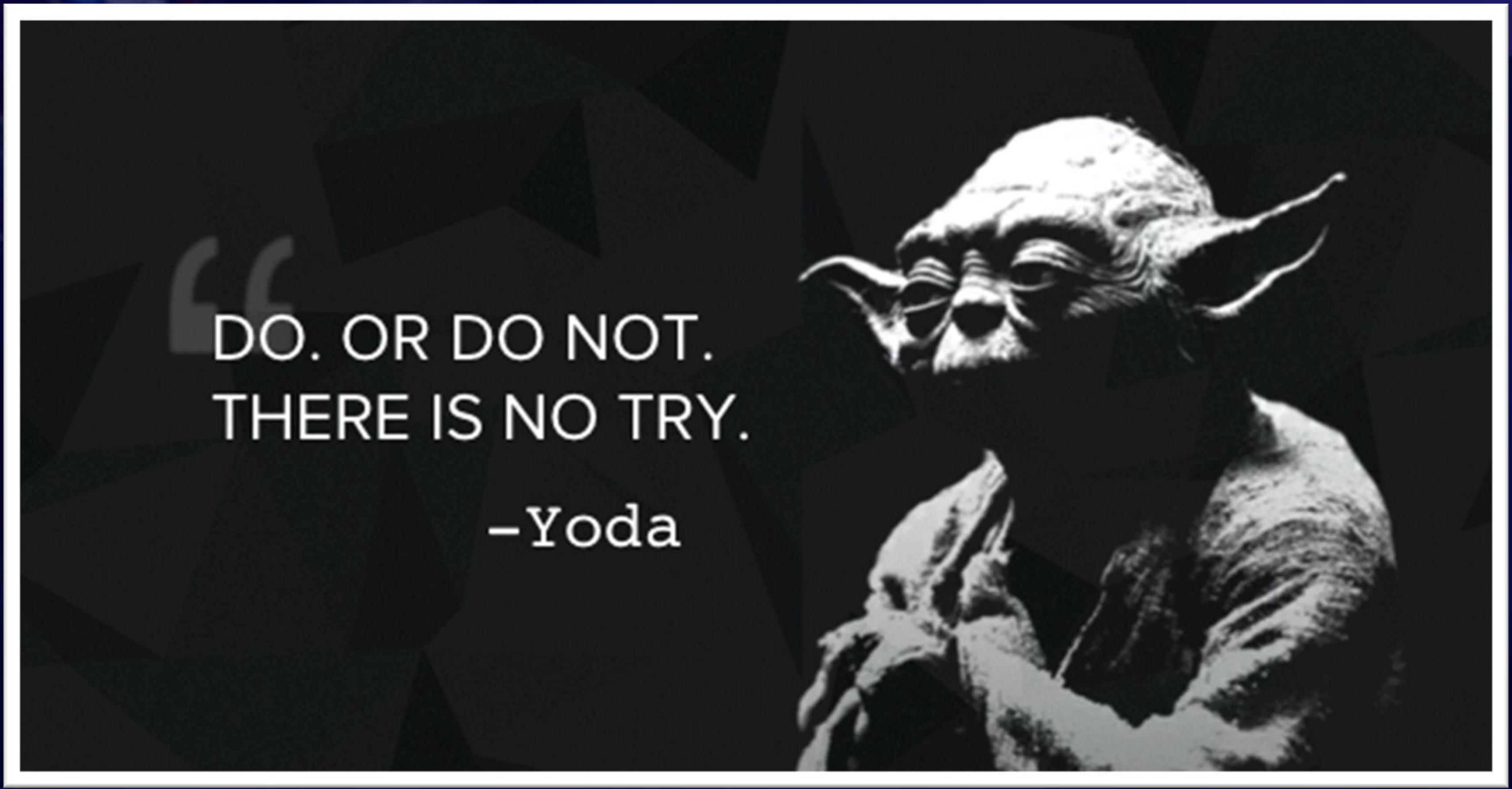
All Patients with Asymptomatic AS Need Treatment - Con

> *"If it ain't broke, don't fix it."*
> —Thomas Bertram Lance in *Nation's Business*, May 1977

Limor Ilan Bushari , MD
Emek Medical Center


DO. OR DO NOT.
THERE IS NO TRY.
–Yoda

- What is the natural history of severe asymptomatic AS?
- Literature review and GL
- How do we define "Asymptomatic" and ways to assess it ?
- What is the surgical outcome of pts with asymptomatic AS?
- Should we stay with wait and watch, or should we intervene?
- Staging asymptomatic AS : Not only symptoms play a role

To treat or not to treat ?

68 y/o man

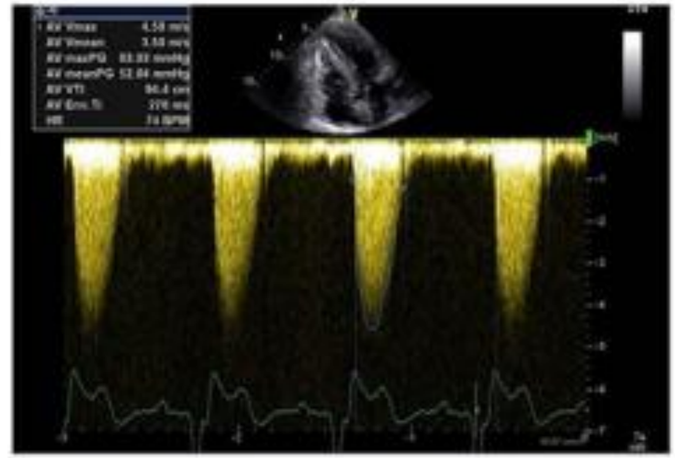
- History of known calcific AS (for the past 3 years)
- Mild HTN
- No evidence for obstructive CAD
- No angina, syncope or dyspnea
- LVEF : 63%
- AVA 0.7 cm2; Gradients 73/46 mmHg (max/mean)

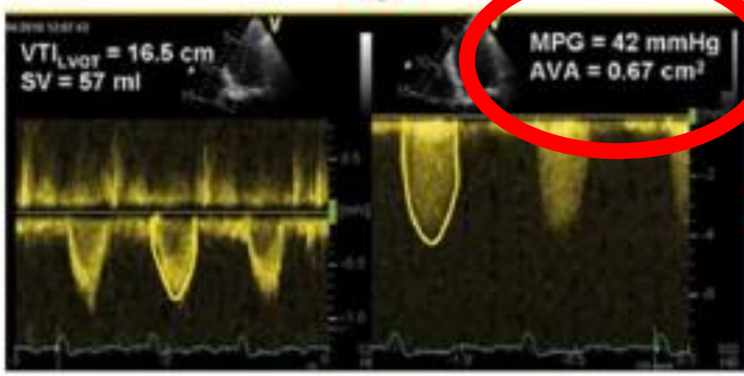
72 y/o woman

- History of known calcific AS (for the past 5 years)
- HTN, NIDDM, HLP
- Obese, OSA (Bipap at night)
- No angina, syncope or dyspnea
- LVEF : 63%
- AVA 0.7 cm2; Gradients 73/46 mmHg (max/mean)

Echocardiography for Aortic stenosis

- Maximum systolic velocity across the aortic valve
- Mean aortic valve pressure gradient
- Aortic valve area (AVA) calculation

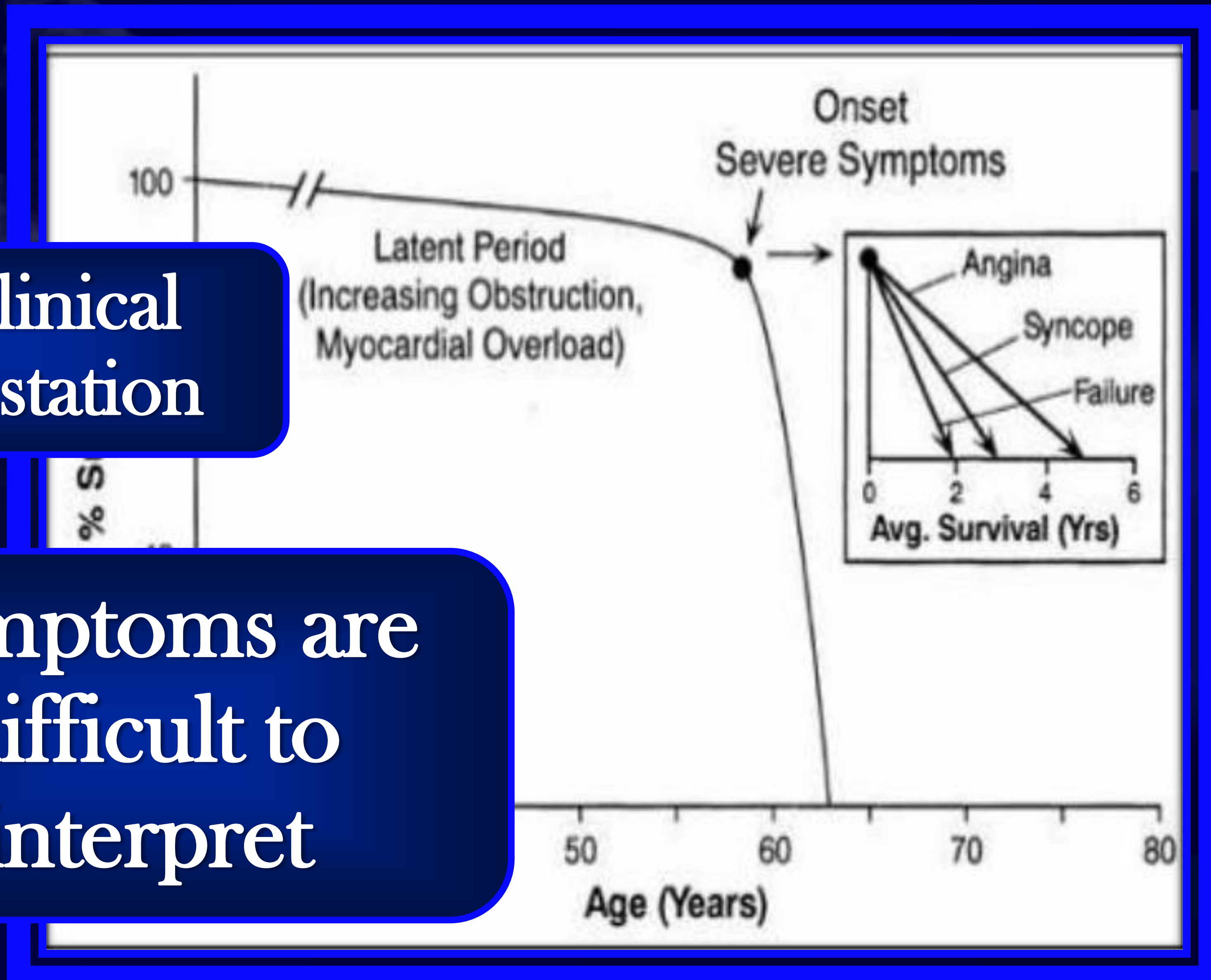




$$AVA = \frac{\pi(LVOT/2)^2 \times LVOT\ VTI}{AV\ VTI}$$

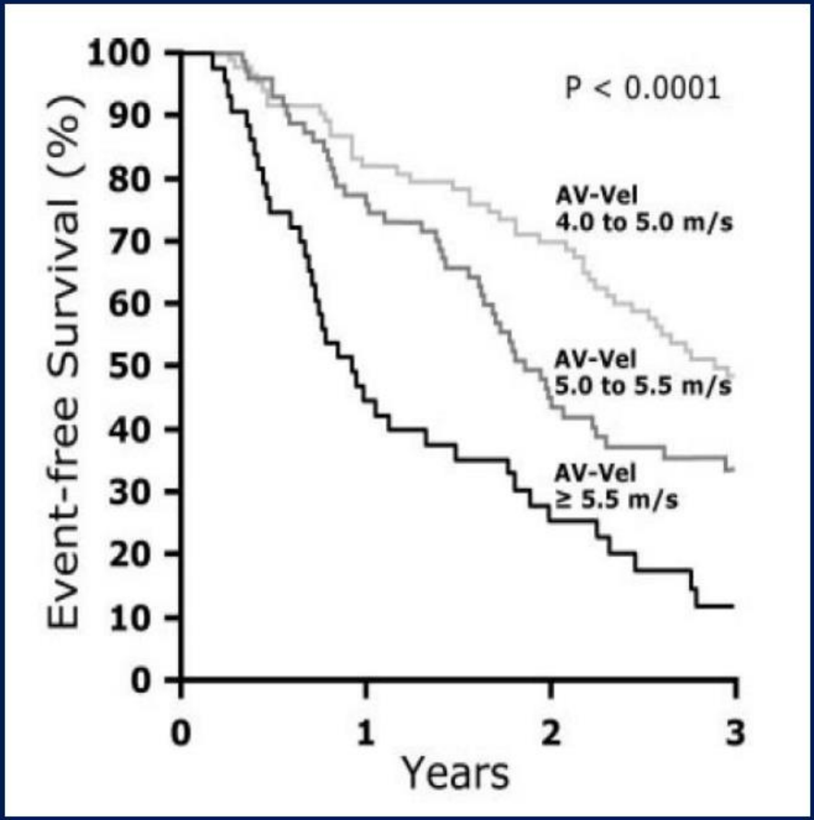
Late clinical manifestation

Symptoms are difficult to interpret



Ross & Branwald, Circulation 1968

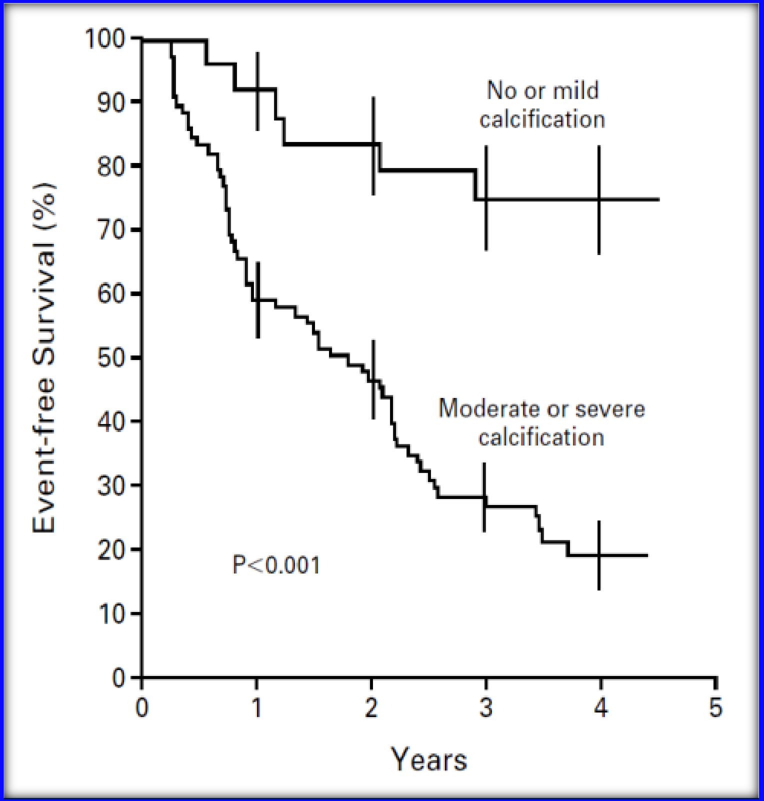
Natural history of very severe AS

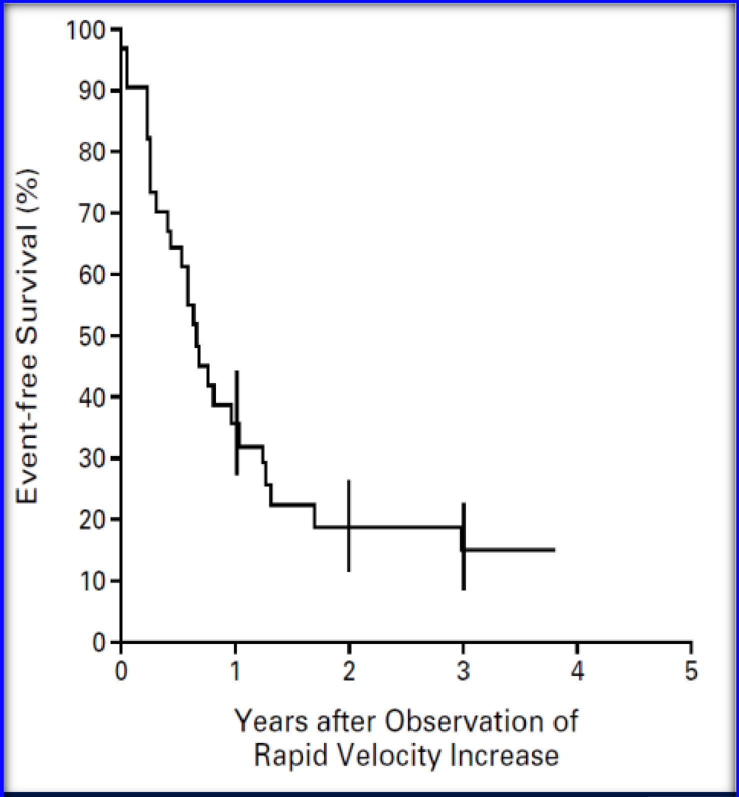


Rosenhek et al. Circulation.,2010

Rapid Stenosis Progression
V ≥ 0.3 m/s/ per year

Valve Calcifications





Rosenhek et al, N Engl J Med , 2000

When should we offer valve intervention?

Aortic stenosis progression

TOO EARLY

UNECESSARY EXPOSURE TO RISK OF:

- Complications of surgery / TAVI
- Living with a prosthetic valve
- Anticoagulation
- Repeat intervention for structural valve deterioration

OPTIMAL TIMING

JUST AS LEFT VENTRICULAR DECOMPENSATION IS STARTING TO DEVELOP

TOO LATE

IRREVERSIBLE DAMAGE TO THE MYOCARDIUM:

- Sudden cardiac death
- Increased peri-operative risk
- Heart failure
- Hospital admissions
- Increased mortality
- Major financial burden

Table 3 Estimates of clinical risks associated with watchful waiting or early intervention strategies

Risks associated with watchful waiting	Risk estimate	Risks associated with early intervention	Risk estimate
Sudden cardiac death	1.0%–1.5% per year [46–48]	Perioperative mortality	1%–3% (refine using validated risk calculator)
Death while awaiting elective intervention once symptoms develop	4% at 1 month, 12% at 6 months [49]	Perioperative complications (SAVR): ▶ Stroke. ▶ Pacemaker requirement. ▶ Major bleeding. ▶ New atrial fibrillation.	 2.4%–8.1%[33–35] 1.5%–8.6%[32] 9%–26%[36 39] 17%–43%[34 36 39]
Increased perioperative mortality: ▶ Impaired left ventricular function. ▶ No contractile reserve.	(Refine using validated risk calculator) 9%–19%[10 20 50] 22%–32%[11 52]	Periprocedural complications (TAVI): ▶ Stroke. ▶ Pacemaker requirement. ▶ Major vascular complications. ▶ Major bleeding. ▶ New atrial fibrillation.	 2.2%–2.6%.[40] 7%–25%[38–40] 2.0%–4.5%[40] 12%–15%[36 39] 10%–13%[34 36 39]
Lack of improvement in ejection fraction following intervention	25%–50%[10 11]	Long-term prosthetic valve complications: ▶ Thromboembolism. ▶ Major bleeding with anticoagulation.	 0.7%–1.0% per year[42] 1.8%–2.6% per year[42]
Incomplete resolution of symptoms	Approximately 50%[50]	Prosthetic valve endocarditis	1%–3% in first year then <0.5% per year[43]
Increased late postintervention mortality: ▶ Impaired ejection fraction. ▶ Myocardial fibrosis.	HR 2.0[20] HR 1.25–5.25[21 51 57]	Reoperation for structural valve degeneration: ▶ <65 years of age. ▶ >65 years of age.	 46%–55% at 20 years 8%–15% at 20 years[45]

SAVR, surgical aortic valve replacement; TAVI, transcatheter aortic valve implantation.

ORIGINAL RESEARCH

Sudden cardiac death in asymptomatic patients with aortic stenosis

Table 2 Risk of sudden cardiac death—Cox regression

	Univariate			Multivariate*		
	HR	95% CI	P value	HR	95% CI	P value
Age (per year)	1.065	1.016 to 1.116	0.009	1.059	1.011 to 1.109	0.016
Female	0.542	0.229 to 1.281	0.163			
Body mass index (per kg/m^2)	0.889	0.802 to 0.986	0.025	0.870	0.780 to 0.971	0.013
Blood pressure diastolic (per mm Hg)	1.008	0.674 to 1.008	0.674			
Blood pressure systolic (per mm Hg)	1.008	0.990 to 1.026	0.386			
Hypertension	1.389	0.645 to 2.994	0.402			
Pulse rate (per beat/min)	1.011	0.976 to 1.047	0.554			
Ejection fraction (per %)	1.007	0.949 to 1.069	0.816			
LV end diastolic diameter (per mm)	1.141	0.606 to 2.149	0.693			
LV end systolic diameter (per mm)	1.113	0.549 to 2.260	0.766			
LVMI (per 10 g/m^2)	1.173	1.076 to 1.280	<0.001	1.205	1.103 to 1.318	<0.001
Jet velocity (per m/s)	1.106	0.532 to 2.298	0.787			
Jet velocity >3.0 m/s	1.027	0.482 to 2.190	0.945			
Mean pressure gradient (per mm Hg)	1.008	0.962 to 1.055	0.750			
Aortic valve area (per cm^2)	0.520	0.199 to 1.357	0.182			

*Variables with $p<0.05$ on univariate were included in the multivariate analysis.
LV, left ventricular; LVMI, left ventricular mass index.

Minners J, *et al*. *Heart* 2020;**106**:1646–1650. doi:10.1136/heartjnl-2019-316493

Key messages

What is already known on this subject?

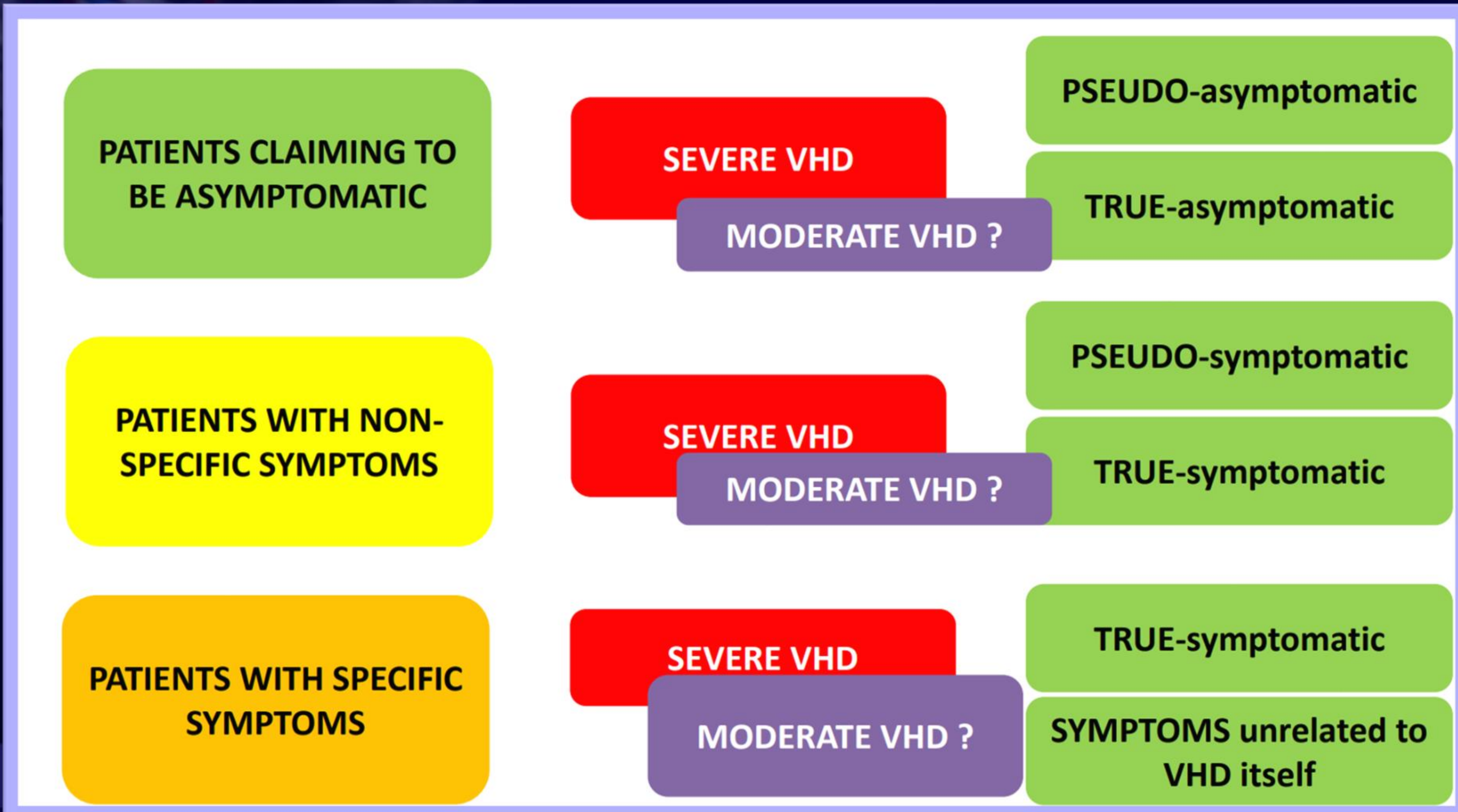
- Sudden cardiac death (SCD) is a significant concern in asymptomatic patients with aortic stenosis (AS) with a reported incidence of up to 3%/year. However, whether AS alone puts patients at risk independent of non-valve related factors, including coronary heart disease, is unclear.

What might this study add?

- The current trial demonstrates that SCD is rare (0.4%/patient-year) in asymptomatic patients with mild to moderate AS who do not have non-valve-related risk factors. Similarly, patients who develop severe stenosis during follow-up have a low risk of SCD (0.6%/patient-year).

How might this impact on clinical practice?

- Since the risk of sudden cardiac death in asymptomatic patients with AS is low and not primarily related to stenosis severity, alternative risk factors for SCD should actively be investigated to reduce the incidence of this serious complication.


PATIENTS CLAIMING TO BE ASYMPTOMATIC
SEVERE VHD
MODERATE VHD ?
PSEUDO-asymptomatic
TRUE-asymptomatic
PATIENTS WITH NON-SPECIFIC SYMPTOMS
SEVERE VHD
MODERATE VHD ?
PSEUDO-symptomatic
TRUE-symptomatic
PATIENTS WITH SPECIFIC SYMPTOMS
SEVERE VHD
MODERATE VHD ?
TRUE-symptomatic
SYMPTOMS unrelated to VHD itself

Education in Heart

VALVULAR HEART DISEASES

Timing of intervention in aortic stenosis: a review of current and future strategies

Russell James Everett,[1] Marie-Annick Clavel,[2] Philippe Pibarot,[2] Marc Richard Dweck[1]

Table 2 Symptomatology of severe aortic stenosis

Symptom	Aetiology	Potential questions to ask:
Angina	Supply–demand imbalance: coexistent coronary disease and fixed cardiac output versus hypertrophied myocardium.	'Do you get chest pain or discomfort when walking or doing other activities?'
Breathlessness/reduced exercise capacity	Reduced LV compliance, increased left ventricular end-diastolic and pulmonary capillary pressures.	'Can you walk ask many stairs as this time last year?' 'Can you keep up with your friends?'
Presyncope/syncope *(important to elicit any exertional component)*	Fixed cardiac output, skeletal muscle vasodilation on exertion and resultant cerebral hypoperfusion.	'Have you felt lightheaded like you might faint?' 'Have you had any fainting or blackout episodes?'
Palpitations	Development of atrial or ventricular arrhythmia, myocardial scarring.	'Are you aware of your heart racing?'

LV, left ventricular.

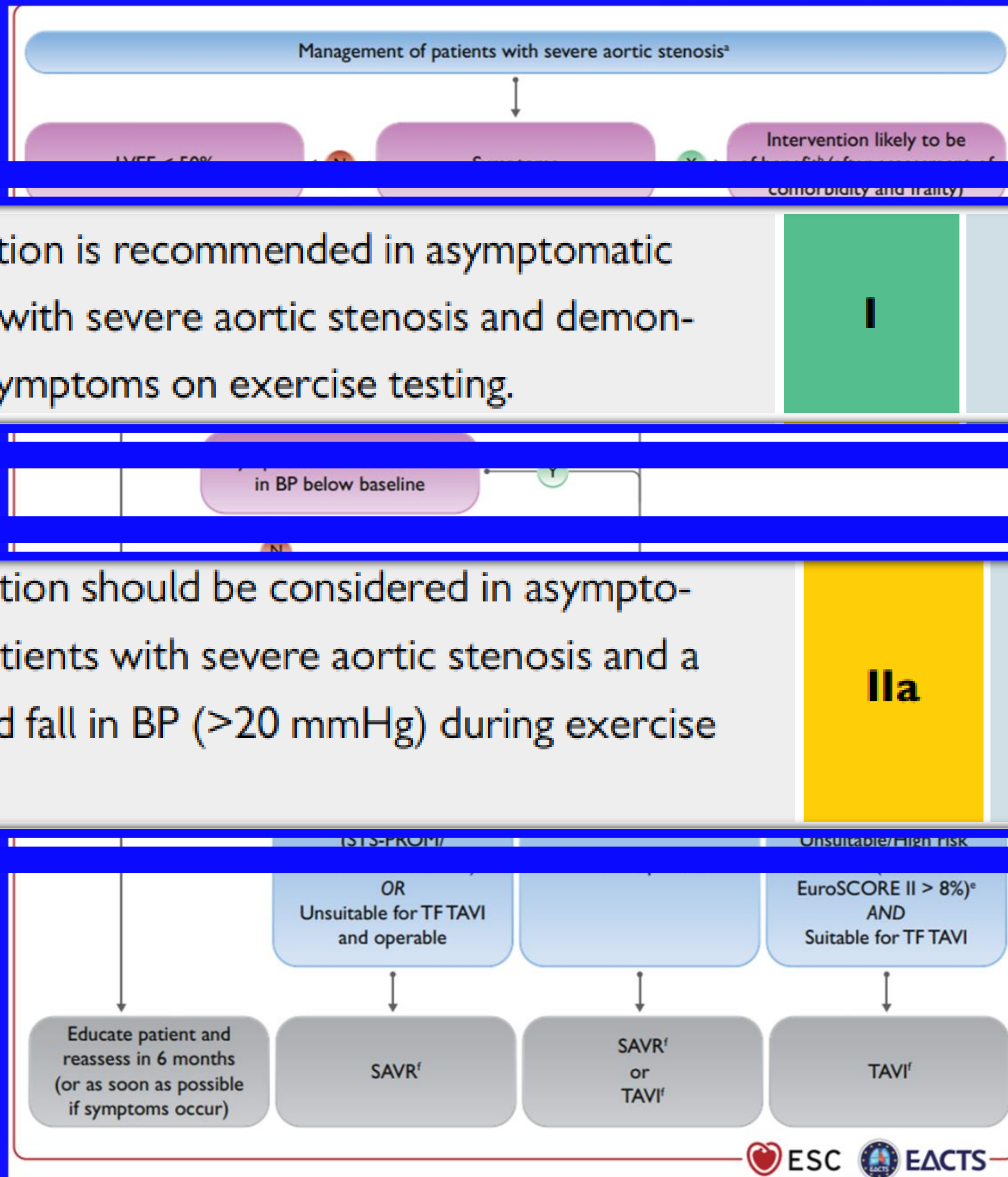
ESC
European Society
of Cardiology

European Heart Journal (2022) **43**, 561–632
https://doi.org/10.1093/eurheartj/ehab395

ESC/EACTS GUIDELINES

2021 ESC/EACTS Guidelines for the management of valvular heart disease

Developed by the Task Force for the management of valvular heart disease of the European Society of Cardiology (ESC) and the European Association for Cardio-Thoracic Surgery (EACTS)



Intervention is recommended in asymptomatic patients with severe aortic stenosis and demonstrable symptoms on exercise testing.	I	C

Intervention should be considered in asymptomatic patients with severe aortic stenosis and a sustained fall in BP (>20 mmHg) during exercise testing.	IIa	C

JOURNAL OF THE AMERICAN COLLEGE OF CARDIOLOGY

PUBLISHED BY ELSEVIER

VOL. 7

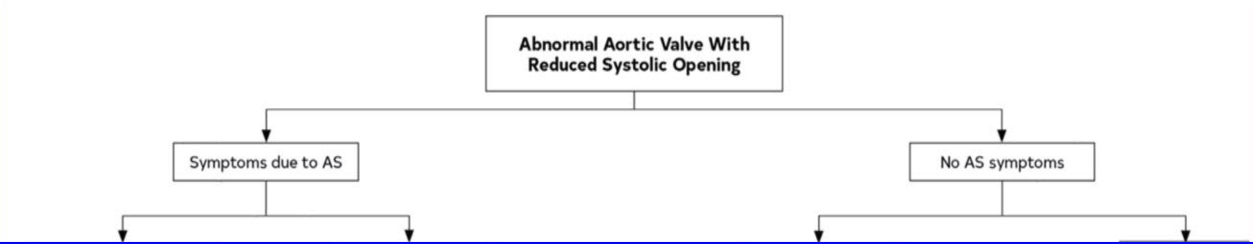
CLINICAL PRACTICE GUIDELINE: FULL TEXT

2020 ACC/AHA Guideline for the Management of Patients With Valvular Heart Disease

A Report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines

Developed in collaboration with and endorsed by the American Association for Thoracic Surgery, American Society of Echocardiography, Society for Cardiovascular Angiography and Interventions, Society of Cardiovascular Anesthesiologists, and Society of Thoracic Surgeons

FIGURE 2 Timing of intervention for AS



COR	LOE	RECOMMENDATIONS
2a	B-NR	1. In asymptomatic patients with severe AS (Stage C1), exercise testing is reasonable to assess physiological changes with exercise and to confirm the absence of symptoms (1-4).

2a	B-NR	6. In apparently asymptomatic patients with severe AS (Stage C1) and low surgical risk, AVR is reasonable when an exercise test demonstrates decreased exercise tolerance (normalized for age and sex) or a fall in systolic blood pressure of ≥10 mm Hg from baseline to peak exercise.[13,28–30]

surgical aortic valve replacement; SVI, stroke volume index; TAVI, transcatheter aortic valve implantation; TAVR, transcatheter aortic valve replacement; and V_{max}, maximum velocity.

2.3.5. Diagnostic Testing: Exercise Testing

In a subset of patients, exercise stress testing will be of additional value in determining optimal therapy. Because of the slow, insidious rate of progression of many valve lesions, patients may deny symptoms as they gradually

Exercise echocardiography may identify the cardiac origin of dyspnoea. The prognostic impact has been shown mainly for aortic stenosis and mitral regurgitation.[9]

capacity and blood pressure response) is of prognostic value in patients with asymptomatic valve disease and provides further information about the timing of a potential intervention (3-11). It is important that exercise

Stress Testing in Asymptomatic Aortic Stenosis

Circulation. 2017;135:1956–1976. DOI: 10.1161/CIRCULATIONAHA.116.025457

ABSTRACT: Aortic stenosis is 1 of the most common heart valve diseases among adults. When symptoms develop, prognosis is poor, and current guidelines recommend prompt aortic valve replacement. Depending of the severity of the aortic stenosis and the presence of concomitant heart disease and medical comorbidities, stress testing represents a reasonable strategy to help better risk stratify asymptomatic patients. The present report provides a comprehensive review of the current available data on stress testing in aortic stenosis and subsequently summarizes its potential for guiding the optimal timing of aortic valve replacement.

Björn Redfors, MD, PhD
Philippe Pibarot, DVM, PhD
Linda D. Gillam, MD, MPH
Daniel Burkhoff, MD, PhD
Jeroen J. Bax, MD, PhD
Brian R. Lindman, MD, MSCI
Robert O. Bonow, MD, MS
Patrick T. O'Gara, MD
Martin B. Leon, MD
Philippe Généreux, MD

Table 2. Abnormal Stress Test Among Large Observational Series of Aortic Stenosis

Studies	Type of Stress Test	Abnormal Stress Test	Aortic Stenosis Severity		
			Mild	Moderate	Severe
Treadmill stress test					
Otto et al[54]	Treadmill, Bruce	15% (N=104)*		×	×
Amato et al[55]	Treadmill, Ellestad	67% (44/66)			×
Das et al[56]†	Treadmill, modified Bruce	29% (19/65)‡		×	×
Das et al[57]	Treadmill, modified Bruce	37% (46/125)		×	×
Peidro et al[58]	Treadmill, modified Naughton	63% (67/106)		×	×
Lafitte et al[59]	Treadmill, modified Bruce	65% (39/60)			×
Rajani et al[60]	Treadmill, modified Bruce	26% (10/38)		×	×
Stress echocardiogram					
Takeda et al[28]	Dobutamine stress echo	27% (13/49)		×	×
Alborino et al[29]	Dobutamine stress echo	60% (18/30)		×	×
Lancellotti et al[30]	Exercise echocardiography, bicycle	38% (26/69)			×
Maréchaux et al[31]	Exercise echo, bicycle	48% (24/50)			×
Lancellotti et al[32]	Exercise echocardiography, bicycle	47% (60/128)			×
Maréchaux et al[33]	Exercise echocardiography, bicycle	27% (51/186)		×	×
Donal et al[34]	Exercise echocardiography, bicycle	34% (69/205)		×	×
Sonaglioni et al[35]§	Exercise echocardiography, bicycle	36% (32/90)	×	×	
Cardiopulmonary testing					
Olaf et al[61]†	Bicycle, cardiopulmonary testing	23% (9/39)		×	×
Dulgheru et al[62]	Treadmill, modified Bruce, cardiopulmonary testing	N=62		×	×
Levy et al[63]	Bicycle, cardiopulmonary testing	28% (12/43)			×
Dulgheru et al[64]	Treadmill, modified Bruce, cardiopulmonary testing	N=44		×	×
van Le et al[65]§	Bicycle, cardiopulmonary testing	19% (25/130)		×	×

Exercise Stress Echo in Aortic Stenosis

JACC: CARDIOVASCULAR IMAGING VOL. 11, NO. 6, 2018

PUBLISHED BY ELSEVIER

ORIGINAL RESEARCH

Prognostic Value of Exercise-Stress Echocardiography in Asymptomatic Patients With Aortic Valve Stenosis

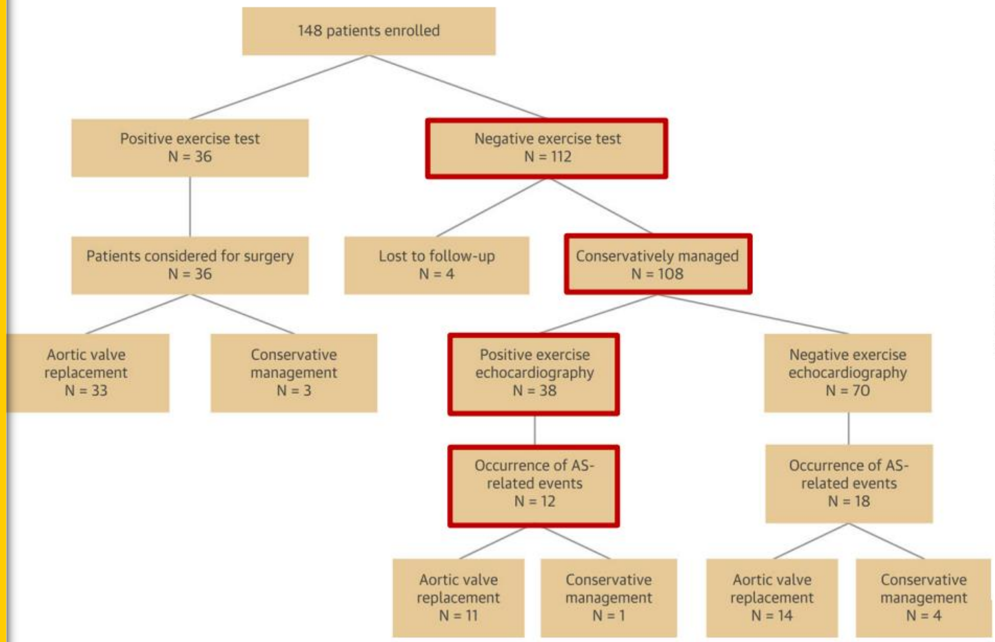
Coppelia Goublaire, MD,[a] Maria Melissopoulou, MD,[a] David Lobo, MD,[b] Naozumi Kubota, MD, PhD,[a] Constance Verdonk, MD,[a] Claire Cimadevilla, MD,[a] Isabelle Codogno, MS,[a] Eric Brochet, MD,[a] Alec Vahanian, MD, PhD,[a,c,d] David Messika-Zeitoun, MD, PhD[a,c,d]

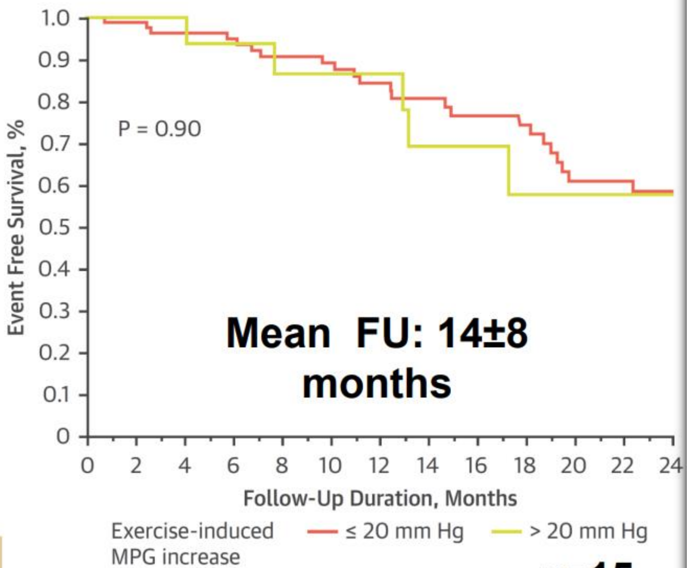
TABLE 1 Clinical, Hemodynamic, and Echocardiographic Characteristics of the Overall Population and According to Exercise Test Results

		Exercise Test			Negative Exercise Test		
	Overall (N = 148)	Positive Results (n = 36)	Negative Results (n = 112)	p Value	Positive Exercise Echocardiography Results (n = 38)	Negative Exercise Echocardiography Results (n = 70)	p Value
Male	110 (74)	24 (60)	86 (80)	0.02	28 (74)	58 (83)	0.33
Age, yrs	67 ± 13	67 ± 14	67 ± 12	0.79	67 ± 14	67 ± 11	0.65
History of coronary artery disease	30 (21)	6 (16)	24 (23)	0.34	9 (25)	15 (22)	0.81
Atrial fibrillation	18 (12)	6 (15)	12 (11)	0.4	5 (13)	7 (10)	0.75
Pacemaker	2 (1)	0 (0)	2 (2)	1	1 (3)	1 (2)	1
Chronic respiratory failure	8 (6)	1 (3)	7 (7)	0.68	3 (8)	4 (6)	0.69
Diabetes mellitus	20 (14)	7 (18)	13 (13)	0.28	5 (14)	8 (12)	0.76
BMI, kg/m^2	26 ± 4	24 ± 3	26 ± 4	0.001	25 ± 3	27 ± 5	0.12
Echocardiography at rest							
Pressure gradient, mm Hg	47 ± 13	52 ± 13	45 ± 13	0.0008	48 ± 15	43 ± 11	0.07
Peak velocity, m/s	4.3 ± 0.6	4.7 ± 0.5	4.2 ± 0.6	<0.0001	4.4 ± 0.7	4.1 ± 0.5	0.02
Aortic valve area, cm^2	0.97 ± 0.23	0.88 ± 0.17	1 ± 0.23	0.001	0.99 ± 0.26	1.01 ± 0.22	0.72
Indexed aortic valve area, cm^2/m^2	0.52 ± 0.11	0.49 ± 0.08	0.53 ± 0.12	0.03	0.53 ± 0.12	0.52 ± 0.11	0.7
Left ventricular hypertrophy	93 (70)	27 (73)	66 (69)	0.83	26 (79)	40 (64)	0.17
LVEF, %	70 ± 9	69 ± 8	70 ± 9	0.55	70 ± 9	70 ± 9	0.78
SPAP, mm Hg	34 ± 6	35 ± 5	34 ± 6	0.11	35 ± 6	33 ± 6	0.14
Exercise echocardiography							
Percent predicted heart rate	83 ± 11	84 ± 11	83 ± 12	0.64	84 ± 11	83 ± 12	0.56
Mean gradient at peak exercise, mm Hg	59 ± 18	67 ± 19	56 ± 17	0.0004	65 ± 20	52 ± 13	0.0005
Gradient variation, mm Hg	13 ± 10	15 ± 12	12 ± 9	0.05	16 ± 10	9 ± 7	0.0006
Gradient variation >20 mm Hg	23 (17)	8 (22)	15 (15)	0.18	15 (41)	0 (0)	NA
SPAP variation, mm Hg	21 ± 11	23 ± 11	20 ± 11	0.38	28 ± 8	14 ± 8	<0.0001
SPAP >60 mm Hg at peak exercise	37 (25)	12 (30)	25 (23)	0.19	25 (66)	0 (0)	NA

Values are n (%) or mean ± SD.
BMI = body mass index; LVEF = left ventricular ejection fraction; NA = not applicable; SPAP = systolic pulmonary artery pressure.

Prognostic Impact of Exercise Echo in AS

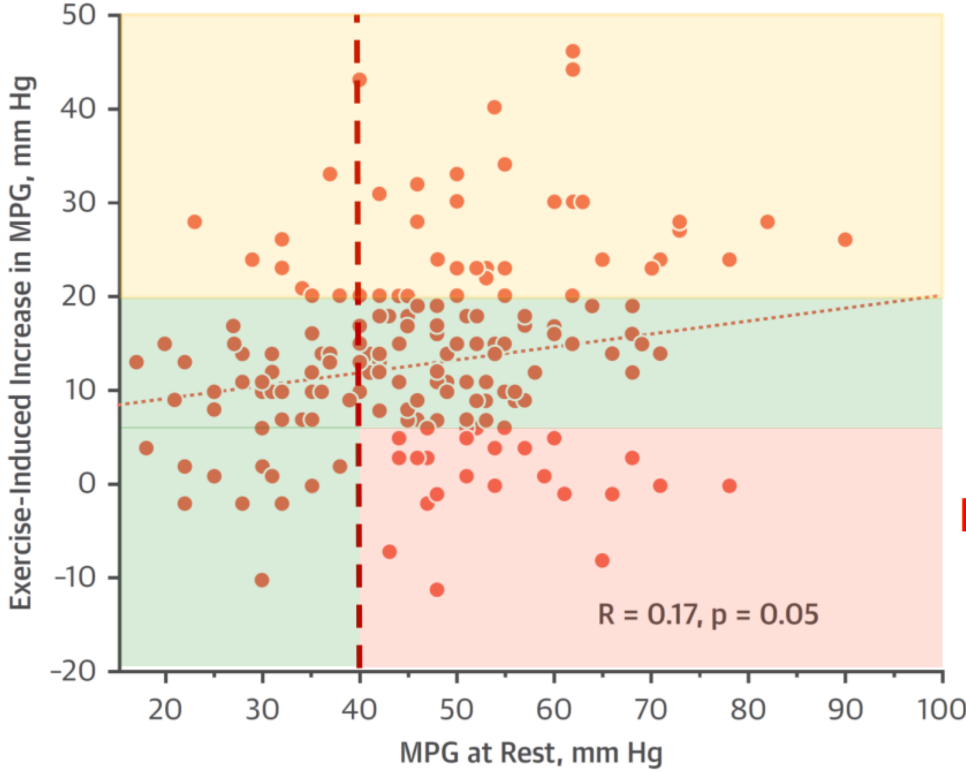




n=15

Goublaire et al. JACC CVI, 2017

Prognostic Impact of No changes in MPG?



Increase in MPG

Physiologic changes in MPG

Decrease in MPG

Goublaire et al. JACC CVI, 2017

Changes in Recommendations

Stress echocardiography-derived parameters in Asymptomatic patients

	2012	2017 / 2021
AS	**IIb C** Increase of mean pressure gradient with exercise by >20 mmHg.	Taken out

Level of evidence C	Consensus of opinion of the experts and/ or small studies, retrospective studies, registries.

Vahanian et al. EHJ, 2012
Baumgartner et al. EHJ, 2017

JOURNAL OF THE AMERICAN COLLEGE OF CARDIOLOGY
VOL. 7

PUBLISHED BY ELSEVIER

CLINICAL PRACTICE GUIDELINE: FULL TEXT

2020 ACC/AHA Guideline for the Management of Patients With Valvular Heart Disease

A Report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines

Developed in collaboration with and endorsed by the American Association for Thoracic Surgery, American Society of Echocardiography, Society for Cardiovascular Angiography and Interventions, Society of Cardiovascular Anesthesiologists, and Society of Thoracic Surgeons

2a	B-NR	6. In apparently asymptomatic patients with severe AS (Stage C1) and low surgical risk, AVR is reasonable when an exercise test demonstrates decreased exercise tolerance (normalized for age and sex) or a fall in systolic blood pressure of ≥10 mm Hg from baseline to peak exercise.[13,28–30]
2a	B-R	7. In asymptomatic patients with very severe AS (defined as an aortic velocity of ≥5 m/s) and low surgical risk, AVR is reasonable.[15,31–35]
2a	B-NR	8. In apparently asymptomatic patients with severe AS (Stage C1) and low surgical risk, AVR is reasonable when the serum B-type natriuretic peptide (BNP) level is >3 times normal.[32,36–38]
2a	B-NR	9. In asymptomatic patients with high-gradient severe AS (Stage C1) and low surgical risk, AVR is reasonable when serial testing shows an increase in aortic velocity ≥0.3 m/s per year.[39,40]
2b	B-NR	10. In asymptomatic patients with severe high-gradient AS (Stage C1) and a progressive decrease in LVEF on at least 3 serial imaging studies to <60%, AVR may be considered.[8–11,33]

ESC European Society of Cardiology

European Heart Journal (2022) **43**, 561–632
https://doi.org/10.1093/eurheartj/ehab395

ESC/EACTS GUIDELINES

2021 ESC/EACTS Guidelines for the management of valvular heart disease

Developed by the Task Force for the management of valvular heart disease of the European Society of Cardiology (ESC) and the European Association for Cardio-Thoracic Surgery (EACTS)

B) Asymptomatic patients with severe aortic stenosis		
Intervention is recommended in asymptomatic patients with severe aortic stenosis and systolic LV dysfunction (LVEF <50%) without another cause.[9,238,239]	I	B
Intervention is recommended in asymptomatic patients with severe aortic stenosis and demon- strable symptoms on exerci	I	C
Intervention should be cons matic patients with severe a systolic LV dysfunction (LVE another cause.[9,240,241]		
Intervention should be cons matic patients with severe a sustained fall in BP (>20 mm testing.		

Intervention should be considered in asympto- matic patients with LVEF >55% and a normal exercise test if the procedural risk is low and one of the following parameters is present: • Very severe aortic stenosis (mean gradient ≥60 mmHg or V_{max} >5 m/s).[9,242] • Severe valve calcification (ideally assessed by CCT) and V_{max} progression ≥0.3 m/s/ year.[164,189,243] • Markedly elevated BNP levels (>3× age- and sex-corrected normal range) confirmed by repeated measurements and without other explanation.[163,171]	IIa	B

JACC: CARDIOVASCULAR IMAGING
VOL. 12, NO. 1, 2019

ORIGINAL RESEARCH

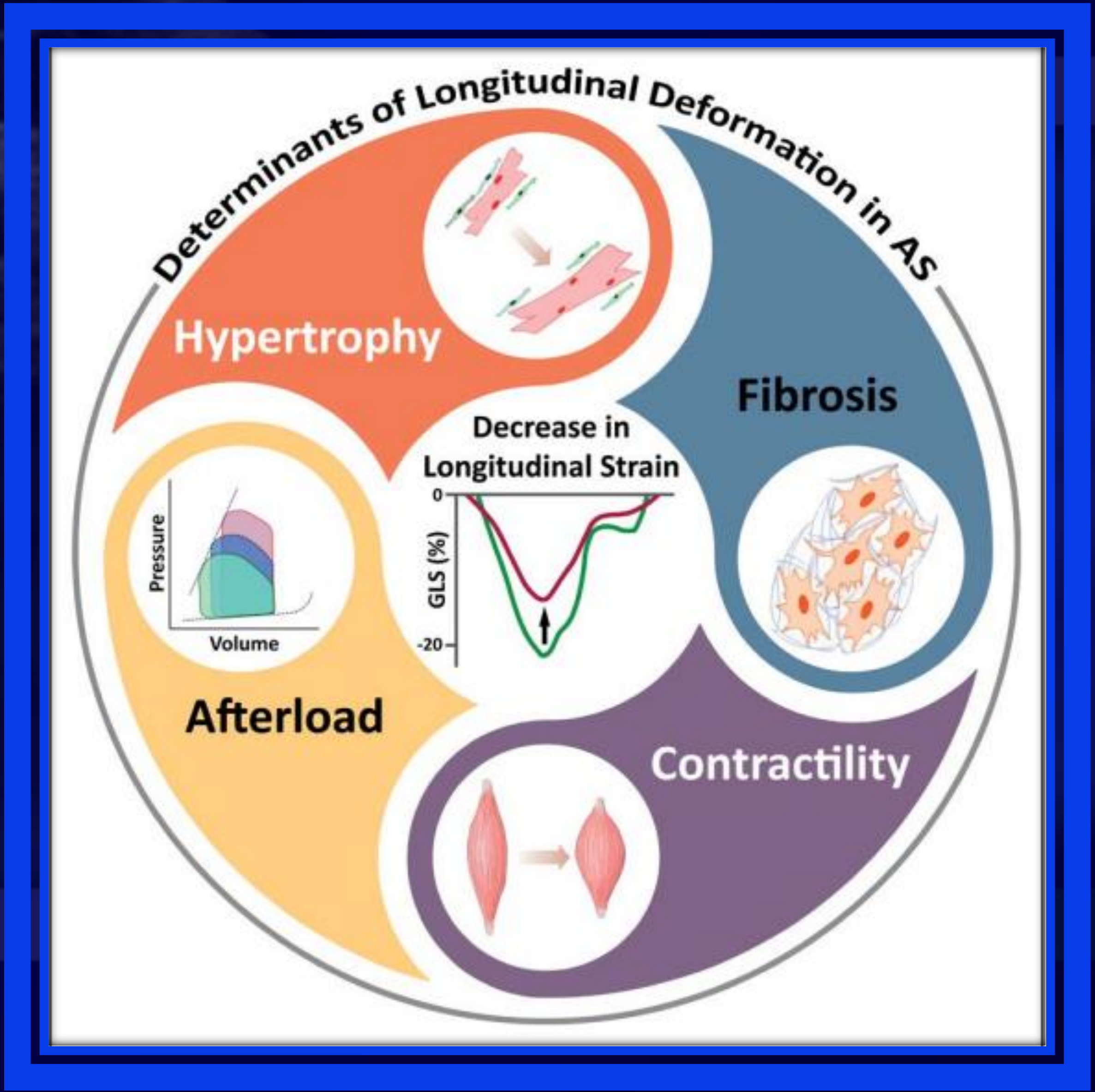
Distribution and Prognostic Significance of Left Ventricular Global Longitudinal Strain in Asymptomatic Significant Aortic Stenosis

An Individual Participant Data Meta-Analysis

TABLE 1 Description of Selected Studies

First Author (Ref. #)	Year	Design	Population Available (n = 1,067)	AVAi (cm^2/m^2)	Vendor	LVGLS Cutoff	Outcome
Lancellotti et al. (32)	2010	Prospective/bicentric	163	0.45 ± 0.09	GE	15.9%	MACE
Zito et al. (33)	2011	Prospective/monocentric	82	0.40 ± 0.10	GE	18%	MACE
Dahl et al. (18)	2012	Prospective/monocentric	65	0.46 ± 0.19	GE	Quartile	MACE
Kearney et al. (34)	2012	Prospective/monocentric	77	0.56 ± 0.23	GE	15%	All-cause death
Yingchoncharoen et al. (17)	2012	Prospective/monocentric	78	0.39 ± 0.13	Siemens	15%	MACE
Kusunose et al. (35)	2014	Retrospective/monocentric	137	0.42 ± 0.2	Siemens	Quartile	All-cause death
Sato et al. (16)	2014	Retrospective/multicentric	142	0.42 ± 0.11	GE	17%	MACE
Carstensen et al. (36)	2015	Prospective/multicentric	104	0.49 ± 0.13	GE	15%	MACE
Nagata et al. (37)	2015	Prospective/multicentric	102	0.42 ± 0.10	TomTec	17%	MACE
Salaun et al. (38)	2017	Prospective/multicentric	117	0.47 ± 0.11	GE	Tertile	All-cause death

AVAi = indexed aortic valve area; GE = General Electric; LVGLS = left ventricular global longitudinal strain; MACE = major adverse cardiac event.



Circ Cardiovasc Imaging. 2020;13:e010711. DOI: 10.1161/CIRCIMAGING.120.010711

FIGURE 2 **Distribution of LV Global Longitudinal Strain According to Studies**

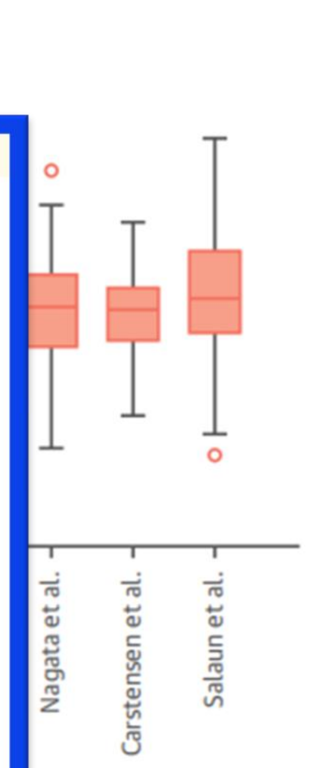
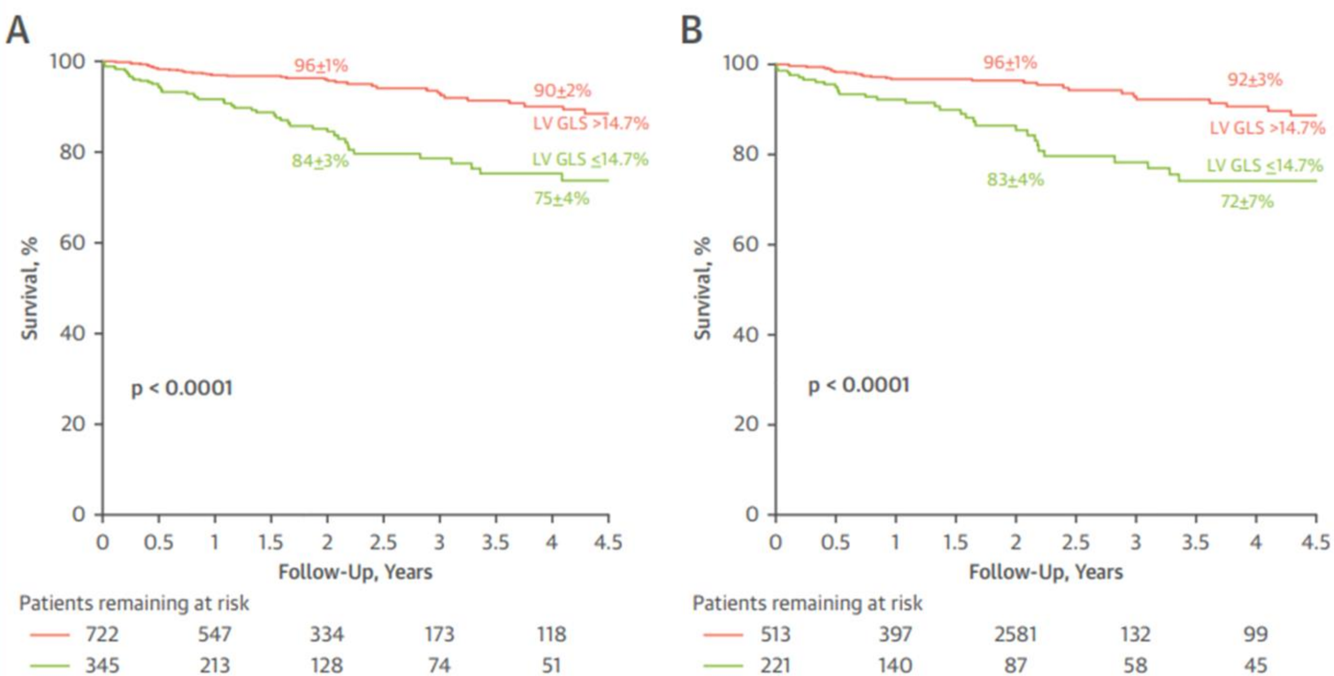


FIGURE 4 **Kaplan-Meier Survival Curves**



Kaplan-Meier survival curves stratified according to left ventricular global longitudinal strain in the whole cohort **(A)** and in patients with left ventricular ejection fraction ≥60% **(B)**. Percentage in the graphs are survival rate at 2- and 4-year follow-up. LVGLS = left ventricular global longitudinal strain.

JOURNAL OF THE AMERICAN COLLEGE OF CARDIOLOGY
VOL. 74, NO. 4, 2019

PUBLISHED BY ELSEVIER

Staging Cardiac Damage in Patients With Asymptomatic Aortic Valve Stenosis

Lionel Tastet, MS,[a] Christophe Tribouilloy, MD,[b] Sylvestre Maréchaux, MD,[c] E. Mara Vollema, MD,[d] Victoria Delgado, MD,[d] Erwan Salaun, MD,[a] Mylène Shen, MS,[a] Romain Capoulade, PhD,[e] Marie-Annick Clavel, DVM, PhD,[a] Marie Arsenault, MD,[a] Élisabeth Bédard, MD,[a] Mathieu Bernier, MD,[a] Jonathan Beaudoin, MD,[a] Jagat Narula, MD,[f] Patrizio Lancellotti, MD,[g] Jeroen J. Bax, MD,[d] Philippe Généreux, MD,[h,i,j] Philippe Pibarot, DVM, PhD[a]

CENTRAL ILLUSTRATION Association Between Cardiac Damage Staging Classification and Risk of Mortality

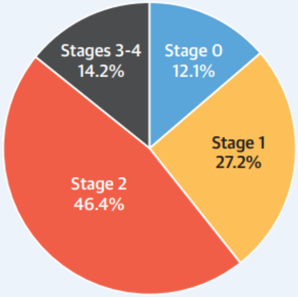
Staging Classification

Stages 3-4: Pulmonary or tricuspid valve damage, or RV damage or subclinical heart failure
- Pulmonary hypertension (SPAP ≥60 mm Hg)
- Tricuspid regurgitation (≥moderate)
- RV systolic dysfunction (≥moderate)
- Moderate to severe low-flow (stroke volume index <30 ml/m²)

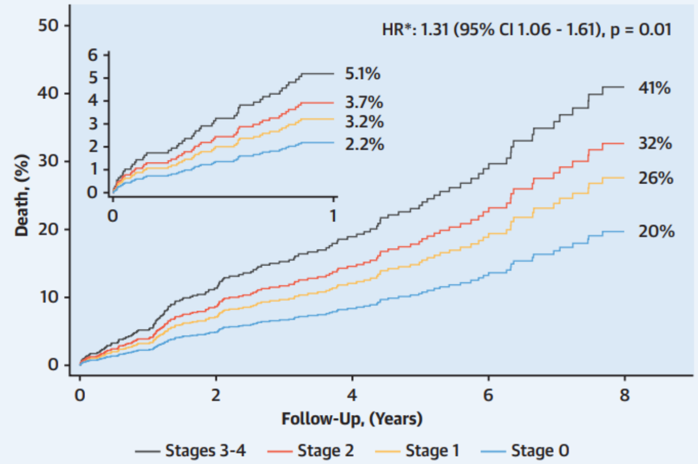
Stage 2: LA or mitral valve damage
- Left atrial enlargement (LA volume >34 ml/m²)
- Atrial fibrillation
- Mitral regurgitation (≥moderate)

Stage 1: LV damage
- LV hypertrophy (LV mass index >95 g/m² women; >115 g/m² men)
- Grade ≥ II LV diastolic dysfunction
- Impaired LV global longitudinal strain (≤|15%|)
- Subclinical LV systolic dysfunction (LVEF <60%)

Stage 0: No cardiac damage



All-Cause Mortality



Tastet, L. et al. J Am Coll Cardiol. 2019;74(4):550-63.

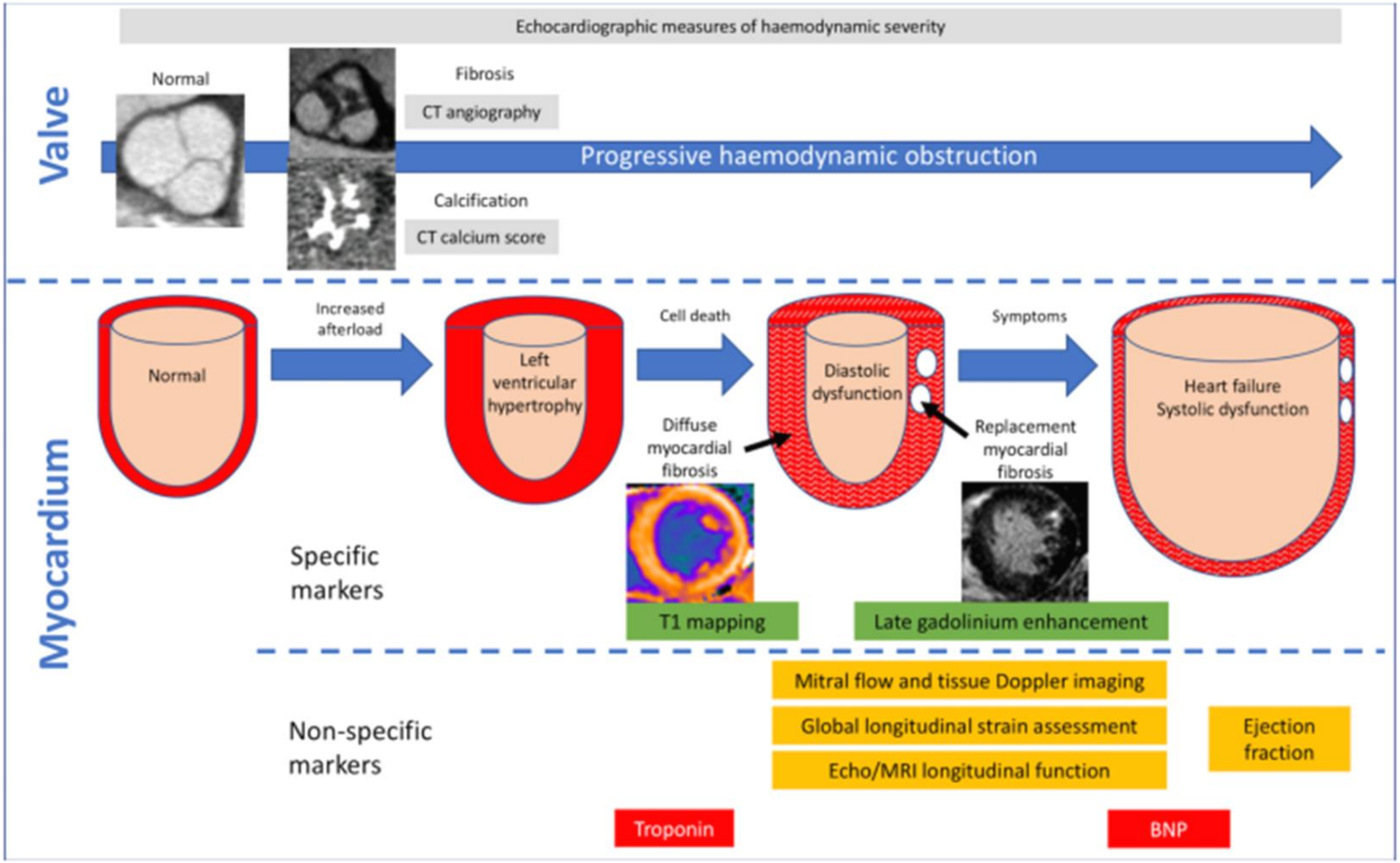
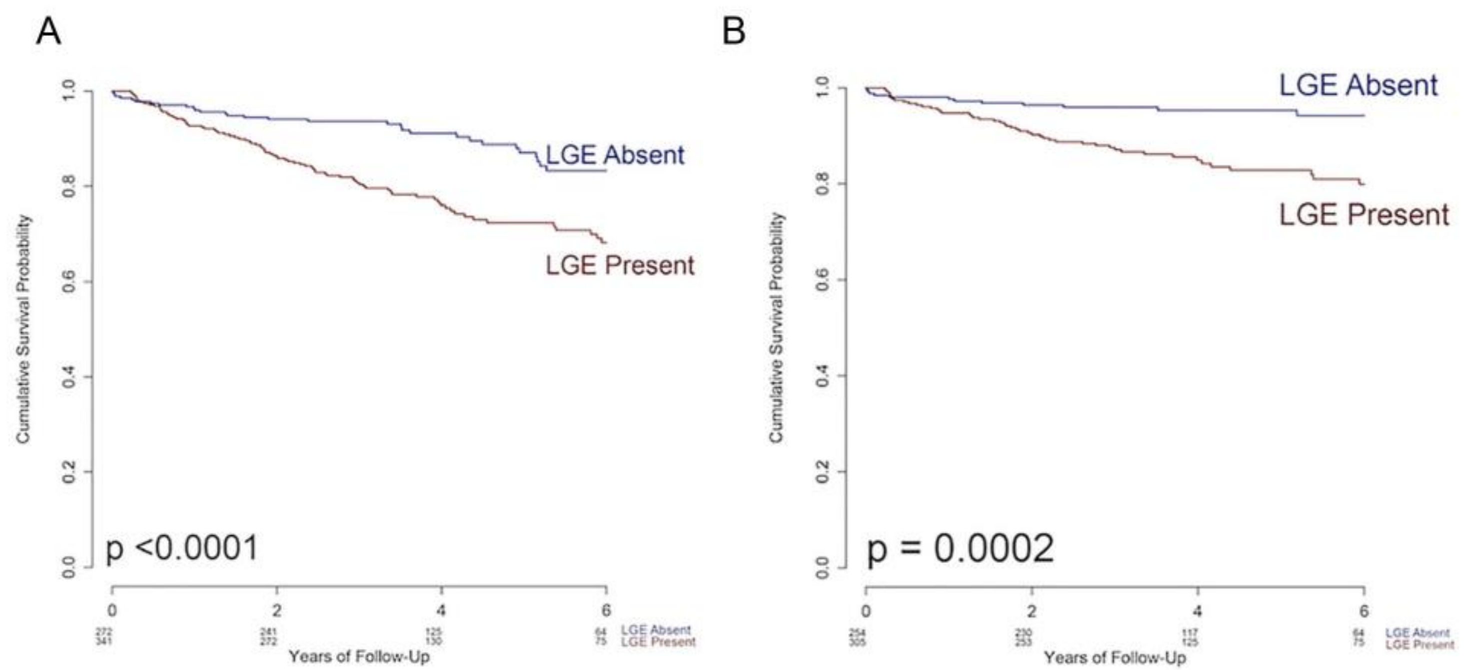

Echocardiographic measures of haemodynamic severity
Valve
Normal
Fibrosis
CT angiography
Progressive haemodynamic obstruction
Calcification
CT calcium score
Myocardium
Normal
Increased afterload
Left ventricular hypertrophy
Cell death
Diastolic dysfunction
Symptoms
Heart failure
Systolic dysfunction
Diffuse myocardial fibrosis
Replacement myocardial fibrosis
Specific markers
T1 mapping
Late gadolinium enhancement
Non-specific markers
Mitral flow and tissue Doppler imaging
Global longitudinal strain assessment
Echo/MRI longitudinal function
Ejection fraction
Troponin
BNP

Figure 2

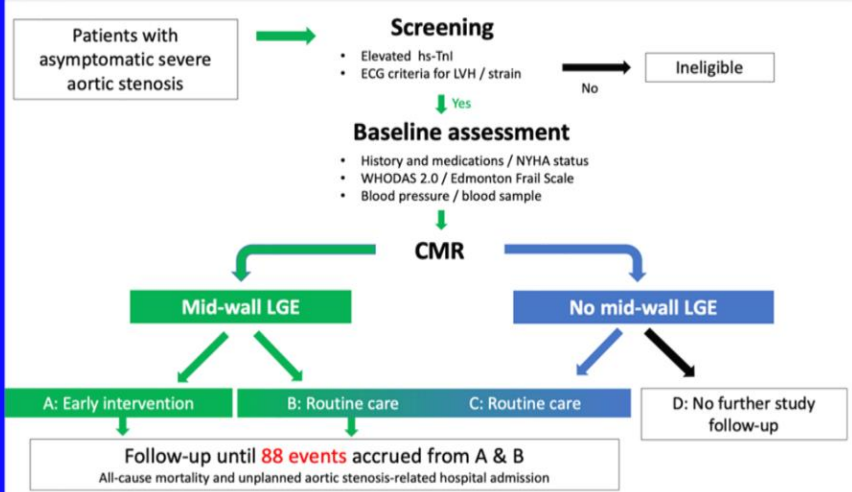


Late gadolinium enhancement and all-cause and cardiovascular mortality. Kaplan-Meier curves demonstrating the association between late gadolinium enhancement on cardiac magnetic resonance and all-cause (**A**) and cardiovascular (**B**) mortality in patients with severe AS. Figures from Musa et al.[21]

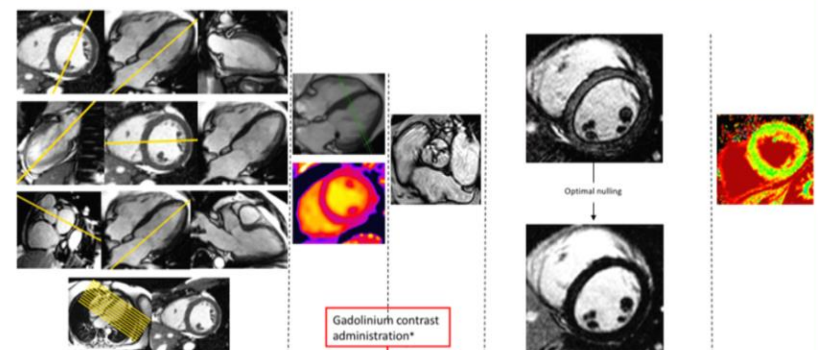
Rationale and design of the randomized, controlled Early Valve Replacement Guided by Biomarkers of Left Ventricular Decompensation in Asymptomatic Patients with Severe Aortic Stenosis (EVOLVED) trial

Rong Bing,[a,1] Russell J. Everett,[a,1] Christopher Tuck,[b] Scott Semple,[a] Steff Lewis,[b] Ronnie Harkess,[b] Nicholas L. Mills,[a] Thomas A. Treibel,[c] Sanjay Prasad,[d] John P. Greenwood,[e] Gerry P. McCann,[f] David E. Newby,[a] and Marc R. Dweck,[a]
Edinburgh, London, Leeds and Leicester, United Kingdom

Figure 3



tudy flowchart. The sample size has been calculated based on an event rate of 25.0% in the routine care arm and 13.4% in the early intervention rm over the first 2 years; 88 observed primary outcome events will give 90% power at 5% significance level.



	Positioning, localisers	LV cine	Native T1^	LV cine	LGE imaging	Post-contrast T1^
		4C, 3C, 2C, SAX	3-3-5 MOLLI	LVOT, valve	GRE-LGE SAX or PSIR, phase swap, long-axis	
Minutes	5	12-15	1-2	7	15	2

ardiac magnetic resonance protocol. The EVOLVED CMR scanning protocol with representative images from different sequences. * The preferred adolinium-based contrast agent and dose are gadobutrol 0.15 mmol/kg. ^ Pre- and postcontrast T1 imaging is optional. *LV*, left ventricular; *C*, 4-chamber; *3C*, 3-chamber; *2C*, 2-chamber; *SAX*, short axis; *MOLLI*, modified Look-Locker inversion recovery; *GRE*, gradient echo; *SIR*, phase sensitive inversion recovery.

Original research

Early surgical intervention versus conservative management of asymptomatic severe aortic stenosis: a systematic review and meta-analysis

Gonçalo Nuno Ferraz Costta,[1,2] João Fernandes Lopes Cardoso,[3] Bárbara Oliveiros,[2] Lino Gonçalves,[1,2] Rogerio Teixeira[1,2]

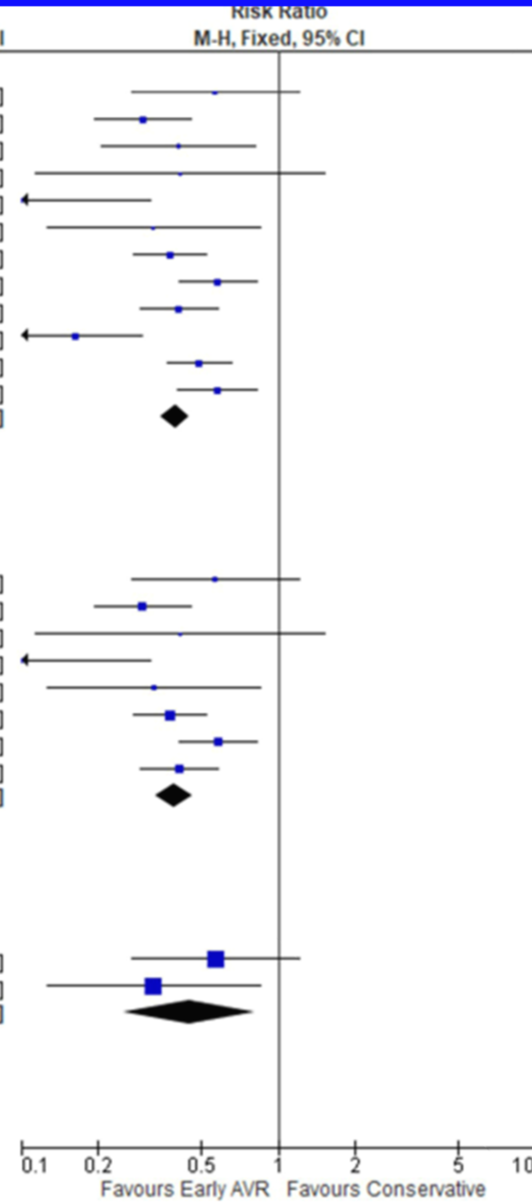
Costa GNF, *et al*. *Heart* 2023;**109**:314–321. doi:10.1136/heartjnl-2022-321411

Table 3 Study characteristics

Study	Design	Aortic stenosis criteria*	LVEF criteria	Stress test	Asymptomatic status†	Number of patients: Early AVR	Number of patients: WW
Banovic *et al*[36] (AVATAR)	Randomised clinical trial	AVA ≤1.0 cm^2 or maximum velocity ≥4.0 m/s or mean gradient ≥40 mm Hg	≥50%	Yes (100% patients)	Negative exercise testing	78	79
Çelik *et al*[35]	Retrospective cohort	AVA ≤1 cm^2 or jet maximal velocity Vmax ≥4.0 m/s	≥50%	Yes (NR)	No cardiac symptoms at baseline visit	4	3
Kang *et al*[9] (RECOVERY)	Randomised clinical trial	AVA ≤0.75 cm^2 and (jet maximum velocity ≥4.5 m/s or mean gradient ≥50 mm Hg)	≥50%	Yes (NR)	No cardiac symptoms at baseline visit OR negative exercise testing in non-specific symptoms	72	73
Campo *et al*[33]	Retrospective cohort	AVA ≤1.0 cm^2 or maximum velocity ≥4.0 m/s or mean gradient ≥40 mm Hg	None	Yes (30% patients)	No cardiac symptoms at index echocardiography	104	161
Kim *et al*[34]	Retrospective cohort	AVA ≤1.0 cm^2 or iAVA ≤0.6 cm^2/m^2 or maximum velocity ≥4.0 m/s or mean gradient ≥40 mm Hg	≥50%	No	No cardiac symptoms from electronic patient file review	221	247
Bohbot *et al*[32]	Retrospective cohort	Mean gradient ≥40 mm Hg	≥50%	Yes (64% patients)	No cardiac symptoms from electronic patient file review	192	247
Masri *et al* 2016[31]	Prospective cohort	iAVA ≤0.6 cm^2/m^2	≥50%	Yes (100% patients)	Negative exercise testing	341	192
Taniguchi *et al*[30]	Retrospective cohort	AVA <1.0 cm^2 or maximum velocity >4.0 m/s or mean gradient >40 mm Hg	None	No	No cardiac symptoms from electronic patient file review	291	291
Le Tourneau *et al*[29]	Retrospective cohort	Maximum velocity ≥4.0 m/s	None	No	No cardiac symptoms from electronic patient file review	160	514
Kang *et al*[28]	Prospective cohort	AVA ≤0.75 cm^2 and maximum velocity ≥4.5 m/s or mean gradient ≥50 mm Hg	≥50%	No	No cardiac symptoms from electronic patient file review	98	186
Pai *et al*[20]	Retrospective cohort	AVA ≤0.8 cm^2	None	No	No cardiac symptoms from electronic patient file review	99	239
Pellikka *et al*[6]	Retrospective cohort	Maximum velocity ≥4.0 m/s	None	No	No cardiac symptoms from electronic patient file review	145	180

*Aortic stenosis severity was assessed by cardiac Doppler echocardiography.
†Cardiac symptoms defined as absence of angina, dyspnoea or lightheadness/syncope attributable to aortic stenosis.
AVA, aortic valve area; AVR, aortic valve replacement; iAVA, indexed aortic valve area; LVEF, left ventricle ejection fraction; NR, not reported; Vmax, maximum velocity; WW, watchful waiting.

Study or Subgroup	Early AVR Events	Early AVR Total	Conservative Events	Conservative Total	Weight	Risk Ratio M-H, Fixed, 95% CI
1.1.1 All Studies						
Banovic 2021	9	78	16	79	2.4%	0.57 [0.27, 1.21]
Bohbt 2018	21	192	91	247	11.8%	0.30 [0.19, 0.46]
Campo 2019	9	104	34	161	3.9%	0.41 [0.21, 0.82]
Çelik 2021	1	3	4	4	0.6%	0.42 [0.11, 1.53]
Kang 2010	3	102	28	95	4.3%	0.10 [0.03, 0.32]
Kang 2020	5	73	15	72	2.2%	0.33 [0.13, 0.86]
Kim 2019	37	221	109	247	15.2%	0.38 [0.27, 0.53]
Le Tourneau 2010	30	160	165	514	11.6%	0.58 [0.41, 0.83]
Masri et al 2016	44	341	60	192	11.4%	0.41 [0.29, 0.58]
Pai 2006	10	99	148	239	12.8%	0.16 [0.09, 0.30]
Pellaki 2005	41	145	103	180	13.6%	0.49 [0.37, 0.66]
Tanigu chu 2015	40	291	69	291	10.2%	0.58 [0.41, 0.83]
Subtotal (95% CI)		**1809**		**2321**	**100.0%**	**0.40 [0.35, 0.45]**
Total events	250		842			
Heterogeneity: Chi² = 28.19, df = 11 (P = 0.003); I² = 61%						
Test for overall effect: Z = 13.94 (P < 0.00001)						
1.1.2 Preserved Ejection Fraction Criteria Only						
Banovic 2021	9	78	16	79	4.0%	0.57 [0.27, 1.21]
Bohbt 2018	21	192	91	247	19.8%	0.30 [0.19, 0.46]
Çelik 2021	1	3	4	4	1.0%	0.42 [0.11, 1.53]
Kang 2010	3	102	28	95	7.2%	0.10 [0.03, 0.32]
Kang 2020	5	73	15	72	3.8%	0.33 [0.13, 0.86]
Kim 2019	37	221	109	247	25.6%	0.38 [0.27, 0.53]
Le Tourneau 2010	30	160	165	514	19.5%	0.58 [0.41, 0.83]
Masri et al 2016	44	341	60	192	19.1%	0.41 [0.29, 0.58]
Subtotal (95% CI)		**1170**		**1450**	**100.0%**	**0.40 [0.33, 0.47]**
Total events	150		488			
Heterogeneity: Chi² = 13.16, df = 7 (P = 0.07); I² = 47%						
Test for overall effect: Z = 10.89 (P < 0.00001)						
1.1.3 Randomised Controlled Trials Only						
Banovic 2021	9	78	16	79	51.3%	0.57 [0.27, 1.21]
Kang 2020	5	73	15	72	48.7%	0.33 [0.13, 0.86]
Subtotal (95% CI)		**151**		**151**	**100.0%**	**0.45 [0.25, 0.82]**
Total events	14		31			
Heterogeneity: Chi² = 0.79, df = 1 (P = 0.38); I² = 0%						
Test for overall effect: Z = 2.64 (P = 0.008)						



Test for subgroup differences: Chi² = 0.19, df = 2 (P = 0.91), I² = 0%

Study or Subgroup	Early AVR Events	Early AVR Total	Conservative Events	Conservative Total	Weight	Odds Ratio M-H, Random, 95% CI
1.2.1 Heart Failure Hospitalization						
Banovic 2021	1	78	7	79	10.4%	0.13 [0.02, 1.11]
Kang 2020	0	73	8	72	5.8%	0.05 [0.00, 0.91]
Kim 2019	2	221	3	247	14.2%	0.74 [0.12, 4.49]
Tanigu chu 2015	10	291	50	291	69.6%	0.17 [0.09, 0.35]
Subtotal (95% CI)		**663**		**689**	**100.0%**	**0.19 [0.10, 0.39]**
Total events	13		68			
Heterogeneity: $Tau^2 = 0.06$; $Chi^2 = 3.23$, df = 3 (P = 0.36); $I^2 = 7\%$						
Test for overall effect: Z = 4.63 (P < 0.00001)						
1.2.2 Myocardial Infarction						
Banovic 2021	1	78	2	79	15.2%	0.50 [0.04, 5.63]
Kang 2020	0	73	1	72	8.6%	0.32 [0.01, 8.09]
Kim 2019	2	221	4	247	30.5%	0.55 [0.10, 3.06]
Tanigu chu 2015	3	291	6	291	45.7%	0.49 [0.12, 2.00]
Subtotal (95% CI)		**663**		**689**	**100.0%**	**0.49 [0.19, 1.27]**
Total events	6		13			
Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 0.08$, df = 3 (P = 0.99); $I^2 = 0\%$						
Test for overall effect: Z = 1.46 (P = 0.14)						
1.2.3 Stroke						
Banovic 2021	2	78	1	79	5.4%	2.05 [0.18, 23.11]
Kang 2010	1	73	3	72	6.1%	0.32 [0.03, 3.15]
Kim 2019	4	221	2	247	10.9%	2.26 [0.41, 12.45]
Tanigu chu 2015	23	291	18	291	77.6%	1.30 [0.69, 2.47]
Subtotal (95% CI)		**663**		**689**	**100.0%**	**1.30 [0.74, 2.29]**
Total events	30		24			
Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 1.99$, df = 3 (P = 0.57); $I^2 = 0\%$						
Test for overall effect: Z = 0.92 (P = 0.36)						
1.2.4 Cardiovascular Mortality						
Banovic 2021	7	78	7	79	13.8%	1.01 [0.34, 3.04]
Kang 2010	0	102	18	95	3.2%	0.02 [0.00, 0.34]
Kang 2020	1	73	11	72	5.5%	0.08 [0.01, 0.61]
Kim 2019	26	221	74	247	25.6%	0.31 [0.19, 0.51]
Pellaki 2005	35	352	82	270	26.9%	0.25 [0.16, 0.39]
Tanigu chu 2015	25	291	46	291	25.0%	0.50 [0.30, 0.84]
Subtotal (95% CI)		**1117**		**1054**	**100.0%**	**0.33 [0.19, 0.56]**
Total events	94		238			
Heterogeneity: $Tau^2 = 0.23$; $Chi^2 = 13.93$, df = 5 (P = 0.02); $I^2 = 64\%$						
Test for overall effect: Z = 4.05 (P < 0.0001)						

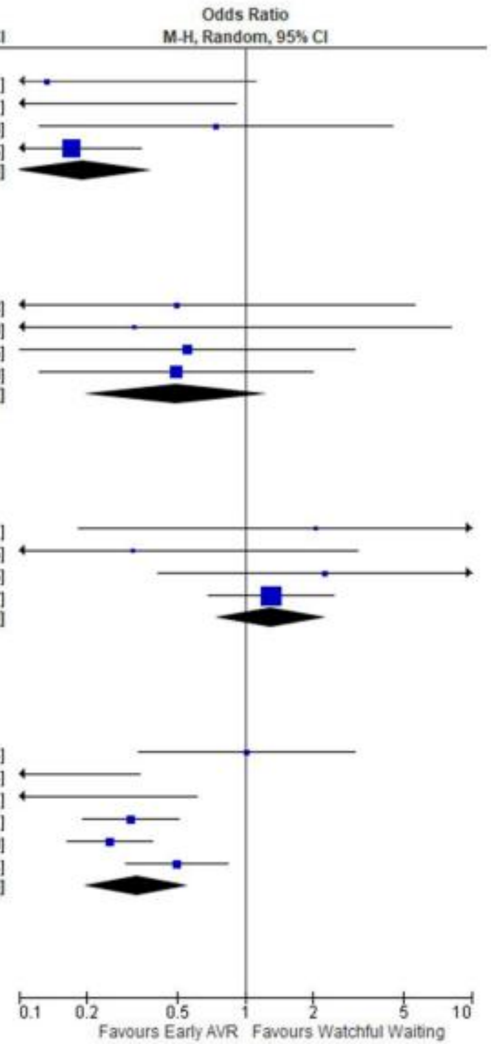


Figure 3 Forest plot of heart failure hospitalisation, myocardial infarction, stroke or cardiovascular mortality comparing early AVR strategy versus watchful waiting. AVR, aortic valve replacement; M-H, Mantel-Haenszel.

Although all these studies point in the same direction, their results **must be analyzed cautio**usly. All showed significant **heterogeneity** between studies; the meta-analyses are exposed to publication bias, but their main limitation is that their quality depends on the quality of the studies they included, many of which **were retrospective studies**. In addition, the **stress test was not universally performed** in the studies included, so there is no way to determine whether all patients were truly asymptomatic, and the **follow-up of patients in the conservative group was not protocolized**.

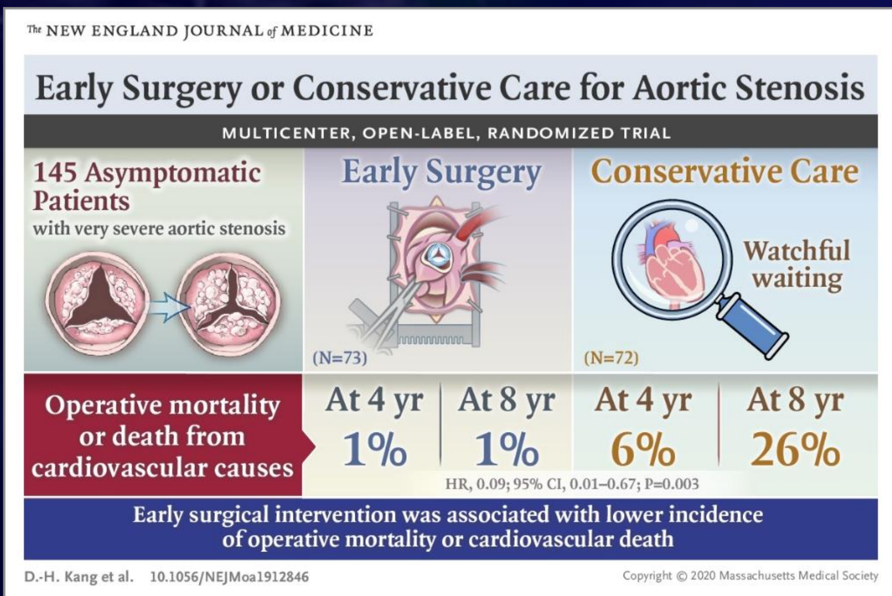
Thus, although the conservative strategy is often known as 'watchful waiting,' we have no evidence that, in these cases, the waiting was watchful.

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 JANUARY 9, 2020 VOL. 382 NO. 2

Early Surgery or Conservative Care for Asymptomatic Aortic Stenosis

Duk-Hyun Kang, M.D., Ph.D., Sung-Ji Park, M.D., Ph.D., Seung-Ah Lee, M.D., Sahmin Lee, M.D., Ph.D., Dae-Hee Kim, M.D., Ph.D., Hyung-Kwan Kim, M.D., Ph.D., Sung-Cheol Yun, Ph.D., Geu-Ru Hong, M.D., Ph.D., Jong-Min Song, M.D., Ph.D., Cheol-Hyun Chung, M.D., Ph.D., Jae-Kwan Song, M.D., Ph.D., Jae-Won Lee, M.D., Ph.D., and Seung-Woo Park, M.D., Ph.D.



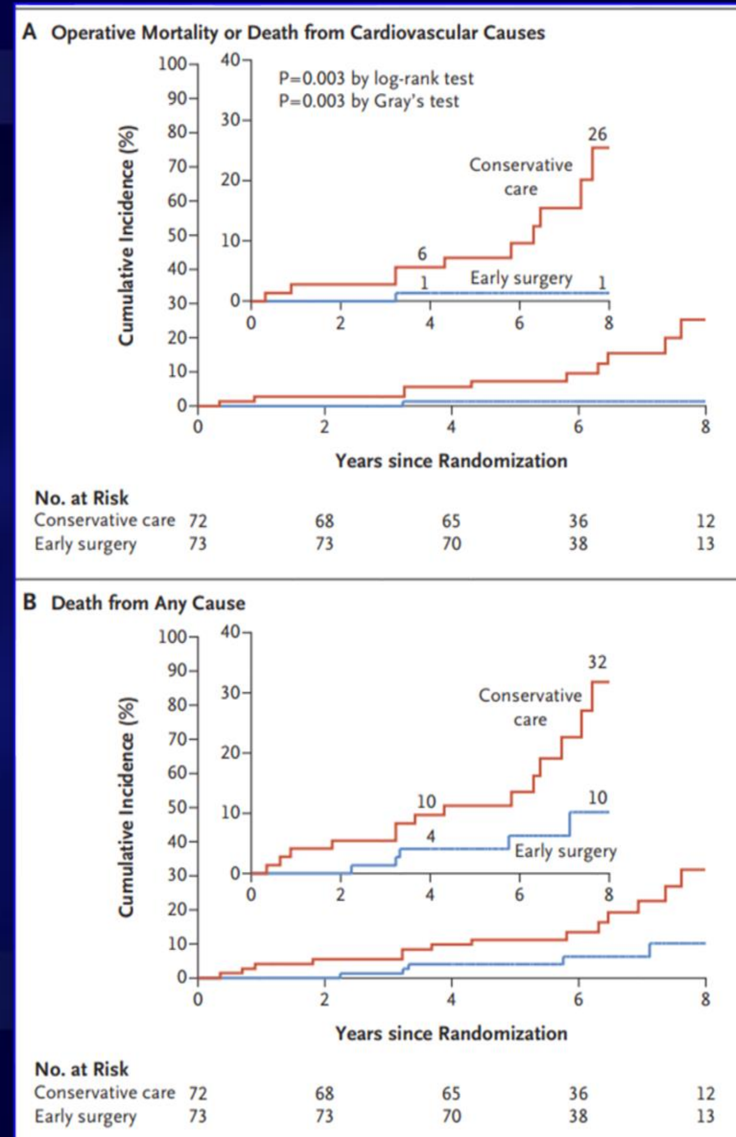


Figure 2. Time-to-Event Curves for the Primary Composite End Point and Death from Any Cause.

Although the surgical risk of these patients was low, there were zero operative deaths, which is likely a reflection of experienced operators/institutions.

Pts in the watchful waiting arm could go as long as 8 years without crossing over (only two cross-overs to surgery), despite having such severe aortic stenosis.

This cohort had a very high proportion of bicuspid aortic stenosis patients, which may be a partial reason for this.

Exercise testing was only selectively employed; thus, some patients could have "hidden" symptomatic aortic stenosis, which would have been unmasked with a stress test.

The EARLY-TAVR trial is looking to enroll a similar asymptomatic population – all patients are required to undergo exercise testing for this reason.
These results are not applicable to TAVR;

The RECOVERY trial randomized 145 patients with asymptomatic very severe AS to early surgery or conservative care [38]. The cardiovascular mortality rate after a median follow-up period of 6 years was 1% in the early surgery group and 15% in the conservative care group. Several aspects of that study deserve to be mentioned.

- **Patients >80 years of age were excluded**. The mean age was 64±9 years.
- **More than half the patients had a bicuspid aortic valve**, so this population differs considerably from what a real clinical scenario of severe AS represents nowadays [36]. Probably due to this selected population, operative mortality was zero, and the mortality in the follow-up period was also strikingly low (7% of all-cause mortality). These figures are far from the 5% and 15% reported in the observational studies.
- **The small number of deaths represents a statistical limitation** of the RECOVERY trial.
- The surgical outcomes reflect the surgical excellence of the participant centers, but the results may **not be extrapolated to less-experienced centers**.

It is also surprising that 22% of patients in the conservative arm never underwent surgery despite the long follow-up period. This reflects that patients with asymptomatic AS are a heterogeneous population for whom a one-size-fits-all strategy may not be the best approach.

Circulation

ORIGINAL RESEARCH ARTICLE

Aortic Valve Replacement Versus Conservative Treatment in Asymptomatic Severe Aortic Stenosis: The AVATAR Trial

Marko Banovic, MD, PhD; Svetozar Putnik, MD, PhD; Martin Penicka, MD, PhD; Gheorghe Doros, PhD; Marek A. Deja, MD, PhD; Radka Kockova, MD, PhD; Martin Kotrc, MD; Sigita Glaveckaite, MD, PhD; Hrvoje Gasparovic, MD, PhD; Nikola Pavlovic, MD, PhD; Lazar Velicki, MD, PhD; Stefano Salizzoni, MD, PhD; Wojtek Wojakowski, MD, PhD; Guy Van Camp, MD, PhD; Serge D. Nikolic, PhD; Bernard Iung, MD; Jozef Bartunek, MD, PhD; on behalf of the AVATAR Trial Investigators*

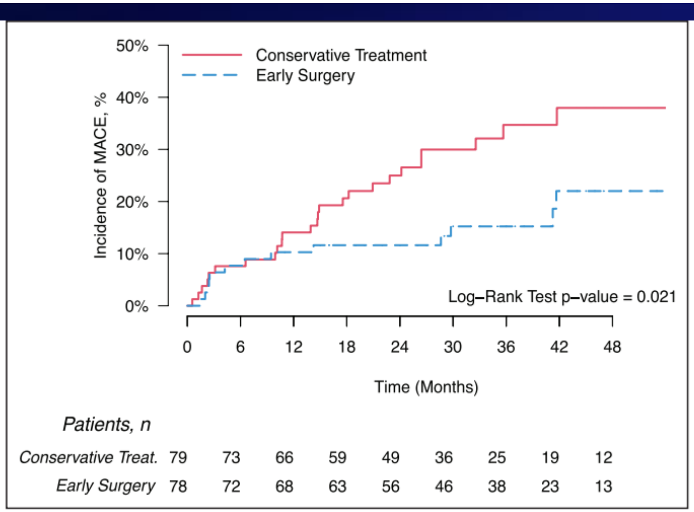


Figure 2. Kaplan-Meier cumulative incidence rates estimates of the primary composite end point as analyzed by intention-to-treat analysis.
MACE indicates major adverse cardiovascular event; and Treat., treatment.

Table 3. Primary and Secondary Outcomes

Primary outcome: Time to first MACE			
Outcome	Early surgery group 3-y KM estimate (%)	Conservative treatment group 3-y KM estimate (%)	Hazard ratio (95% CI)
Primary end point	15.22%	34.70%	0.46 (0.23–0.90)
Time-to-event secondary outcomes			
All cause death rate	9.54%	20.11%	0.56 (0.24–1.27)
HF hospitalization	4.01%	12.94%	0.32 (0.08–1.19)
SAE	17.31%	27.50%	0.57 (0.28–1.12)
Cardiovascular death	9.54%	9.09%	1.02 (0.40–2.58)
Binary secondary outcomes	Early surgery group n/N (%)	Conservative treatment group n/N (%)	Odds ratio (95% CI)
Intraoperative or 30-day mortality*	1/72 (1.4%)	1/25 (4%)	0.34 (0.02–5.61)
Repeated MACE	3/78 (3.8%)	7/79 (8.9%)	0.41 (0.10–1.65)
Thromboembolic complication	2/78 (2.6%)	2/79 (2.5%)	1.03 (0.14–7.67)
Major bleeding complications	4/78 (5.1%)	1/79 (1.3%)	3.52 (0.37–32.68)

HF indicates heart failure; IQR, interquartile range; MACE, major adverse cardiovascular event; and SAE, serious adverse event.

*Mortality counted in all patients undergoing with valve surgery in early surgery (n=72) and in the conservative group (n=25). For other binary secondary events, the denominator is 78 in the early surgery group and 79 in the conservative treatment group.

Valvular heart disease

Management of asymptomatic severe aortic stenosis: a systematic review and meta-analysis

Vasiliki Tsampasian ,[1,2] Ciaran Grafton-Clarke,[1,2]
Abraham Edgar Gracia Ramos ,[3,4] George Asimakopoulos,[5,6] Pankaj Garg,[1,2]
Sanjay Prasad,[5,6] Liam Ring,[7] Gerry P McCann ,[8,9] James Rudd,[10]
Marc R Dweck,[11] Vassilios S Vassiliou[1,2]

Table 1 Main characteristics of the two randomised controlled trials

	AVATAR	RECOVERY
Trial design	Multinational, randomised, controlled, parallel-group, event-driven	Multicentre, randomised, controlled, parallel-group, open-label
Recruitment sites	Nine medical centres, seven European Union countries	Four medical centres, one country
Recruitment period	June 2015–September 2020	July 2010–April 2015
Follow-up period (median)	32 months	73 months
Inclusion criteria	▶ Asymptomatic patients. ▶ Severe AS (AVA <1 cm^2, Vmax >4 m/s or MG >40	▶ Asymptomatic patients. ▶ Very severe AS (AVA <0.75 cm^2, Vmax >4.5 m/s or MG >50 mm
Aetiology of aortic stenosis	▶ Degenerative valvular disease: 133 patients (84.7%). ▶ Bicuspid aortic valve: 22 patients (14.0%). ▶ Rheumatic valvular disease: 2 patients (1.3%).	▶ Degenerative valvular disease: 48 (33%). ▶ Bicuspid aortic valve: 88 patients (61%). ▶ Rheumatic valvular disease: 9 patients (6%).
Primary endpoints	▶ All-cause mortality or major adverse cardiovascular events comprised all-cause death, acute myocardial infarction, stroke and unplanned heart failure hospitalisation needing intravenous treatment with diuretics or inotropes.	▶ Operative mortality (death during or within 30 days after surgery) or death from cardiovascular causes during the entire follow-up period.

Data are presented as available by the relevant published studies.
AS, aortic stenosis; AVA, aortic valve area; AVATAR, Aortic Valve Replacement versus Conservative Treatment in Asymptomatic Severe Aortic Stenosis; LVEF, left ventricular ejection fraction; MG, mean gradient; RECOVERY, Randomized Comparison of Early Surgery versus Conventional Treatment in Very Severe Aortic Stenosis; Vmax, maximal velocity across the aortic valve.

Study or Subgroup	log[Hazard Ratio]	SE	Favours early surgery Total	Favours conservative Tx Total	Weight	Hazard Ratio IV, Random, 95% CI
AVATAR	-0.5798	0.4323	78	79	58.8%	0.56 [0.24, 1.31]
RECOVERY	-1.1087	0.5161	73	72	41.2%	0.33 [0.12, 0.91]
Total (95% CI)			**151**	**151**	**100.0%**	**0.45 [0.24, 0.86]**

Heterogeneity: Tau² = 0.00; Chi² = 0.62, df = 1 (P = 0.43); I² = 0%
Test for overall effect: Z = 2.41 (P = 0.02)

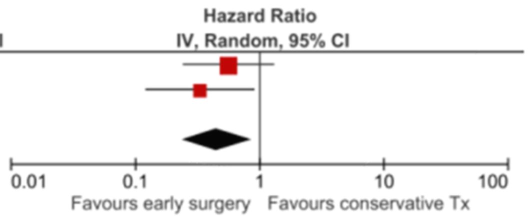


Figure 1 Meta-analysis of AVATAR and RECOVERY trials focusing on all-cause mortality: the effect of early intervention on all-cause mortality. AVATAR, Aortic Valve Replacement versus Conservative Treatment in Asymptomatic Severe Aortic Stenosis. RECOVERY, Randomized Comparison of Early Surgery versus Conventional Treatment in Very Severe Aortic Stenosis; IV, interval variable; Tx, treatment.

Table 4 Main study characteristics of the ongoing randomised controlled trials

	EASY-AS[38]	EARLY TAVR[39]	DANAVR[40]	EVoLVeD[41]
Identifier	NCT04204915	NCT03042104	NCT03972644	NCT03094143
Estimated enrolment	2844 participants	900 participants	1700 participants	1000 participants
Estimated completion date	October 2029	March 2024	September 2029	October 2024
Intervention	AVR	TAVR	SAVR or TAVR	SAVR or TAVR (participants will be randomised based on the presence or absence of fibrosis on CMR)
Primary outcomes	Cardiovascular death and hospitalisation for heart failure	All-cause death, all stroke and unplanned cardiovascular hospitalisation	All-cause mortality	All-cause mortality or unplanned aortic stenosis-related hospitalisation
Key inclusion criteria	▶ Asymptomatic severe AS. ▶ Age >18 years. ▶ LVEF ≥50%.	▶ Asymptomatic severe AS. ▶ Age ≥65 years. ▶ LVEF ≥50%. ▶ STS risk score <10.	▶ Asymptomatic severe AS. ▶ Age ≥18 and ≤85 years. ▶ LVEF ≥50%.	▶ Asymptomatic severe AS. ▶ Age >18 years. ▶ LVEF ≥50% on CMR.

AS, aortic stenosis; AVR, aortic valve replacement; CMR, cardiac magnetic resonance; DANAVR, Danish National Randomized Study on Early Aortic Valve Replacement in Patients with Asymptomatic Severe Aortic Stenosis; EARLY-TAVR, Evaluation of TAVR Compared to Surveillance for Patients with Asymptomatic Severe Aortic Stenosis; EASY-AS, Early Valve Replacement in Severe Asymptomatic Aortic Stenosis Study; EVoLVeD, Early Valve Replacement Guided by Biomarkers of LV Decompensation in Asymptomatic Patients with Severe AS; LVEF, left ventricular ejection fraction; SAVR, surgical aortic valve replacement; STS, Society of Thoracic Surgeons; TAVR, transcatheter aortic valve replacement.

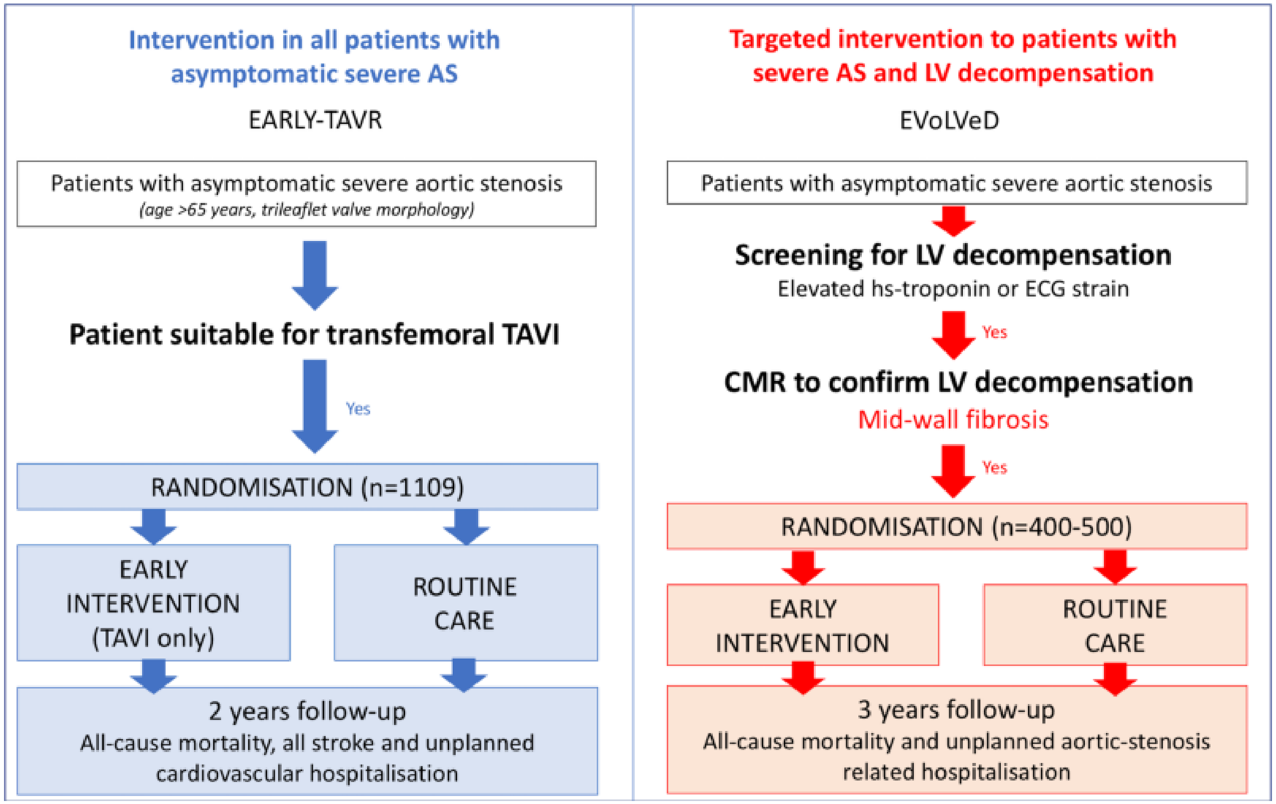


Figure 3 Comparison of EARLY-TAVR and EVoLVeD randomised controlled trial designs. Currently, recruiting randomised controlled trials generally fall into two groups: those investigating valve intervention in all asymptomatic patients with severe AS (eg, EARLY-TAVR) and those looking to target intervention based on measures of left ventricular decompensation (eg, EVoLVeD). AS, aortic stenosis; CMR, cardiac magnetic resonance; EARLY-TAVR, Evaluation of Transcatheter Aortic Valve Replacement Compared to SurveilLance for Patients with AsYmptomatic Severe Aortic Stenosis; EVoLVeD, Early Valve Replacement Guided by Biomarkers of Left Ventricular Decompensation in Asymptomatic Patients with Severe AS; hs, high-sensitivity; LV, left ventricular; TAVI, transcatheter aortic valve insertion.

Timing of Intervention in Aortic Stenosis

Patrizio Lancellotti, M.D., Ph.D., and Mani A. Vannan, M.B., B.S.

Key messages

- Aortic stenosis is a disease of both the valve and the myocardium, characterised by fibrosis and calcification of valve leaflets, progressive left ventricular hypertrophy and myocardial fibrosis.
- Although no randomised controlled trial data exist, current clinical guidelines recommend valve intervention when severe aortic stenosis is accompanied by evidence of left ventricular decompensation.
- Timing of valve intervention is crucial. Too early and the patient will be unnecessarily exposed to risks of intervention and prosthetic valve complications; too late and irreversible myocardial damage can lead to persistent symptoms and risk of adverse events. Ideally valve replacement would be performed just as left ventricular decompensation is starting to develop.
- Improved surgical methods and perioperative care, as well as transcatheter aortic valve implantation techniques have resulted in major reductions in procedural risk. As such, earlier valve intervention in asymptomatic patients could be contemplated, and randomised controlled trials are underway that will help inform our future management.

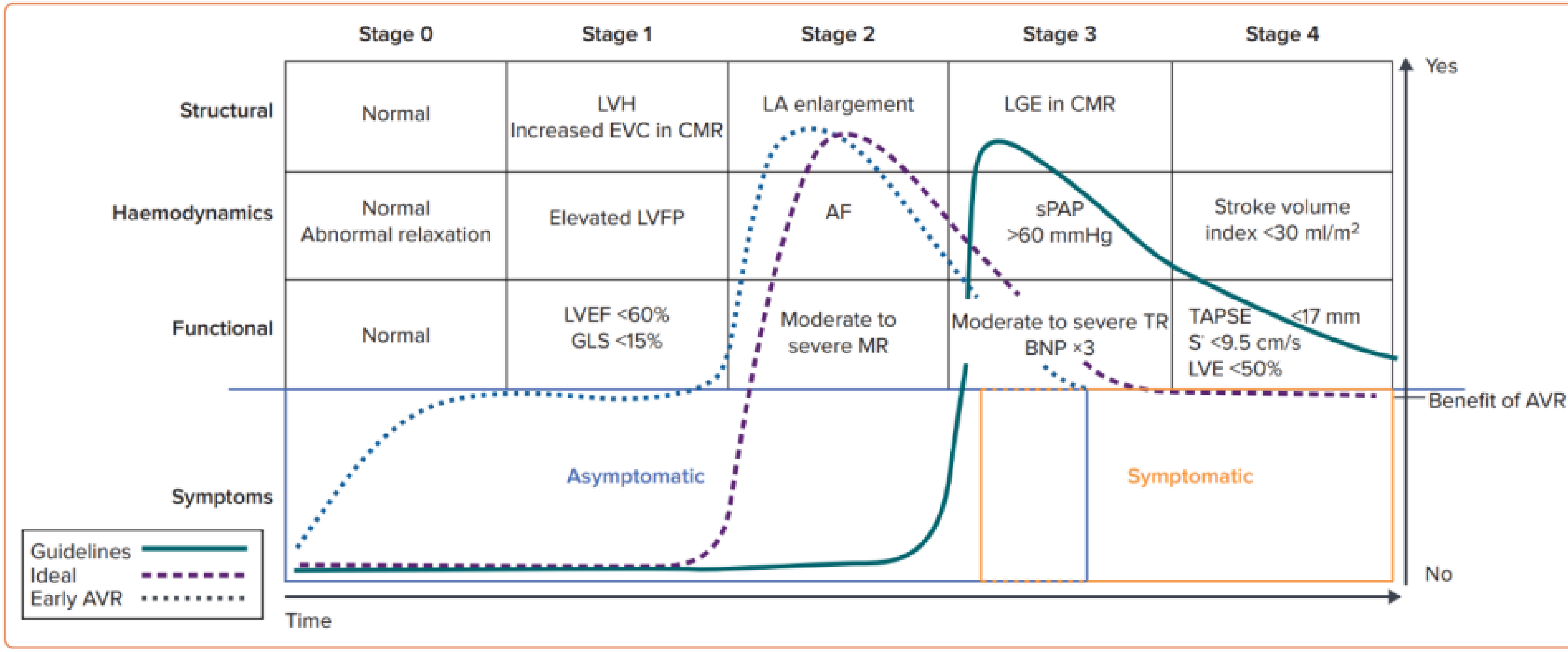
Severe Aortic Stenosis	Disease Consequences or Cardiac Damage: Hemodynamic Changes	Disease Consequences or Cardiac Damage: Structural Changes	Disease Consequences or Cardiac Damage: Symptoms
Stage 0–1: Compensated Disease	Normal LVFP Abnormal LV relaxation	LVH (LV mass >115 g/m^2 in men; >95 g/m^2 in women)	Asymptomatic
Stage 1–2: Subclinical LV Dysfunction	Elevated LVFP Moderate-to-severe mitral regurgitation	GLS <15% LVEF <60% Increased cardiac MRI ECV LA volume >34 ml/m^2	Asymptomatic
	Markedly elevated BNP level		Asymptomatic
Stage 3–4: Decompensated Disease	SVI <30 ml/m^2 Moderate-to-severe tricuspid regurgitation PSAP ≥60 mm Hg	Cardiac MRI LGE LVEF <50% RV dysfunction (TAPSE <17 mm, tricuspid annular systolic velocity <9.5 cm/sec)	Symptomatic

Disease Progression

Management Options

- Wait for symptoms
- Active follow-up at clinic for patients with valvular disease
- Early aortic-valve replacement

Figure 1. An Approach to Staging in Severe Aortic Stenosis.



Stage 0
Stage 1
Stage 2
Stage 3
Stage 4
Structural
Haemodynamics
Functional
Symptoms
Normal
LVH
Increased EVC in CMR
LA enlargement
LGE in CMR
Normal
Abnormal relaxation
Elevated LVFP
AF
sPAP
>60 mmHg
Stroke volume
index <30 ml/m²
Normal
LVEF <60%
GLS <15%
Moderate to
severe MR
Moderate to severe TR
BNP ×3
TAPSE <17 mm
S' <9.5 cm/s
LVE <50%
Yes
No
Benefit of AVR
Asymptomatic
Symptomatic
Guidelines
Ideal
Early AVR
Time

Cases Study

68 y/o man

- History of known calcific AS (for the past 5 years)
- Mild HTN
- No evidence for obstructive CAD
- No angina, syncope or dyspnea
- LVEF : 63%
- AVA 0.7 cm2; Gradients 73/46 mmHg (max/mean)

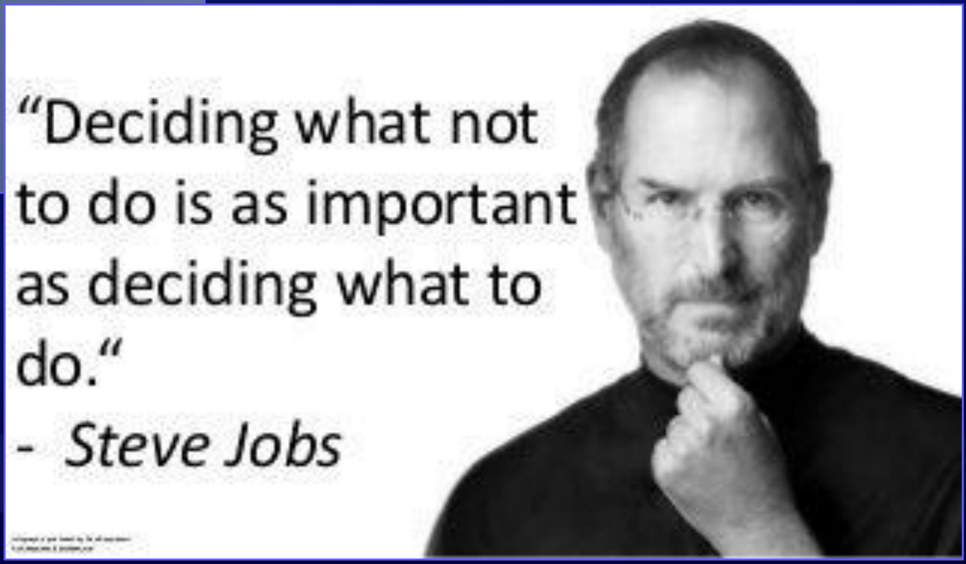
72 y/o woman

- History of known calcific AS (for the past 8 years)
- HTN, NIDDM, HLP
- Obese, OSA (Bipap at night)
- No angina, syncope or dyspnea
- LVEF : 63%
- AVA 0.7 cm2; Gradients 73/46 mmHg (max/mean)

Take Home Message

- AS is a disease of the valve and the myocardium
- Timing of intervention is crucial in Asymptomatic AS
- Lack of symptoms doesn't rule need for intervention
- Perform stress test, comprehensive TTE, GLS
- Further Imaging modalities: CCT ; CMR
- Take BNP !!
- Not all asymptomatic patients are the same
- The decision is tailor made for each patient


YOUR WAY
MY WAY


“Deciding what not to do is as important as deciding what to do.“
- Steve Jobs

To Be Continued....