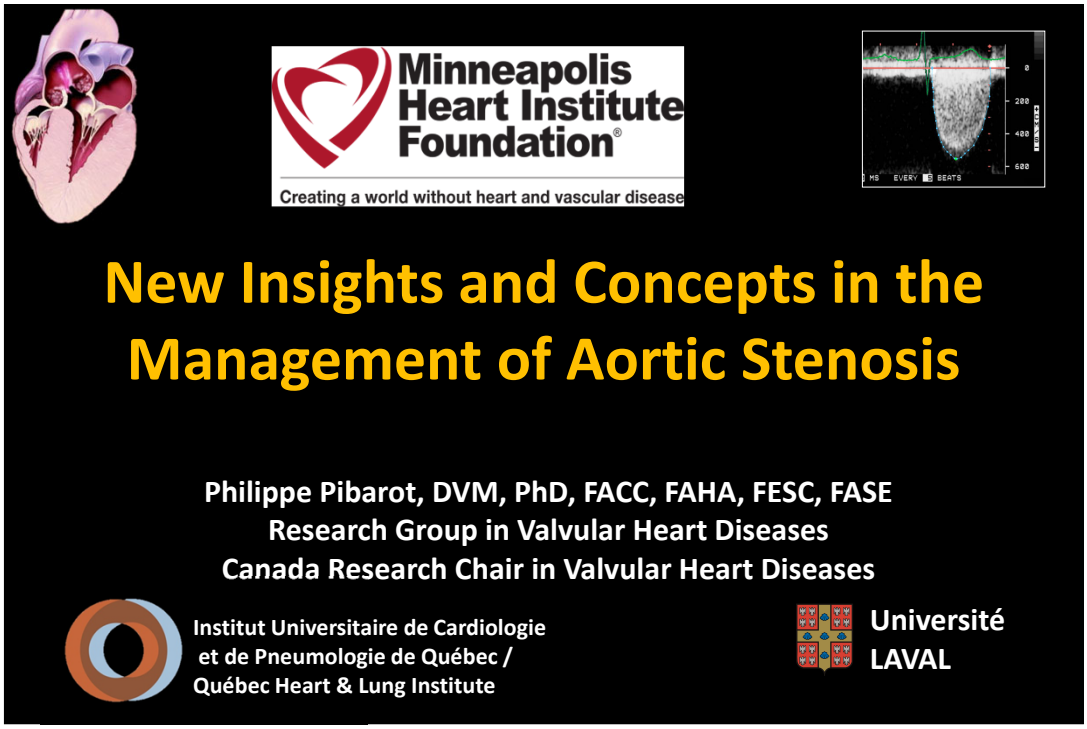

Minneapolis
Heart Institute
Foundation
GRAND ROUNDS

1


Minneapolis
Heart Institute
Foundation
Creating a world without heart and vascular disease
New Insights and Concepts in the Management of Aortic Stenosis
Philippe Pibarot, DVM, PhD, FACC, FAHA, FESC, FASE
Research Group in Valvular Heart Diseases
Canada Research Chair in Valvular Heart Diseases
Institut Universitaire de Cardiologie
et de Pneumologie de Québec /
Québec Heart & Lung Institute
Université
LAVAL

2

Disclosure: Philippe Pibarot

Financial relationship with industry:

- Edwards Lifesciences: Echo CoreLab for PARTNER 2– SAPIEN 3, PARTNER 3, TAVR-UNLOAD, EARLY-TAVR, PROGRESS, ALLIANCE X4 trials
- Edwards Lifesciences: Steering committee of PROGRESS trial
- Cardiac Phoenix: Echo CoreLab for BACE FIM Study
- Pi-Cardia: Echo CoreLab for Leaflex Study

Other financial disclosure:

- Research Grants from Canadian Institutes of Health
- Research and Heart & Stroke Foundation of Quebec

Off label Use: None

3

Aortic Stenosis: Progression Stage and When to Intervene?

- At risk for AS (BAV, Aortic Sclerosis) (Stage A)
- Mild / Moderate AS (Stage B)

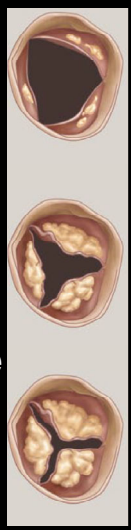
→ Follow

- Severe AS – Asymptomatic No LV Dysfunction (Stage C1)

→ Early AVR vs. Surveillance

- Severe AS – Asymptomatic LV Dysfunction (EF<50%) (Stage C2)
- Severe AS – Symptomatic Stage D

→ AVR Now



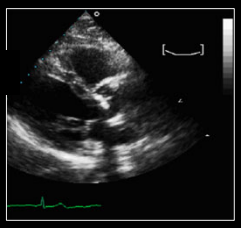
4

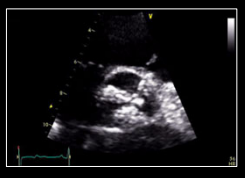
Concept #1: Early AVR vs. Clinical Surveillance in Asymptomatic Severe AS (Stage C1)

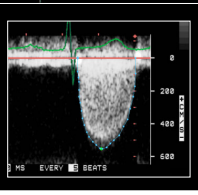
5

Case #1: Asymptomatic Patient with Severe AS (Stage C1)

- 75 y.o. woman with calcific AS
- Asymptomatic (confirmed by ETT)
- BNP: 190 pg/ml; ratio: 2
- LVEF: 60%
- Grading of AS severity on echo:
  - Severely calcified valve
  - Peak jet velocity: 5.1 m/s (1 Yr ago: 4.8 m/s)
  - Peak/mean gradient: 104/64 mmHg
  - AVA: 0.65 cm^2 Indexed AVA: 0.35 cm^2/m^2







6

Clinical Dilemna in True Asymptomatic Severe AS (C1 Stage)

Early « Prophylactic » AVR?

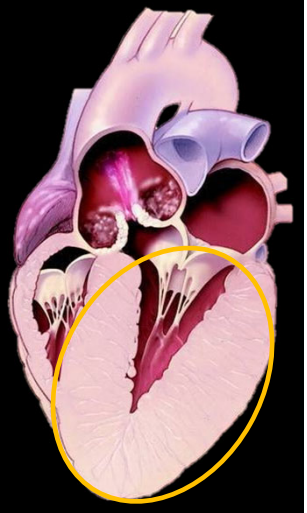
OR

Watchful waiting?

7

Look at the Left Ventricle!

Beyond the LV ejection fraction



8

CARDIOLOGY

Editorial Comment

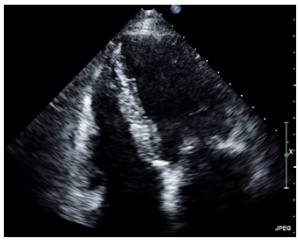
Cardiology 2008;109:122–125
DOI: 10.1159/000105553

Received: January 11, 2007
Accepted: January 12, 2007
Published online: August 21, 2007

What Our Eyes See Is Not Necessarily What Our Heart Feels

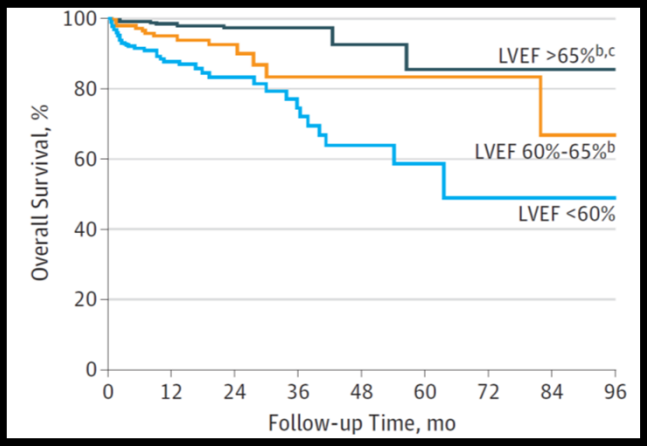
Philippe Pibarot Éric Larose

Laval Hospital Research Center/Quebec Heart Institute, Laval University, Quebec, Que., Canada



9

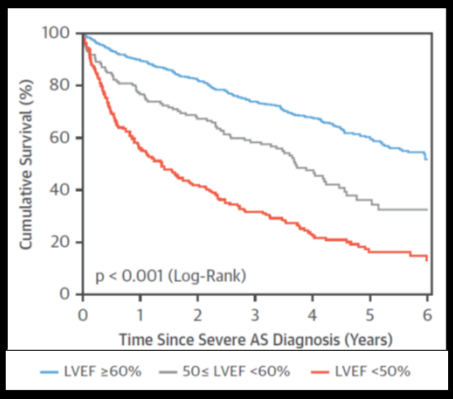
Outcomes of Patients With Asymptomatic AS Followed Up in Heart Valve Clinics



Lancellotti et al. JAMA Cardiology 2018

10

LVEF<50% to define LV systolic dysfunction in AS: Is it too low?

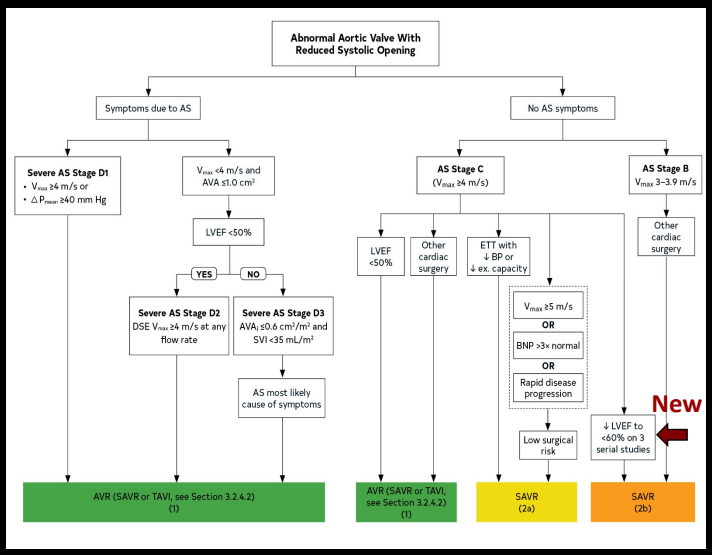


LVEF<60% more appropriate to define LV dysfunction and trigger AVR?

Ito et al. J Am Coll Cardiol 2018;71:1313–21)

11

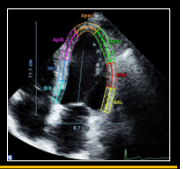
LVEF<50% to define LV systolic dysfunction in AS: Is it too low?



ESC Guidelines LVEF<55% (IIa)

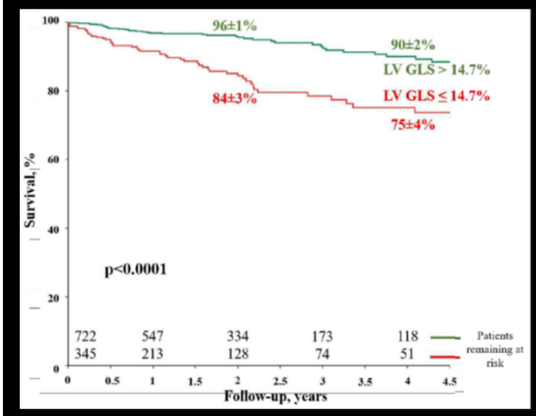
12

Distribution and Prognostic Significance of GLS in Asymptomatic AS: A Meta-analysis

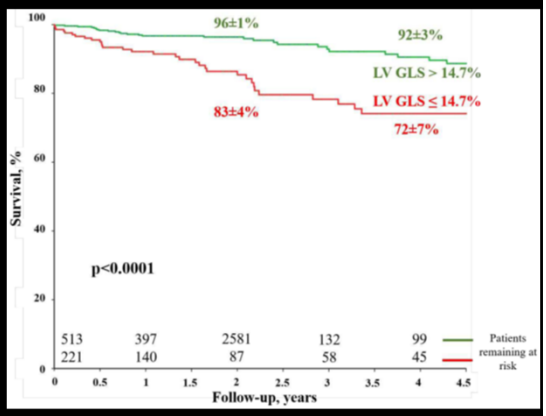


Case: GLS= -13%

Whole Cohort



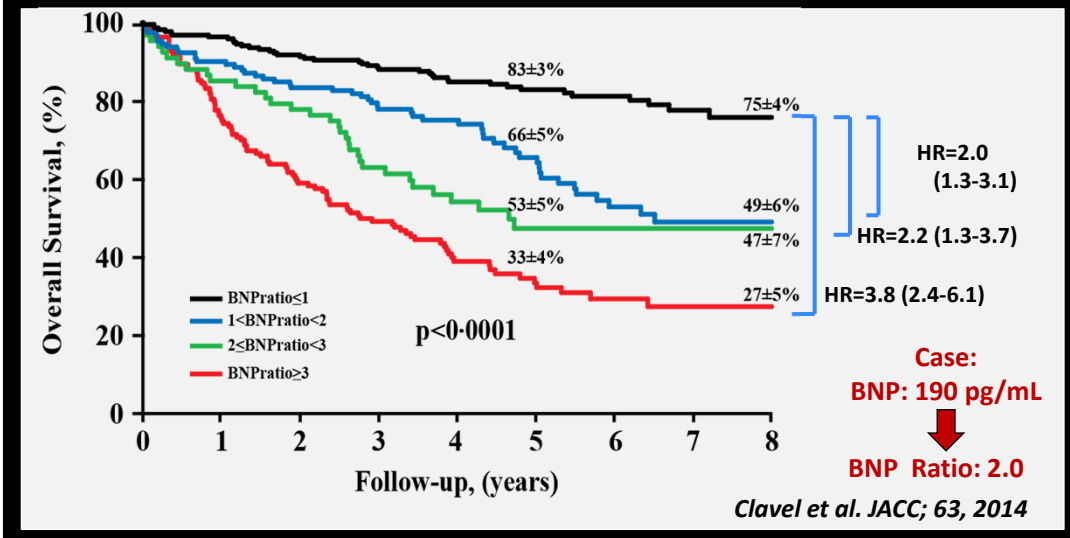
LVEF ≥ 60%



Magne et al. JACCi 2019

13

Risk of Mortality according to BNP "Activation": Ratio of Measured BNP / normal value of BNP in Asymptomatic AS

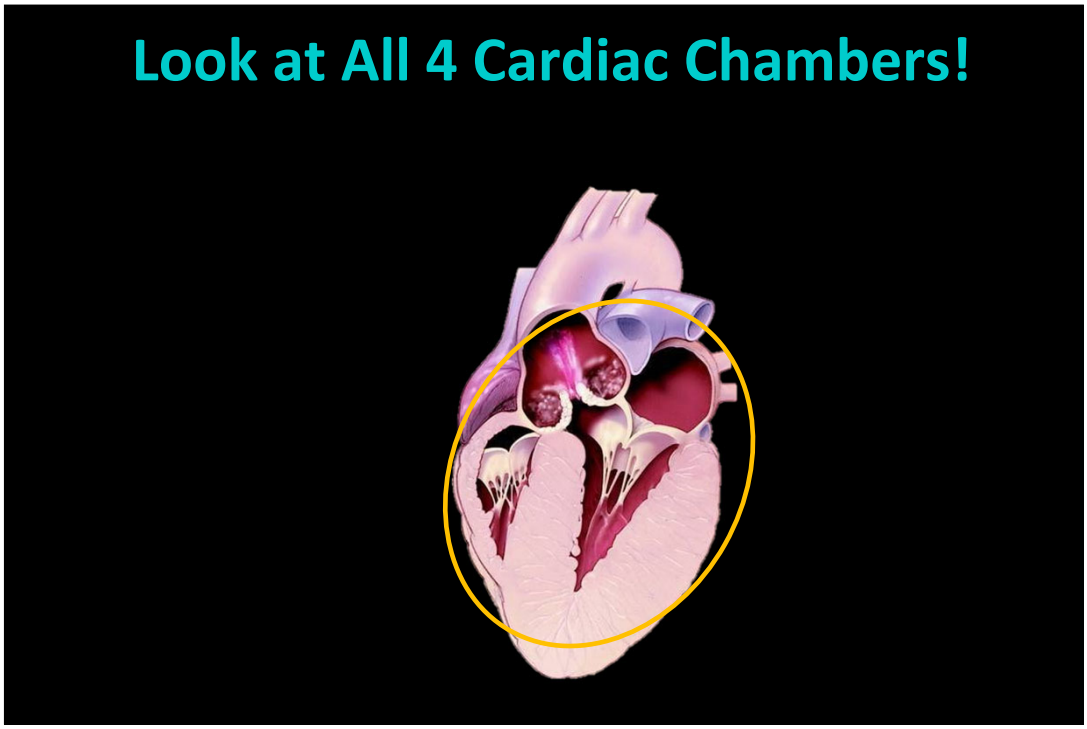


Case:
BNP: 190 pg/mL

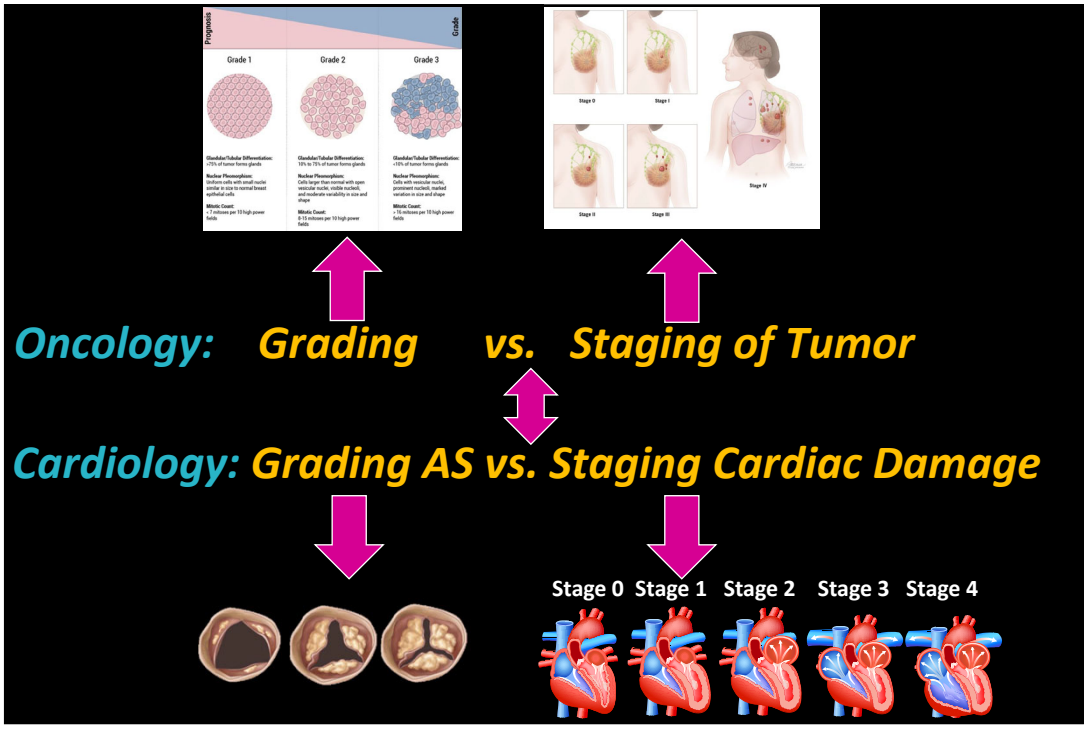
BNP Ratio: 2.0

Clavel et al. JACC; 63, 2014

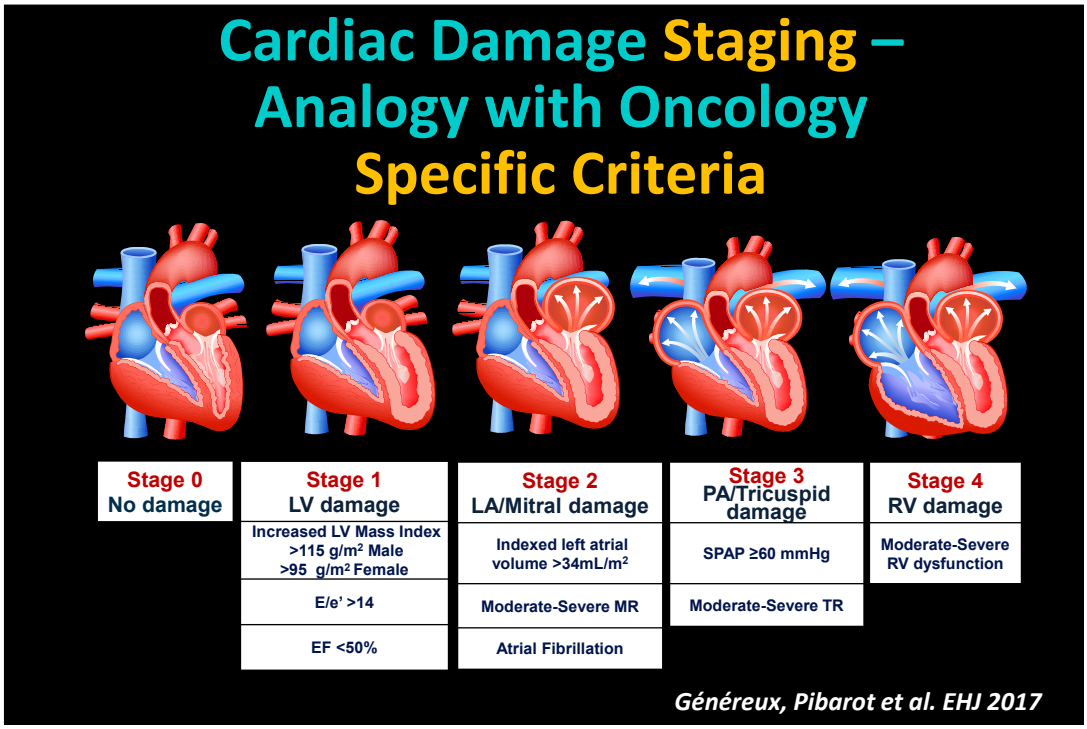
14


Look at All 4 Cardiac Chambers!

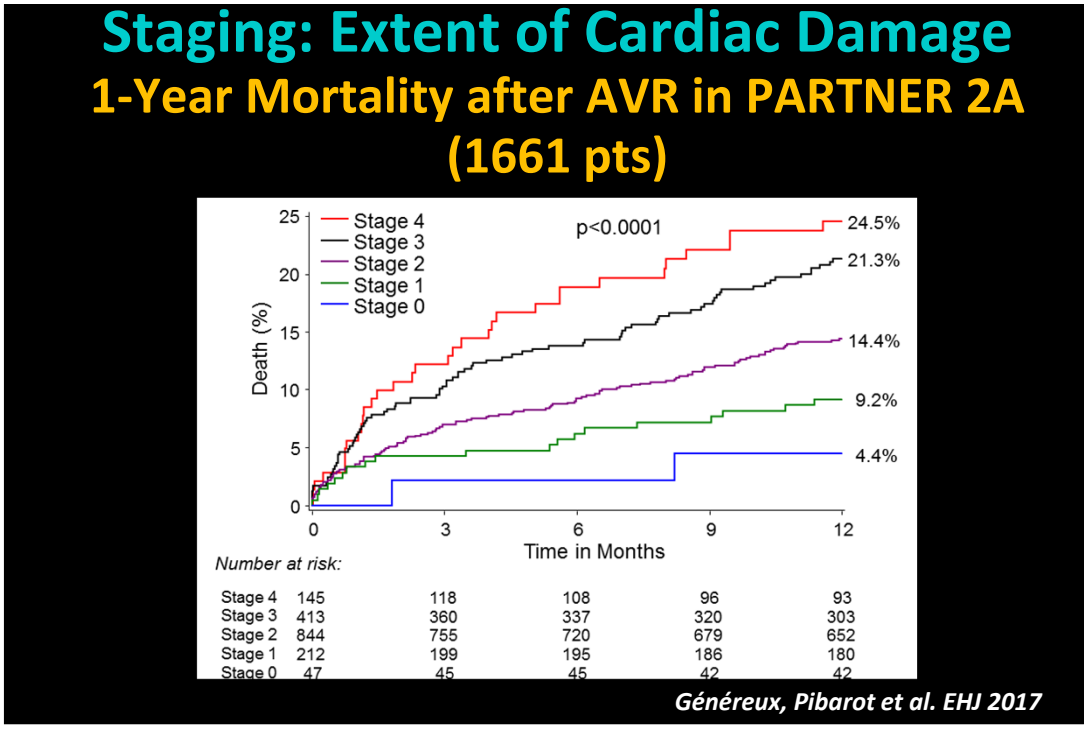
15


Prognosis
Grade
Grade 1
Grade 2
Grade 3
Oncology: Grading vs. Staging of Tumor
Cardiology: Grading AS vs. Staging Cardiac Damage
Stage 0 Stage 1 Stage 2 Stage 3 Stage 4

16


Cardiac Damage Staging – Analogy with Oncology
Specific Criteria
Stage 0
No damage
Stage 1
LV damage
Increased LV Mass Index >115 g/m² Male >95 g/m² Female
E/e' >14
EF <50%
Stage 2
LA/Mitral damage
Indexed left atrial volume >34mL/m²
Moderate-Severe MR
Atrial Fibrillation
Stage 3
PA/Tricuspid damage
SPAP ≥60 mmHg
Moderate-Severe TR
Stage 4
RV damage
Moderate-Severe RV dysfunction
Généreux, Pibarot et al. EHJ 2017

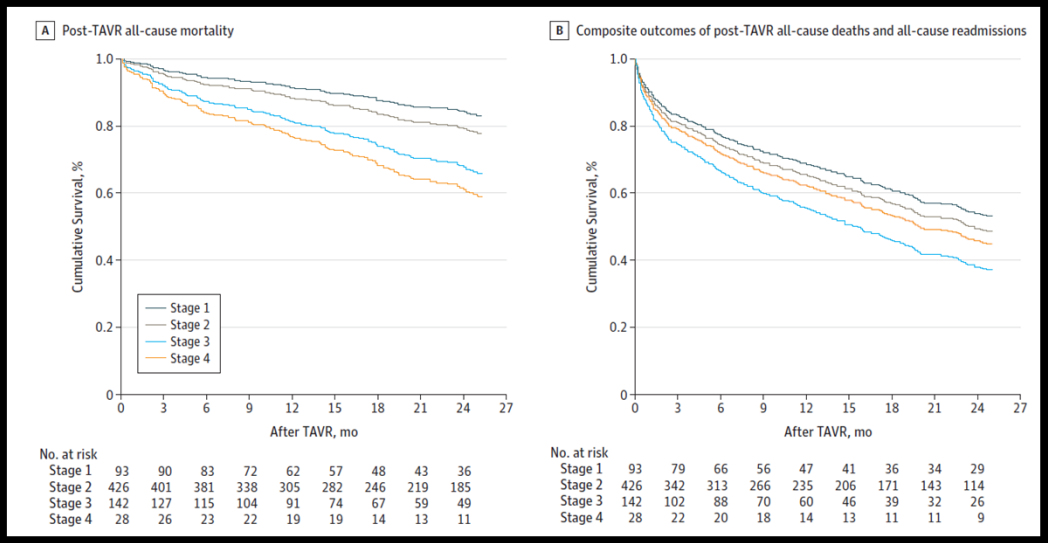
17


Staging: Extent of Cardiac Damage
1-Year Mortality after AVR in PARTNER 2A (1661 pts)
Stage 4
Stage 3
Stage 2
Stage 1
Stage 0
p<0.0001
24.5%
21.3%
14.4%
9.2%
4.4%
Death (%)
Time in Months
Number at risk:
Stage 4 145 118 108 96 93
Stage 3 413 360 337 320 303
Stage 2 844 755 720 679 652
Stage 1 212 199 195 186 180
Stage 0 47 45 45 42 42
Généreux, Pibarot et al. EHJ 2017

18

Cardiac Damage Staging vs. Outcomes

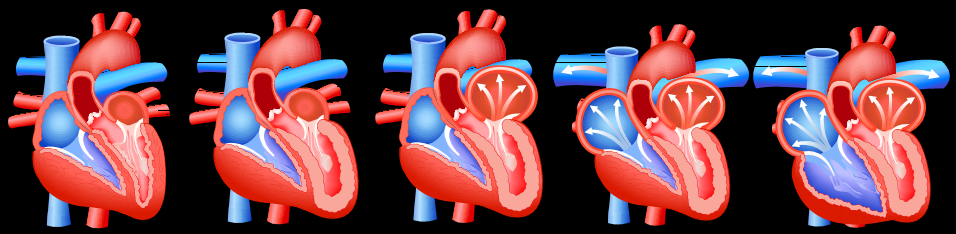
2-Year Outcomes after TAVR in UPMC Cohort (689 pts)



Fukui et al. JAMA Cardiology 2019

19

Modification of Cardiac Damage Staging for Asymptomatic Severe AS: Specific Criteria

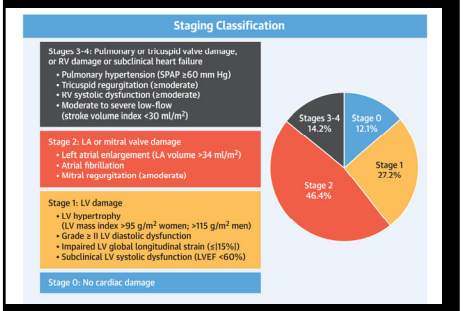


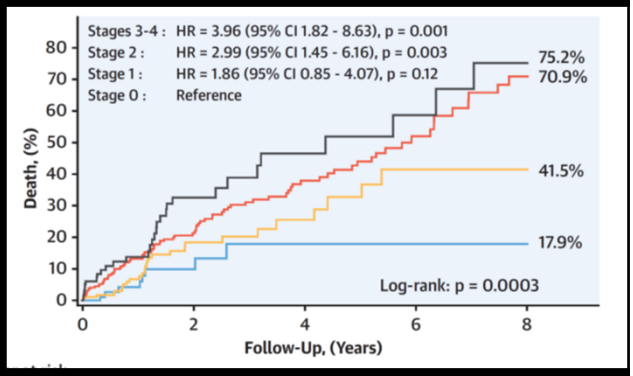
Stage 0	Stage 1	Stage 2	Stage 3	Stage 4
No damage	LV damage	LA/Mitral damage	PA/Tricuspid damage	RV damage
	Increased LV Mass Index >115 g/m² Male >95 g/m² Female	Indexed left atrial volume >34mL/m²	PAS ≥ 60mmHg	Moderate-Severe RV dysfunction
	≥ Grade 2 Diast. Dysf.	Moderate-Severe MR	Moderate-Severe TR	SVi < 30 mL/m²
	EF <60%	Atrial Fibrillation		
	GLS < 15%			

Tastet al. JACC; 2019: 74: 550-563

20

Cardiac Damage Staging in Asymptomatic AS



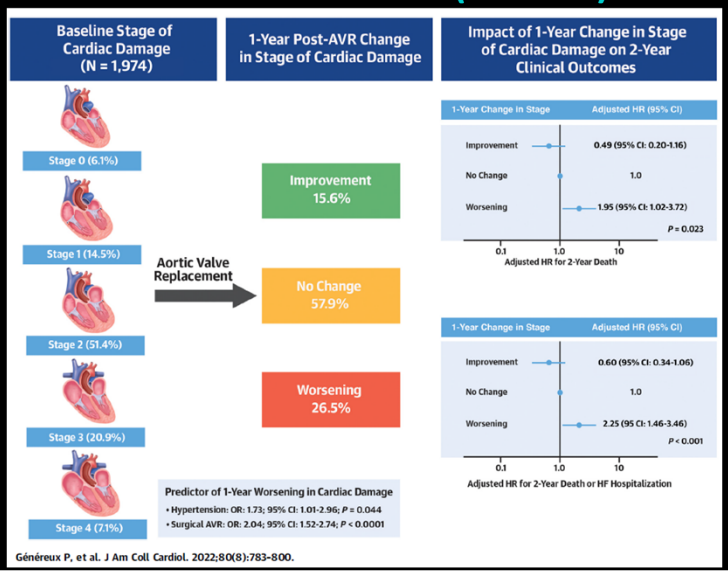


61% of Asymptomatic Patients with Severe AS were in Stage ≥2

Tastet al. JACC; 2019: 74: 550-563

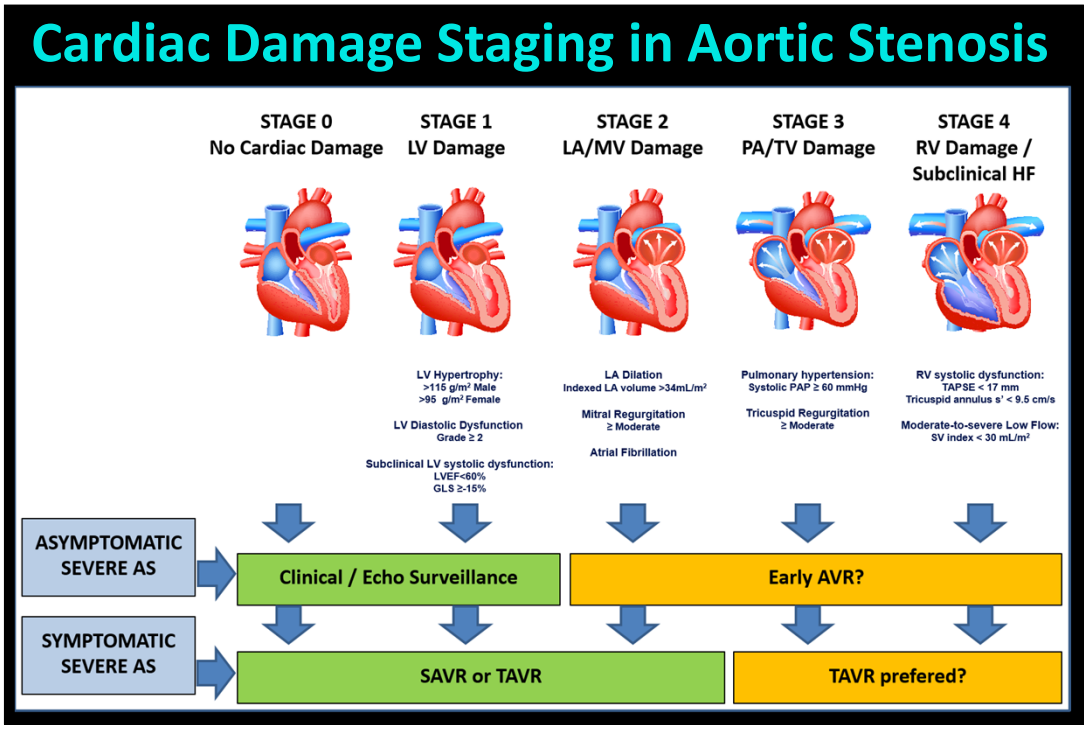
21

Evolution and Prognostic Impact of Cardiac Damage Stage from Baseline to 1 year:
PARTNER 2 and 3 (n=1974)

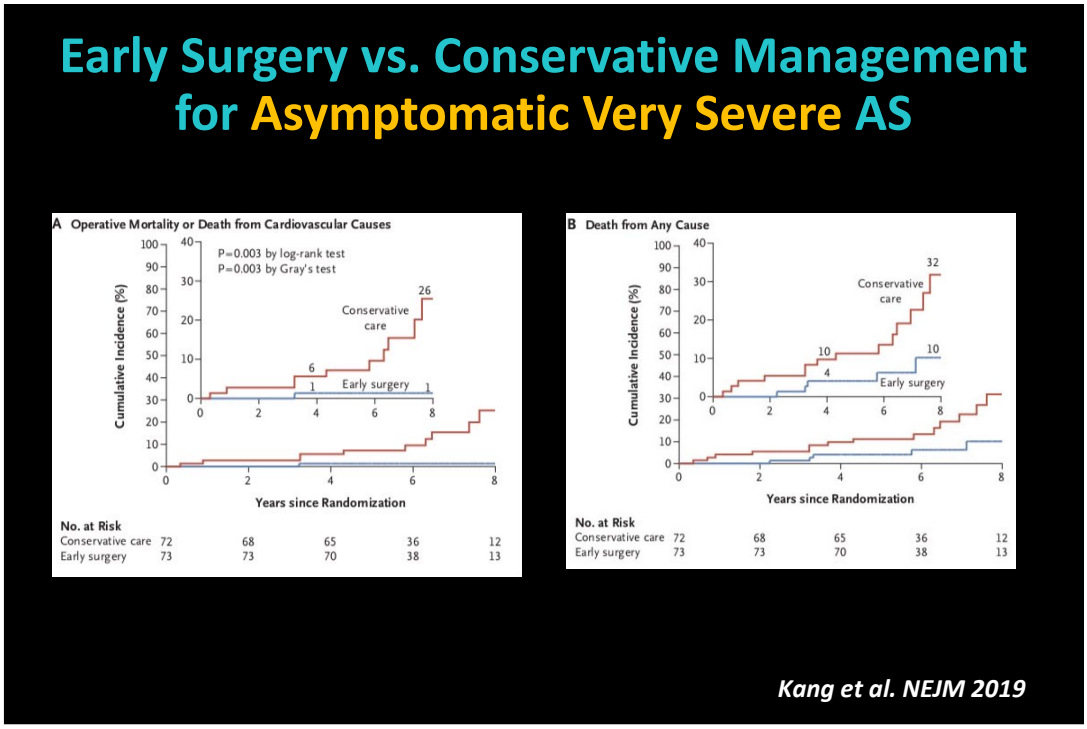


Généreux et al. JACC 2022

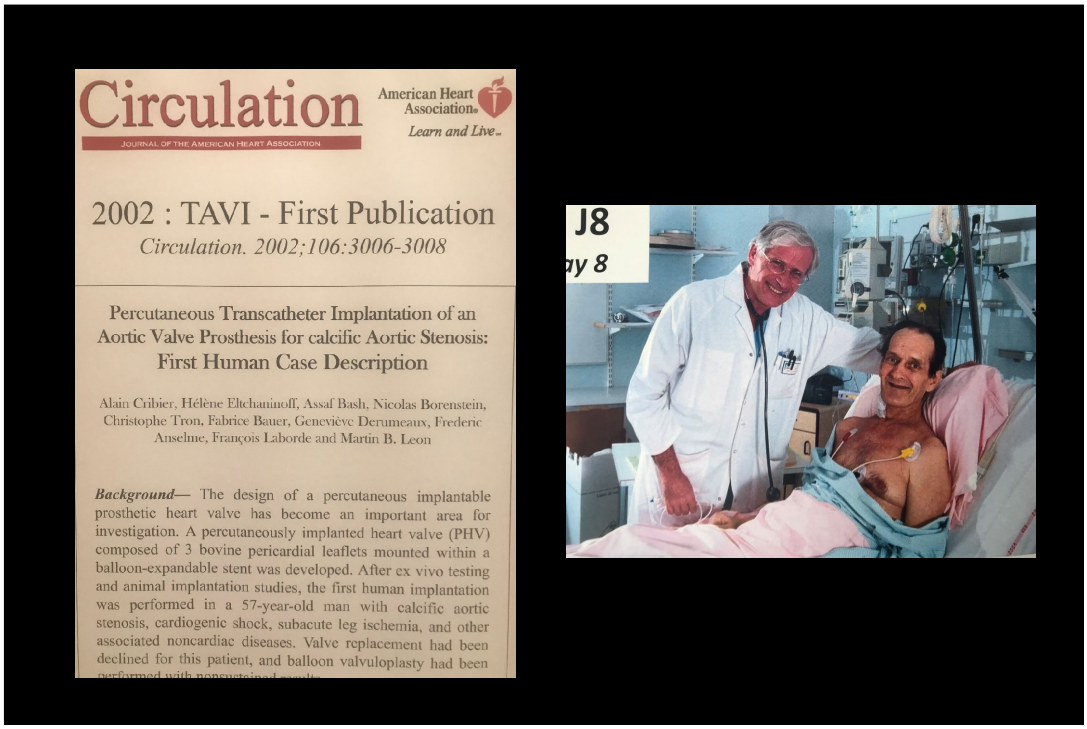
22


Cardiac Damage Staging in Aortic Stenosis
STAGE 0
No Cardiac Damage
STAGE 1
LV Damage
STAGE 2
LA/MV Damage
STAGE 3
PA/TV Damage
STAGE 4
RV Damage / Subclinical HF
LV Hypertrophy:
>115 g/m² Male
>95 g/m² Female
LV Diastolic Dysfunction
Grade ≥ 2
Subclinical LV systolic dysfunction:
LVEF<60%
GLS ≥-15%
LA Dilation
Indexed LA volume >34mL/m²
Mitral Regurgitation
≥ Moderate
Atrial Fibrillation
Pulmonary hypertension:
Systolic PAP ≥ 60 mmHg
Tricuspid Regurgitation
≥ Moderate
RV systolic dysfunction:
TAPSE < 17 mm
Tricuspid annulus s' < 9.5 cm/s
Moderate-to-severe Low Flow:
SV index < 30 mL/m²
ASYMPTOMATIC SEVERE AS
Clinical / Echo Surveillance
Early AVR?
SYMPTOMATIC SEVERE AS
SAVR or TAVR
TAVR prefered?

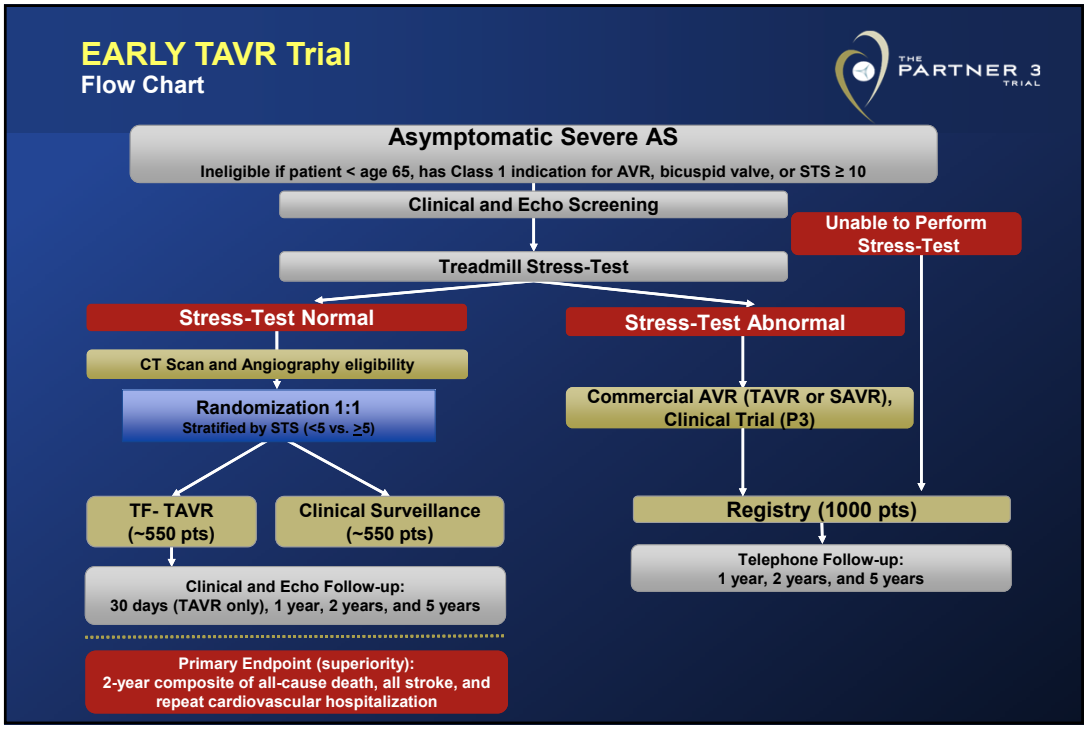
23


Early Surgery vs. Conservative Management for Asymptomatic Very Severe AS
A Operative Mortality or Death from Cardiovascular Causes
P=0.003 by log-rank test
P=0.003 by Gray's test
Cumulative Incidence (%)
Conservative care
Early surgery
26
6
1
1
Years since Randomization
No. at Risk
Conservative care 72 68 65 36 12
Early surgery 73 73 70 38 13
B Death from Any Cause
Cumulative Incidence (%)
Conservative care
Early surgery
32
10
4
10
Years since Randomization
No. at Risk
Conservative care 72 68 65 36 12
Early surgery 73 73 70 38 13
Kang et al. NEJM 2019

24


Circulation
American Heart Association
Learn and Live
JOURNAL OF THE AMERICAN HEART ASSOCIATION
2002 : TAVI - First Publication
Circulation. 2002;106:3006-3008
Percutaneous Transcatheter Implantation of an Aortic Valve Prosthesis for calcific Aortic Stenosis: First Human Case Description
Alain Cribier, Hélène Eltchaninoff, Assaf Bash, Nicolas Borenstein, Christophe Tron, Fabrice Bauer, Geneviève Derumeaux, Frederic Anselme, François Laborde and Martin B. Leon
Background— The design of a percutaneous implantable prosthetic heart valve has become an important area for investigation. A percutaneously implanted heart valve (PHV) composed of 3 bovine pericardial leaflets mounted within a balloon-expandable stent was developed. After ex vivo testing and animal implantation studies, the first human implantation was performed in a 57-year-old man with calcific aortic stenosis, cardiogenic shock, subacute leg ischemia, and other associated noncardiac diseases. Valve replacement had been declined for this patient, and balloon valvuloplasty had been
J8
ay 8

25


EARLY TAVR Trial
Flow Chart
THE PARTNER 3 TRIAL
Asymptomatic Severe AS
Ineligible if patient < age 65, has Class 1 indication for AVR, bicuspid valve, or STS ≥ 10
Clinical and Echo Screening
Unable to Perform Stress-Test
Treadmill Stress-Test
Stress-Test Normal
Stress-Test Abnormal
CT Scan and Angiography eligibility
Randomization 1:1
Stratified by STS (<5 vs. ≥5)
Commercial AVR (TAVR or SAVR), Clinical Trial (P3)
TF- TAVR (~550 pts)
Clinical Surveillance (~550 pts)
Registry (1000 pts)
Telephone Follow-up: 1 year, 2 years, and 5 years
Clinical and Echo Follow-up: 30 days (TAVR only), 1 year, 2 years, and 5 years
Primary Endpoint (superiority): 2-year composite of all-cause death, all stroke, and repeat cardiovascular hospitalization

26

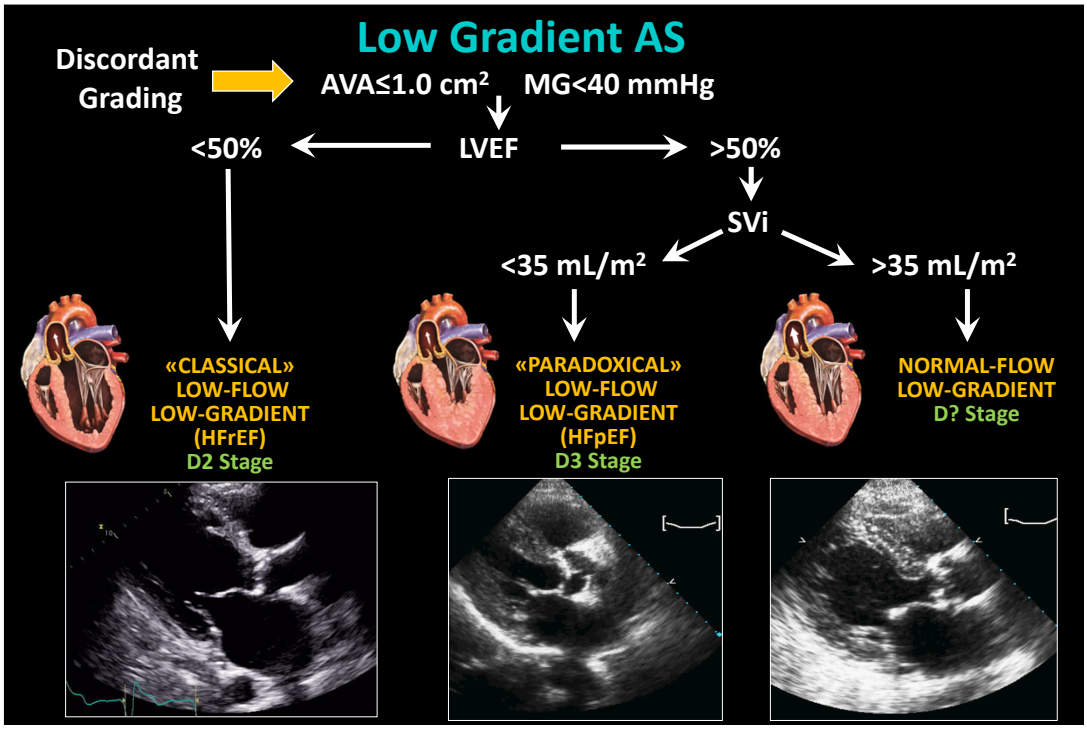
Conclusion #1: Aymptomatic Severe AS (Stage C1)

- There is no Class I indication for AVR in patients with asymptomatic severe AS unless LVEF < 50% or indication for other cardiac surgery
- Class IIa indication for AVR if: very severe AS, fast stenosis progression, elevated BNP
- Class IIb (IIa) indication for AVR if: LVEF< 60% (55%) on 3 serial imaging studies
- Usefulness of cardiac damage staging in risk stratification and timing for intervention: Stage ≥2: Consider early AVR; Stage ≥3: Consider TAVR vs. SAVR
- The benefit of early TAVI in asymptomatic severe AS is currently being tested in the EARLY-TAVR (NCT03042104)

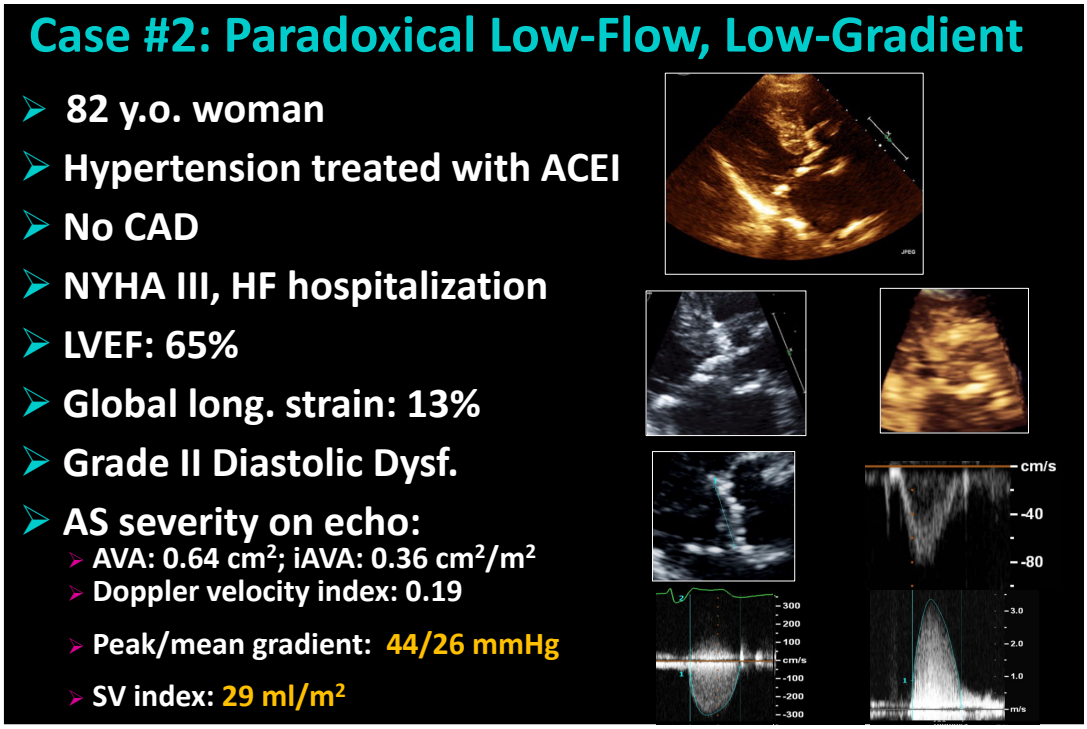
27

Concept #2: Confirming Stenosis Severity and Indication of AVR in Low-flow, low-gradient AS (Stage D2, D3)

28


Low Gradient AS
Discordant Grading
AVA≤1.0 cm²
MG<40 mmHg
LVEF
<50%
>50%
SVi
<35 mL/m²
>35 mL/m²
«CLASSICAL» LOW-FLOW LOW-GRADIENT (HFrEF) D2 Stage
«PARADOXICAL» LOW-FLOW LOW-GRADIENT (HFpEF) D3 Stage
NORMAL-FLOW LOW-GRADIENT D? Stage

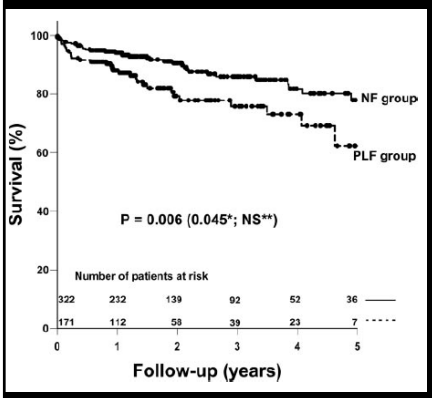
29


Case #2: Paradoxical Low-Flow, Low-Gradient
82 y.o. woman
Hypertension treated with ACEI
No CAD
NYHA III, HF hospitalization
LVEF: 65%
Global long. strain: 13%
Grade II Diastolic Dysf.
AS severity on echo:
AVA: 0.64 cm²; iAVA: 0.36 cm²/m²
Doppler velocity index: 0.19
Peak/mean gradient: 44/26 mmHg
SV index: 29 ml/m²
cm/s
-40
-80

30

Paradoxical Low-Flow, Low-Gradient Severe Aortic Stenosis Despite Preserved Ejection Fraction Is Associated With Higher Afterload and Reduced Survival

Zeineb Hachicha, MD; Jean G. Dumesnil, MD; Peter Bogaty, MD; Philippe Pibarot, DVM, PhD



512 Patients with severe AS and preserved LVEF

18% had "paradoxical LF-LG" severe AS :
AVA< 1.0 cm^2, Indexed AVA<0.6 cm^2/m^2
MG<40 mmHg, SV index < 35 ml/m^2

Associated with worse prognosis

Hachicha Z et al., Circulation. 115:2856-2864, 2007

31

AORTIC STENOSIS
± HYPERTENSION

Pronounced Concentric Remodeling

Impaired Diastolic Filling

Impaired Longitudinal systolic function

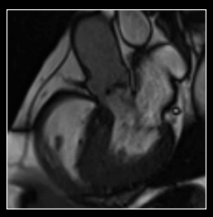
Atrial Fibrillation

Mitral Stenosis

Mitral Regurgitation

Tricuspid Regurgitation

Cardiac Amyloidosis (Up to 15%)



Reduced Forward Stroke Volume (SVi<35 mL/m^2)

Low-Flow Despite Preserved LVEF

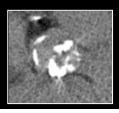
Low-Gradient Despite Severe AS

Pibarot & Dumesnil, Circulation 2013

32

Circulation 2007	American and European guidelines	American and European guidelines
Discovery of the paradoxical LFLG entity	Class IIa Indication of AVR for paradoxical LFLG severe AS	Class I Indication of AVR for paradoxical LFLG severe AS
2007	2012	2021

Diagnostic testing: AVC score by CT imaging is reasonable to confirm severity (IIa): >1200 AU in ♀ and > 2000 AU in ♂

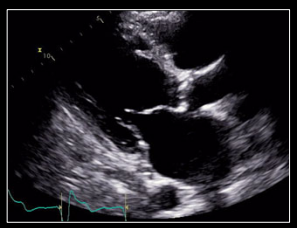


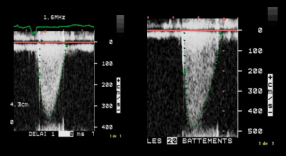
Guidelines	Recommendation for AVR	Class
ACC-AHA 2021	AVR is recommended in **symptomatic** patients who have low-flow, low-gradient **severe** AS with normal LVEF (Stage D3) if AS is the most likely cause of symptoms	I

33

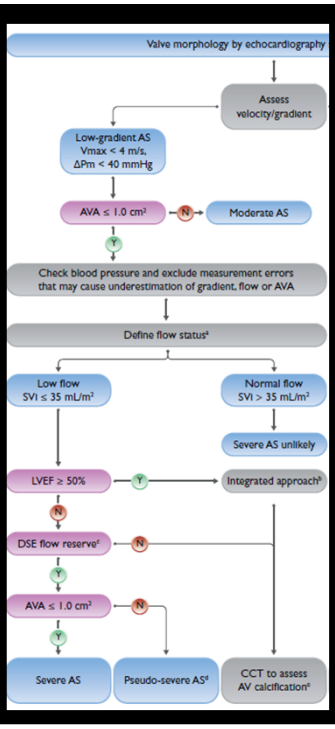
2021 Guidelines for Management of Low-Gradient AS

Classical LF-LG AS with Low LVEF

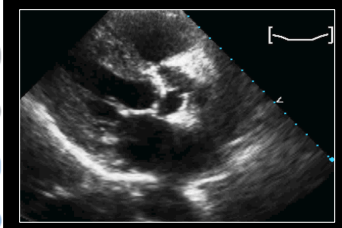


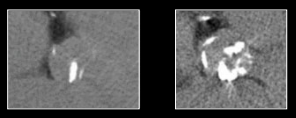


True-severe AS by DSE:
Stress AVA < 1.0 cm²
Stress MG ≥ 40 mmHg



Paradoxical LF-LG AS with Normal LVEF



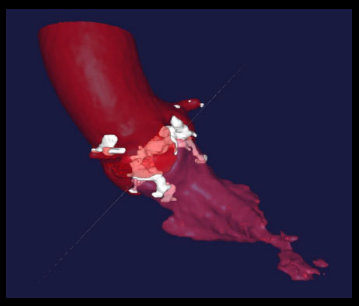


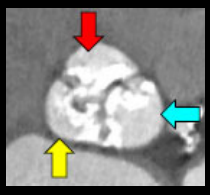
Baumgartner et al. EHJ 2017
Otto et al. JACC 2021

True-severe AS by CT:
AVC Score: > 2000 AU in ♂
> 1200 AU in ♀

34

Case #2: Aortic Valve Calcium Scoring by MDCT





AVC Score: 3200 AU

Confirms Severe AS: Patient underwent TAVR

35

Aortic Stenosis and Cardiac Amyloidosis

Cardiac Amyloidosis

CA Red Flags

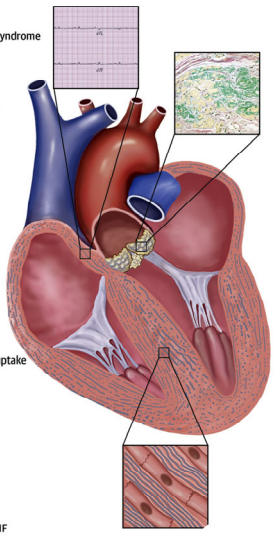
- **Clinical:** ≥65 years, Male, carpal tunnel syndrome
- **ECG:** Low-voltage despite LVH, Pseudo-infarction pattern
- **Biomarkers:** Disproportionate elevation of troponin and BNP
- **TTE:** Severe biventricular hypertrophy, Myocardial granular sparkling, Severe LV longitudinal systolic dysfunction with apical sparing
- **CMR:** Extensive LV LGE and elevated ECV values

Confirm Diagnosis of CA

- **Confirm TTR-CA:** Grade 2 or 3 cardiac uptake on bone scintigraphy with negative blood or urine monoclonal light chain
- **Exclude CA Diagnosis:** Grade 0 cardiac uptake on bone scintigraphy with negative blood or urine monoclonal light chain
- **Prevalence of TTR-CA in AS:** up to 15%

Therapeutic Management of CA

- **AL-CA:** Chemotherapy
- **TTR-CA:** TTR stabilizer in patients with HF
- **Heart Management: CHAD-STOP**



Aortic Stenosis

AS Features in Patients with CA

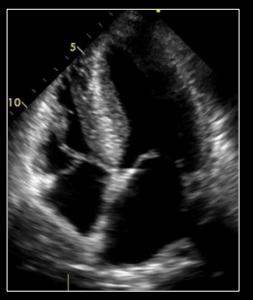
- High prevalence of paradoxical low-flow, low-gradient AS
- Aortic valve amyloid infiltration
- Faster AS progression?

Confirm AS Severity

- **AV Calcium Score by Non-Contrast CT**
  - ≥ 1,200 AU in women
  - ≥ 2,000 AU in men

Therapeutic Management of AS

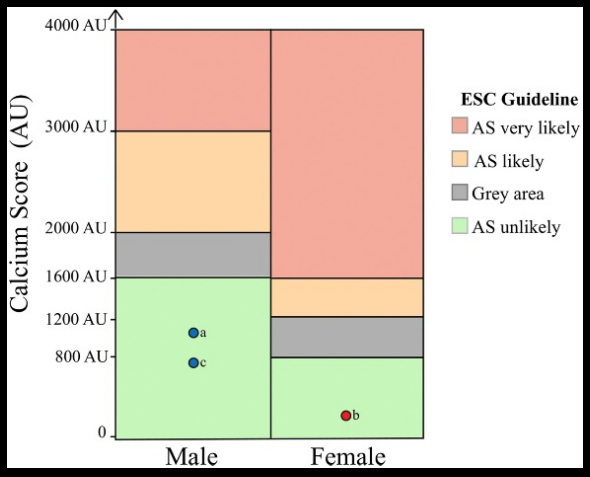
- **Evaluation by Heart Team**
- **TAVR** in low-flow, low-gradient severe AS
- **TAVR** in high-gradient AS with depressed LV systolic function
- **SAVR or TAVR** according to surgical risk in high-gradient AS with preserved LV systolic function
- **Medical treatment** alone in patients with high risk of AVR futility

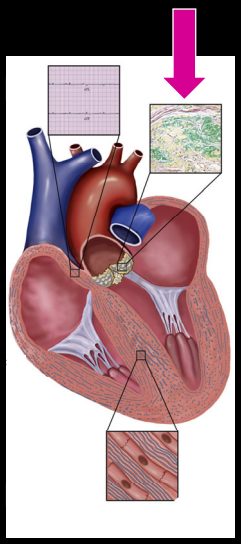


Ternacle, J. et al. J Am Coll Cardiol. 2019;74(21):2638-51.

36

Risk of False Negative Cases of Severe AS with non-contrast CT in Patients with LFLG AS + CA

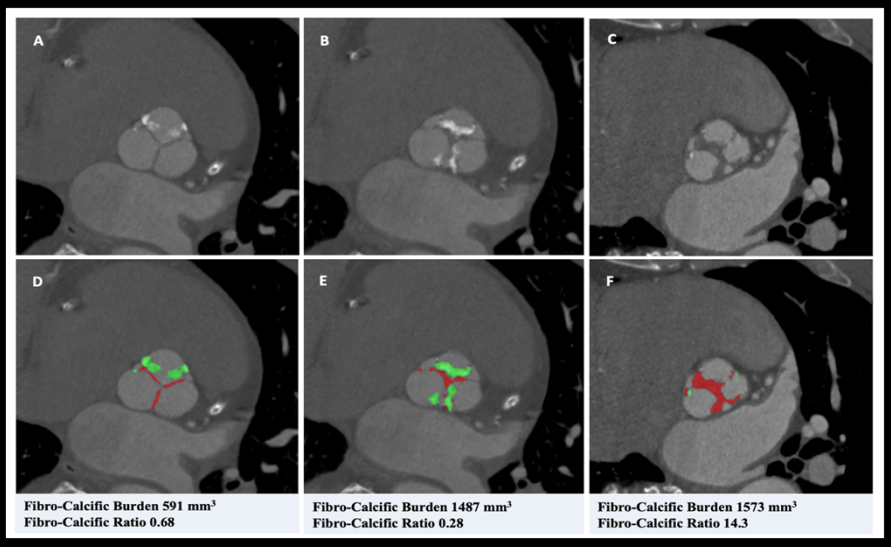




JACC Case Rep 2020, 2 (14) 2205–2209

37

Future perspectives: Contrast CT to Assess AoV Fibro-Calcific Burden

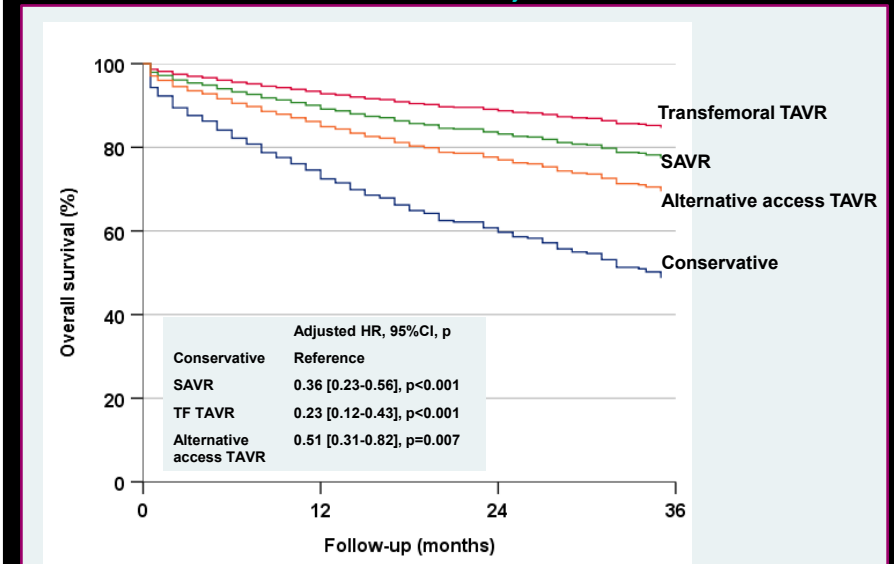


Calcium
Fibrosis

Cartlidge et al. Heart 2021

38

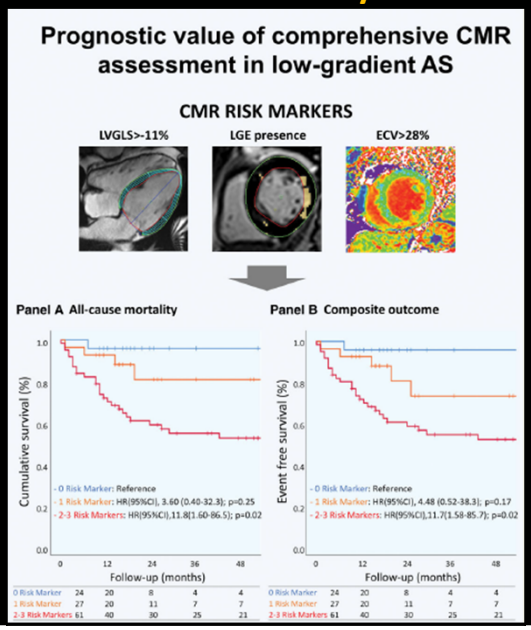
Early SAVR vs. TAVI vs. Conservative Management in (Classical and Paradoxical) Low-flow, Low-Gradient AS



Annabi et al. JAHA 2020

39

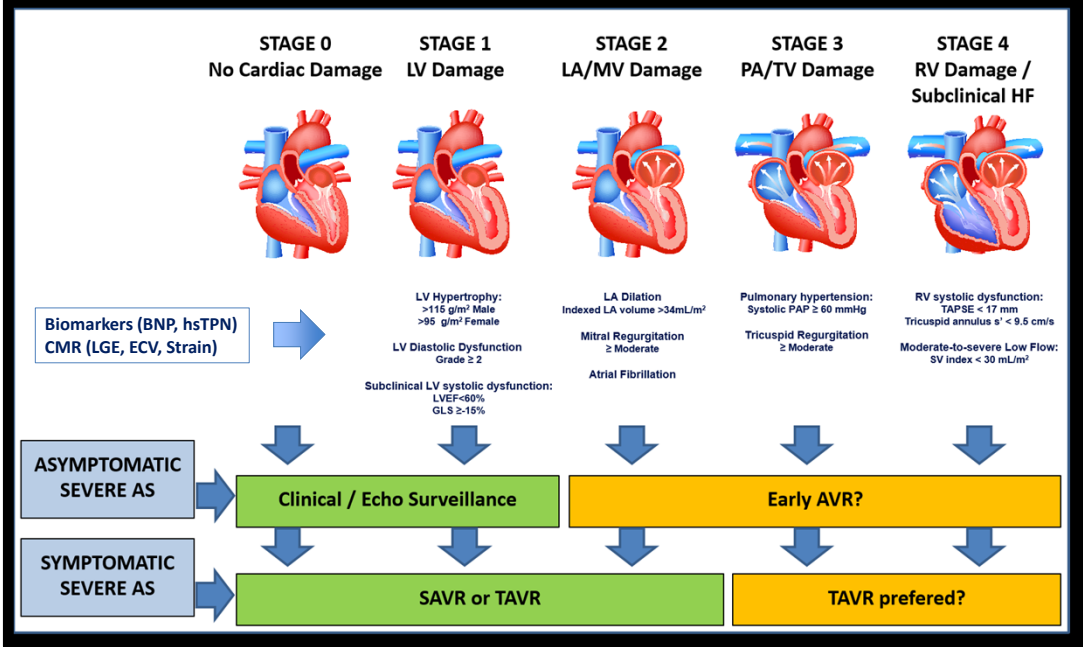
CMR for Risk Stratification in Low-Gradient AS: The TOPAS Study



Fukui et al. EHJ CVI 2022

40

Cardiac Damage Staging in Aortic Stenosis



41

Conclusion #2: Low-Flow, Low-Gradient AS (Stage D2, D3)

- **DSE** is useful to confirm stenosis severity in classical (reduced LVEF) LFLG AS
- **Non-contrast MDCT** AoV calcium scoring is useful **(Class IIa)** to confirm stenosis severity in all types of LG AS
- **AVR is recommended (Class I)** in patients with classical or paradoxical LFLG severe AS
- **Transfemoral TAVR** is preferred vs. SAVR in classical or paradoxical LFLG severe AS

42

Future Perspectives: Low-Flow, Low-Gradient AS (Stage D2, D3)

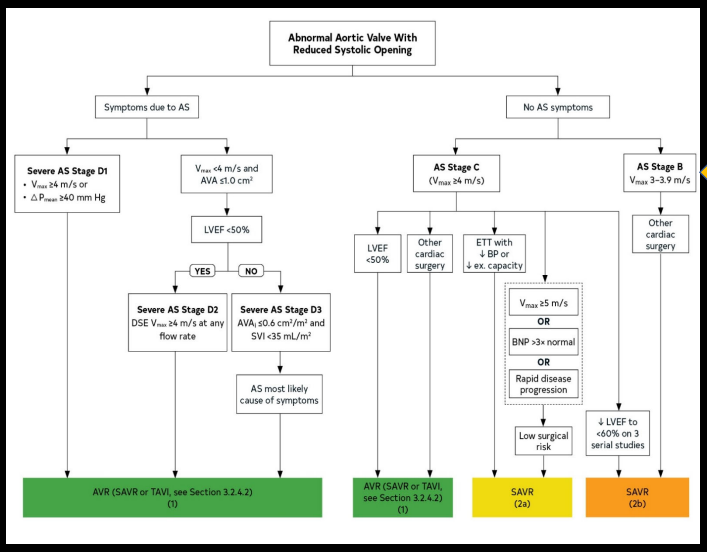
- Patients with LFLG AS should be screened for cardiac amyloidosis
- CT angiography may improve the quantitation of aortic valve fibro-calcific burden and confirm stenosis severity in LG AS patients

43

Concept #3: Early AVR vs. Clinical Surveillance Symptomatic 'at-risk' moderate AS (Stage B)

44

Timing of Intervention for AS



45

Case #3: Moderate AS with Low LVEF and HF Symptoms

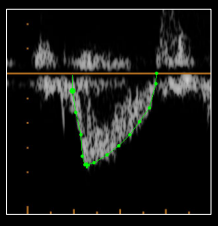
Rest

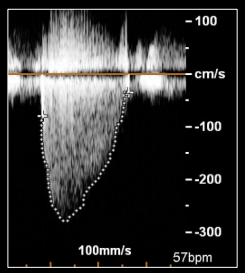
SV= 36 ml
Q_{mean}=139 ml/s
LVEF=20%
ΔP= 35 / 22 mmHg
AVA= 0.85 cm^2

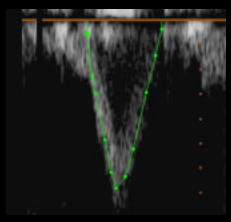
→

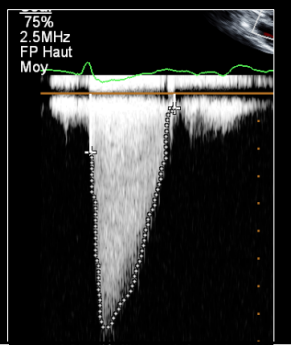
DSE

SV= 55 ml
Q_{mean}=243 ml/s
LVEF=30%
ΔP= 63 / 32 mmHg
AVA= 1.2 cm^2



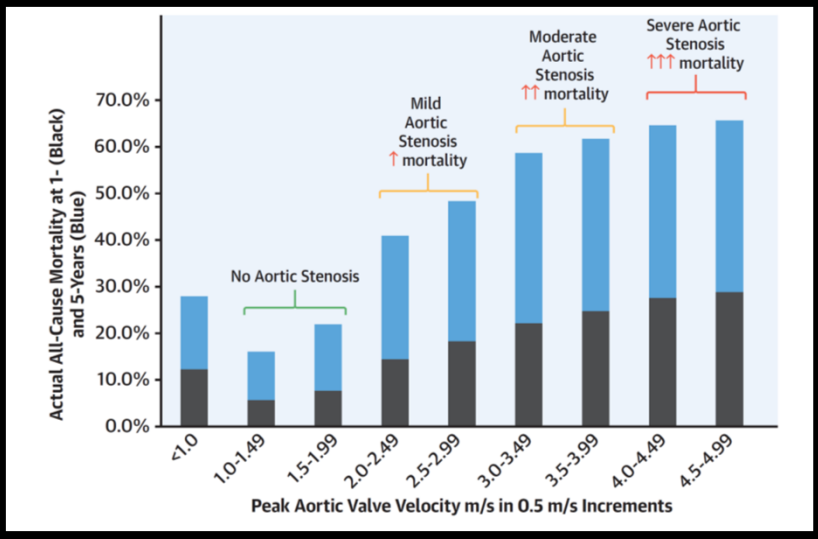






46

Outcome of Patients with Moderate AS

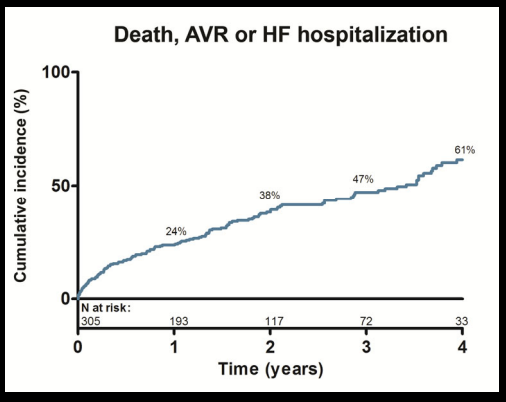


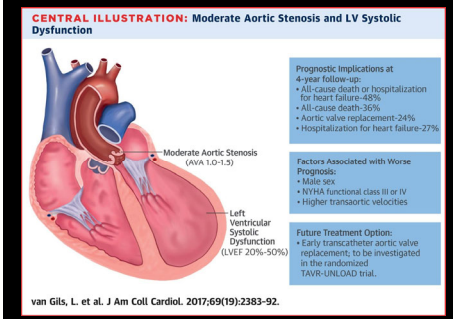
Strange et al. JACC 2019

47

Outcome of Patients with Moderate AS and Reduced LVEF

Retrospective 3-center study of 305 patients with moderate AS and LVEF<50%



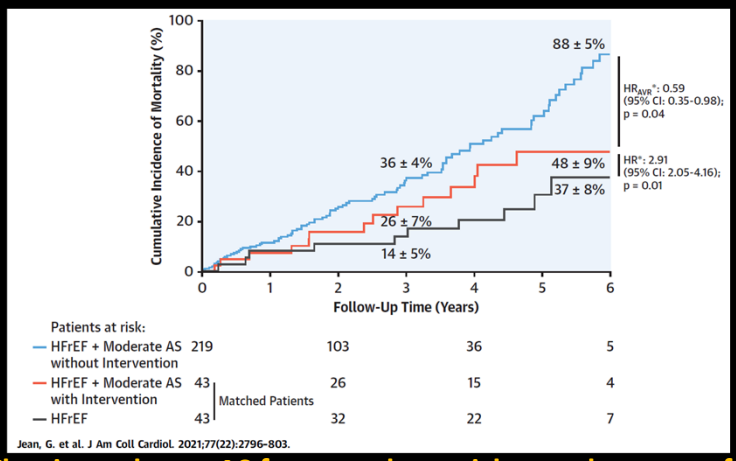


Van Gils et al. JACC 2017

48

Outcome of Patients with Moderate AS and Reduced LVEF

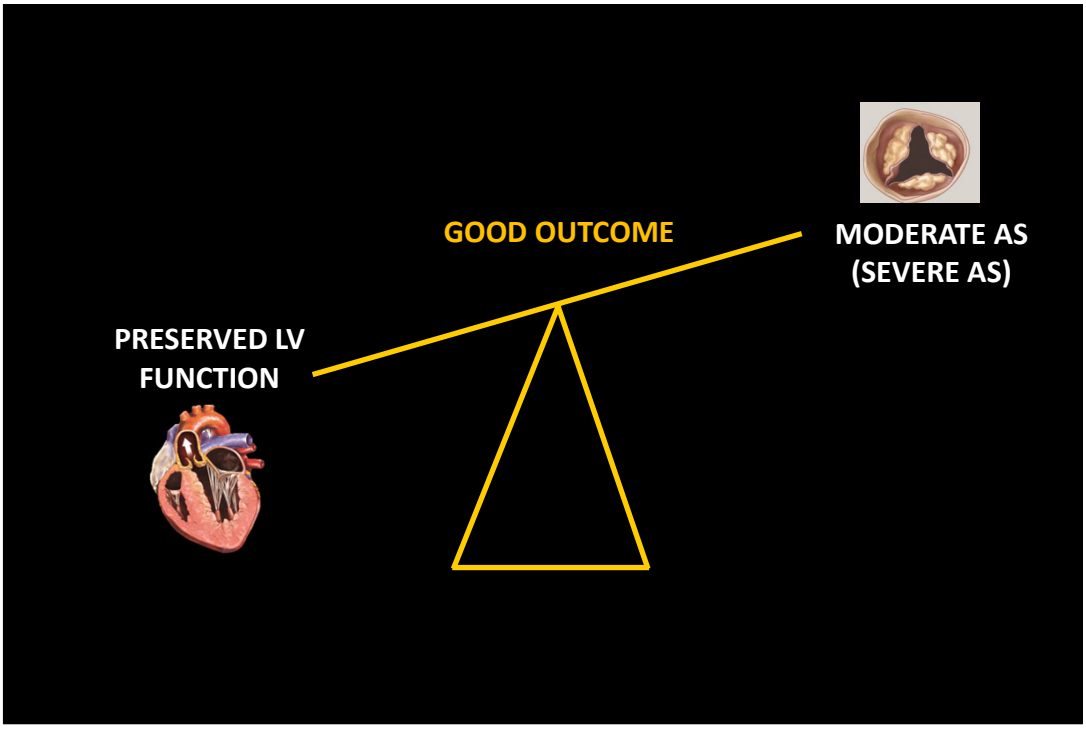
Propensity score matched study of 262 pts. with moderate AS HFrEF vs. 262 pts. With HFrEF and no AS



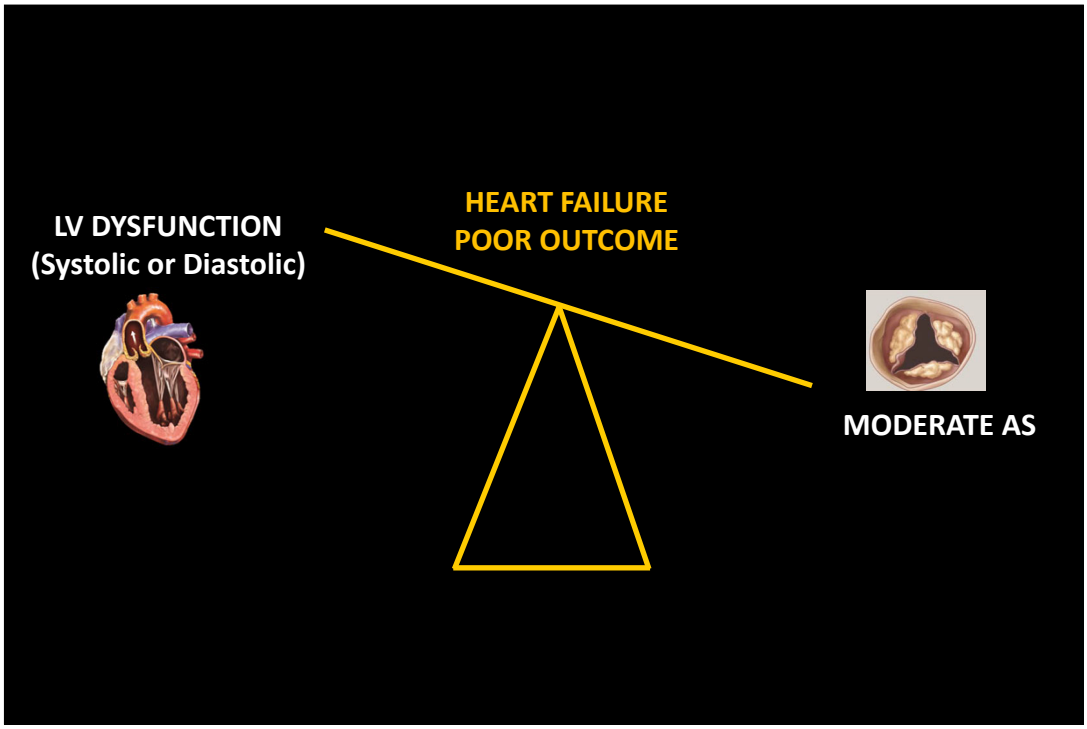
What is moderate AS for a good ventricle may be severe for a depressed ventricle!

Jean et al. JACC 2021

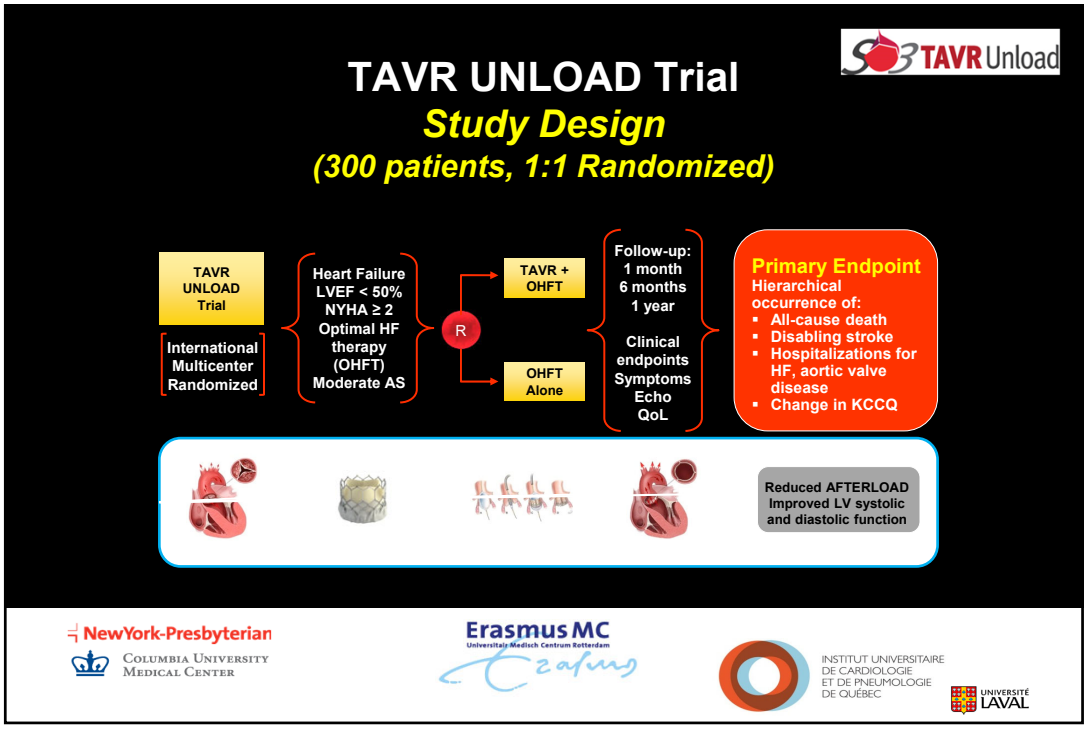
49



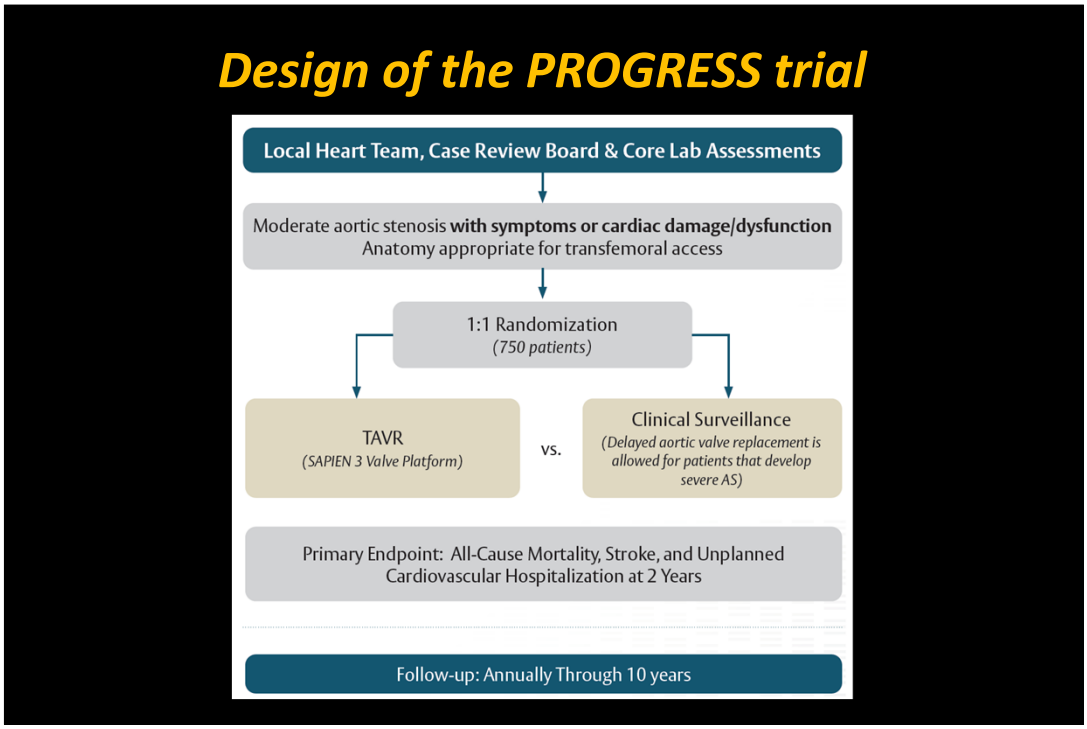
50


LV DYSFUNCTION
(Systolic or Diastolic)
HEART FAILURE
POOR OUTCOME
MODERATE AS

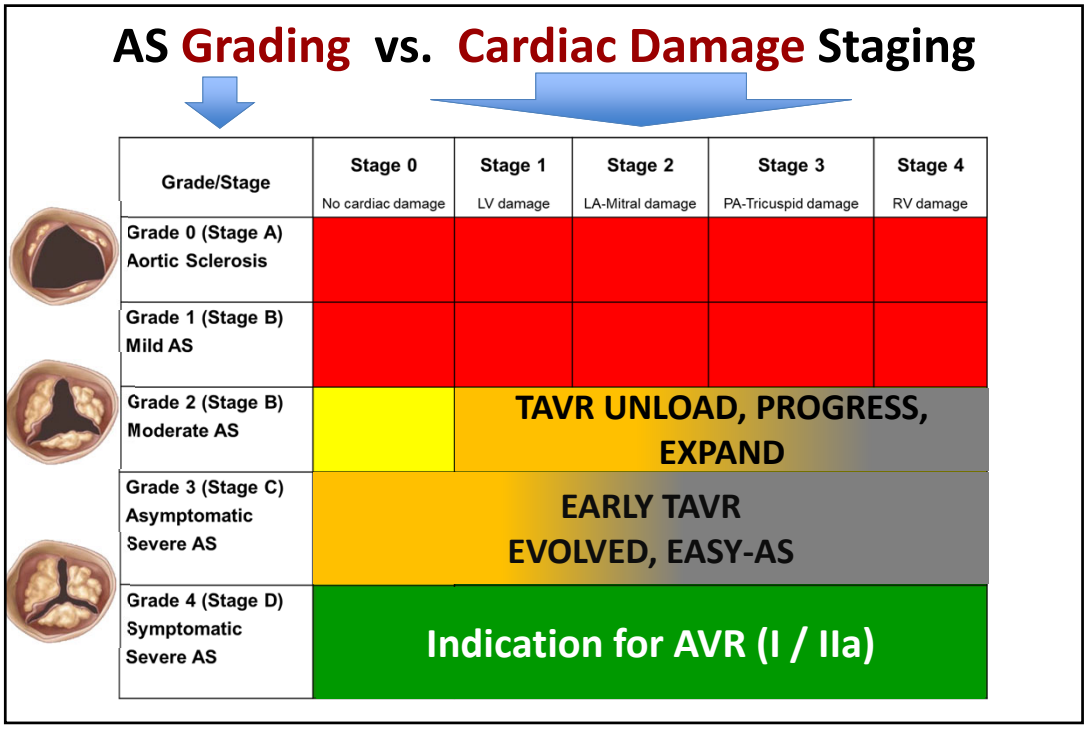
51


TAVR Unload
TAVR UNLOAD Trial
Study Design
(300 patients, 1:1 Randomized)
TAVR UNLOAD Trial
International Multicenter Randomized
Heart Failure
LVEF < 50%
NYHA ≥ 2
Optimal HF therapy (OHFT)
Moderate AS
R
TAVR + OHFT
OHFT Alone
Follow-up:
1 month
6 months
1 year
Clinical endpoints
Symptoms
Echo
QoL
Primary Endpoint
Hierarchical occurrence of:
All-cause death
Disabling stroke
Hospitalizations for HF, aortic valve disease
Change in KCCQ
Reduced AFTERLOAD
Improved LV systolic and diastolic function
NewYork-Presbyterian
Columbia University Medical Center
Erasmus MC
Universitair Medisch Centrum Rotterdam
INSTITUT UNIVERSITAIRE DE CARDIOLOGIE ET DE PNEUMOLOGIE DE QUÉBEC
UNIVERSITÉ LAVAL

52


Design of the PROGRESS trial
Local Heart Team, Case Review Board & Core Lab Assessments
Moderate aortic stenosis with symptoms or cardiac damage/dysfunction
Anatomy appropriate for transfemoral access
1:1 Randomization
(750 patients)
TAVR
(SAPIEN 3 Valve Platform)
vs.
Clinical Surveillance
(Delayed aortic valve replacement is allowed for patients that develop severe AS)
Primary Endpoint: All-Cause Mortality, Stroke, and Unplanned Cardiovascular Hospitalization at 2 Years
Follow-up: Annually Through 10 years

53


AS Grading vs. Cardiac Damage Staging
Grade/Stage
Stage 0
No cardiac damage
Stage 1
LV damage
Stage 2
LA-Mitral damage
Stage 3
PA-Tricuspid damage
Stage 4
RV damage
Grade 0 (Stage A)
Aortic Sclerosis
Grade 1 (Stage B)
Mild AS
Grade 2 (Stage B)
Moderate AS
TAVR UNLOAD, PROGRESS, EXPAND
Grade 3 (Stage C)
Asymptomatic
Severe AS
EARLY TAVR
EVOLVED, EASY-AS
Grade 4 (Stage D)
Symptomatic
Severe AS
Indication for AVR (I / IIa)

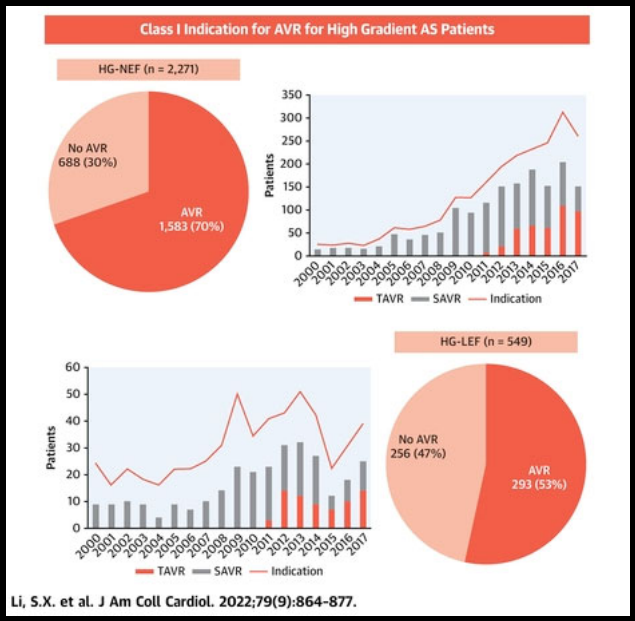
54

Conclusion #3: Symptomatic at-risk moderate AS (Stage B)

- Moderate AS is well tolerated by a good ventricle but poorly tolerated by a failing ventricle
- Moderate AS with HF is associated with poor prognosis
- There is no indication for AVR in patients with moderate AS and HF unless they have an indication for cardiac surgery (e.g. CABG)
- Closer clinical/ echo FU (every year) is recommended for at-risk moderate AS
- The benefit of early TAVI in at-risk moderate AS is currently being tested in the TAVR-UNLOAD (NCT02661451), PROGRESS (NCT04889872), and EXPAND (NCT05149755) trial

55

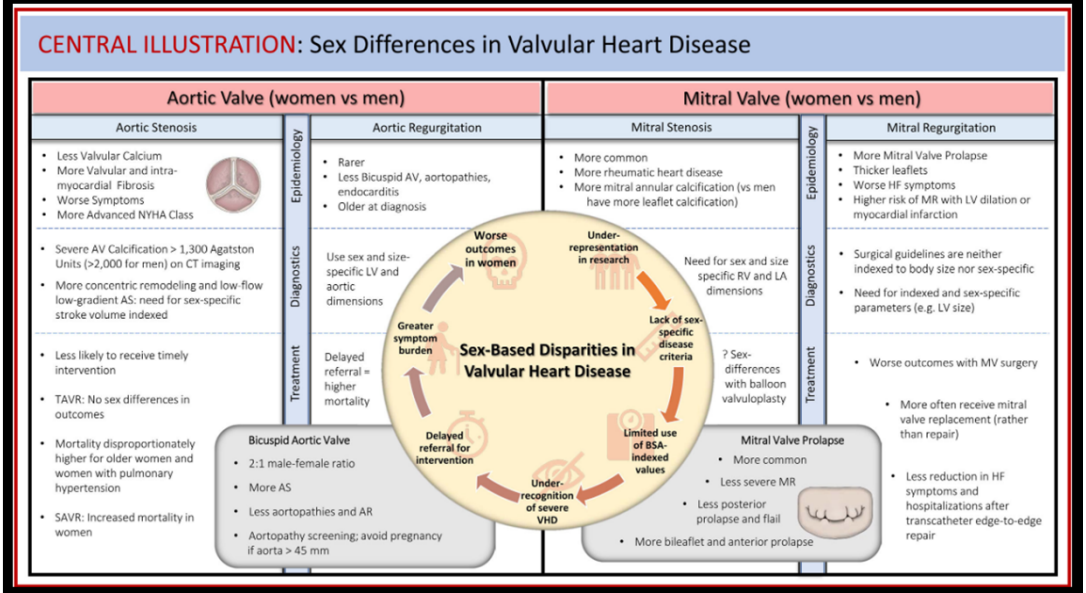
Temporal trends in AVR Utilization



Li, S.X. et al. J Am Coll Cardiol. 2022;79(9):864-877.

56

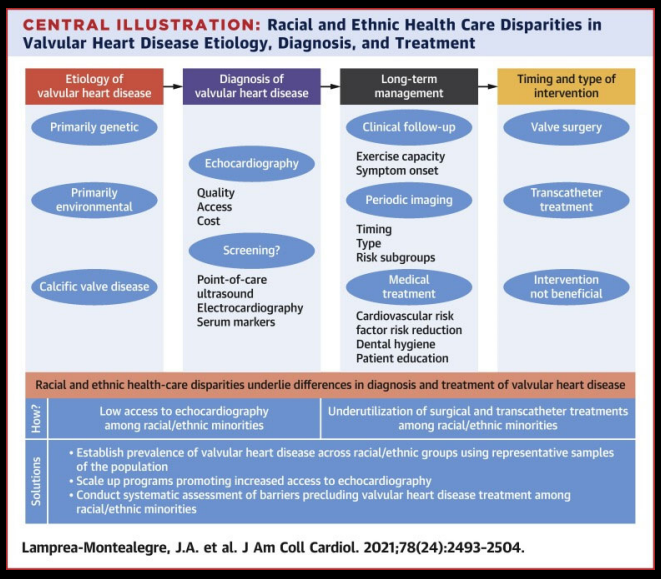
Sex Differences and Disparities in VHD



Desjardins et al. Circulation Research 2022

57

Risk of under-diagnosis and under-treatment is higher in racial/ethnic minorities



Lamprea-Montealegre, J.A. et al. J Am Coll Cardiol. 2021;78(24):2493-2504.

58

Conclusion #3: Expanding AVR indications to lower risk populations: Yes, but….

Before expanding indication of TAVR / SAVR to other lower risk populations, we should first put a priority on treating under-served populations with already established indication of AVR

59

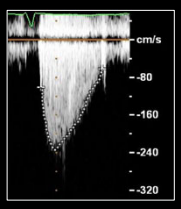
Concept #4: Pharmacotherapy for Aortic Stenosis

60

Case #4: Patient with Mild AS and Rapid Progression during FU (B Stage)

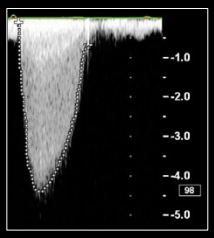
57 y.o. man with mild calcific AS

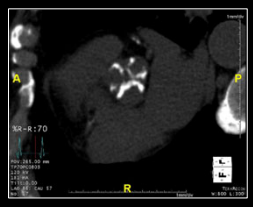
Baseline



- V_{Peak}: 2.3 m/s
- Peak/mean gradients: 22/12 mmHg
- AVA: 1.6 cm^2
- Calcium score: 901 AU

2.5 years later





- V_{Peak}: 4.4 m/s (progression 0.8 m/s/yr)
- Peak/mean gradients: 77/44 mmHg
- AVA: 0.88 cm^2
- Calcium score: 2007 AU

Lipoprotein (a) level: 147 mg/dl

61

The NEW ENGLAND JOURNAL of MEDICINE

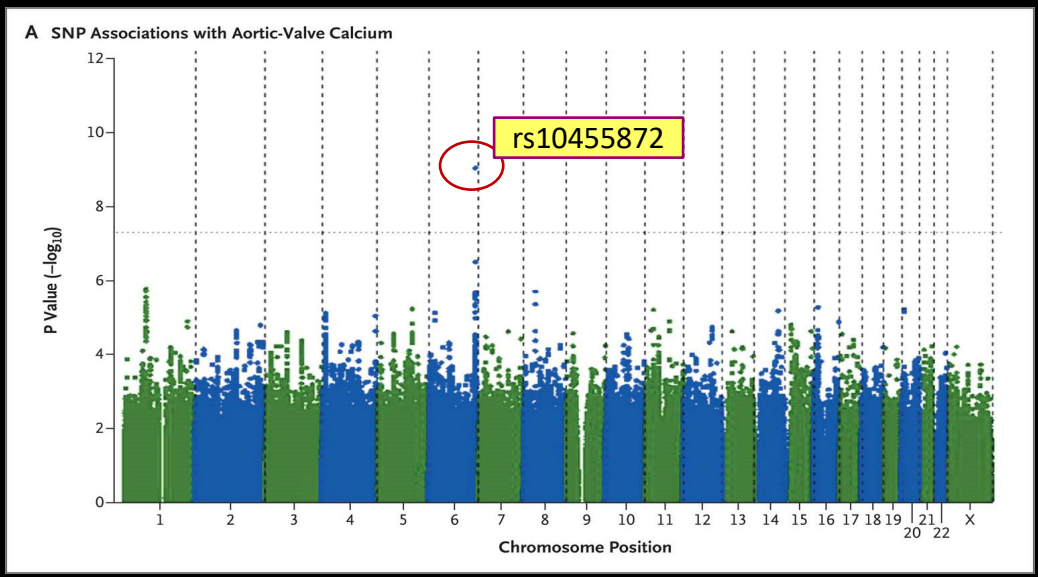
ESTABLISHED IN 1812 FEBRUARY 7, 2013 VOL. 368 NO. 6

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

62

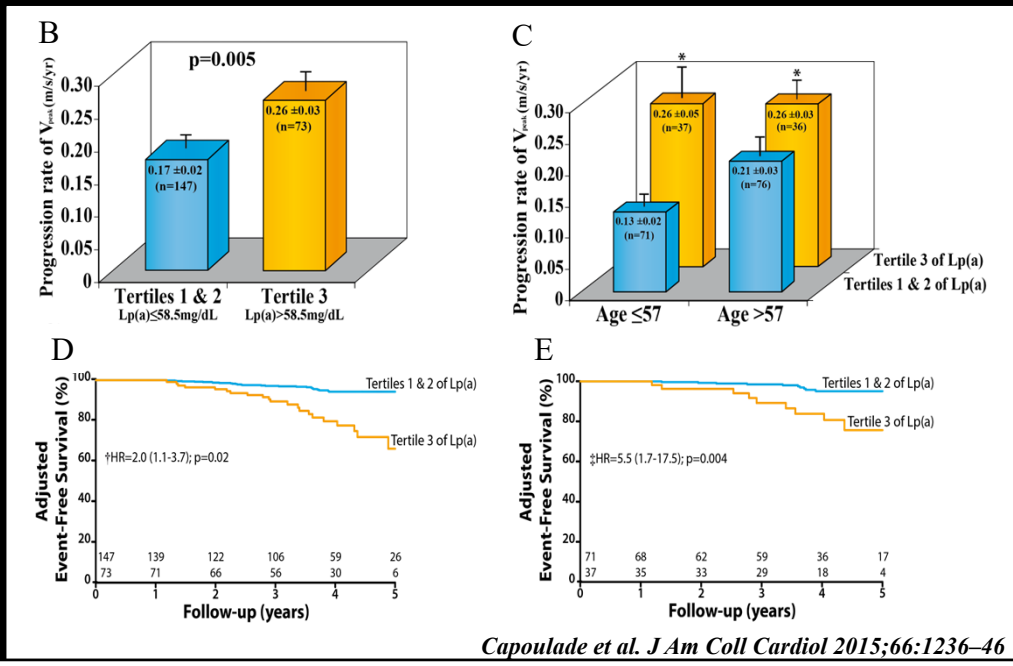
Association between LPA and Aortic Valve Calcification



Genomewide significance prespecified = $P<5.0\times10^{-8}$

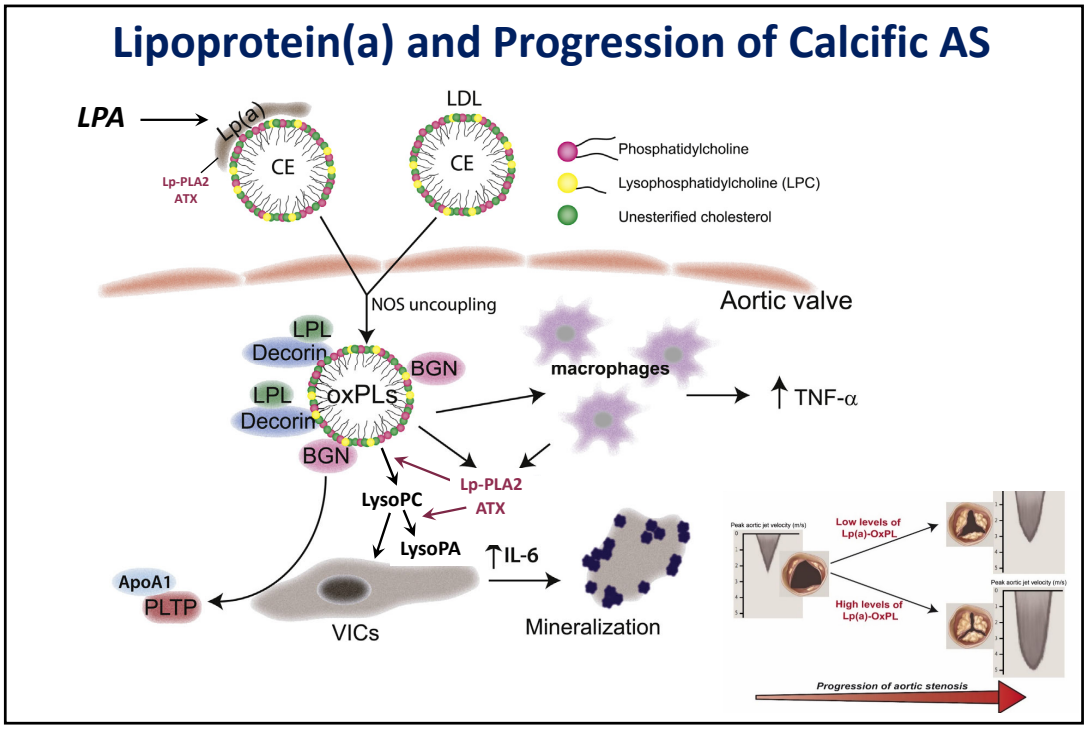
63

Lipoprotein(a) and AS Progression: Astronomer Trial

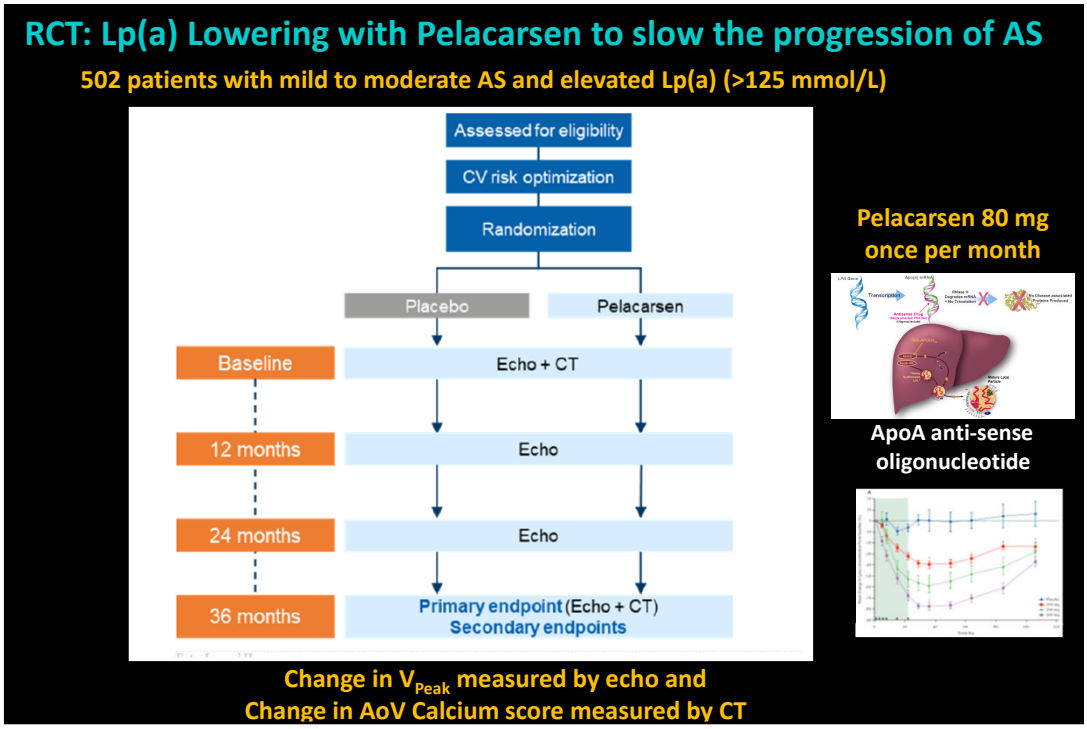


Capoulade et al. J Am Coll Cardiol 2015;66:1236–46

64


Lipoprotein(a) and Progression of Calcific AS
LPA
Lp(a)
CE
Lp-PLA2
ATX
LDL
CE
Phosphatidylcholine
Lysophosphatidylcholine (LPC)
Unesterified cholesterol
NOS uncoupling
Aortic valve
LPL
Decorin
BGN
LPL
oxPLs
Decorin
BGN
macrophages
TNF-α
Lp-PLA2
ATX
LysoPC
LysoPA
IL-6
ApoA1
PLTP
VICs
Mineralization
Low levels of Lp(a)-OxPL
High levels of Lp(a)-OxPL
Progression of aortic stenosis

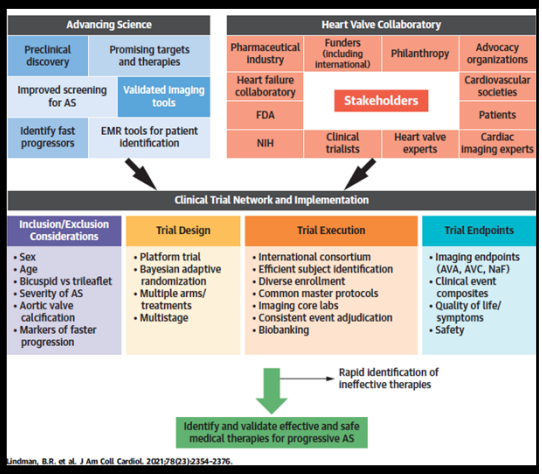
65


RCT: Lp(a) Lowering with Pelacarsen to slow the progression of AS
502 patients with mild to moderate AS and elevated Lp(a) (>125 mmol/L)
Assessed for eligibility
CV risk optimization
Randomization
Placebo
Pelacarsen
Baseline
Echo + CT
12 months
Echo
24 months
Echo
36 months
Primary endpoint (Echo + CT)
Secondary endpoints
Pelacarsen 80 mg once per month
ApoA anti-sense oligonucleotide
Change in V Peak measured by echo and
Change in AoV Calcium score measured by CT

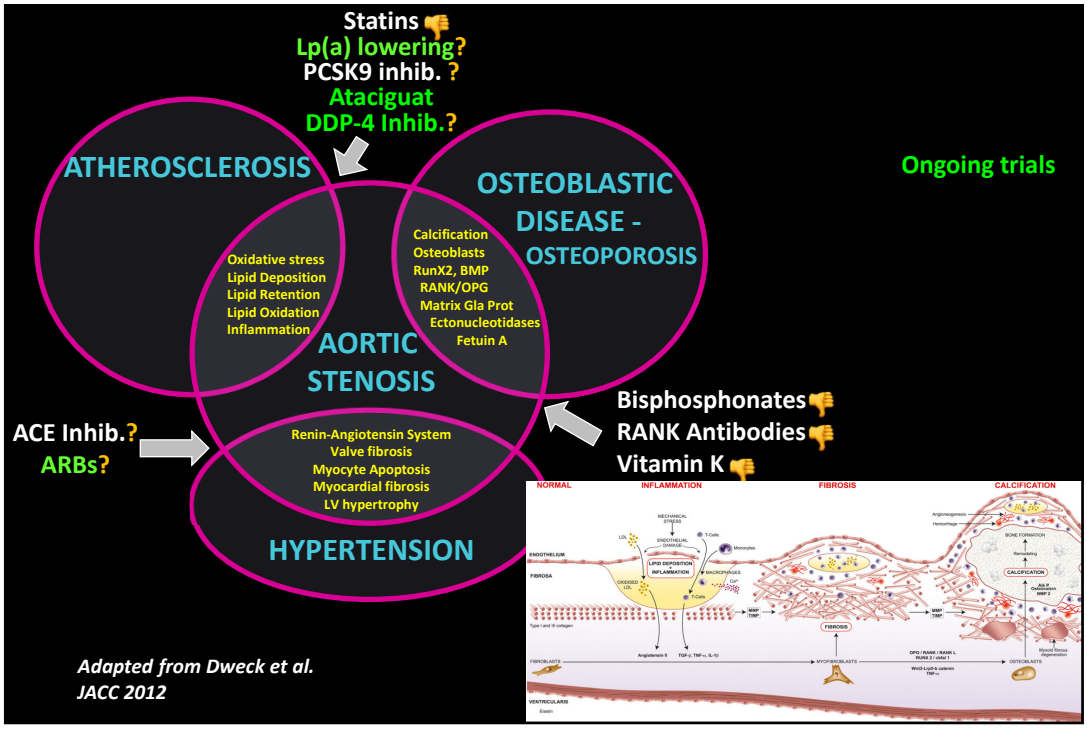
66

Endpoints for Pharmacotherapy RCTs in AS

- **Primary Endpoints:**
  - Change in V_{Peak} or AVA (echo) Baseline to 3 Yr
  - Change in AVC (CT) Baseline to 3 Yr
- **Secondary Endpoints:**
  - Change in NaF (PET-CT) Baseline to 1 Yr
  - Change in patient's health status (KCCQ) Baseline to 3 Yr
  - Clinical endpoints: death, AVR, valve-related hospit. Baseline to 3 Yr



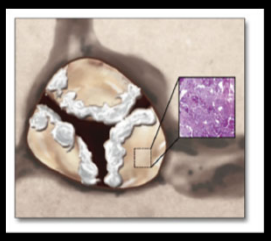
67

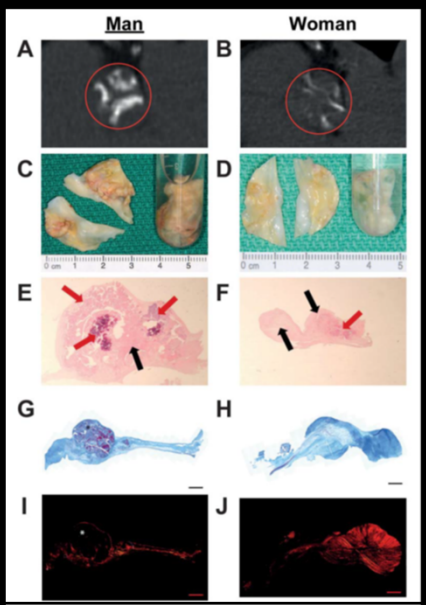


68

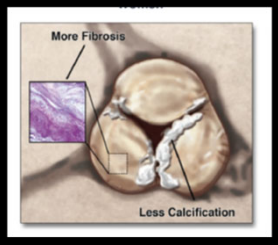
Women have less AoV calcification but more fibrosis compared to men

Men





Women

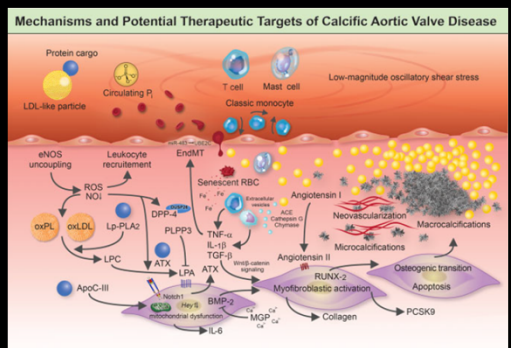


Simard et al.
Circ Res 2016

69

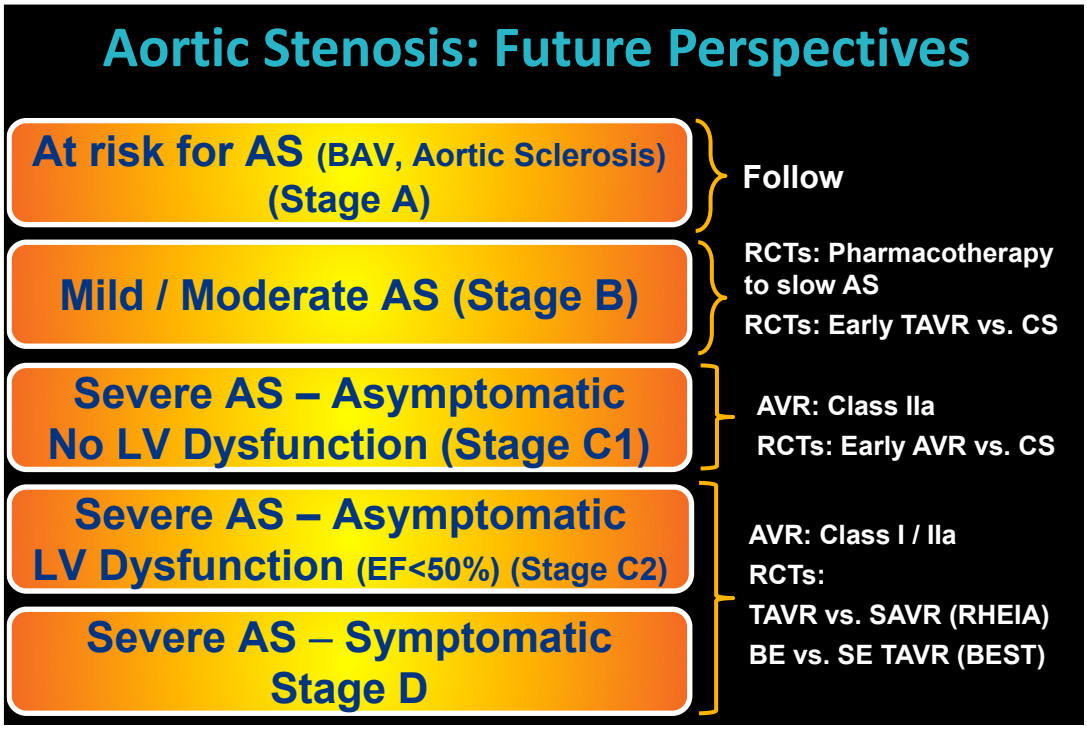
Conclusion #4: Pharmacotherapy for AS?

- Not yet but several promising targets (Lp(a), PCSK9, ARBs) have been identified and several RCTs are ongoing
- The « One drug fits all » will not work for AS
- Need to tailor therapy according to age, sex, and AS severity

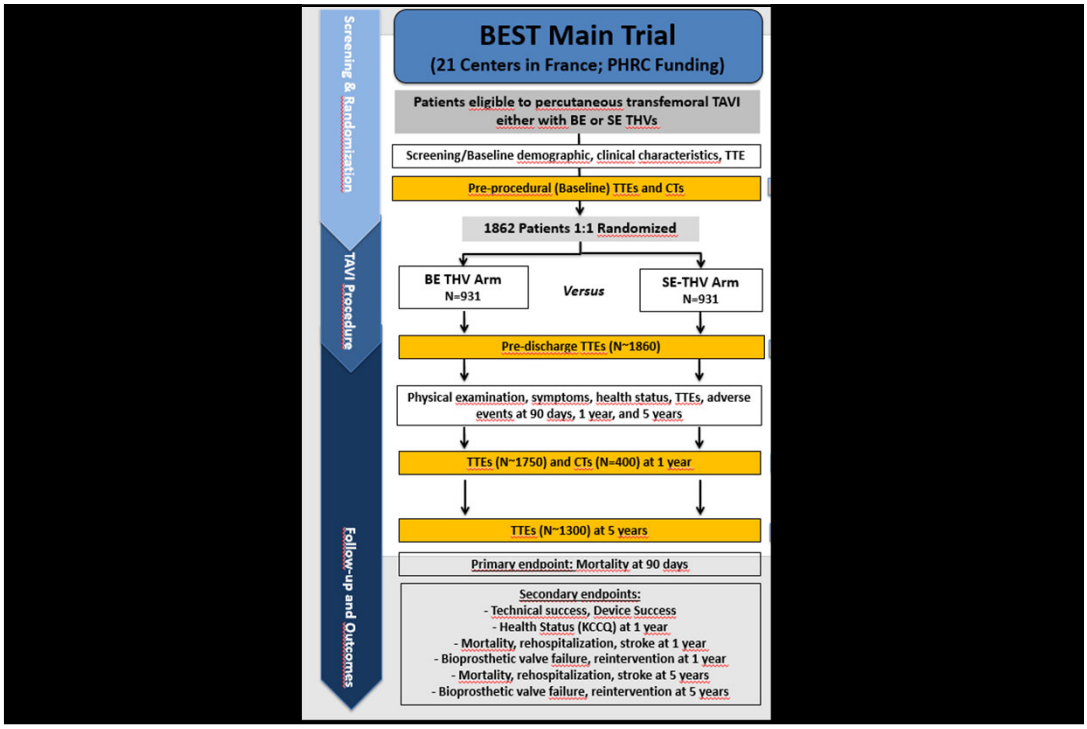


Target	Pharmacotherapy	Randomized Controlled Trial(s)
PCSK9/Lp(a)	PCSK9 inhibitor, Niacin	Ongoing
Matrix gla-protein (MGP)	Vitamin-K	↓ Calcification, hemodynamic effects t.b.d.
Soluble guanylyl cyclase (sGC)	HMR-1766 (Ataciguat)	Ongoing
Dipeptidyl peptidase-4 (DPP-4)	DA-1229	Ongoing
Angiotensin-II receptor	Fimasartan	Ongoing
Hydroxyapatite crystal formation	SNF472	↓ Calcification, hemodynamic effects t.b.d.
RANKL/osteoclastic activity	Denosumab/alendronic acid	Negative

70


Aortic Stenosis: Future Perspectives
At risk for AS (BAV, Aortic Sclerosis) (Stage A)
Follow
Mild / Moderate AS (Stage B)
RCTs: Pharmacotherapy to slow AS
RCTs: Early TAVR vs. CS
Severe AS – Asymptomatic No LV Dysfunction (Stage C1)
AVR: Class IIa
RCTs: Early AVR vs. CS
Severe AS – Asymptomatic LV Dysfunction (EF<50%) (Stage C2)
AVR: Class I / IIa
RCTs:
TAVR vs. SAVR (RHEIA)
BE vs. SE TAVR (BEST)
Severe AS – Symptomatic Stage D

71


BEST Main Trial
(21 Centers in France; PHRC Funding)
Screening & Randomization
Patients eligible to percutaneous transfemoral TAVI either with BE or SE THVs
Screening/Baseline demographic, clinical characteristics, TTE
Pre-procedural (Baseline) TTEs and CTs
1862 Patients 1:1 Randomized
BE THV Arm N=931
Versus
SE-THV Arm N=931
TAVI Procedure
Pre-discharge TTEs (N~1860)
Physical examination, symptoms, health status, TTEs, adverse events at 90 days, 1 year, and 5 years
TTEs (N~1750) and CTs (N=400) at 1 year
TTEs (N~1300) at 5 years
Follow-up and Outcomes
Primary endpoint: Mortality at 90 days
Secondary endpoints:
- Technical success, Device Success
- Health Status (KCCQ) at 1 year
- Mortality, rehospitalization, stroke at 1 year
- Bioprosthetic valve failure, reintervention at 1 year
- Mortality, rehospitalization, stroke at 5 years
- Bioprosthetic valve failure, reintervention at 5 years

72


CIHR
IRSC
Canadian Institutes of Health Research
Instituts de recherche en santé du Canada
Canada Research Chairs
www.chairs-chaires.gc.ca
HEART & STROKE FOUNDATION OF CANADA
Finding answers. For life.
Heart Valve COLLABORATORY
WORKING TOGETHER TO ADVANCE THE SCIENCE AND TREATMENT OF VALVULAR HEART DISEASE
HEART VALVE DISEASE
Working together to create a better patient journey
Heart Valve Voice Canada

73


The Team!

74