Leiden University Medical Center

Στένωση Αορτής: Νεότερα στη Διάγνωση

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Clinical research fellow in Cardiology

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Θεσσαλονίκη, 11 Απριλίου 2014

Disclosures

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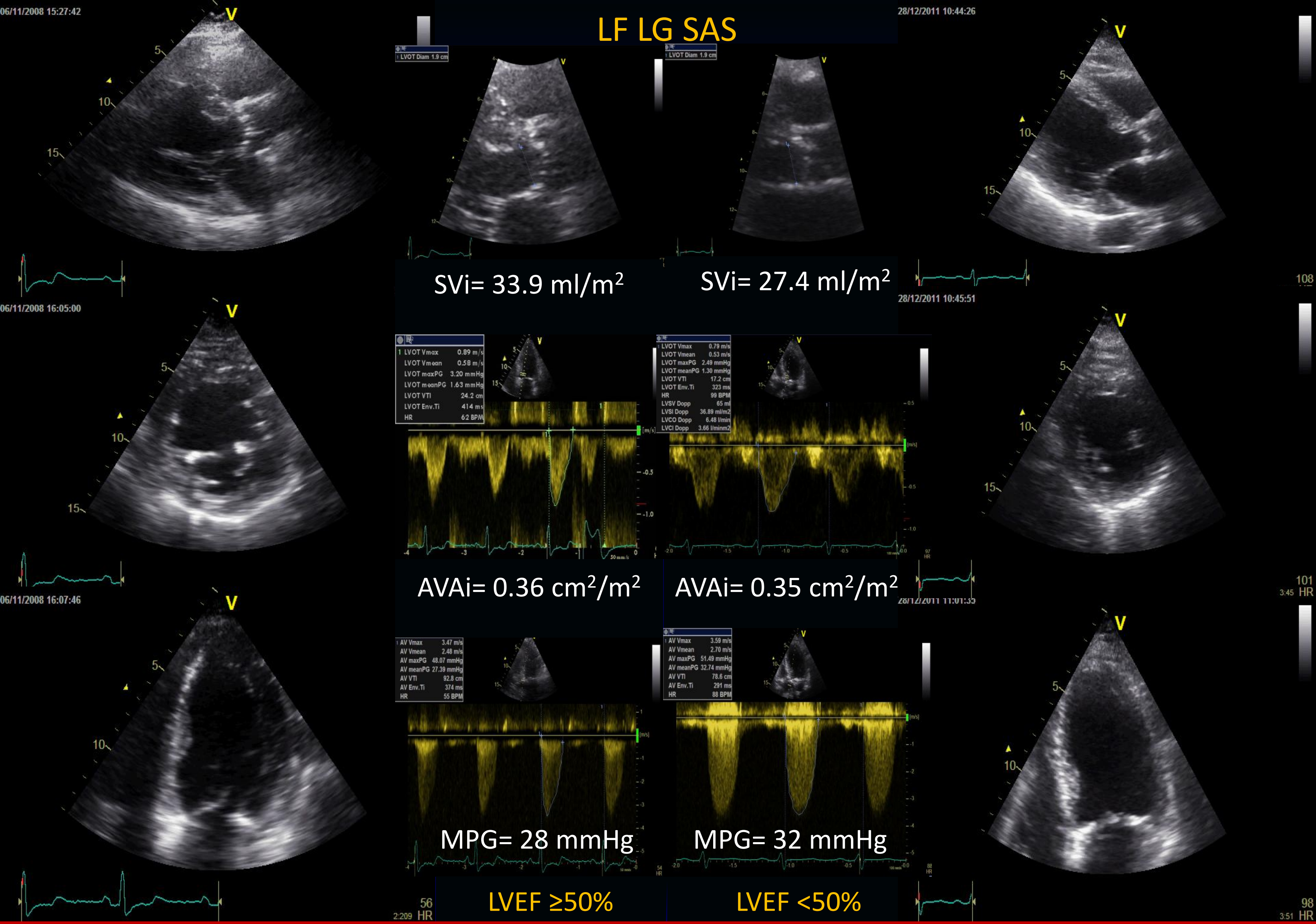
- ESC training grant
- EACVI research grant
- HCS training grant
- ELIKAR research grant


LF LG SAS
SVi= 33.9 ml/m2
SVi= 27.4 ml/m2
AVAi= 0.36 cm2/m2
AVAi= 0.35 cm2/m2
MPG= 28 mmHg
MPG= 32 mmHg
LVEF ≥50%
LVEF <50%

Stage	Definition	Valve Anatomy	Valve Hemodynamics	Hemodynamic Consequences	Symptoms
A	At risk of AS	• Bicuspid aortic valve (or other congenital valve anomaly) • Aortic valve sclerosis	• Aortic V_{max} <2 m/s	• None	• None
B	Progressive AS	• Mild-to-moderate leaflet calcification of a bicuspid or trileaflet valve with some reduction in systolic motion or • Rheumatic valve changes with commissural fusion	• Mild AS: Aortic V_{max} 2.0–2.9 m/s or mean ΔP <20 mm Hg • Moderate AS: Aortic V_{max} 3.0–3.9 m/s or mean ΔP 20–39 mm Hg	• Early LV diastolic dysfunction may be present • Normal LVEF	• None
C: Asymptomatic severe AS					
C1	Asymptomatic severe AS	• Severe leaflet calcification or congenital stenosis with severely reduced leaflet opening	• Aortic V_{max} ≥4 m/s or mean ΔP ≥40 mm Hg • AVA typically is ≤1.0 cm^2 (or AVAi ≤0.6 cm^2/m^2) • Very severe AS is an aortic V_{max} ≥5 m/s or mean ΔP ≥60 mm Hg	• LV diastolic dysfunction • Mild LV hypertrophy • Normal LVEF	• None: Exercise testing is reasonable to confirm symptom status
C2	Asymptomatic severe AS with LV dysfunction	• Severe leaflet calcification or congenital stenosis with severely reduced leaflet opening	• Aortic V_{max} ≥4 m/s or mean ΔP ≥40 mm Hg • AVA typically ≤1.0 cm^2 (or AVAi ≤0.6 cm^2/m^2)	• LVEF <50%	• None
D: Symptomatic severe AS					
D1	Symptomatic severe high-gradient AS	• Severe leaflet calcification or congenital stenosis with severely reduced leaflet opening	• Aortic V_{max} ≥4 m/s or mean ΔP ≥40 mm Hg • AVA typically ≤1.0 cm^2 (or AVAi ≤0.6 cm^2/m^2) but may be larger with mixed AS/AR	• LV diastolic dysfunction • LV hypertrophy • Pulmonary hypertension may be present	• Exertional dyspnea or decreased exercise tolerance • Exertional angina • Exertional syncope or presyncope
D2	Symptomatic severe low-flow/low-gradient AS with reduced LVEF	• Severe leaflet calcification with severely reduced leaflet motion	• AVA ≤1.0 cm^2 with resting aortic V_{max} <4 m/s or mean ΔP <40 mm Hg • Dobutamine stress echocardiography shows AVA ≤1.0 cm^2 with V_{max} ≥4 m/s at any flow rate	• LV diastolic dysfunction • LV hypertrophy • LVEF <50%	• HF • Angina • Syncope or presyncope
D3	Symptomatic severe low-gradient AS with normal LVEF or paradoxical low-flow severe AS	• Severe leaflet calcification with severely reduced leaflet motion	• AVA ≤1.0 cm^2 with aortic V_{max} <4 m/s or mean ΔP <40 mm Hg • Indexed AVA ≤0.6 cm^2/m^2 and • Stroke volume index <35 mL/m^2 • Measured when patient is normotensive (systolic BP <140 mm Hg)	• Increased LV relative wall thickness • Small LV chamber with low stroke volume • Restrictive diastolic filling • LVEF ≥50%	• HF • Angina • Syncope or presyncope

Nishimura et al. Circulation 2014; in press

Low-Gradient AS: survival analysis

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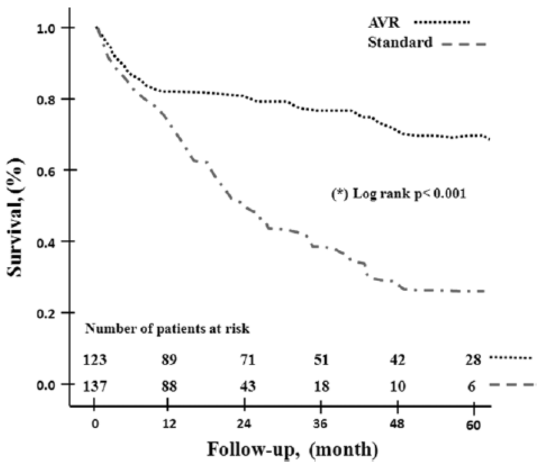


Figure 2. Unadjusted analysis of survival of patients who underwent aortic valve replacement (AVR) and those who received standard medical therapy.

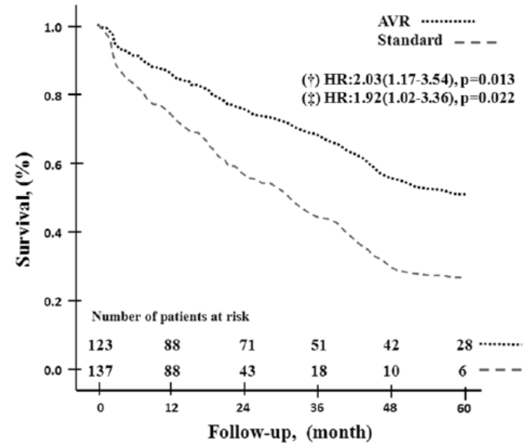


Figure 3. After adjustment for demographic variables (†) and a Society of Thoracic Surgeons score–based model (‡), aortic valve replacement (AVR) was found to be independently associated with better outcome (please see the text and Table 3 for models). HR indicates hazard ratio.

Low-Gradient

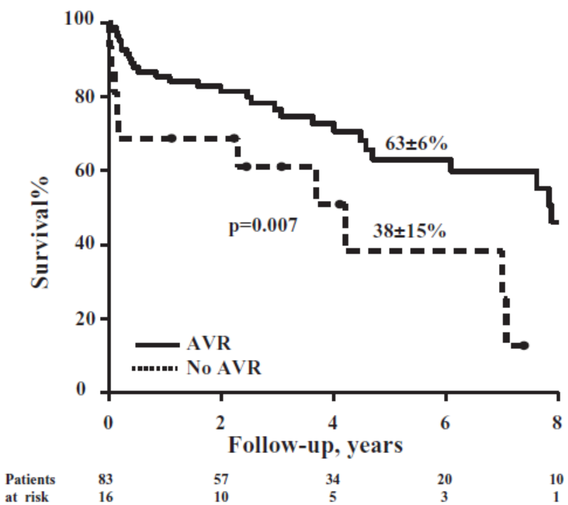
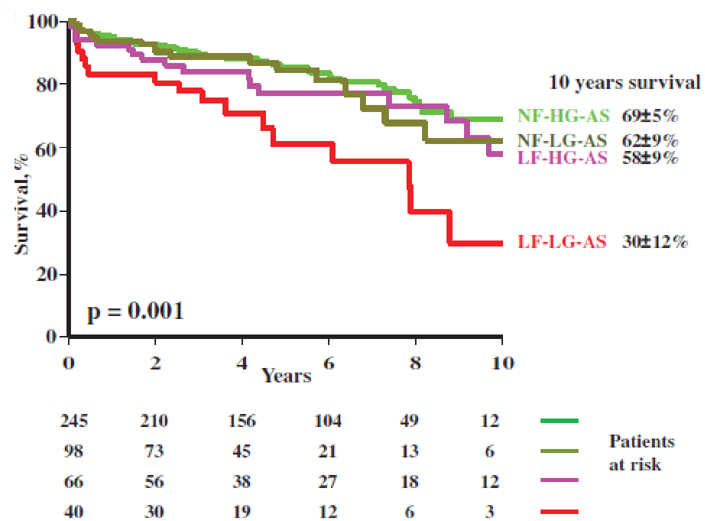
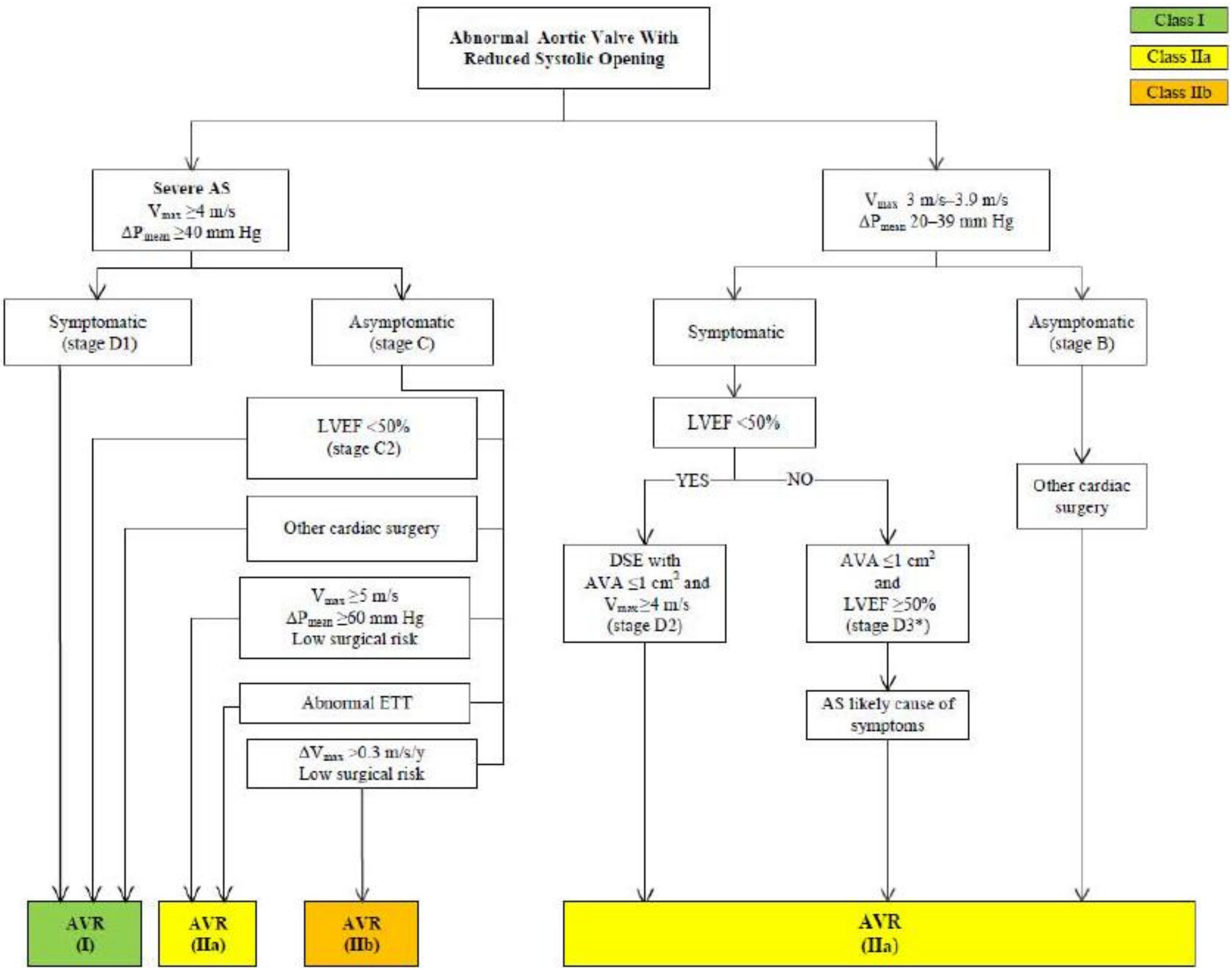


Figure 2. Overall survival in patients with low-flow, low-gradient aortic stenosis group according to the management: aortic valve replacement (AVR) vs conservative.



Paradoxical Low-flow Low-Gradient

Ozkan et al. Circulation 2013;128:622-631
Mohty et al. Circulation 2013;128:S235-42



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Nishimura et al. Circulation 2014; in press

Pathophysiology of adverse outcomes in AS

Imbalance between

- ❑ LV hemodynamic load
  - ➢ Aortic valve obstruction
    - ➢ Elevated arterial pressure
- ❑ LV capacity to overcome the increased load

Pibarot P, Dumesnil. JACC 2012;60:169-80

Multimodality Imaging for AS diagnosis

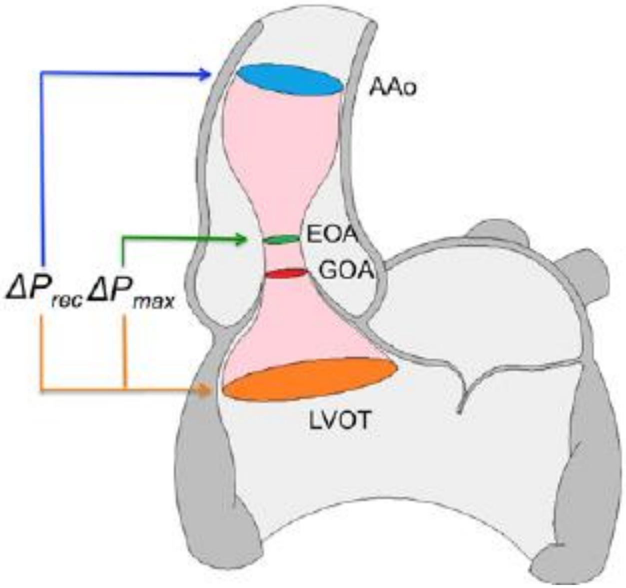
Modalities Used for Diagnosis of AS

Diagnostic Modality	Advantages	Disadvantages
Doppler echocardiography	• Non/ minimally invasive • Moderate spatial resolution • Provides both flow and anatomy	• Does not provide pressure directly • Need LVOT measurements • Need good imaging windows for accurate measurements
Cardiac catheterization	• Direct pressure measurement • Can resolve inconsistencies in echo diagnosis	• Invasive • Time-averaged CO measure • Cannot provide valve anatomy
CT	• Highest spatial resolution • Can provide 3D anatomy	• No hemodynamic data • Radiation exposure
MRI	• Provides 3D anatomy and flow • No radiation risks	• Low spatial and temporal resolution • Aliasing in severe AS • Expensive

Metric	Units	Method	Severe AS Cutoff
AS jet velocity*	m/s	Direct measure	> 4.0
Mean pressure gradient*	mm Hg	Direct measure (Cath) Bernoulli equation (Echo)	> 40
EOA*	cm^2	Gorlin equation (Cath) Continuity equation (Echo)	< 1.0
Indexed EOA*	cm^2/m^2	EOA normalized by BSA	< 0.6
Dimensionless index (DI)*	None	Ratio of LVOT velocity and VC velocity	< 0.25
Energy loss index	cm^2/m^2	Indexed EOA accounting for ascending aorta size	< 0.5–0.6
Valvuloarterial impedance	$mm\,Hg \cdot mL^{-1} \cdot m^{-2}$	Global systolic LV load, including arterial pressure	4.5–5
AV resistance	$dynes \cdot s^{-1} \cdot cm^{-5}$	Resistance of AV to flow	> 280
Projected valve area at normal flow	cm^2	Estimated EOA at normal flow	< 1.0
Calcium score	AU	Measured from CT data	> 1651

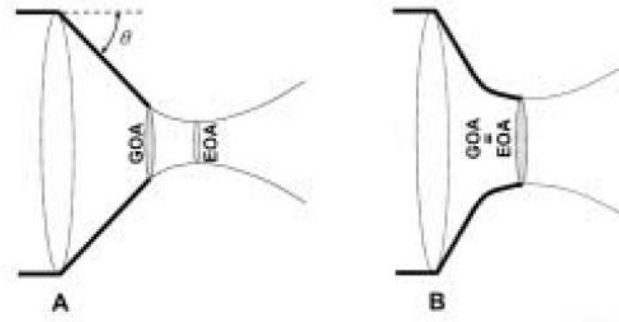
Saikrishnan et al. Circulation 2014

AS: which aortic valve area



$$C_c = \frac{EOA}{GOA}$$

$$EOA = \frac{A_{LVOT} VTI_{LVOT}}{VTI_{VC}}$$



Diagnostic method	AVA	Definition
Echocardiographic or CMR planimetry	GOA	Anatomic area of the valve aperture
Doppler echocardiography	EOA	Cross-sectional area of the vena contracta
Cardiac catheterization	$EOA\ A_A/(A_A - EOA)$	Area characterizing the flow energy loss

Saikrishnan et al. Circulation 2014

Anatomic aortic valve area

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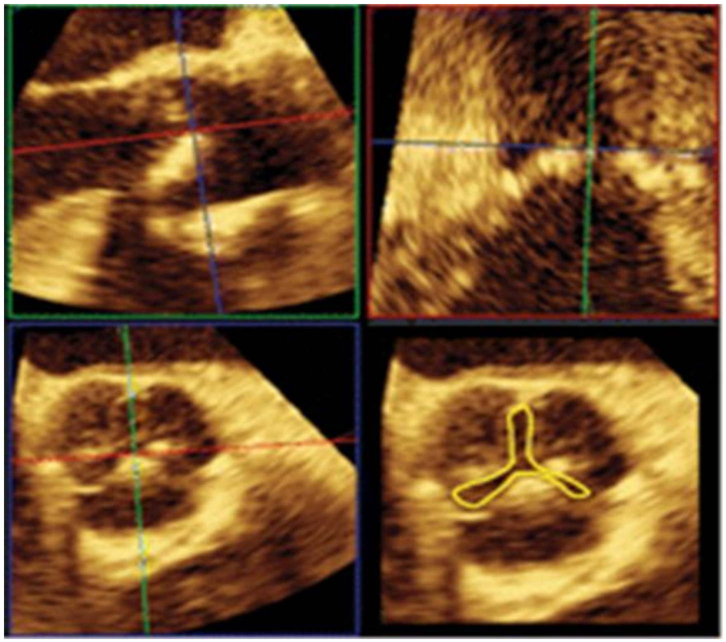
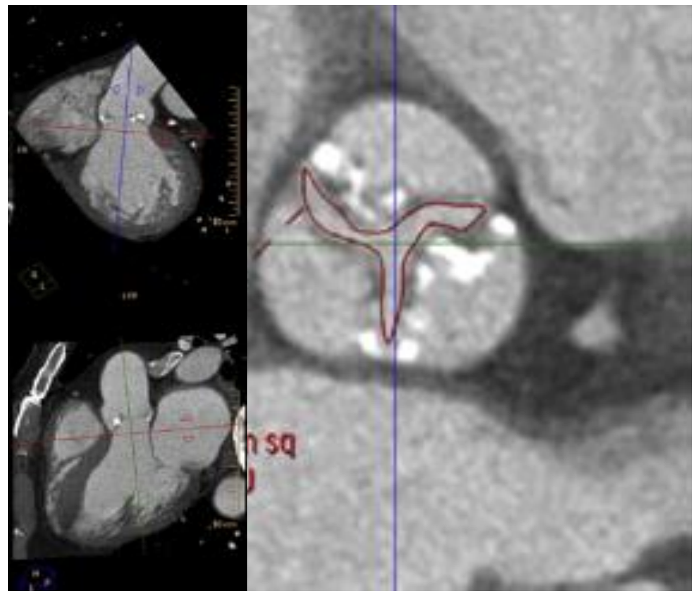
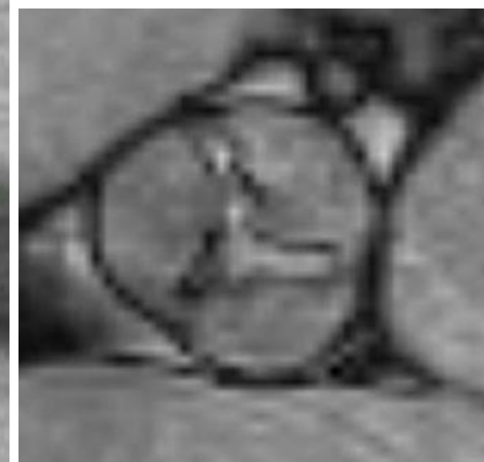
3D Echo



MDCT

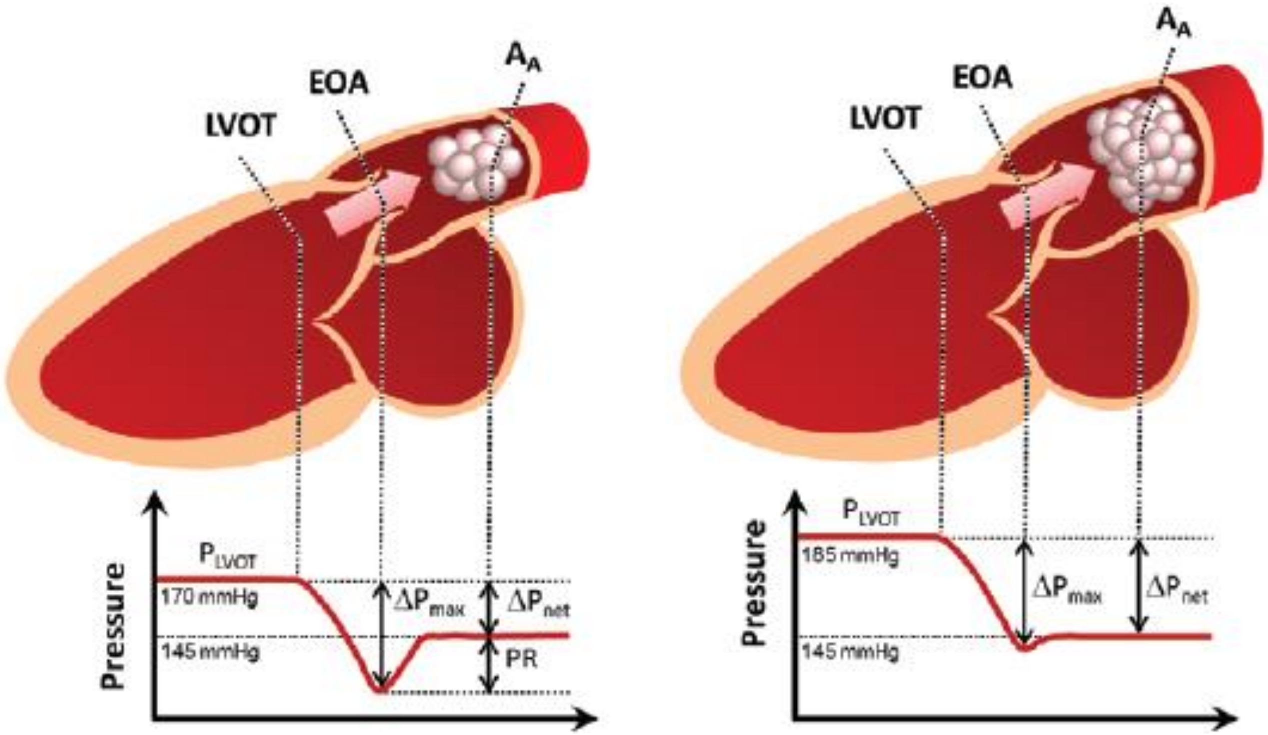


MRI



Gaspar et al. JASE 2012
Myerson. J Cardiovasc MR 2012

Pressure Recovery - Energy loss index



ELI=[(AVA×AA)/(AA−AVA)]/BSA

Becomes particularly relevant in patients with moderate to severe AS and small aortas, in whom measurement of AVA by Doppler echocardiography may lead to overestimation of severity

Pibarot. Circulation 2013;127:1101-4

Energy loss index

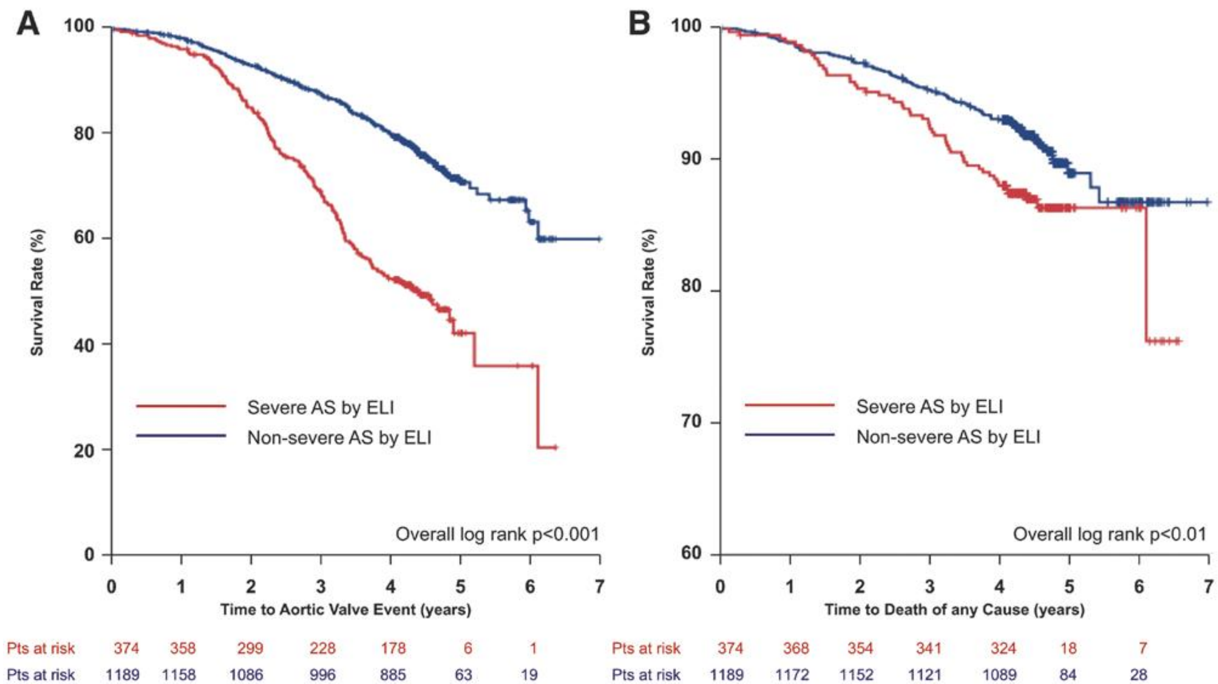


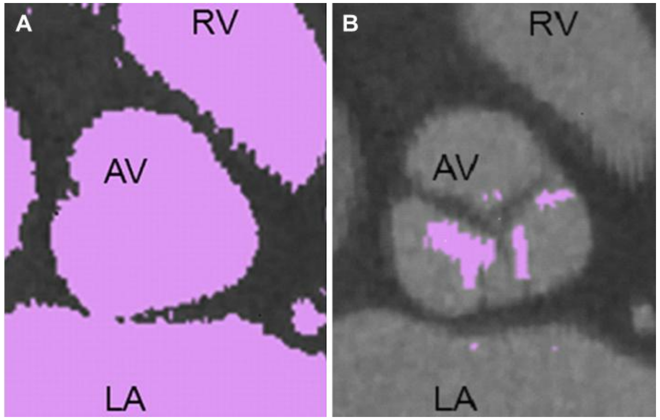
Figure 1. Kaplan-Meier plot of event-free survival (**A**) and overall survival (**B**) in groups of aortic stenosis (AS) patients (Pts) with or without severe AS by energy loss index (ELI) at baseline.

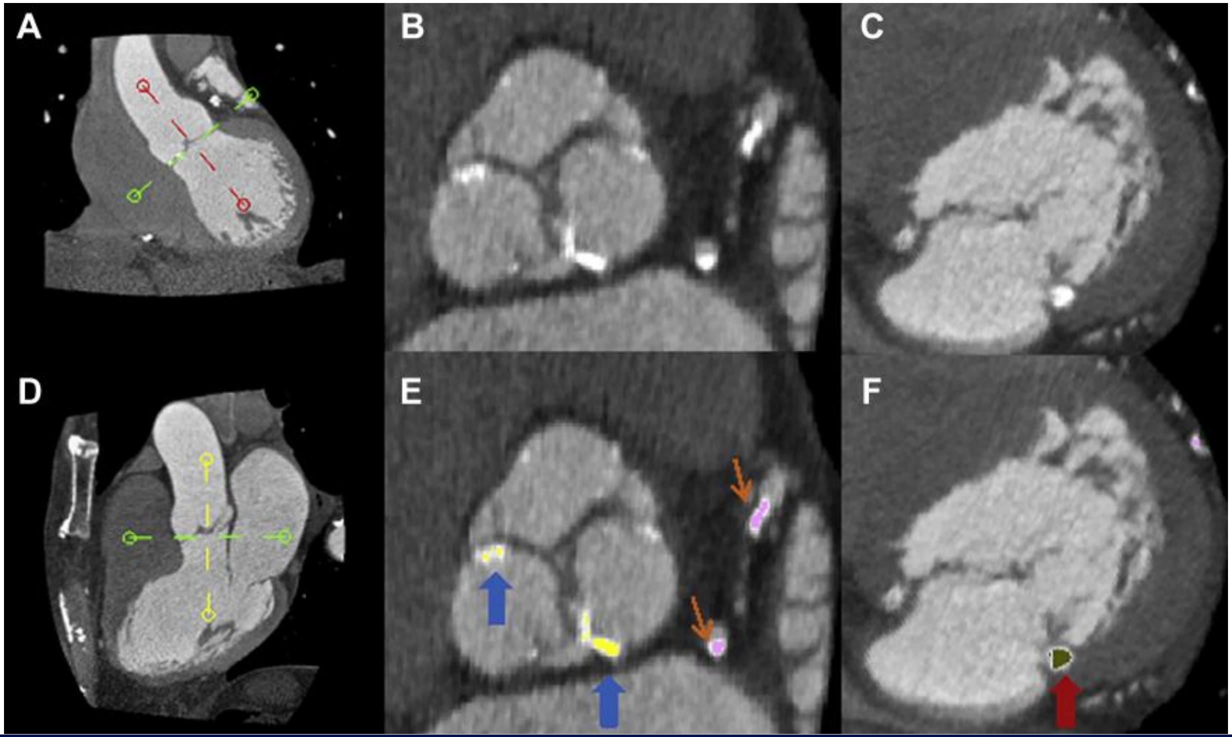
value <0.6 cm^2/m^2 was used as the cutoff for diagnosing severe AS by ELI

ELI improved the prediction of aortic valve events by 13% (95% confidence interval 5–19)

Pibarot. Circulation 2013;127:1101-4

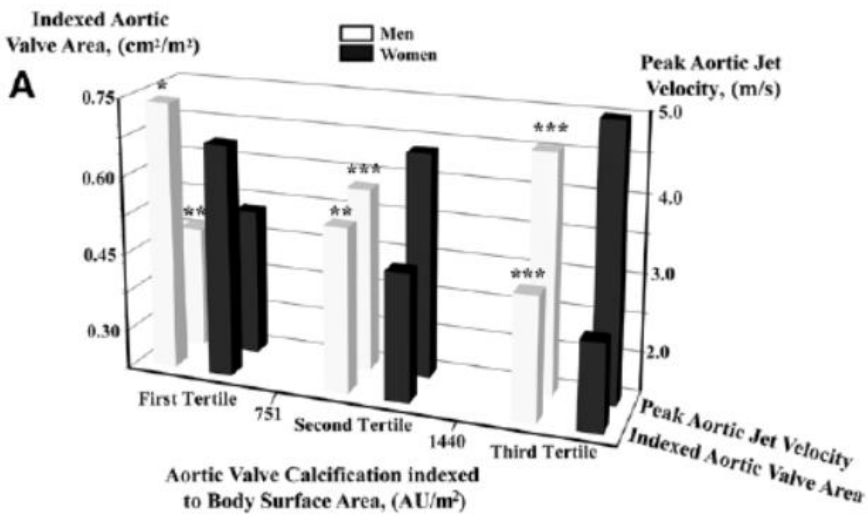
MDCT
valve calcification



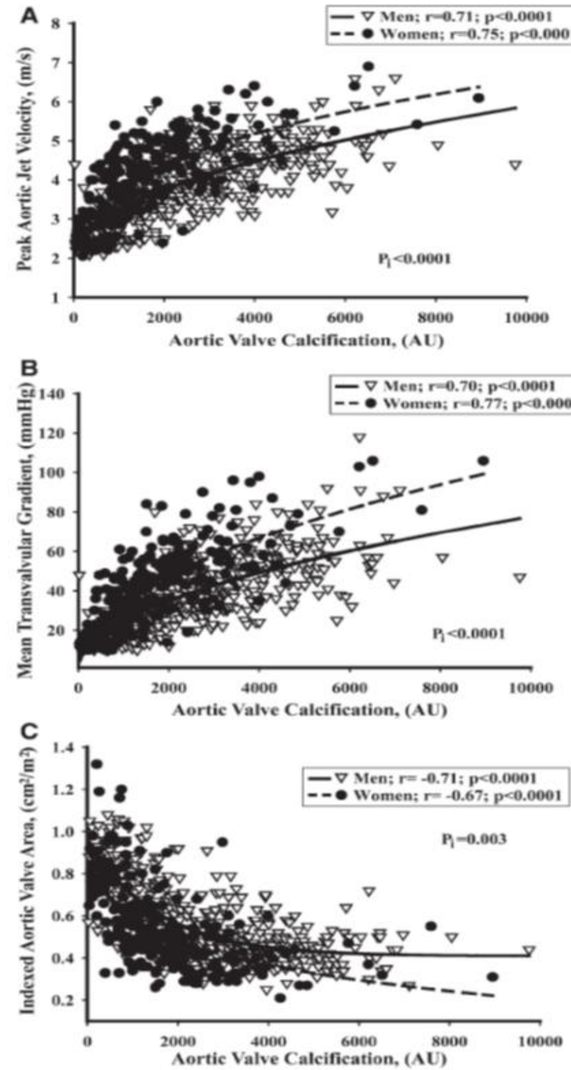


Kamperidis et al. AJC 2014

Aortic valve calcification in AS



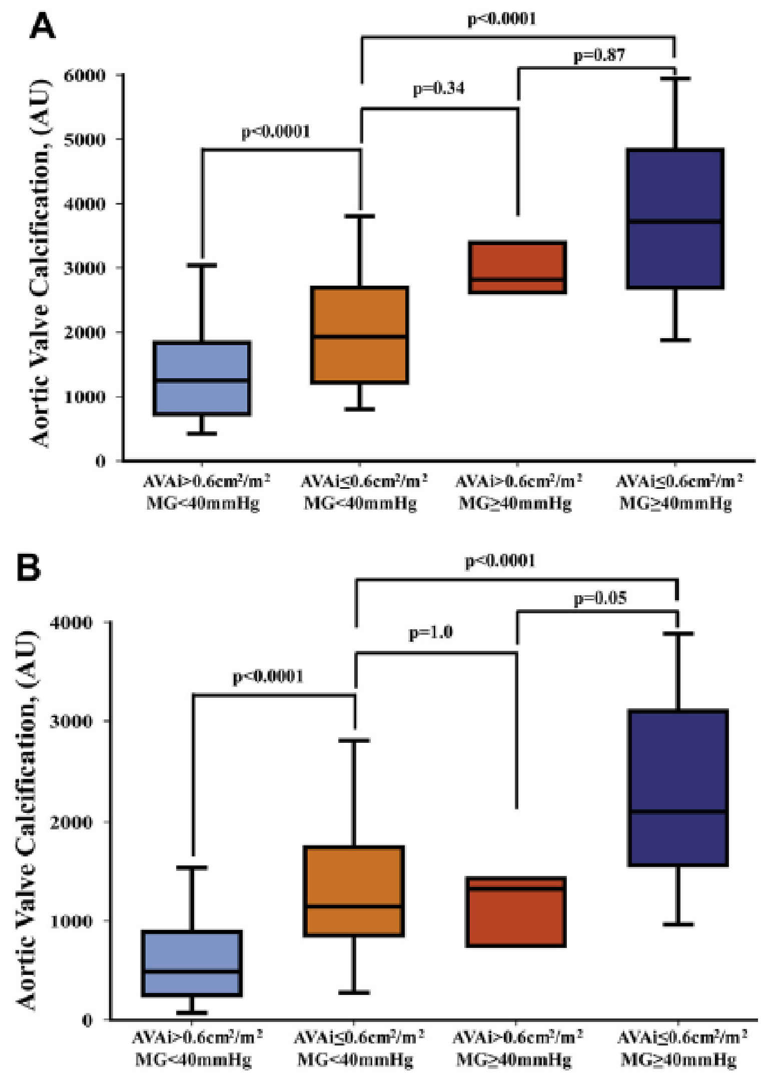
Aortic Valve Calcification >1650 AU



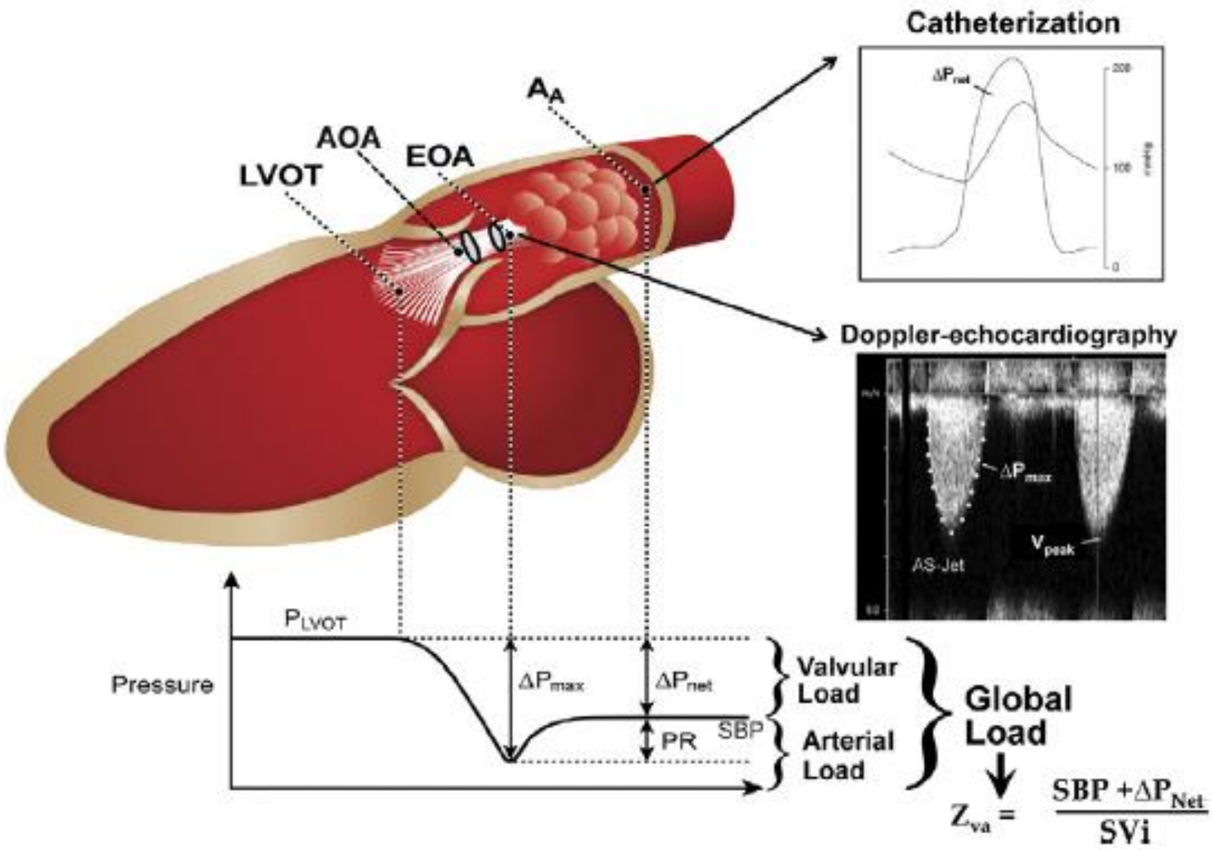
Aortic valve calcification in AS

Table 4 Accuracy of AVC, AVCi, and AVCd to Identify Severe AS

Sex	AUC	Threshold	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
AVC						
Women	0.91					
	Specific threshold	1,681*	69	95	95	65
	Best threshold	1,274*	86	89	93	79
	Sensitive threshold	791*	95	63	81	88
Men	0.90					
	Specific threshold	3,381*	59	95	95	59
	Best threshold	2,065*	89	80	88	82
	Sensitive threshold	1,661*	95	70	84	90
AVCi						
Women	0.91					
	Specific threshold	1,071†	59	95	96	59
	Best threshold	637†	91	85	91	85
	Sensitive threshold	476†	95	69	84	89
Men	0.89					
	Specific threshold	1,733†	55	95	95	57
	Best threshold	1,067†	86	79	87	77
	Sensitive threshold	776†	95	61	80	88
AVCd						
Women	0.93					
	Specific threshold	580‡	73	95	96	68
	Best threshold	292‡	92	81	87	86
	Sensitive threshold	228‡	95	68	83	89
Men	0.92					
	Specific threshold	727‡	65	95	95	63
	Best threshold	476‡	90	80	88	82
	Sensitive threshold	402‡	95	70	84	90



Afterload in AS



Pibarot. Circulation 2013;127:1101-4

Valvulo-arterial impedance

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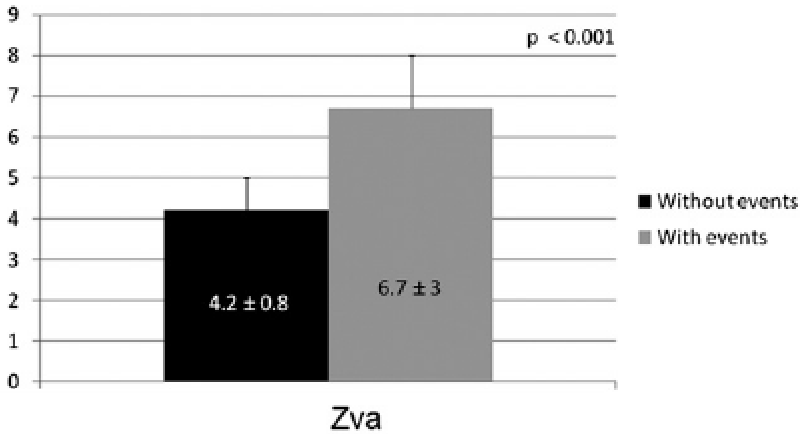

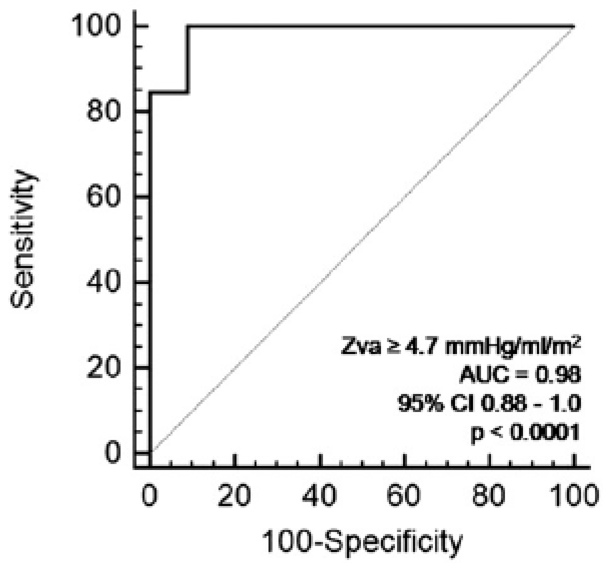

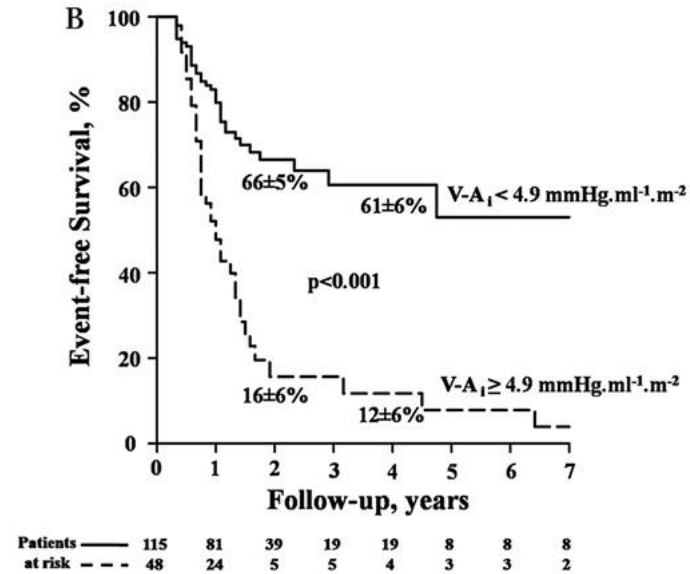

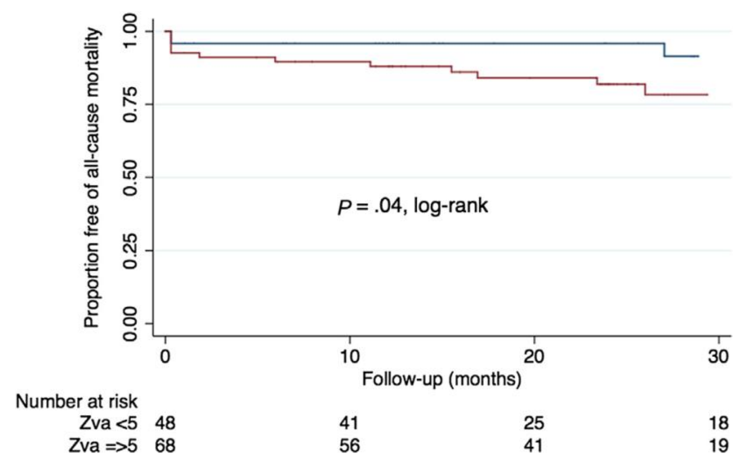

Katsanos et al. JASE 2013
Zito et al. AJC 2011
Lancellotti et al. Heart 2010

TYPES OF SEVERE AORTIC STENOSIS

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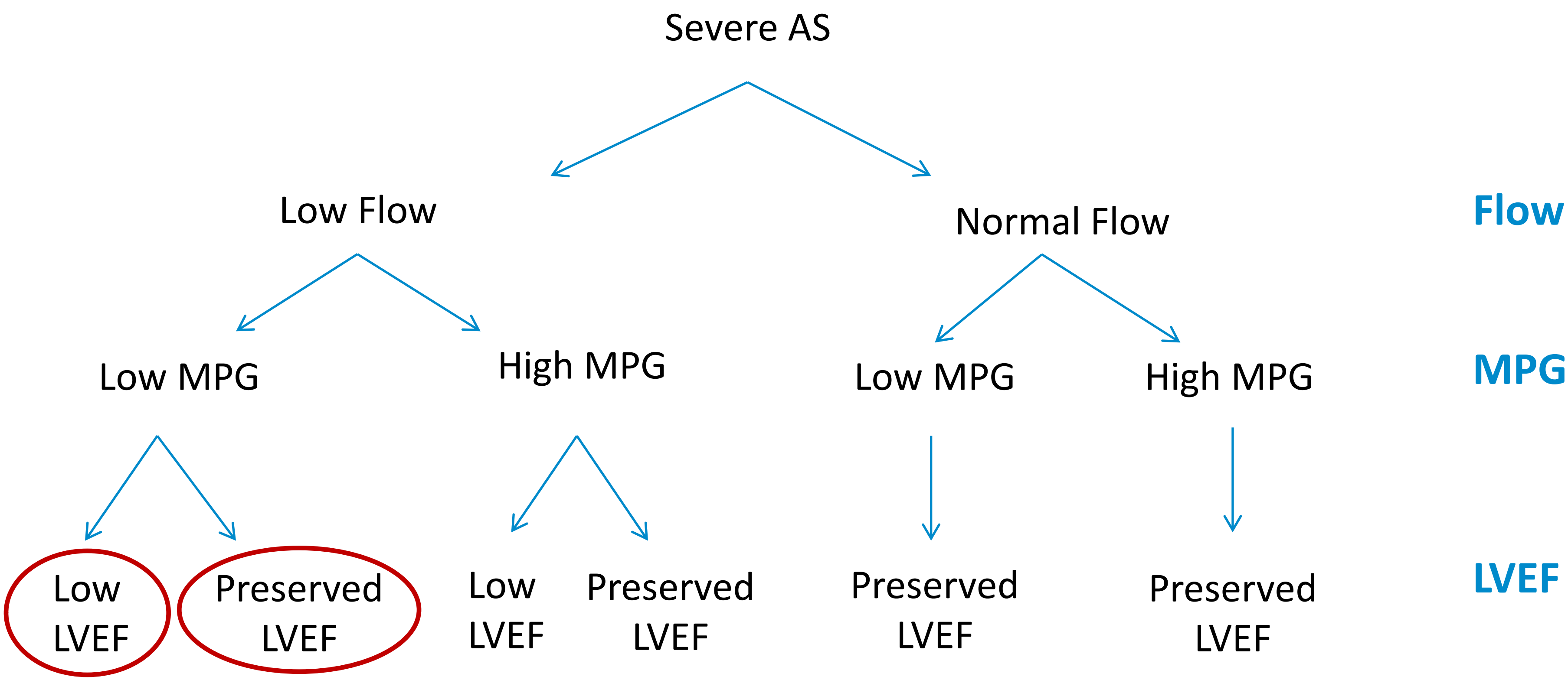
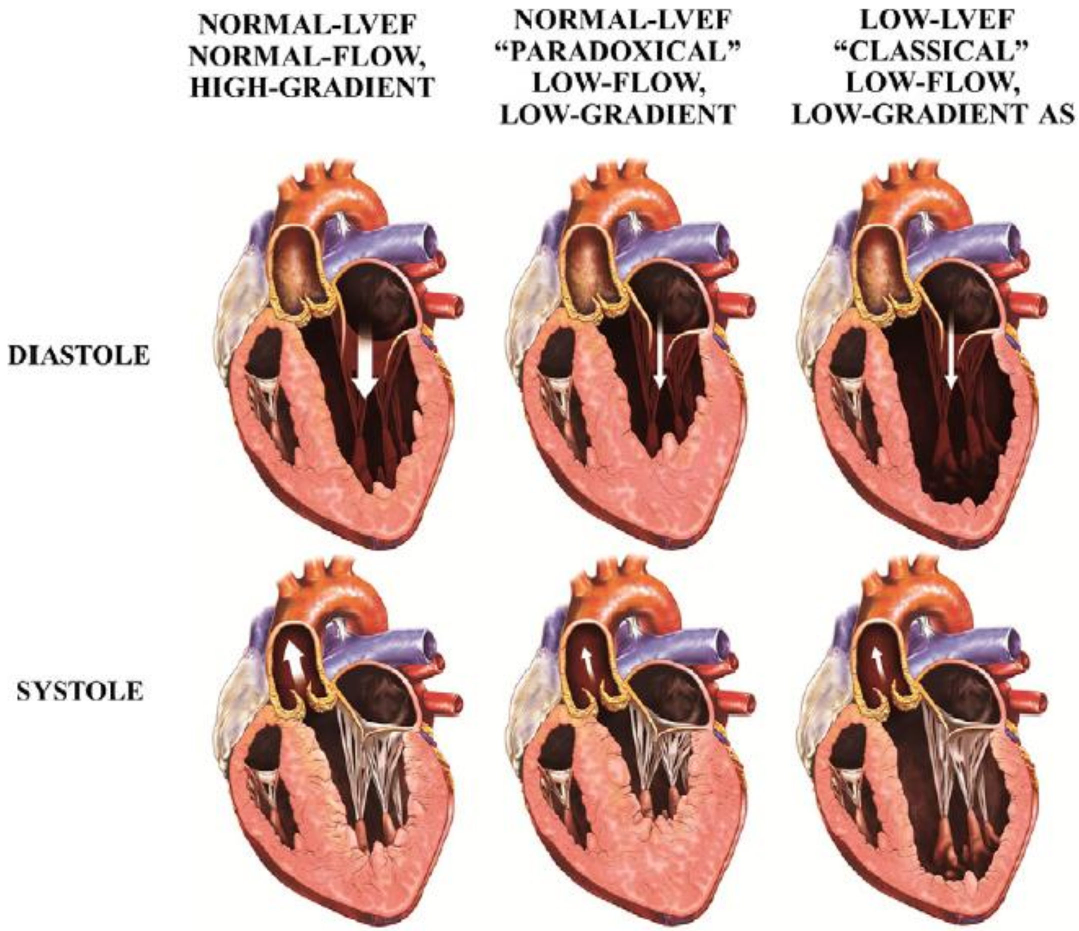
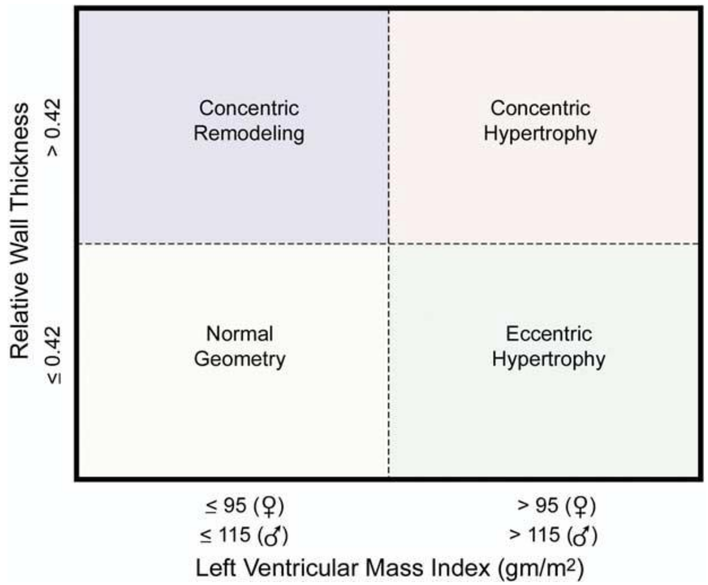


Herrmann HC et al. Circulation 2013;127:2316-26

Adda J et al. Circ Cardiovasc Imaging 2012;5:27-35

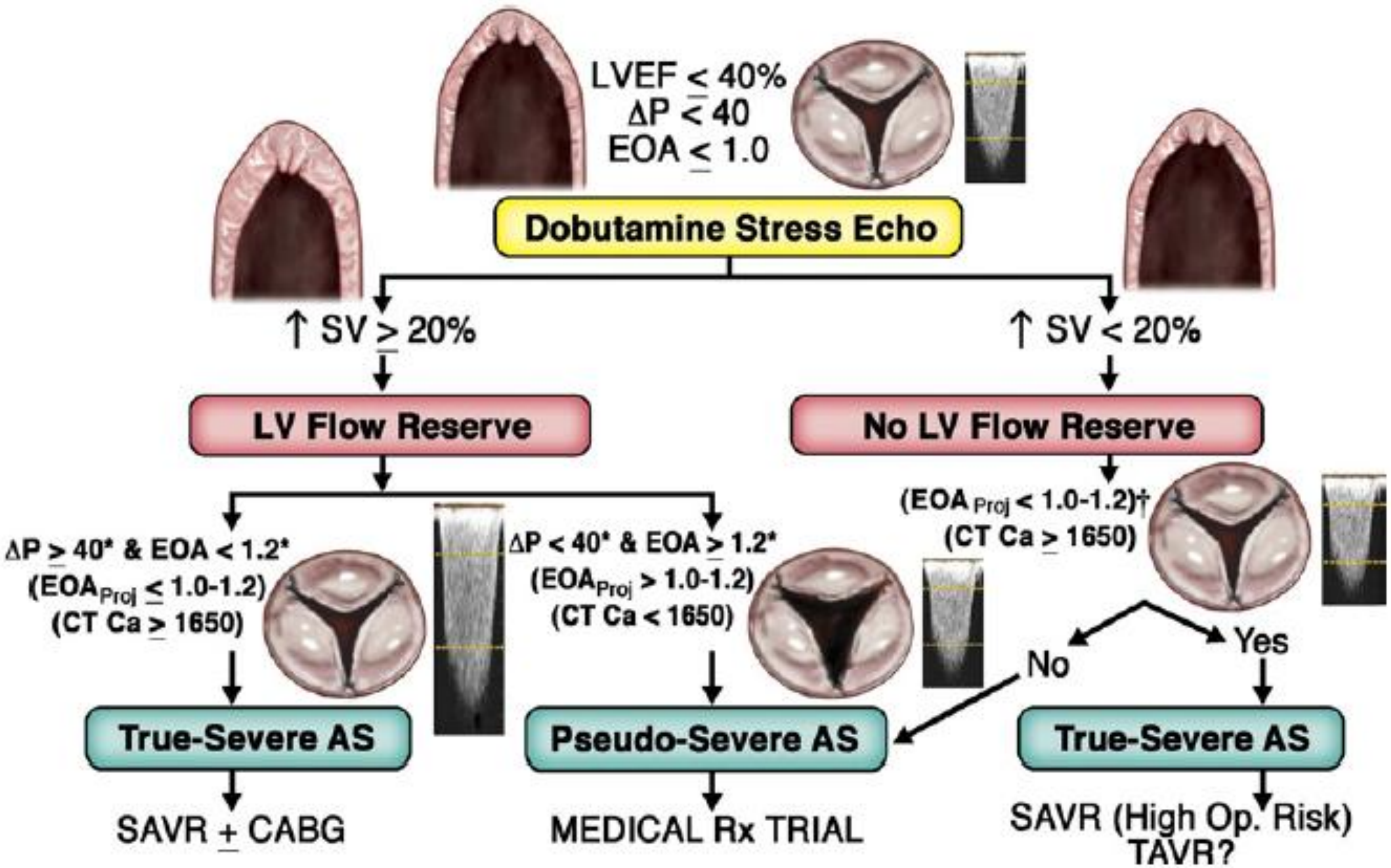
LV remodeling





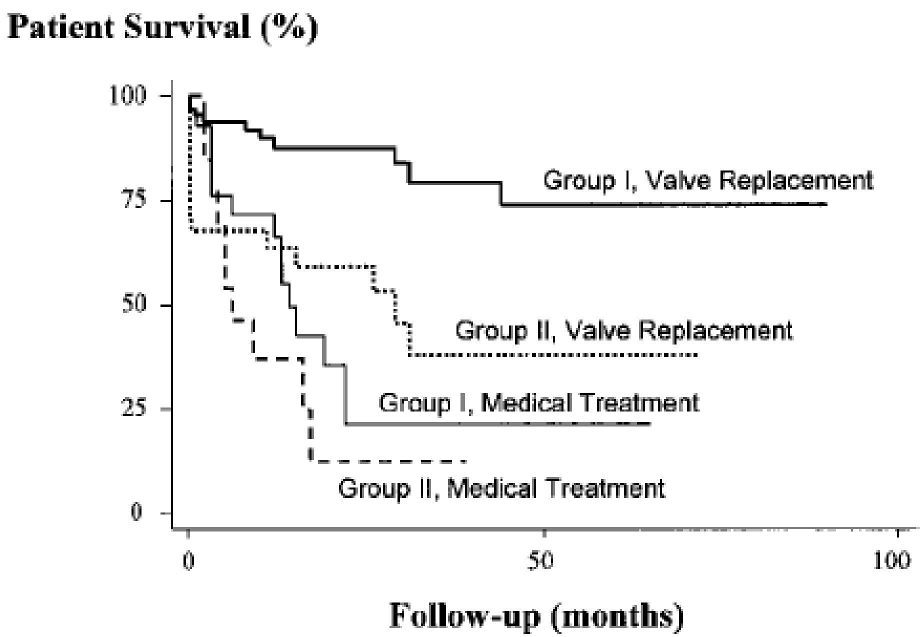
Pibarot et al. JACC 2012;60:1845-53

Stress Echo
Classical low-flow low-gradient AS



Pibarot et al. JACC 2012;60:1845-53

Flow reserve: impact on decision making



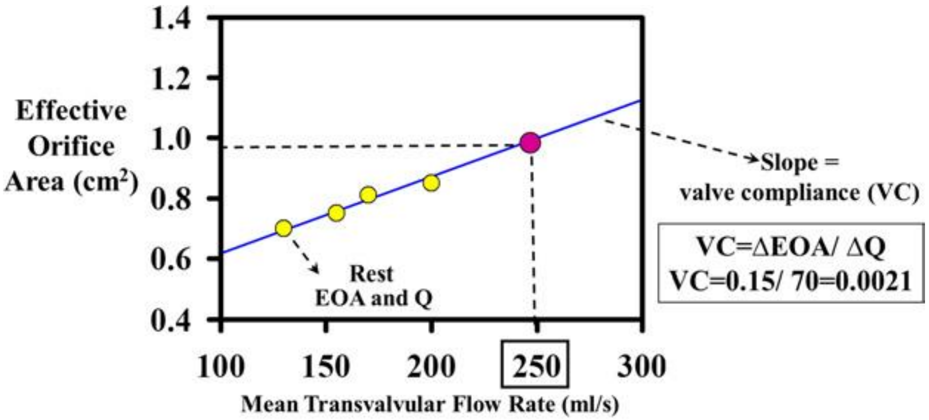
Kaplan-Meier survival estimates by group and treatment.

Group I : Contractile reserve on DSE
Group II: No contractile reserve on DSE

Stress Echo
Paradoxical low-flow low-gradient AS

Low dose dobutamine stress Echocardiography

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



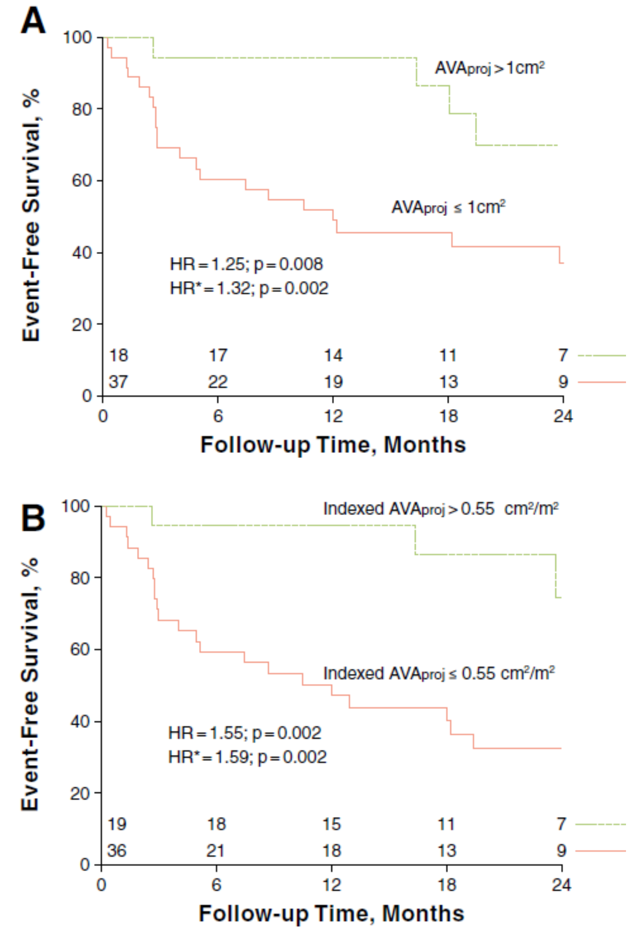
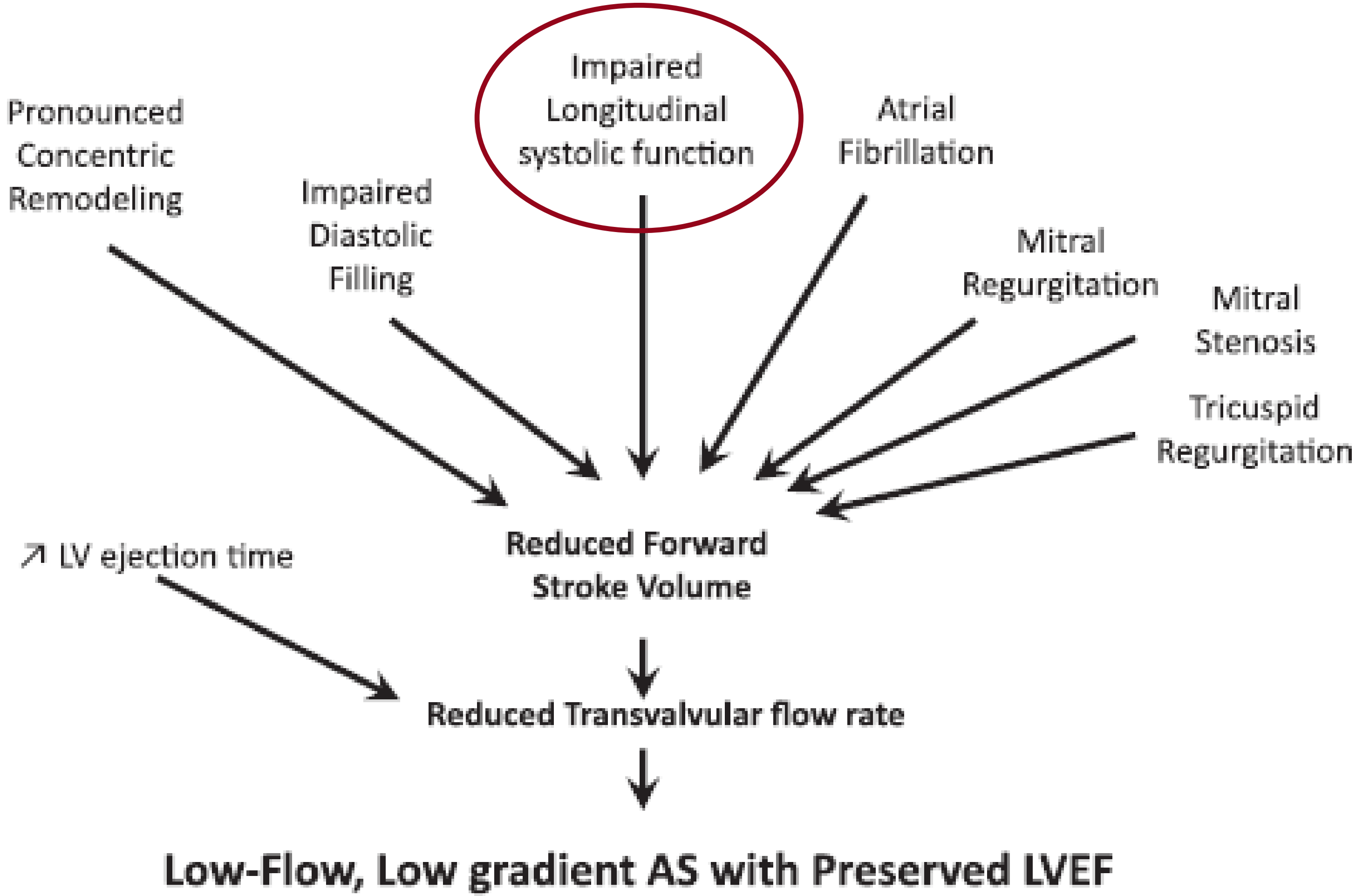


Figure 3. Event-Free Survival According to AVA_{Proj}

Event-free survival according to (A) projected aortic valve area (AVA_{Proj}) at normal flow rate and (B) indexed AVA_{proj} during stress echocardiography. *Hazard ratio (HR) adjusted for age and sex.

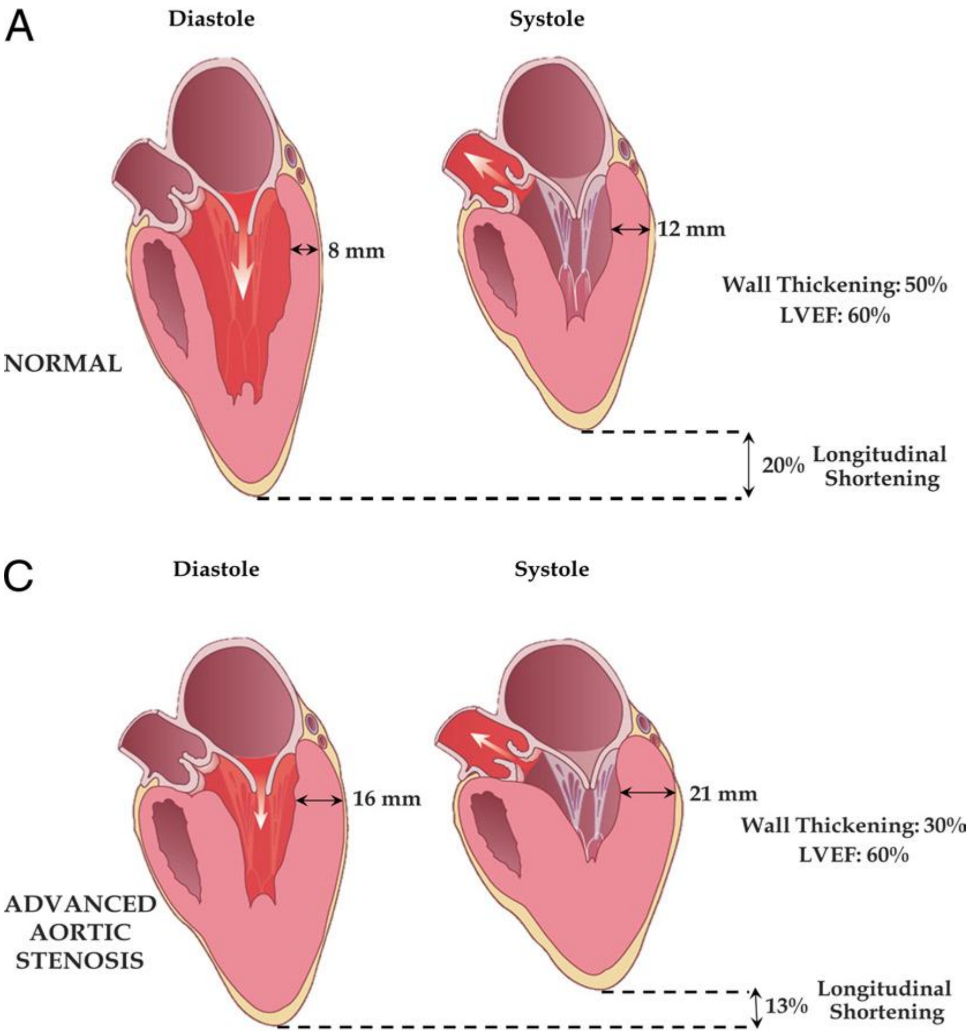
Clavel et al. JACC Cardiovasc Im 2013

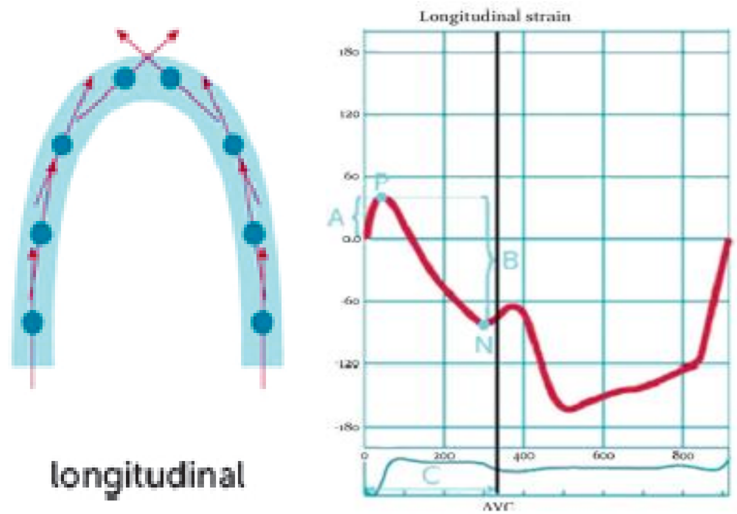
Paradoxical low-flow low-gradient AS



Pibarot. Circulation 2013;128:1729-32

Systolic function in AS





Pibarot P et al. JACC 2012;60:169-80
Blessberger et al. Heart 2010;96:716-722

Global longitudinal Stain & Strain rate in AS

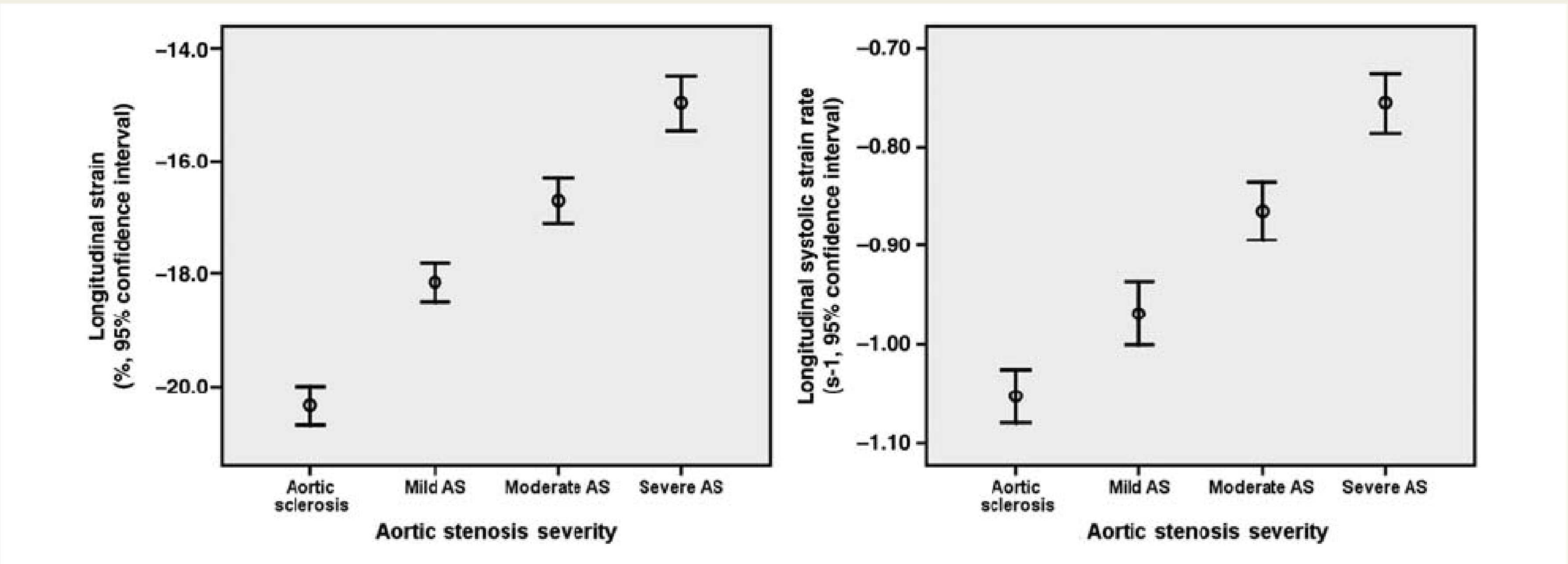


Figure 1 Impairment of left ventricular longitudinal strain and systolic strain rate with increasing aortic stenosis severity ($P < 0.001$ by ANOVA). Left ventricular longitudinal function progressively decline from mild to severe aortic stenosis. Post hoc analysis with Bonferroni correction showed that with each categorical increase in aortic stenosis severity grade from sclerosis to severe stenosis, there was an associated progressive impairment of longitudinal strain and strain rate (all $P < 0.05$).

Ng et al. EHJ 2011

Table 1. Characterization of 340 Patients Based on Flow (≤ or >35 mL/m²) and Gradient (≤ or>40 mm Hg)

AVA≤0.6 cm^2/m^2	Normal Flow SVi>35 mL/m^2	Low Flow SVi≤35 mL/m^2	
High gradient MG>40 mm Hg	Group 1 Normal flow, high gradient n=213 (62.7%) LVEF: 66.8±8 % MG: 57±13.5 mm Hg AVA: 0.79±0.17 cm^2 AVAi: 0.44±0.08 cm^2/m^2 Z_{va}: 4.1±0.8 mm Hg/ml/m^2 GLS: −16.5±3.4 %	Group 2 Low flow, high gradient n=45 (13.2%) LVEF: 63.7 ±8.2 % MG: 64.4 ±16.3 mm Hg AVA: 0.46 ±0.11 cm^2 AVAi: 0.26 ±0.05 cm^2/m^2 Z_{va}: 6.7 ±1.3 mm Hg/ml/m^2 GLS: −14.1 ±3.5 %	n=258 (75.9%)
Low gradient MG≤40 mm Hg	Group 3 Normal flow, low gradient n=52 (15.3%) LVEF: 64.6±7.3 % MG: 34.4±4.6 mm Hg AVA: 0.86±0.14 cm^2 AVAi: 0.49±0.07 cm^2/m^2 Z_{va}: 4±0.8 mm Hg/ml/m^2 GLS: −16.5±3.5 %	Group 4 Low flow, low gradient n=30 (8.8%) LVEF: 63 ±9.3 % MG: 32.7 ±5.7 mm Hg AVA: 0.7 ±0.12 cm^2 AVAi: 0.38 ±0.08 cm^2/m^2 Z_{va}: 5.5 ±1.1 mm Hg/ml/m^2 GLS: −15.5 ±4.1 %	n=82 (24.1%)
	n=265 (78%)	n=75 (22%)	n=340 (100%)

	Group 1 SVi>35 MG>40 n=213	Group 2 SVi≤35 MG>40 n=45	Group 3 SVi>35 MG≤40 n=52	Group 4 SVi≤35 MG≤40 n=30
GLS (%)	−16.5±3.4†††	−14.1±3.5***,‡‡	−16.5±3.5††	−15.5±4.1
LS base (%)	−13.6±3.2†††,§	−10.9±2.8***,‡‡‡	−14.8±3†††,§§§	−11.6±3.4*,‡‡‡
LS mid-LV (%)	−15.8±3.1†††	−13.7±3***,‡‡‡	−16.8±3.2†††,§	−14.4±3.3‡
LS apex (%)	−22±5.5†	−19.5±4.9*	−21.2±6.1	−20.1±6.5
RS (%)	35.9±16.8	33±21	36.7±14.5§	27.9±10.5‡
CS (%)	−19.6±6 ns	−17.7±6.1	−18.3±5.6	−16.1±4.7

Adda. Circ Cardiovasc Imaging. 2012;5:27-35

GLS in AS

preserved LVEF

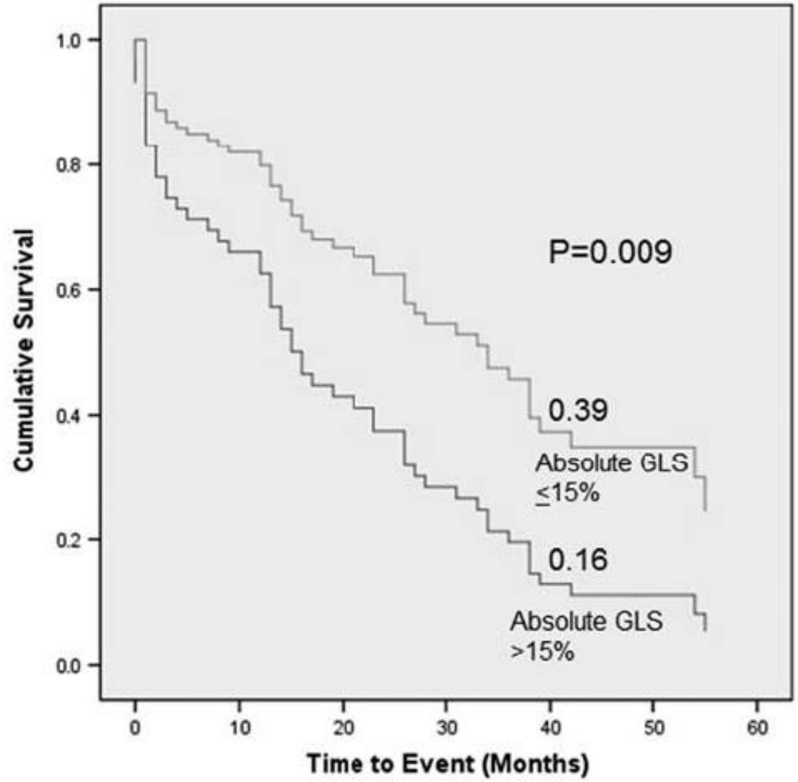


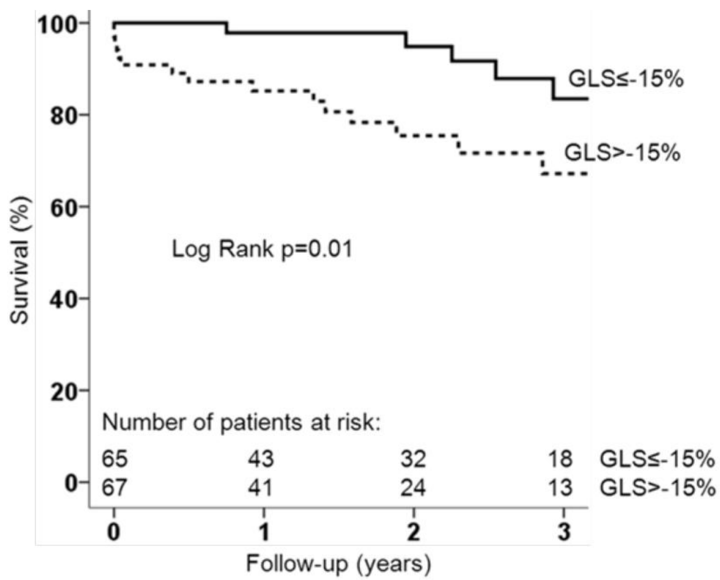
Table 3. Multivariate Analysis of Event-Free Survival. GLS Remains Associated With Survival After Correcting for Clinical Risk, Peak Gradient, Calcification, and Impedance

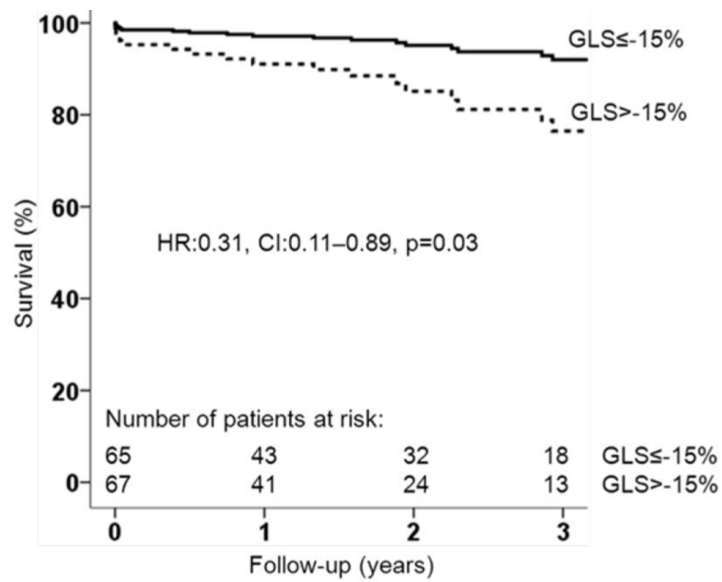
	Gradient Model (R^2=0.47)		AV Calcification Model (R^2=0.26)		Impedance Model (R^2=0.28)	
Variable	HR (95% CI)	*P*	HR (95% CI)	*P*	HR (95% CI)	*P*
STS-PRMM	0.95 (0.90–1.00)	0.06	0.95 (0.90–1.00)	0.07	0.95 (0.90–0.997)	0.04
Global longitudinal strain	1.13 (1.03–1.25)	0.01	1.13 (1.02–1.25)	0.02	1.15 (1.04–1.27)	0.01
Transaortic peak pressure gradient	1.02(1.01–1.04)	0.005	…	…	…	…
AV calcification score 3 or 4	…	…	2.63 (1.27–5.44)	0.009	…	…
Valvulo-arterial impedance	…	…	…	…	1.35 (1.08–1.67)	0.01

Yingchoncharoen. Circ Cardiovasc Imaging. 2012;5:719-725

GLS in AS

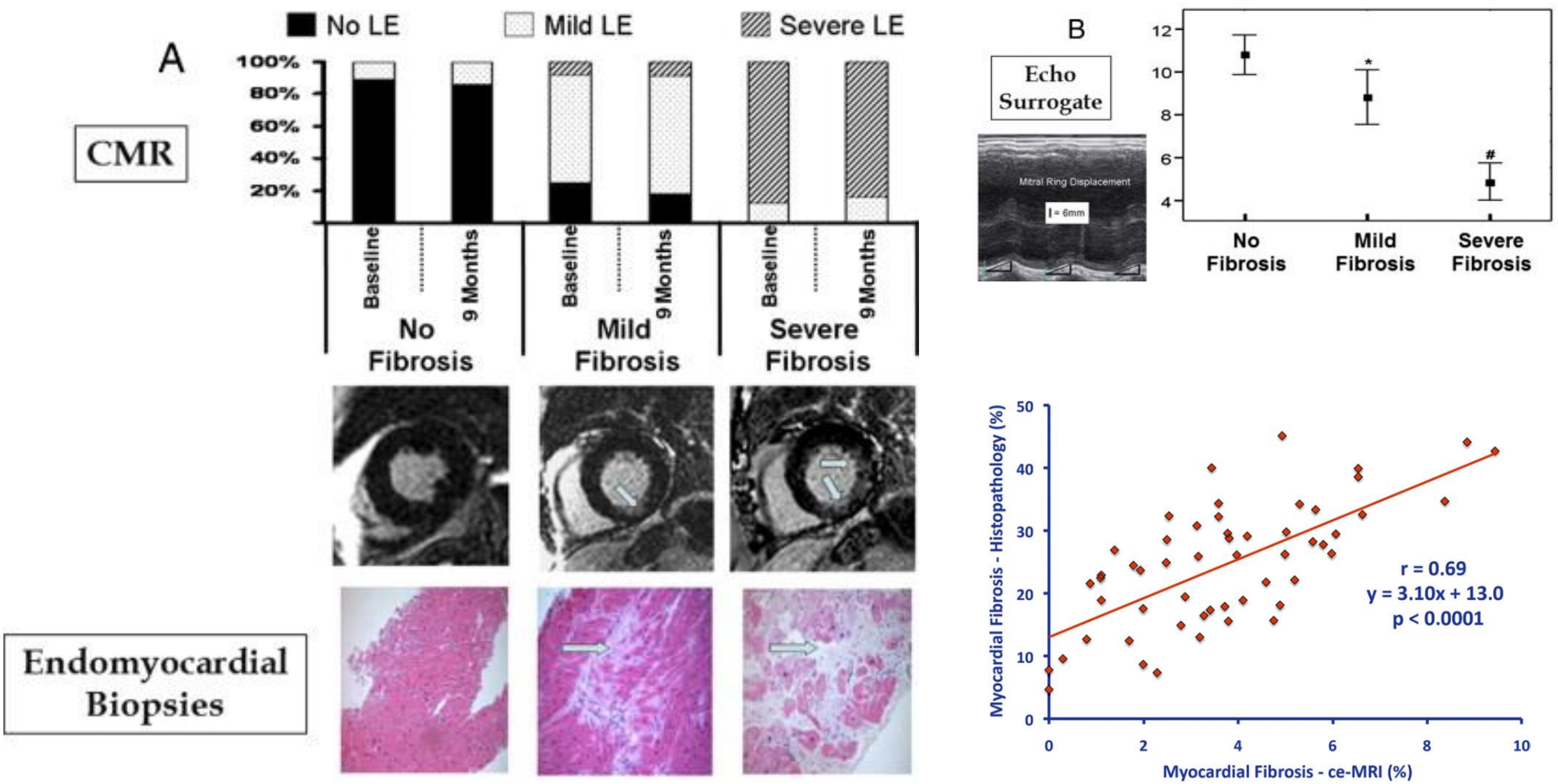
Low-Gradient & preserved LVEF





Kamperidis et al. ACC.14

Myocardial fibrosis in AS



Pibarot et al. JACC 2012
Hermann et al. JACC 2011

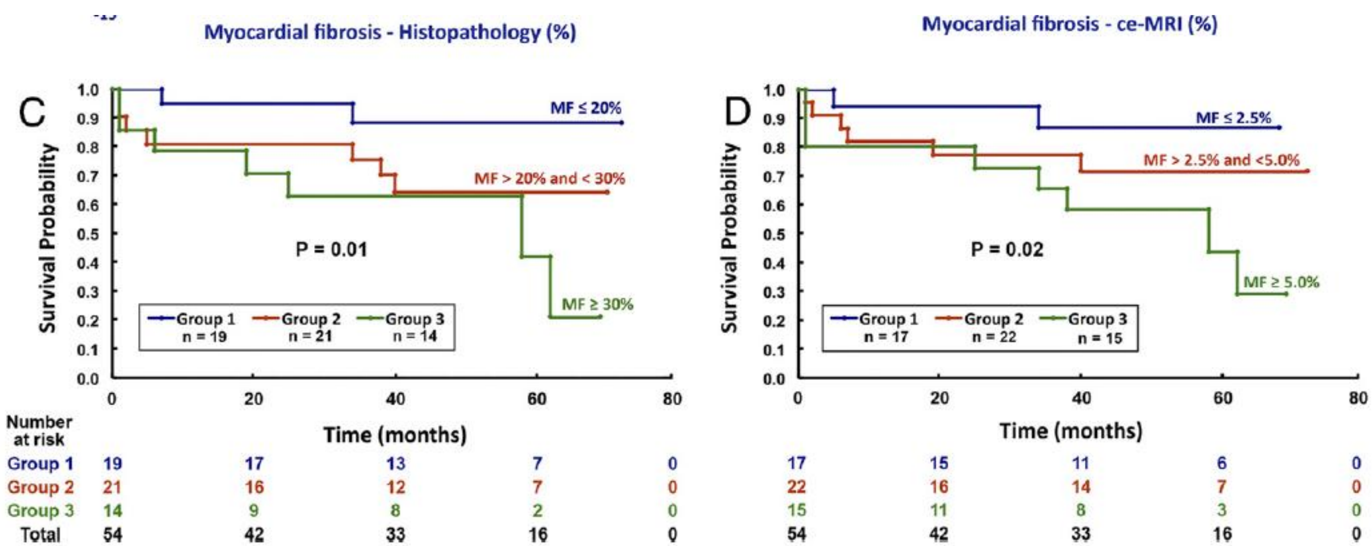
MRI for fibrosis

HEART LUNG CENTER LEIDEN

	Severe AS, High Gradient (n = 49)	Severe AS, Low Gradient, EF ≥50% (n = 11)	Severe AS, Low Gradient, EF <50% (n = 9)
Left heart catheterization			
Aortic valve area, cm^2	0.7 ± 0.1	0.7 ± 0.2	0.8 ± 0.1
Indexed aortic valve area, $cm^2 \cdot m^{-2}$	0.39 ± 0.12	0.41 ± 0.14	0.46 ± 0.11
Pulmonary capillary wedge pressure, mm Hg	14 ± 7	15 ± 7	18 ± 7
Stroke volume, ml	72 ± 12	56 ± 13	63 ± 13
Stroke volume index, $ml \cdot m^{-2}$	40 ± 5	31 ± 4	34 ± 3
Mean aortic pressure gradient, mm Hg	53 ± 8	37 ± 8*	27 ± 8*†
Transvalvular flow rate, ml/s	241 ± 40	179 ± 30*	184 ± 20*
Central venous oxygen saturation, %	69 ± 4	63 ± 4*	59 ± 4*†
cMRI			
Ejection fraction, %	55 ± 13	56 ± 12	38 ± 17*†
Late enhancement–positive segments: 0/1/>1, %	47/19/34	0/20/80	0/23/77
Myocardial histology			
Interstitial fibrosis, %	1.8 ± 0.8	3.9 ± 0.6*	4.8 ± 0.6*
Myocyte diameter, μm	12.2 ± 1.3	13.1 ± 1.5	13.7 ± 1.3*
Cardiac biomarkers			
NT-proBNP, pg/ml	1,418 (377–1,505)	3,730 (1,858–5,671)*	5,016 (4,182–5,704)*

Hermann et al. JACC 2011

Myocardial fibrosis in AS



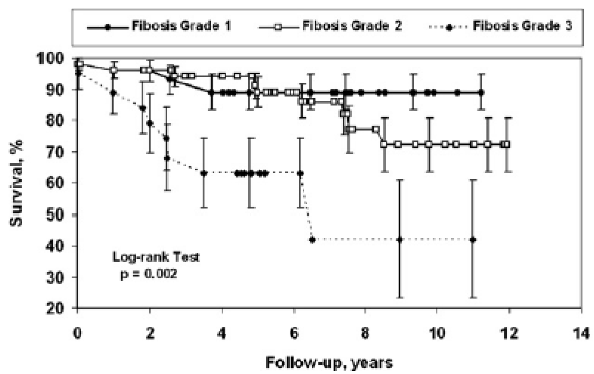


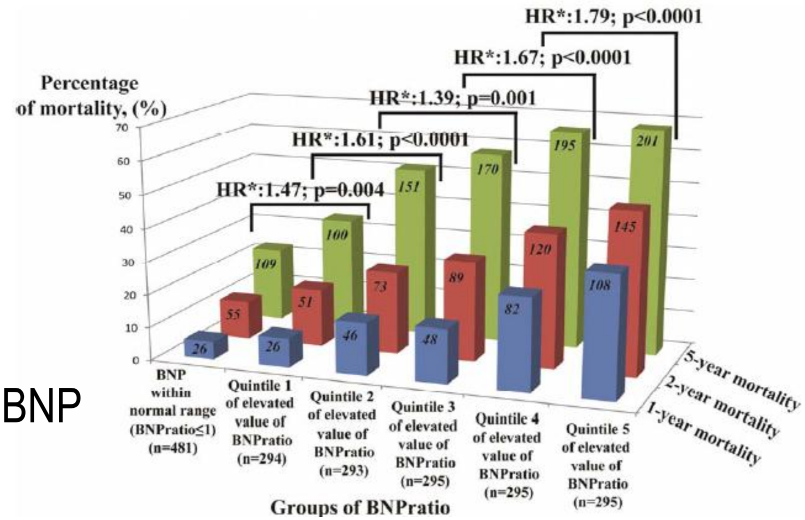
FIGURE 4. Actuarial freedom from cardiac death at 10 years according to myocardial fibrosis grade.

Higher fibrosis → worse survival after AVR

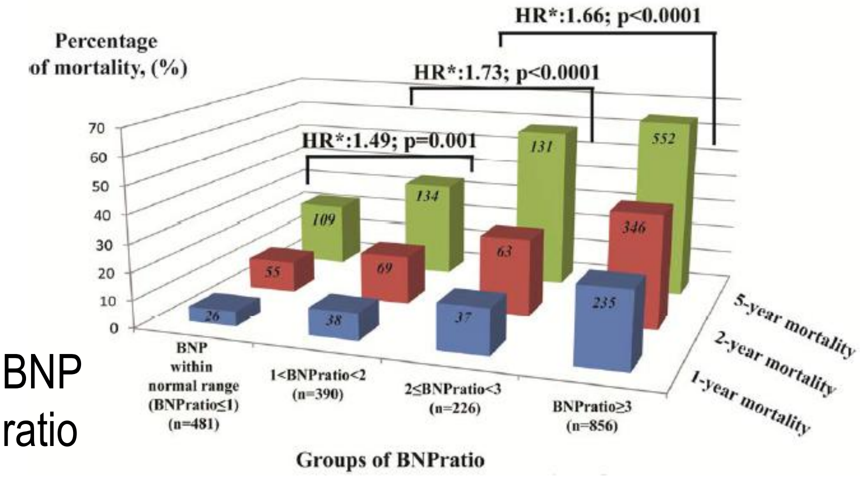
Azavedo et al. JACC 2010
Milano et al. J Thorac Cardiovasc Surg 2012

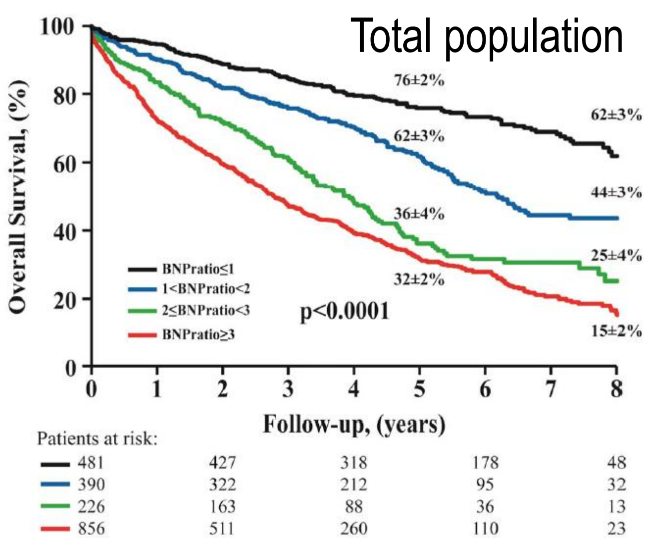
BNP in AS

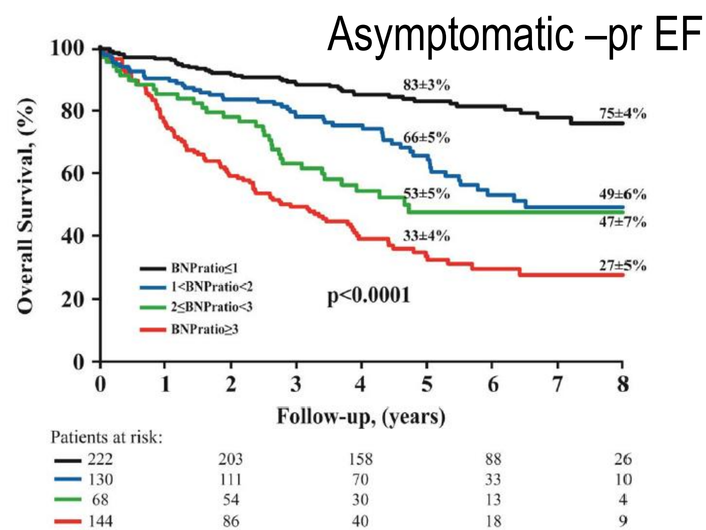
BNP



BNP ratio







Quantification of valvular obstruction			
Mean gradient*†	>40 mm Hg	Same as peak aortic jet velocity	Same as peak aortic jet velocity
Valve effective orifice area*† $EOA = SV_{LVOT}/VTI_{Ao}$ Indexed EOA* $EOAI = EOA/BSA$	≤1.0 cm^2 ≤0.6 cm^2/m^2	Less flow dependent than gradient or peak velocity Reflects intrinsic severity of valvular obstruction	Susceptible to measurements errors Over-estimates LV energy loss in patients with small aortas May under- or over-estimate stenosis severity in presence of hypertension May over-estimate stenosis severity in low flow states EOA may over-estimate severity in patients with small body size. Indexed EOA may over-estimate severity in obese patients
Energy loss index $ELI = [EOA \times A_A/A_A - EOA]/BSA$	≤0.5–0.6 cm^2/m^2	Less flow dependent than gradient or peak velocity Takes into account pressure recovery and is ± equivalent to EOA measured by catheter Reflects true LV energy loss caused by stenosis Should be measured in patients with small aortas	Susceptible to measurements errors May under- or over-estimate stenosis severity in presence of hypertension May over-estimate stenosis severity in low flow states
Aortic valve calcification score†	Echo 4/4† CT >1,650 AU	Can be estimated by echo and quantitatively measured by multislice CT Correlates well with stenosis severity and predicts rapid stenosis progression Independent of hemodynamic conditions Useful in low flow states when echo assessment of stenosis hemodynamic severity is inconclusive	Echo, semiquantitative assessment CT, exposure to radiation
Quantification of global LV hemodynamic load			
Valvuloarterial impedance (Z_{va})* $Z_{va} = SBP + \Delta P_{Mean}/SVI$	>4.5 $mm\ Hg \cdot ml^{-1} \cdot m^2$	Can be measured by Doppler echocardiography Reflects global (valvular+arterial) load imposed on LV Potentially superior to predict occurrence of symptoms and events	Susceptible to measurements errors Does not permit to discriminate the valvular versus the arterial contribution to the global LV load

Pibarot et al. JACC 2012

Quantification of LV systolic dysfunction			
LVEF*†	<50%	Widely used and validated with regard to outcome data	Susceptible to measurements errors Also influenced by LV geometry Under-estimates the degree of myocardial systolic dysfunction in presence of LV concentric remodeling
Global longitudinal strain*	<15%	Less influenced by LV geometry Superior to LVEF to assess intrinsic myocardial function	Cutoff values need to be further validated
Myocardial fibrosis		Can be measured by CMR Predicts poor outcomes after AVR	High cost and low availability of CMR
Plasma natriuretic peptides* BNP or NT-ProBNP		Easy and inexpensive to measure Reflects total burden of disease on myocardium Correlates well with myocardial systolic dysfunction and symptoms Predicts poor outcomes before and after AVR	High variability in the threshold values reported in the literature to predict poor outcomes Increase in BNP during serial follow-up may be superior to isolated measure Does not permit discriminating impact of valvular stenosis versus hypertension versus other cardiovascular disease NT-ProBNP may be more sensitive to detect early LV systolic dysfunction but more age dependent

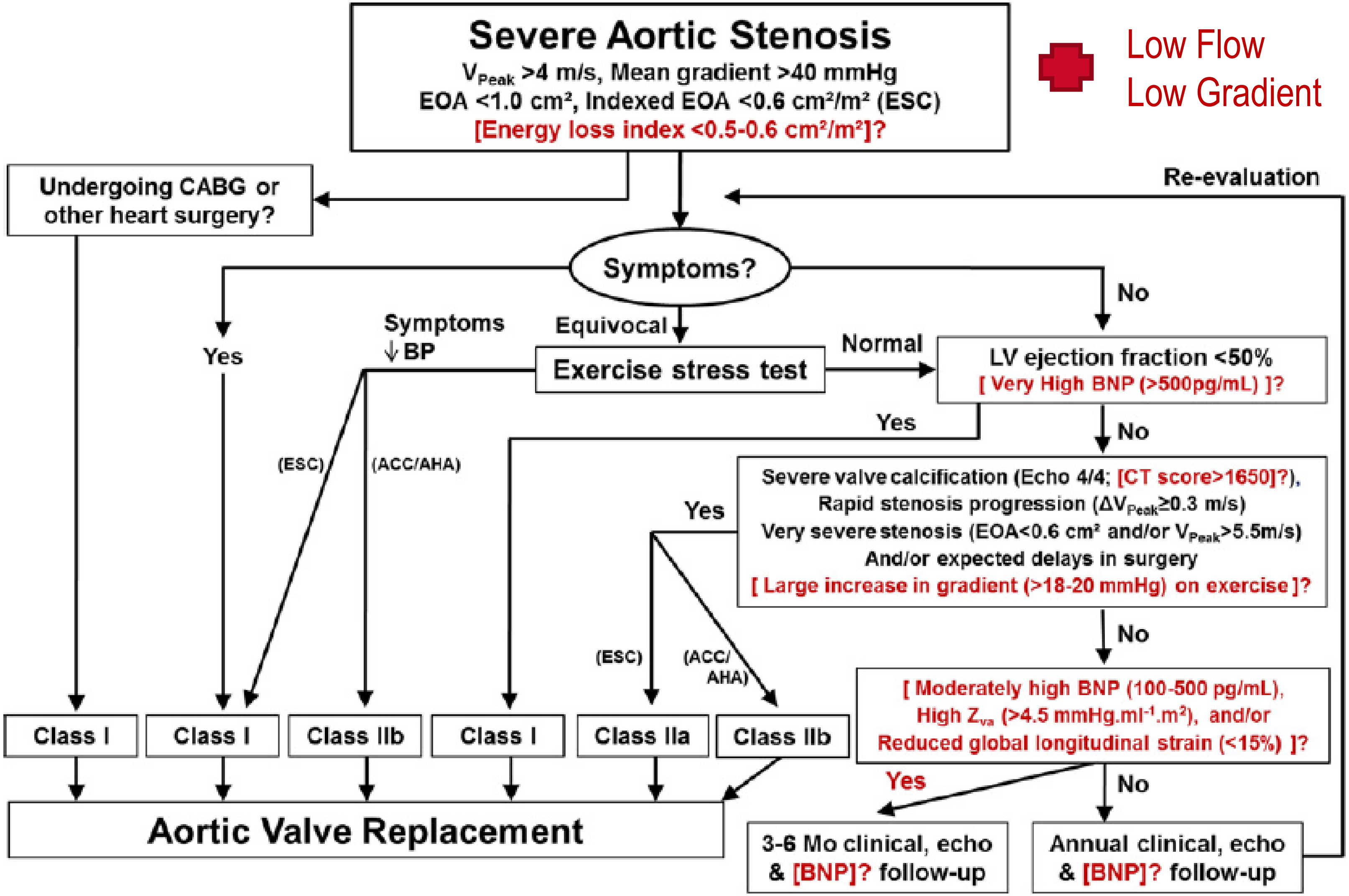
Forward Flow - SVi <35ml/m^2

Stress echocardiography - Projected AVA <1cm^2

LV remodeling - Concentric remodeling or hypertrophy

Pibarot et al. JACC 2012

AS: New in diagnosis



Low Flow
Low Gradient

Pibarot et al. JACC 2012

Ευχαριστώ

Table 2: Hazard ratio, 95% confidence interval and p-value for different variables and threshold of BNP

		Overall mortality - Univariate Analysis	Multivariate Analysis[§]		
			Overall mortality[†] - Whole cohort	Mortality Under medical treatment – Whole cohort	Overall mortality[†] - Asymptomatic isolated AS*
Ln BNP	HR (95%CI)	1.68 (1.60-1.77)	1.40 (1.31-1.50)	1.41 (1.30-1.54)	1.61 (1.36-1.91)
	p	<0.0001	<0.0001	<0.0001	<0.0001
LnBNPratio	HR (95%CI)	1.54 (1.47-1.62)	1.40 (1.31-1.50)	1.41 (1.30-1.54)	1.61 (1.37-1.91)
	p	<0.0001	<0.0001	<0.0001	<0.0001
Activated BNP	HR (95%CI)	3.08 (2.59-3.69)	1.91 (1.55-2.35)	1.84 (1.44-2.35)	2.35 (1.57-3.56)
	p	<0.0001	<0.0001	<0.0001	<0.0001
Activated BNP less than twice normal[‡]	HR (95%CI)	1.80 (1.44-2.25)	1.49 (1.17-1.90)	1.43 (1.08-1.90)	2.10 (1.32-3.36)
	p	<0.0001	0.001	0.008	0.002
Activated BNP 2 to 3 time normal[‡]	HR (95%CI)	3.13 (2.48-3.96)	2.12 (1.63-2.75)	2.10 (1.55-2.86)	2.25 (1.31-3.87)
	p	<0.0001	<0.0001	<0.0001	0.003
Activated BNP more than 3 times normal[‡]	HR (95%CI)	4.06 (3.38-4.91)	2.43 (1.94-3.05)	2.21 (1.69-2.88)	3.93 (2.40-6.43)
	p	<0.0001	<0.0001	<0.0001	<0.0001

*Asymptomatic isolated AS group was defined as asymptomatic AS with normal Ejection Fraction and no previous myocardial infarction; [‡]compared to normal BNP; [§]Adjusted for Age, Gender, Body Surface Area, Atrial Fibrillation, Charlson Score Index, Symptoms, Creatinine, Hemoglobin, Systolic Blood Pressure, Indexed Aortic Valve Area, indexed stoke volume and LV Ejection Fraction. [†]Further adjustment for Aortic Valve Replacement as a time dependent variable