

September 12-14

**2018**

Les Comtes de Méan  
Liège, Belgium

# 6<sup>th</sup> International Meeting on Aortic Diseases

New insights into an old problem CHU Liège, APF

[www.chuliege-ima.be](http://www.chuliege-ima.be)

## How Does Current Knowledge on BAV Aortopathy Impact Valve Repair?

Alessandro Della Corte, MD, PhD

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Naples, Italy





# Disclosure of Interest

Speaker name: Alessandro Della Corte

- I do not have any potential conflict of interest



# The current understanding of BAV aortopathy: searching for knowledge to translate into clinical management...

## Thursday September 13

### **I What's new in research on bicuspid aortopathy?**

**Simon Body, Bart Loeys**

- 08.30 The complex genetic architecture of bicuspid aortic valve related aortopathy, **Bart Loeys**
- 08.38 Protein-altering and regulatory genetic variants near GATA4 implicated in BAV, **Simon Body**
- 08.46 New insights in the genetics of aortopathy and BAV in Turner syndrome, **Aline Verstraeten**
- 08.54 Circulating microRNAs in bicuspid aortopathy, **Evaldas Girdauskas**
- 09.02 TGF- $\beta$ /ENG ratio in bicuspid aortopathy, **Alessandro Della Corte**
- 09.10 Discussion

### **I What's new in management of bicuspid aortopathy?**

**Alessandro Della Corte, Hector Michelena**

- 09.35 Fluid dynamics simulations to understand BAV aortopathy mechanisms and risks, **Luca Koechlin**
- 09.43 Searching for early biomechanically-driven indexes of aortic remodeling: where are we at? **Emiliano Votta**
- 09.51 Advanced imaging biomarkers in bicuspid aortic valve disease surveillance, **Malenka Bissell**
- 09.59 Gender-related differences in bicuspid aortopathy history and outcomes, **Hector Michelena**



# Towards Personalized Surgical Indications for BAV aortopathy?



Heart 2014 Jan;100(2):96-7

Editorial

## Phenotypic heterogeneity of bicuspid aortopathy: a potential key to decode the prognosis?

Alessandro Della Corte

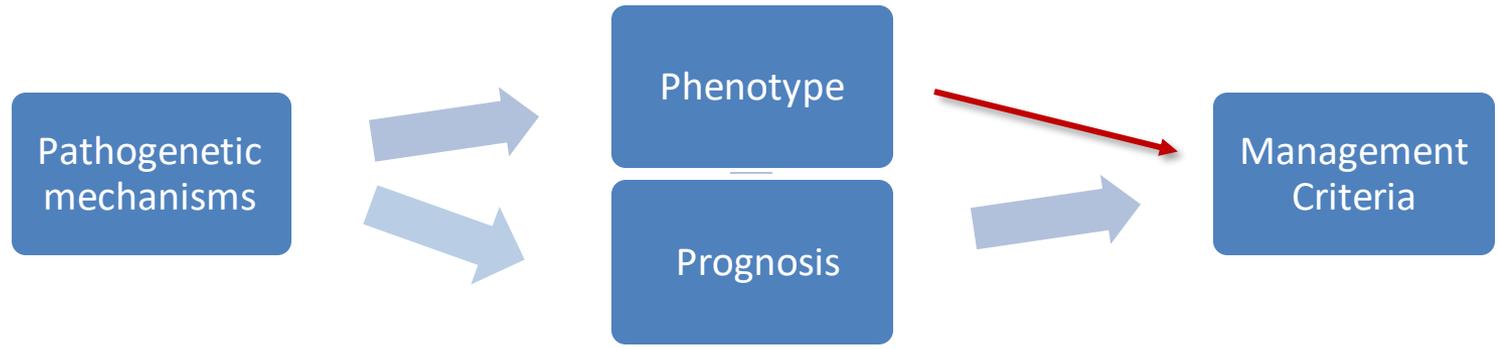
**KNOWLEDGE–PRACTICE INTERCONNECTION**

The clinical and basic research on bicuspid aortic valve (BAV) and associated conditions is an exponentially expanding field. As of 23 October 2013, according to a PubMed article search for the ‘bicuspid aortic valve? (BAV)’, the number of articles published in the

replacement of the ascending aorta from the American Heart Association (AHA)/ American College of Cardiology (ACC)<sup>2</sup> do include BAV among those syndromic aortopathies, when recommending prophylactic surgery at a diameter between 40 and 50 mm. A recent survey among cardiac surgeons has demonstrated that a considerable

genetic risk markers for BAV aortopathy, these predictors could be distinguished into phenotypic predictors or functional predictors (these latter including functional imaging parameters such as aortic wall distensibility or shear stress).

Also in our above-mentioned recent study,<sup>5</sup> baseline diameter did not predict the progression of the aortopathy; however, the pattern of aortic dimensions (the so-called ‘aortic phenotype’) did: the only independent determinant of a fast growth (>0.9 mm/year) of the tubular ascending aorta in BAV patients was the root phenotype, that is, a dilated aorta with diameter at Valsalva sinuses exceeding the diameter of the tubular tract. The root





# Classification of BAV-associated aortopathy

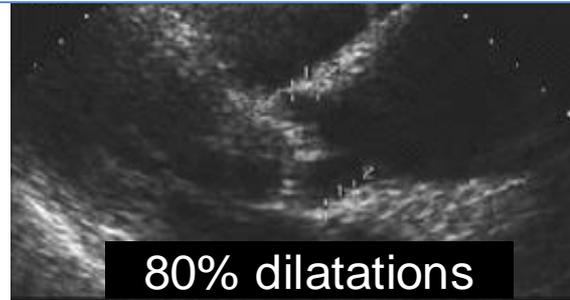
Predictors of ascending aortic dilatation with bicuspid aortic valve:  
a wide spectrum of disease expression<sup>☆</sup>

Alessandro Della Corte<sup>\*,1</sup>, Ciro Bancone, Cesare Quarto, Giovanni Dialetto,  
Franco E. Covino, Michelangelo Scardone, Giuseppe Caianiello, Maurizio Cotrufo

Non-dilated Aorta

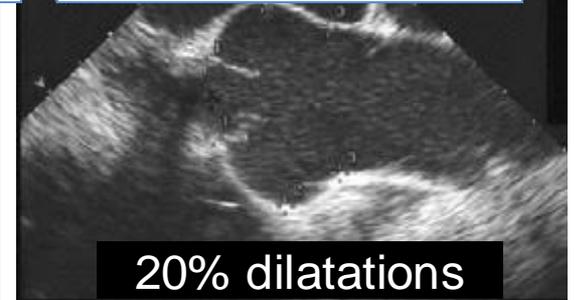


Ascending phenotype  
(dilated, asc>root)



80% dilatations

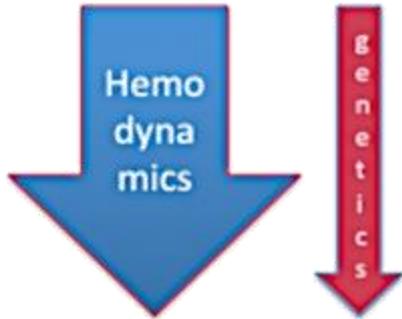
Root phenotype  
(dilated, root>asc)



20% dilatations

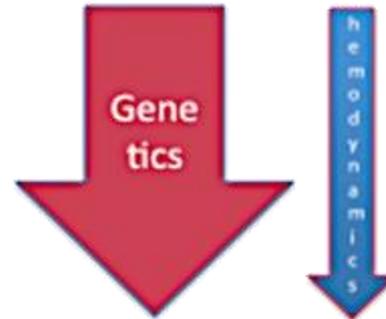
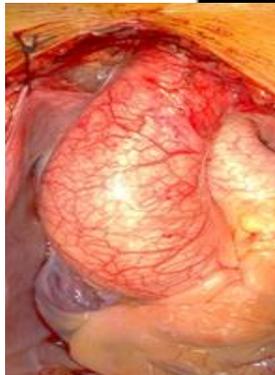
Della Corte A, et al. EJCTS 2007;31:397-405

# Combinations of different causative mechanisms



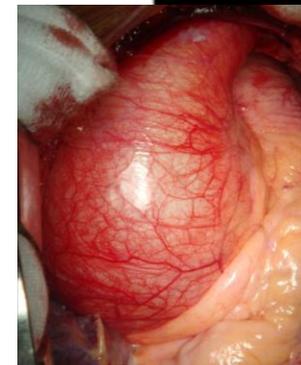
## Ascending phenotype

- Aortic stenosis
- Older age
- Hypertension
- (RN type)



## Root phenotype

- No AV stenosis
- Younger age
- Male sex
- RL type
- Taller stature





# Ascending phenotype: regional aortopathy, probably predictable by flow imaging

J Cardiovasc Med 2009

## **The association of bicuspid aortic valve disease with asymmetric dilatation of the tubular ascending aorta: identification of a definite syndrome**

Maurizio Cotrufo<sup>a</sup> and Alessandro Della Corte<sup>b</sup>

EJCTS 2014

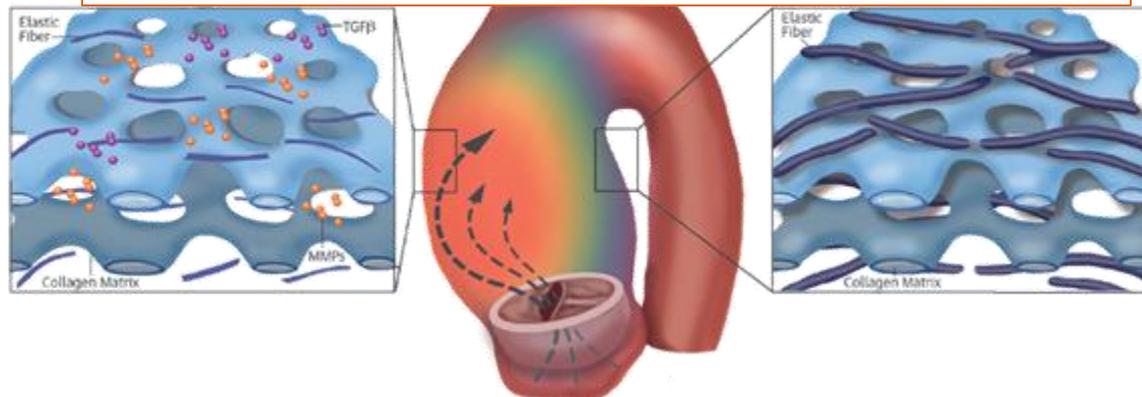
## **Correlation between systolic transvalvular flow and proximal aortic wall changes in bicuspid aortic valve stenosis<sup>†</sup>**

Evaldas Girdauskas<sup>a,\*</sup>, Mina Rouman<sup>a</sup>, Kushtrim Disha<sup>a</sup>, Thorsten Scholle<sup>b</sup>, Beatrix Fey<sup>b</sup>, Bernhard Theis<sup>c</sup>, Iver Petersen<sup>c</sup>, Michael A. Borger<sup>d</sup> and Thomas Kuntze<sup>a</sup>

JACC 2015

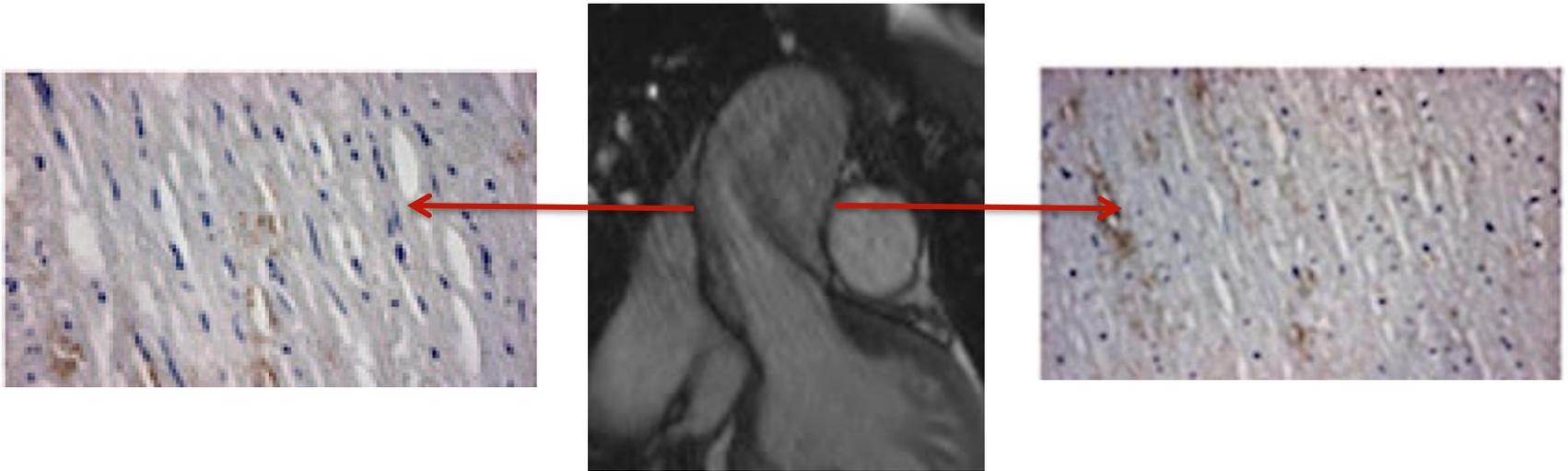
## **Valve-Related Hemodynamics Mediate Human Bicuspid Aortopathy**

Insights From Wall Shear Stress Mapping

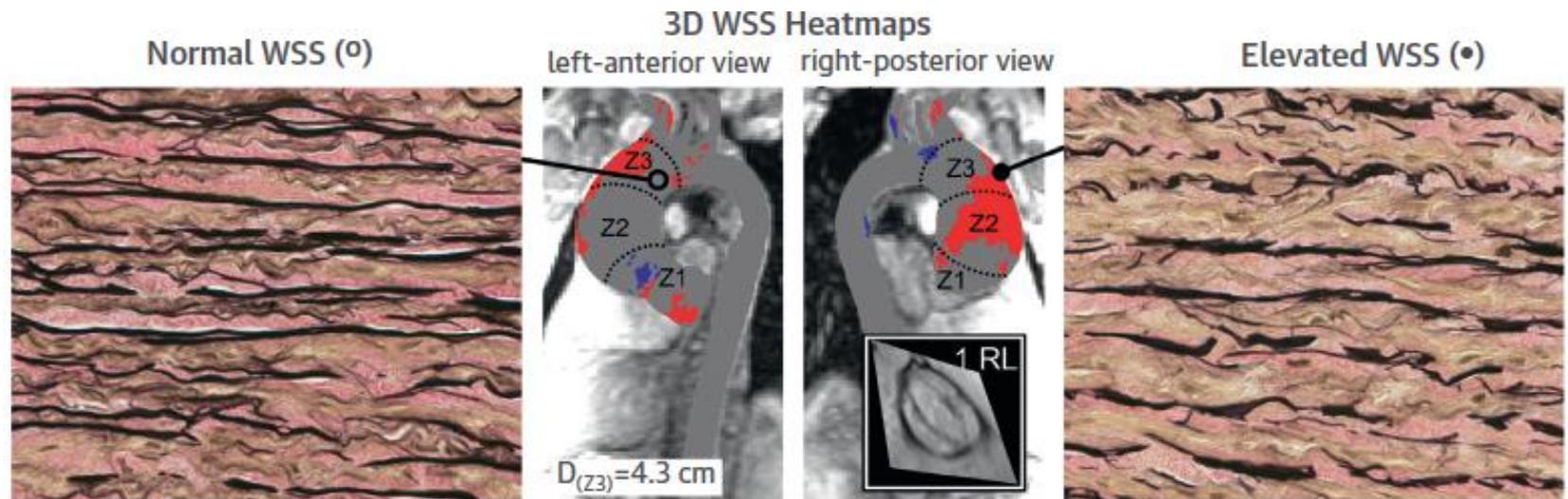




Della Corte et al. JTCVS 2012 – Forte et al. Clin Sci 2013



Guzzardi et al. JACC 2015





# Root phenotype: diffuse asc aortopathy, probably more genetically homogeneous

Pepe et al. *BMC Medical Genetics* 2014, **15**:23  
<http://www.biomedcentral.com/1471-2350/15/23>



**RESEARCH ARTICLE**

**Open Access**

## Identification of fibrillin 1 gene mutations in patients with bicuspid aortic valve (BAV) without Marfan syndrome

Guglielmina Pepe<sup>1,2\*</sup>, Stefano Nistri<sup>1,3</sup>, Betti Giusti<sup>1,2</sup>, Elena Sticchi<sup>1,2</sup>, Monica Attanasio<sup>1,2</sup>, Cristina Porciani<sup>1,2</sup>, Rosanna Abbate<sup>1,2</sup>, Robert O Bonow<sup>4</sup>, Magdi Yacoub<sup>5</sup> and Gian Franco Gensini<sup>1,2,6</sup>

Pepe G, et al. *BMC Med Gen* 2014

European Journal of Cardio-Thoracic Surgery 0 (2017) 1-7  
doi:10.1093/ejcts/ezx065

**ORIGINAL ARTICLE**

Cite this article as: Girdauskas E, Geist L, Disha K, Kazakbaev I, Groß T, Schulz S et al. Genetic abnormalities in bicuspid aortic valve root phenotype: preliminary results. *Eur J Cardiothorac Surg* 2017; doi:10.1093/ejcts/ezx065.

## Genetic abnormalities in bicuspid aortic valve root phenotype: preliminary results<sup>†</sup>

Evaldas Girdauskas<sup>a,\*</sup>, Lisa Geist<sup>b</sup>, Kushtrim Disha<sup>c</sup>, Iliaz Kazakbaev<sup>c</sup>, Tatiana Groß<sup>a</sup>, Solveig Schulz<sup>b</sup>, Martin Ungelenk<sup>b</sup>, Thomas Kuntze<sup>c</sup>, Hermann Reichenspurner<sup>a</sup> and Ingo Kurth<sup>b,d</sup>

Girdauskas E, et al. *EJCTS* 2017



## Pattern of Ascending Aortic Dimensions Predicts the Growth Rate of the Aorta in Patients With Bicuspid Aortic Valve

Alessandro Della Corte, MD, PhD,\*  
Ciro Bancone, MD, PhD,\*  
Marianna Buonocore, MD,\*  
Giovanni Dialetto, MD,\*  
Franco E. Covino, MD,\*  
Sabrina Manduca, MD,\*  
Giancarlo Scognamiglio, MD,†  
Veronica D'Oria, MD,\*  
Marisa De Feo, MD, PhD\*

Della Corte A, et al. JACC Img 2013

## Aortic events after isolated aortic valve replacement for bicuspid aortic valve root phenotype: echocardiographic follow-up study<sup>†</sup>

Evaldas Girdauskas<sup>a,\*</sup>, Kushtrim Disha<sup>a</sup>, Mina Rouman<sup>a</sup>, Andres Espinoza<sup>a</sup>,  
Michael A. Berger<sup>b</sup> and Thomas Kuntze<sup>a</sup>

<sup>a</sup> Department of Cardiac Surgery, Heart Center, Central Hospital Bad Berka, Bad Berka, Germany

<sup>b</sup> Cardiovascular Institute, Columbia University Medical Center, New York, USA

Girdauskas E, et al.  
EJCTS 2015

## Impact of Aortic Insufficiency on Ascending Aortic Dilatation and Adverse Aortic Events After Isolated Aortic Valve Replacement in Patients With a Bicuspid Aortic Valve

Yongshi Wang, MD,\*  
Boting Wu, MD,\*  
Jun Li, MD,  
Lili Dong, MD,  
Chunsheng Wang, MD,  
and Xianhong Shu, MD, PhD

Wang Y, et al. Ann Thorac Surg 2016



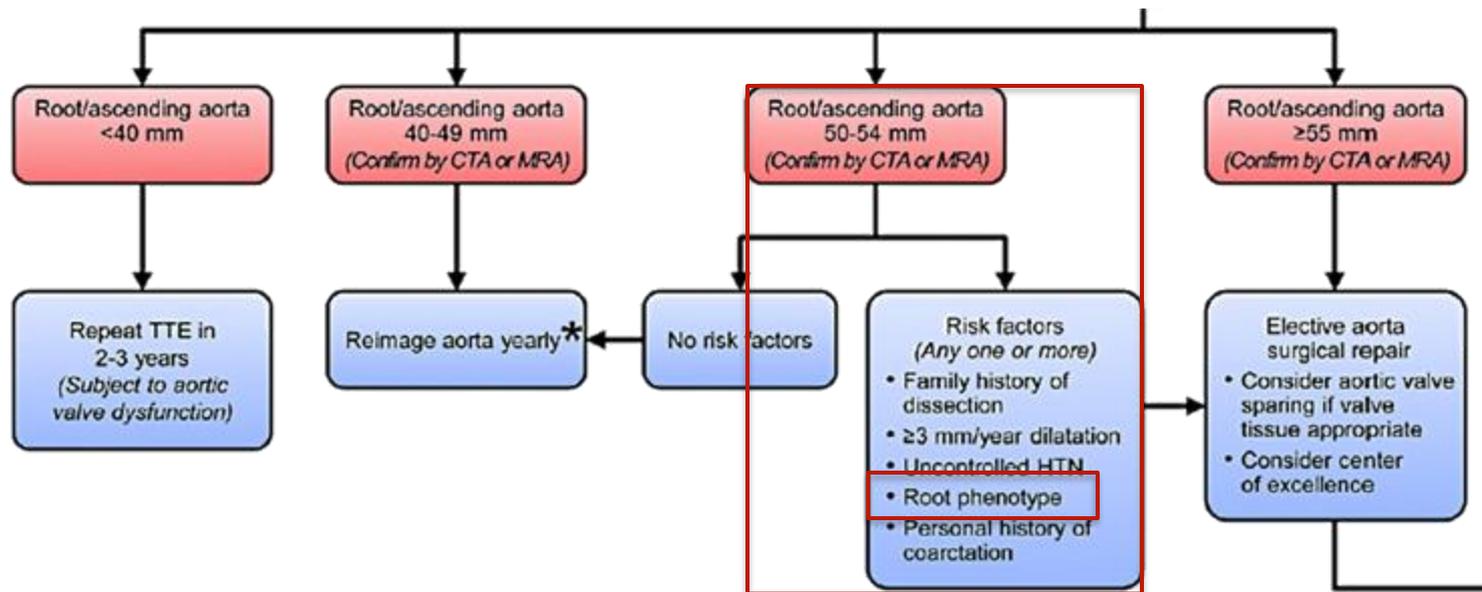
# How does Knowledge of Phenotypic Heterogeneity Impact on Aorta Repair?

Int J Cardiol 2015

Review

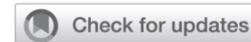
## Bicuspid aortic valve aortopathy in adults: Incidence, etiology, and clinical significance

Hector I. Michelena <sup>a,\*</sup>, Alessandro Della Corte <sup>b</sup>, Siddharth K. Prakash <sup>c</sup>, Dianna M. Milewicz <sup>c</sup>, Artur Evangelista <sup>d</sup>, Maurice Enriquez-Sarano <sup>a</sup>



\*If first-time patient, may reimage at 6 months and if no progression then yearly

## The American Association for Thoracic Surgery consensus guidelines on bicuspid aortic valve–related aortopathy: Full online-only version



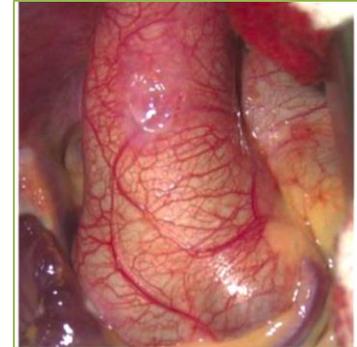
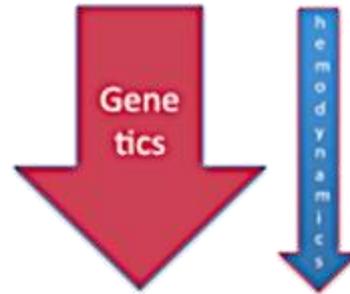
Michael A. Borger, MD, PhD,<sup>a</sup> Paul W. M. Fedak, MD, PhD,<sup>b</sup> Elizabeth H. Stephens, MD, PhD,<sup>c</sup> Thomas G. Gleason, MD,<sup>d</sup> Evaldas Girdauskas, MD, PhD,<sup>e</sup> John S. Ikonomidis, MD, PhD,<sup>f</sup> Ali Khoynezhad, MD, PhD,<sup>g</sup> Samuel C. Siu, MD,<sup>h</sup> Subodh Verma, MD, PhD,<sup>i</sup> Michael D. Hope, MD,<sup>j</sup> Duke E. Cameron, MD,<sup>k</sup> Donald F. Hammer, MD,<sup>l</sup> Joseph S. Coselli, MD,<sup>m</sup> Marc R. Moon, MD,<sup>n</sup> Thoralf M. Sundt, MD,<sup>o</sup> Alex J. Barker, PhD,<sup>p</sup> Michael Markl, PhD,<sup>q</sup> Alessandro Della Corte, MD, PhD,<sup>r</sup> Hector I. Michelena, MD,<sup>s</sup> and John A. Elefteriades, MD<sup>t</sup>

**TABLE 5. Recommendations for aortic repair in patients with bicuspid aortic valve aortopathy**

Recommendation	Class/LOE
Repair of the ascending aorta/root is recommended when the aortic diameter is $\geq 55$ mm in patients without risk factors	I/B <sup>26,27,33,155,226</sup>
Repair of the ascending aorta/root should be performed when the aortic diameter is $\geq 50$ mm in patients with <b>risk factors</b> (ie, <u>root phenotype</u> or predominant AI, uncontrolled hypertension, family history of aortic dissection/sudden death, coarctation, aortic growth $>3$ mm/y)	IIa/B <sup>26,27,33,155,226</sup>



# How does Knowledge of Phenotypic Heterogeneity Impact on Valve Repair?



## Root phenotype

- No AV stenosis
- Younger age
- Male sex
- RL type
- Taller stature
- Faster aortic growth
- Post-AVR events
- Familial forms
- (AML prolapse)
- Higher dissection risk?
- Connective tissue disease?
- Earlier indications for surgery?



This is the phenotypic context in which BAV repair is considered, indicated and practiced



## Timing of Operation

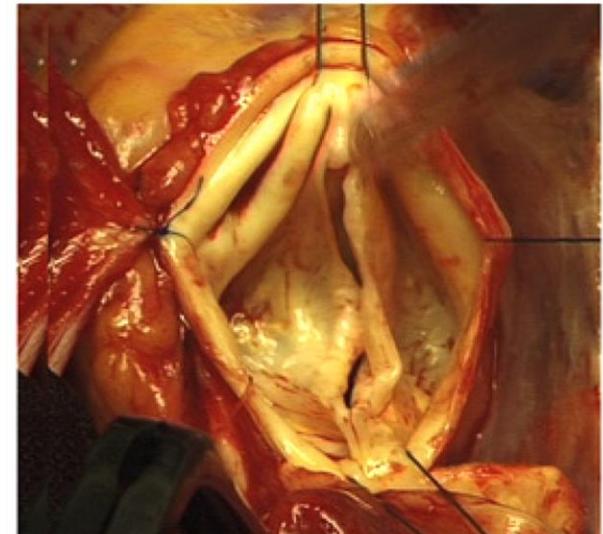
The current knowledge of the 'malignant behaviour' of dilatation in patients with **root phenotype** justifies a more aggressive timing (diameter >50 mm if BAV is not severely regurgitant, otherwise >45mm)



- Young patients (prosthesis-related complications)
- Increased chances to repair the valve

### **Surgical treatment of bicuspid aortic valve disease: Knowledge gaps and research perspectives**

Alessandro Della Corte, MD, PhD,<sup>a</sup> Simon C. Body, MBChB, MPH,<sup>b</sup> Anna M. Booher, MD,<sup>c</sup> Hans-Joachim Schaefer, MD,<sup>d</sup> Rita K. Milewski, MD, PhD,<sup>e</sup> Hector I. Michelena, MD,<sup>f</sup> Arturo Evangelista, MD, PhD,<sup>g</sup> Philippe Pibarot, DVM, PhD,<sup>h</sup> Patrick Mathieu, MD,<sup>h</sup> Giuseppe Limongelli, MD, PhD,<sup>i</sup> Prem S. Shekar, MD,<sup>j</sup> Sary F. Aranki, MD,<sup>j</sup> Andrea Ballotta, MD,<sup>k</sup> Giuseppe Di Benedetto, MD,<sup>l</sup> Natzi Sakalihan, MD, PhD,<sup>m</sup> Gianantonio Nappi, MD,<sup>a</sup> Kim A. Eagle, MD,<sup>c</sup> Joseph E. Bavaria, MD,<sup>e</sup> Alessandro Frigiola, MD,<sup>k</sup> and Thoralf M. Sundt, MD,<sup>n</sup> on behalf of the International Bicuspid Aortic Valve Consortium (BAVCon) Investigators



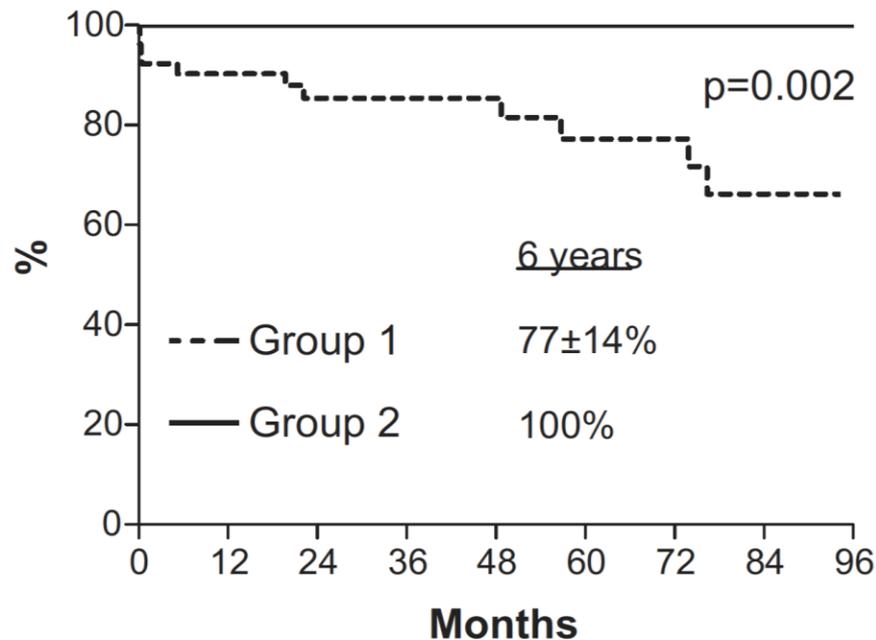


# Associated Reimplantation Technique

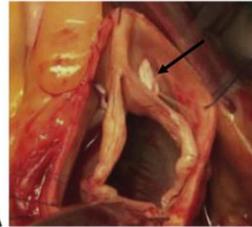
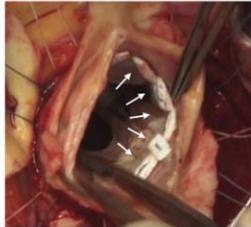
## Valve sparing-root replacement with the reimplantation technique to increase the durability of bicuspid aortic valve repair

Laurent de Kerchove, MD,<sup>a</sup> Munir Boodhwani, MD, MMSC,<sup>d</sup> David Glineur, MD,<sup>a</sup> Michel Vandyck, MD,<sup>b</sup> Jean-Louis Vanovershelde, MD, PhD,<sup>c</sup> Philippe Noirhomme, MD,<sup>a</sup> and Gebrine El Khoury, MD<sup>a</sup>

JTCVS 2011



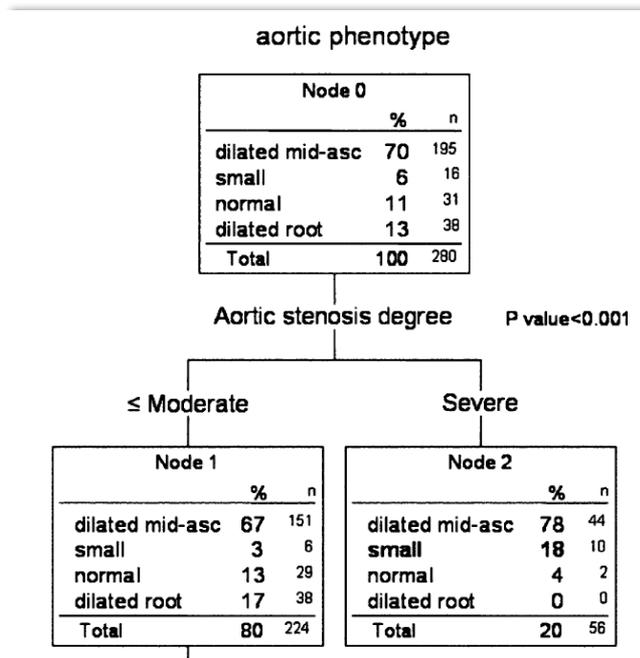
No. at risk	0	12	24	36	48	60	72	84	96
Group 1	53	42	33	27	21	18	15	10	8
Group 2	53	39	29	23	20	14	9	6	2

Group 1 (unmatched, n= 87)		Group 2 (unmatched, n= 74)	
<b>Definition:</b> BAV repair without VAJ annuloplasty or with subcommissural annuloplasty (SCA)		<b>Definition:</b> BAV repair with circumferential VAJ annuloplasty	
- No annuloplasty (cusp repair only)	5 (6%)	- Valve sparing reimplantation technique <sup>2</sup> 74 (100%)	
- SCA	48 (55%)		
- Ascending aorta replacement	4 (5%)		
- Ascending aorta replacement + SCA	13 (15%)		
- Aortic root remodeling <sup>1</sup>	7 (8%)		
- Aortic root remodeling <sup>1</sup> + SCA	10 (11%)	 	

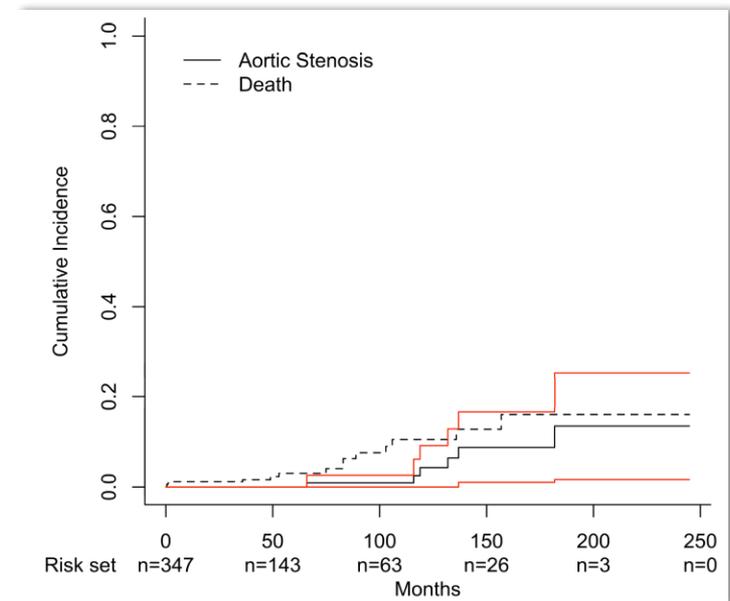
Freedom from recurrent aortic insufficiency greater than 2+

# Concerns of post-BAV-repair calcification and stenosis?

- Awareness of the differences between the patient phenotypes (probably subtended by different genetic background)
- “Root phenotype”: association with AS very uncommon → Very low risk of evolution to calcific stenosis following BAV repair as long as performed in root phenotype patients?



Della Corte A et al., EJCTS 2007



Schneider U et al., JTCVS 2017

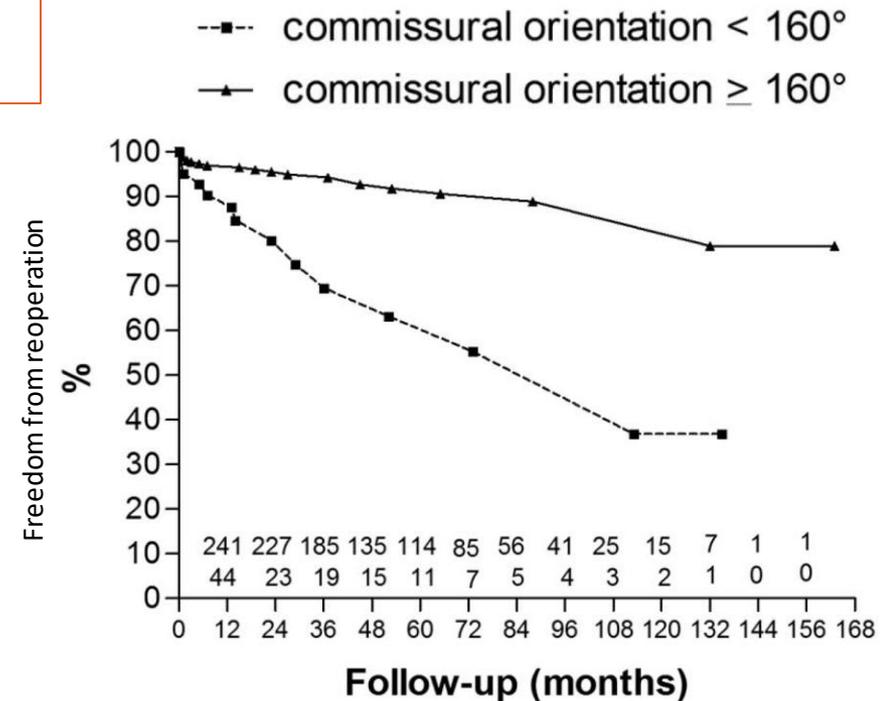
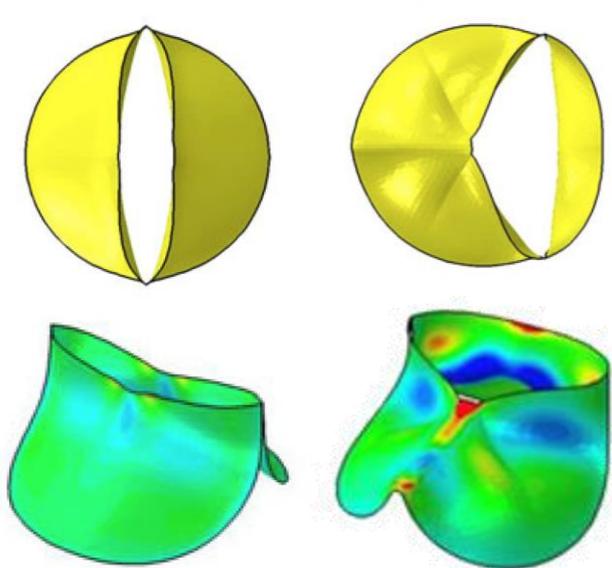
# Need to re-configure commissural orientation?

Cardiovascular Engineering and Technology, Vol. 2, No. 1, March 2011 (© 2011) pp. 48-56  
 DOI: 10.1007/s13239-011-0035-9

## Cardiovasc Engin Technol 2011

### Effect of Geometry on the Leaflet Stresses in Simulated Models of Congenital Bicuspid Aortic Valves

PAUL N. JERMIHOV,<sup>1</sup> LU JIA,<sup>2</sup> MICHAEL S. SACKS,<sup>3</sup> ROBERT C. GORMAN,<sup>4</sup>  
 JOSEPH H. GORMAN III,<sup>4</sup> and KRISHNAN B. CHANDRAN<sup>1</sup>



### Valve Configuration Determines Long-Term Results After Repair of the Bicuspid Aortic Valve

Diana Aicher, MD; Takashi Kunihara, MD; Omar Abou Issa, MD; Brigitte Brittner, MD;  
 Stefan Gräber, MD; Hans-Joachim Schäfers, MD

Circulation 2011



## Morpho-functional features of the BAV

- Commissural orientation
- RL vs RN
- Presence and completeness of the raphe
- Indentation of the fused cusp free margin (“restrictive raphe”)
- Height of the false commissure
- *Others?*



ELSEVIER

European Journal of Cardio-thoracic Surgery 37 (2010) 1015–1020

EUROPEAN JOURNAL OF  
CARDIO-THORACIC  
SURGERY

[www.elsevier.com/locate/ejcts](http://www.elsevier.com/locate/ejcts)

Bicuspid aortic valve: differences in the phenotypic continuum affect the repair technique<sup>☆</sup>

Andrea Mangini<sup>\*</sup>, Massimo Lemma, Monica Contino, Matteo Pettinari,  
Guido Gelpi, Carlo Antona

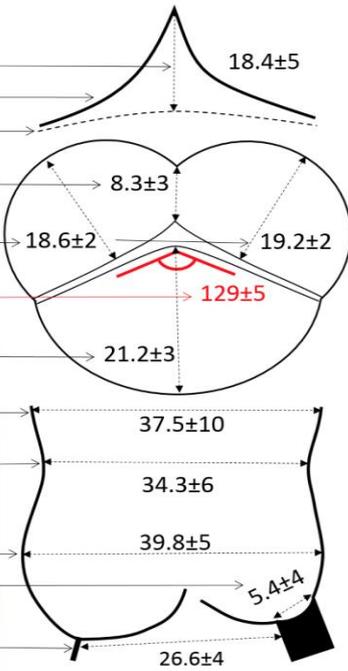
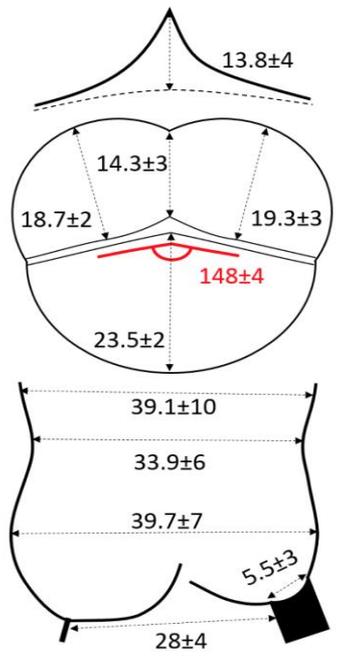
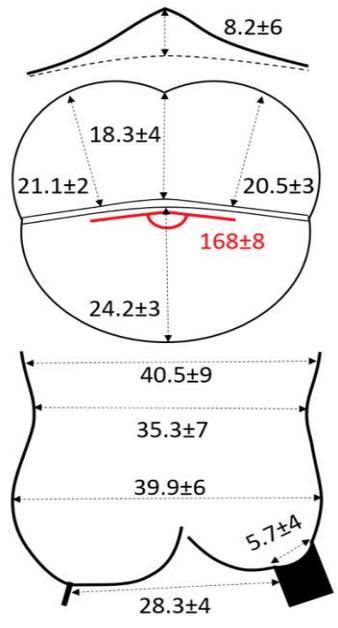
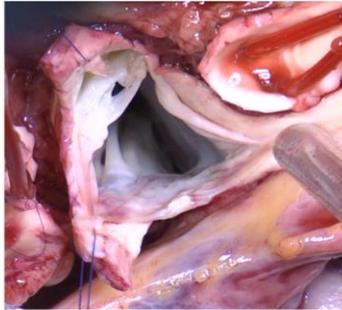
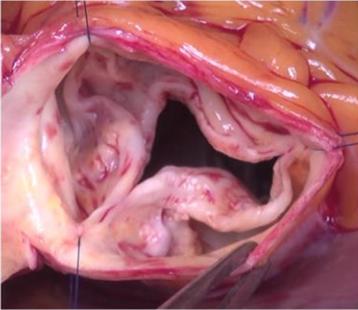
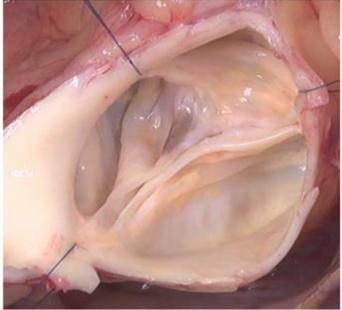
JAMA Cardiology | **Original Investigation**

### Prognostic Implications of Raphe in Bicuspid Aortic Valve Anatomy

William K. F. Kong, MD; Victoria Delgado, MD, PhD; Kian Keong Poh, MD; Madelien V. Regeer, MD; Arnold C. T. Ng, MBBS, PhD; Louise McCormack, MBBS; Tiong Cheng Yeo, MD; Miriam Shanks, MD, PhD; Sarah Parent, MD; Roxana Enache, MD, PhD; Bogdan A. Popescu, MD, PhD; Michael Liang, MD; James W. Yip, MD; Lawrence C. W. Ma, MBBS; Vasileios Kamperidis, MD, PhD; Philippe J. van Rosendaal, MD; Enno T. van der Velde, PhD; Nina Ajmone Marsan, MD, PhD; Jeroen J. Bax, MD, PhD



# Morpho-functional features of the BAV

	Group 1: 120°-139° Asymmetric BAV n=20	Group 2: 140°- 159° Intermediate BAV n=53	Group 3: 160°-180° Symmetric BAV n=42
1. Type of cusp fusion (R:right, N:non, L:left coronary cusp)	R/L 75%, R/N 20%, N/L 5%	R/L 87%, R/N 11%, N/L 2%	R/L 79%, R/N 21%, N/L 0%
2. Height of non functional commiss. (Cusp insertion) (Basal ring line)	18.4±5	13.8±4	8.2±6
3. Length of fusion	8.3±3	14.3±3	18.3±4
4. gH fused cusp (2 measures)	18.6±2, 19.2±2	18.7±2, 19.3±3	21.1±2, 20.5±3
5. Commissure angle	129±5	148±4	168±8
6. gH non-fused cusp	21.2±3	23.5±2	24.2±3
7. Ascending aorta	37.5±10	39.1±10	40.5±9
8. Sino-tubular junction	34.3±6	33.9±6	35.3±7
9. Sinus of Valsalva	39.8±5	39.7±7	39.9±6
10. Muscular inclusion (Right sinus)	5.4±4	5.5±3	5.7±4
11. Aorto-ventricular junction	26.6±4	28±4	28.3±4
			
			



## Conclusions

- As long as clinical and basic research elucidates more and more aspects of this disease (e.g. phenotypic heterogeneity), our surgical approach can improve (e.g. phenotypic stratification)
- In BAV repair, there is still space for improvement: optimization of indications (e.g. timing), patient selection (e.g. root phenotype patients), technical aspects (e.g. commissural reorientation)...
- In-depth understanding of the **morpho-functional heterogeneity** of the valve is expected to provide the basis for such an improvement