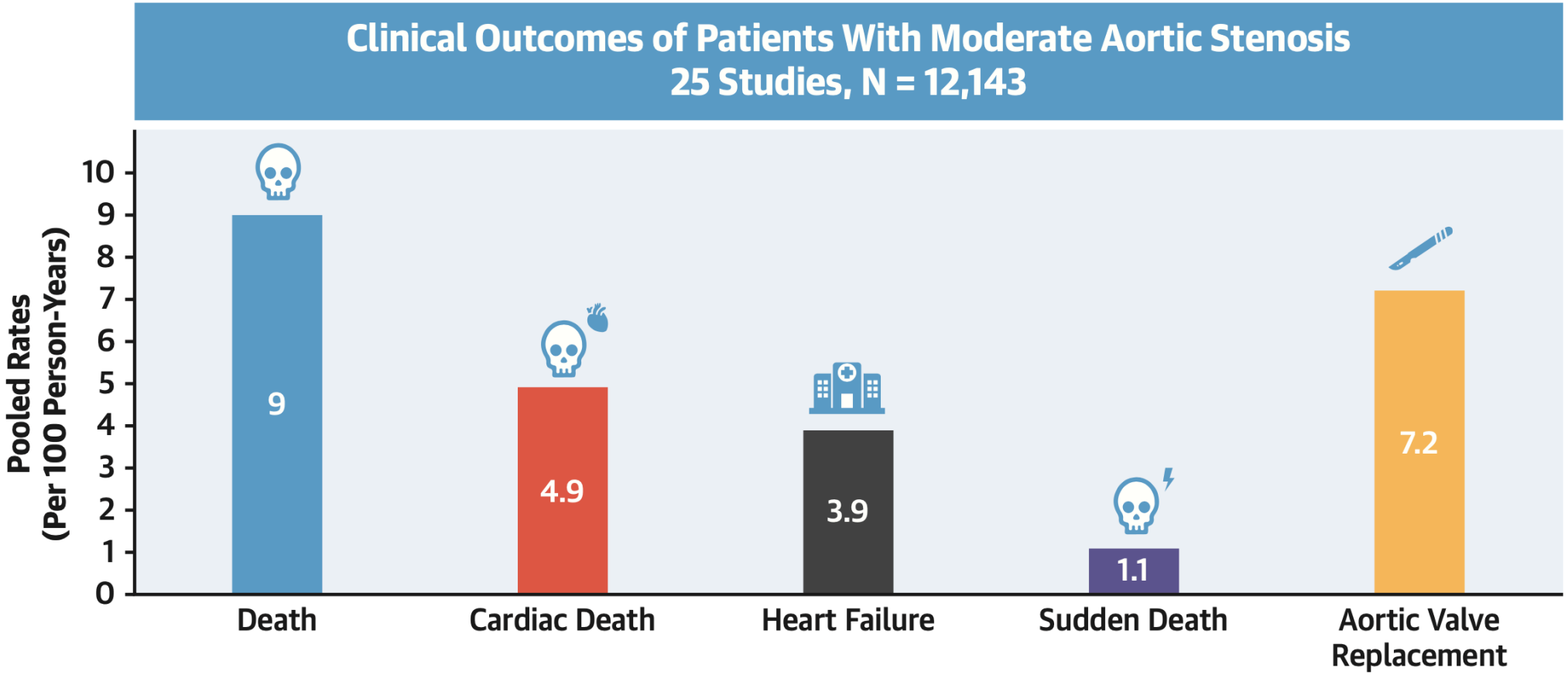
TAVR Role in Moderate AS: Current State and Future Perspectives

Juan F. Granada, MD
President and CEO
Cardiovascular Research Foundation
New York

Moderate AS – No Innocent Bystander

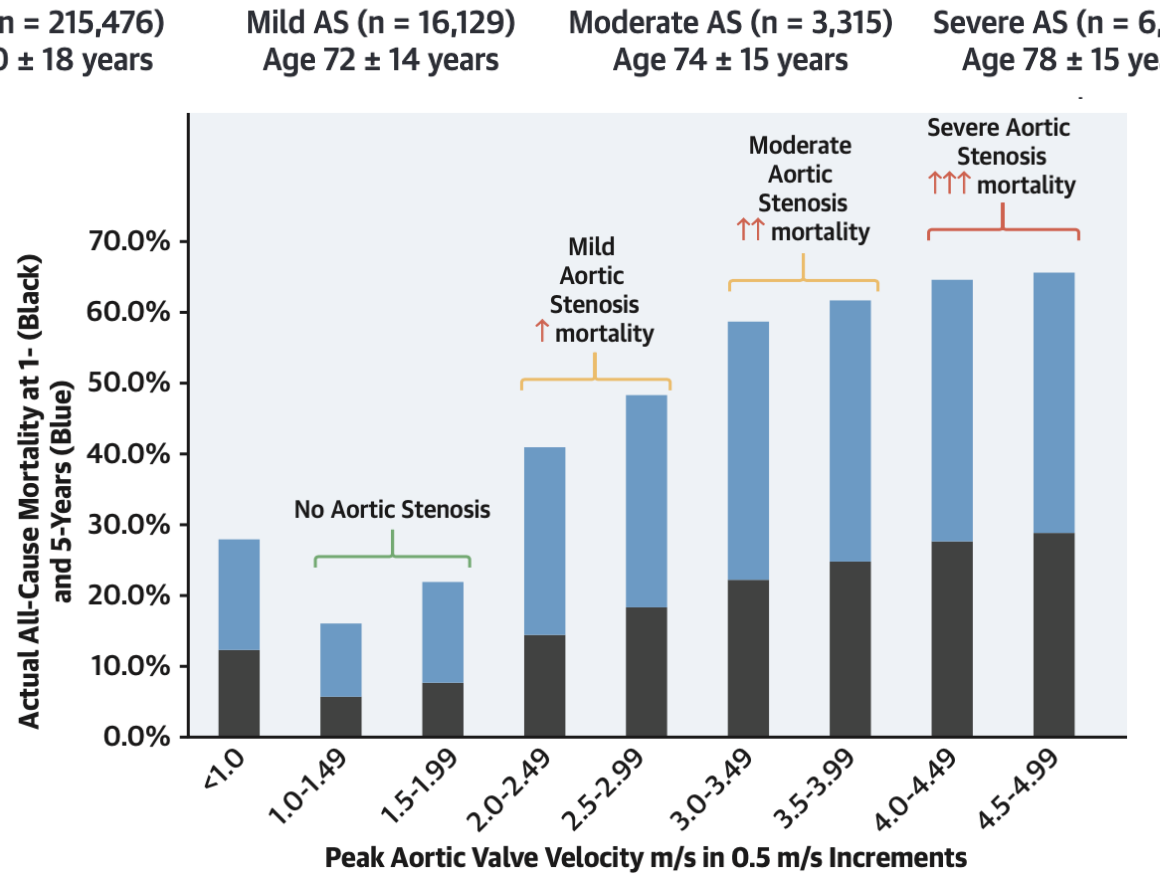
Meta-analysis of 25 studies (n= 12,143). Mean follow up 3.8 ± 1.7 years
Mean age 74 years (40% women)



Coisne, Granada et al. JACC CVI 2022;15:1664-74

Outcome After Diagnosis of Aortic Stenosis

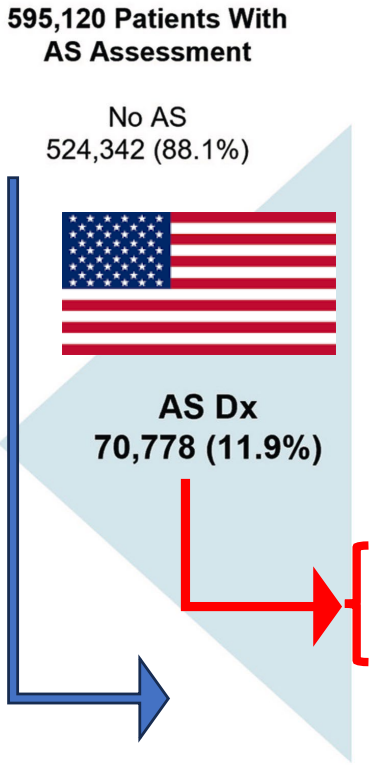
National Echocardiography Database of Australia
N = 241,303, Median 1,208 days of FU

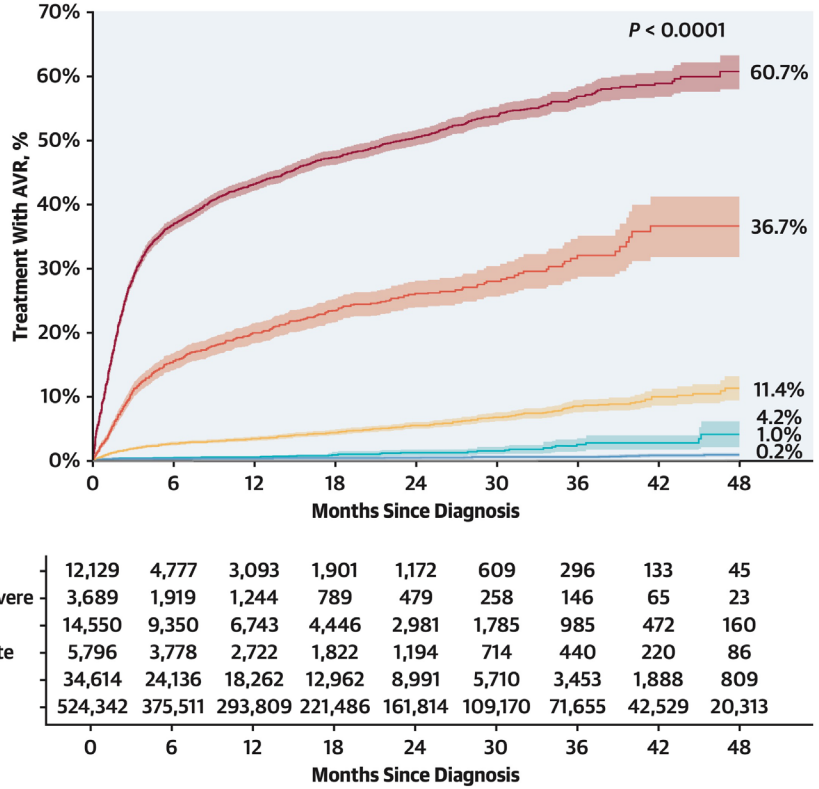


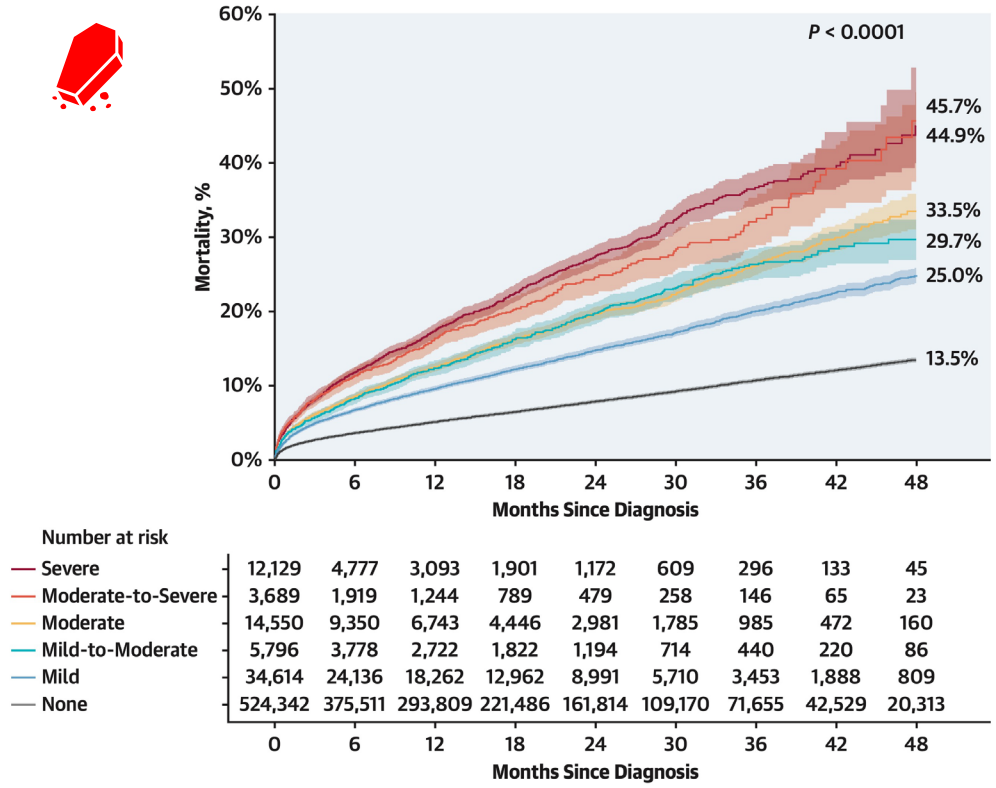
Strange et al. JACC 2019;74:1851-63

Outcome After Diagnosis of Aortic Stenosis

Real-world data set including 1,669,536 echocardiographic reports (1,085,850 patients) from 24 U.S. hospitals (egnite Database)







Genereux et al. JACC 2023;82:2101-09

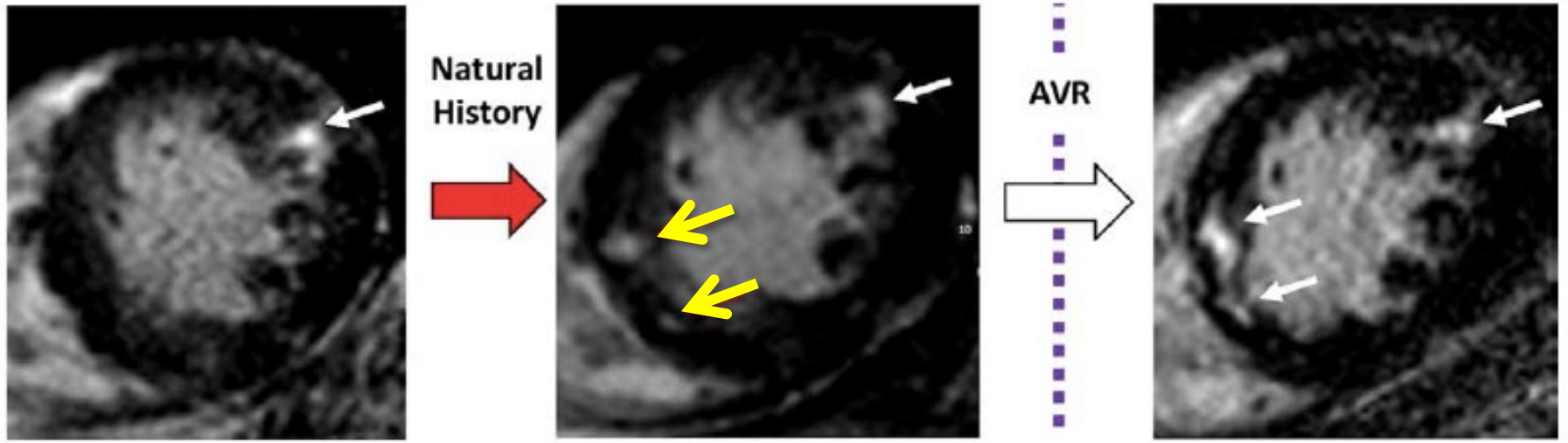
Circulation: Cardiovascular Imaging

ORIGINAL ARTICLE

Progression of Hypertrophy and Myocardial Fibrosis in Aortic Stenosis

A Multicenter Cardiac Magnetic Resonance Study

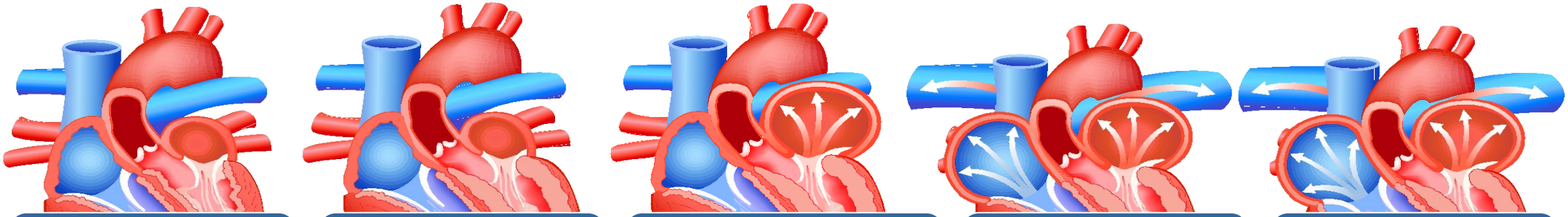
Russell J. Everett, MD, BSc*
Lionel Tastet, MSc*
Marie-Annick Clavel, DVM, PhD
Calvin W.L. Chin, MD, PhD
Romain Capoulade, PhD
Vassilios S. Vassiliou, MD
Jacek Kwiecinski, MD
Miquel Gomez, MD, PhD
Edwin J.R. van Beek, MD, PhD
Audrey C. White
Sanjay K. Prasad, MD
Eric Larose, DVM, MD
Christopher Tuck, BSc
Scott Semple, PhD
David E. Newby, MD, DSc, PhD
Philippe Pibarot, DVM, PhD†
Marc R. Dweck, MD, PhD†



Everett et al. *Circ Cardiovasc Imaging* 2018;11:e007461

Circ Cardiovasc Imaging. 2018;11:e007451. DOI: 10.1161/CIRCIMAGING.117.007451

Staging Classification of Patients with AS Specific Criteria and Prevalence (n= 1974)

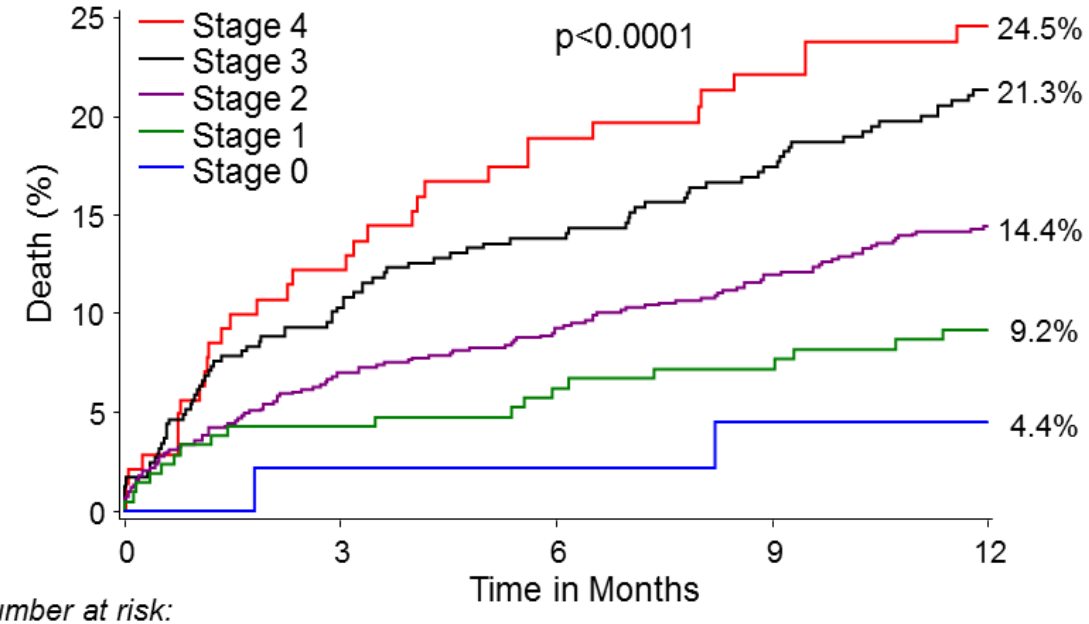


Stage 0 N=121 (6.1%)	Stage 1 N=287 (14.5%)	Stage 2 N=1014 (51.4%)	Stage 3 N=412 (20.9%)	Stage 4 N=140 (7.1%)
Stage 0 **No damage**	**Stage 1** **LV damage**	**Stage 2** **LA/Mitral damage**	**Stage 3** **PA/Tricuspid damage**	**Stage 4** **RV damage**
	Increased LV Mass Index **>115 g/m² Male** **>95 g/m² Female**	**Indexed left atrial volume** **>34mL/m²**	**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)

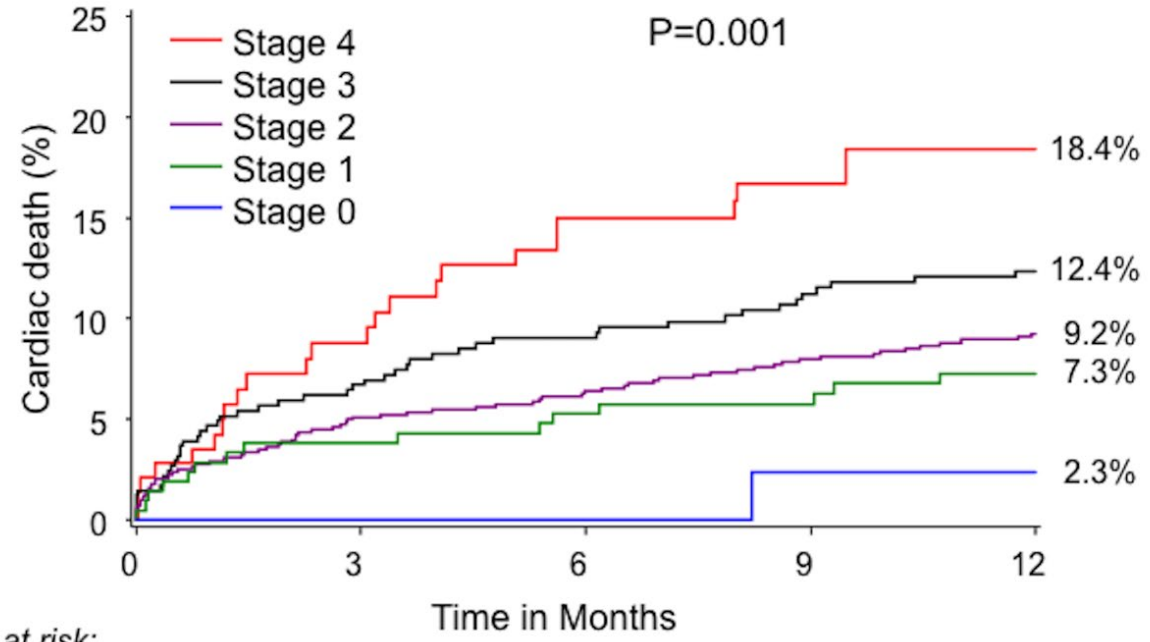
Généreux et al. Eur Heart J 2017;38(45):3351-3358

Extent of Cardiac Damage and Outcomes
1-Year Death After AVR (N= 1661)



Number at risk:

Stage 4	145	118	108	96	93
Stage 3	413	360	337	320	303
Stage 2	844	755	720	679	652
Stage 1	212	199	195	186	180
Stage 0	47	45	45	42	42



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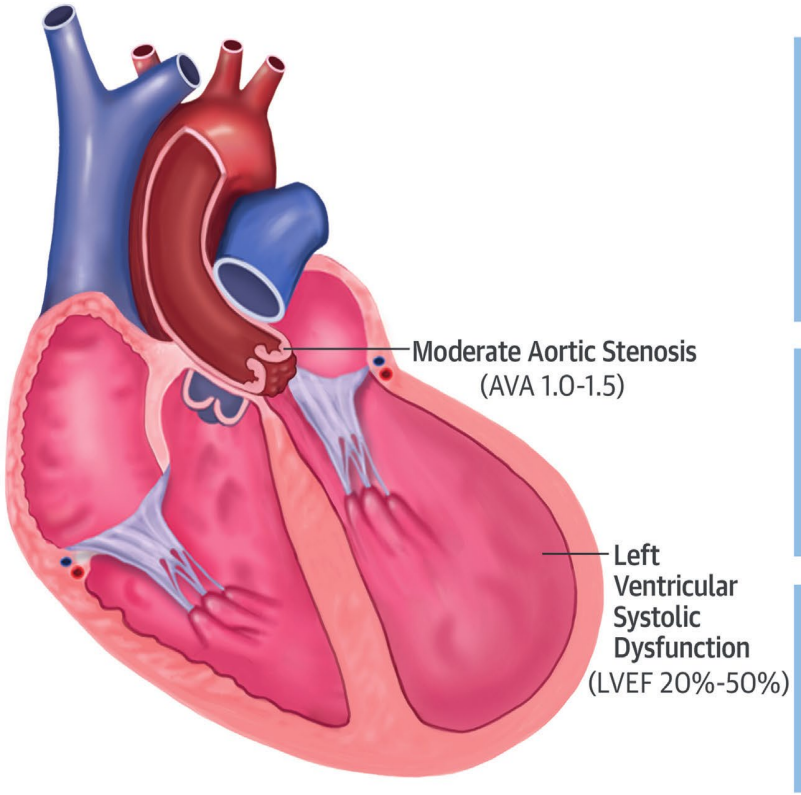
Généreux et al. Eur Heart J 2017;38(45):3351-3358

HFrEF May be Exquisitely Sensitive to Increased Afterload of Moderate AS

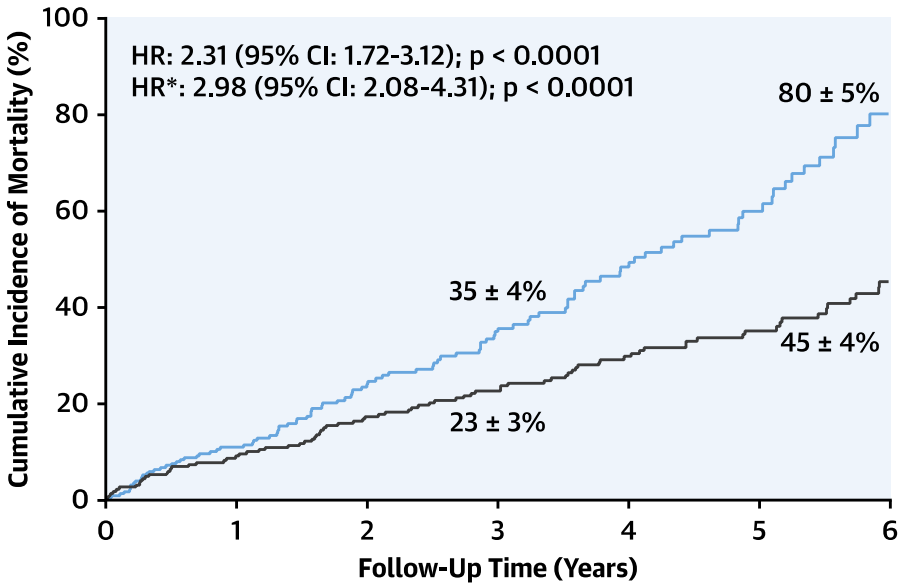


Prognostic Implications at 4-year follow-up:
- All-cause death or hospitalization for heart failure-48%
- All-cause death-36%
- Aortic valve replacement-24%
- Hospitalization for heart failure-27%

Factors Associated with Worse Prognosis:
- Male sex
- NYHA functional class III or IV
- Higher transaortic velocities

Future Treatment Option:
- Early transcatheter aortic valve replacement; to be investigated in the randomized TAVR-UNLOAD trial.

A

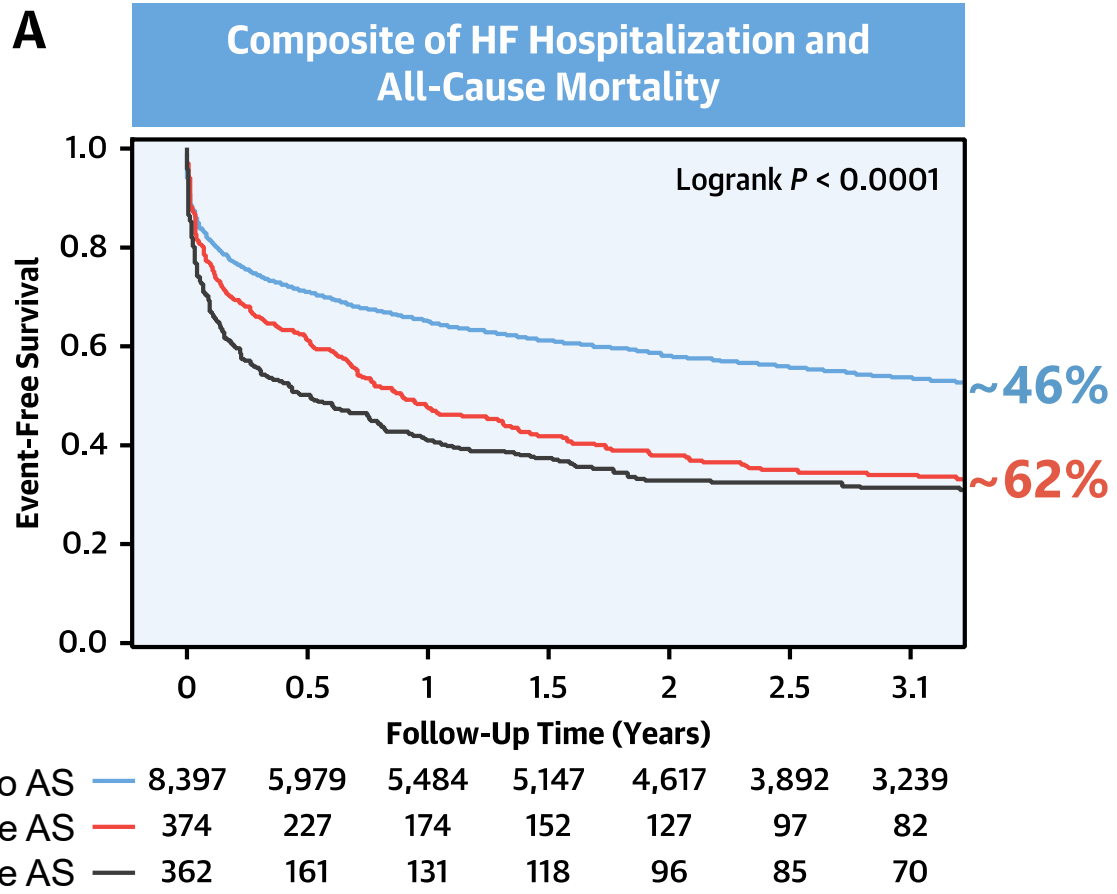


Patients at risk:				
— HFrEF	262	178	117	44
— HFrEF + Moderate AS	262	129	51	9

Jean, G. et al. J Am Coll Cardiol. 2021;77(22):2796-803.

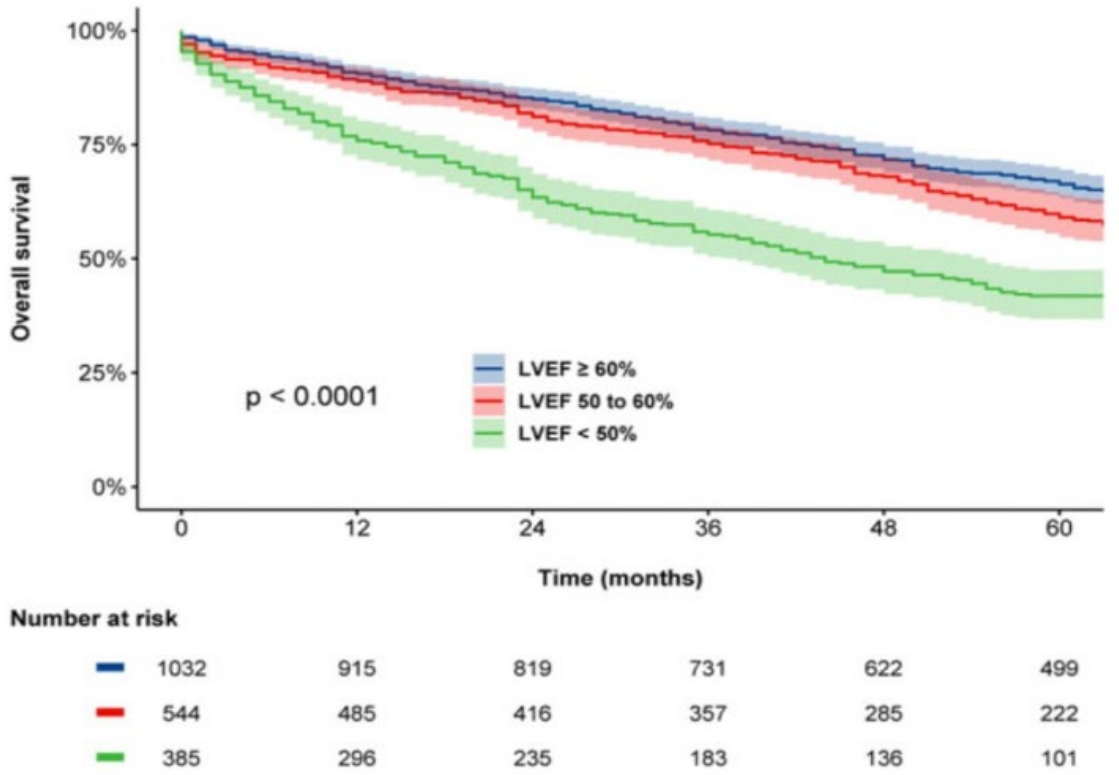
Impact of AS Severity in HFrEF

9,133 patients
Median follow-up 3.1 Years



Khan KR. J Am Coll Cardiol. 2023;81:1235-44.

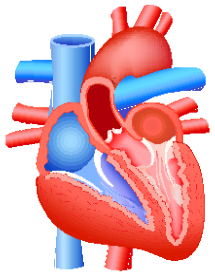
1961 patients with moderate AS
EF < 50% in 385 patients (20%)



Stassen et al. EHJ CV Imaging 2022;23:790-9

Change in Cardiac Damage Post AVR at 1-Year

Early Cardiac Damage at Baseline



Stage 0
No damage

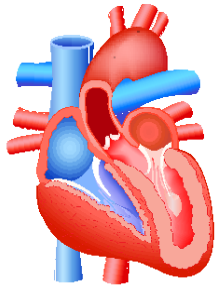
STAGE 0
N = 81/1352
(6.0%)

N = 35/78 (44.9%) → STAGE 0
N = 16/78 (20.5%) → STAGE 1
N = 14/78 (17.9%) → STAGE 2
N = 8/78 (10.3%) → STAGE 3
N = 5/78 (6.4%) → STAGE 4
N = 3 (3.7%) → Death

65.4%
Stage 0-1
~35% > stage 2

Baseline

1 Year Post AVR



Stage 1
LV damage

Increased LV Mass Index > 115 g/m² Male > 95 g/m² Female
E/e' > 14
EF < 50%

STAGE 1
N = 180/1352
(13.3%)

N = 25/167 (15.0%) → STAGE 0
N = 57/167 (34.1%) → STAGE 1
N = 59/167 (35.3%) → STAGE 2
N = 15/167 (9.0%) → STAGE 3
N = 11/167 (6.6%) → STAGE 4
N = 13 (7.2%) → Death

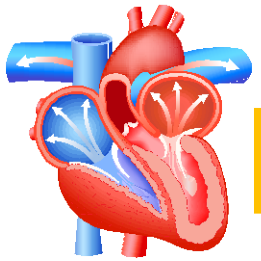
49%
Stage 0-1
~51% > stage 2

Baseline

1 Year Post AVR

Généreux et al. J Am Coll Cardiol 2022;80:783–800.

Change in Cardiac Damage Post AVR at 1-Year Advanced Cardiac Damage at Baseline



Stage 3
PA/Tricuspid damage
PAS ≥ 60mmhg
Moderate-Severe TR

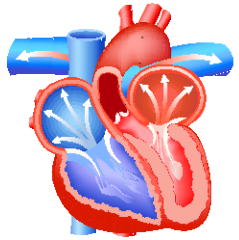
Baseline

STAGE 3
N=296/1352
(21.9%)

4.7%
Stage 0-1
72.2%
Stage 3-4

N = 4/216 (1.9%)	STAGE 0
N = 6/216 (2.8%)	STAGE 1
N = 50/216 (23.1%)	STAGE 2
N = 133/216 (61.6%)	STAGE 3
N = 23/216 (10.6%)	STAGE 4
N = 80 (27.0%)	Death

1 Year Post AVR



Stage 4
RV damage
Moderate-Severe RV dysfunction

Baseline

STAGE 4
N = 98/1352
(7.2%)

2.9%
Stage 0-1
~69.1%
Stage 3-4

N = 2/68 (2.9%)	STAGE 0
N = 0/68 (0.0%)	STAGE 1
N = 19/68 (27.9%)	STAGE 2
N = 13/68 (19.1%)	STAGE 3
N = 34/68 (50.0%)	STAGE 4
N = 30 (30.6%)	Death

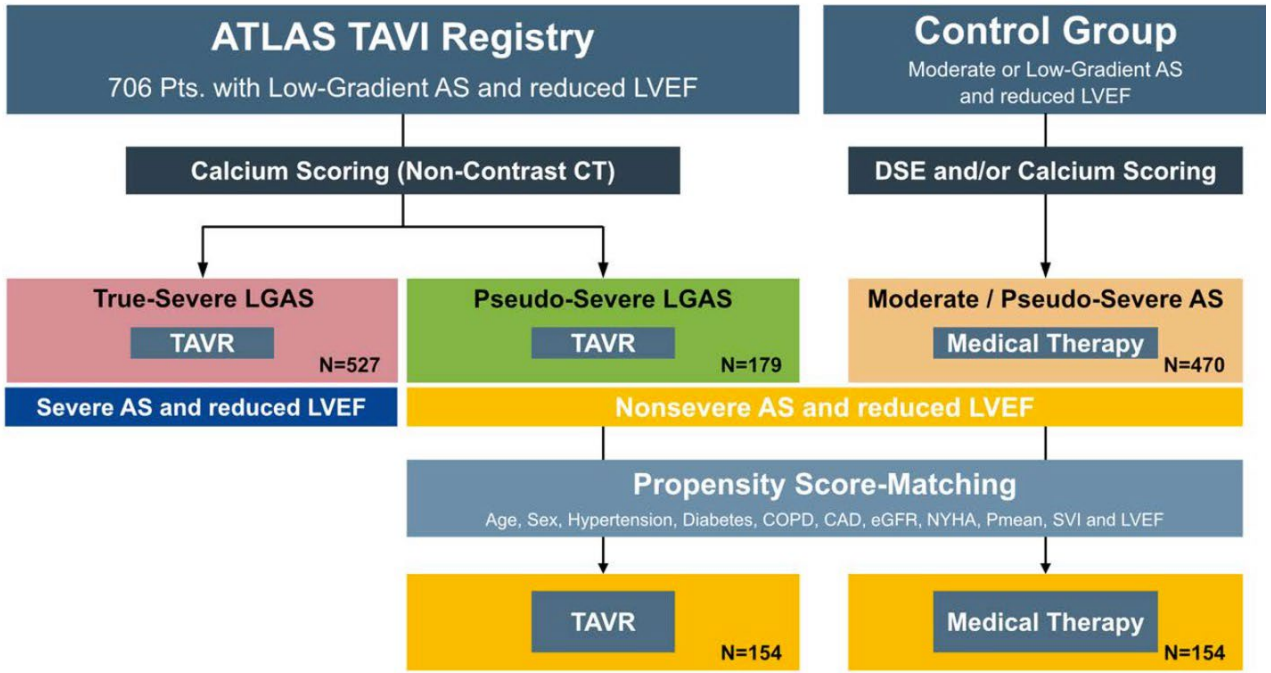
1 Year Post AVR

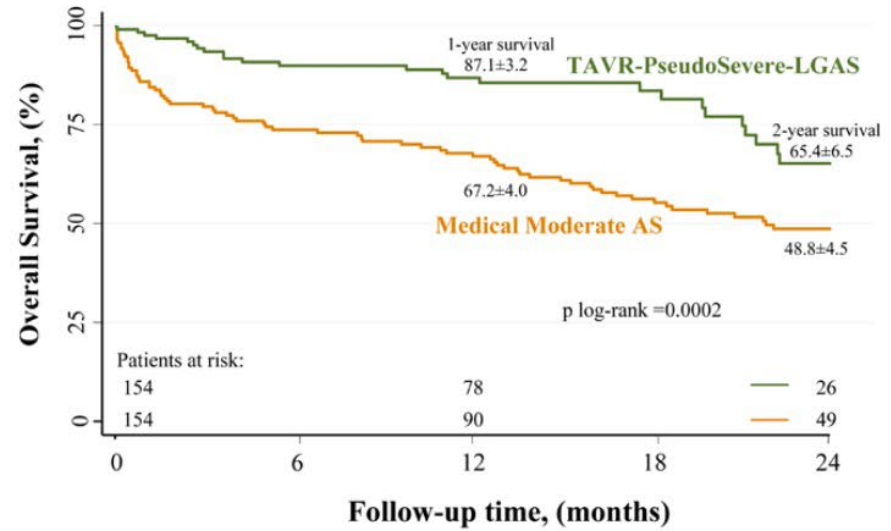
Généreux et al. J Am Coll Cardiol 2022;80:783–800.

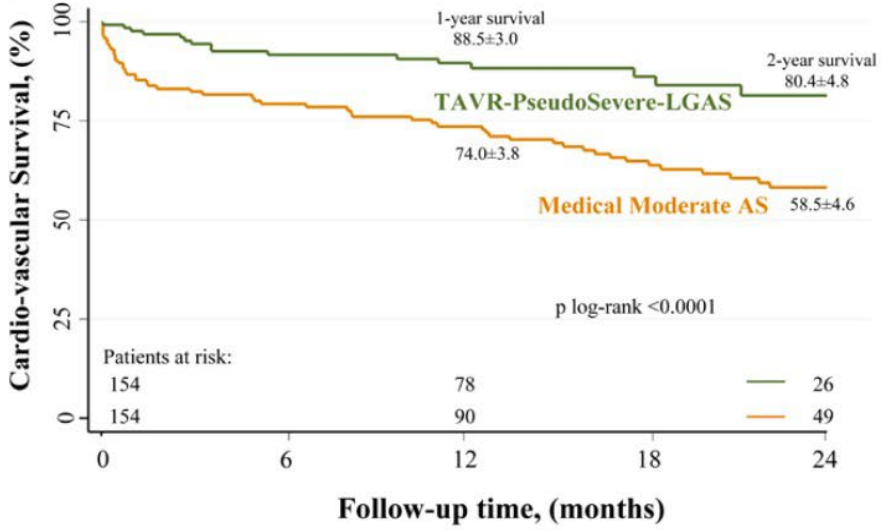
TAVR for Moderate AS & HFrEF

Transcatheter Aortic Valve Replacement in Patients With Reduced Ejection Fraction and Nonsevere Aortic Stenosis

Sebastian Ludwig, MD*; Niklas Schofer, MD*; Mohamed Abdel-Wahab, MD; Marina Urena, MD; Guillaume Jean, MD; Matthias Renker, MD; Christian W. Hamm, MD; Holger Thiele, MD; Bernard Iung, MD; Joris F. Ooms, MD; Maya Wiessman, MD; Nils S.B. Mogensen, MD; Benjamin Longère, MD; Nils Perrin, MD; Walid Ben Ali, MD, PhD; Augustin Coisne, MD, PhD; Jordi S. Dahl, MD, PhD; Nicolas M. Van Mieghem, MD; Ran Kornowski, MD; Won-Keun Kim, MD; Marie-Annick Clavel, DVM, PhD







Ludwig et al. Circ CVI 2023;16

RCTs in Moderate AS Are Already Underway

TAVR Unload

TAVR UNLOAD study design

- International, multicentre trial
- Study cohort: patients with heart failure with LVEF <50% and moderate aortic stenosis

Randomization 1:1

N = 309

Transfemoral TAVI plus optimal heart failure therapy

Optimal heart failure therapy

- Follow-up at 1 month, 6 months, 1 year and 2 years
- Clinical parameters: symptoms, echocardiography and quality of life

- Enrollment ended 12/2022
- 178 subjects
- Follow up complete Feb. 2024
- Results TCT this year.

THE PROGRESS TRIAL

PROGRESS study design

Local Heart Team, Case Review Board & Core Lab Assessments

Moderate aortic stenosis **with symptoms or cardiac damage / dysfunction**
Anatomy appropriate for transfemoral access

1:1 Randomization

TAVR

vs.

Clinical Surveillance

Primary Endpoint: All-Cause Mortality, Stroke, and Unplanned Cardiovascular Hospitalization at 2 Years

Follow-up Annually Through 10 years

The EXPAND TAVR II

EXPAND TAVR II RCT

Patients with moderate AS, EF > 20%, NYHA≥2 &

- **HF event < 1 calendar year prior to qualifying echo**
- **NT proBNP ≥ 600 pg/ml**
- **GLT ≤15% or**
- **E/e' ≥ 14.0**

1:1 Randomization N = 650

TAVR + GDMT

GDMT

- **Safety Composite rate @ 30 days of all-cause mortality, all-stroke, life threatening or fatal bleeding, acute kidney injury, hospitalization due to device or procedure-related complication, or valve dysfunction requiring reintervention.**
- **Efficacy Composite rate @ 2 years of all-cause mortality or unplanned procedure-related or aortic valve related hospitalization.**

JACC: CARDIOVASCULAR IMAGING
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VOL. 14, NO. 9, 2021

ORIGINAL RESEARCH

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

Partho P. Sengupta, MD, DM,[a] Sirish Shrestha, MS,[a] Nobuyuki Kagiyama, MD, PhD,[a] Yasmin Hamirani, MD,[a] Hemant Kulkarni, MD,[a,b] Naveena Yanamala, PhD,[a] Rong Bing, MBBS,[c] Calvin W.L. Chin, MD, PhD,[d] Tania A. Pawade, MD, PhD,[c] David Messika-Zeitoun, MD,[e] Lionel Tastet, MSc,[f] Mylène Shen, PhD,[f] David E. Newby, MD, PhD,[c] Marie-Annick Clavel, DVM, PhD,[f] Phillippe Pibarot, DVM, PhD,[f] Marc R. Dweck, MD, PhD,[c] on behalf of the Artificial Intelligence for Aortic Stenosis at Risk International Consortium

J Am Coll Cardiol Img 2021;14:1707-1720

JACC: CARDIOVASCULAR IMAGING
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VOL. 16, NO. 6, 2023

ORIGINAL RESEARCH

Machine Learning to Optimize the Echocardiographic Follow-Up of Aortic Stenosis

Antonio Sánchez-Puente, BSc, PhD,[a,b,*] P. Ignacio Dorado-Díaz, BE, PhD,[a,b,*] Jesús Sampedro-Gómez, BE,[a,b] Javier Bermejo, MD, PhD,[b,c] Pablo Martinez-Legazpi, BE, PhD,[d] Francisco Fernández-Avilés, MD, PhD,[b,c] Javier Sánchez-González, BE, PhD,[e] Candelas Pérez del Villar, MD, PhD,[a,b] Víctor Vicente-Palacios, BE, PhD,[e,†] Pedro L. Sanchez, MD, PhD[a,b,†]

J Am Coll Cardiol Img 2023;16:733-744

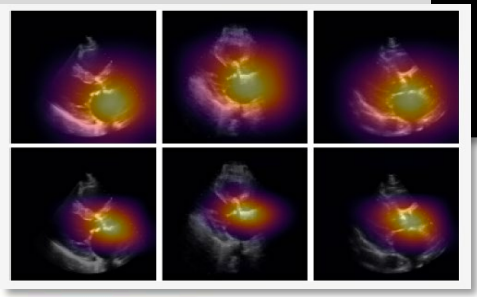
ESC European Society of Cardiology
European Heart Journal (2023) **44**, 4592–4604
https://doi.org/10.1093/eurheartj/ehad456

CLINICAL RESEARCH
Digital health and innovation

Severe aortic stenosis detection by deep learning applied to echocardiography

Gregory Holste [1,2†], Evangelos K. Oikonomou [2†], Bobak J. Mortazavi[3,4], Andreas Coppi[2,4], Kamil F. Faridi[2], Edward J. Miller [2], John K. Forrest[2], Robert L. McNamara[2], Lucila Ohno-Machado [5], Neal Yuan[6,7], Aakriti Gupta[8], David Ouyang[8,9], Harlan M. Krumholz[2,4,10], Zhangyang Wang[1], and Rohan Khera [2,4,5,11*]

European Heart Journal (2023) **44**, 4592–4604



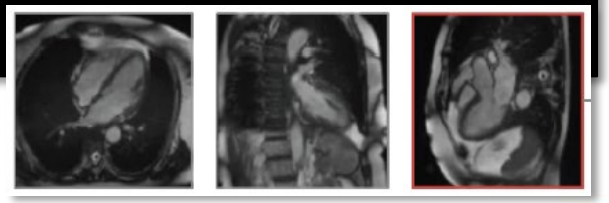
Research

JAMA Cardiology | Original Investigation | AI IN CARDIOLOGY

A Multimodal Video-Based AI Biomarker for Aortic Stenosis Development and Progression

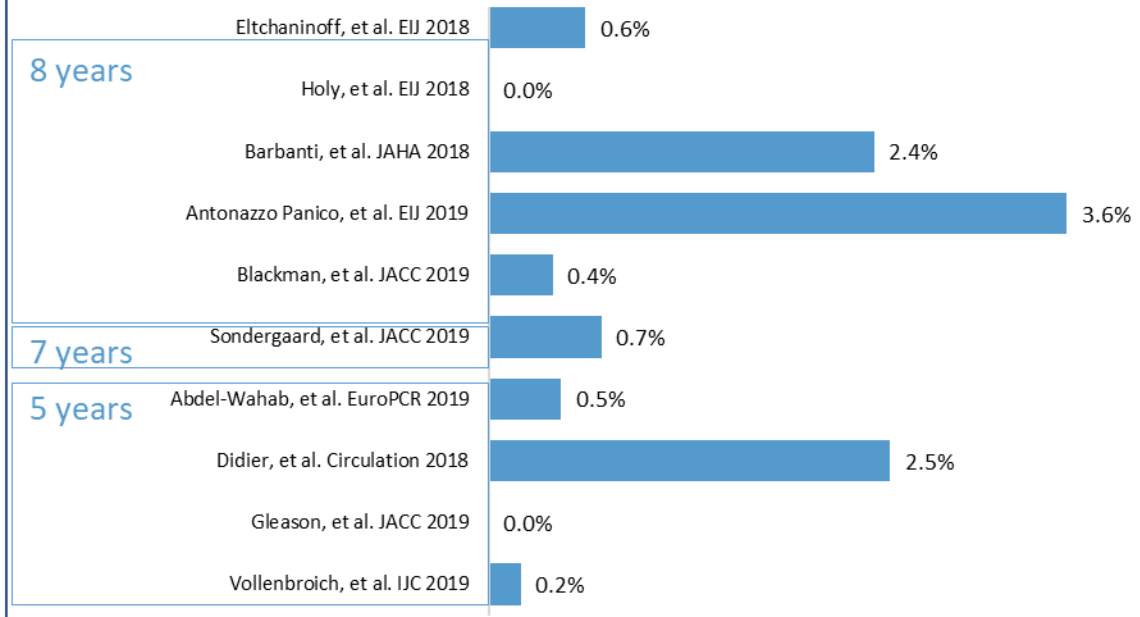
Evangelos K. Oikonomou, MD, DPhil; Gregory Holste, BA; Neal Yuan, MD; Andreas Coppi, PhD; Robert L. McNamara, MD, MHS; Norrisa A. Haynes, MD, MPH; Amit N. Vora, MD, MPH; Eric J. Velazquez, MD; Fan Li, PhD; Venu Menon, MD; Samir R. Kapadia, MD; Thomas M. Gill, MD; Girish N. Nadkarni, MD, MPH; Harlan M. Krumholz, MD, SM; Zhangyang Wang, PhD; David Ouyang, MD; Rohan Khera, MD, MS

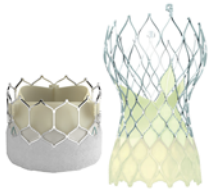
JAMA Cardiol. 2024; 10.1001/jamacardio.2024.0759



10-Year TAVR Durability Needs to be Established!

Severe SVD

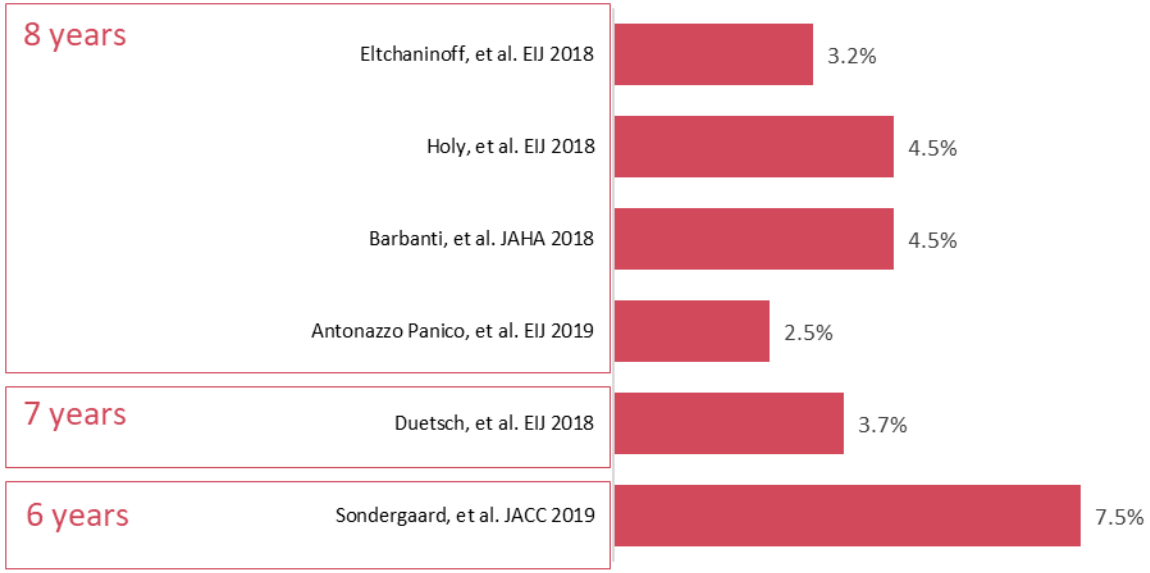




SVD at 5 to 8 years
Weighted incidence

1.3%
(95% CI 0.7-1.9)

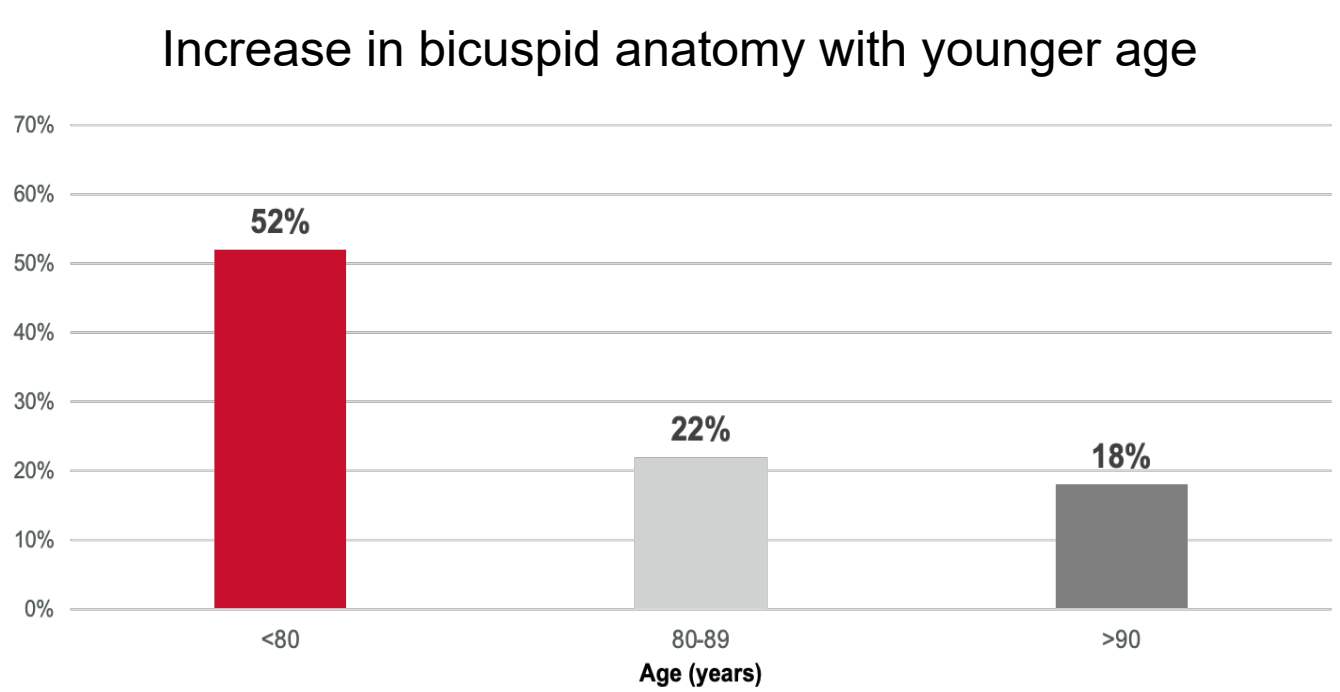
Bioprosthetic valve failure (BVF)

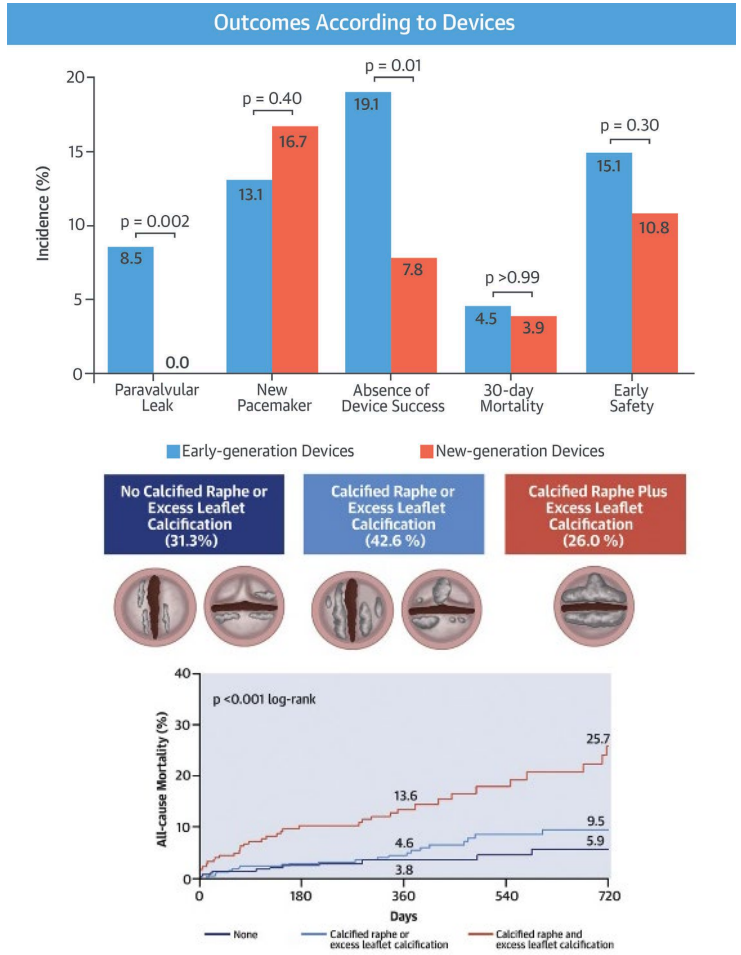


BVF at 6 to 8 years
Weighted incidence

3.7%
(95% CI 2.7-4.6)

Bicuspid AS More Common In Younger Patients And May Present A Challenge For TAVR





Patient selection and safety of TAVR for Bicuspid AS Needs to be defined!

Yoon et al. JACC 2016;68:1195-205; Yoon et al. JACC. 2020;76:1018-1030

Interventional Management of Moderate AS

- The clinical impact of moderate AS is substantial and can be explained by effects on cardiac performance, underlying damage and hemodynamics
- There is early evidence that the early treatment of AS may have an impact on mortality, HFH and future cardiac damage
- There are still many open questions regarding valve durability, patient selection (i.e., BAV) and frame selection (re-intervention)
- Detecting AS before irreversible cardiac damage develops is critically needed, greater precision in selecting patients for intervention is greatly needed
- RCT data will start to emerge soon, TAVR UNLOAD data will be presented at TCT this year!