TAVR in Moderate AS with Heart Failure

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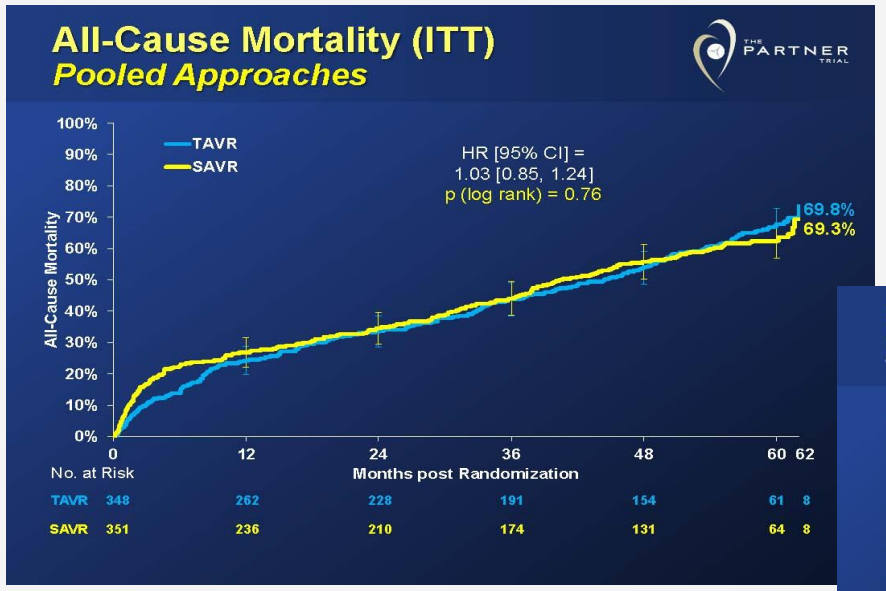
Disclosure

Speaker's name : Michael Kang-Yin Lee

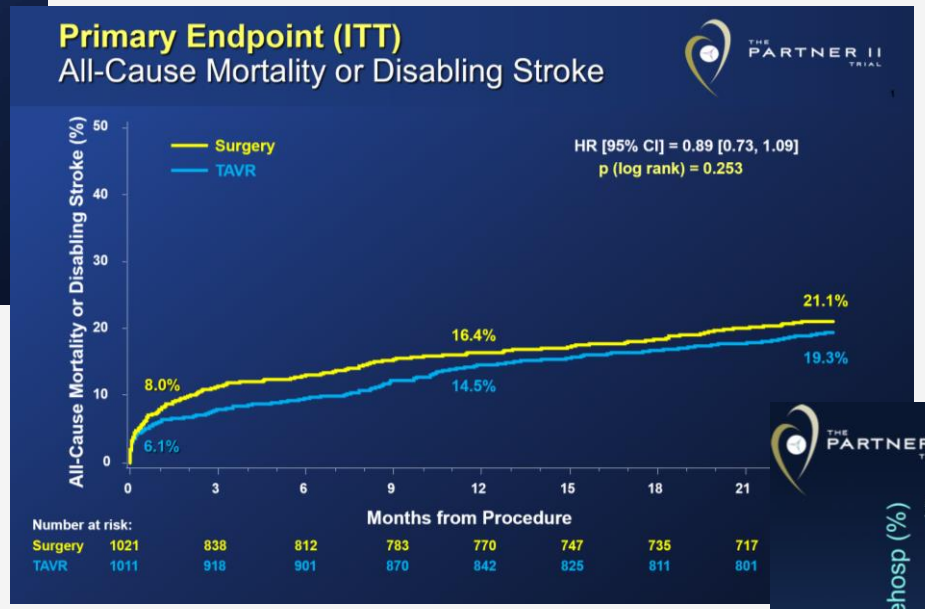
☑ TAVI Proctor: Medtronic, Edwards, Abbott, TricValve, JenaValve Trilogy

☑ LAAO Proctor: Abbott, Boston Scientific

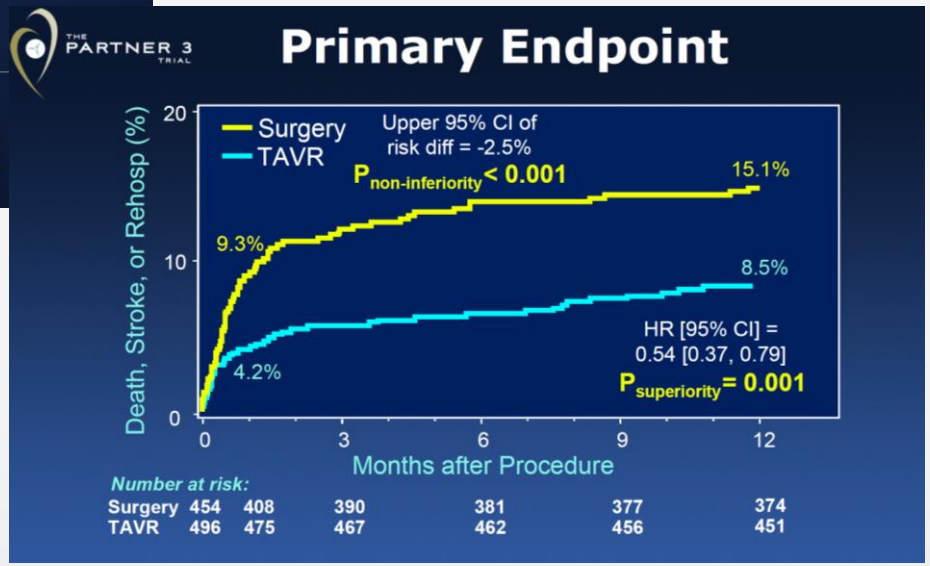
Balloon-expandable valve



"High-risk"

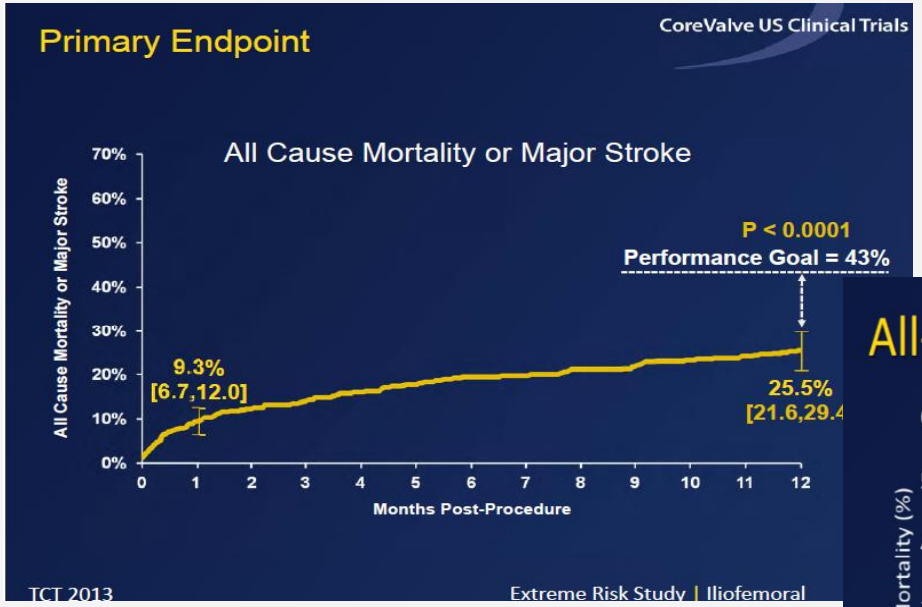


"Intermediate-risk"

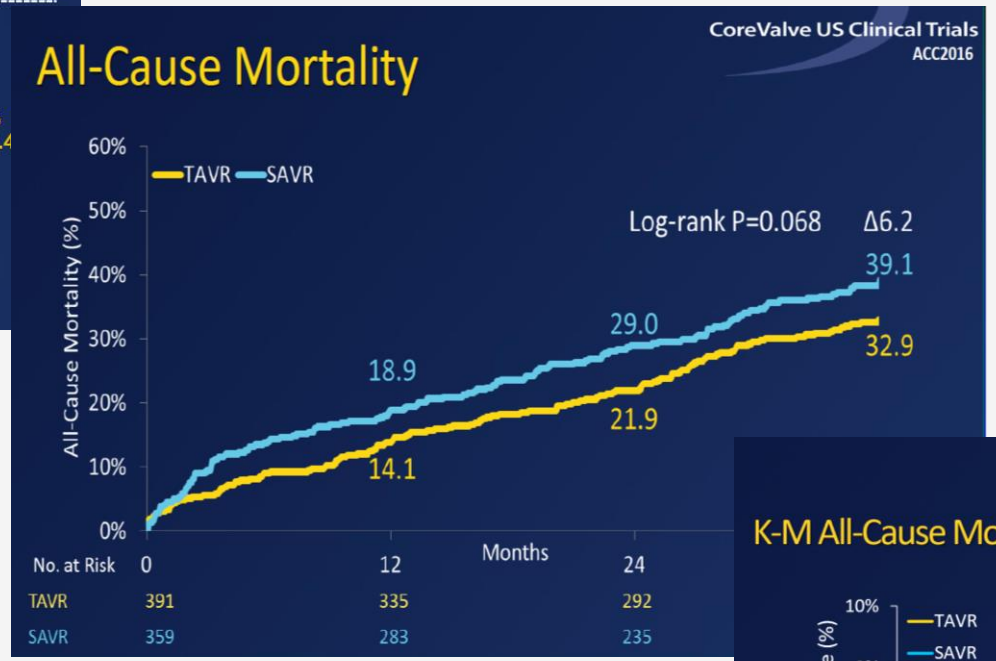


"Low-risk"

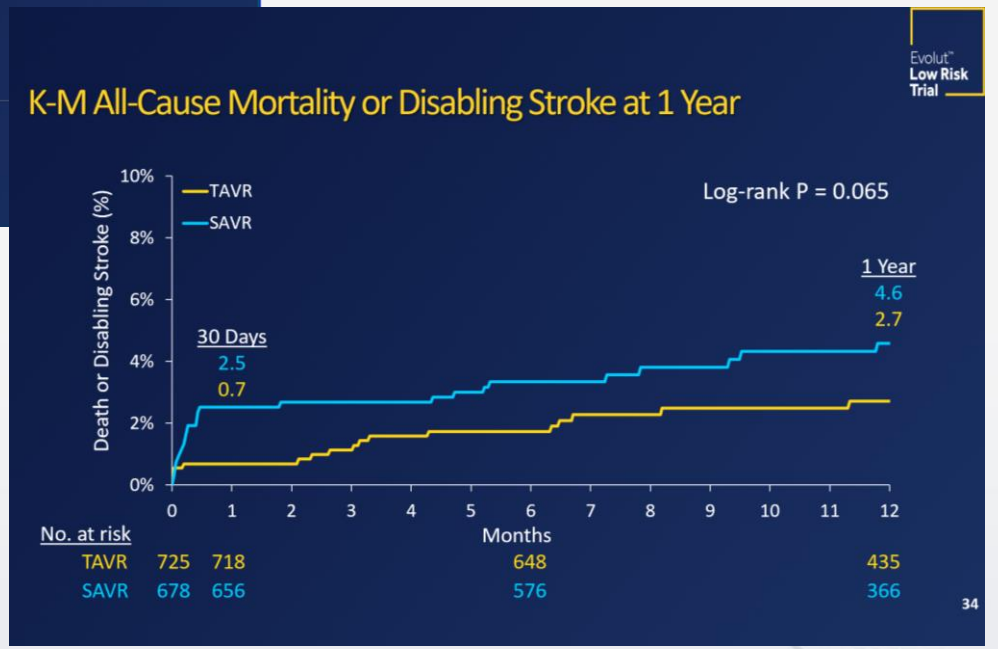
Self-expanding valve



"Extreme-risk"



"High-risk"



"Low-risk"

29th TCTAP2024
CVRF

Grading of AS severity

	Sclerosis	Mild AS	Moderate AS	Severe AS
Maximum velocity (m/s)	≤2.5	2.6–2.9	3.0–4.0	≥4.0
Mean pressure gradient (mmHg)		<20	20–40	≥40
AVA (cm^2)		>1.5	1.0–1.5	<1.0
AVA indexed (cm^2/m^2)		>0.85	0.60–0.85	<0.60
Dimensionless index		>0.50	0.25–0.50	<0.25
CT calcium score			Men 800–2000 AU Women 400–1200 AU	Men ≥ 2000 AU Women ≥ 1200 AU
Valvulo-arterial impedance ($mmHg/mL/m^2$)		<3.5	3.5–4.5	>4.5

J. Bax, et al. Eur Heart J, Volume 45, Issue 11, 14 March 2024, Pages 912–921, https://doi.org/10.1093/eurheartj/ehae050

Recommendations for Timing of Intervention of AS
Referenced studies that support the recommendations are summarized in Online Data Supplements 4, 6-10.

COR	LOE	RECOMMENDATIONS
1	A	1. In adults with severe high-gradient AS (Stage D1) and symptoms of exertional dyspnea, HF, angina, syncope, or presyncope by history or on exercise testing, AVR is indicated (74-80).
1	B-NR	2. In asymptomatic patients with severe AS and an LVEF <50% (Stage C2), AVR is indicated (81-84).
1	B-NR	3. In asymptomatic patients with severe AS (Stage C1) who are undergoing cardiac surgery for other indications, AVR is indicated (57,63,85-87).
1	B-NR	4. In symptomatic patients with low-flow, low-gradient severe AS with reduced LVEF (Stage D2), AVR is recommended (88-95).
1	B-NR	5. In symptomatic patients with low-flow, low-gradient severe AS with normal LVEF (Stage D3), AVR is recommended if AS is the most likely cause of symptoms (96-98).
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 (61,63,64,99).
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 (86,100-104).
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 (101,105-107).
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 (108,109).
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 (81-84,102).
2b	C-EO	11. In patients with moderate AS (Stage B) who are undergoing cardiac surgery for other indications, AVR may be considered.

5 Class 1
(Severe AS)

4 Class 2a
(Severe AS)

2 Class 2b
(1 Severe AS)
(1 Moderate AS)

Otto, Nishimura, Bonow et al. J Am Coll Cardiol. 2021 Feb, 77 (4) e25–e197

CVRF

Moderate AS Guidelines: Class 2B

2b	C-EO	11. In patients with moderate AS (Stage B) who are undergoing cardiac surgery for other indications, AVR may be considered.

Otto, Nishimura, Bonow et al. J Am Coll Cardiol. 2021 Feb, 77 (4) e25–e197

Follow-up in Patients With Aortic Stenosis

Aortic Severity	Follow-up Recommendation
Mild (Vmax 2.0–2.9 m/s)	Every 3-5 years
Moderate (Vmax 3.0–3.9 m/s)	**Every 1-2 years**
Severe Asymptomatic (Vmax ≥4 m/s)	Every 6-12 months

Vmax = peak aortic velocity. Adapted from Otto et al.

Otto, Nishimura, Bonow et al. J Am Coll Cardiol. 2021 Feb, 77 (4) e25–e197

AS is a rapidly progressive disease

Annualized increase in:

- Mean pressure gradient of 4.1mmHg
- Decrease in AVA of 0.08cm^2
- Worsening of aortic valve calcification (by CT) of 158.5AU

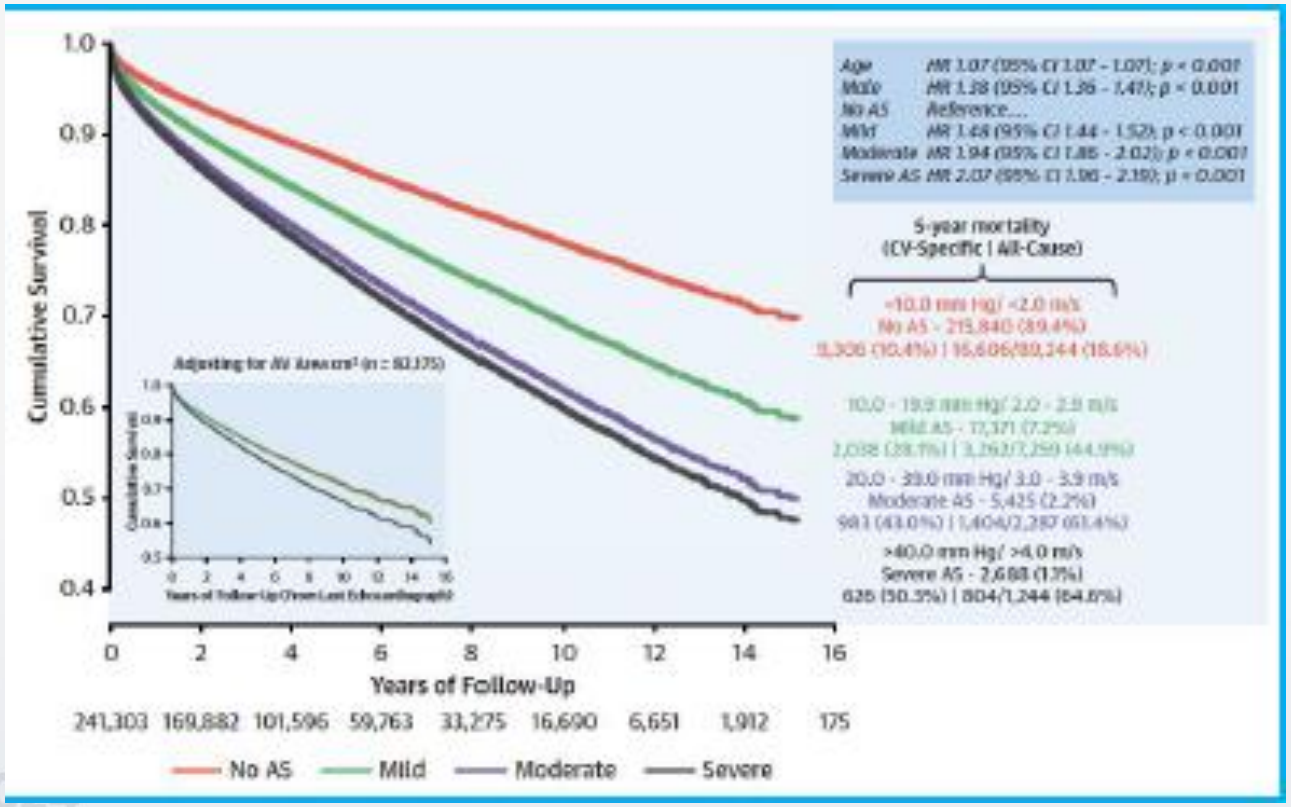
Increasing baseline severity of AS predictive of higher rates of progression

DG Bohbot et al. J Am Heart Assoc 2019;8:e011036

Moderate AS as Bad as Severe AS?

Poor Long-Term Survival in Patients With Moderate Aortic Stenosis

Geoff Strange, PhD,[a] Simon Stewart, PhD,[b] David Celermajer, MD, PhD,[c] David Prior, MBBS, PhD,[d] Gregory M. Scalia, MBBS (Hons), MMedSc,[e] Thomas Marwick, MBBS, PhD,[f] Marcus Ilton, MD,[g] Majo Joseph, MBBS,[h] Jim Codde, PhD,[i] David Playford, MBBS, PhD,[a] on behalf of the National Echocardiography Database of Australia contributing sites



Why?

- Misclassification?

-Challenges of Echocardiogram to diagnose severe AS?

-Rapid conversion to severe AS?

-Already too much cardiac damage?

-Too late intervention?

Strange et al. J Am Coll Cardiol. 2019 Oct 15;74(15):1851-1863.

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Predictors of Mortality or Adverse Cardiac Events in Moderate AS

- **Atrial fibrillation**
- **Low EF (<60%)**
- **Severe Diastolic Dysfunction**
- **Fast progression of AS (>0.3m/s/year PV)**
- **Low SVI (<35cc/m^2)**
- **Elevated BNP**
- **Elevated AV Calcium Score by CT**

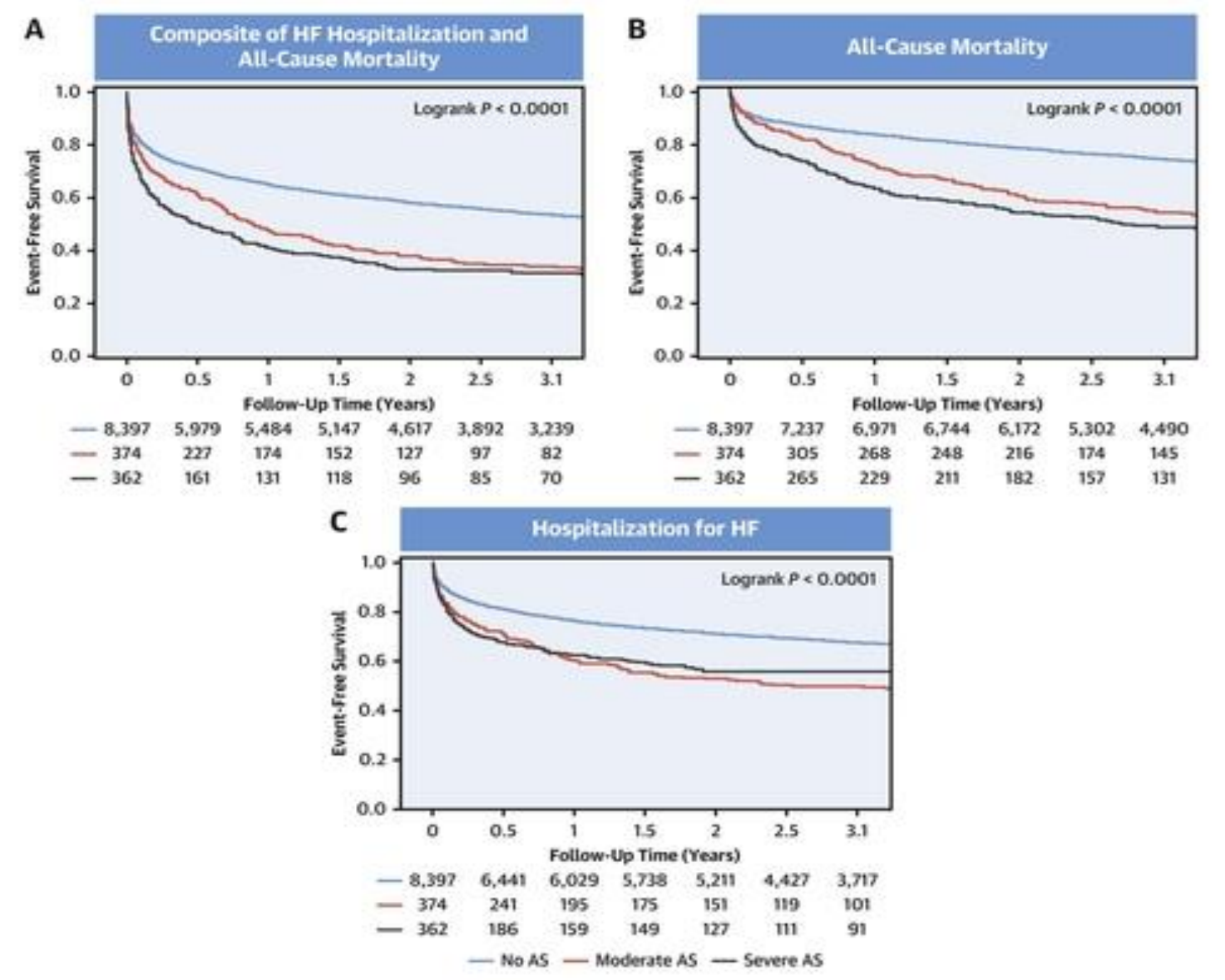
Kennedy et al. JACC 1991;17:313-9
Otto et al. Circulation 1997 95;9,2262-2220
Rosenhek et al. EHJ. 2004; 25,199-205
Yechoor et al. JTCS 2013; 145:25,1550-3

Lancelotti et al. JAMA Cardiol. 2018; 3 (11);1060-8
Strange et al. J Am Coll Cardiol 2019;74:1851–63
Delesalle et al. JAHA 2019;8

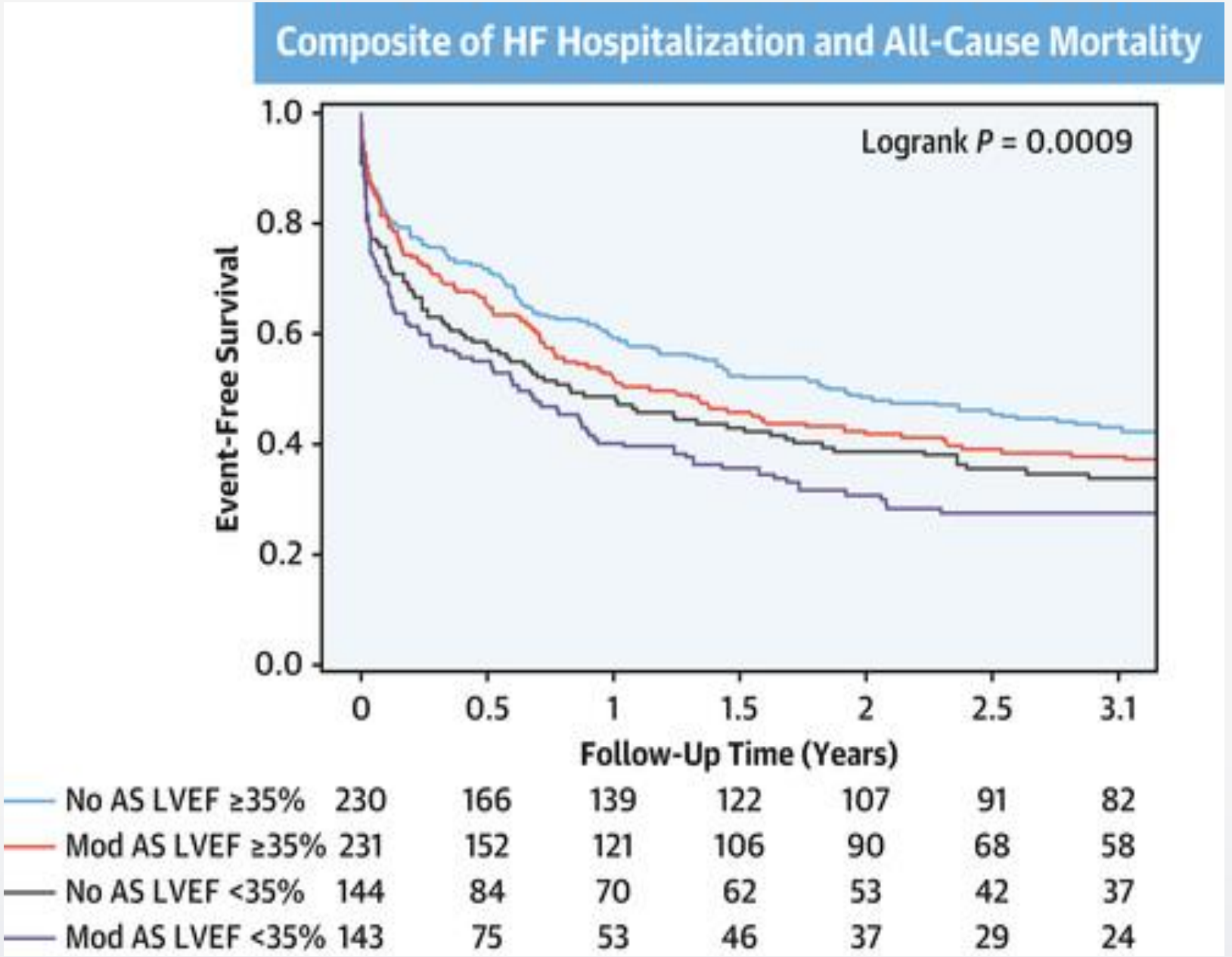
Murphy et al. Am J Cardiol.2019;124:1924−1931
Benfari et al. JASE; 2019:34 ;3:237-244
Ito et al. JASE 2021; 34(3):248-256

Samad et al. EHJ; 2016: 37, 2276–2286
Van Gils et al. JACC 2017;69:2383–92
Moon et al. KCJ; 2020 50(9):791-800

Patients with HFrEF stratified by AS severity



Kathleen R. Khan et al. *J Am Coll Cardiol* 2023; 81:1235-1244.



Kathleen R. Khan et al. *J Am Coll Cardiol* 2023; 81:1235-1244.

JACC: CARDIOVASCULAR INTERVENTIONS
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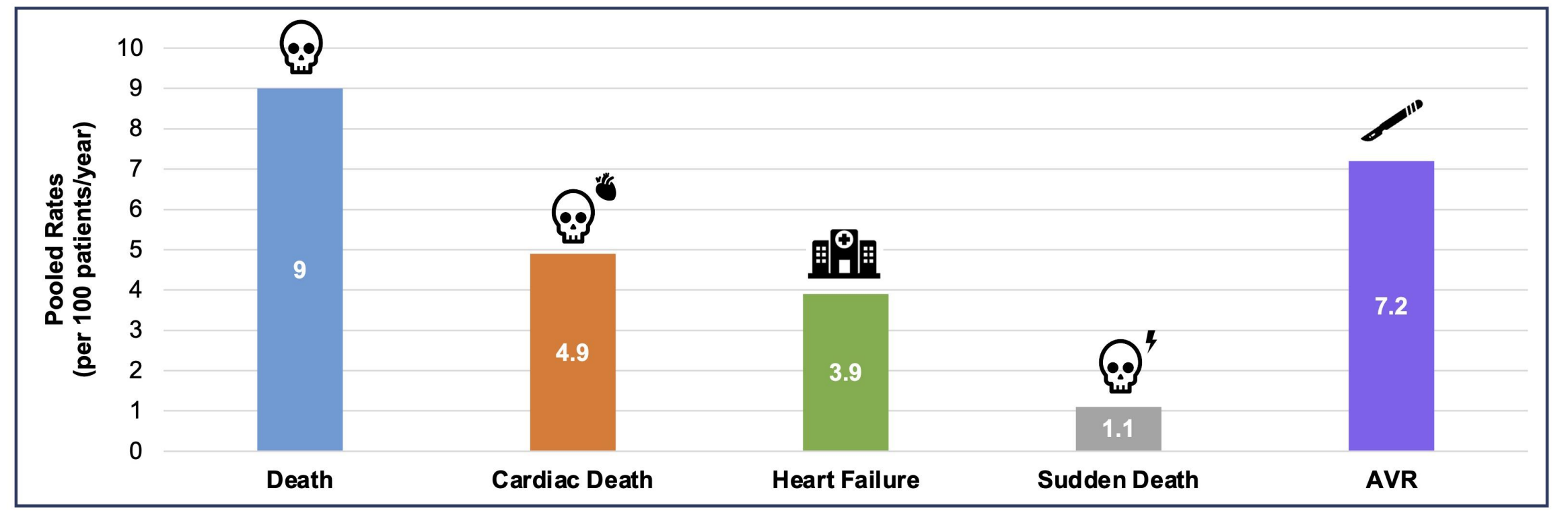
Impact of Moderate Aortic Stenosis on Long-Term Clinical Outcomes

A Systematic Review and Meta-Analysis

Augustin Coisne, MD, PhD,[a,b,c,*] Andrea Scotti, MD,[a,b,*] Azeem Latib, MD,[b] David Montaigne, MD, PhD,[c] Edwin C. Ho, MD,[b] Sebastian Ludwig, MD,[a,d] Thomas Modine, MD, PhD,[e] Philippe Généreux, MD,[f] Jeroen J. Bax, MD, PhD,[g] Martin B. Leon, MD,[a] Christophe Bauters, MD,[h] Juan F. Granada, MD[a]

25 studies
12,143 moderate AS patients
3.7 years of follow-up

Meta-analysis of adverse events



Similar results were obtained performing an alternative meta-analysis excluding the studies using definitions of moderate AS no longer supported by current guidelines (n=4)

Augustin Coisne et al. *J Am Coll Cardiol Intv* 2022; 15:1664-1674.

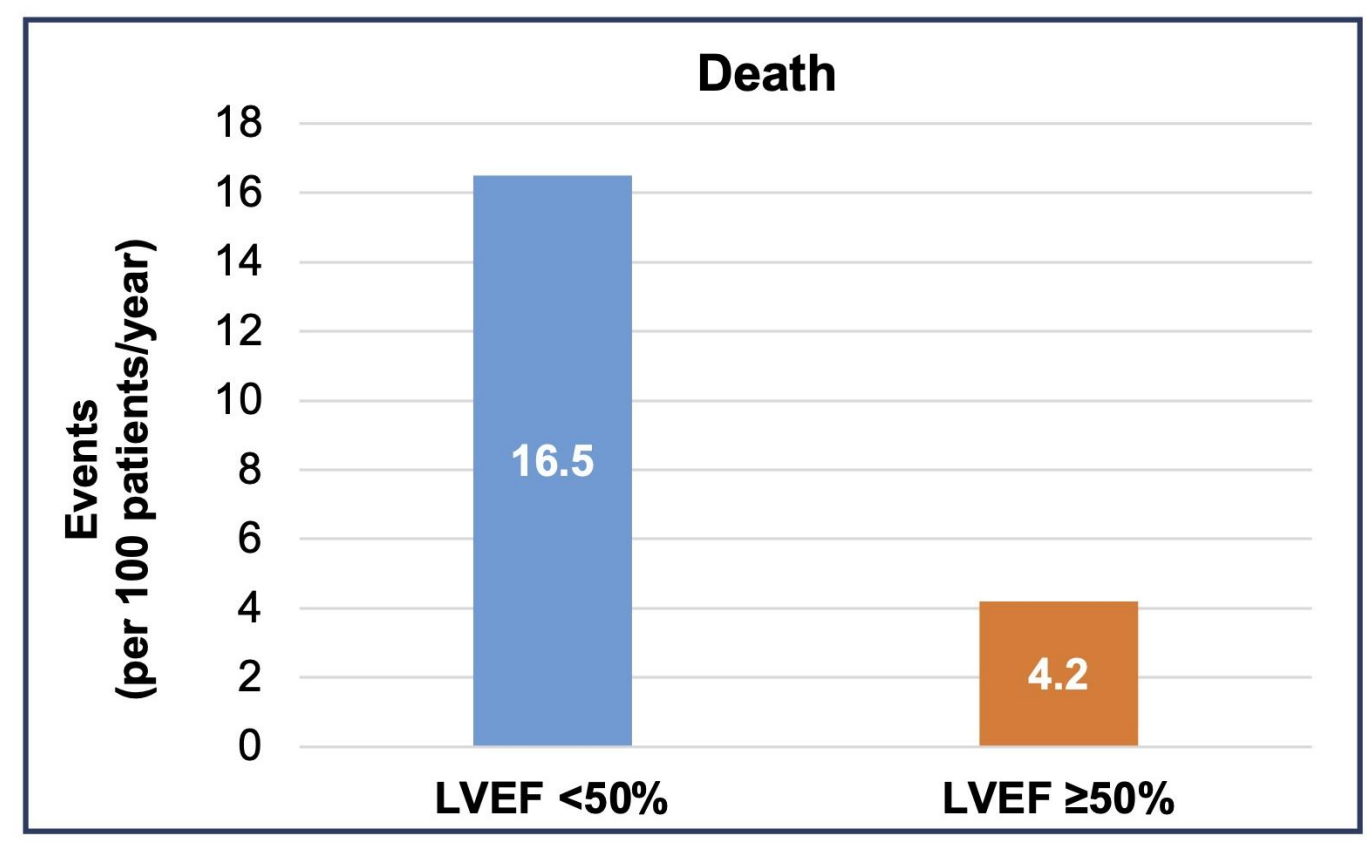
Meta-regression analysis of all-cause mortality

Covariate	β	Standard Error	Lower bound	Upper bound	p value
Year of publication	-0.006	0.014	-0.034	0.023	0.684
Age	0.039	0.034	-0.030	0.109	0.253
BMI	-0.167	0.108	-0.422	0.087	0.164
Sex (female)	-0.005	0.009	-0.024	0.014	0.601
Hypertension	-0.001	0.023	-0.050	0.048	0.967
Diabetes	0.039	0.015	0.007	0.071	0.019
Atrial Fibrillation	0.026	0.019	-0.015	0.067	0.194
Coronary Artery Disease	0.026	0.009	0.006	0.046	0.017
Stroke	0.005	0.024	-0.049	0.059	0.841
Chronic Obstructive Pulmonary Disease	0.024	0.034	-0.058	0.105	0.517
NYHA class III/IV	0.038	0.010	0.015	0.061	0.004
Symptoms	0.017	0.004	0.009	0.025	<0.001
Aortic Valve Area	-0.111	1.349	-2.958	2.736	0.935
Mean Aortic Gradient	-0.025	0.029	-0.086	0.037	0.408
LV Ejection Fraction	-0.049	0.017	-0.085	-0.014	0.009

Diabetes, coronary artery disease, presence of symptoms, and LV dysfunction were associated with a significant impact on the overall estimate of all-cause death

Augustin Coisne et al. *J Am Coll Cardiol Intv* 2022; 15:1664-1674.

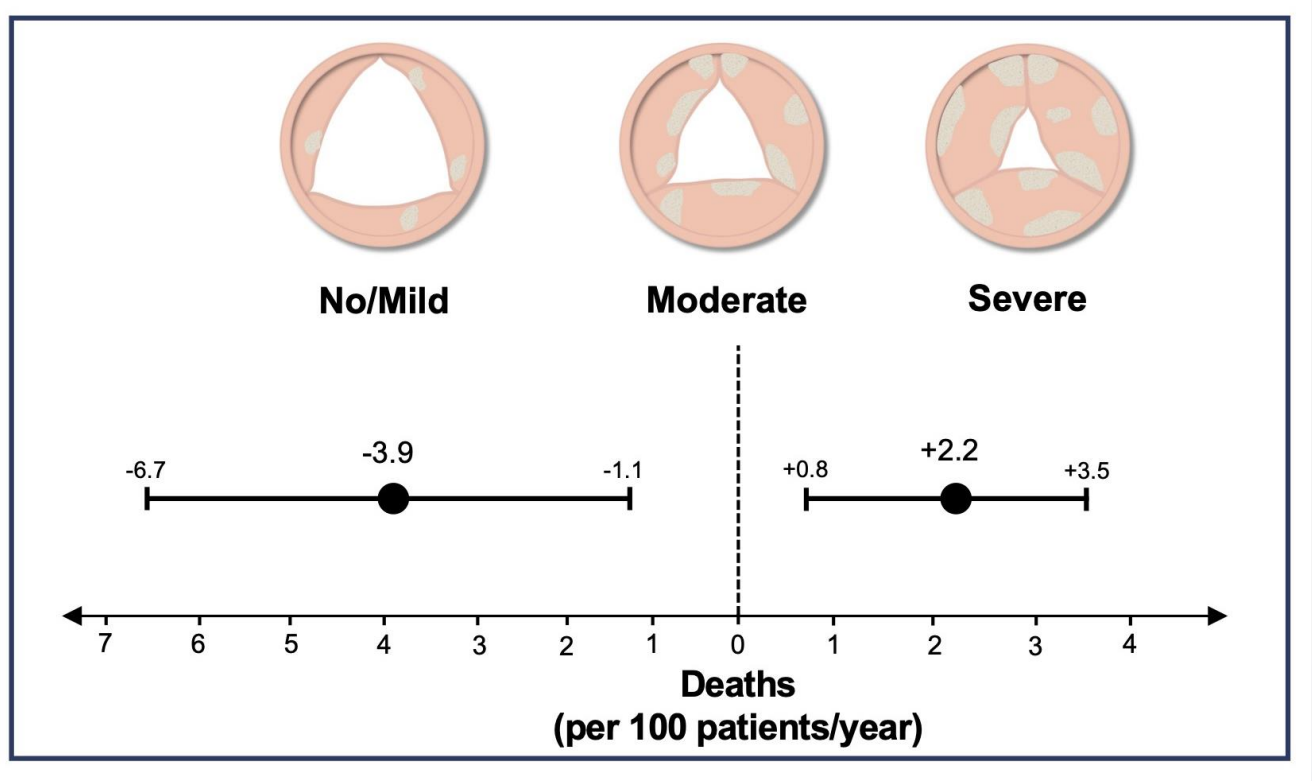
Subgroup analysis



All-cause mortality was higher in patients with reduced LVEF (<50%) than with normal LVEF, respectively 16.5 (95%CI: 5.2-52.3) and 4.2 (95%CI: 1.4-12.8) per 100 patients/year.

Augustin Coisne et al. *J Am Coll Cardiol Intv* 2022; 15:1664-1674.

Meta-analysis on the comparison with other stages of aortic stenosis



Compared to patients with moderate AS, the incidence rate difference of all-cause mortality was

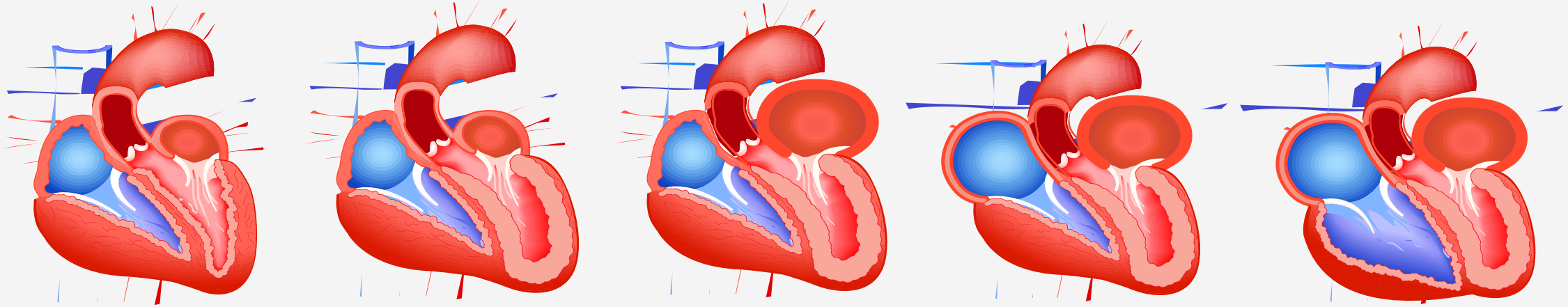
-3.9 per 100 patients/year for patients with no/mild AS

+2.2 per 100 patients/year for patients with severe AS

Augustin Coisne et al. *J Am Coll Cardiol Intv* 2022; 15:1664-1674.

Staging Classification of Patients with AS:

Specific Criteria



Stage 0 No damage	Stage 1 LV damage	Stage 2 LA/Mitral damage	Stage 3 PA/Tricuspid damage	Stage 4 RV damage
	Increased LV Mass Index >115 g/m^2 Male >95 g/m^2 Female	Indexed left atrial volume >34mL/m^2	PAS ≥60mmhg	Moderate-Severe RV dysfunction
	E/e' >14	Moderate-Severe MR	Moderate-Severe TR	
	EF <50%	Atrial Fibrillation		

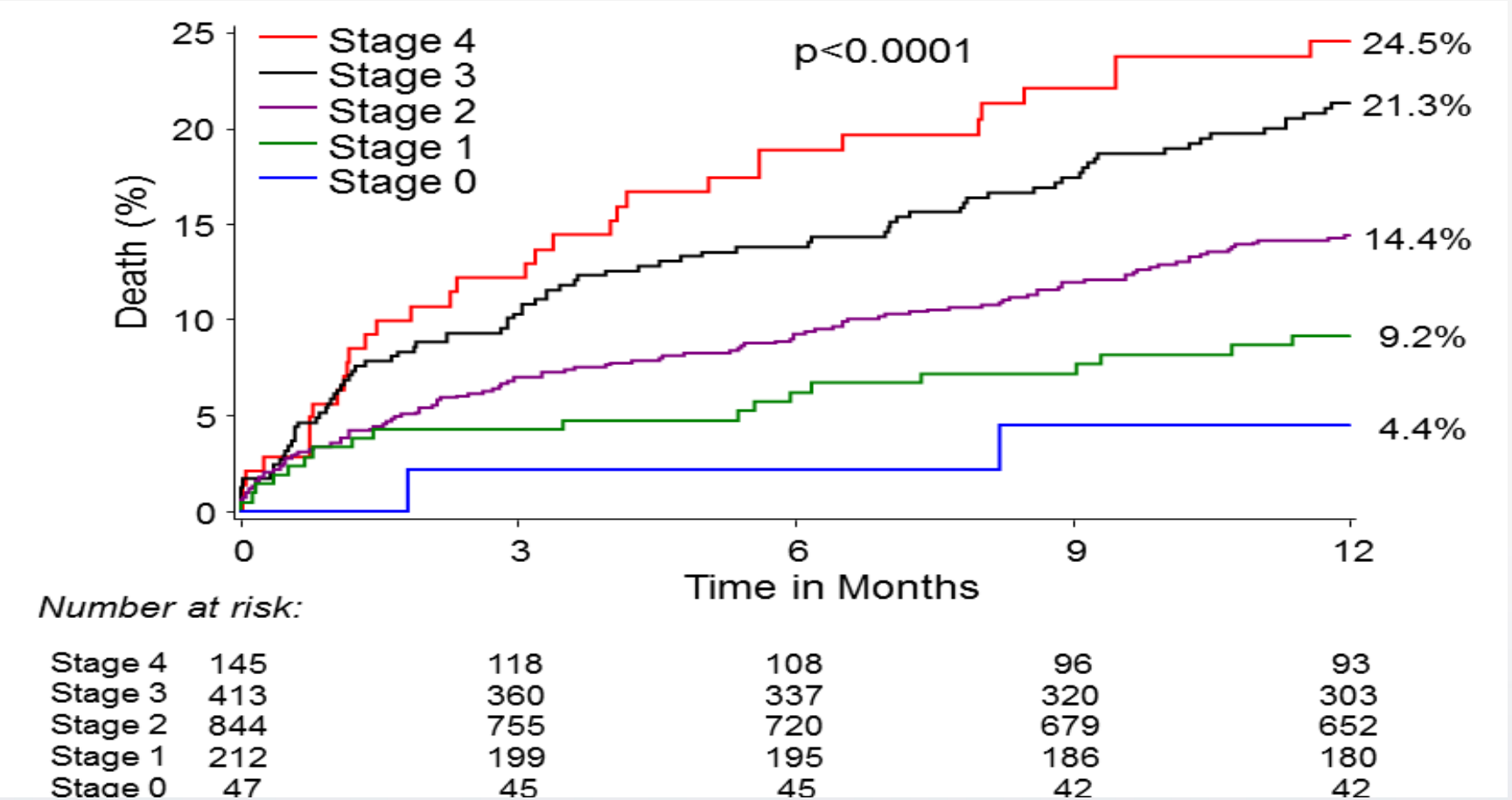
Patients hierarchically classified based on the presence of at least one variable in the highest stage (independent, not additive)

Généreux et al. Eur Heart J 2017 Jul 21

Extent of Cardiac Damage

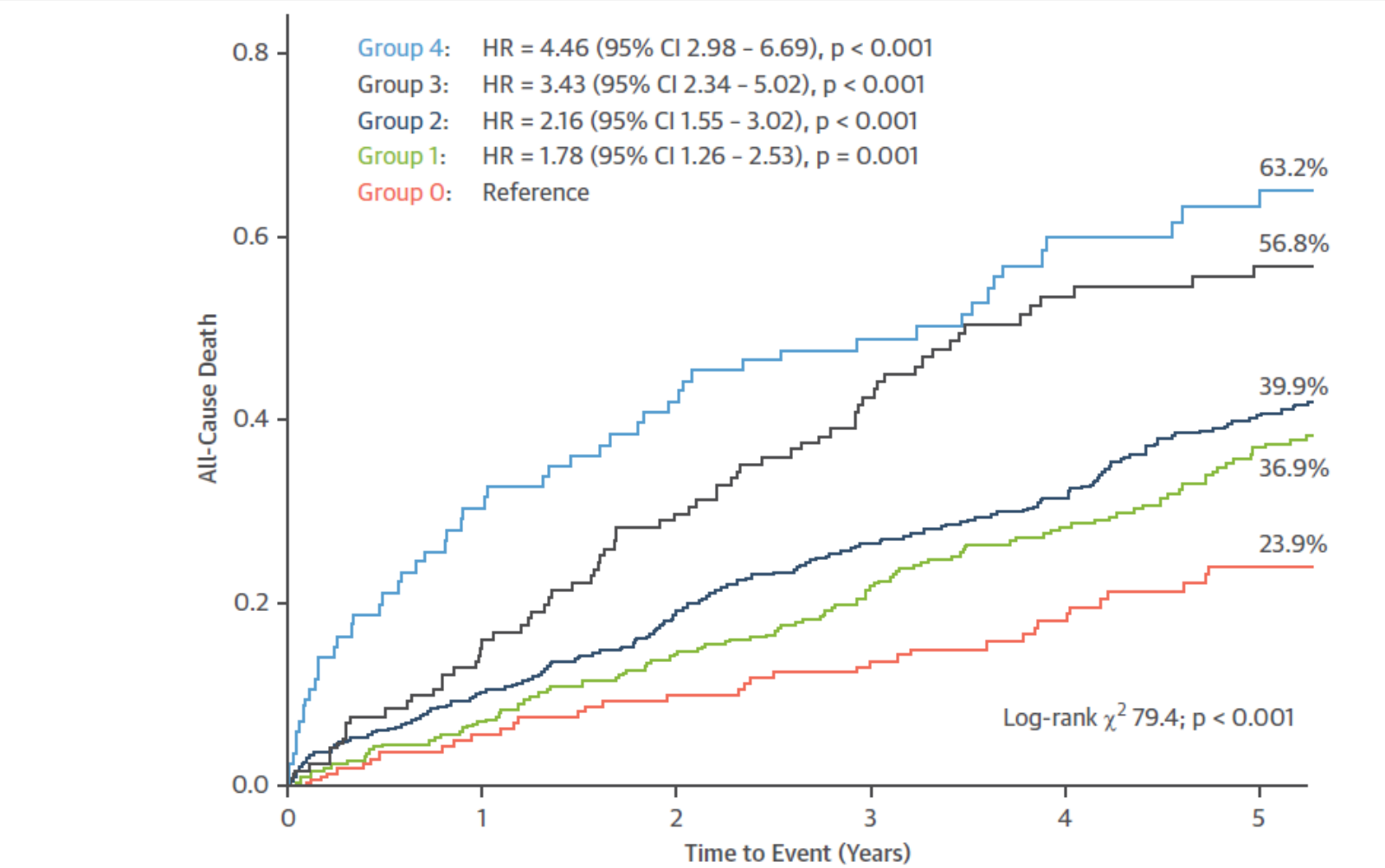
1-Year Death After AVR; N=1,661 pts.

Severe AS with Symptoms



Généreux et al. Eur Heart J 2017 Jul 21

Extent of Cardiac Damage Among Moderate AS
5-Year Death; N=1,245 pts.



Amanullah et al. JACC Imaging 2021

Symptomatic moderate aortic stenosis should undergo intervention

Pro

- High mortality in patients with moderate aortic stenosis was found in several studies including large registries
- Analyses of observational data suggest association of intervention with improved survival
- Moderate stenosis can rapidly progress to severe stenosis
- Risk of intervention has become low
- Risk factors may help identifying patients likely to benefit from intervention

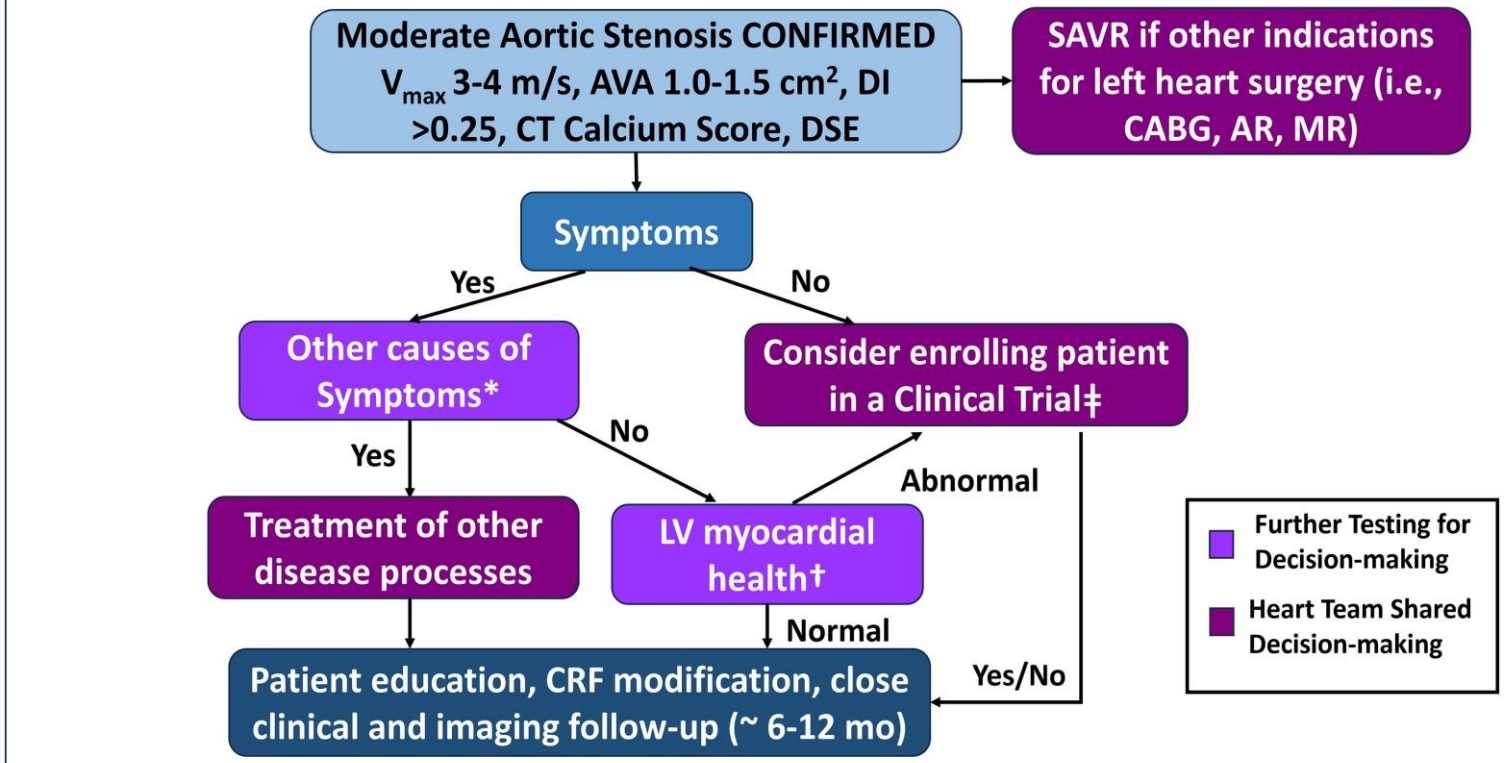
Symptomatic moderate aortic stenosis

Contra

- Increased mortality may be related to important comorbidities. Causative relationship between valve stenosis and outcome?
- Required randomized controlled trials are still not available
- Early and late risks of valve intervention must be weighed against potential benefit
- Severe stenosis may be misclassified as moderate:
  - low flow-low gradient
  - failure to capture highest velocity
  - failure to calculate valve area
  - additional tests not performed (f.e. CT)
  - failure to consider patient's size

J. Bax, et al. Eur Heart J, Volume 45, Issue 11, 14 March 2024, Pages 912–921, https://doi.org/10.1093/eurheartj/ehae050

Approach to evaluation of patients with moderate aortic stenosis



* Coronary artery disease, hypertension, diastolic dysfunction, atrial fibrillation, amyloid, chronic obstructive pulmonary disease, renal disease, diabetes, obesity, concomitant aortic regurgitation, mitral regurgitation or tricuspid regurgitation.

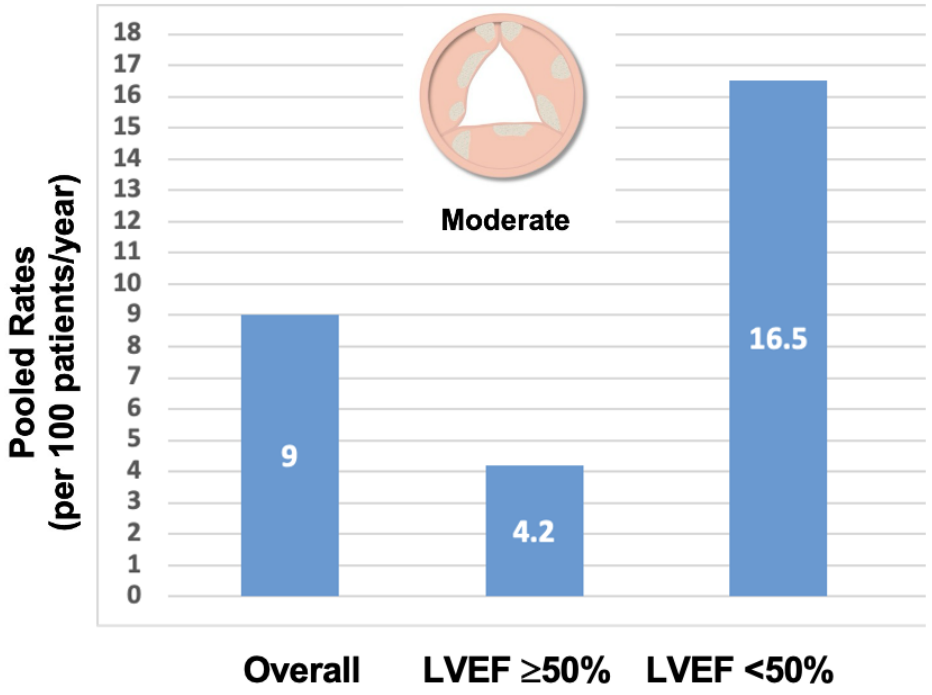
† Reduced LVEF or evidence of myocardial structural changes by imaging or heart failure by biomarkers

‡ Enrollment in a clinical trial may be considered to evaluate: 1) the effect of medical therapy on patients with asymptomatic moderate aortic stenosis, and 2) the benefit of transcatheter aortic valve intervention in patients with symptomatic moderate aortic stenosis and evidence of structural myocardial changes.

Abbreviations: AR = aortic regurgitation, AS = aortic stenosis, AVA = aortic valve area, CABG = coronary artery bypass grafting, CRF = cardiac risk factors, CT = computed tomography, DI = Doppler index, DSE = dobutamine stress echocardiography, Dx = diagnosis, MR = mitral regurgitation, Rx = treatment, SAVR = surgical aortic valve replacement, V_{max} = maximum velocity

J. Bax, et al. Eur Heart J, Volume 45, Issue 11, 14 March 2024, Pages 912–921, https://doi.org/10.1093/eurheartj/ehae050

Moderate AS Clinical Trials



TAVR UNLOAD	*recruiting*
PROGRESS	*recruiting*
EXPAND TAVR II	*recruiting*

Augustin Coisne et al. *J Am Coll Cardiol Intv* 2022; 15:1664-1674.

TAVR UNLOAD

TAVR UNLOAD Trial

International Multicenter Randomized

LV-EF< 50% & Moderate AS

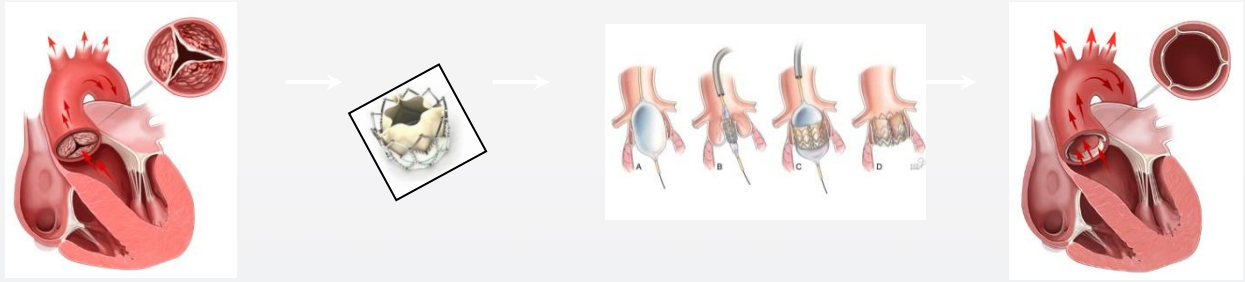
R

TAVR + OHFT

OHFT alone

Follow-up: 1, 6 months 1 & 2 years

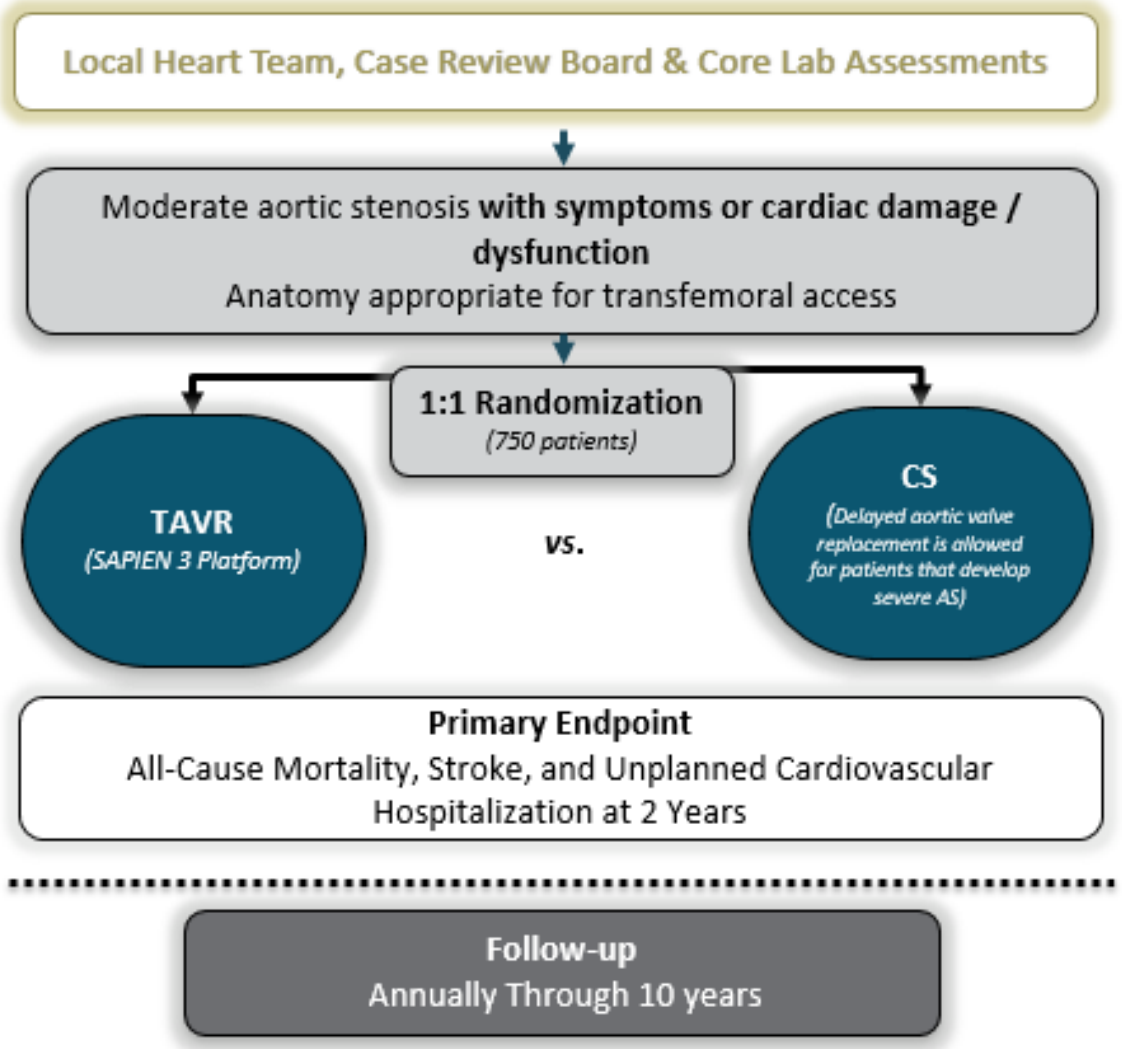
Clinical endpoints Symptoms Echo QoL



Spitzer et al. AHJ 2016;182:80-88

Study Design

THE PROGRESS TRIAL



Inclusion Criteria

THE PROGRESS TRIAL

1

- **≥65 Years**

2

- **Moderate AS**

1. Moderate AVA

AVA 1.0 – 1.5cm² OR

AVA < 1.0 cm² with AVAi > 0.6 cm²/m² if BMI <30kg/m²; OR

AVA < 1.0 cm² with AVAi > 0.5 cm²/m² if BMI ≥30kg/m²

AND

2. Moderate peak aortic velocity or gradient:

Peak velocity 3.0 to < 4.0 m/s OR

Mean gradient 20 to < 40mmHg

3

- **Symptoms**
- **-or-**
- **Cardiac Damage or Dysfunction**

1. Evidence of Symptoms

NYHA ≥2, dyspnea, angina, syncope

OR

2. Evidence of Cardiac Damage or Dysfunction

LVEF <60%

Diastolic dysfunction ≥ Grade 2

Stroke volume index < 35 mL/m²

Persistent atrial fibrillation or any paroxysmal episode within 6 months

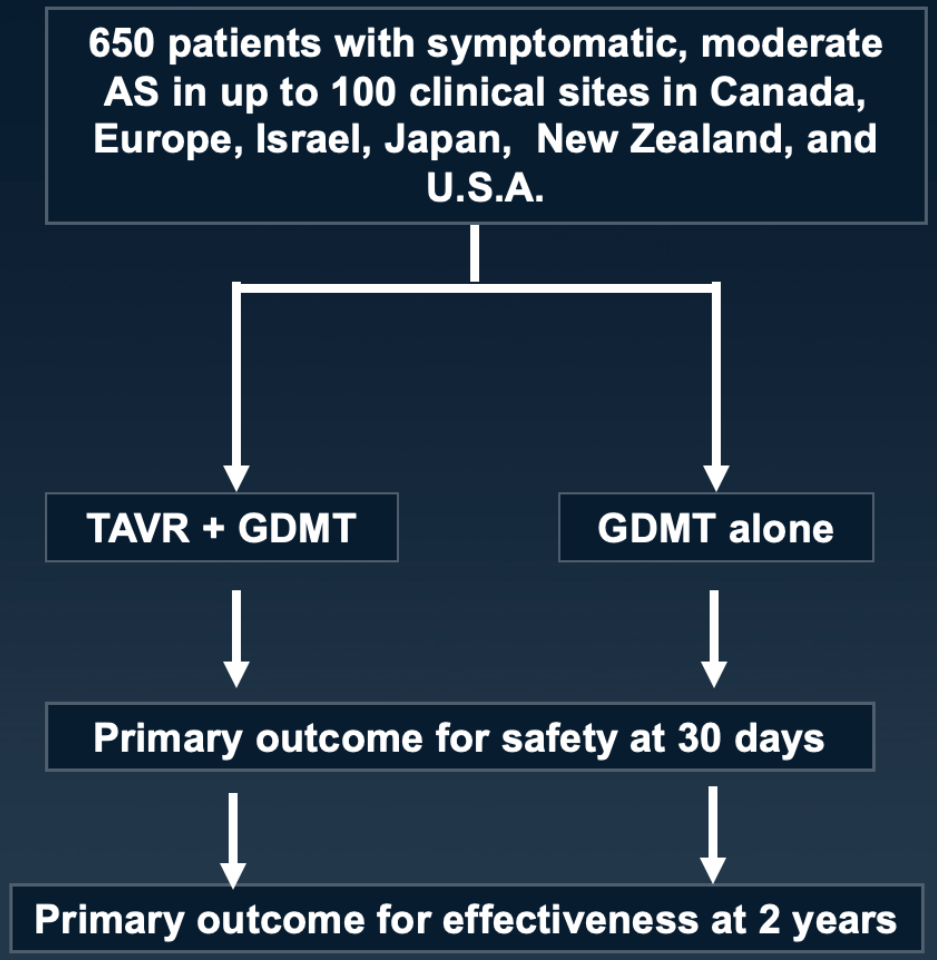
NT-ProBNP >3x normal

Elevated calcium score (>1200 AU for females, >2000 AU for males)

EXPAND TAVR II Pivotal

Design

- **DESIGN:** Prospective, randomized, parallel-assignment, two-arm, multi-center clinical evaluation of the Medtronic Evolut Pro+ or FX System vs. GDMT alone
- **OBJECTIVE:** To determine safety and effectiveness of Medtronic TAVR in patients with moderate, symptomatic AS
- **PRINCIPAL INVESTIGATORS**
  Josep Rodes-Cabau, Paul Sorajja, Stephan Windecker



EXPAND TAVR II Pivotal

Key inclusion criteria

- Symptoms
- Moderate AS
  - Mean grad, ≥20 to <40 mmHg, *and*
  - Peak vel., ≥3 to <4 m/s, *and*
  - AVA, ≥1 to <1.5 cm^2
- On GDMT
- EF >20%
- HFH in prior yr, GLS ≤15%, E/e' ≥14, or NT-proBNP ≥600

Key exclusion criteria

- Age <65 years
- Class I surgical indication
- Type 0 or 2 bicuspid
- Type 1 bicuspid w aorta >4.5 cm
- Not suitable for TF TAVR
- Needs coronary revascularization
- Amyloidosis

Take Home Message

- Moderate AS is not benign, esp. with Heart Failure symptoms
- Patients with diabetes, coronary artery disease, presence of symptoms, and reduced LVEF were at higher risk of death.
- Moderate AS with Heart Failure might be as bad as severe AS and warrant earlier AV intervention
- Randomized clinical trials are eagerly awaited to investigate whether moderate AS patients might benefit from an early intervention with a reasonable risk-benefit ratio in specific population subsets