

Moderate and Moderate to Severe Aortic Stenosis: Echocardiography and Treatment

Rafael Kuperstein MD

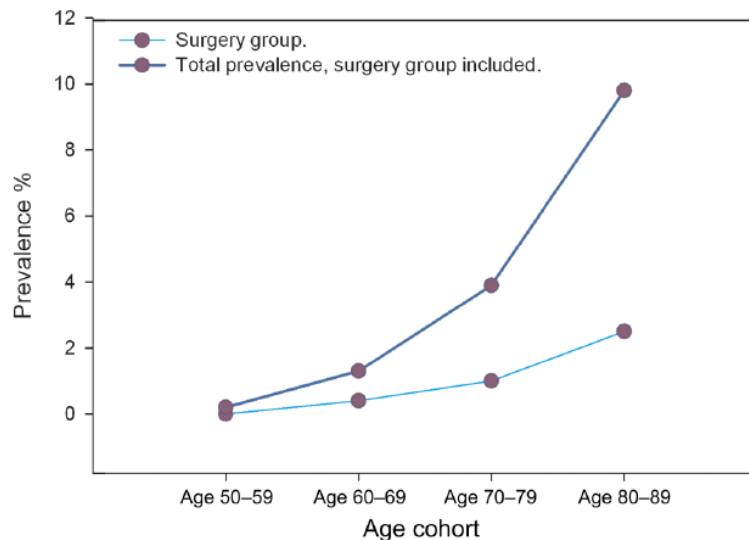
Director: Echocardiography and Valvular Heart Disease Clinics

Sheba Medical Center

Israel

Aortic Stenosis

- Very common pathology in the elderly
- Prevalence increases with age
- From 0.2% (50-59 years old) to 9.8%(80-89 years old)



Eveborn GW et al, Heart 2013

Aortic Stenosis

- Rate of progression is variable
- Guidelines recommend yearly echocardiographic follow up for patients with Moderate AS

Moderate Aortic Stenosis Echocardiographic Diagnosis

	Mild	Moderate	Severe
Jet Velocity(m/sec)	2.0-2.9	3.0-4.0	>4.0
Mean Gradient (mmHg)	<20	20-40	>40
Valve Area (cm ²)	>1.5	1.0-1.5	<1.0
Valve Area Index(cm ² /m ²)	>0.85	0.6-0.85	<0.6*

- Normal Flow(SVI> 35ml/Kg)
- Low Flow(SVI ≤ 35 ml/Kg)
- LVEF ≥ 50%
- LVEF <50%

* <0.5 when BMI>30 Kg/m²



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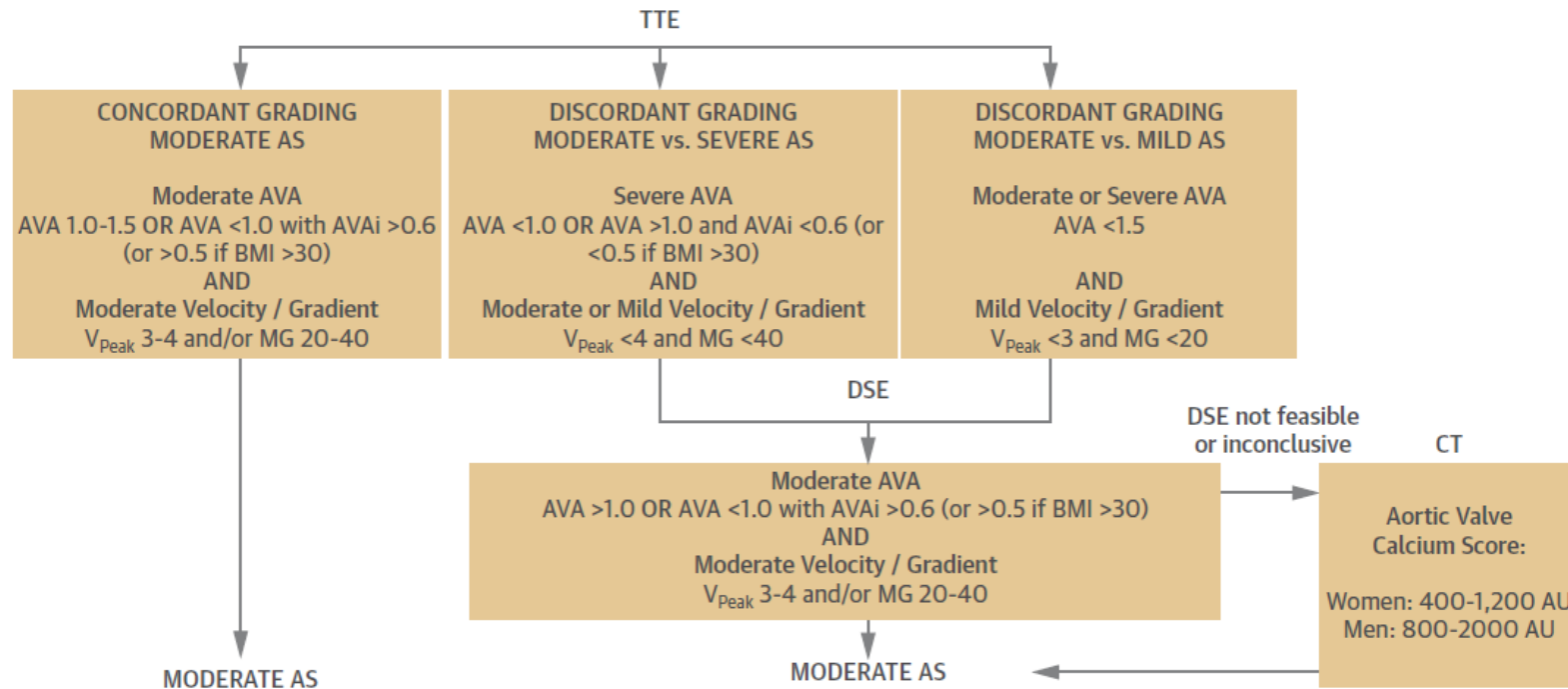
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Moderate Aortic Stenosis Echocardiographic Diagnosis

Discordant echocardiographic findings

- Exclude measurement errors
- Calculate Dimensionless index
- Calculate valvulo-arterial impedance(Z)?
- Planimetry by TEE?
- Hybrid imaging (still under investigation)

Aortic Stenosis Echocardiographic Diagnosis: Measurement Errors Excluded



Moderate Aortic Stenosis: Management

ACC Guidelines	In patients with moderate AS who are undergoing cardiac surgery for other indications, AVR may be considered	2B C-EO
ESC Guidelines (2021)	SAVR should be considered in patients with moderate AS undergoing CABG or surgical intervention on the ascending aorta or another valve after heart team consultation	2AC

Why do the Guidelines Recommend Conservative Treatment

- Low overall risk for sudden death with moderate AS
- Historically high risk associated with AVR

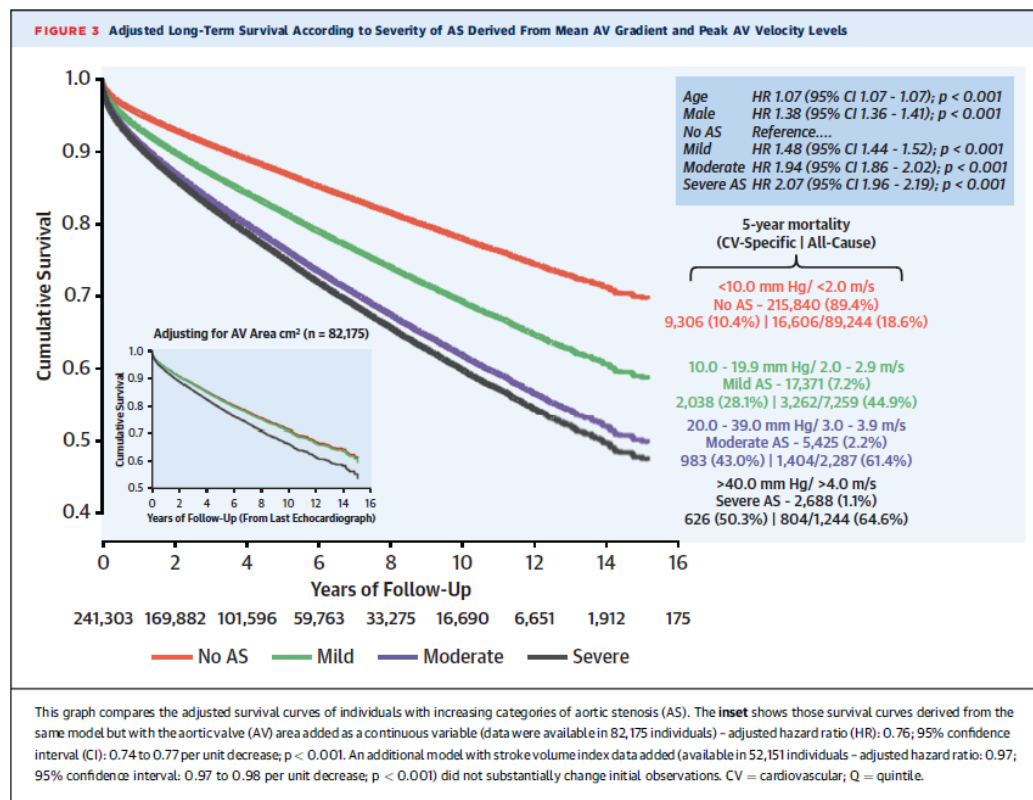
Is the prognosis of Moderate AS so benign?



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Survival of Patients with Aortic Stenosis



- No AS
- Mild AS
- Moderate AS
- Severe AS

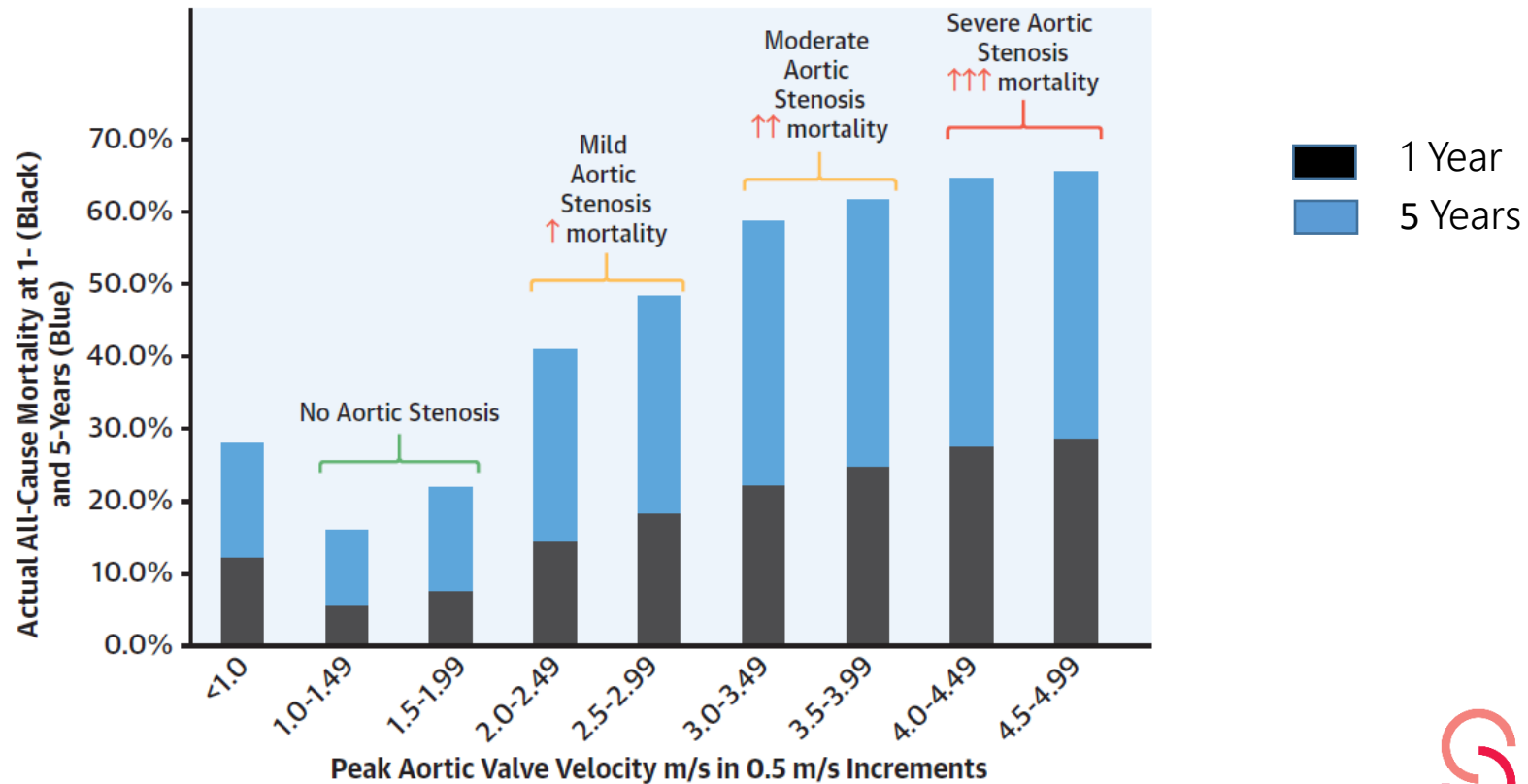
n=25,827

Median Follow-up: 1208 days (598-2177)

Strange et al, JACC 2019

Survival of Patients with Aortic Stenosis

One and 5 year mortality per Increment in Peak AV Velocity

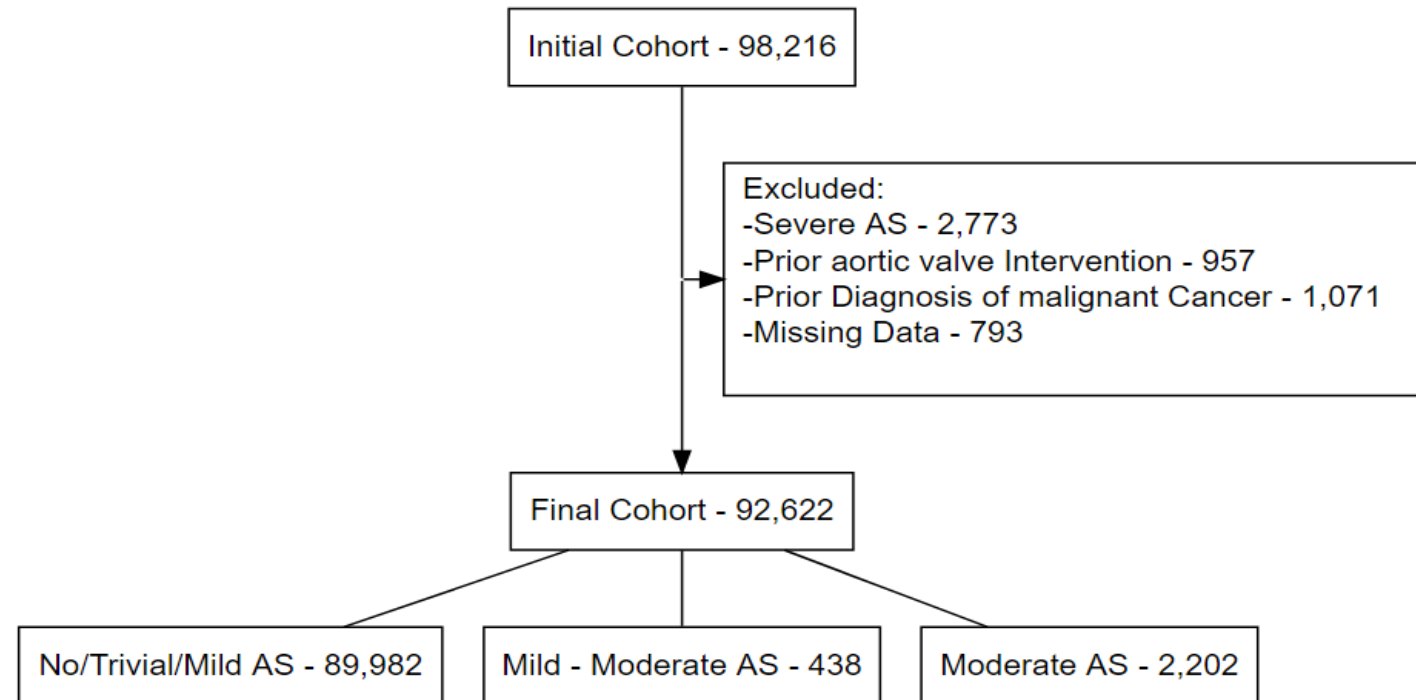


Strange et al, JACC 2019

The Association of Moderate Aortic Stenosis with Poor Survival Is Modified by Age and Left Ventricular Function: Insights from SHEBAHEART Big Data



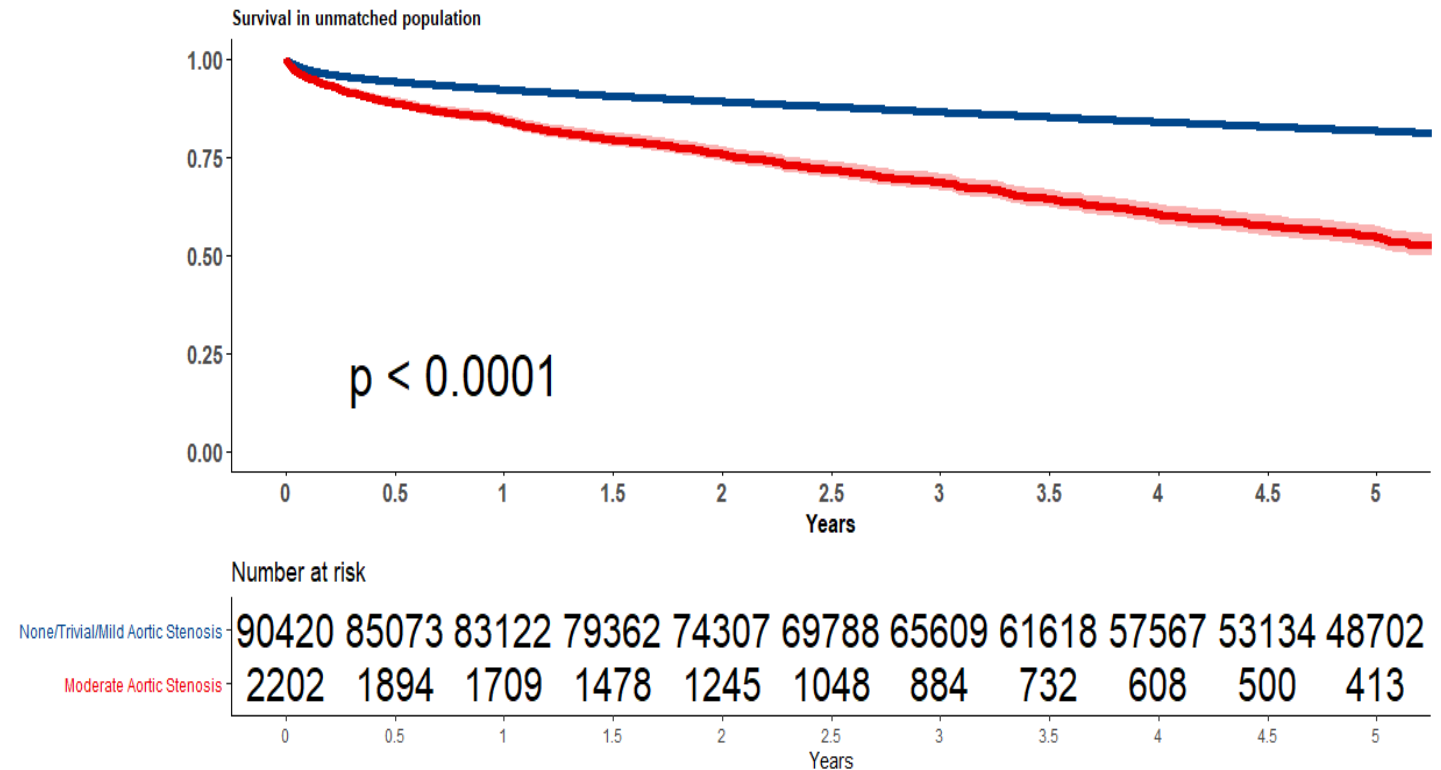
- Consecutive patients who underwent echocardiographic evaluation between 2007 and 2019.
- All-cause mortality and cancer data were available for all patients from national registries.
- Cox regression survival models were applied with censoring of patients who developed metastatic cancer, developed > moderate AS, or underwent aortic valve intervention during follow-up





Overall Survival

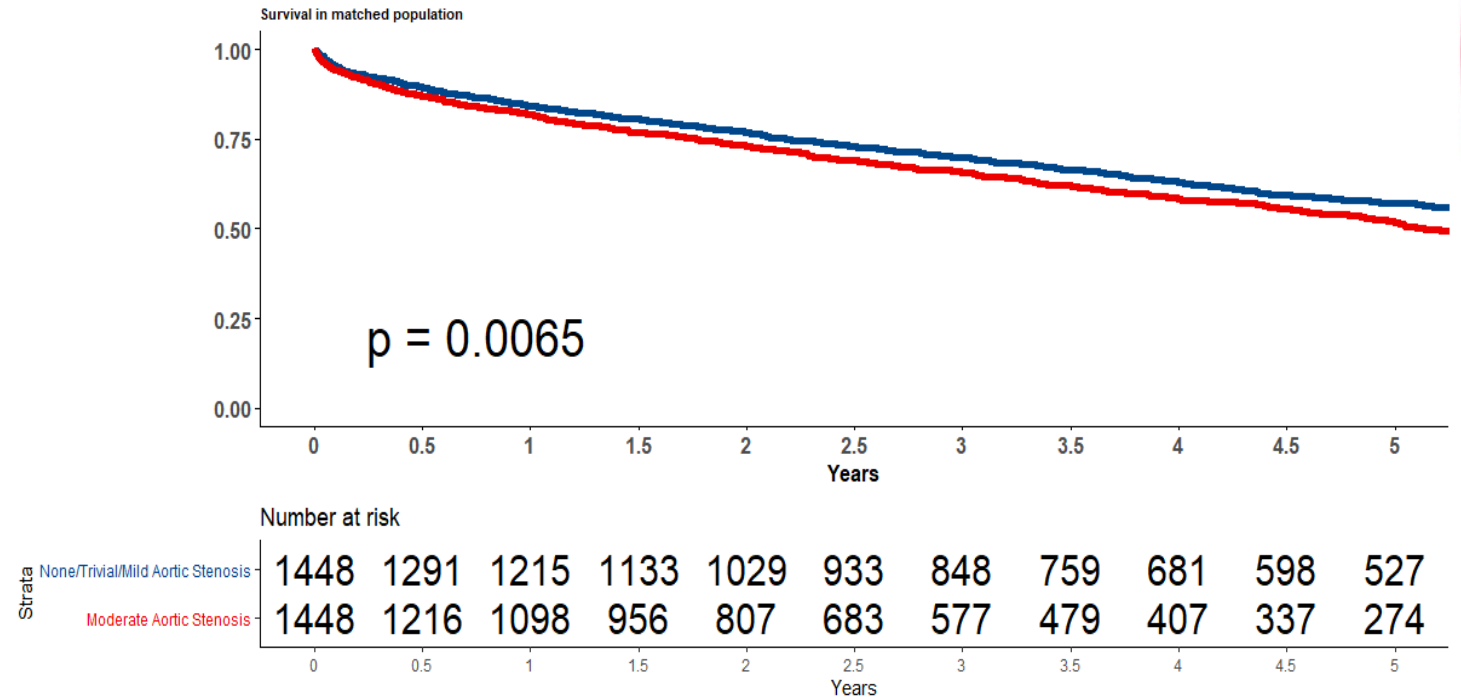
- During a median follow-up of 5 (IQR 2-8) years, 19,171 (21%) patients died.
- We observed event rates of 3.7 cases 100 person-years in the <moderate AS group vs and 12.7 per in the moderate AS group





Propensity Matching

- A total of 1,448 moderate AS patients with comprehensive clinical, laboratory, and echocardiographic data were identified and matched with control patients
- Regression model showed that compared with $\leq$ mild AS, patients with moderate AS were 17% more likely to die during follow-up (95% CI 1.04-1.30, $p = 0.007$).



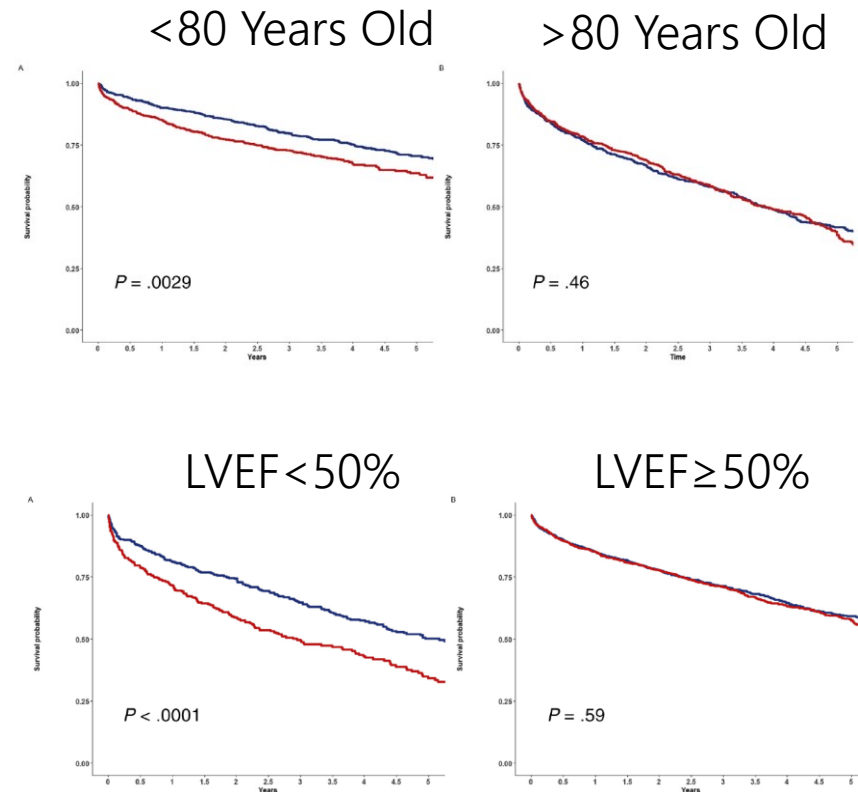
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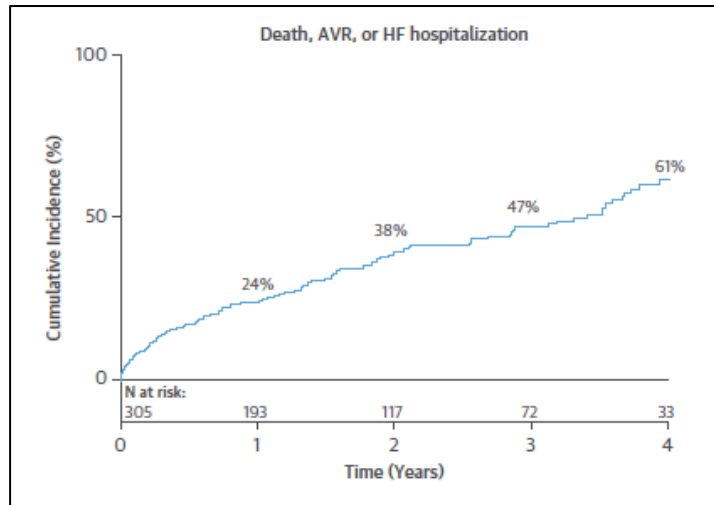
Subgroup Analysis and Interaction

- There was a significant interaction with respect to two important subgroups:
 - Non-octogenarians patients (age < 80)
 - Patients with LVEF < 50%).

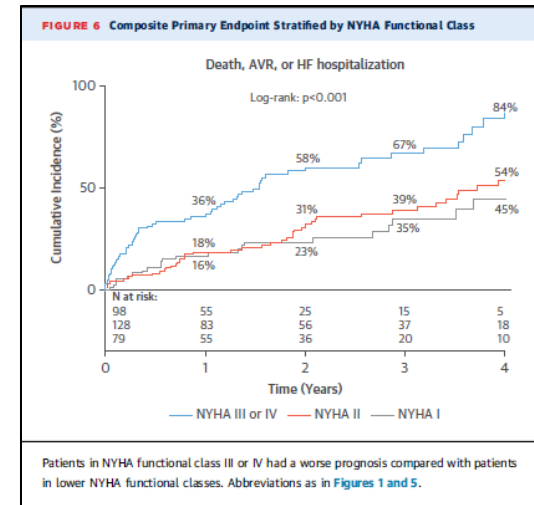


Prognostic Implications of Moderate Aortic Stenosis in Patients With Left Ventricular Systolic Dysfunction

Death AVR or HF Hospitalizations



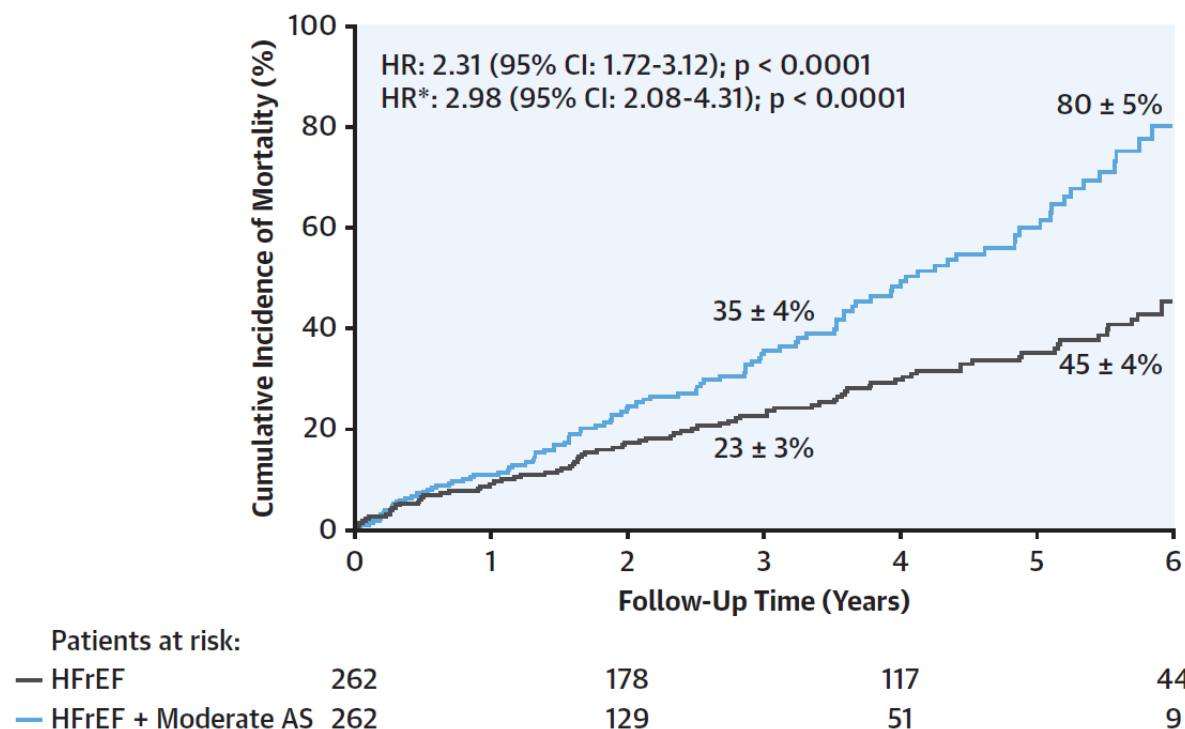
Per NYHA Class



- $n=305$
- Age 73 ± 11 years
- AVA 1.2 ± 0.16 cm²
- Mean gradient 14 ± 4 mmHg
- LVEF: $38 \pm 9\%$
- Median Follow up: 638 days

Moderate Aortic Stenosis in Patients With Heart Failure and Reduced Ejection Fraction

A



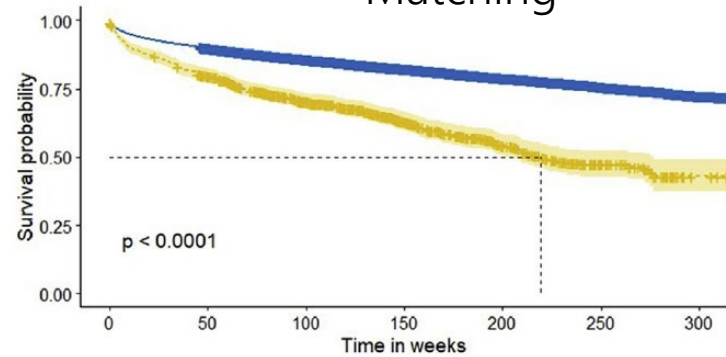
- $n=262$
- Mean age: 73 ± 10 years
- AVA: 1.2 ± 0.2 cm²
- Mean Gradient: 15 ± 5 mmHg
- LVEF: $38.5 \pm 9.6\%$
- Follow-up: 2.9 ± 2.2 years

Jean G, JACC 2021

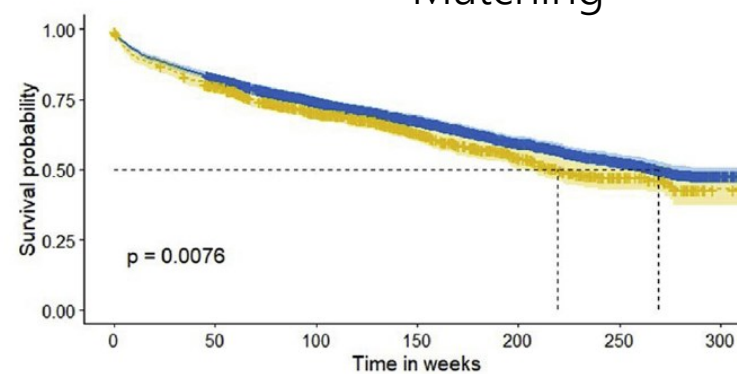
Natural History of Moderate Aortic Stenosis with Preserved and Low Ejection Fraction



Survival Probability before Propensity Matching

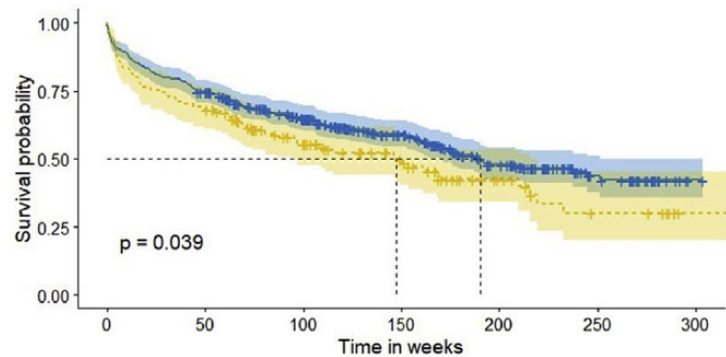


Survival Probability after Propensity Matching

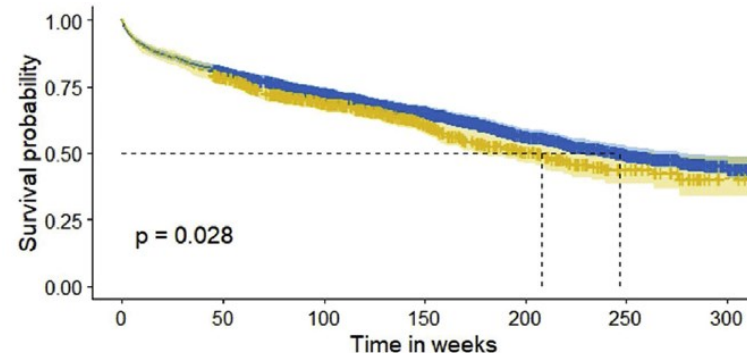


- $n=952$
- Mean age 78 ± 12 years
- Mean AVA 1.3 ± 0.1 cm²
- Mean Gradient 20 ± 9 mmHg
- Mean LVEF $55 \pm 8\%$
- Follow-up 181 Weeks

Survival Probability Propensity Matched with LVEF <50%



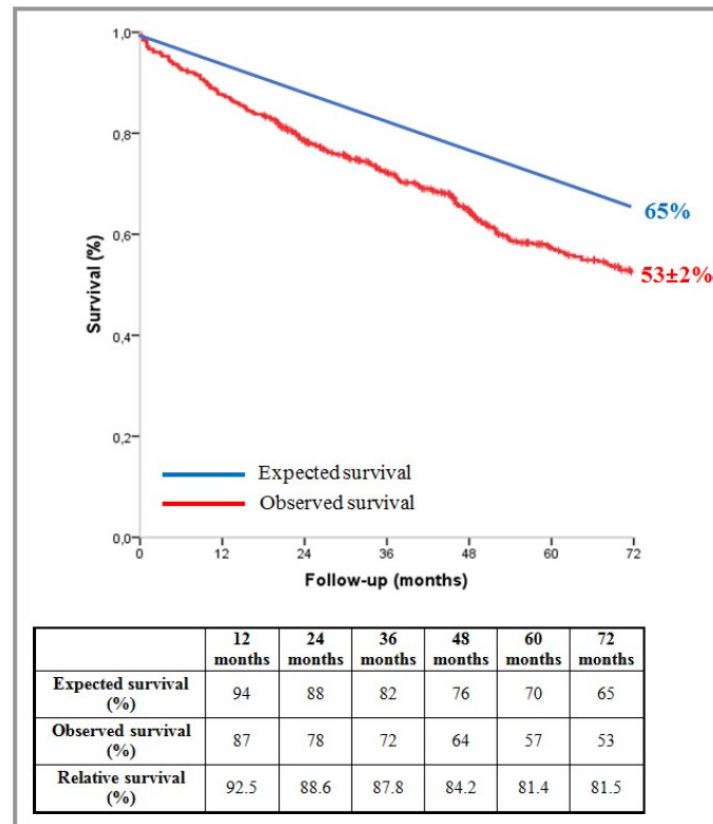
Survival Probability Propensity Matched with Low Gradient



Mean gradient and LVEF did not interact with the effects of moderate AS on survival

Characteristics and Prognosis of Patients With Moderate Aortic Stenosis and Preserved Left Ventricular Ejection Fraction

n=508
Age 75 ± 11 years
AVA 1.2 ± 0.15 cm²
Mean Gradient 25 ± 9 mmHg
Follow-up time 47 months



- Expected survival
- Moderate AS survival

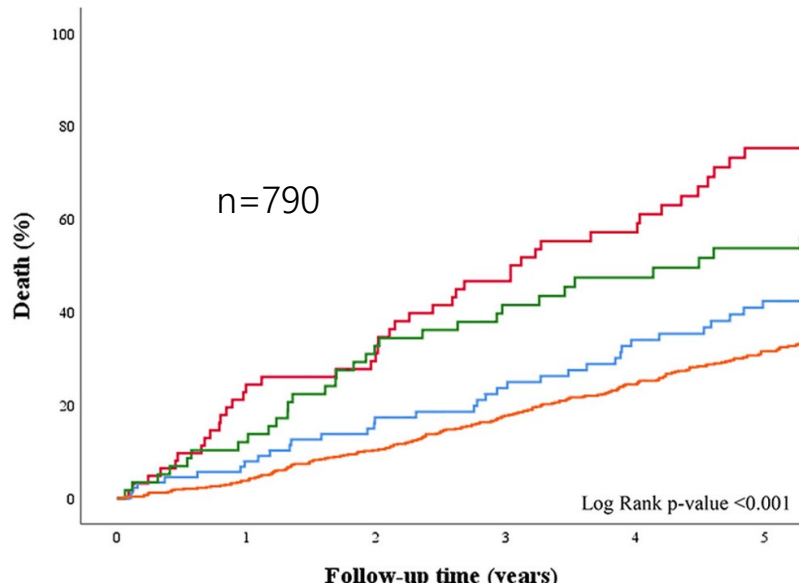
Delesalle G et al, JAHA2019

Characteristics and Prognosis of Patients With Moderate Aortic Stenosis and Preserved Left Ventricular Ejection Fraction

Independent Predictors of Mortality

- Age(CI: 1.02-1.05) $p < 0.001$
- Prior AF (CI 1.05-1.73) $p < 0.019$
- Charlson Comorbidity Index (CI: 1.05-1.18) $p < 0.001$
- AVR according to current guidelines (CI:0.23-0.54) $p < 0.001$

Prognostic Significance of Discordant Severity Criteria In Moderate AS

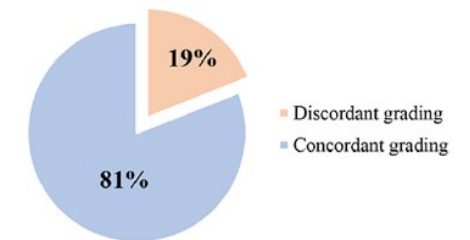


Mortality according to concordance and LVEF

- Discordant ,LVEF< 50%
- Concordant ,LVEF<50%
- Discordant,LVEF≥50%
- Concordant ,LVEF≥50%

	Aortic valve area	Mean gradient
Concordant grading	1.0 – 1.5 cm ²	≥20 mmHg
Discordant grading	1.0 – 1.5 cm ²	<20 mmHg

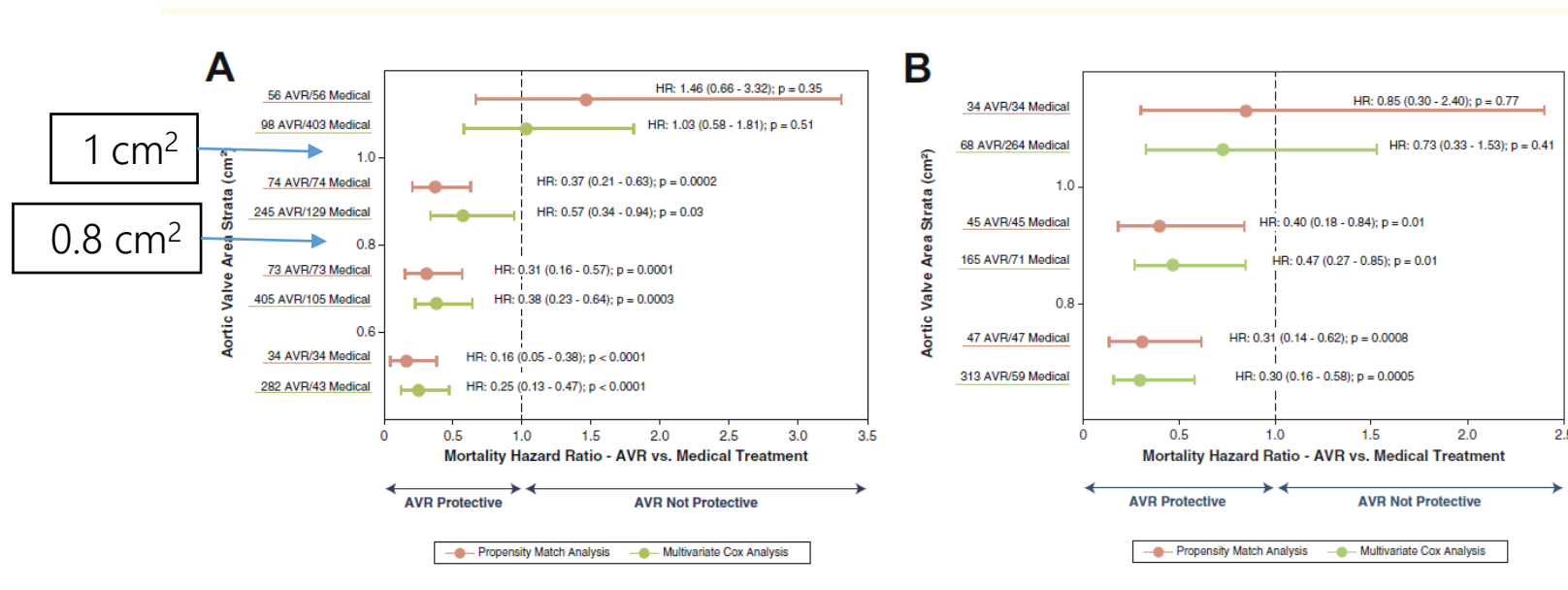
Discordant, LVEF<50%	HR:2.78(2.00-3.87)	P<0.001
Concordant LVEF<50%	HR:1.58(1.06-2.36)	P<0.025



Discordant Grading of Aortic Stenosis Severity

Echocardiographic Predictors of Survival Benefit Associated With Aortic Valve Replacement

Mortality Hazard Ratio for AVR Vs. Medical Treatment according to AVA Strata



Whole Cohort

Normal LV Function and Flow

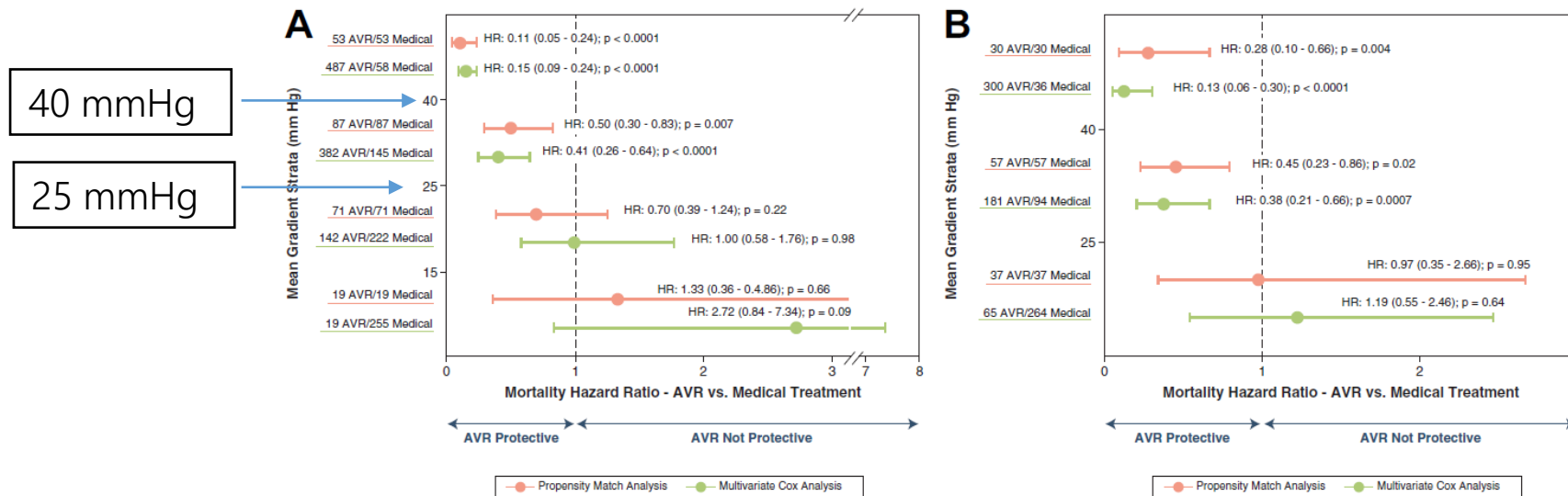
- n=1710
- AVA 0.9 ± 0.3 cm²
- Mean Gradient 33 ± 18 mmHg
- Mean LVEF $59 \pm 14\%$
- F/U time 4.4 ± 3 years

Berthelot-Richer M et al, JACC Imaging 2016

Discordant Grading of Aortic Stenosis Severity

Echocardiographic Predictors of Survival Benefit Associated With Aortic Valve Replacement

Mortality Hazard Ratio for AVR Vs. Medical Treatment according to Mean Gradient Strata



Whole Cohort

Normal LV Function and Flow

- n=1710
- AVA $0.9 \pm 0.3 \text{ cm}^2$
- Mean Gradient $33 \pm 18 \text{ mmHg}$
- Mean LVEF $59 \pm 14\%$
- F/U time $4.4 \pm 3 \text{ years}$

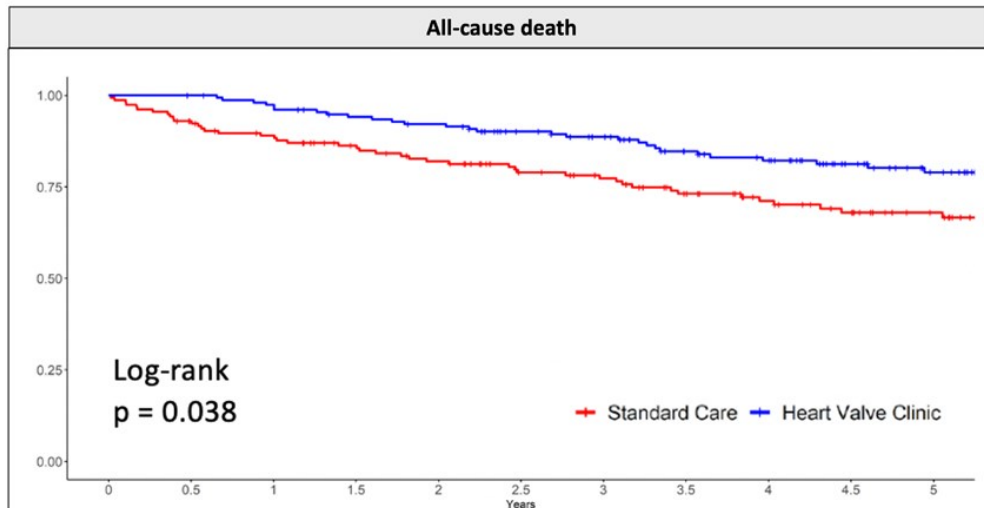
Berthelot-Richer M et al, JACC Imaging 2016

Summary for Now

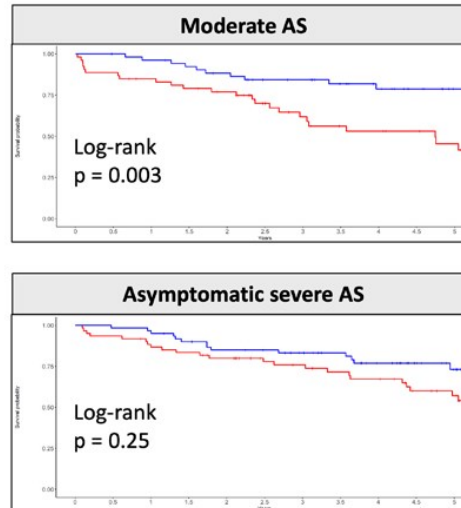
- Moderate Aa is associated with a poor prognosis, which is more pronounced in patients with LV dysfunction
- In patients with normal function the $\uparrow$ risk seems to be related to comorbidities
- More data is needed in patients with discordant findings and normal function and flow

Original research

Outcomes in patients with moderate and asymptomatic severe aortic stenosis followed up in heart valve clinics



HVC is a significant predictor of reduced mortality in patients with moderate Aortic Stenosis



- Age 76.5 ± 12.8 YO
 - F/U Time: 4.8 ± 1.8 Y
 - 57% Moderate AS
- Heart Valve Clinic
 - Standard Cardiology Care
- More consults
 - More BNP
 - More EST
 - More CT
 - Earlier Surgery

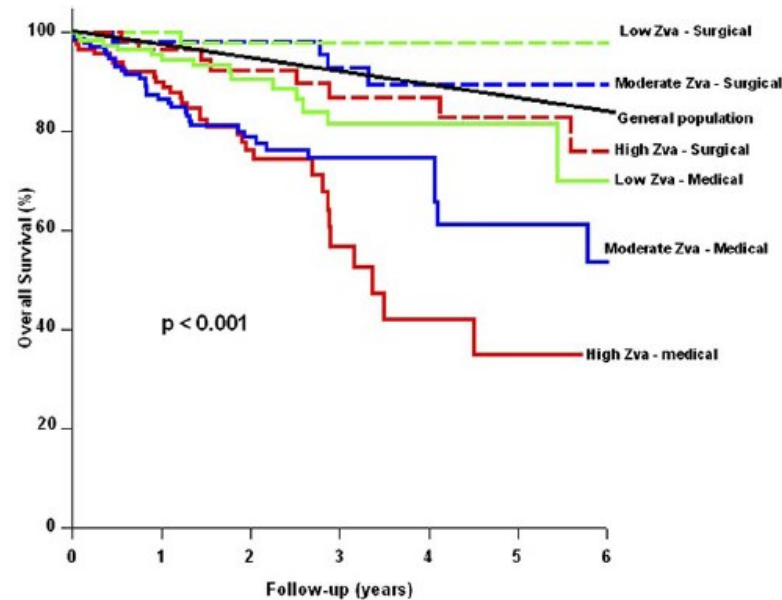


Can we risk stratify patients with moderate
aortic stenosis?

Moderate Aortic Stenosis: Risk Stratification

Impact of Valvulo-Arterial Impedance on Overall Survival

n=544
Asymptomatic
≥ Moderate
Aortic Stenosis



Valvulo-Arterial Impedance

$$Z_{va} = \frac{LVSP}{SVi} = \frac{SAP + \Delta P_{Mean}}{SVi}$$

Hachicha et al, JACC 2009



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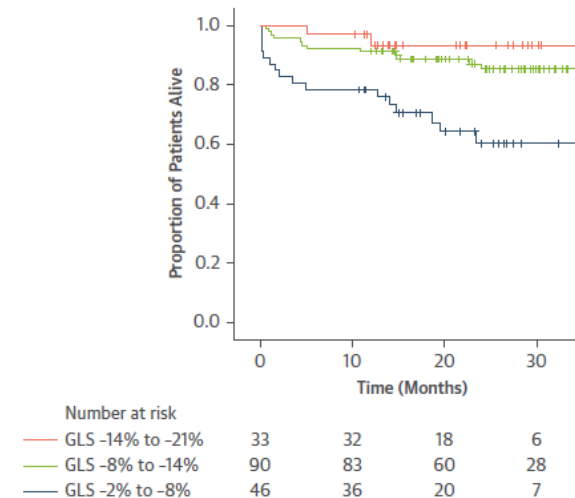
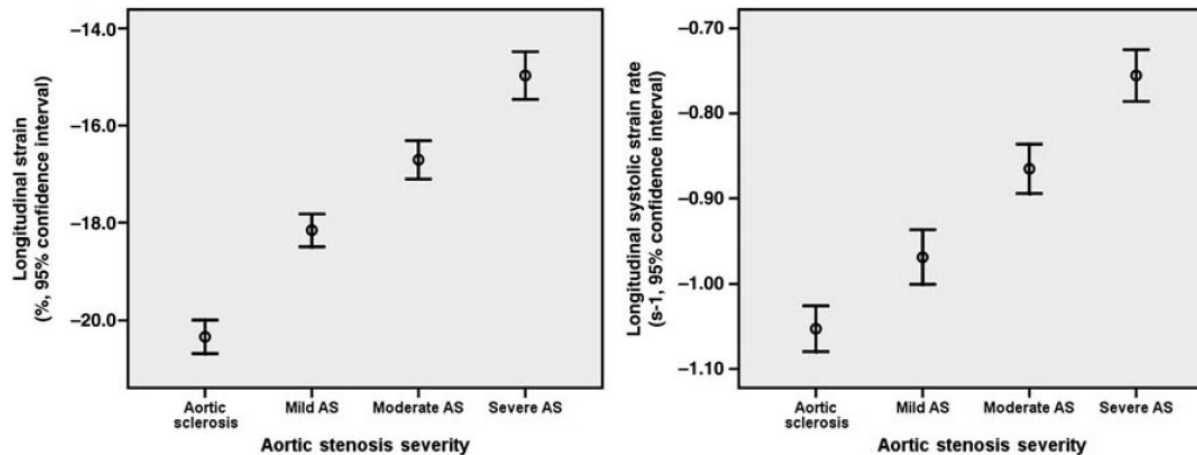
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Moderate Aortic Stenosis: Risk Stratification

- Strain Imaging for early assessment of LV dysfunction

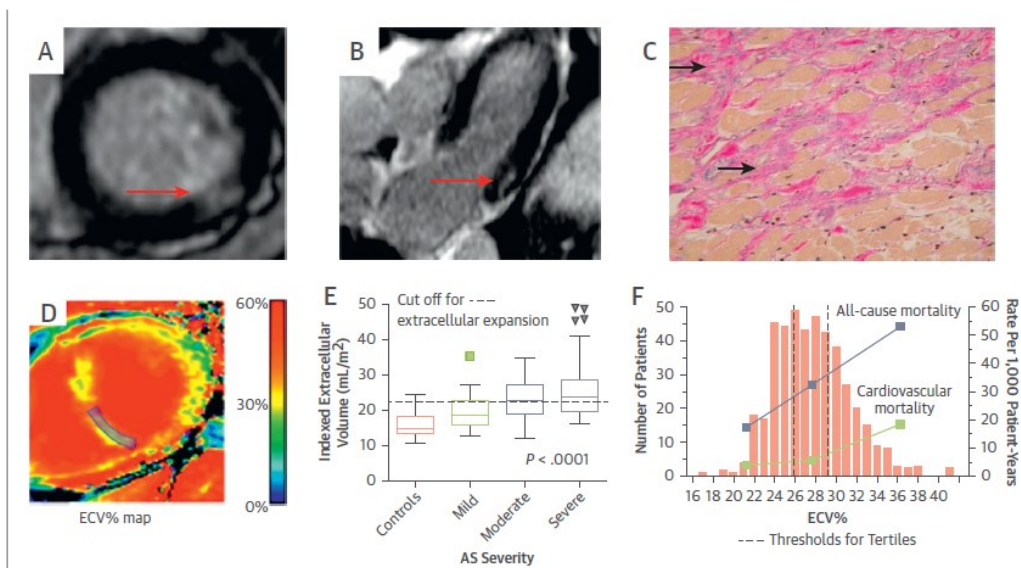
Impairment of GLS and Systolic Strain Rate with Increasing Severity of AS

Survival in Moderate AS and LV dysfunction according to GLS



Moderate Aortic Stenosis: Risk Stratification

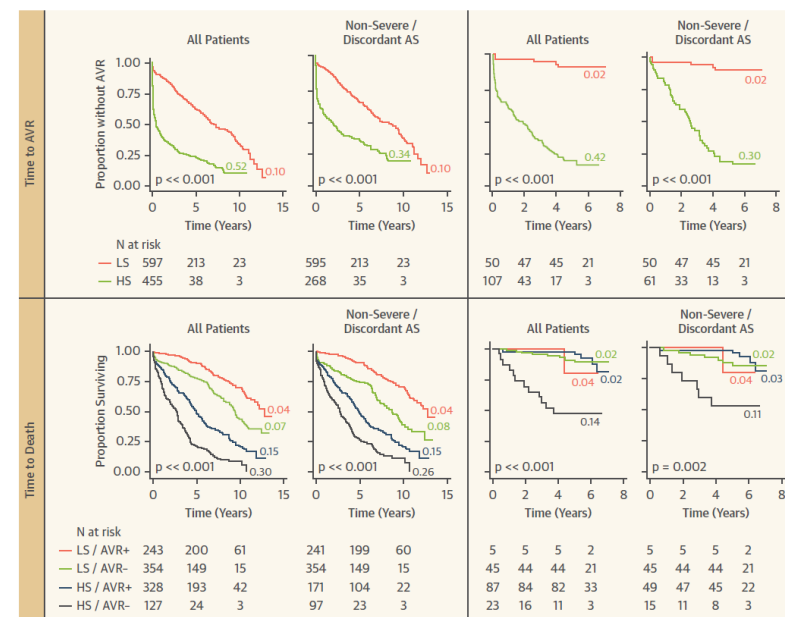
- MRI for early assessment of LV fibrosis
 - Reactive interstitial fibrosis(reversible)
 - Focal replacement fibrosis (irreversible)



Moderate Aortic Stenosis: Risk Stratification

Artificial Intelligence

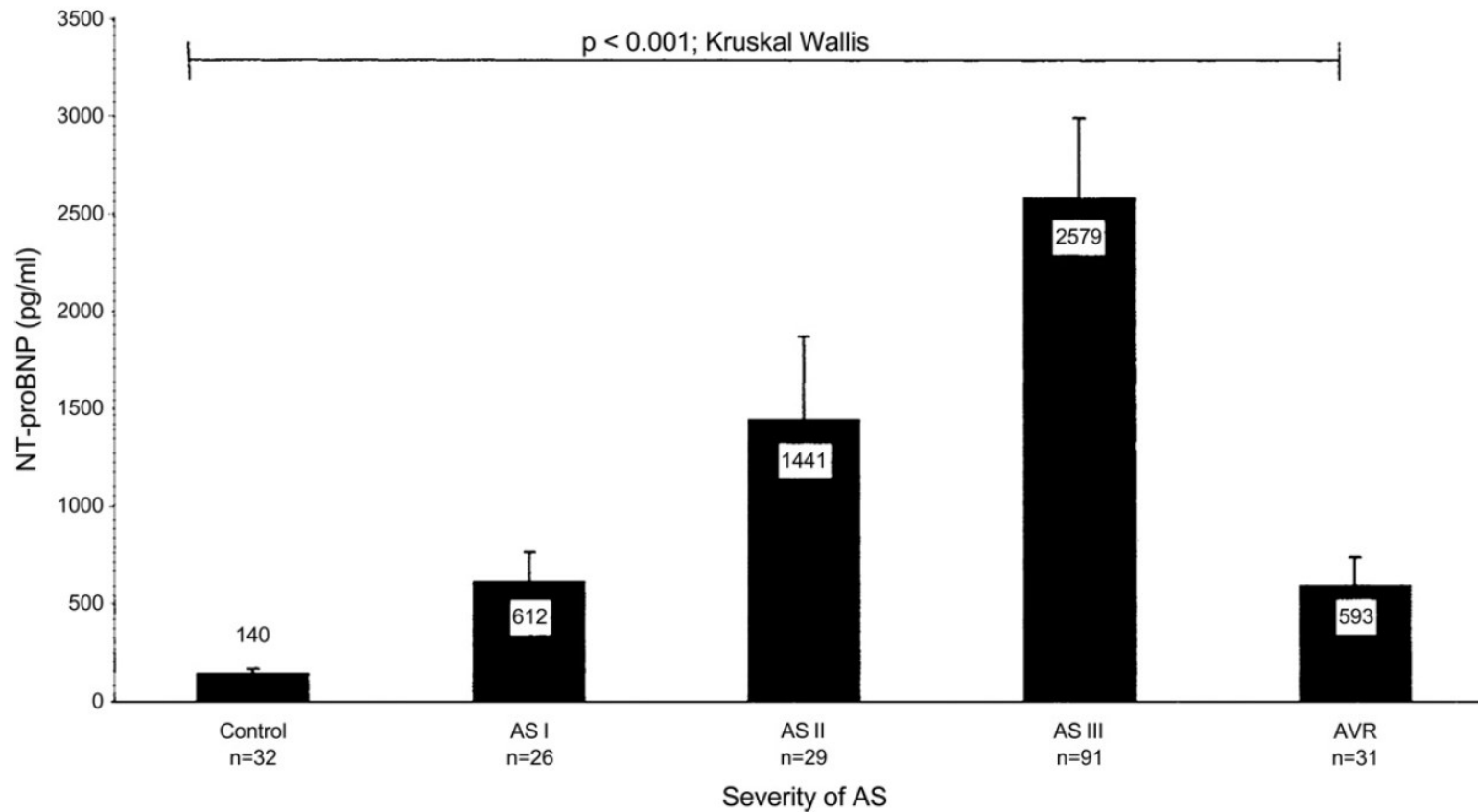
A Machine-Learning Framework to Identify Distinct Phenotypes of Aortic Stenosis Severity



Segupta PP et al, JACC 2021

Moderate Aortic Stenosis: Risk Stratification

- NT-pro BNP Levels According to Severity of AS



Steadman CD et al, JACC 2010



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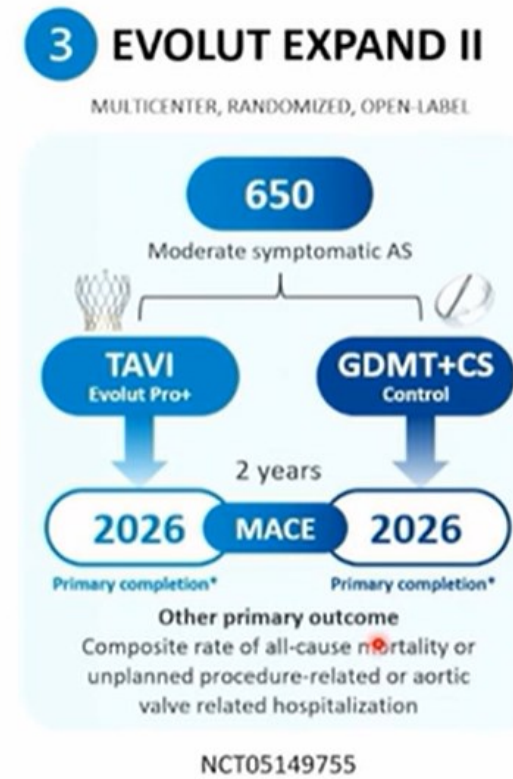
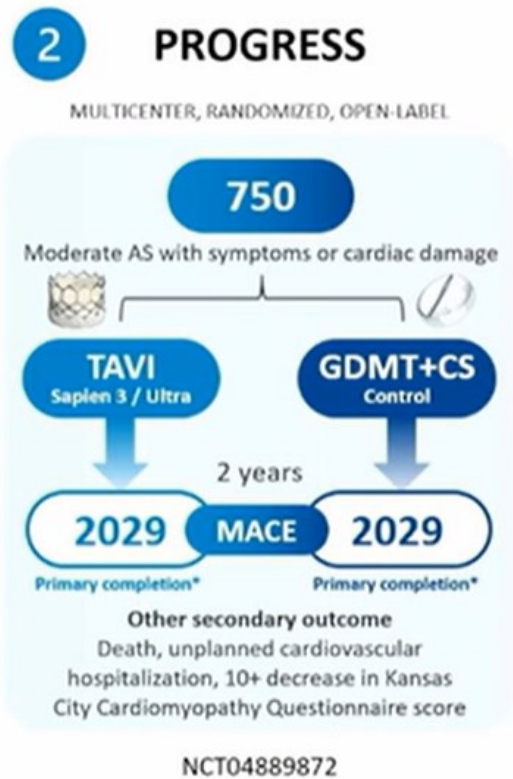
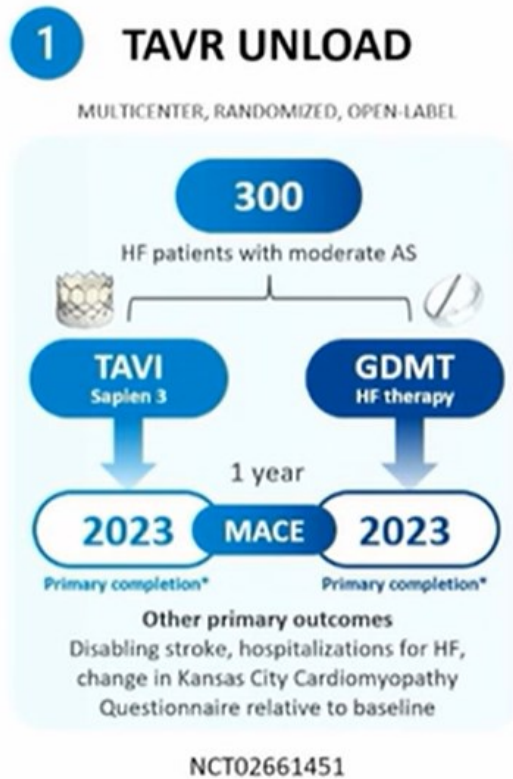
Conclusions(1)

- Aortic Stenosis is a valvular and a ventricular disease
- Moderate AS is associated with increased mortality
- The diagnosis of Moderate AS can be difficult and complicated due to discordant grading
- The high mortality rates seems to be mainly related to co-morbidities and LV dysfunction

Conclusions(2)

- Patients with Moderate AS need to be followed in specialized valvular heart disease clinics
- Advanced risk stratification with strain imaging ,CT, MRI, artificial intelligence and biological markers may help in advising for early intervention in patients with aortic stenosis

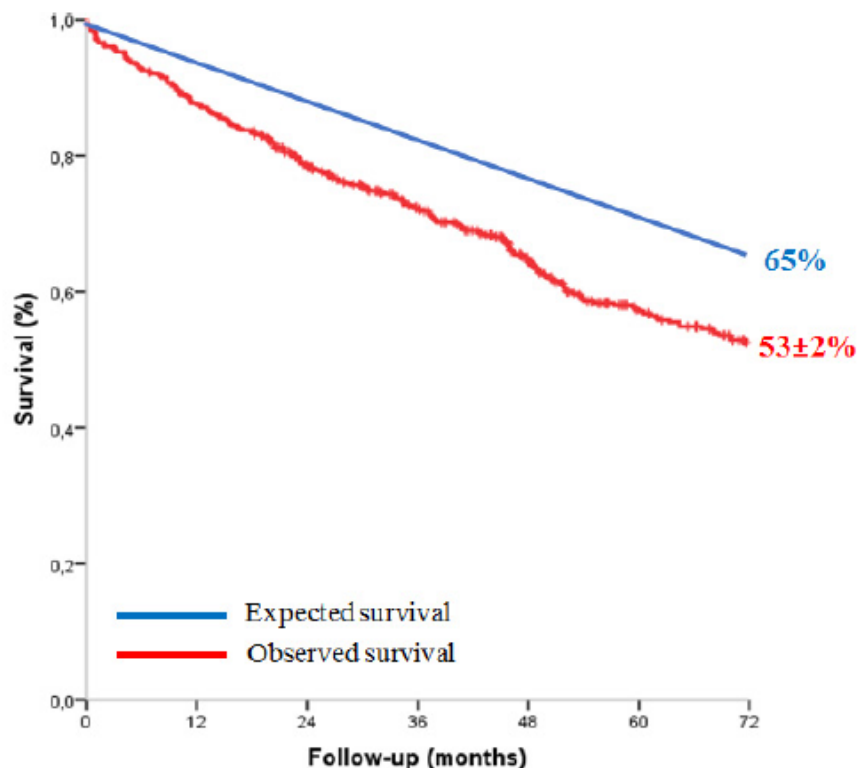
The Future: TAVR Trials in Moderate Aortic Stenosis



Thank You!



Survival of Patients with Moderate AS



	12 months	24 months	36 months	48 months	60 months	72 months
Expected survival (%)	94	88	82	76	70	65
Observed survival (%)	87	78	72	64	57	53
Relative survival (%)	92.5	88.6	87.8	84.2	81.4	81.5

Variables	Surgery	
	Multivariable Analysis	
	HR (95% CI)	P Value
Model 1		
Age (per 1-y increment)	1.05 (1.04–1.07)	<0.001
Male sex (yes vs no)	0.92 (0.70–1.22)	0.563
BSA (per 1-cm ² decrement)	0.70 (0.35–1.44)	0.337
NYHA class (III–IV vs I–II)	1.10 (0.78–1.55)	0.600
Prior atrial fibrillation (yes vs no)	1.36 (1.05–1.76)	0.019
Mean pressure gradient (per 1-mm Hg increment)	1.01 (0.99–1.02)	0.760
Left ventricular ejection fraction (per 1% decrement)	0.99 (0.98–1.01)	0.584
Prior myocardial infarction (yes vs no)	1.04 (0.62–1.76)	0.880
Moderate-to-severe valve calcification (yes vs no)	1.19 (0.90–1.57)	0.222
Charlson comorbidity index (per 1-unit increment)	1.13 (1.07–1.22)	<0.001

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



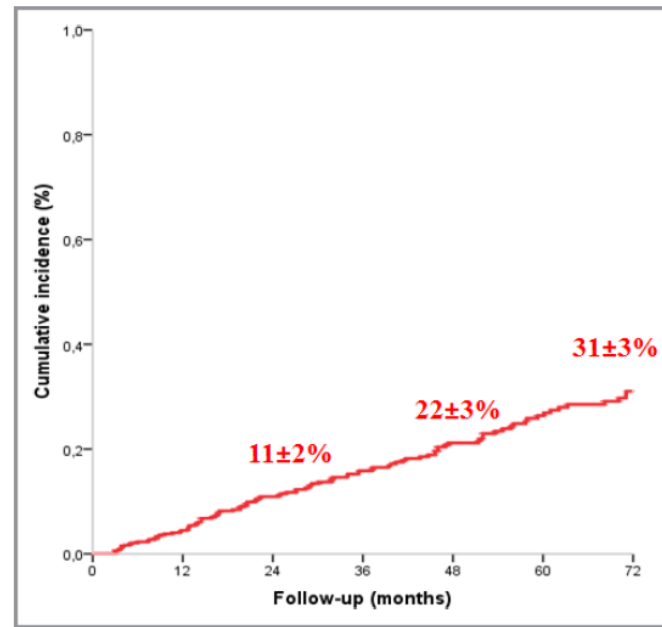
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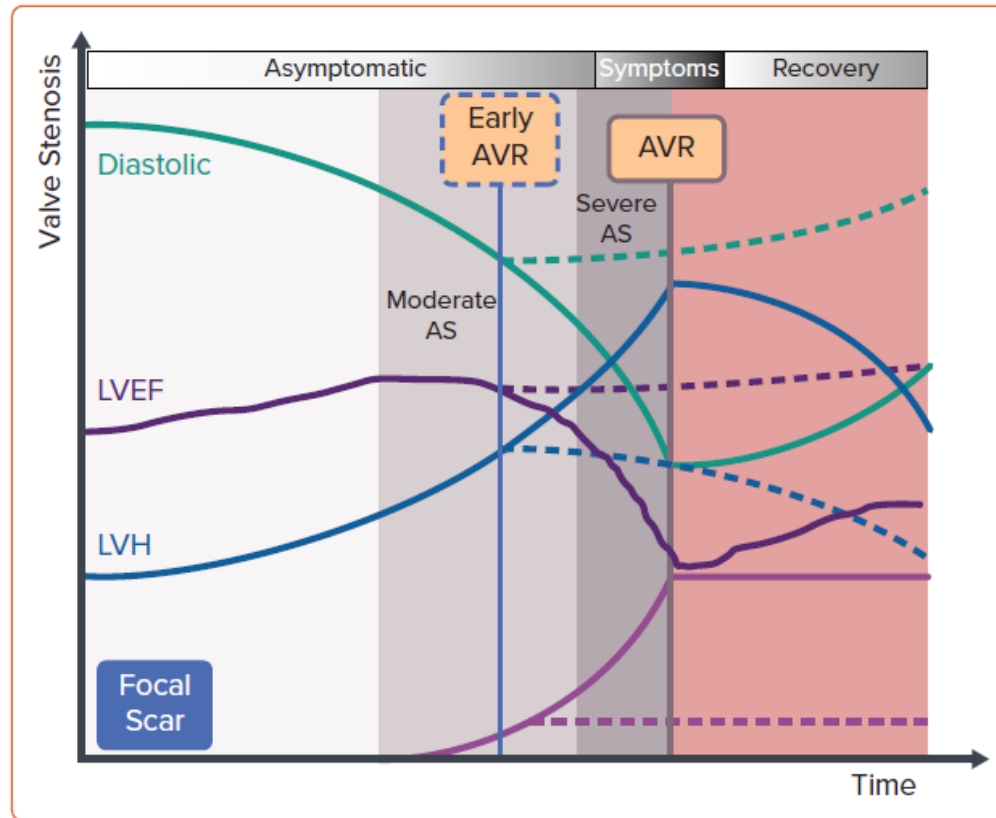
Characteristics and Prognosis of Patients With Moderate Aortic Stenosis and Preserved Left Ventricular Ejection Fraction

Cumulative Incidence of Surgery

n=508
Age 75 ± 11 years
Follow-up time 47 months



Imaging Parameters in Aortic Stenosis



Prognostic Significance of Discordant Severity Criteria In Moderate AS

Table 4 Uni- and multivariate Cox proportional hazard analyses for the identification of independent correlates of all-cause mortality

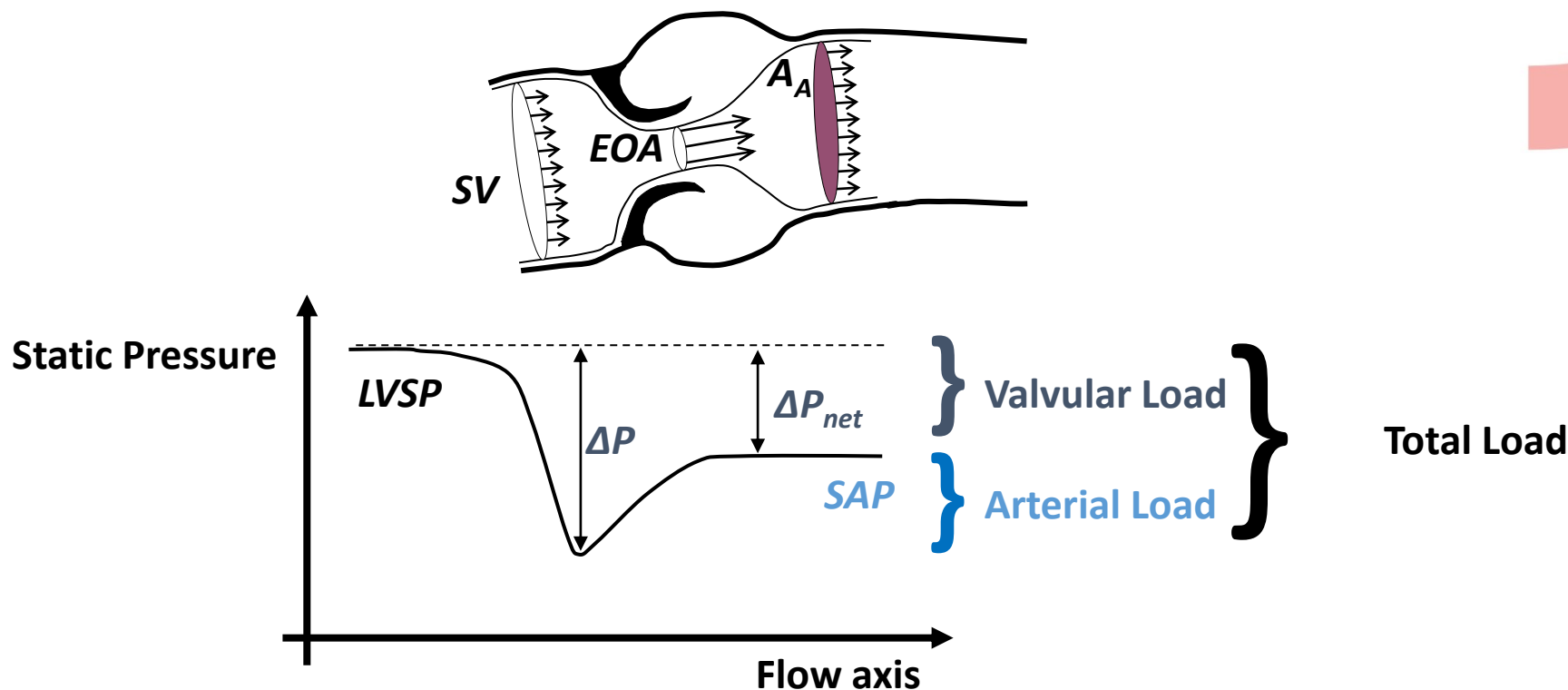
	Univariate analysis		Multivariate analysis	
	Hazard ratio (95% CI)	P value	Hazard ratio (95% CI)	P value
Age (per 1 year increase)	1.05 (1.03 to 1.06)	<0.001	1.04 (1.02 to 1.05)	<0.001
Male	1.00 (0.81 to 1.22)	0.973		
Previous MI (yes/no)	1.72 (1.33 to 2.22)	<0.001		
eGFR <60 mL/min/1.73 m ² (yes/no)	2.55 (2.07 to 3.15)	<0.001	2.15 (1.71 to 2.70)	<0.001
LV hypertrophy (yes/no)	1.75 (1.39 to 2.20)	<0.001	1.67 (1.30 to 2.15)	<0.001
LVEDV index (per 1 mL/m ² increase)	1.007 (1.003 to 1.011)	0.001		
Moderate/severe MR (yes/no)	1.50 (1.05 to 2.13)	0.025		
Stroke volume index (per unit increase)	0.986 (0.977 to 0.996)	0.005		
TAPSE <1.7 cm (yes/no)	1.71 (1.18 to 2.47)	0.004		
Type of moderate AS				
Concordant moderate AS +LVEF≥50%	Reference	...	Reference	...
Discordant moderate AS +LVEF<50%	3.11 (2.26 to 4.27)	<0.001	2.78 (2.00 to 3.87)	<0.001
Discordant moderate AS +LVEF≥50%	1.46 (1.06 to 2.01)	0.022	1.01 (0.78 to 1.56)	0.595
Concordant moderate AS +LVEF<50%	2.12 (1.49 to 3.01)	<0.001	1.58 (1.06 to 2.36)	0.025



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Left Ventricular Afterload in Aortic Stenosis = Valvular Load + Arterial Load



Valvulo-Arterial Impedance

$$Z_{va} = \frac{LVSP}{SVi} = \frac{SAP + \Delta P_{Mean}}{SVi}$$

>3.5: Moderate
>4.5: Severe

Briand et al, JACC, 2005
Hachicha et al., Circulation, 2007



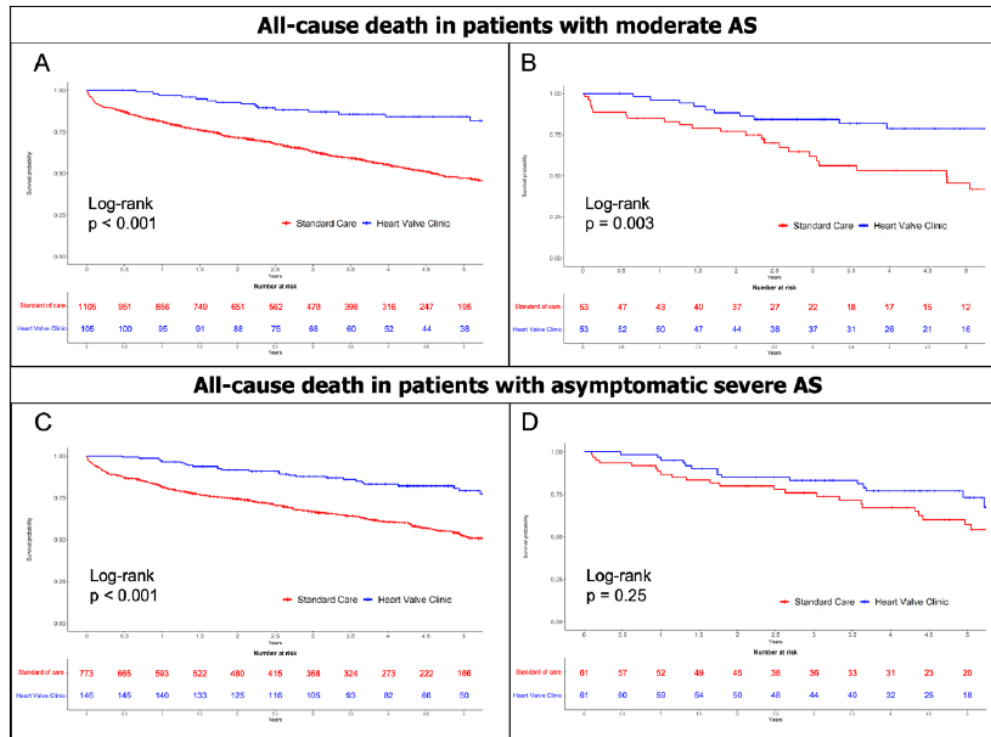
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Original research

Outcomes in patients with moderate and asymptomatic severe aortic stenosis followed up in heart valve clinics

n=1210



n=919

Unmatched

Matched

n=106

- Age 76.5 ± 12.8 YO
- F/U Time: 4.8 ± 1.8 Y

- Heart Valve Clinic
- Standard Care

n=122

HVC was significant predictor of reduced mortality in patients with moderate AS