The Upstream Management of Aortic Stenosis

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Disclosure Statement of Financial Interest

Within the past 12 months, I or my spouse/partner have had a financial interest/arrangement or affiliation with the organization(s) listed below.

Affiliation/Financial Relationship	Company
• Grant/Research Support	• Edwards Lifesciences, Abbott
• Scientific Advisory Board	• Medtronic
• Executive Physician Council	• Boston Scientific Corp

Upstream Management of Aortic Stenosis

?

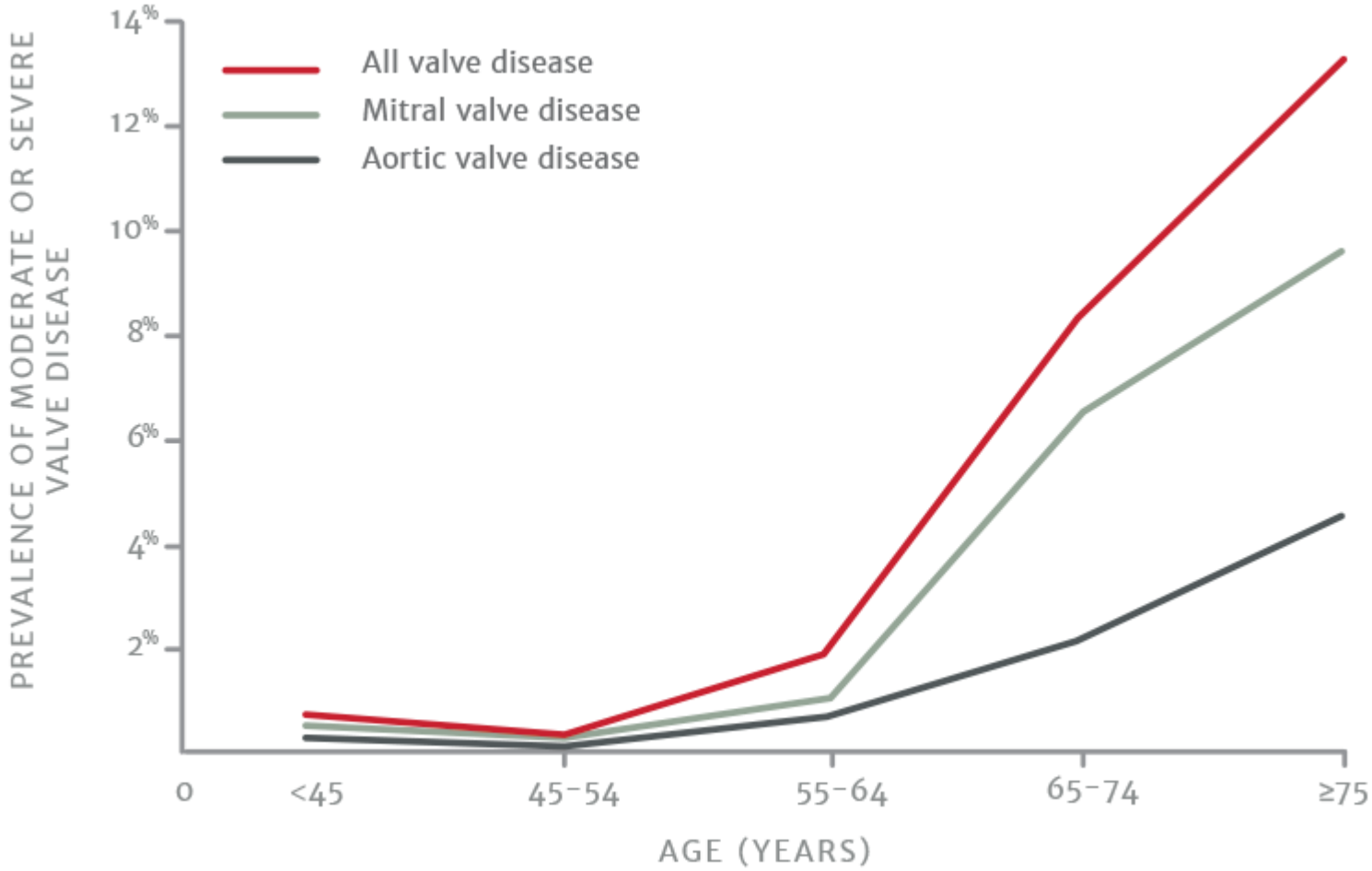
Upstream Management of CAD

- Pathophysiology
- Risk Factor Modification (i.e. lipids, smoking etc)
- Detection (CAC, CCTA, stress testing, Invasive angio)
- Criterion for Treatment (symptoms, anatomy, FFR)
- Treatment Options (Medical, PCI, CABG)
- Effectiveness and Durability of Treatment Options

Upstream Management of Aortic Stenosis

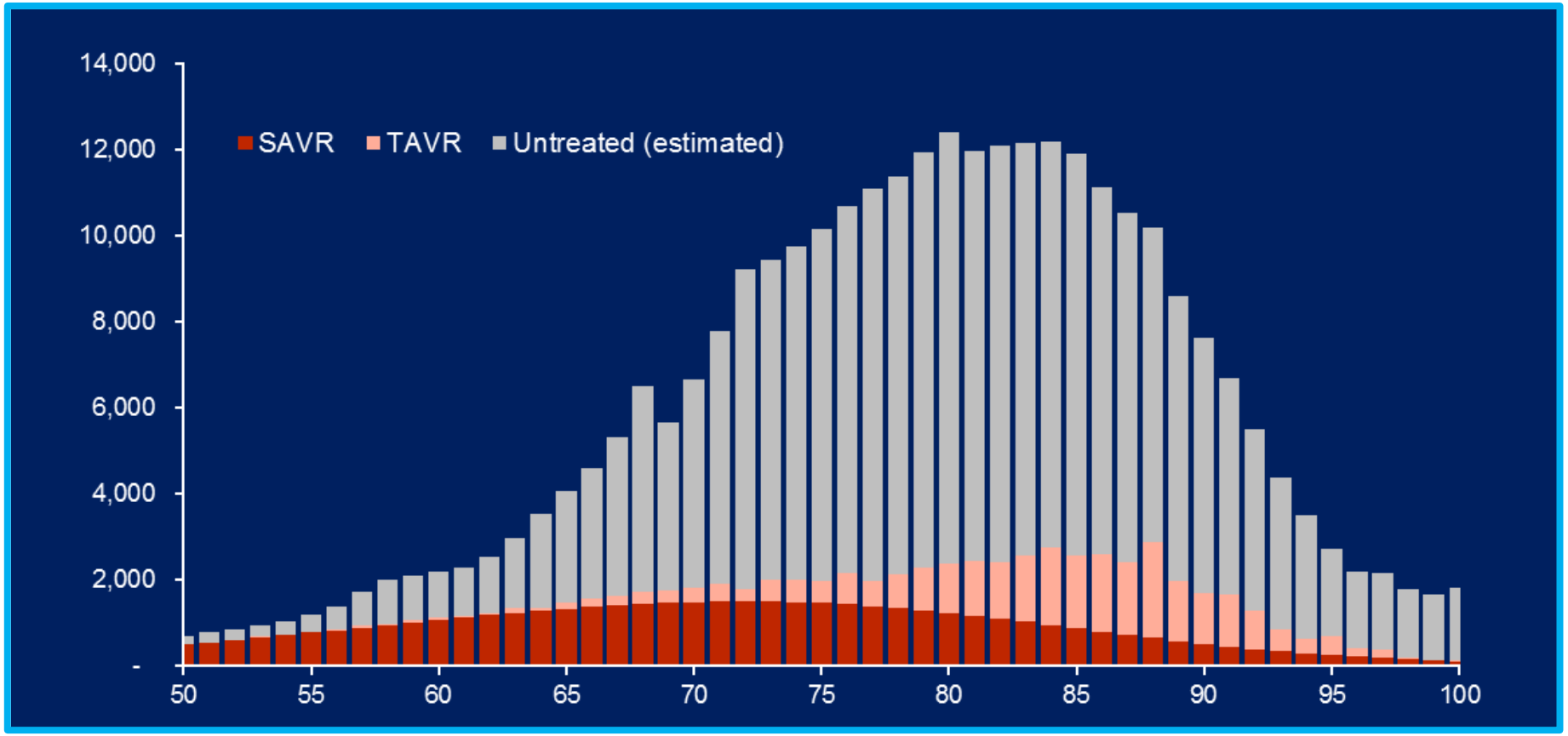
- Pathophysiology
- Risk Factors

Incidence of AS according to Age

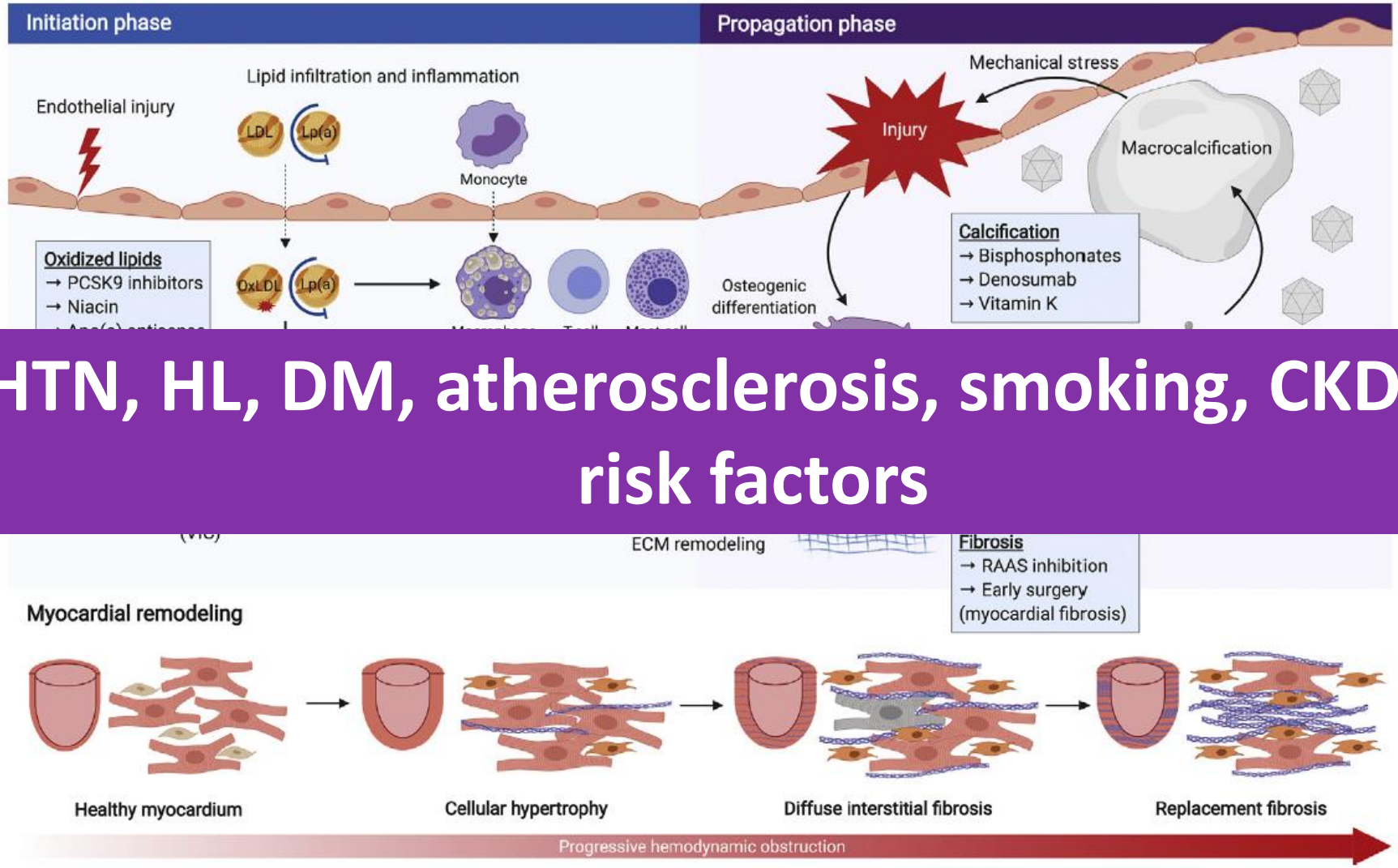


Incidence of AS according to Age (6% above age 75)

2015 Severe Symptomatic AS Patients in the U.S.



Pathophysiology of Aortic Stenosis



HTN, HL, DM, atherosclerosis, smoking, CKD are risk factors

Statin Trials to Treat CAVD

Study (year)	Participants	Outcomes
Retrospective study (2001)[73]	180 participants aged >60 years	Significant decrease in peak systolic pressure gradient (a marker of aortic valve function) in patients taking statins
Retrospective study (2001)[75]	174 patients with mild-to-moderate CAVD (57 statin-treated, 117 not taking statins)	Patients taking statins had a slight improvement in aortic valve remodelling
Prospective analysis (2002)[82]	156 patients (38 statin-treated, 118 not receiving any lipid-lowering treatment)	Patients taking statins had a slight improvement in aortic valve area
SALTIRE trial (2005)[83]	Randomized, double-blind trial of 155 patients given atorvastatin or placebo (mean follow-up 25 months)	No significant difference in aortic jet velocity or valve calcification between atorvastatin and placebo
RAAVE trial (2007)[74]	Prospective study of 121 patients with moderate-to-severe CAVD (61 patients received rosuvastatin, 60 received no treatment)	Statin treatment seemed to slow haemodynamic progression of CAVD, as indicated by changes in aortic jet velocity
SEAS trial (2008)[84]	Randomized, double-blind trial of 1,873 patients with mild-to-moderate asymptomatic aortic stenosis receiving either simvastatin or placebo daily	Statin treatment did not reduce cardiovascular events associated with CAVD
SEAS follow-up (2010)[85]	1,763 patients from the SEAS trial divided into tertiles according to CAVD severity on the basis of peak aortic jet velocity	Statins did not improve CAVD outcomes regardless of initial severity of disease
ASTRONOMER trial (2010)[86]	Randomized, double-blind trial of 269 patients given rosuvastatin or placebo	Statin treatment did not reduce deterioration in peak aortic pressure gradient

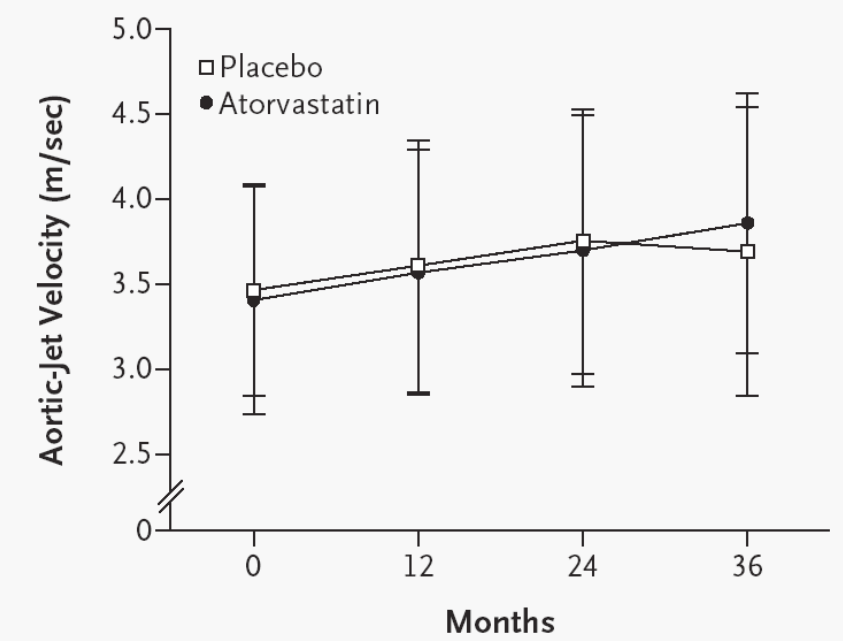
Abbreviation: CAVD, calcific aortic valve disease.

JD Hutcheson, E Aikawa and WD Merryman. Nat. Rev. Cardiol. 11, 218–231 (2014)

Failure of Statin Rx to Treat CAVD

SALTIRE (2005)

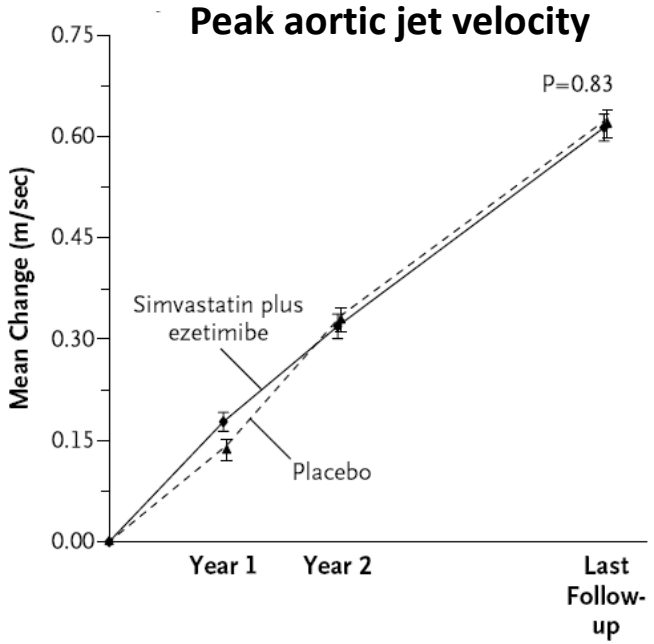
N = 155 pts



Cowell et al, NEJM, 352:2389-97,2005

SEAS (2008)

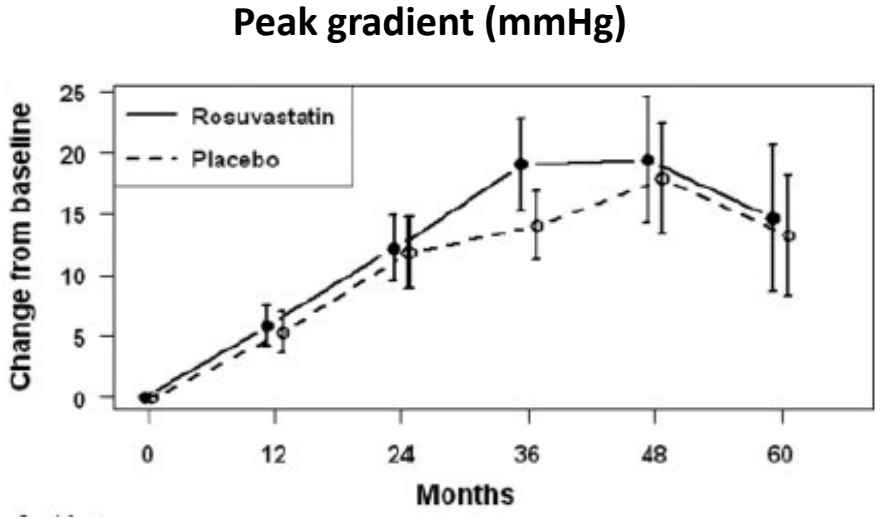
N = 1,873 pts



Rossebo et al, NEJM, 359:1343-56, 2008

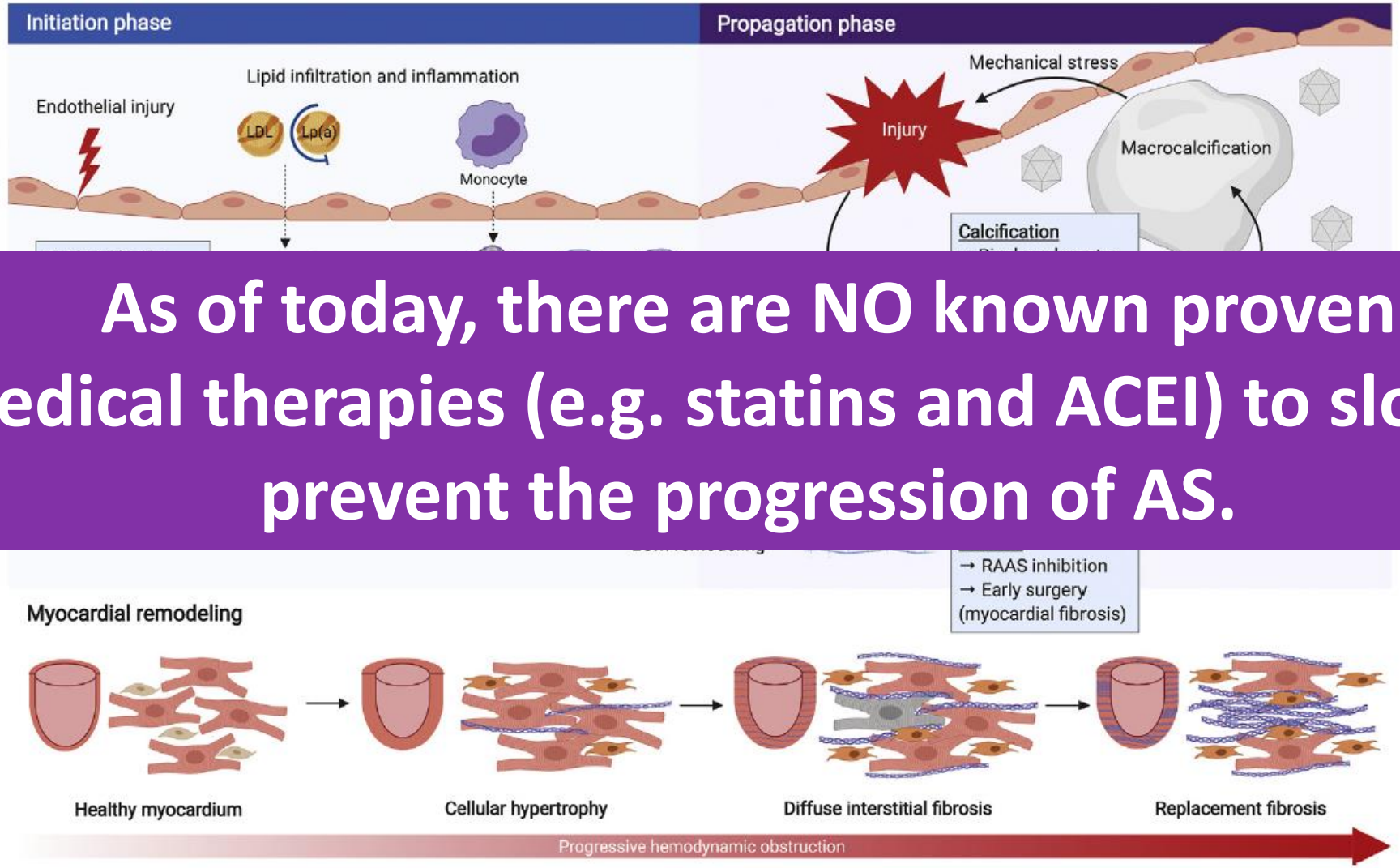
ASTRONOMER (2010)

N = 269 pts



Chan et al, Circulation 121:306-314, 2010

Pathophysiology of Aortic Stenosis



As of today, there are NO known proven medical therapies (e.g. statins and ACEI) to slow or prevent the progression of AS.

The NEW ENGLAND JOURNAL of MEDICINE

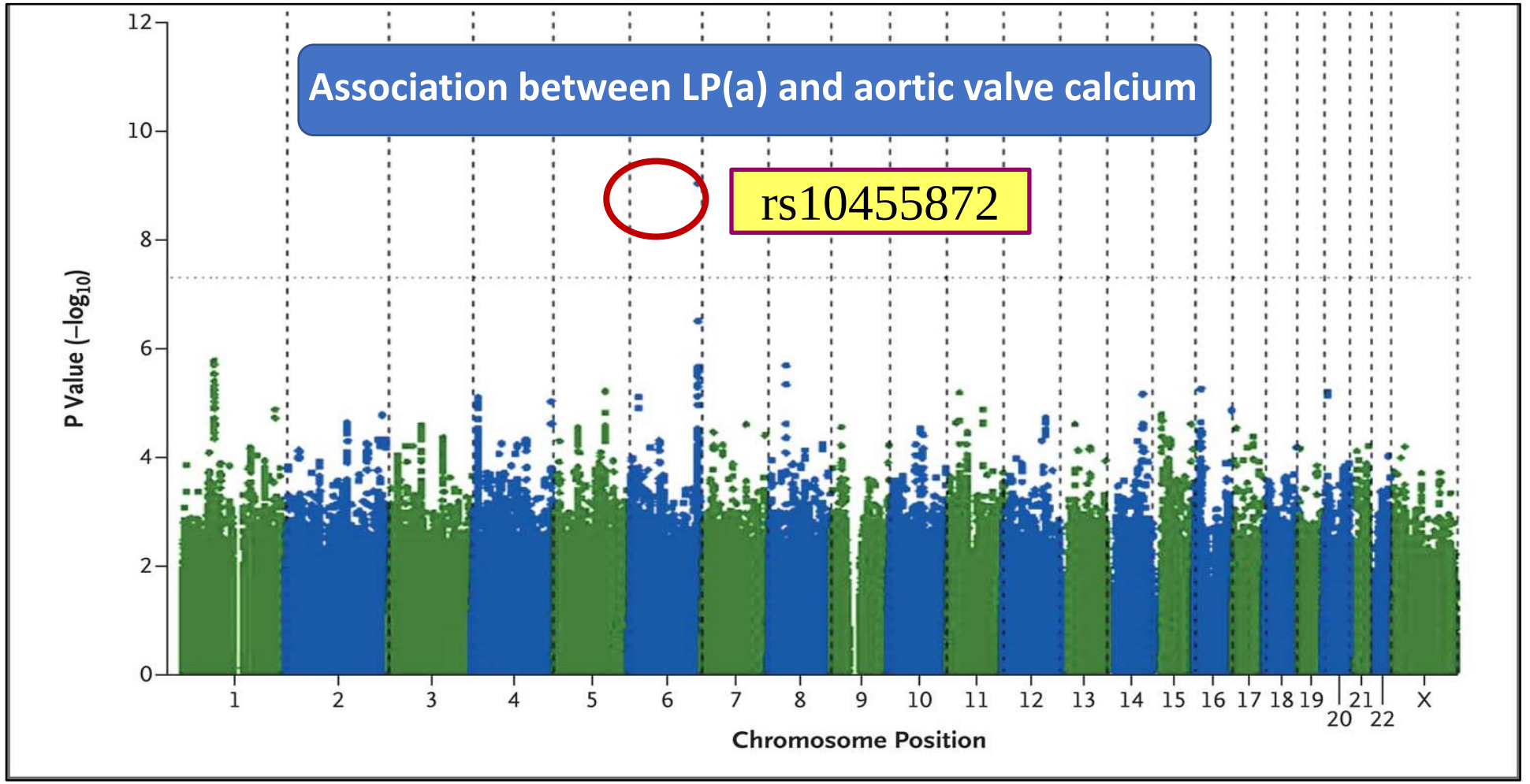
ESTABLISHED IN 1812 FEBRUARY 7, 2013 VOL. 368 NO. 6

Genetic Associations with Valvular Calcification and Aortic Stenosis

George Thanassoulis, M.D., Catherine Y. Campbell, M.D., David S. Owens, M.D., J. Gustav Smith, M.D., Ph.D., Albert V. Smith, Ph.D., Gina M. Peloso, Ph.D., Kathleen F. Kerr, Ph.D., Sonali Pechlivanis, Ph.D., Matthew J. Budoff, M.D., Tamara B. Harris, M.D., Rajeev Malhotra, M.D., Kevin D. O'Brien, M.D., Pia R. Kamstrup, M.D., Ph.D., Børge G. Nordestgaard, M.D., D.M.Sc., Anne Tybjaerg-Hansen, M.D., D.M.Sc., Matthew A. Allison, M.D., M.P.H., Thor Aspelund, Ph.D., Michael H. Criqui, M.D., M.P.H., Susan R. Heckbert, M.D., Ph.D., Shih-Jen Hwang, Ph.D., Yongmei Liu, Ph.D., Marketa Sjogren, Ph.D., Jesper van der Pals, M.D., Ph.D., Hagen Kälsch, M.D., Thomas W. Mühleisen, Ph.D., Markus M. Nöthen, M.D., L. Adrienne Cupples, Ph.D., Muriel Caslake, Ph.D., Emanuele Di Angelantonio, M.D., Ph.D., John Danesh, F.R.C.P., Jerome I. Rotter, M.D., Sigurdur Sigurdsson, M.Sc., Quenna Wong, M.S., Raimund Erbel, M.D., Sekar Kathiresan, M.D., Olle Melander, M.D., Ph.D., Vilmundur Gudnason, M.D., Ph.D., Christopher J. O'Donnell, M.D., M.P.H., and Wendy S. Post, M.D., for the CHARGE Extracoronary Calcium Working Group

Thanassoulis G et al. NEJM 2013; 368: 503-12

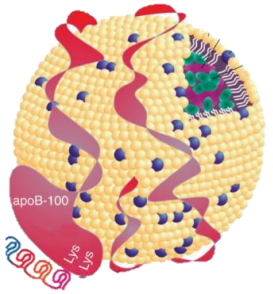
Lp (a) Reigns Supreme in GWAS!

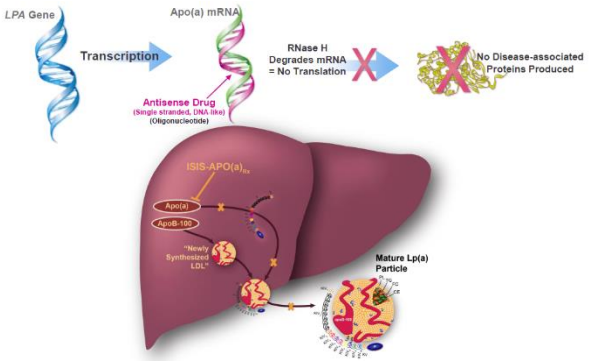


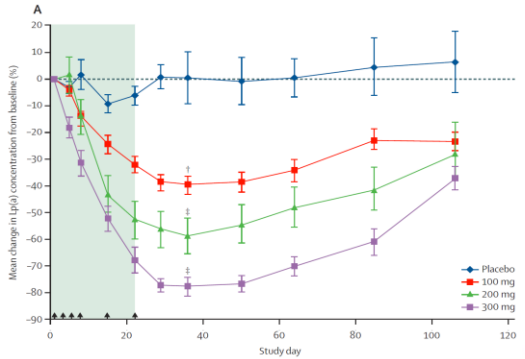
Thanassoulis G et al. NEJM 2013; 368: 503-12

Lp (a) Reigns Supreme!

- About 20% of the general population (65 Million people in North America) have elevated Lp(a)
- Lp(a) circulating levels are determined genetically and currently available drugs (Niacin) only achieve modest reduction in Lp(a)
- Phase I and II trials report that oligonucleotide antisense directed to Apo(a), reduces Lp(a) levels by >80% with minimal side effects

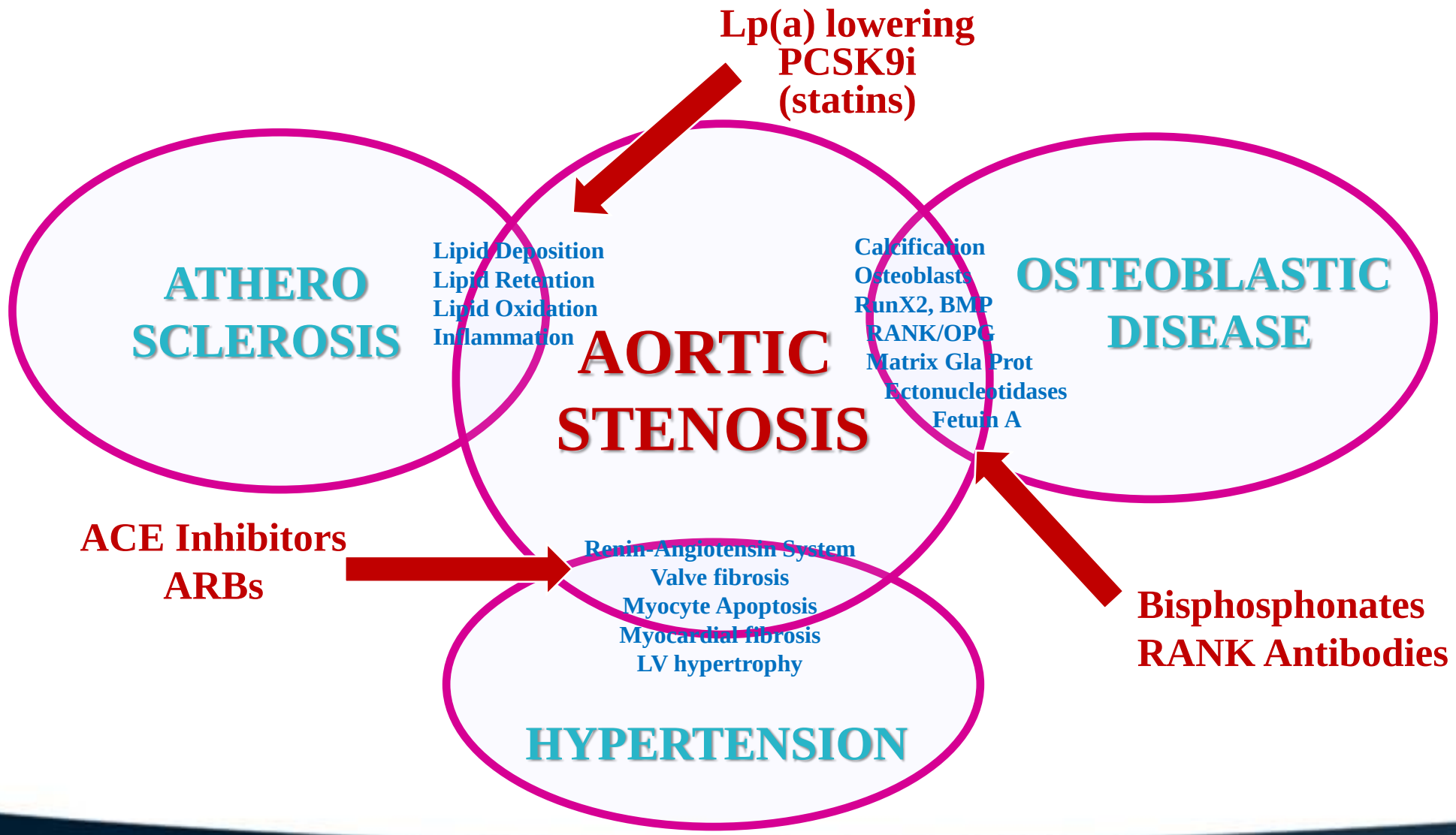






Tsimikas et al. Lancet 2015

Modern Thinking – Medical Rx for AS



Adapted from… Dweck et al. JACC 2012

Future Perspectives on Medical Rx for CAVD

Table 1
Ongoing randomized clinical trials in aortic stenosis

Study	Target	Treatment	Main Inclusion Criteria	Follow-up	Primary Efficacy Endpoints
PCSK9 inhibitors in the progression of aortic stenosis (NCT03051360)	ApoB-containing lipoproteins; PCSK9	Biweekly injection of PCSK9 inhibitor vs placebo	Mild-moderate aortic stenosis (n = 140)	2 years	Change in aortic valve CT calcium score and 18F-NaF uptake
EAVaLL—Early Aortic Valve Lipoprotein (a) Lowering (NCT02109614)	Lipoprotein(a)	Daily extended-release niacin 1500–2000 mg vs Placebo	Aortic sclerosis or mild aortic stenosis + elevated Lp(a) levels (>50 mg/dL) (n = 150)	2 years	Change in aortic valve CT calcium score
SALTIRE II—Study Investigating the Effect of Drugs Used to Treat Osteoporosis on the Progression of Calcific Aortic Stenosis (NCT02132026)	Mineral metabolism	• Alendronic acid (n = 50) vs placebo tablets (n = 25) • Denosumab (n = 50) vs placebo injections (n = 25)	Aortic stenosis (V_{max} >2.5 m/s)	2 years	Change in aortic valve calcium score, aortic valve 18F-NaF uptake
BASIK2—Bicuspid Aortic Valve Stenosis and the Effect of vItamin K2 on calcium metabolism on 18F-NaF PET/MRI (NCT02917525)	Vitamin K2-Matrix Gla protein	Daily vitamin K2 360 μg (n = 22) vs placebo (n = 22)	Bicuspid aortic valve and calcified mild to moderate aortic stenosis	18 months	Change in aortic valve 18F-NaF uptake at 6 mo; change in aortic valve calcium score (secondary endpoint at 6 + 18 mo)
EvoLVeD—Early Valve Replacement Guided by Biomarkers of LV Decompensation in Asymptomatic Patients With Severe AS (NCT03094143)	Midwall fibrosis and timing of intervention	Early aortic valve replacement vs routine care	Asymptomatic severe aortic stenosis (V_{max} >4.0 m/s; or V_{max} >3.5 with AVA <0.6 cm^2/m^2)	± 3 y (until 88 events accrue)	Composite of all-cause mortality or unplanned aortic stenosis–related hospitalisation

Abbreviations: ApoB, apolipoprotein B; AVA, aortic valve area; V_{max}, peak aortic jet velocity.

Incomplete Understanding of Pathogenesis

- Are there octogenarian with pristine aortic valves?
- Are risk factor modifications occur early enough in trials?
- Should we be studying aortic stenosis progression or prevention?
- Are all tricuspid valves born equal?
- LV reserve/response to aortic stenosis variations

Upstream Management of Aortic Stenosis

- Pathophysiology
- Risk Factors
- Detection

Future Screening Tools for Valvular Heart Disease

Artificial Intelligence/Machine Learning

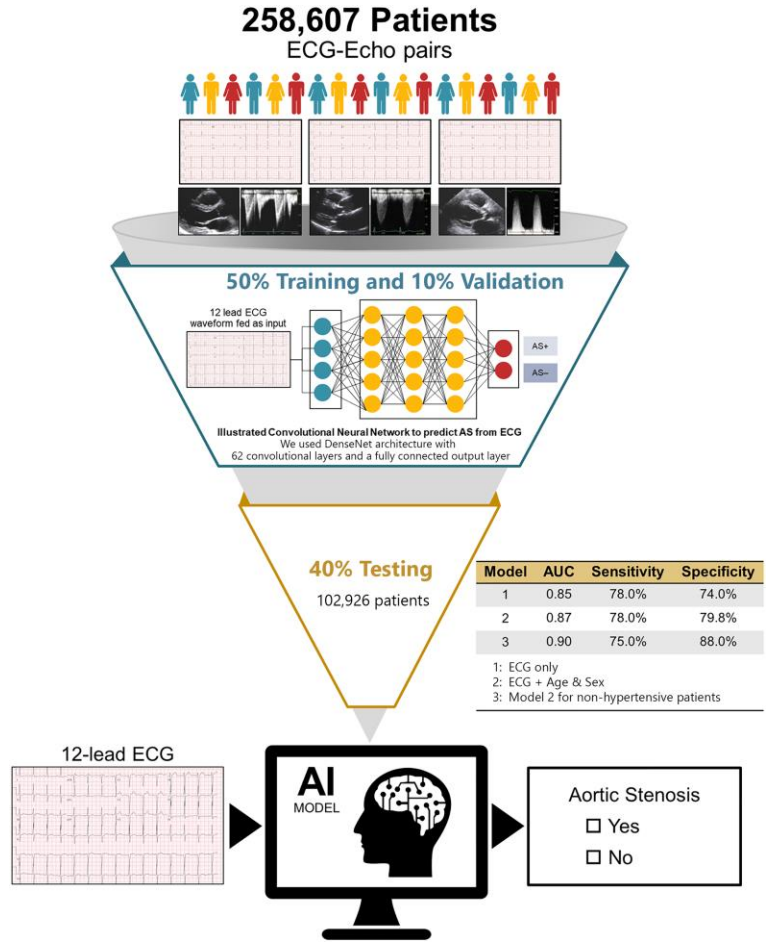
ESC European Society of Cardiology
European Heart Journal (2021) **00**, 1–12
doi:10.1093/eurheartj/ehab153

CLINICAL RESEARCH
Valvular heart disease

Electrocardiogram screening for aortic valve stenosis using artificial intelligence

Michal Cohen-Shelly [1], Zachi I. Attia [1], Paul A. Friedman[1], Saki Ito[1], Benjamin A. Essayagh [1], Wei-Yin Ko[1],Dennis H. Murphree [1], Hector I. Michelena [1], Maurice Enriquez-Sarano[1], Rickey E. Carter [2], Patrick W. Johnson [2], Peter A. Noseworthy[1], Francisco Lopez-Jimenez [1], and Jae K. Oh[1]*

In the test group, the AI-ECG labelled 3833 (3.7%) patients as positive with the area under the curve (AUC) of 0.85. The sensitivity, specificity, and accuracy were 78%, 74%, and 74%, respectively.



Future Screening Tools for Valvular Heart Disease

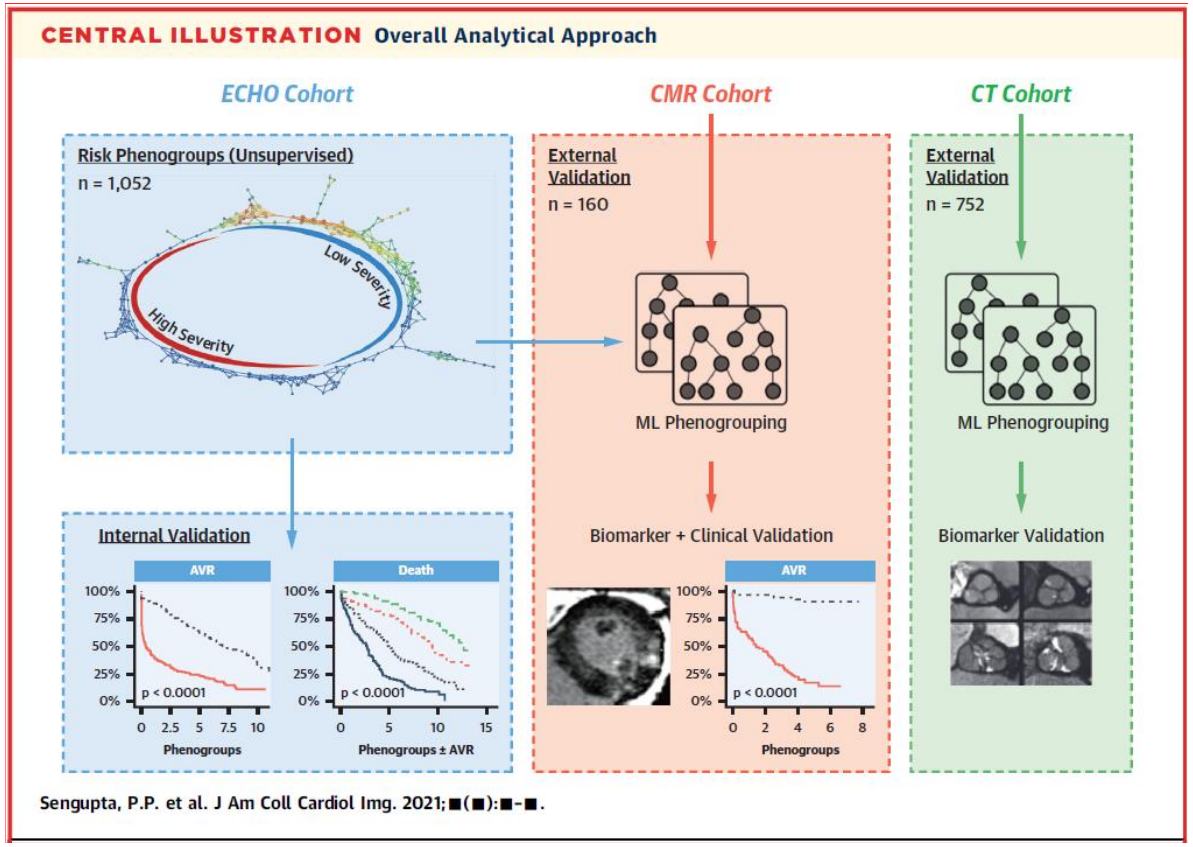
Artificial Intelligence/Machine Learning

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] for the Artificial Intelligence for Aortic Stenosis at Risk International Consortium

Conclusions:

Machine learning can integrate ECHO measurements to augment the classification of disease severity in most patients with AS, with major potential to optimize the timing of AVR. (JACC Imaging 2021)



Upstream Management of Aortic Stenosis

- Pathophysiology
- Risk Factor Modification
- Detection
  - Is there a CAC score equivalent for early aortic stenosis?
    - Score of 1648 is associated with severe AS

Upstream Management of Aortic Stenosis

- Pathophysiology
- Risk Factor Modification
- Detection
- Criteria for Treatment

Traditional Thinking – Aortic Stenosis

Aortic Stenosis

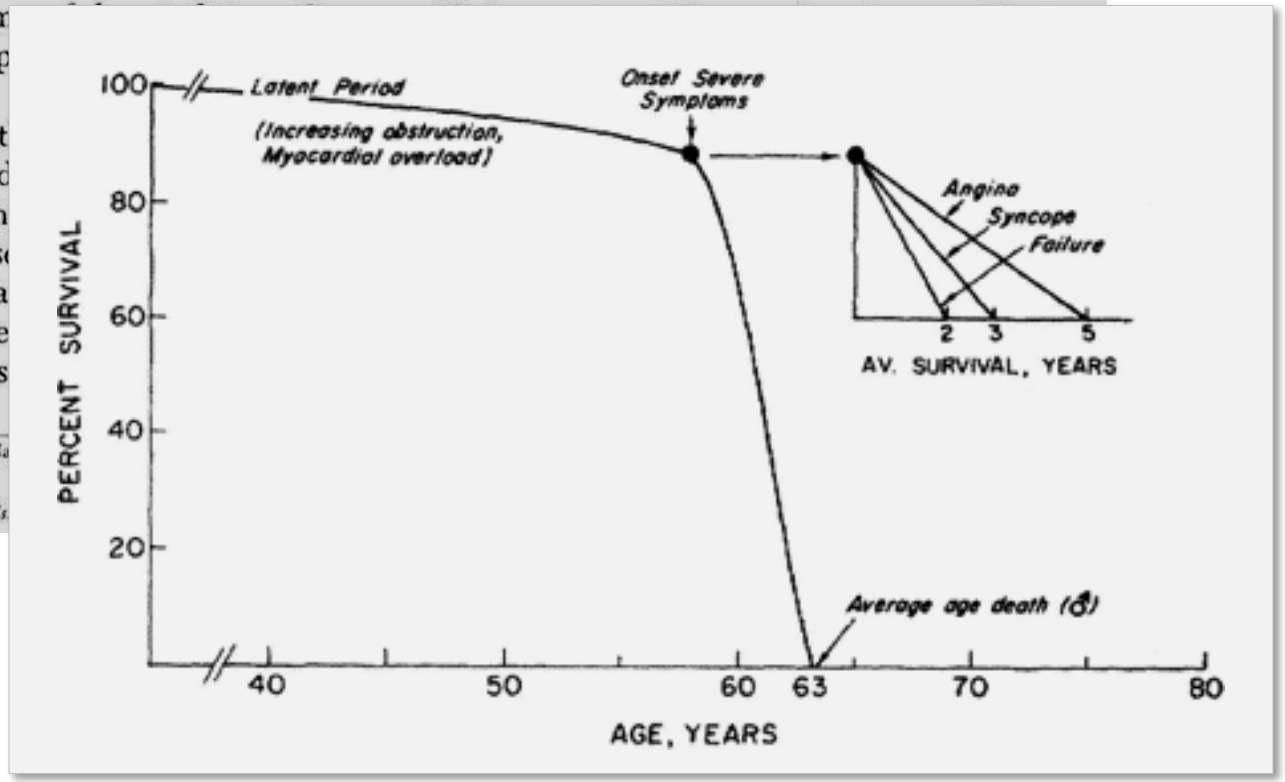
By John Ross, Jr., M.D. and Eugene Braunwald, M.D.

THE ADVENT of corrective operations for various form placed increasing emp accurate information history of patients wit lesions. An understand assumes particular im aortic stenosis becaus dence of sudden dea disease and the grave to accompany the ons

patients with isolated valvular aortic stenosis

From the Cardiology Branch, Na stitute, Bethesda, Maryland.

Supplement V to Circulation, Vols



Ross and Braunwald, *Circulation* 1968;38:V-61

Traditional Thinking – Aortic Stenosis

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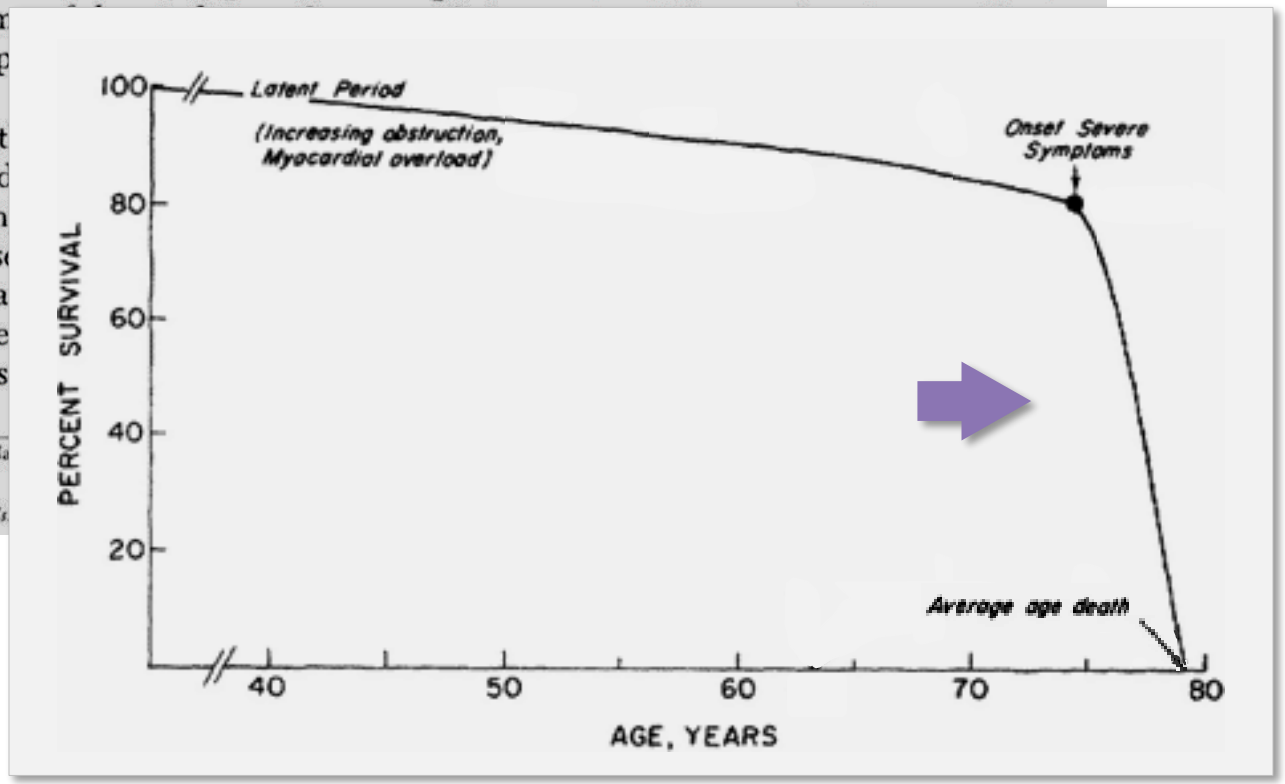
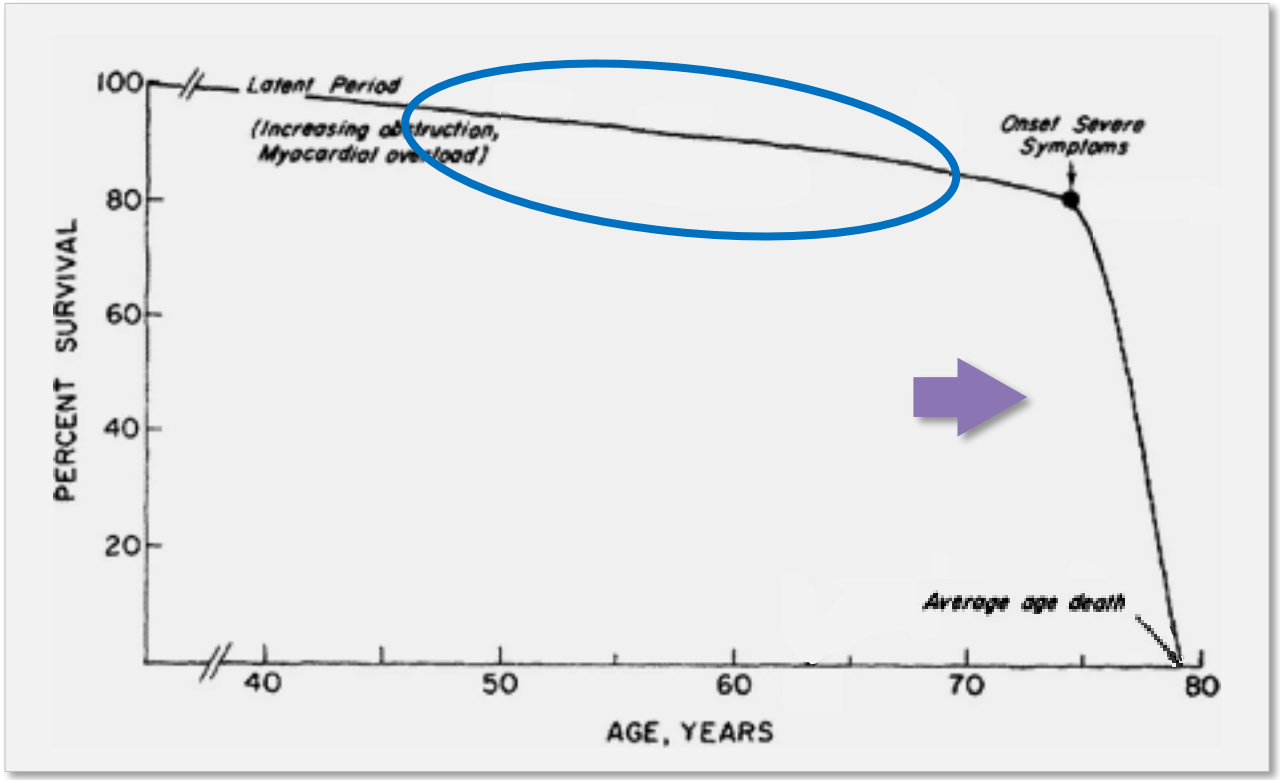


Ross and Braunwald, *Circulation* 1968;38:V-61

Traditional Thinking – Aortic Stenosis

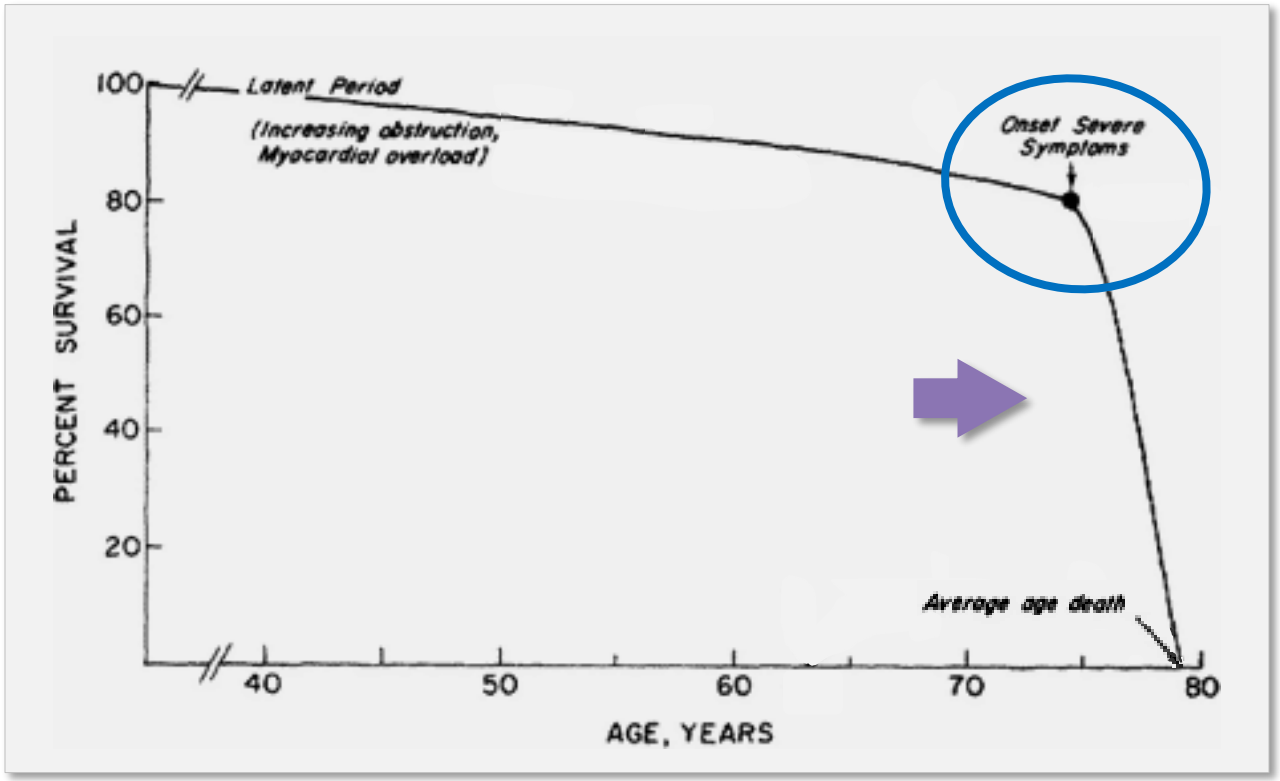
Fundamental fallacies: 1. there are no important reversible and irreversible structural changes during the so-called latent period which negatively impact subsequent clinical outcomes



Ross and Braunwald, *Circulation* 1968;38:V-61

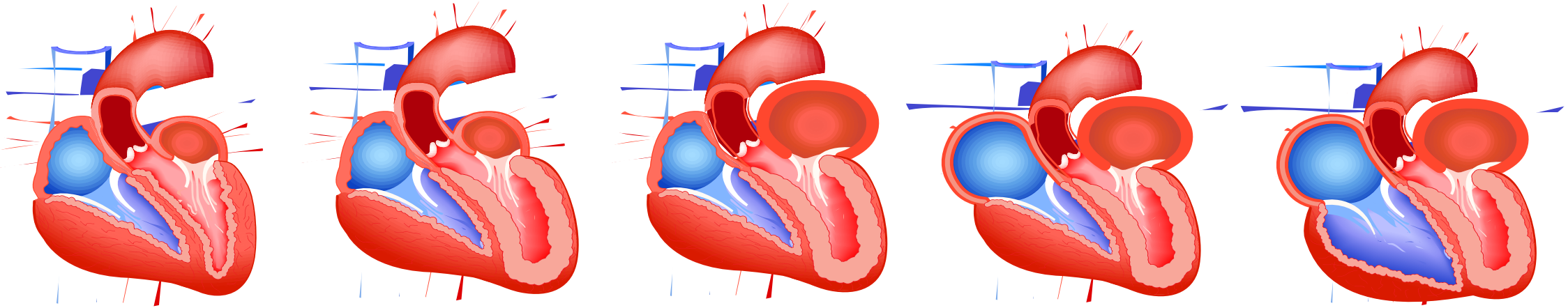
Traditional Thinking – Aortic Stenosis

Fundamental fallacies: 2. the onset of symptoms is discrete, easily identifiable (even in the elderly), and is inexorably linked to aortic stenosis severity



Ross and Braunwald, *Circulation* 1968;38:V-61

Staging Classification in Severe AS (n=1,661 pts)

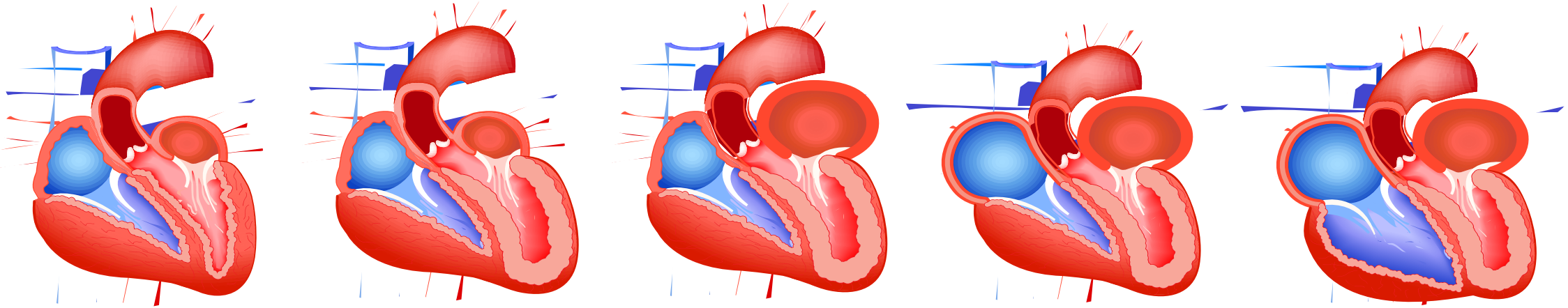


Stage 0 No damage	Stage 1 LV damage	Stage 2 LA/Mitral damage	Stage 3 PA/Tricuspid damage	Stage 4 RV damage
	Increased LV Mass Index >115 g/m^2 Male >95 g/m^2 Female	Indexed left atrial volume >34mL/m^2	PAS ≥60mmhg	Moderate-Severe RV dysfunction
	E/e' >14	Moderate-Severe MR	Moderate-Severe TR	
	EF <50%	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 Jul 21

Staging Classification in Severe AS (n=1,661 pts)



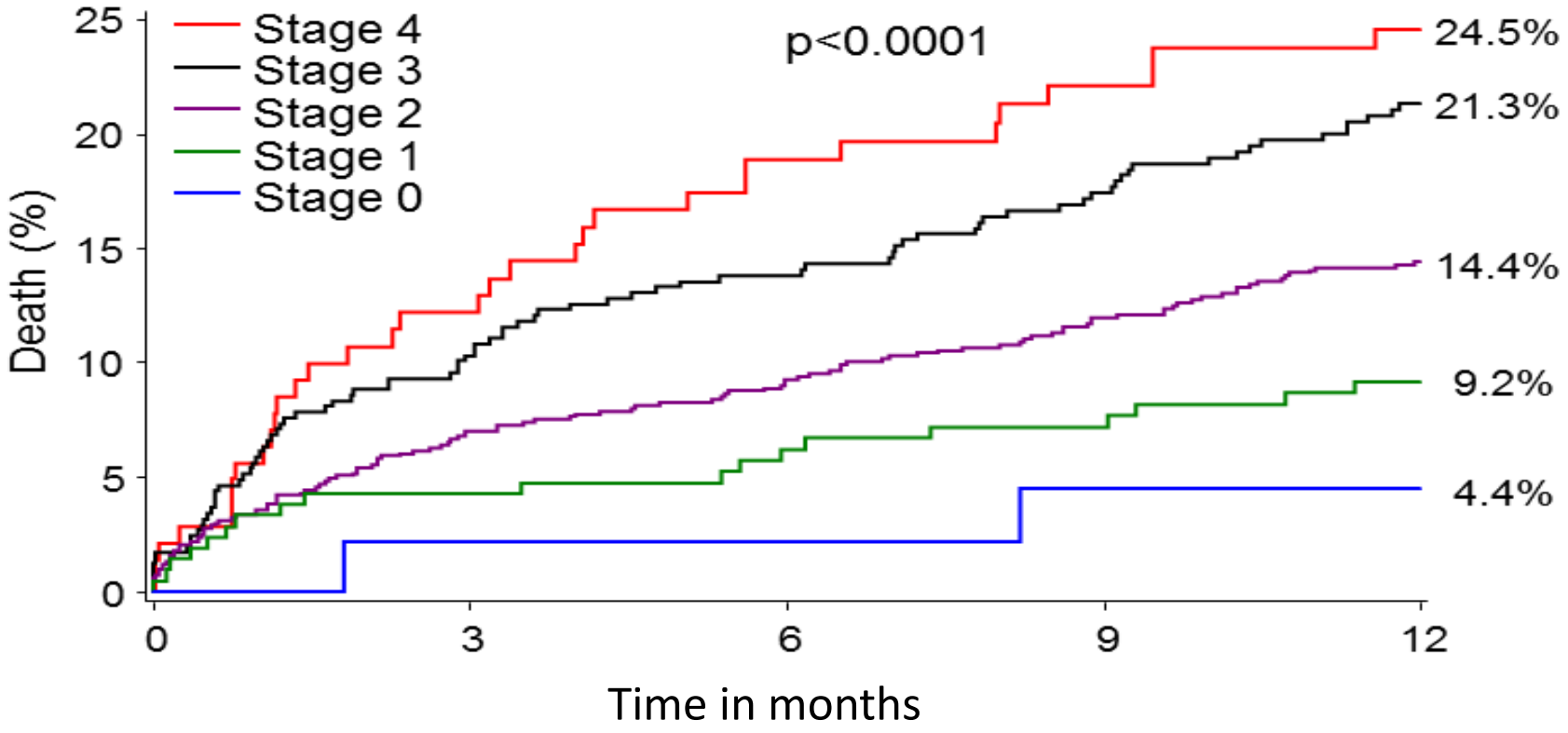
N=47 (2.8%)	N=212 (12.8%)	N=844 (50.8%)	N=413 (24.9%)	N=145 (8.7%)
	EF <50%	Atrial Fibrillation		

Patients hierarchically classified based on the presence of at least one variable in the highest stage (independent, not additive) ; Severe AS: AVA 1.0 cm2; mean gradient 40 mmHg

Généreux et al. *Eur Heart J* 2017 Jul 21

Staging Classification in Severe AS (n=1,661 pts)

One-year Mortality after AVR



Généreux et al. *Eur Heart J* 2017 Jul 21

NEW RESEARCH PAPER

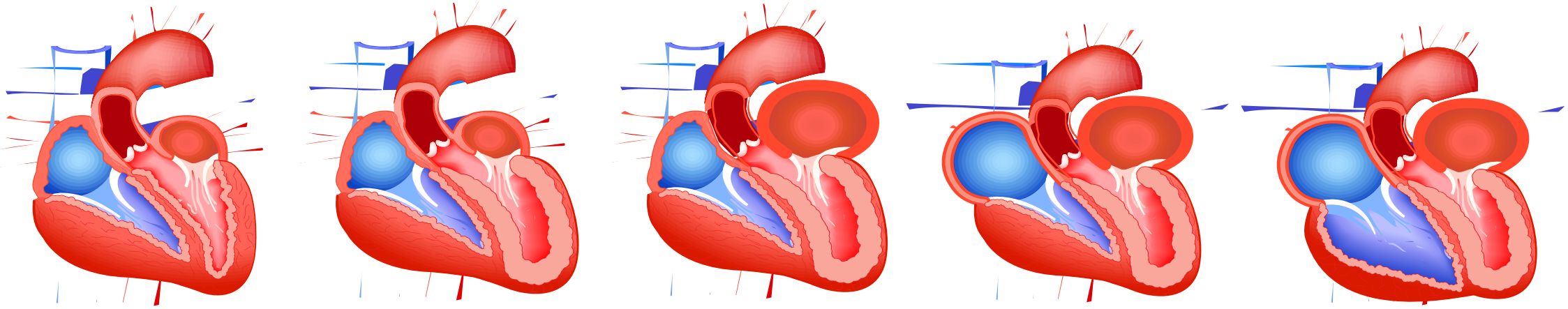
Prognostic Implications of Associated Cardiac Abnormalities Detected on Echocardiography in Patients With Moderate Aortic Stenosis

Mohammed Rizwan Amanullah, MBBS,[a,*] Stephan Milhorini Pio, MD,[b,*] Arnold C.T. Ng, MBBS, PhD,[c] Kenny Y.K. Sin, MBBS,[d] Nina Ajmone Marsan, MD, PhD,[b] Zee Pin Ding, MBBS,[a] Martin B. Leon, MD,[e] Philippe Généreux, MD,[f] Victoria Delgado, MD, PhD,[b] See Hooi Ewe, MBBS, PhD,[a] Jeroen J. Bax, MD, PhD[b]

- 1245 patients with moderate AS followed in a longitudinal database
- Patients grouped according to index echocardiograms into 5 categories of severity of cardiac damage
- Significant higher mortality rates with increasing extent of extra-aortic valvular cardiac abnormalities (log-rank $p < 0.001$)

Amanullah MR et al. JACC Imaging 2021

Staging Classification in Moderate AS (n=1,245 pts)



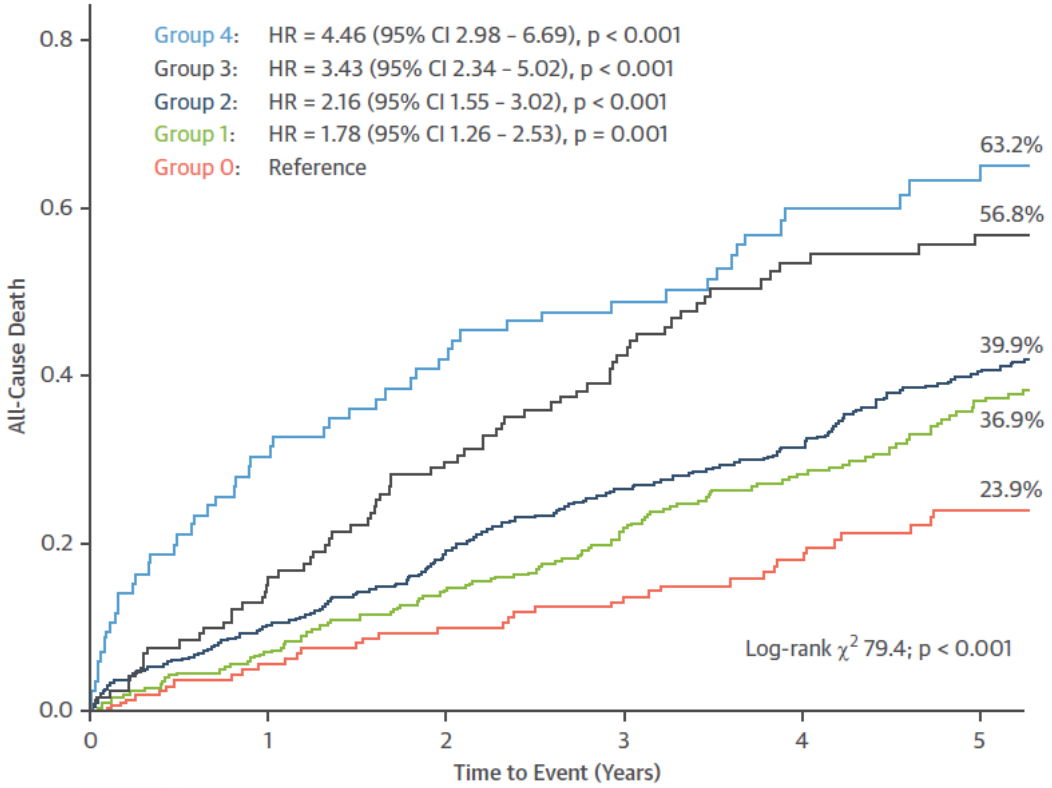
N=163 (13.1%)	N=334 (26.8%)	N=530 (42.6%)	N=132 (10.6%)	N=86 (6.4%)
	EF <50%	Atrial Fibrillation		

Patients hierarchically classified based on the presence of at least one variable in the highest stage (independent, not additive) ; Moderate AS: AVA 1.2 cm2; mean gradient 24.4mmHg

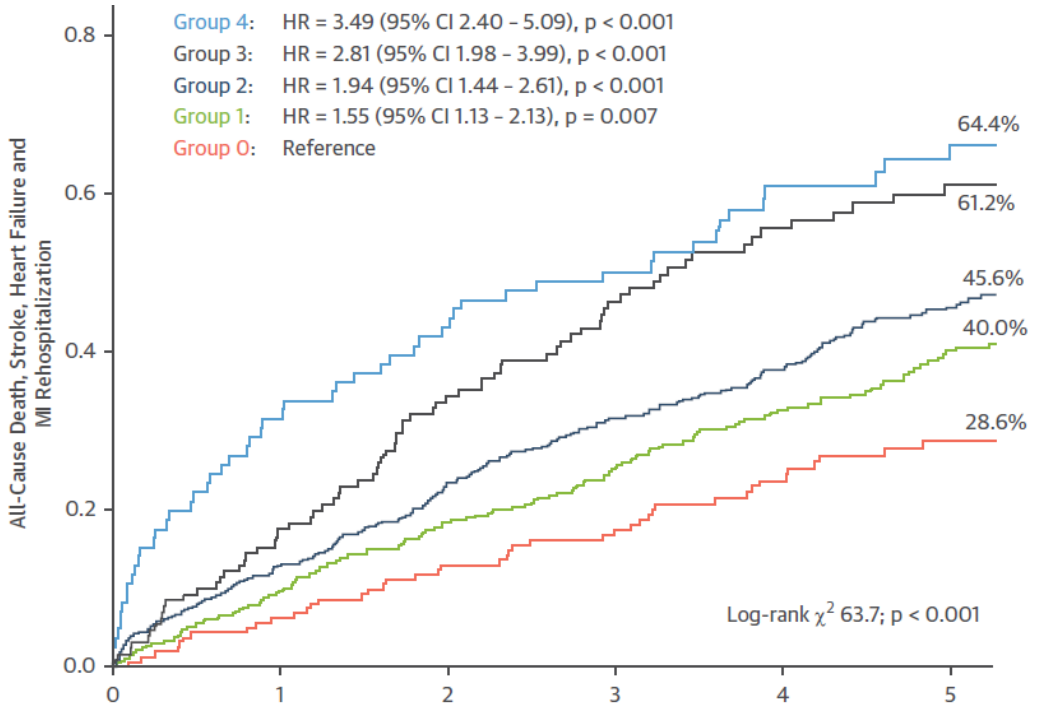
Amanullah MR et al. JACC Imaging 2021

Staging Classification in Moderate AS (n=1,245 pts)

5-yr Mortality



5-yr Mortality, Stroke or Rehosp

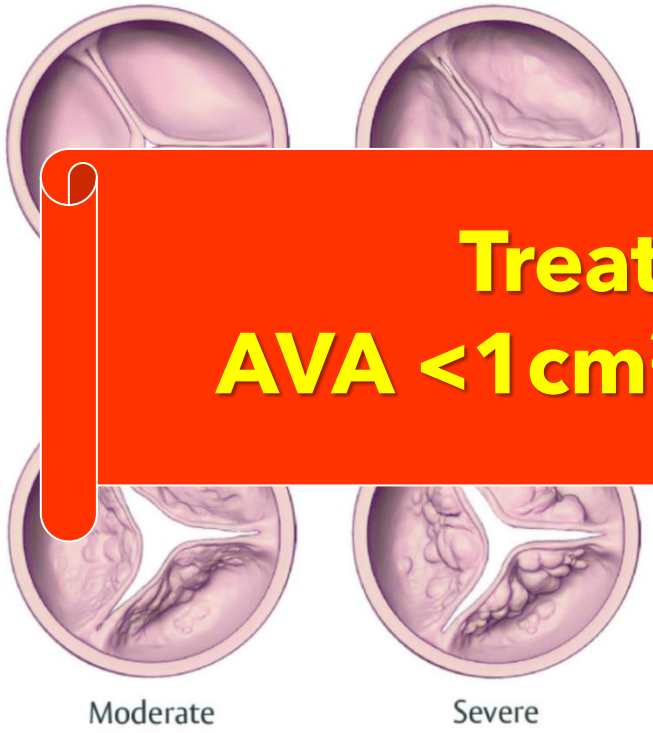


Amanullah MR et al. JACC Imaging 2021

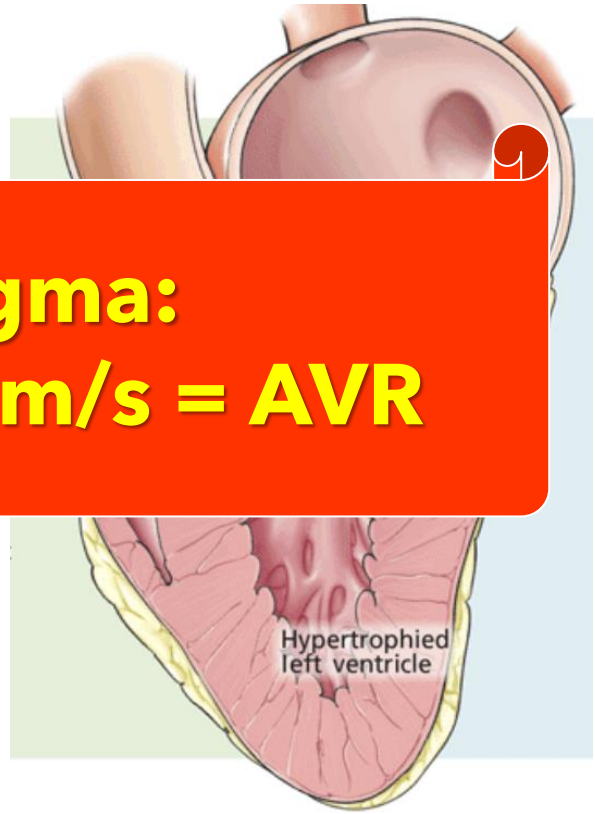
Aortic Valve Therapies: The Future?

UPSTREAM AS Treatment

Two parallel processes with 'variable' linkage



Treatment Dogma:
AVA <1 cm^2 or PV ≥4 m/s = AVR



The RECOVERY Surgical AVR Trial

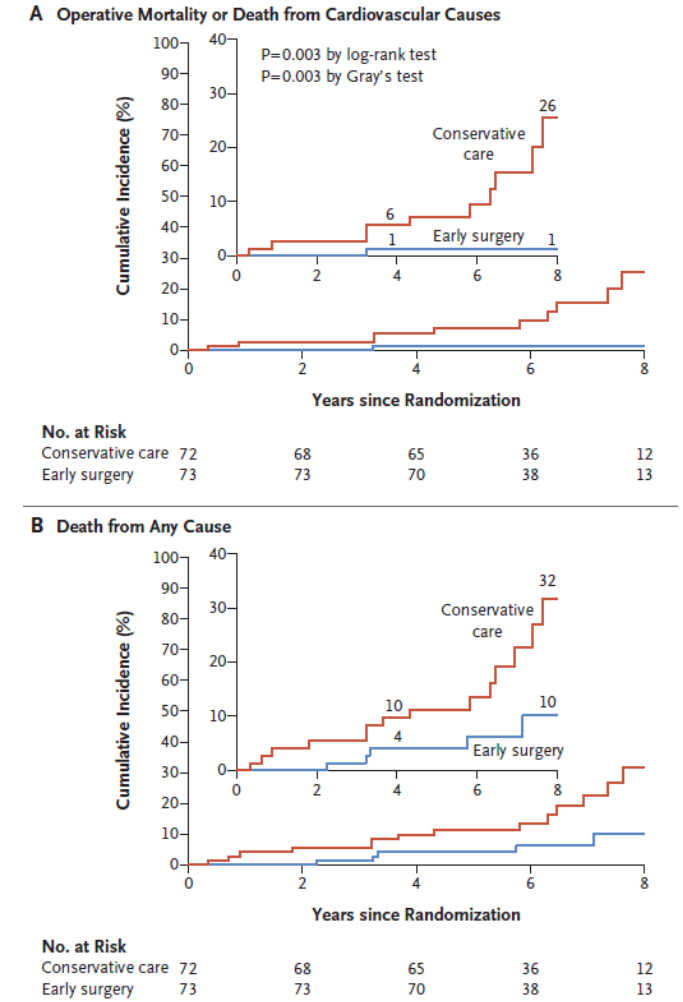
The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 JANUARY 9, 2020 VOL. 382 NO. 2

Early Surgery or Conservative Care for Asymptomatic Aortic Stenosis

Duk-Hyun Kang, M.D., Ph.D., Sung-Ji Park, M.D., Ph.D., Seung-Ah Lee, M.D., Sahmin Lee, M.D., Ph.D., Dae-Hee Kim, M.D., Ph.D., Hyung-Kwan Kim, M.D., Ph.D., Sung-Cheol Yun, Ph.D., Geu-Ru Hong, M.D., Ph.D., Jong-Min Song, M.D., Ph.D., Cheol-Hyun Chung, M.D., Ph.D., Jae-Kwan Song, M.D., Ph.D., Jae-Won Lee, M.D., Ph.D., and Seung-Woo Park, M.D., Ph.D.

- 145 asymptomatic patients w very severe AS randomized to early surgery or conservative care
- 1^{ry} endpoint (operative and FU death) was 1% vs. 15% in early surgery vs. conservative care (P=0.003)

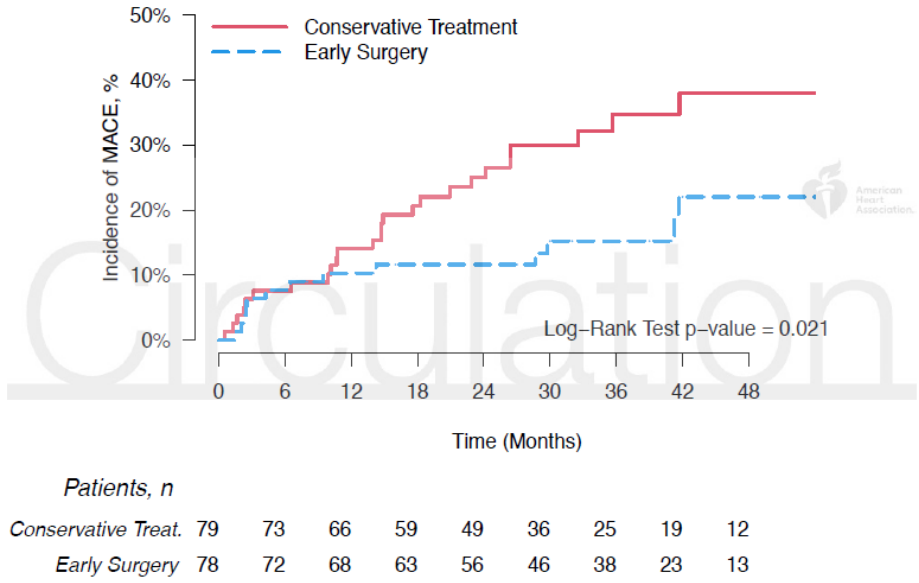


Kang DH et al, NEJM 2020

The AVATAR Surgical AVR Trial

Aortic Valve Replacement versus Conservative Treatment In Asymptomatic Severe Aortic Stenosis: The AVATAR Trial

- 157 asymptomatic patients (ETT confirmed) w severe AS, randomized to early surgery or conservative care at 9 centers from 7 EU countries; median FU 32 months
- Early surgery operative mortality 1.4%
- 1^{ry} endpoint (MACE = death, MI, stroke and HF rehosp) was lower with early surgery vs. conservative care (HR 0.46, 95% CI 0.23-0.90; p=0.02)

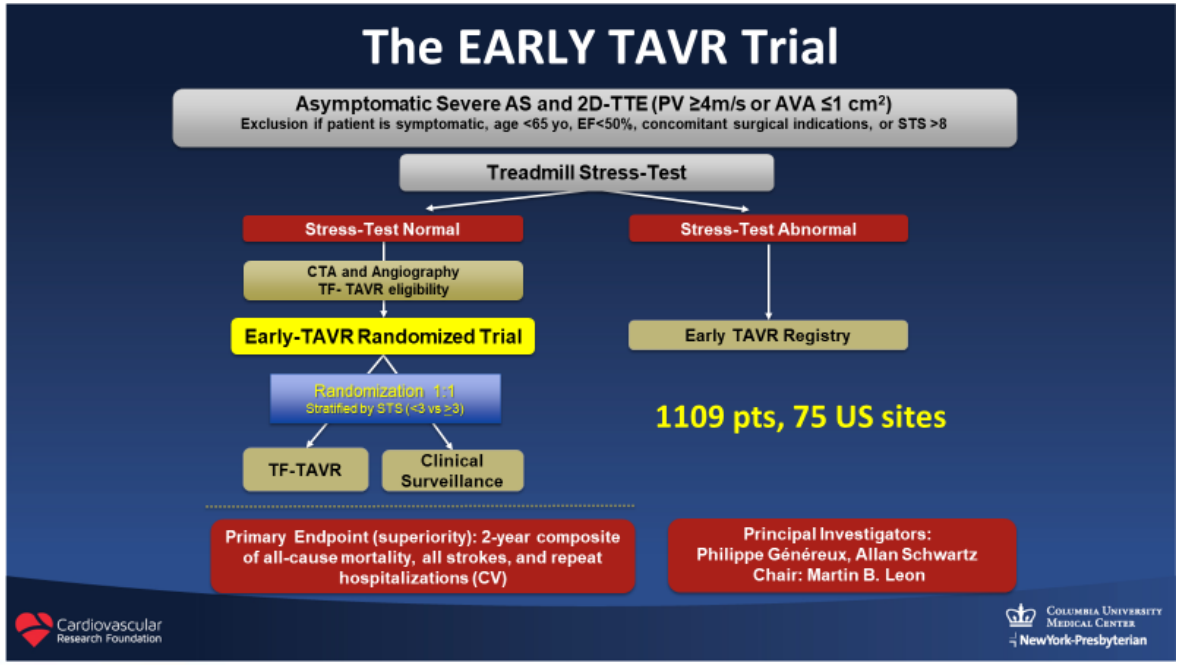


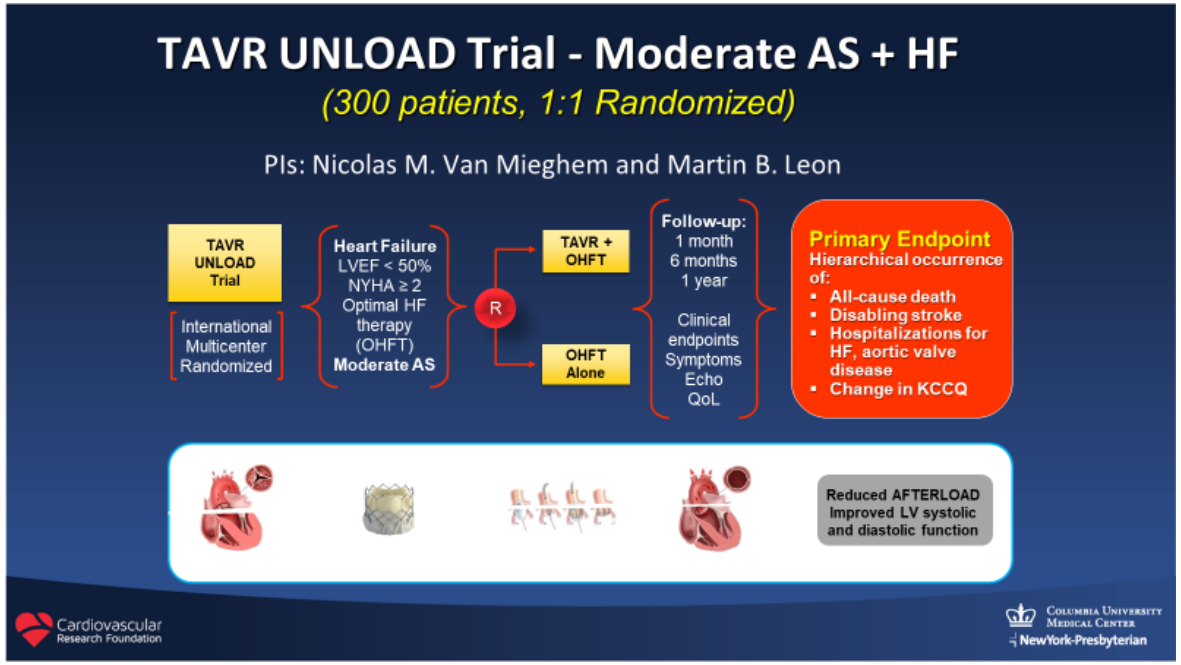
Banovic, M, AHA 2021 and Circulation 2021

Pre-emptive (earlier) TAVR

EARLY TAVR and UNLOAD Trials

Expanding TAVR Clinical Indications to 'Earlier' Treatment Scenarios





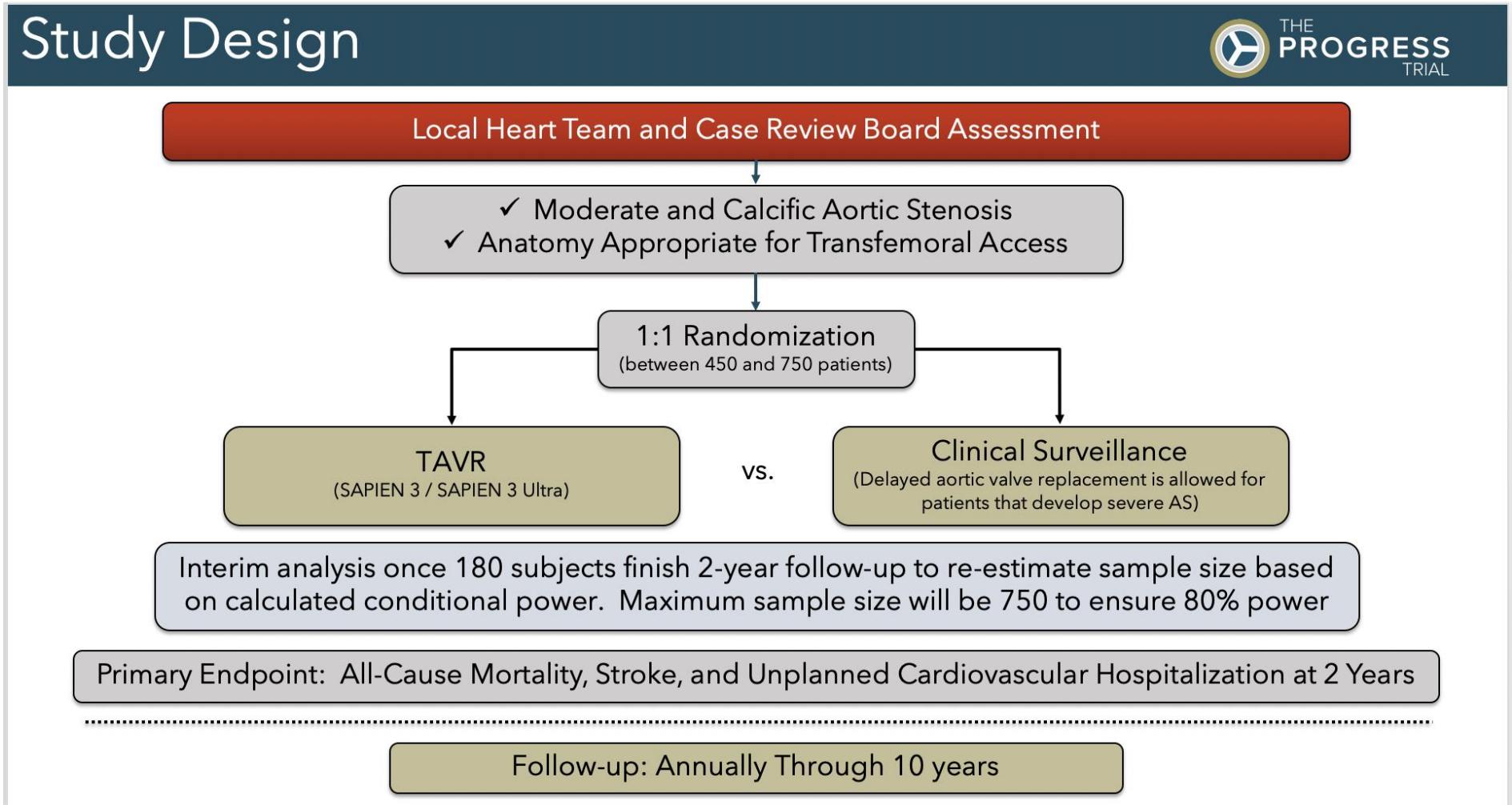
Upstream Mod AS Treatment

"At Risk" Predictors

- Cardiac symptoms (esp. heart failure NYHA 3 or 4)
- Low ejection fraction (< 60% LVEF)
- Atrial fibrillation (persistent or recent paroxysmal)
- Low stroke volume (SVI < 35 cc/m^2)
- Severe diastolic dysfunction (by echo criteria)
- Rapid AS progression (increase PV > 0.3 m/sec/year)
- Elevated cardiac biomarkers (BNP)
- Elevated AV calcium score by CT

Upstream Mod AS Treatment: The Future?

The PROGRESS Trial



Study PIs: Philippe Genereux, Raj Makkar and Jeroen Bax; Study Chairman: Martin B. Leon

AS Severity Grading and Cardiac Staging

Grade or Stage	Stage 0 None	Stage 1 LV	Stage 2 LA-mitral	Stage 3 PA-tricuspid	Stage 4 RV
Grade 0 V_{max} <2m/s					
Grade 1 V_{max} 2-2.9m/s					
Grade 2 V_{max} 3-3.9m/s					
Grade 3 V_{max} ≥.4m/s					

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Grade 1 V_{max} 2-2.9m/s					
Grade 2 V_{max} 3-3.9m/s	PROGRESS	PROGRESS	PROGRESS	PROGRESS	PROGRESS
Grade 3 V_{max} ≥.4m/s	EARLY TAVR				

AS Severity Grading and Cardiac Staging

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Grade 0 V_{max} <2m/s	?Multi-drug 'precision' medical Rx				
Grade 1 V_{max} 2-2.9m/s					
Grade 2 V_{max} 3-3.9m/s	PROGRESS	PROGRESS	PROGRESS	PROGRESS	PROGRESS
Grade 3 V_{max} ≥.4m/s	EARLY TAVR	AVR	AVR	AVR	AVR