Moderate Aortic Stenosis: Bridging Clinical Practice & Innovation

November 19, 2025

Meeting Reminders

Please Note:

- This webinar is being recorded.
- All participants will be muted upon entry.
- Recordings of today's sessions will be enduring resources in a few weeks on www.heart.org

Questions?

- We encourage an open, conversational discussion, so please engage and share your thoughts!
- Q&A is scheduled at the end of the webinar.
- Submit your questions in the chat anytime—they will be addressed during the designated Q&A.

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Welcome & Introductions

Devin Marie Keating
Director of Operations, Clinical Studies
American Heart Association

Thank you to

Kardigan, Inc.

for being a supporter of the

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Heart Valve Initiative

Today's Speakers

Sreekanth Vemulapalli, MD

Duke University Health System

Associate Professor of Medicine/Cardiology;

Medical Director, Duke Echo Lab and Cardiac Diagnostic Unit;

Member, Duke Clinical Research Institute;

Member, Duke-Margolis Center for Health Policy

Professor Marc Dweck

University of Edinburgh

Personal Chair of Clinical Cardiology;

BHF Senior Clinical Research Fellow;

Vice-President European Association of Cardiovascular Imaging

Brian R. Lindman, MD, MSc

Vanderbilt University Medical Center

Medical Director, Structural Heart and Valve Center;

Associate Professor of Medicine

Disclosures

American Heart Association Statement

- The recommendations and opinions presented by our guest speakers may not represent the official position of the American Heart Association. The materials are for educational purposes only, and do not constitute an endorsement or instruction by AHA/ASA. The AHA/ASA does not endorse any product or device.

Sreekanth Vemulapalli, MD

- Grants / Contracts: National Institutes of Health (R01 and UG3/UH3), Food and Drug Administration, Edwards Lifesciences, Abbott Vascular, American College of Cardiology, American Heart Association
- Consulting / Advisory: Edwards Lifesciences, Medtronic, Abbott Vascular, Cytokinetics, Astra Zeneca, Boehringer-Ingelheim

Professor Marc Dweck

- Speaker fees from Pfizer, Radcliffe Cardiology, Bristol Myers Squibb, Edwards and Novartis. He has received consultancy fees from Novartis, Jupiter Bioventures, Beren and Silence therapeutics.
- Director of Image Analysis Core Lab within the Edinburgh Clinical Research Facility, University of Edinburgh

Brian R. Lindman, MD, MSc

- Investigator-Initiated Research Grants: Edwards Lifesciences
- Consulting / Advisory: Edwards Lifesciences, Medtronic, Anteris, Kardigan, Inc., AstraZeneca

Agenda:

1. Moderate Aortic Stenosis Disease Burden & Treatment Need
2. Medical Therapy for Valve Disease and The Role of ATA-301
3. Expanding Research Capacity for Medical Therapy in Moderate Aortic Stenosis
4. Panel Discussion: Real-World Considerations and Clinical Implementation
5. Q&A and Closing Remarks

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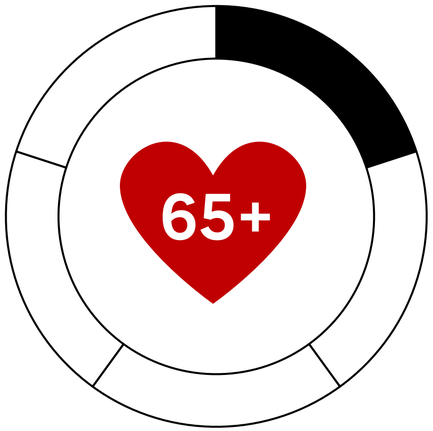
Opening Remarks

Sreekanth Vemulapalli, MD

Duke University, Duke University Health System
Associate Professor of Medicine / Cardiology;
Medical Director, Duke Echo Lab and Cardiac Diagnostic Unit;
Member, Duke Clinical Research Institute;
Member, Duke-Margolis Institute for Health Policy

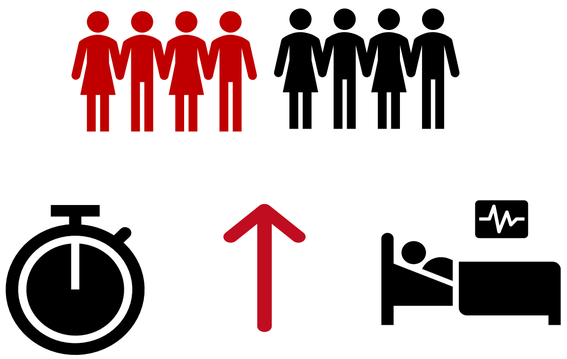
THE UNMET NEED IN HEART VALVE DISEASE

High Prevalence



Nearly **1 in 5** Americans **aged 65+** have significant valvular heart disease
(PREVUE Valve Study, TCT 2025)

Under Treatment or Delayed Treatment

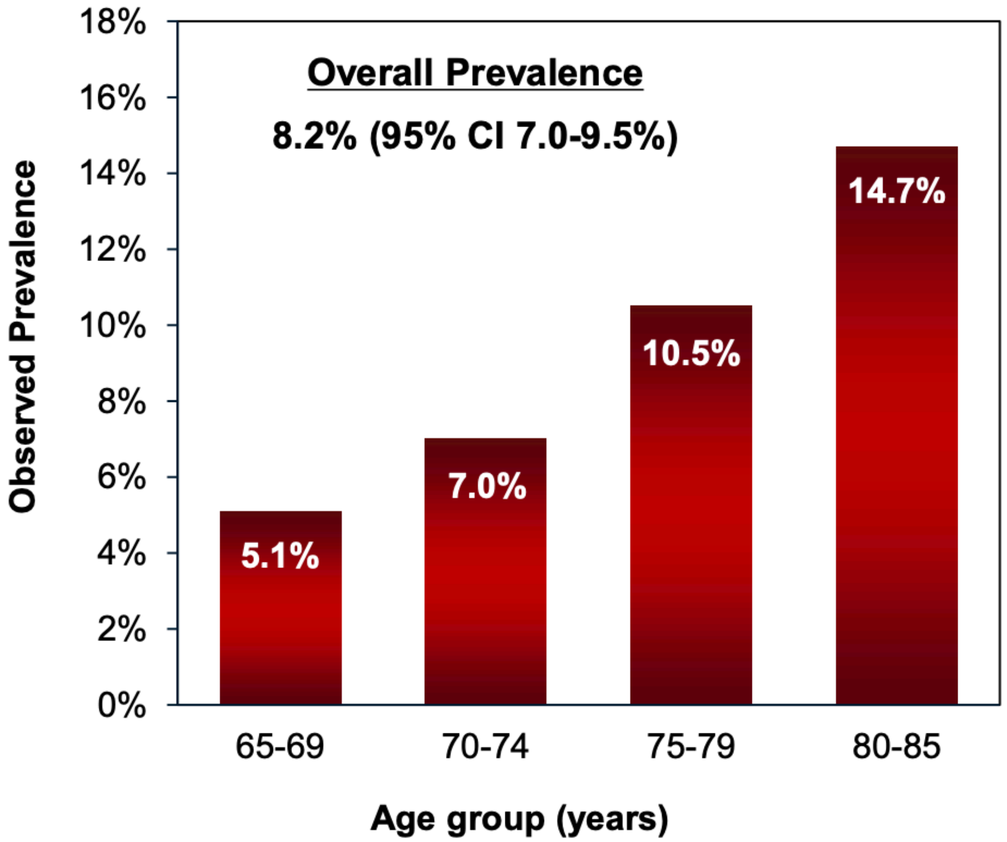


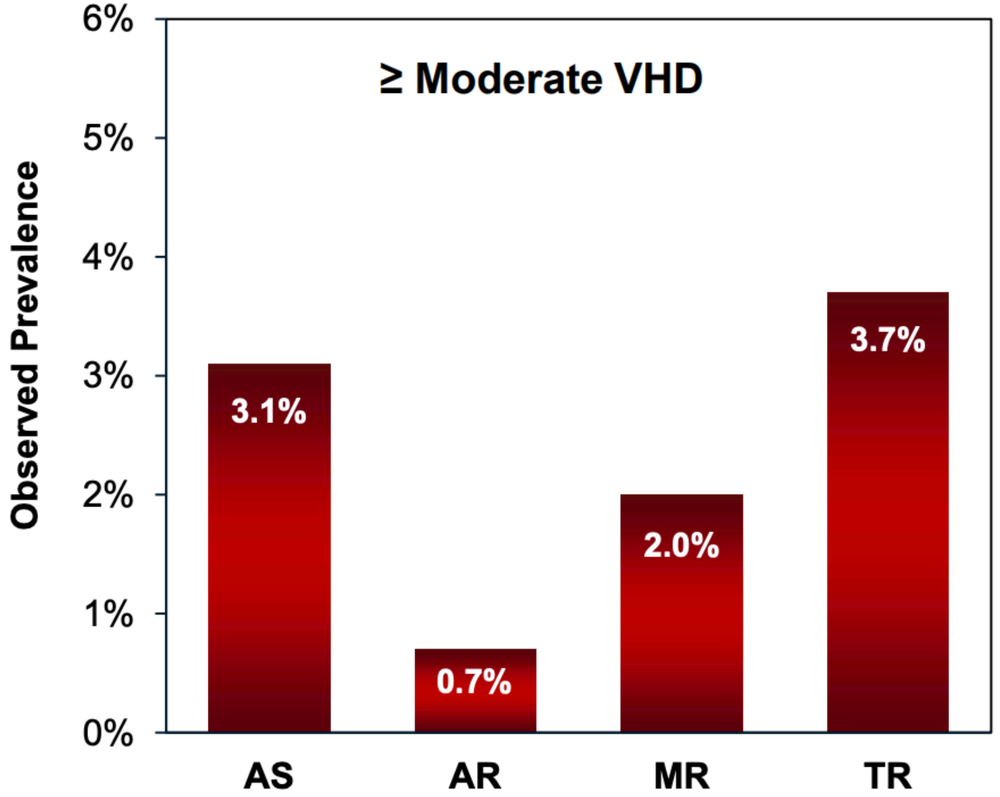
50% of all patients with symptomatic severe aortic **stenosis remain untreated. Delayed or missed treatment** increases mortality, and reduces quality of life
(Li et al., JACC, 2022)

Disparities in Care

Treatment gaps disproportionately affect **older adults, women, and underrepresented populations.**
(Nathan, JAMA Cardiology, 2022; Tanguturi et al., Circulation, 2025)

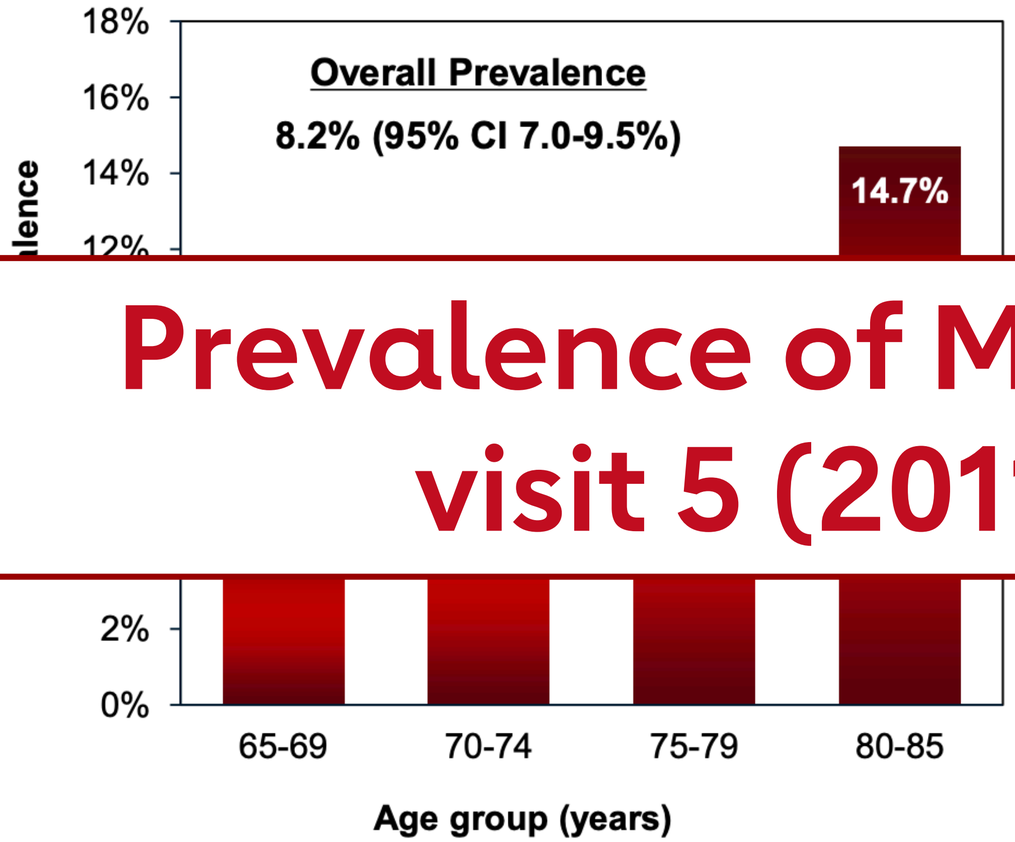
PREVUE-VALVE

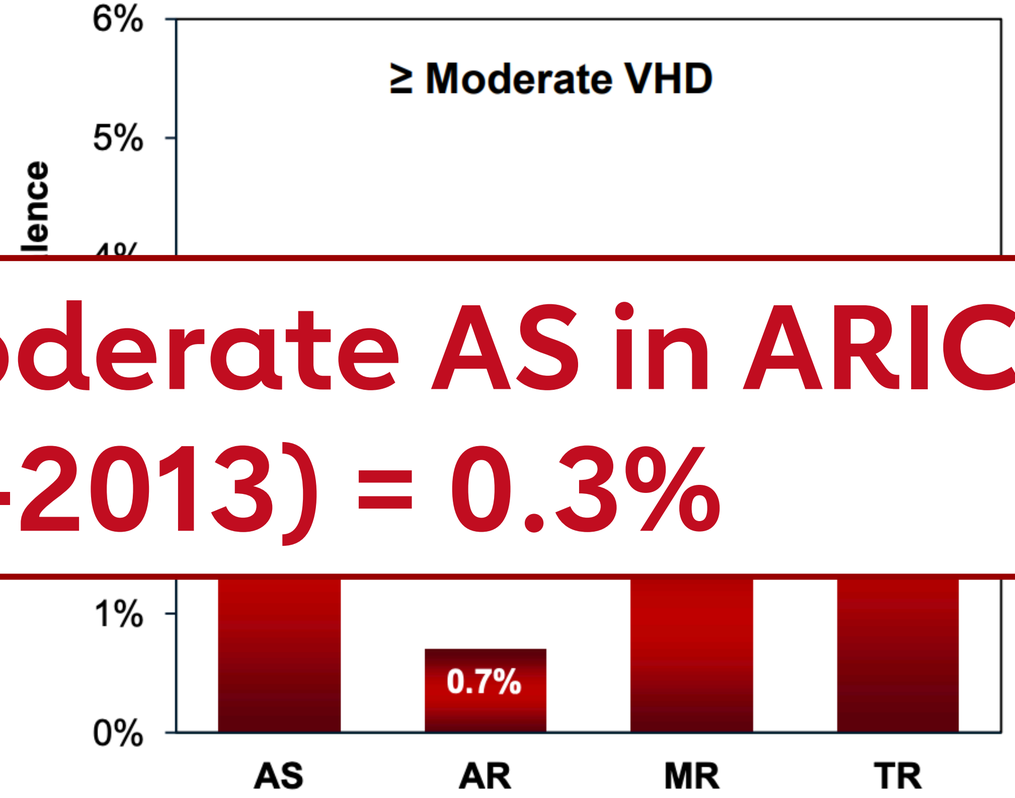




Cohen DJ. Prevue-Valve. TCT 2025
Shelbaya et al. Circulation. 2023

PREVUE-VALVE

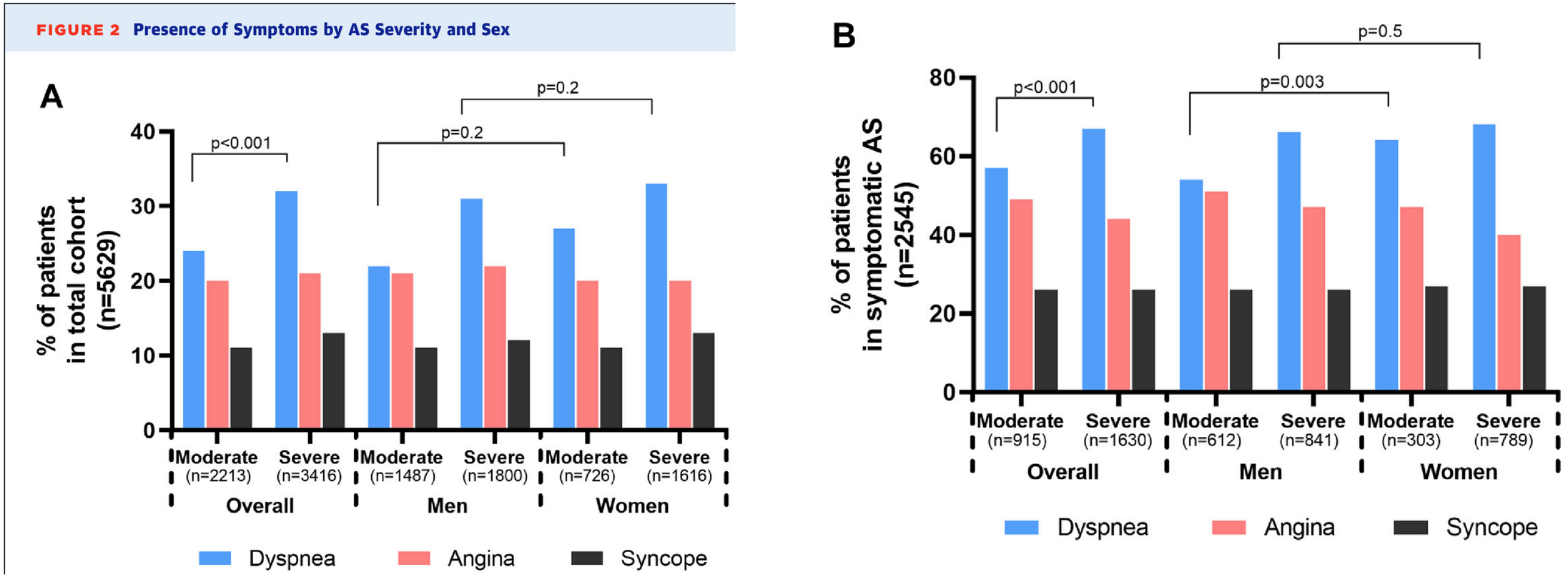




Prevalence of Moderate AS in ARIC visit 5 (2011-2013) = 0.3%

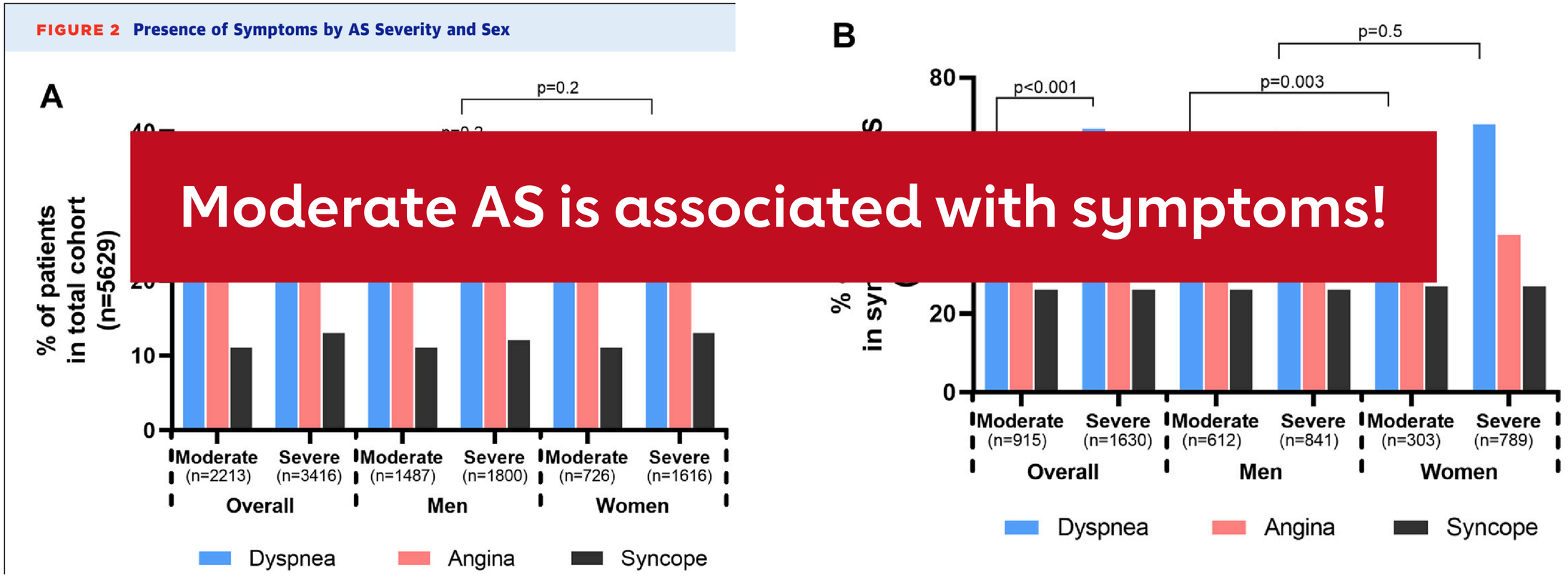
Cohen DJ. Prevue-Valve. TCT 2025
Shelbaya et al. Circulation. 2023

THE BURDEN OF MODERATE AORTIC STENOSIS: SYMPTOMS



Playford D. Comorbidities and Symptom Status in Moderate and Severe AS. JACC Adv. 2023

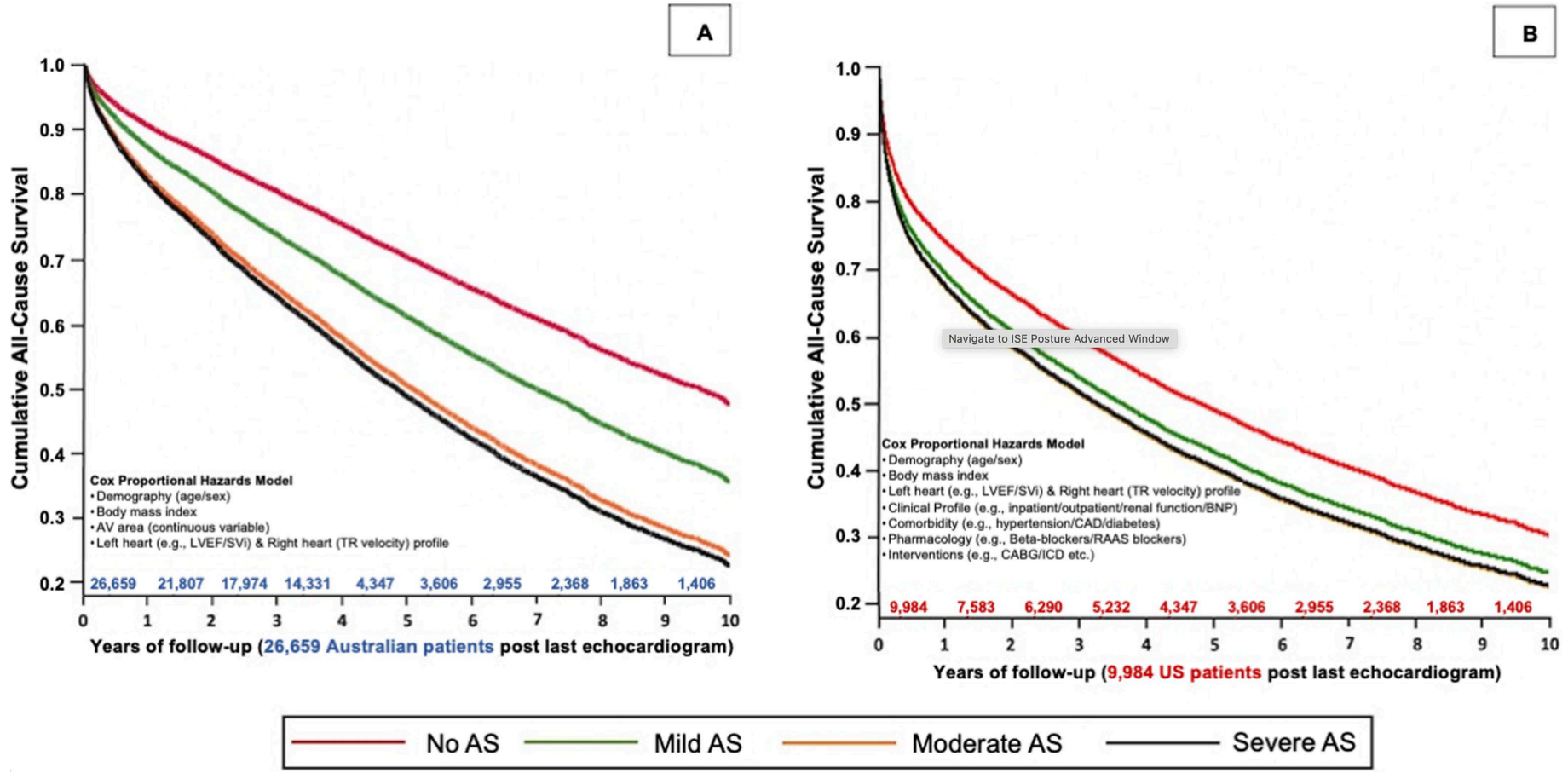
THE BURDEN OF MODERATE AORTIC STENOSIS: SYMPTOMS



Moderate AS is associated with symptoms!

Playford D. Comorbidities and Symptom Status in Moderate and Severe AS. JACC Adv. 2023

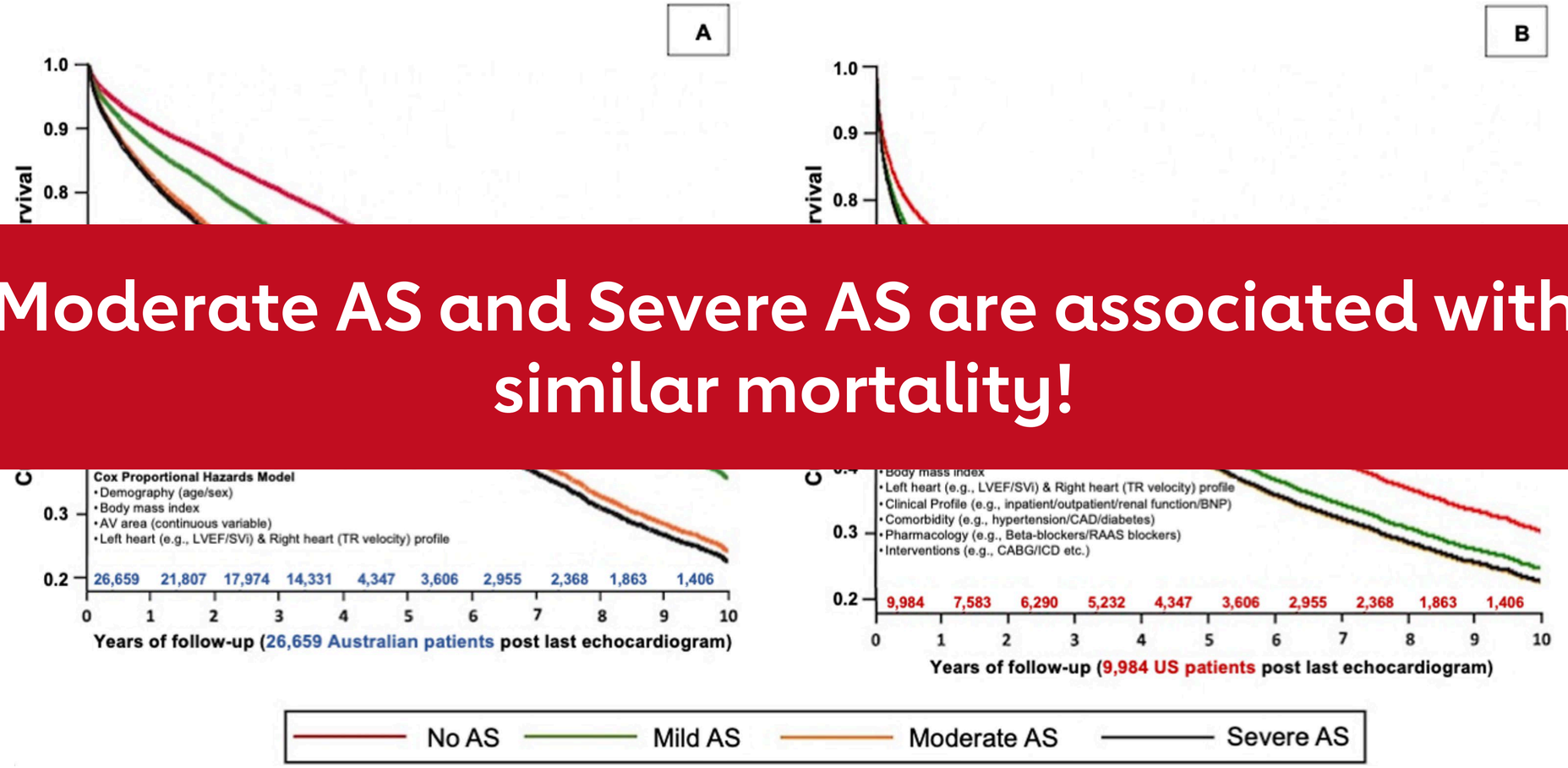
THE BURDEN OF MODERATE AORTIC STENOSIS: OUTCOMES



Strom et al. PLOS ONE 2022

THE BURDEN OF MODERATE AORTIC STENOSIS: OUTCOMES

Moderate AS and Severe AS are associated with similar mortality!



Strom et al. PLOS ONE 2022

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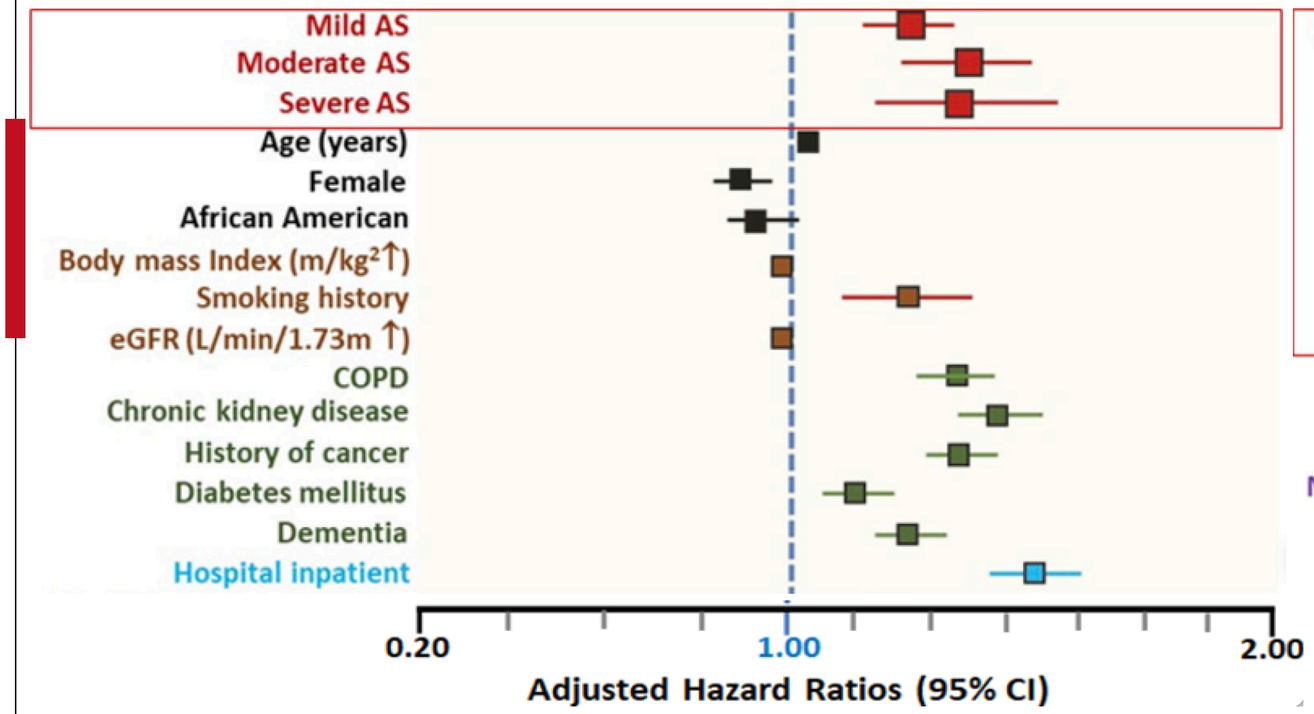
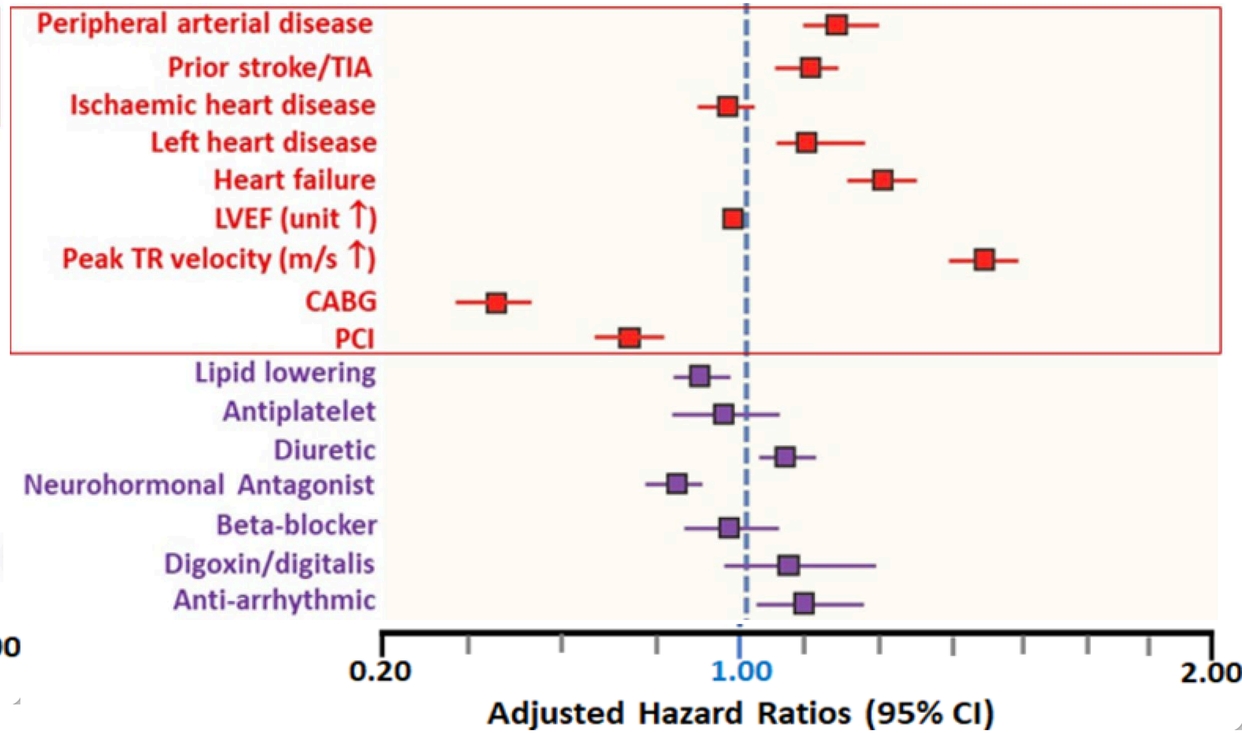
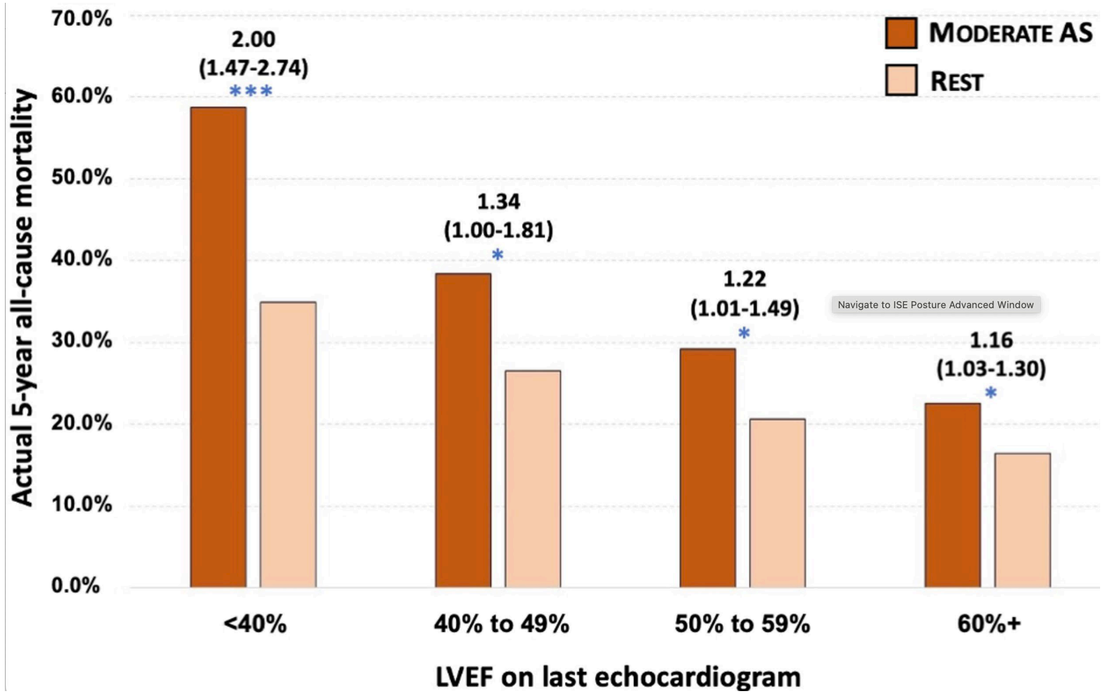
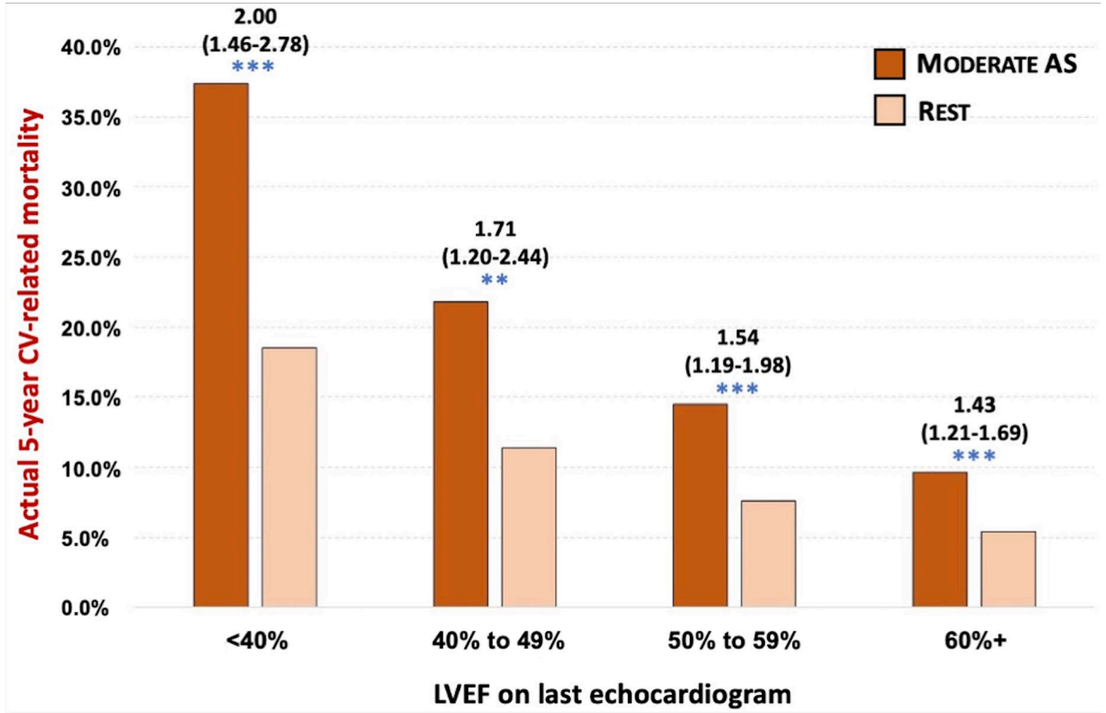




Strom et al. PLOS ONE 2022

ALL CAUSE AND CV MORTALITY IN MODERATE AS BY LVEF





Strom et al. PLOS ONE 2022

OPPORTUNITIES FOR RESEARCH IN MODERATE AS

Excess **Mortality**

Symptoms: Dyspnea on exertion

Prevention of **Cardiac Damage**

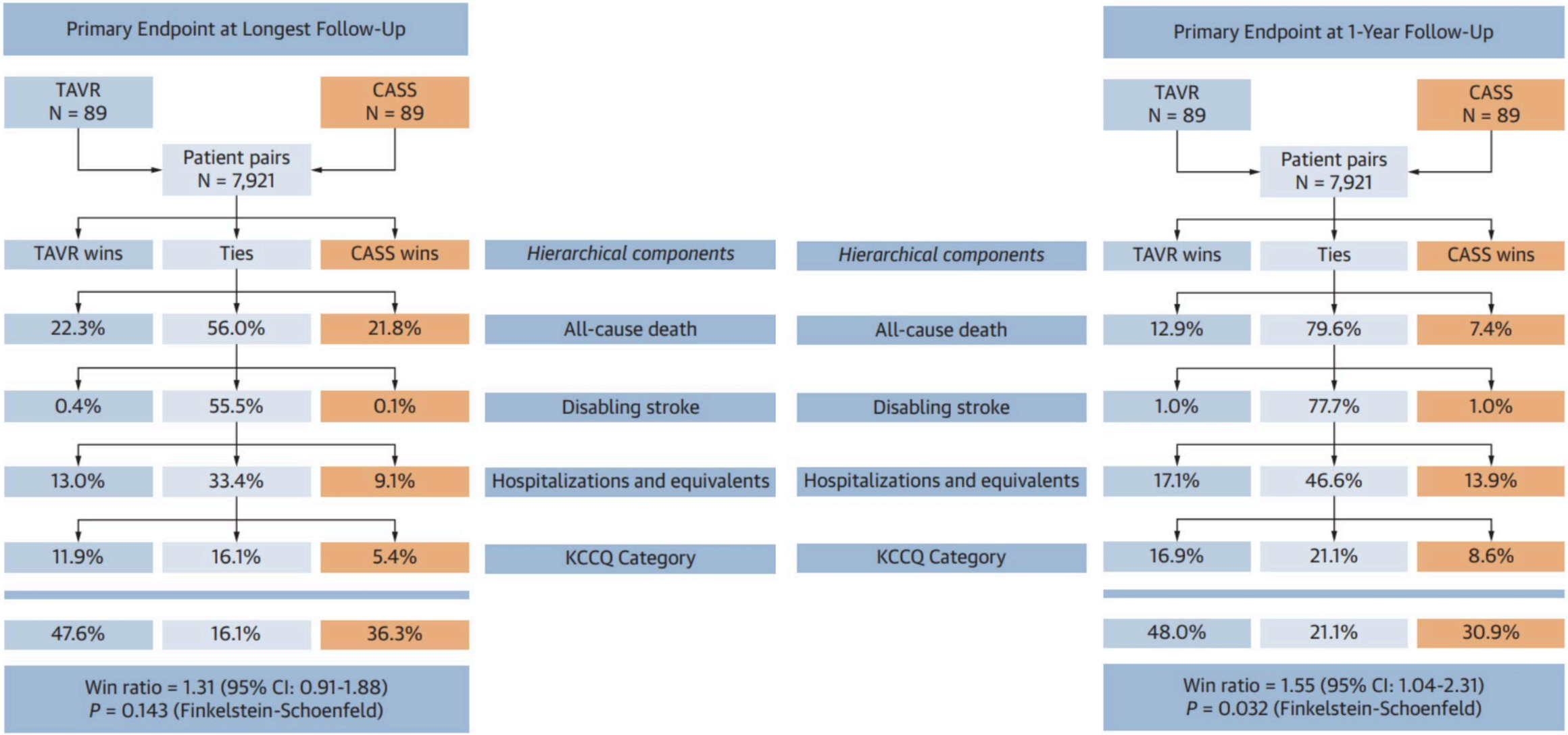
TAVR UNLOAD: DESIGN

- Prospective Randomized Trial examining the efficacy of TAVR vs. continued clinical aortic stenosis surveillance (CASS) in patients with moderate AS and HFrEF on optimal medical therapy

- Patients randomized 1:1 to receive transfemoral balloon expandable TAVR vs. clinical surveillance

Van Mieghem NM, Elmariah S, Spitzer E, et al. J Am Coll Cardiol. 2025;85:878-890. PMID: 39480381.

TAVR UNLOAD: RESULTS



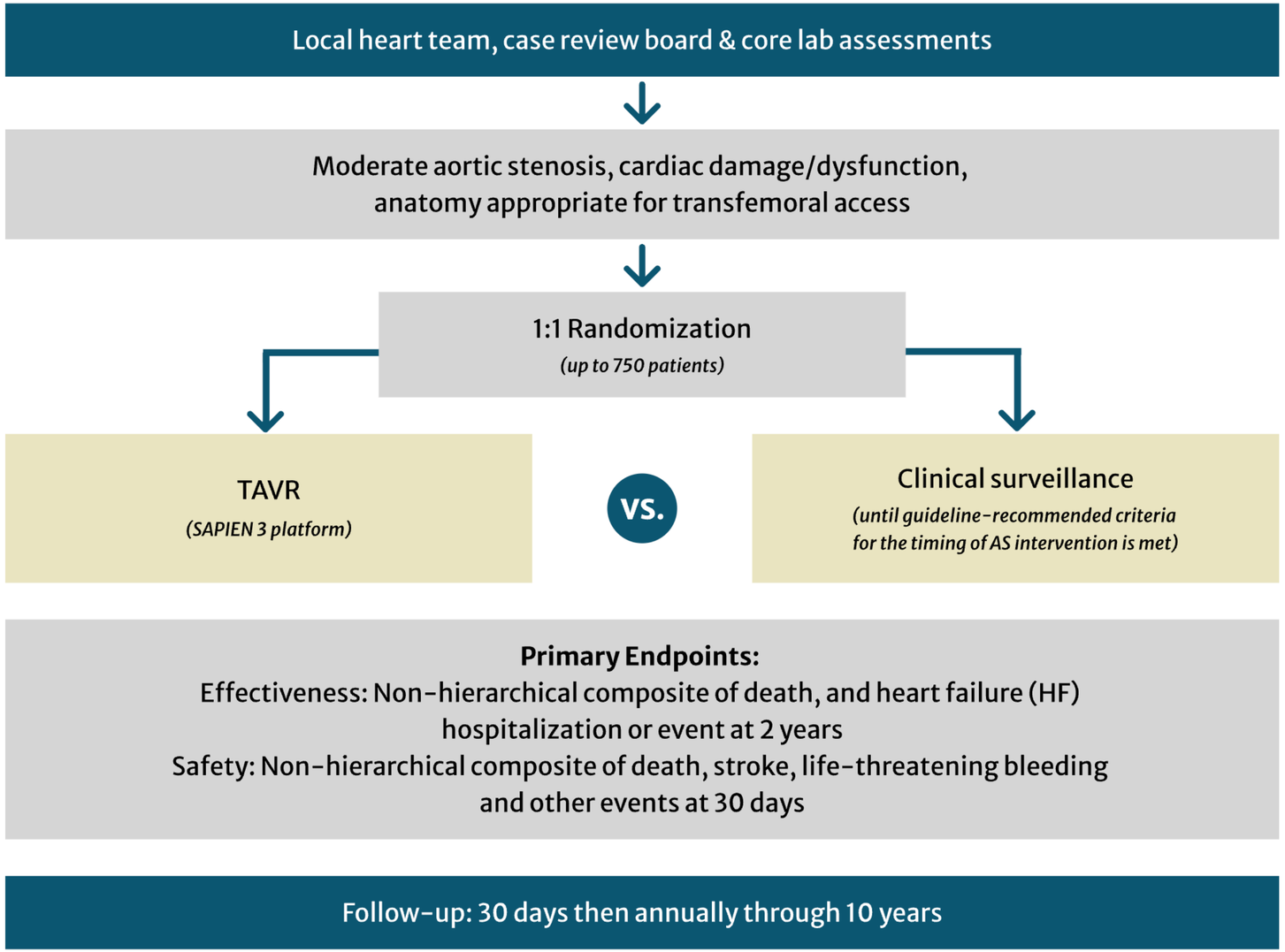
Van Mieghem NM, Elmariah S, Spitzer E, et al. J Am Coll Cardiol. 2025;85:878-890. PMID: 39480381.

TAVR UNLOAD: RESULTS

1. Underpowered
2. High Crossover from Surveillance to TAVR
3. Medical Therapy in Surveillance was Suboptimal

Van Mieghem NM, Elmariah S, Spitzer E, et al. J Am Coll Cardiol. 2025;85:878-890. PMID: 39480381.

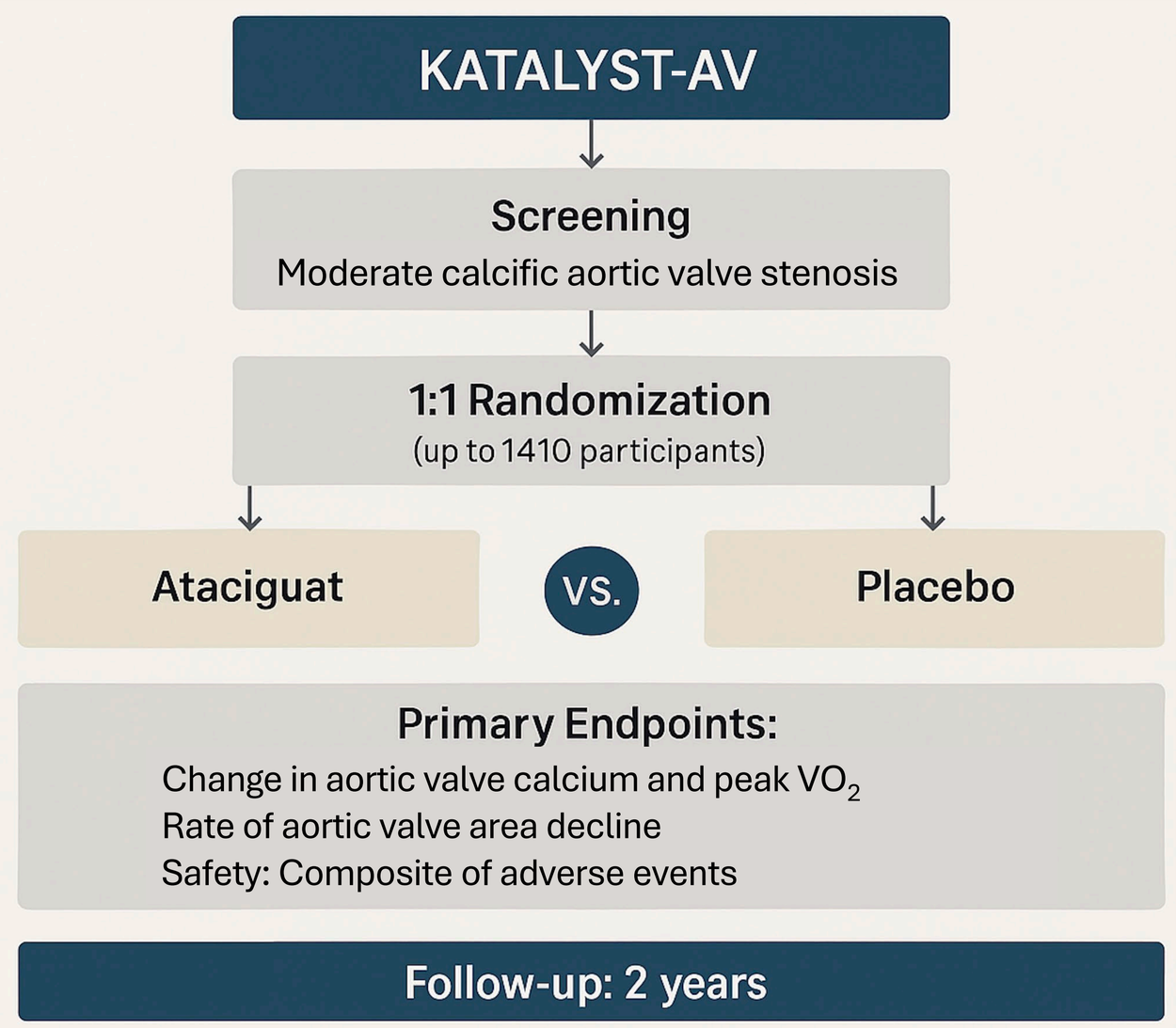
PROGRESS TRIAL: DESIGN



Will help to answer role of TAVR in select patients with moderate AS

https://clinicaltrials.gov/study/NCT04889872

KATALYST-AV TRIAL: DESIGN



Endpoints of peak VO_2 and aortic valve area uniquely target physical function

https://clinicaltrials.gov/study/NCT07001800

CONCLUSIONS

Moderate AS is associated with **dyspnea**

Moderate AS is associated with **increased mortality,** similar to severe AS

TAVR Unload showed improved QOL but was underpowered

PROGRESS Trial will investigate the role of TAVR in moderate AS with cardiac damage / dysfunction

KATALYST-AV Trial will evaluate if ataciguat slows the progression and investigate the symptoms of moderate CAVS by measuring functional capacity

American Heart Association®

Moderate Aortic Stenosis Disease Burden & Treatment Need

Professor Marc Dweck

University of Edinburgh

Personal Chair of Clinical Cardiology;

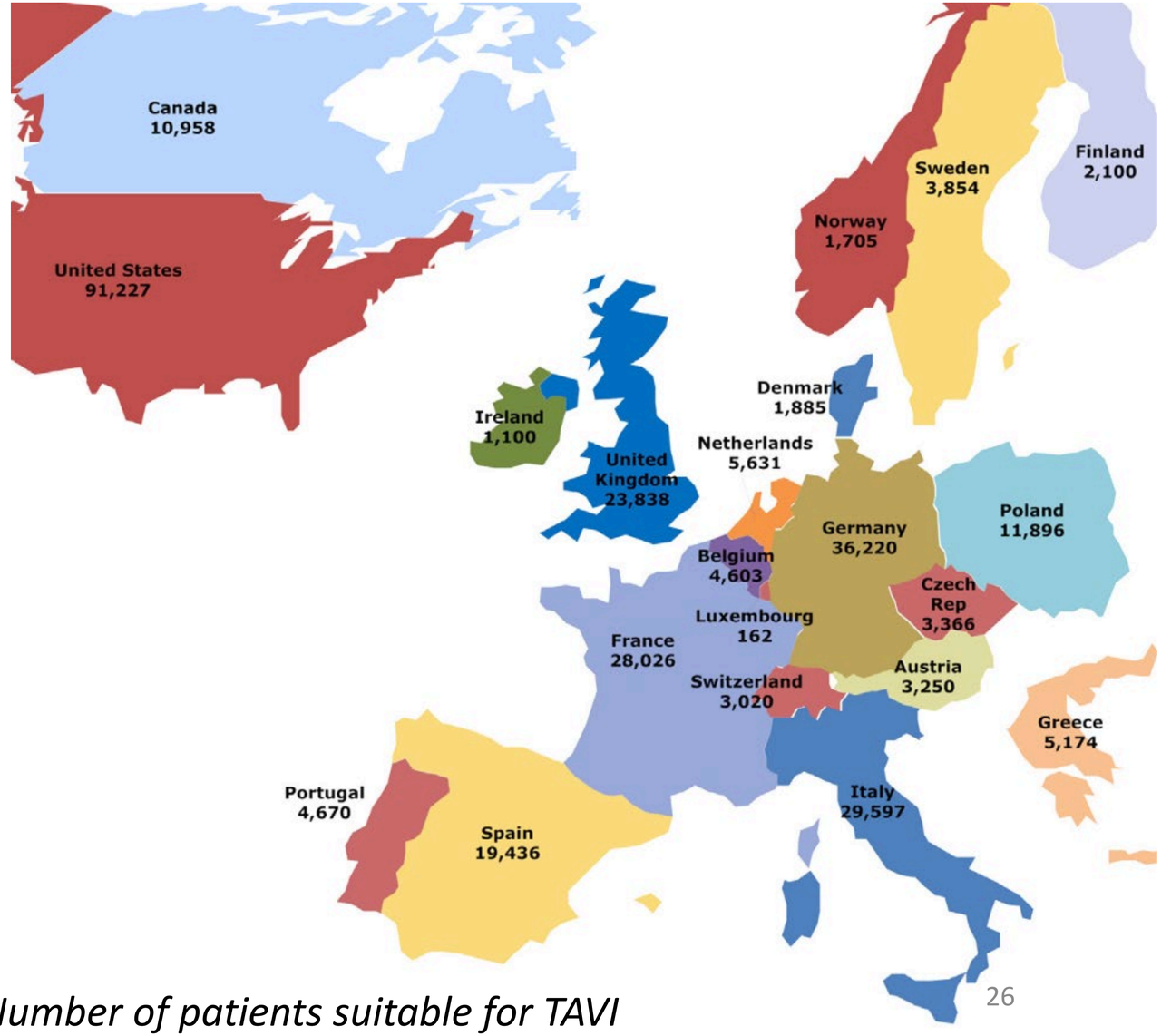
BHF Senior Clinical Research Fellow;

Vice-President European Association of Cardiovascular Imaging

A Looming Heart Valve Epidemic

- Aortic Stenosis a common cardiac condition
  - 5-10% patients >65
  - Globally each year it is responsible for ~125,000 deaths and loss of 1.8 million disability-adjusted life years

Prevalence set to triple by 2050



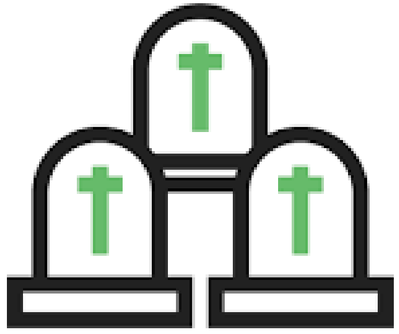
Number of patients suitable for TAVI

Nkomo, Lancet 2006
Osnabrugge JACC 2013

Last Major Cardiovascular Condition Without an Effective Medical Therapy

- Patients don’t want to undergo AVR or TAVI and desperately want the option of a preventative medical therapy
- Clinicians frustrated at lack of therapeutic options for their patients
- Large and growing potential market
- No competition (no drugs work)

CLINICAL TRIAL GRAVEYARD



The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

A Randomized Trial of Intensive Lipid-Lowering Therapy in Calcific Aortic Stenosis

S. Joanna Cowell, B.M., David E. Newby, M.D., Robin J. Prescott, Ph.D., Peter Bloomfield, M.D., John Reid, M.B., Ch.B., David B. Northridge, M.D., and Nicholas A. Boon, M.D., for the Scottish Aortic Stenosis and Lipid Lowering Trial, Impact on Regression (SALTIRE) Investigators

The NEW ENGLAND JOURNAL of MEDICINE

Circulation

Volume 143, Issue 25, 22 June 2021; Pages 2418-2427

https://doi.org/10.1161/CIRCULATIONAHA.121.053708

ORIGINAL RESEARCH ARTICLE

Effect of Denosumab or Alendronic Acid on the Progression of Aortic Stenosis: A Double-Blind Randomized Controlled Trial

ORIGINAL ARTICLE

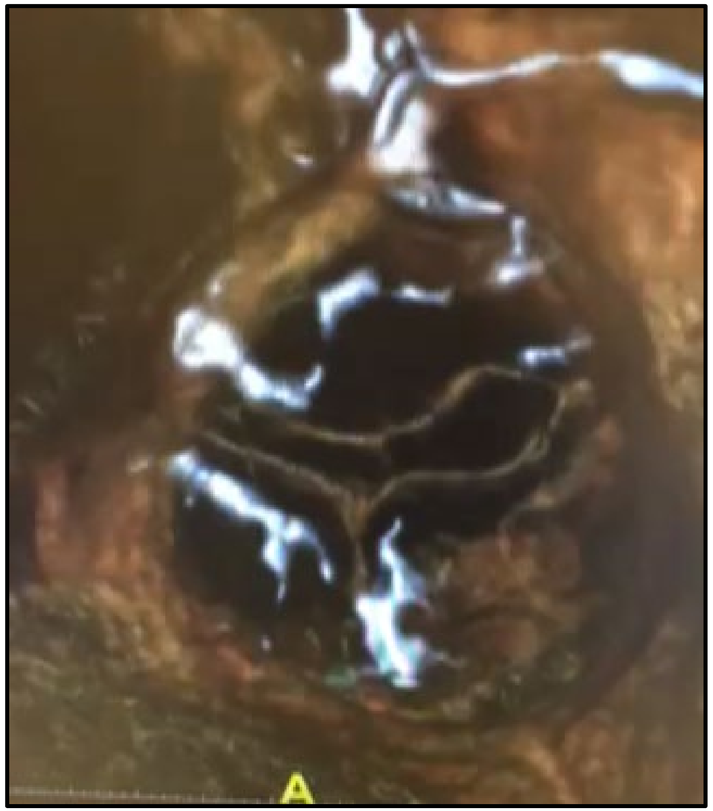
Intensive Lipid Lowering with Simvastatin and Ezetimibe in Aortic Stenosis

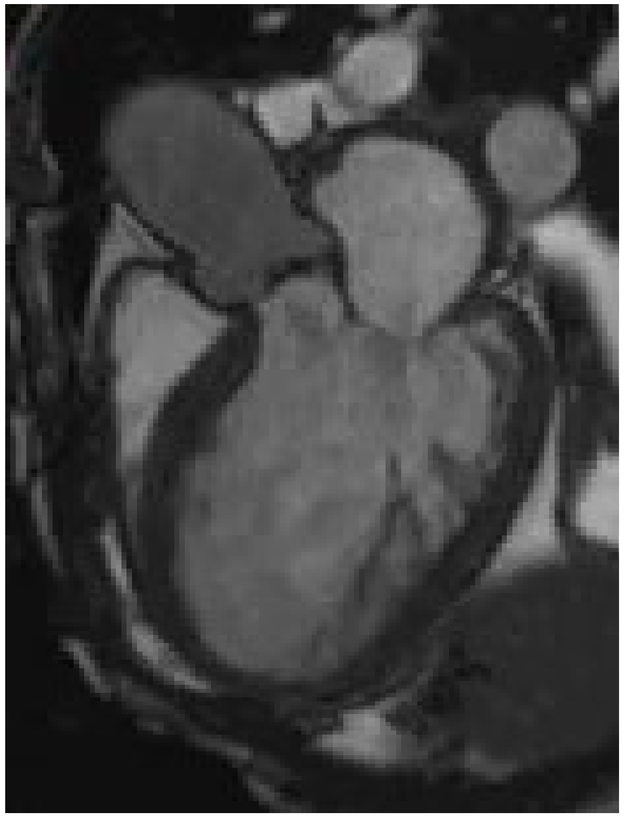
Anne B. Rossebø, M.D., Terje R. Pedersen, M.D., Ph.D., Kurt Boman, M.D., Ph.D., Philippe Brudi, M.D., John B. Chambers, M.D., Kenneth Egstrup, M.D., Ph.D., Eva Gerdts, M.D., Ph.D., Christa Gohlke-Bärwolf, M.D., Ingar Holme, Ph.D., Y. Antero Kesäniemi, M.D., Ph.D., William Malbecq, Ph.D., Christoph A. Nienaber, M.D., Ph.D., Simon Ray, M.D., Terje Skjærpe, M.D., Ph.D., Kristian Wachtell, M.D., Ph.D., and Ronnie Willenheimer, M.D., Ph.D., for the SEAS Investigators*

Edinburgh Heart Centre

Aortic Stenosis

A Disease of the Valve and the Myocardium





Pathophysiology

Potential Treatment Targets

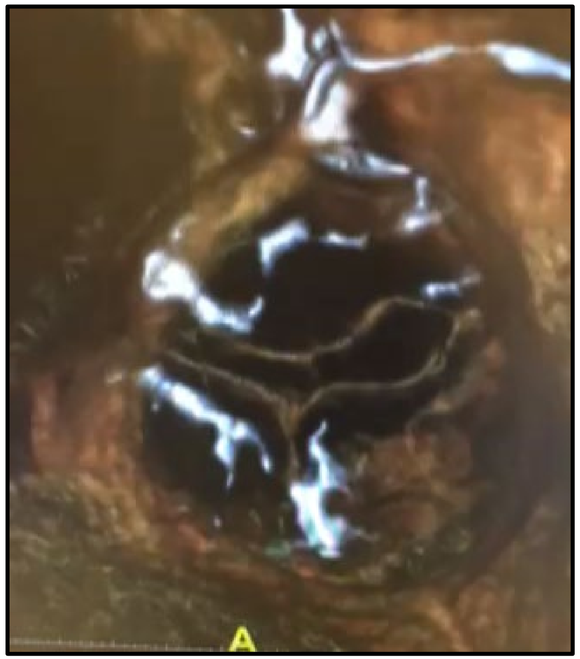
Trial design

Ongoing / Planned Studies

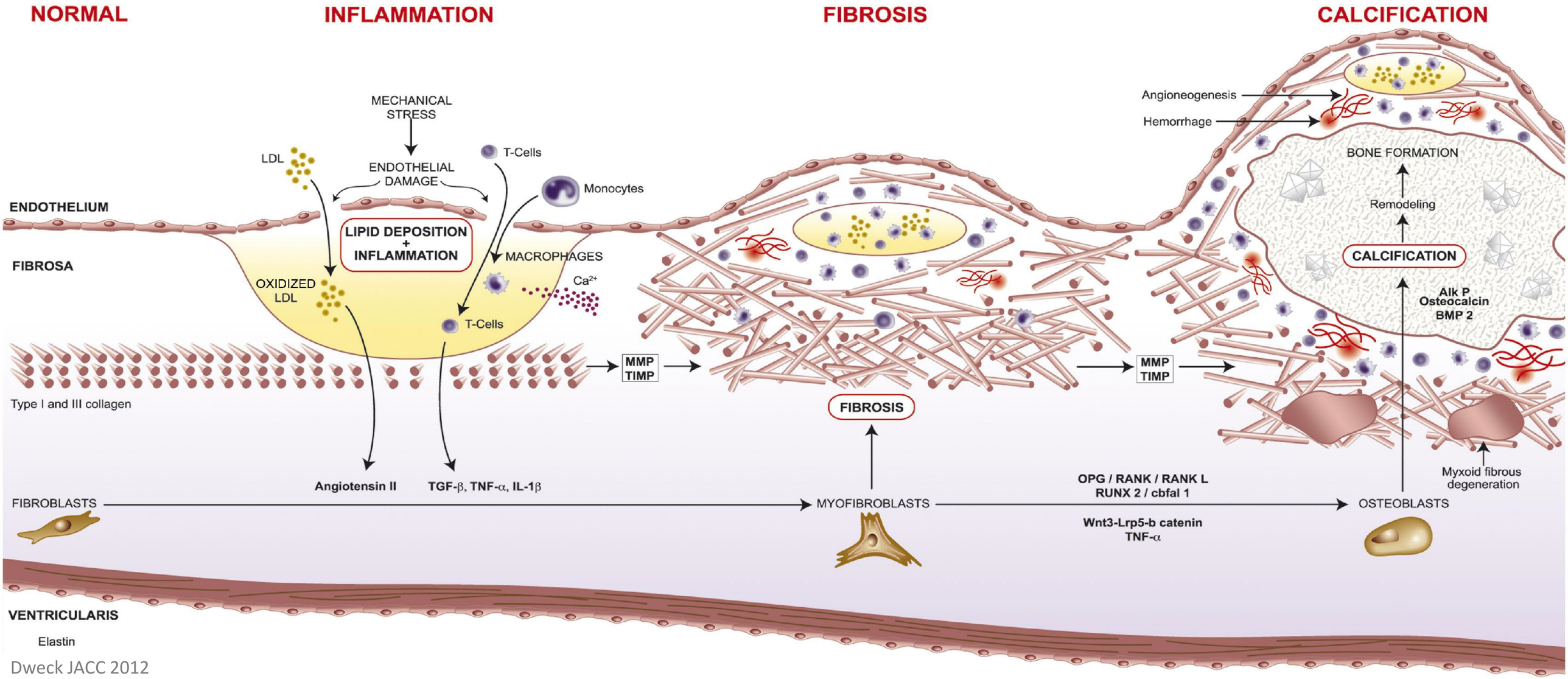
Dweck JACC 2012

Edinburgh Heart Centre

The Valve



The Valve – Pathogenesis



Dweck JACC 2012

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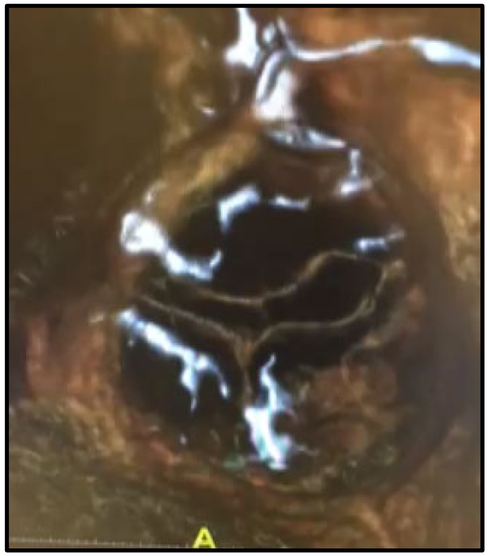
Design of Trials



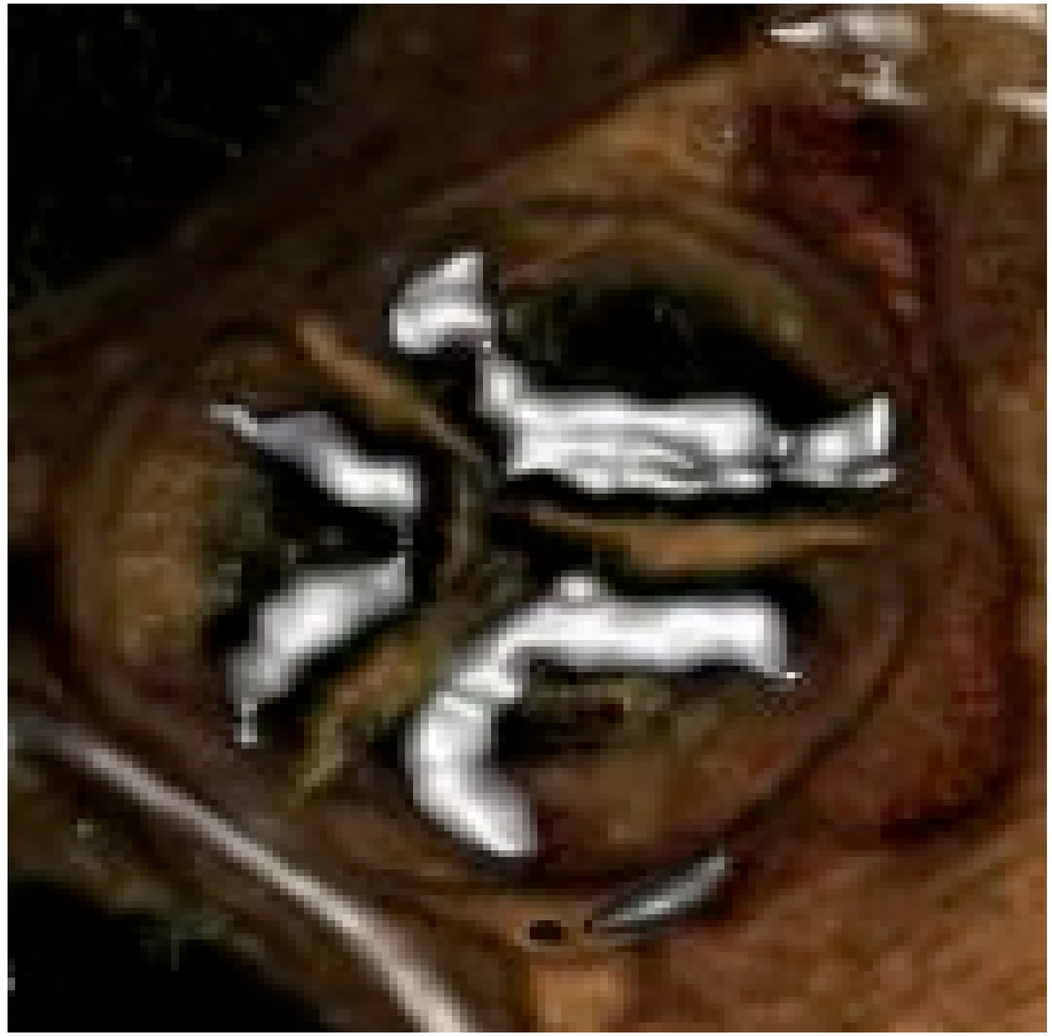
Clinical Endpoints

Phase 2 vs Phase 3 Trials

- AVR and Death
- Take many years if not decades to accrue
- Moving straight to phase 3 trials is a brave and expensive
- Strong need for Phase 2 Clinical Trials demonstrating an effect of the drug on disease progression
- AVR is dependent on the patients progressing to severe aortic stenosis

Assessing Disease Progression

- Echocardiography
- CT Calcium Scoring
- CT Fibrocalcific Scoring
- Positron Emission Tomography



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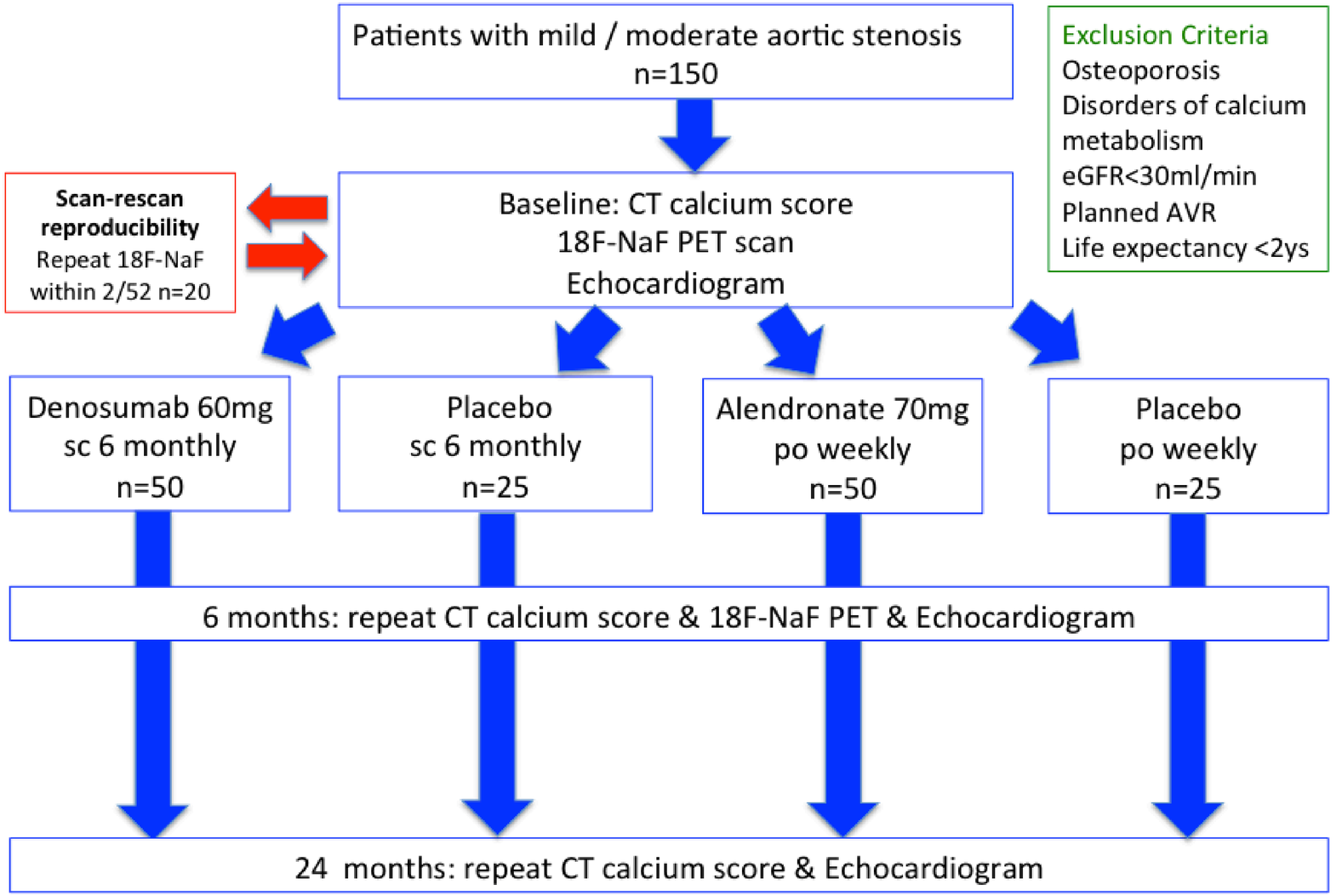
Recent & Ongoing Trials Using this Approach

SALTIRE 2

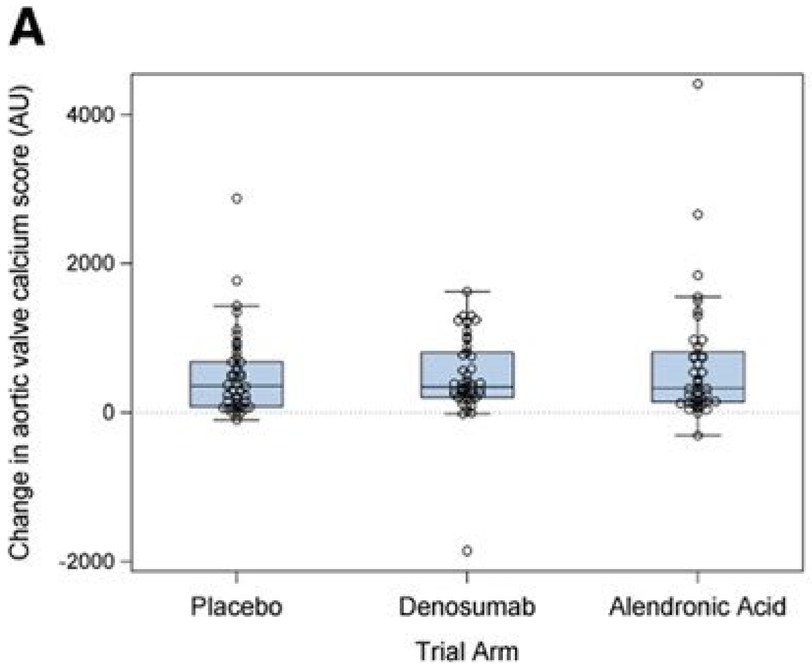


Pawade Circulation 2022

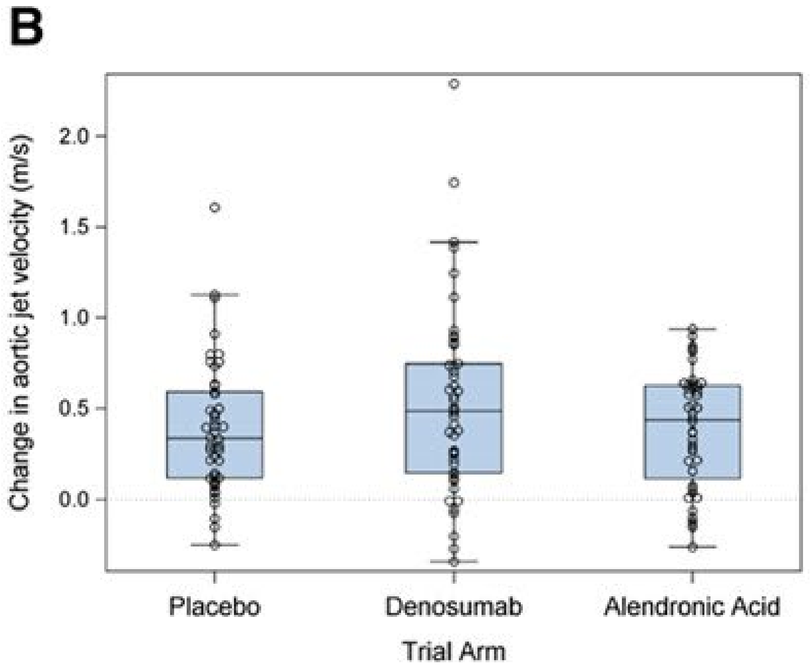
ClinicalTrials.gov NCT02132026

SALTIRE 2 – Neutral Outcomes

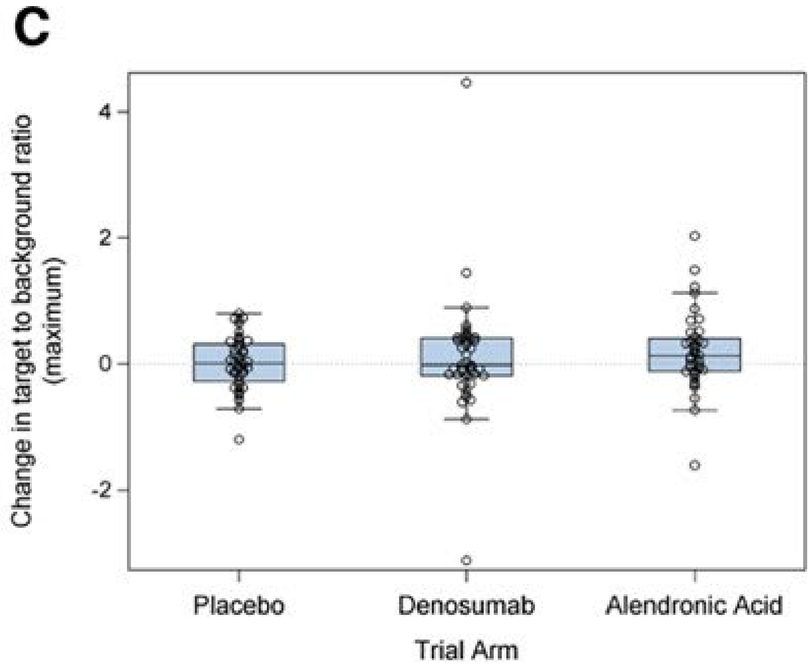
CT Calcium Score



Echo Peak Velocity



18F-Fluoride PET



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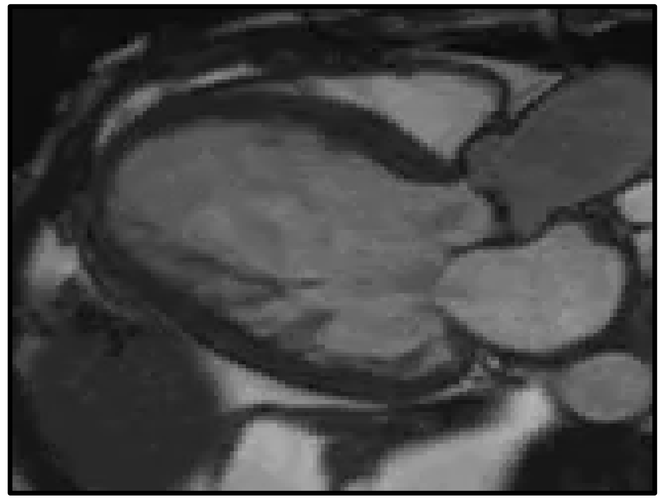
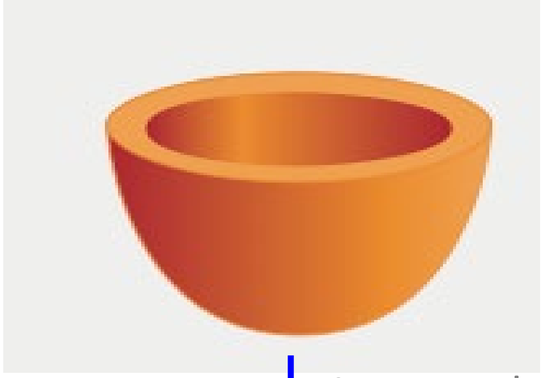
The Myocardium

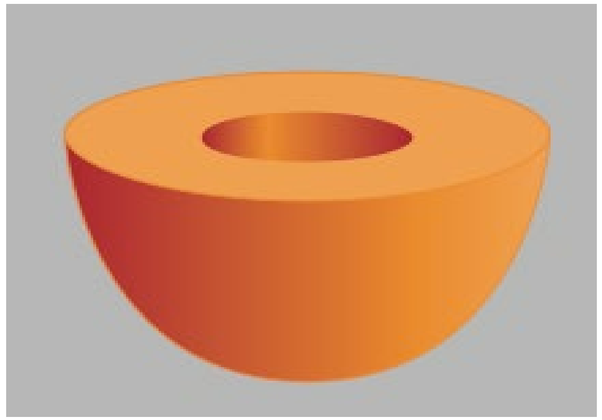


Normal

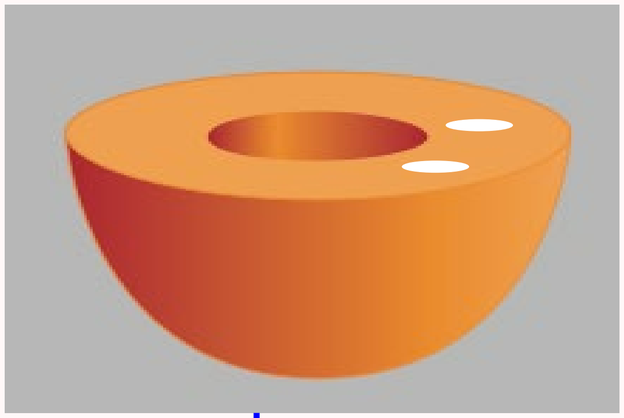


Increased afterload

LVH

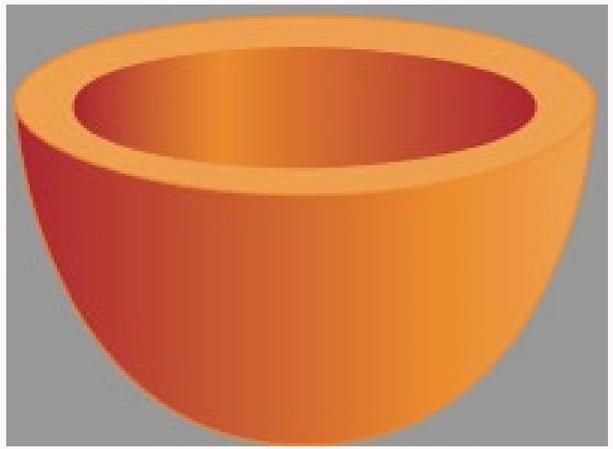


Myocyte Cell Death



Fibrosis

SYMPTOMS → AVR



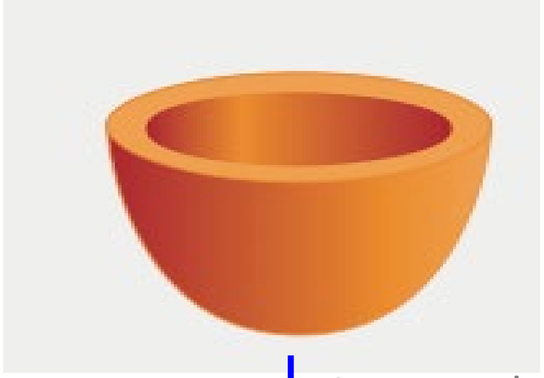
Heart Failure

Impact of Aortic Stenosis on the Myocardium

DECOMPENSATION

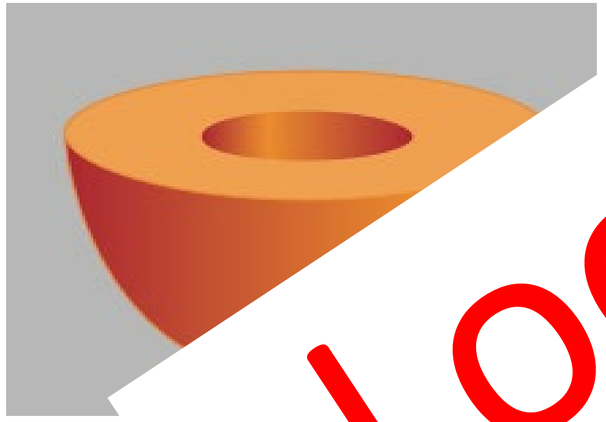
Adapted Dweck MR Aortic stenosis: a disease of the valve and the myocardium. J Am Coll Cardiol. 2012;60:1854-63 .

Normal



Increased afterload

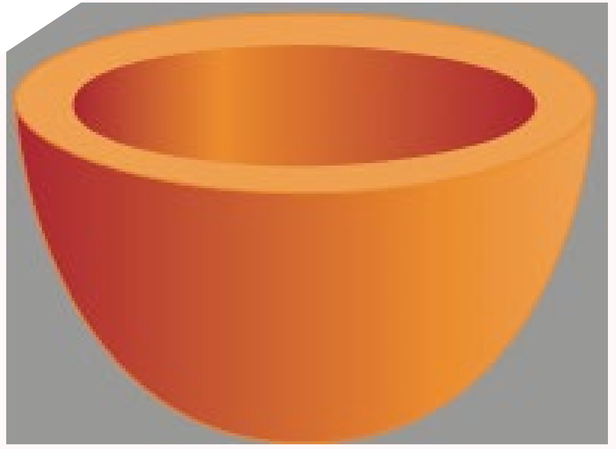
LVH



ATION

ibrosis

SYMPTOMS → AVR



Heart Failure

Looks a lot like HFpEF

Impact of Aort
Myoca

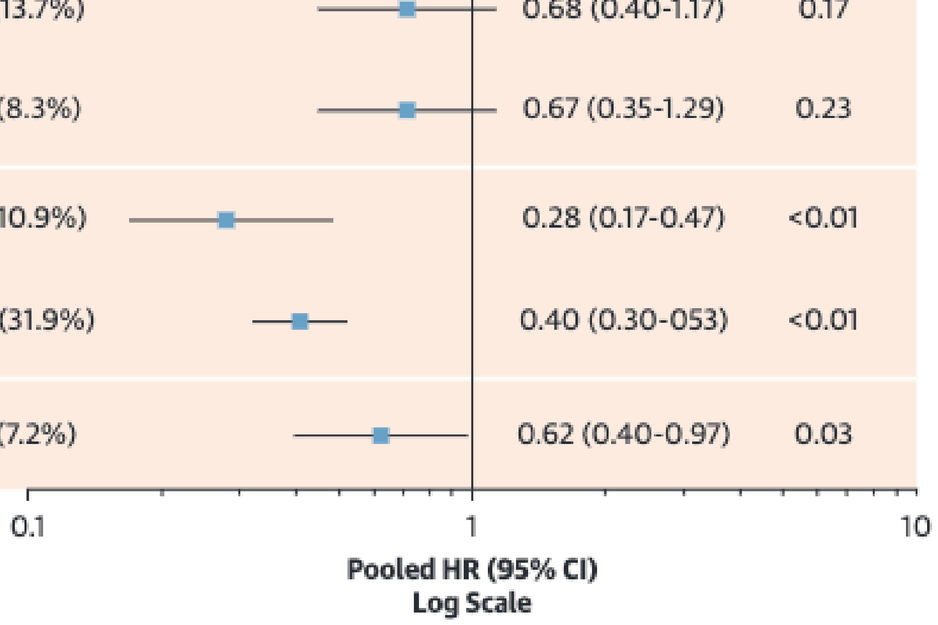
Adapted Dweck MR Aortic stenosis: a disease of the v myocardium.
J Am Coll Cardiol. 2012;60:1854-63 .

META-ANALYSIS

Consistent reduction in heart failure with early intervention

CENTRAL ILLUSTRATION Systematic Review and Study-Level Meta-Analysis of AVR vs Clinical Surveillance in Asymptomatic Severe Aortic Stenosis

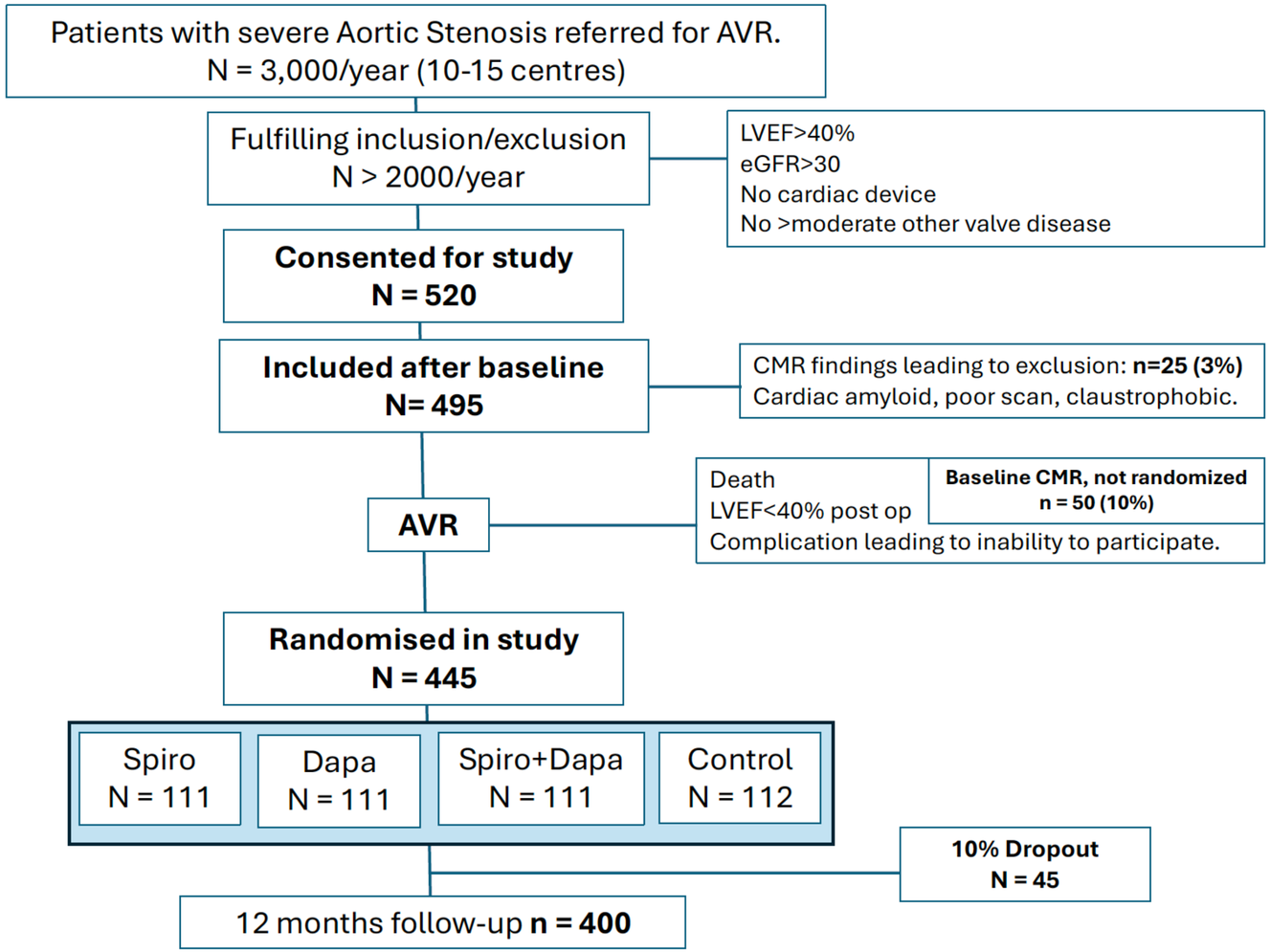
	Early AVR n/N (%)	Clinical Surveillance n/N (%)	Pooled HR* (95% CI)	*P* Value
All-Cause Mortality	70/719 (9.7%)	97/708 (13.7%)	0.68 (0.40-1.17)	0.17
Cardiovascular Mortality	37/719 (5.1%)	59/708 (8.3%)	0.67 (0.35-1.29)	0.23
Heart Failure Hospitalization	18/606 (3.0%)	65/597 (10.9%)	0.28 (0.17-0.47)	<0.01
Unplanned CV or HF Hospitalization	105/719 (14.6%)	226/708 (31.9%)	0.40 (0.30-053)	<0.01
Stroke	32/719 (4.5%)	51/708 (7.2%)	0.62 (0.40-0.97)	0.03



Généreux P, et al. JACC. 2025;85(9):912-922.

RELIEF-AS TRIAL

Can Dapagliflozin and Spironolactone Improve myocardial health in aortic stenosis?



NIHR170907

Conclusions

- Aortic stenosis remains perhaps the last major cardiovascular disease without a medical therapy
- The pathogenesis of aortic stenosis involves the valve and the myocardium
- In the valve it is useful to think in terms of the initiation and propagation phases – the latter is the better target for therapy
- The myocardial response shows many similar features to heart failure with preserved ejection fraction and therefore multiple candidate drugs
- There are multiple ongoing trials aiming to develop novel treatments that target both the valve and the myocardium

Medical Therapy for Valve Disease and The Role of ATA-301

Brian R. Lindman, MD, MSc

Vanderbilt University Medical Center

Medical Director, Structural Heart and Valve Center;
Associate Professor of Medicine

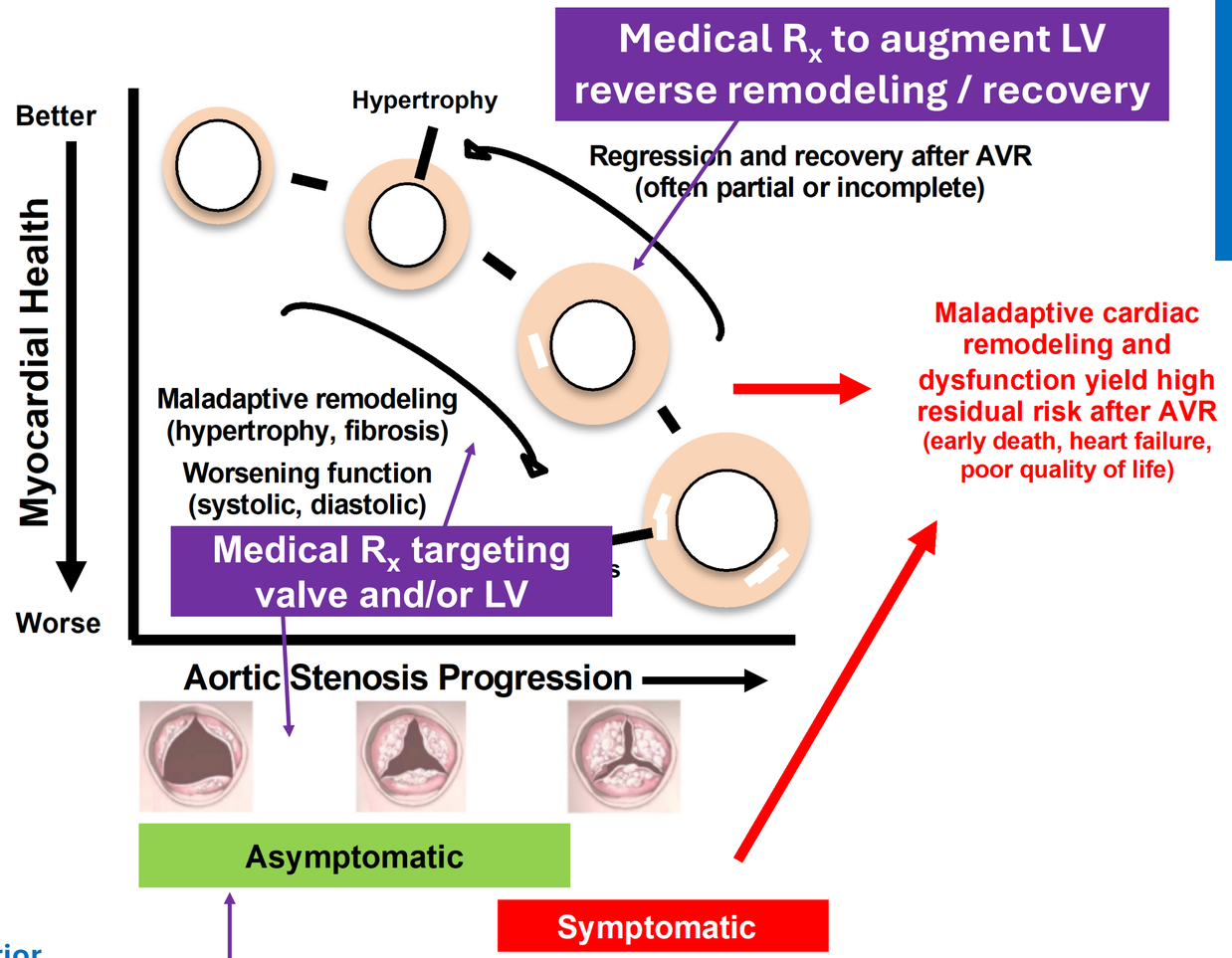
Strategies to Prevent and Mitigate Risk of Heart Failure in Calcific Aortic Stenosis

AS is a precipitant of and precursor to HF

Patients with progressive AS have stage B HF → usually transitions to stage C HF before or after AVR

Stage B HF: Structural heart disease but without signs or symptoms of HF

Stage C HF: Structural heart disease with prior or current symptoms of HF



Mitigating HF after AVR

Most patients treated with AVR have stage C HF with or without persistent HF symptoms or "HF in remission"

Modified from Lindman BR, Lindenfeld J. JAMA Cardiol. 2021;6:993-994

Opportunities For Medical Therapy Along The Spectrum Of AS Severity

AVA

Trials would need to be unreasonably large and long

1.8 - 2.0

1.3

1.0

AVR

Aortic sclerosis

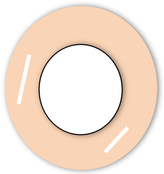
Mild AS & early moderate AS

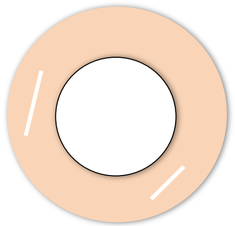
Late moderate AS

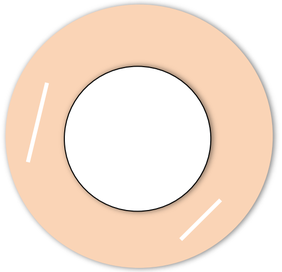
AVR?? (symptomatic or remodeling/dysfxn)

Post-AVR

Size of valve or ventricle represents size of opportunity

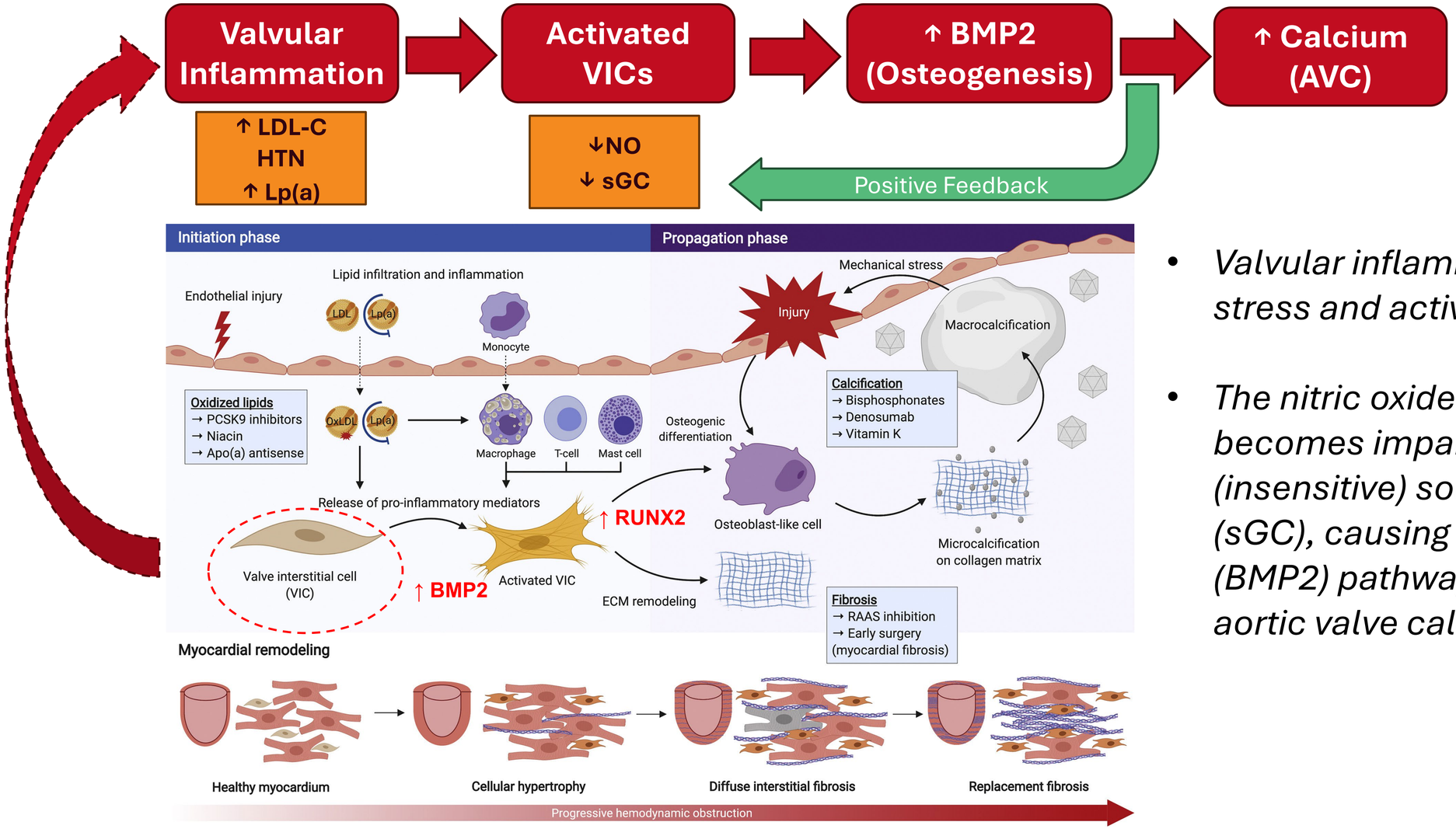






Ataciguat Overview

CAVS: Mechanism of Disease Activation & Propagation of valvular interstitial cells (VICs) is central to CAVS



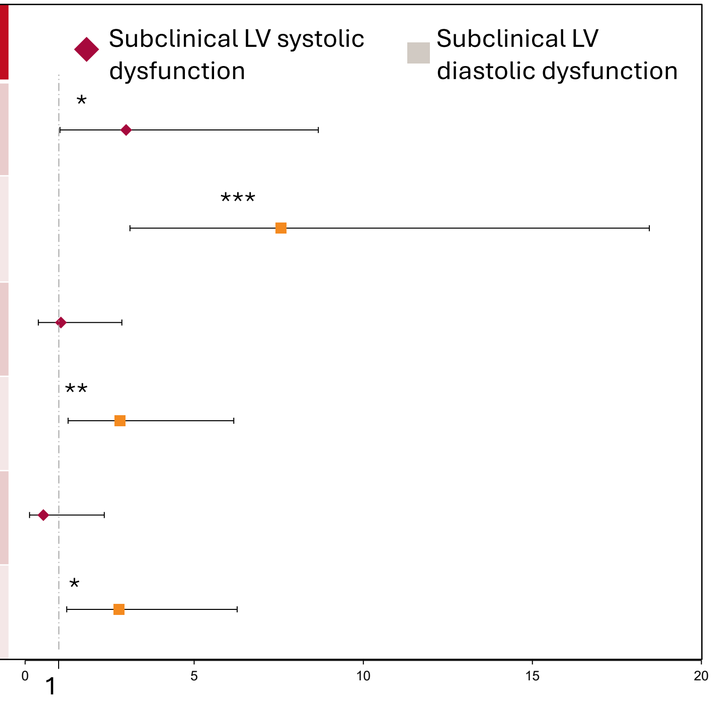
- *Valvular inflammation causes oxidative stress and activates VICs*
- *The nitric oxide (NO) signaling pathway becomes impaired from oxidized (insensitive) soluble guanylate cyclase (sGC), causing activation of osteogenic (BMP2) pathways and an increase in aortic valve calcium (AVC) deposition*

Modified from Zheng KH, et al. Cardiol Clin. 2020 MID: 31753168.

Correlation of AVC Deposition with Cardiac Function

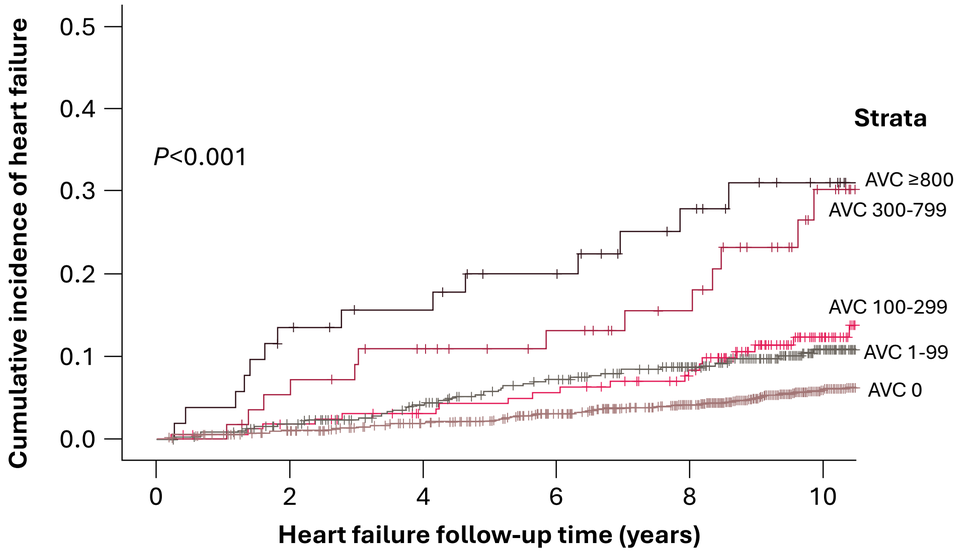
Left ventricle functionality[1]

AVS Characteristic	Odds Ratio (95% CI)
Calcification, ≥2 leaflets	2.99 (1.03–8.67)
	7.57 (3.10–18.46)
Calcification, one leaflet	1.06 (0.39–2.86)
	2.8 (1.27–6.17)
Thickening	0.54 (0.13–2.34)
	2.78 (1.23–6.27)



* *P* <0.05; ** *P* ≤0.01; *** *P* <0.001

Cumulative incidence of heart failure according to the AVC categories[2]



Number at risk

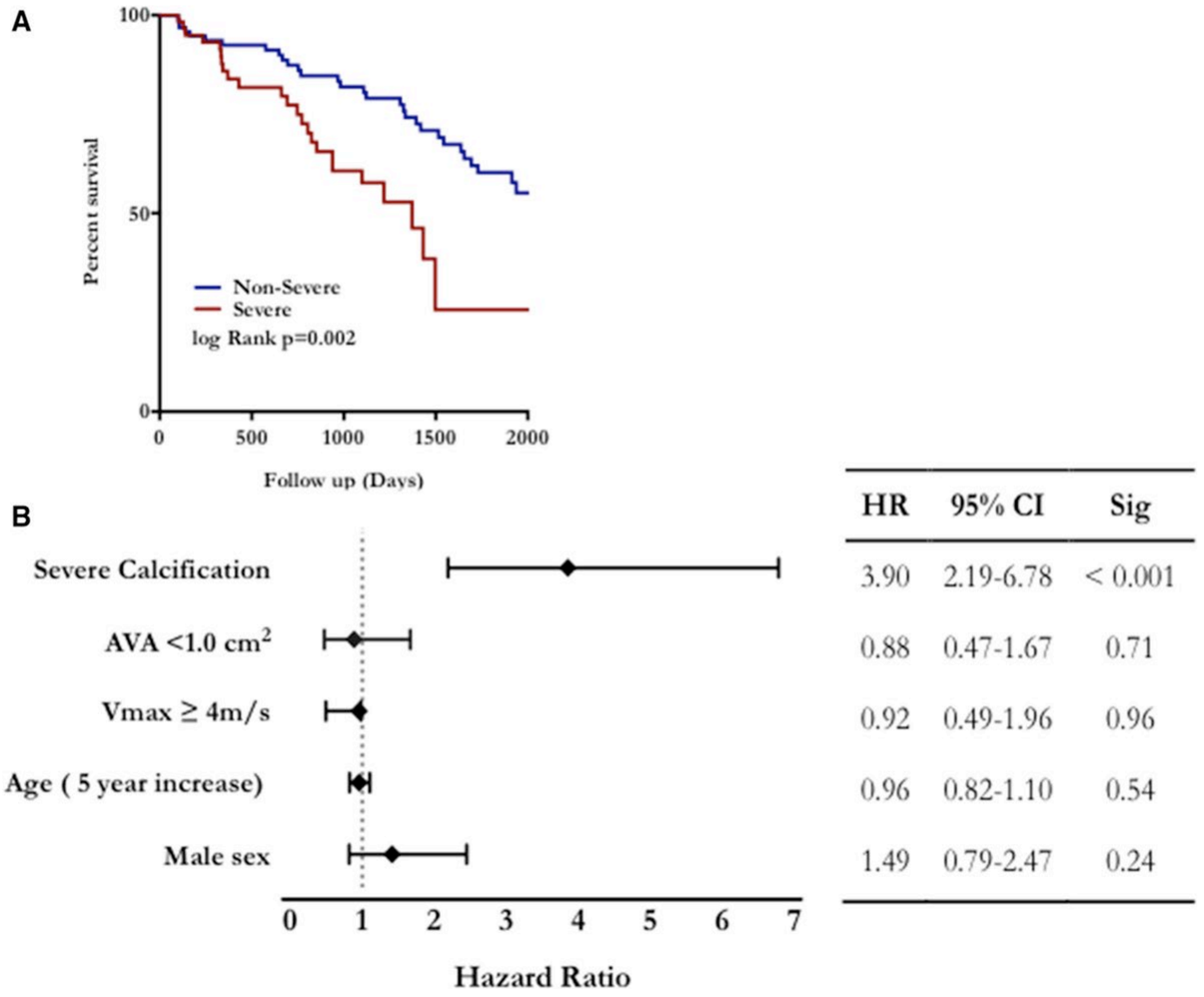
Strata						
AVC 0	1601	1562	115	1445	1347	714
AVC 1-99	474	454	420	390	356	203
AVC 100-299	165	159	150	145	130	74
AVC 300-799	56	52	46	40	34	18
AVC ≥800	52	44	39	34	26	19

As CAVS progresses, AVC deposition correlates with impairment of cardiac structure and decline in function[1,2]

[1]Yoshida et al. *European Journal of Preventative Cardiology* (2023).
[2]Zhu et al. *Circulation: Cardiovascular Imaging* (2023).

Aortic Valve Calcification (AVC) is Strongest Predictor of Risk - Higher than AVA and Vmax

- Severe calcification associated with adverse prognosis
- AVC was only independent predictor of:
  - Aortic valve replacement
  - Death
- Severe AVC had 3- to 4-fold increased risk

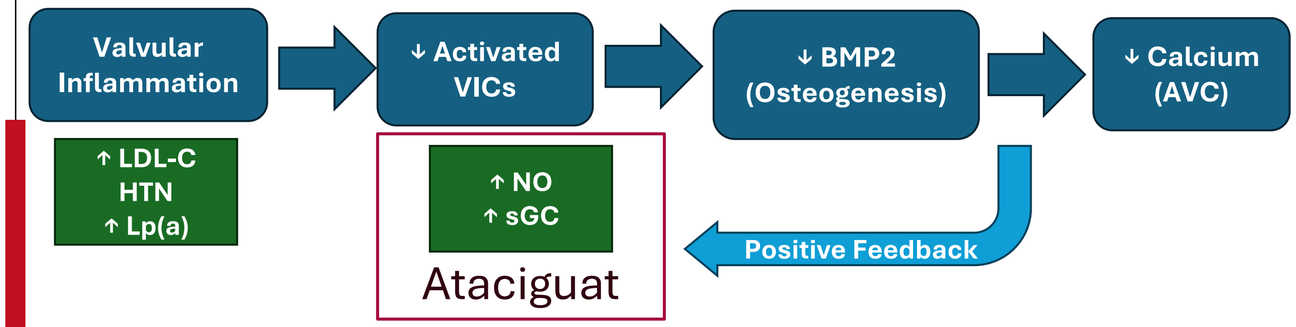


	HR	95% CI	Sig
Severe Calcification	3.90	2.19-6.78	< 0.001
AVA <1.0 cm²	0.88	0.47-1.67	0.71
Vmax ≥ 4m/s	0.92	0.49-1.96	0.96
Age (5 year increase)	0.96	0.82-1.10	0.54
Male sex	1.49	0.79-2.47	0.24

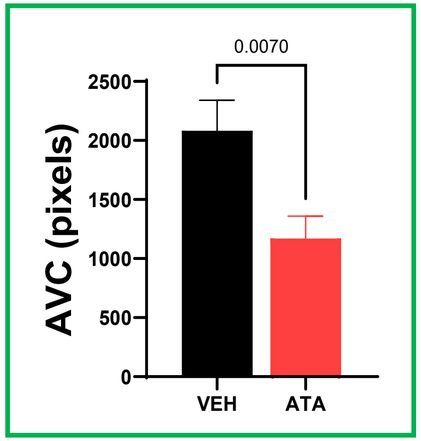
Pawade, Circ Imaging, 2018
DOI: 10.1161/CIRCIMAGING.117.007146

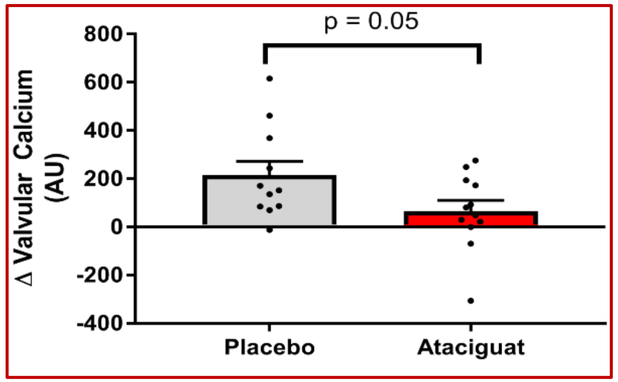
Ataciguat for CAVS: Therapeutic Hypothesis

Ataciguat Mechanism of Action



Preclinical & Clinical Evidence with Ataciguat





- Ataciguat is a unique sGC activator/stimulator that preferentially targets valvular oxidized sGC, unlike previously approved sGC stimulators
- Ataciguat reactivates the NO signaling pathway in VICs, reducing osteogenesis & aortic valve calcium

- Preclinical evidence demonstrates an ~50% reduction in aortic valve calcium (AVC) in CAVS mice
- In a phase II study of patients with moderate CAVS, treatment with Ataciguat resulted in a 50-60% reduction in AVC compared to placebo after 6 months and was associated with improvements in ventricular structure & function without observed effects on blood pressure

Summary of ATA Clinical Experience

- Ataciguat: NO-independent soluble guanylate cyclase activator with negligible systemic vascular effects
- No inotropic effects
- Dosed orally, 200 mg, once daily
- Hepatic clearing; potential for CYP and P-gp drug-drug interaction

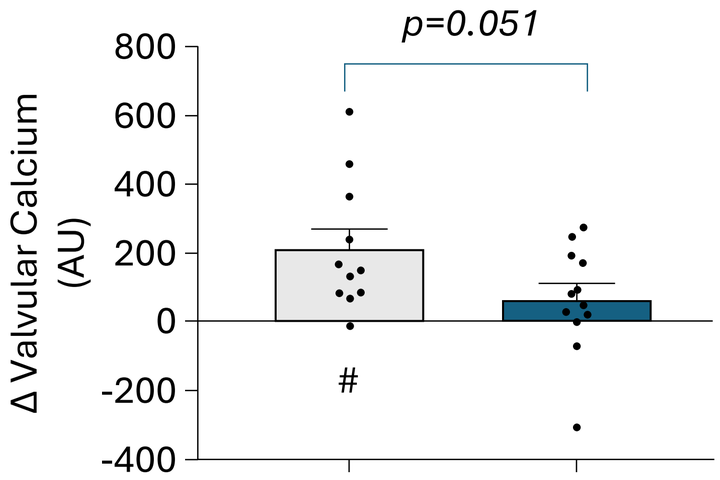
- **A total of 22 clinical studies (n= 999 patients)**
  - Mean SBP reduction – 1mmHg
  - 4 indications: peripheral arterial disease (N=330), coronary artery disease (N=32), angina (N=257), neuropathic pain (N=59)
    - No unfavorable safety signals
- **Two clinical studies in AS (n= 67 patients)**
  - Phase 1b: orthostatic BP
    - No Hypotension in mild/mod AS
  - Phase 2: moderate calcific Aortic Stenosis
    - Reduced AVC progression at 6m

Kardigan data on file

Key Endpoints

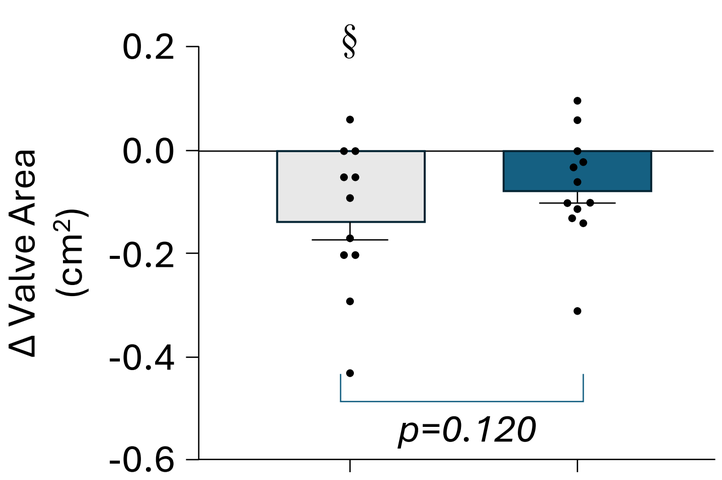
Change from baseline to 6 months

Primary endpoint: AVC



	Placebo	Ataciguat
N	11	12
Baseline values	1208	1056

AVA_{CE}



Placebo	Ataciguat
11	12
1.33	1.36

But there was little mean change in **transvalvular parameters:**

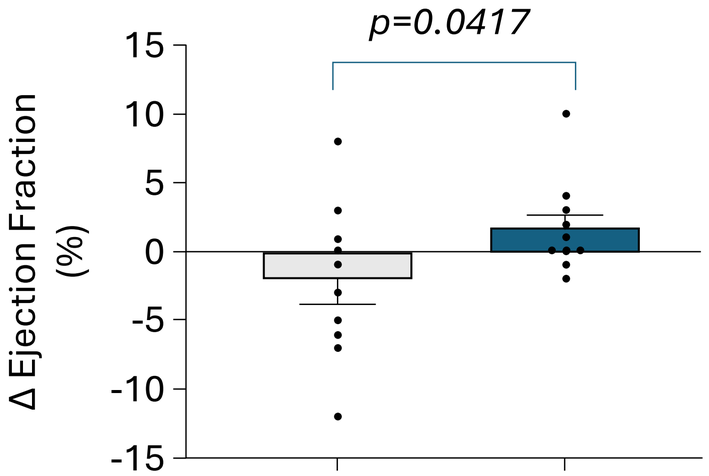
	Placebo (n=11)		**Ataciguat** (n=12)	
	Baseline	**6 mo**	**Baseline**	**6 mo**
Peak gradient	26±7	28±8	26±7	29±9
Peak velocity	3.3±0.4	3.4±0.5	3.2±0.4	3.4±0.6

Zhang et al, *Circulation*. 2025.
#, change from baseline *P*=0.004; §, change from baseline *P*=0.015.
AVA_{CE}, aortic valve area by continuity equation; AVC, aortic valve calcium; mo, months.

Measures of Cardiac Function

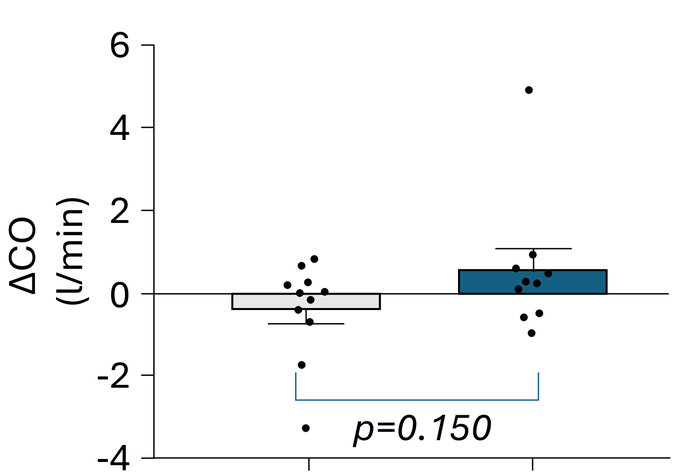
Change from baseline to 6 months

LVEF[1]



	Placebo	Ataciguat
N	11	12
Baseline values	64%	65%

Cardiac output[2]



Placebo	Ataciguat
11	10
6.3	6.3

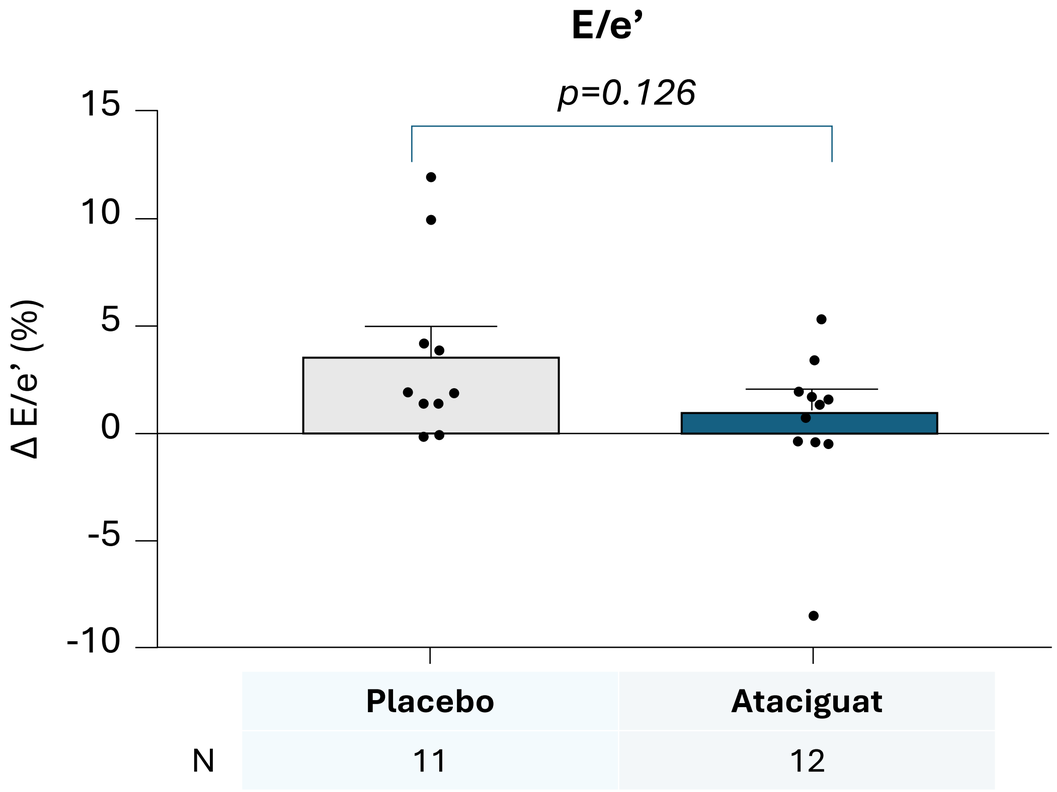
Ataciguat treatment improved LVEF and tended towards improved CO[1,2]

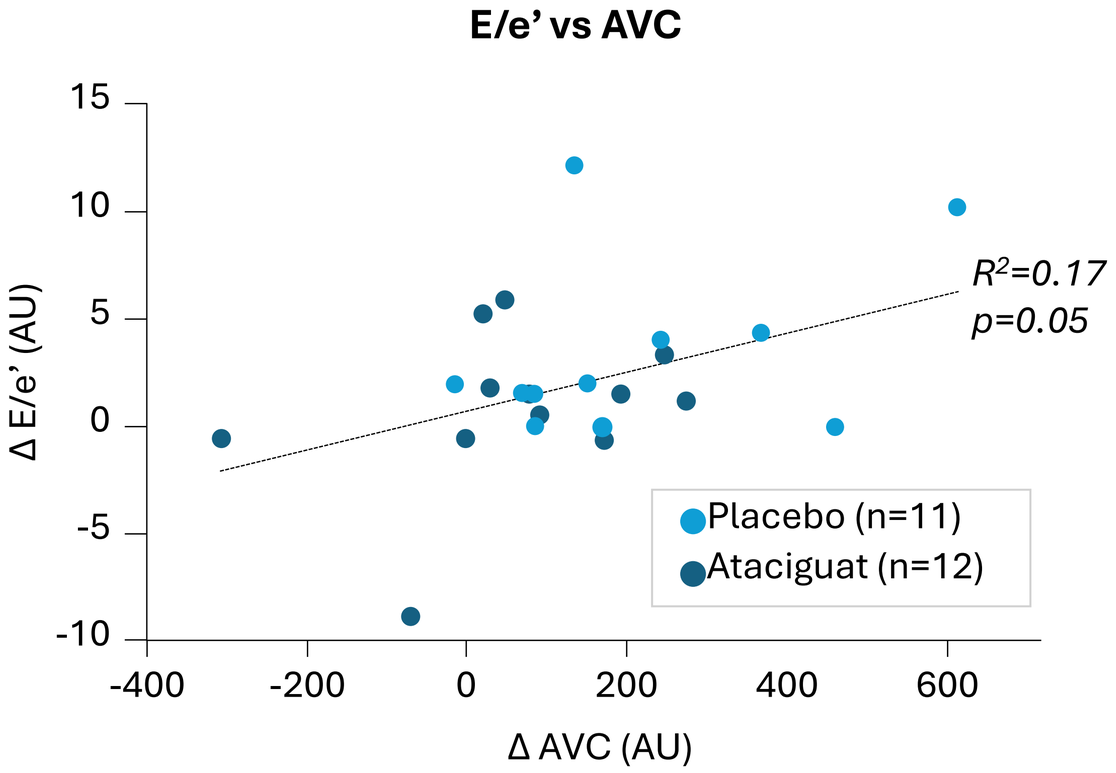
Participants with the least increase in AVC generally had the largest increase in CO, and improvements in CO were more frequent in those treated with ataciguat compared with placebo[2]

[1]Zhang et al, *Circulation*. 2025. [2]Data on file.
AVC, aortic valve calcium; CO, cardiac output; LVEF, left ventricle ejection fraction.

Changes in Diastolic Dysfunction

Change from baseline to 6 months





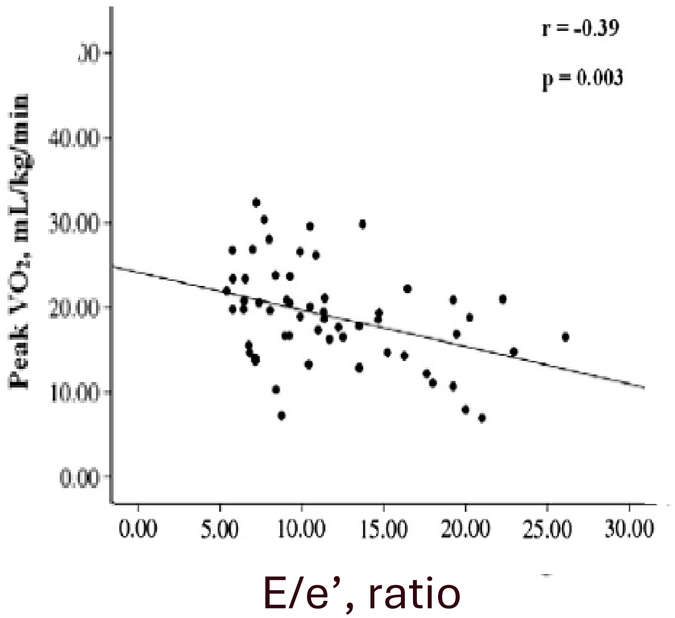
Ataciguat tended to slow worsening of E/e', and increases in AVC correlated with worsening E/e'

Zhang et al, *Circulation*. 2025.

AU, arbitrary units; AVC, aortic valve calcium; E/e', ratio early mitral inflow velocity to mitral annular diastolic velocity.

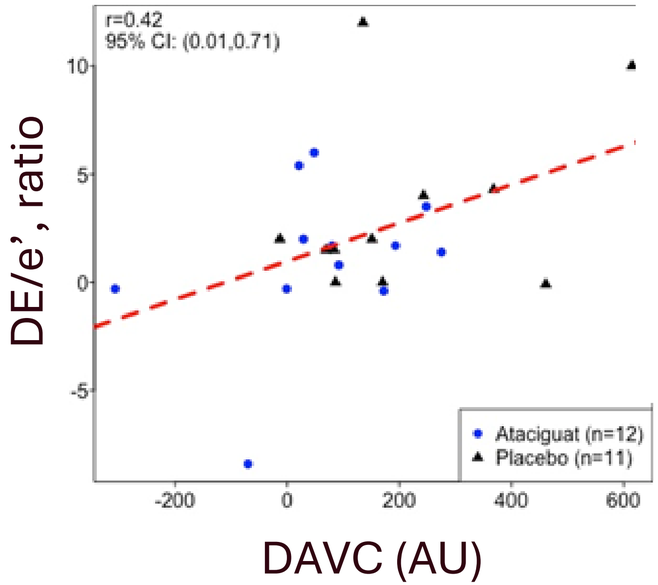
Hypothesis: Slowing AVC deposition associated with preserved pVO2

pVO_2 Correlates w/ Diastolic Function



Dulgheru, Intl J Cardiol. 2013
DOI: 10.1016/j.ijcard.2013.01.205

- **AVC Progression Correlate w/ Diastolic Function**



Kardigan data on file

Slowing AVC Progression w/ Ataciguat Projected to Preserve Cardiopulmonary Function

Addition Ataciguat Projections:

- **Reduced LV mass increase**
- **Reduced Symptoms**
- **Reduced Diastolic Dysfunction**
- **Reduced Systolic Dysfunction**
- **Reduced AVA narrowing**
- **Prolonged time before AVR**

Changes in Calcific Aortic Stenosis Associated with Changes in AV and Cardiac Measures

Δ Aortic Valve Calcification

→ Δ Aortic Valve Function
(Thickening, Compliance and Area)

→ Δ Cardiac Structure & Function
(Systolic and Diastolic Fx, LV Mass)

→ Projected Benefits
Δ Symptoms
Δ Cardiopulmonary Fx

KATALYST-AV

A Two-Part Adaptive Phase 3, Randomized, Double-Blinded Placebo Controlled Study Checking the Efficacy and Safety of Ataciguat to Slow the Progression of Valvular Dysfunction in Participants with Moderate Calcific Aortic Valve Stenosis

- **What is the effect of ataciguat on slowing the progression of AVC?**
- **How does the change in AVC correlate with echocardiographic measures (e.g., diastolic function)?**
- **How do these changes relate to symptoms and cardiopulmonary function?**
- **What is the direct effect of ataciguat on cardiopulmonary function?**

https://clinicaltrials.gov/study/NCT07001800

Phase 3 KATALYST-AV Clinical Trial (Currently Recruiting)

A phase 3, randomized, double-blind, placebo-controlled trial investigating the efficacy of ataciguat in slowing the progression of valvular dysfunction in adults with moderate CAVS

N=1410 (estimated)

KATALYST-AV Phase III Trial Design, NCT07001800[1]

Inclusion Criteria

- ≥50 years of age
- Moderate CAVS as defined by:
  - AVA ≥1 cm^2 to ≤1.50 cm^2
  - AVC score ≥600 to 1200 AU (women) or ≥600 to 2000 AU (men)
- LVEF ≥45% at screening
- Can perform CPET
- No prior or planned AV intervention
- No known congenital AV disease
- No evidence of heart failure

$R_{1:1}$

Ataciguat
QD ≤156 weeks

Placebo
QD ≤156 weeks

Part A

Primary Endpoints:
- Change in AVC at week 24

Secondary Endpoints:
- Change in AVC and pVO_2 correlation at week 48
- Change in pVO_2 at week 48
- Change in LVMI at week 48
- Change in KCCQ-23 at week 48

Part B

Primary Endpoints:
- Change in pVO_2 at week 48
- Percent change in AVA at week 48

Secondary Endpoints:
- Change in AVC at week 48
- TTD to proceed with TAVR/SAVR or all-cause death
- Percent with progression to AVA <1.0 cm^2 at week 48

*Safety, tolerability, and pharmacokinetics will also be evaluated.

https://clinicaltrials.gov/study/NCT07001800

American Heart Association®

Expanding Research Capacity for Medical Therapy in Moderate Aortic Stenosis

Sreekanth Vemulapalli, MD

Duke University, Duke University Health System
Associate Professor of Medicine / Cardiology;
Medical Director, Duke Echo Lab and Cardiac Diagnostic Unit;
Member, Duke Clinical Research Institute;
Member, Duke-Margolis Institute for Health Policy

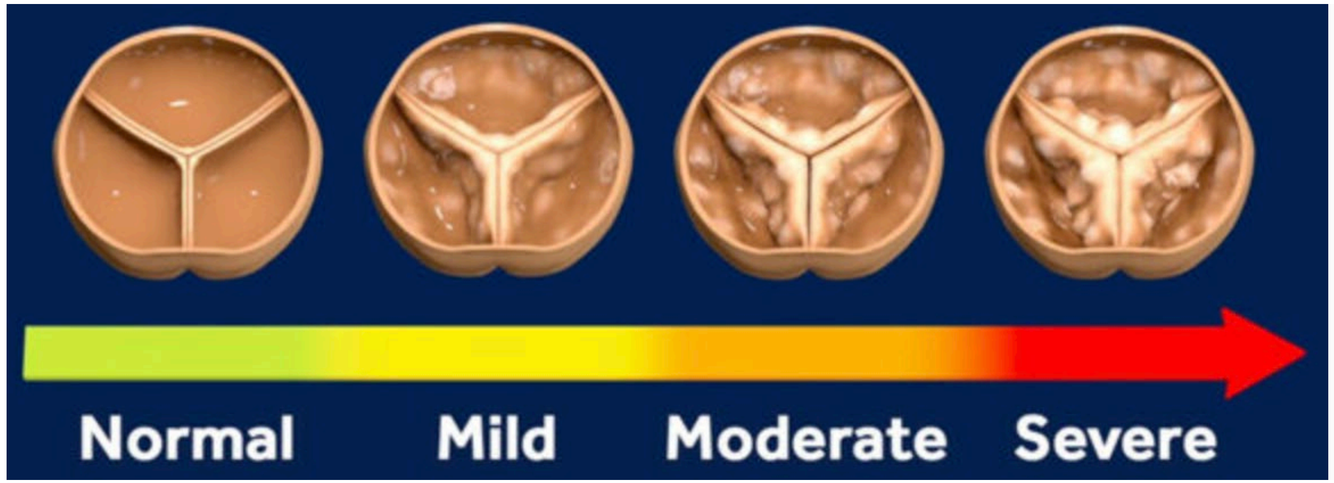
OUTLINE

Advancing medical therapy in a space **historically dominated by interventional trials**

Leveraging registry-to-trial strategies to **identify eligible patients based on real-world data**

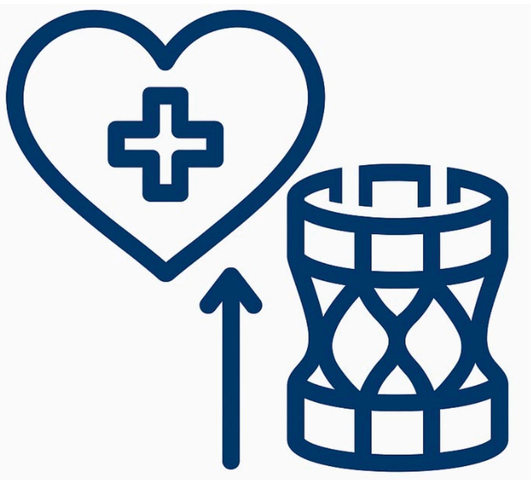
Building **Research Capacity** and **Quality in Moderate Aortic Stenosis**

ROLES FOR MEDICAL THERAPY IN AORTIC STENOSIS



Lp(a)* Ataciguat*

AVR



SGLT2i

ACEi/ARB

**Investigational, Ongoing clinical trial in progress*

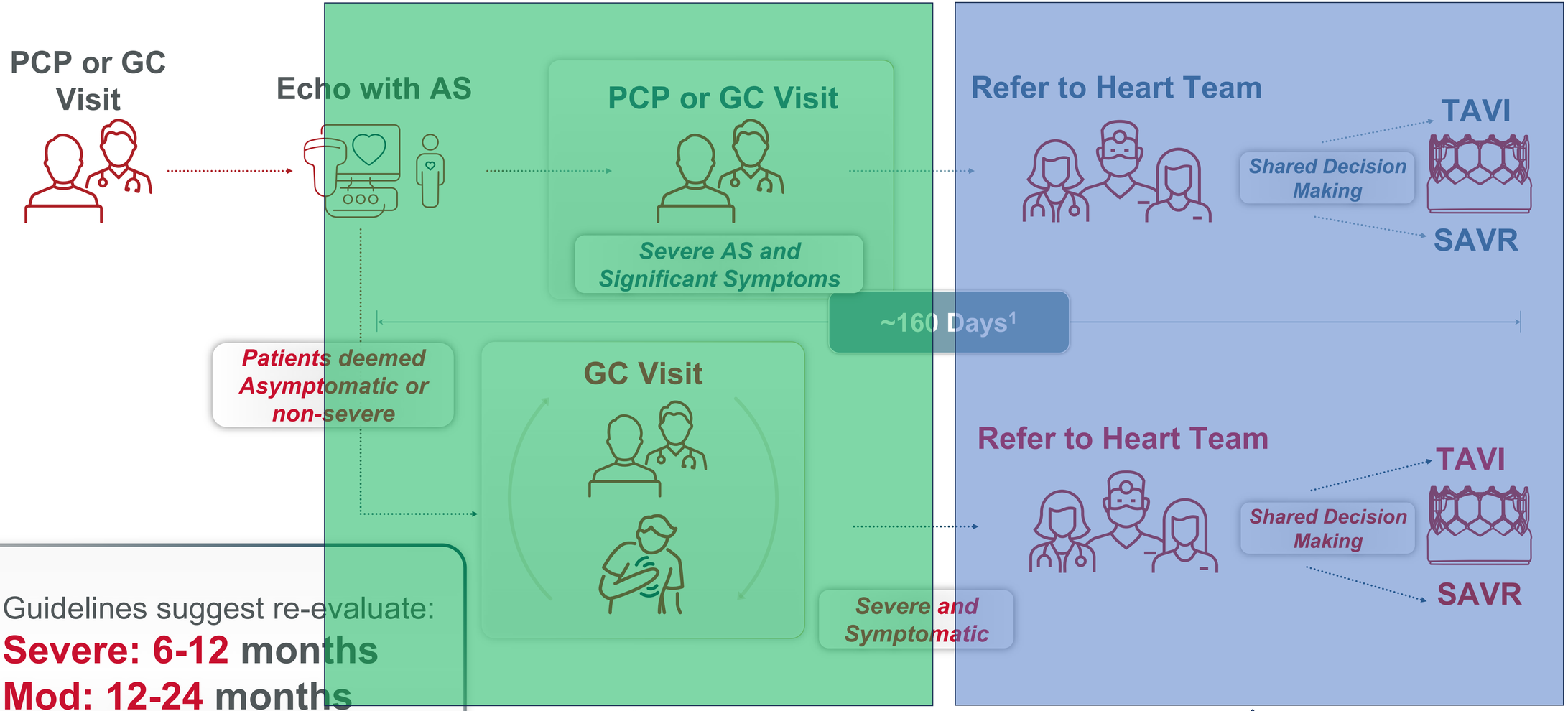
Raposeiras-Roubín S, Amat-Santos IJ, Rossello X, et al. N Engl J Med. 2025;392:1396-1405. PMID: 40162639.
Inohara T, Manandhar P, Kosinski AS, et al. JAMA. 2018;320:2231-2241. PMID: 30512100.

MEDICAL THERAPY VS. DEVICE TRIALS IN MODERATE AS

	PROGRESS	EXPAND TAVR II	KATALYST-AV
Inclusion Criteria	Age ≥ 65	Age ≥ 65	Age ≥ 50
	Moderate AS	AVA ≥ 1.0, ≤ 1.5 cm^2 and max velocity ≥ 3.0, < 4.0 or Mean gradient ≥ 20, < 40 mm hg	AVA ≥ 1 to ≤ 1.5 cm^2
	Symptoms or cardiac damage	Symptoms or Ca++ score or NYHA class	LVEF ≥ 45%
Exclusion Criteria	Not anatomically suitable for transfemoral TAVR	Not anatomically suitable for transfemoral TAVR	CAD or expected coronary stenting
	Severe AR	Cardiac amyloidosis	Moderate, moderate to severe, or severe mitral stenosis, mitral regurgitation, and/or aortic regurgitation
	AVR or prior AV intervention	Class I indication for cardiac surgery	Long-standing permanent or persistent AFib
	LVEF < 20%	LVEF < 20	NYHA III or IV

American Heart Association®
Target: Aortic Stenosis™

The Current Treatment Pathway for Severe AS



Guidelines suggest re-evaluate:

Severe: 6-12 months

Mod: 12-24 months

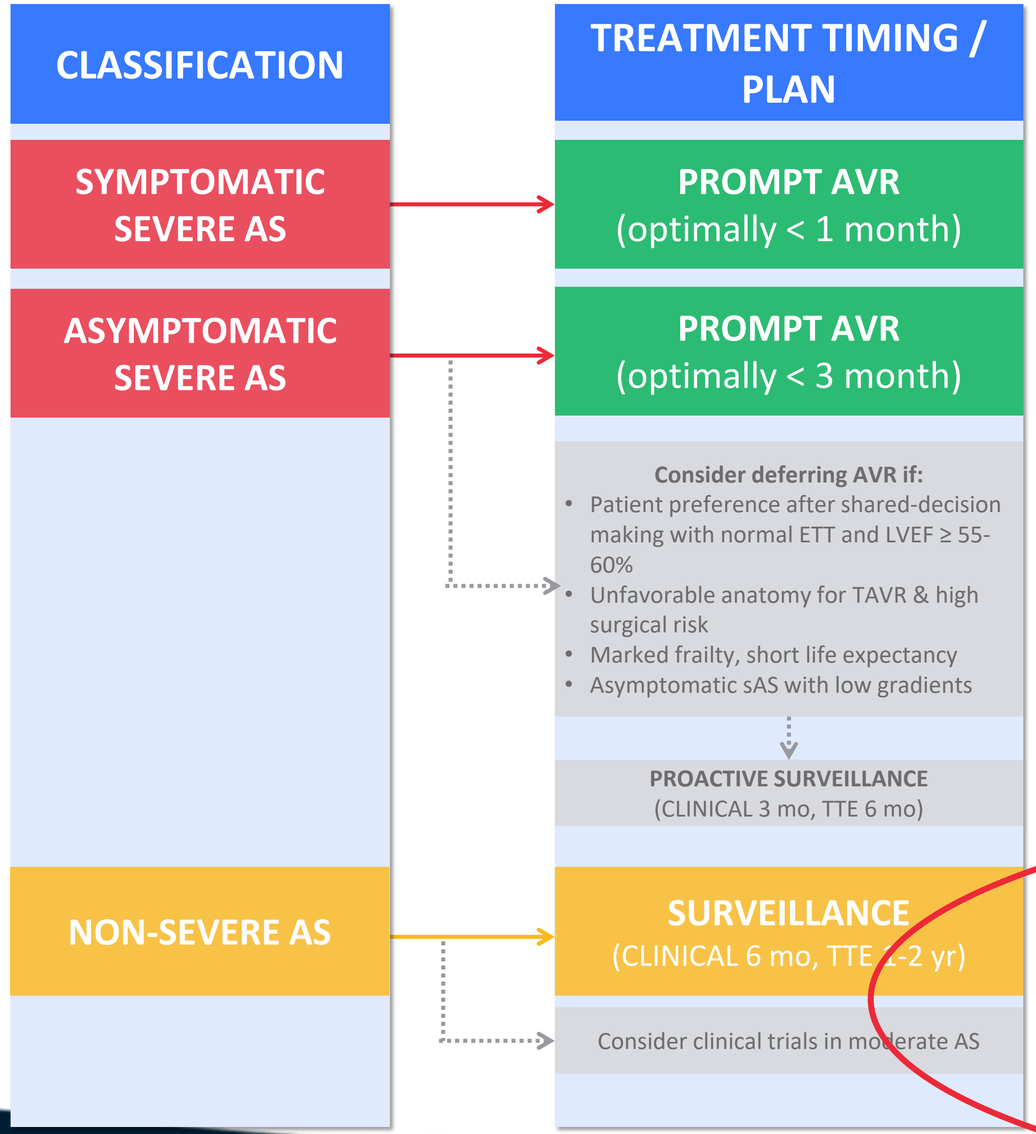
Mild: 3-5 years

Moderate AS Trials

Severe AS / Device Trials

Sethi et al, The Cost of Waiting for a Transcatheter Aortic Valve Replacement in Medicare Beneficiaries With Severe Aortic Stenosis, Structural Heart 2024.

Treatment Timing and Plan



Symptomatic severe AS

- AVR within 1 month, prioritization if needed
- Mortality cost to delay

Asymptomatic severe AS

- Favor prompt AVR, <3 months
- Consider deferral in selected patients

Proactive surveillance

- Partnership between HVT and referrer
- More vigilant than every 6-12 months
- Incorporate digital tools for scale

Moderate AS

- Clinical surveillance
- Clinical trials testing AVR or medical therapy in select patients

Cook et al. International Expert Perspective on Early Referral, Streamlined Evaluation, and Prompt Treatment of Patients with Aortic Stenosis. JACC 2025 (in press).

HOW TO IDENTIFY PATIENTS WITH MODERATE AS

ICD 10 coding: Low sensitivity for severity < severe

Echo databases

Egnite / Tempus, etc.: Software using NLP to identify severity of AS

Existing Registry Data:

- **Society of Thoracic Surgeons (STS):** Majority of patients undergoing AVR have severe AS
- **Transcatheter Valve Therapies (TVT):** Currently essentially all severe AS
- **Target: Aortic Stenosis™ (Target: AS):** Sample of patients with moderate and severe AS

EXAMPLE: KATALYST-AV Trial

Inclusion
Age ≥ 50
AVA ≥ 1 to ≤ 1.5 cm^2
AVC score ≥ 600 – 1200 AU (Women); AVC score ≥ 600 – 2000 AU (Men)
LVEF ≥ 45%
Able to perform CPET
Exclusion
Prior AV replacement / repair / intervention
Moderate, moderate to severe, or severe mitral stenosis, mitral regurgitation, and/or aortic regurgitation
Bicuspid aortic valve / congenital aortic valve disease
NYHA III or IV
Cardiomyopathy or myocarditis or congenital heart disease
Coronary artery disease or anticipating coronary stenting
Abnormal ECG or long-standing persistent or permanent Afib

EXAMPLE: KATALYST-AV Trial

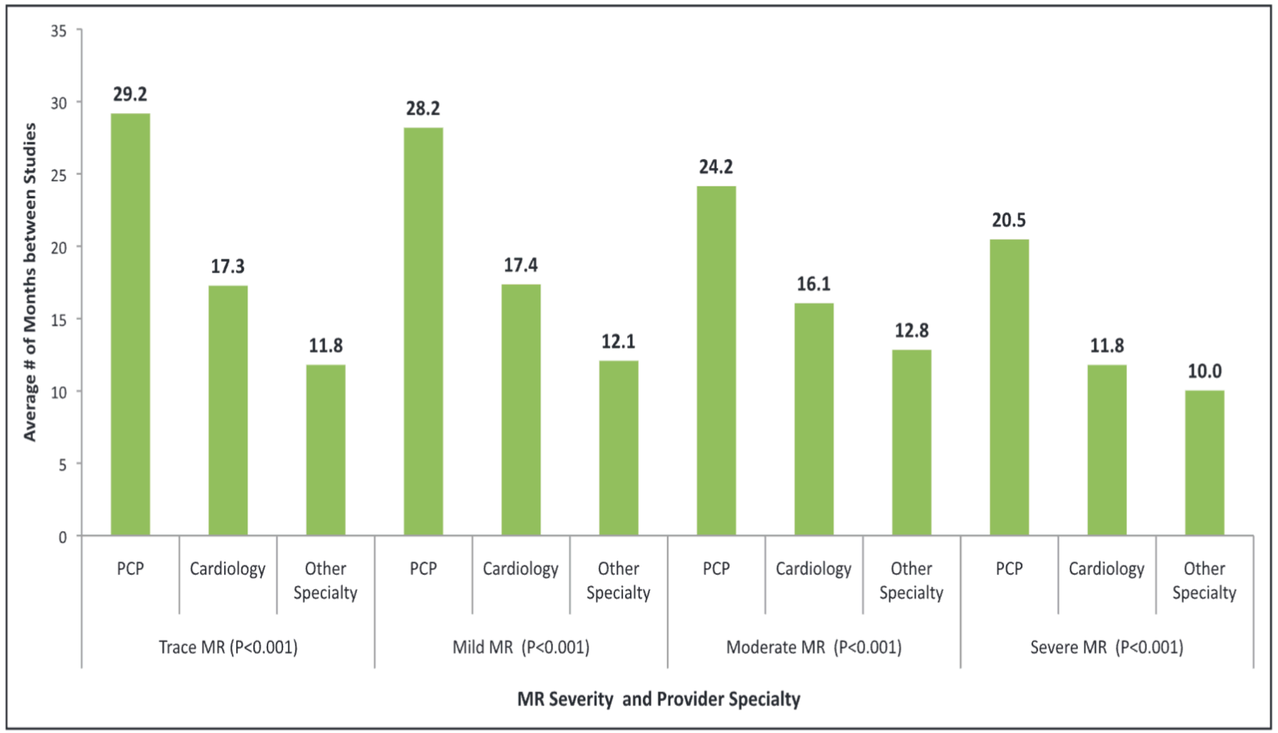
Inclusion	Echo Database
Age ≥ 50	Yes
AVA ≥ 1 to ≤ 1.5 cm^2	Yes
AVC score ≥ 600 – 1200 AU (Women); AVC score ≥ 600 – 2000 AU (Men)	No
LVEF ≥ 45%	Yes
Able to perform CPET	No
Exclusion	**Echo Database**
Prior AV replacement / repair / intervention	No
Moderate, moderate to severe, or severe mitral stenosis, mitral regurgitation, and/or aortic regurgitation	Yes
Bicuspid aortic valve / congenital aortic valve disease	Yes
NYHA III or IV	No
Cardiomyopathy or myocarditis or congenital heart disease	No
Coronary artery disease or anticipating coronary stenting	No
Abnormal ECG or long-standing persistent or permanent Afib	No

EXAMPLE: KATALYST-AV Trial

Inclusion	Echo Database	Target: AS
Age ≥ 50	Yes	Yes
AVA ≥ 1 to ≤ 1.5 cm^2	Yes	Yes
AVC score ≥ 600 – 1200 AU (Women); AVC score ≥ 600 – 2000 AU (Men)	No	Yes
LVEF ≥ 45%	Yes	Yes
Able to perform CPET	No	No
Exclusion	**Echo Database**	**Target: AS**
Prior AV replacement / repair / intervention	No	Yes
Moderate, moderate to severe, or severe mitral stenosis, mitral regurgitation, and/or aortic regurgitation	Yes	Yes
Bicuspid aortic valve / congenital aortic valve disease	Yes	Yes
NYHA III or IV	No	No
Cardiomyopathy or myocarditis or congenital heart disease	No	No
Coronary artery disease or anticipating coronary stenting	No	Yes
Abnormal ECG or long-standing persistent or permanent Afib	No	Yes

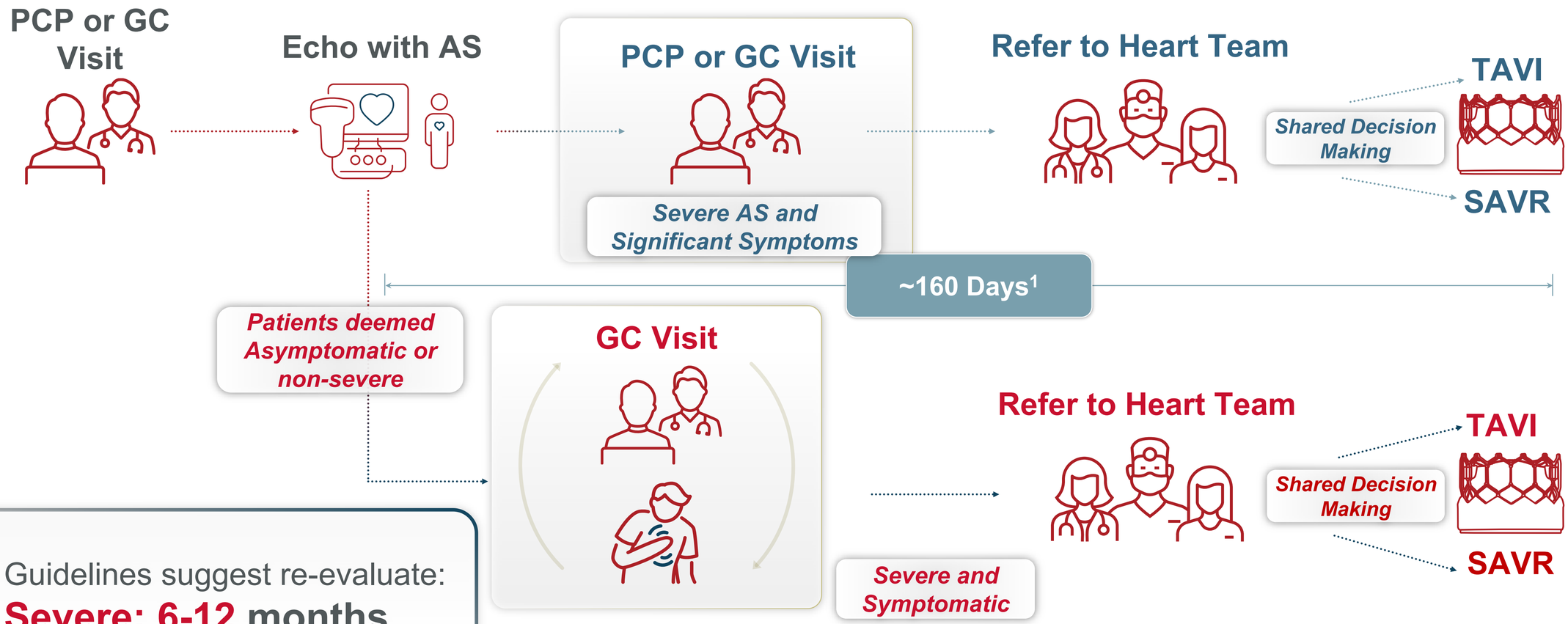
CHALLENGES IN THE CARE AND RESEARCH OF AS

- **Under-recognition** of disease
- **Poor surveillance**: No recommendations in echo report for surveillance intervals
- **No "system" for** ensuring appropriate **surveillance** and **referral** of patients with valvular disease



Tanguturi et al. Variation in the Echocardiographic Surveillance of Primary Mitral Regurgitation. Circ Imaging. 2017

The Current Treatment Pathway for Severe AS



Guidelines suggest re-evaluate:

Severe: 6-12 months

Mod: 12-24 months

Mild: 3-5 years

Sethi et al, The Cost of Waiting for a Transcatheter Aortic Valve Replacement in Medicare Beneficiaries With Severe Aortic Stenosis, Structural Heart 2024.

The Echo Lab And The Heart Valve Team Are The Backbone Of Care And Research In Valve Disease

GUIDELINES AND STANDARDS

Guidelines for the Standardization of Adult Echocardiography Reporting: Recommendations From the American Society of Echocardiography

As an example, the following language may be considered:
"This patient has significant aortic stenosis that, according to the current American College of Cardiology/American Heart Association/ASE valvular heart disease guidelines, may warrant treatment. As clinically appropriate, further evaluation and/or referral should be considered.'

Backbone of clinical care and research for non-severe AS

HVT RESPONSIBILITIES

- Confirm/clarify AS severity
- Procedural risk assessment
- Determine treatment strategy and timing
- Proactive surveillance if no prompt AVR
- Lifetime Management

Taub et al. JASE 2025
Cook et. al. JACC 2025 (in press)

CONCLUSIONS

- **Moderate AS** is an emerging frontier in valvular heart disease research and treatment
  - Medical therapies
  - Device therapies

- The **Target: Aortic Stenosis™ Registry** focuses on pre-AVR care and represents an opportunity for both quality improvement and patient identification for **moderate AS trials**

- With an increased focus on recommendations regarding surveillance and further evaluation, the **echo lab will become the hub for clinical care and research** on non-severe AS

American Heart Association®

Panel Discussion:

Real-World Considerations and Clinical Implementation

Panel Discussion

Sreekanth Vemulapalli, MD

Duke University Health System

Associate Professor of Medicine/Cardiology;

Medical Director, Duke Echo Lab and Cardiac Diagnostic Unit;

Member, Duke Clinical Research Institute;

Member, Duke-Margolis Center for Health Policy

Professor Marc Dweck

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Personal Chair of Clinical Cardiology;

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Vice-President European Association of Cardiovascular Imaging

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Vanderbilt University Medical Center

Medical Director, Structural Heart and Valve Center;

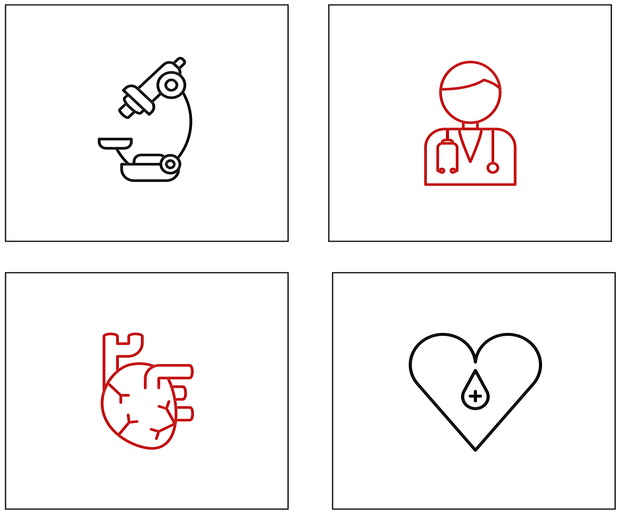
Associate Professor of Medicine

Q & A

WE WANT TO HEAR FROM YOU!

Please take **5-10 minutes** to complete a brief survey. Your insights are critical in helping us:

- **Understand** how clinicians **identify and manage** patients with moderate AS
- **Evaluate** site **research readiness for medical therapy trials** in a space historically led by interventional studies
- **Inform** the design of future **outreach, education, and site engagement** strategies led by the AHA and national collaborators



The results of this survey will help shape real-world solutions to overcome care gaps and accelerate trial access for patients with moderate AS.

Scan the QR code to Complete the Survey

Your input is essential to advancing care for patients with moderate AS!

American Heart Association®

Thank you for joining us today!

Recordings of today's sessions will be enduring resources in a few weeks on www.heart.org

Connect with Us! Scan to email ClinicalStudies@heart.org