Debate: How Should we Manage “at risk” Moderate AS?

Conservative Management

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FACULTY DISCLOSURE

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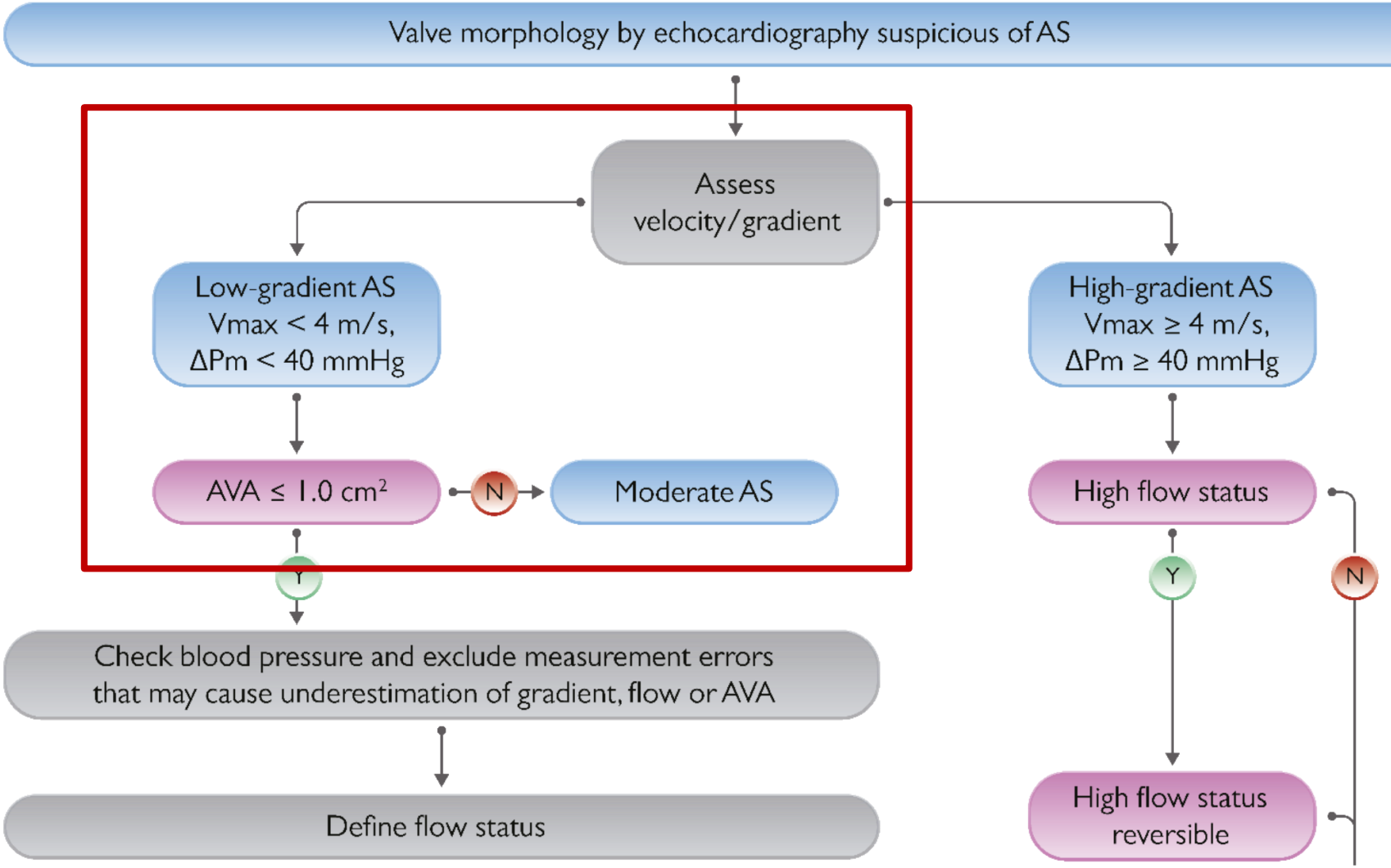
I have no financial relationships to disclose

Quantification of Aortic Stenosis

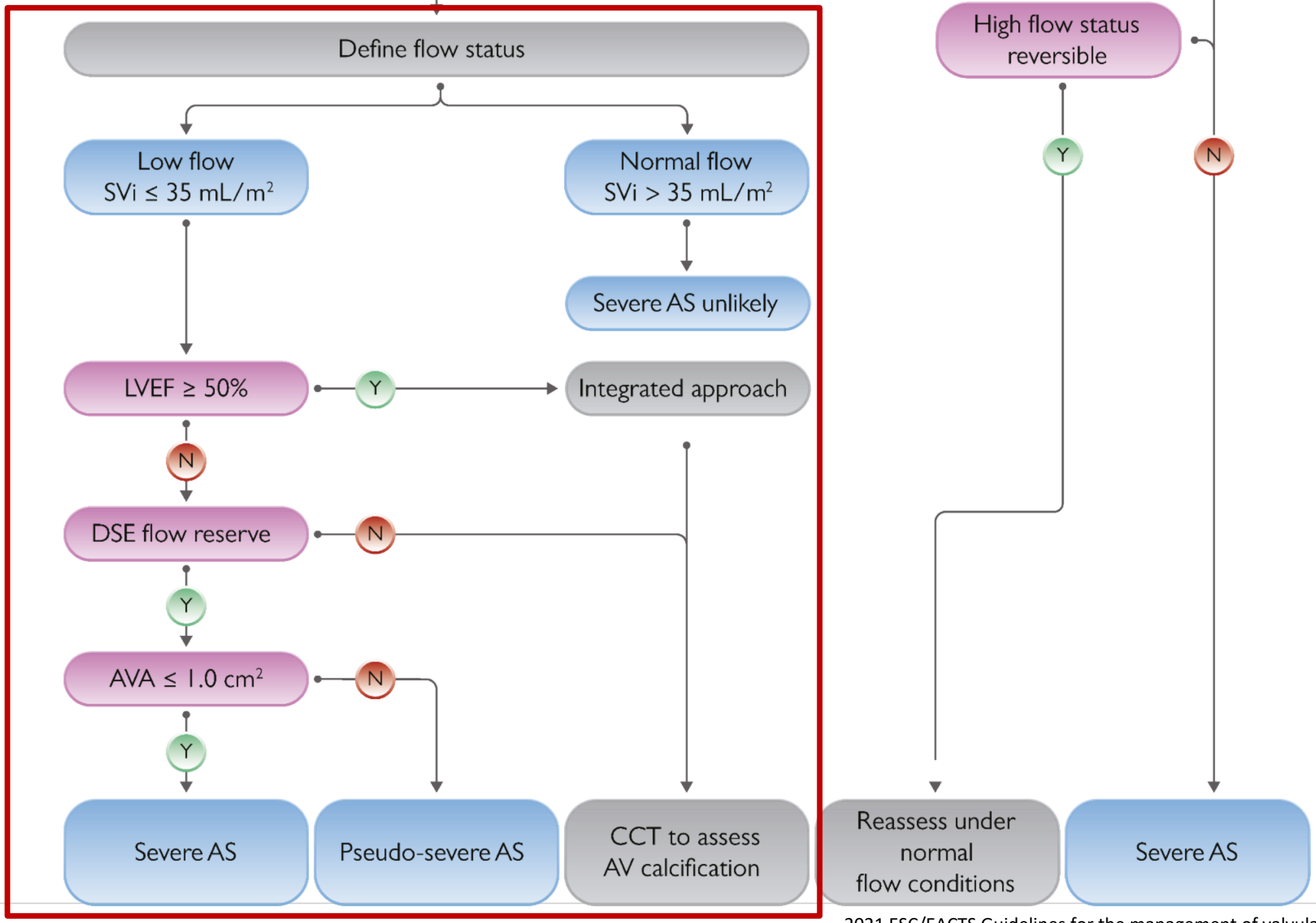
Integrative approach

	Aortic sclerosis	Mild	Moderate	Severe
Peak velocity (m/s)	≤2.5 m/s	2.6–2.9	3.0–4.0	≥4.0
Mean gradient (mmHg)	–	<20	20–40	≥40
AVA (cm^2)	–	> 1.5	1.0–1.5	<1.0
Indexed AVA (cm^2/m^2)	–	>0.85	0.60–0.85	<0.6
Velocity ratio	–	> 0.50	0.25–0.50	<0.25

(Baumgartner et al. Eur Heart J Cardiovasc Imaging 2017;18:254-75)



2021 ESC/EACTS Guidelines for the management of valvular heart disease
(European Heart Journal; 2021 – doi: 10.1093/eurheartj/ehab395; European Journal of Cardio-Thoracic Surgery; 2021 – doi: 10.1093/ejcts/ezab389)



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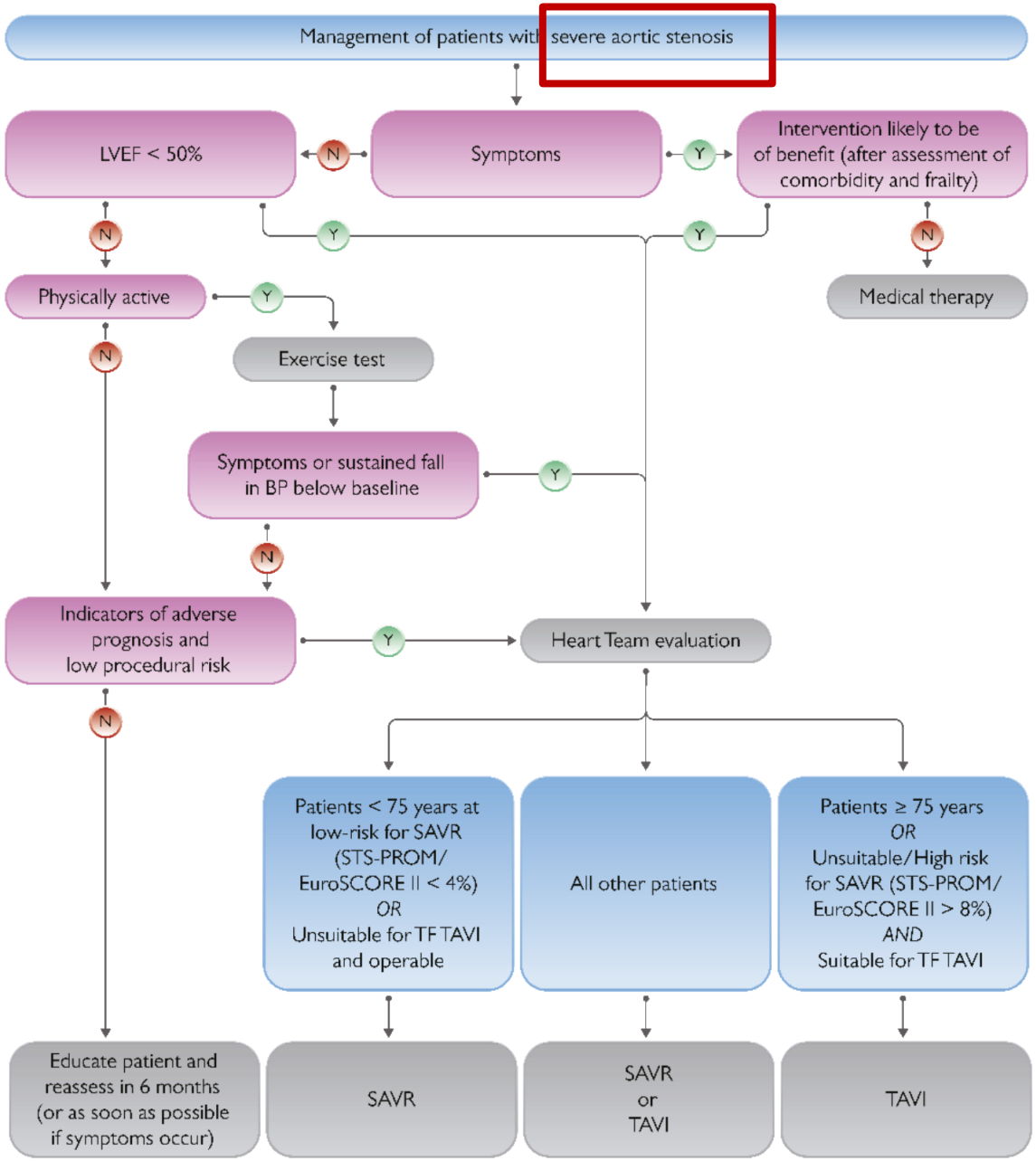

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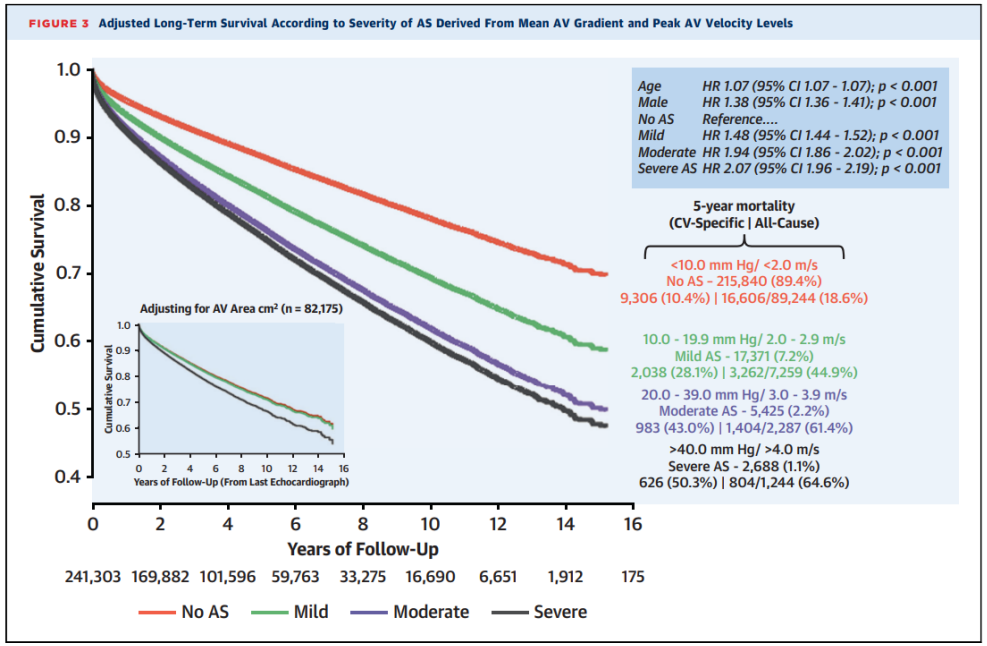
Outcome of Aortic Stenosis / Severity

- 241,303 subjects from the NEDA echocardiographic database (2000-2017)
  - 215,476 no AS
  - 16,129 mild AS, 3315 moderate AS, 6383 severe AS

- Available measurements of AS severity
  - Peak velocity, n=235,430
  - Mean gradient n=110,197
  - Valve area n=82,175

➢Survival analysis adjusted on age and sex after mean follow-up of 3.3 years

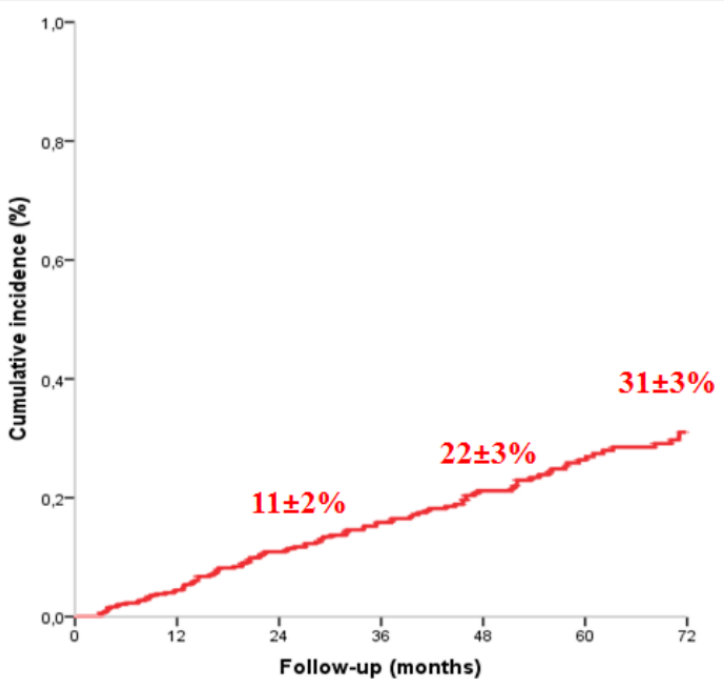
- **No data** on risk factors, comorbidities, symptoms, intervention on aortic valve during follow-up



(Strange et al. J Am Coll Cardiol 2019;74:1851-63)

Outcome of Moderate Aortic Stenosis

- 508 patients with moderate aortic stenosis (valve area 1.1-1.5 cm^2) and LVEF ≥ 50% from 2 French centres (2000-2014), median follow-up 4 years
- Mean gradient 25±9 mmHg, peak velocity 3.2±0.5 m/sec.
- 86% in NYHA class I-II
- 78% hypertension, 36% diabetes, 48% dyslipidemia
- Mean Charlson Comorbidity Index 2.04±2.03
- **31% intervention at 6 years**



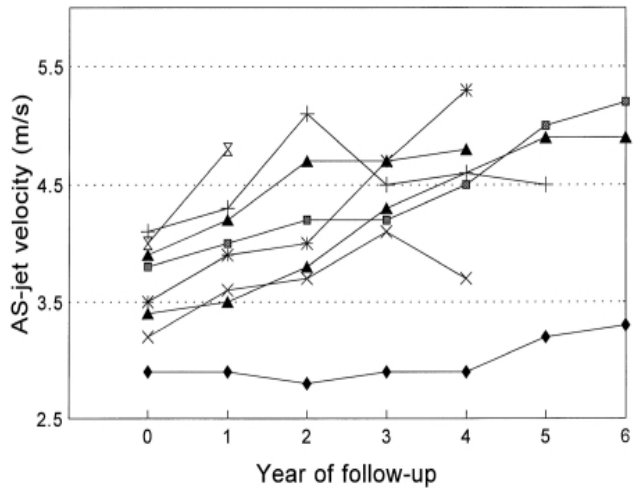
Cumulative incidence of surgery

(Delesalle et al. J Am Heart Assoc 2019;8:e011036)

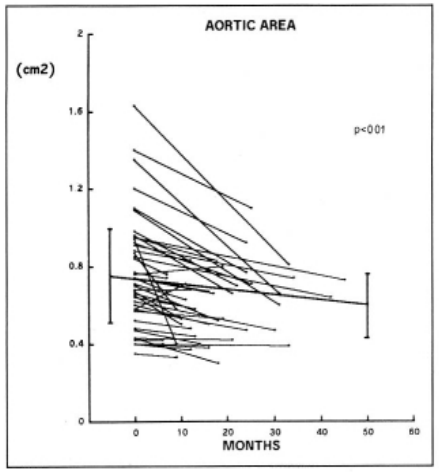
Progression of Aortic Stenosis

- ***Mean*** progression
  - 0.1 cm^2 / yr.
  + 7 mmHg / yr.

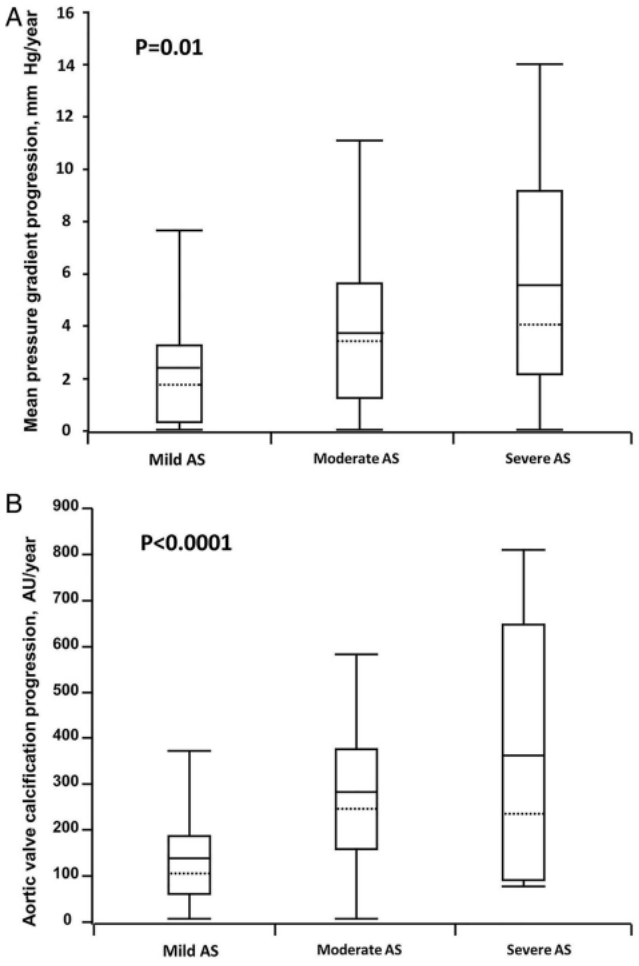
- Individual variability



(Otto et al. Circulation 1997;95:2262-70)



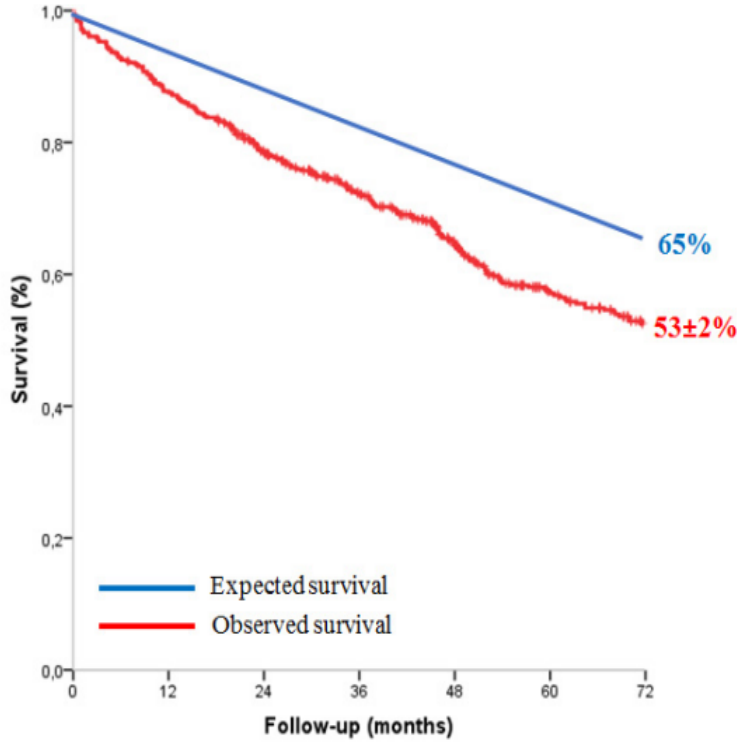
(Faggiano et al. Am J Cardiol 1992;70:229-33)



(Nguyen et al. Heart 2015;101:943-7)

Outcome of Moderate Aortic Stenosis

- Survival and associated factors (multivariate analysis)



Model 2		
Age (per 1-y increment)	1.04 (1.02–1.05)	<0.001
Male sex (yes vs no)	0.92 (0.70–1.21)	0.569
BSA (per 1-cm^2 decrement)	0.82 (0.41–1.61)	0.558
NYHA class (III–IV vs I–II)	1.04 (0.89–1.21)	0.614
Prior atrial fibrillation (yes vs no)	1.35 (1.05–1.73)	0.019
Mean pressure gradient (per 1–mm Hg increment)	1.01 (0.99–1.02)	0.543
Left ventricular ejection fraction (per 1% decrement)	0.99 (0.98–1.01)	0.783
Prior myocardial infarction (yes vs no)	1.01 (0.61–1.67)	0.980
Charlson comorbidity index (per 1-unit increment)	1.11 (1.05–1.18)	0.002
Moderate-to-severe valve calcification (yes vs no)	1.15 (0.86–1.51)	0.316
Aortic valve replacement (yes vs no)*	0.38 (0.27–0.54)	<0.001

(Delesalle et al. J Am Heart Assoc 2019;8:e011036)

Mortality Associated with Aortic Sclerosis

- Prospective study of 5621 subjects aged ≥ 65 years with echocardiographic evaluation, mean follow-up 5 years
  - Normal valve in 3919 (70%)
  - Aortic sclerosis in 1610 (29%)
  - Aortic stenosis in 92 (2%)

- Relative risks of death according to aortic valve sclerosis adjusted on age, sex and cardiovascular risk factors

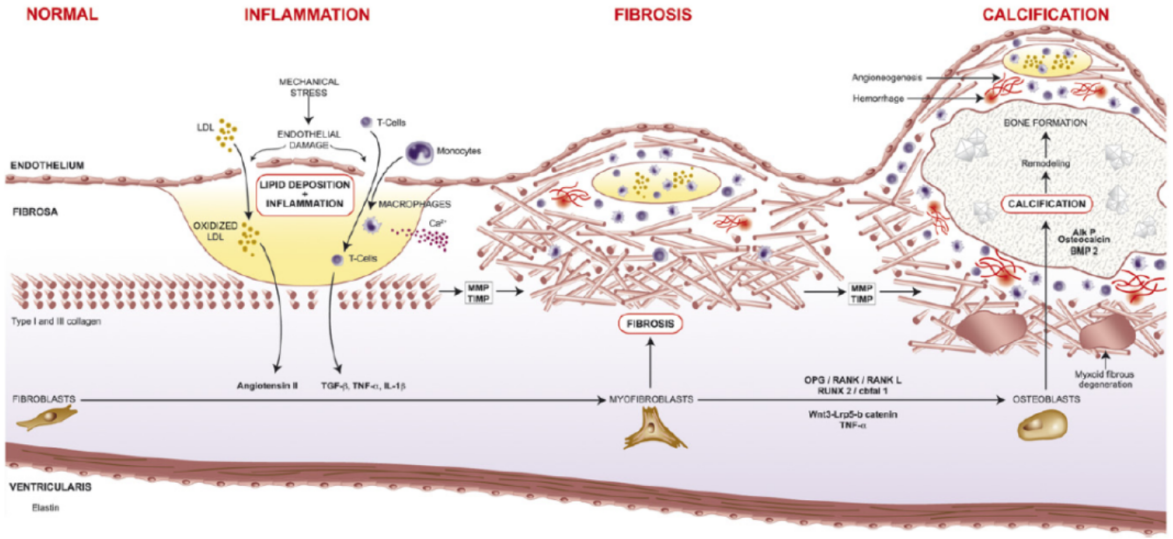
No coronary disease	Relative Risk [95% CI]
All-cause death	1.35 [1.12–1.61]
Cardiovascular death	1.52 [1.12–2.05]
Coronary disease	**Relative Risk [95% CI]**
All-cause death	1.14 [0.92–1.41]
Cardiovascular death	1.21 [0.91–1.61]

(Otto et al. N Engl J Med 1999;341:142-7)

Moderate Aortic Stenosis and Mortality: which Relationships?

- Moderate aortic stenosis, aortic sclerosis and mortality: cause or marker?

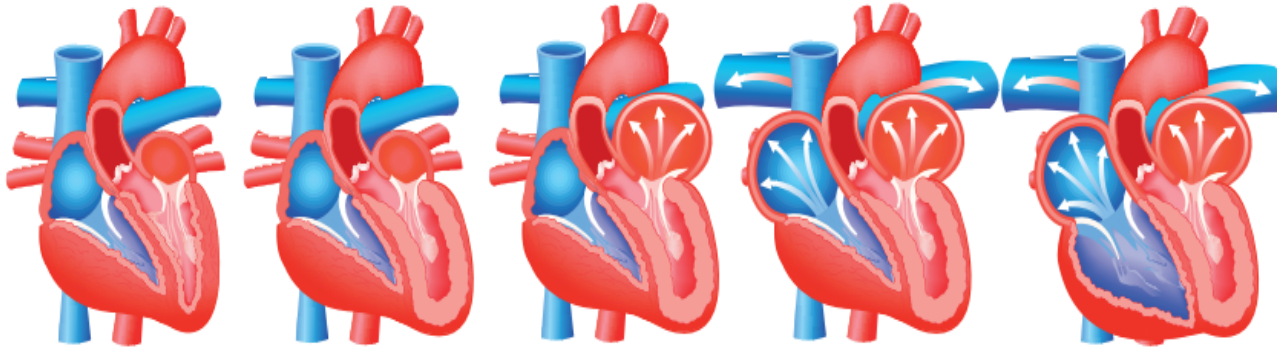
- Demonstrated relationship between CV risk factors and AS progression



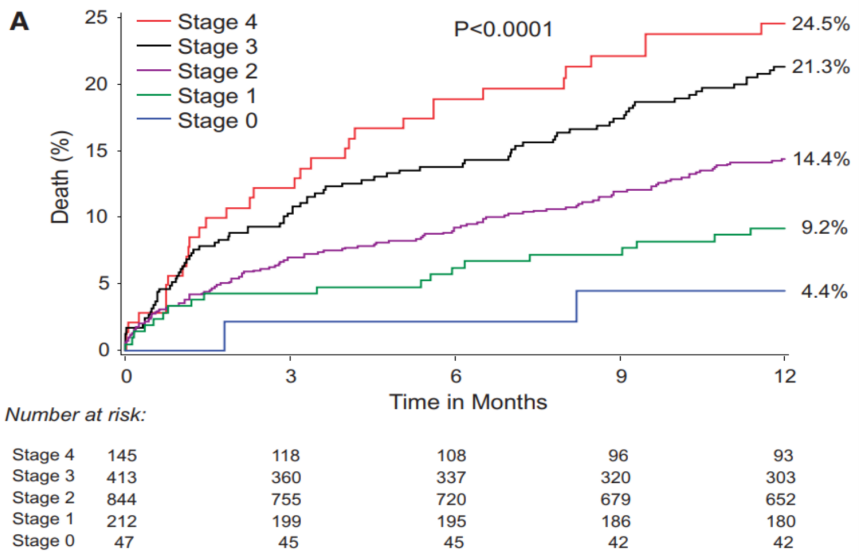
(Dweck et al. J Am Coll Cardiol 2012;60:1854-63)

Cardiac Staging in Severe Aortic Stenosis

1661 patients from PARTNER 2A et 2B (surgery or TAVI for severe symptomatic AS)



Stages/Criteria	Stage 0	Stage 1	Stage 2	Stage 3	Stage 4
	No Cardiac Damage	LV Damage	LA or Mitral Damage	Pulmonary Vasculature or Tricuspid Damage	RV Damage
Echocardiogram		Increased LV Mass Index >115 g/m² (Male) >95 g/m² (Female)	Indexed left atrial volume >34mL/m²	Systolic Pulmonary hypertension ≥60 mmhg	Moderate-Severe right ventricular dysfunction
		E/e' >14	Moderate-Severe mitral regurgitation	Moderate-Severe tricuspid regurgitation	
		LV Ejection Fraction <50%	Atrial Fibrillation		



Predictive value on mortality

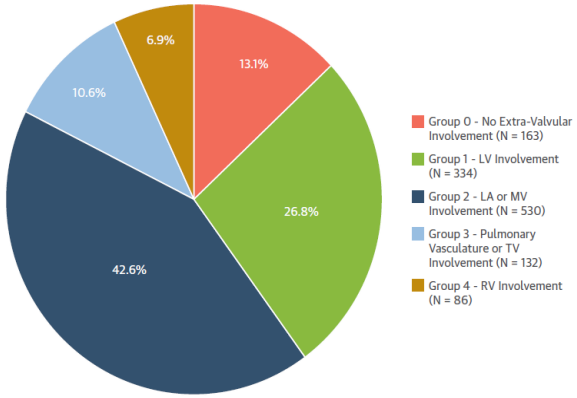
(HR 1.46 / 1 stage, 95% CI 1.27-1.67, p < 0.0001)

(Généreux et al. Eur Heart J 2017;38:3351-8)

Cardiac Staging in Moderate Aortic Stenosis

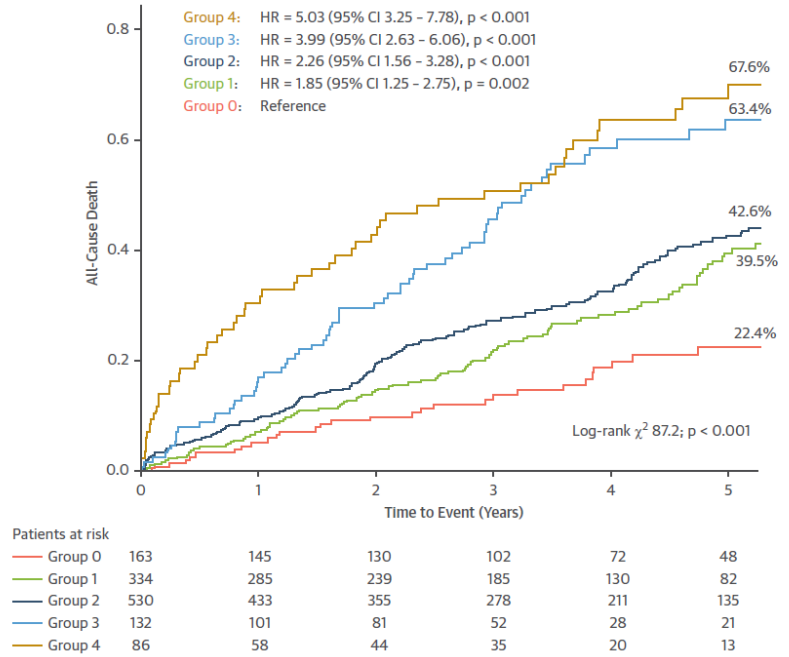
- 1245 patients with moderate aortic stenosis (valve area 1.0-1.5 cm^2) and dimensionless velocity index ratio ≥ 0.25 from 2 centres (2001-2018), median follow-up 4.3 years
- Mean gradient 24±8 mmHg, peak velocity 3.2±0.5 m/sec., 82% LVEF ≥ 50%
- 88% in NYHA class I-II
- 79% hypertension, 35% diabetes, 80% dyslipidemia
- 30% aortic intervention during follow-up

➢87% had extra-valvular involvement (stages 1-4)



Extra-Aortic Valvular Cardiac Abnormalities					
	Group 0	Group 1	Group 2	Group 3	Group 4
Involvement	No Extra-Valvular	Left Ventricular	Left Atrial or Mitral	Pulmonary or Tricuspid	Right Ventricular
Echo-cardiographic criteria		LV mass index ♂ >115 g/m^2 ♀ >95 g/m^2 LV ejection fraction <50% E/e' ratio >14	Left atrial volume index >34 ml/m^2 Atrial fibrillation Moderate or severe mitral regurgitation	Systolic pulmonary arterial pressure >60 mm Hg Moderate or severe tricuspid regurgitation	TAPSE <16 mm

Survival censored at the time of AVR

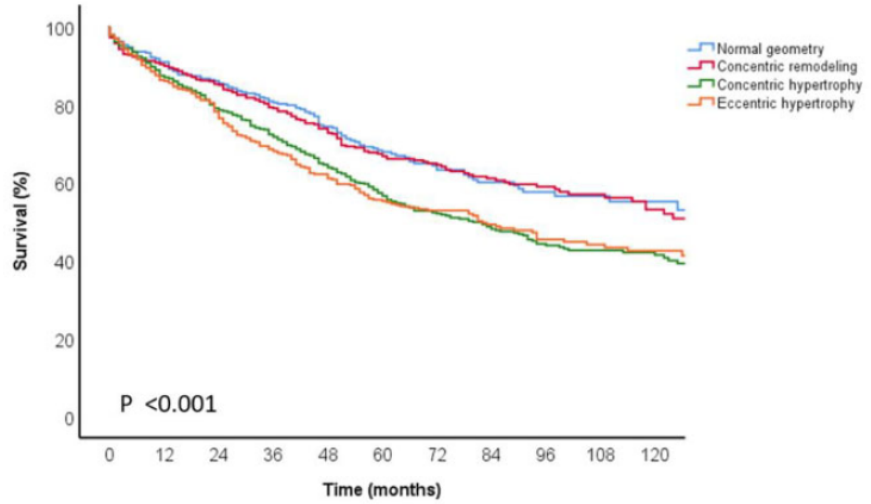


(Amanullah et al. J Am Coll Cardiol Img 2021;14:1724-37)

Left Venticular Remodelling in Moderate Aortic Stenosis

- 1931 patients with moderate aortic stenosis (valve area 1.0-1.5 cm^2) from 3 centres (2001-2019), median follow-up 51 months
- LV geometry
  - 18% Normal geometry
  - 24% Concentric remodelling
  - 36% Concentric hypertrophy
  - 22% Eccentric hypertrophy
- Negative impact of concentric hypertrophy

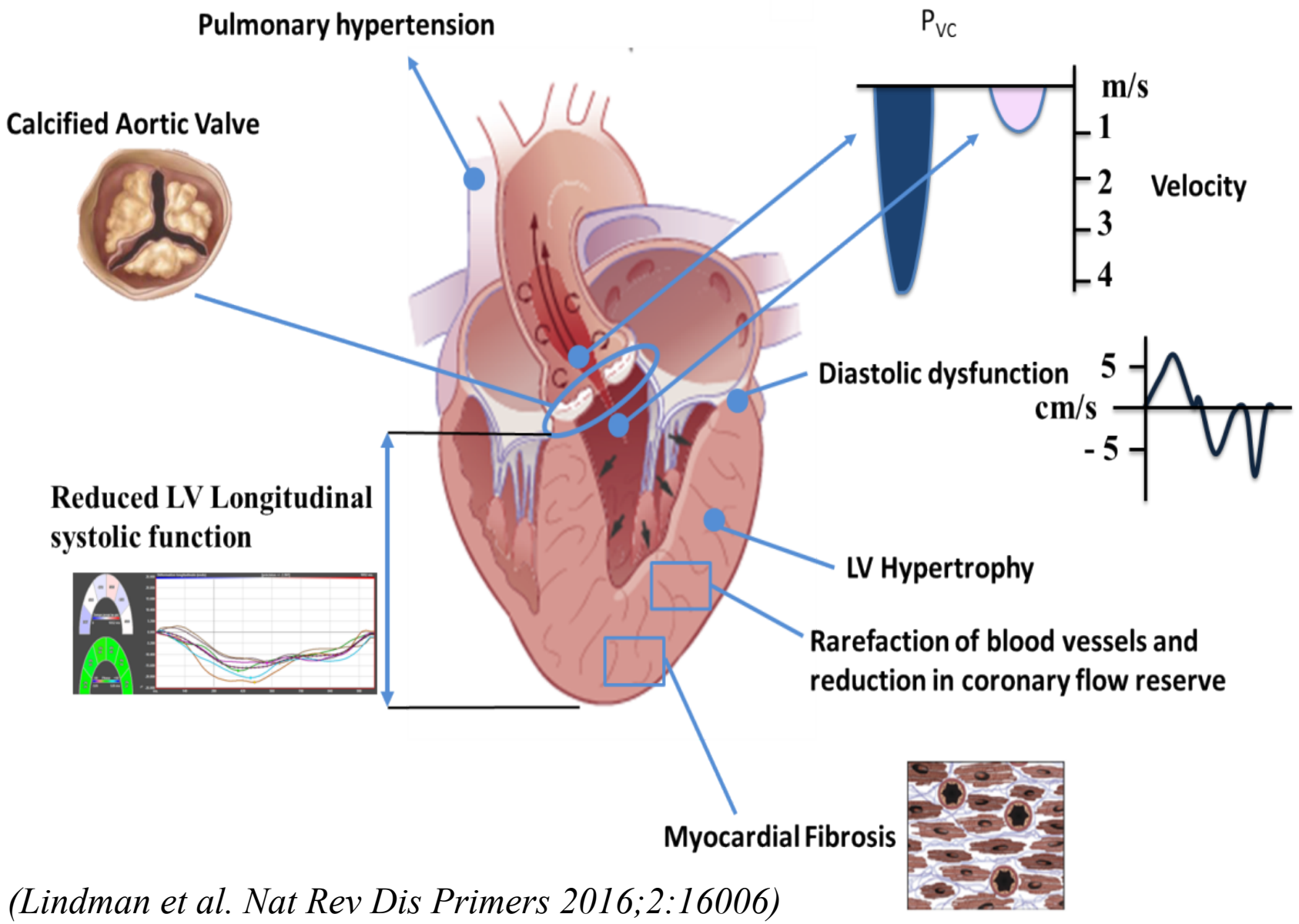
	All-cause mortality		AVR or all-cause mortality	
	HR (95% CI)	*P* value	HR (95% CI)	*P* value
	Univariable analysis		**Univariable analysis**	
Normal geometry	*Reference group*		*Reference group*	
Concentric remodelling	0.976 (0.773–1.233)	0.840	1.103 (0.922–1.319)	0.282
Concentric hypertrophy	1.410 (1.147–1.734)	0.001	1.285 (1.091–1.513)	0.003
Eccentric hypertrophy	1.435 (1.148–1.793)	0.002	1.300 (1.087–1.555)	0.004
	Multivariable analysis[a]		**Multivariable analysis**[b]	
Normal geometry	*Reference group*		*Reference group*	
Concentric remodelling	0.973 (0.763–1.240)	0.825	1.111 (0.921–1.342)	0.272
Concentric hypertrophy	1.258 (1.016–1.558)	0.035	1.291 (1.088–1.532)	0.003
Eccentric hypertrophy	1.244 (0.987–1.568)	0.065	1.217 (1.008–1.470)	0.042



Number at risk											
Normal geometry	344	307	270	237	191	149	112	82	57	38	29
Concentric remodeling	469	415	365	313	258	198	159	122	93	66	49
Concentric hypertrophy	698	598	509	447	356	278	204	156	111	86	59
Eccentric hypertrophy	420	356	306	259	215	168	131	100	72	57	41

(Stassen et al. Eur Heart J Cardiovasc Imaging 2022;23:1326-35)

Maladaptive remodelling and impaired function of LV in Aortic Stenosis

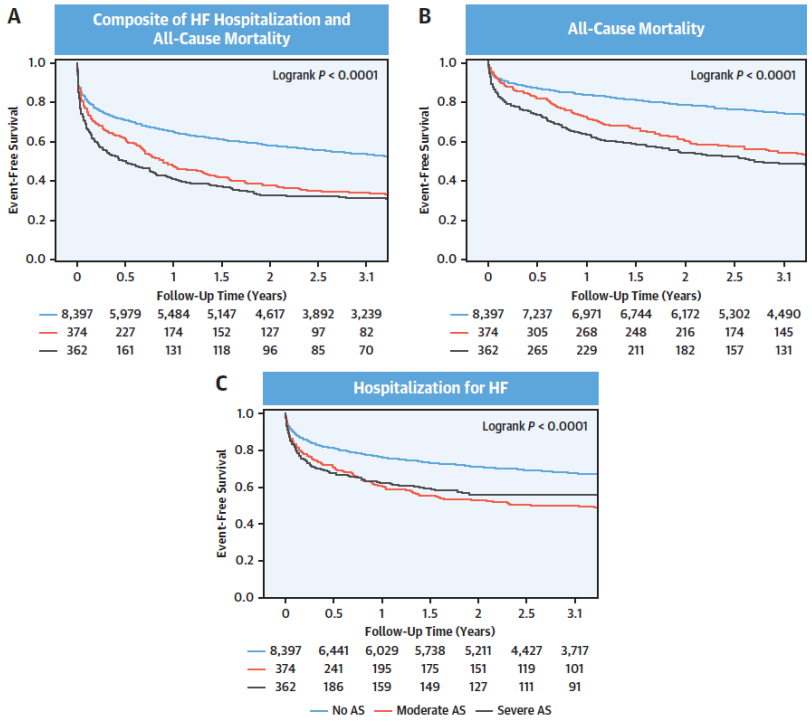


(Lindman et al. Nat Rev Dis Primers 2016;2:16006)

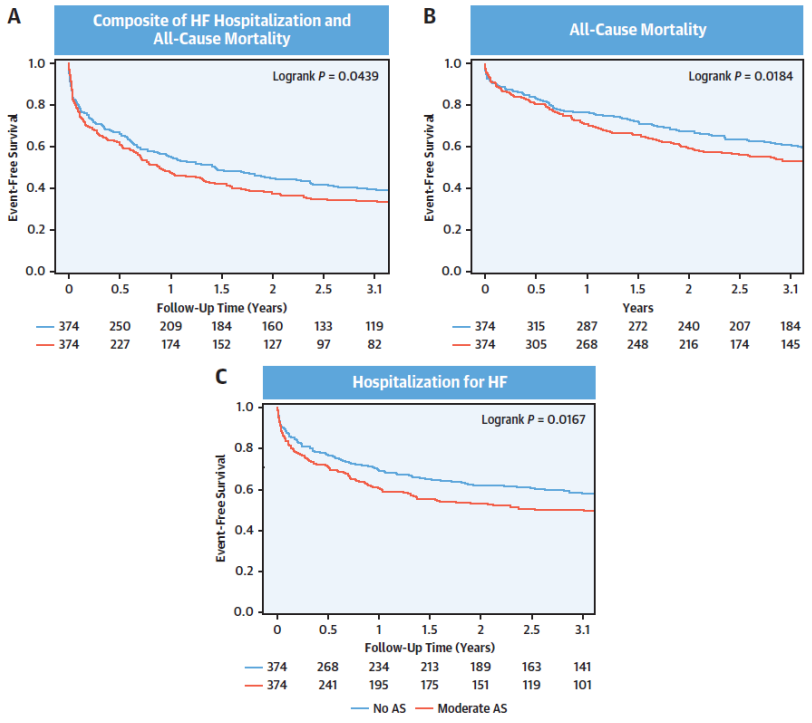
Moderate Aortic Stenosis with Heart Failure

- 9133 patients with HFrEF (374 with moderate AS, 362 with severe AS)

- Outcome of HFrEF according to AS



Propensity-matched analysis



- Adjusted HR for all-cause mortality, moderate AS vs. no AS: 1.32 [95% CI 1.07-1.63], p<0.01

(Khan et al. J Am Coll Cardiol 2023;81:1235-44)

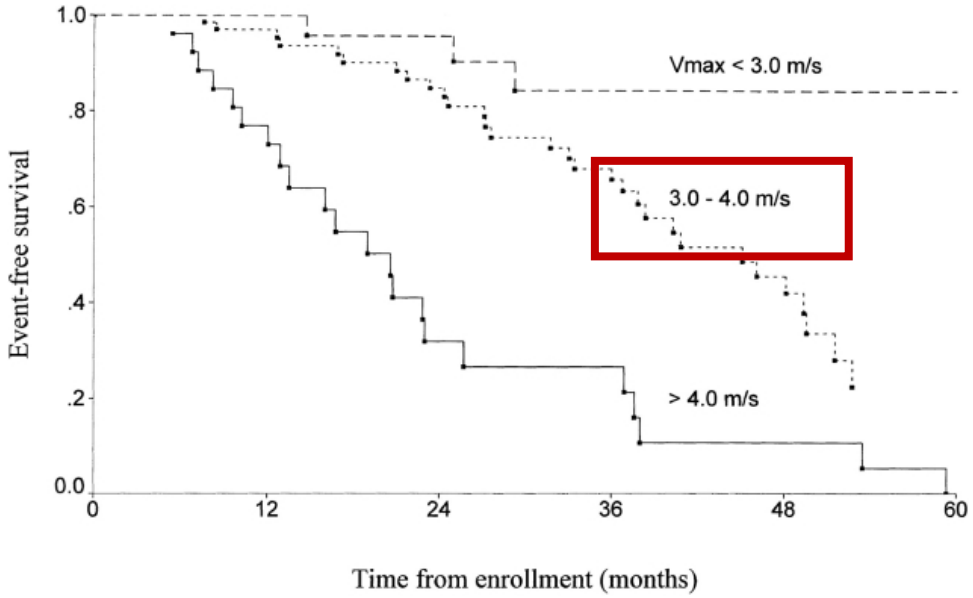
Outcome of Aortic Stenosis: Timing of Intervention

- 123 asymptomatic patients with V. max. ≥ 2.5 m/s (max. gradient ≥ 25 mmHg)

  Age 63 ± 16 yrs

  Annual stress test

- Death or AVR / peak velocity



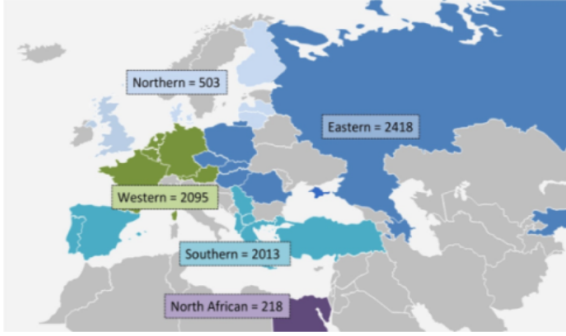
(Otto et al. Circulation 1997;95:2262-70)

- Confounding issue related to follow-up and timing of intervention

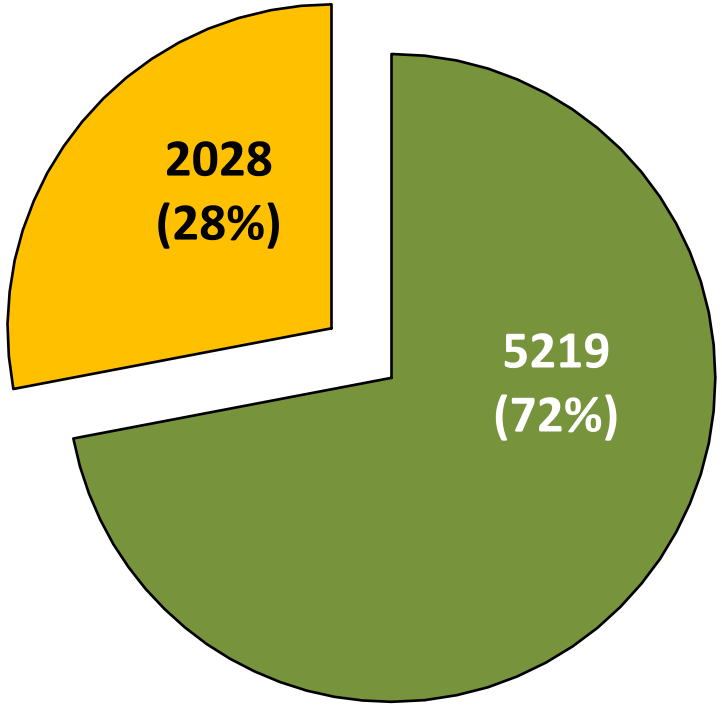
  A third of asymptomatic patients with known severe AS are followed less than once a year and experience higher mortality.

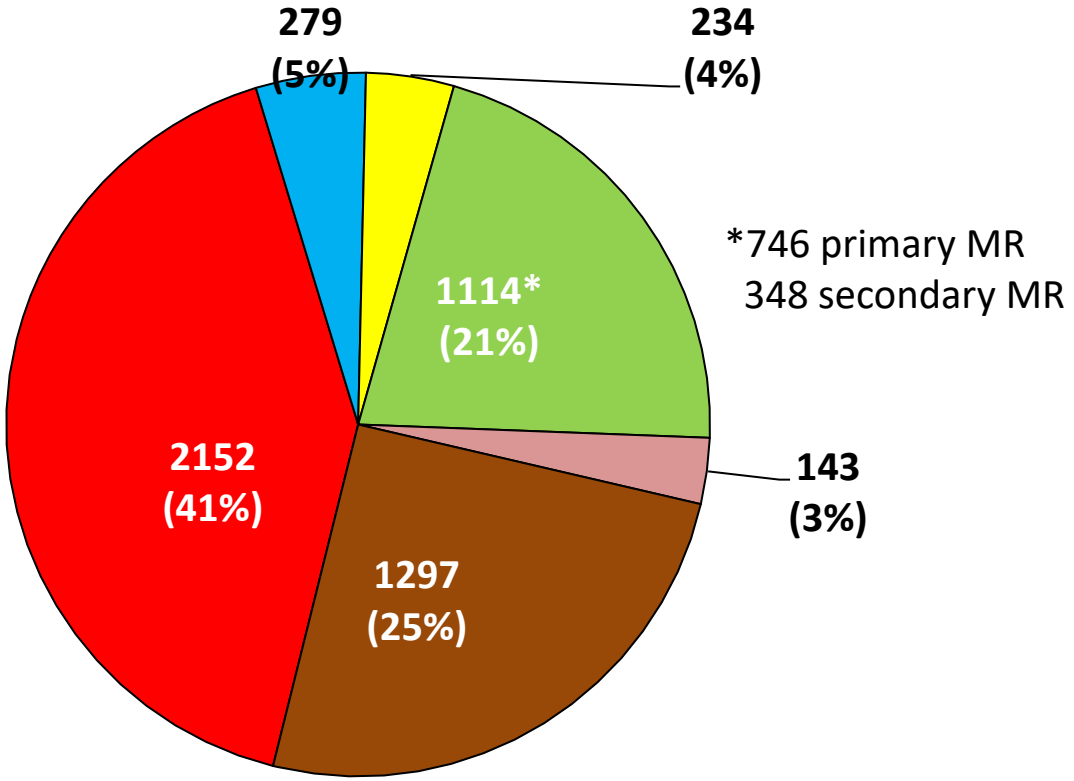
(Ahmed et al. JAMA Cardiol 2017;2:1141-6)

EORP VHD Survey on Valvular Disease



7247 patients included in 28 countries (January-August 2017)
Previous intervention or severe native valvular disease





(Iung et al. Circulation 2019;140:1156-69)

Patient Characteristics

	AS	AR	MS	MR	Multiple left	Isolated right	Previous Interv.
Age (years)	76 [67-83]	58 [48-69]	59 [45-68]	68 [60-77]	75 [65-82]	74 [65-81]	70 [59-78]
≥ 80 yrs (%)	38	6	6	17	33	26	36
Female (%)	43	19	75	44	54	59	21
HF < 1 yr. (%)	16	11	17	27	24	25	17
NYHA III-IV (%)	37	19	45	47	50	52	26
A. Fib (%)	14	6	46	35	30	57	32
Charlson index	4 [3-6]	2 [1-3]	2 [1-3]	3 [2-5]	4 [3-6]	4 [3-6]	3 [2-5]
Euroscore II	1.9 [1.1-3.4]	1.0 [0.6-1.9]	1.2 [0.8-2.2]	2.0 [1.0-4.0]	2.3 [1.3-4.7]	2.3 [1.4-4.3]	3.0 [1.6- 6.0]

What have we Learnt on Moderate Aortic Stenosis?

- Obervational data strongly suggest a poor prognosis of moderate aortic stenosis

- Limitations of available studies
  - Retrospective analyses with inclusions during a long time span (change of practices, guidelines…)
  - Inhomogeneous definitions of moderate AS (gradient, valve area, stroke volume). Possible inclusion of patients with low-flow low-gradient severe aortic stenosis
  - Major confounding factors: risk factors, comorbidities
  - Frequent occurrence of aortic intervention at mid-term follow-up
  - Inhomogeneous left ventricular remodelling and cardiac damage

- Too early intervention exposes to higher cumulative risk of prosthesis-related complications

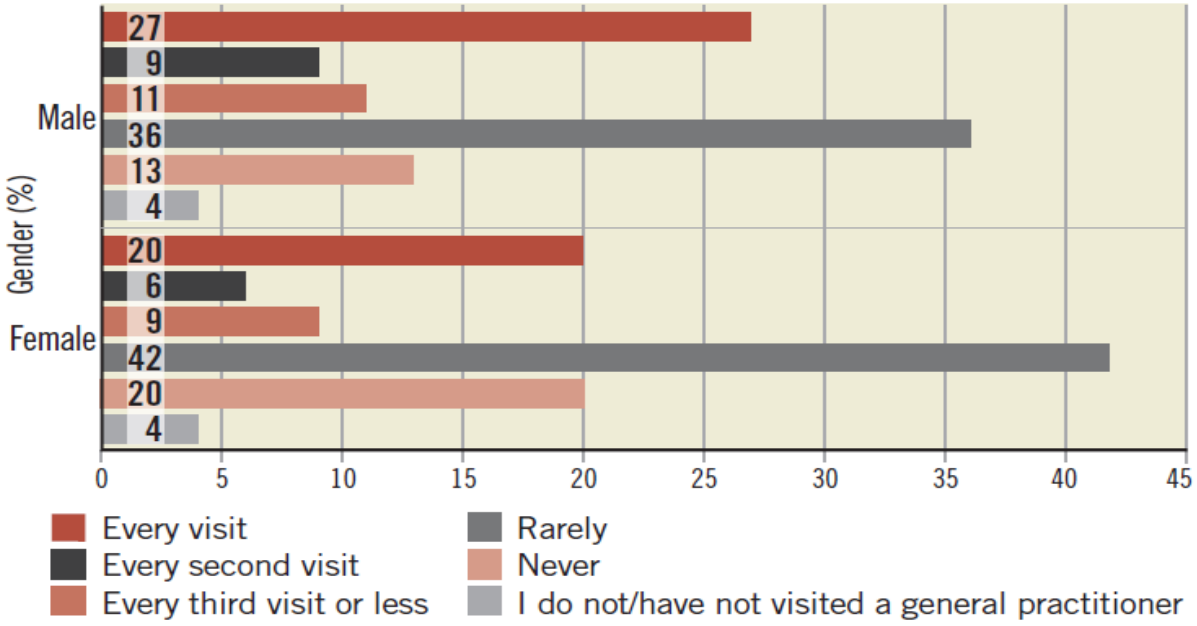
How to Manage Moderate Aortic Stenosis?

- Agressive assessment and management of cardiovascular risk factors
- Comprehensive echocardiographic evaluation ± multimodality imaging, not to miss severe low-gradient aortic stenosis
- Close follow-up for timely intervention according to undisputed indications
- Intervention may be beneficial in a subset of highly selected patients
  - Cardiac damage, left ventricular remodelling
  - Heart failure
  - ➢ But the benefit of intervention remains to be proven

Detection of Aortic Stenosis

Survey performed in 2015 in 8860 patients ≥ 60 years in 9 European countries

- Only 2% were concerned by heart valve disease
- 54% stated that their GP rarely or never used a stethoscope



(Gaede et al. Eurointervention 2016;12:883-9)