

AHA'S MODERATE AORTIC STENOSIS VIRTUAL GRAND ROUNDS SERIES: SESSION #3

Medical Therapy Trials in Valvular Heart Disease: Challenges & Lessons

September 25, 2026

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/ModerateAS

Questions?

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

If you are having issue with audio, please call in using the appropriate number below.

Dial by your location:

+1 (301) 715-8592	(Washington DC)
+1 (312) 626-6799	(Chicago)
+1 (646) 876-9923	(New York)
+1 (253) 215-8782	(Tacoma)
+1 (346) 248-7799	(Houston)
+1 (669) 900-6833	(San Jose)

Meeting ID: 86747122854
Passcode: 858496

Welcome & Introductions

Inara Valliani, MPH
Program Implementation Manager, Clinical Studies
American Heart Association

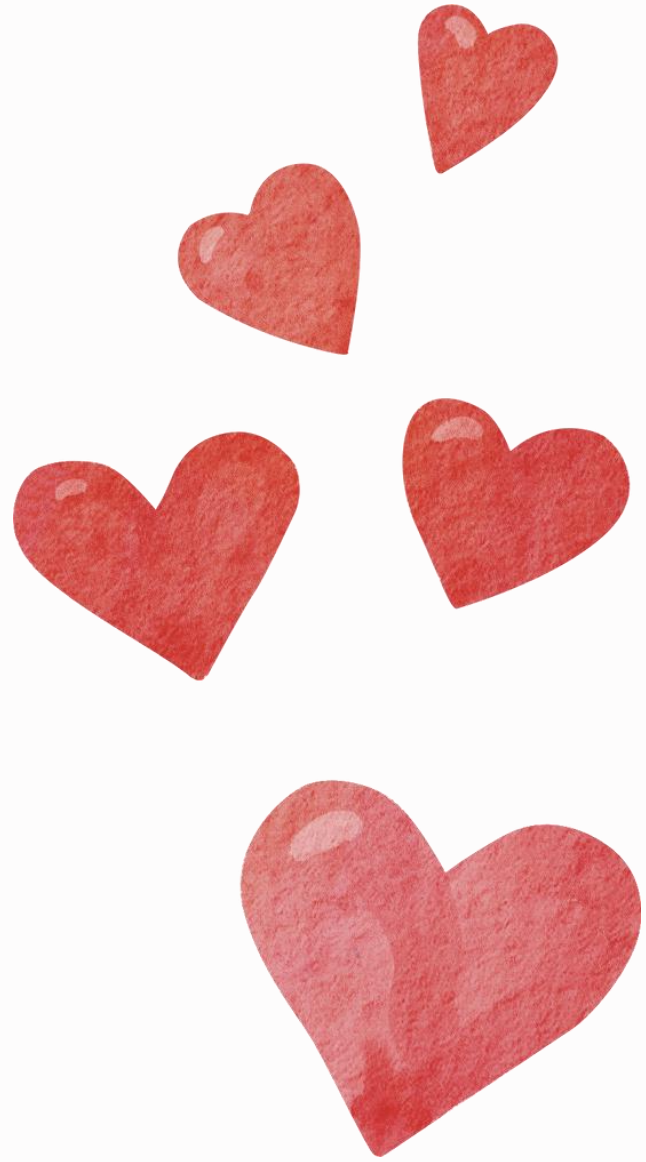
Thank you to

Kardigan, Inc.

for being a supporter of the

American Heart Association's

Heart Valve Initiative



Today's Speakers



Professor Marc Dweck

University of Edinburgh

Personal Chair of Clinical Cardiology

BHF Senior Clinical Research Fellow

Vice-President European Association of Cardiovascular Imaging



Yee-Ping Sun, MD

Brigham and Women's Hospital

Harvard Medical School

Director, Cardiovascular Medicine Fellowship Program

Director, Structural Heart Disease Imaging Program

Assistant 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 the Heart Association. The American Heart Association does not endorse any product or device.

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

Agenda:

1. Welcome & Introductions
2. Medical Therapy Trials: Rationale & Opportunity
3. The Foundational Role of Imaging for Patient Identification & Enrollment
4. Understanding the Patient Population for Medical Therapy Trials
5. Addressing Enrollment Challenges & Practical Guidance for Medical Therapy Trials
6. Moderated Panel Discussion, Q&A, and Closing Remarks



Medical Therapy Trials: Rationale & Opportunity

Professor Marc Dweck
University of Edinburgh
Personal Chair of Clinical Cardiology;
BHF Senior Clinical Research Fellow;
Vice-President European Association of Cardiovascular Imaging

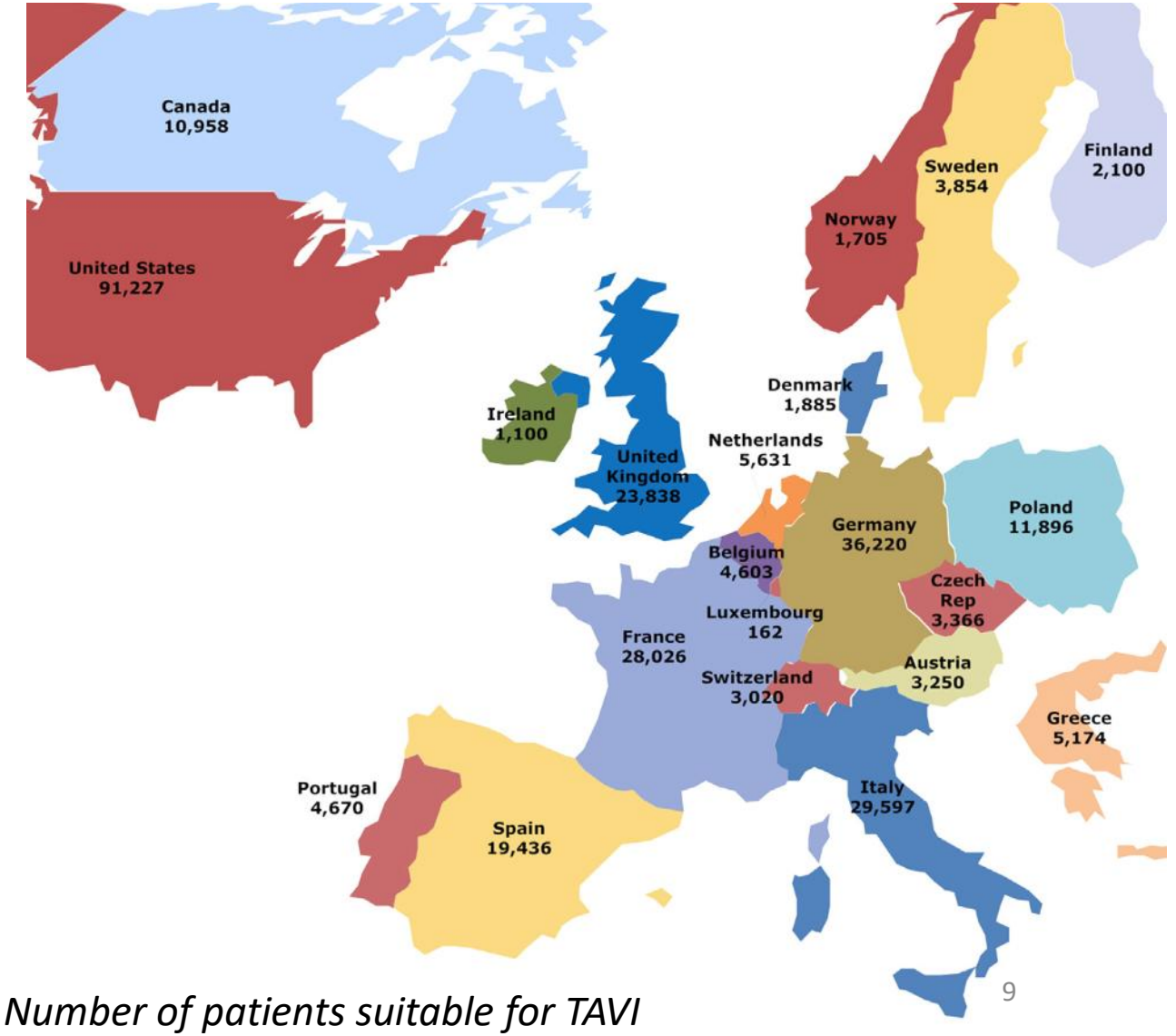


A Looming Heart Valve Epidemic

Aortic stenosis is a common and growing global cardiovascular disease

- Global prevalence **more than doubled** from **~5.0 million** people in 1992 to **~13.3 million** in 2021
- Associated with **140,000 deaths** annually worldwide

Prevalence set to double by 2050



Number of patients suitable for TAVI

Yagdir Circulation 2020
Nkomo, Lancet 2006
Osnabrugge JACC 2013
Gupta, BMJ 2026

One of the Last Major Cardiovascular Conditions Without an Effective Medical Therapy

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



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

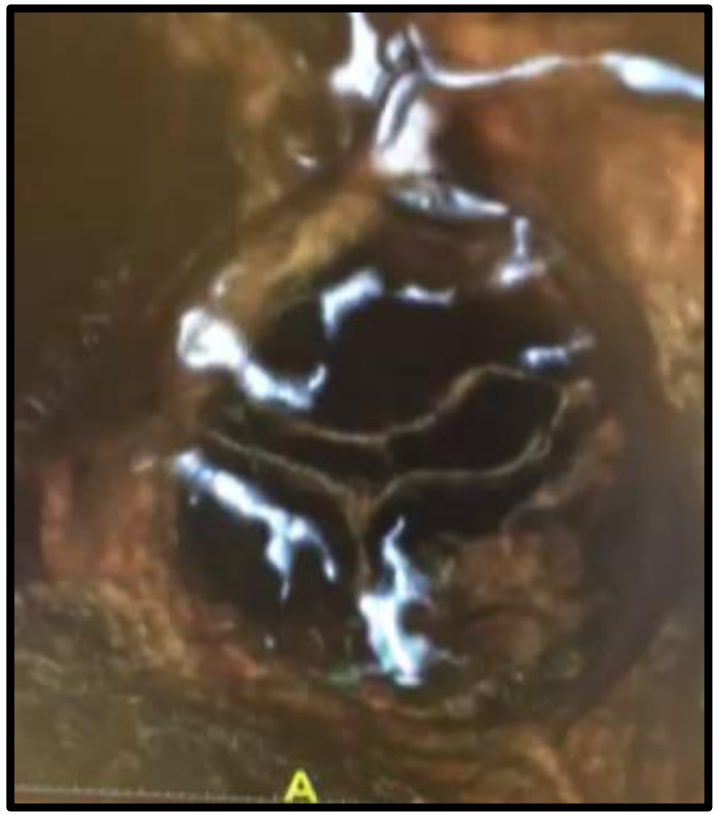
Intensive Lipid Lowering with Simvastatin and Ezetimibe in Aortic Stenosis

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

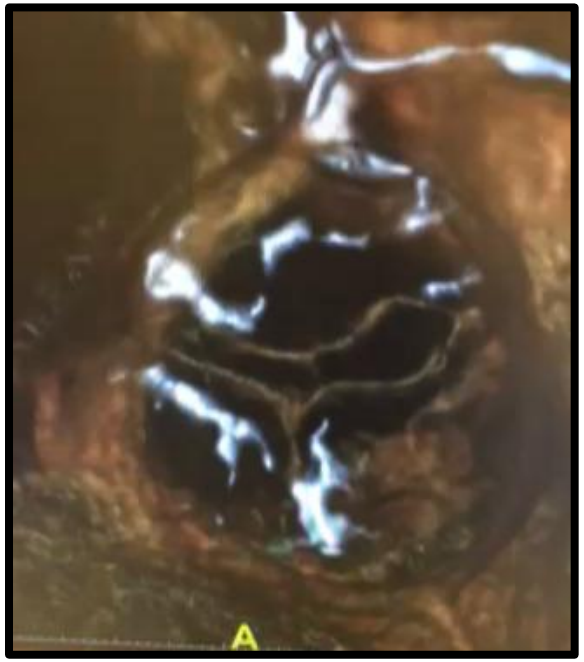
Trial Design

Ongoing / Planned Studies

Dweck JACC 2012

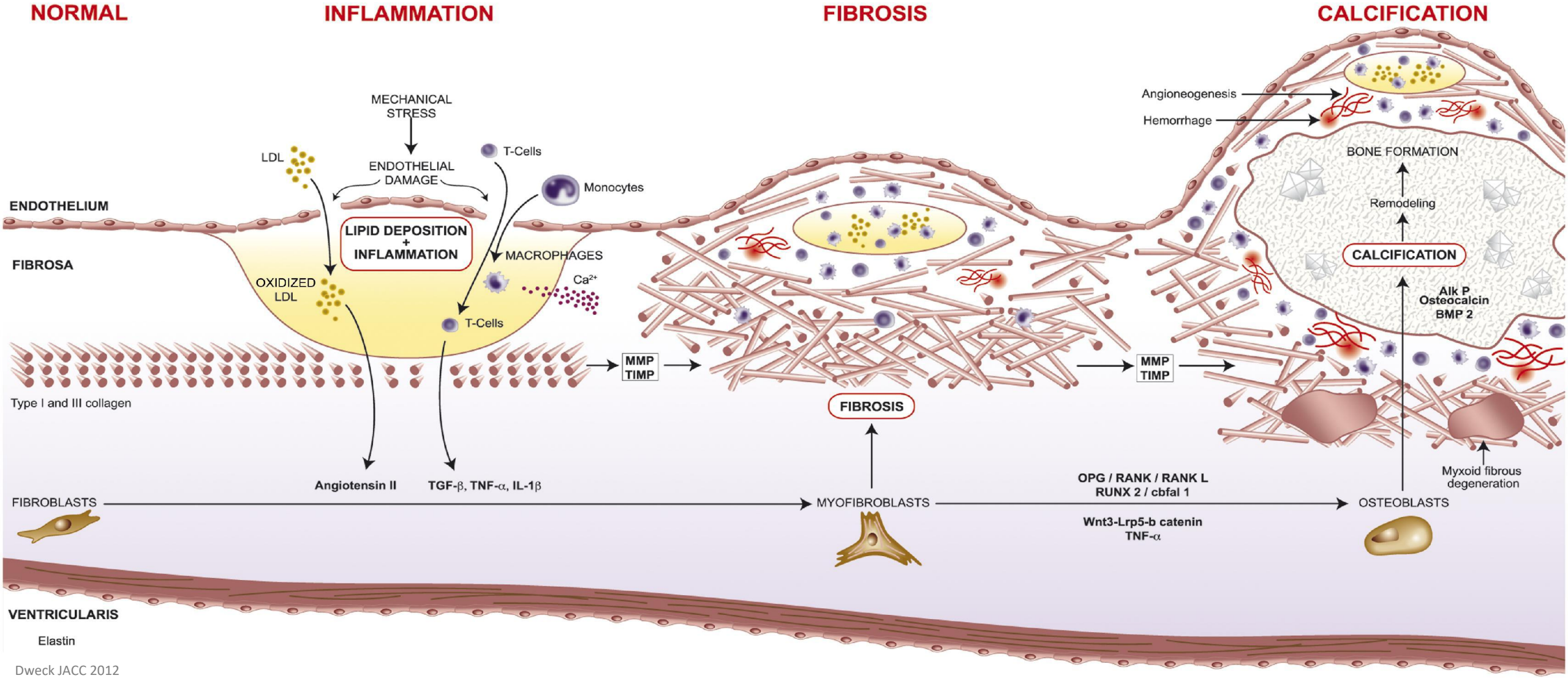
Edinburgh Heart Centre

The Valve





The Valve – Pathogenesis

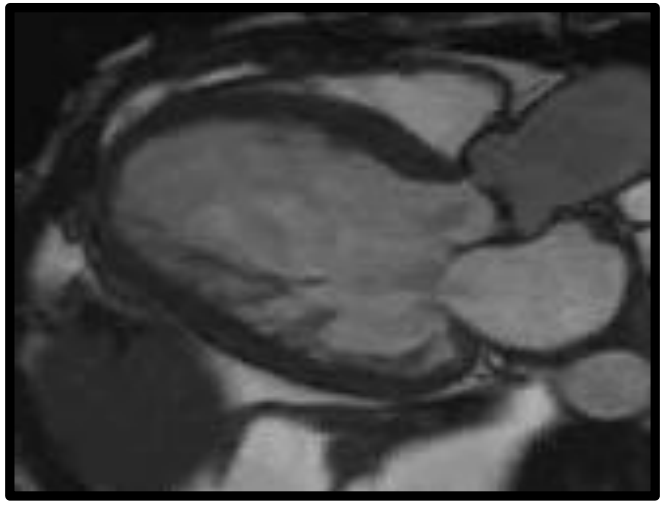


Dweck JACC 2012

Edinburgh Heart Centre

THE UNIVERSITY OF EDINBURGH

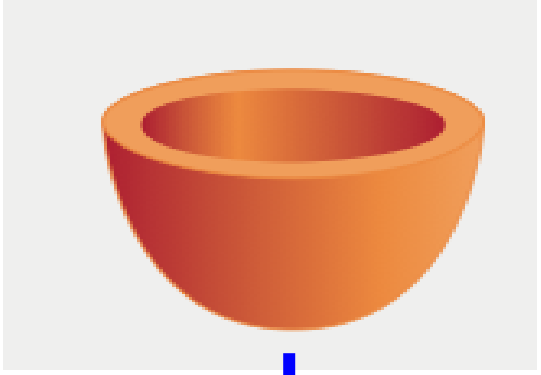
The Myocardium





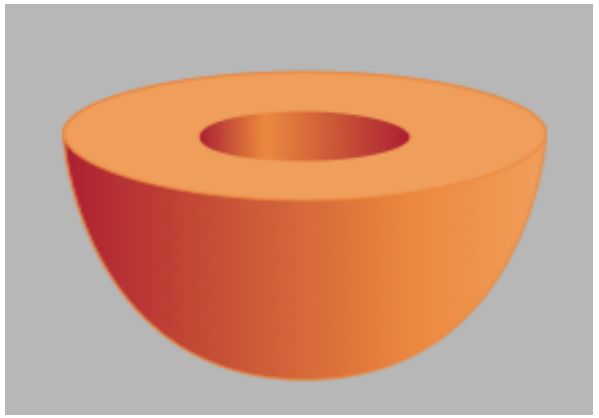
Impact of Aortic Stenosis on the Myocardium

Normal



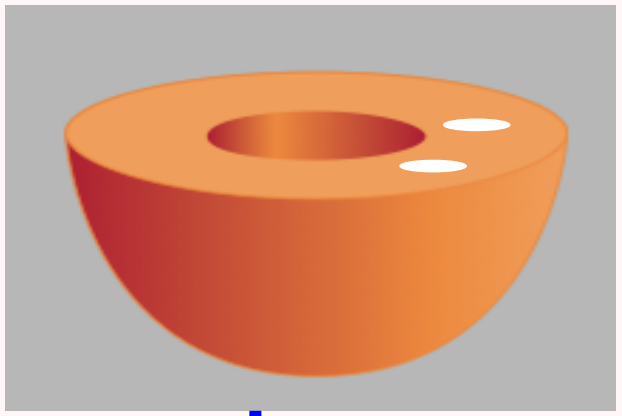
Increased afterload

LVH



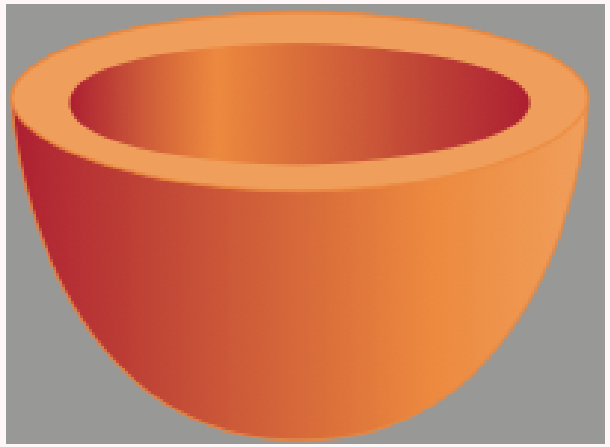
Myocyte Cell Death

DECOMPENSATION



Fibrosis

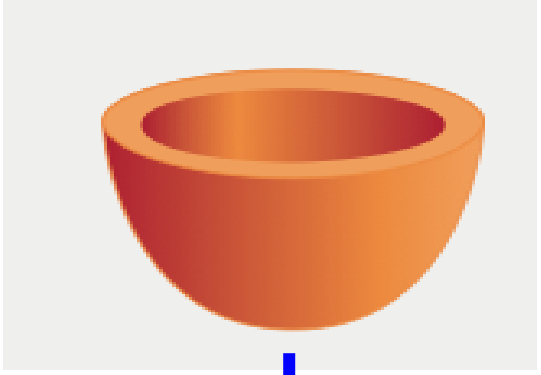
SYMPTOMS → **AVR**



Heart Failure

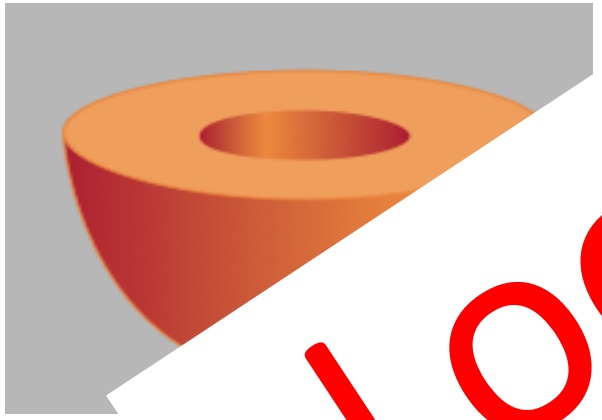
Adapted Dweck MR Aortic stenosis: a disease of the valve and the myocardium.
J Am Coll Cardiol. 2012;60:1854-63.

Normal



Increased afterload

LVH



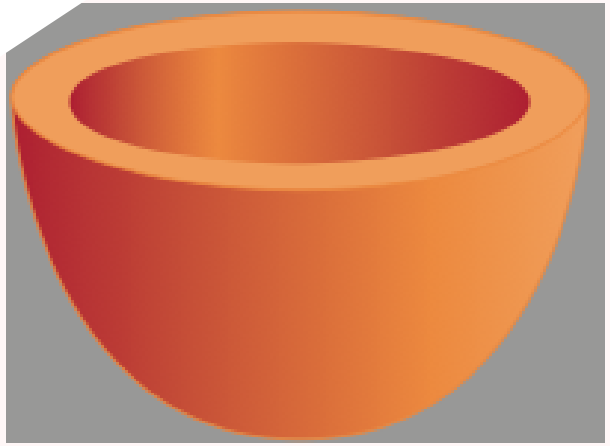
ATION

ibrosis



Looks a lot like HFpEF

SYMPTOMS → AVR



Heart Failure

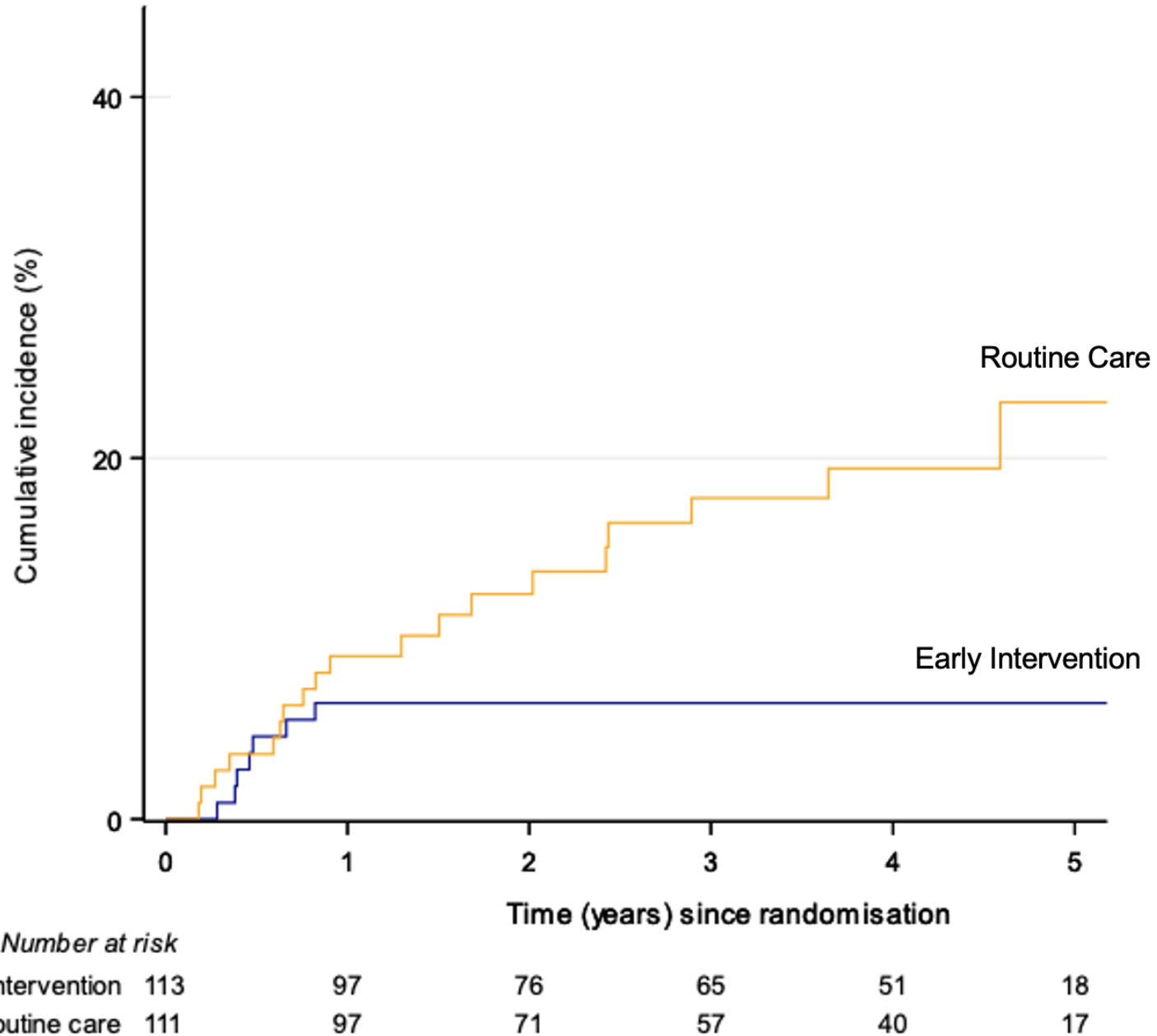
Impact of Aort
Myoca

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

Secondary Endpoint

Unplanned aortic hospitalization

Hazard Ratio 0.37
(95% CI 0.16 to 0.88)

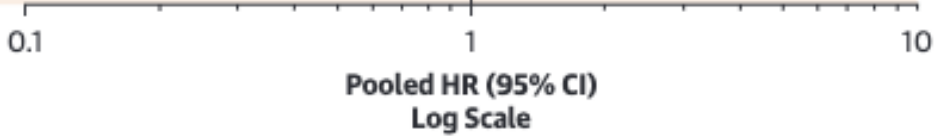


META-ANALYSIS

Consistent reduction in heart failure with early aortic valve 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.

The Foundational Role of Imaging for Patient Identification & Enrollment

Edinburgh Heart Centre

THE UNIVERSITY OF EDINBURGH

Design of Trials





Clinical Endpoints

Phase 2 vs Phase 3 Trials

CLINICAL ENDPOINTS

- AVR and Death (Valve)
- Heart failure hospitalisation and Death (Myocardium)
- Take many years to accrue
- Moving straight to phase 3 trials is expensive

PHASE 2 Trials

- Demonstrate initial proof of concept.
- Valve- aortic stenosis progression (echo and/or CT)
- Myocardium- left ventricular mass and or fibrosis (Echo or CMR)

Assessing Disease Progression

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



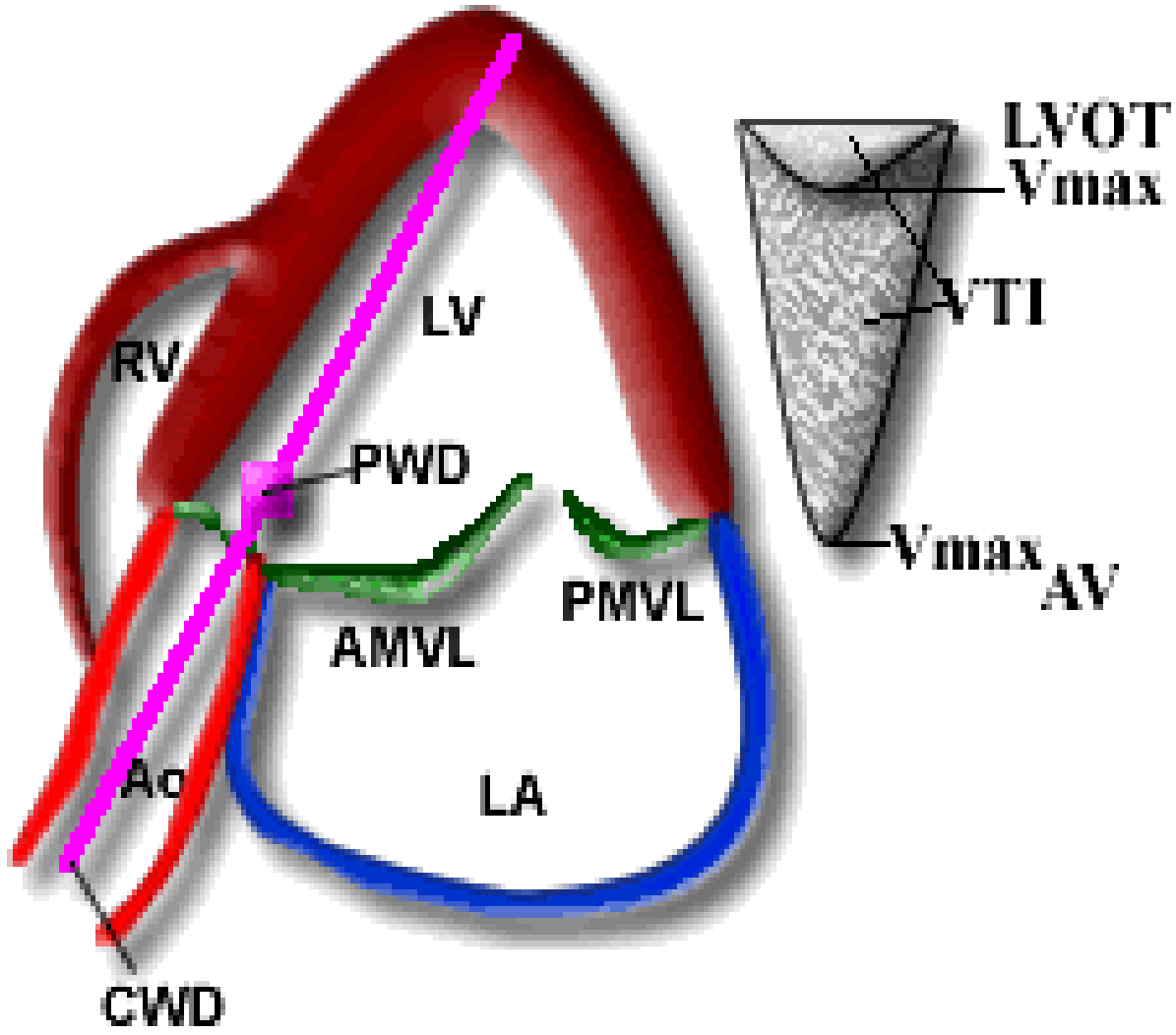
Echocardiography

Peak Aortic Jet Velocity

Mean Gradient

Aortic Valve Area

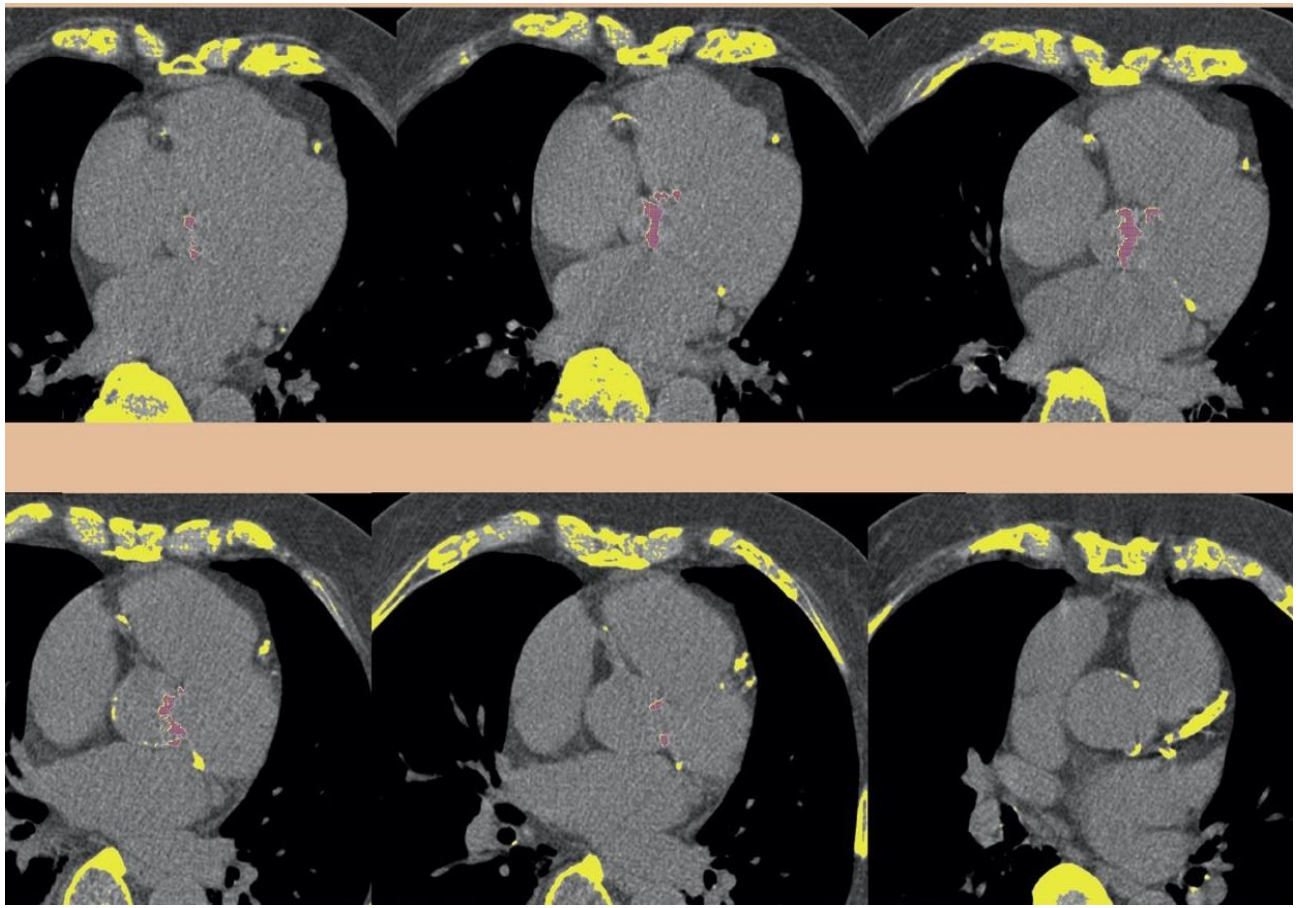
- Continuity equation

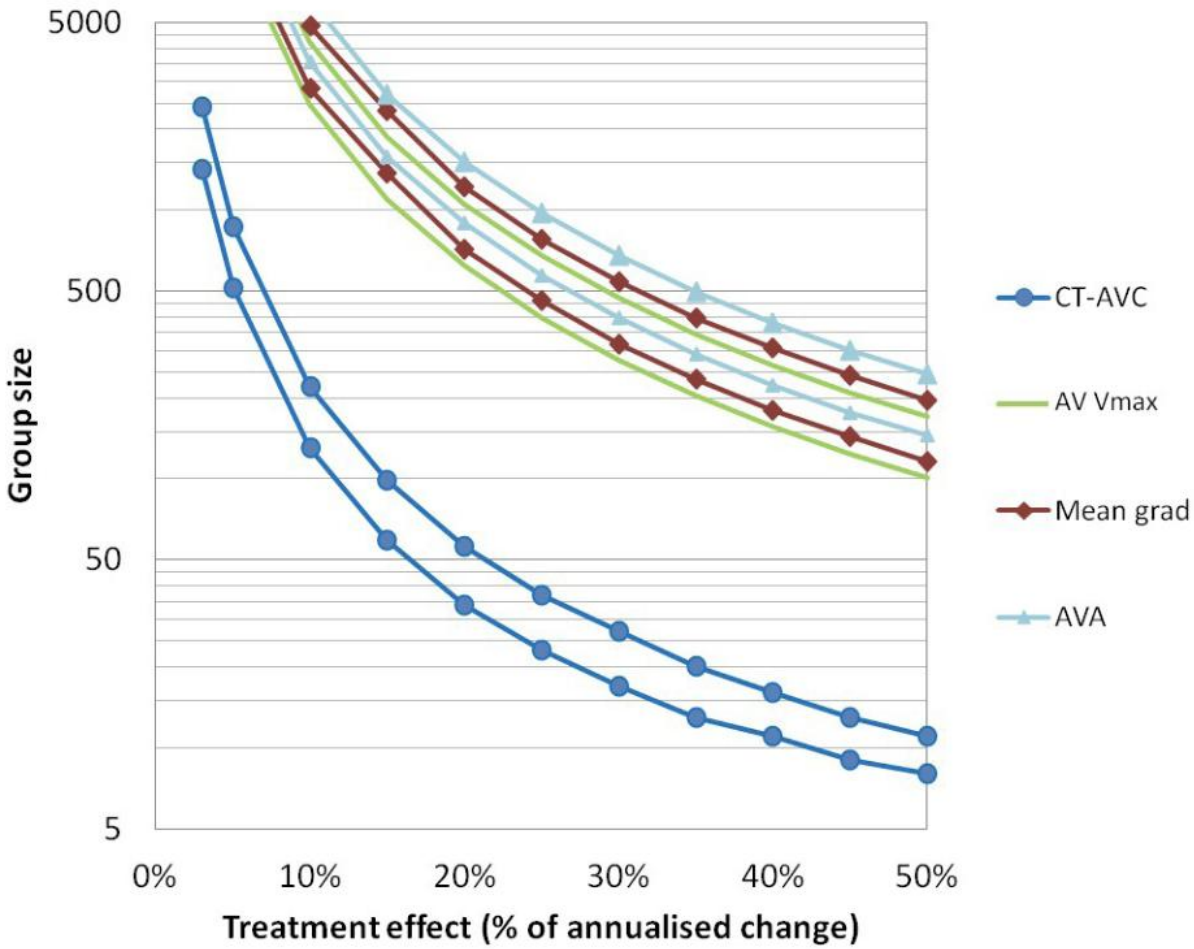


- THE clinical reference standard used to guide management worldwide
  - Must be included; key driver to patient treatment decisions

- Precision of measurements is similar to the annual progression

CT-Calcium Scoring

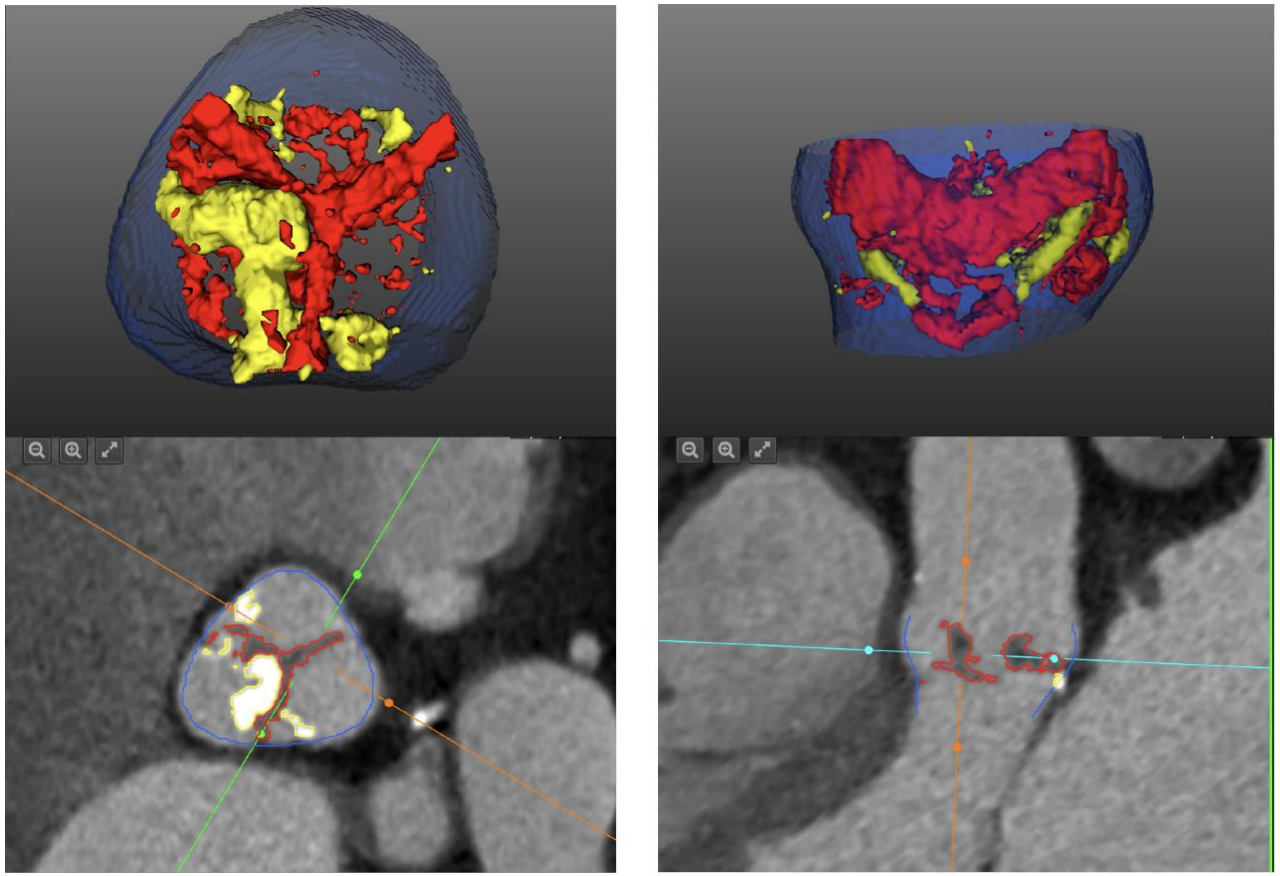


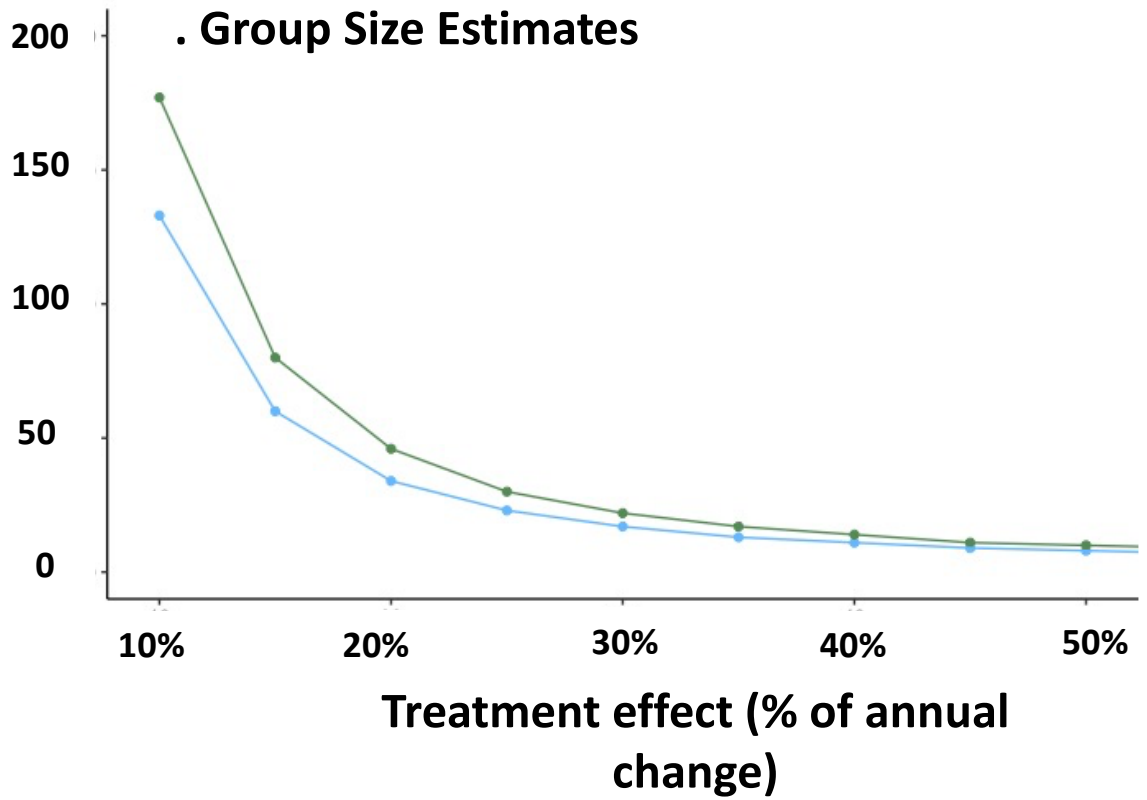


- Fewer patients required to demonstrate a treatment effect
- Only focuses on valve calcification

Doris MK, Jenkins W, Robson P, et al. *Heart 2020*;106:1906-1913.

CT-Fibrocalcific Scoring





- Measures valve fibrosis & calcification
- Can also assess coronary plaque

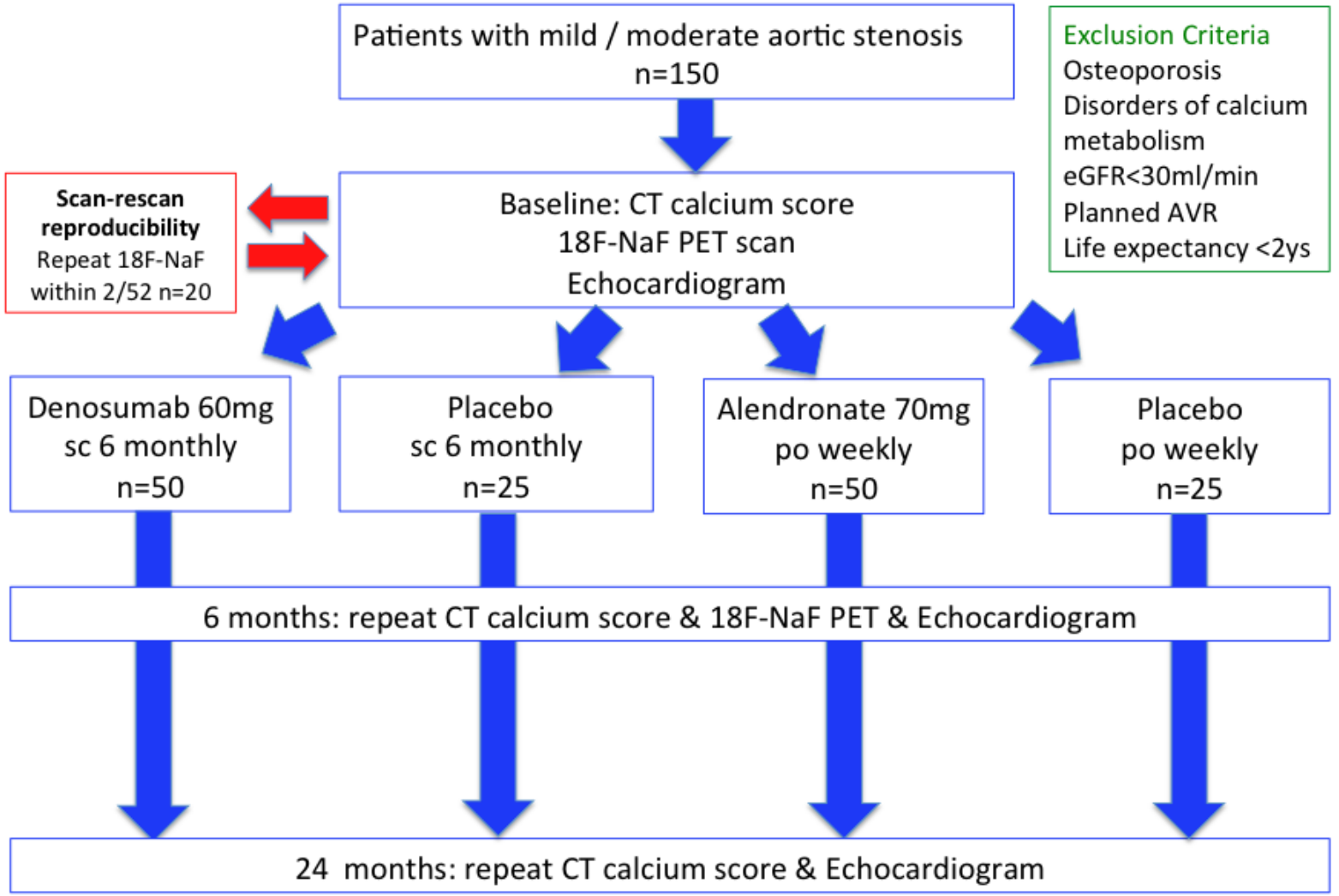
- Novel technique, not used in clinical practice

Edinburgh Heart Centre

Recent & Ongoing Trials Using this Approach

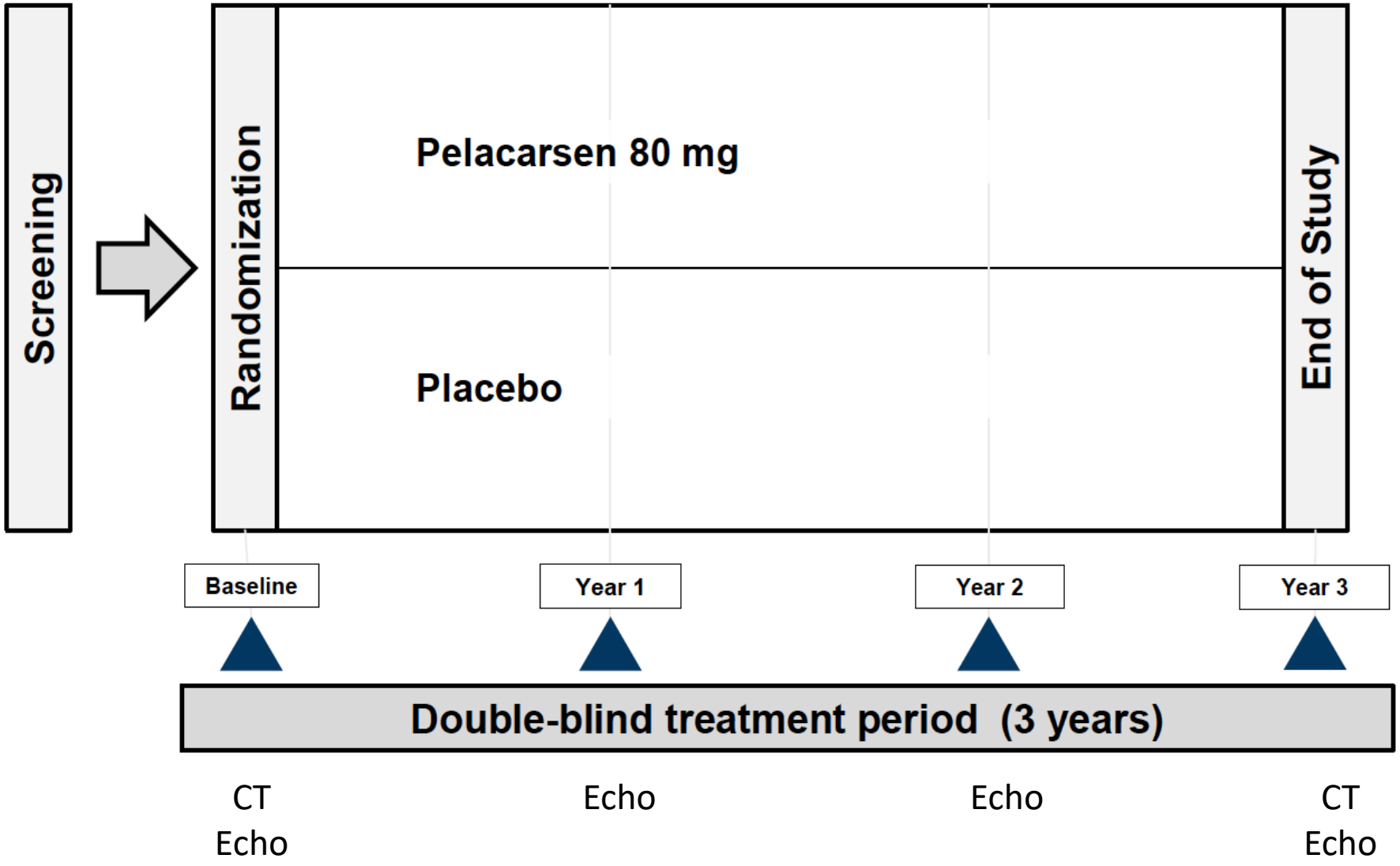


SALTIRE 2



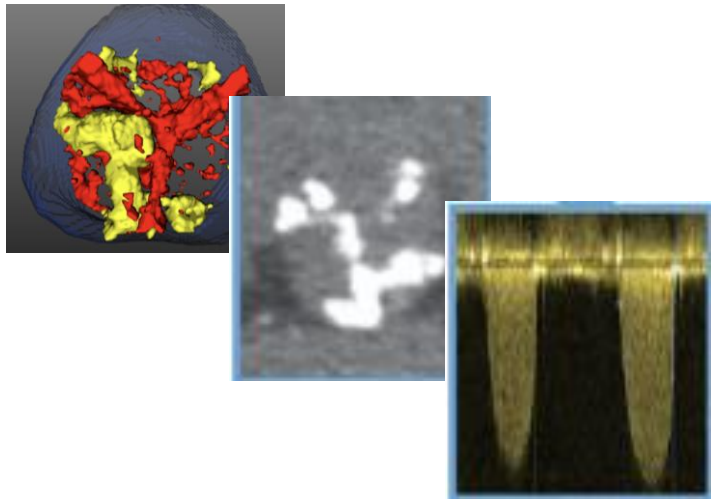
ClinicalTrials.gov NCT02132026

Lp(a)FRONTIERS CAVS: Study design



Aims:

- To assess the impact of Lp(a) lowering with pelacarsen on CAVS progression

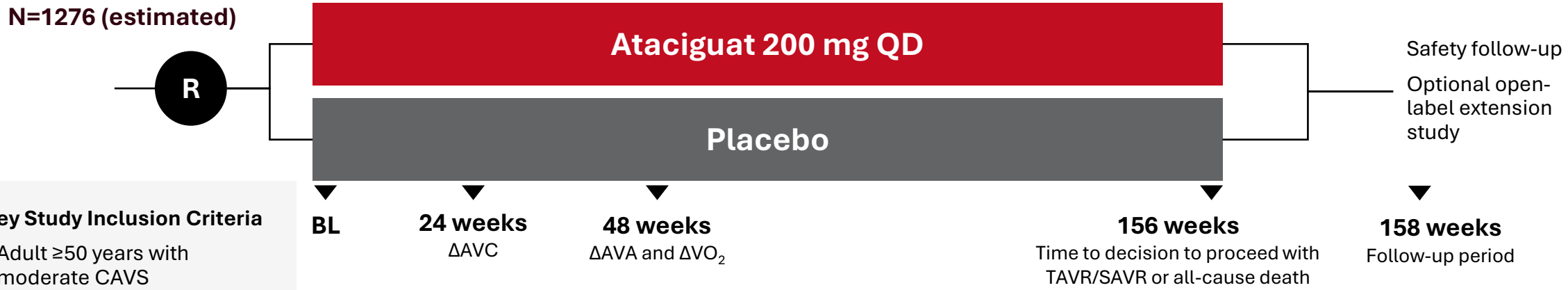


Cho et al. American heart journal, 287, 1–9. https://doi.org/10.1016/j.ahj.2025.03.019

Phase 2b/3 KATALYST-AV Clinical Trial (Currently Recruiting)[1]

A phase 2b/3, randomized, double-blind, placebo-controlled trial investigating the efficacy of ataciguat in slowing the progression of valvular dysfunction in adults with moderate CAVS (NCT07001800)

Design and Inclusion Criteria



Key Study Inclusion Criteria

- Adult ≥50 years with moderate CAVS
- AVA of ≥1.0 cm^2 to ≤1.50 cm^2
- AVC 600-1200 AU (women) or 600-2000 AU (men)
- LVEF ≥ 45% at screening
- No contraindication to completing CPET (Part A sub-study, Part B)

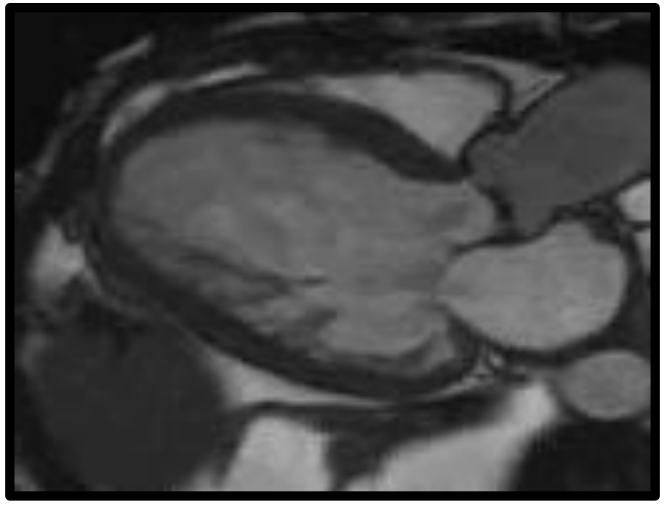
	Part A (n=132)	Part B (n=1144)
Primary endpoint(s)	• Change in AVC at Week 24	• Change in AVA at week 48 • Change in pVO_2 at week 48
Secondary endpoints	• Change in eVO_2 at week 48 (ATA vs PBO) • Change in AVC and VO_2 correlation at week 48 • Change in VO_2 at week 48 • Change in LVMI at week 48 • Change in KCCQ-23 at week 48	• 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
CPET Sub-study (n~50)	• Change in pVO_2 at week 48 (ATA vs PBO) • Borg RPF at peak exertion	N/A

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

1. Protocol ATA-301, Version 3.0. December 12, 2025.

Edinburgh Heart Centre

The Myocardium

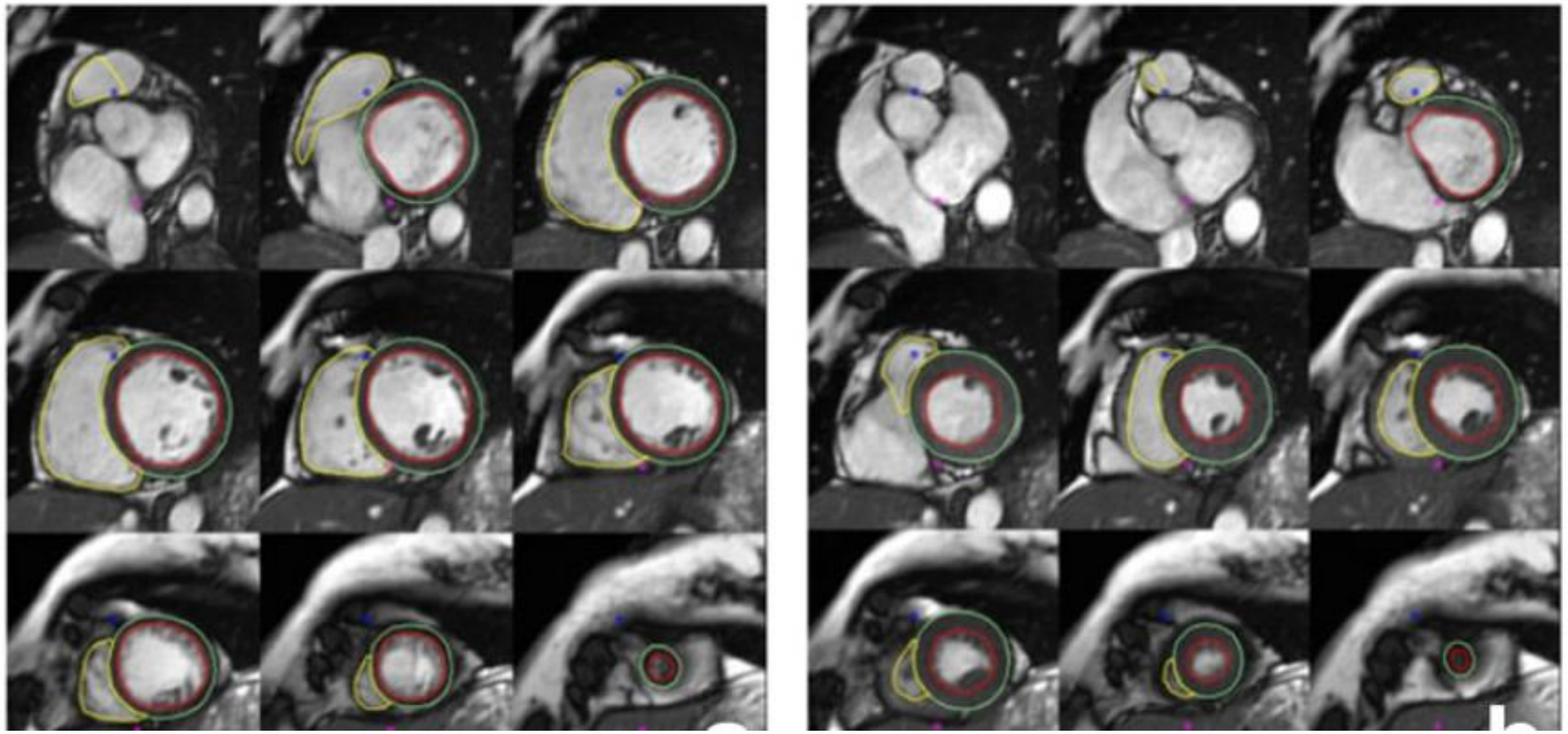




Assessing LV Mass and Volumes (cine stack)

Diastole

Systole

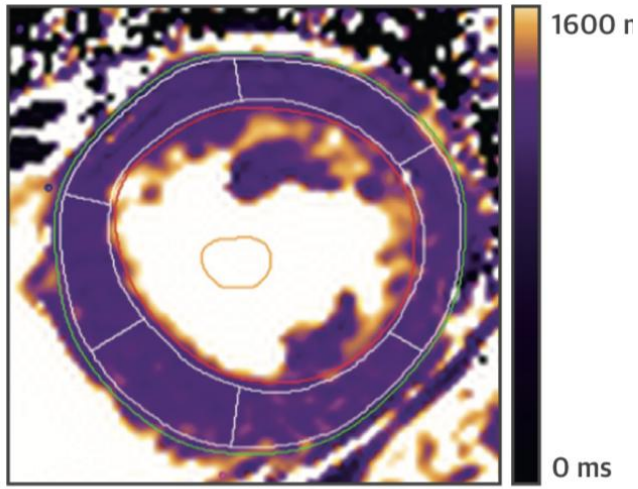


LV hypertrophy

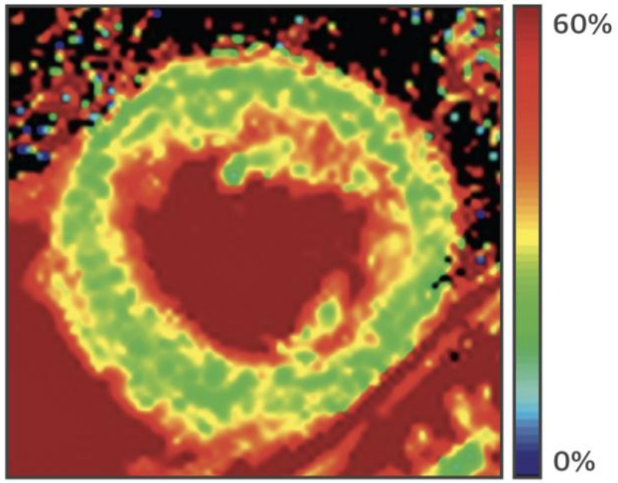
Ejection fraction

CMR - Interstitial Diffuse Fibrosis (reversible)

T1 Mapping



Native T1 Map

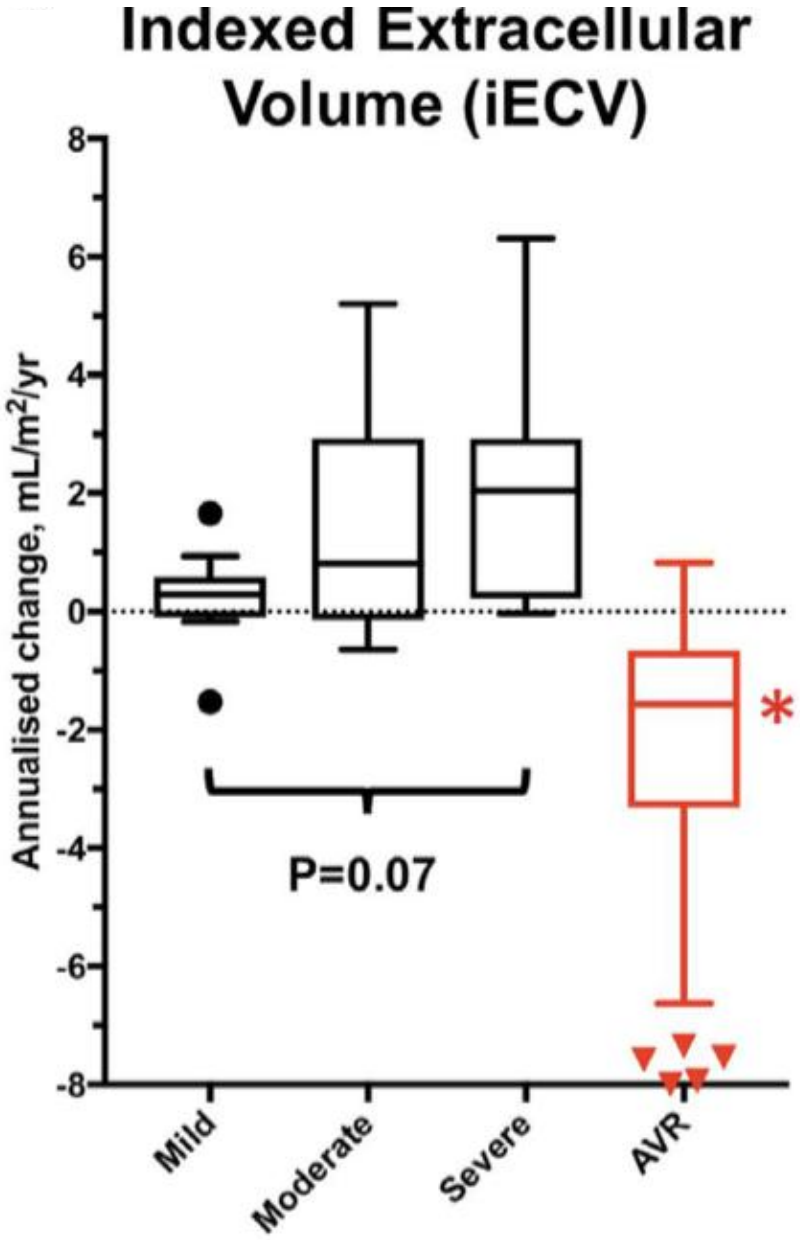


ECV% Map

iECV = ECV% * LV volume

= total burden of myocardial fibrosis in LV

Increases slowly before AVR but then reverses to a degree post AVR



Everett et al. 2018. Circulation. *Cardiovascular imaging*, 11(6), e007451. https://doi.org/10.1161/CIRCIMAGING.117.007451

SGLT2 Inhibitors to Improve Myocardial Health in Aortic Stenosis

National Institute for Health and Care Research

University of East Anglia

Rationale:

- Aortic stenosis affects the myocardium. Left ventricular fibrosis is associated with mortality and precedes systolic dysfunction
- No available medical therapy to protect the myocardium of patients with aortic stenosis
- SGLT2 inhibitors have been shown to attenuate myocardial diffuse fibrosis in patients with heart failure

Hypothesis:

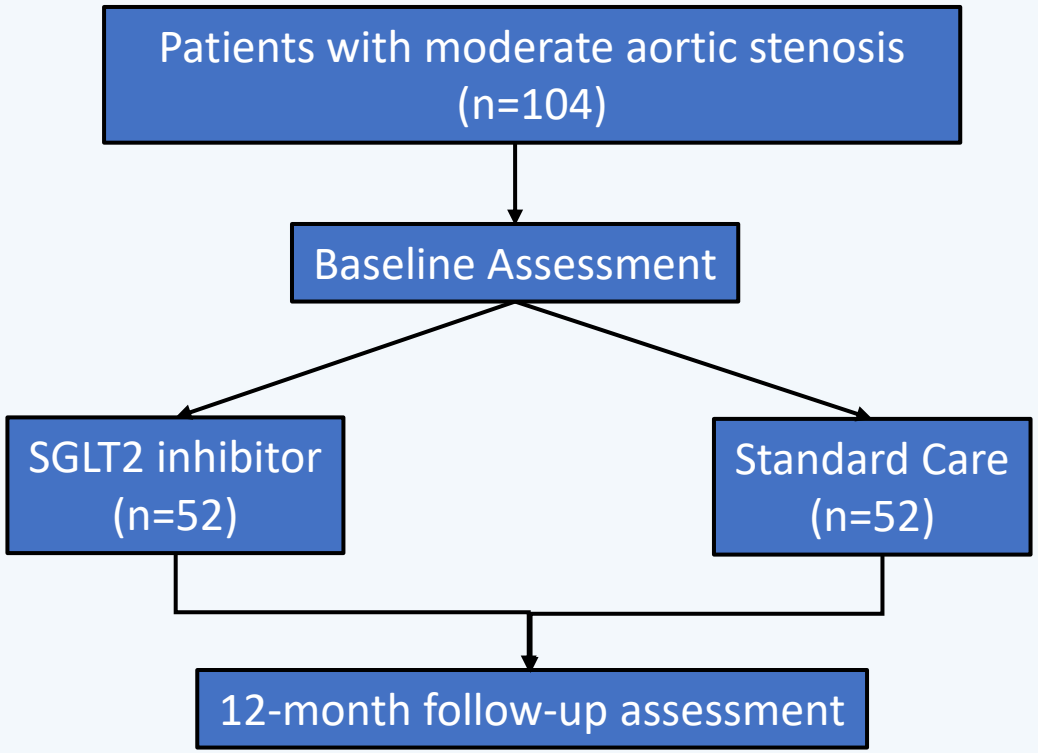
- SGLT2 inhibitors will attenuate myocardial hypertrophy and diffuse fibrosis in patients with aortic stenosis

Study Design:









Recruitment and eligibility assessment

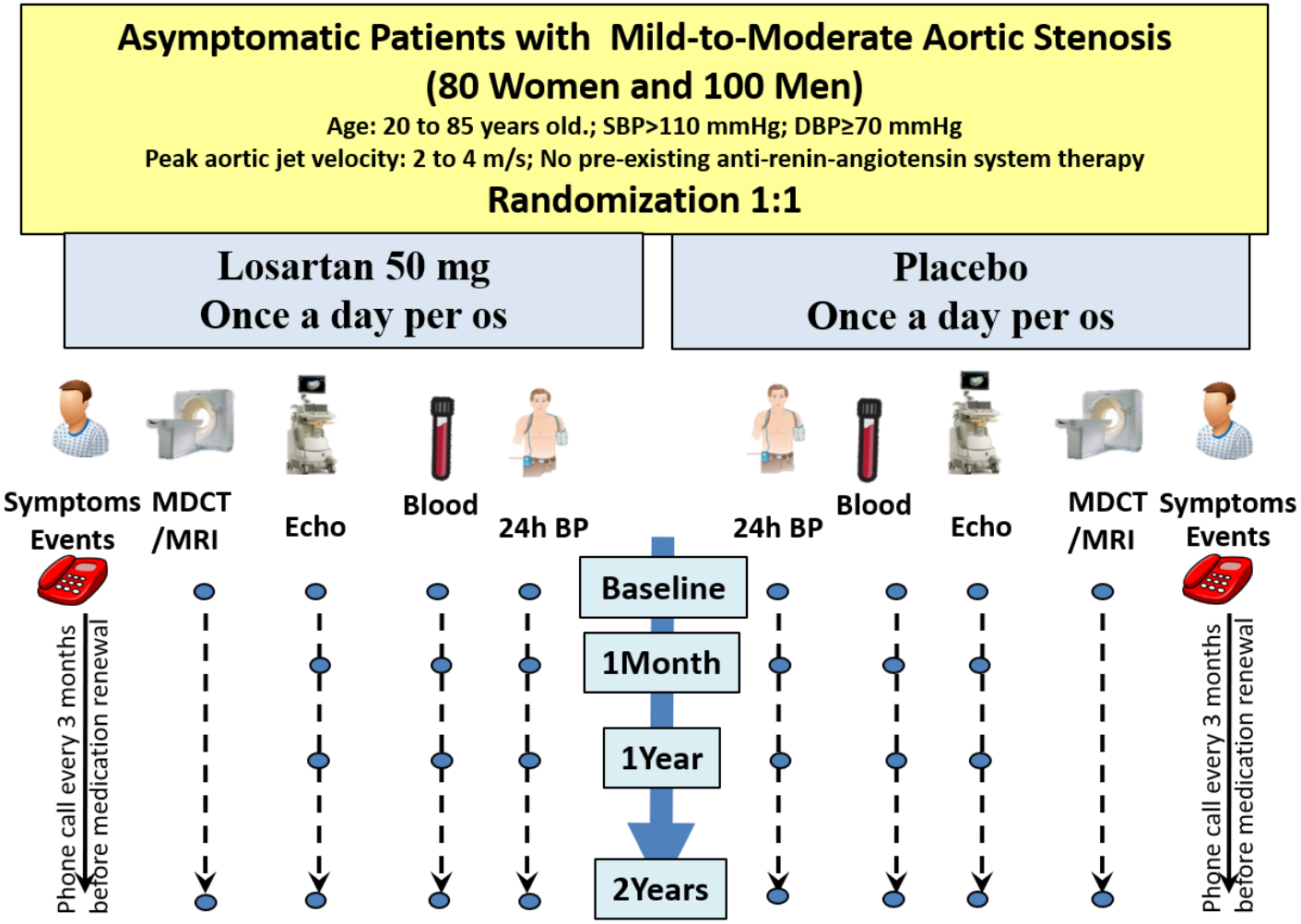
Randomisation

- Cardiac MRI
- Clinical assessment
- ECG
- Echocardiography
- CPET

ARBAS TRIAL

- Targeting the renin angiotensin aldosterone axis
- Losartan
- May have benefits with respect to both the valve and the myocardium

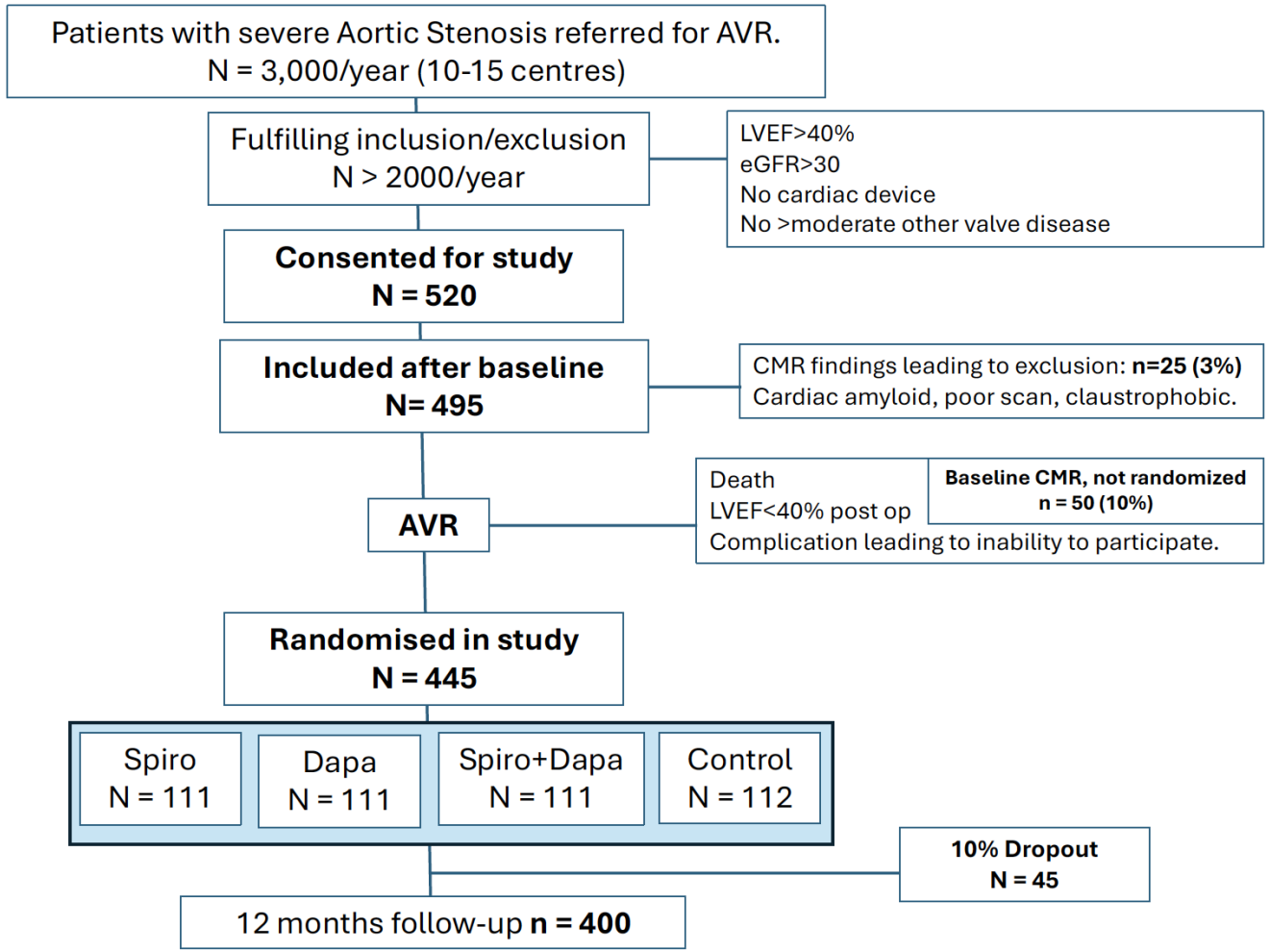




ClinicalTrials.gov NCT04913870

RELIEF-AS TRIAL

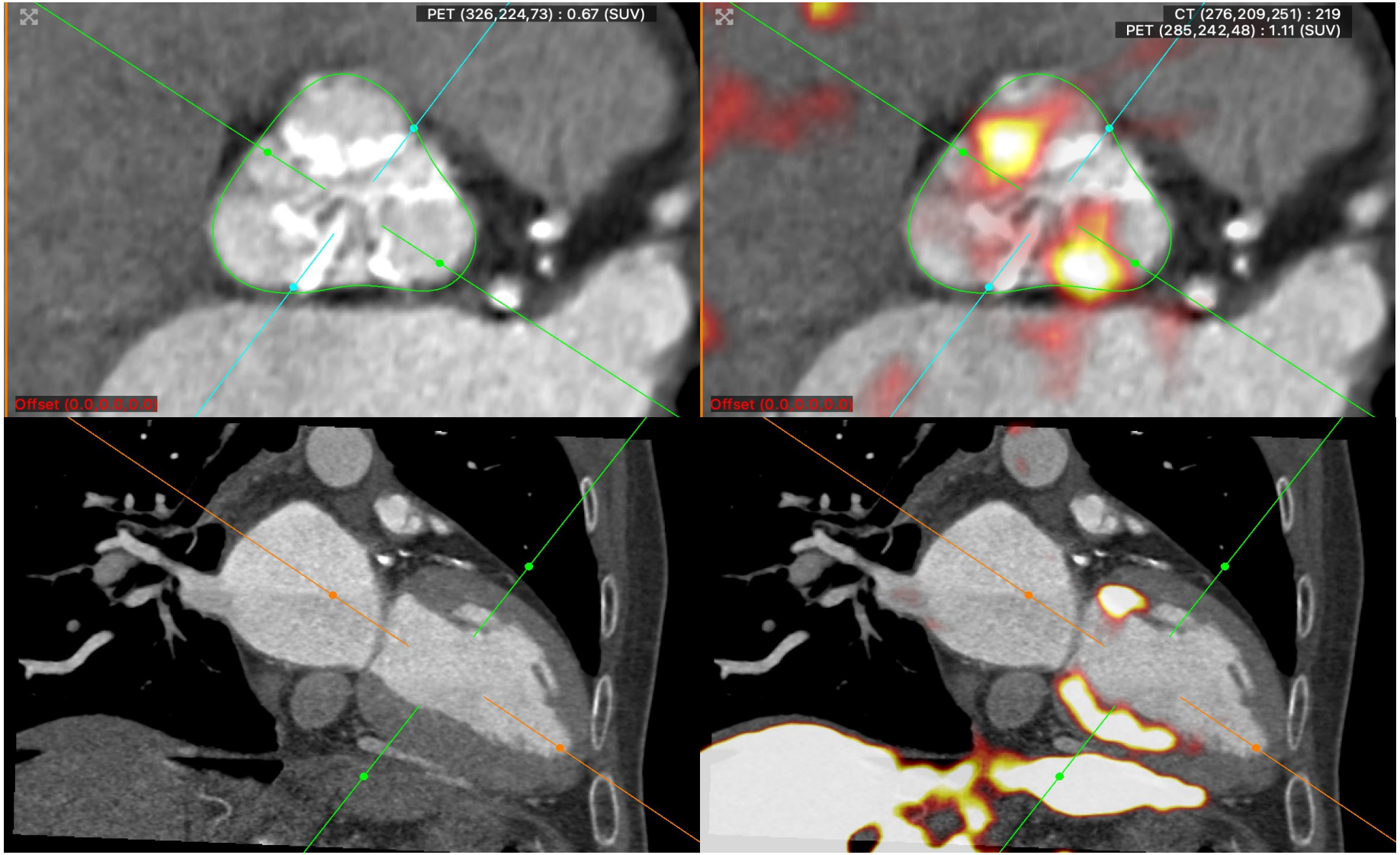
Can Dapagliflozin and Spironolactone Improve myocardial health in aortic stenosis



NIHR170907

^{68}Ga-FAPI PET

Activated Fibroblasts & Fibrosis Activity



Edinburgh Heart Centre

Conclusions

- Aortic stenosis remains perhaps one of 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

American Heart Association.

Understanding the Patient Population for Medical Therapy Trials

Yee-Ping Sun, MD

Brigham and Women's Hospital

Harvard Medical School

Director, Cardiovascular Medicine Fellowship Program

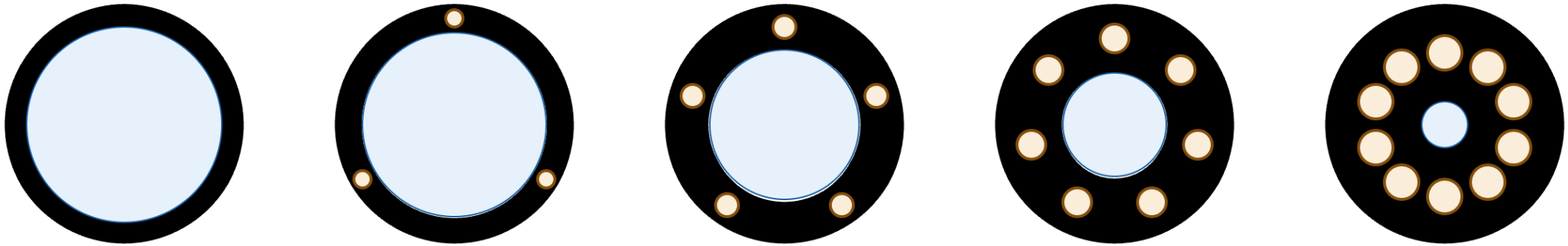
Director, Structural Heart Disease Imaging Program

Assistant Professor of Medicine



Management of Patients with Aortic Stenosis (AS)

PCP → PCP/General Cardiologist → General Cardiologist/ Heart Valve Team

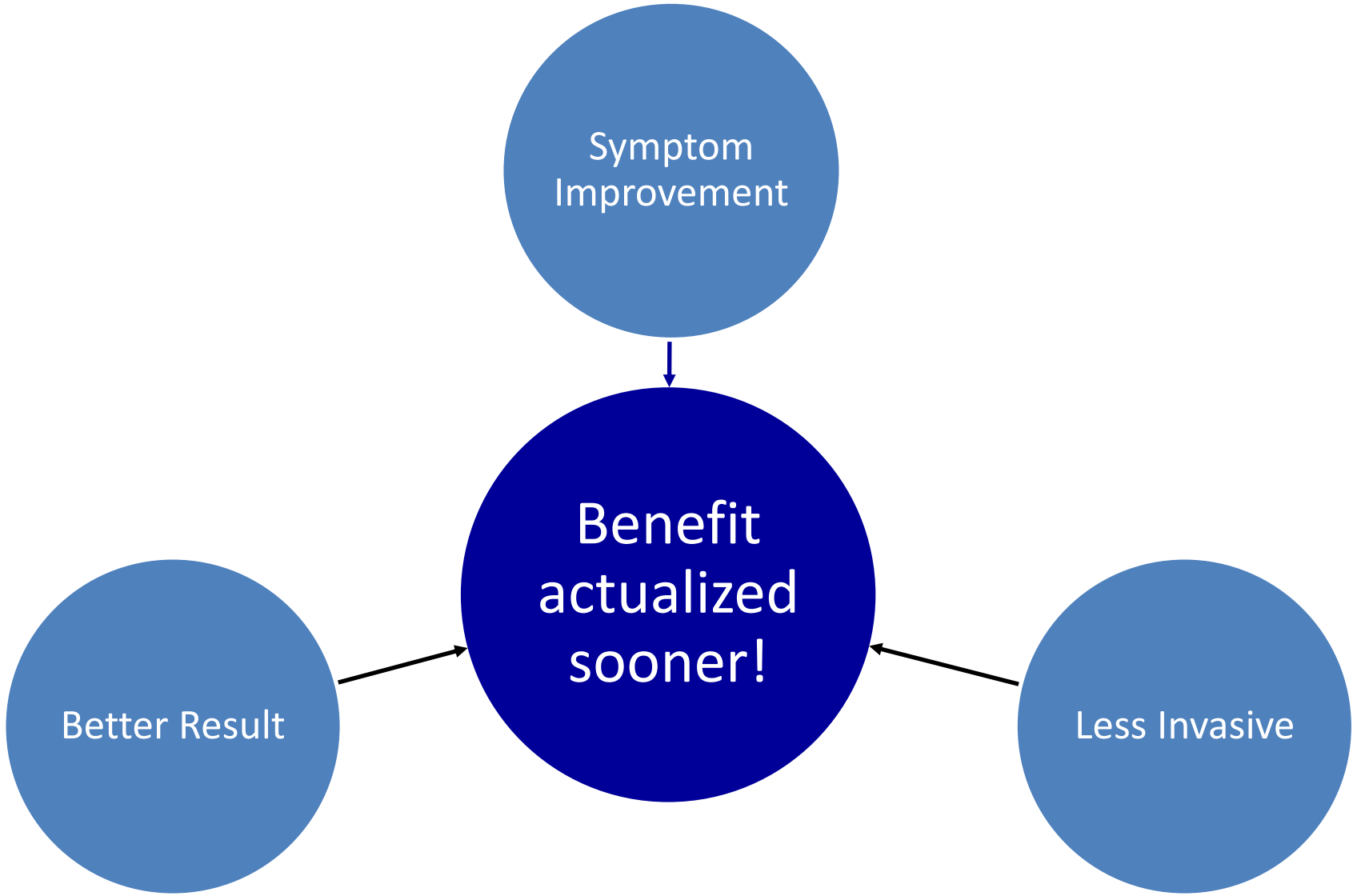


Normal	Sclerotic	Mild AS	Moderate AS	Severe AS
No obstruction	No obstruction	AVA >1.50 cm^2	AVA ≥1.01 - ≤1.50 cm^2	AVA < 1.00 cm^2

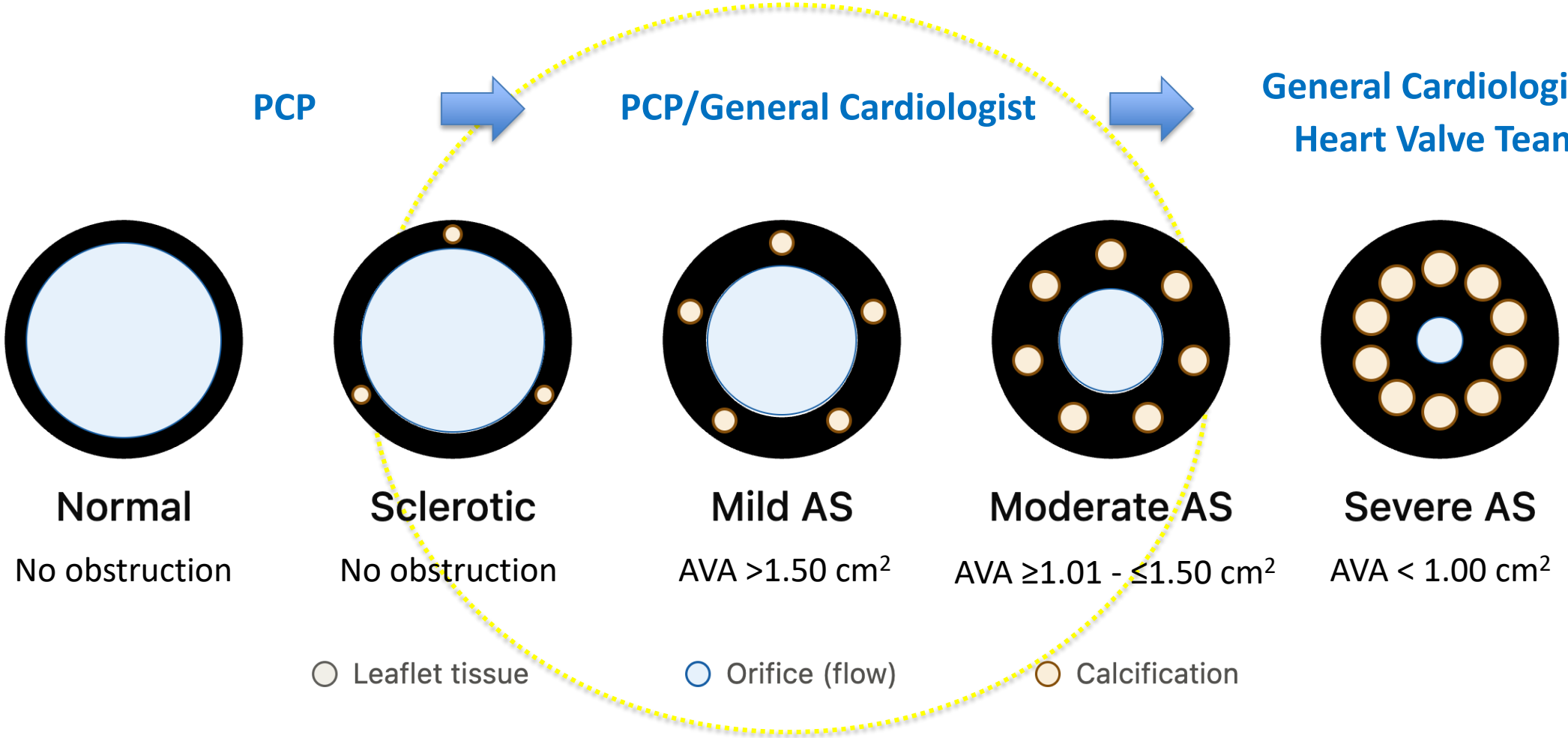
Leaflet tissue Orifice (flow) Calcification

2020 ACC/AHA Valvular Heart Disease Guideline, J of ACC. Vol. 77,4 (2021)

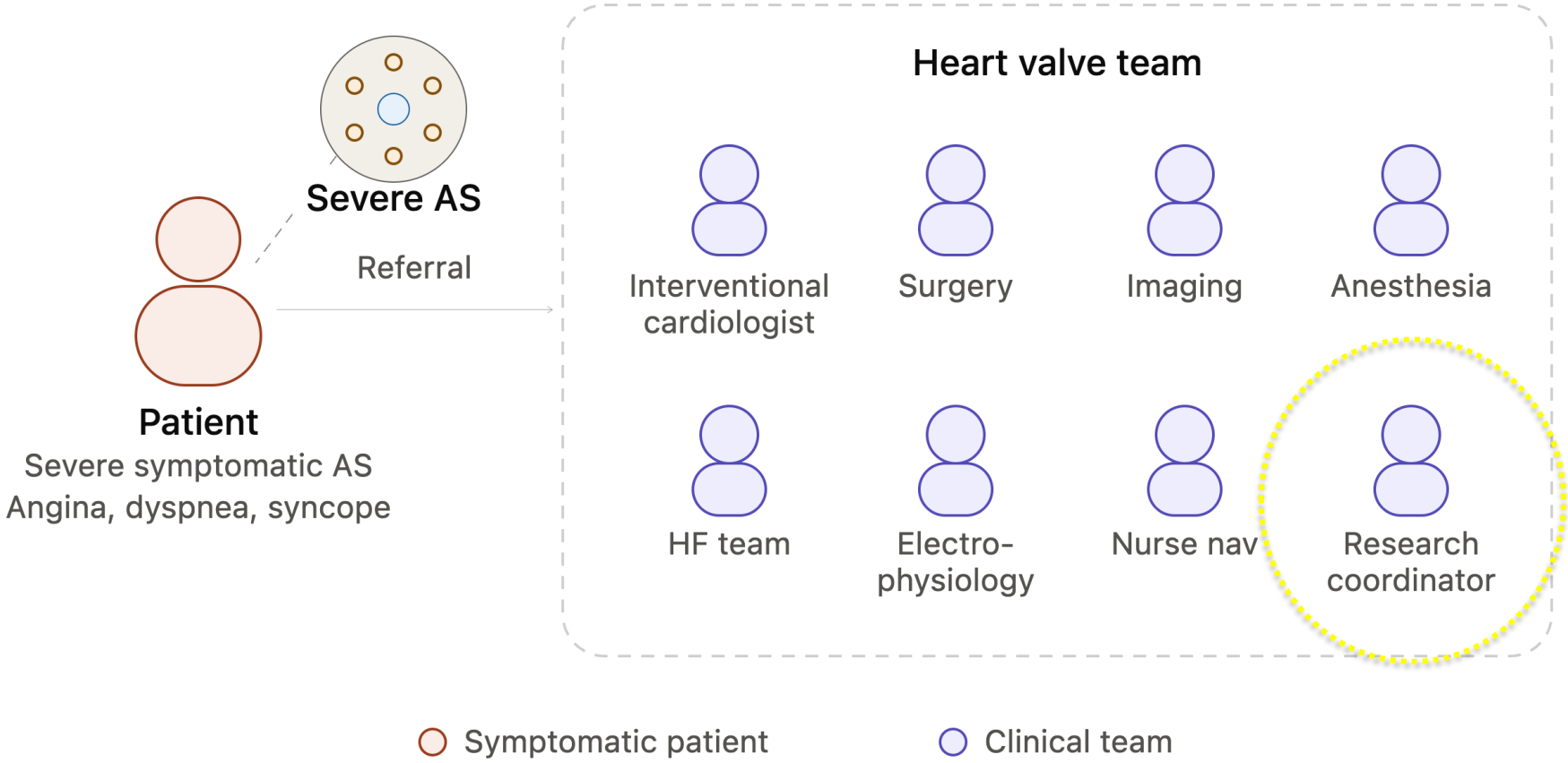
Motivations For Participation in Transcatheter Trial



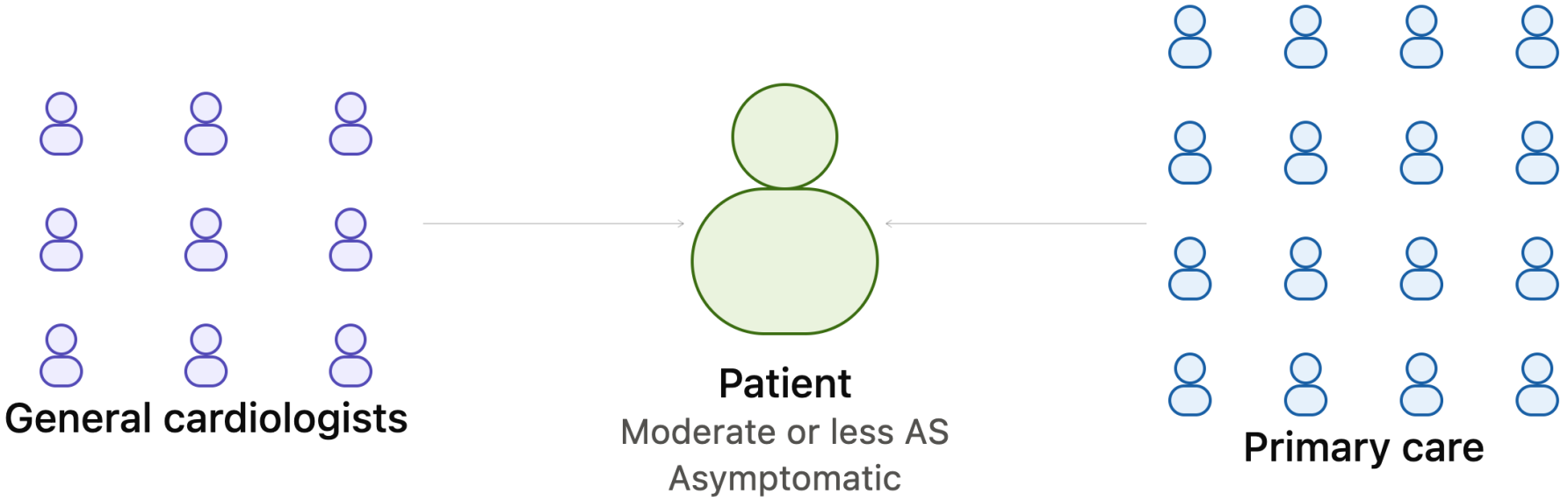
Optimal Patients for Medical Therapy Trials



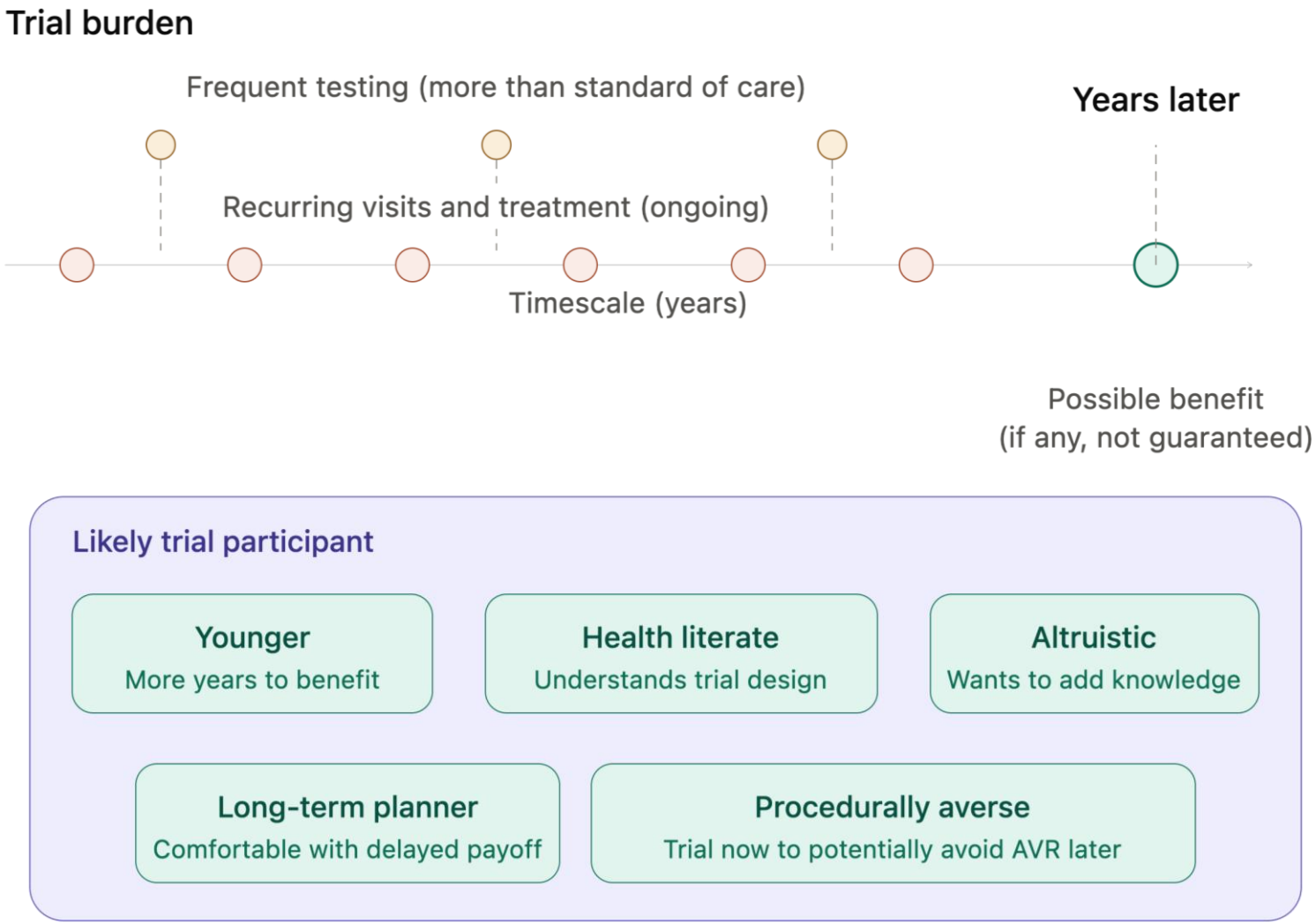
Identification of Patients for Transcatheter Trials



Identification of Patients for Medical Rx AS Trials



What Type of Patient is Likely to Participate?



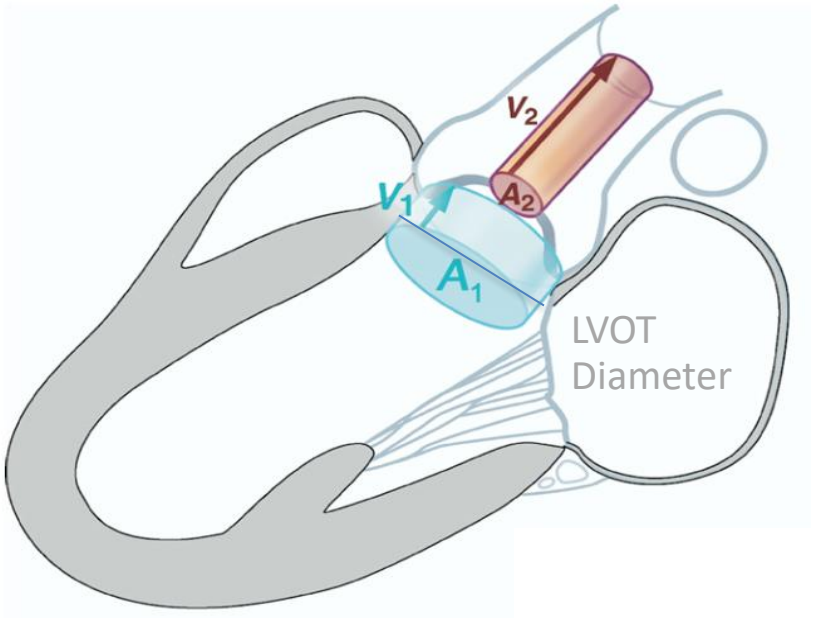
Finding the Right Patient by Echo!

- **Want patients who have:**
  - AVA > 1 cm^2
  - Peak velocity < 4 m/s
  - Mean gradient < 40 mmHg
- Defining AS by **AVA criteria** (AVA > 1 cm^2)
- Ensure not missing **higher gradients**

Measuring AVA Correctly

- **Severe AS** defined as **AVA < 1 cm²** by TTE for **trial/research purposes**
  - ***In real-life***, severe AS is most reliably captured by high gradient AS
  - ***In trials***, we want to exclude low gradient AS
- Prevalence of **low gradient AS** is **highly variable**
  - As low as 5%, as high as 50%
  - This is likely due to contribution of **LVOT measurement error**

AVA Measurement Must Be Accurate

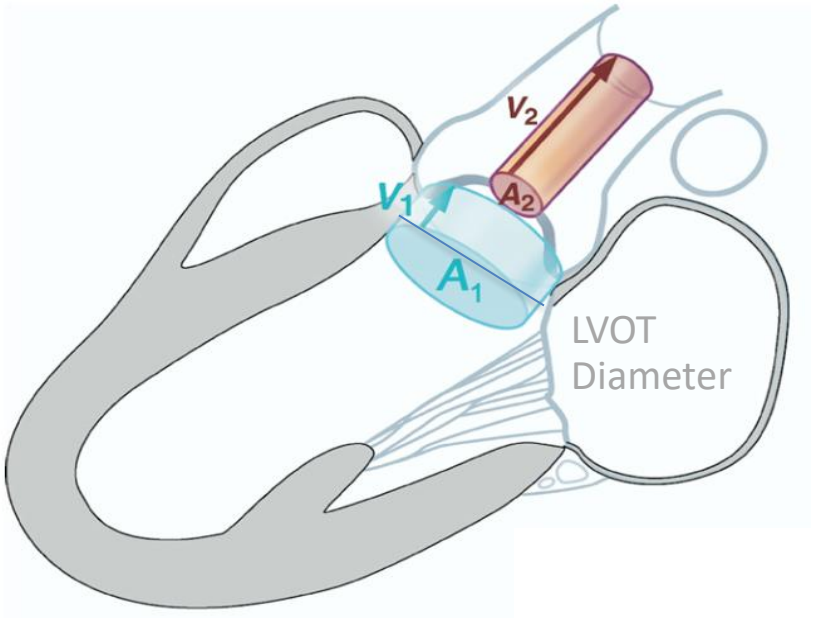


$$A_2 = (A_1 \times v_1)/v_2$$

$$AVA = (A_{LVOT} \times v_{LVOT})/v_{AV}$$

$$AVA = \frac{\left(\frac{D_{LVOT}}{2}\right)^2 \pi \times VTILVOT}{VTI_{AV}}$$

Don’t Undermeasure the LVOT!



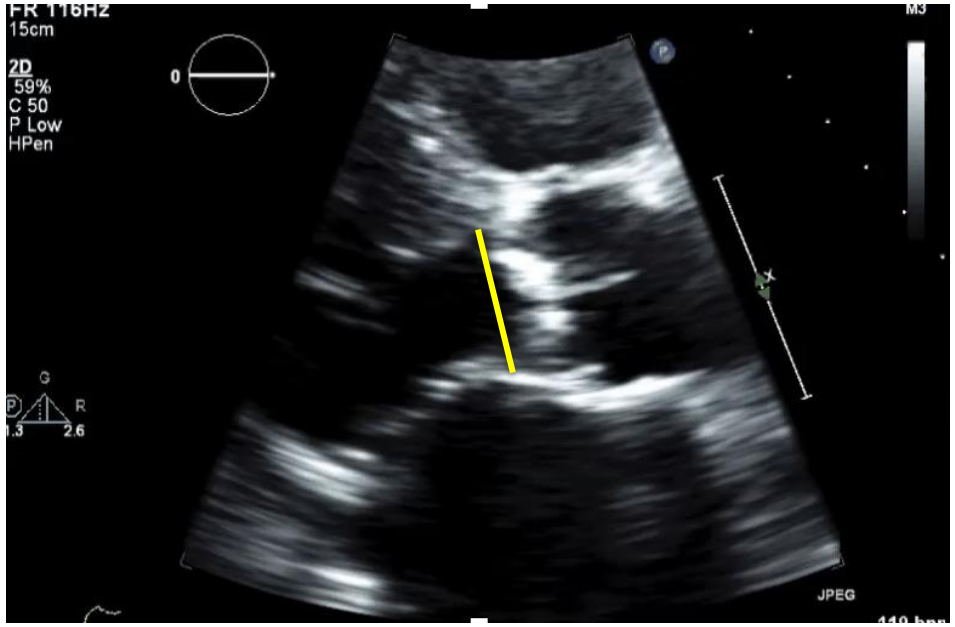
$$A_2 = (A_1 \times v_1)/v_2$$

$$AVA = (A_{LVOT} \times v_{LVOT})/v_{AV}$$

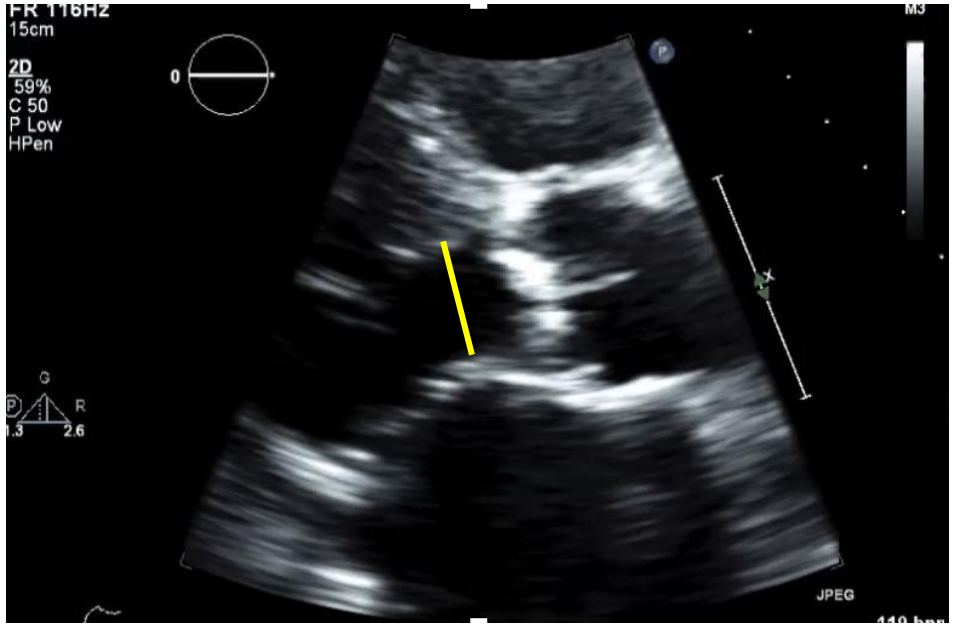
$$AVA = \frac{\left(\frac{D_{LVOT}}{2}\right)^2 \pi \times VTILVOT}{VTI_{AV}}$$

Undermeasurement of LVOT Diameter → Undermeasurement of AVA → Inappropriate characterization of severe AS

Where to Measure LVOT is Controversial



At the annulus



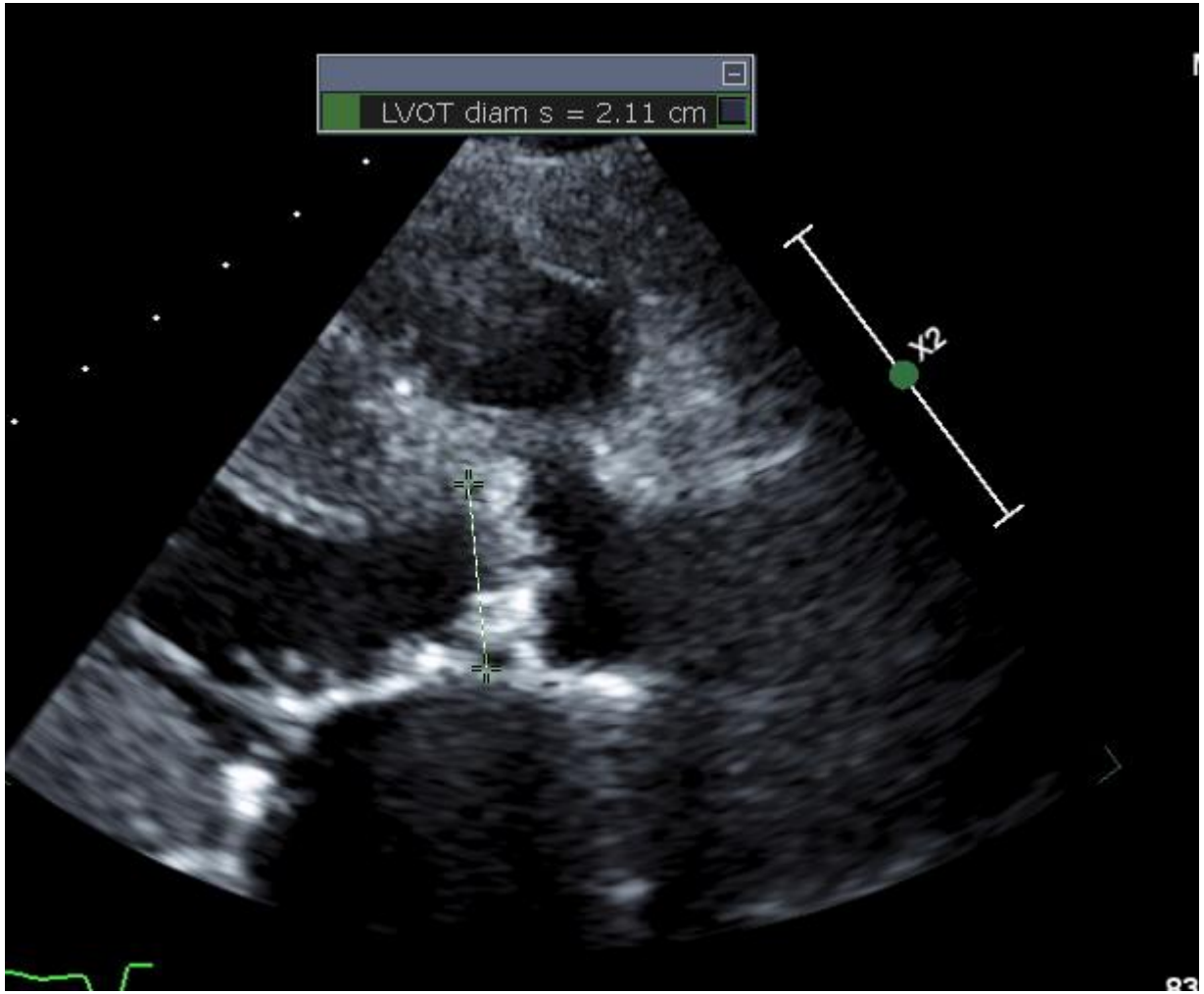
0.5-1 cm below annulus

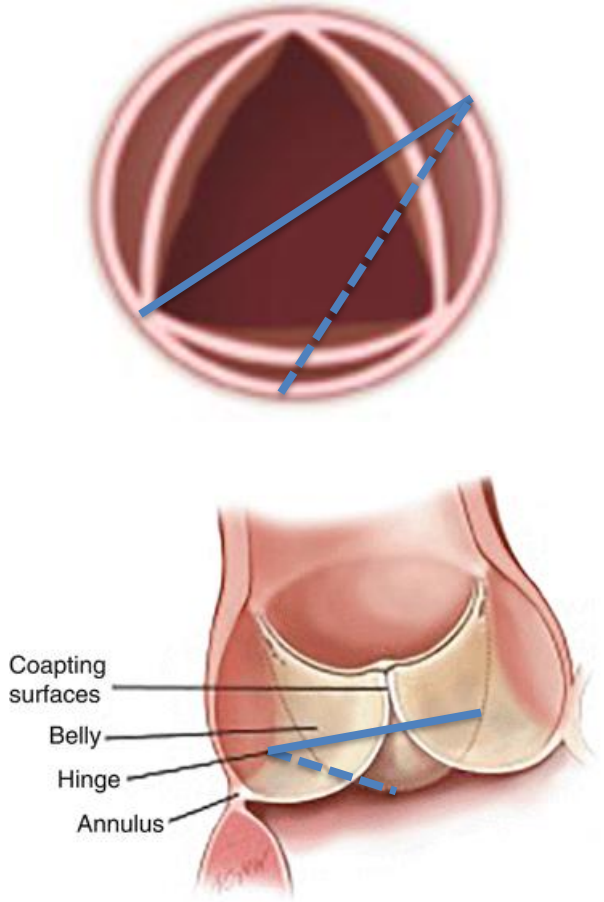
Measure the LVOT at the Annulus

- Prior outcomes studies looking at **AVA by continuity** have measured it this way
- Annulus **does not vary** much in the cardiac cycle
- **LVOT** is **very elliptical** in severe AS while **annulus remains circular**

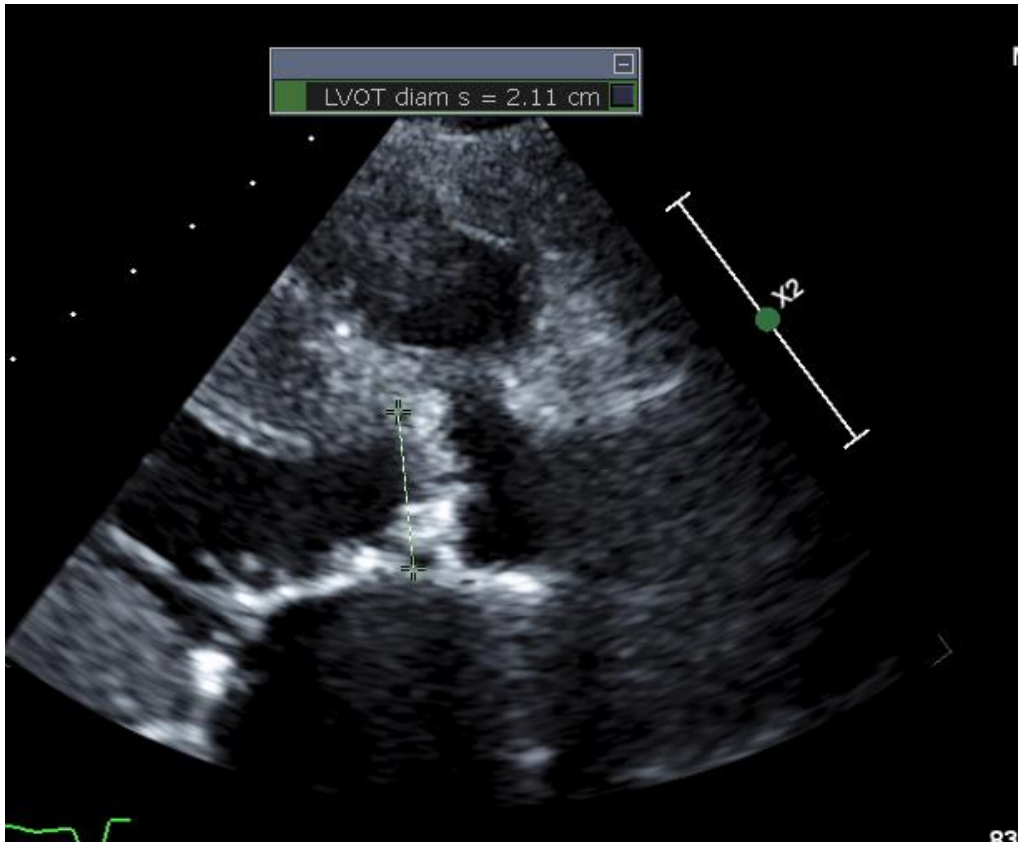
Hahn RT and Pibarot P. JASE 2015.

Don’t Measure at the Hingepoints



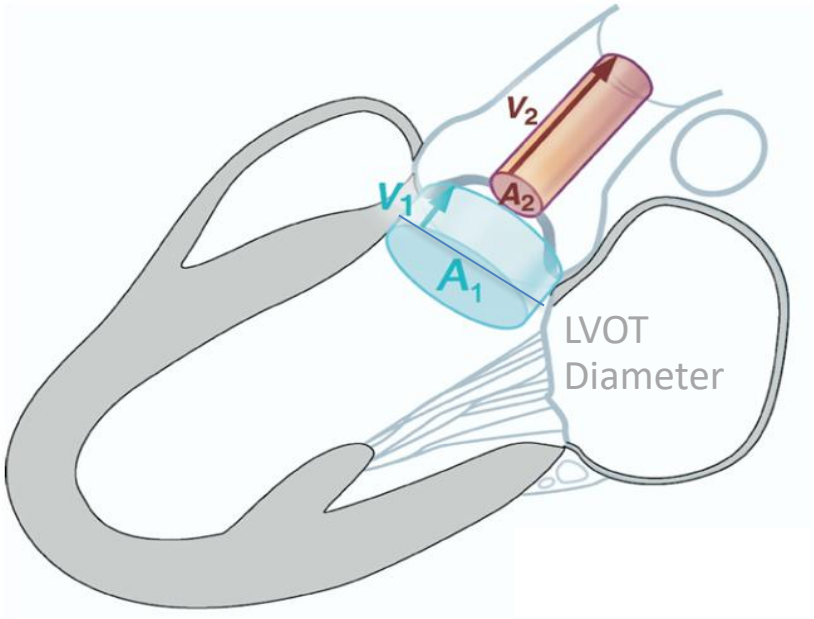


LVOT Measurement Tips



- Use zoomed view
- Measure mid-systole
- Ideal image show 1 hinge point
- Measure from hinge point to annulus beyond other hinge point

Don’t Mismeasure the LVOT VTI!



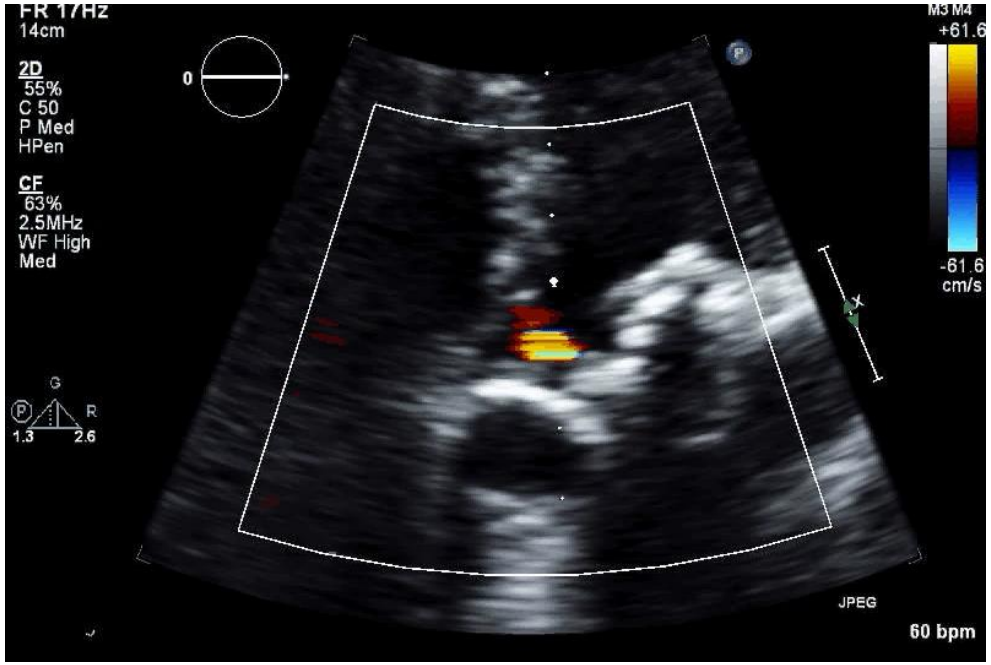
$$A_2 = (A_1 \times v_1)/v_2$$

$$AVA = (A_{LVOT} \times v_{LVOT})/v_{AV}$$

$$AVA = \frac{\left(\frac{D_{LVOT}}{2}\right)^2 \pi \times VTILVOT}{VTI_{AV}}$$

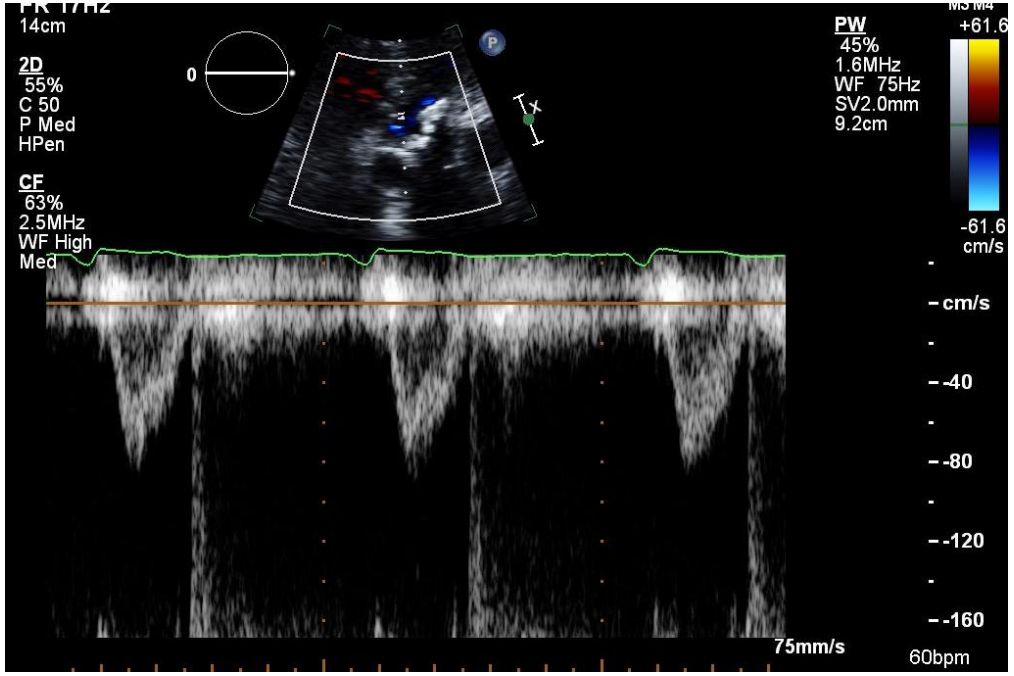
Mismeasurement of VTI_{LVOT} → Mismeasurement of AVA → Inappropriate characterization of AS

Measurement of LVOT VTI



- Sample volume should be *just proximal* to flow acceleration
  - If you measure within the flow acceleration → overestimation of AVA
  - If you measure to far into LV → underestimation of AVA

Measurement of LVOT VTI



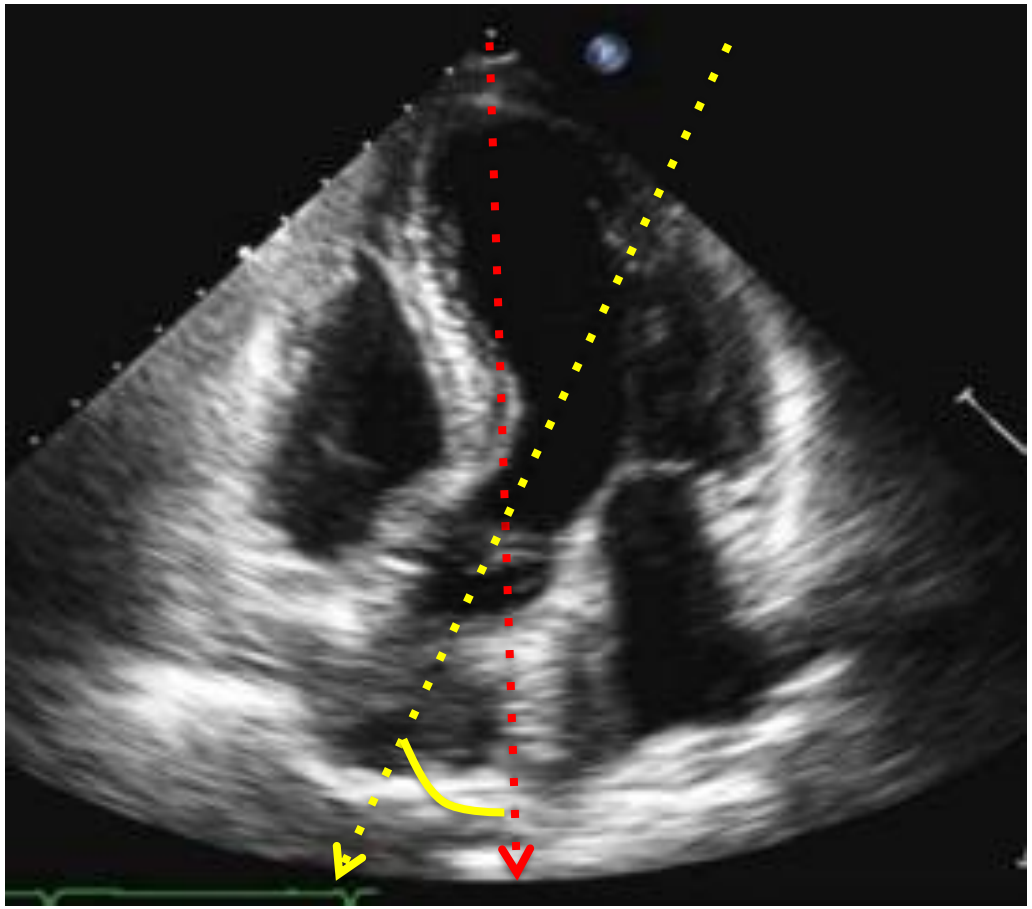
- Modal (white border, black interior) ideal
- No AV opening spike
- Visualize closure spike then move sample volume slightly ventricular

Don’t Underestimate Gradients!

- **High flow** (peak velocity > 4 m/s, mean gradient < 40 mmHg) with AVA > 1 cm^2 associated with **worse outcomes***
  - Medical trials do **NOT** want to include these patients
- Make sure that you’re not missing a high gradient

Unger et al. JACC. 2024.

Optimize Alignment



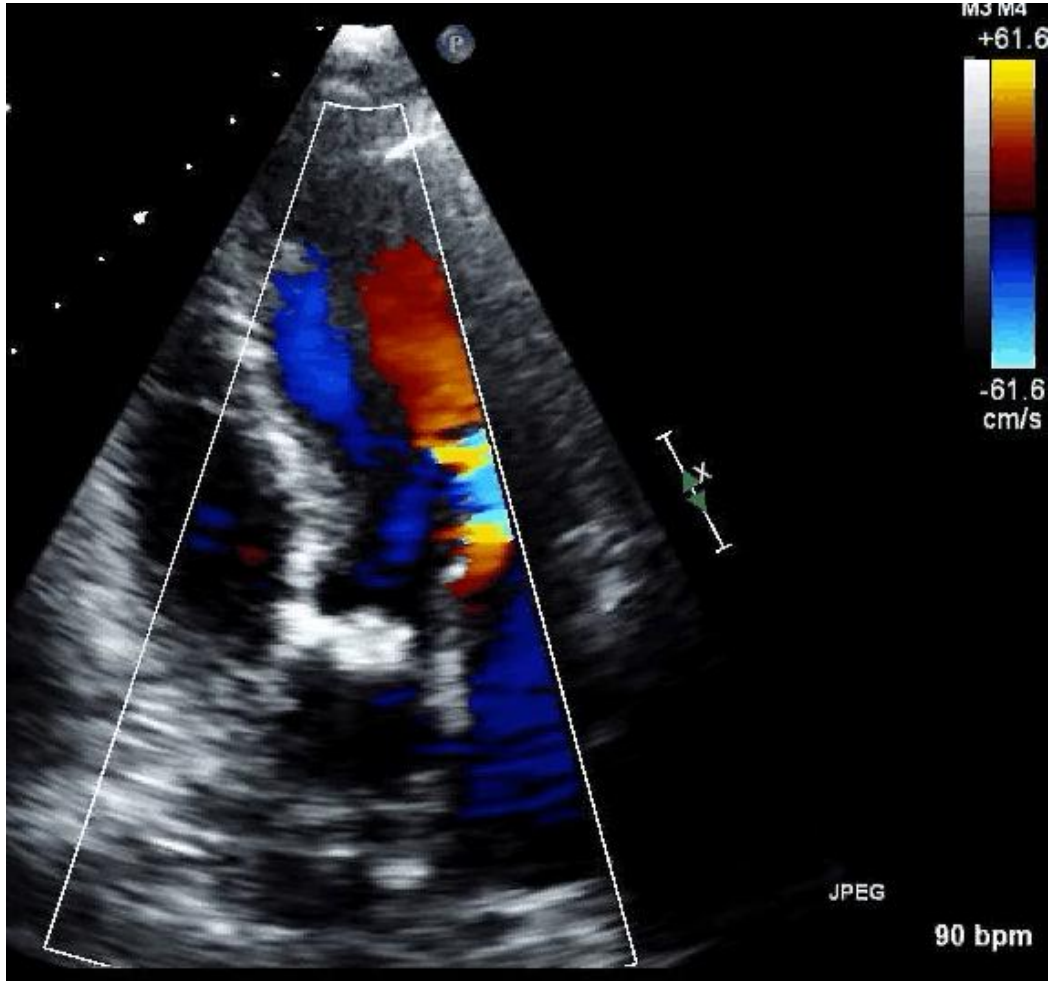
20° Misalignment

Peak velocity 3.7 m/s

Mean gradient 36 mmHg

AVA 1.1 cm^2

Optimize Alignment



< 10° Misalignment

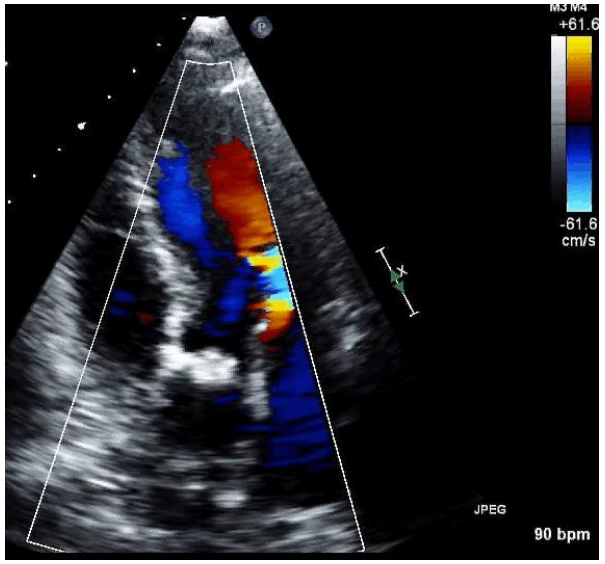
Peak velocity 4.2 m/s

Mean gradient 44 mmHg

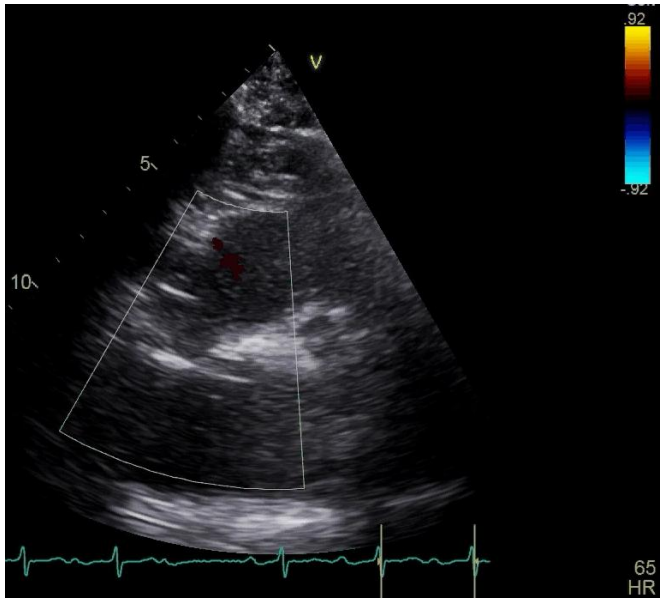
AVA 1 cm^2

Use All Views!

A5c



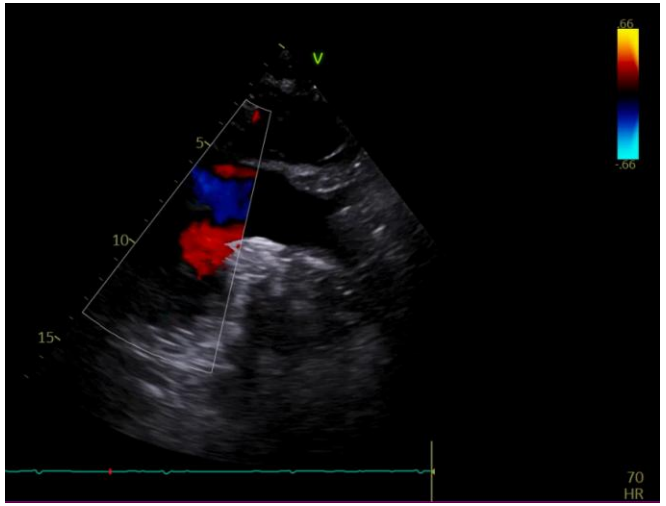
RSB



A3c



SSN



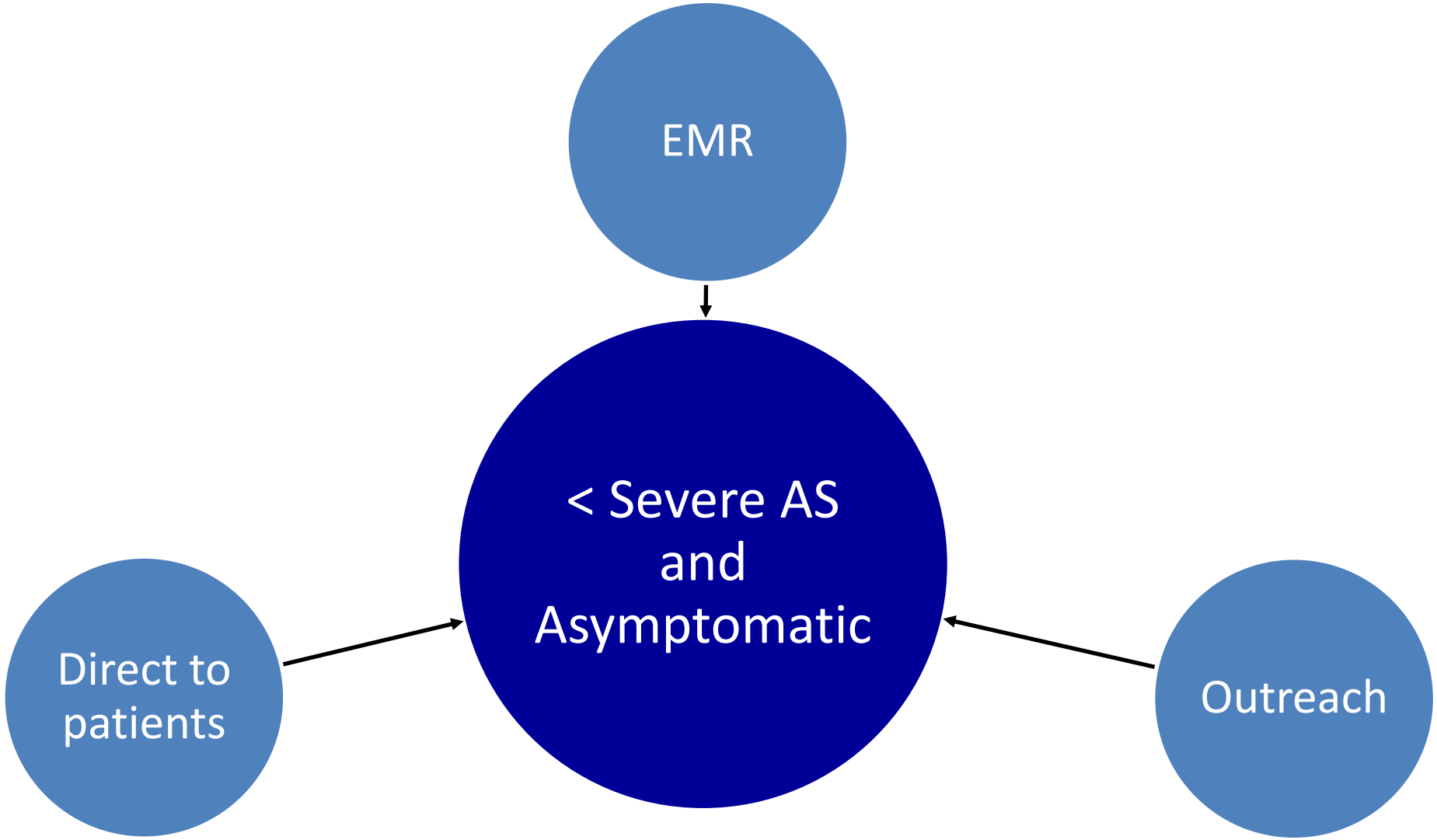
Dimensionless Index

- Dimensionless index = $LVOT_{VTI}/AV_{VTI}$
- Avoids LVOT measurement and angle issues
- Assessment:
  - Severe: < 0.25
  - Moderate: 0.25-.5
  - Mild: > 0.5
- DI < 0.25 has prognostic value in all-comers with AS and specifically in low gradient AS

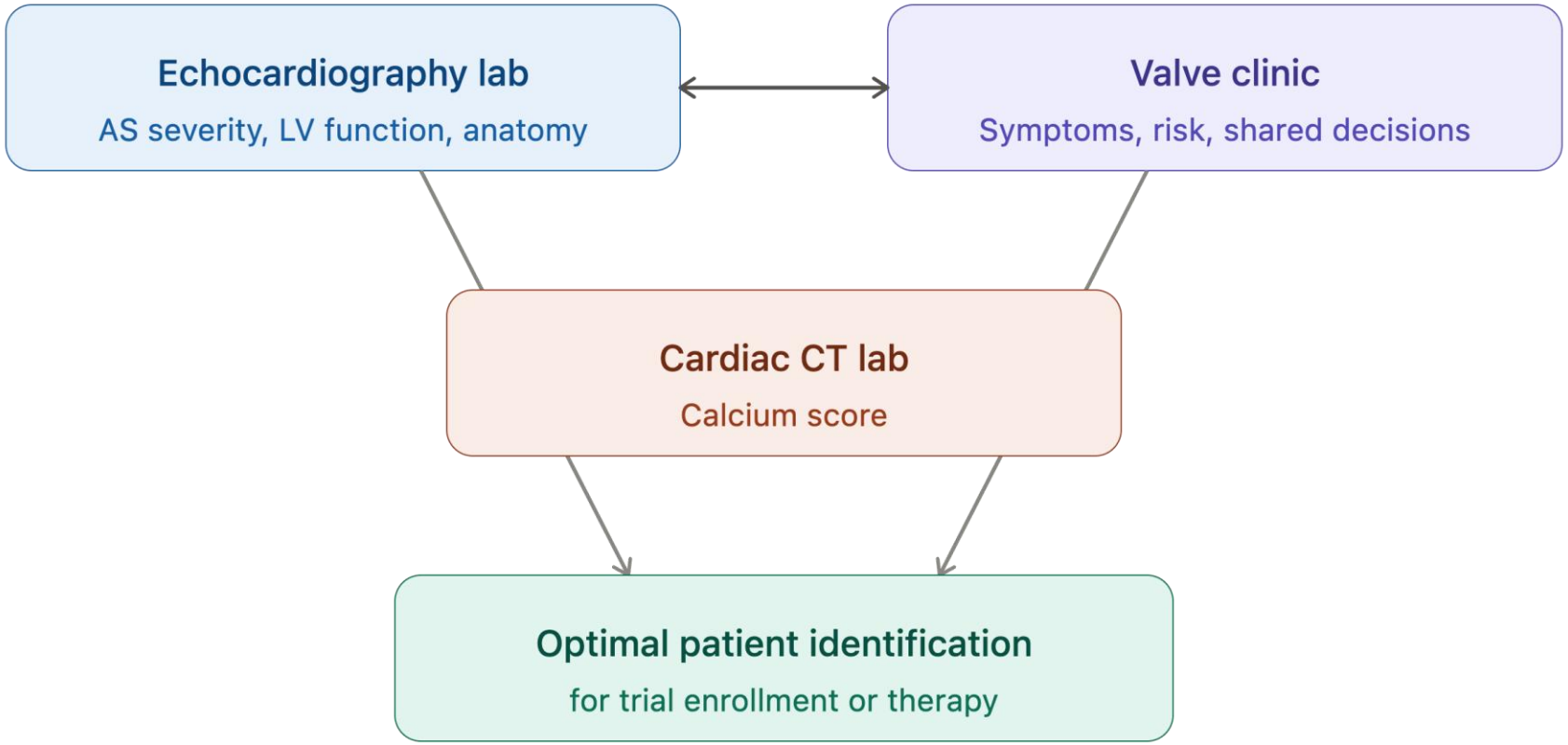
Baumgartner et al. J. Am Soc Echo 2017.
Altes et al. Circ CV Imaging 2021.
Rusinaru et al. JACC Imaging 2015.

Addressing Enrollment Challenges & Practical Guidance for Medical Therapy Trials

How to reach eligible patients?



Echo Lab and Valve Clinic Collaboration



Suggested Screening Criteria for Moderate AS

Screen EMR for:

- LVEF > 50%
- Native aortic valve
- AVA: .8 cm^2 – 1.7 cm^2 AND
- DI > 0.25 AND
- Peak velocity < 4 m/s AND
- Mean Gradient < 40 mmHg



Re-review by Trial Echocardiographer

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

University of Edinburgh

Personal Chair of Clinical Cardiology;

BHF Senior Clinical Research Fellow;

Vice-President European Association of Cardiovascular Imaging



Yee-Ping Sun, MD

Brigham and Women's Hospital

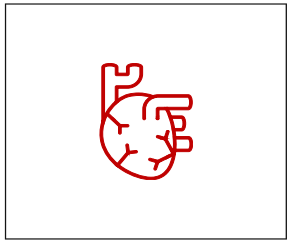
Harvard Medical School

Director, Cardiovascular Medicine Fellowship Program

Director, Structural Heart Disease Imaging Program

Assistant Professor of Medicine

INTERESTED IN LEARNING MORE?

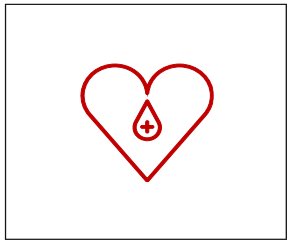


Join our upcoming Moderate AS Virtual Grand Rounds Sessions!

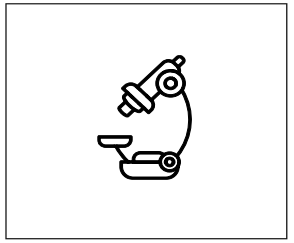


COMING SOON:

- **Session #4:** Engaging the Patient Voice & Driving Trial Participation – ***December 2026***



Sessions will encourage cross-disciplinary dialogue and discuss opportunities available across the moderate AS care pathway.



Scan to visit http://www.heart.org/ModerateAS for a recording of today's session, additional resources, and information on future Virtual Grand Round sessions!

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/ModerateAS

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