EUROVALVE

Sept 25-26, LIEGE

Session: the best approach for “at risk moderate AS"

EARLY INTERVENTION: ACTING BEFORE IT’S TOO LATE

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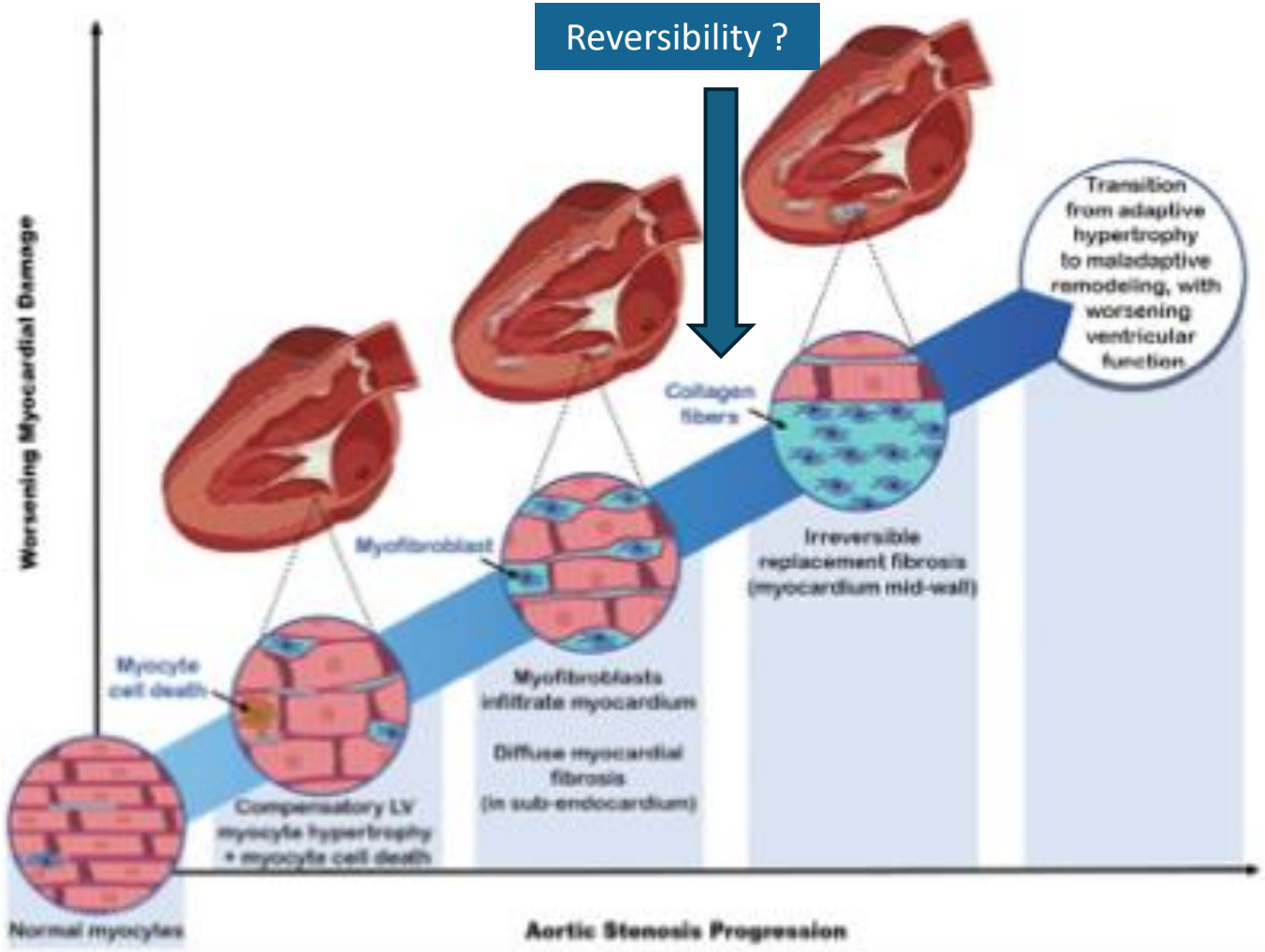
Pedara-Catania

Italy

Pathophysiology of Cardiac Damage Secondary to AS



Maznyczka et al JACC Cardiovasc Interv. 2024

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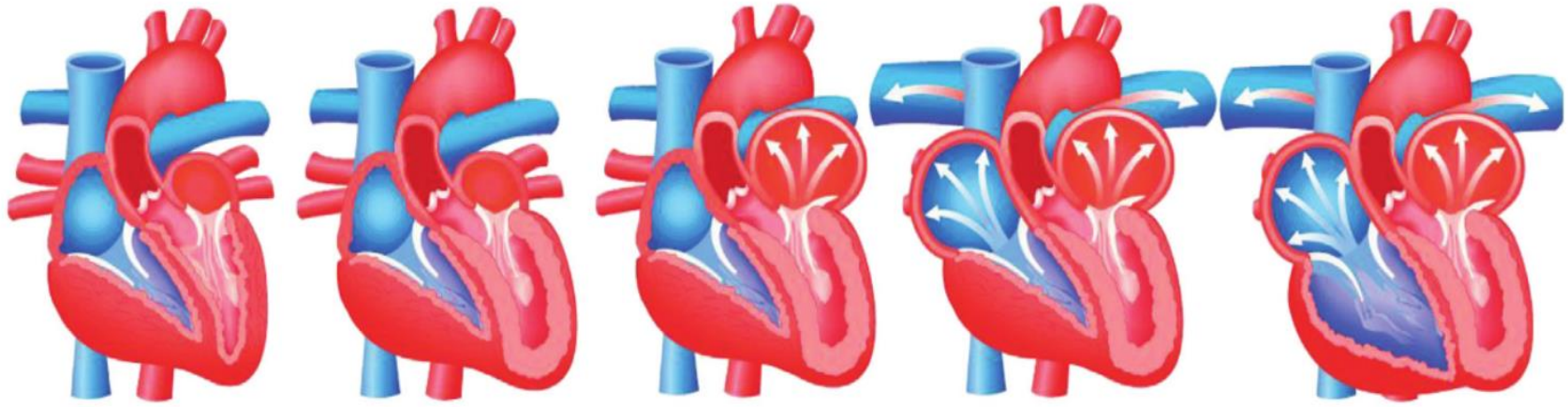
Natural History of Cardiac Damage Secondary to AS



Stage 0	Stage 1 LV damage	Stage 2 LA/MV damage	Stage 3 Pulm. vessel TV damage	Stage 4 RV damage
	increased LV mass index E/e' >14 LVEF <50%	LAVi >35 ml/m^2 MR 3/4 AF	PAPs < 60 mmHg TR 3/4	Moderate-severe RV dysfunction

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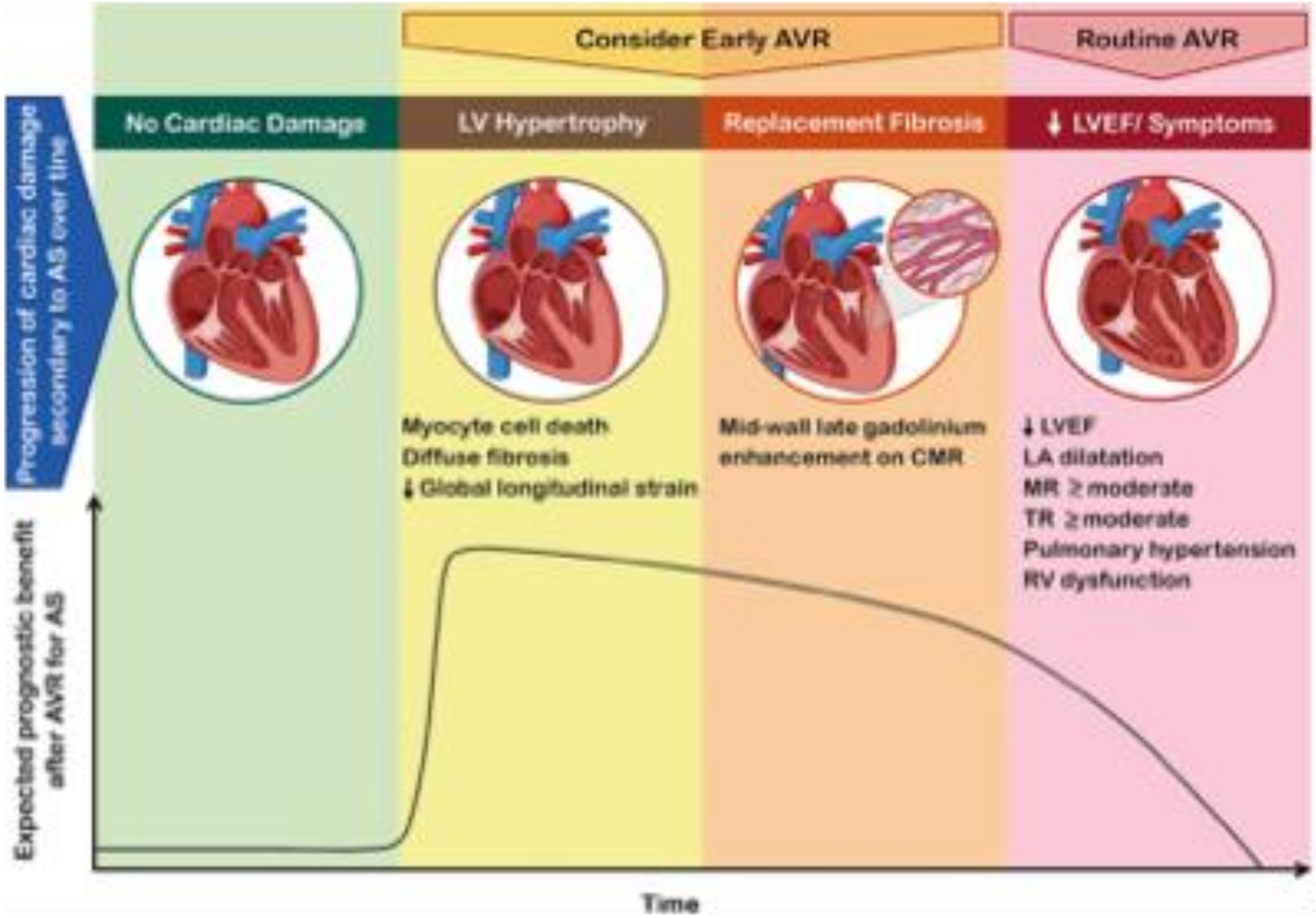
Natural History of Cardiac Damage Secondary to AS and the rational for Earlier AVR



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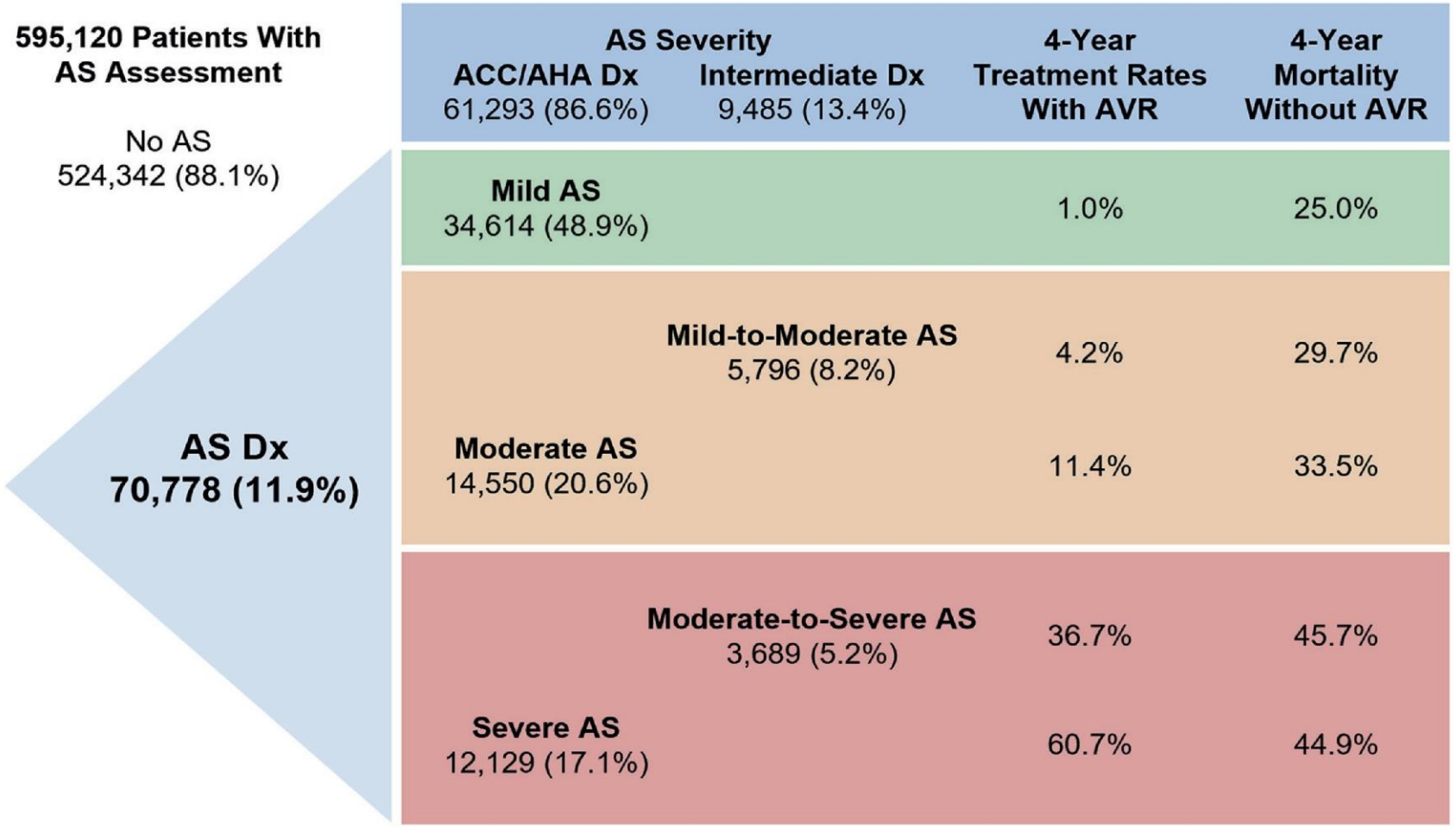
Prospective RCTs in patients with moderate aortic stenosis

	PROGRESS (NCT04889872)	EXPAND TAVR II (NCT05149755)	TAVR UNLOAD (NCT02661451)
Study population	Moderate AS	Moderate AS	Moderate or pseudo-severe AS and HF (EF <50%)
Sponsor	Edwards Lifesciences	Medtronic	Cardiovascular Research Foundation
TAVI device	SAPIEN 3 SAPIEN 3 Ultra SAPIEN 3 Ultra RESILIA	Evolut PRO+ Evolut FX	SAPIEN 3
Randomisation	N=750 TAVI vs clinical surveillance (1:1)	N=650 TAVI+GDMT vs GDMT alone (1:1)	N=600 TAVI vs GDMT (1:1)
Key inclusion criteria	Symptoms (NYHA ≥II) or evidence of cardiac damage	Symptoms (NYHA ≥II or reduced functional capacity) or HFH in previous year, EF <60% GLS ≤16% E/e' ≥14, or NT-proBNP ≥600 ng/L	Symptoms (NYHA ≥II) and EF ≥20% and <50%
Primary effectiveness endpoint	Composite endpoint (non-hierarchical): - Death, - HFH or HF event	Composite endpoint (non-hierarchical): - Death, - HFH or HF event, - Medical instability leading to AVR or reintervention	Composite endpoint (hierarchical): 1) Death, 2) Disabling stroke, 3) HFH or HFH equivalent, 4) Change in KCCQ
Time frame	2 years	2 years	1 year

N=178

CENTRAL ILLUSTRATION: Mortality Associated With Untreated Aortic Stenosis



Généreux P, et al. J Am Coll Cardiol. 2023

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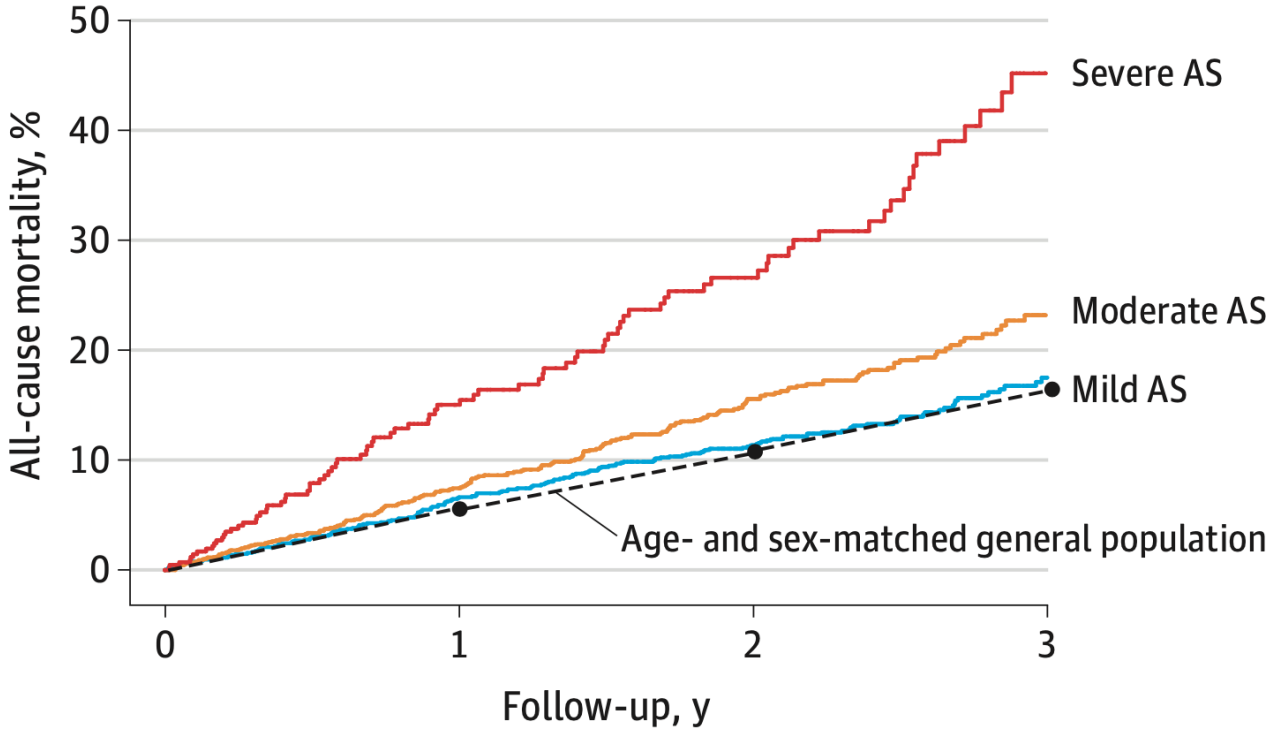
Moderate AS

What's the prognosis?



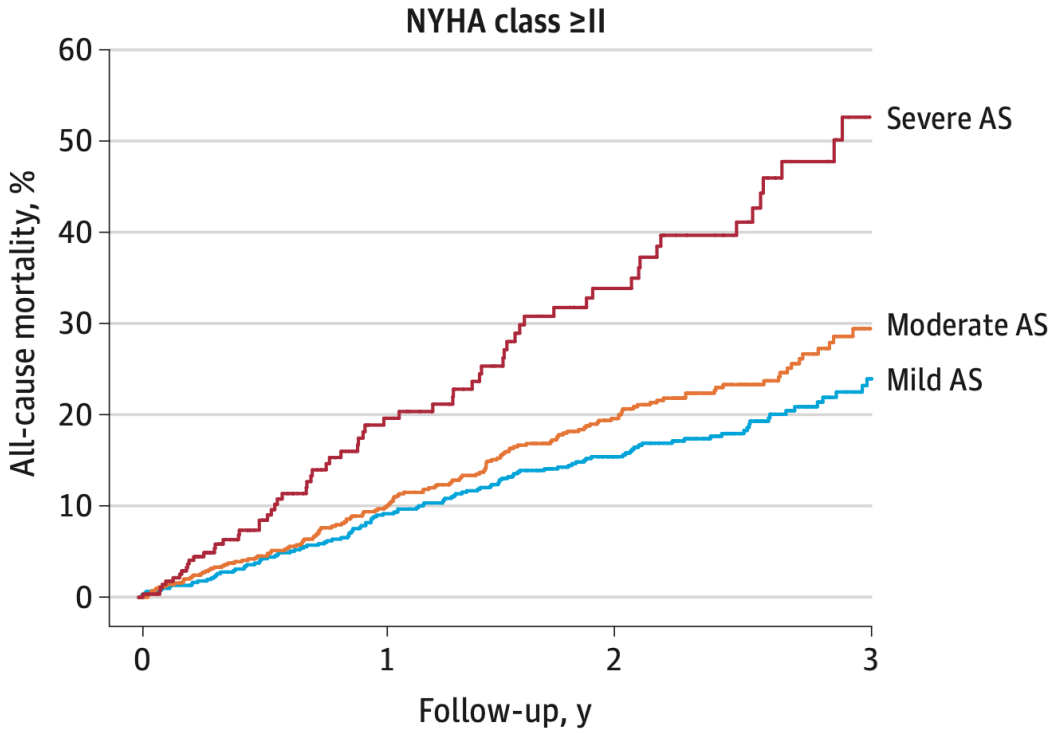
No. at risk				
Mild	1154	1063	815	203
Moderate	1122	930	620	117
Severe	427	189	114	23

HR 3.12 (2.39-4.06) for severe vs. mild, p<0.001

HR 1.44 (1.17-1.78) for moderate vs. mild, p=0.001

Moderate AS

What's the prognosis in symptomatics?



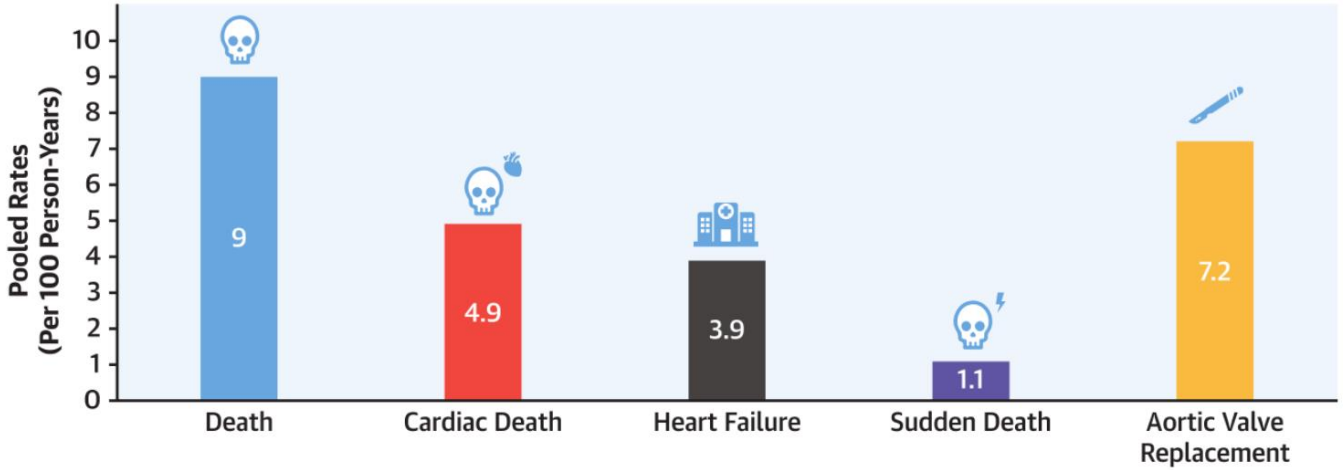
No. at risk				
Mild	618	550	401	99
Moderate	709	556	364	64
Severe	293	109	60	15

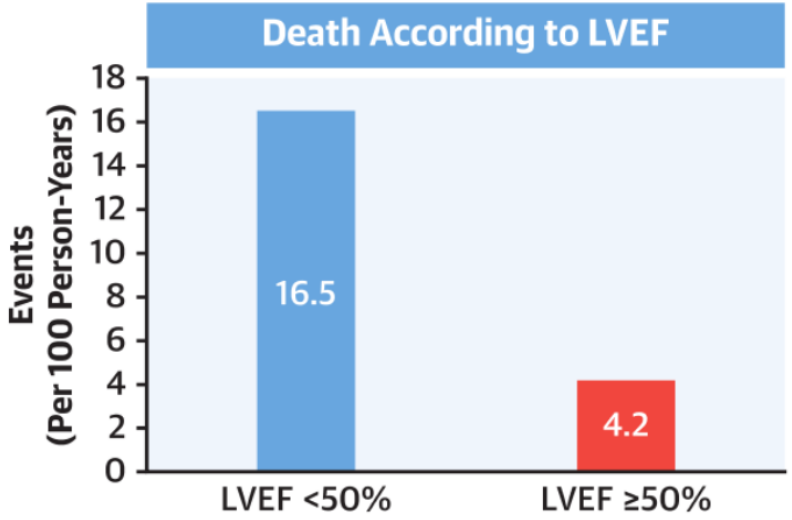
HR 2.60 (1.92-3.52) for severe vs. mild, p<0.001

HR 1.33 (1.04-1.69) for moderate vs. mild, p=0.02

Long-term impact of moderate AS

A meta-analysis of 25 studies, 12’143 patients with moderate AS





RESEARCH LETTER

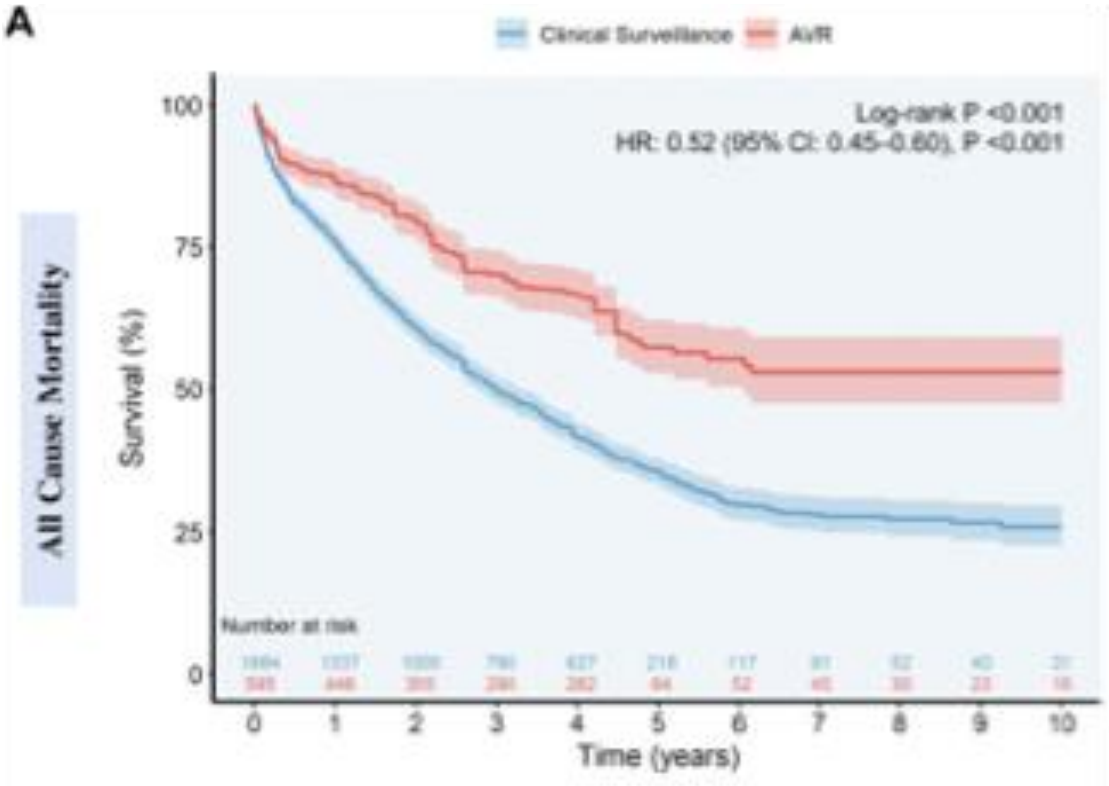
Early Aortic Valve Replacement in Moderate Aortic Stenosis

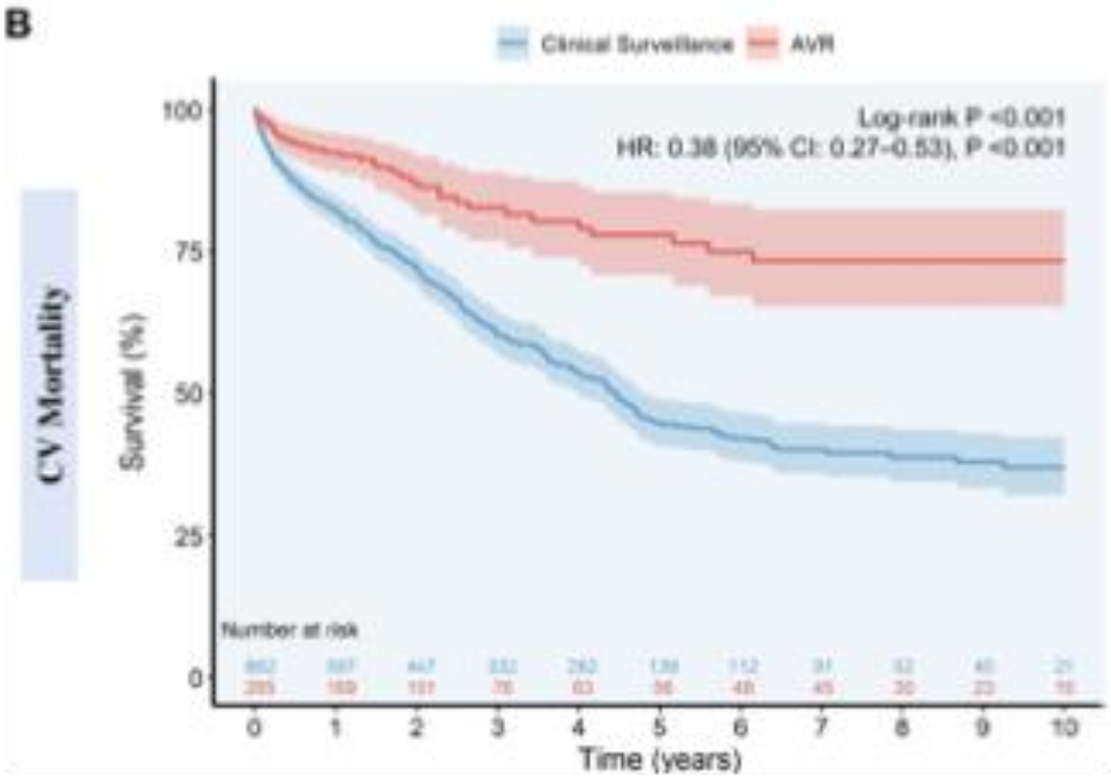
Kaplan-Meier meta-analysis to compare AVR to clinical surveillance in moderate AS with LVEF ≤ 50%.

Five observational studies (2,479 pts: 595 AVR [24%] and 1,884 clinical surveillance [76%]) with 2.4 years (IQR: 0.8–5.0 years) median follow-up

1. Jean G, Van Mieghem NM, Gegenava T, et al. Moderate aortic stenosis in patients with heart failure and **reduced ejection fraction**. J Am Coll Cardiol. 2021;77:2796–2803.
2. Samad Z, Vora AN, Dunning A, et al. Aortic valve surgery and survival in patients with moderate or severe aortic stenosis and **left ventricular dysfunction**. Eur Heart J. 2016;37:2276–2286.
3. Hariri EH, Badwan O, Kassab J, et al. Role of aortic valve replacement in moderate aortic stenosis: a 10-year outcomes study. Open Heart. 2024;11:e002616.
4. Ludwig S, Schofer N, Abdel-Wahab M, et al. Transcatheter aortic valve replacement in patients with **reduced ejection fraction** and nonsevere aortic stenosis. Circ Cardiovasc Interv. 2023;16:e012768.
5. Moon I, Kim M, Choi J-W, et al. Early surgery versus watchful waiting in patients with moderate aortic stenosis and **left ventricular systolic dysfunction**. Korean Circ J. 2020;50:791.

Mortality According to Aortic Valve Replacement Versus Clinical Surveillance in Patients With **Moderate Aortic Stenosis and Reduced Ejection Fraction**





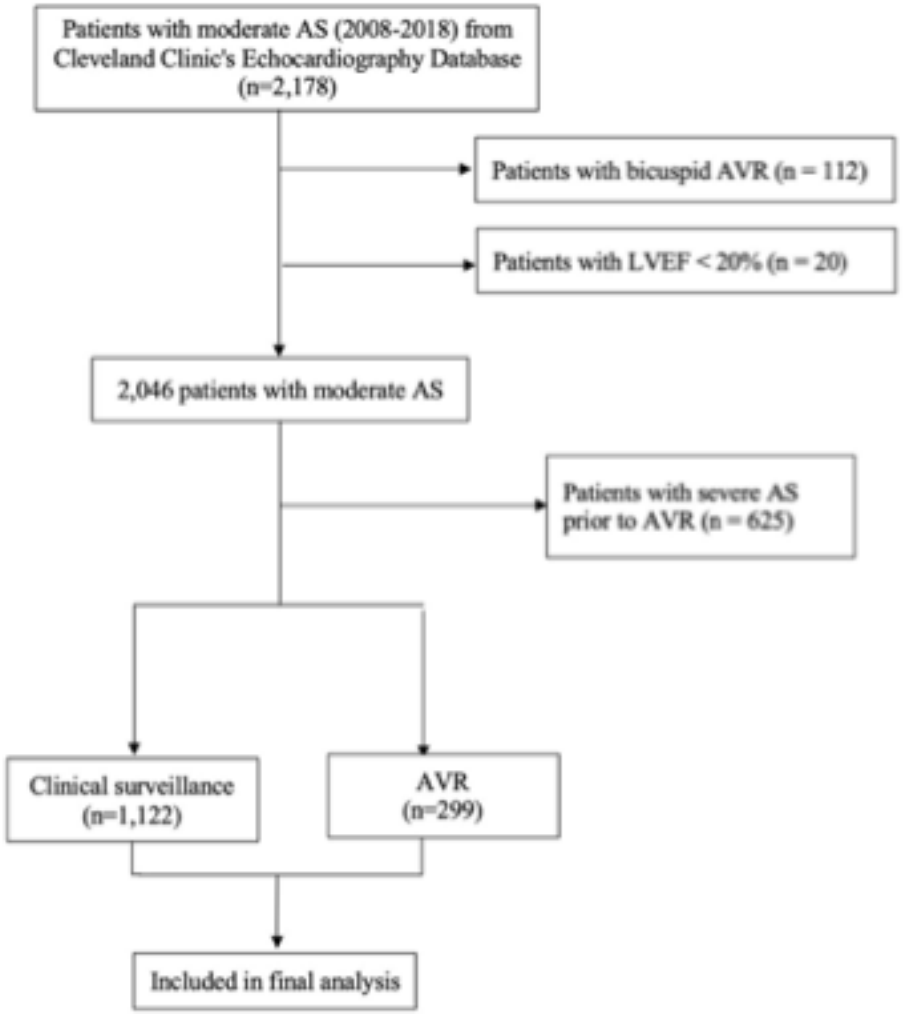
CONCLUSIONS

- This Kaplan Meier (KM) reconstructed meta-analysis of 5 observational studies with **2,479 moderate AS** patients with **LVEF ≤50%** demonstrated that **AVR (TAVI or SAVR) is associated with a significantly lower risk of all-cause and CV mortality, compared to clinical surveillance**.
- However, given the **observational** nature of the included studies, **caution in the interpretation of results is warranted given the possible unaddressed confounders that might introduce bias**.
- Further long-term and **randomized data are required** to confirm the bene ts of early AVR in this unique population and its impact on long-term outcomes.

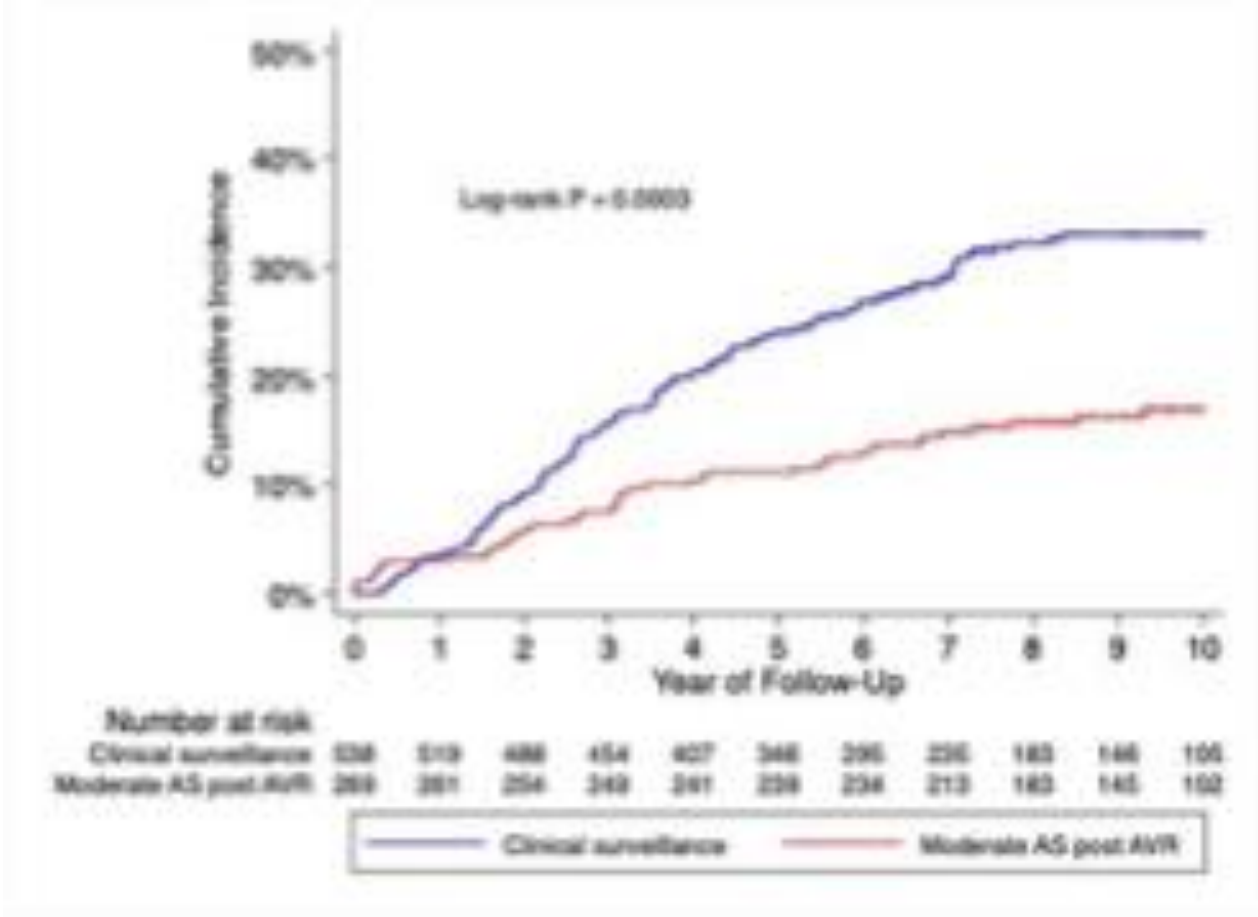
Role of aortic valve replacement in moderate aortic stenosis: a 10- year outcomes study

Patients aged 65 years or greater with native moderate native AS, defined as aortic valve area (AVA) between 1.0 and 1.5 cm2 at index echocardiogram, were identified from the **Cleveland Clinic Echocardiography Database** from January 2008 to June 2018

CONSORT diagram for study population selection. Patients aged 18 years or older with native moderate AS between 2008 and 2018 were selected from Cleveland Clinic's echocardiography database. We excluded patients with bicuspid AS (n=112) and left ventricular ejection fraction <20% (n=20) at baseline. We also excluded patients who underwent AVR with severe AS (n=265). **Final population included 1421 patients, among which 299 underwent AVR with moderate AS prior to surgery and 1122 underwent clinical surveillance during the study period.**



Role of aortic valve replacement in moderate aortic stenosis: a 10- year outcomes study



Kaplan- Meier curves of the cumulative incidence of all- cause mortality in 2:1 propensity-matched group of patients who underwent AVR versus clinical surveillance

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Clinical Impact of Cardiac Damage Across the Spectrum of Severity in Aortic Stenosis Patients

A. Coisne, D. Montaigne, R. Groulez, C. Diharce, S. Aghezzaf, S. Ninni, G. Lemesle, A. Sudre, T. Modine, A. Vincentelli, M. Jungling, P. Généreux, M. B. Leon, J.F. Granada, C. Bauters

on behalf of the VALVENOR investigators

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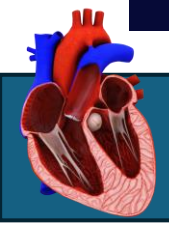
Lille University Hospital



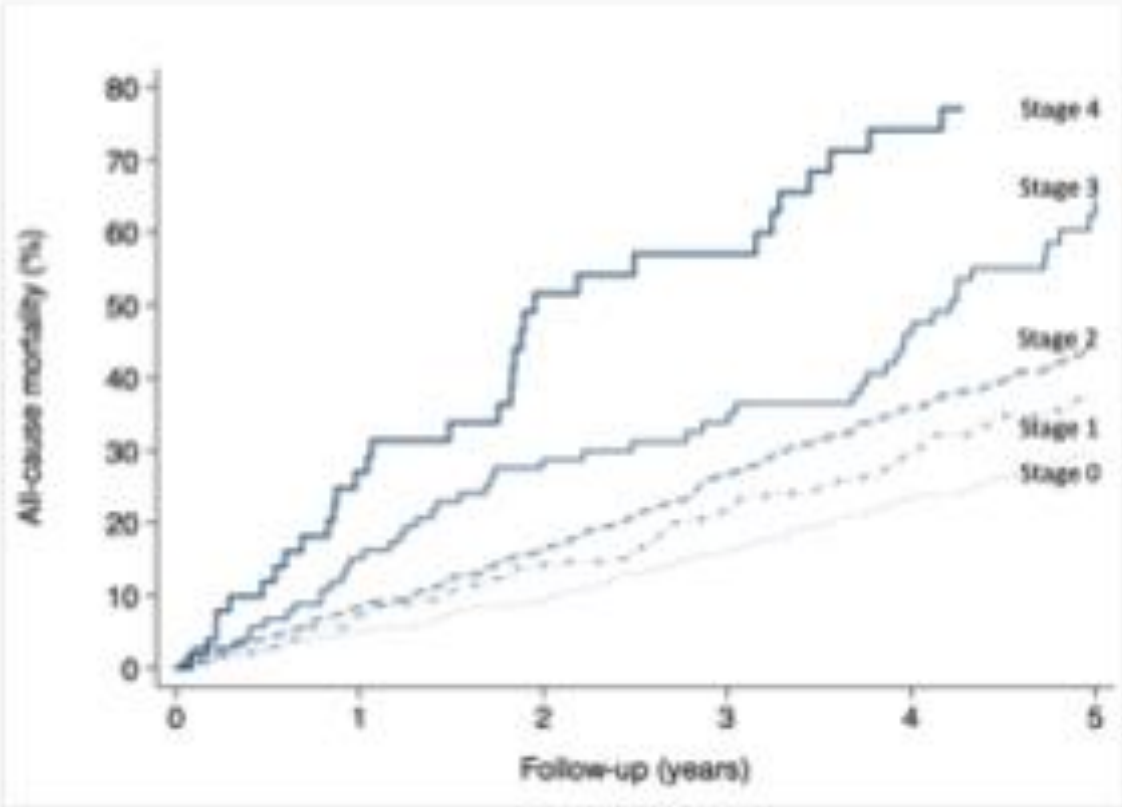
VALVENOR registry

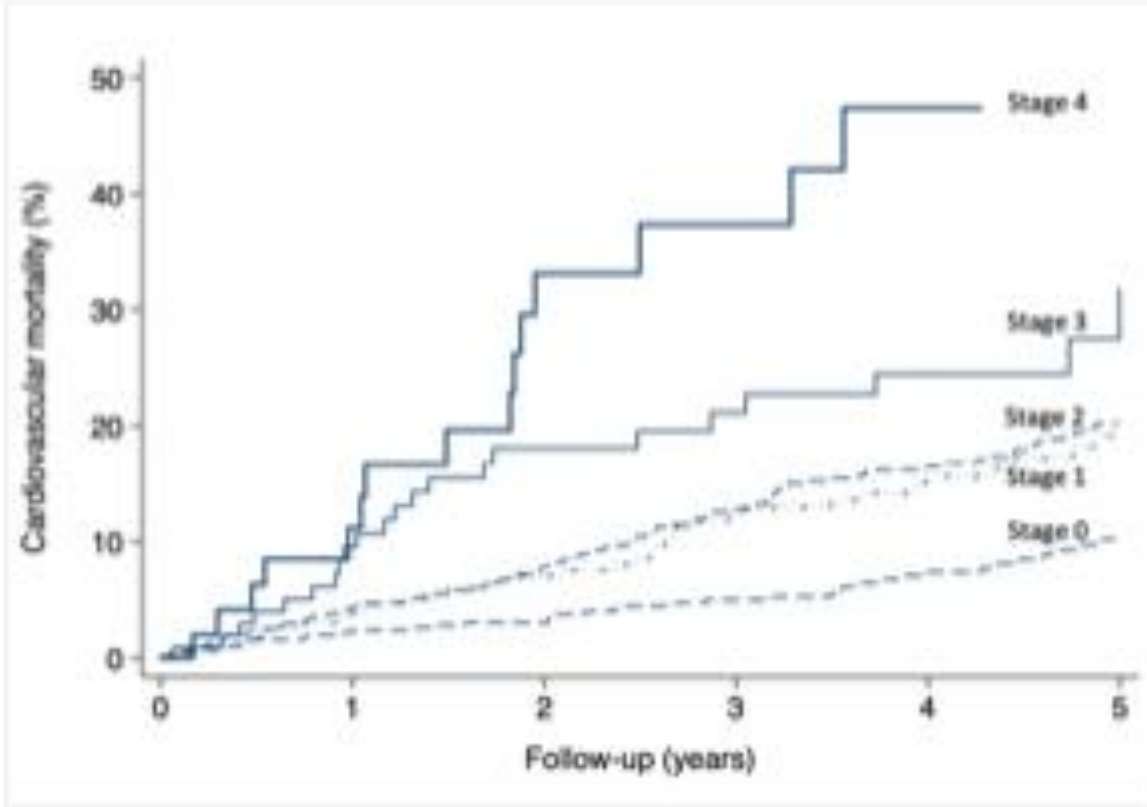
- **2,704 outpatients** with **Vmax >2.5m/s**
- between May 2016 and December 2017
- by **117 cardiologists**
- **FU at 5 years**

Main objective of the study

To explore the **clinical impact of extravalvular CD** across the overall **spectrum of AS** (mild, moderate and severe AS) as well as the correlation between CD and **AS severity**.

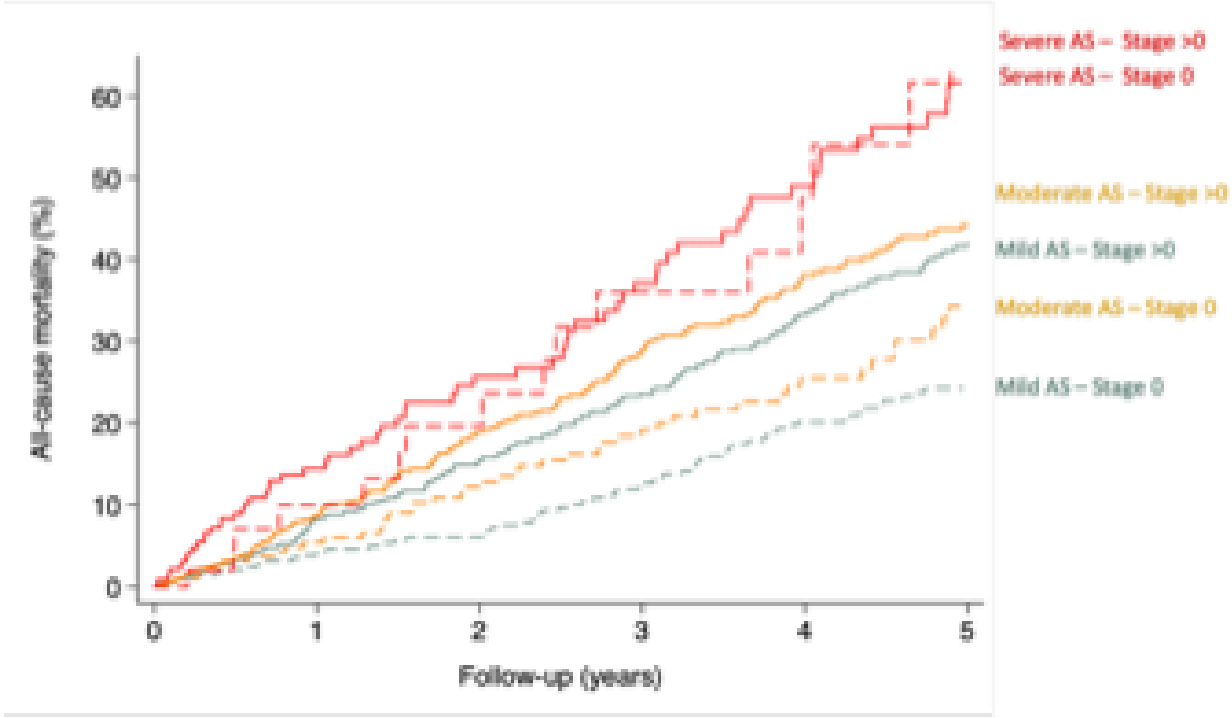
Results

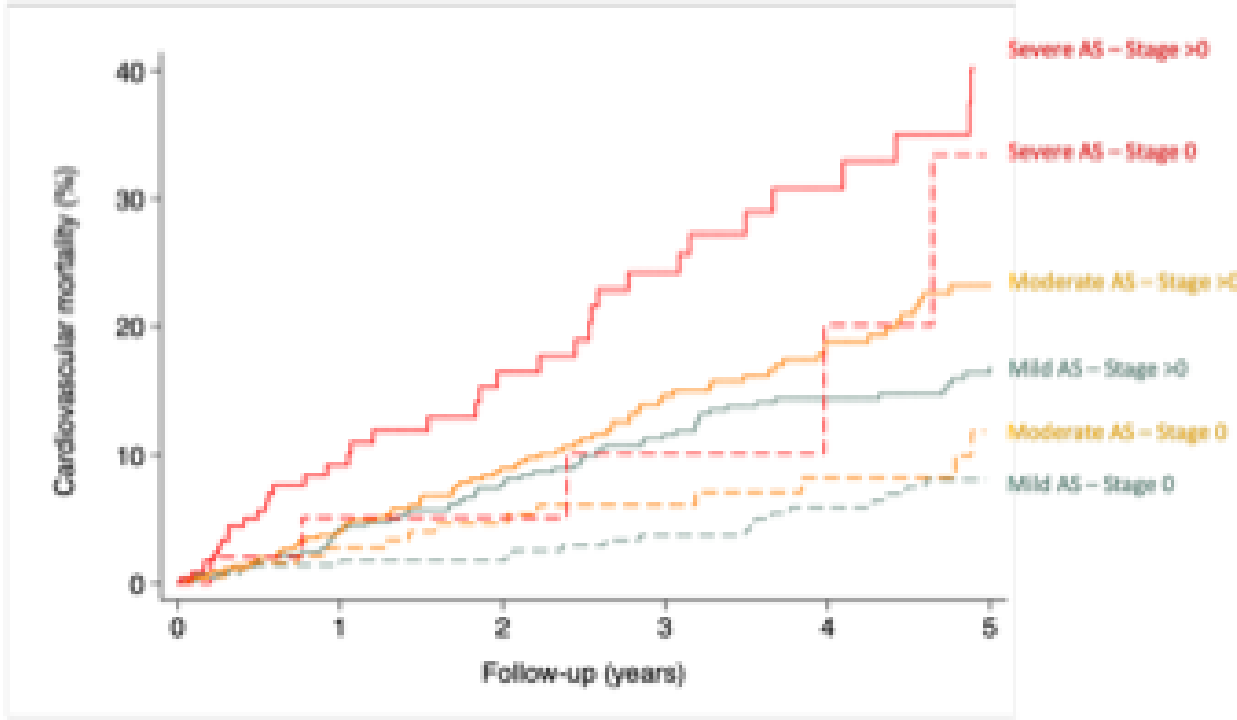




The 5-year all-cause and cardiovascular mortality rates were 30% and 10% in patients with CD stage 0, 34% and 18% in stage 1, 41% and 19% in stage 2, 58% and 30% in stage 3 and 71% and 41% in stage 4, respectively

Results



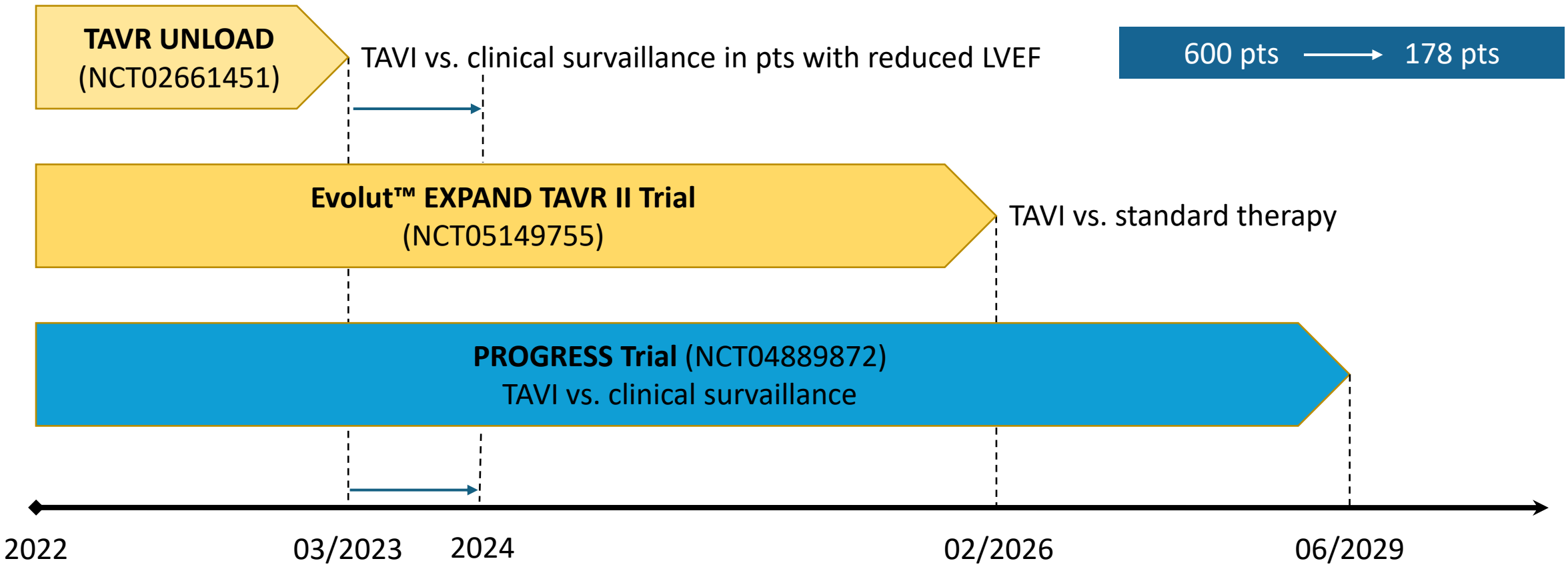


Both all-cause mortality and cardiovascular mortality were higher in patients in stage >0 than in patients in stage 0 across all AS stages

Conclusions

- 1747 outpatients across the spectrum of AS included in a prospective regionwide registry, followed-up for 5 years and compared according to Généreux's classification
- The extent of extravalvular CD correlates with AS severity and is associated with clinical outcomes across all AS stages
- Further research is warranted to determine whether assessing CD should be integrated in the management of patients with AS

Ongoing RCTs in symptomatic, moderate AS



TAVR UNLOAD Trial

Study Design

Investigator-initiated, international, randomized controlled, open label, superiority trial

TAVR UNLOAD

Symptomatic patients with HFrEF on GDMT & moderate AS

LV EF < 50% at rest

R

TF TAVR (n=89)

CASS (n=89)

Clinical AS surveillance and AVR upon progression to severe AS

Primary Endpoint

Hierarchical * occurrence of:

1. All-cause death
2. Disabling stroke
3. Hospitalizations and equivalents
4. Change in KCCQ

1st Key Secondary EP

Time-to-event analysis of:

Major adverse cardiac or cerebrovascular events (MACCE) defined as the composite of:

- All-cause death
- All stroke
- Hospitalizations and equivalents

TAVR UNLOAD Trial

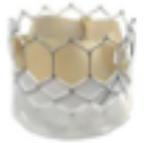
AS Fate in Clinical AS Surveillance

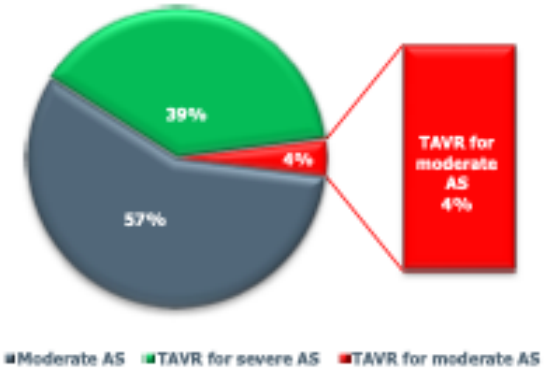
➢ **Progression to severe AS**

- ✓ 35/89 patients (39%*)
- ✓ 16 patients in year 1
- ✓ + 13 patients in year 2
- ✓ + 5 patients in year 3
- ✓ + 1 patient in year 4
- ○ All underwent TAVR
- ○ 17 /35 (= 49%) with HF event*

➢ **TAVR**

- ✓ 38/89 patients (43%*)

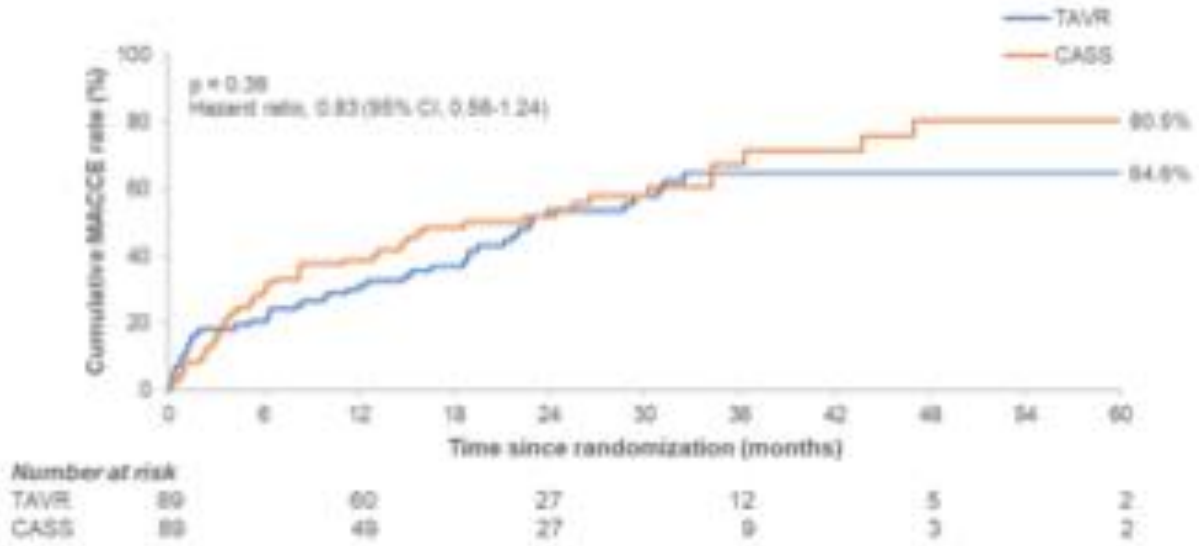




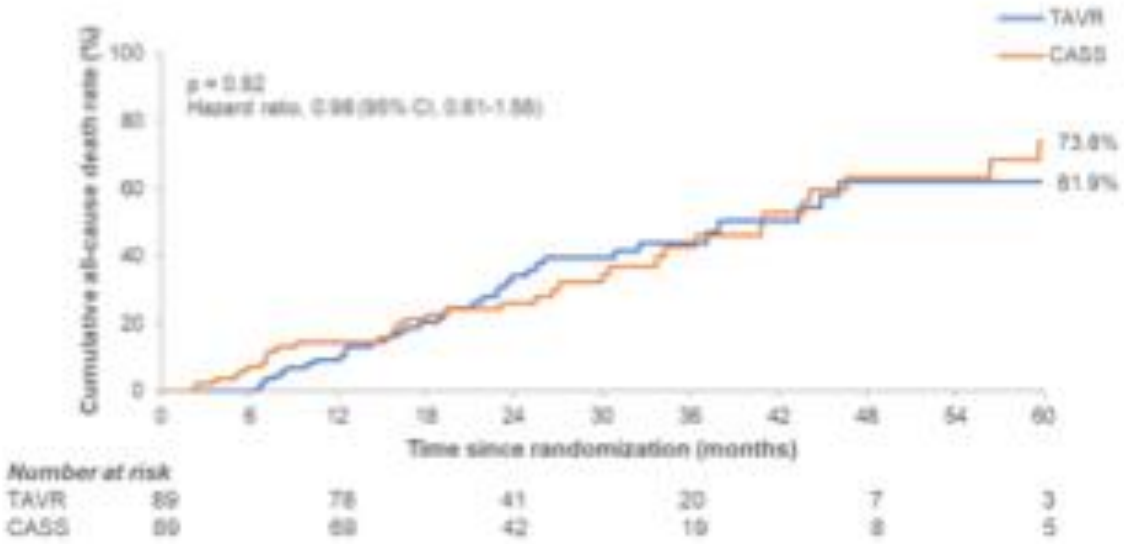
* Not considering death as competing risk
** 18/35 were treated with TAVR upon TTE confirmation of severe AS

TAVR UNLOAD Trial

MACCE



All-cause Death



* MACCE = composite of all-cause death, all stroke, and HF hospitalizations and equivalents

TAVR UNLOAD Trial

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CONCLUSION

- TAVR for **moderate AS in patients with HFrEF** on GDMT was safe but **did not affect the primary hierarchical composite endpoint** at a median follow up of 23 months
- TAVR resulted in more wins in the primary hierarchical composite endpoint at one year follow **clinically meaningful improvement in quality of life** up driven by compared with clinical AS surveillance
- During the trial, **43% of the clinical AS surveillance group underwent TAVR** predominantly because of disease progression to severe AS.
- The **cardiac damage framework may identify** a broader patient phenotype with moderate AS that may benefit from upstream TAVR. This concept is under investigation in the PROGRESS and EXPAND TAVR II trials.

CONCLUSIONS

- In patients with asymptomatic severe aortic stenosis and myocardial fibrosis, **early intervention did not reduce the incidence of the composite primary endpoint of all-cause death or unplanned aortic stenosis hospitalization**.

- The principal benefit of early intervention appears to be in the reduction of unplanned hospitalizations and in preventing the development of limiting symptoms.

Impact of Cardiac Damage Staging in Patients With Moderate Aortic Stenosis and Reduced Left Ventricular Ejection Fraction: Insights From the TAVR UNLOAD Trial

Yukari Kobayashi, MD

On behalf of TAVR UNLOAD Investigators

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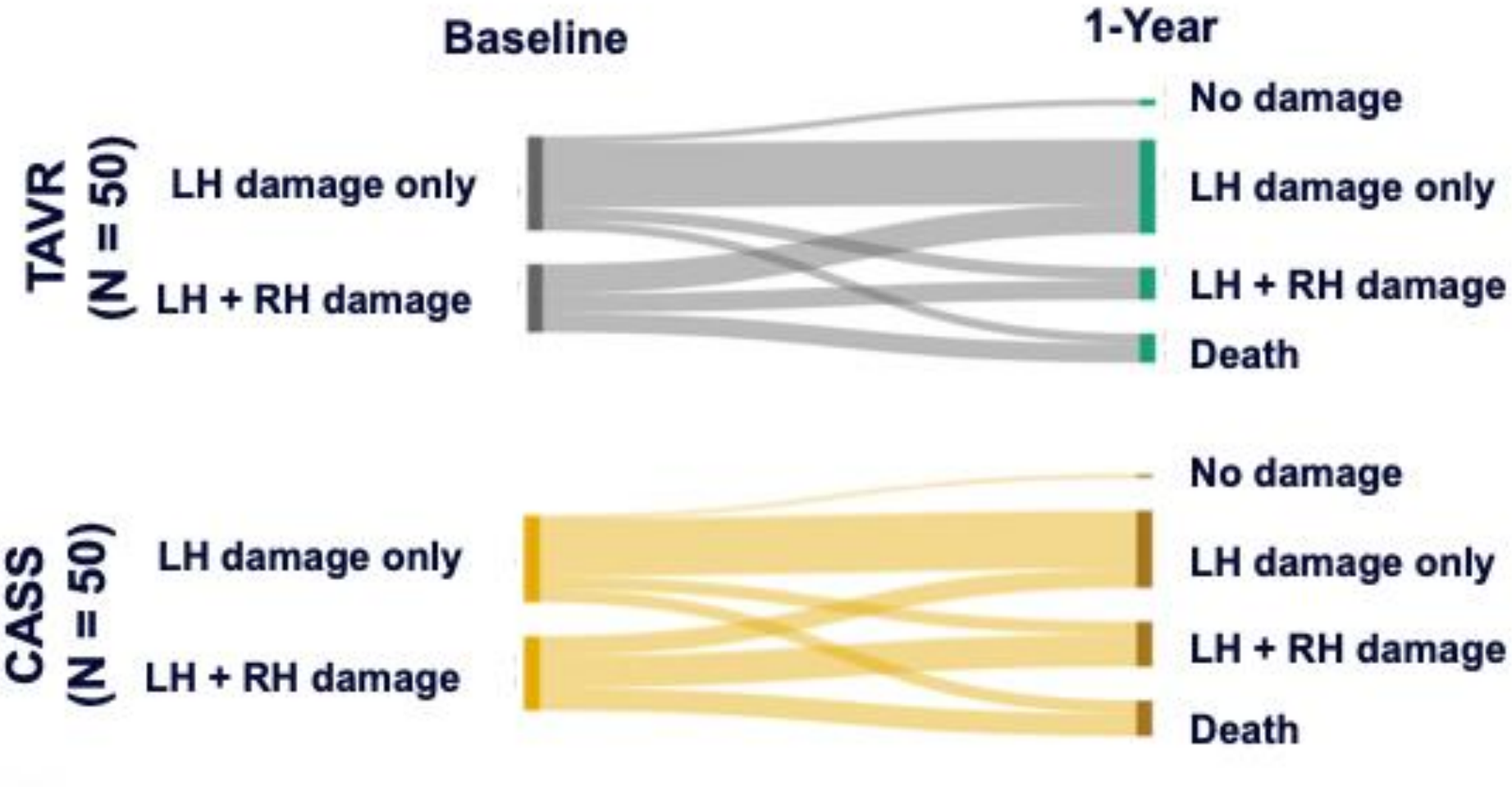
Change in Cardiac Damage Staging at 1 Year



X^2 of change
P = 0.63

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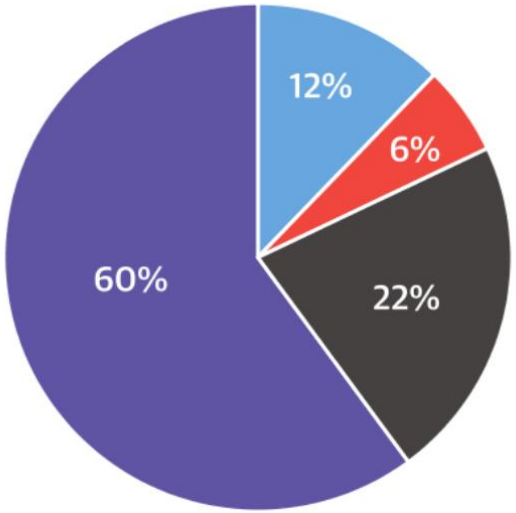
Conclusions

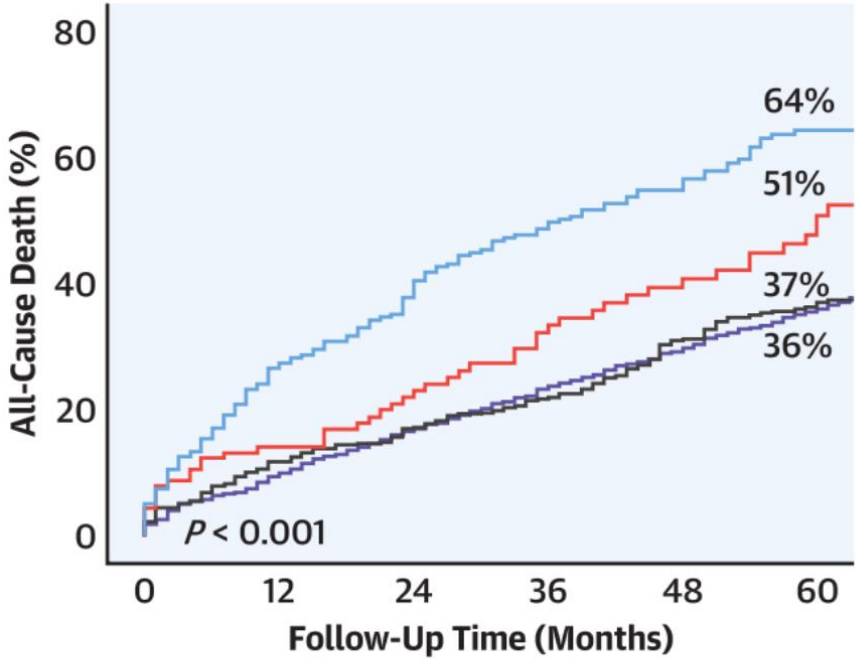
- TAVR **did not significantly impact the cardiac damage change** compared to CASS at 1 year
- **RH damage was associated with worse clinical outcomes** and health status
- The association between RH damage and outcome was consistent across TAVR and CASS
- The **positive effect of TAVR on health status was consistent in patients with and without RH damage**

Not all moderate AS are equal

The impact of flow status



Classical Low-Flow, Low-Gradient, Discordant MAS
Paradoxical Low-Flow, Low-Gradient, Discordant MAS
Normal-Flow, Low-Gradient, Discordant MAS
Concordant MAS



Number at risk						
	1,186	1,058	939	825	685	556
	433	369	317	283	224	165
	114	94	72	55	45	30
	241	174	133	101	72	49

Moderate AS
AVA 1,0-1,5 cm^2

Low-gradient (<20 mmHg)

Low-flow (SVi <35 ml/m^2)

Moderate aortic stenosis

- AVA >1 and ≤ 1,5 cm2
- MG < 40 mmHg
- Vmax < 4m/s

DEFINITION	VALVE HEMODYNAMICS
Concordant moderate AS	MG ≥ 20mmHg and < 40 mmHg
Discordant moderate AS	
normal-flow, low-gradient	MG < 20 mmHg, SVi ≥35mL/m2, LVEF ≥ 50%
«paradoxical» low-flow, low-gradient	MG< 20 mmHg, SVi <35 mL/m2, LVEF ≥50%
«classical» low-flow, low-gradient	MG< 20 mmHg, LVEF <50%

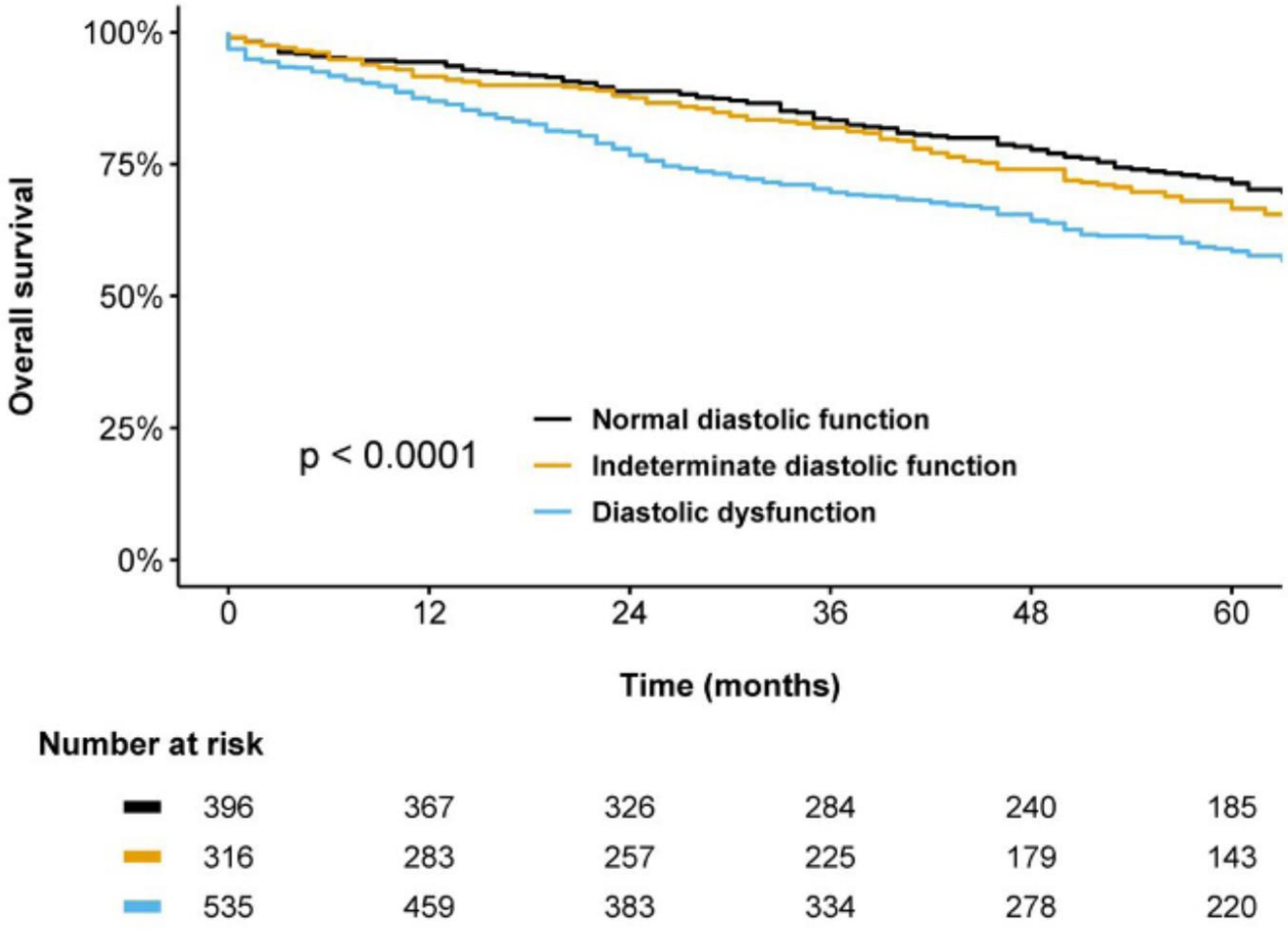
Not all moderate AS are equal

The impact of diastolic function

Patients with moderate AS and preserved LVEF (n=1247)
mean age 74 years

Evaluation of diastolic function
1. Average E/e' > 14
2. Septal e' velocity <7cm/s or lateral e' <10 cm/s
3. TR velocity > 2.8 m/s
4. LAVi > 34 ml/m^2

Normal	Indeterminate	Dysfunction
<50% positive	50% positive	>50% positive



The value of early intervention in moderate AS

not endorsed by 2025 ESC/EACTS guidelines

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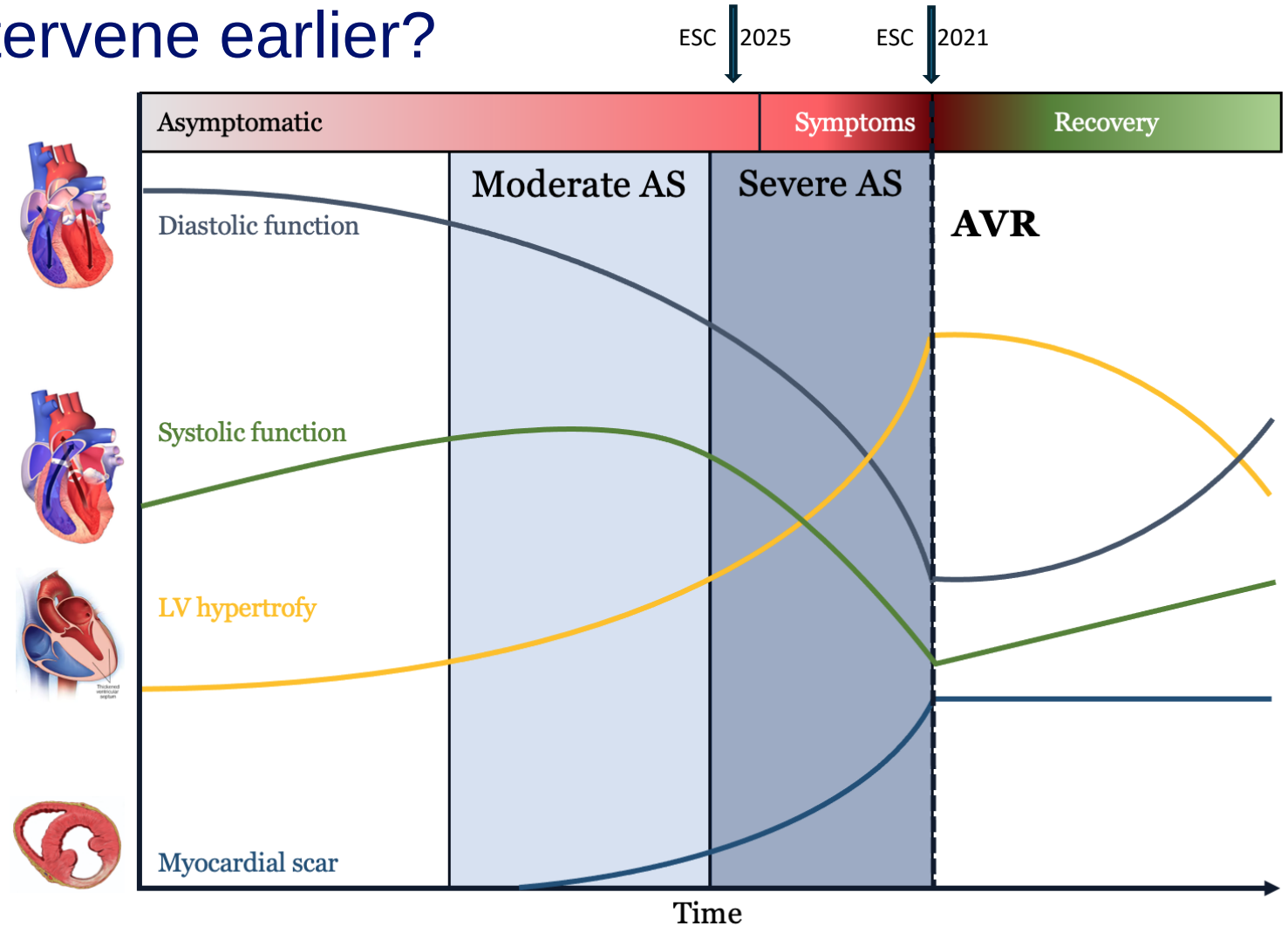
The progression of aortic stenosis

Should we intervene earlier?



Adapted from Badiani S et al. Interv Card Rev 2021

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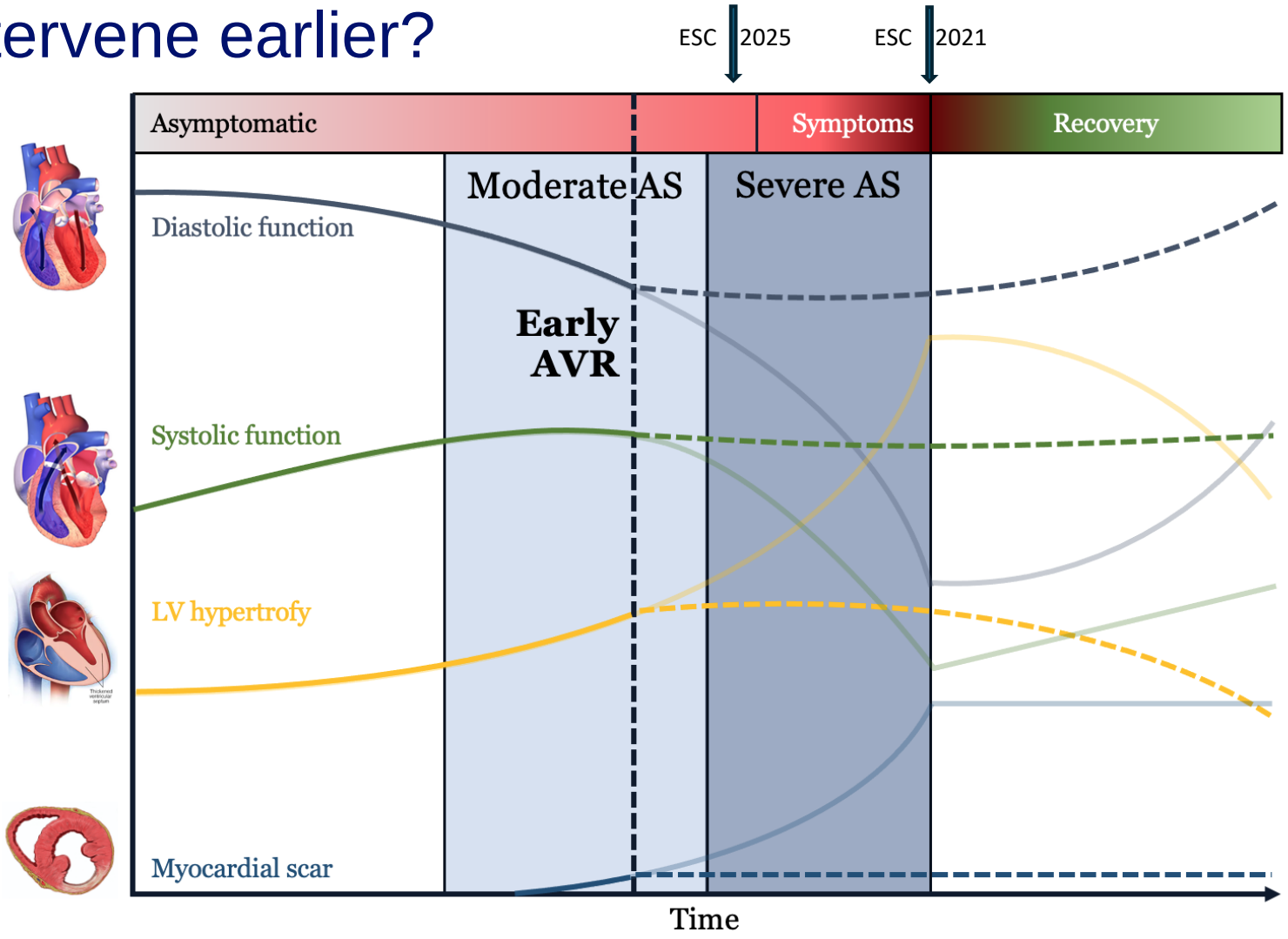
The progression of aortic stenosis

Should we intervene earlier?



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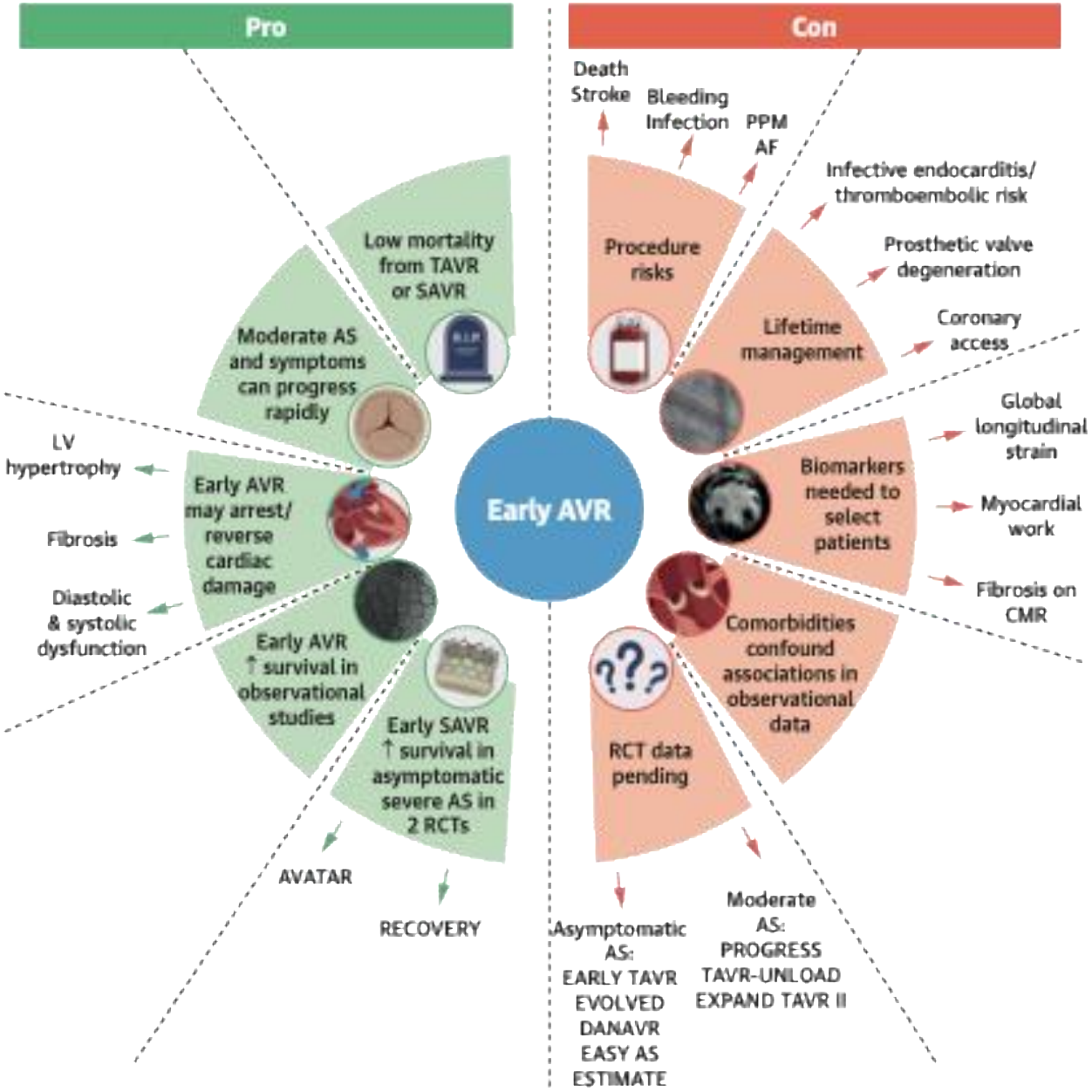
Pros and Cons of Earlier Aortic Valve Replacement in Patients With Aortic Stenosis



Take-home messages

Early AVR in moderate AS **might be considered** if operative risk is low and few concerns about long-term management

Silent ventricular abnormalities (i.e. midwall fibrosis at MRI) **might identify a subset** of patients that may benefit from an early intervention

Moderate AS impact on patients' outcomes and **intervention should be considered** especially when other conditions affect the left ventricle

Ongoing **trials** will establish the benefit of an early intervention before the stage of severe, symptomatic AS, but **long-term considerations** will be fundamental in the final decision

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