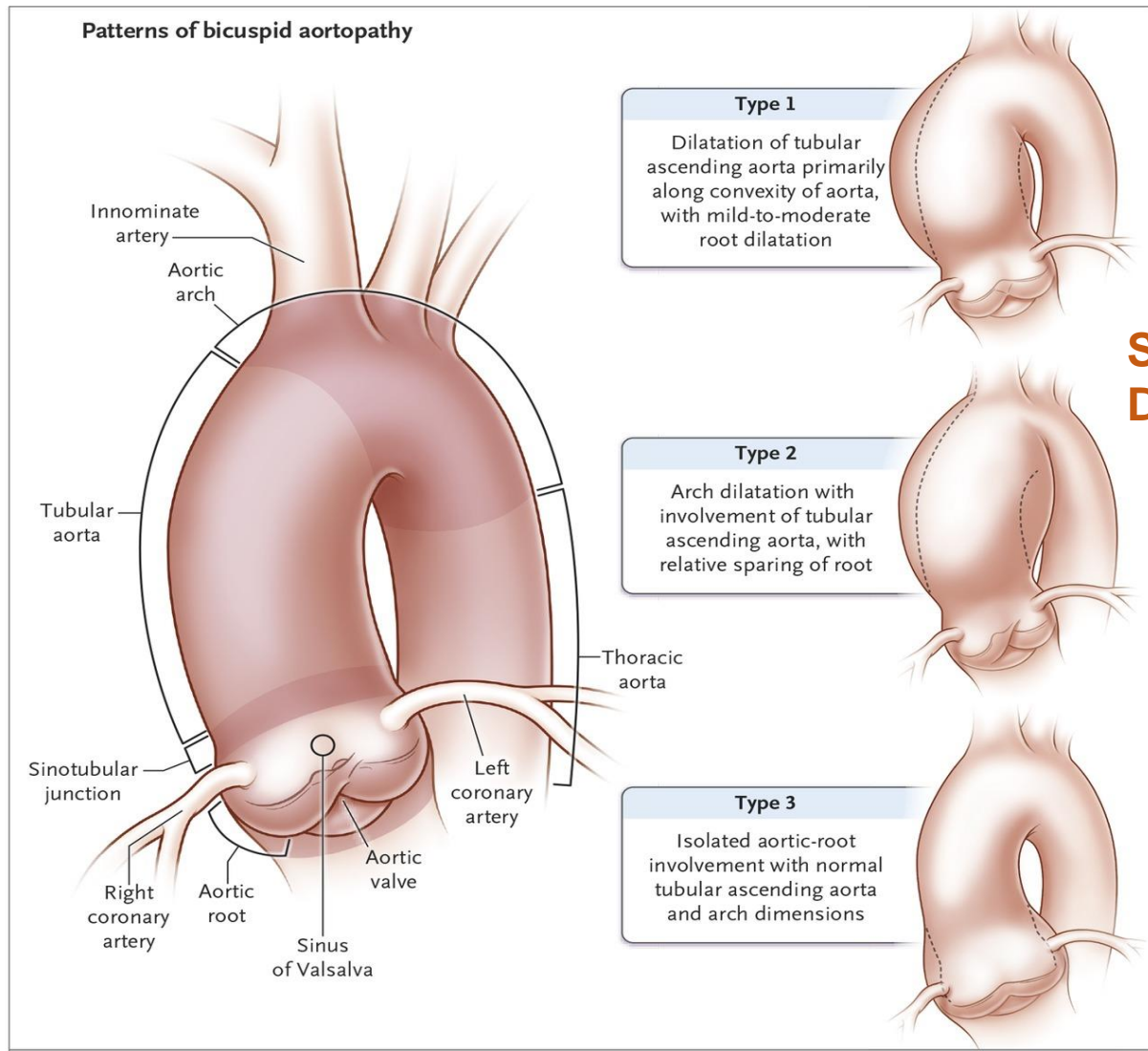
Etz CD, Zoli S, Brenner R, Roder F, Bischoff M, Bodian CA, DiLuozzo G and Griep RB. When to operate on the bicuspid valve patient with a modestly dilated ascending aorta. Ann Thorac Surg. 2010;90:1884-90; discussion 1891-2.

# Bicuspid Aortopathy



Verma S and Siu SC. Aortic dilatation in patients with bicuspid aortic valve. N Engl J Med. 2014;370:1920-9.

# Bicuspid Aortopathy



**STJ  
Definition**

# The aortopathy of bicuspid aortic valve disease has distinctive patterns and usually involves the transverse aortic arch

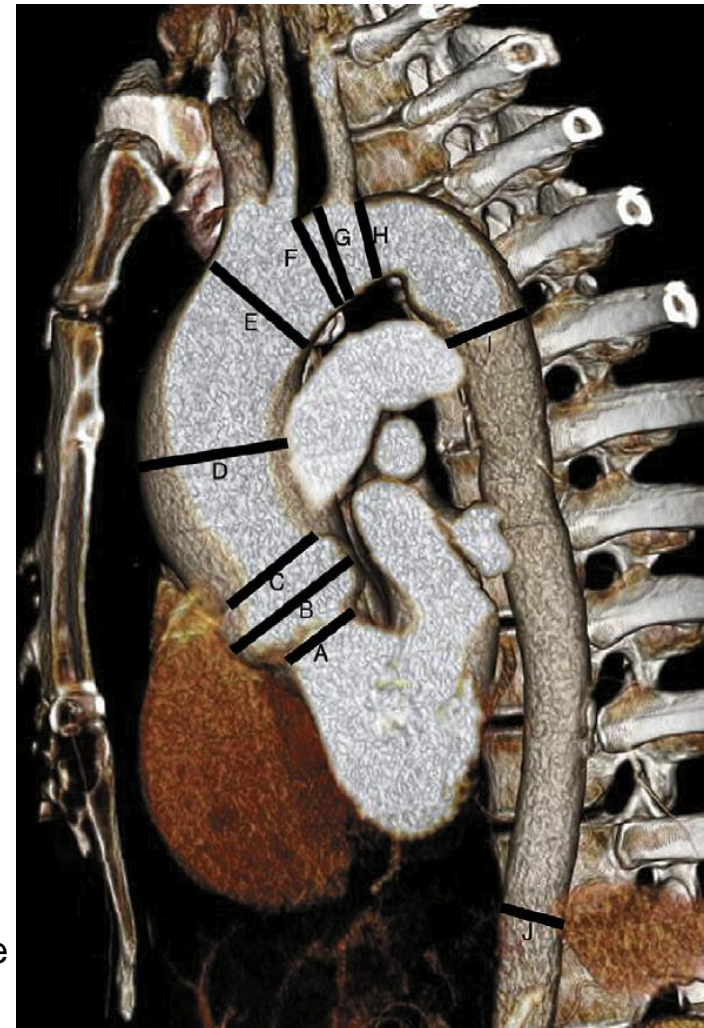
Shafie S. Fazel, MD, PhD,<sup>a</sup> Hari R. Mallidi, MD,<sup>a</sup> Richard S. Lee, MD,<sup>a</sup> Michael P. Sheehan, MSN, RN, FNP,<sup>a</sup> David Liang, MD, PhD,<sup>c</sup> Dominik Fleischman, MD,<sup>b</sup> Robert Herfkens, MD,<sup>b</sup> R. Scott Mitchell, MD,<sup>a</sup> and D. Craig Miller, MD<sup>a</sup>

**J Thorac Cardiovasc Surg 135: 901,**

N= 64 BAV patients

CTA or MRA of thoracic aorta

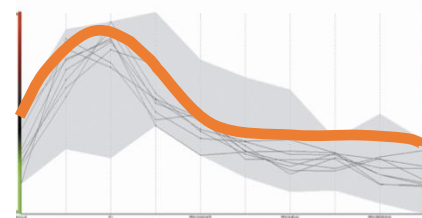
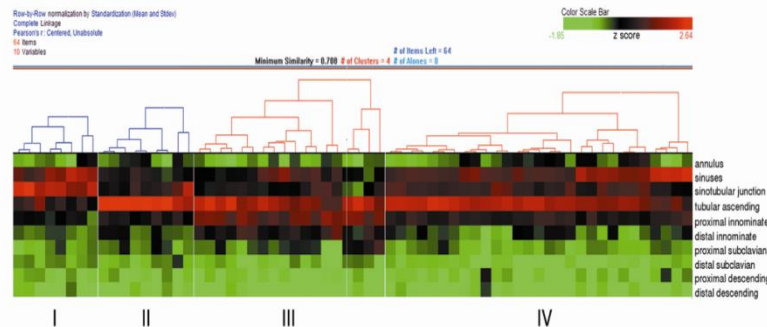
- Aortoventricular junction
- Sinuses of Valsalva
- Sinotubular junction
- Tubular ascending aorta
- Proximal to innominate artery
- Distal to innominate artery
- Proximal to LSCA
- Distal to LSCA
- Proximal descending aorta



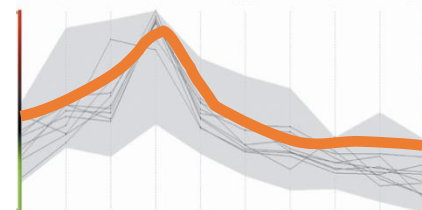
Fazel SS, Mallidi HR, Lee RS, Sheehan MP, Liang D, Fleischman D, Herfkens R, Mitchell RS and Miller DC. The aortopathy of bicuspid aortic valve disease has distinctive patterns and usually involves the transverse aortic arch. J Thorac Cardiovasc Surg. 2008;135:901-7, 907 e1-2.



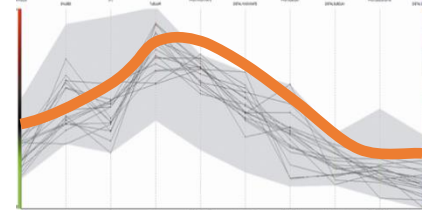
# Cluster I



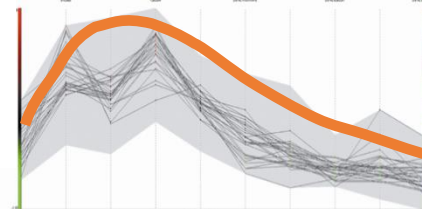
40.9+/-10.6 yrs  
 38% female  
 38% bovine arch  
 Mean AS gradient 15.3 mmHg  
 Mean AI grade 1.25  
 Fusion pattern R/L 75%, R/N 13%, L/N 0%  
 Naturally perfect 13%



48.4+/- 11.2 yrs  
 13% female  
 13% bovine arch  
 Mean AS gradient 6.9 mmHg  
 Mean AI grade 1.00  
 Fusion pattern R/L 100%, R/N 0%, L/N 0%  
 Naturally perfect 0%



44.4+/-10.3 yrs  
 28% female  
 22% bovine arch  
 Mean AS gradient 24.9 mmHg  
 Mean AI grade 1.35  
 Fusion pattern R/L 73%, R/N 21%, L/N 0%  
 Naturally perfect 6%



46.1+/-13.2 yrs  
 24% female  
 35% bovine arch  
 Mean AS gradient 11 mmHg  
 Mean AI grade 1.23  
 Fusion pattern R/L 79%, R/N 10%, L/N 3%  
 Naturally perfect 7%

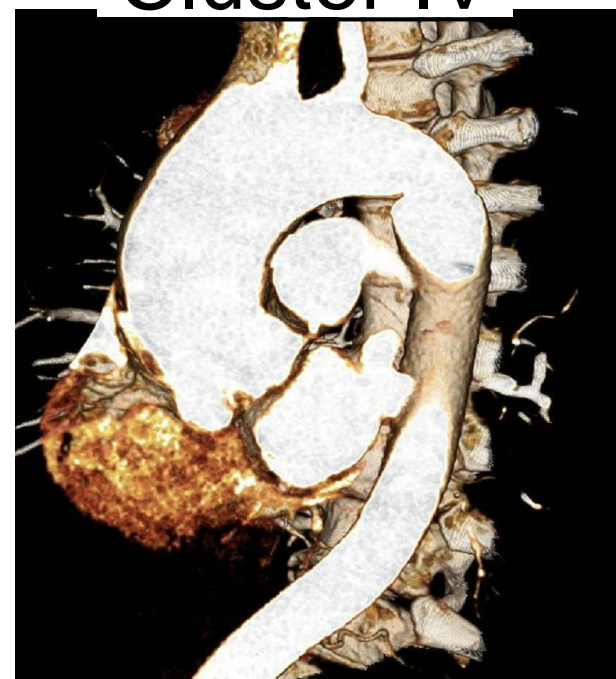
# Cluster II



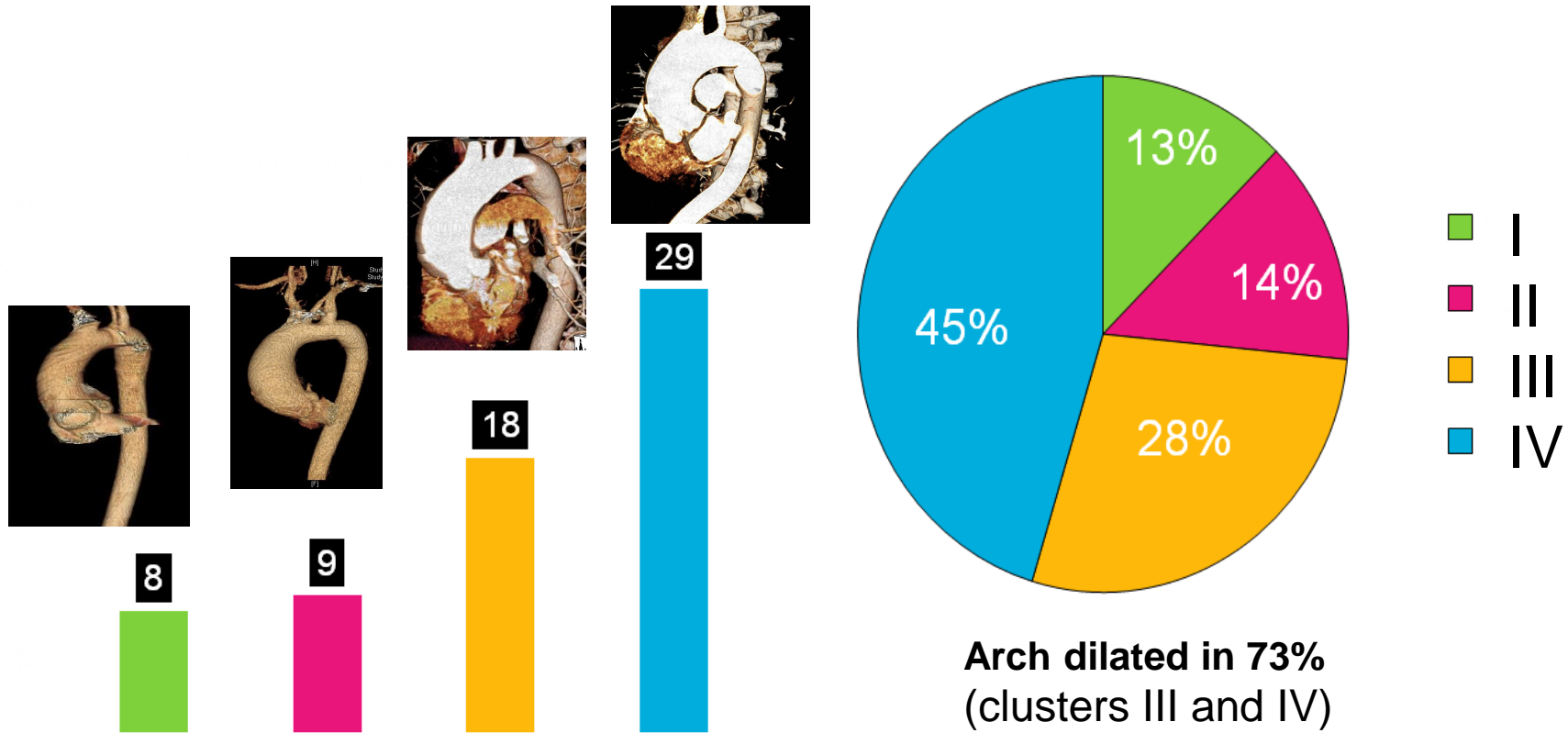
# Cluster III



# Cluster IV

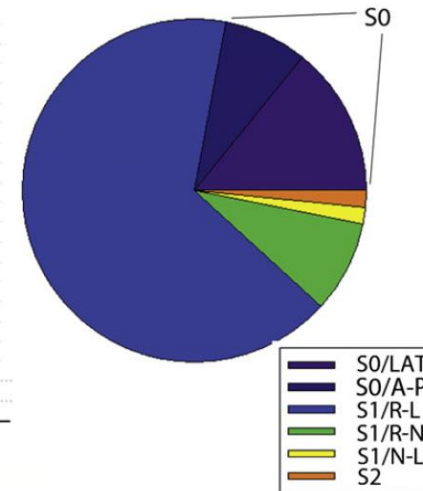
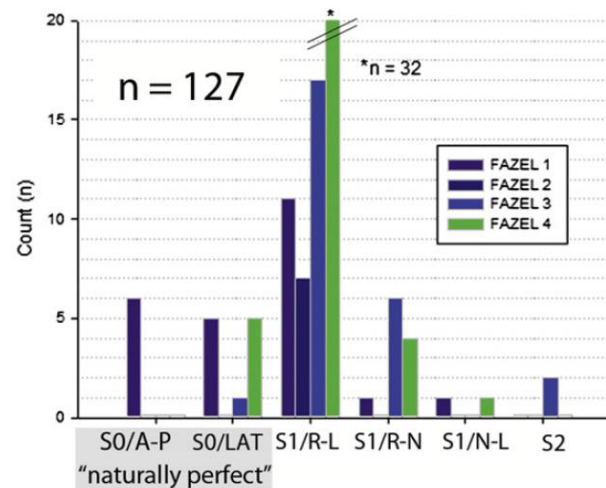
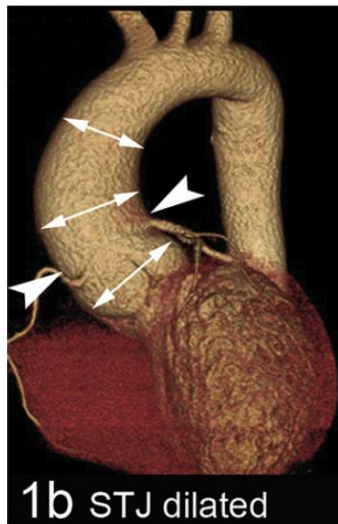
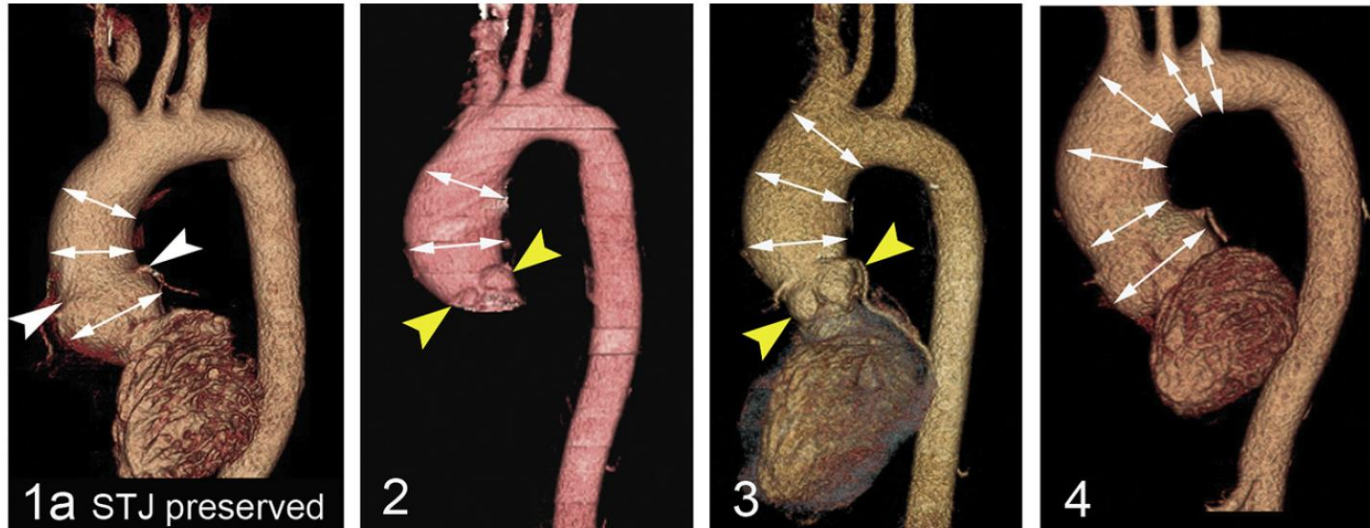


# Morphology Clusters: BAV-Associated Aortopathy Transverse Arch Involvement



Fazel SS, Mallidi HR, Lee RS, Sheehan MP, Liang D, Fleischman D, Herfkens R, Mitchell RS and Miller DC. The aortopathy of bicuspid aortic valve disease has distinctive patterns and usually involves the transverse aortic arch. J Thorac Cardiovasc Surg. 2008;135:901-7, 907 e1-2.

# Bicuspid Aortopathy – related to valve type?

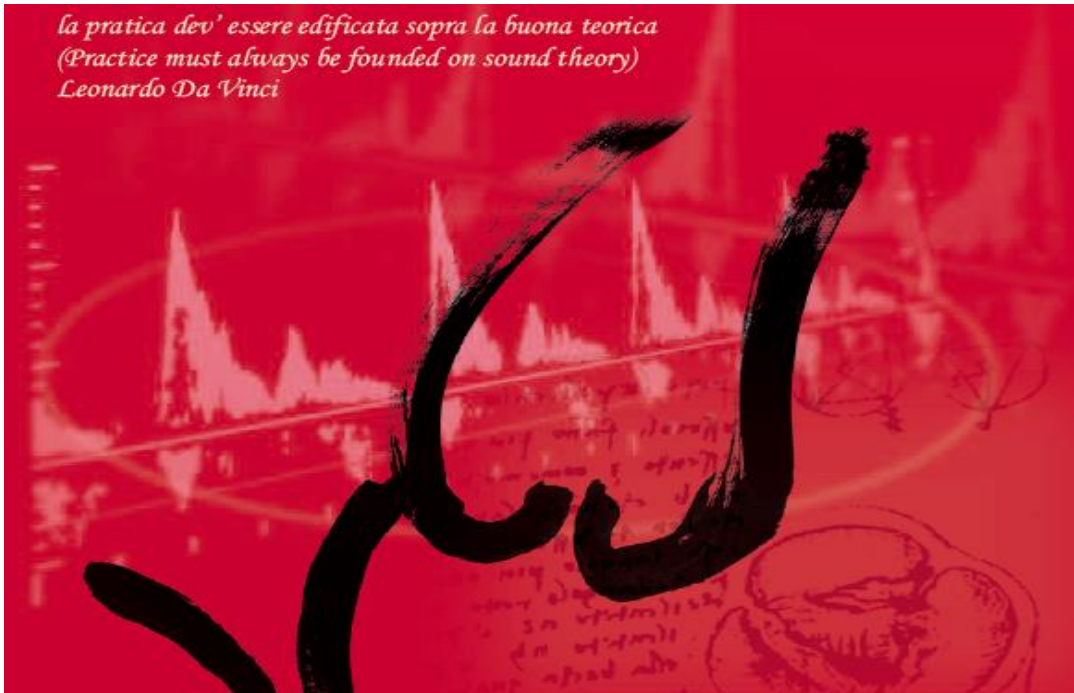


Kari FA, Fazel SS, Mitchell RS, Fischbein MP and Miller DC. Bicuspid aortic valve configuration and aortopathy pattern might represent different pathophysiologic substrates. J Thorac Cardiovasc Surg. 2012;144:516-7.



# III. Guidelines

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*(Practice must always be founded on sound theory)*  
*Leonardo Da Vinci*



# III. Guidelines

Decision in aortic diameters **50-55mm** based on

- Patient age
- Body size
- Comorbidities
- Type of surgery
- Risk factors:
  - Family history
  - Hypertension
  - Coarctation
  - Rapid growth > 2mm/year

Aortic diameters  $\geq$  **55mm**  
surgery should be performed  
irrespective  
of valve function

advising against pregnancy [72]. Patients with Marfanoid manifestations due to connective tissue disease, without complete Marfan criteria, should be treated as Marfan patients. In indivi-

Vahanian A, Alfieri O, Andreotti F, et al. Joint Task Force on the Management of Valvular Heart Disease of the European Society of C and European Association for Cardio-Thoracic S. Guidelines on the management of valvular heart disease (version 2012): the Joint Task Force on the Management of Valvular Heart Disease of the European Society of Cardiology (ESC) and the European Association for Cardio-Thoracic Surgery (EACTS). Eur J Cardiothorac Surg. 2012;42:S1-44.



# I. Back to Clinical Scenario

- 62 y/o male, NYHA II, FH: positive BAV, one unclear sudden death, CVRF: arterial hypertension
  - Bicuspid combined valvular dysfunction with leading stenotic component (4 m/sec)
  - Valve Type: One Raphe, fused left-right coronary cusps
  - Root Geometry: unbalanced (150 degrees)
  - Sinotubular definition
  - Aortic annulus: elliptical, max. **29mm** – Aortic root: **42mm**, Ascending Aorta: **45mm**, rate last 2 years: **1mm/year**
- **Valvular indication: ascending aorta indicated**
  - **Without valvular indication: ascending indicated (risk factors)**
  - **With or without valvular indication: root not indicated (?)**

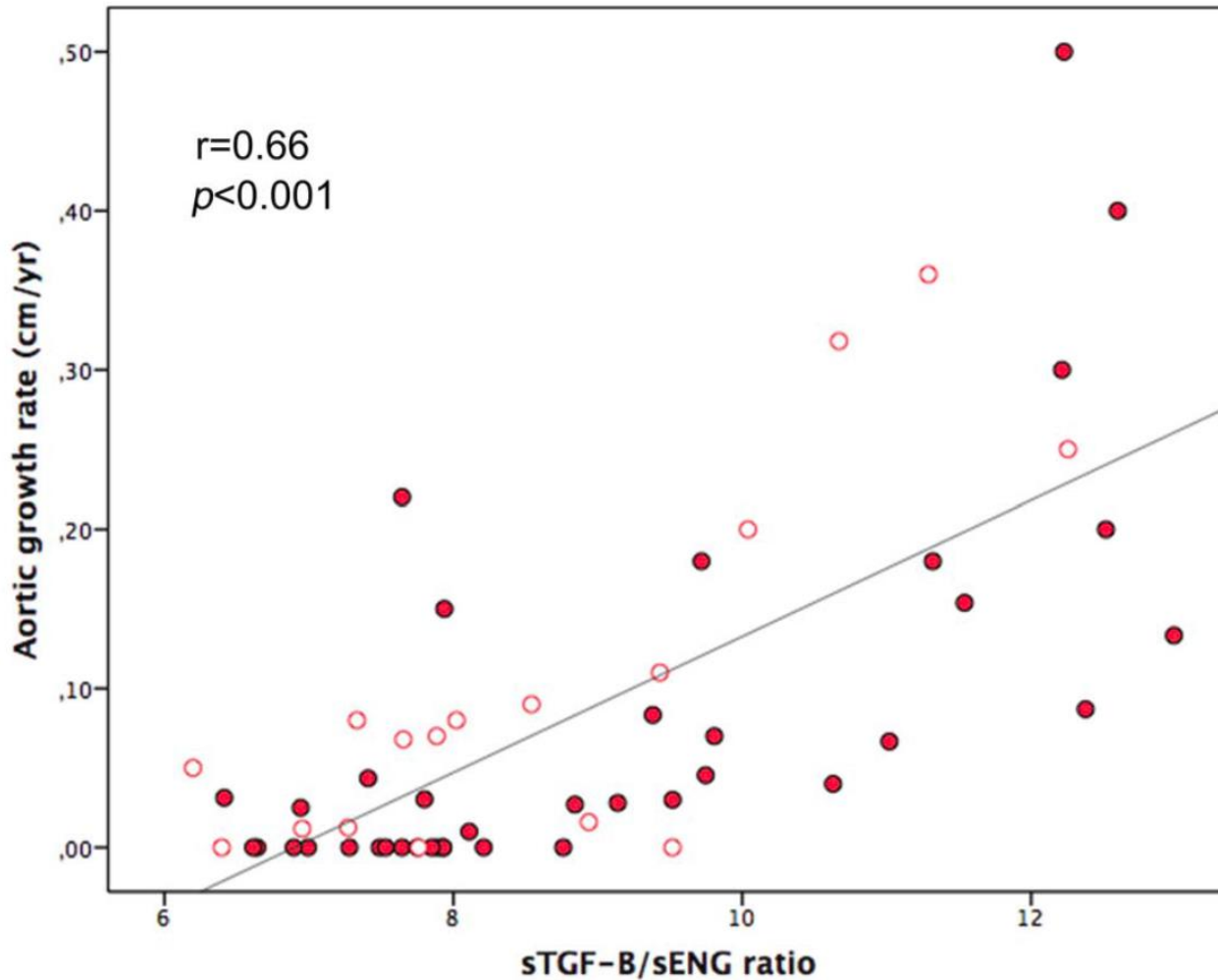
# IV. New Markers

- Serum Enzyme Ratios
- Biomechanics





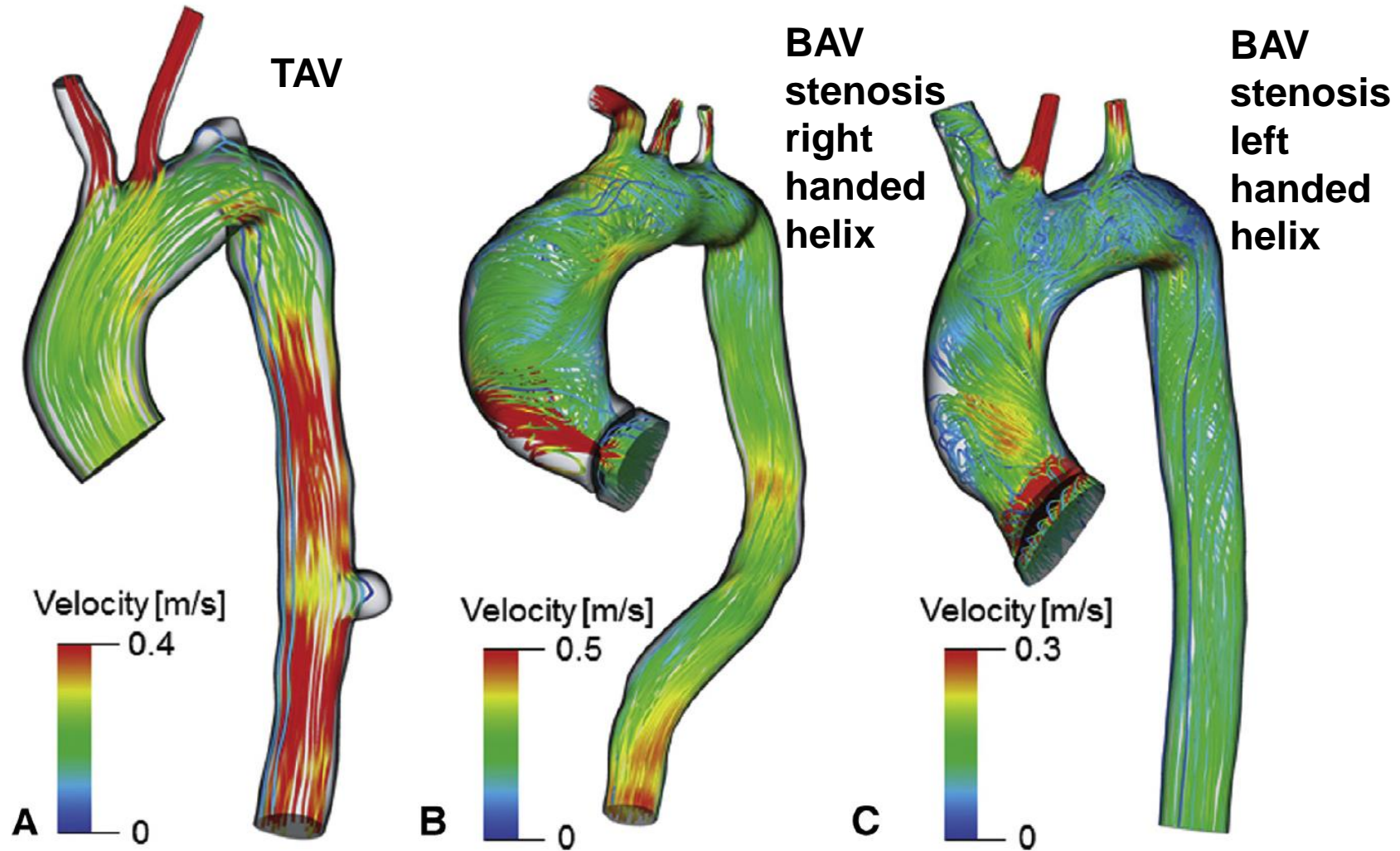
# IV. New Markers: Serum Enzyme Ratios



Forte A, Bancone C, Cobellis G, Buonocore M, Santarpino G, Fischlein T, Cipollaro M, De Feo M and Della Corte A. A Possible Early Biomarker for Bicuspid Aortopathy: Circulating Transforming Growth Factor Beta-1 to Soluble Endoglin Ratio. *Circ Res.* 2017.



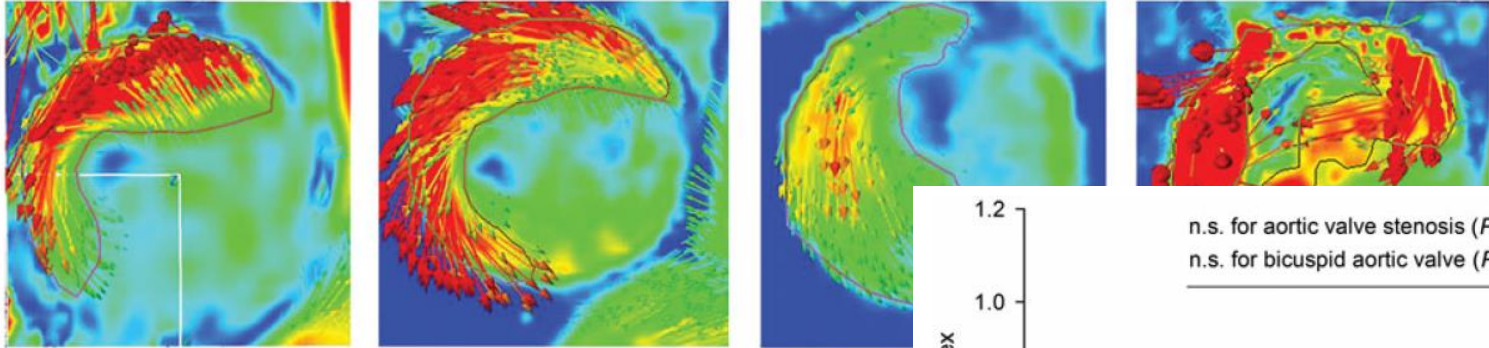
# IV. Biomechanics: Flow Patterns



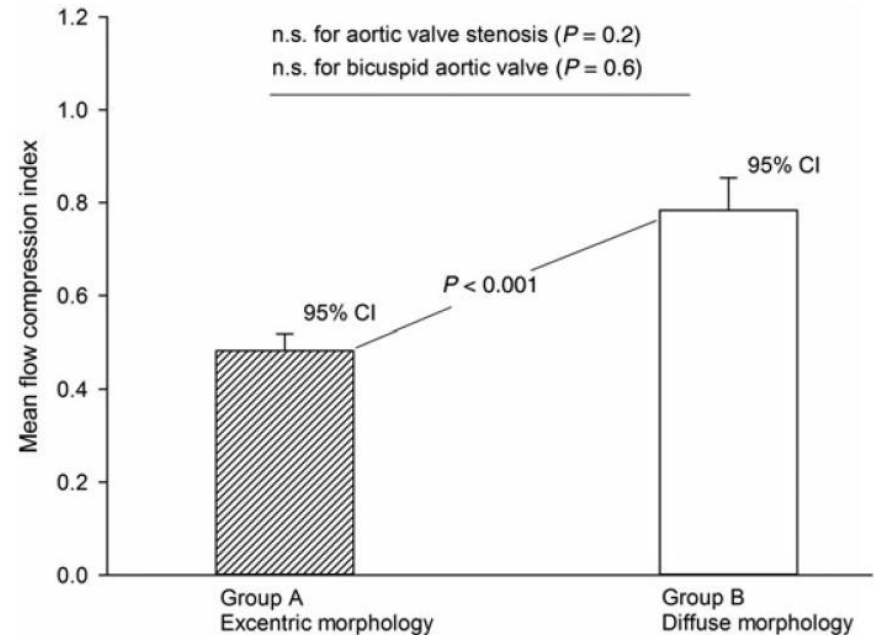
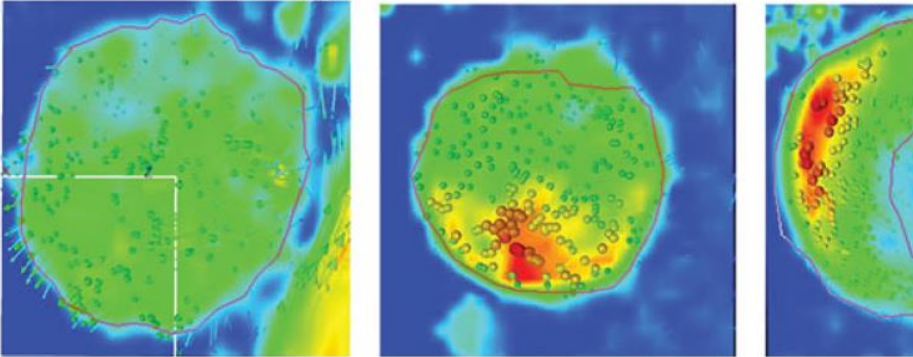
Kimura N, Nakamura M, Komiya K, Nishi S, Yamaguchi A, Tanaka O, Misawa Y, Adachi H and Kawahito K. Patient-specific assessment of hemodynamics by computational fluid dynamics in patients with bicuspid aortopathy. J Thorac Cardiovasc Surg. 2017;153:S52-S62 e3.

# IV. Biomechanics: Flow Patterns

Excentric ascending aortic morphology: small root, tubular enlargement



Non-excentric morphology: diffuse root and tubular enlargement



Kari FA, Kocher N, Beyersdorf F, Tscheuschler A, Meffert P, Rylski B, Siepe M, Russe MF and Hope MD. Four-dimensional magnetic resonance imaging-derived ascending aortic flow eccentricity and flow compression are linked to aneurysm morphology. *Interact Cardiovasc Thorac Surg.* 2015;20:582-7; discussion 587-8.

# IV. Biomechanics - WSS

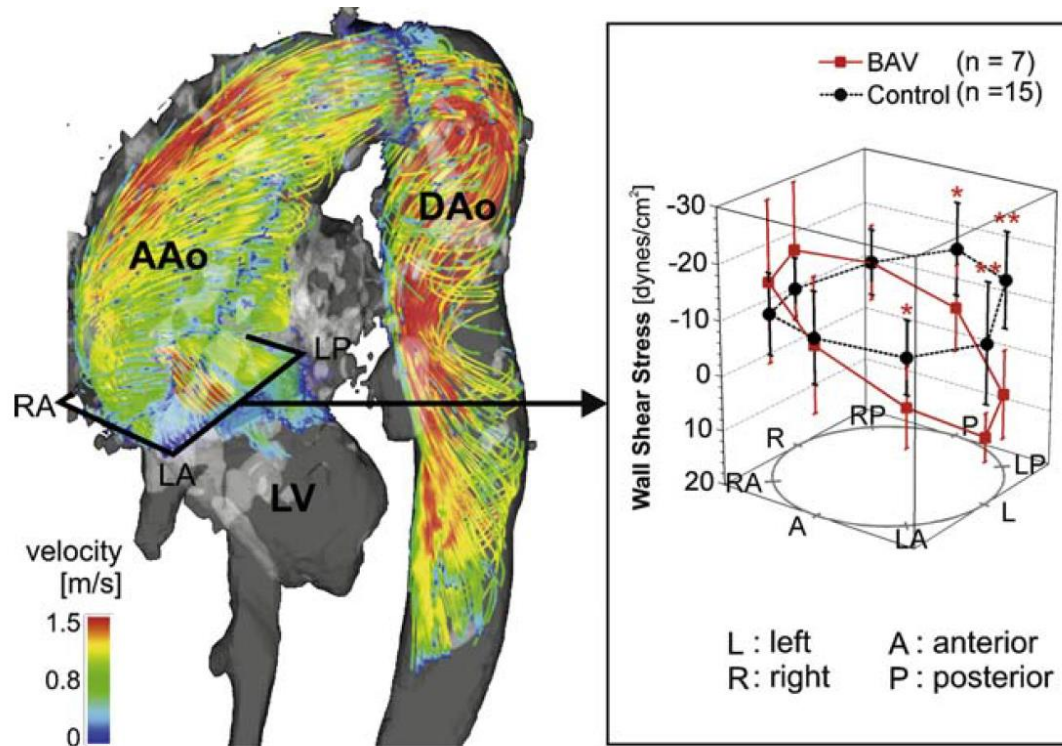


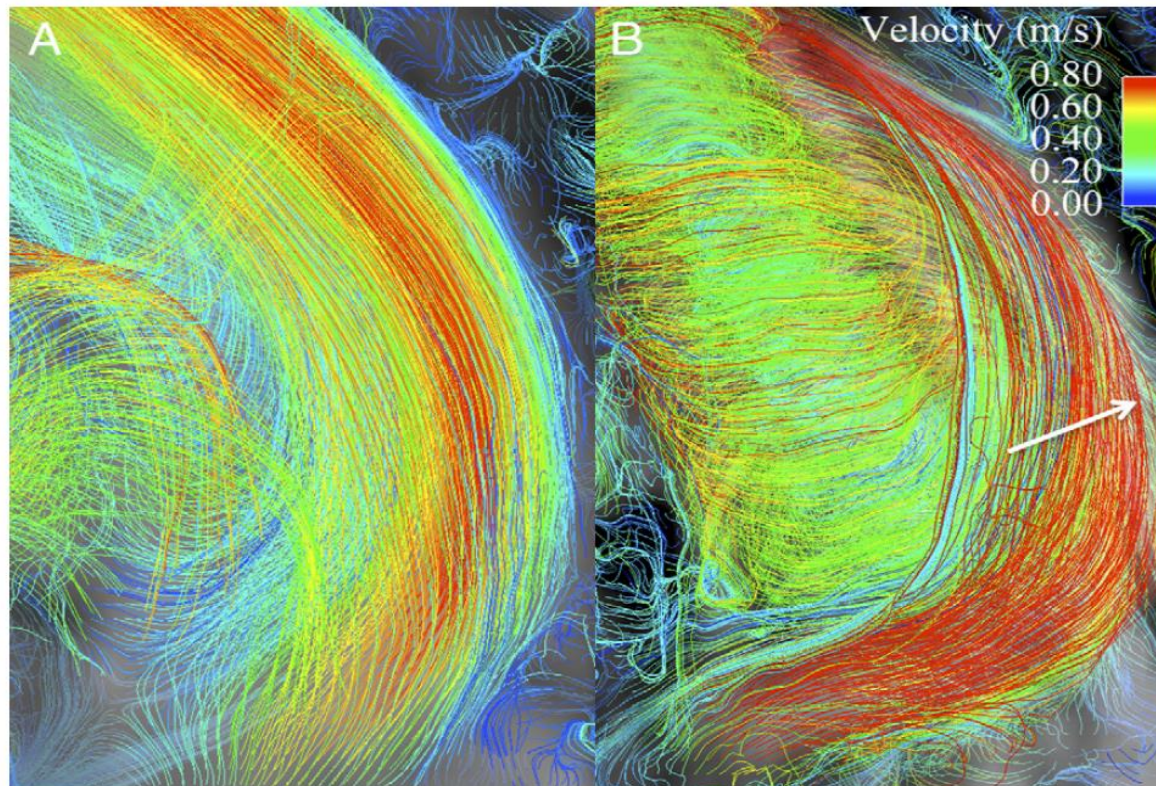
Fig. 1. Volumetric pathline representation of systolic 3D blood flow characteristics in the aortic arch of an insufficient BAV patient. The pattern of exaggerated helical flow in the dilated ascending aorta (AAo) of BAV patients led to significant measured WSS differences (at the level of the sinus of Valsalva) between BAV patients and controls ( $*p < 0.05$ ,  $**p < 0.001$ ). DAo: descending aorta and LV: left ventricle.

Barker AJ, Markl M, Burk J, Lorenz R, Bock J, Bauer S, Schulz-Menger J and von Knobelsdorff-Brenkenhoff F. Bicuspid aortic valve is associated with altered wall shear stress in the ascending aorta. *Circ Cardiovasc Imaging*. 2012;5:457-66.



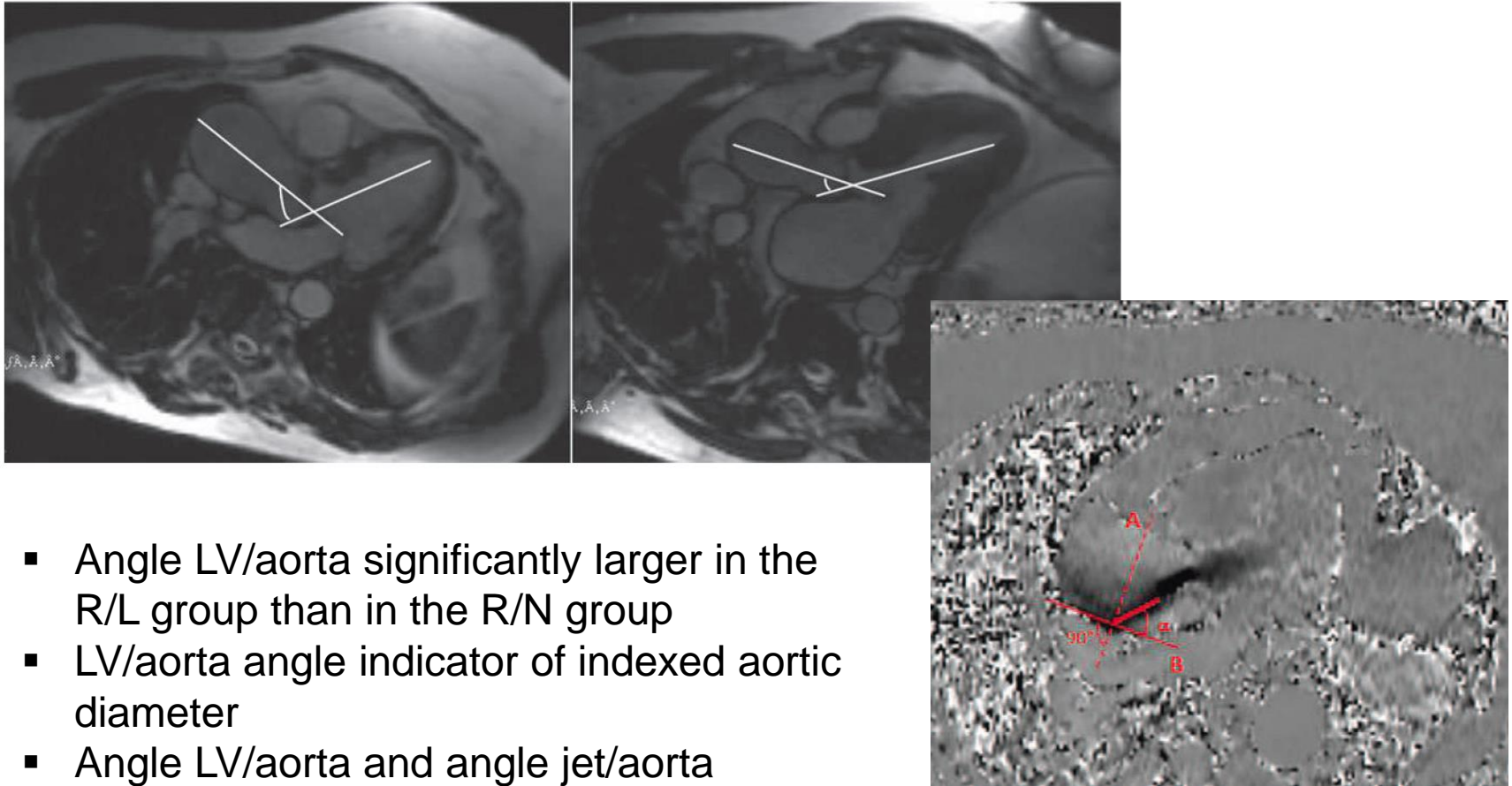
## IV. Biomechanics: Flow Patterns

- Normalized displacement of flow from vessel center
- 25 patients, no significant valve dysfunction, F-U 4.5 years
- Faster aortic growth in pts with displaced flow



Hope MD, Wrenn J, Sigovan M, Foster E, Tseng EE and Saloner D. Imaging biomarkers of aortic disease: increased growth rates with eccentric systolic flow. *J Am Coll Cardiol.* 2012;60:356-7.

# IV. Biomechanics - Geometry



- Angle LV/aorta significantly larger in the R/L group than in the R/N group
- LV/aorta angle indicator of indexed aortic diameter
- Angle LV/aorta and angle jet/aorta predictive of mid-ascending phenotype

Girdauskas E, Rouman M, Disha K, Dubslaff G, Fey B, Theis B, Petersen I, Borger MA, von Kodolitsch Y, Kuntze T and Reichenspurner H. Aortopathy in Bicuspid Aortic Valve Stenosis with Fusion of Right-Left versus Right-Non-Coronary Cusps: Are These Different Diseases? *J Heart Valve Dis.* 2016;25:262-269.

# Take Home Messages

- Diameters + Growth rate + Risk factors
- All guidelines: level of evidence C
- No differentiation between root / ascending aorta
- Serum Enzyme Ratios
- Biomechanics: Flow patterns, shear stress, root geometry, valve type



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(Practice must always be founded on sound theory)  
Leonardo Da Vinci*

# Thank You

## Bicuspid Aortopathy- to replace or not to?

Dr. Fabian A. Kari

Universitäts-Herzzentrum Freiburg-Bad Krozingen

Klinik für Herz- und Gefäßchirurgie





Hardikar AA, Marwick TH. Surgical thresholds for bicuspid aortic valve associated aortopathy. JACC Cardiovasc Imaging 2013;6(12):1311-1320.

# Stress – MMP2/TIMP1-4 - Stiffness

## Hypotheses

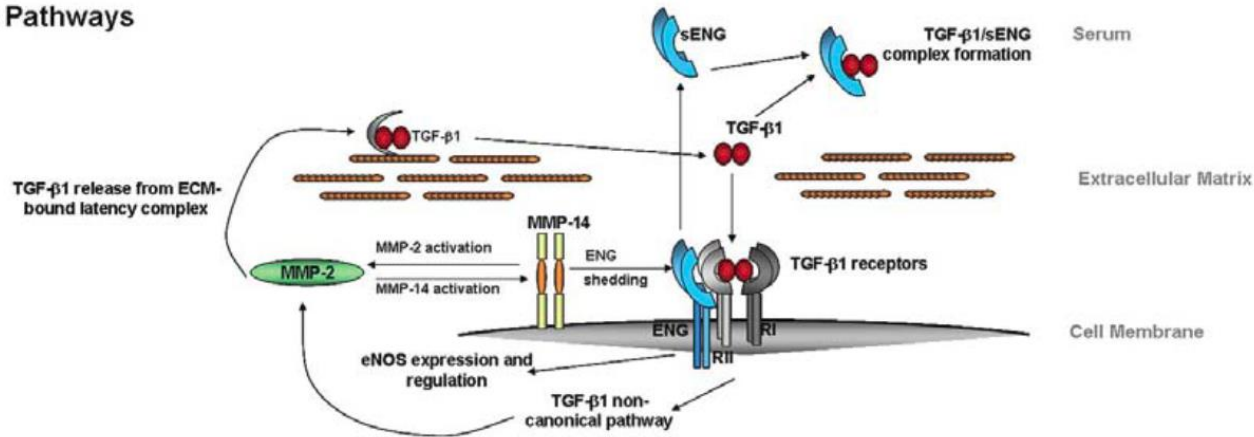
- Stretch regulates MMP-2 activity and TIMP-1-4 protein levels in ascending aortic tissue
- Modulation of MMP-2 activity in human and murine *ex vivo* tissue is sufficient to alter tissue stiffness and regulate TIMP-1-4 protein expression
- TIMP-1-4 are released from aortic tissue and their serum levels are related to aortic mechanical properties

Dr. Anke Tscheuschler  
Postdoctoral Research Fellow  
Institution: Department of Cardiovascular Surgery  
University Heart Centre Freiburg · Bad Krozingen (UHZ), Freiburg, Germany

Dr. Remi Peyronnet  
Head of Cell Biophysics  
Institution: Institute for Experimental Cardiovascular Medicine (IEKM)  
University Heart Centre Freiburg Bad Krozingen (UHZ), Freiburg, Germany

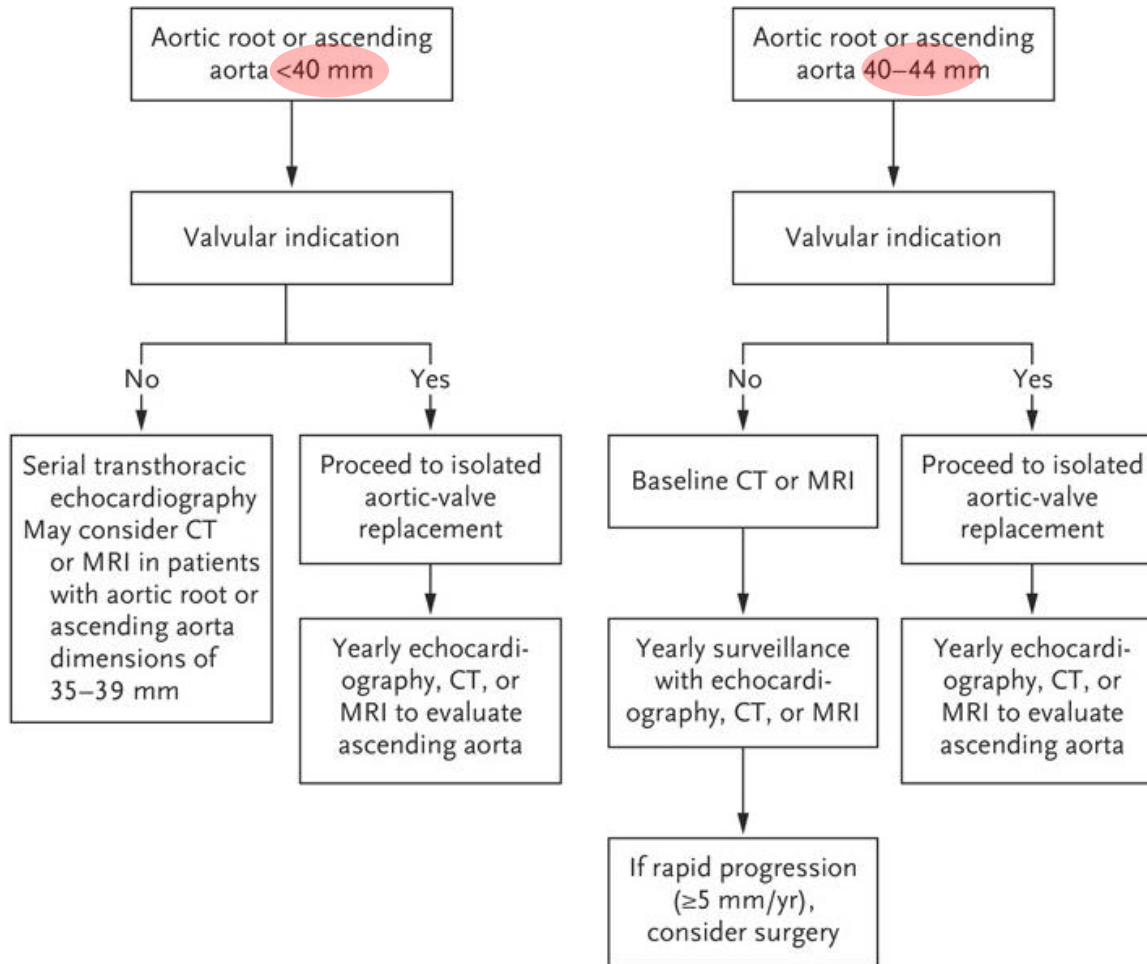
# IV. New Markers: Serum Enzyme Ratios

The Pathways



Forte A, Bancone C, Cobellis G, Buonocore M, Santarpino G, Fischlein T, Cipollaro M, De Feo M and Della Corte A. A Possible Early Biomarker for Bicuspid Aortopathy: Circulating Transforming Growth Factor Beta-1 to Soluble Endoglin Ratio. *Circ Res.* 2017.

# III. Guidelines





# III. Guidelines

