"Thus, the task is not so much to see what no one yet has seen, but to think what nobody yet has thought about that which everybody sees.”

Schopenhauer
### Current guidelines

<table>
<thead>
<tr>
<th>Severity</th>
<th>Velocity (m/s)</th>
<th>Mean gradient (mmHg)</th>
<th>AVA (cm²)</th>
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<tr>
<td>Normal</td>
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</tr>
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<tr>
<td>Severe</td>
<td>≥ 4</td>
<td>≥ 40</td>
<td>≤ 1</td>
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</tbody>
</table>

Nishimura RA et al. Circ 2014

### Low flow AS

<table>
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Nishimura RA et al. Circ 2014
Discrepant AV Hemodynamics with low flow condition

Classic low-flow low-gradient AS: EF < 50%

Paradoxical low-flow low-gradient AS: EF > 50%

Low-Flow, Low gradient AS with Preserved LVEF

Pibarot, JACC. 2014
Low-flow low-gradient AS with low EF

- LVEF < 50%
- MG < 40 mmHg
- AVA ≤ 1 cm²

**LFLG AS**

**Severe AS**
AVA ≤ 1 cm², MG ≥ 40 mmHg

**Non-severe AS**
AVA > 1 cm², MG < 40 mmHg
62 year-old with ischemic CM

AVA = 0.81 cm²
MG = 24 mmHg

Low-Flow, Low-Gradient AS
Echo Data for Analysis

<table>
<thead>
<tr>
<th>Dobutamine</th>
<th>Baseline</th>
<th>10 mcg</th>
<th>20 mcg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stroke Volume</td>
<td>Mean Gradient</td>
<td>Stroke Volume</td>
<td>Mean Gradient</td>
</tr>
<tr>
<td>Ao Valve Area</td>
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</tbody>
</table>

$\text{Stroke Volume} = \text{LVOT Area} \times \text{LVOT TVI}$
Response to dobutamine- Severe AS

SV: 42 ml
MG: 22 mmHg
AVA: 0.86 cm²

SV: 60 ml
MG: 41 mmHg
AVA: 0.95 cm²

Response to Dobutamine- Non-severe AS

SV: 55 ml
MG: 20 mmHg
AVA: 0.90 cm²

SV: 73 ml
MG: 24 mmHg
AVA: 1.25 cm²
Response to Dobutamine- No CR

SV: 44 ml
MG: 18 mmHg
AVA: 0.73 cm²

SV: 44 ml
MG: 25 mmHg
AVA: 0.7 cm²

What is contractile reserve?

- This was defined in the literature as a 20% increase in stroke volume from baseline at any point during stress test.

- It has been shown in the European database to be a strong predictor of overall mortality as well surgical mortality in patients with LFLG AS.
Group I: Normal CR
Group II: No CR

Tribouilloy C, Monin JL et al. JACC 2009

LG AS: AVA ≤ 1, MG < 40, LVEF < 50%

AVA ≥ 1, MG ≥ 40

Severe AS

AVA ≤ 1, MG < 40, No CR

AVA > 1, MG < 40

Non-severe AS
But

Do all patients with EF < 50% have low stroke volume?

Normal SVi low EF low gradient AS

SV=82 ml   SV=95 ml
SVi= 47 ml/m2  SVi= 55 ml/m2
AVA= 0.81 cm2  AVA= 0.9 cm2
MG= 24 mmHg  MG = 42 mmHg
50-year-old female with chest radiation

SV = 39 ml
SVi = 26 ml/m²
MG = 24 mmHg
AVA = 0.64 cm²

Definition of low flow

- This has been defined in the literature as stroke volume indexed (SVi) of < 35 ml/m².
- This is only being used in patients with normal ejection fraction.
- The number is more arbitrary than evidence-driven.
What is flow rate?

- Flow rate is the amount of blood ejected across the aortic valve every second.
- Flow happens during the systolic ejection period of the cardiac cycle.
- Most common method of measuring flow is:

$$ FR = \frac{SV}{ET} $$

FR (ml/sec)

Normal = 200-250 ml/sec

Wolfram V et al. Circ. 1994
Resting Aortic Valve Area at Normal Transaortic Flow Rate Reflects True Valve Area in Suspected Low Gradient Severe Aortic Stenosis

Naveen C. Chahal, MBBS,† Maria Iakovopoulou, MD,‡ Ana M. Gonzalez-Gonzalez, MD,∥ Ramasamy Maranmane, MBBS,§ Rajdeep Khattar, MBBS,¶ Roxy Senior, MD

| TABLE 2 Change in AVA During Stress, Stratified by Resting LVEF, SVI, and Flow Rate State |
|----------------------------------|----------------------------------|----------------------------------|-------------------------|
| LVEF <50%                        | 37                              | 0.75 ± 0.14                      | 0.87 ± 0.21             | <0.001                 |
| LVEF >50%                        | 30                              | 0.79 ± 0.10                      | 0.93 ± 0.23             | 0.007                  |
| SVI <35 ml/m²                    | 47                              | 0.74 ± 0.12                      | 0.86 ± 0.23             | <0.001                 |
| SVI >35 ml/m²                    | 20                              | 0.83 ± 0.10                      | 0.98 ± 0.21             | 0.016                  |
| Qa <200 ml/s                     | 48                              | 0.74 ± 0.12                      | 0.89 ± 0.25             | <0.001                 |
| Qa >200 ml/s                     | 19                              | 0.85 ± 0.09                      | 0.99 ± 0.12             | 0.19                   |

Values are mean ± SD.
Qa = flow rate; other abbreviations as in Table 1.
FR ≠ SV ≠ EF

Mayo Clinic data

- 70 patients with EF < 50% with at least AV hemodynamics at rest and peak dobutamine were identified

- Survival analysis using log-rank Kaplan-Meier curves were performed.

- Hypothesis: Flow rate will better risk stratify patients with LFLG AS than SV derived CR.
70 patients with LG AS: AWA ≤ 1 cm², MG < 40 mmHg

53 patients with severe LG AS: Peak AWA ≤ 1

17 patients with non-severe AS: Peak AWA > 1

27 patients with CR, MG ≥ 40

26 patients with No CR, MG < 40

14 Medical Rx

13 patients AVR

14 patients AVR

12 Medical Rx

11 SAVR

2 TAVR

7 SAVR

7 TAVR

53 patients with severe LG AS: Peak AWA ≤ 1

P<0.001
53 patients with severe LG AS: Peak AVA ≤ 1

Baseline flow survival data

No CR

P=0.31

No CR

P=0.001

AVR

P=0.04

P=0.072

Baseline Q > 200

P=0.06

Baseline Q > 220

Baseline Q > 230

Baseline Q > 230

P=0.03*

Baseline Q > 220

Baseline Q > 230

Baseline Q > 220

Baseline Q > 230
Response to dobutamine data

Baseline Q < 230
peak Q > 230
peak Q < 230
P=0.004

“Flow Reserve”

Benefit from AVR by rest flow
Baseline Q < 200
Baseline Q > 200

Baseline Q < 200
baseline Q > 200
AVR
No AVR
P=0.13
P<0.001

Surviving
0
1
2
3
4
5
6
7
8
9
TTD year

Surviving
0
1
2
3
4
5
6
7
8
9
TTD year

P=0.13
P<0.001
Conclusion

- Flow $\neq$ SV $\neq$ EF
- Flow rate is an emerging concept and was shown in our database to be a better prognosticator than SV derived CR.
- Whether we should refer patients with normal SVI or flow rate for dobutamine echo is still to be determined.

74-year-old male

- Known aortic valve stenosis
- Chronic atrial fibrillation
- S/P dual chamber PPM for heart block
- Develops CHF and hospitalized three times from worsening aortic valve stenosis
  - LV EF 35%
  - AVA 0.8 cm$^2$ MG 22 mmHg
  - Moderate AR
  - Moderate-severe MR
74-year-old male

- High surgical risk
- Referred for TAVR
74-year-old male

BP: 137/90
HR: 90
AS murmur
NT-Pro BNP 23407
Creatinine 1.8

74-year-old male

[Image of ECG]

[Image of chest X-ray]
What would you recommend next?

1. TAVR?
2. Aortic valve balloon valvuloplasty?
3. TEE for MitraClip candidacy?
4. Dobutamine echocardiogram for hemodynamic assessment of AS?
5. Cardiac catheterization for hemodynamic assessment of AS?

Dobutamine echocardiogram
5 mcg/kg/min - 20 mcg/kg/min @ 5 min stages

LVOT = 2.2 cm

REST

TVI 13 cm SV 49 cc SVI 26 cc/m²

PEAK

TVI 17 cm SV 65 cc SVI 34 cc/m²

SV ↑ 20% /

AVA ≤ 1 cm²
MG ≥ 40 mmHg
OR
AVA > 1 cm²
MG < 40 mmHg
What would you recommend next?

1. Aortic valve balloon valvuloplasty?
2. TAVR?
3. Cardiac catheterization for hemodynamic assessment?
4. Hospice?
5. Maybe something else?

Dobutamine echocardiogram
5 mcg/kg/min - 20 mcg/kg/min @ 5 min stages

<table>
<thead>
<tr>
<th>LVOT = 2.2 cm</th>
<th>REST</th>
<th>PEAK</th>
</tr>
</thead>
<tbody>
<tr>
<td>TVI 13 cm SV 49 cc SVI 28cc/m²</td>
<td>TVI 17 cm SV 65 cc SVI 34cc/m²</td>
<td></td>
</tr>
<tr>
<td>Flow = 144 cc/s</td>
<td>Flow = 163 cc/s</td>
<td></td>
</tr>
<tr>
<td>Vel 3 m/s MG 20mmHg AVA 0.8 cm²</td>
<td>Vel 3.5 m/s MG 28mmHg AVA 0.87 cm²</td>
<td></td>
</tr>
</tbody>
</table>
Pibarot et al, circ 2006.

**Dobutamine echocardiogram**

5 mcg/kg/min - 20 mcg/kg/min @ 5 min stages

LVOT = 2.2 cm  
REST  
TVI 13 cm SV 49 cc SVI 28 cc/m²  
Flow = 144 cc/s

PEAK  
TVI 17 cm SV 65 cc SVI 34 cc/m²  
Flow = 163 cc/s

AVAproj = 1.1 cm²
Baseline LVEF 27%

1 month LVEF 33%

4 months LVEF 58%
74-year-old male (4 months following)

NT-Pro BNP
2544
Creatinine
1.4

Atrial fibrillation and aortic stenosis assessment
Prevalence of AF in AS patients

- AF in general affects 1-2% of the general population (Chugh 2001)

- It affects 9% of patients with moderate AS with an incidence of 1.2%/year (Greve 2013).

- In patients referred for TAVR in the French database, 26% had AF at time of referral (Chopard 2015) and 37% in PARTNER I trial (Biviano 2016).

- And up to 35-50% in patients with LFLG AS with reduced EF (Levy 2006, Eleid 2012).

- Atrial fibrillation makes grading of aortic stenosis severity complex and time-consuming.

- This is due to significant beat-beat variability resulting in different mean gradient and peak velocity from beat to beat.

- Should we average signals?
Expert consensus.

Case:

- 73-year-old patient with known aortic valve stenosis and persistent AF.
- Referred to Valve Clinic for an opinion on her AS.
Case 1:

**MG:** 40 mmHg

**AVA:** 0.77 cm²

**SV:** 71 ml

**SVi:** 50 ml/m²
She was referred from Valve Clinic for a surgical evaluation.

Surgery gave the patient the option of surgery vs 3 months follow-up. She chose to follow-up.

Presented to ER with sudden cardiac death after one month.

Final Impressions

1. Moderate-severe calcific aortic valve stenosis.
2. Aortic valve systolic mean Doppler gradient, 38 mmHg.
3. Aortic valve area by Doppler, 0.77 cm².
5. Moderate mitral valve stenosis.
6. Mitral valve diastolic mean Doppler gradient, 8 mmHg (heart rate 70 BPM).
7. Mitral valve area by continuity equation, 1.27 cm².
• This example raises 2 questions:

1. Should we average?

2. Is MG more important than AVA?

• From the Mayo Clinic database, we identified patients with aortic valve stenosis with AVA ≤ 1 cm² and atrial fibrillation at the time of echocardiogram between 1/2012 and 12/2014.

• Grading of severity of AS based on averaging signals.

• Clinical outcomes including rates of referral to AVR and overall survival with and without AVR.
AVA ≤1 + AF (n=768)

Average MG < 40 and V < 4 (LGAS) (373, 49%)

LGAS - HS (264, 71%)

Average MG ≥ 40 or V ≥ 4 (395, 51%)

LGAS + HS (109, 29%)

Severe HGAS

Grading of AS severity

- Severe
- Mod-Sev
- Moderate
AVA ≤ 1 + AF (n=768)

Average MG < 40 and V ≤ 4 (LGAS) (373, 49%)

LGAS - HS (264, 71%)

Severe 25%
Mod-sev 35%
Mod 35%
Nild-mod 5%

LGAS + HS (109, 29%)

Severe 40%
Mod-sev 45%
Mod 15%

Severe HGAS

Average MG ≥ 40 or V ≥ 4 (395, 51%)

Severe HGAS 100%

Severe 40%
Mod-sev 35%
Mod 35%
Nild-mod 5%

P=0.16

Medical Management arm
AVA ≤ 1 + AF (n=768)

Average MG < 40 and V ≤ 4 (LGAS) (373, 49%)

LGAS - HS (264, 71%)

Severe 25%
Mod-sev 35%
Mod 35%
Nild-mod 5%

LGAS + HS (109, 29%)

Severe 40%
Mod-sev 45%
Mod 15%

Severe HGAS

Average MG ≥ 40 or V ≥ 4 (395, 51%)

Severe 100%

Average MG ≥ 40 or V ≥ 4

P=0.17
Referral to AVR

Rate of referral to AVR

- HGAS
- LGAS
- LGAS+HS
- LGAS-HS

P < 0.001
Severe HGAS
LGAS
LGAS + HS
LGAS - HS
AVR
AVA ≤ 1 + AF
(n=768)
Average MG < 40
and V < 4 (LGAS)
(373, 49%)
Average MG ≥ 40
or V ≥ 4
(395, 51%)
LGAS - HS
(264, 71%)
LGAS + HS
(109, 29%)
Severe HGAS
AVR (64, 24%)
AVR (54, 50%)
AVR (243, 63%)
P<0.0001
Multi-variate analysis for predictors of mortality

<table>
<thead>
<tr>
<th>Variable</th>
<th>Hazard Ratio</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>1.031623</td>
<td>0.001*</td>
</tr>
<tr>
<td>Gender</td>
<td>M/F: 1.3</td>
<td>0.0111*</td>
</tr>
<tr>
<td>AVA</td>
<td>6.35</td>
<td>0.0002*</td>
</tr>
<tr>
<td>EF</td>
<td>1.001034</td>
<td>0.8139</td>
</tr>
<tr>
<td>MG</td>
<td>0.990257</td>
<td>0.517</td>
</tr>
<tr>
<td>RVSP</td>
<td>0.995923</td>
<td>0.3008</td>
</tr>
<tr>
<td>SVi</td>
<td>1.3</td>
<td>0.004*</td>
</tr>
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AVA ≥ 1 + AF (n=768)

Average MG < 40 and V < 4 (LGAS) (373, 49%)

LGAS - HS (264, 71%)
AVR (64, 24%)

LGAS + HS (109, 29%)
AVR (54, 50%)

Average MG ≥ 40 or V ≥ 4 (395, 51%)

Severe HGAS
AVR (243, 63%)
How does the gradient in AF compare to that in sinus rhythm in the same patient?

Case 4:

- 72-year-old male with known calcified aortic stenosis.
- Developed palpitations and shortness of breath and presented to ER.
In SR: SVi: 51 ml/m²
AVA: 0.73 cm²

In AF: SVi: 37 ml/m²
AVA: 0.85 cm²

Case 5:

• 75-year-old female with HTN and shortness of breath for 6 months comes in with palpitations.
Conclusion:

- Averaging under-estimates the severity of aortic valve stenosis.
- We are under-referring patients with AS and AF by averaging their signals.
- AVA is the strongest predictor of mortality in patients with AS and AF. Patients with $\text{AVA} \leq 1 \text{ cm}^2$ had the worst outcomes regardless of MG.
- The highest signal should be used to grade AS in these patients.
Future directions:

- Prospective study where patients with any degree of AS are referred for cardioversion.

- Patients will need a limited echocardiogram before the cardioversion focused on AV hemodynamics.

- Patients will need a limited echocardiogram right after cardioversion to reassess hemodynamics and compare signals.

Future directions:

- Patients with AS and frequent PVCs where MG augments to severe range with a PVC. Outcomes?

- Identify these patients who also had a Holter monitor and determine number of PVCs that will change the outcomes.
Future directions:

Questions/discussion