

Medical Therapy for Aortic Stenosis

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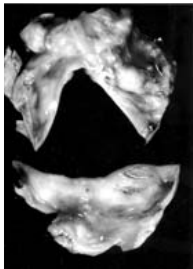
Heart Valve Summit 2008

Valve Director **Bluhm Cardiovascular Institute** Division of Cardiology,
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Disclosure: Two patents owned by the Mayo Clinic: Mechanisms of Heart Valve
Degeneration, Bioprosthetic Heart Valve,
Off Label Indication for the use of statins
National Institute of Health R01 Grant Funding

Bicuspid Aortic Valve Disease



Roberts et al, Circulation. 2005 Feb 22;111(7):920-5. Epub 2005 Feb 14

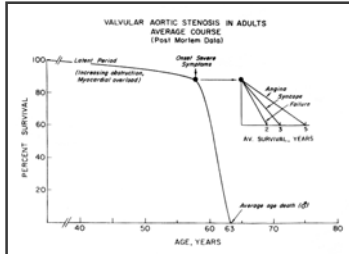
Bicuspid Valves

- **Most common congenital cardiac malformation**
- **Affects 1-2% of population**
- **Associated with other congenital disorders of the aorta (PDAs, Coarctation)**
- **Associated with aortic dilation, aneurysms, and dissection later in life**
- **Deficient microfibrillar proteins, elevated matrix metalloproteinases (MMPs)**

Ortiz, Shin, Rajamannan, Current Opinions, 2006

Natural History

- Ross and Braunwald, Circulation 1968



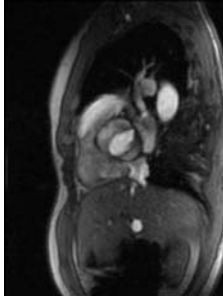
Recommendations for Aortic Valve Replacement in Aortic Stenosis

Indication	Class
1. Symptomatic patients with severe AS	I
2. Patients with severe AS before undergoing coronary artery bypass surgery	I
3. Patients with severe AS undergoing surgery on the aorta or other heart valves	I
4. Patients with moderate AS undergoing coronary artery bypass surgery or surgery on the aorta or other heart valves	IIa
5. Asymptomatic patients with severe AS and:	
• LV systolic dysfunction	IIa
• Abnormal response to exercise (eg, hypotension)	IIa
• Ventricular tachycardia	IIb
• Marked or excessive LV hypertrophy (≥ 15 mm)	IIb
• Valve area < 0.6 cm ²	IIb
6. Prevention of sudden death in asymptomatic patients with none of the findings listed under indication 5	III

Bonow, et. al., *Circulation* 2006 (118): 1949-84

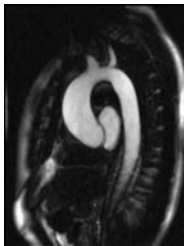
Valvular Heart Disease MultiModality Imaging

Bicuspid Aortic Valve



Ortiz, Rajamannan, Current Opinions, 2006

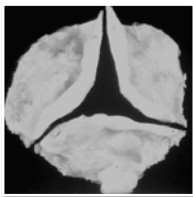
Aortic Root Evaluation



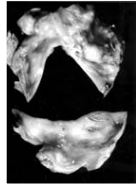
Ortiz, Rajamannan, Current Opinions, 2006

**What is the Next
Step Towards
Understanding
this Disease?**

What are the mechanisms involved in the development of valve calcification = disease progression?

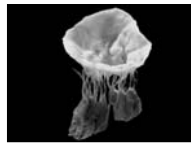


Calcific Aortic Stenosis

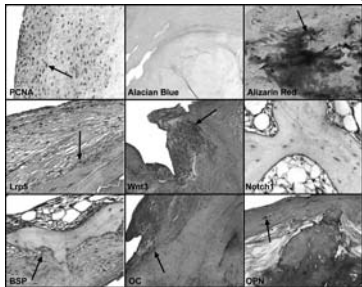


Calcific Aortic Bicuspid Stenosis

Degenerative Mitral Valve

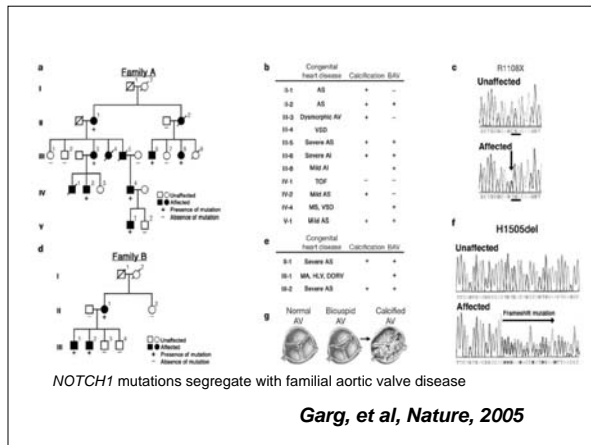


Bicuspid Aortic Valve Immunohistochemistry



Caira et al, JACC, April 2006

Understanding the Cellular Mechanisms of the Bicuspid Aortic Valve Phenotype



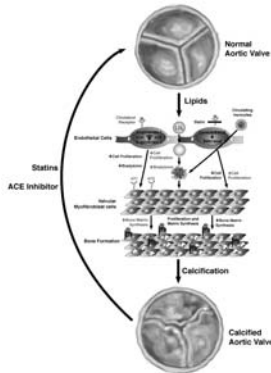
Hypothesis

Whether the eNOS null mouse with bicuspid aortic valves develop stenosis and calcification via a Notch1/Wnt signaling pathways?

Is There Medical Therapy for Calcific Aortic Stenosis?

To Answer this Question:
Experimental Studies

Is there Medical Therapy for Aortic Stenosis: Lessons Learned from Experimental Models



- *Rajamannan, Atorvastatin, Rabbit Model, In vitro Model, Circulation, Heart*
- *Osman, Atorvastatin, In Vitro Model, Circulation*
- *Wu, Prav and Simvastatin, In vitro, ATVB*
- *Ashiro, ARB, Rabbit Model, JACC*

Rajamannan, ATVB, In Review, 2007

Question: Do you treat Bicuspid Aortic Valves Patients with Medical Therapy?

Is There Medical Therapy for Calcific Aortic Stenosis?

To Answer this Question:
Clinical Trials

Prospective Clinical Trials to Date

Trial/University	Location	Hypothesis	Medication
SALTIRE NEJM, 2006	Edinburgh, Scotland	The Scottish Aortic Stenosis and Lipid Lowering Trial. Impact on Regression	Atorvastatin
RAAVE JACC, 2007	Porto, Portugal	Rosuvastatin Affecting Aortic Valve Endothelium	Rosuvastatin
ASTRONOMER	Multicenter Canadian	The Aortic Stenosis Progression Observation: Measuring the Effect of Rosuvastatin	Rosuvastatin
SEAS	Multicenter, European	The Simvastatin and Ezetimide in Aortic Stenosis Study	Simvastatin and Ezetimide
University of Leipzig	Leipzig, Germany	Statin Therapy in Asymptomatic Mild to Moderate Aortic Stenosis	Fluvastatin
Odense University Hospital	Odense, Denmark	Effect of Angiotensin II Receptor Blockers Remodelling (ARB) on Left Ventricular Reverse After Aortic Valve Replacement in Severe Valvular Aortic Stenosis	Candesartan
ACCESS	Rigshospitalet, Copenhagen, Denmark	Acute Hemodynamic Effects of Treatment With ACE-inhibitors in Patients With Symptomatic Aortic Stenosis AASK-1.0	Captopril and Trandolapril
AORTICA Group	Salamanca, Spain	Randomized Study to Evaluate the Efficacy of Fluvastatin on Inflammatory Markers in Patients with Aortic Stenosis	Fluvastatin
STOP-AS	Cleveland, Ohio	STOP Aortic Stenosis	Atorvastatin

Rajamannan, ATVB, In Review, 2007

RAAVE: Rosuvastatin Affecting Aortic Valve Endothelium

***RAAVE INVESTIGATORS: Moura,
Ramos, Zamorano, Barros,
Azevedo, Rocha-Gonçalves,
Rajamannan***

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School of Medicine

Conclusion

- Prospective Hypothesis Driven Study demonstrating the effect of Lipid Lowering Therapy in the treatment of Aortic Stenosis:
- 1) Rosuvastatin Slowed Hemodynamic Progression of Aortic Stenosis
- 2) Rosuvastatin reduced Inflammatory Markers
- Large Scale Randomized Clinical Trials are necessary in the future for the treatment of this disease
