Low Gradient Severe AS: Who Qualifies for TAVR?

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Disclosures

- Chiesi Pharma-Consultant

Background

- Aortic valve stenosis
  - One of the most prevalent valvular heart disease in developed countries
  - 85,000 valve procedures
  - 15,000 deaths per year in North America
  - AVR is indicated for severe AS and either symptoms or LV dysfunction. Certain asymptomatic patients.

Severity Grading

AHA Guidelines for Severity of Aortic Stenosis

	Valve Area (cm2)	Maximum Aortic Velocity (mmHg)	Mean Pressure Gradient (mmHg)
Mild	1.5-2	2.5-3.0	< 25
Moderate	1.0-1.5	3.0-4.0	25-40
Severe	0.6-1.0	>4.0	>40
Critical	< 0.6		

- AVA<1.0 cm2, mean gradient >40 mmHg, Vmax >4 m/s

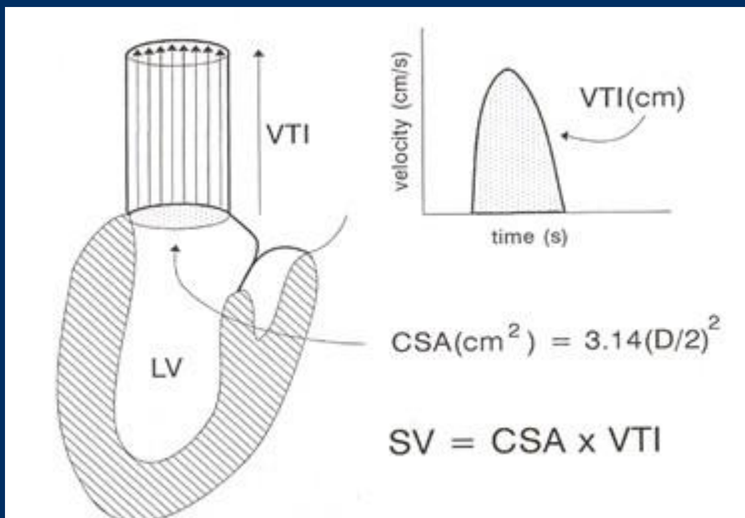
- Up to 40% patient have discordant Doppler findings
  - AVA<1.0 cm2, mean gradient <40 mmHg, Vmax <4 m/s

Hemodynamic characteristics

Aortic stenosis	Flow	Gradient
Classic AS (EF>50%)	NL (Svi>35ml/m2)	High (>40 mmHg)
Classic LF,LG (EF<50%)	Reduced (CI <3 L/m/m2, Svi<35 ml/m2)	Low (<40mmHg)
Paradoxical LFLG (EF>50%)	Reduced (CI <3 L/m/m2, Svi<35 ml/m2)	Low (<40mmHg)
NFLG (EF>50%)	NL	Low (<40 mmHg)

Normal SV 60-100 ml/m (120-200 ml/min with exercise),
Stroke volume index 35-65 ml/m2

ECHO calculation for SV(i)



Stroke volume and aortic stenosis severity

The Doppler-derived SVi was calculated as follows:

$$SVi = \frac{LVOT\ CSA \times VTI}{BSA}$$

Not so classic aortic stenosis

1. Low Flow, Low Gradient Severe AS

2. Paradoxical Low Flow, Low Gradient Severe AS

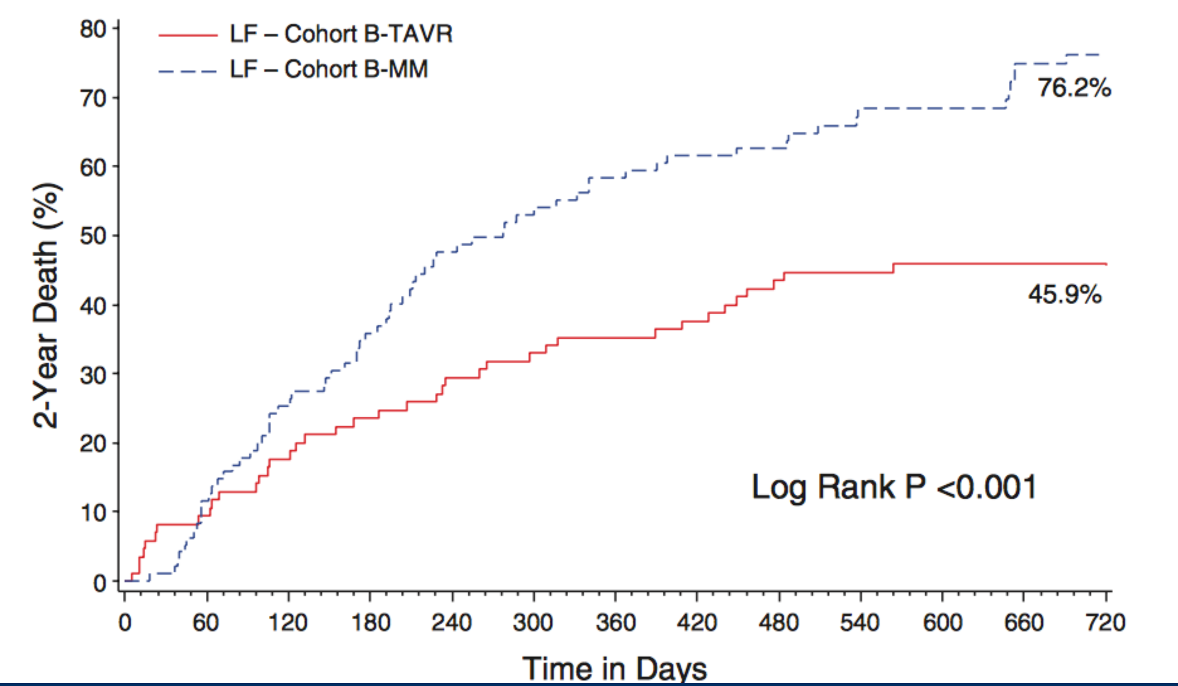
Low flow, low gradient AS with low EF

- EF<50%, AVA <1.0 cm2, mean gradient <40 mmHg
- 5-10% of severe AS
- Low flow state – gradient may be pseudo-normalized (underestimate stenosis severity)
- AVA may be pseudo-severe (overestimate severity)
- Often associated with CAD (Syntax>22 worse outcomes)
- Enlarged cavity with low ejection fraction
- More often functional MR
- Intrinsic cardiomyopathy

Marie-Annick Clavel et al. JIMG 2017;10:185-202

Predictors of Mortality and Outcomes of Therapy in Low-Flow Severe Aortic Stenosis

A Placement of Aortic Transcatheter Valves (PARTNER) Trial Analysis



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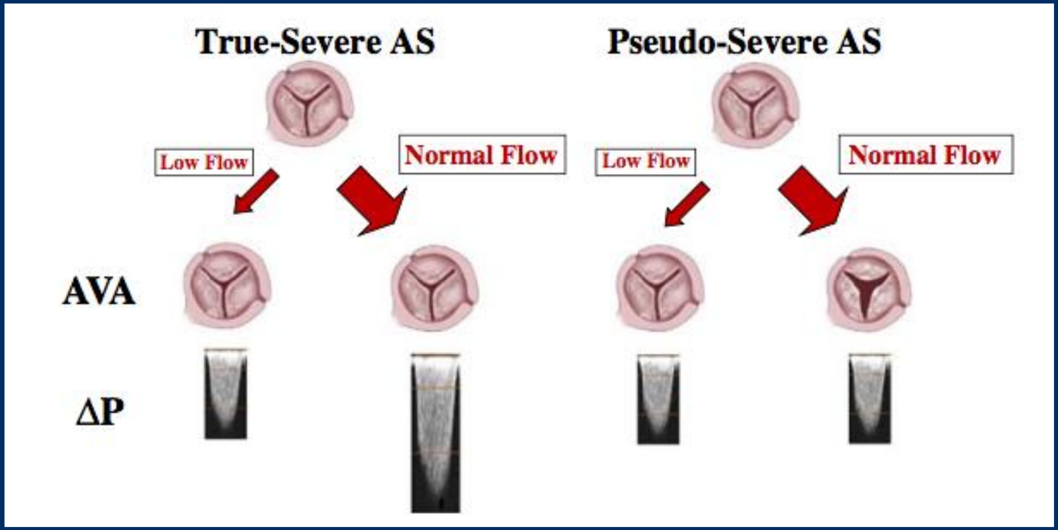
Dobutamine stress ECHO

- Low dose up 20 mcg/kg/min
- Attempt to increase flow volume across the AV

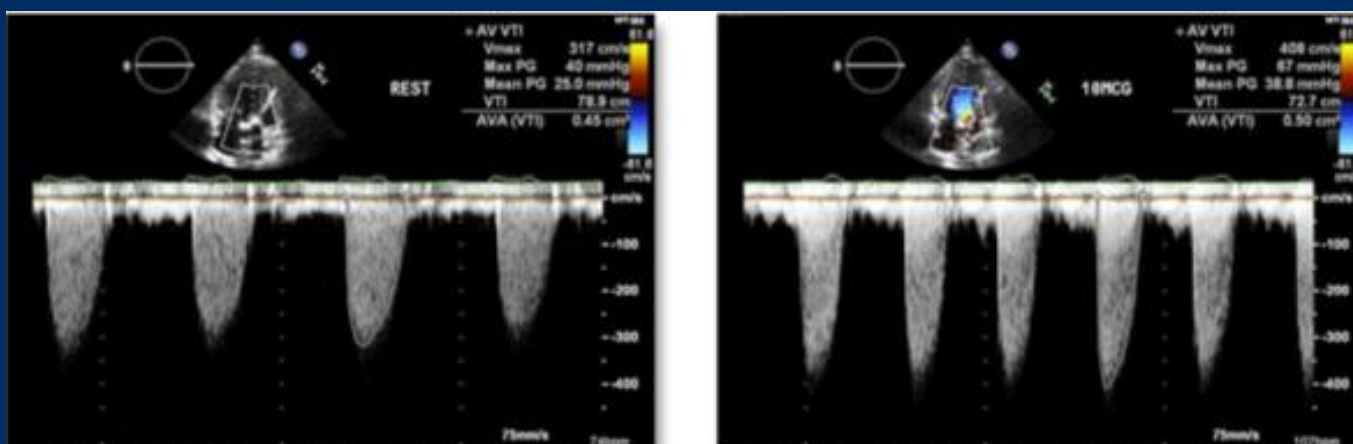


Parameter cut offs:
Peak stress mean gradient, mm Hg ≥40*
Peak stress AVA, cm2 ≤1.0–1.2*
Absolute increase in AVA cm2 <0.3

Circ Cardiovasc Imaging. 2014;7:545-551

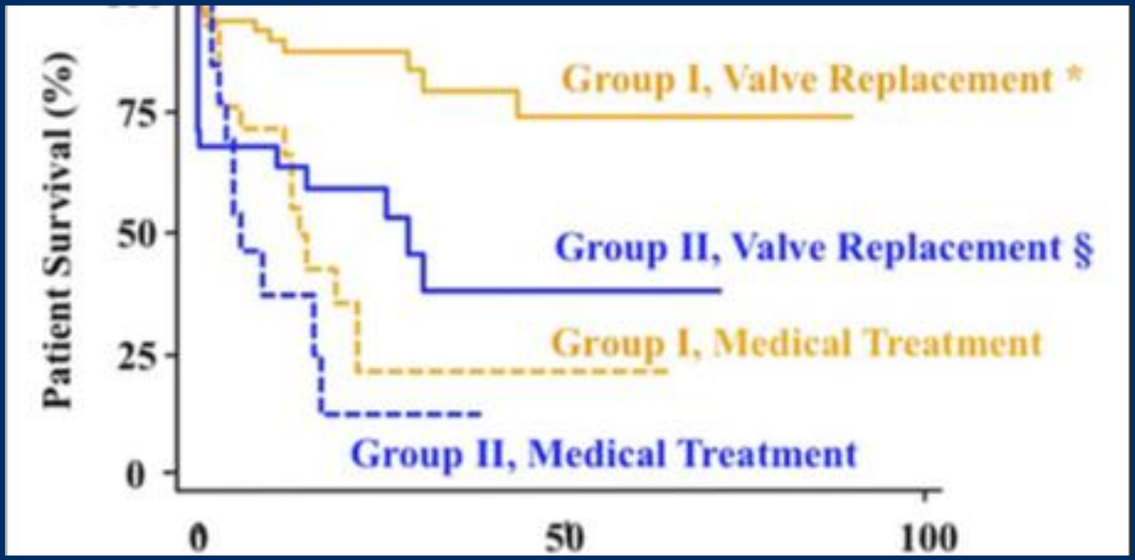
Contractile reserve

- Dobutamine up to 20 mcg/kg/min
  - Stroke volume increase >20%
  - Vmax> 0.6 m/s
  - Mean gradient increase >10 mmHg



JACC Imaging 2013;6:184-95

Importance Contractile (flow) Reserve



Group 1= contractile reserve (survival benefit p=0.001)
Group II= No contractile reserve (trend of survival benefit p=0.07)

BUT!! Higher surgical mortality rate of 22-33% (no reserve) vs 5-8% (flow reserve)

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JACC 2012;60:1845-53

- What if DSE shows inadequate flow reserve?
- What if patient has adverse reaction to Dobutamine?
- What if patient has poor echo windows?
- Variable flow response to Dobutamine
- Paradoxical LFLG AS

Contractile (flow) reserve

If no contractile reserve, can we predict the valve area by artificially normalizing flow?

TOPAS Study

- Projected AVA
  - Extrapolation of what the EOA would at standardized flow rate chosen to be 250 ml/s based on observed flow rates found in patients with severe AS and normal flow.
- EOA and mean trans-valvular flow is proposed to represent valvular compliance

$$AVA_{proj} = \frac{AVA_{peak} - AVA_{rest}}{Q_{peak} - Q_{rest}} \times (250 - Q_{rest}) + AVA_{rest}$$

Q=VTI

J Am Soc Echocardiogr 2010;23:380 – 6.

Projected AVA

$$AVA_{proj} = \frac{AVA_{peak} - AVA_{rest}}{Q_{peak} - Q_{rest}} \times (250 - Q_{rest}) + AVA_{rest}$$

New parameter has been shown to be more closely related to actual AS severity, impairment of myocardial blood flow, LV flow reserve, and survival than the traditional DSE parameters.

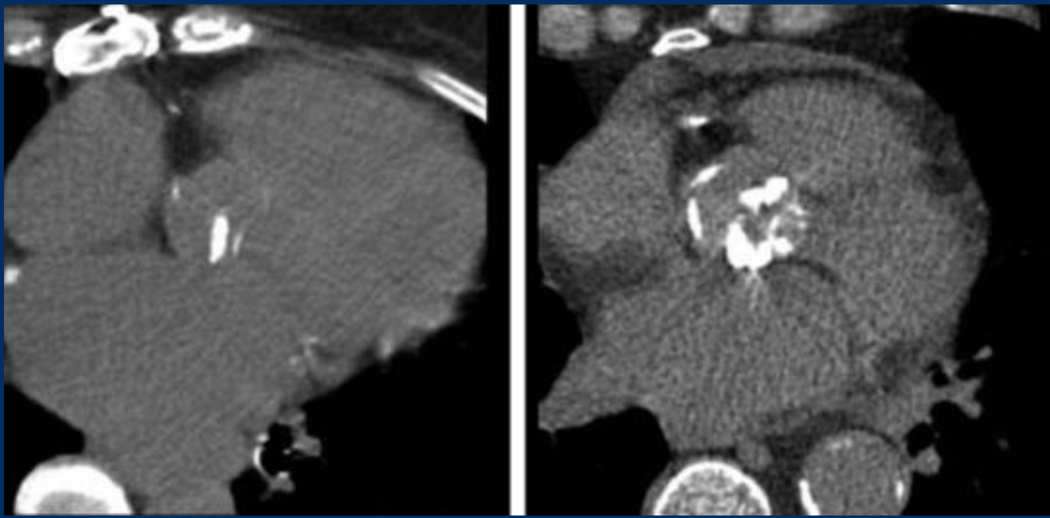
The full potential of the EOA_{Proj} remains to be determined by future studies

Circulation 2008;118:S234–42.
J Am Soc Echocardiogr 2010;23:380 – 6.

Multi-slice CT and valvular calcium score

Aortic valve calcium load, AU
Women >1200†
Men >2000†

Aortic valve calcium density, AU/cm2
Women >300†
Men >500



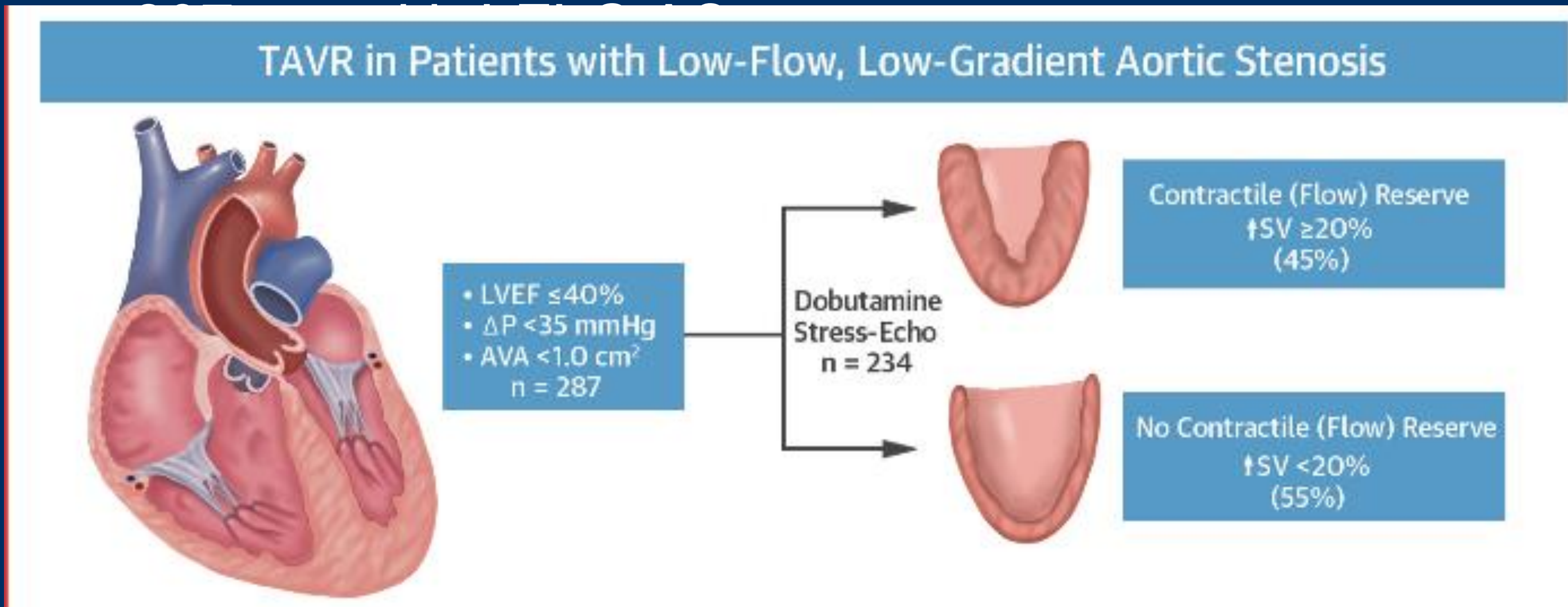
TAVR may be attractive in LFLG AS

Table. Theoretical Advantages of TAVR Versus Surgical Aortic Valve Replacement

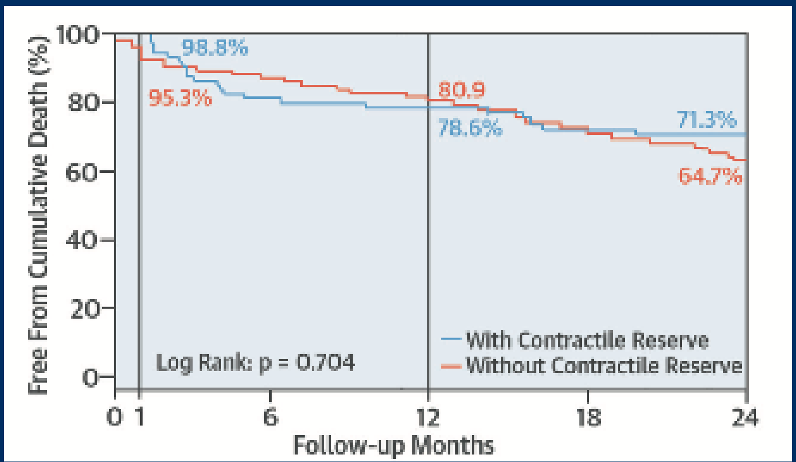
Advantage of TAVR	Result
TAVR is less invasive	Faster recovery time
	Less pericardial irritation
	Lower risk of atrial fibrillation
	Less healing (lower risk for infection)
	Shorter or no ventilator dependency
TAVR does not require cardiopulmonary bypass	Lower risk of systemic inflammatory response syndrome
	Lower risk of adverse cerebral effects
	Lower levels of procedural anticoagulation
	No need for cardiac standstill with cardioplegia and hypothermia
TAVR associated with a larger EOA	Less PPM
	PPM may be more important in LF, low EF (patients are more reliant on afterload)

***Circ Cardiovasc Interv*. 2017;10:1-9**

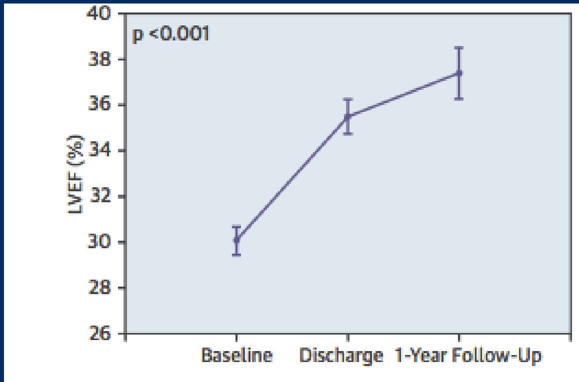
TOPAS-TAVI Registry (true or pseudo-severe AS)

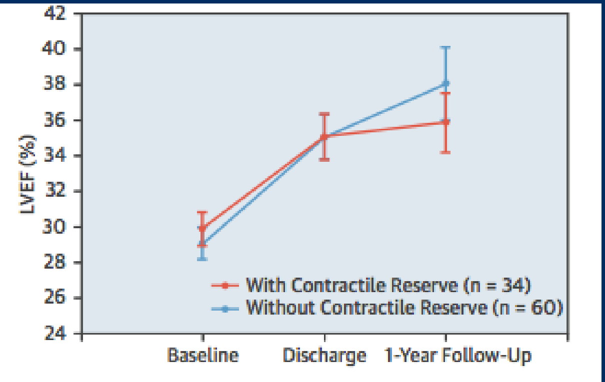


TOPAS-TAVI Registry



- 30 day mortality of 3.8%
- Significant EF improved in >50% patients
- Lack of contractile reserve did not influence outcomes
- Late mortality 39%





JACC 2018;71:1297–308

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Paradoxical LFLG AS

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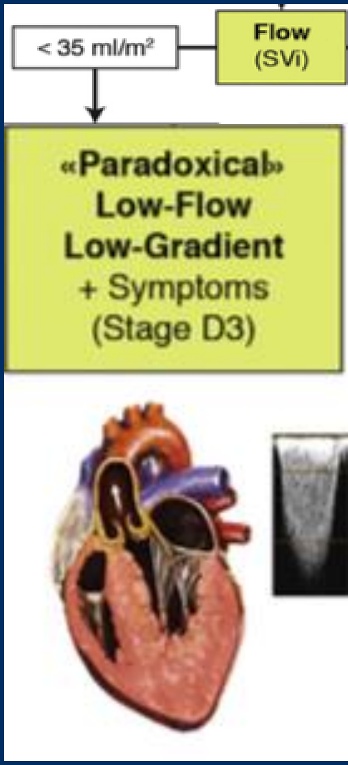
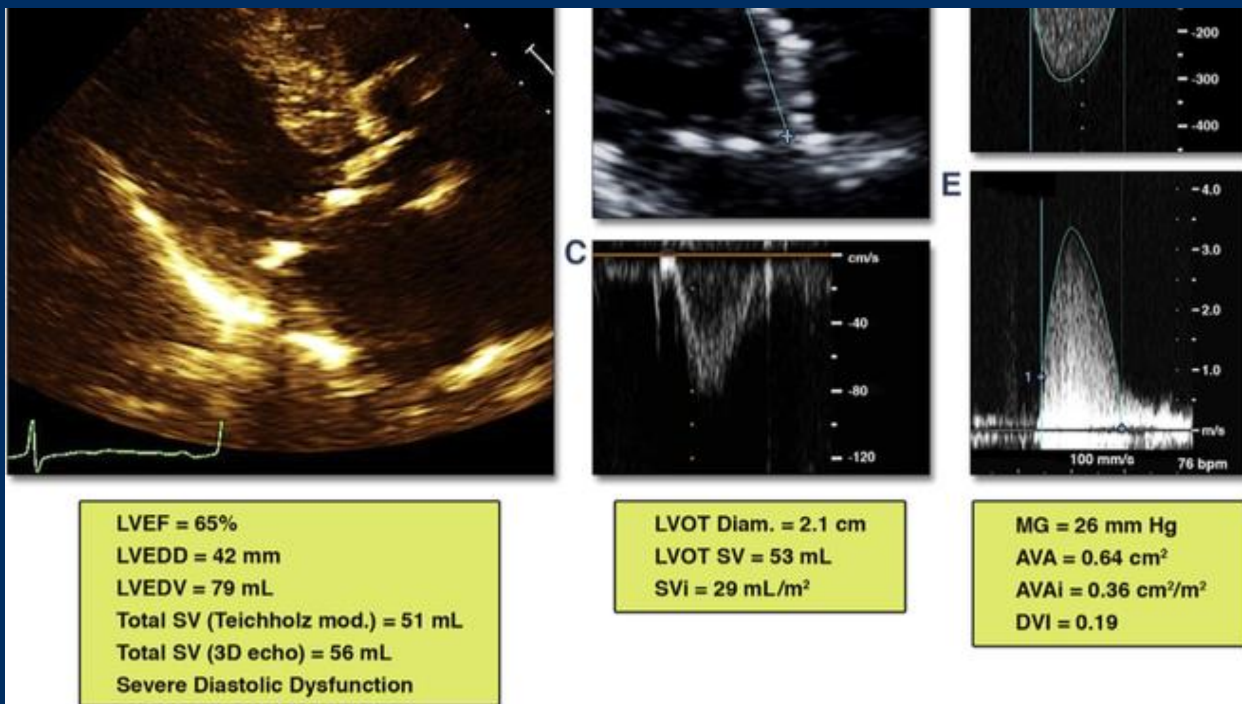
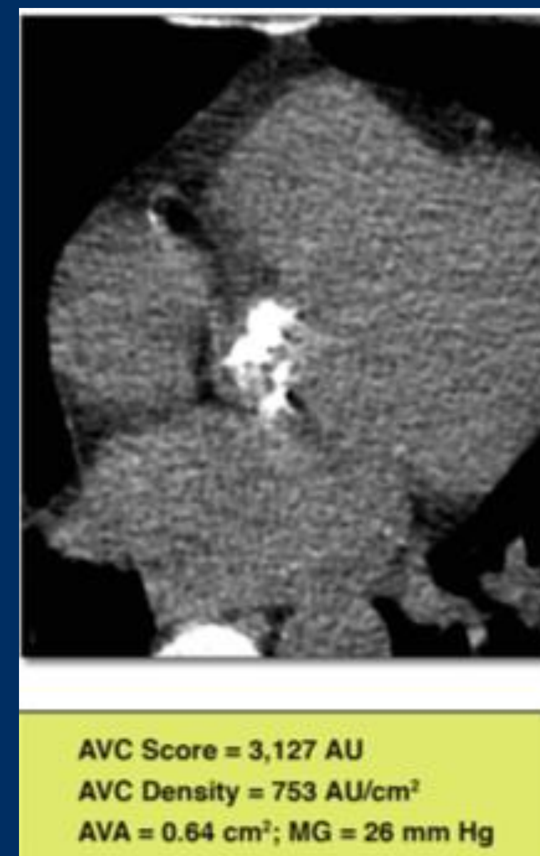
Paradoxical LF-LG AS

- LVEF>50%
- Low stroke volume (Svi<35 ml/m2)
- AVA <1.0 cm2 (AVAi <0.6cm2/m2)
- Mean gradient <40 mmHg
- 5-15% of patients (F>Male) usually elderly
- Small LV cavities with LVH
- Other factors- MR,MS, atrial fibrillation, TR



PLFLG Aortic stenosis





JACC Imaging 2017;10:185– 202

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Valvular Heart Disease

Clinical Outcome in Asymptomatic Severe Aortic Stenosis

Insights From the New Proposed Aortic Stenosis Grading Classification

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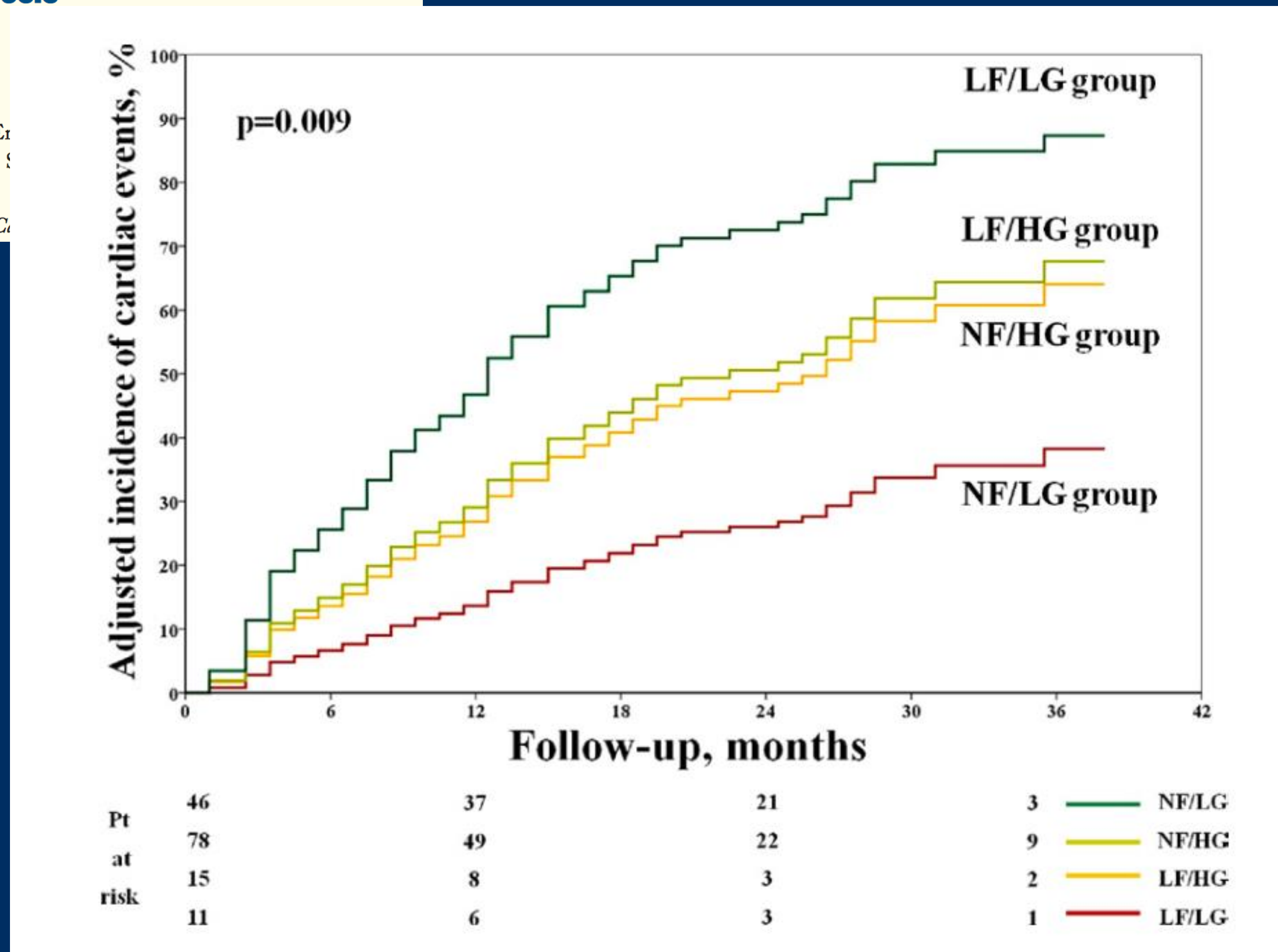
Kim O'Connor, MD,*‡ Monica Rosca, MD,* Catherine
Luc A. Piérard, MD, PHD*

Liège and Brussels, Belgium; Rennes, France; and Quebec, C



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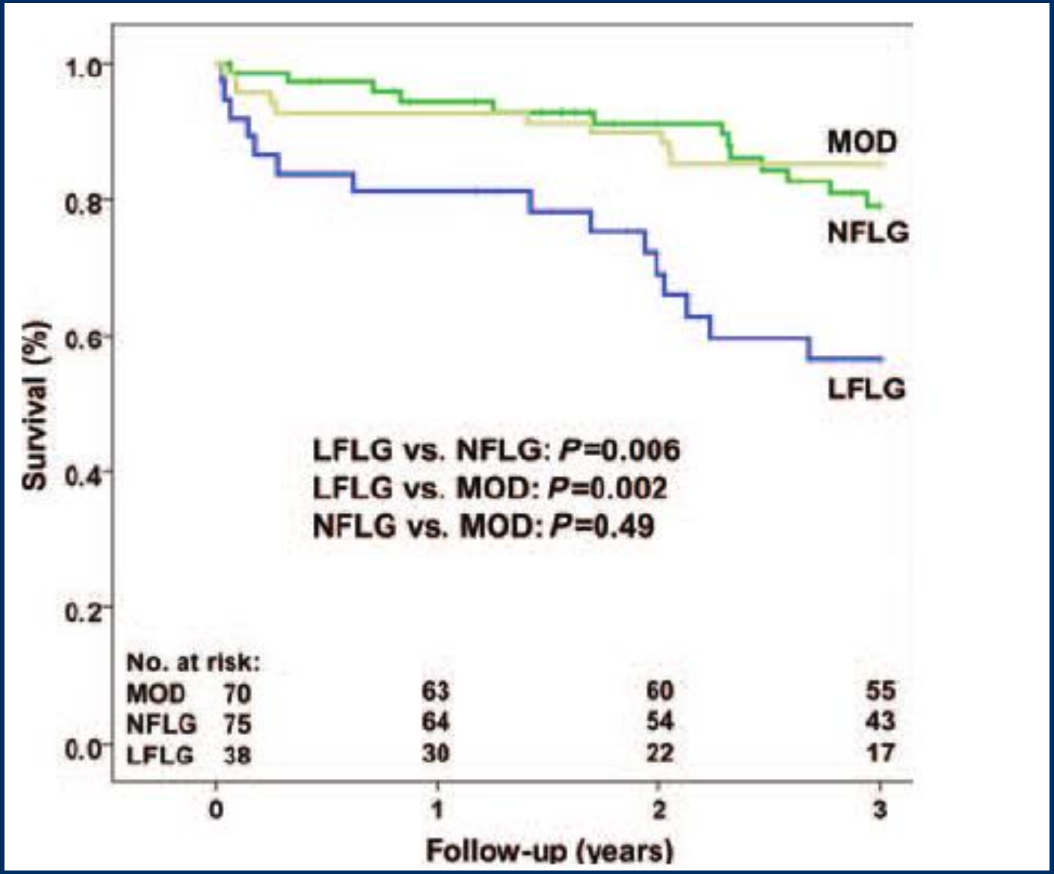
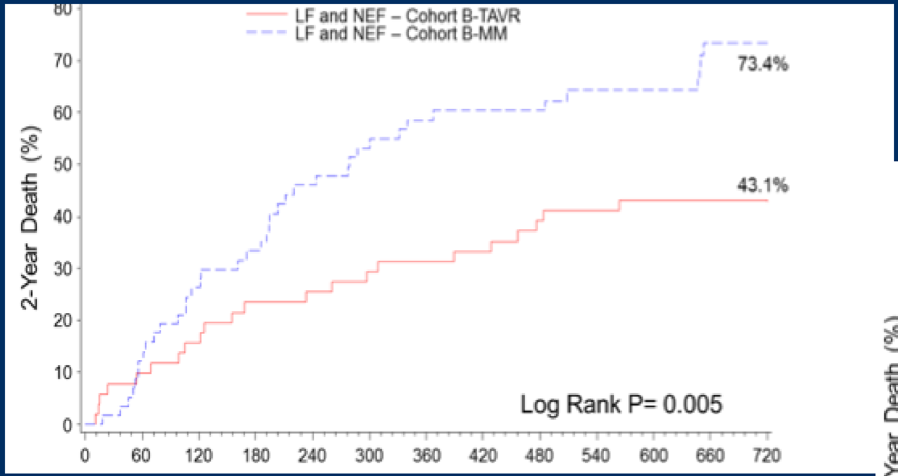
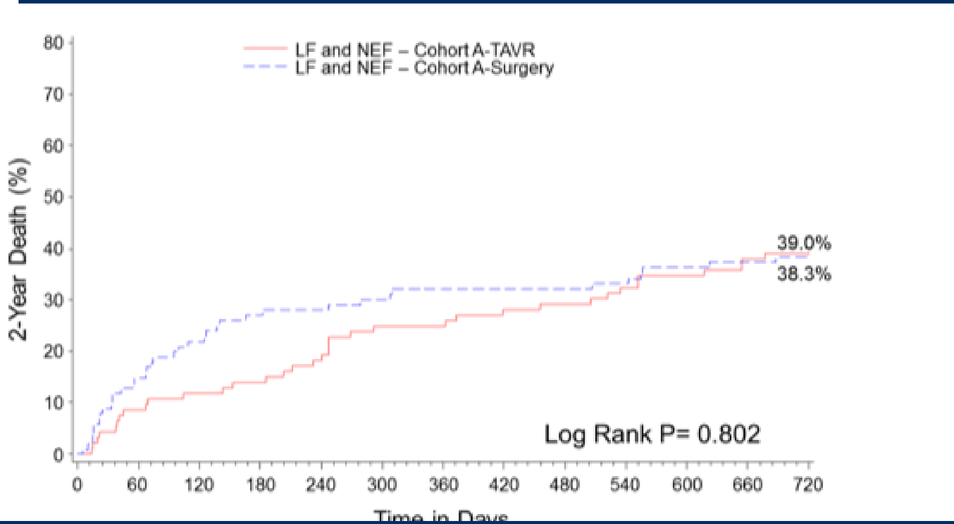
Differential left ventricular remodelling and longitudinal function distinguishes low flow from normal-flow preserved ejection fraction low-gradient severe aortic stenosis

Article (PDF Available) in European Heart Journal 34(25) · March



PARTNER I Trial Analysis in PLFLG AS





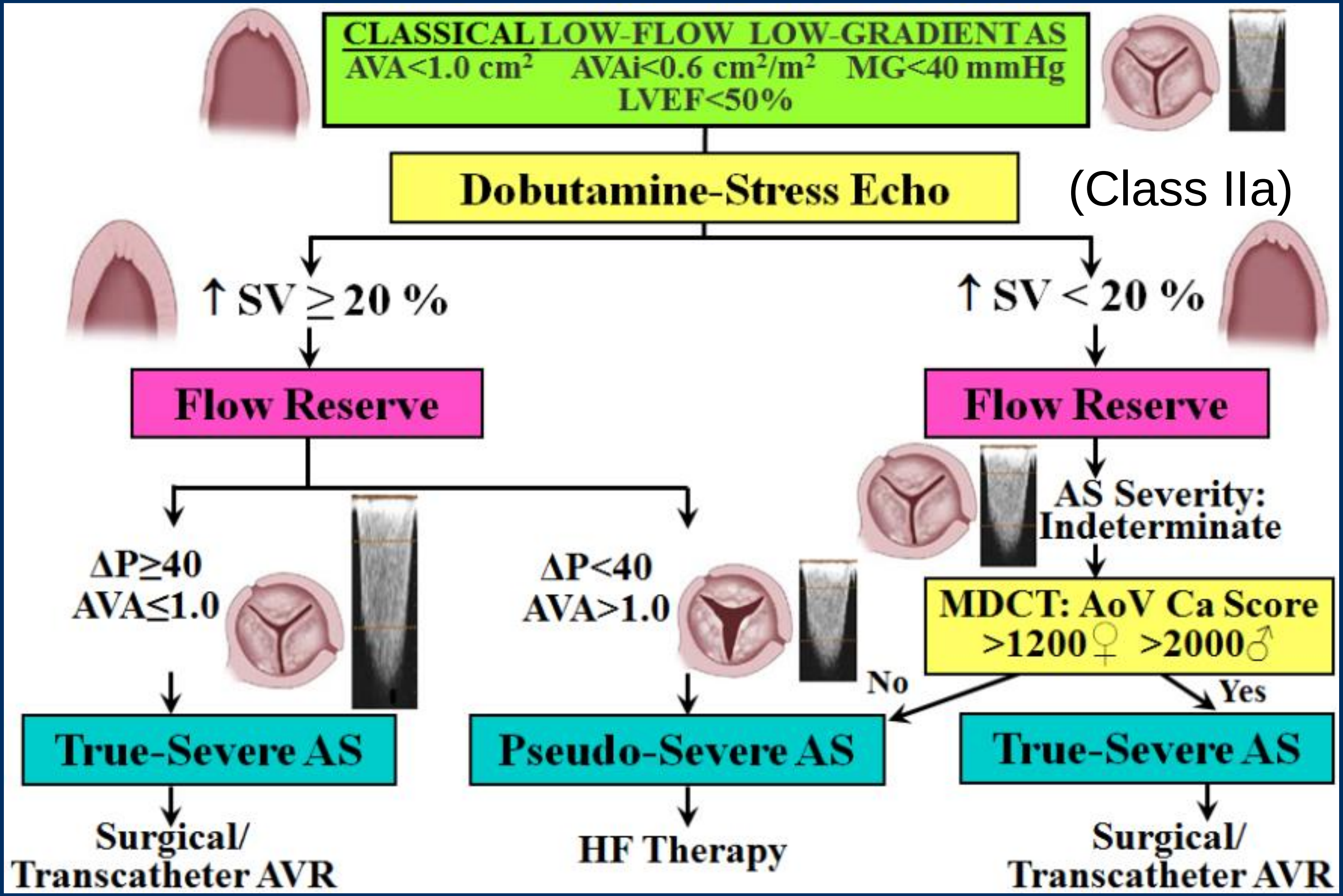
Circulation. published online May 9, 2013

PLFLG AS

- Based on anatomical and hemodynamic features
  - Prevalence in women, small LV cavity with restrictive physiology, small annulus.
  - At risk for patient prosthesis mismatch (AVAi<0.85 cm2/m2 post surgery).
  - TAVR offers a larger EOA.
- Post hoc analysis of PARTNER 1A suggests that TAVR is superior to SAVR in PLFLG AS

Circ Cardiovasc Imaging. 2014;7:545-551

Circulation.2013;127:2316-26



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Circ Cardiovasc Imaging. 2014;7:545-551

TABLE 1 Multimodality Imaging for Identification of Low Flow and Confirmation of Stenosis Severity in Low-Gradient AS

Imaging Modality	Imaging Parameter and Criteria	Advantages	Limitations
	Low Flow		
Doppler-echocardiography	Stroke volume index <35 ml/m^2*	Good marker of LV pump function and prognosis	Does not account for the effect of ejection duration on the gradient. May overestimate the prevalence of low-flow state in obese patients.
	Mean transvalvular flow rate <200 ml/s	Better determinant of gradient than stroke volume index	Potentially inferior to stroke volume index to predict prognosis.
	Severe AS		
Doppler-echocardiography	Peak aortic jet velocity ≥ 4 m/s* Mean gradient ≥ 40 mm Hg*	Less subject to measurement error than the AVA	Highly flow-dependent. May underestimate AS severity in low-flow states.
	AVA <1.0 cm^2* Indexed AVA <0.6 cm^2/m^2* (<0.5 cm^2/m^2 if BMI ≥ 30 kg/m^2) Doppler velocity index <0.25	Less flow-dependent than the gradient or peak velocity	Subject to measurement error. May overestimate AS severity in low-flow states.
	Severe valve leaflet thickening and calcification. Severely reduced leaflet mobility.		Reduced leaflet mobility may overestimate AS severity in low-flow states. Often difficult to assess by TTE; better assessed by TEE.
Dobutamine-stress echocardiography	Peak aortic jet velocity ≥ 4 m/s Mean gradient ≥ 40 mm Hg* Mean gradient ≥ 30 mm Hg	Less subject to measurement error than the AVA	Highly flow-dependent. May underestimate AS severity if flow rate remains below normal with dobutamine stress or overestimate AS severity if supra-normal response to dobutamine stress.
	AVA<1.0 cm^2* AVA<1.2 cm^2 Doppler velocity index <0.25 Increase in AVA<0.3 cm^2	Less flow-dependent than the gradient or peak velocity	Subject to measurement error. May overestimate AS severity if flow rate remains below normal with dobutamine stress
	Projected AVA <1.0 cm^2 Indexed Projected AVA <0.55 cm^2/m^2	Standardized for flow	Subject to measurement error. Not measurable if increase in flow rate $<15\%$ with dobutamine stress.
MDCT	Aortic valve calcium score $>2,000$ AU in men $>1,200$ AU in women Aortic valve calcium density >500 AU/cm^2 in men >300 AU/ cm^2 in women	Highly accurate and reproducible. Independent of flow and hemodynamics. Does not require administration of stress or contrast agent.	Reflects anatomic rather than hemodynamic severity. Does not take into account valvular fibrosis and therefore may underestimate AS severity.

JACC Imaging 2017;10:185– 202

Severe AS

Guidelines Recommendations for AVR in Low-Flow, Low-Gradient AS

	Recommendation for AVR	Class
CLASSICAL LF-LG (D2 Stage)	AVR is reasonable in symptomatic patients with low LVEF, low-flow/low-gradient severe AS with a DSE that shows a mean gradient ≥40 mm Hg with an AVA ≤1.0 cm^2 at any dobutamine dose	**IIa**
PARADOXICAL LF-LG (D3 Stage)	AVR is reasonable in symptomatic patients who have low-flow, low-gradient severe AS who are normotensive and have an LVEF ≥50% if clinical, hemodynamic, and anatomic data support valve obstruction as the most likely cause of symptoms	**IIa**

Nishimura, Otto et al. JACC 2014

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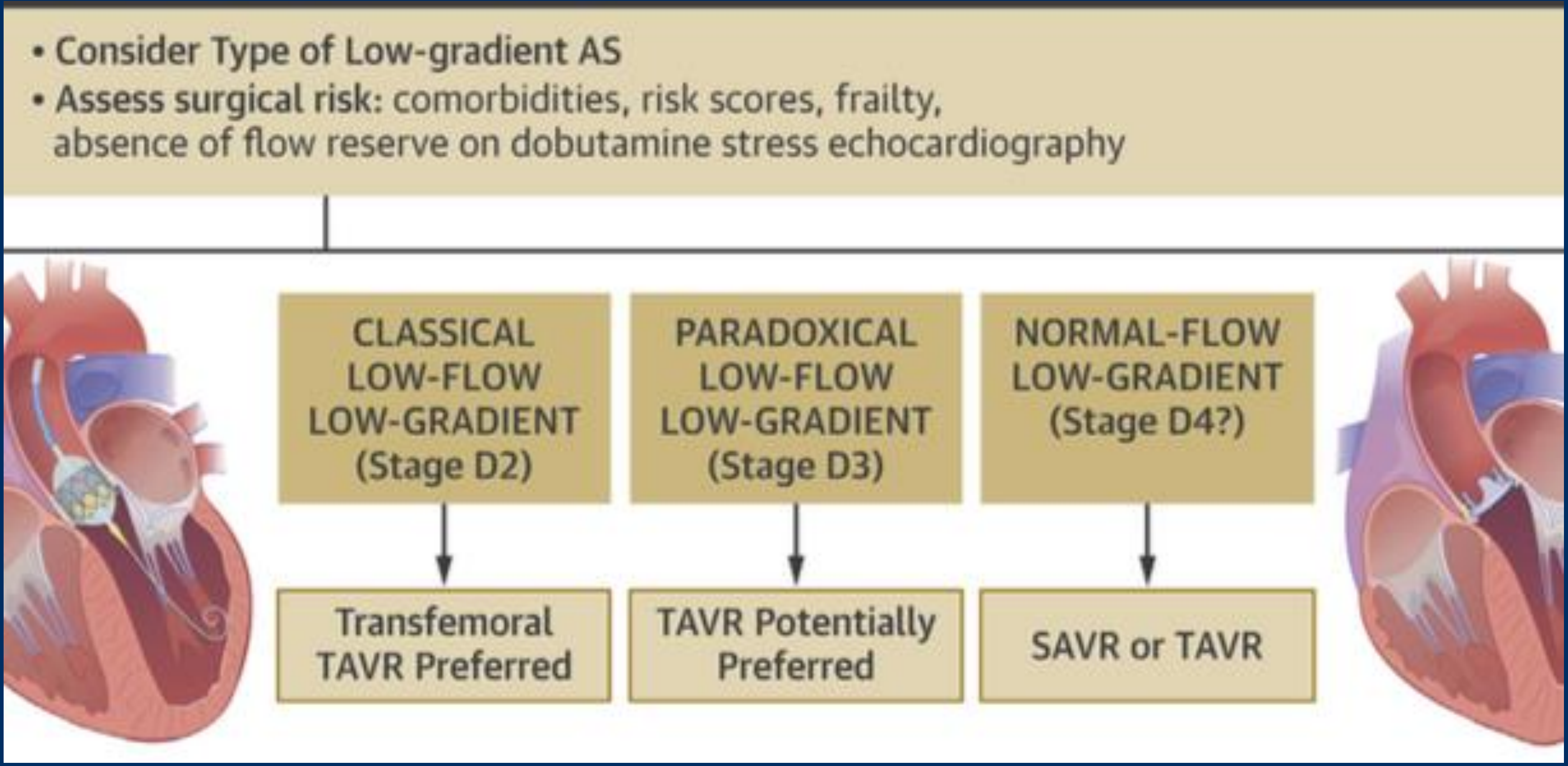
Select type of AVR



JAmCollCardiolImg2017;10:185– 202

Conclusions

- Low EF, low flow, low gradient AS have poor outcomes.
- TAVR improves mortality regardless of flow, gradient or EF.
- Given lower procedural risk and superior valve hemodynamics of TAVR. This may be preferred over SAVR for low flow or EF.
-

Questions:

- Which statement regarding Classic low flow, low gradient AS is true?
  a. Mortality is similar to normal flow, high gradient AS
  b. Predominantly not associated with CAD
  c. No mortality benefit is AVR with no contractile reserve
  d. Transcatheter AVR may be the preferred interventional treatment modality over SAVR

Question 2

- What is the preferred supporting test for the diagnosis of paradoxical LFLG aortic valve stenosis?
  a. Abnormal exercise treadmill stress
  b. Aortic valve density score >300 in women
  c. Elevated Pro-BNP
  d. Coronary calcium score >2000 AU in men

Question 3

- Which statement is false regarding the TOPAS-TAVI registry?

a. TAVR was associated with low 30 day mortality

b. Dobutamine stress echo failed to predict clinical outcomes

c. TAVR was associated with worsening LVEF

d. Anemia, pulmonary disease and residual PVL was associated with poorer outcomes

References

- Clavel et al. Cardiac Imaging for assessing low-gradient severe aortic valve stenosis. JACC Imaging 2017;10:185-202.
- Ribeiro et al. Transcatheter Aortic Valve Replacement in Patients with Low-Flow, low gradient Aortic Valve stenosis. JACC 2018;71:1297-308.
- Nishimura et al. 2014 AHA/ACC Guideline for the Management of Patients with Valvular Heart Disease. JACC 2014;63(22):e57-185