Low Gradient Severe (?) Aortic Stenosis

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Disclosure: Philippe Pibarot

Financial relationship with industry:

- Edwards Lifesciences: Echo CoreLab for PARTNER 2–SAPIEN 3, PARTNER 3, TAVR-UNLOAD trials
- V-Wave Ltd: Echo CoreLab for FIM Study
- Cardiac Phoenix: Echo CoreLab for BACE FIM Study

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- Research Grants from Canadian Institutes of Health
- Research and Heart & Stroke Foundation of Quebec

Off label Use: None
Low Gradient AS

AVA ≤ 1.0 cm²  MG < 40 mmHg

<50%  ← LVEF  →  >50%

<35 mL/m²  SVi  >35 mL/m²

«CLASSICAL» LOW-FLOW LOW-GRADIENT D2 Stage

«PARADOXICAL» LOW-FLOW LOW-GRADIENT D3 Stage

NORMAL-FLOW LOW-GRADIENT D? Stage
“Classical” Low-Flow, Low-Gradient AS with Reduced LVEF (D2 Stage)
Low-Flow, Low-Gradient Severe(?) AS

True-Severe AS

Normal Flow

Low Flow

Pseudo-Severe AS

Normal Flow

Low Flow

AVA

ΔP

Gradient = \frac{Q^2}{K \times AVA^2}
Change in stroke volume during DSE

Dobutamine (μg/kg/min)

<table>
<thead>
<tr>
<th>Baseline</th>
<th>5</th>
<th>10</th>
<th>15</th>
<th>20</th>
</tr>
</thead>
<tbody>
<tr>
<td>14</td>
<td>14</td>
<td>18</td>
<td>20</td>
<td>22</td>
</tr>
</tbody>
</table>

LVOT Time Velocity Integral (cm)
Change in Gradient during DSE

Dobutamine (μg/kg/min)

Baseline

5

10

15

20

Mean Pressure Gradient (mm Hg)
Case #1

Resting Echo

LVEF=40%  SV= 53 ml
AVA= 0.77 cm²
ΔP= 49 / 29 mmHg

DSE

LVEF=50%  SV= 73 ml
AVA= 0.75 cm²
ΔP= 92 / 52 mmHg
**Case #2**

**Resting Echo**

- SV = 34 ml
- LVEF = 15%
- Peak $\Delta P$ = 18 mmHg
- Mean $\Delta P$ = 12 mmHg
- AVA = 0.85 cm$^2$

**DSE**

- SV = 46 ml
- LVEF = 25%
- Peak $\Delta P$ = 21 mmHg
- Mean $\Delta P$ = 13 mmHg
- AVA = 1.35 cm$^2$
Outcome of Pseudo-Severe AS Under Conservative Treatment

Pseudo Severe AS:
$\Delta P < 40 \ & \ AVA \geq 1.2$ at DSE

29 % had PSAS

Fougères et al.
Eur Heart J. 2012
**Case #3**

**Resting Echo**
- SV= 36 ml
- LVEF=20%
- Peak ∆P= 35 mmHg
- Mean ∆P= 22 mmHg
- AVA= 0.85 cm²

**DSE**
- SV= 46 ml
- LVEF=28%
- Peak ∆P= 63 mmHg
- Mean ∆P= 32 mmHg
- AVA= 1.1 cm²
Predictors of Mortality in Patients with Low-LVEF, Low-Flow, Low-Gradient AS Treated Medically – TOPAS Study

What is moderate AS for a good ventricle may be severe for a depressed ventricle!
TAVR UNLOAD Trial

Heart Failure
LVEF < 50%
NYHA ≥ 2
Optimal HF therapy (OHFT)
Moderate AS

TAVR + OHFT

OHFT alone

Follow-up:
1 month
6 months
1 & 2 years

Clinical endpoints
Symptoms
Echo
QoL

International Multicenter Randomized
Case #4

- 76 y.o. woman
- Risk factors:
  - Obese, Hyperchol.
  - Hypertension, COPD
  - 3-vessel CAD
- CABG × 3: Aug 95
- MI: Jan 96
- CHF: LVEDD:64 mm, LVEF: 25%, BNP: 832 pg/ml
- Aortic stenosis, mild mitral regurgitation
- Current medication: ASA, ARBs, Statin, Digoxin, Brochodil.
Case #4

**Resting Echo**

- LVEF = 25%
- SV = 51 ml
- AVA = 0.8 cm²
- ΔP = 46 / 27 mmHg

**DSE**

- LVEF = 30%
- SV = 57 ml
- AVA = 0.8 cm²
- ΔP = 52 / 30 mmHg
AoV Ca Scoring by MDCT to Differentiate True vs. Pseudo- Severe Stenosis in LF-LGAS

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
Dobutamine-Stress Echo

LVEF ≤ 40%
AVA ≤ 1.0
ΔP < 40

↑ SV ≥ 20%

Contractile (Flow) Reserve

ΔP ≥ 40
AVA < 1.0

True-Severe AS
SAVR ± CABG
TAVR ± PCI

ΔP < 40
AVA ≥ 1.0

Pseudo-Severe AS
HF Therapy

↑ SV < 20%

No Contractile (Flow) Reserve

AS Severity: Indeterminate

MSCT: AoV Ca Score
♀ > 1200
♂ > 2000

True-Severe AS
SAVR (High Op. Risk)
TAVR? BAV+TAVR?
Outcome After Aortic Valve Replacement for Low-Flow/Low-Gradient Aortic Stenosis Without Contractile Reserve on Dobutamine Stress Echocardiography

Christophe Tribouilloy, MD, PhD,* Franck Lévy, MD,† Dan Rusinaru, MD,‡ Pascal Guéret, MD,‡ Hélène Petit-Eisenmann, MD,§ Serge Baleynaud, MD,‖ Yannick Jobic, MD,¶ Catherine Adams, MD,# Bernard Lelong, MD,** Agnès Pasquet, MD,†† Christophe Chauvel, MD,‡‡ Damien Metz, MD,§§ Jean-Paul Quéré, MD,* Jean-Luc Monin, MD, PhD‡

A

**Total Population**

Survival (%)

AVR

Medical management

Follow-up (months)

log rank p = 0.001

B

**Matched Patients**

Survival (%)

AVR

Medical management

Follow-up (months)

p = 0.019

Tribouilloy et al. JACC, 53; 1865-1873, 2009
Preoperative Contractile/Flow Reserve vs. Postoperative Ejection Fraction

Quere et al, Circulation 2006;113:1738-1734
### 2014 ACC/AHA Guidelines on Management of VHD: Indications for AVR in AS

**Definition:**
- $\text{AVA} \leq 1.0 \text{ cm}^2$
- Mean gradient $< 40 \text{ mmHg}$
- LVEF $< 50\%$

**Stage:** D2

<table>
<thead>
<tr>
<th>Recommendation</th>
<th>Class</th>
<th>Level</th>
</tr>
</thead>
<tbody>
<tr>
<td>AVR is reasonable in symptomatic patients with low LVEF, low-flow/low-gradient severe AS with a DSE that shows a mean gradient $\geq 40 \text{ mm Hg}$ with an AVA $\leq 1.0 \text{ cm}^2$ at any dobutamine dose</td>
<td>IIa</td>
<td>B</td>
</tr>
</tbody>
</table>

*Nishimura, Otto et al.*

*JACC 2014*
**2012 ESC/EACTS Guidelines on Management of VHD: Indications for AVR in AS**

<table>
<thead>
<tr>
<th>Indication</th>
<th>Grade</th>
<th>Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>AVR should be considered in symptomatic patients with severe AS, low flow, low gradient with reduced EF, and evidence of flow reserve.</td>
<td>IIA</td>
<td>C</td>
</tr>
<tr>
<td>AVR may be considered in symptomatic patients with severe AS low flow, low gradient, and LV dysfunction without flow reserve.</td>
<td>IIB</td>
<td>C</td>
</tr>
</tbody>
</table>

Severe AS on DSE: Increase in AVA < 0.2 cm² with final AVA < 1 cm²; mean gradient > 40 mmHg

Flow reserve: >20% increase in stroke volume

*Vahanian et al. EHJ 2012*
**Key Messages: Classical Low-Flow, Low-Gradient AS with Reduced LVEF**

- **Dobutamine stress echo** is essential for risk stratification and clinical decision making.
- Absence of flow reserve **should not preclude** consideration of AVR.
- Use **different cut-points of AVA** and gradient to define severe AS?
- **Aortic valve calcium scoring** may be useful to corroborate stenosis severity in patients with no flow reserve.
- **TAVR** may provide a valuable alternative in these patients.
“Paradoxical” Low-Flow, Low-Gradient AS with Preserved LVEF (Stage D3)

↑Age
Women
Hypertension
MetS – Diabetes

Hachicha Z et al., Circulation, 2007
Dumesnil et al. Eur Heart J, 2009
Pibarot & Dumesnil JACC, in press, 2012
AORTIC STENOSIS ± HYPERTENSION

- Pronounced Concentric Remodeling
- Impaired Diastolic Filling
- Impaired Longitudinal systolic function
- Atrial Fibrillation
- Mitral Stenosis
- Mitral Regurgitation
- Tricuspid Regurgitation
- Constrictive Pericarditis

Reduced Forward Stroke Volume (SVi<35 mL/m²)

- Reduced Transvalvular flow rate

Low-Flow, Low-gradient AS Despite Preserved LVEF

Pibarot & Dumesnil, Circulation 2013
Case #5

- 82 y.o. woman
- Hypertension treated with ACEI
- No CAD
- NYHA III, HF hospitalization
- LVEF: 65%
- Global longit. strain: 13%
- Severe Diastolic Dysf.
- AS severity on echo:
  - AVA: 0.64 cm²; iAVA: 0.36 cm²/m²
  - Peak/mean gradient: 44/26 mmHg
  - SV index: 29 ml/m²
Potential Causes of Discordance between AVA (e.g. 0.8) and gradient (e.g. 30) in Pts. With Preserved LVEF

- Measurement errors
- Small body size
- Normal-flow, low-gradient AS
  Inconsistency in guidelines criteria
- Paradoxical low-flow, low-gradient severe? AS

Aortic Valve Area: Anatomic vs. Effective

**Effective Orifice Area (EOA)**

**Anatomic Orifice Area (AOA)**

**AS Severity**
- Mild  > 1.5 cm$^2$
- Moderate  1.0-1.5 cm$^2$
- Severe  < 1.0 cm$^2$

**AVA** = \[
\frac{\text{CSA}_{LVOT} \times \text{VTI}_{LVOT}}{\text{VTI}_{Ao}}
\]

**Continuity Equation**
Measurement Pitfalls: LVOT Diameter

- **Underestimation**
  - Poor echogenicity
  - Image truncated
  - LVOT elliptical

- **Overestimation**
  - Oblique measure
Low gradient severe aortic stenosis with preserved ejection fraction: reclassification of severity by fusion of Doppler and computed tomographic data

191 patients with symptomatic severe AS undergoing TAVR

16 % reclassified as non-severe by hybrid CT-echo method

<table>
<thead>
<tr>
<th>Aortic Stenosis</th>
<th>Normal Flow – High Gradient</th>
<th>Low Flow – High Gradient</th>
<th>Normal Flow – Low Gradient</th>
<th>Low Flow – Low Gradient</th>
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<tr>
<td>Severe, n (%)</td>
<td>72 (100)</td>
<td>70 (97)</td>
<td>31 (100)</td>
<td>46 (100)</td>
</tr>
<tr>
<td></td>
<td>2 (3)</td>
<td>0 (0)</td>
<td>22 (48)</td>
<td>42 (100)</td>
</tr>
<tr>
<td>Moderate, n (%)</td>
<td>2 (3)</td>
<td>0 (0)</td>
<td>24 (52)</td>
<td>5 (12)</td>
</tr>
</tbody>
</table>

Kamperidis et al. Eur Heart J 2015
Calculation of AVA by MDCT and Echo

- Cut-point of AVA to predict mortality
  - Echo AVA: $1.0 \text{ cm}^2$ vs. Hybrid (MDCT-Echo) AVA: $1.2 \text{ cm}^2$

Clavel et al., JACC Imaging 2015
Low gradient severe aortic stenosis with preserved ejection fraction: reclassification of severity by fusion of Doppler and computed tomographic data

191 patients with symptomatic severe AS undergoing TAVR

If an AVA cut-point of 1.2 cm² had been used: 3 % reclassified as non-severe by hybrid CT-echo method

<table>
<thead>
<tr>
<th>Aortic Stenosis</th>
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<th>Low Flow – High Gradient</th>
<th>Normal Flow – Low Gradient</th>
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<td></td>
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<td>31 (100)</td>
<td>22 (48)</td>
<td>37 (88)</td>
</tr>
<tr>
<td>Moderate, n (%)</td>
<td>2 (3)</td>
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<td>24 (52)</td>
<td>5 (12)</td>
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</tbody>
</table>
Doppler-Echo Features of Paradoxical Low-Flow, Low-Gradient AS

The Aortic Valve:
- AVA < 1.0 cm²  AVAi < 0.6 cm²/m²  DVI < 0.25
- Severely thickened/calcified valve
- Mean gradient < 40 mmHg
- Valvulo-arterial impedance > 4.5

The Left Ventricle
- EDD < 47 mm  EDV < 55 mL/m²
- RWT ratio > 0.50
- Myocardial fibrosis
- Impaired LV filling
- LVEF > 50%
- GLS < 15%
- SVi < 35 mL/m²

Pibarot & Dumesnil, JACC 58;413-415, 2011
Case #6: Normal-Flow, Low-Gradient AS (Stage ?)

LVOT
Vmax: 96 cm/s
SV: 72 ml
SVI: 37 ml/m²

Aortic valve
Vmax: 372 cm/s
MG: 35 mmHg
AVA: 0.81 cm²
Outcome and Impact of AVR in Low-Gradient AS: A Meta-Analysis

- 18 studies, 7,459 patients

Paradoxical LF-LG AS:
- Increased risk of mortality compared to moderate AS and high-gradient AS
- Outcome is improved by AVR

Normal Flow, Low-Gradient AS:
- Outcome similar to high-gradient AS but improved by AVR

Dayan JACC; 66:2594-03, 2015
Treatment Comparison in Paradoxical Low-flow, low-gradient AS

Cohort B: Inoperable Patients

log rank p = 0.003

Numbers at Risk

<table>
<thead>
<tr>
<th>Days</th>
<th>B – TAVR</th>
<th>B – Std Rx</th>
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</thead>
<tbody>
<tr>
<td>0</td>
<td>23</td>
<td>29</td>
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<tr>
<td>60</td>
<td>21</td>
<td>22</td>
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<tr>
<td>120</td>
<td>19</td>
<td>15</td>
</tr>
<tr>
<td>180</td>
<td>17</td>
<td>10</td>
</tr>
<tr>
<td>240</td>
<td>15</td>
<td>9</td>
</tr>
<tr>
<td>300</td>
<td>13</td>
<td>9</td>
</tr>
<tr>
<td>360</td>
<td>11</td>
<td>6</td>
</tr>
<tr>
<td>420</td>
<td>10</td>
<td>5</td>
</tr>
<tr>
<td>480</td>
<td>10</td>
<td>4</td>
</tr>
</tbody>
</table>

Herrmann et al. Circulation 2013
Treatment Comparison in Paradoxical Low-flow, low-gradient AS

Cohort A: High Risk Patients

<table>
<thead>
<tr>
<th>Days</th>
<th>LF NEF LG – A - TAVR</th>
<th>LF NEF LG – A - Surgery</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>60</td>
<td></td>
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<td>120</td>
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<tr>
<td>540</td>
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<tr>
<td>600</td>
<td></td>
<td></td>
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<tr>
<td>660</td>
<td></td>
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<tr>
<td>720</td>
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</tbody>
</table>

Numbers at Risk

<table>
<thead>
<tr>
<th></th>
<th>A – TAVR</th>
<th>A – Surgery</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 – 60 Days</td>
<td>43</td>
<td>44</td>
</tr>
<tr>
<td>61 – 120 Days</td>
<td>39</td>
<td>33</td>
</tr>
<tr>
<td>121 – 180 Days</td>
<td>38</td>
<td>30</td>
</tr>
<tr>
<td>181 – 240 Days</td>
<td>34</td>
<td>30</td>
</tr>
<tr>
<td>241 – 300 Days</td>
<td>34</td>
<td>28</td>
</tr>
<tr>
<td>301 – 360 Days</td>
<td>33</td>
<td>27</td>
</tr>
<tr>
<td>361 – 420 Days</td>
<td>29</td>
<td>27</td>
</tr>
<tr>
<td>421 – 480 Days</td>
<td>26</td>
<td>26</td>
</tr>
<tr>
<td>481 – 540 Days</td>
<td>22</td>
<td>23</td>
</tr>
<tr>
<td>541 – 600 Days</td>
<td></td>
<td></td>
</tr>
<tr>
<td>601 – 660 Days</td>
<td></td>
<td></td>
</tr>
<tr>
<td>661 – 720 Days</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

log rank p = 0.01

Herrmann et al. Circulation 2013
### Guidelines on Management of VHD: Indications for AVR in Paradoxical Low-Flow, Low-Gradient AS

**Definition:**

- \( \text{AVA} \leq 1.0 \text{ cm}^2 \), Indexed \( \text{AVA} \leq 0.6 \text{ cm}^2/\text{m}^2 \)
- Mean gradient < 40 mmHg,
- LVEF ≥ 50%, SVi < 35 mL/m²

**Stage:** D3

<table>
<thead>
<tr>
<th>Guidelines</th>
<th>Recommendation for AVR</th>
<th>Class</th>
</tr>
</thead>
<tbody>
<tr>
<td>ESC-EACTS 2012</td>
<td>AVR should be considered in <strong>symptomatic</strong> patients with low flow, low gradient (&lt;40 mmHg) AS with normal EF only after careful confirmation of severe AS.</td>
<td>IIa</td>
</tr>
<tr>
<td>ACC-AHA 2014</td>
<td>AVR is reasonable in <strong>symptomatic</strong> patients who have low-flow, low-gradient severe AS who are <strong>normotensive</strong> and have an LVEF ≥ 50% if clinical, hemodynamic, and anatomic data support valve obstruction as the most likely cause of symptoms</td>
<td>IIa</td>
</tr>
</tbody>
</table>

Vahanian et al. EHJ 2012  
Nishimura, Otto et al. JACC 2014
Case #5: Aortic Valve Calcium Scoring by MDCT

AVC Score: 3200 AU
Doppler-Echocardiography Post-TAVR
With a SAPIEN 3 Valve
LVOTD: 2.07 cm
LVOT TVI: 18.7 cm
LVOT SV: 63 mL (vs. 53 ml pre-TAVR);  indexed SV: 35 mL/m²
(RVOT SV: 65 mL)
Positive LV Remodeling and Improvement in Flow Following AVR in Paradoxical Low-Flow, Low-Gradient AS

Dahou et al. JACC CV Imaging 2016 in press
Evolution and Prognostic Impact of Low Flow after TAVR

LeVen F et al. Heart 2015
Evolution and Prognostic Impact of Low Flow after TAVR in Low-Flow AS

Anjan et al. JAMA Cardiol. 2016
Key Messages: Paradoxical Low-Flow, Low-Gradient AS with Preserved LVEF

- It is important to rule-out:
  1. Measurement errors
  2. Small body size
  3. Normal-flow, low-gradient AS (inconsistency in guidelines criteria)
  4. Pseudo-severe AS (MDCT, DSE)

- AVR improves outcome in patients with true paradoxical low-flow, low-gradient severe AS

- TAVR may provide a valuable alternative to SAVR in these patients