Keynote lecture…

UPSTREAM management of aortic stenosis

Martin B. Leon, MD

Columbia University/NYP Hospital
Cardiovascular Research Foundation
New York City

TCTAP

April 20-23, 2022
Seoul, Korea

15 mins

Financial Disclosures - Martin B. Leon, MD

TCTAP 2022; Seoul, Korea; April 20-23, 2022

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

Financial Relationship	Company
• Research Support	Abbott, Boston Scientific, Edwards Lifesciences, Medtronic
• Advisory Boards*	Abbott, Boston Scientific, Edwards Lifesciences, Gore, Medtronic
• Equity	Alta, Ancora, Conveyor, East End Medical, K2, Medinol, Pi-cardia, Triventures, Venus MedTech, Valve Medical, XenterMD

*Medical or scientific advisory boards (no direct physician payments)

Roadmap for this Lecture

- UPSTREAM conceptual framework
- Under-diagnosis/treatment issues
- Screening tools for aortic stenosis
- Pre-emptive (earlier) AVR
- Pharmaco-therapeutics for AVD

Roadmap for this Lecture

UPSTREAM conceptual framework

Under-diagnosis/treatment issues

Screening tools for aortic stenosis

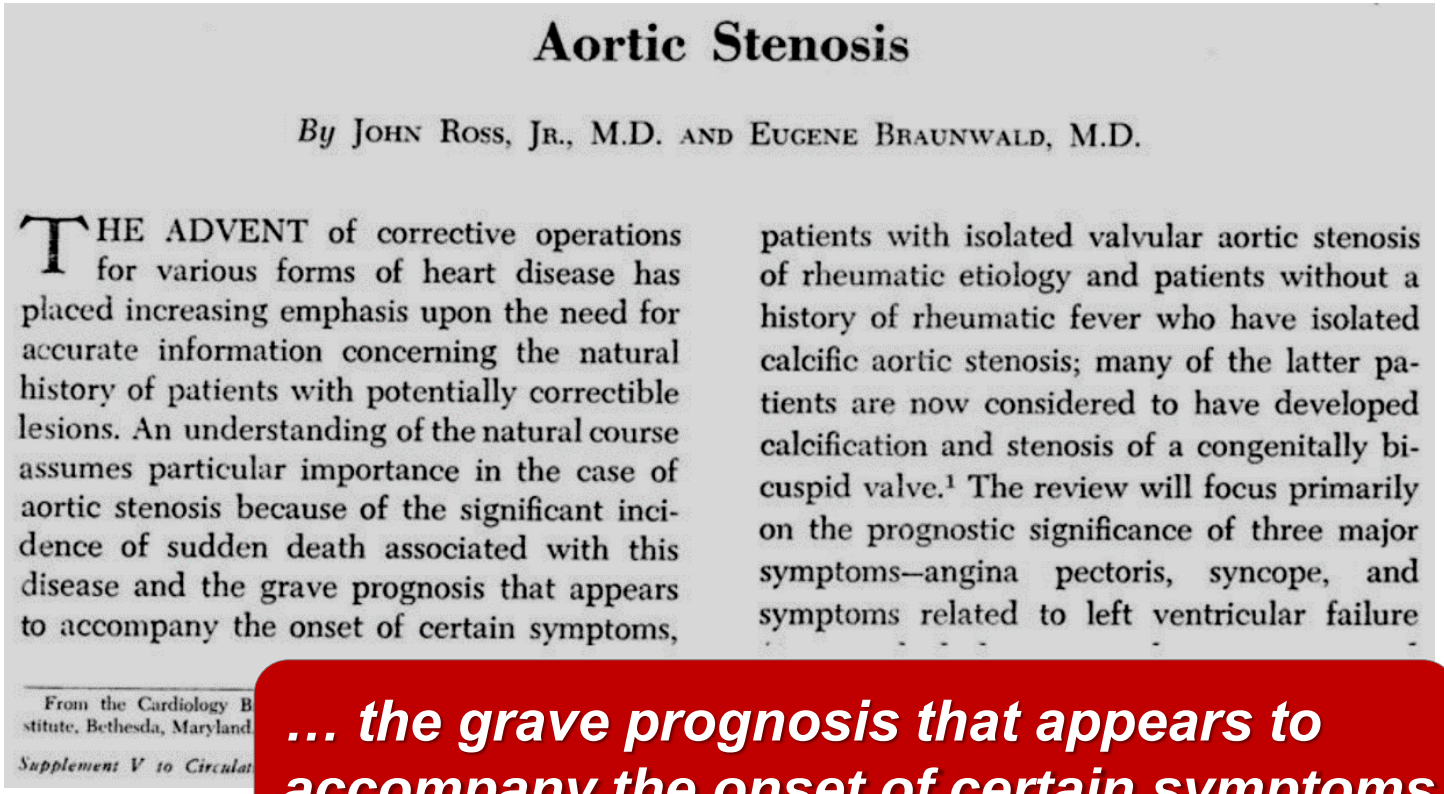
Pre-emptive (earlier) AVR

Pharmaco-therapeutics for AVD

UPSTREAM Conceptual Framework

- Aortic stenosis is a *continuous disease process* (both congenital bicuspid and senile calcific degenerative forms) *punctuated* by various clinical events (e.g. AF, cardiac symptoms) and structural changes (e.g. LVH, PAH, RH failure).
- *Earlier management*, both diagnosis and treatment, leads to optimal clinical outcomes.
- *Delaying progression* of calcific AS before the onset of symptoms or need for AVR should be an aspirational goal.
- Clinical research efforts should shift from late-stage reactive AVR to *early-stage pre-emptive AVR and other complementary therapy approaches.*
- The availability of less-invasive low-risk transcatheter technologies combined with more durable heart valves (a work in progress) coupled to enhanced (easily accessible) early diagnosis will *transform AS patient management paradigms in the future!*

Traditional Thinking – Aortic Stenosis



Aortic Stenosis

By JOHN ROSS, JR., M.D. AND EUGENE BRAUNWALD, M.D.

THE ADVENT of corrective operations for various forms of heart disease has placed increasing emphasis upon the need for accurate information concerning the natural history of patients with potentially correctible lesions. An understanding of the natural course assumes particular importance in the case of aortic stenosis because of the significant incidence of sudden death associated with this disease and the grave prognosis that appears to accompany the onset of certain symptoms,

patients with isolated valvular aortic stenosis of rheumatic etiology and patients without a history of rheumatic fever who have isolated calcific aortic stenosis; many of the latter patients are now considered to have developed calcification and stenosis of a congenitally bicuspid valve.[1] The review will focus primarily on the prognostic significance of three major symptoms—angina pectoris, syncope, and symptoms related to left ventricular failure

From the Cardiology B
stitute, Bethesda, Maryland.

Supplement V to Circulat

… the grave prognosis that appears to accompany the onset of certain symptoms

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

Traditional Thinking – Aortic Stenosis

Aortic Stenosis

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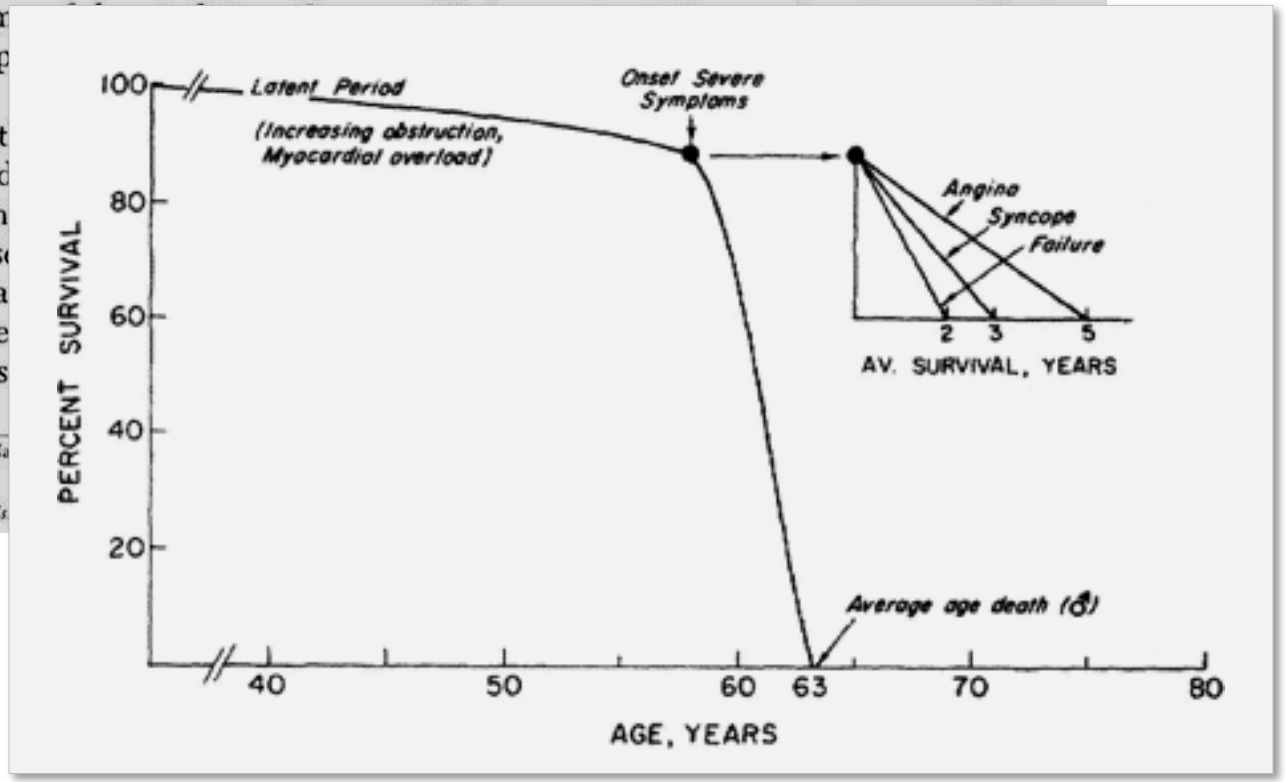

Ross and Braunwald, *Circulation* 1968;38:V-61

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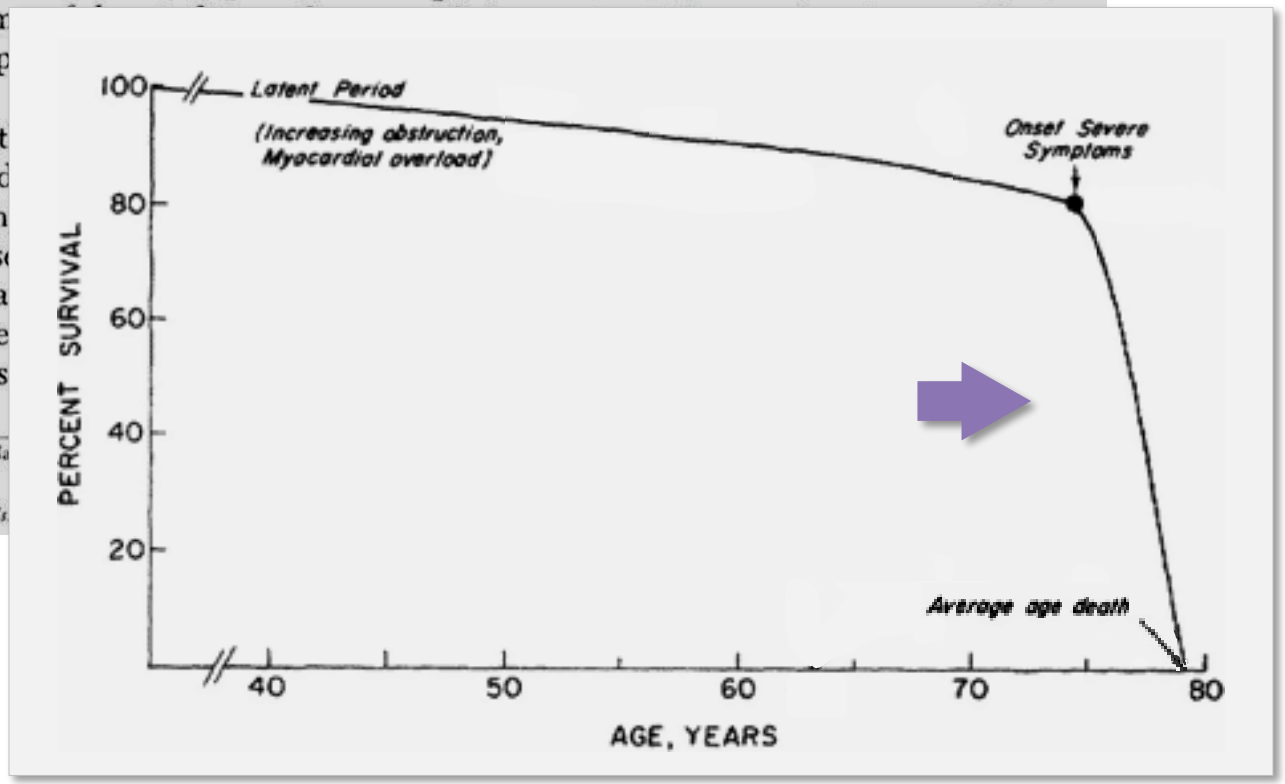
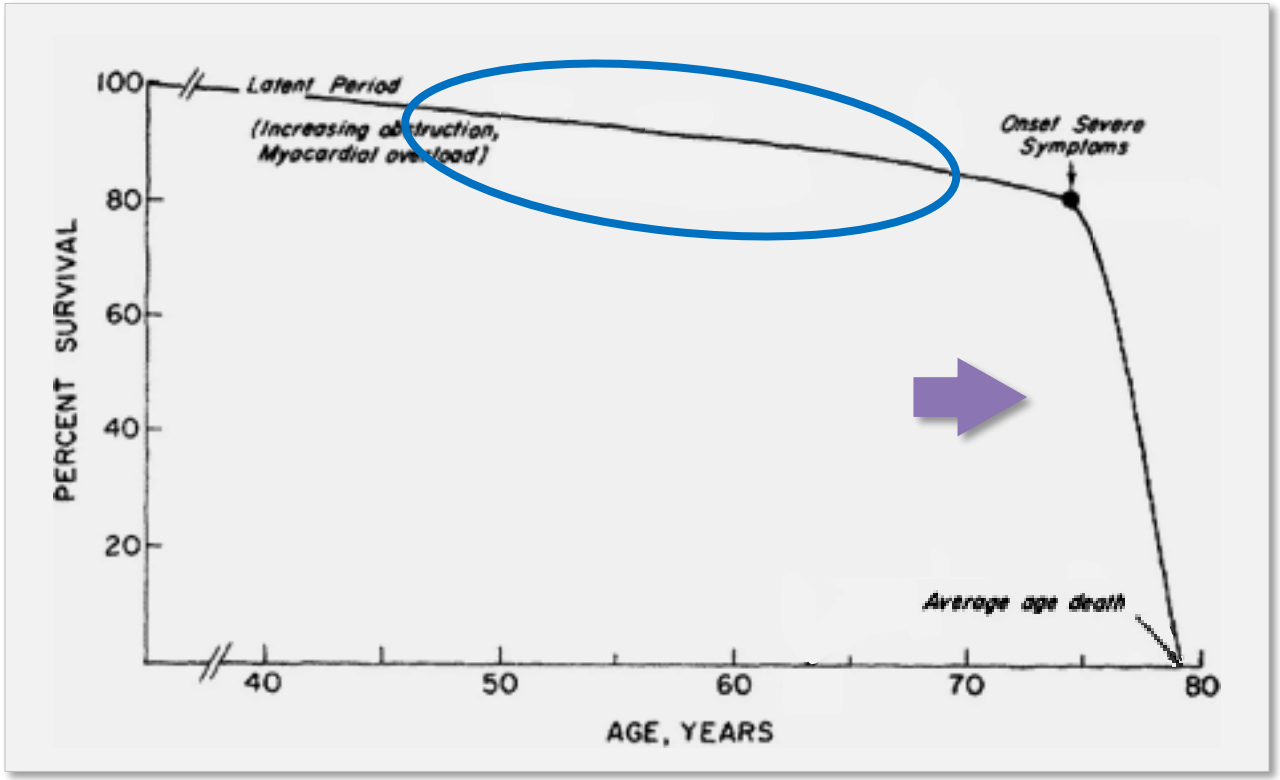


Ross and Braunwald, *Circulation* 1968;38:V-61

Traditional Thinking – Aortic Stenosis

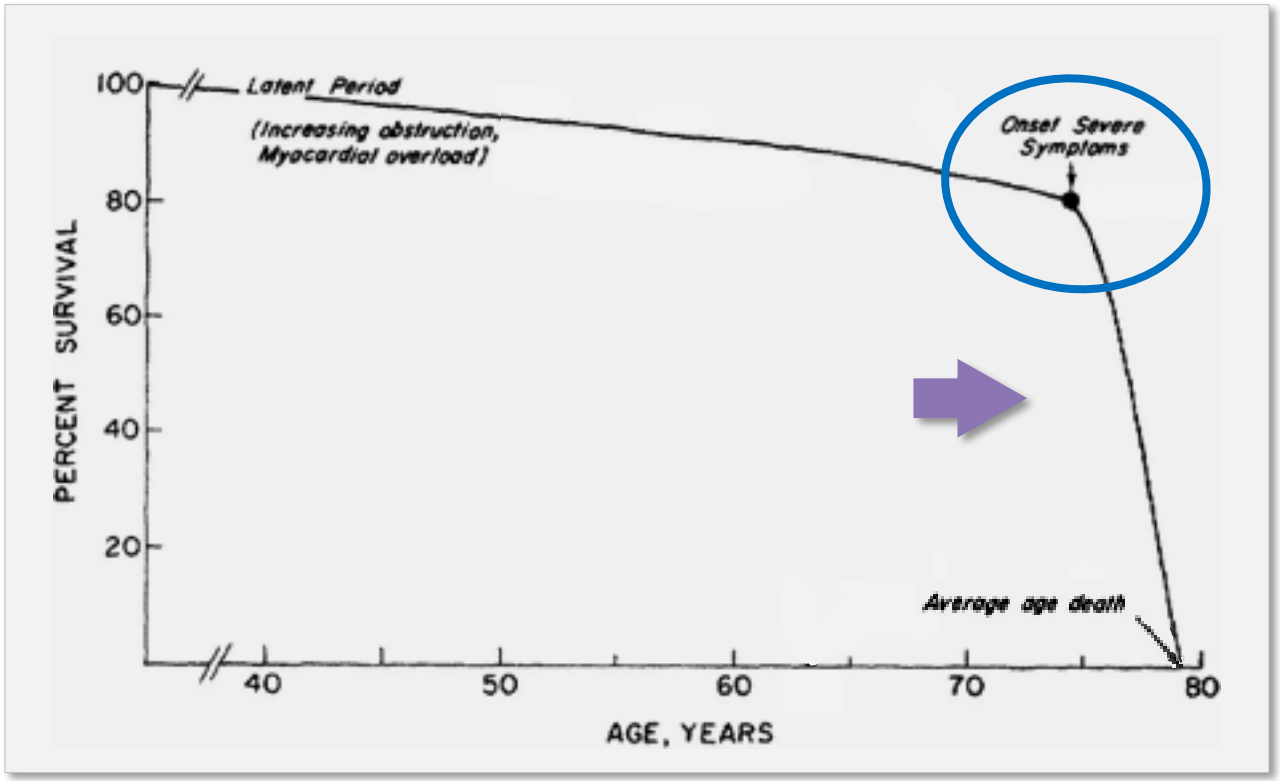
Fundamental fallacies: *1. there are no important reversible and irreversible structural changes during the so-called latent period which negatively impact subsequent clinical outcomes*



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

UPSTREAM Thinking – Aortic Stenosis

Aortic Stenosis

By JOHN

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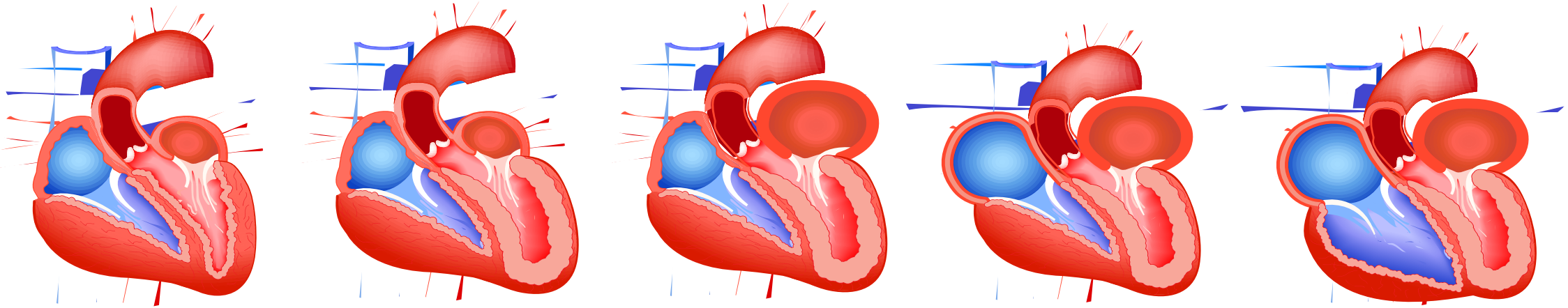
Supplement V to Circulation, Vols. XXXV

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

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

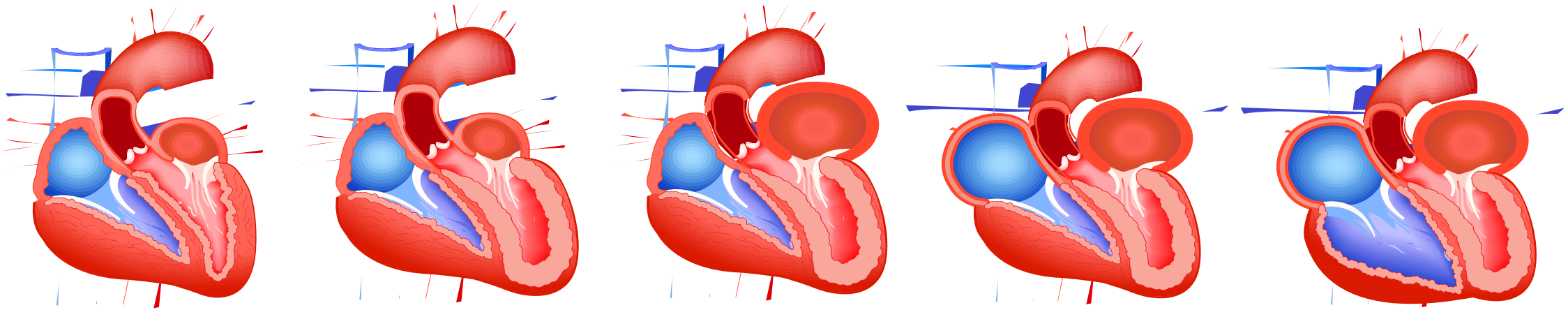


Stage 0 No damage	Stage 1 LV damage	Stage 2 LA/Mitral damage	Stage 3 PA/Tricuspid damage	Stage 4 RV damage
	Increased LV Mass Index >115 g/m^2 Male >95 g/m^2 Female	Indexed left atrial volume >34mL/m^2	PAS ≥60mmhg	Moderate-Severe RV dysfunction
	E/e' >14	Moderate-Severe MR	Moderate-Severe TR	
	EF <50%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



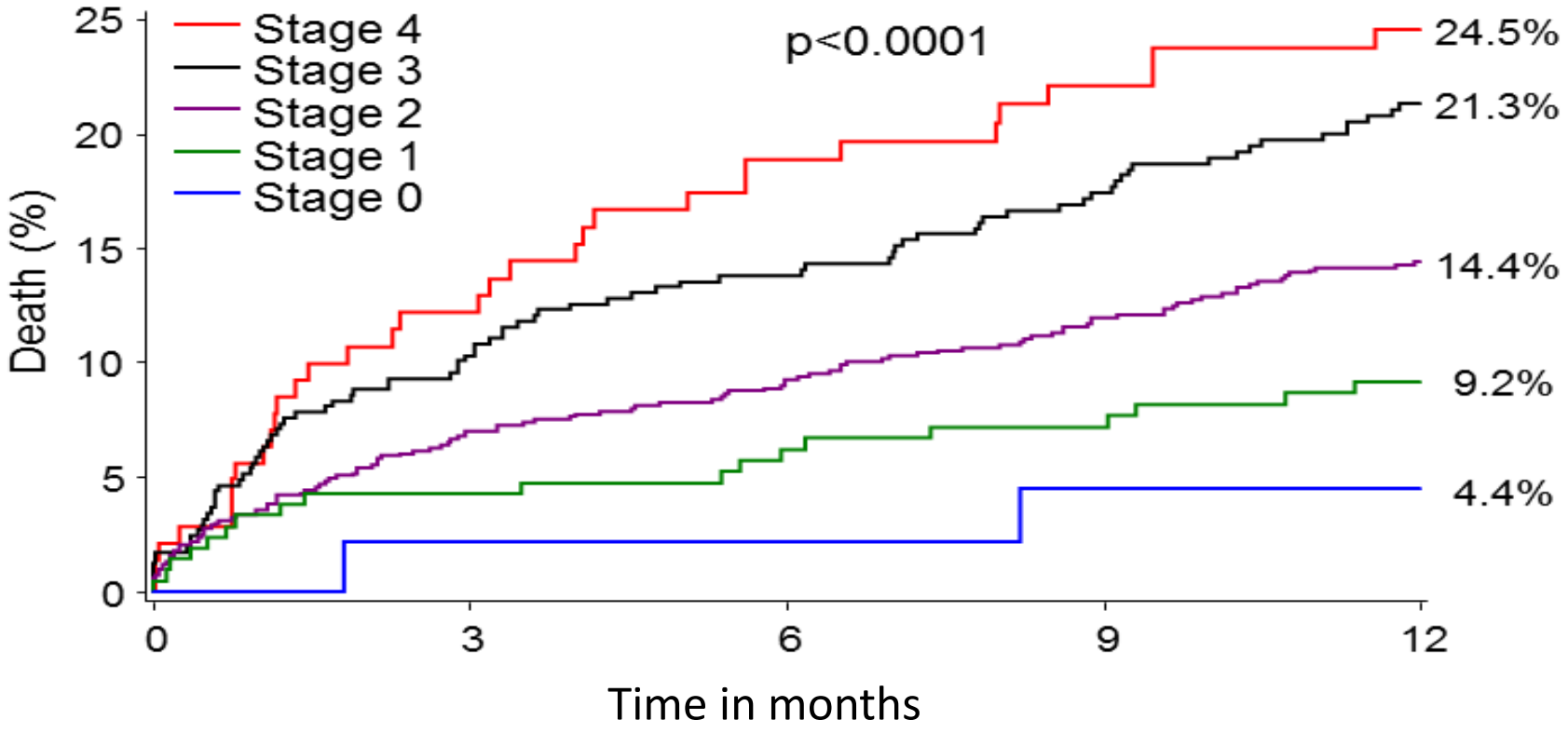
N=47 (2.8%)	N=212 (12.8%)	N=844 (50.8%)	N=413 (24.9%)	N=145 (8.7%)
	EF <50%	Atrial Fibrillation		

Patients hierarchically classified based on the presence of at least one variable in the highest stage (independent, not additive)

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

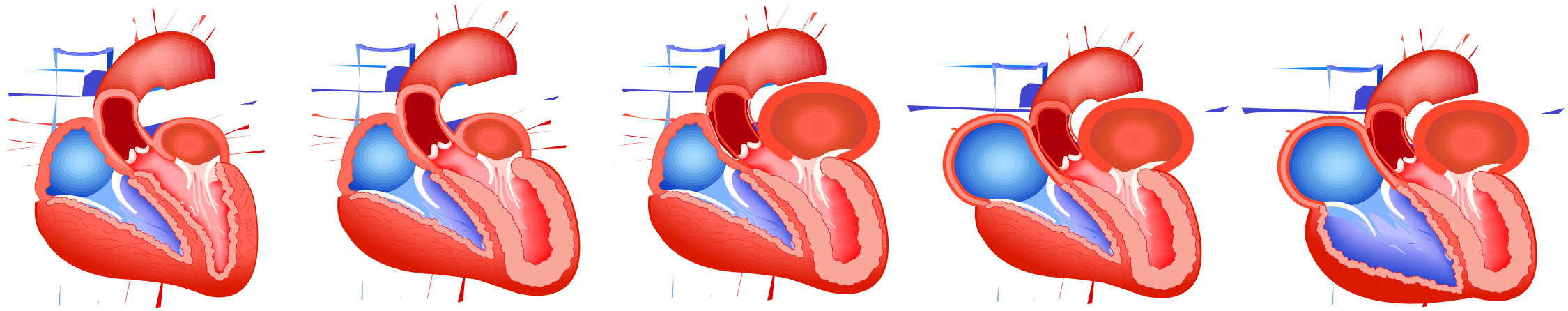
Prognostic Implications of Associated Cardiac Abnormalities Detected on Echocardiography in Patients With Moderate Aortic Stenosis

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)



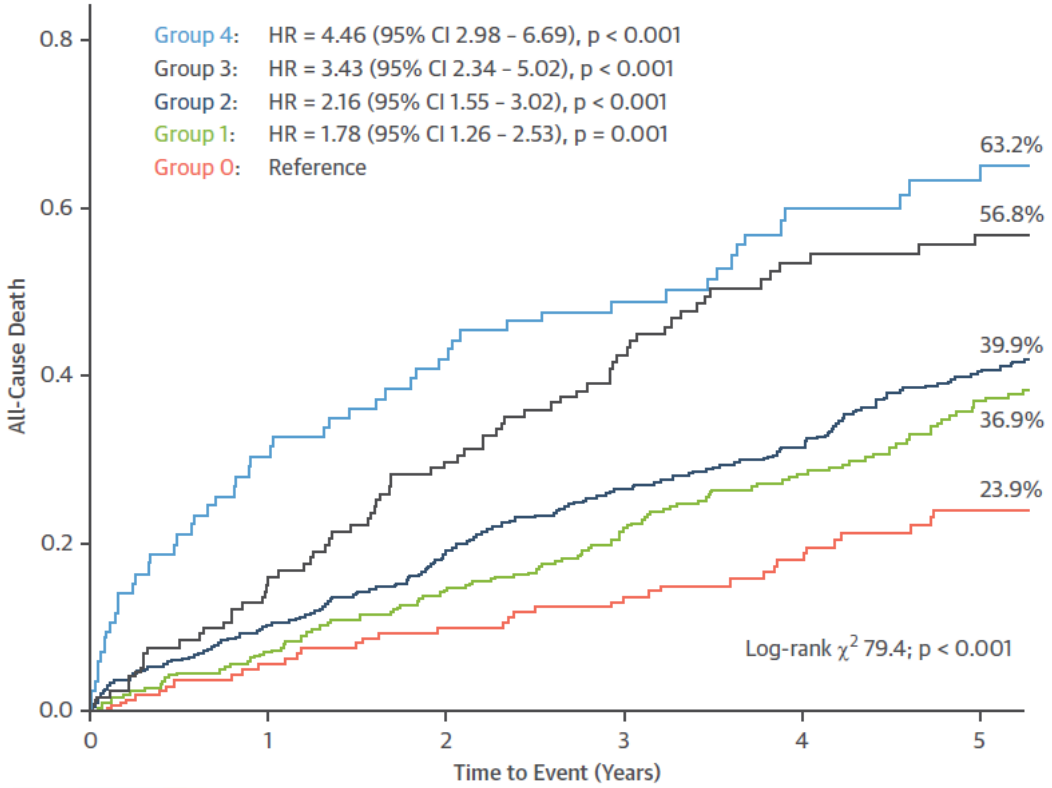
N=163 (13.1%)	N=334 (26.8%)	N=530 (42.6%)	N=132 (10.6%)	N=86 (6.4%)
	EF <50%	Atrial Fibrillation		

Patients hierarchically classified based on the presence of at least one variable in the highest stage (independent, not additive)

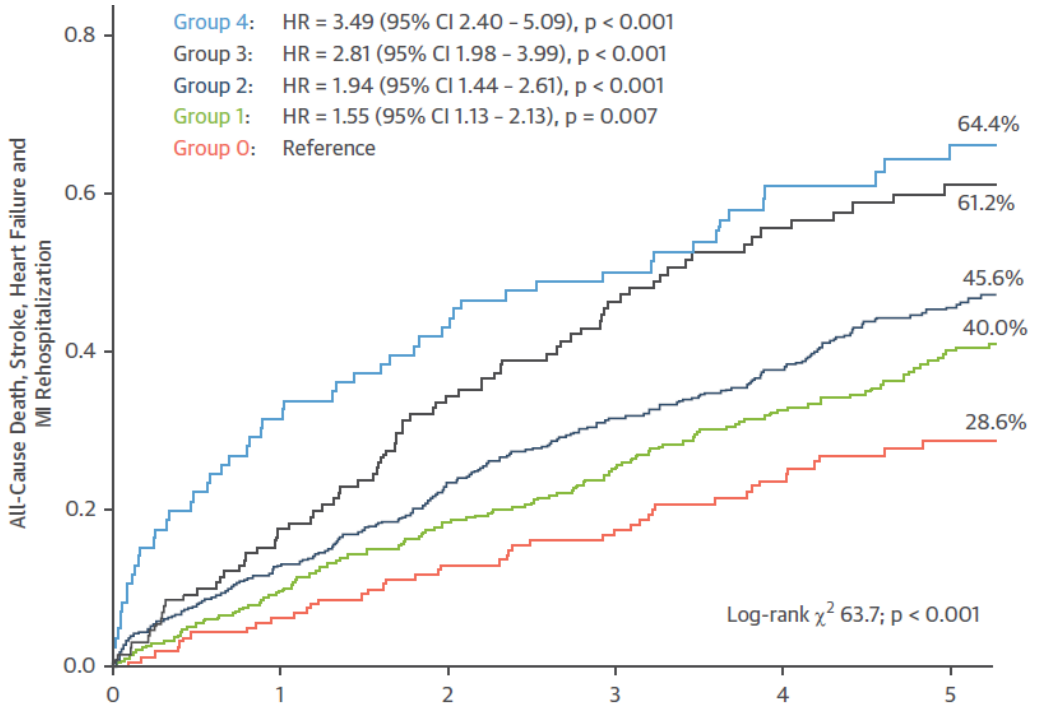
Amanullah MR et al. JACC Imaging 2021

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

5-yr Mortality



5-yr Mortality, Stroke or Rehosp

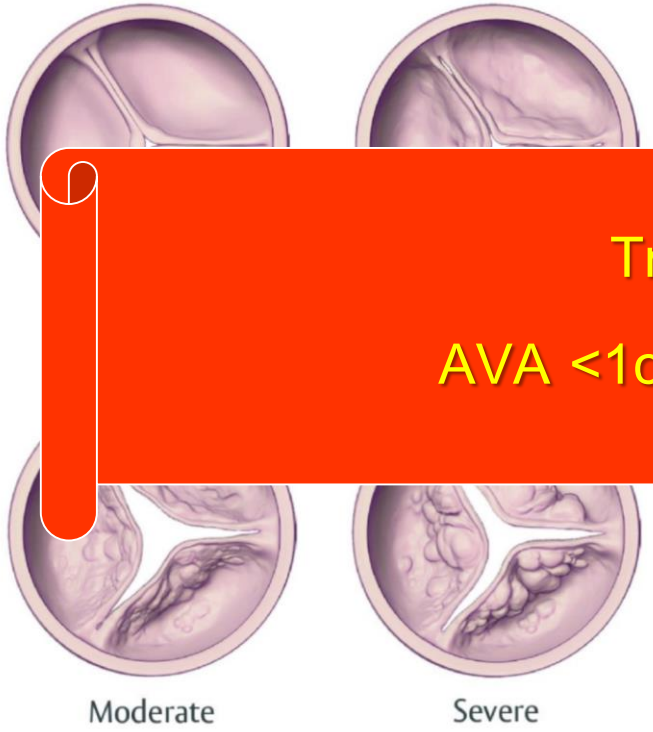


Amanullah MR et al. JACC Imaging 2021

Aortic Valve Therapies: The Future?

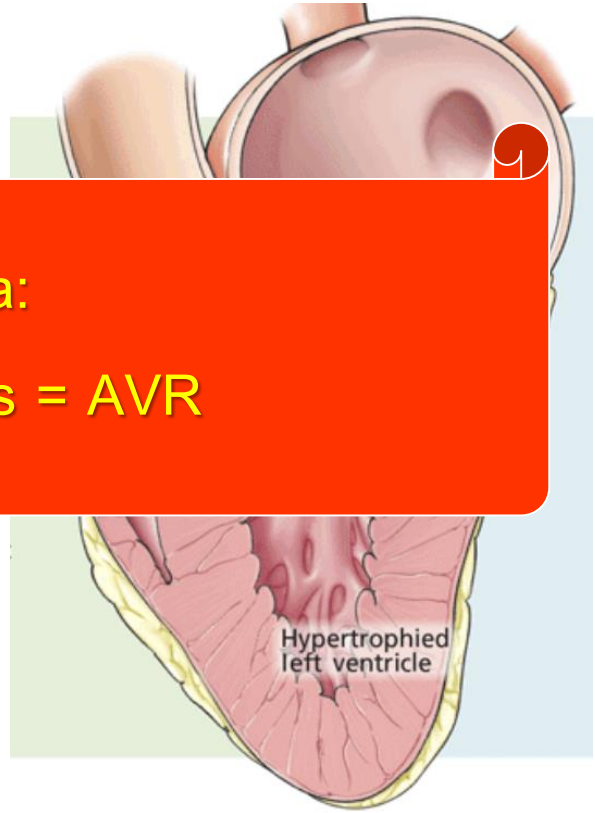
UPSTREAM AS Treatment

Two parallel processes with 'variable' linkage



Treatment Dogma:

AVA <1cm^2 or PV ≥4m/s = AVR



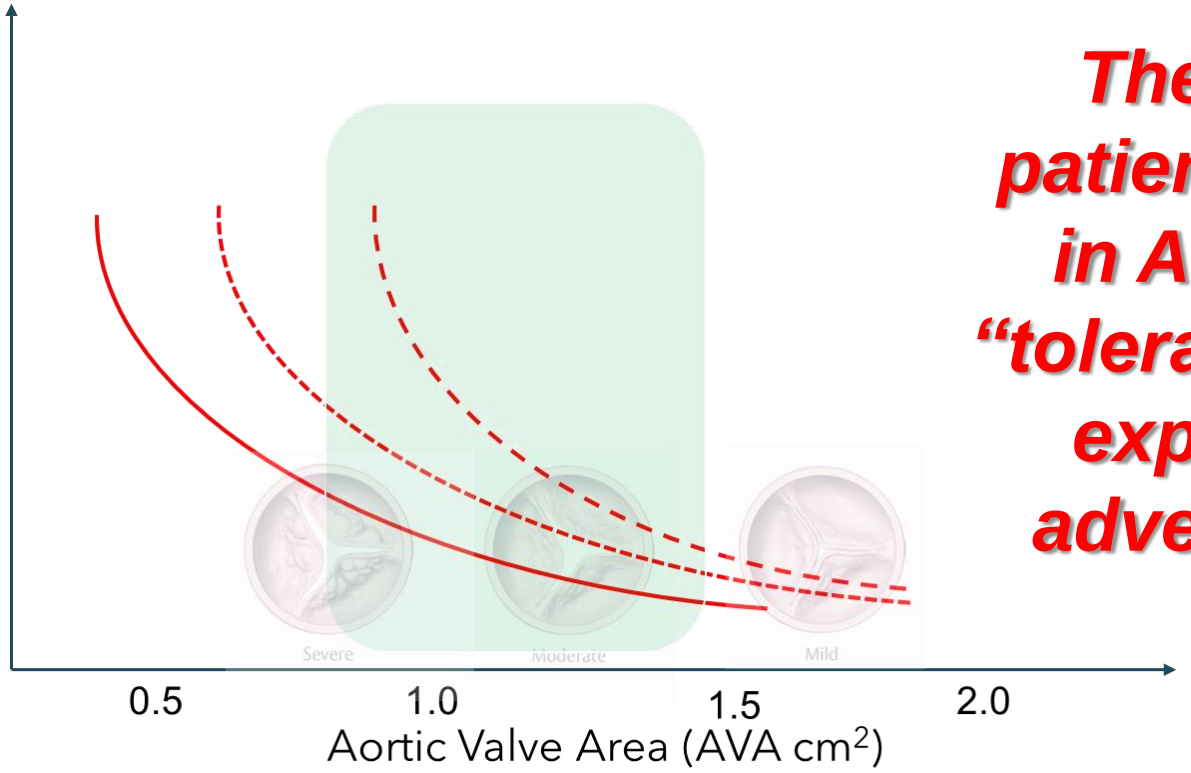
Aortic Valve Therapies: The Future?

UPSTREAM AS Treatment

At what AS severity do adverse events occur?

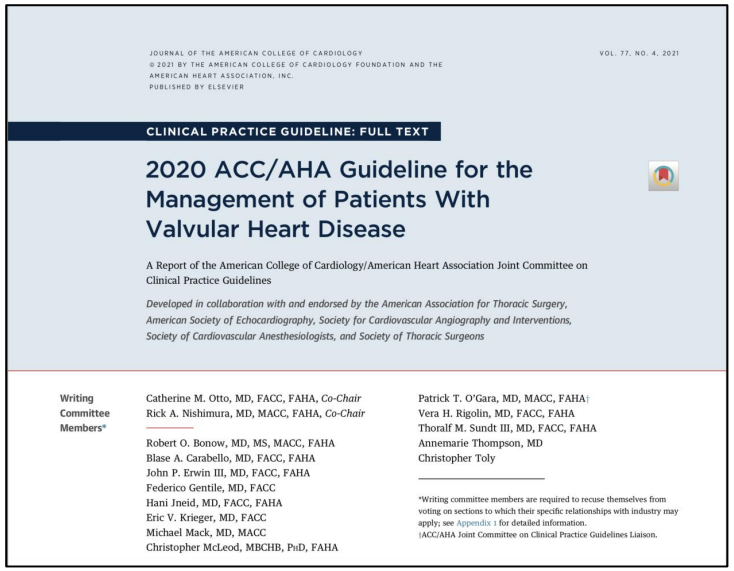
Adverse Events

- Mortality
- Valve-related symptoms
- Cardiac damage



There is wide patient variability in AS afterload "tolerance" and the expression of adverse events!

VHD Guidelines - Timing of Intervention for AS



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VOL. 77, NO. 4, 2021

CLINICAL PRACTICE GUIDELINE: FULL TEXT

2020 ACC/AHA Guideline for the Management of Patients With Valvular Heart Disease

A Report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines

Developed in collaboration with and endorsed by the American Association for Thoracic Surgery, American Society of Echocardiography, Society for Cardiovascular Angiography and Interventions, Society of Cardiovascular Anesthesiologists, and Society of Thoracic Surgeons

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Christopher Toly

*Writing committee members are required to recuse themselves from voting on sections to which their specific relationships with industry may apply; see Appendix 1 for detailed information.
†ACC/AHA Joint Committee on Clinical Practice Guidelines Liaison.

COR	LOE	RECOMMENDATIONS
1	A	1. In adults with severe high-gradient AS (Stage D1) and symptoms of exertional dyspnea, HF, angina, syncope, or presyncope by history or on exercise testing, AVR is indicated (74-80).
1	B-NR	2. In asymptomatic patients with severe AS and an LVEF <50% (Stage C2), AVR is indicated (81-84).
1	B-NR	3. In asymptomatic patients with severe AS (Stage C1) who are undergoing cardiac surgery for other indications, AVR is indicated (57,63,85-87).
1	B-NR	4. In symptomatic patients with low-flow, low-gradient severe AS with reduced LVEF (Stage D2), AVR is recommended (88-95).
1	B-NR	5. In symptomatic patients with low-flow, low-gradient severe AS with normal LVEF (Stage D3), AVR is recommended if AS is the most likely cause of symptoms (96-98).

5 Class 1 recommendations

All severe AS and 3/5 with symptoms

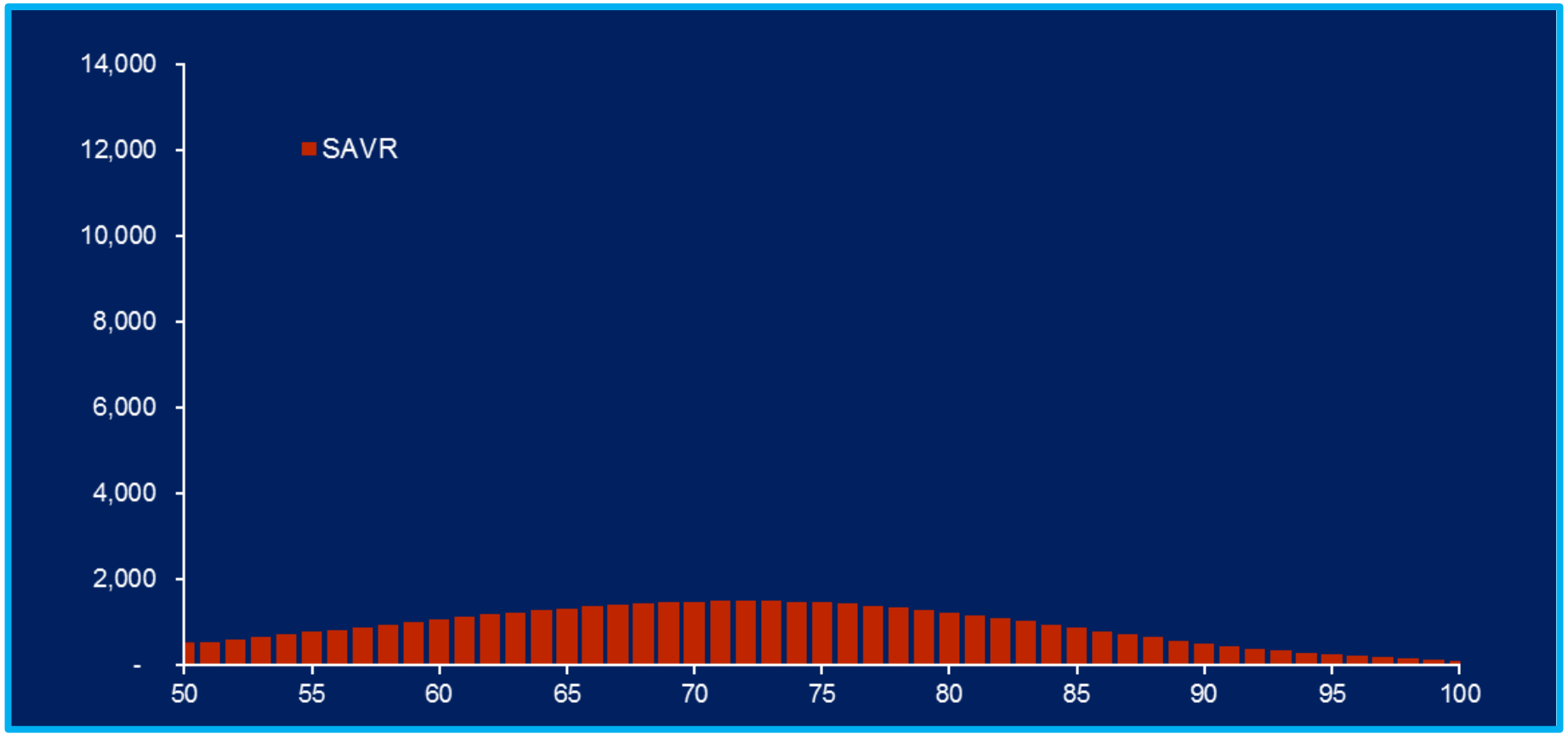
Otto, Nishimura, Bonow et al. J Am Coll Cardiol. 2021 Feb, 77 (4) e25–e197

Roadmap for this Lecture

- UPSTREAM conceptual framework
- ***Under-diagnosis/treatment issues***
- Screening tools for aortic stenosis
- Pre-emptive (earlier) AVR
- Pharmaco-therapeutics for AVD

Underdiagnosis and Undertreatment Issues

2015 Severe Symptomatic AS Patients in the U.S.



Nkomo 2006, Iivanainen 1996, Aronow 1991, Bach 2007, Freed 2010, Iung 2007, Pellikka 2005, Brown 2008, Thourani 2015

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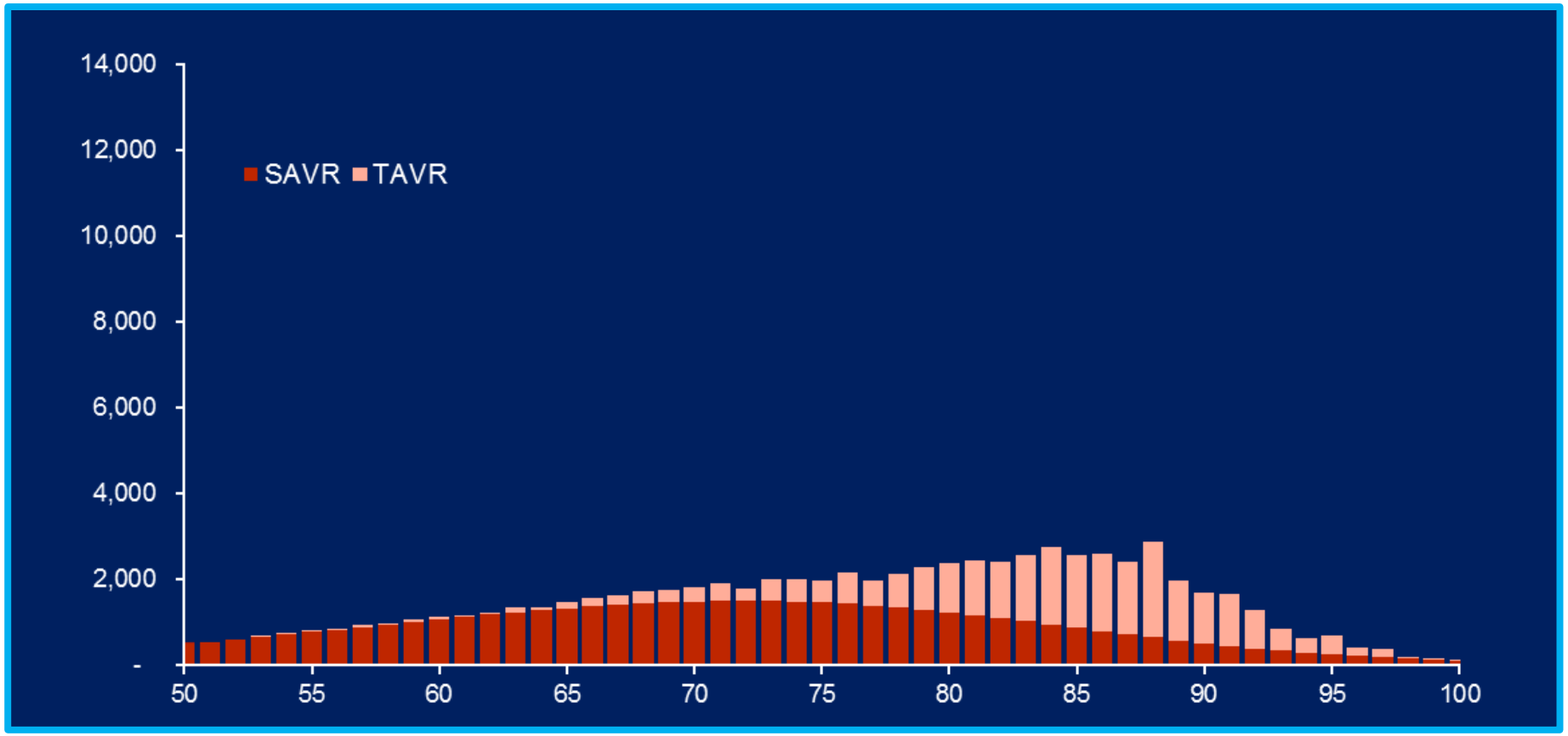

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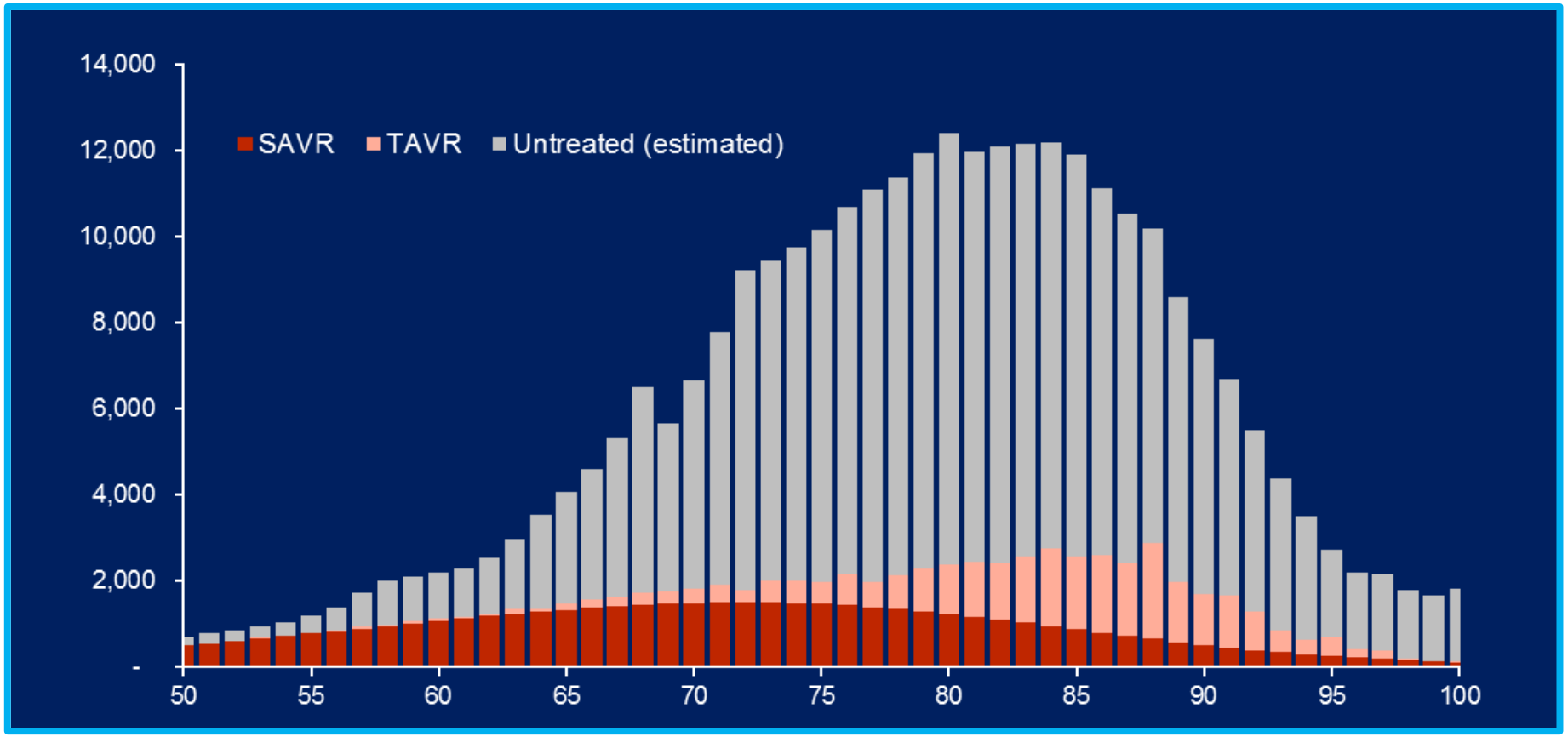
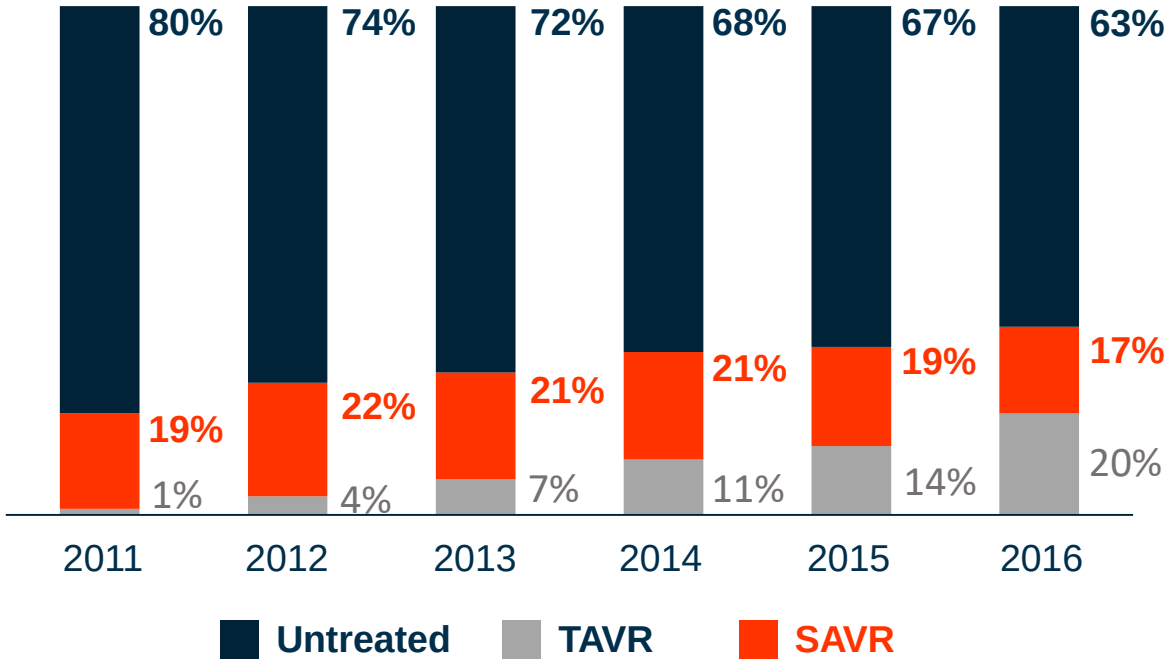


Nkomo 2006, Iivanainen 1996, Aronow 1991, Bach 2007, Freed 2010, Iung 2007, Pellikka 2005, Brown 2008, Thourani 2015

Severe Symptomatic AS Undertreatment

OPTUM database (80 million people)

AVR treatment rate 1 year **after diagnosis** for cohort of patients with **diagnosed ssAS** (%)[1]



Over 60% **of diagnosed** symptomatic severe Aortic Stenosis (ssAS) patients went ***untreated*** **in 2016**

Treatment rates of ssAS have risen → As **TAVR volume** has grown

Matthew Brennan, J., et al. "Racial differences in the use of aortic valve replacement for treatment of symptomatic severe aortic valve stenosis in the transcatheter aortic valve replacement era." *Journal of the American Heart Association* 9.16 (2020): e015879.

Underdiagnosis and Undertreatment Issues

JAMA Cardiology | Original Investigation

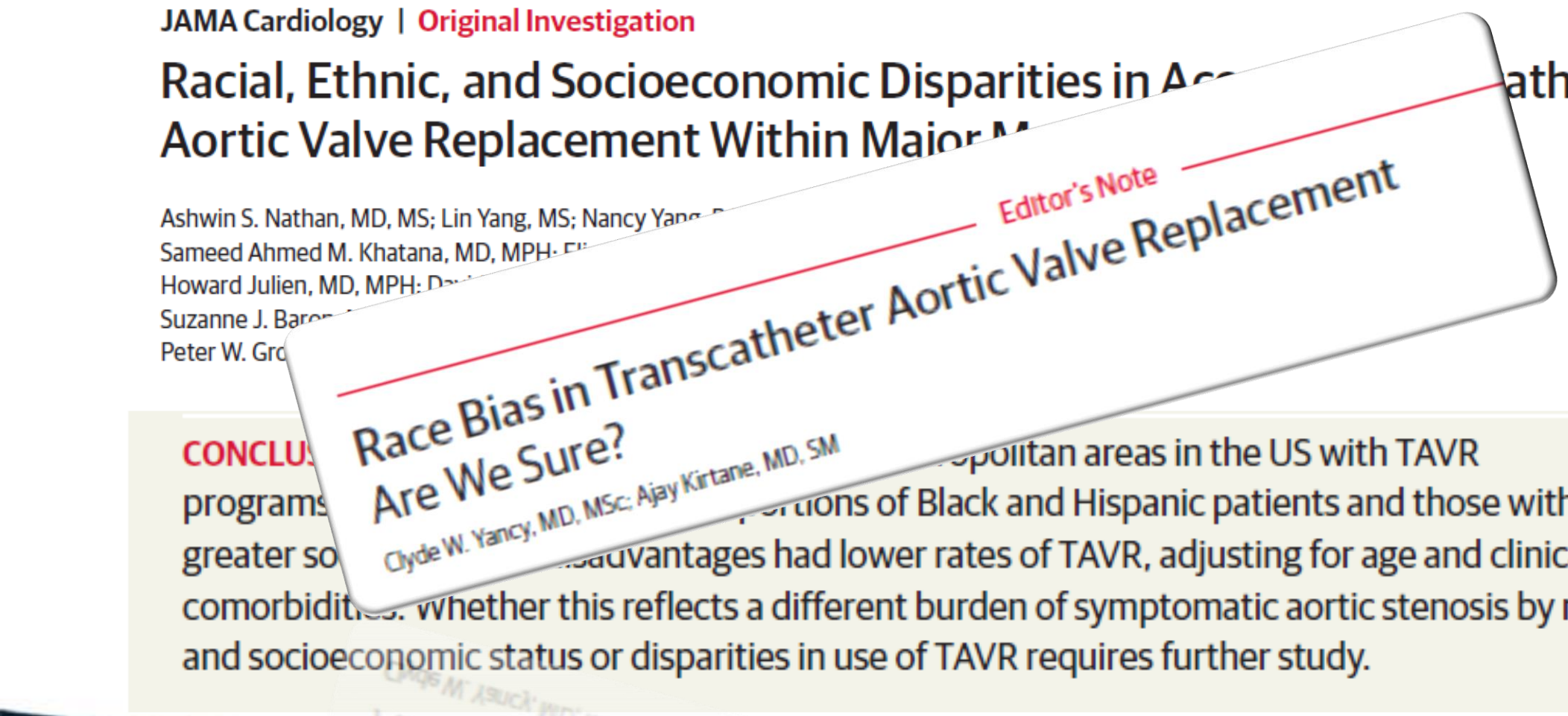
Racial, Ethnic, and Socioeconomic Disparities in Access to Transcatheter Aortic Valve Replacement Within Major Metropolitan Areas

Ashwin S. Nathan, MD, MS; Lin Yang, MS; Nancy Yang, BA; Lauren A. Eberly, MD, MPH; Sameed Ahmed M. Khatana, MD, MPH; Elias J. Dayoub, MD, MPP, MS; Sreekanth Vemulapalli, MD; Howard Julien, MD, MPH; David J. Cohen, MD, MSc; Brahmajee K. Nallamothu, MD, MPH; Suzanne J. Baron, MD, MSc; Nimesh D. Desai, MD, PhD; Wilson Y. Szeto, MD; Howard C. Herrmann, MD; Peter W. Groeneveld, MD, MS; Jay Giri, MD, MPH; Alexander C. Fanaroff, MD, MHS

DESIGN, SETTING, AND PARTICIPANTS This multicenter, nationwide cross-sectional analysis of Medicare claims data between January 1, 2012, and December 31, 2018, included beneficiaries of fee-for-service Medicare who were 66 years or older living in the 25 largest metropolitan core-based statistical areas.

Nathan AS et al. JAMA Cardiol 2021

Underdiagnosis and Undertreatment Issues



JAMA Cardiology | Original Investigation

Racial, Ethnic, and Socioeconomic Disparities in A… atheter Aortic Valve Replacement Within Major M…

Ashwin S. Nathan, MD, MS; Lin Yang, MS; Nancy Yang…
Sameed Ahmed M. Khatana, MD, MPH; El…
Howard Julien, MD, MPH; Da…
Suzanne J. Baron…
Peter W. Gro…

Editor's Note

Race Bias in Transcatheter Aortic Valve Replacement Are We Sure?

Clyde W. Yancy, MD, MSc; Ajay Kirtane, MD, SM

CONCLU… …politan areas in the US with TAVR programs… …portions of Black and Hispanic patients and those with greater so… …disadvantages had lower rates of TAVR, adjusting for age and clinical comorbidities. Whether this reflects a different burden of symptomatic aortic stenosis by race and socioeconomic status or disparities in use of TAVR requires further study.

Nathan AS et al. JAMA Cardiol 2021

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- ***Screening tools for aortic stenosis***
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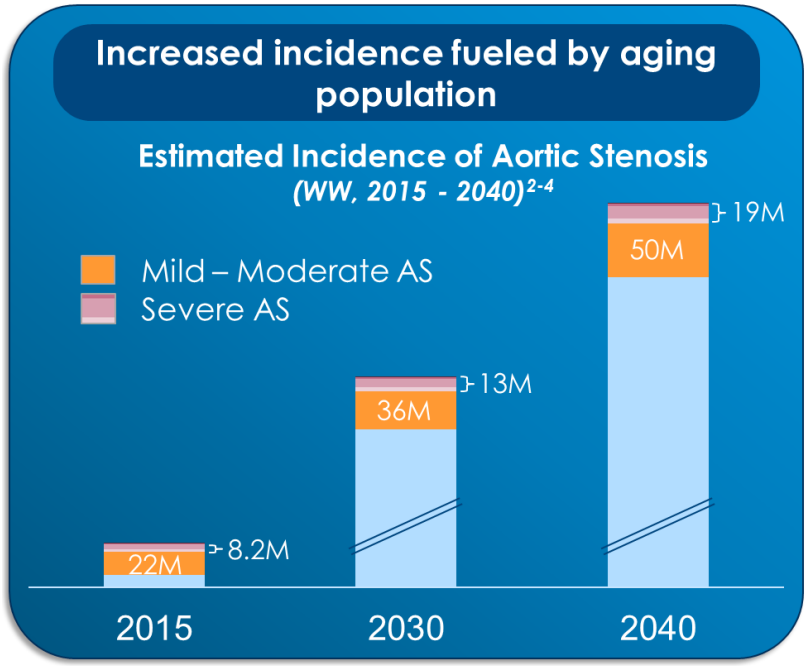
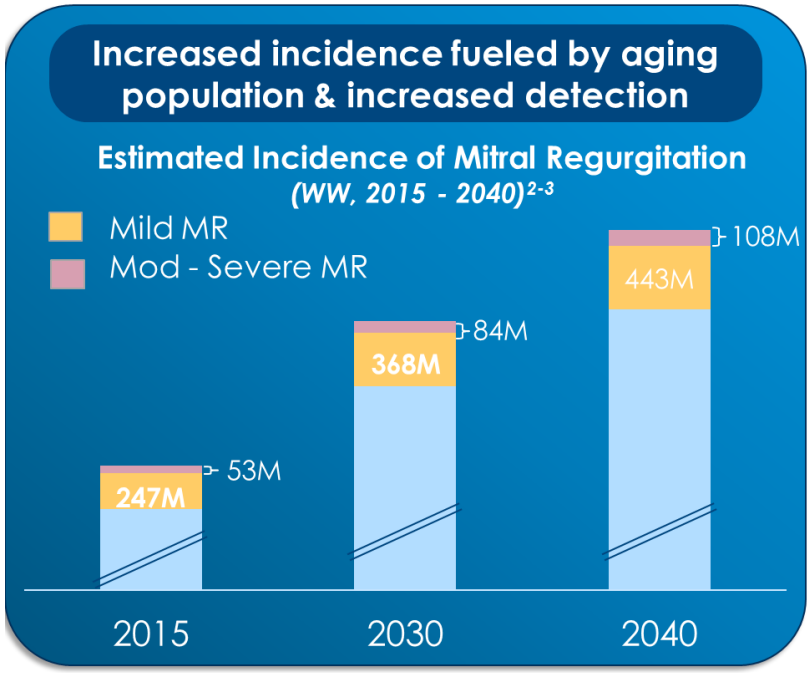
Valvular Heart Disease Therapies: The Future?

Growth and Access to Care

Global mod-severe AS/MR incidence >150 million in 2040





Access to care CRISIS: under-diagnosis and under-treatment; Example: in the U.S., < 30% pts with severe symp AS receive AVR (surgery or TAVR) within 1yr of diagnosis!

Future Screening Tools for Valvular Heart Disease

Artificial Intelligence/Machine Learning

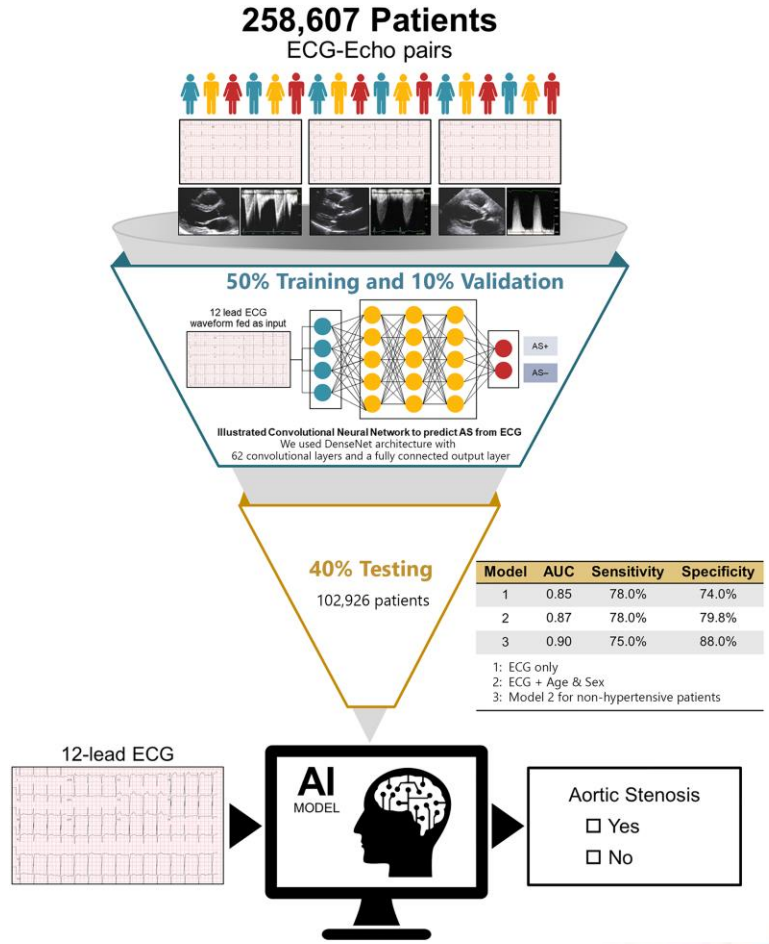
ESC European Society of Cardiology
European Heart Journal (2021) **00**, 1–12
doi:10.1093/eurheartj/ehab153

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.

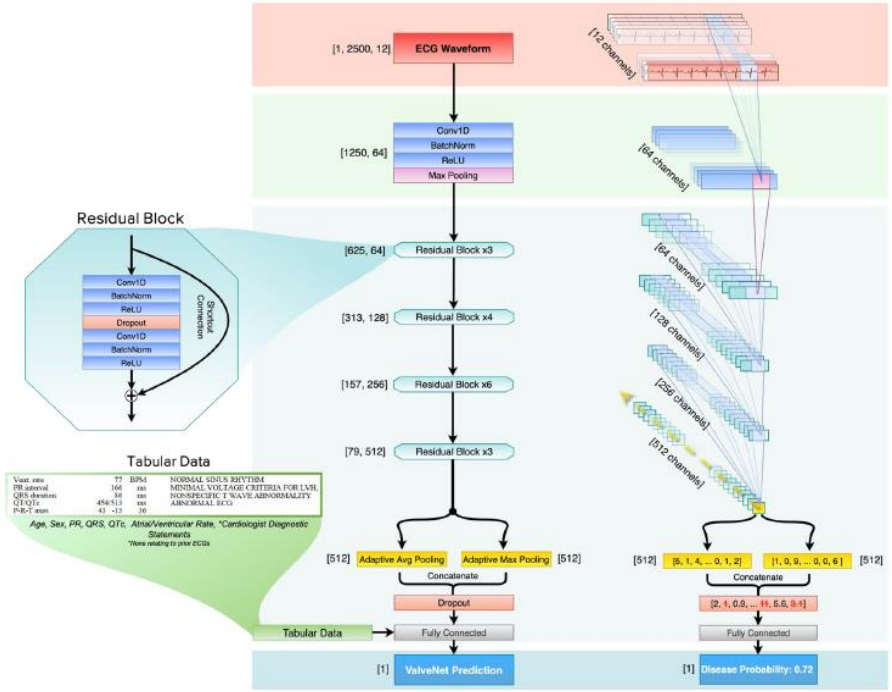


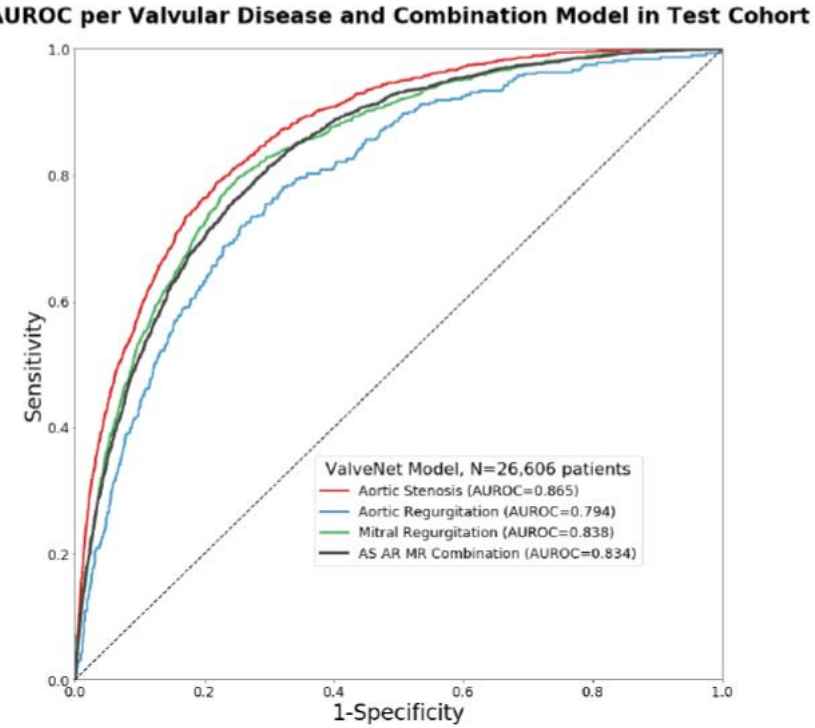
Future Screening Tools for Valvular Heart Disease

Artificial Intelligence/Machine Learning

JACC and TVT 2021

An artificial intelligence model for the detection of aortic stenosis, aortic regurgitation, and mitral regurgitation from electrocardiograms





Columbia test set model performance:

AU-ROC for AS was 0.865 (95% CI 0.850-0.878), AR 0.794 (0.760-0.826), MR 0.838 (0.822-0.853) and AS/AR/MR 0.834 (0.822-0.846)

Elias P, Poterucha TJ et al; Submitted to JACC 2021

Future Screening Tools for Valvular Heart Disease

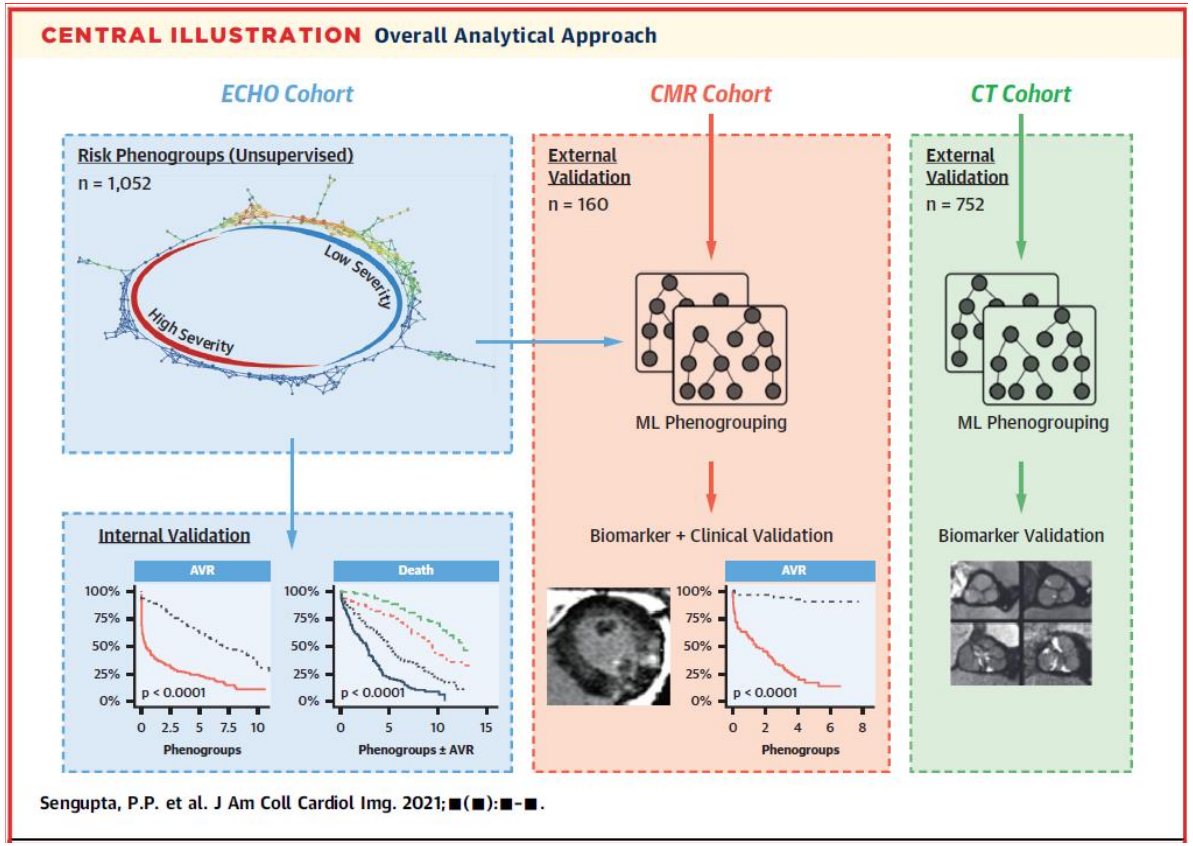
Artificial Intelligence/Machine Learning

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)



Roadmap for this Lecture

- UPSTREAM conceptual framework
- Under-diagnosis/treatment issues
- Screening tools for aortic stenosis
- ***Pre-emptive (earlier) AVR***
- Pharmaco-therapeutics for AVD

The RECOVERY Surgical AVR Trial

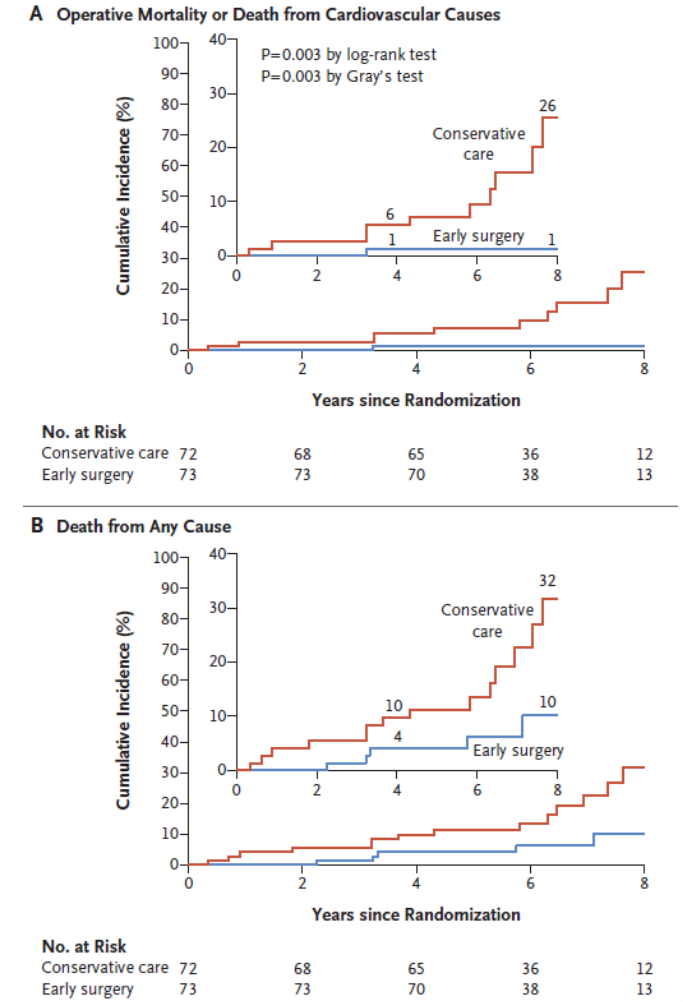
The NEW ENGLAND JOURNAL of MEDICINE

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)

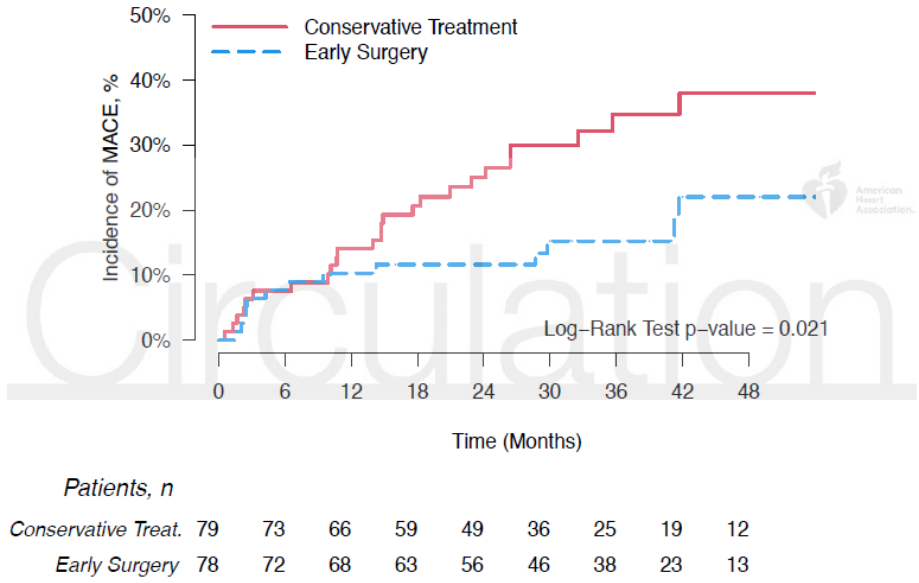


Kang DH et al, NEJM 2020

The AVATAR Surgical AVR Trial

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

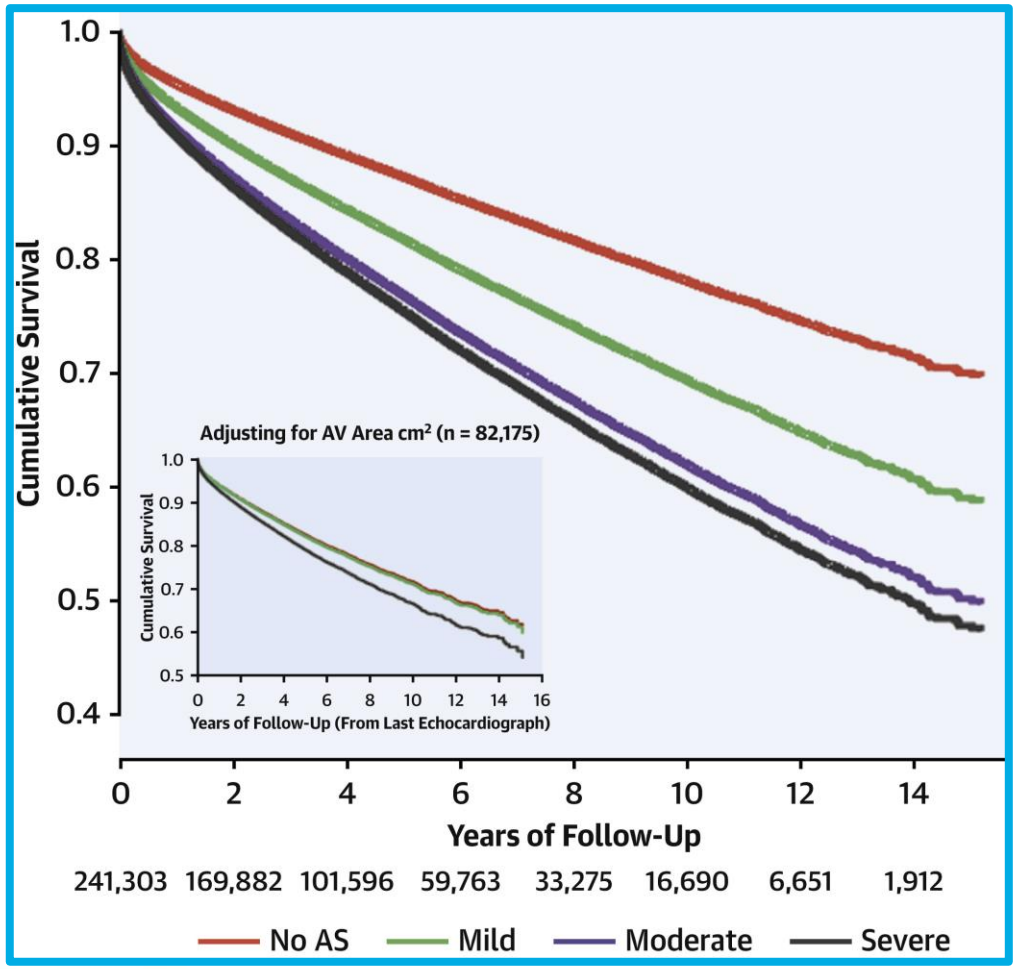
- 157 asymptomatic patients (ETT confirmed) w severe AS, randomized to early surgery or conservative care at 9 centers from 7 EU countries; median FU 32 months
- Early surgery operative mortality 1.4%
- 1^{ry} endpoint (MACE = death, MI, stroke and HF rehosp) was lower with early surgery vs. conservative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



Banovic, M, AHA 2021 and Circulation 2021

Natural History of Untreated Mod AS

National Echo Database



Poor Long-Term Survival in Patients With Moderate Aortic Stenosis

Geoff Strange, PhD,[a] Simon Stewart, PhD,[b] David Celermajer, MD, PhD,[c] David Prior, MBBS, PhD,[d] Gregory M. Scalia, MBBS (Hons), MMedSc,[e] Thomas Marwick, MBBS, PhD,[f] Marcus Ilton, MD,[g] Majo Joseph, MBBS,[h] Jim Codde, PhD,[i] David Playford, MBBS, PhD,[a] on behalf of the National Echocardiography Database of Australia contributing sites

Reasons…

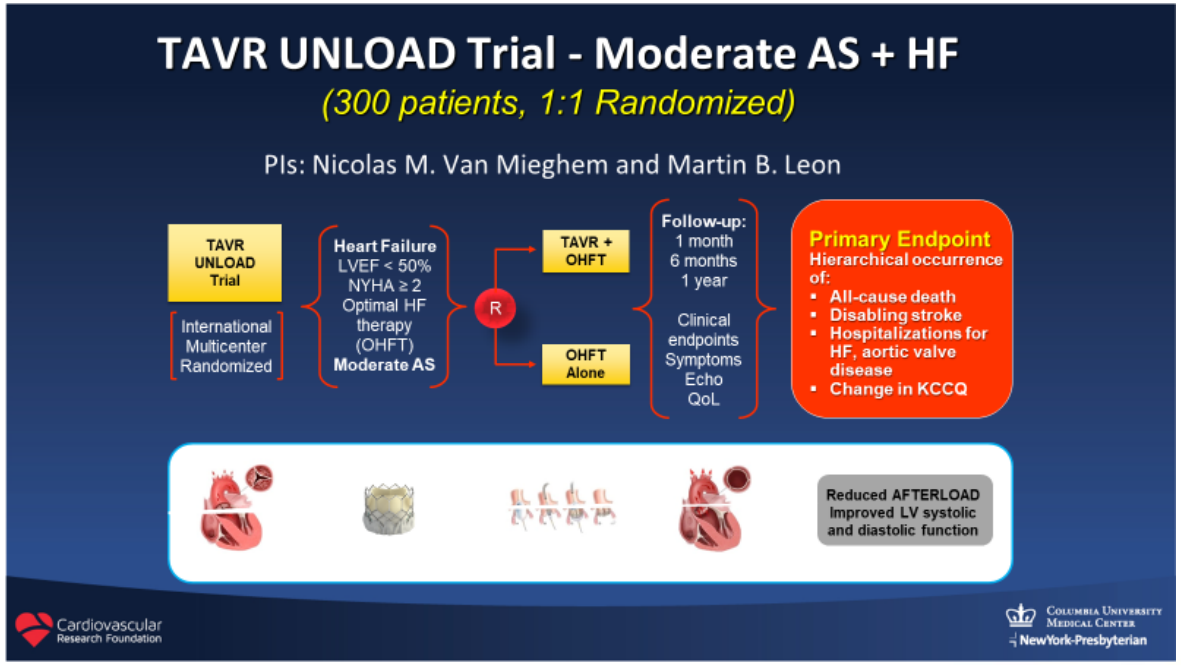
- Misclassification issues?
- Echocardiography challenges
- Rapid progression to severe AS
- Already too much cardiac damage
- Intervention too late (missed opportunities) with limitations of active surveillance strategy

Strange G et al. JACC 2019; 74:1851–63

Pre-emptive (earlier) TAVR

EARLY TAVR and UNLOAD Trials

Expanding TAVR Clinical Indications to 'Earlier' Treatment Scenarios



Upstream Mod AS Treatment

"At Risk" Predictors

Natural History of Moderate Aortic Stenosis

KELLEY D. KENNEDY, MD, RICK A. NISHIMURA, MD, FACC, DAVID R. HOLMES, JR., MD, FACC, KENT R. BAILEY, PHD

Early Surgery versus Watchful Waiting in Patients with Moderate Aortic Stenosis and Left Ventricular Systolic Dysfunction

ARTICLE

Prospective Study of Asymptomatic Valvular Aortic Stenosis

Clinical, Echocardiographic, and Exercise Predictors of Outcome

The natural history of moderate aortic stenosis in a veteran population

JAMA Cardiology | Original Investigation

Outcomes of Patients With Asymptomatic Aortic Stenosis Followed Up in Heart Valve Clinics

Poor Long-Term Survival in Patients With Moderate Aortic Stenosis

Characteristics and Prognosis of Patients With Moderate Aortic Stenosis and Preserved Left Ventricular Ejection Fraction

Clinical and Echocardiographic Predictors of Outcomes in Patients With Moderate (Mean Transvalvular Gradient 20 to 40 mm Hg) Aortic Stenosis

Excess Mortality Associated with Progression Rate in Asymptomatic Aortic Valve Stenosis

Prognostic Risk Stratification of Patients with Moderate Aortic Stenosis

Aortic valve surgery and survival in patients with moderate or severe aortic stenosis and left ventricular dysfunction

Prognostic Implications of Moderate Aortic Stenosis in Patients With Left Ventricular Systolic Dysfunction

Mild and moderate aortic stenosis

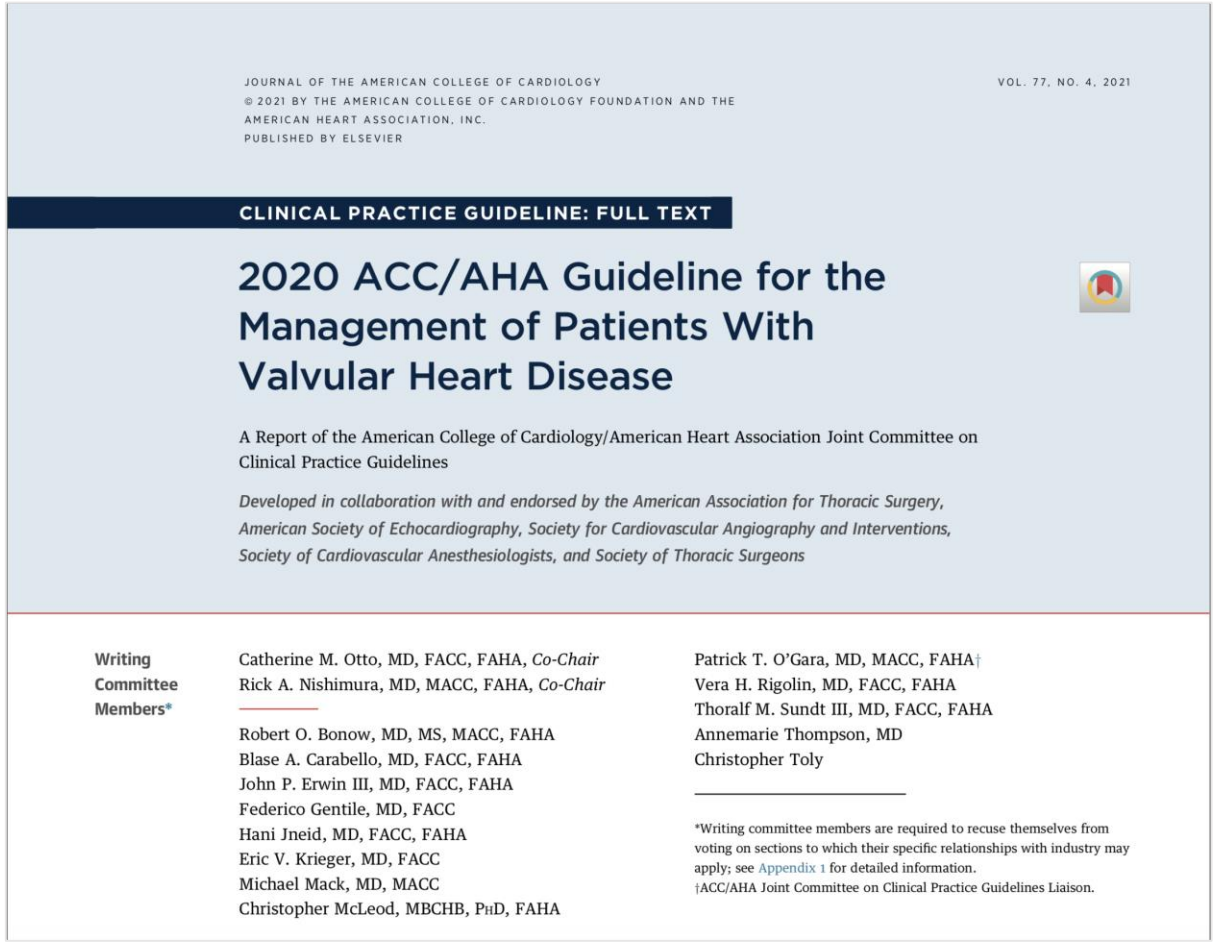
Natural history and risk stratification by echocardiography

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

Get with the Guidelines (Moderate AS)



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VOL. 77, NO. 4, 2021

CLINICAL PRACTICE GUIDELINE: FULL TEXT

2020 ACC/AHA Guideline for the Management of Patients With Valvular Heart Disease

A Report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines

Developed in collaboration with and endorsed by the American Association for Thoracic Surgery, American Society of Echocardiography, Society for Cardiovascular Angiography and Interventions, Society of Cardiovascular Anesthesiologists, and Society of Thoracic Surgeons

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*Writing committee members are required to recuse themselves from voting on sections to which their specific relationships with industry may apply; see Appendix 1 for detailed information.
†ACC/AHA Joint Committee on Clinical Practice Guidelines Liaison.

Grading Moderate AS

	Aortic sclerosis	Mild	Moderate	Severe
Peak velocity (m/s)	≤2.5 m/s	2.6–2.9	3.0–4.0	≥4.0
Mean gradient (mmHg)	–	<20	20–40	≥40
AVA (cm^2)	–	> 1.5	1.0–1.5	<1.0
Indexed AVA (cm^2/m^2)	–	>0.85	0.60–0.85	<0.6
Velocity ratio	–	> 0.50	0.25–0.50	<0.25

J Am Soc Echo 2017;30:372-92.

Otto, Nishimura, Bonow et al. J Am Coll Cardiol. 2021 Feb, 77 (4) e25–e197

VHD Mod AS Guidelines- Timing and Follow-Up

Timing of Intervention Recommendations

2b	C-EO	11. In patients with moderate AS (Stage B) who are undergoing cardiac surgery for other indications, AVR may be considered.

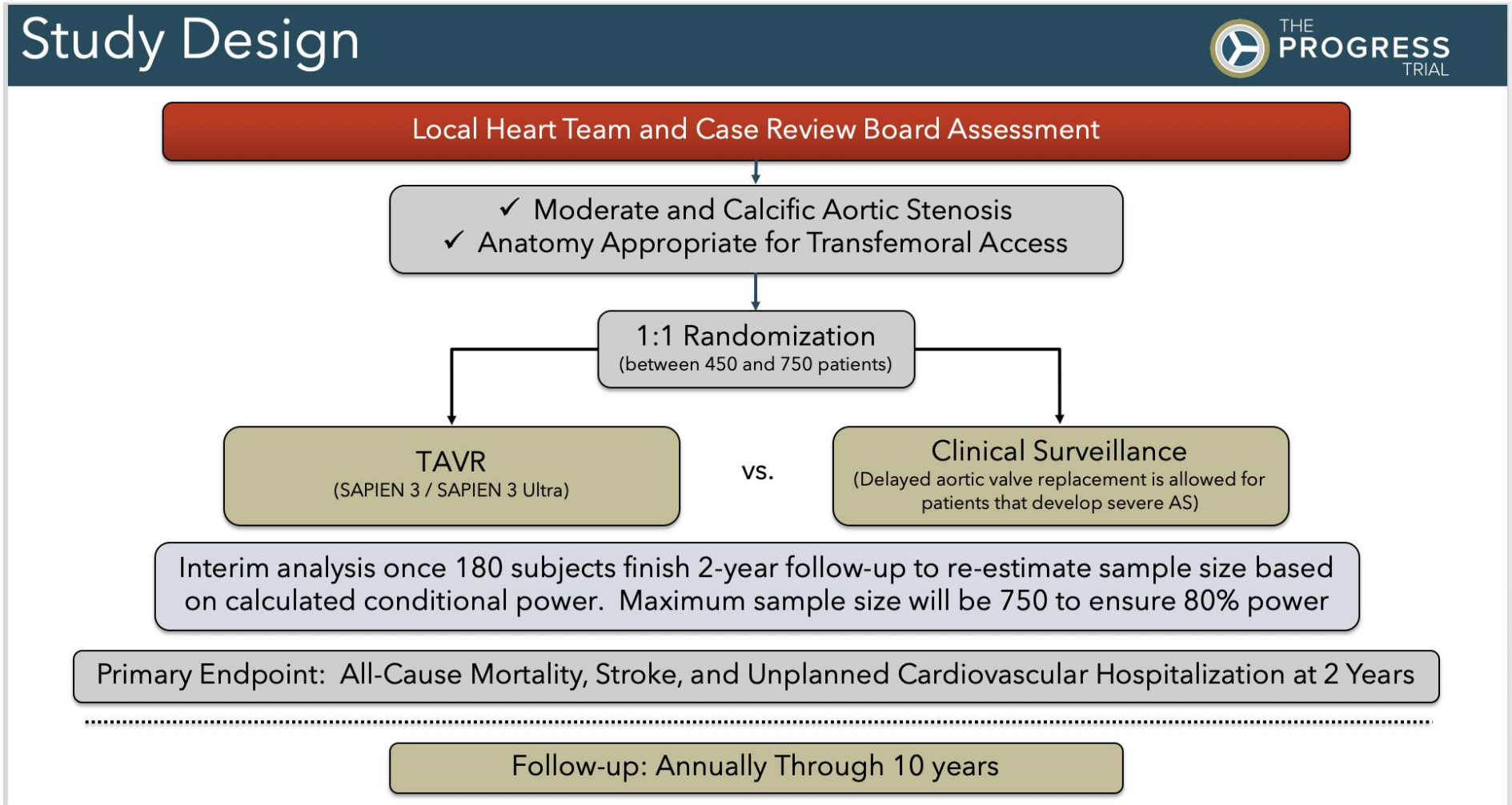
Follow-Up Recommendations

Mild (Vmax 2.0–2.9 m/s)	Every 3-5 years
Moderate (Vmax 3.0–3.9 m/s)	**Every 1-2 years**
Severe Asymptomatic (Vmax ≥4 m/s)	Every 6-12 months

Otto, Nishimura, Bonow et al. J Am Coll Cardiol. 2021 Feb, 77 (4) e25–e197

Upstream Mod AS Treatment: The Future?

The PROGRESS Trial

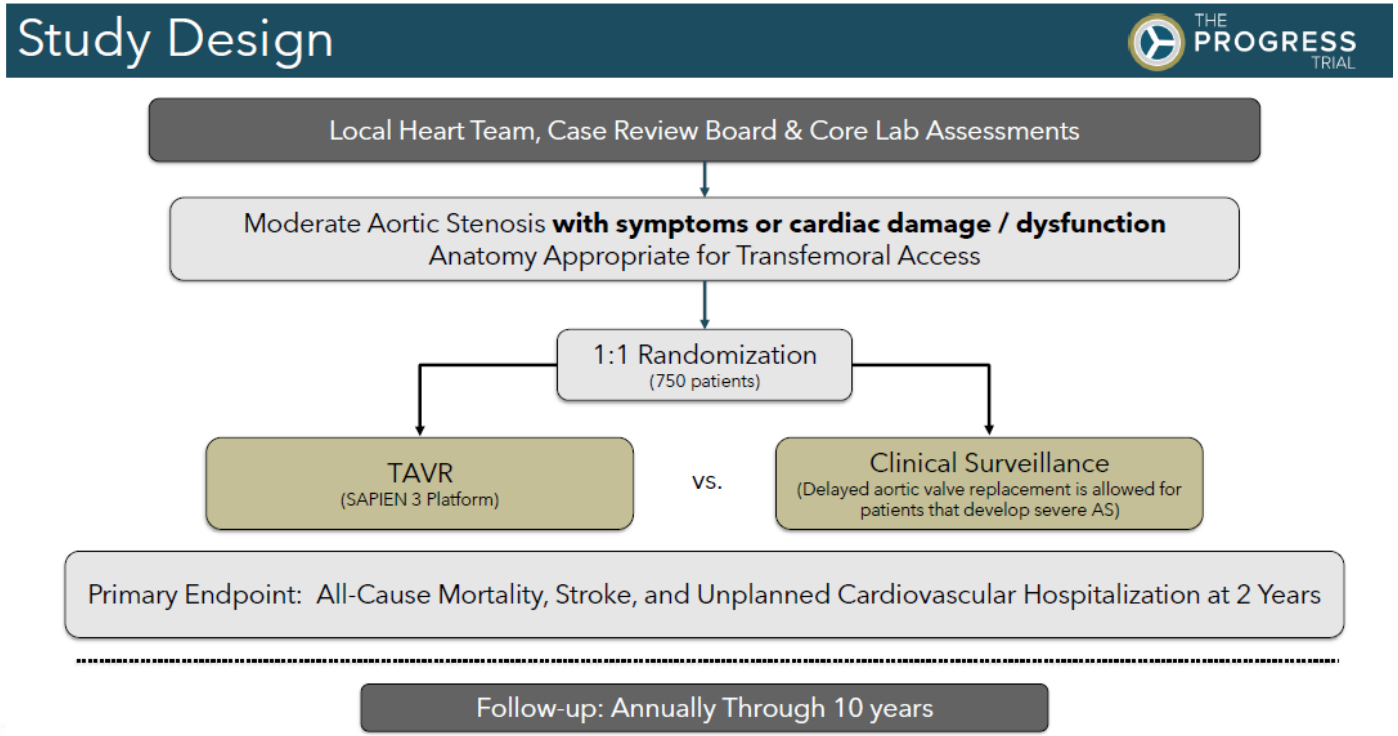


Study PIs: Philippe Genereux, Raj Makkar and Jeroen Bax; Study Chairman: Martin B. Leon

Upstream Mod AS Treatment: The Future?

The PROGRESS Trial

The PROGRESS Trial (750 pts)



Inclusion Criteria (1)

Patients must be **≥65** years old

Moderate AS is defined as:

1. Moderate AVA

AVA 1.0 – 1.5cm^2 **OR**

AVA < 1.0 cm^2 with AVAi > 0.6 cm^2/m^2 if BMI <30kg/m^2; **OR**

AVA < 1.0 cm^2 with AVAi > 0.5 cm^2/m^2 if BMI ≥30kg/m^2

AND

2. Moderate peak aortic velocity or gradient:

Peak velocity 3.0 to < 4.0 m/s **OR**

Mean gradient 20 to < 40mmHg

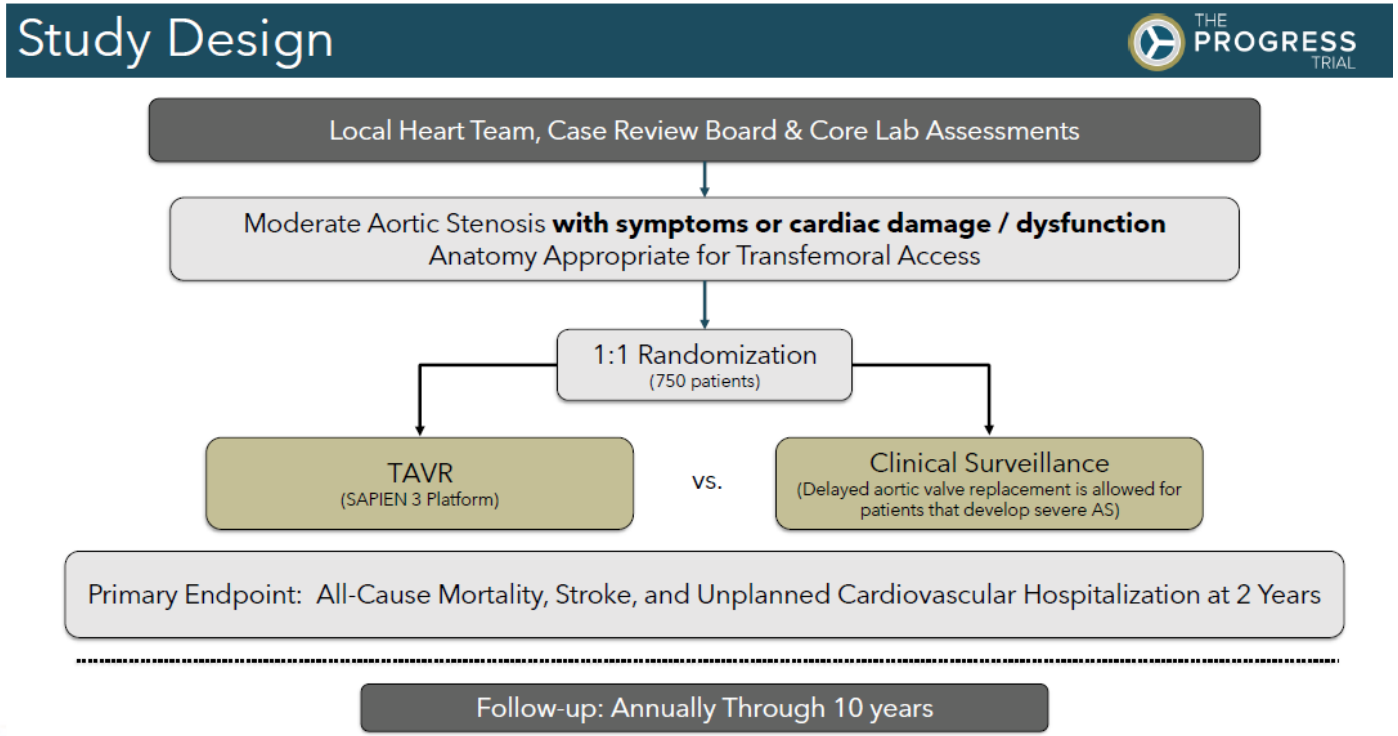
Subjects who only meet **one of the above criteria** on resting TTE are **eligible** if both criteria are met following **dobutamine stress echo (DSE)**

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

Upstream Mod AS Treatment: The Future?

The PROGRESS Trial

The PROGRESS Trial (750 pts)



Inclusion Criteria (2)

1. Evidence of Symptoms

NYHA ≥2, dyspnea, angina, syncope

OR

2. Evidence of Cardiac Damage or Dysfunction

LVEF <60%

Diastolic dysfunction ≥ Grade 2

Stroke volume index < 35 mL/m^2

Persistent atrial fibrillation or any paroxysmal episode within 6 months

NT-ProBNP >3x normal

Elevated calcium score (>1200 AU for females, >2000 AU for males)

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					

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		AVR	AVR	AVR	AVR

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	PROGRESS	PROGRESS	PROGRESS	PROGRESS	PROGRESS
Grade 3 V_{max} ≥.4m/s	EARLY TAVR				

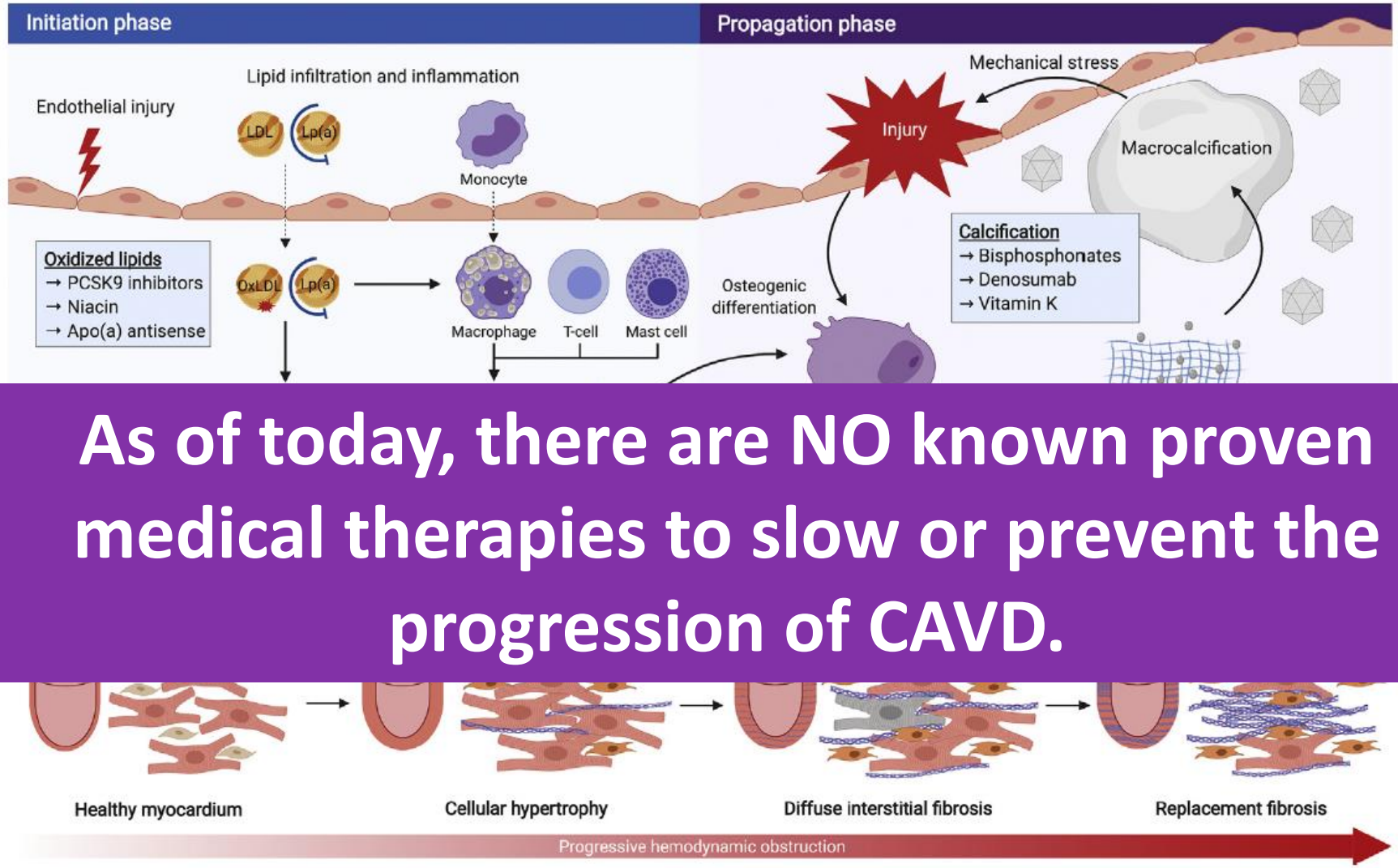
First PROGRESS Patient Enrolled

Philippe Généreux & Morristown Med. Ctr. Team

Roadmap for this Lecture

- UPSTREAM conceptual framework
- Under-diagnosis/treatment issues
- Screening tools for aortic stenosis
- Pre-emptive (earlier) AVR
- ***Pharmaco-therapeutics for AVD***

Pathophysiology of Aortic Stenosis



As of today, there are NO known proven medical therapies to slow or prevent the progression of CAVD.

KH Zheng, E Tzolos, MR Dweck. Cardiol Clin 38 (2020) 1-12

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.

KH Zheng, E Tzolos, MR Dweck. Cardiol Clin 38 (2020) 1-12

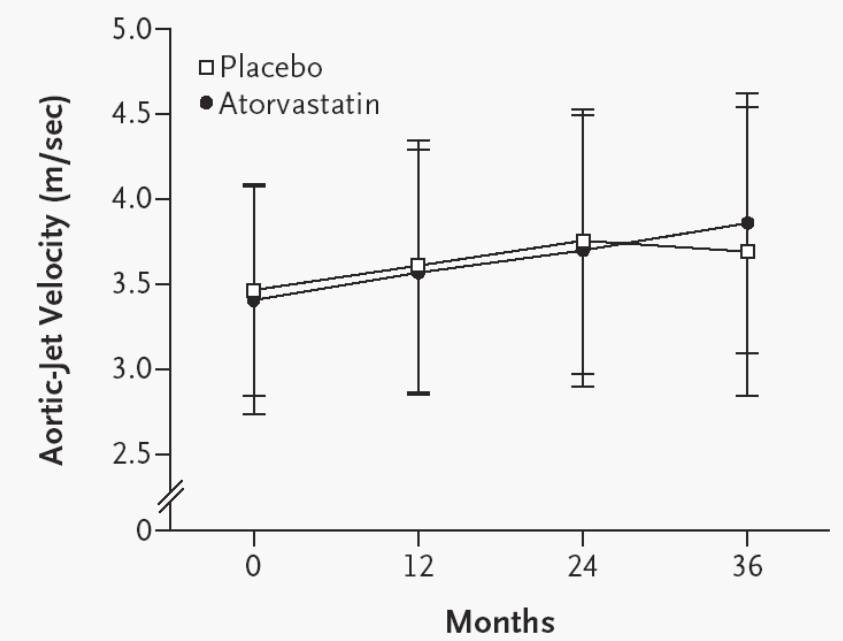
The “Statin Era” of Medical Rx for CAVD

- AS is a degenerative process resulting from “wear and tear”, predominantly of the valve leaflets.
- AS shares many similarities with atherosclerosis (risk factors, mechanisms).
- *Thus, AS is a potentially modifiable atherosclerotic disease.*
- Hope for pharmacotherapy in AS: STATINS!

Failure of Statin Rx to Treat CAVD

SALTIRE (2005)

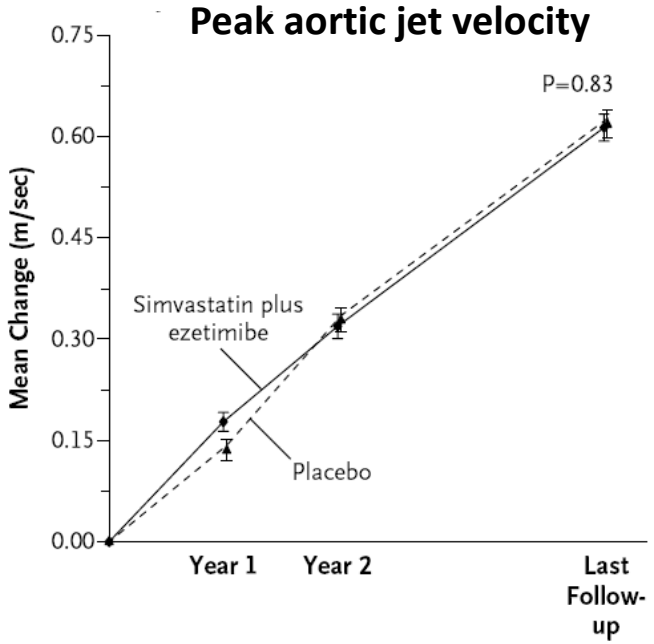
N = 155 pts



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

SEAS (2008)

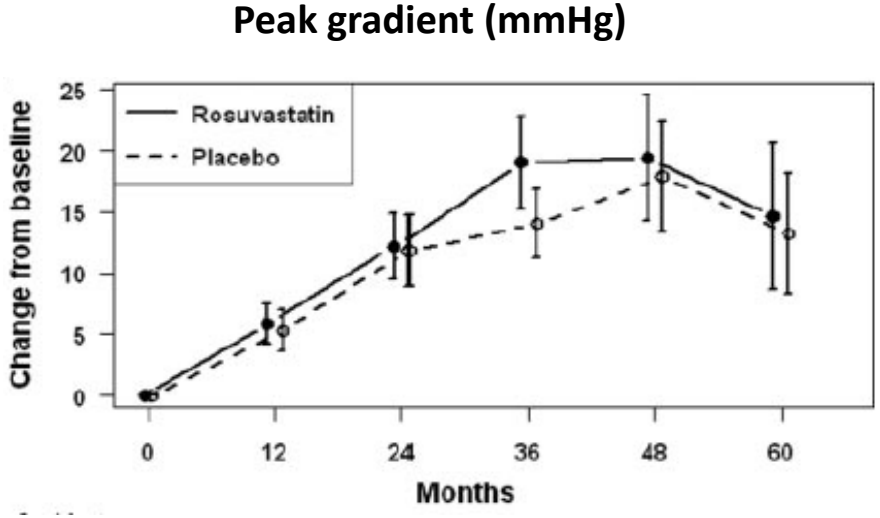
N = 1,873 pts



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

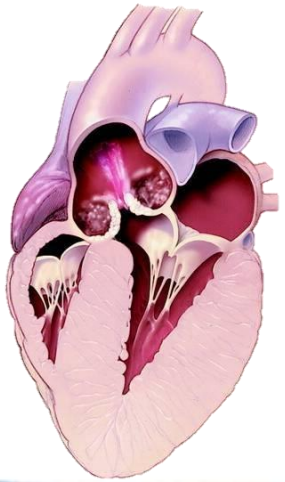
ASTRONOMER (2010)

N = 269 pts



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

Modern Thinking – Medical Rx for CAVD



- Several promising targets have been identified and several RCTs are planned or ongoing
- The « one drug fits all » concept will not be effective for all AS patients
- Need to tailor therapy according to age, sex, AoV Phenotype, and AS severity

Adapted from Pibarot

Modern Thinking – Medical Rx for CAVD

Lp(a) lowering
PCSK9i

Young age
BAV
Mild/moderate AS

ARBs
Antifibrotic therapy

Young/ old age
TAV/ BAV
Women

Bisphosphonates
RANK Ab, Vit K

Old age
TAV/ BAV
Mild/Moderate AS

Adapted from Pibarot

Medical Therapies for CAVD

Circulation

PERSPECTIVE

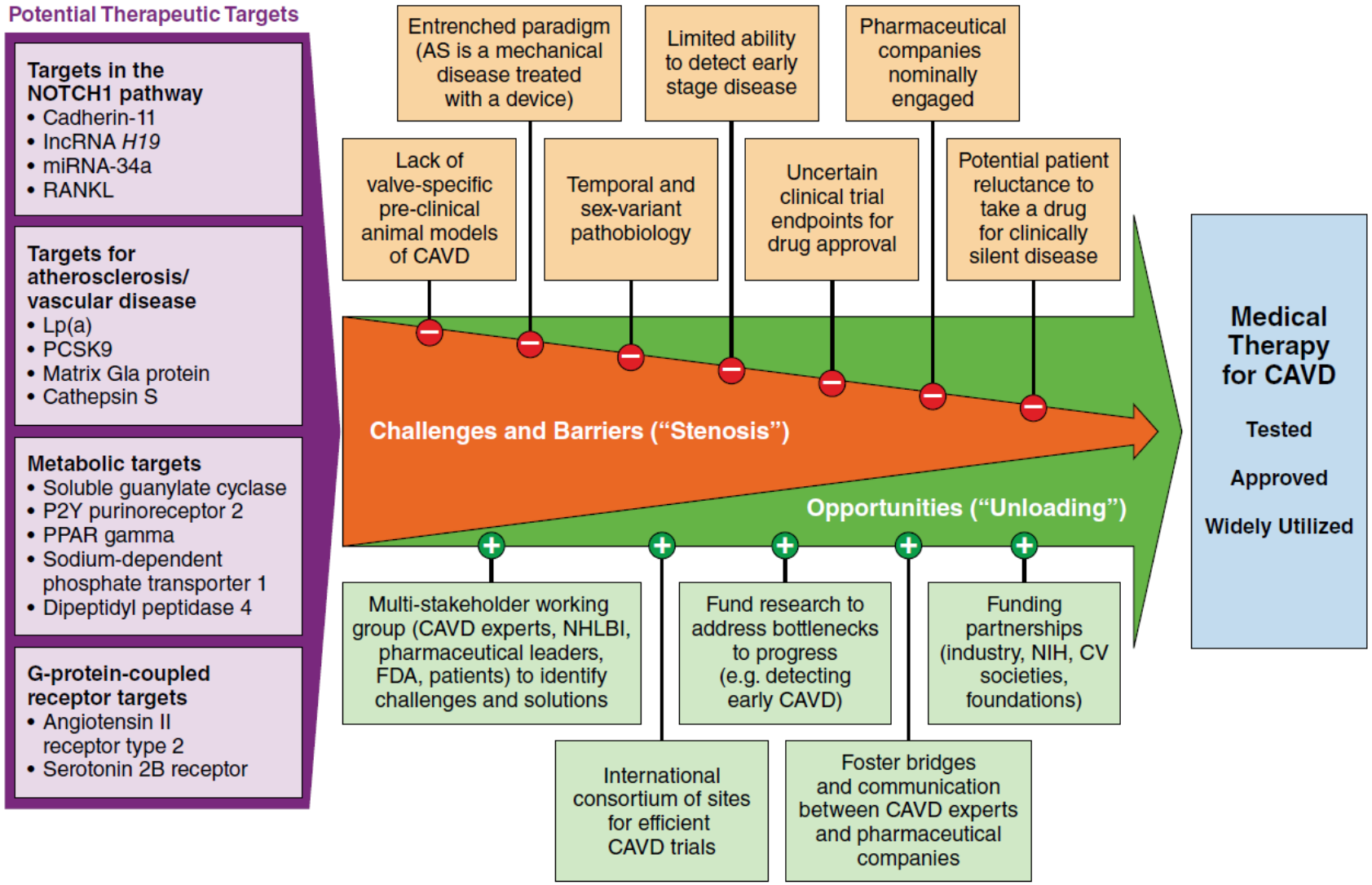
Unloading the Stenotic Path to Identifying Medical Therapy for Calcific Aortic Valve Disease

Barriers and Opportunities

Brian R. Lindman, MD, MSc and W. David Merryman, PhD

Circulation 2021; 143:1455-57

Medical Therapies for CAVD



Medical Therapies for CAVD

Prevention and Mitigation of Heart Failure in the Treatment of Calcific Aortic Stenosis
A Unifying Therapeutic Principle

- After TAVR, up to 50% of patients are dead, have residual heart failure (HF) symptoms or poor QoL at 1 year
- HF is the most common admitting diagnosis during the first year after TAVR with rates only slightly lower in the year after TAVR compared to the year before
- **Residual risk from HF is primarily due to cardiac remodeling and irreversible injury**
- Before the onset of symptoms and before AS is “severe”, chronic pressure overload from years of AS leads to a series of molecular and tissue-level myocardial alterations (e.g., fibrosis, apoptosis, inflammation, microvascular dysfunction, etc.) that presage global/macroscopic changes in cardiac structure and function

Brian R. Lindman, MD, MSc and JoAnn Lindenfeld, MD; JAMA Cardiology 2021

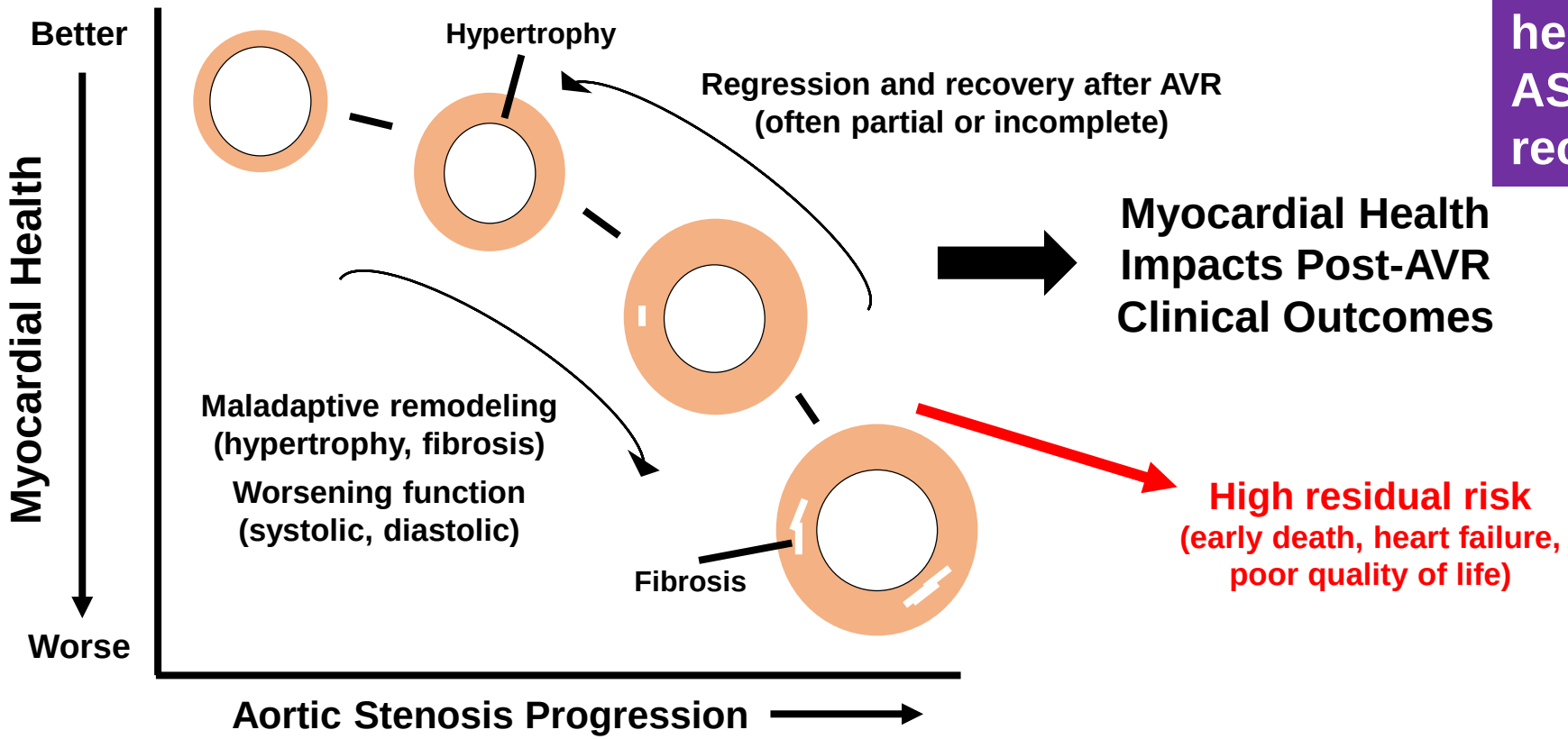
Medical Therapies for CAVD

RAAS inhibition?

Entresto?

SGLT2i?

Adjunctive medical therapy to protect the heart during progressive AS and augment its recovery after AVR



Myocardial Health Impacts Post-AVR Clinical Outcomes

High residual risk
(early death, heart failure, poor quality of life)

Asymptomatic

Symptomatic

Symptom-based trigger for AVR (too late)

Increased mortality, residual heart failure, poor QoL

Medical Therapies for CAVD

Key Points

- Aortic stenosis is a disease of both the valve and the myocardium.
- Currently, there are no medical therapies that have been proven to slow down or halt disease progression in aortic stenosis.
- Novel insights in the valve and myocardial pathophysiology of aortic stenosis progression have identified numerous molecular targets related to oxidized lipids, calcification, and fibrosis, although only a few have thusfar been translated to clinical trials.
- A multi-drug approach to precisely target disease stage and patient phenotype is the most realistic and promising.
- The clinical trial process must be rejuvenated including the use of non-invasive imaging modalities such as CT calcium scoring, 18F-NaF PET, and MRI to assist in risk stratification and as surrogate clinical endpoints.

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					

Multi-drug ‘precision’ medical Rx

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	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

UPSTREAM Management of AS

(Martin B. Leon)