Update on the Pathophysiology of Aortic Stenosis

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Disclosure
Philippe Pibarot

Financial relationship with industry:

- Edwards Lifesciences: Echo CoreLab - SAPIEN 3
- V-Wave: Echo CoreLab
- Cardiac Phoenix: Research Grant for Echo CoreLab
- Ionis Pharmaceuticals

Other financial disclosure:

- Research Grants from Canadian Institutes of Health
- Research and Heart & Stroke Foundation of Quebec
Aortic Stenosis:
Most frequent CVD after CAD and Hypertension

Prevalence in Population

<table>
<thead>
<tr>
<th>Age Range</th>
<th>Normal</th>
<th>Aortic Sclerosis</th>
<th>Mild-to-Moderate Aortic Stenosis</th>
<th>Severe Aortic Stenosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age 18-45</td>
<td>2%</td>
<td>0.2%</td>
<td>0.2%</td>
<td>0.2%</td>
</tr>
<tr>
<td>Age 46-55</td>
<td>2%</td>
<td>0.2%</td>
<td>0.2%</td>
<td>0.2%</td>
</tr>
<tr>
<td>Age 56-65</td>
<td>10%</td>
<td>1%</td>
<td>2%</td>
<td>3%</td>
</tr>
<tr>
<td>Age 66-75</td>
<td>20%</td>
<td>2%</td>
<td>2%</td>
<td>3%</td>
</tr>
<tr>
<td>Age &gt;75</td>
<td>30%</td>
<td></td>
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</tr>
</tbody>
</table>
The Natural History of Aortic Stenosis

Asymptomatic period (increasing obstruction, myocardial overload)

Onset of severe symptoms

Average death age (male)

Average survival (yr)

0 2 4 6

0 40 50 60 70 80

Age (year)

Symptomatic severe AS : indication of AVR (class I)

Angina

Syncope

Failure
The Burden of Aortic Stenosis

- Afflicts about 1 million people in North America
- Prevalence increases with age:
  In population >65 y.o: 25% sclerosis and 3% stenosis
- No medical therapy to reduce AS progression!
- Severe symptomatic AS: SAVR or TAVR
- AS responsible for 20,000 deaths and 80,000 AVRs per year in North America
2014 ACC-AHA Guidelines: Progression Stages

**A Stage**
At Risk of AS
- MG < 15 mmHg
- AVA > 2 cm²

**B Stage**
Mild to Moderate AS
- MG < 40 mmHg
- AVA > 1 cm²

**C Stage**
Asymptomatic Severe AS
- MG ≥ 40 mmHg
- LVEF ≤ 50%

**BICUSPID VALVE**
AORTIC SCLEROSIS
A Stage

**MILD / MODERATE AS**
B Stage
AVR, Class III

**HIGH GRADIENT**
ASYMPTOMATIC
NORMAL LVEF
C1 Stage
AVR, Class IIa/IIb

**HIGH GRADIENT**
ASYMPTOMATIC
LOW LVEF
C2 Stage
AVR, Class I

At Risk of AS
- A Stage
- MG < 15 mmHg
- AVA > 2 cm²

Mild to Moderate AS
- B Stage
- MG < 40 mmHg
- AVA > 1 cm²

Asymptomatic Severe AS
- C Stage
- MG ≥ 40 mmHg
- LVEF ≤ 50%

**1.8 m/s**

**3.6 m/s**

**5.4 m/s**

**5.4 m/s**

**NORMAL LVEF**

**LOW LVEF**

**HIGH GRADIENT**

**ASYMPTOMATIC**

**MILD / MODERATE AS**

**BICUSPID VALVE**

**AORTIC SCLEROSIS**

**A Stage**

**B Stage**

**C Stage**

**AVR, Class III**

**AVR, Class IIa/IIb**

**AVR, Class I**

**AVR, Class I**
2014 ACC-AHA Guidelines: Progression Stages

D Stage
Symptomatic Severe AS

MG ≥ 40 mmHg

MG < 40 mmHg
AVA ≤ 1 cm²
LVEF < 50%

MG < 40 mmHg
AVA ≤ 1 cm²
LVEF ≥ 50%

MG < 40 mmHg
AVA ≤ 1 cm²
LVEF ≥ 50%

MG < 40 mmHg
AVA ≤ 1 cm²
LVEF ≥ 50%

SVI > 35 mL/m²

«CLASSICAL»
LOW-FLOW
LOW-GRADIENT
D2 Stage
AVR, Class IIa

«PARADOXICAL»
LOW-FLOW
LOW-GRADIENT
D3 Stage
AVR, Class IIa

NORMAL -FLOW
LOW-GRADIENT
Stage ?
AVR ?

HIGH GRADIENT
SYMPTOMATIC
D1 Stage
AVR, Class I

Symptomatic Severe AS

5.4 m/s

3.6 m/s

3.6 m/s

3.6 m/s
The Changing Face of Aortic Stenosis

- “Degenerative” process as a result of wear and tear?
- AS shares many cellular similarities with vascular atherosclerosis
- AS has been linked to several traditional risk factors for coronary artery disease
- AS: an atherosclerotic disease?
- Is there a hope for pharmacotherapy in AS?
Pharmacological Therapy for AS?
The Failure of Statins in Aortic Stenosis

SALTIRE

Cowell, NEJM, 352:2389-97, 2005

ASTRONOMER


Chan Circulation 121:306-314, 2010
Calcific AS has some similarities but also some dissimilarities with atherosclerosis.
Case #1: Patient with Mild AS and Rapid Progression during FU (B Stage)

57 y.o. man with mild calcific AS

Baseline

- $V_{\text{Peak}}$: 2.3 m/s
- Peak/mean gradients: 22/12 mmHg
- $\text{AVA}$: 1.36 cm$^2$
- Calcium score: 901 AU

2.5 years later

- $V_{\text{Peak}}$: 4.4 m/s (progression 0.8 m/s/yr)
- Peak/mean gradients: 77/44 mmHg
- $\text{AVA}$: 0.88 cm$^2$
- Calcium score: 2007 AU

Lipoprotein (a) level: 147 mg/dl
Genetic Associations with Valvular Calcification and Aortic Stenosis

George Thanassoulis, M.D., Catherine Y. Campbell, M.D., David S. Owens, M.D., J. Gustav Smith, M.D., Ph.D., Albert V. Smith, Ph.D., Gina M. Peloso, Ph.D., Kathleen F. Kerr, Ph.D., Sonali Pechlivanis, Ph.D., Matthew J. Budoff, M.D., Tamara B. Harris, M.D., Rajeev Malhotra, M.D., Kevin D. O'Brien, M.D., Pia R. Kamstrup, M.D., Ph.D., Børge G. Nordestgaard, M.D., D.M.Sc., Anne Tybjaerg-Hansen, M.D., D.M.Sc., Matthew A. Allison, M.D., M.P.H., Thor Aspelund, Ph.D., Michael H. Criqui, M.D., M.P.H., Susan R. Heckbert, M.D., Ph.D., Shih-Jen Hwang, Ph.D., Yongmei Liu, Ph.D., Marketa Sjogren, Ph.D., Jesper van der Pals, M.D., Ph.D., Hagen Kälsch, M.D., Thomas W. Mühleisen, Ph.D., Markus M. Nöthen, M.D., L. Adrienne Cupples, Ph.D., Muriel Caslake, Ph.D., Emanuele Di Angelantonio, M.D., Ph.D., John Danesh, F.R.C.P., Jerome I. Rotter, M.D., Sigurdur Sigurdsson, M.Sc., Quenna Wong, M.S., Raimund Erbel, M.D., Sekar Kathiresan, M.D., Olle Melander, M.D., Ph.D., Vilmundur Gudnason, M.D., Ph.D., Christopher J. O'Donnell, M.D., M.P.H., and Wendy S. Post, M.D., for the CHARGE Extracoronary Calcium Working Group
Association between LPA and Aortic Valve Calcification

Genomewide significance prespecified = $P < 5.0 \times 10^{-8}$
Lipoprotein(a) and AS Progression: Astronomer Trial

**B**

Progression rate of $V_{max}$ (m/s/yr)

<table>
<thead>
<tr>
<th>Tertiles 1 &amp; 2</th>
<th>Tertile 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lp(a)≤58.5mg/dL</td>
<td>Lp(a)&gt;58.5mg/dL</td>
</tr>
<tr>
<td>0.17±0.02 (n=147)</td>
<td>0.26±0.03 (n=73)</td>
</tr>
</tbody>
</table>

$p=0.005$

**C**

Progression rate of $V_{max}$ (m/s/yr)

<table>
<thead>
<tr>
<th>Age ≤57</th>
<th>Age &gt;57</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lp(a)≤58.5mg/dL</td>
<td>Lp(a)&gt;58.5mg/dL</td>
</tr>
<tr>
<td>0.13±0.02 (n=71)</td>
<td>0.26±0.03 (n=37)</td>
</tr>
<tr>
<td>0.21±0.03 (n=76)</td>
<td>0.26±0.03 (n=36)</td>
</tr>
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</table>

**D**

Adjusted Event-Free Survival (%)

<table>
<thead>
<tr>
<th>Follow-up (years)</th>
<th>Tertiles 1 &amp; 2 of Lp(a)</th>
<th>Tertile 3 of Lp(a)</th>
</tr>
</thead>
<tbody>
<tr>
<td>147</td>
<td>73</td>
<td>75</td>
</tr>
<tr>
<td>139</td>
<td>66</td>
<td>71</td>
</tr>
<tr>
<td>122</td>
<td>56</td>
<td>66</td>
</tr>
<tr>
<td>106</td>
<td>30</td>
<td>56</td>
</tr>
<tr>
<td>59</td>
<td>30</td>
<td>30</td>
</tr>
<tr>
<td>26</td>
<td>6</td>
<td>6</td>
</tr>
</tbody>
</table>

†HR=2.0 (1.1-3.7); $p=0.02$

**E**

Adjusted Event-Free Survival (%)

<table>
<thead>
<tr>
<th>Follow-up (years)</th>
<th>Tertiles 1 &amp; 2 of Lp(a)</th>
<th>Tertile 3 of Lp(a)</th>
</tr>
</thead>
<tbody>
<tr>
<td>71</td>
<td>37</td>
<td>37</td>
</tr>
<tr>
<td>68</td>
<td>35</td>
<td>35</td>
</tr>
<tr>
<td>62</td>
<td>33</td>
<td>33</td>
</tr>
<tr>
<td>59</td>
<td>29</td>
<td>29</td>
</tr>
<tr>
<td>36</td>
<td>18</td>
<td>18</td>
</tr>
<tr>
<td>17</td>
<td>4</td>
<td>4</td>
</tr>
</tbody>
</table>

§HR=5.5 (1.7-17.5); $p=0.004$

*Capoulade et al. J Am Coll Cardiol 2015;66:1236–46*
Lipoprotein(a) and Progression of Calcific AS

A - Cellular level

Lipoprotein(a)

Aortic valve

Endothelium

macrophages

Mineralization

Lp-PLA2

OxPLA2

LPC

OxFFA

B - Patients level

Low levels of Lp(a)-OxPL

High levels of Lp(a)-OxPL

Progression of aortic stenosis
There is now a strong body of evidence to support the hypothesis that Lp(a) and its associated OxPL are involved in AS progression.

About 20% of the general population (65 Million people in North America) have elevated Lp(a).

Lp(a) circulating levels are determined genetically and currently available drugs only achieve modest reduction in Lp(a) and have significant side effects.

Recent Phase I and II trials report that oligonucleotide antisense directed to Apo(a), reduces Lp(a) levels by >75% with minimal side effects.
Lipid Deposition
Lipid Retention
Lipid Oxidation
Inflammation
Renin-Angiotensin System
Valve fibrosis
Myocyte Apoptosis
Myocardial fibrosis
LV hypertrophy
Calcification
Osteoblasts
RunX2, BMP
RANK/OPG
Matrix Gla Prot
Ectonucleotidases
Fetuin A

Lp(a) lowering
PCSK9 inhib.
(statins)

ACE Inhibitors
ARBs

Adapted from Dweck et al. JACC 2012
**Congenital Bicuspid Aortic Valve**

- Most frequent congenital CV disease: 0.5-1 % of the population
- More frequent in males
- Life-time risk of AVR for AS is about 50%
- Develop AS 10 years earlier compared to subjects with tricuspid valve
Correlation Between AoV Calcification and AS Hemodynamic Severity in Patients with a Bicuspid Aortic Valve

Patients > 50 y.o.  Patients < 50 y.o.

Shen et al. Heart 2016
Case #2: 62 y.o. Patient with Bicuspid AS (C1 Stage)

62 y.o. man
Asymptomatic

Gradients: 63 / 45 mmHg
AVA (EOA): 0.89 cm²

AVA (AOA): 0.97 cm²
AVC Score: 5313 AU
Case #3: Young Patient with Bicuspid AS and High Gradient (C1 Stage)

36 y.o. woman
Asymptomatic

Gradients: 63 / 45 mmHg
AVA (EOA): 0.71 cm²

AVA (AOA/GOA): 1.2 cm²

AVC Score: 0 AU
Role of Jet Eccentricity in Generating Disproportionately Elevated Transvalvular Gradients in Bicuspid AS

Centric Jet

Eccentric Jet

↓ Contraction coefficient (EOA/AOA)
↓ EOA
↑ Gradient

Abbas et al. Echocardiography 2014
In patients with Tricuspid AS: Calcium is the main culprit lesion
AoV Calcification by Echo Predicts Outcomes in AS

Valve Calcification ($\geq 3/4$)

Case #1: Severe AoV Calcification

Quantification of Valvular Calcification by CT

None   Mild

Moderate  Severe

Messika-Zeitoun, JACC, 2004;110:356-362
Correlation between AoV Calcification by CT and Hemodynamic / Clinical Outcomes in AS

- AVC Correlates with hemodynamic severity
- Severe AVC:
  - Predicts hemodynamically severe AS
  - Predicts rapid AS progression
  - Predicts mortality

Aggarwal et al. Circ Img 2012
Clavel et al. JACC 2013
Clavel et al. JACC 2014
Differences in Women vs. Men in the Anatomic vs. Hemodynamic Severity of AS

Clavel et al. JACC 2013
AoV Ca Scor by CT to Differentiate Hemodynamically Severe vs. Non-Severe Stenosis

Pseudo-Severe

AVC score: 1034 AU
AVC density: 220 AU/cm²

True-Severe

AVC score: 3682 AU
AVC density: 980 AU/cm²

AVC Score: >2000 AU in ♂
>1200 AU in ♀

AVC Density: >500 AU/cm² in ♂
>300 AU/cm² in ♀

Clavel et al. JACC 2013
Women have less AoV calcification but more fibrosis compared to men

Naoum et al. JACC CV Imaging 2015
Patients with Calcific AS often have Concomitant Hypertension

30-80% of patients with calcific AS have hypertension. Hypertension doubles mortality in AS.
Impact of Hypertension on LV Systolic Wall Stress in Presence of AS: Animal Study

Catheter Gradient

Doppler Gradient

Peak Systolic Wall Stress

Impact of Hypertension and Anti-Hypertensive Medications on AS Progression and Outcomes

AS Progression

AVR or Death

Impact of Systolic Hypertension on Progression of AS

Progression of Aortic Valve Calcification, AU

<table>
<thead>
<tr>
<th>Group</th>
<th>Mean AU (Range)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>No SHPT (n=64)</td>
<td>157 (58-303)</td>
<td>0.007</td>
</tr>
<tr>
<td>SHPT (n=37)</td>
<td>370 (126-824)</td>
<td></td>
</tr>
</tbody>
</table>

SHPT: Systolic Hypertension
Pathophysiology of AS: Take Home Messages

- Pathophysiology of AS differs in:
  - Younger vs. older patients: lipid-mediated inflammation vs. phosphocalcic dysmetabolism
  - Women versus men: less calcification but more fibrosis
  - Bicuspid versus tricuspid valve

- Next milestones in the management of AS:
  - Tailor management according to age, sex, and valve phenotype
  - Better identify and treat hypertension in AS
  - RCT of ARB in patients with mild-to-moderate AS
  - RCT of Lp(a) lowering in younger patients with mild AS