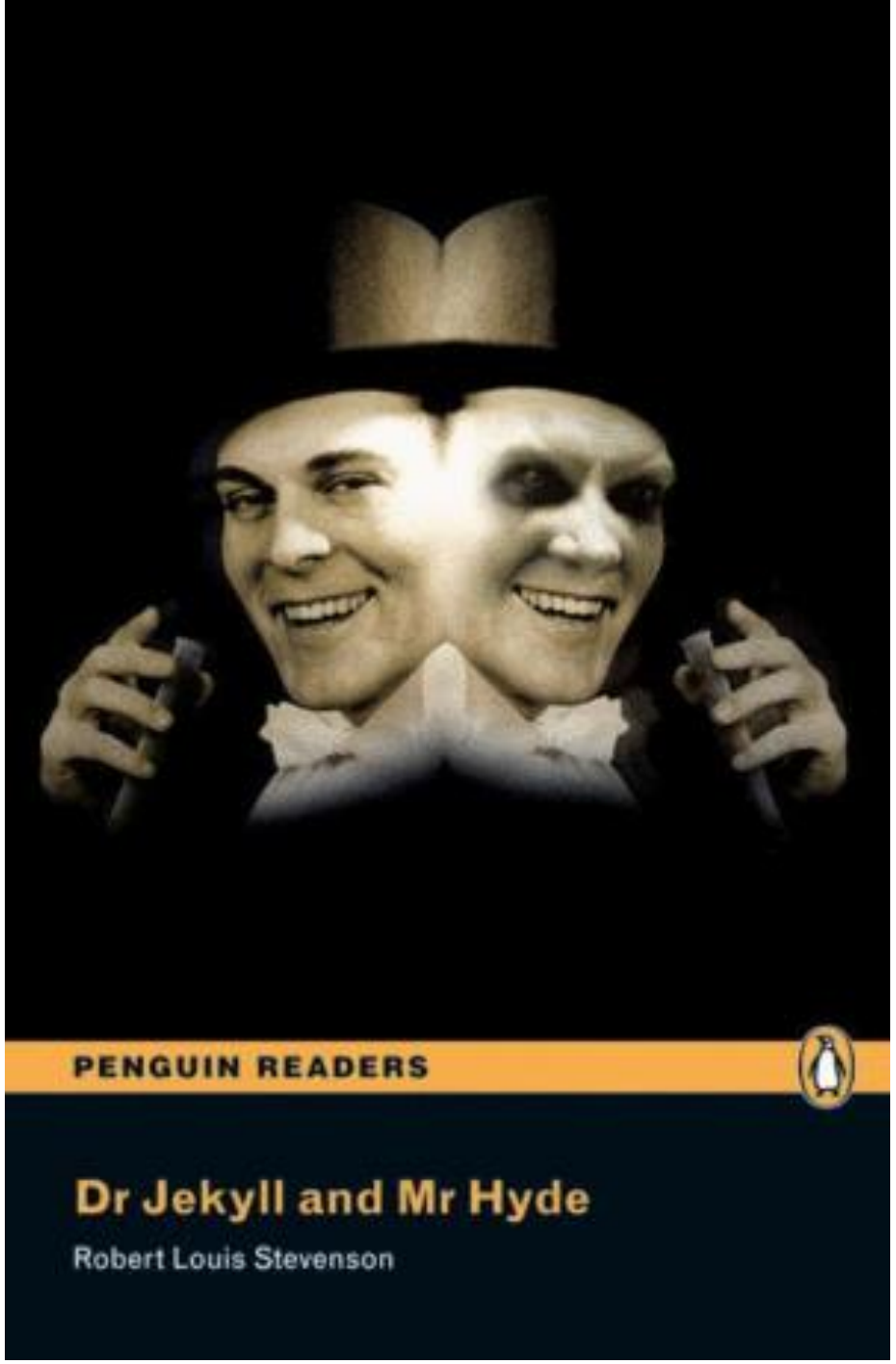


Dr. Jekyll, a respectable scientist, uses a potion to transform himself into the savage and remorseless Mr. Hyde, allowing him to indulge in his wicked impulses in a way his civilized persona cannot.

Asymptomatic severe AS:
Conservative Management:
A Prudent Approach

By Mr. Hyde alias Philippe Pibarot

Canada Research Chair in Valvular Heart Diseases

Institut Universitaire de Cardiologie et de Pneumologie de Québec / Québec Heart & Lung Institute

Doctorate Honoris Causa

LIÈGE université

Université LAVAL

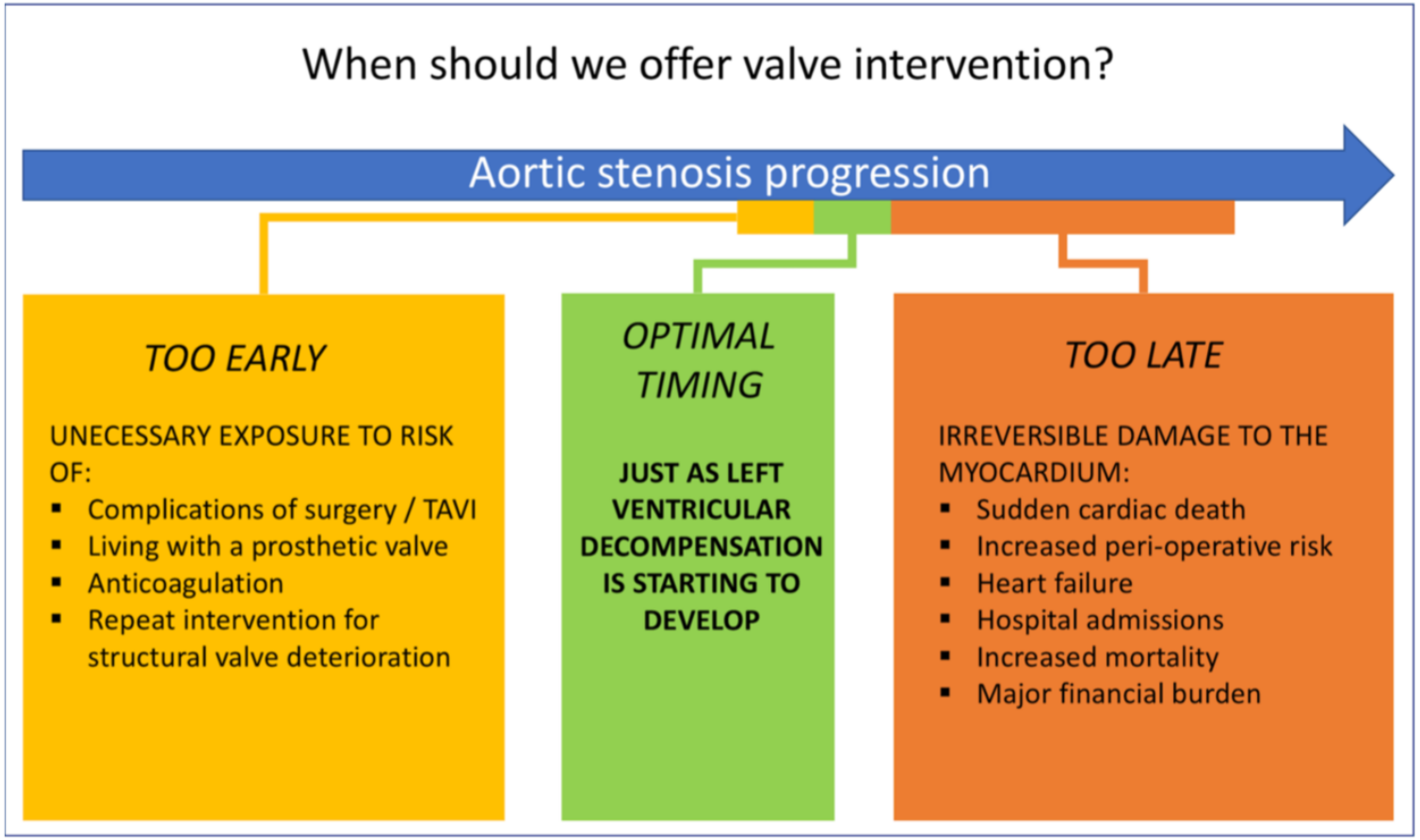
Disclosure: Philippe Pibarot

- **Financial relationship with industry**
  - **Edwards Lifesciences: Echo CoreLab for PARTNER 2– SAPIEN 3, PARTNER 3, TAVR-UNLOAD, EARLY-TAVR, PROGRESS, ALLIANCE X4 trials, RHEIA**
  - **Novartis: Lp(a) FRONTIERS CAVS**
- **Other financial disclosure:**
  - **Research Grants from Canadian Institutes of Health**
  - **Research and Heart & Stroke Foundation of Quebec**
  - **Off label Use: None**

Mr Hyde will defend this strategy:

Clinical surveillance in asymptomatic severe AS and early AVR in selected patients with risk markers

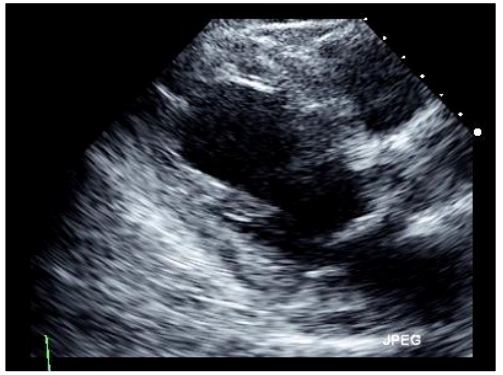
Aortic Valve Replacement (AVR /TAVI): Timing is Everything!

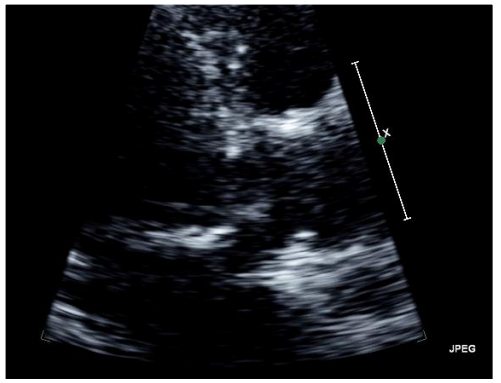


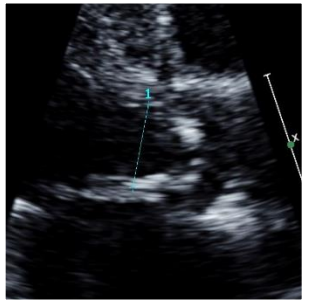
Everett Heart 2018

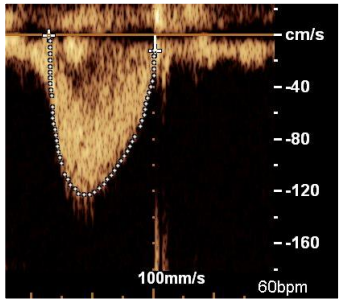
Case: Asymptomatic 78 y.o. Man with Severe AS

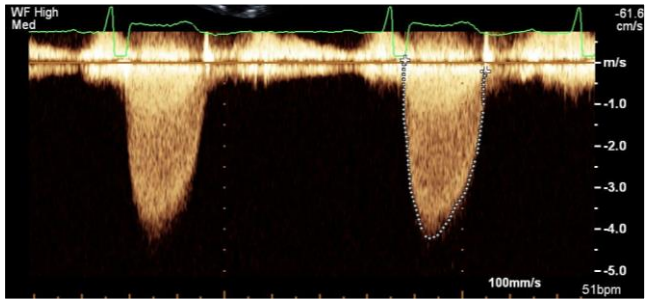
- 78 y.o. man, BSA: 2.02 m^2
- Asymptomatic confirmed by ETT
- No evidence of CV risk factors
- No evidence of CAD, preserved LVEF
- SV: 85 mL, SV index: 42 mL/m^2
- AS severity on echo:
  - Peak jet velocity: 4.25 m/s
  - Peak/mean gradient: 72/46 mmHg
  - AVA: 0.89 cm^2 Indexed AVA: 0.44 cm^2/m^2





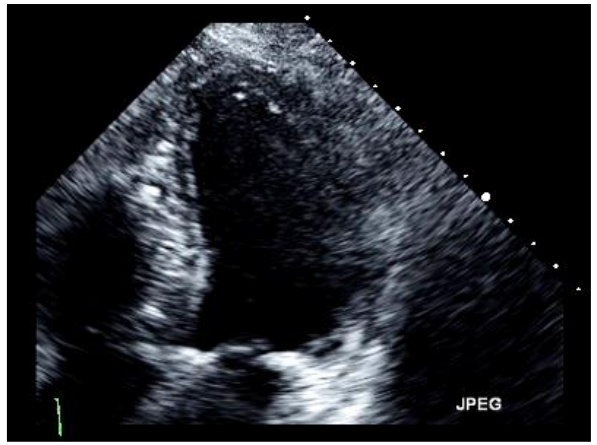


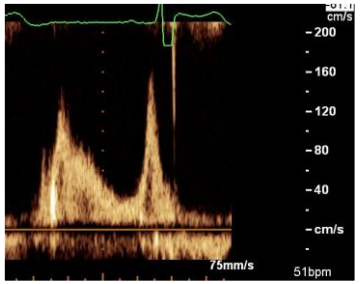


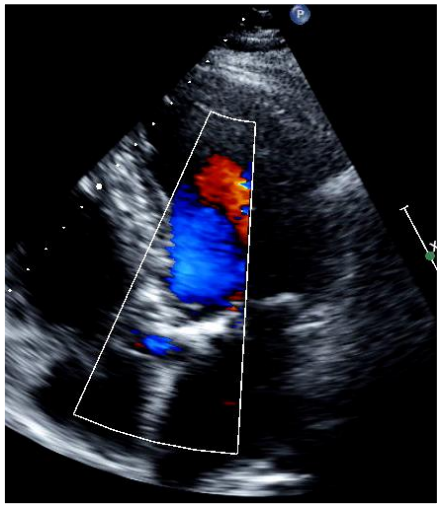


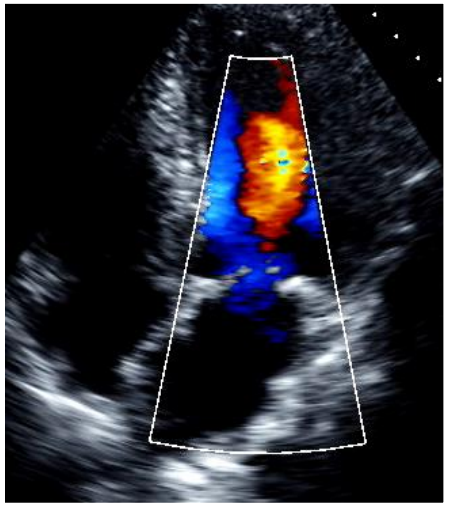
Case: Asymptomatic 78 y.o. Man with Severe AS

- LVEF by Biplane Simpson: 63%
- LV diastolic dysfunction: Grade 1
- Mild MR, MAC
- Trace TR
- Normal systolic PAP









Clinical Dilemna in True Asymptomatic Severe AS

Early « Prophylactic » AVR?

OR

Watchful waiting / Active Clinical Surveillance?

ACC/AHA and ESC/EACTS Guidelines for the Management of Valvular Heart Diseases

JACC Guideline Comparison

Augustin Coisne, MD, PhD,[a,b] Patrizio Lancellotti, MD, PhD,[c,d] Gilbert Habib, MD, PhD,[e] Madalina Garbi, MD,[f] Jordi Sanchez Dahl, MD, PhD,[g] Marco Barbanti, MD,[h] Mani A. Vannan, MD,[i] Vassilios S. Vassiliou, MD,[j] Dariusz Dudek, MD,[k] Ovidiu Chioncel, MD,[l,m] Johannes L. Waltenberger, MD, PhD,[n,o] Victoria L. Johnson, MD,[p] Ruggero De Paulis, MD,[q] Rodolfo Citro, MD, PhD,[r,s] Philippe Pibarot, DVM, PhD,[t]
on behalf of the EuroValve Consortium

TABLE 1 Selected Recommendations on Management of Aortic Stenosis

Recommendation	American	European
Symptoms and:		
High-gradient	I-A	I-B
LFLG, LVEF <50% and flow reserve	I-B	I-B
LFLG, LVEF <50% and no flow reserve	I-B	IIa-C
LFLG, LVEF ≥50%	I-B	IIa-C
No symptoms and:		
LVEF <50%	I-B	I-B
LVEF <55%		IIa-B
LVEF <60%	IIb-B (3 serial imaging)	
Symptoms on exercise test	I-B	I-B
Fall in SBP on exercise test	IIa-B (10 mm Hg)	IIa-B (20 mm Hg)
Very severe AS (Vmax ≥5 m/s) and low risk	IIa-B	IIa-B
Vmax progression ≥0.3 m/s per y	IIa-B (high gradient)	IIa-B (severe calcification and low risk)
3-fold increase in BNP/N-terminal proBNP	IIa-B (low risk)	IIa-B (only BNP)
Severe AS undergoing other cardiac surgery	I-C	I-B
Moderate AS undergoing other cardiac surgery	IIb-C	IIa-C
Percutaneous BAV in severe AS		
In bridge to SAVR/TAVR	IIb-C	IIb-C
Before noncardiac surgery		IIb-C
Severe comorbidities with survival <1 y		III-C

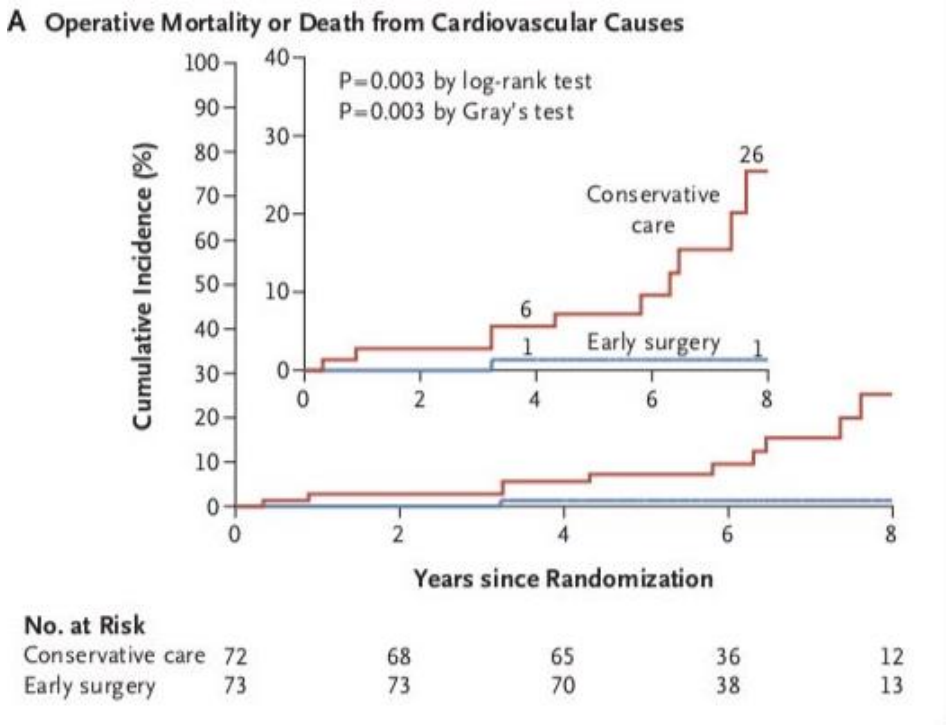
AS = aortic stenosis; BAV = balloon aortic valvuloplasty; BNP = brain natriuretic peptide; LFLG = low flow low gradient; LVEF = left ventricular ejection fraction; SAVR = surgical aortic valve replacement; SBP = systolic blood pressure; TAVR = transcatheter aortic valve replacement.

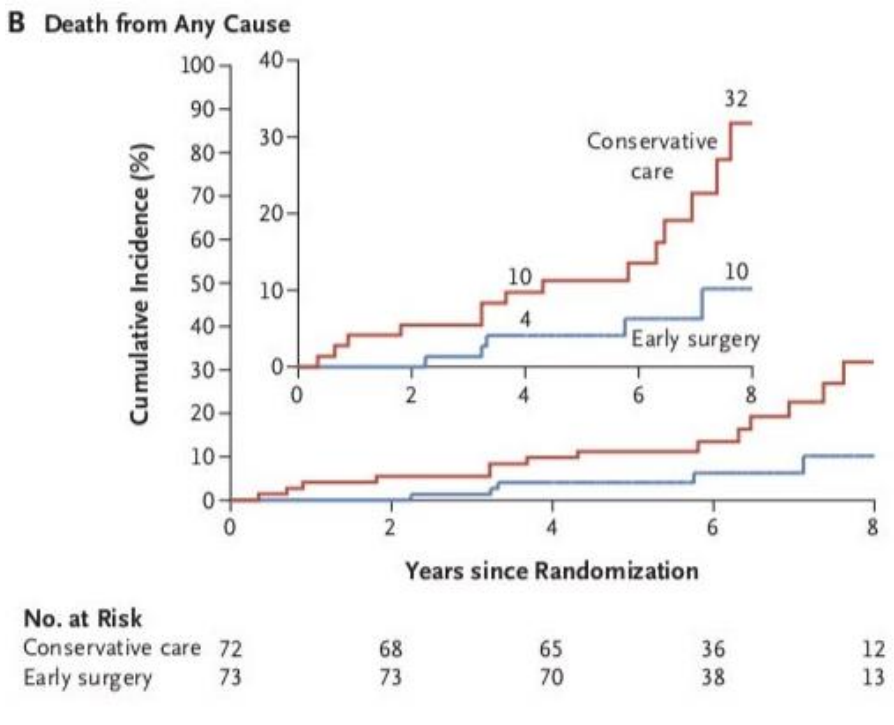
Results

Summary of Randomized Controlled Trials

First Author Year, Study	Country	Study Period	Number of Patients		
			Total	AVR	CS
Genereux 2024 THE EARLY TAVR TRIAL	US & Canada	2017-2021	**901**	**TAVR** 455	446
Dweck 2024 EvoLved-AS	UK	2017-2022	**224**	**SAVR/ TAVR** 113	111
Banovic 2024 AVATAR	Europe	2015-2023	**157**	**SAVR** 78	79
Kang 2020 RECOVERY	Korea	2010-2015	**145**	**SAVR** 73	72

Early Surgery vs. Conservative Management for Asymptomatic Very Severe AS: RECOVERY Trial





Kang et al. NEJM 2019

Aortic Valve Replacement versus Conservative Treatment in Asymptomatic Severe AS – Long-term Follow-up: The AVATAR Trial

AVATAR trial

Aortic valve replacement versus conservative treatment in asymptomatic severe aortic stenosis

Multicenter, multinational, open label, randomized, controlled trial

157

Asymptomatic patients with severe aortic stenosis and normal LV function

Median follow-up of **63** months

78

Early surgery

79

Conservative management with watchful waiting

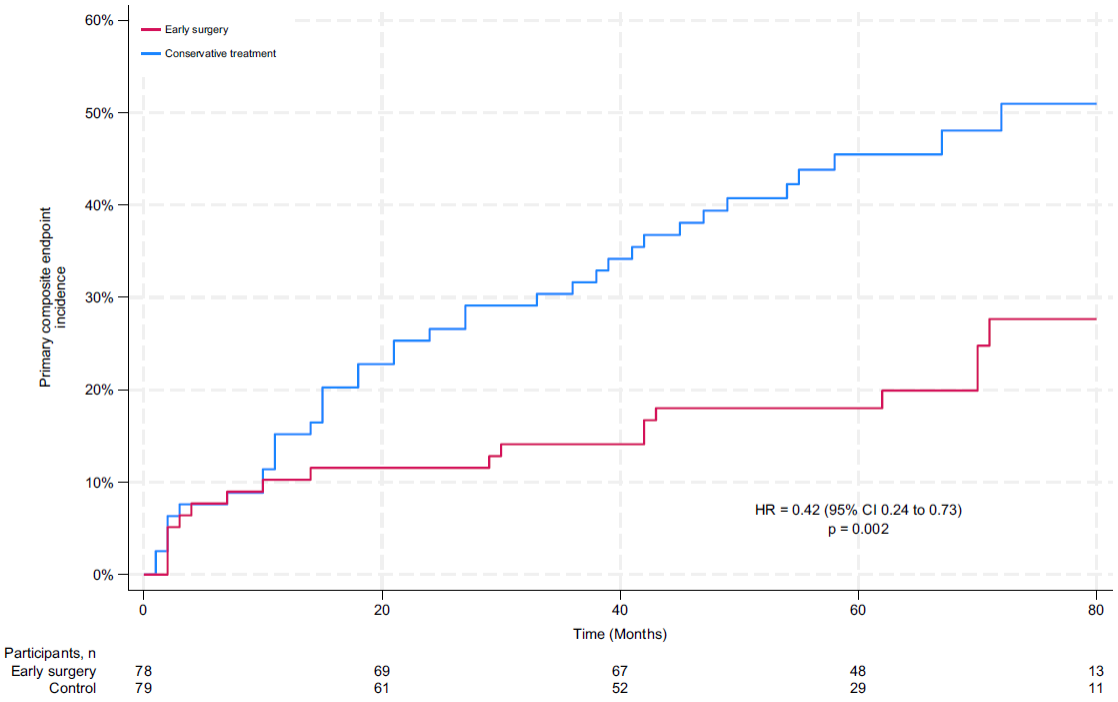
Composite primary outcome comprising all-cause mortality, AMI, stroke or unplanned HF hospitalization

23.1% In early surgery group

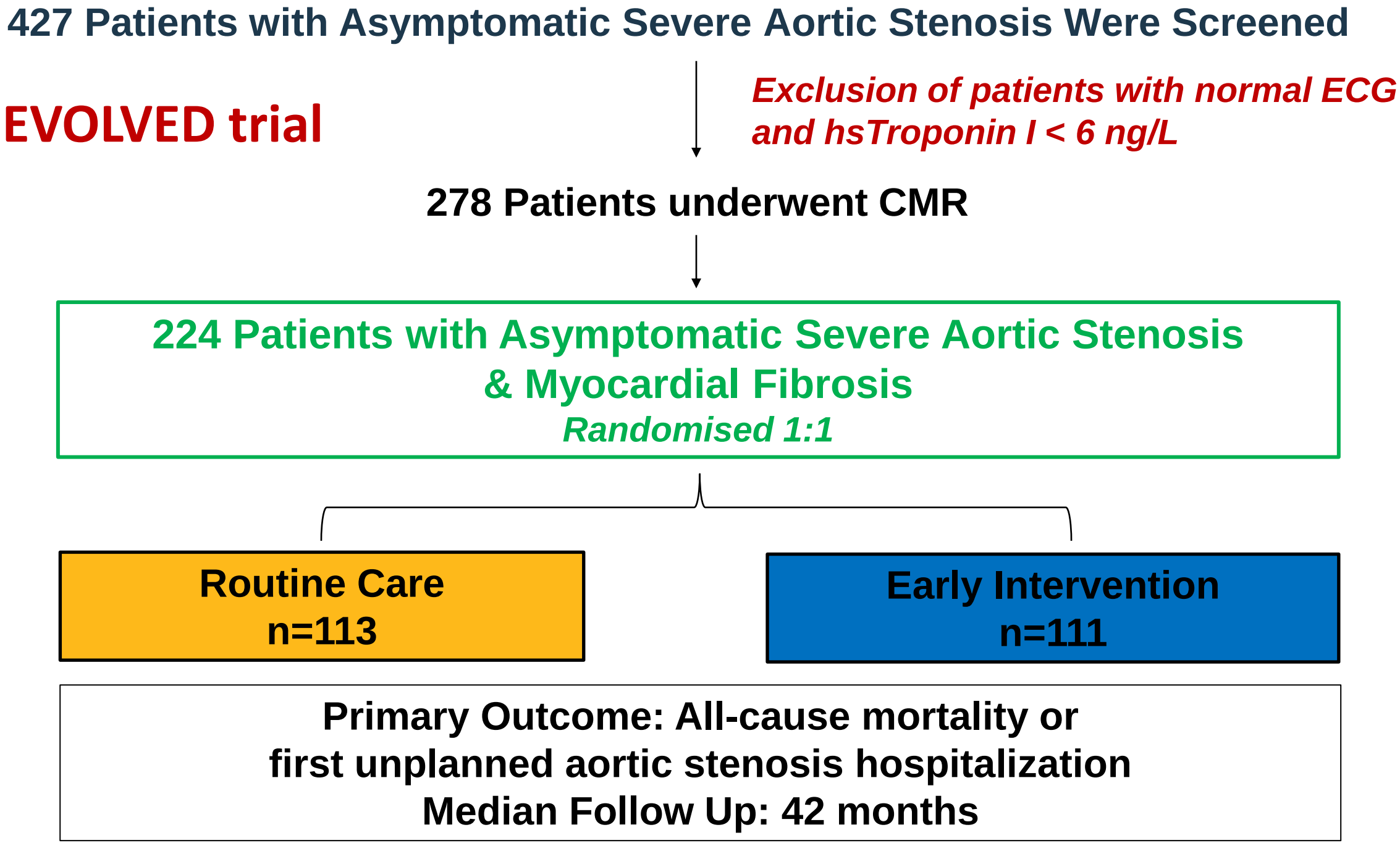
vs

46.8% In conservative management group

(HR 0.42; 95% CI, 0.24–0.73; p = 0.002)



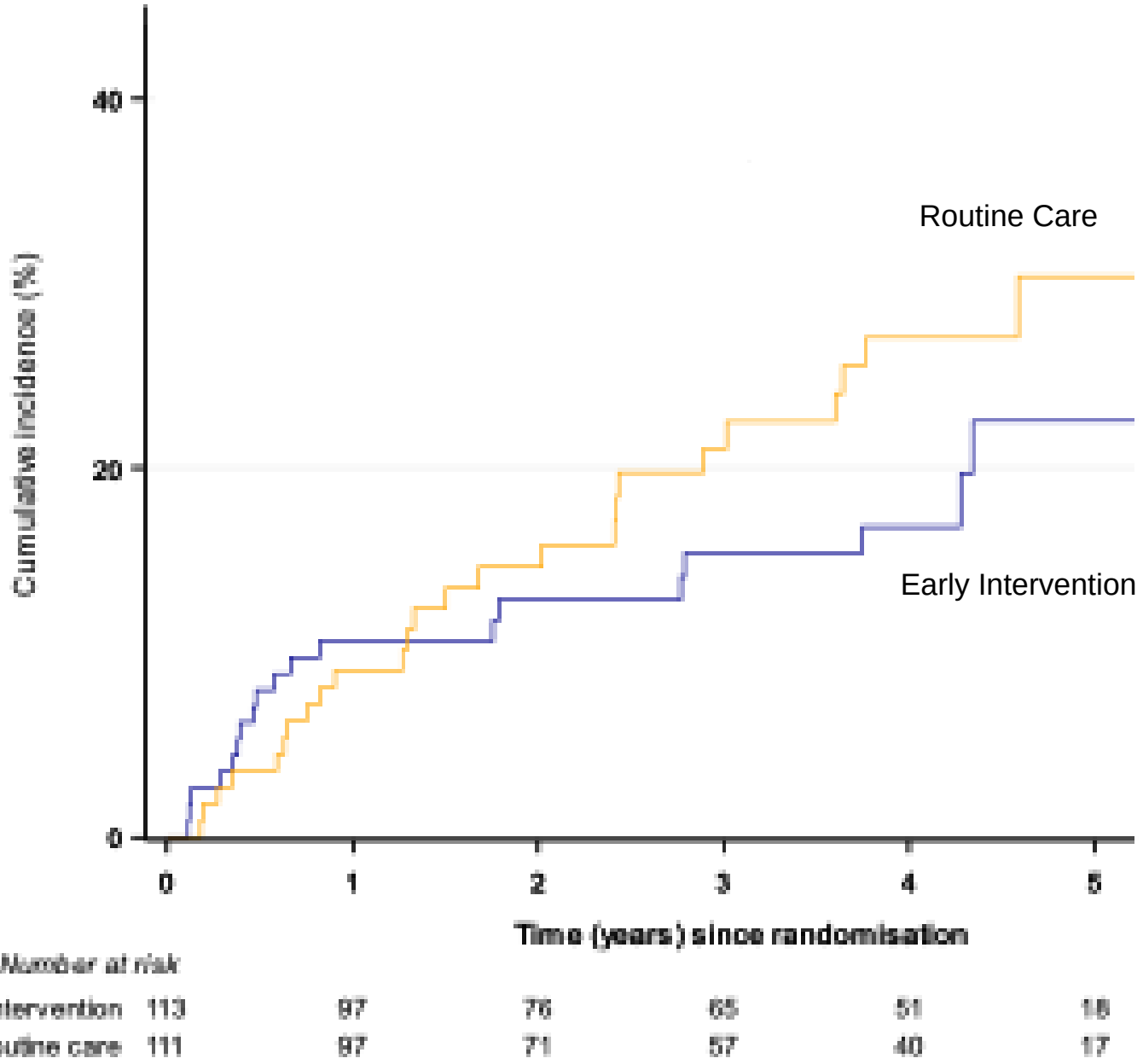
Banovic et al. Eur Heart Journal 2025


427 Patients with Asymptomatic Severe Aortic Stenosis Were Screened
EVOLVED trial
Exclusion of patients with normal ECG and hsTroponin I < 6 ng/L
278 Patients underwent CMR
224 Patients with Asymptomatic Severe Aortic Stenosis & Myocardial Fibrosis
Randomised 1:1
Routine Care n=113
Early Intervention n=111
Primary Outcome: All-cause mortality or first unplanned aortic stenosis hospitalization
Median Follow Up: 42 months

Primary Endpoint

All-cause death or unplanned aortic stenosis hospitalization

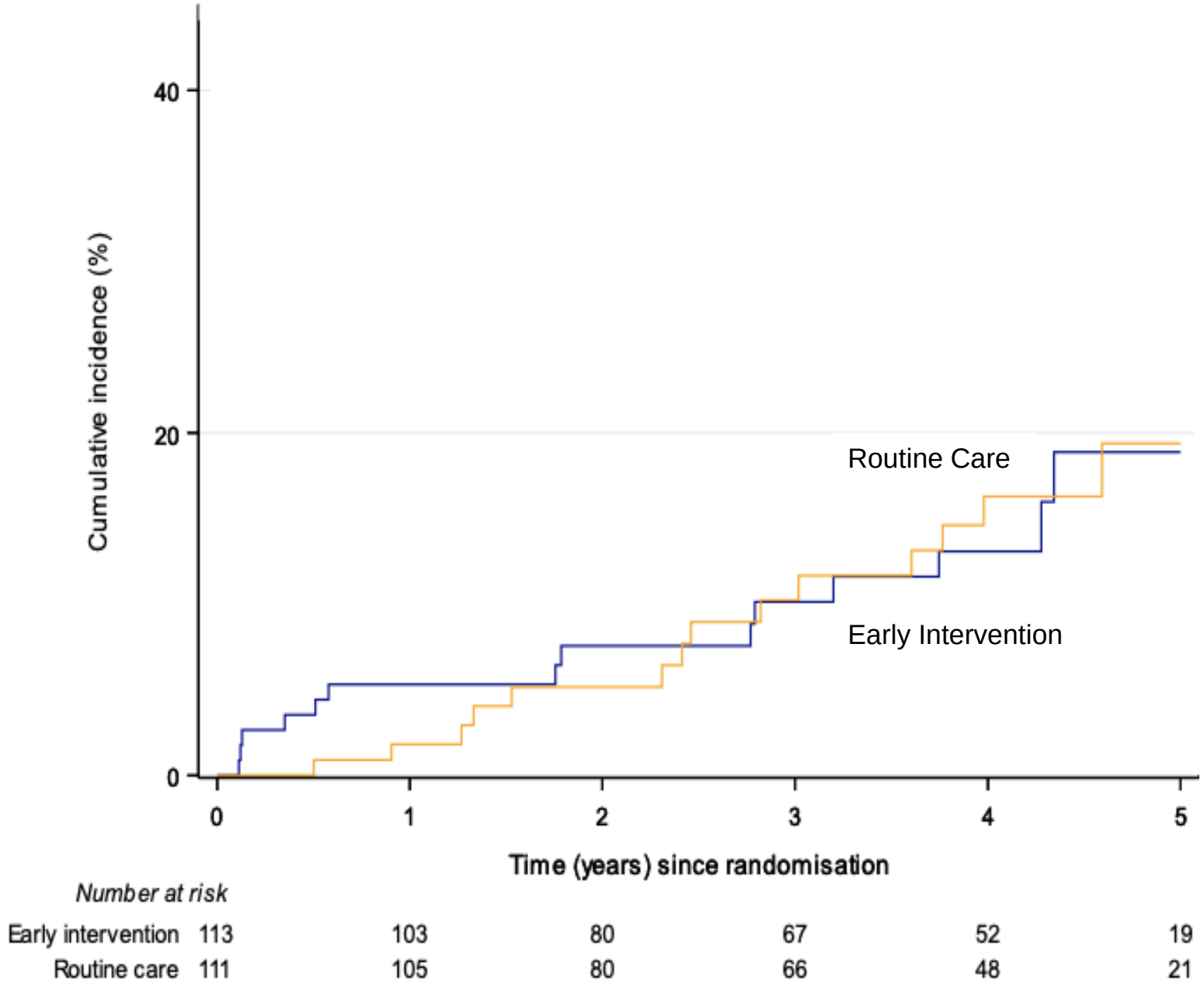
Hazard Ratio 0.79
(95% CI 0.44 to 1.43)
P=0.44



Secondary Endpoint

All-cause death

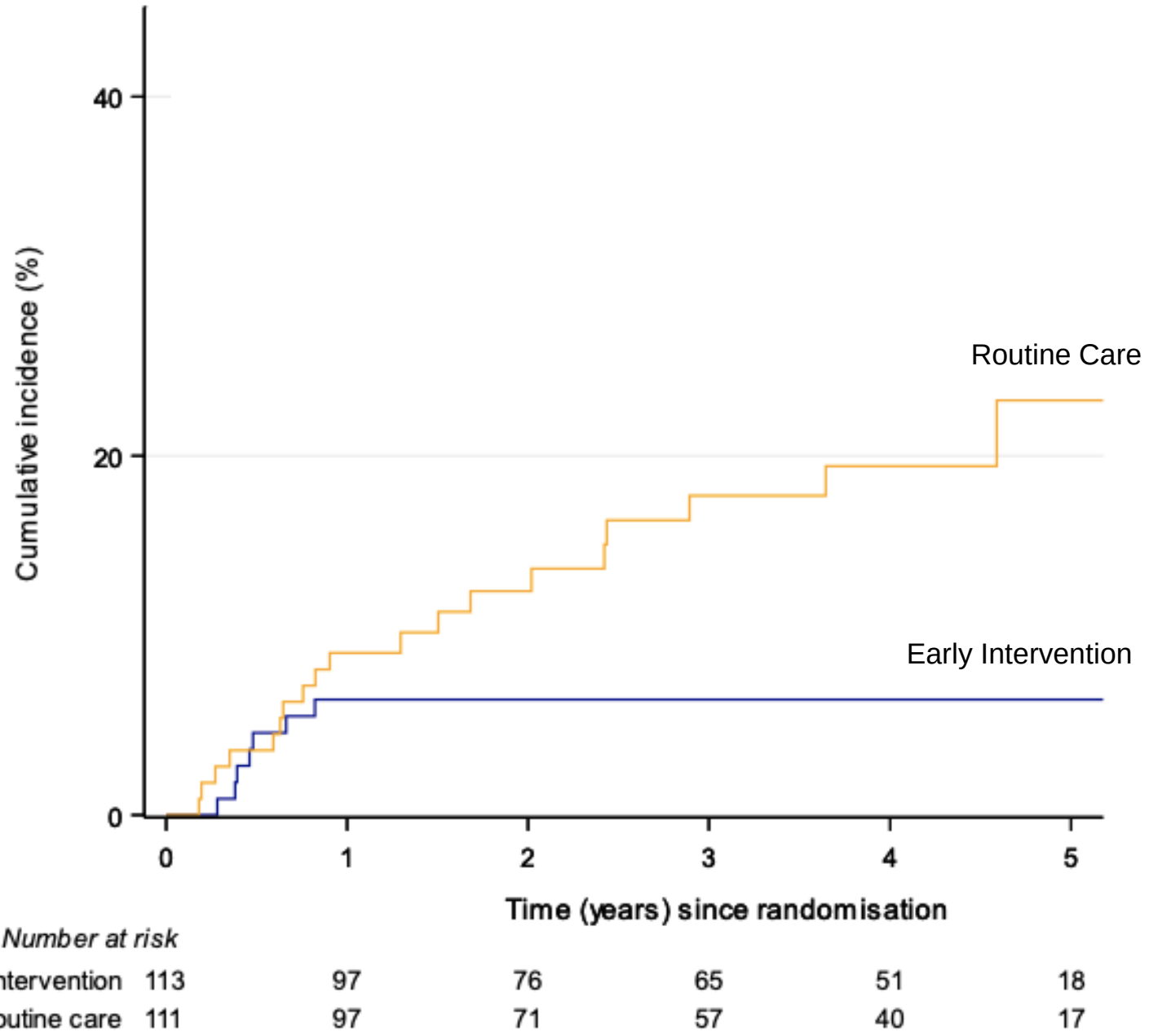
Hazard Ratio 1.22
(95% CI 0.59 to 2.51)



Secondary Endpoint

Unplanned aortic hospitalization

Hazard Ratio 0.37
(95% CI 0.16 to 0.88)



THE EARLY TAVR TRIAL

Study Design

Prospective, multicenter RCT evaluating patients with asymptomatic, severe AS aged ≥ 65 years w/ an STS score ≤ 10% and LVEF ≥ 50%

Asymptomatic Assessment
Confirmed by negative treadmill stress test*

Randomization 1:1

Transfemoral-TAVR
(SAPIEN 3 or SAPIEN 3 Ultra THV)

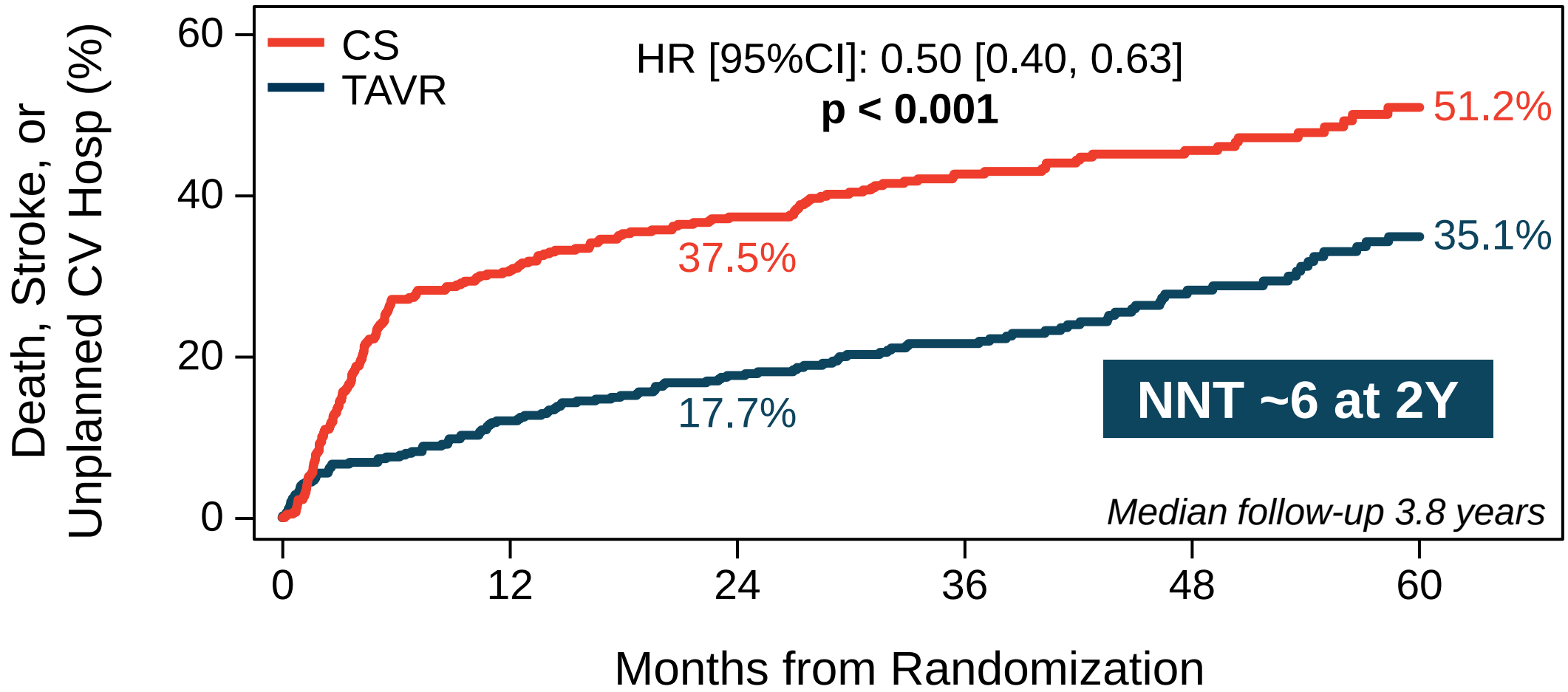
Clinical Surveillance

PRIMARY ENDPOINT (Superiority)
Non-hierarchical composite of all-cause death, any stroke, or unplanned CV hospitalization at a minimum follow-up of 2 years

Généreux et al. NEJM 2024

*Confirmed by detailed clinical history alone if patient was unable to perform stress test

Primary Endpoint



No. at risk:

TAVR	455	390	363	285	142	103
CS	446	305	266	187	117	46

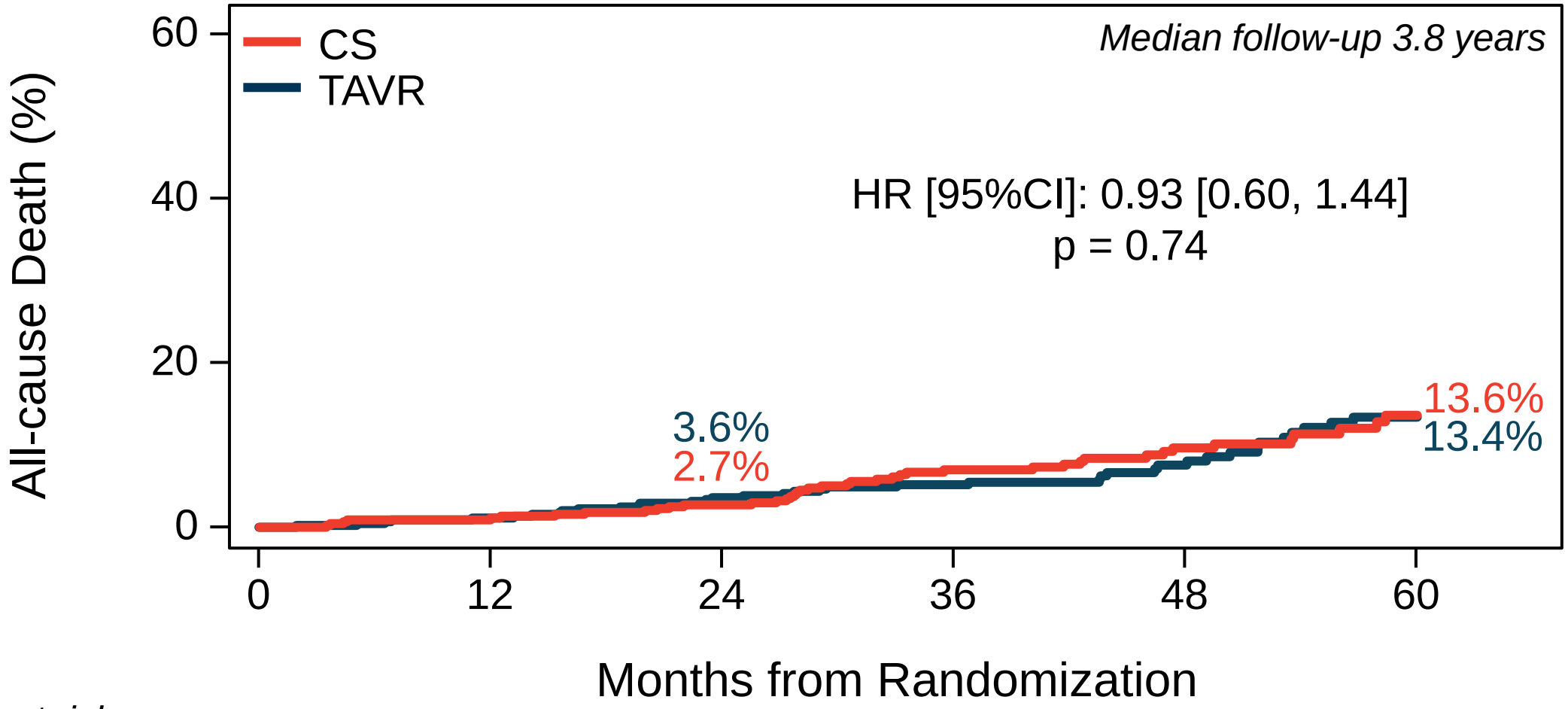
Event rates are Kaplan-Meier estimates

Généreux et al. NEJM 2024

Patients had a minimum follow-up of 2 years

THE EARLY TAVR TRIAL

All-cause Death



No. at risk:

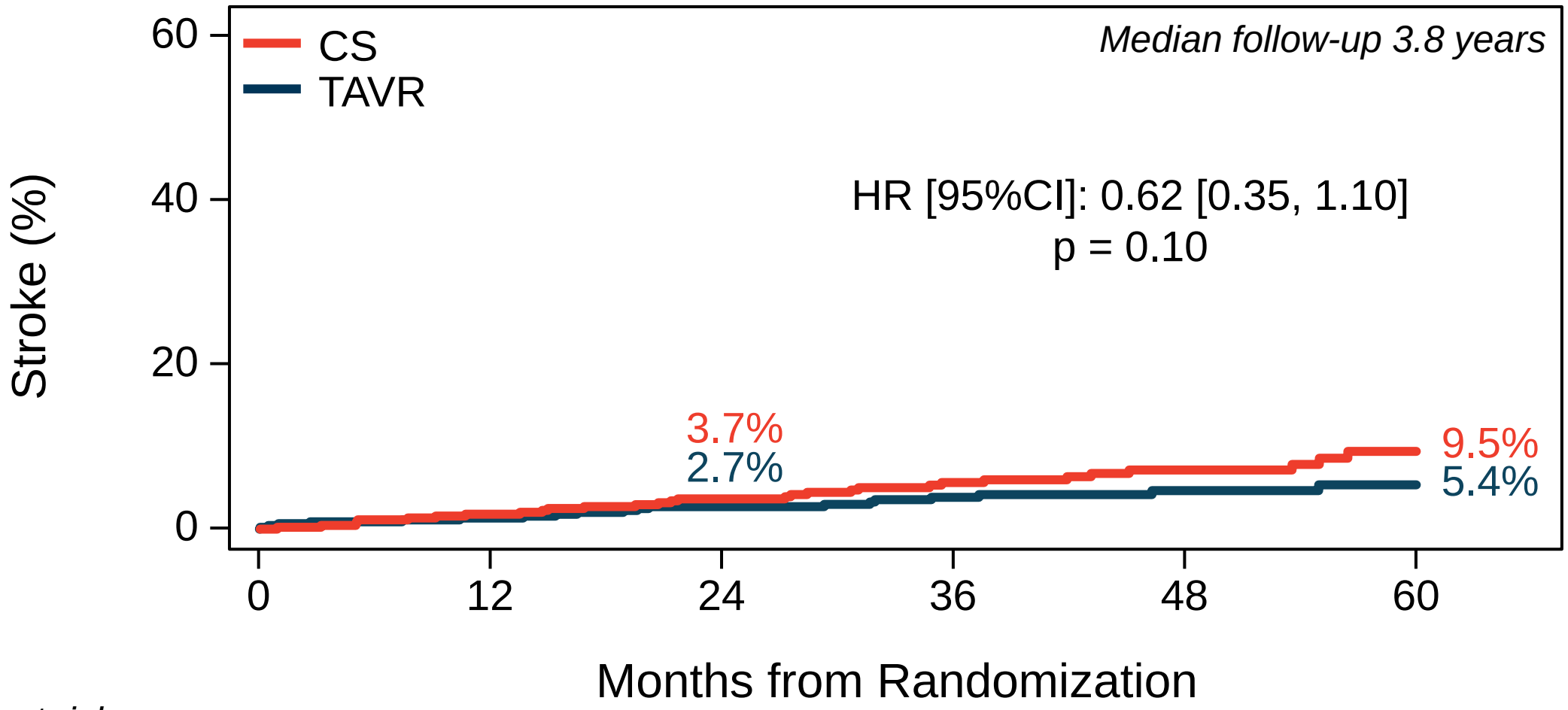
TAVR	455	439	425	346	187	136
CS	446	436	418	310	199	95

Event rates are Kaplan-Meier estimates

Généreux et al. NEJM 2024

Patients had a minimum follow-up of 2 years

Stroke



No. at risk:

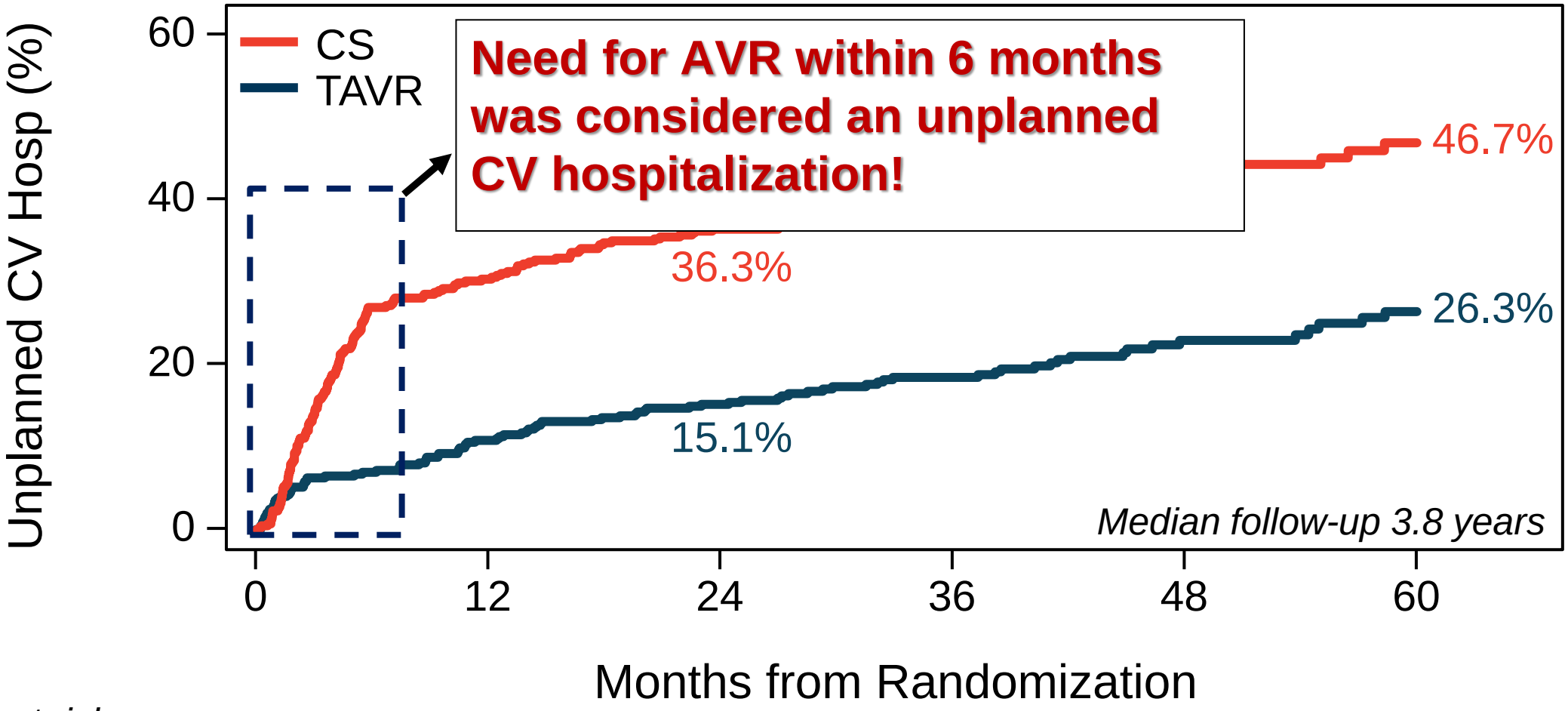
TAVR	455	433	415	335	180	130
CS	446	429	406	295	185	87

Event rates are Kaplan-Meier estimates

Généreux et al. NEJM 2024

Patients had a minimum follow-up of 2 years

Unplanned CV Hospitalization



No. at risk:

TAVR	455	392	365	287	142	103
CS	446	306	267	189	118	46

Event rates are Kaplan-Meier estimates

Généreux et al. NEJM 2024

Patients had a minimum follow-up of 2 years

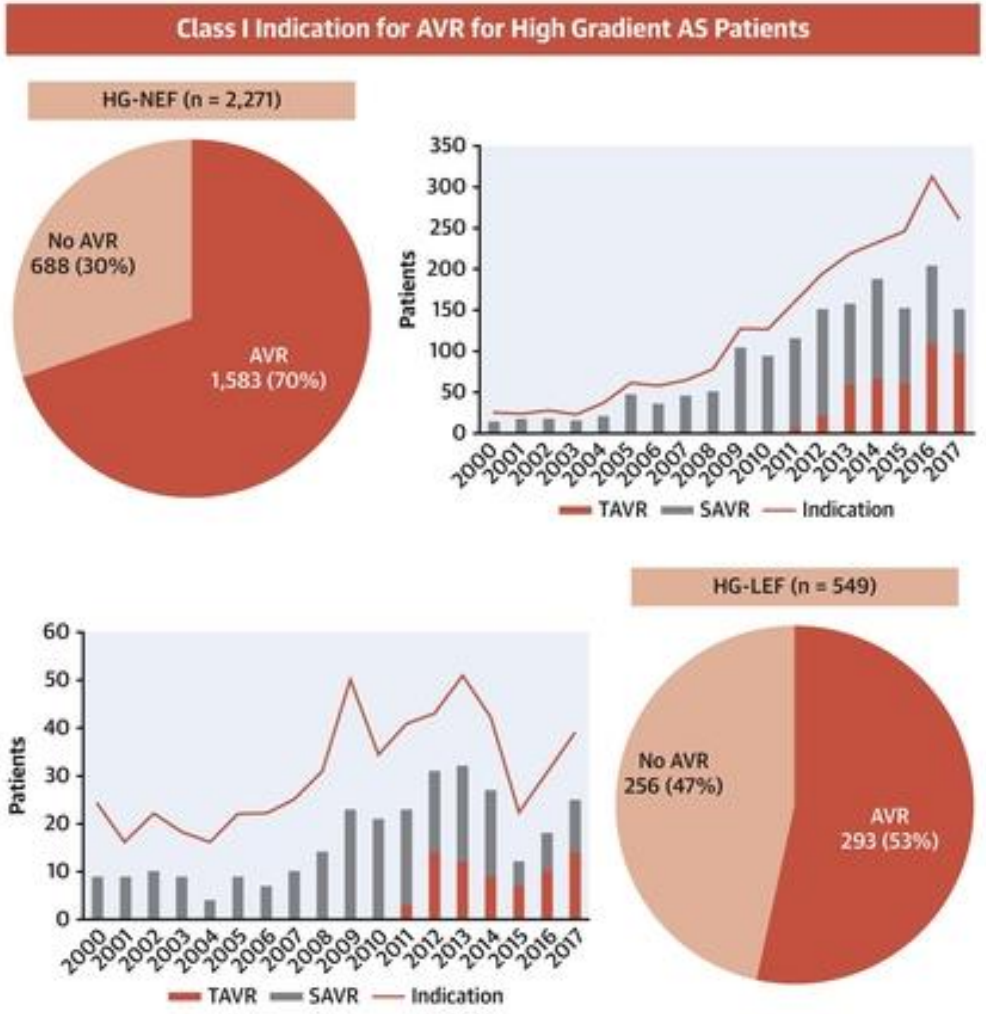
A psychological phenomenon where people change their behavior or performance because they know they are being observed or studied, rather than because of the actual intervention or changes in their environment.

- **Conversion to AVR was often due to anxiety**

Early AVR in all patients with asymptomatic severe AS will overwhelm the HVT and HVC and exceed their bandwidth for TAVI or SAVR

One third of patients with symptomatic severe AS and Class I indication for AVR do not receive AVR, especially in:

- Women
- Elderly patients
- Low-Gradient AS

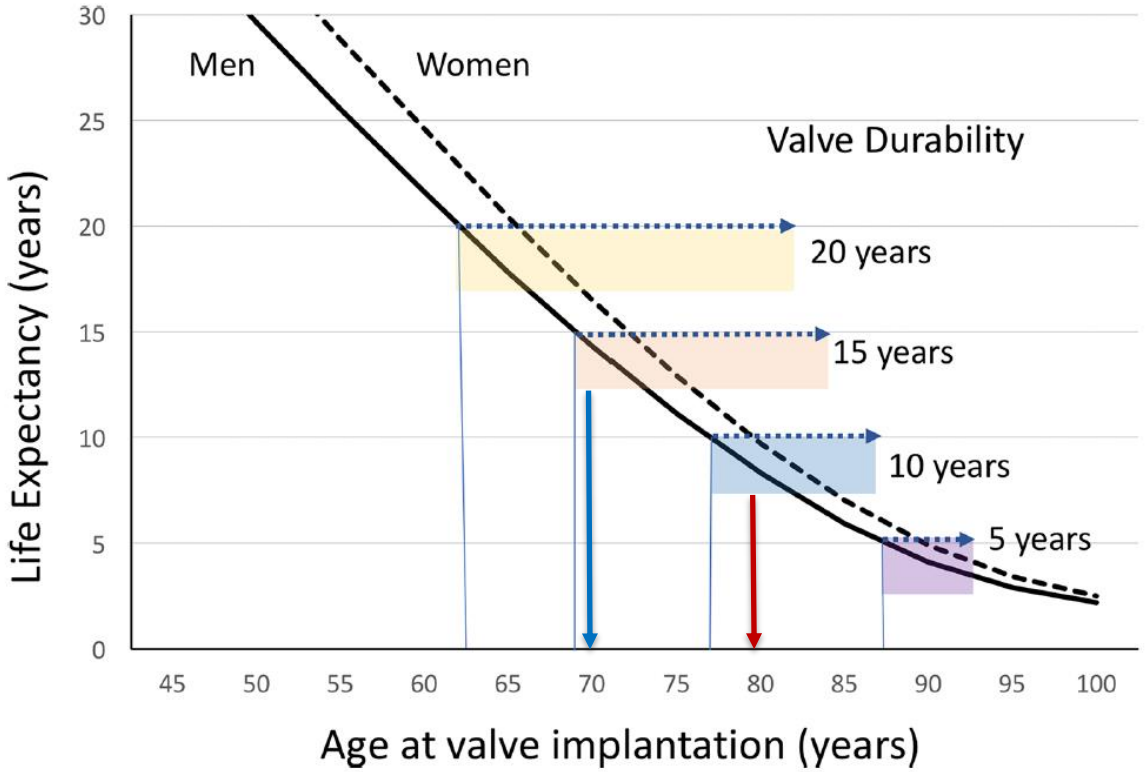


Li, S.X. et al. J Am Coll Cardiol. 2022;79(9):864-877.

Before expanding indication of TAVR / SAVR to asymptomatic severe AS, we should first put a priority on treating patients with symptomatic severe AS

Early AVR in asymptomatic severe AS exposes the patient to earlier SVD and re-intervention

The ‘durability’ clock starts ticking as soon as we implant the bioprosthetic valve



Proven durability of TAVR: 5-8 years

Average age of patients with Asymptomatic Severe AS

Bagur et al. Heart 2017

ESC European Society of Cardiology
European Heart Journal Open (2025) **00**, oeaf114
https://doi.org/10.1093/ehjopen/oeaf114

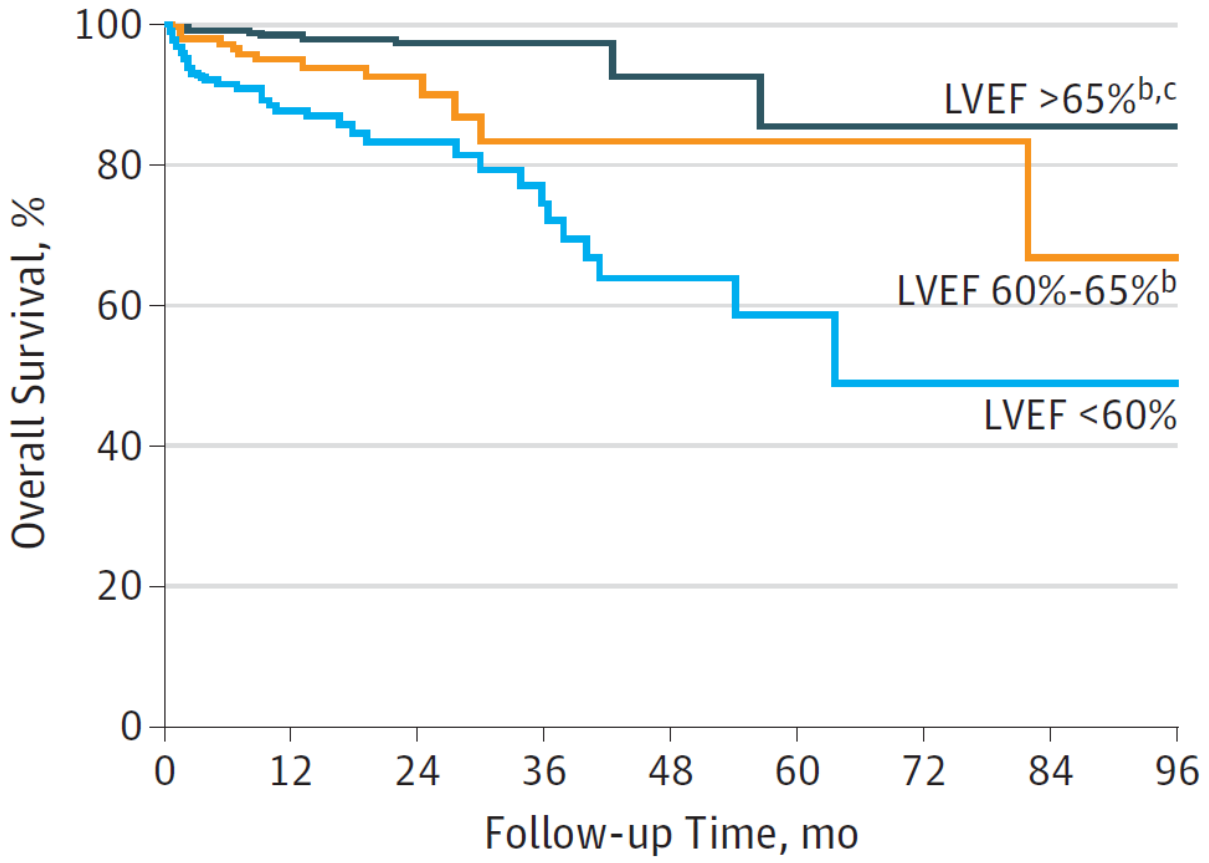
VIEWPOINT
Valvular heart disease

Early aortic valve intervention in asymptomatic severe aortic stenosis: a clinical dilemma in evolution

Patrizio Lancellotti [1,2,*], Augustin Coisne [3,4], Bernard Cosyns[5,6], Raluca Dulgheru[1,2], Madalina Garbi[7], Geu-Ru Hong [8], Jadranka Separovic Hanzevacki[9], Marco Moscarelli [10,11], Tadafumi Sugimoto[12], Erwan Donal [13], Khalil Fattouch [11], Gilbert Habib[14,15], Mani Vannan[16], and Philippe Pibarot [17]; on behalf of the EuroValve Consortium

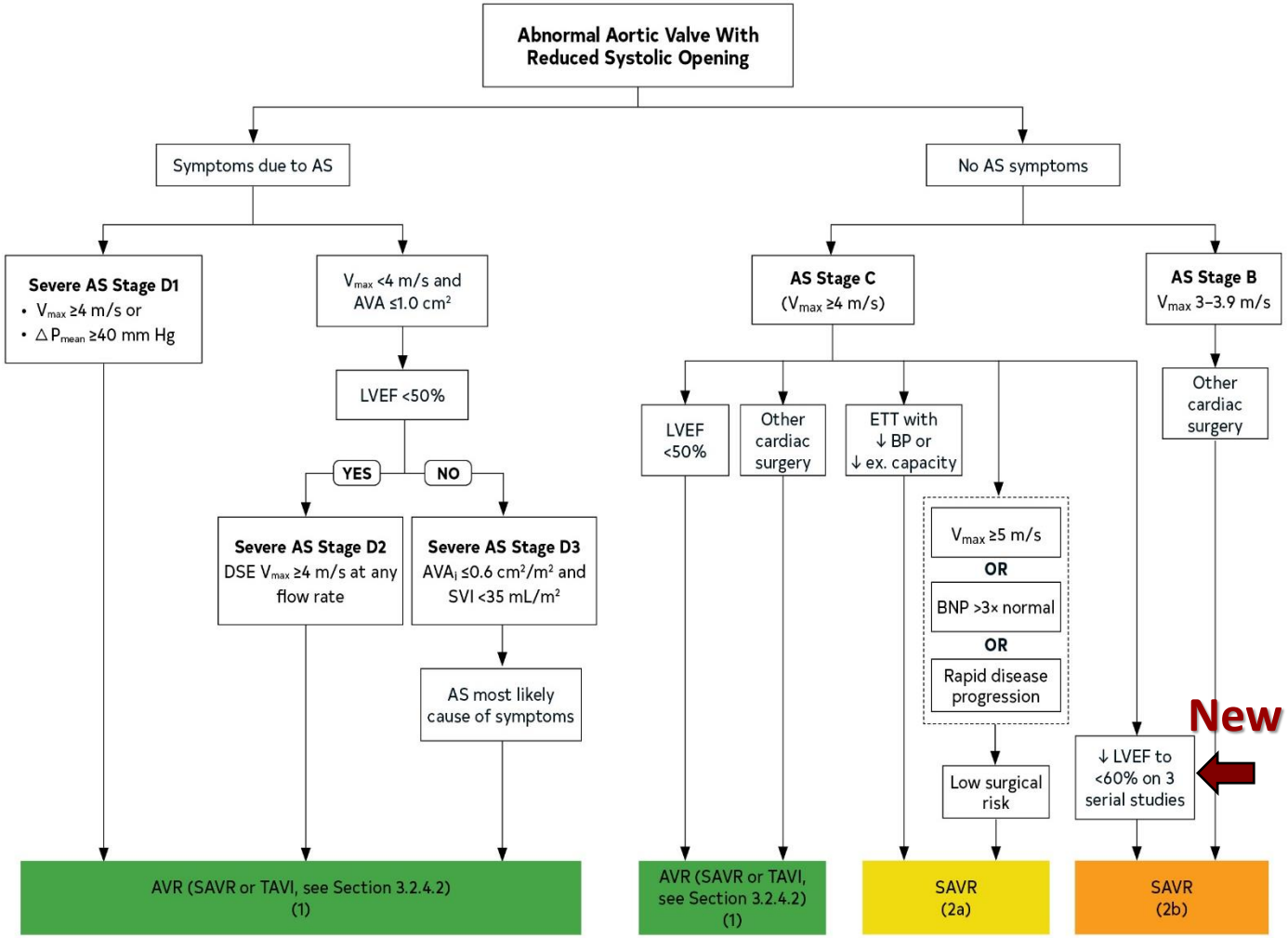
Even if overall results of RCTs favor early AVR in Asymptomatic Severe AS, need to optimize and prioritize timing of AVR based on multimodal risk stratification strategy combining imaging and blood biomarkers of cardiac dysfunction / damage / failure

Outcomes of Patients With Asymptomatic AS Followed Up in Heart Valve Clinics



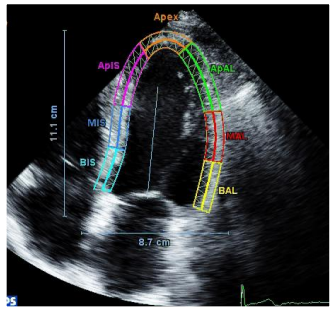
Lancellotti et al. JAMA Cardiology 2018

LVEF<50% to define LV systolic dysfunction in AS: Is it too low?



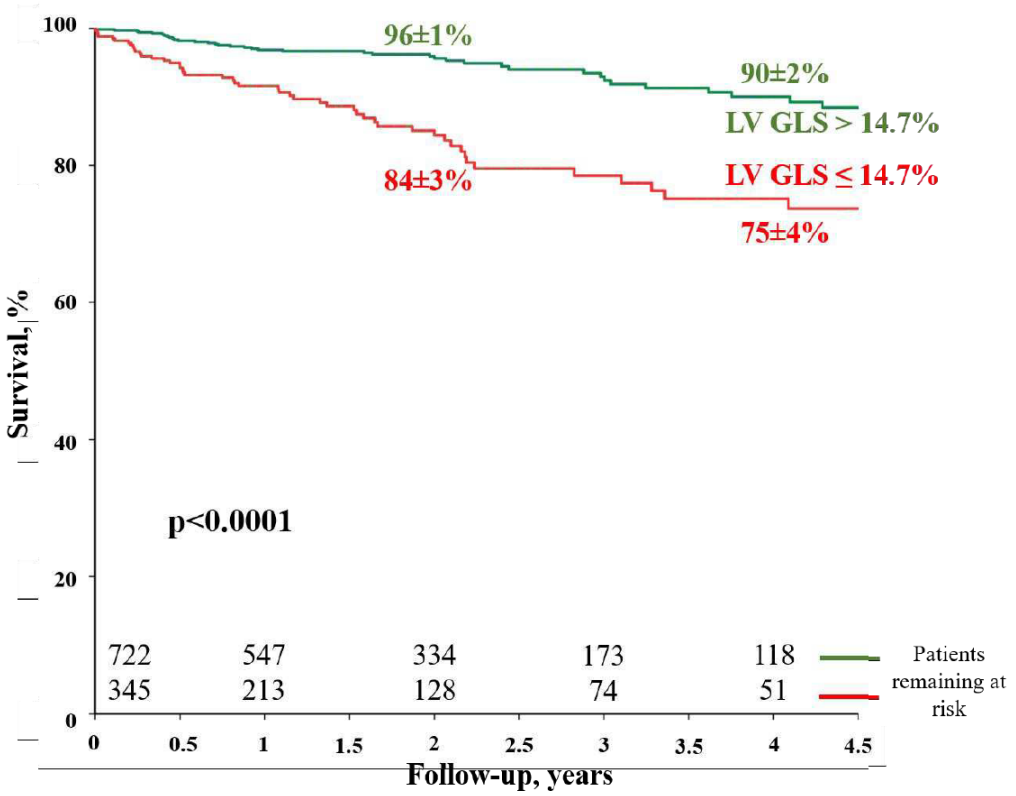
ESC Guidelines
LVEF<55% (IIa)

Distribution and Prognostic Significance of GLS in Asymptomatic AS: A Meta-analysis

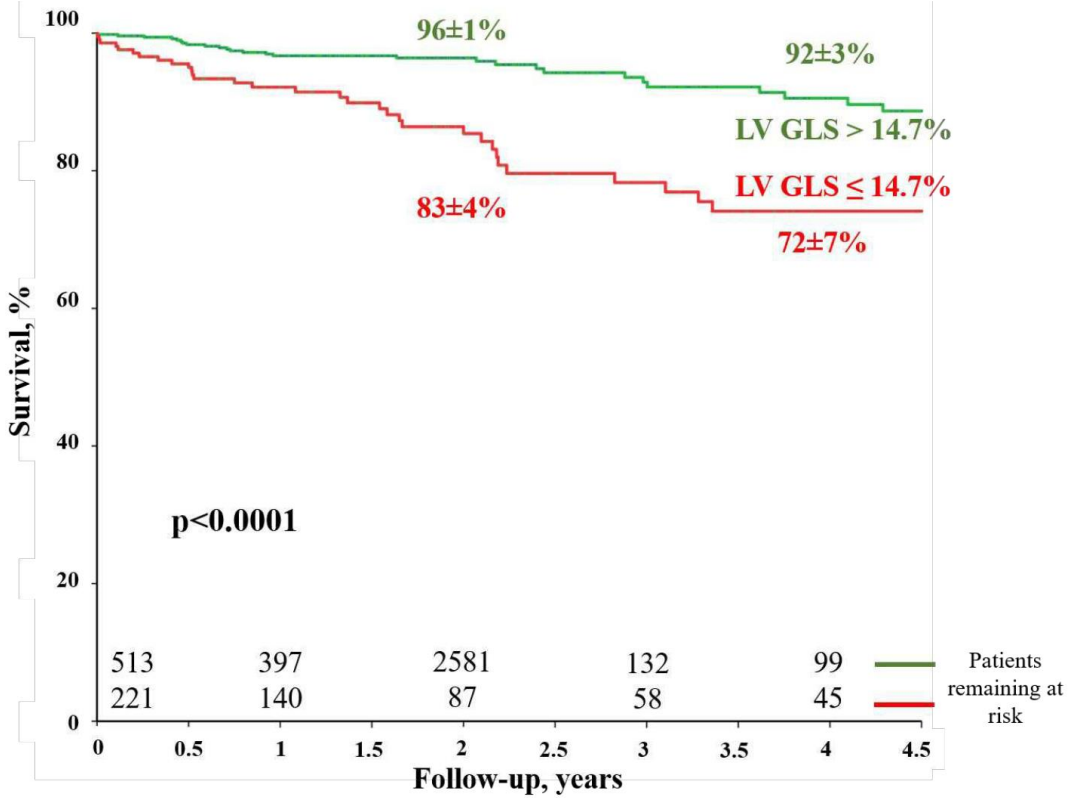


Case: GLS= -13%

Whole Cohort

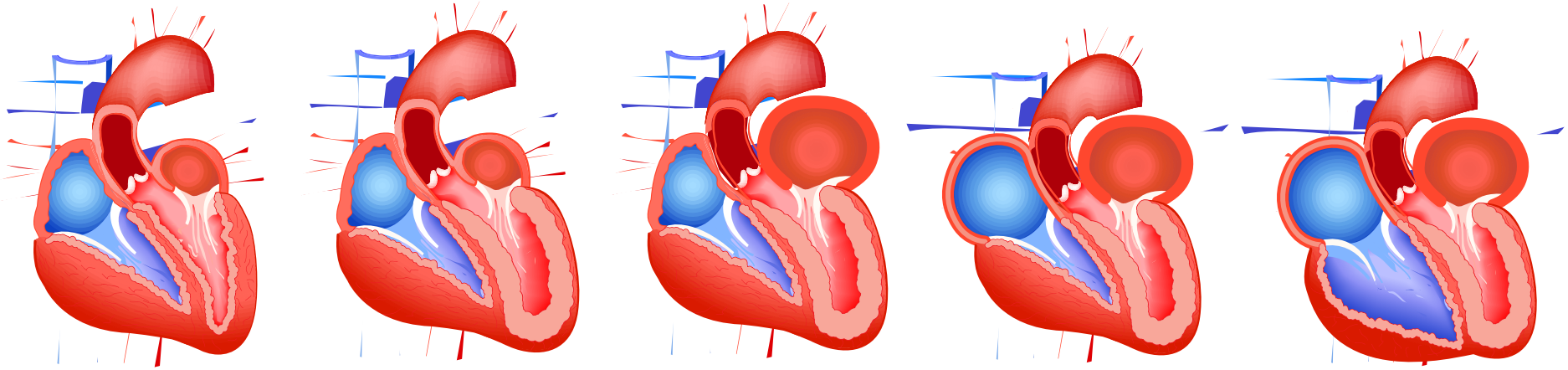


LVEF ≥ 60%



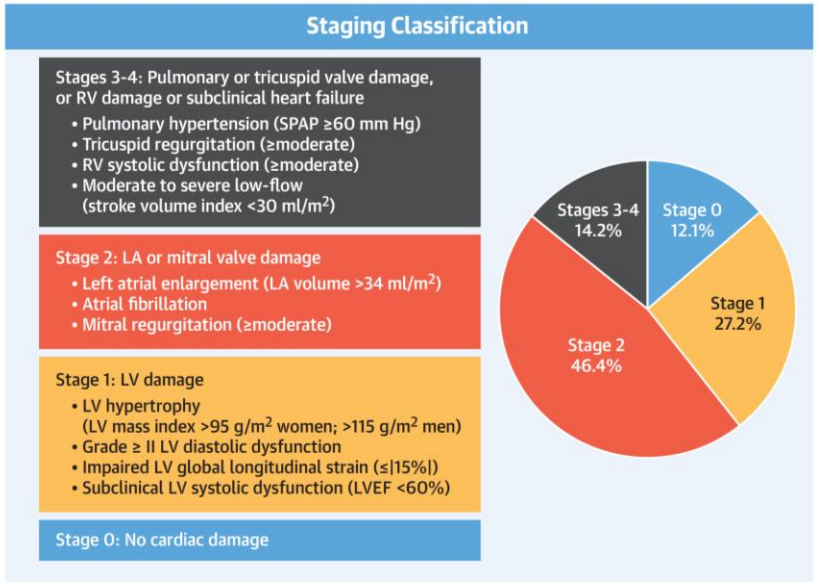
Magne et al. JACCi 2019

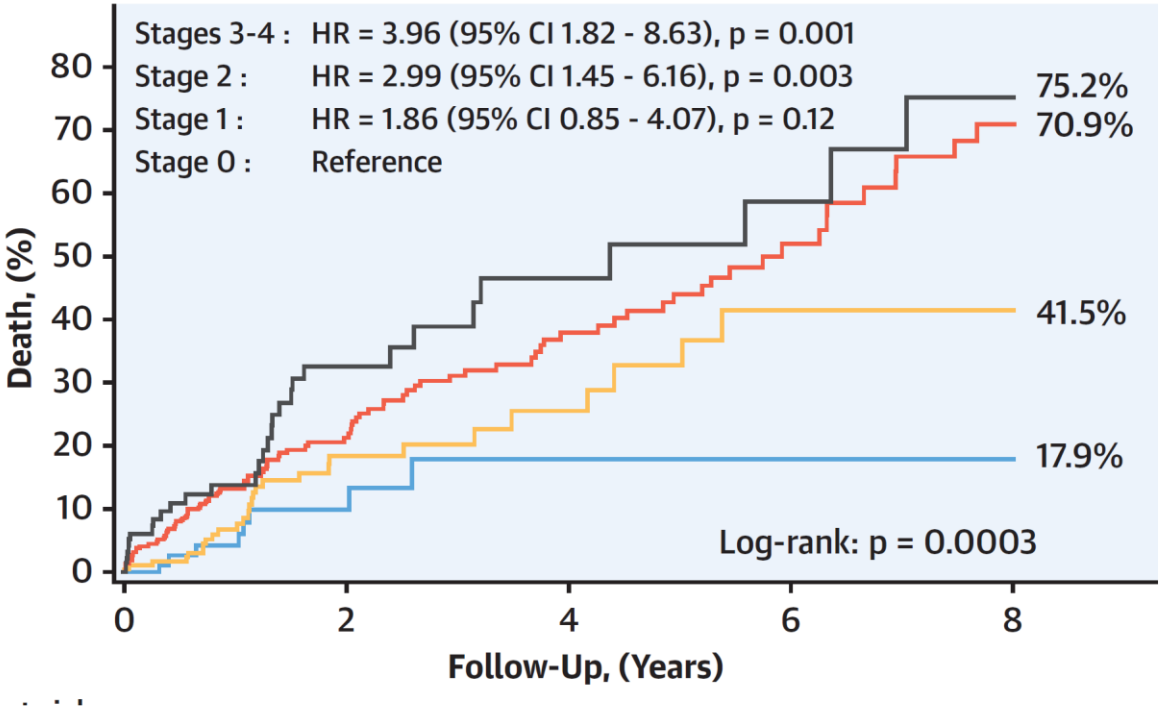
Modification of Cardiac Damage Staging for Asymptomatic Severe AS



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
	≥ Grade 2 Diast. Dysf.	Moderate-Severe MR	Moderate-Severe TR	SVi < 30 mL/m^2
	EF <60%	Atrial Fibrillation		
	GLS < 15%			

Cardiac Damage Staging in Asymptomatic AS



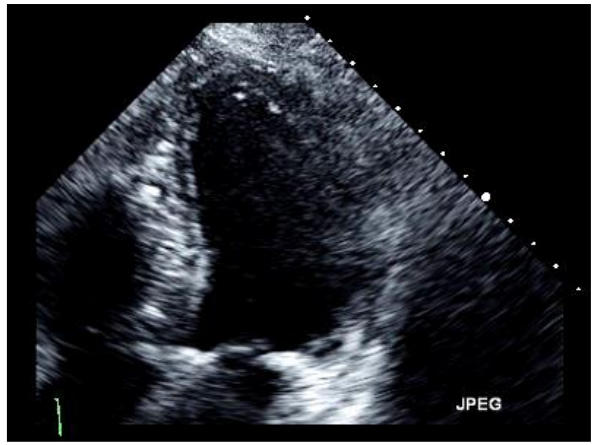


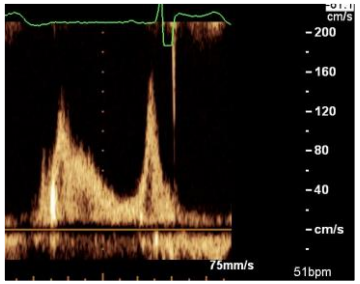
61% of Asymptomatic Patients with Severe AS were in Stage ≥2

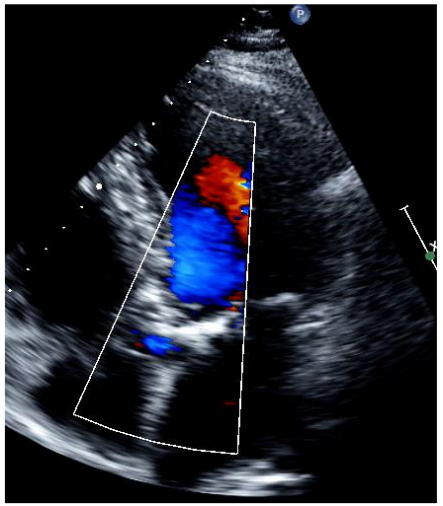
Tastet al. JACC; 2019: 74: 550-563

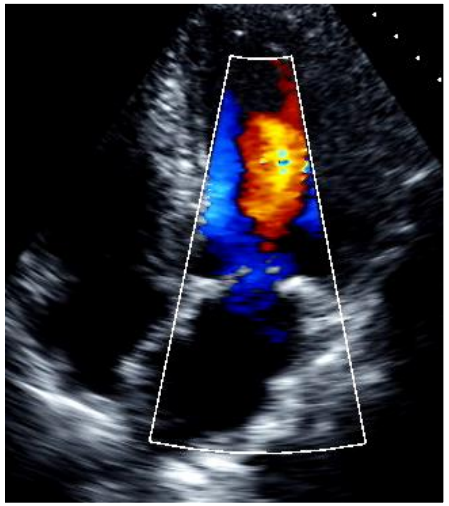
Case: Asymptomatic 78 y.o. Man with Severe AS

- LVEF by Biplane Simpson: 63%
- LV hypertrophy
- LV diastolic dysfunction: Grade 1
- Mild MR, MAC
- Trace TR
- Normal systolic PAP









- Cardiac damage stage 1

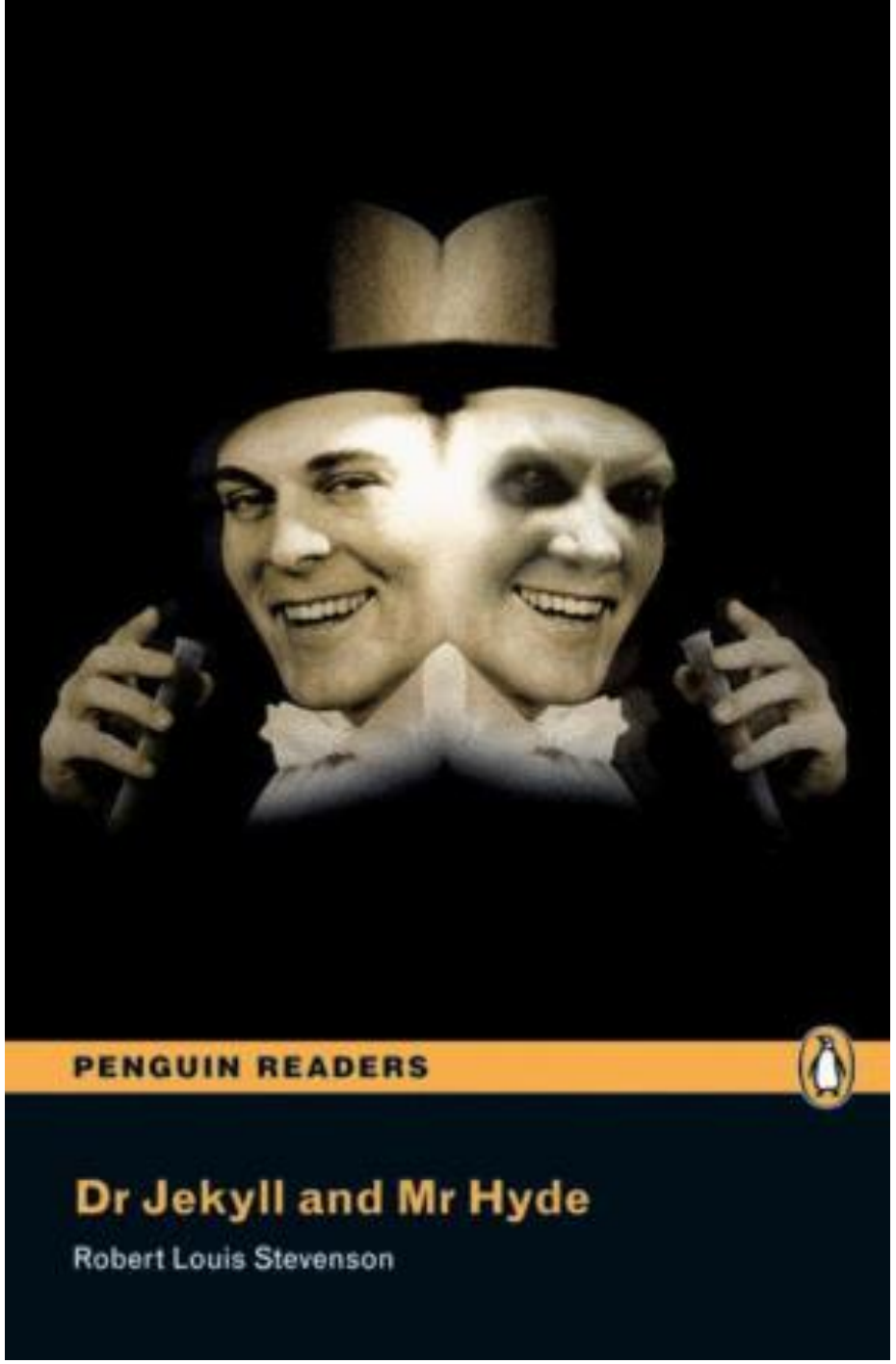
Mr Hyde concludes:

- **<u>Default Strategy:</u> Active clinical surveillance in asymptomatic severe AS**

- **Consider early AVR in selected patients with risk markers:**

  Very severe AS; Fast stenosis progression; Elevated BNP (≥ 3 fold); LVEF <55-60%; Cardiac damage stage ≥ 2

*Strategy recommended by the 2020 ACC-AHA and ESC-EACTS guidelines



Dr. Jekyll, a respectable scientist, uses a potion to transform himself into the savage and remorseless Mr. Hyde, allowing him to indulge in his wicked impulses in a way his civilized persona cannot.

Asymptomatic severe AS:
Early Intervention:
Acting before it is too late

By Dr. Jekyll alias Philippe Pibarot

Canada Research Chair in Valvular Heart Diseases

Institut Universitaire de Cardiologie et de Pneumologie de Québec / Québec Heart & Lung Institute

Doctorate Honoris Causa

LIÈGE université

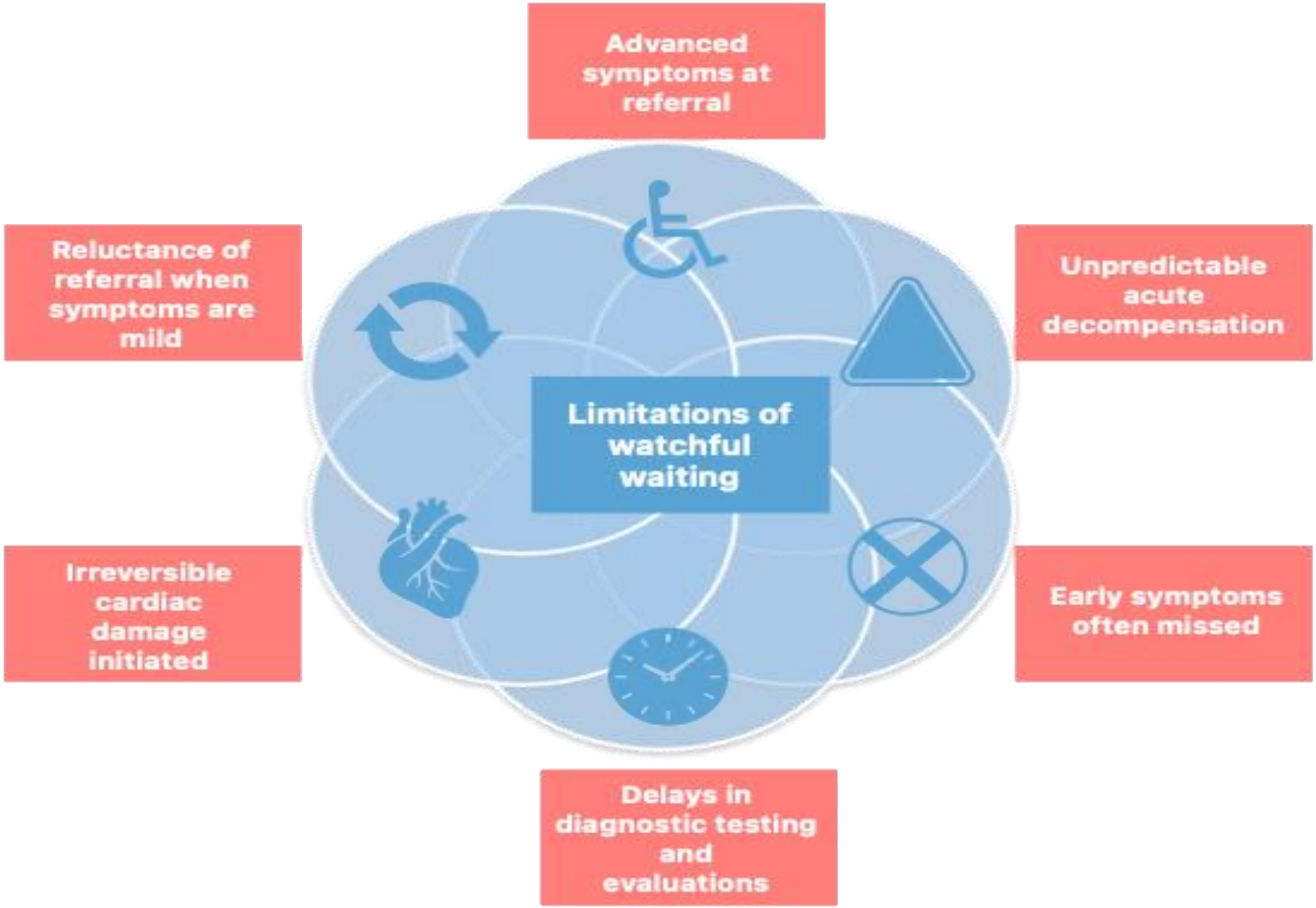
Université LAVAL

Disclosure: Philippe Pibarot

- **Financial relationship with industry**
  - **Edwards Lifesciences: Echo CoreLab for PARTNER 2– SAPIEN 3, PARTNER 3, TAVR-UNLOAD, EARLY-TAVR, PROGRESS, ALLIANCE X4 trials, RHEIA**
  - **Novartis: Lp(a) FRONTIERS CAVS**
- **Other financial disclosure:**
  - **Research Grants from Canadian Institutes of Health**
  - **Research and Heart & Stroke Foundation of Quebec**
  - **Off label Use: None**

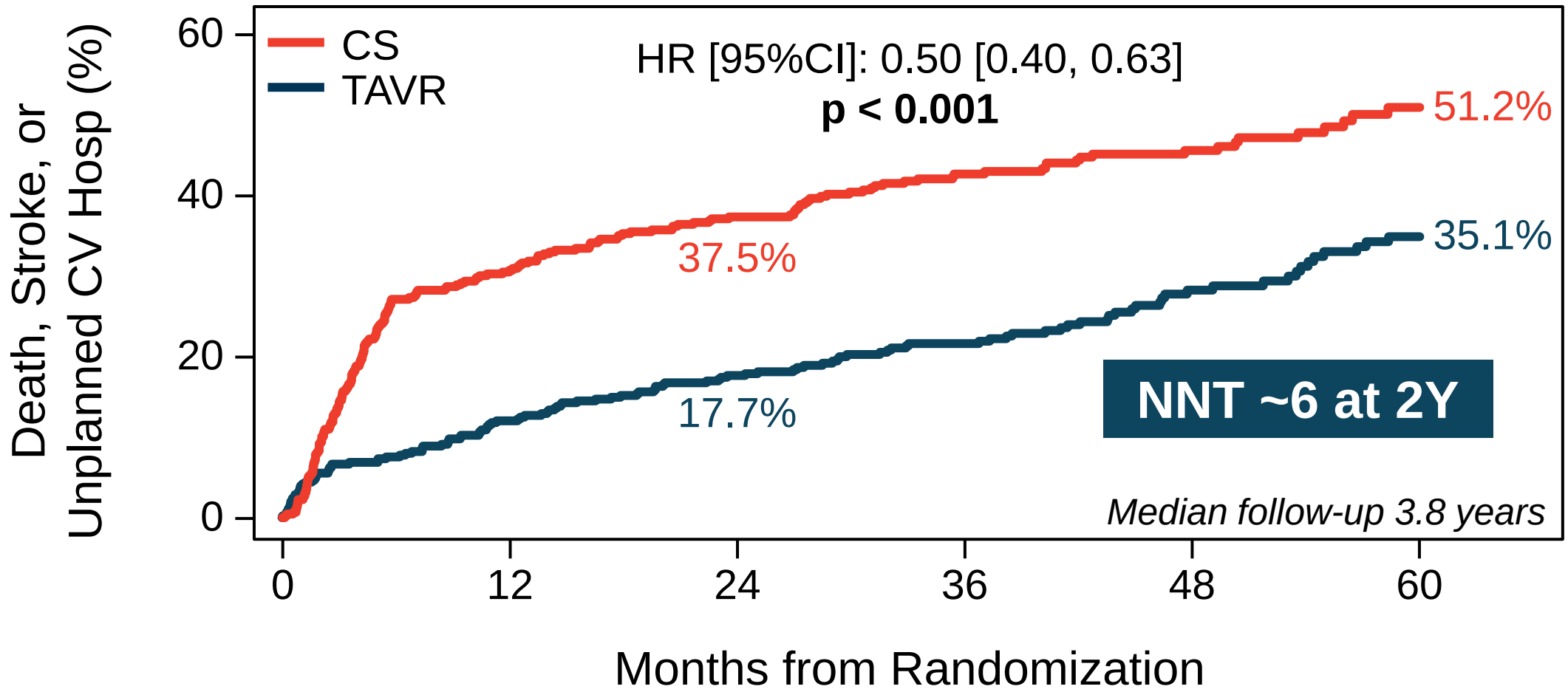
Dr Jekyll will defend this strategy:

Early AVR in asymptomatic severe AS and defer AVR in selected patients with specific criteria


Advanced symptoms at referral
Reluctance of referral when symptoms are mild
Unpredictable acute decompensation
Limitations of watchful waiting
Irreversible cardiac damage initiated
Early symptoms often missed
Delays in diagnostic testing and evaluations

THE EARLY TAVR TRIAL

Primary Endpoint



No. at risk:

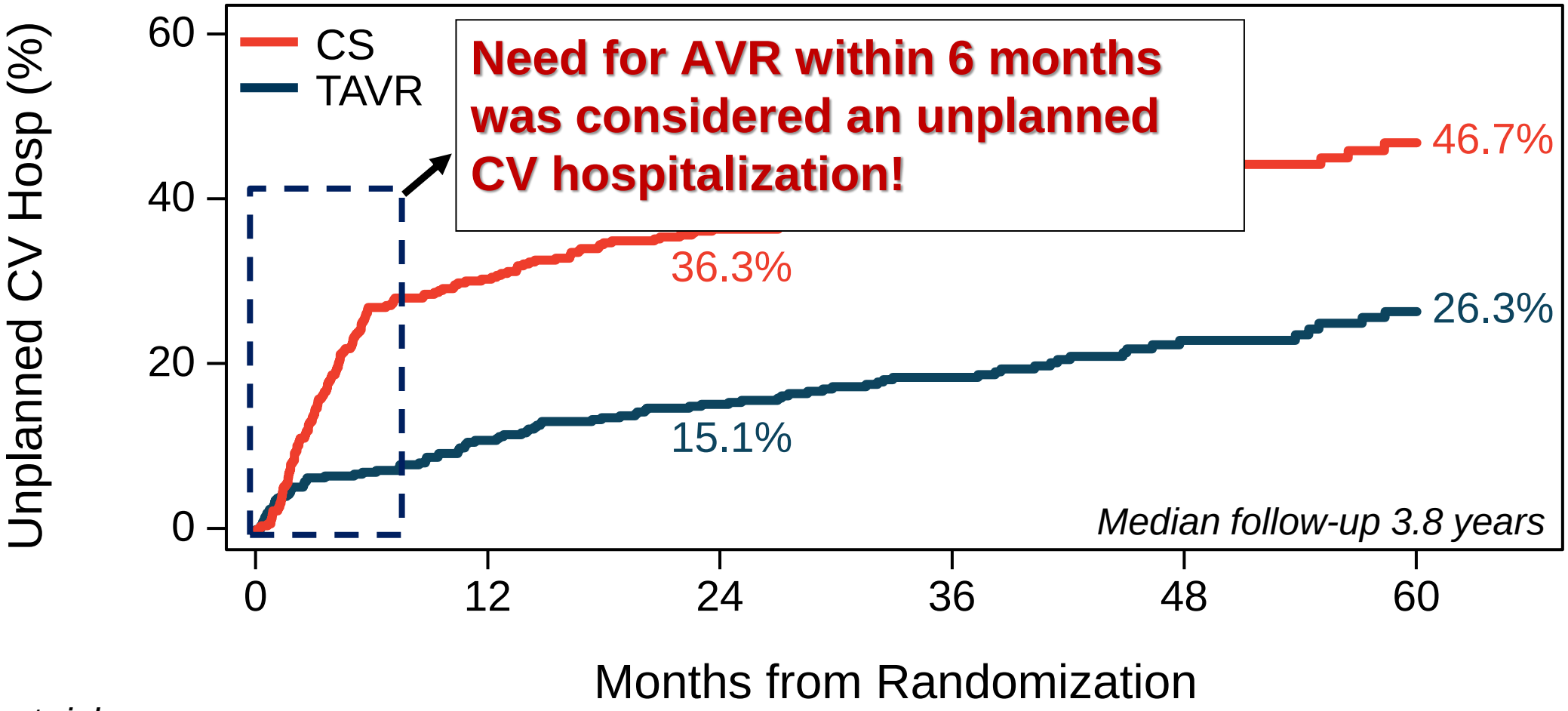
TAVR	455	390	363	285	142	103
CS	446	305	266	187	117	46

Event rates are Kaplan-Meier estimates

Généreux et al. NEJM 2024

Patients had a minimum follow-up of 2 years

Unplanned CV Hospitalization



No. at risk:

TAVR	455	392	365	287	142	103
CS	446	306	267	189	118	46

Event rates are Kaplan-Meier estimates

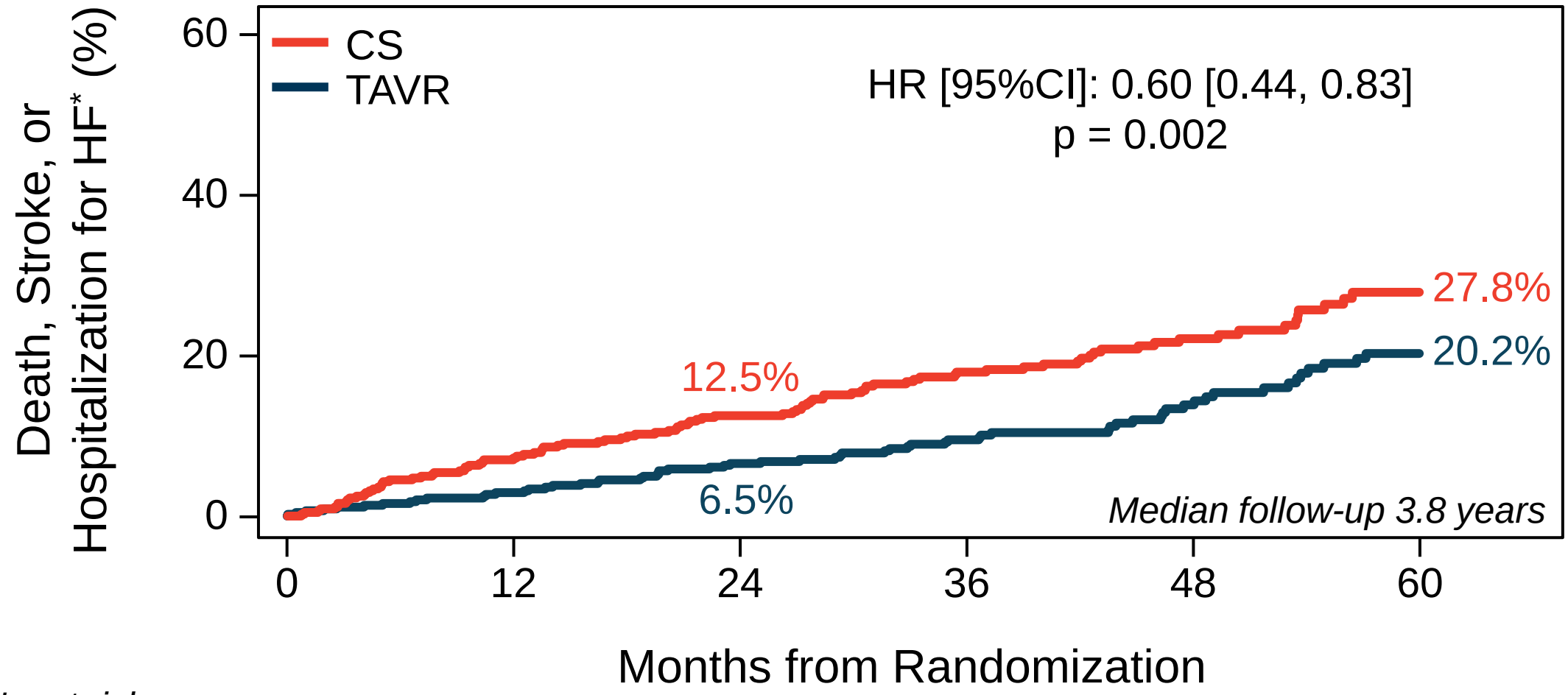
Généreux et al. NEJM 2024

Patients had a minimum follow-up of 2 years

EARLY-TAVR Why did we choose to include the need for AVR within 6 months as an unplanned CV hospitalization?

- Because the ACC/AHA guidelines recommend clinical and echocardiographic follow-up every 6 to 12 months
- The need for AVR before 6 months (the next planned appointment) represents a failure of current guidelines to plan for an uneventful transition to symptoms and AVR.

Death, Stroke, or Hosp. for HF*



No. at risk:

TAVR	455	431	412	331	175	128
CS	446	410	376	268	163	77

Généreux et al. NEJM 2024

*Hosp for symptomatic CHF treated with IV diuresis, inotropic therapy, IABP, ventilation for pulmonary edema, or hemodialysis for vol. overload

- **The frequent, early conversions to AVR in the CS arm of EARLY TAVR (26% at 6 months, 47% at 1 year!) represented more of a Hawthorne effect than real-world clinical experiences**

- **Conversion to AVR was often due to anxiety**

Clinical Presentation at Time of AVR Conversion

Patients classified based on acuity and severity of signs/symptoms

Asymptomatic
Includes pts who may have converted to AVR b/c they required additional medical procedures

Progressive Valve Syndrome
NYHA II
Increase in HF medication from baseline
≥ 1.5- to < 3-fold increase in NT-proBNP from baseline and age-specific threshold*

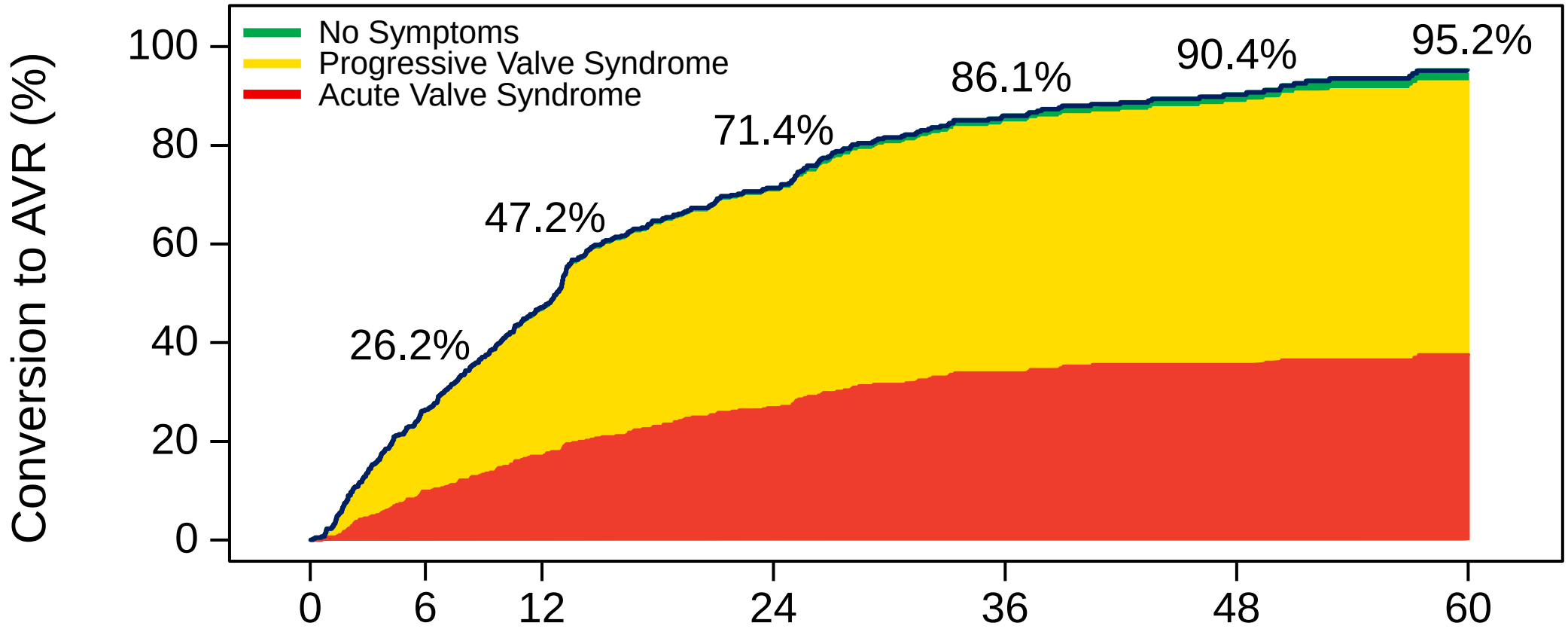
Acute Valve Syndrome
NYHA III/IV
Syncope
Atrial fibrillation
Ventricular arrhythmia
Resuscitated sudden death/cardiac arrest
Hospitalization for HF and/or pulmonary edema
LVEF drops to < 50%
≥ 3-fold increase in NT-proBNP from baseline and age-specific threshold*

*125 pg/mL for patients ≤ 75 years and 450 pg/mL for > 75 years

Adapted from Généreux et al. N Engl J Med 2024;382(2):111-119.

Signs & Symptoms at Time of Conversion to AVR

Median time to delayed AVR: 11.1 months



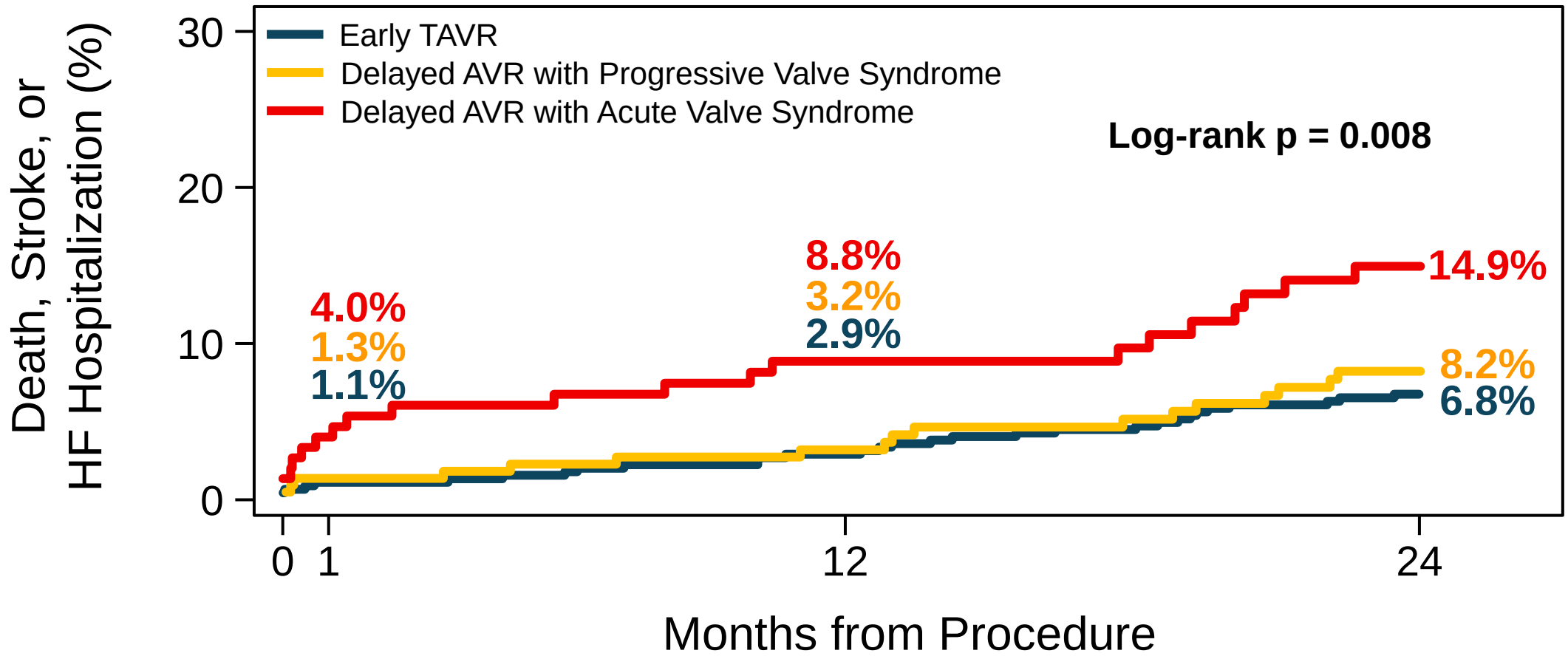
No. at risk:

CS	446	326	231	119	45	22	9

Adapted from Généreux et al. N Engl J Med 2024;382(2):111-119.

Median follow-up 3.8 years.
At the time of analysis, 30 patients were still on study but hadn't converted to AVR

Death, Stroke, or HF Hospitalization*



No. at risk:

Early TAVR	444	439	430	409
Delayed AVR + PVS	227	222	207	175
Delayed AVR + AVS	152	144	125	96

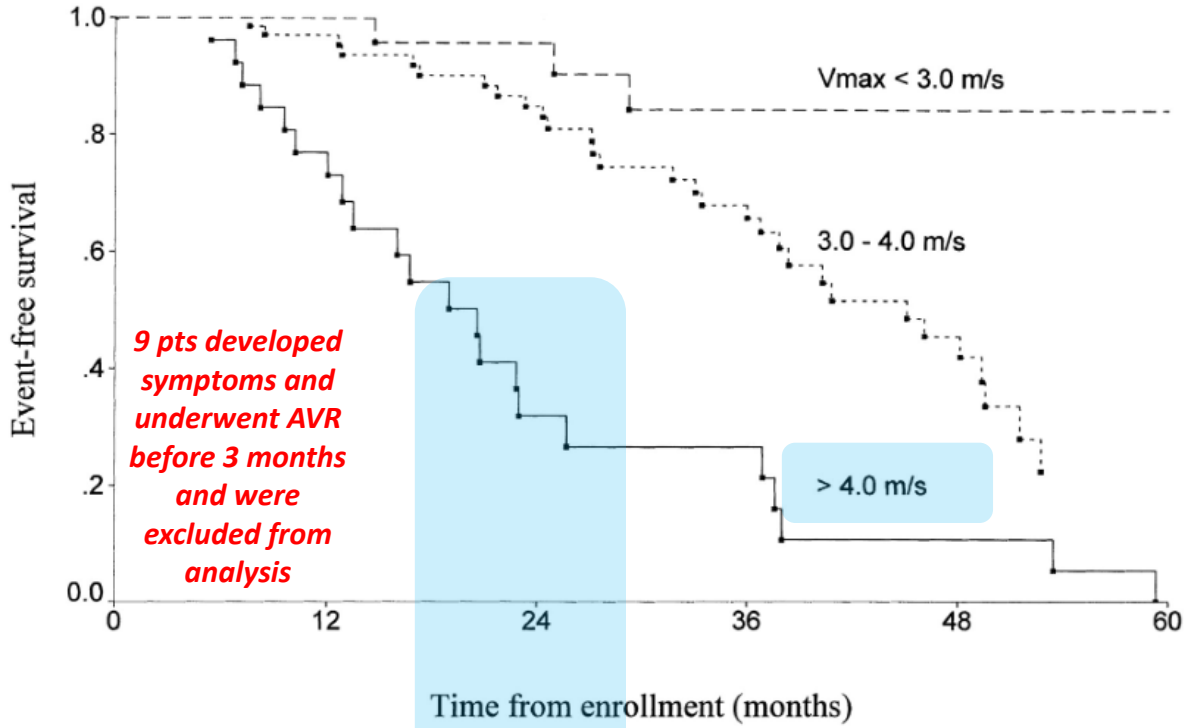
Event rates are Kaplan-Meier estimates

**Hosp for symptomatic CHF treated with IV diuresis, inotropic therapy, IABP, ventilation for pulmonary edema, or hemodialysis for vol. overload*

Circulation

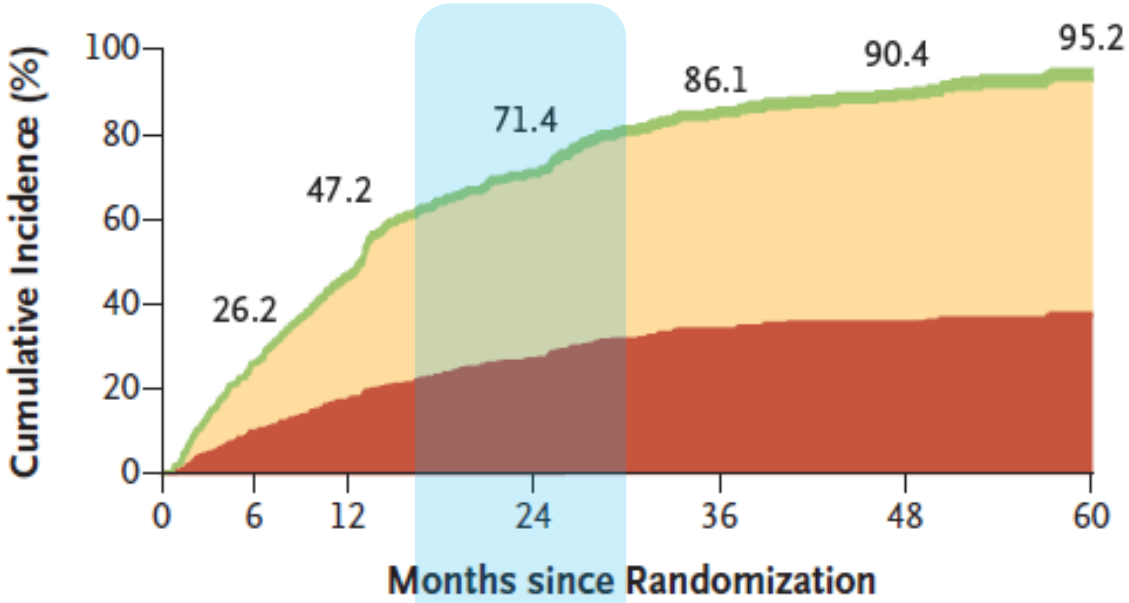
The NEW ENGLAND JOURNAL of MEDICINE

1997; Otto et al.
Prospective Study of Asymptomatic Valvular AS
N=123 pts
AVR or Death



Asymptomatic Severe AS	1 year	2 years	3 years	4 years	5 years
	~30%	~70%	75%	90%	95%

2025; Généreux et al.
TAVR for Asymptomatic Severe AS
N=901 pts
Conversion to AVR



Asymptomatic Severe AS	1 year	2 years	3 years	4 years	5 years
	47.2%	71.4%	86.1%	90.4%	95.2%

Natural History of Asymptomatic Severe AS: Otto et al. 1997 almost identical to Généreux et al. 2025 EARLY TAVR

EARLY AVR vs. Clinical Surveillance: 4 RCTs

Importance of Promptness of Treatment and Quality of Surveillance

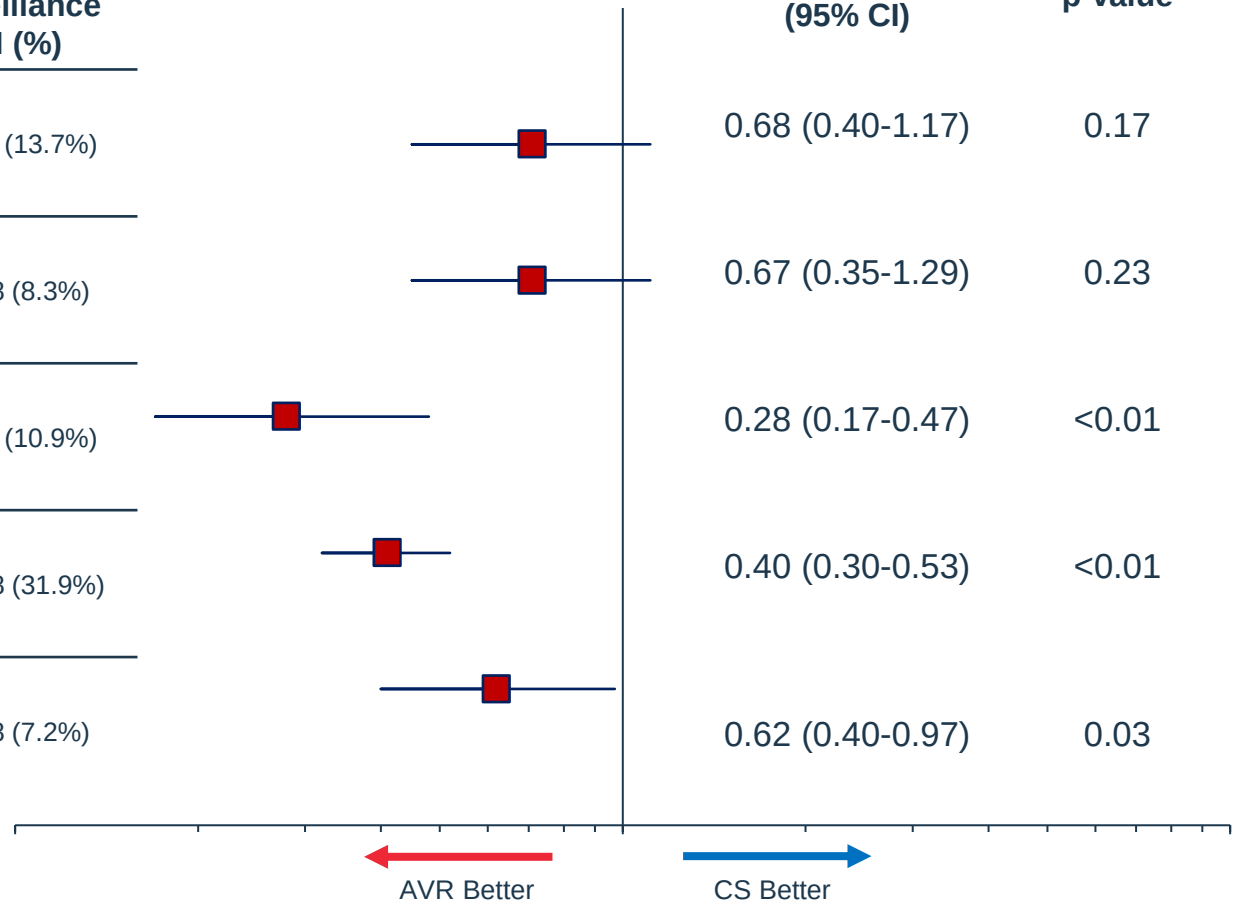
< 3 months for AVR

≥ 3 months for AVR

Study	Time to AVR for pts randomized to early AVR	Time to AVR for pts randomized to clinical surveillance		Mortality
		From randomization	From first symptom/ indication for AVR	
EARLY TAVR *(Genereux 2025)*	**14 days**	332 days	**32 days**	**No difference** (both arms equally good)
AVATAR *(Banovic 2024)*	**55 days**	476 days	**123 days**	**Benefit for early AVR** (delays in treating symptomatic pts)
RECOVERY *(Kang 2020)*	**23 days**	700 days	**Not reported**	**Benefit for early AVR** (~delays in treating symptomatic pts)
EVOLVED-AS *(Loganath 2024)*	**152 days**	614 days	**100 days**	**No difference** (both arms equally bad)

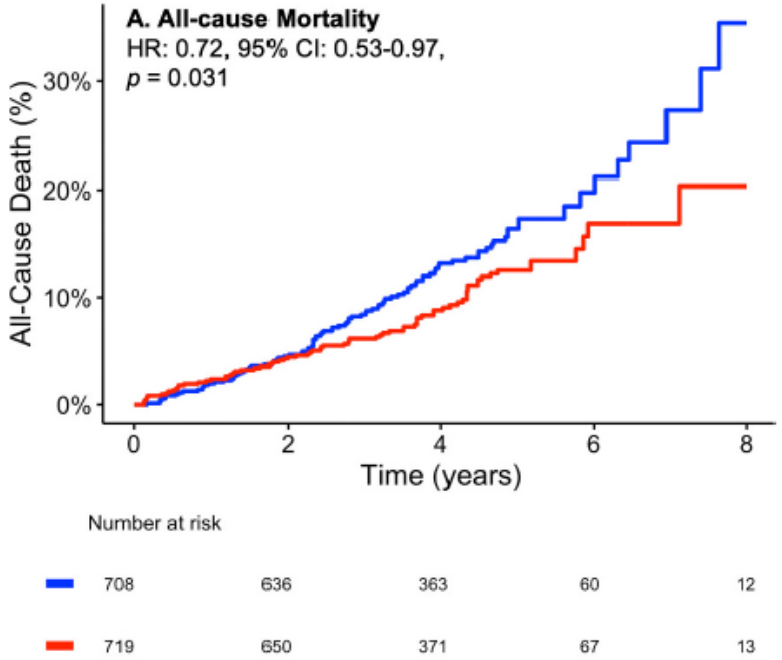
Meta-Analysis 4 RCTs Asymptomatic Severe AS:
EARLY-TAVR, EVOLVED, AVATAR, RECOVERY

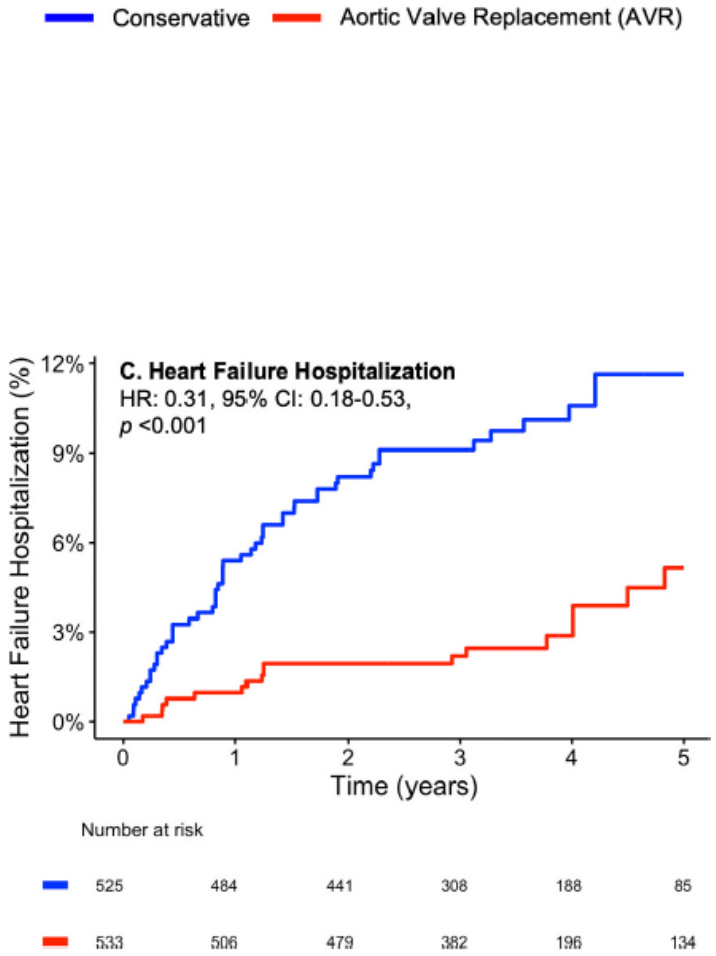
	Early AVR n/N (%)	Clinical Surveillance n/N (%)	Pooled Hazard Ratio* (95% CI)	p-value
All-Cause Mortality	70/719 (9.7%)	97/708 (13.7%)	0.68 (0.40-1.17)	0.17
Cardiovascular Mortality	37/719 (5.1%)	59/708 (8.3%)	0.67 (0.35-1.29)	0.23
Heart Failure Hospitalization	18/606 (3.0%)	65/597 (10.9%)	0.28 (0.17-0.47)	<0.01
Unplanned CV or HF Hospitalization	105/719 (14.6%)	226/708 (31.9%)	0.40 (0.30-0.53)	<0.01
Stroke	32/719 (4.5%)	51/708 (7.2%)	0.62 (0.40-0.97)	0.03

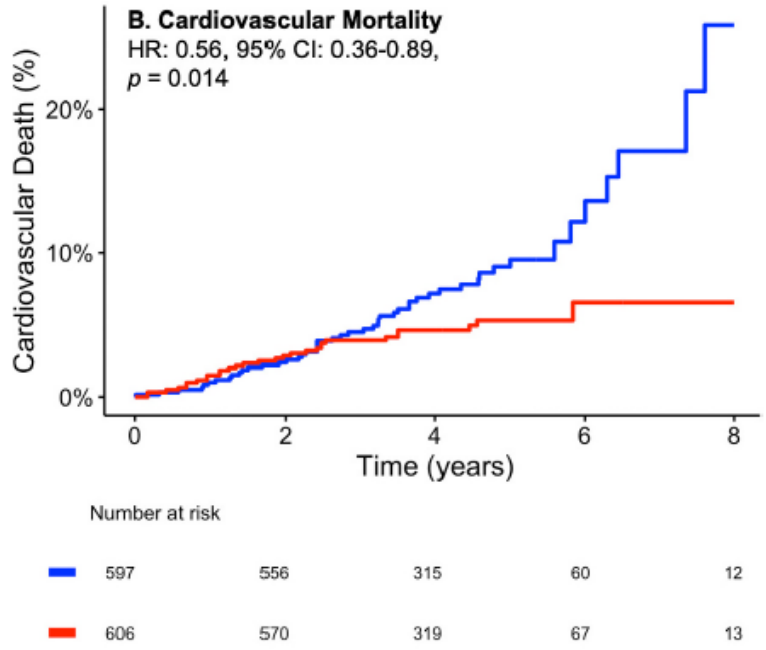


Généreux et al. JACC 2025

Early AVR versus conservative management in asymptomatic severe AS: Meta-analysis of time-to-event data of RCTs







Jacquemyn et al. Int J Cardiol 2025

THE EARLY TAVR TRIAL

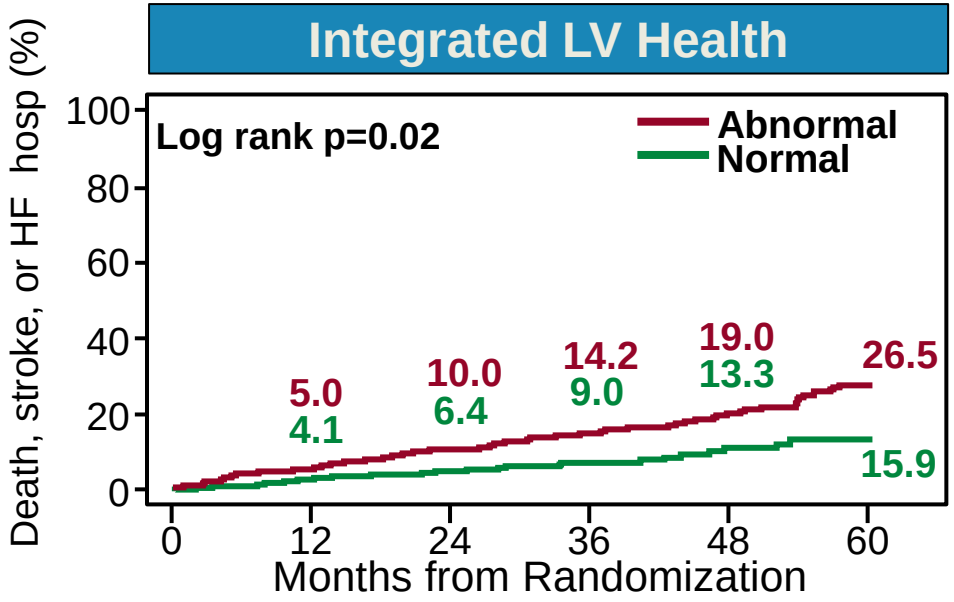
Pre-specified Secondary Endpoints

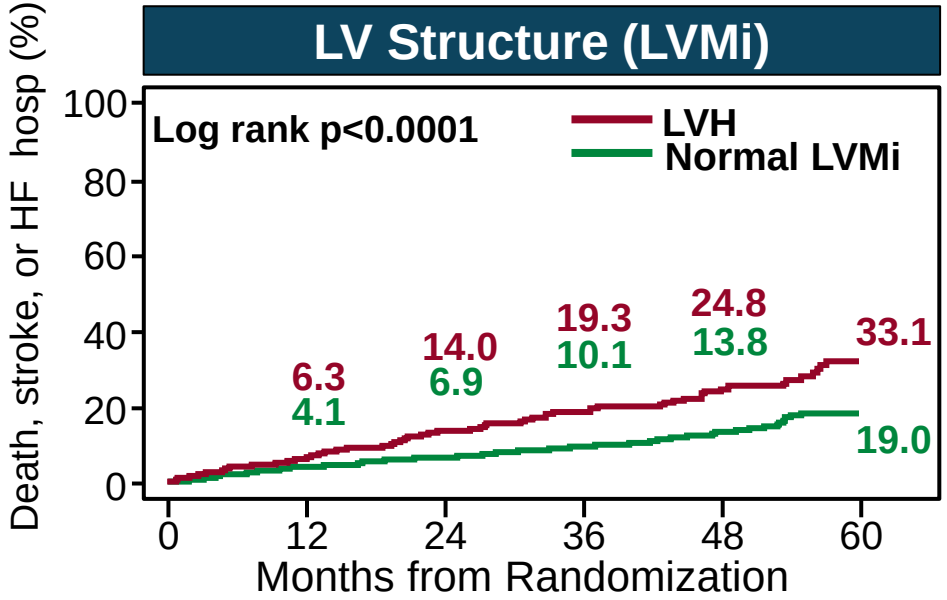
Endpoint — % or mean ± SE	TAVR (N=455)	CS (N=446)	Treatment Effect [95% CI]	P-value
1. Favorable Health Status Outcome*	86.6%	68.0%	Abs Δ: 18.5% [12.6%, 24.3%]	**<0.001**
2. Integrated LV/LA health at 2Y†	48.1%	35.9%	Abs Δ: 12.2% [4.4%, 19.4%]	**0.001**
3. Δ LVEF (%) from baseline to 2Y	-1.2 ± 0.4	-1.3 ± 0.4	Abs Δ: 0.1 [-0.8, 1.3]	0.66
4. New onset atrial fibrillation	13.0%	12.4%	HR: 1.08 [0.73, 1.60]	---
5. Death or disabling stroke	9.7%	11.2%	HR: 0.87 [0.58, 1.31]	---

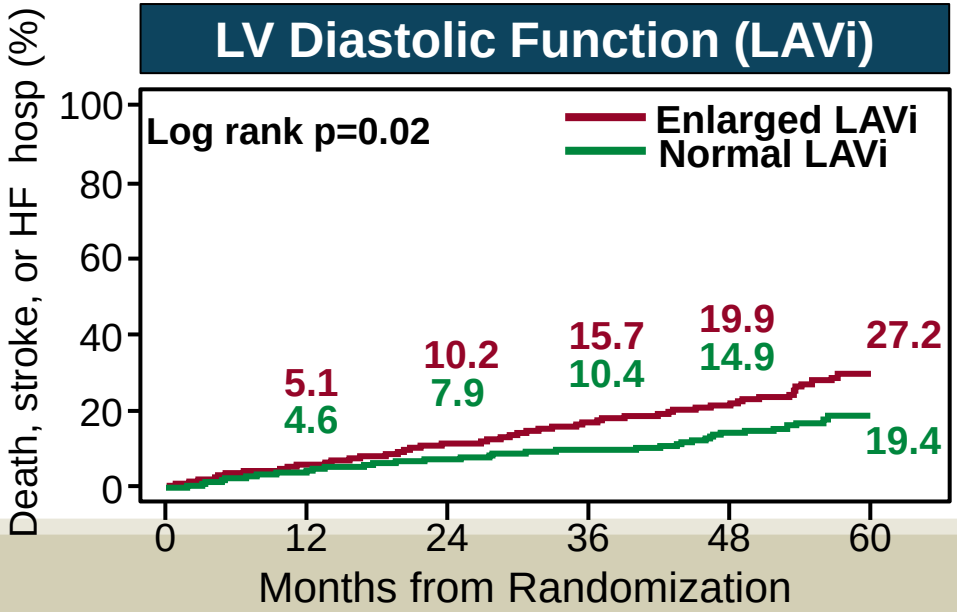
*Evaluated at 2Y and defined as alive w/ a KCCQ score ≥ 75 that did not decrease > 10 points from baseline; if AV intervention/reintervention occurred w/in 6 mos, pre-procedure (CS) or 30-day (TAVR) KCCQ score was used

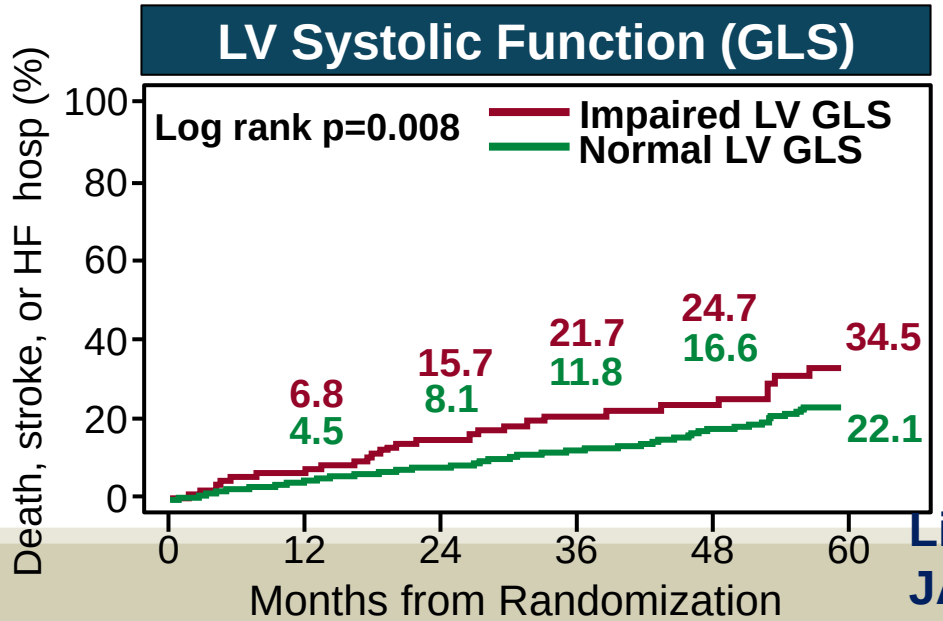
†Defined as meeting all of the following criteria: LV GLS ≥ 15%, LVMi < 115 g/m² for men or <95 g/m² for women, and LAVi ≤ 34 mL/m²

Death, Stroke, or HF Hospitalization





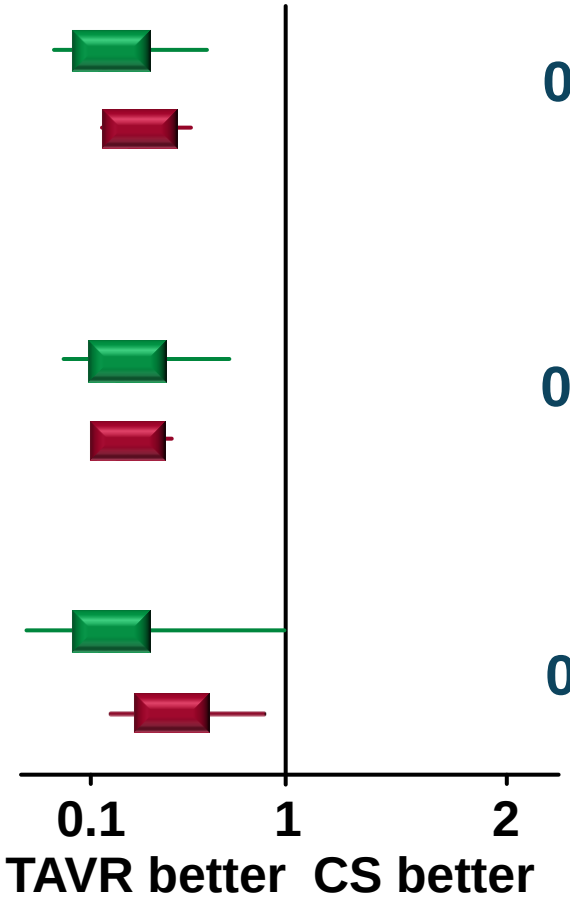




Lindman et al.
JACC 2025

Treatment Effect by Integrated LV Health

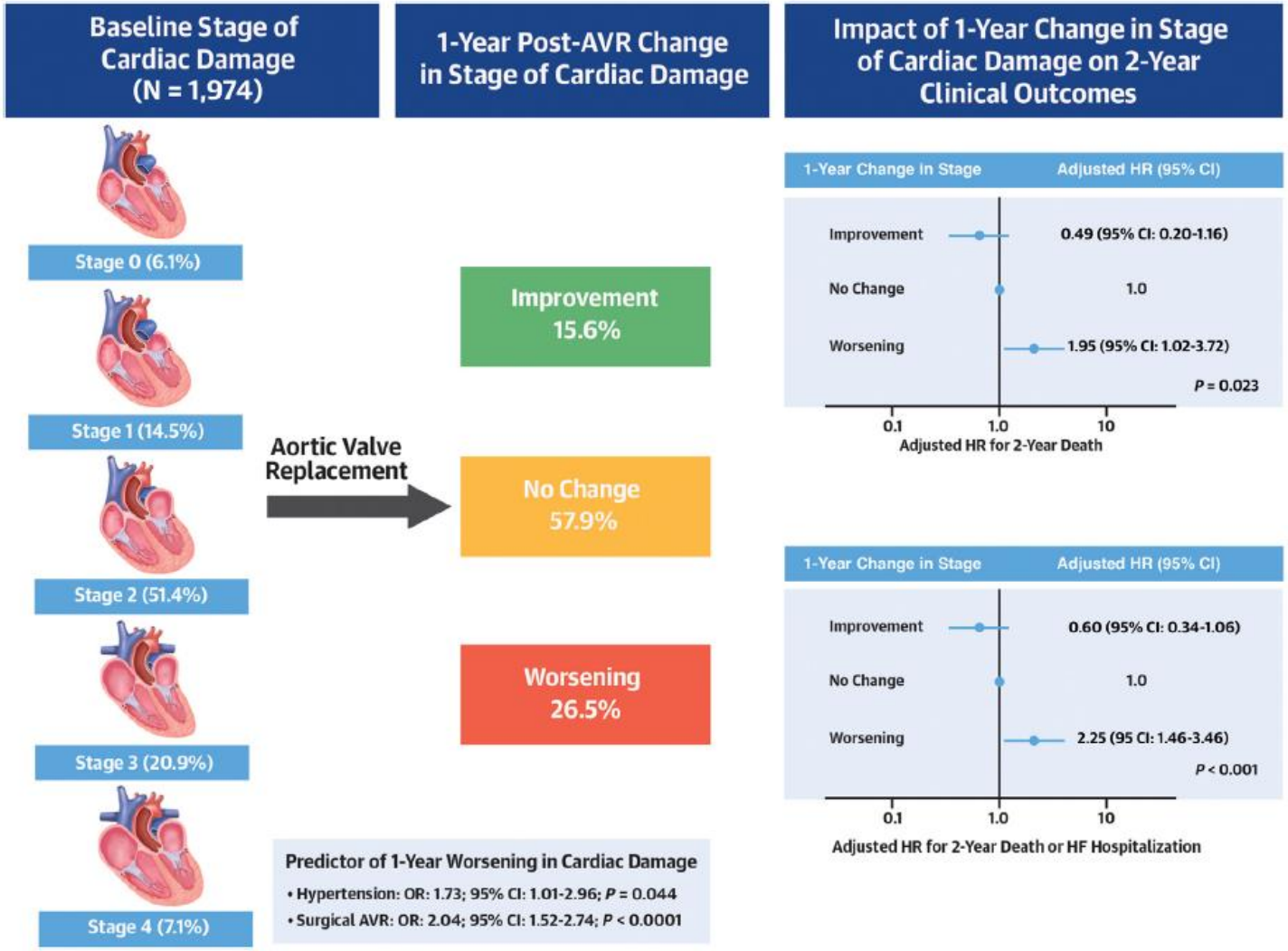
	NNT	HR [95% CI]	Interaction *p*-value
Death, stroke, or unplanned CV hosp			
Integrated LV Health – Normal (N=223)	5	0.44 [0.26,0.74]	**0.48**
Integrated LV Health – Abnormal (N=610)	6	0.53 [0.41,0.69]	
Death, stroke, unplanned CV hosp, or intervention with advanced signs or symptoms			
Integrated LV Health – Normal (N=223)	7	0.49 [0.29,0.81]	**0.96**
Integrated LV Health – Abnormal (N=610)	7	0.49 [0.38,0.63]	
Death, stroke, or HF hospitalization			
Integrated LV Health – Normal (N=223)	19	0.44 [0.19,1.00]	**0.40**
Integrated LV Health – Abnormal (N=610)	19	0.63 [0.44,0.92]	



The benefit of early TAVR is consistent regardless of baseline LV health status

Evolution and Prognostic Impact of Cardiac Damage Stage from Baseline to 1 year:

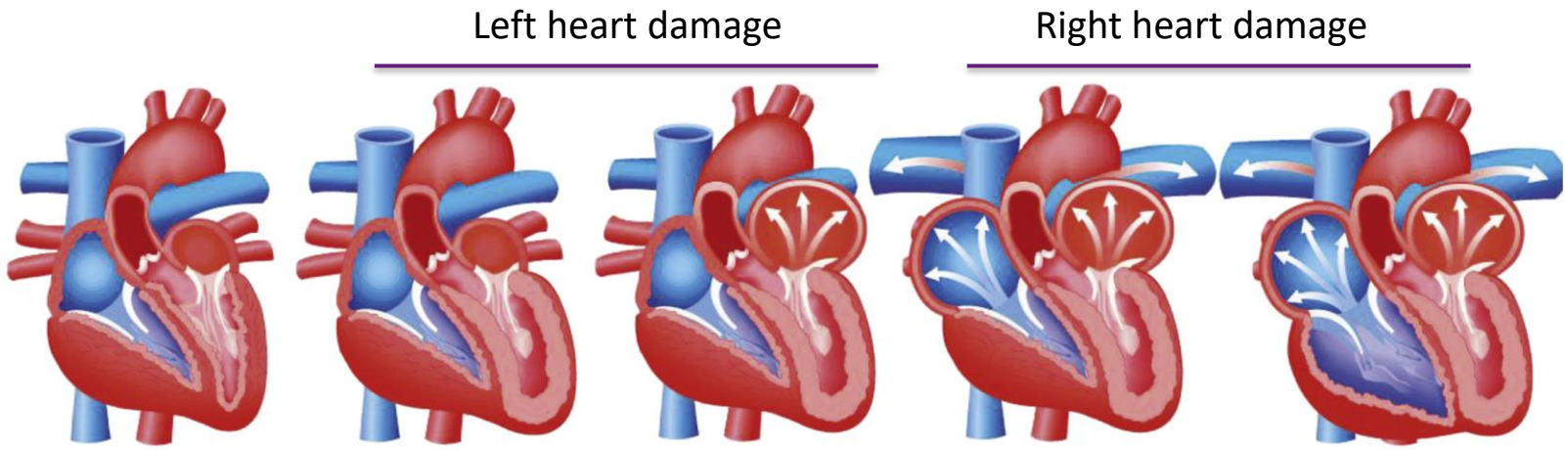
PARTNER 2 and 3 (n=1974)



Généreux P, et al. J Am Coll Cardiol. 2022;80(8):783-800.

Généreux et al.
JACC 2022

EARLY TAVR: Stage of Cardiac Damage at Baseline

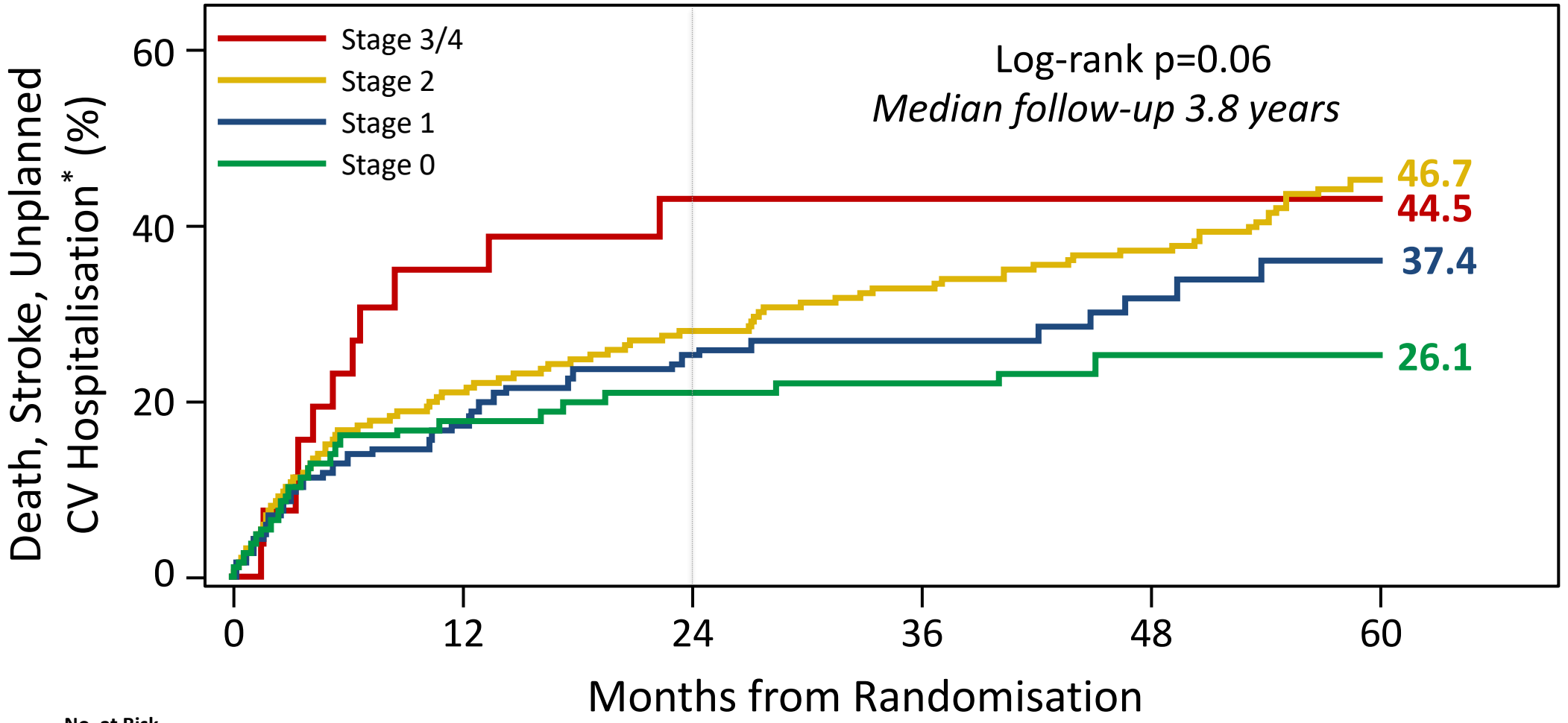


Stage	Stage 0	Stage 1	Stage 2	Stage 3/4	P-value
Total	14.4%	19.6%	62.2%	3.8%	
TAVR	10.9%	22.3%	62.7%	4.1%	0.39
CS	18.2%	16.7%	61.6%	3.5%	

>85% of patients with asymptomatic, severe AS enrolled in the EARLY TAVR trial had existing cardiac damage at baseline

P value is for difference in cardiac damage between Early TAVR and CS, using a Wilcoxon Rank Sum test in a paired analysis.

Death, Stroke, or Unplanned CV Hospitalisation (ITT)



No. at Risk						
Stage 3/4	25	16	13	10	6	5
Stage 2	390	301	271	199	101	54
Stage 1	112	91	81	62	36	24
Stage 0	104	82	79	60	32	19

Evolution of Damage: Early TAVR vs Clinical Surveillance

At 2-year follow-up

Early TAVR (N=220)

Improved*	Stayed the same	Worsened*
24.1%	61.8%	14.1%

p=0.01

Clinical Surveillance (N=198)

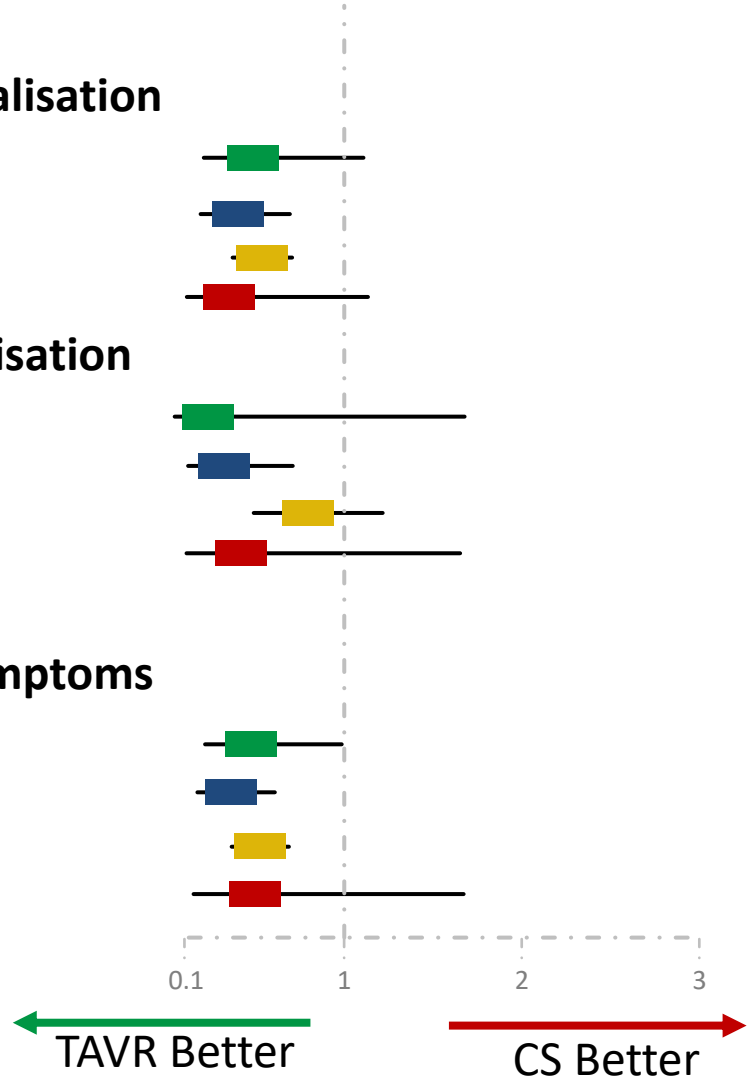
Improved*	Stayed the same	Worsened*
17.7%	58.6%	**23.7%**

The Early TAVR patients were more likely to improve their stage of cardiac damage compared to the CS patients who were more likely to worsen their stage of cardiac damage

*P value is for difference in cardiac damage between Early TAVR and CS, using a Wilcoxon Rank Sum test in a paired analysis. *Improved or Worsened >= 1 stage of cardiac damage from baseline.*

Treatment Effect by Baseline Cardiac Damage

Consistent benefits of the early TAVR strategy across all stages of cardiac damage



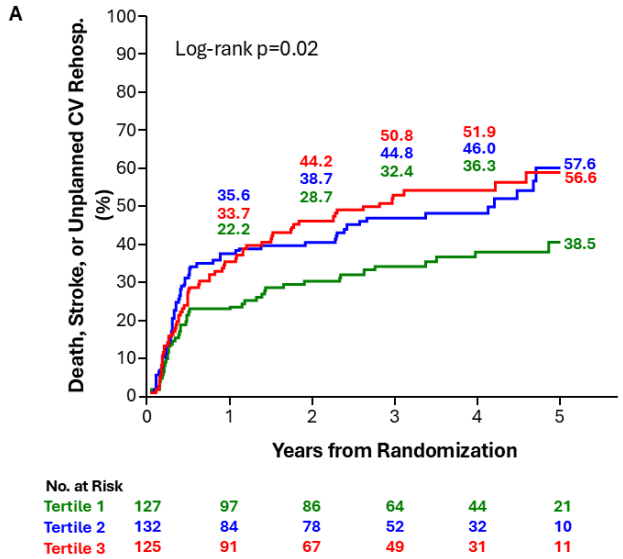
Endpoint	Hazard Ratio [95% CI]	P-value
Death, Stroke or Unplanned CV Hospitalisation		0.68
Stage 0	**0.46** [0.19, 1.09]	
Stage 1	**0.34** [0.17, 0.68]	
Stage 2	**0.49** [0.35, 0.69]	
Stage 3/4	**0.32** [0.09, 1.11]	
Death, Stroke or Heart Failure Hospitalisation		0.13
Stage 0	**0.20** [0.03, 1.66]	
Stage 1	**0.26** [0.10, 0.69]	
Stage 2	**0.75** [0.47, 1.20]	
Stage 3/4	**0.39** [0.09, 1.63]	
Death, Stroke, Unplanned CV Hosp. or Intervention with Advanced Signs/Symptoms		0.63
Stage 0	**0.44** [0.20, 1.00]	
Stage 1	**0.30** [0.15, 0.59]	
Stage 2	**0.48** [0.35, 0.67]	
Stage 3/4	**0.47** [0.13, 1.65]	

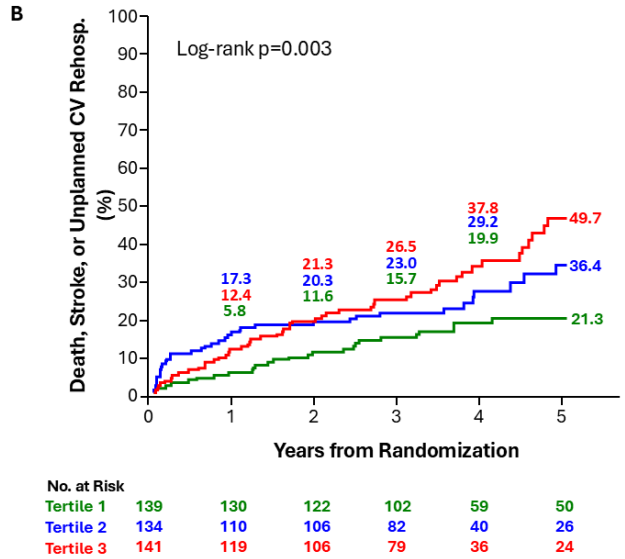
EARLY TAVR: Blood Biomarkers at Baseline

Clinical Surveillance

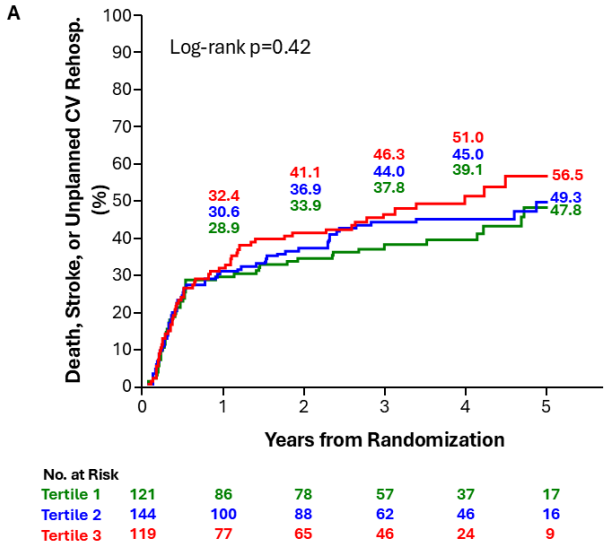
TAVR

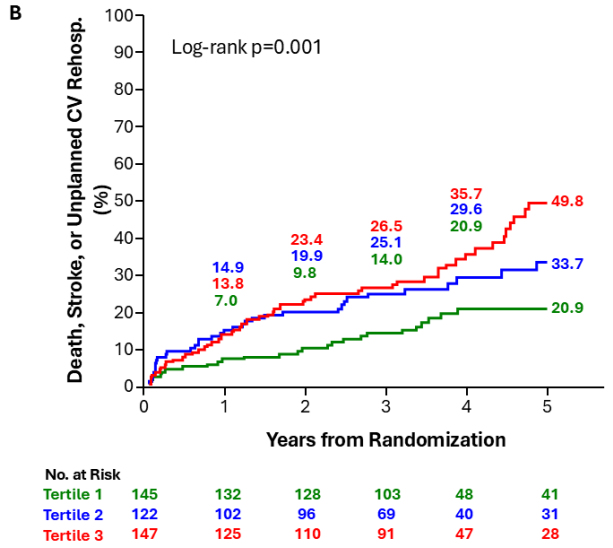
NtProBNP





hs-cTnT





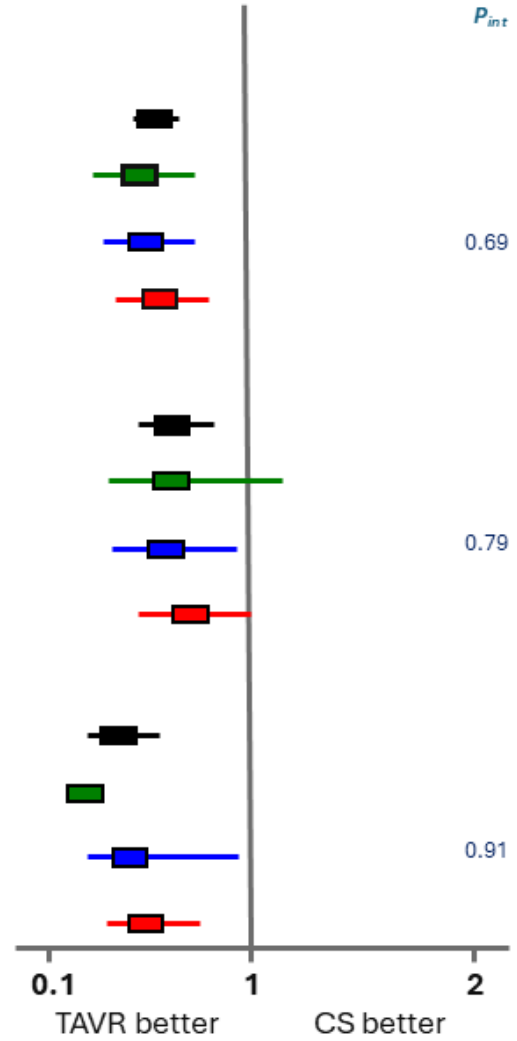
Lindman et al.
Circulation 2025

EARLY TAVR: Blood Biomarkers at Baseline

NtProBNP

A

NT-proBNP	TAVR n events/N analyzed (%)	TAVR Rate per 100 patient years	CS n events/N analyzed (%)	CS Rate per 100 patient years	HR [95% CI]	P_{int}
All-cause death, all stroke, and unplanned CV hospitalization						
All patients (N=798)	113/414 (27.3%)	8.7	173/384 (45.1%)	18.2	0.51 [0.40, 0.65]	
1st Tertile	26/139 (18.7%)	5.3	44/127 (34.6%)	12.3	0.46 [0.28, 0.74]	
2nd Tertile	37/134 (27.6%)	9.3	64/132 (48.5%)	20.9	0.49 [0.33, 0.74]	0.69
3rd Tertile	50/141 (35.5%)	12.2	65/125 (52.0%)	22.6	0.56 [0.39, 0.81]	
All-cause death, all stroke and heart failure hospitalization						
All patients (N=798)	58/414 (14.0%)	3.9	85/384 (22.1%)	6.7	0.59 [0.42, 0.83]	
1st Tertile	10/139 (7.2%)	1.9	16/127 (12.6%)	3.5	0.54 [0.25, 1.19]	
2nd Tertile	15/134 (11.2%)	3.2	28/132 (21.2%)	6.4	0.51 [0.27, 0.95]	0.79
3rd Tertile	33/141 (23.4%)	7.1	41/125 (32.8%)	10.8	0.64 [0.41, 1.02]	
Heart failure hospitalization						
All patients (N=798)	14/414 (3.4%)	0.9	41/384 (10.7%)	3.1	0.30 [0.17, 0.56]	
1st Tertile	0/139 (0.0%)	0	5/127 (3.9%)	1.1	0.00 [0.00, NA]	
2nd Tertile	3/134 (2.2%)	0.6	11/132 (8.3%)	2.4	0.27 [0.07, 0.96]	0.91
3rd Tertile	11/141 (7.8%)	2.3	25/125 (20.0%)	6.4	0.36 [0.18, 0.74]	



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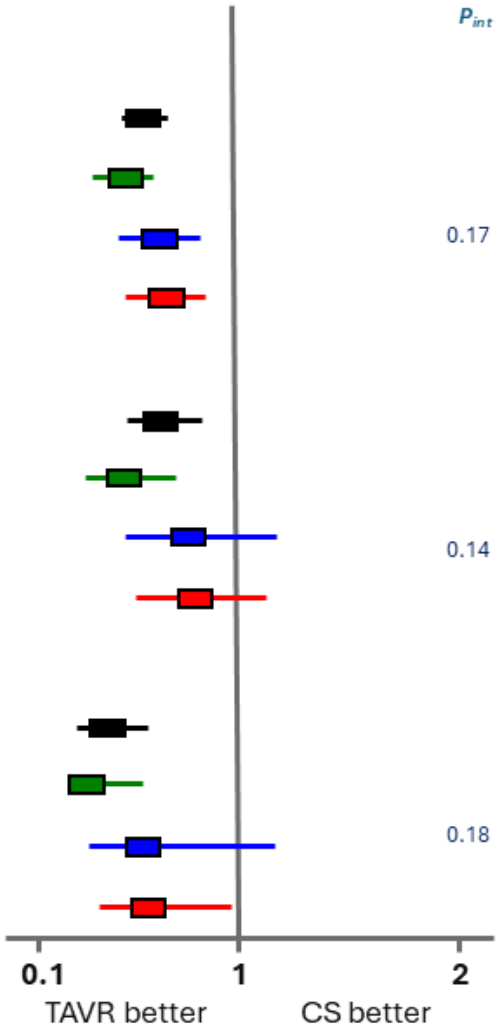
EARLY TAVR: Blood Biomarkers at Baseline

hs-cTnT

B

Hs-cTnT	TAVR n events/N analyzed (%)	TAVR Rate per 100 patient years	CS n events/N analyzed (%)	CS Rate per 100 patient years	HR [95% CI]	P_{int}
All-cause death, all stroke, and unplanned CV hospitalization						
All patients (N=798)	113/414 (27.3%)	8.7	173/384 (45.1%)	18.2	0.51 [0.40, 0.65]	
1st Tertile	25/145 (17.2%)	5.1	50/121 (41.3%)	15.7	0.35 [0.22, 0.57]	
2nd Tertile	34/122 (27.9%)	9.2	65/144 (45.1%)	17.8	0.55 [0.36, 0.83]	0.17
3rd Tertile	54/147 (36.7%)	12.3	58/119 (48.7%)	21.7	0.59 [0.41, 0.86]	
All-cause death, all stroke and heart failure hospitalization						
All patients (N=798)	58/414 (14.0%)	3.9	85/384 (22.1%)	6.7	0.59 [0.42, 0.83]	
1st Tertile	10/145 (6.9%)	1.9	25/121 (20.7%)	6.1	0.31 [0.15, 0.65]	
2nd Tertile	17/122 (13.9%)	4.1	30/144 (20.8%)	6.1	0.67 [0.37, 1.22]	0.14
3rd Tertile	31/147 (21.1%)	6	30/119 (25.2%)	8.1	0.71 [0.43, 1.17]	
Heart failure hospitalization						
All patients (N=798)	14/414 (3.4%)	0.9	41/384 (10.7%)	3.1	0.30 [0.17, 0.56]	
1st Tertile	1/145 (0.7%)	0.2	14/121 (11.6%)	3.4	0.06 [0.01, 0.45]	
2nd Tertile	4/122 (3.3%)	0.9	12/144 (8.3%)	2.3	0.40 [0.13, 1.23]	0.18
3rd Tertile	9/147 (6.1%)	1.7	15/119 (12.6%)	3.9	0.42 [0.19, 0.97]	



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2025 ESC/EACTS Guidelines

Recommendations	Class	Level
Asymptomatic patients with severe aortic stenosis		
Intervention is recommended in asymptomatic patients with severe AS and LVEF <50% without another cause.	I	B
Intervention should be considered in asymptomatic patients (confirmed by a normal exercise test, if feasible) with severe, high-gradient AS and LVEF ≥50% as an alternative to close active surveillance, if the procedural risk is low.	IIa	A
Intervention should be considered in asymptomatic patients with severe AS and LVEF ≥50% if the procedural risk is low and one of the following parameters is present: •Very severe AS (mean gradient ≥60 mmHg or V_{max} >5.0 m/s) •Severe valve calcification (ideally assessed by CCT) and V_{max} progression ≥0.3 m/s/year. •Markedly elevated BNP/NT-proBNP levels (more than three times age- and sex-corrected normal range, confirmed on repeated measurement without other explanation). •LVEF <55% without another cause.	IIa	B
Intervention should be considered in asymptomatic patients with severe AS and a sustained fall in BP (>20 mmHg) during exercise testing.	IIa	C

ESC Guidelines for the management of valvular heart disease
(European Heart Journal; 2025 – doi: 10.1093/eurheartj/ehaf194)

Dr. Jekyll concludes:
Paradigm Shift in Asymptomatic Severe AS

FROM Mr. Hyde:

Clinical surveillance in asymptomatic severe AS and early AVR in selected patients with risk markers*

***Strategy recommended by the 2020 ACC-AHA and ESC-EACTS guidelines**

TO Dr. Jekyll:

Early AVR in asymptomatic severe AS and defer AVR in selected patients with specific criteria*

***Strategy recommended (IIa-A) by the 2025 ESC-EACTS guidelines**

Philippe Pibarot / Mr. Hyde

ESC European Society of Cardiology
European Heart Journal Open (2025) **00**, oeaf114
https://doi.org/10.1093/ehjopen/oeaf114

VIEWPOINT
Valvular heart disease

Early aortic valve intervention in asymptomatic severe aortic stenosis: a clinical dilemma in evolution

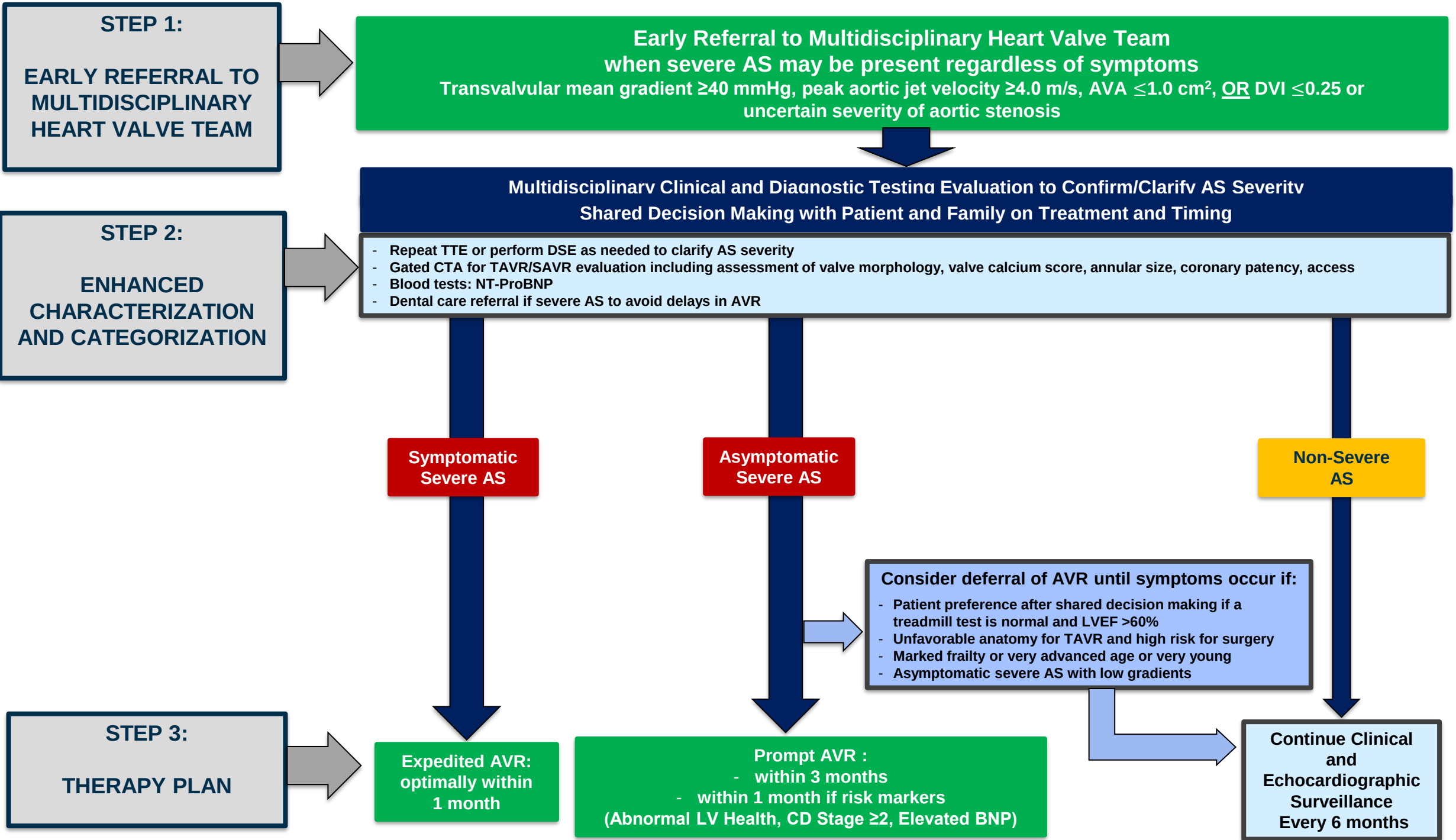
Patrizio Lancellotti [1,2,*], Augustin Coisne [3,4], Bernard Cosyns[5,6], Raluca Dulgheru[1,2], Madalina Garbi[7], Geu-Ru Hong [8], Jadranka Separovic Hanzevacki[9], Marco Moscarelli [10,11], Tadafumi Sugimoto[12], Erwan Donal [13], Khalil Fattouch [11], Gilbert Habib[14,15], Mani Vannan[16], and Philippe Pibarot [17], on behalf of the EuroValve Consortium

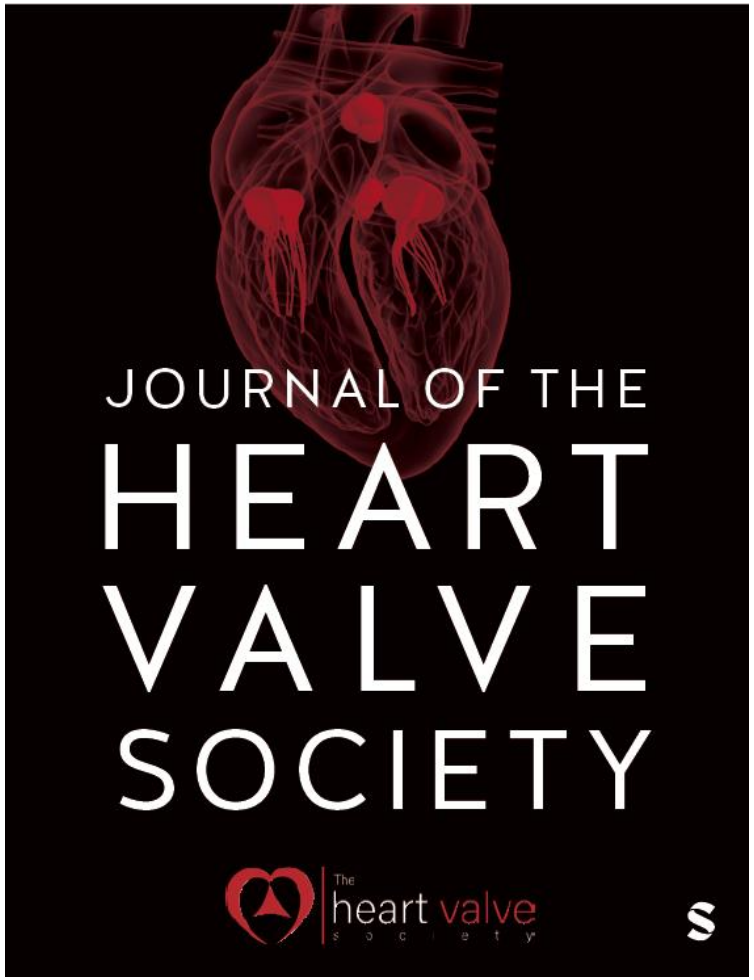
Philippe Pibarot / Dr. Jekyll

International Expert Perspective on Early Referral, Streamlined Evaluation, and Prompt Treatment of Patients with Aortic Stenosis

Running title: *Expert Perspective on Proactive Management of AS*

Christopher M. Cook, MBBS, PhD, Philippe Pibarot, PhD, DVM, Philippe Généreux, MD, Giuseppe Tarantini, MD, Victoria Delgado, MD, Kentaro Hayashida, MD, Radoslaw Parma, MD, Tsuyoshi Kaneko, MD, Tanja Rudolph, MD, João L. Cavalcante, MD, David A. Wood, MD, Jeroen J. Bax, MD, PhD, Thomas Pilgrim, MD, Francesco Saia, MD, Sreek Vemulapalli, MD, Patricia Pellikka, MD, Bernard Iung, MD, Kim Guibone, DNP, APRN, Marc R Dweck, MD, Sammy Elmariah, MD, Hélène Eltchaninoff, MD, Gorav Ailawadi, MD, Simon Cheung-Chi Lam, MD, Karl Poon, MD, Axel Unbehaun, MD, Allan Schwartz, MD, Vinod Thourani, MD, Michael Joner, MD, Bernard Prendergast, MD, Michael Mack, MD, Rebecca T. Hahn, MD, Stephan Windecker, MD, Martin B. Leon, MD, Brian R. Lindman, MD, MSc


STEP 1:
EARLY REFERRAL TO MULTIDISCIPLINARY HEART VALVE TEAM
Early Referral to Multidisciplinary Heart Valve Team
when severe AS may be present regardless of symptoms
Transvalvular mean gradient ≥40 mmHg, peak aortic jet velocity ≥4.0 m/s, AVA ≤1.0 cm², OR DVI ≤0.25 or uncertain severity of aortic stenosis
STEP 2:
ENHANCED CHARACTERIZATION AND CATEGORIZATION
Multidisciplinary Clinical and Diagnostic Testing Evaluation to Confirm/Clarify AS Severity
Shared Decision Making with Patient and Family on Treatment and Timing
- Repeat TTE or perform DSE as needed to clarify AS severity
- Gated CTA for TAVR/SAVR evaluation including assessment of valve morphology, valve calcium score, annular size, coronary patency, access
- Blood tests: NT-ProBNP
- Dental care referral if severe AS to avoid delays in AVR
Symptomatic Severe AS
Asymptomatic Severe AS
Non-Severe AS
Consider deferral of AVR until symptoms occur if:
- Patient preference after shared decision making if a treadmill test is normal and LVEF >60%
- Unfavorable anatomy for TAVR and high risk for surgery
- Marked frailty or very advanced age or very young
- Asymptomatic severe AS with low gradients
STEP 3:
THERAPY PLAN
Expedited AVR: optimally within 1 month
Prompt AVR :
- within 3 months
- within 1 month if risk markers
(Abnormal LV Health, CD Stage ≥2, Elevated BNP)
Continue Clinical and Echocardiographic Surveillance Every 6 months



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