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Aortic Stenosis:
TAVR Lifetime Management

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Financial Disclosure

I, Eberhard Grube have the following financial interest/arrangement that could be perceived as a real or apparent conflict of interest in the context of the subject of this presentation

Speaker Bureau/ SAB: Medtronic, Boston Scientific, HighLife, Jena Valve, Protembis, Anteris, Valve Medical

Equity Interest: Cardiovalve, Claret, Shockwave, Valve medical, CardioMech, Millipede, Pi-Cardia, Jena Valve, Ancora, Laminar, ReNiva Medical

Roadmap of my Presentation
“Lifetime “ Management of AS Patients

- Expanding Indications

Asymptomatic/ Moderate AS

- Failed THV’s
- ViV

Durability/ Future Interventions

- Coronary Access / PCI in TAVR
- Future THVs

CAD/ New Valves

Lifetime Management of AS

Decisions for AVR have changed based on different long-term Priorities

Shift of Focus

ER/HR/IR ← → Low Risk

PROCEDURAL SUCCESS METRICS

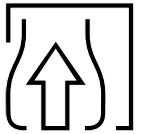
Outcomes
Mortality/Stroke/AV Block

Imaging & Measurements

Minimalistic Approach

	ER/HR/IR	Low Risk
AGE	80+	65+, CAD
ANATOMY	Tri-leaflet	More Bicuspid
ACTIVITY	Low	High(er)

MANAGEMENT METRICS



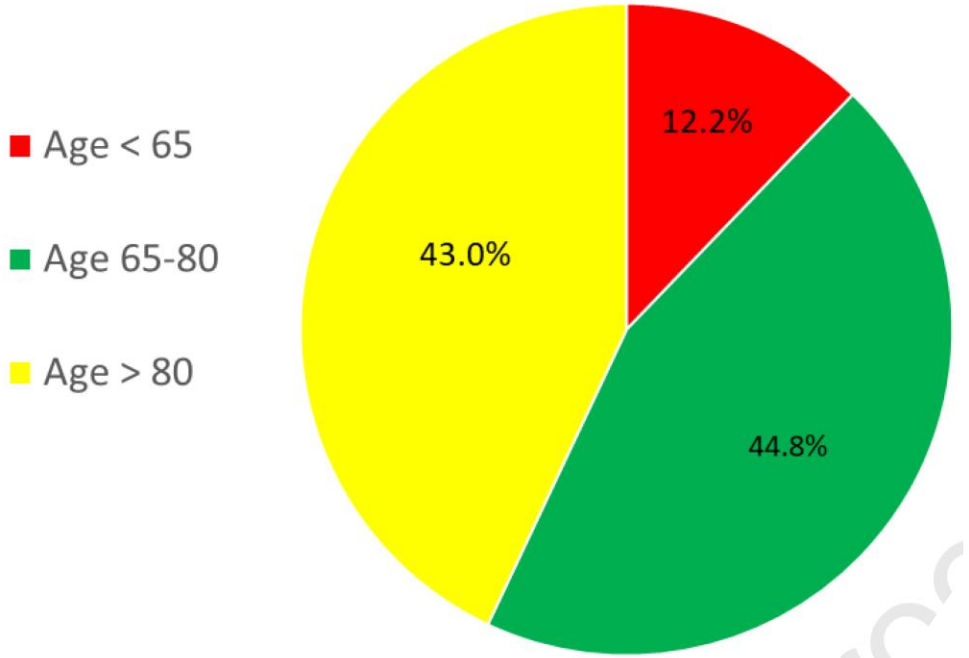
Hemodynamics & PPM

Durability <
Life Expectancy

Coronary Access (PCI)
& TAV-in-TAV

Lifetime Management in Patients with Aortic Stenosis

AGE < 65: TAVR ROSE FROM 17% TO 48% FROM 2015 TO 2021



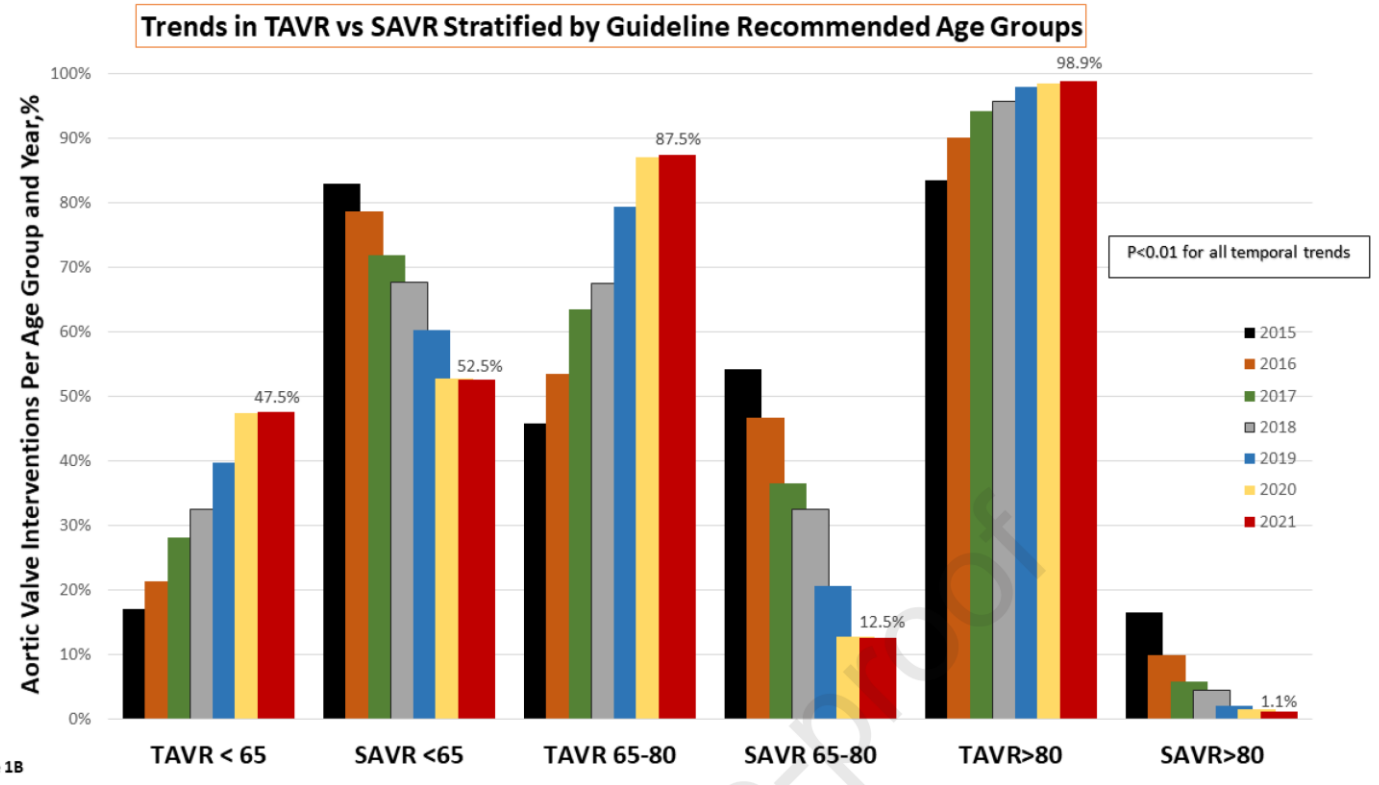


Figure 1B

Age < 65: TAVR rose from 17% to 48%; *SAVR fell from 83% to 52%.*
Age 65-80: TAVR rose from 46% to 87%; *SAVR fell from 54% to 12%.*
Age > 80: TAVR rose from 83% to 99%; *SAVR fell from 16% to 1%.*

Impact of TAVR in the Modern Era

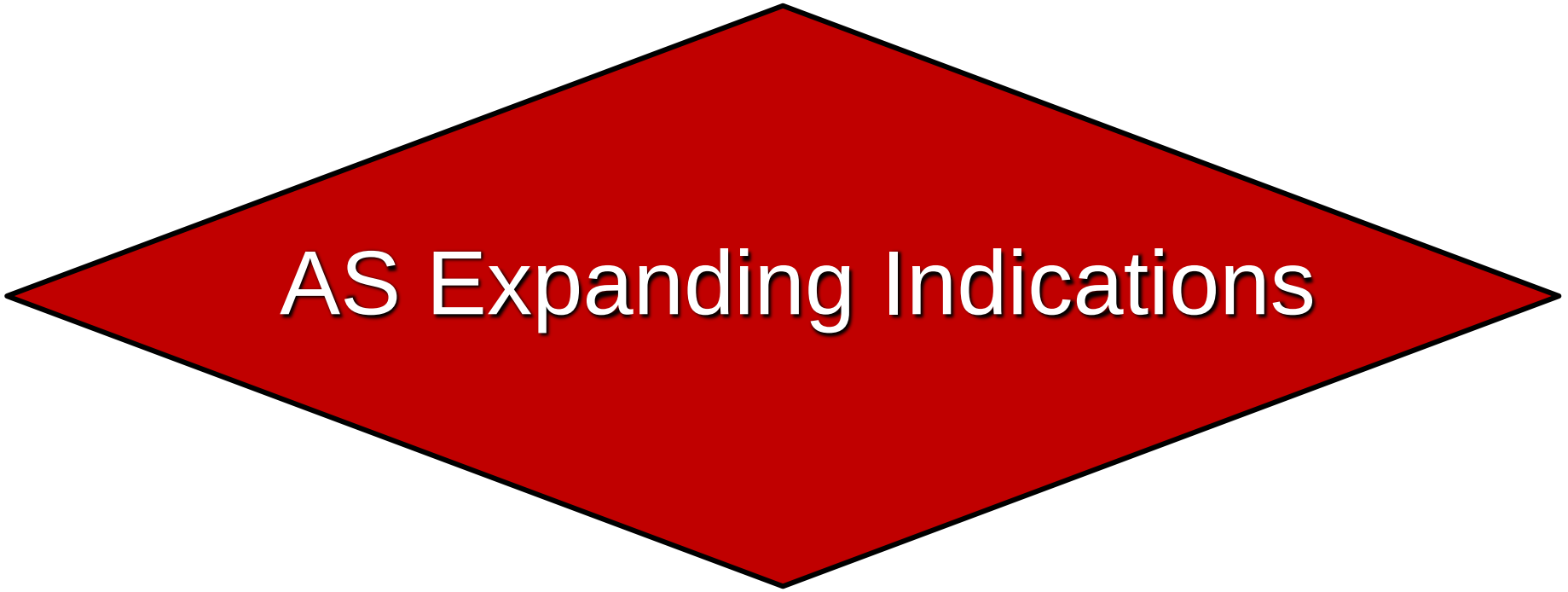
3 Foundational Pillars

Heart Team

Image-Guided Therapy

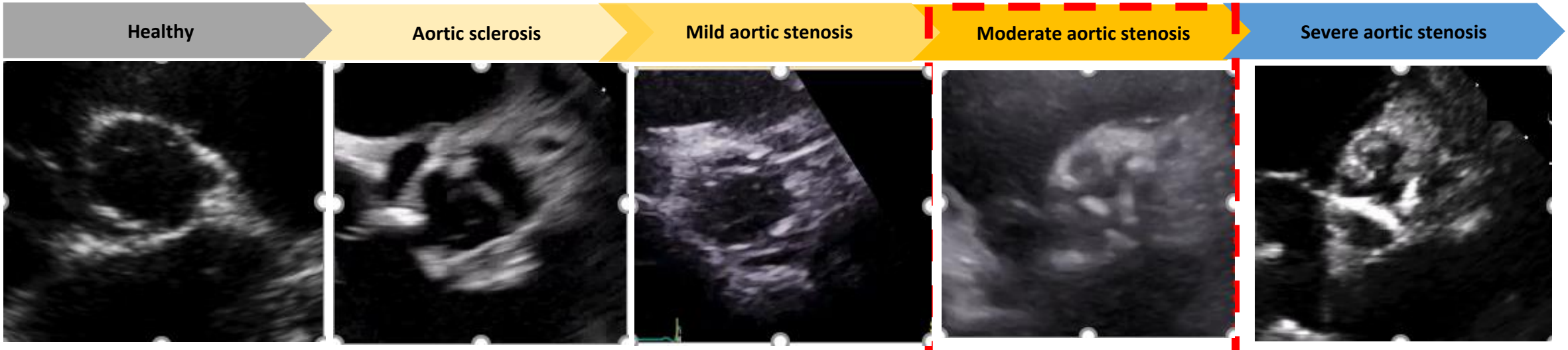
Life Journey

TAVR Journey



Aortic Stenosis is a Progressive Disease

Current treatment paradigm for Moderate AS is to wait for stenosis to be severe before intervention[1-3]



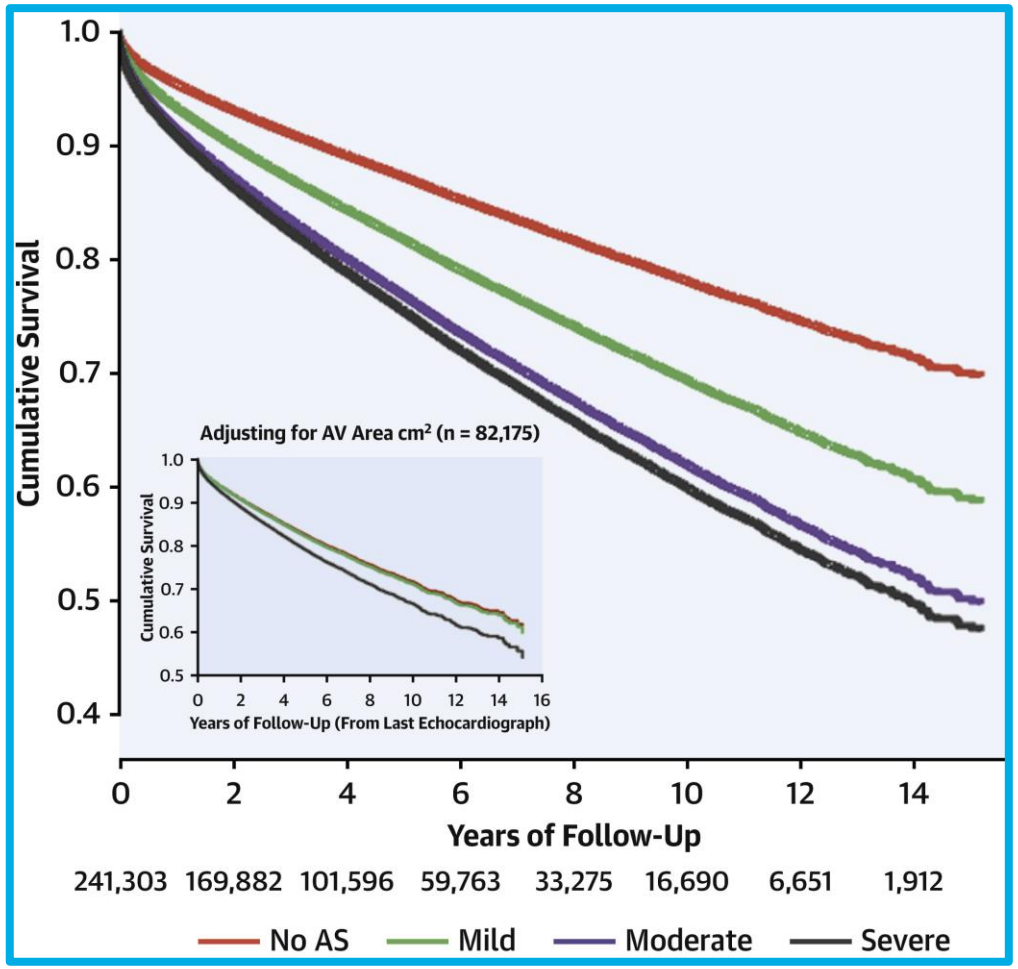
	Sclerosis	Mild	Moderate	Severe
Max velocity (m/s)	≤ 2.5	2.6–2.9	3.0–4.0	≥ 4.0 (m/sec(
Mean gradient (mm Hg)	-	< 20	20–40	≥ 40 (mmHg)
AVA (cm^2)	-	> 1.5	1.0–1.5	< 1.0 (cm^2)

Watchful Waiting?

[1] Vahanian A, et al. Eur Heart J. 2022
[2] Otto CM, et al. Circulation. 2021
[3] Izumi C, et al. Circ J. 2021

Natural History of Untreated Moderate AS

National Echo Database (241,303 pts; median 1208 dys FU)



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

Moderate AS is NOT a Benign Disease!

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

Current Treatment Paradigm for Moderate Aortic Stenosis

Watchful waiting is ingrained in clinical practice

Current Guidelines

- Clinical and echo follow-up every 1-2 years for progression of AS, and medical therapy for hypertension and other cardiovascular conditions[1-3]
- AVR may be considered for patients undergoing cardiac surgery for another reason (IIb)

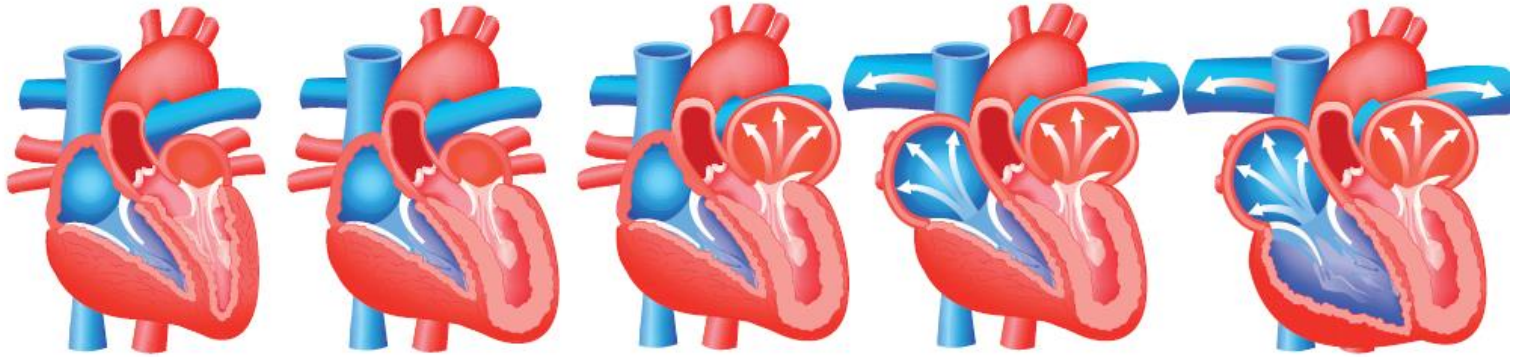
Issues with watchful waiting for moderate AS

- Rate of stenosis progression is highly variable[1,2]
- Moderate AS has been associated with significant cardiovascular events and mortality in observational studies.[4,5]
- Waiting for AS to progress to severe before intervening may result in irreversible cardiac damage and worse prognosis even with AVR[6]

Aortic Valve Therapies: Life Journey Considerations

Aiming for Earlier Intervention

We must investigate earlier intervention to avoid myocardial damage and further improve lifetime outcomes for these patients.

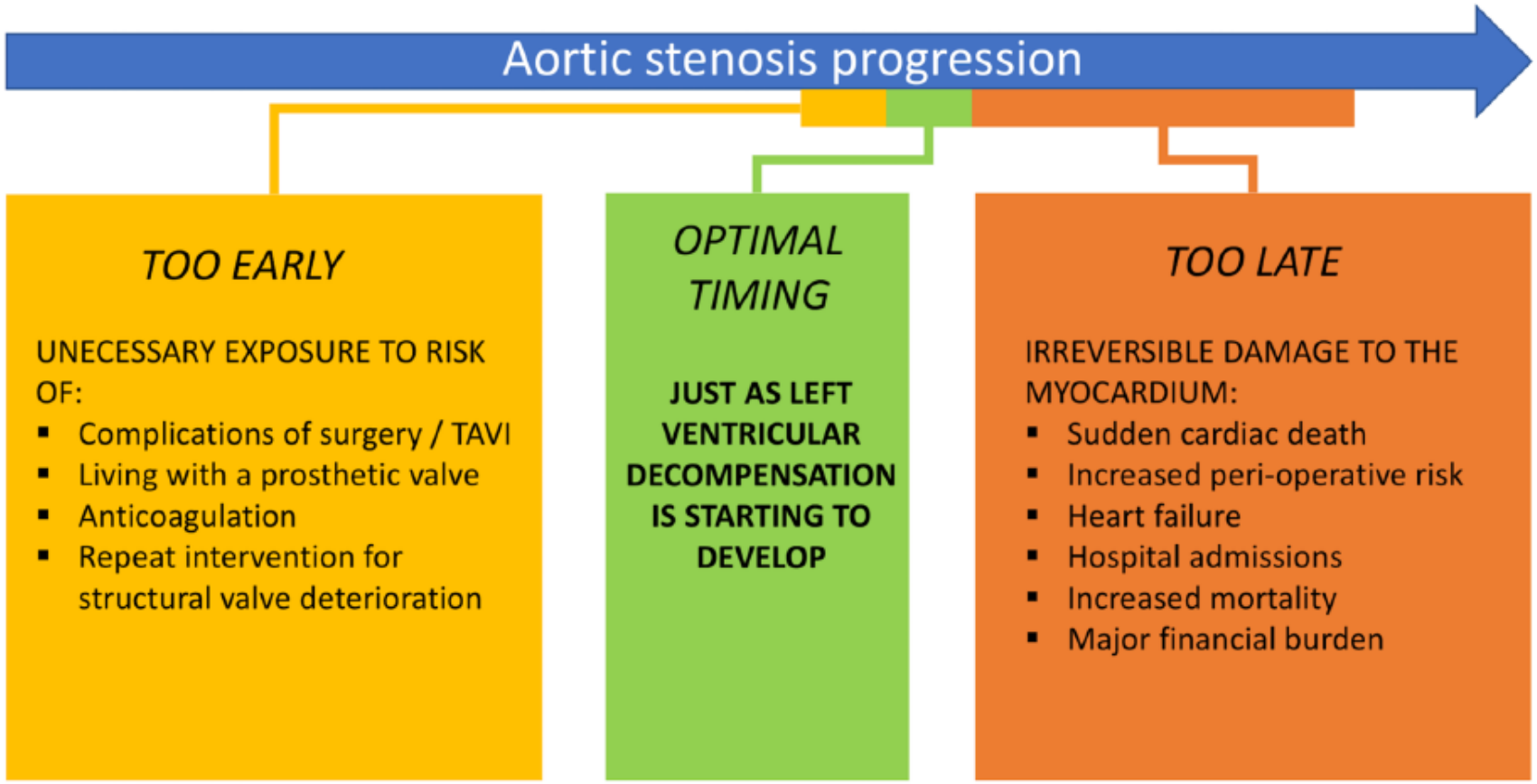


Stages/Criteria	Stage 0	Stage 1	Stage 2	Stage 3	Stage 4
	No Cardiac Damage	LV Damage	LA or Mitral Damage	Pulmonary Vasculature or Tricuspid Damage	RV Damage
Echocardiogram		Increased LV Mass Index >115 g/m² (Male) >95 g/m² (Female)	Indexed left atrial volume >34mL/m²	Systolic Pulmonary hypertension ≥60 mmhg	Moderate-Severe right ventricular dysfunction
		E/e' >14	Moderate-Severe mitral regurgitation	Moderate-Severe tricuspid regurgitation	
		LV Ejection Fraction <50%	Atrial Fibrillation		

Earlier Intervention| Challenges in Timing

Defining cardiac markers for timing AS intervention is an enduring question for earlier treatment.

When should we offer valve intervention?

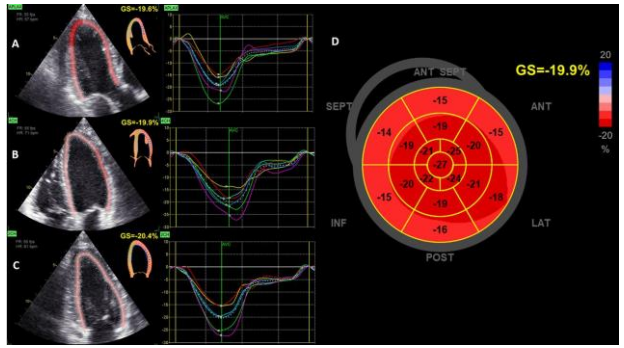


Everett RJ, et al. Heart 20

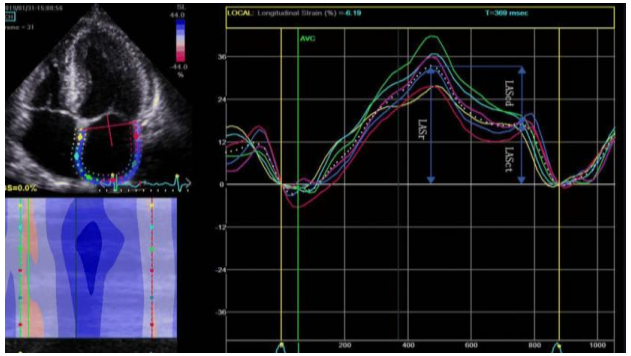
Earlier Intervention| Challenges in Evaluating Cardiac Function

Multi-modalities to evaluate impact of intervention and enhance prognostic risk stratification

Echocardiography
(Baseline and follow-up)

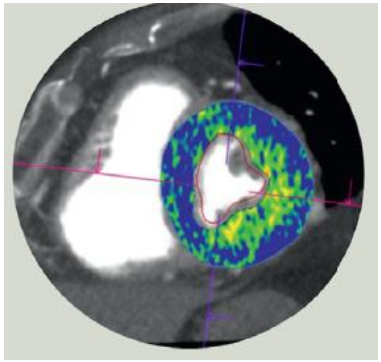


Left Ventricular Global Longitudinal Strain

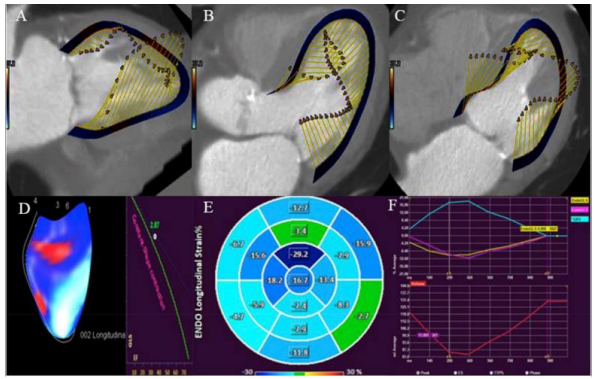


Left Atrial Strain

MDCT
(Baseline)

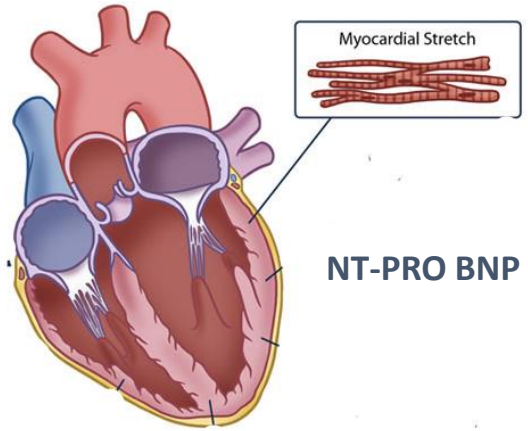


Extra-Cellular Volume



Left Ventricular Global Longitudinal Strain

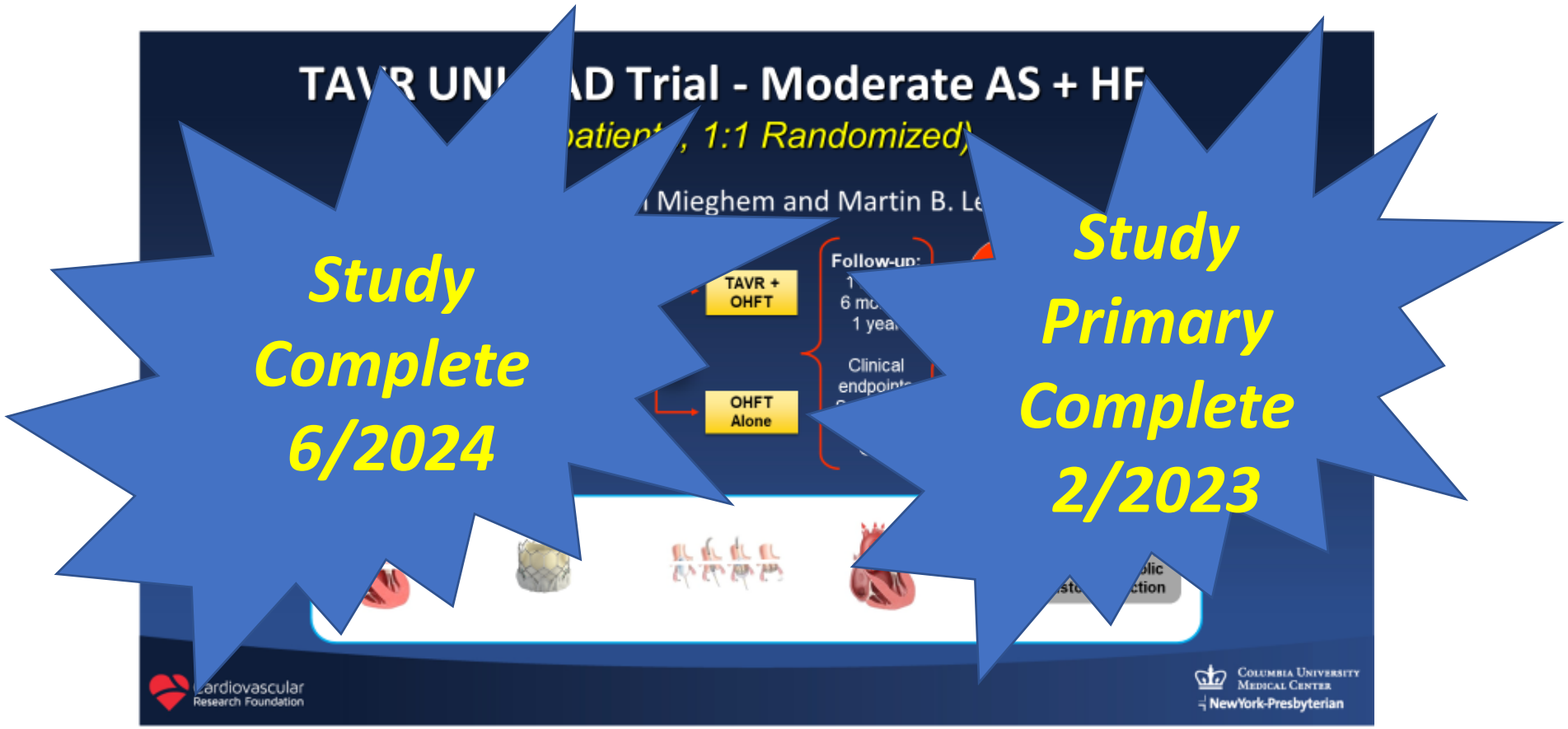
Bio-markers
(Baseline and follow-up)



NT-PRO BNP

Earlier TAVR Trial I TAVR UNLOAD Trial

TAVR vs GDMT and TAVR vs Afterload Reduction and GDMT



Moderate Aortic Stenosis

TAVR Studies

The PROGRESS Trial

Randomized, prospective trial
450 to 750 patients

1:1 Randomization
TAVR (Sapien3 Ultra) vs Clinical Surveillance

Interim Analysis (180 pts finish 2 yr f/u)

Primary Endpoint
All cause Mortality, Stroke and unplanned CV Hospitalisation at 2 years

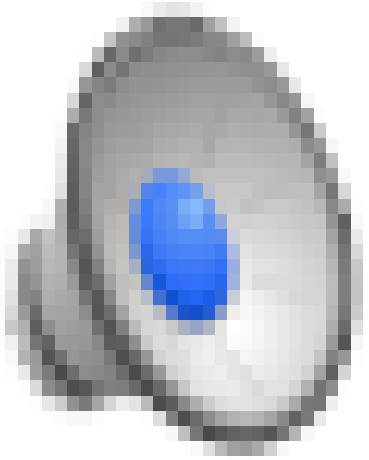
The EXPAND II Trial

Randomized, prospective trial
550 patients

1:1 Randomization
TAVR (Evolut + GDMT) vs GDMT (delayed AVR allowed)

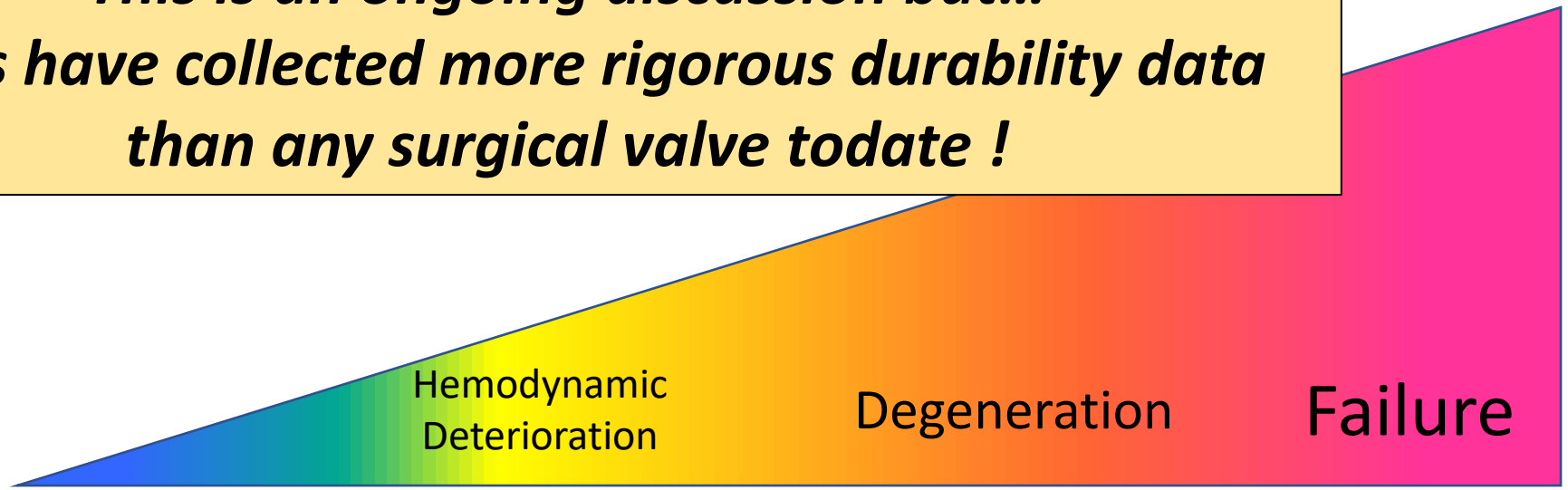
Primary Endpoint
All cause Mortality, HF events or Medical Instability leading to AVR at 2 years

Bioprosthetic Valve Durability



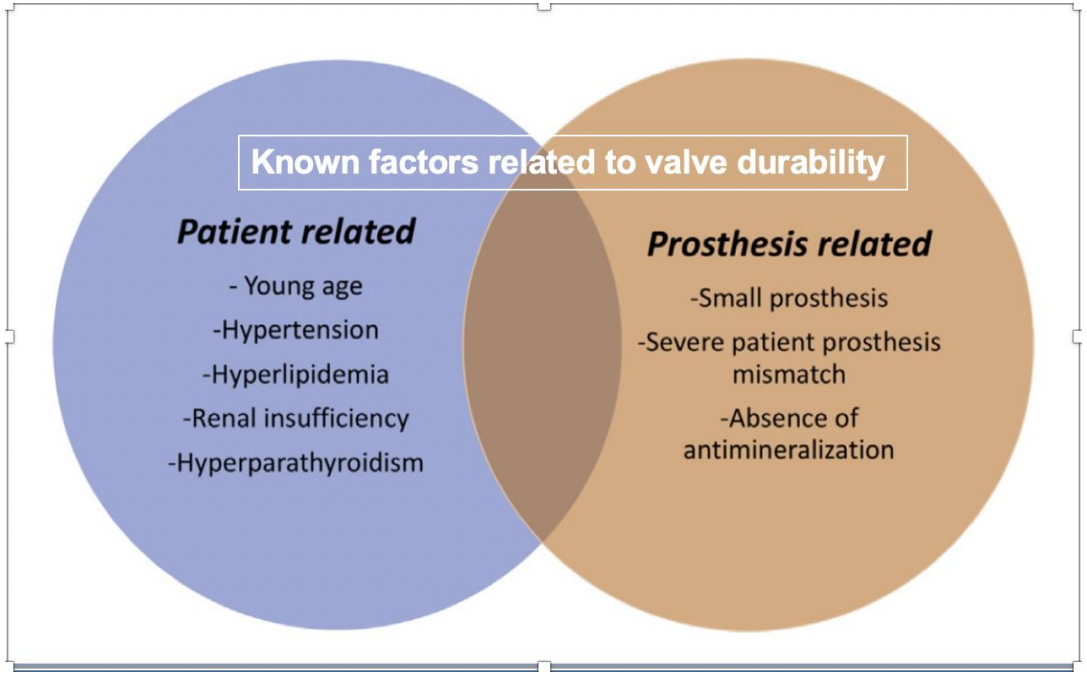
Bioprosthetic Valve Durability

This is an ongoing discussion but…
THVs have collected more rigorous durability data than any surgical valve todate !



Bioprosthetic Valve Durability

Multi-Factorial impacts on expected Valve Durability



Yerasi, et al. JACC 2021;14:1169-80.

- **An ideal THV should replicate a healthy aortic valve going through 40 million cycles per year with unfaltering function.**

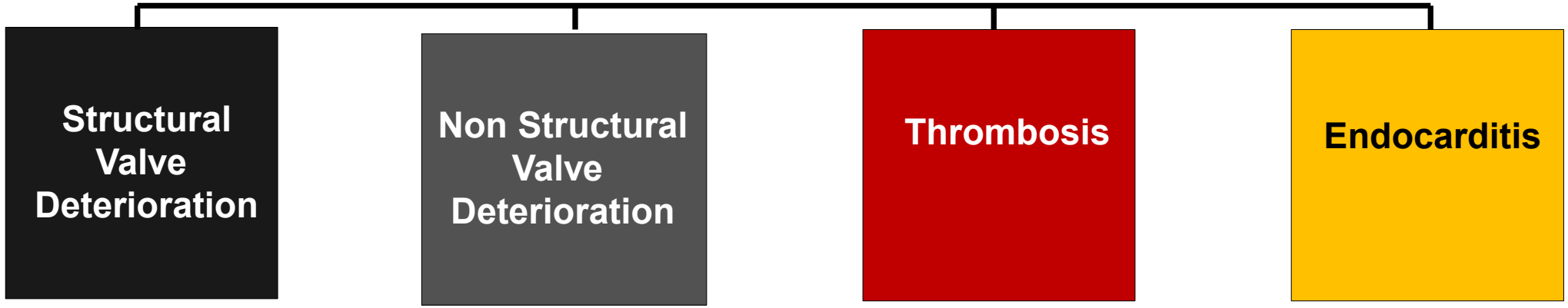
Bioprosthetic Valve Durability

The Problems

- *One of the central issues regarding valve durability* ***is the*** ***lack of a universal definition***.
- ***The VARC-3 and EAPCI consensus documents*** *define four modes of bioprosthetic valve dysfunction: Structural valve deterioration (SVD), non-structural valve dysfunction, thrombosis, and endocarditis*

EAPCI-ESC-EACTS CONSENSUS DOCUMENT

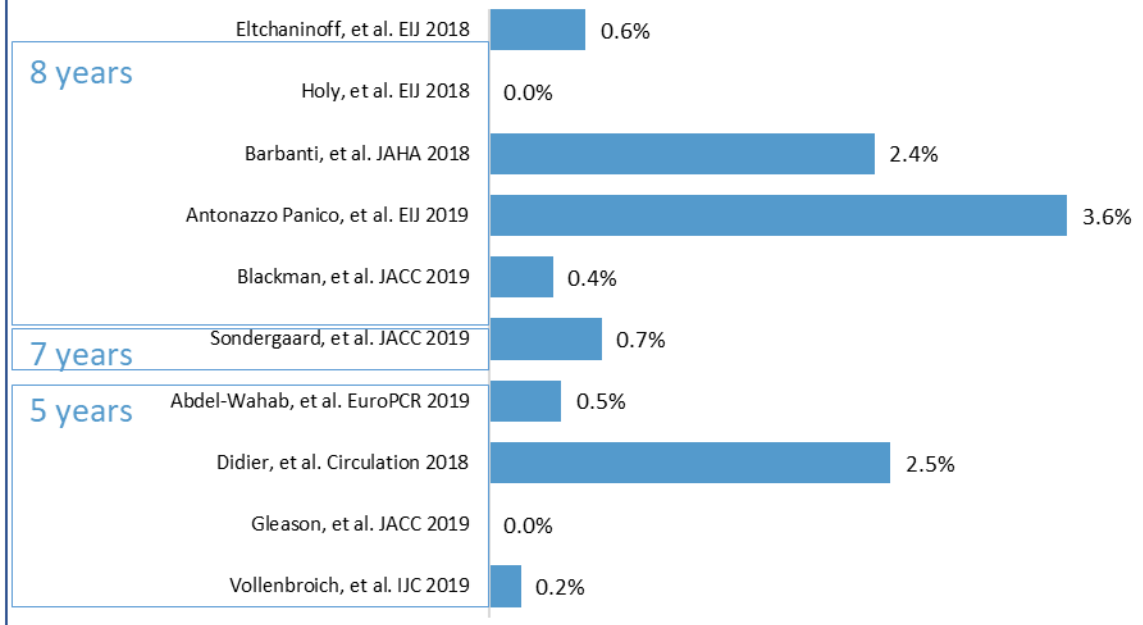
Bioprosthetic Valve Dysfunction

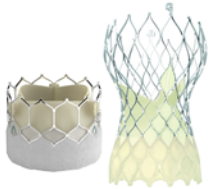


Capodanno D, et al. Eur J Cardiothorac Surg. 2017;52:408-417.

Bioprosthesis Durability (ESC/EACTS Definitions)

Severe SVD

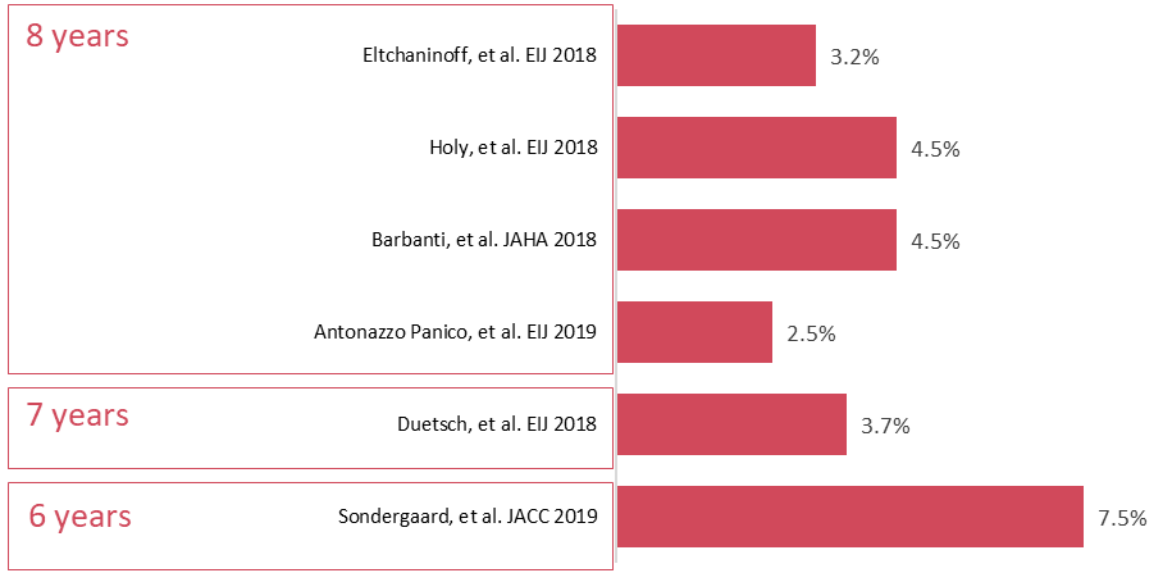




SVD at 5 to 8 years
Weighted incidence

1.3%
(95% CI 0.7-1.9)

Bioprosthetic valve failure (BVF)

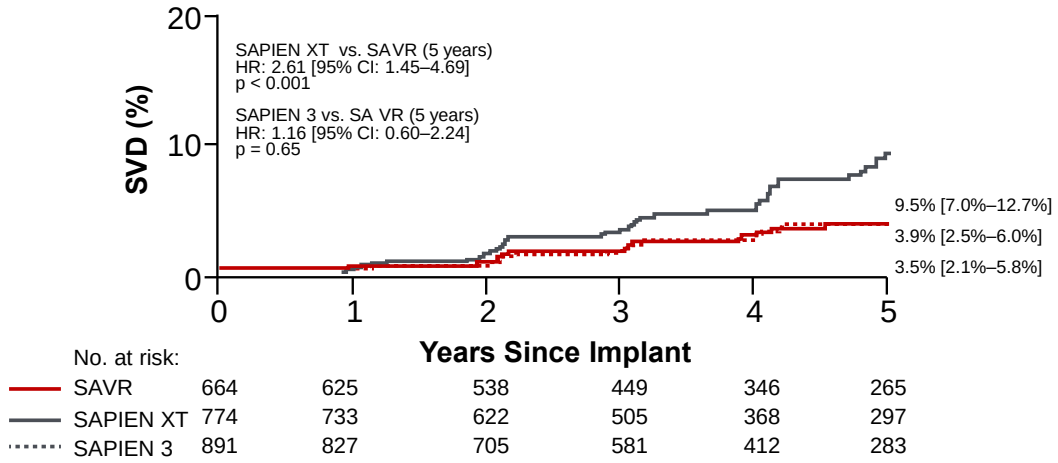


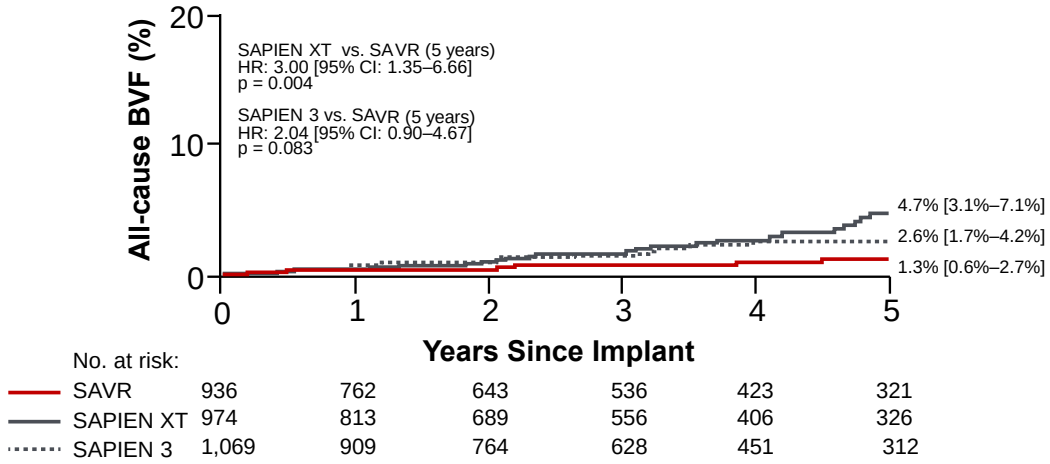
BVF at 6 to 8 years
Weighted incidence

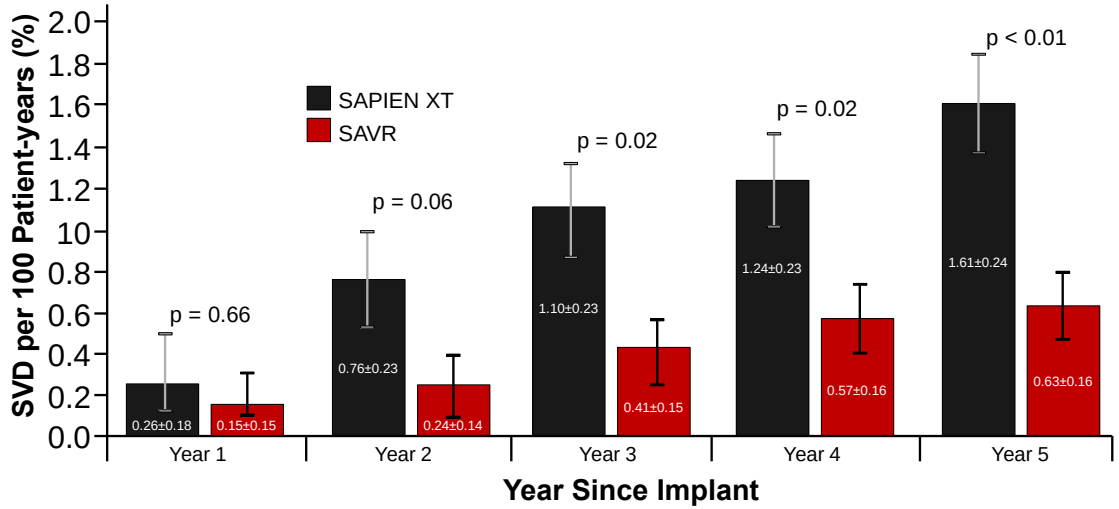
3.7%
(95% CI 2.7-4.6)

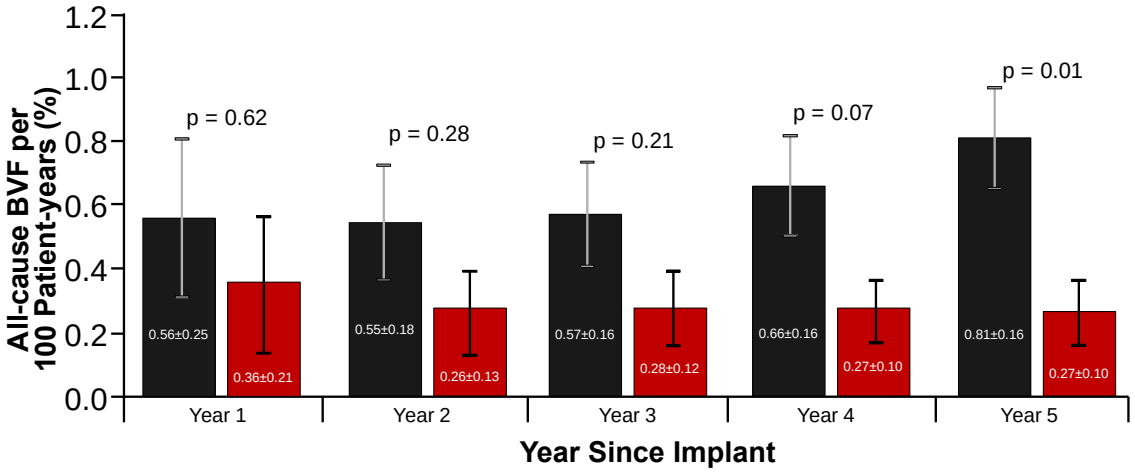
PARTNER 2: 5-YEAR FOLLOW-UP FOR SVD

SAPIEN XT VERSUS SURGERY (RANDOMIZED DATA)







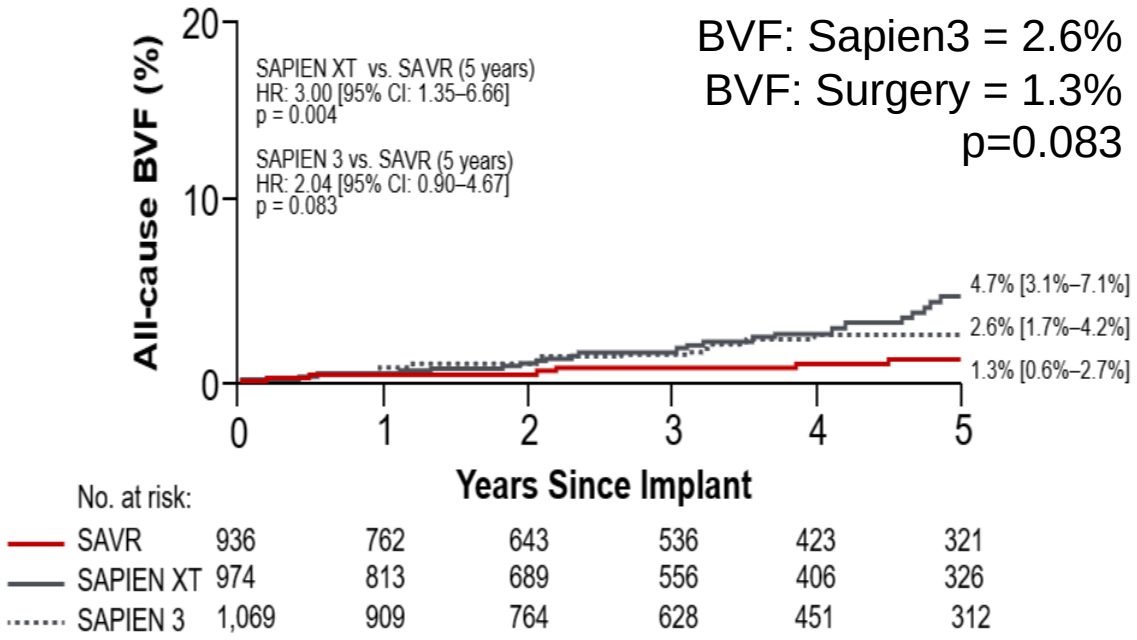


Pibarot P, et al. *JACC*. 2020;76:1830-1843.

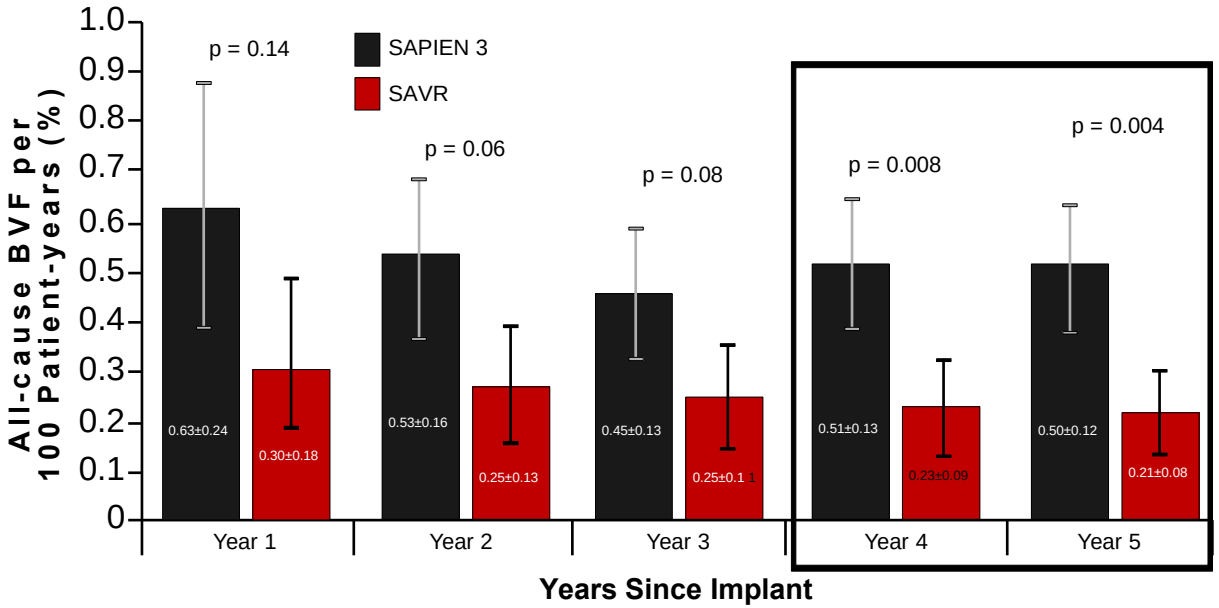
BIOPROSTHETIC VALVE FAILURE

SAPIEN 3 VERSUS SURGERY AT 5 YEARS (DATA NOT RANDOMIZED; PROPENSITY MATCHED)

BVF: Sapien 3 versus Surgery



BVF: Sapien 3 versus Surgery



*Inverse Probability Treatment Weighting (IPTW) to account for non-randomized comparison of surgery with Sapien3.

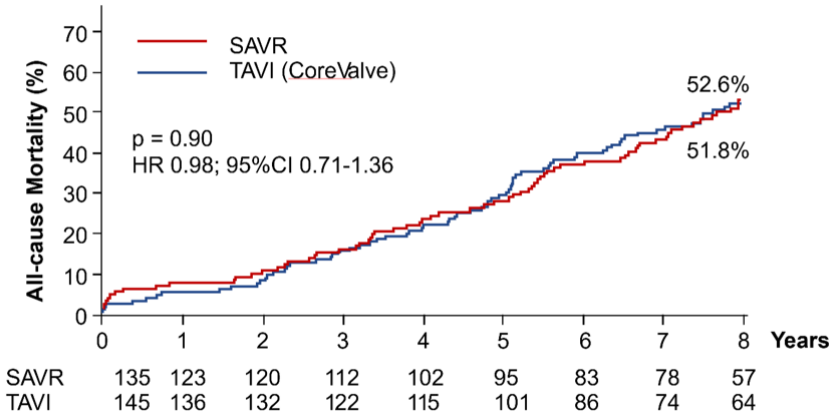
The rate of BVF at 5 years trended to be higher with Sapien 3 than surgery (P=0.083) and the all cause BVF in terms of 100 Patient Years was significantly increased at 4 and 5 years after the procedure.

Pibarot P, et al. *JACC*. 2020;76:1830-1843.

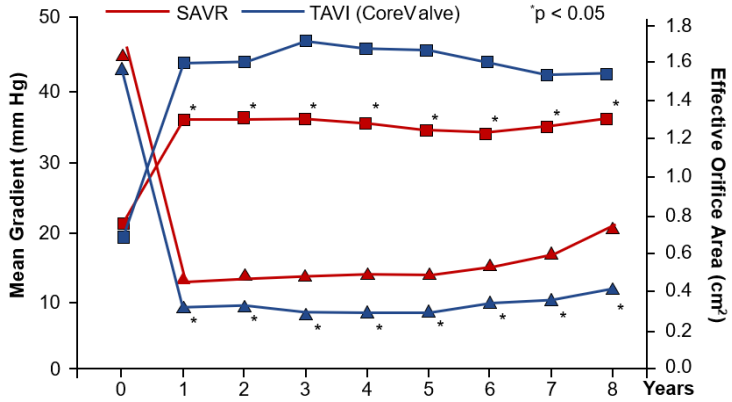
BIOPROSTHETIC VALVE DURABILITY

CORE VALVE / EVOLUT NOTION 8-YEAR ALL COMERS

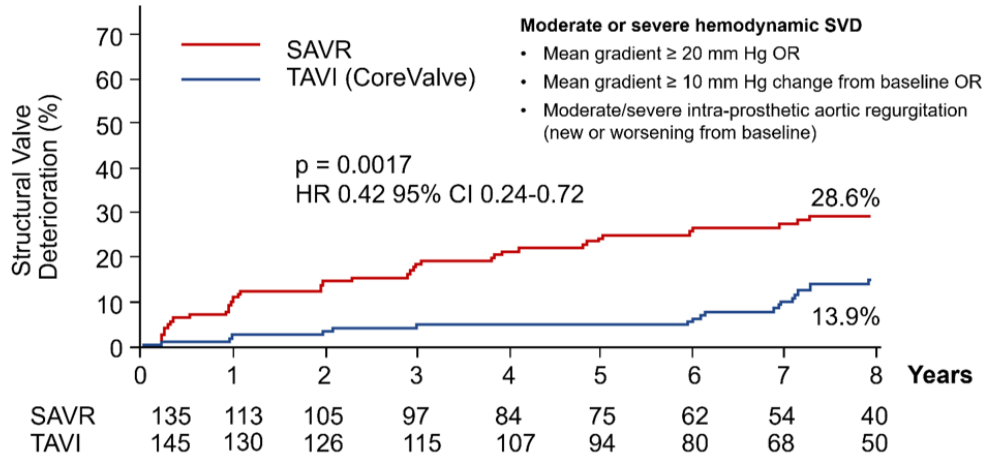
All Cause Mortality



Transthoracic Hemodynamics



Structural Valve Deterioration

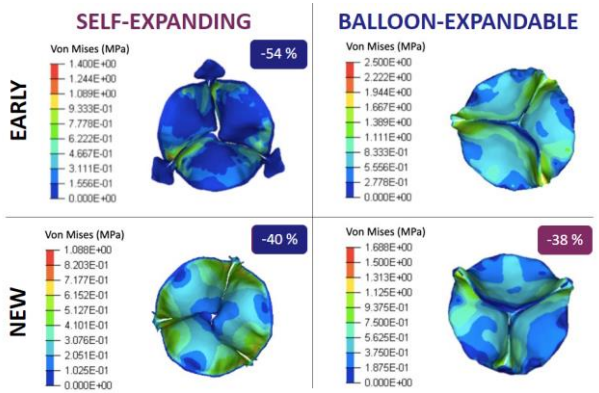


Jorgensen, et al. Eur Heart J. 2021;42:2912-9

BIOPROSTHETIC VALVE DURABILITY

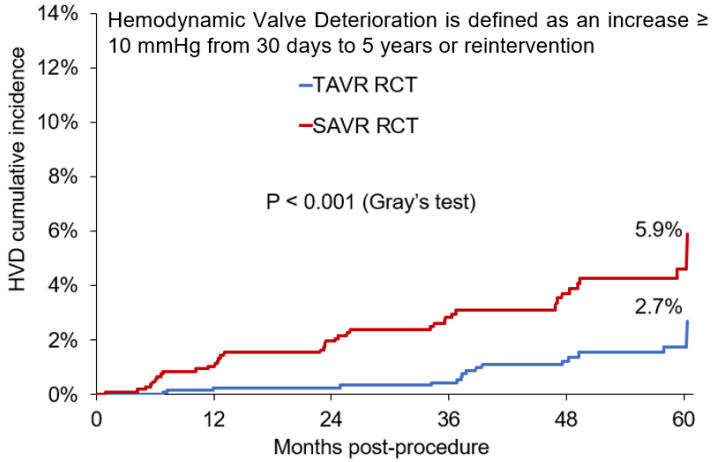
CORE VALVE /EVOLUT DURABILITY

Lower Leaflet Stress with EV



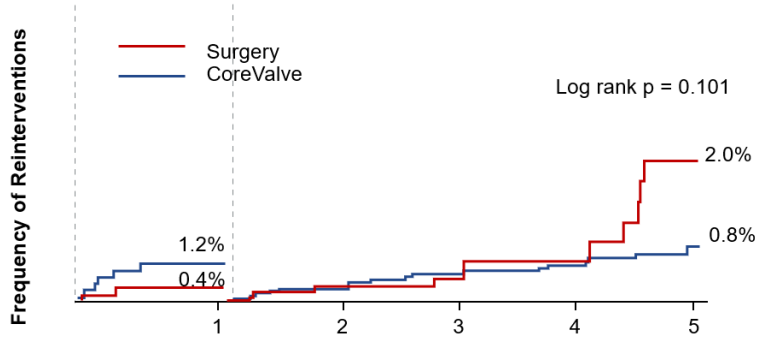
Stanova V, et al. Abstract EuroPCR2021

Gradients correlate with Hemodaynamic Valve Deterioration



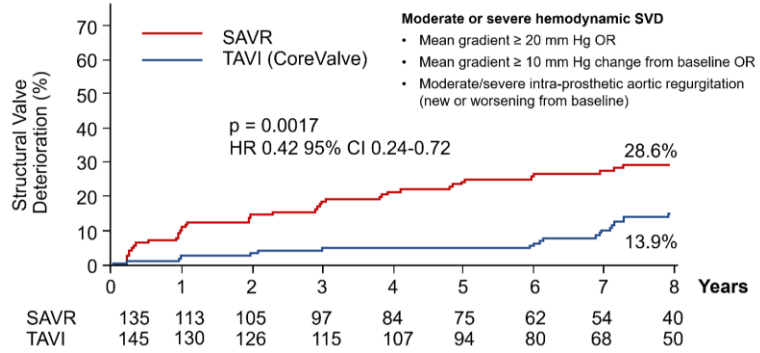
O'Hair et al Abstract ACC 2021

Reintervention Randomized Data)



Grubb, et al. TCT 2020

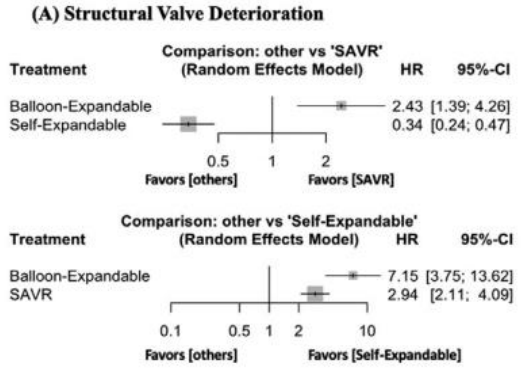
SVD with CoreValve (P=001) (Randomized Data)



Søndergaard L et al. JACC. 2019;73(5):546–53.

Jorgensen, et al. Eur Heart J. 2021;42:2912-9

Meta-analysis of SVD in SEV



Ueyama, et al., Am J Cardiol 2021;158:104-111

TAVR Durability

DOES HALT AND RELM AFFECT DURABILITY?

The Low Risk studies ***did not show*** an association between ***HALT and increased stroke/TIA events***, however both analyses were statistically underpowered.

It is also ***unknown*** whether or how subclinical thrombosis and reduced leaflet motion will ***affect the valve leaflet integrity and durability*** over time.

For these reasons, the prognostic value of ***routine 4D CTA*** and its relationship to subclinical valve thrombosis and clinical events ***remains unclear***.

?

Subclinical Thrombosis/HALT → **Impact to the Patient**

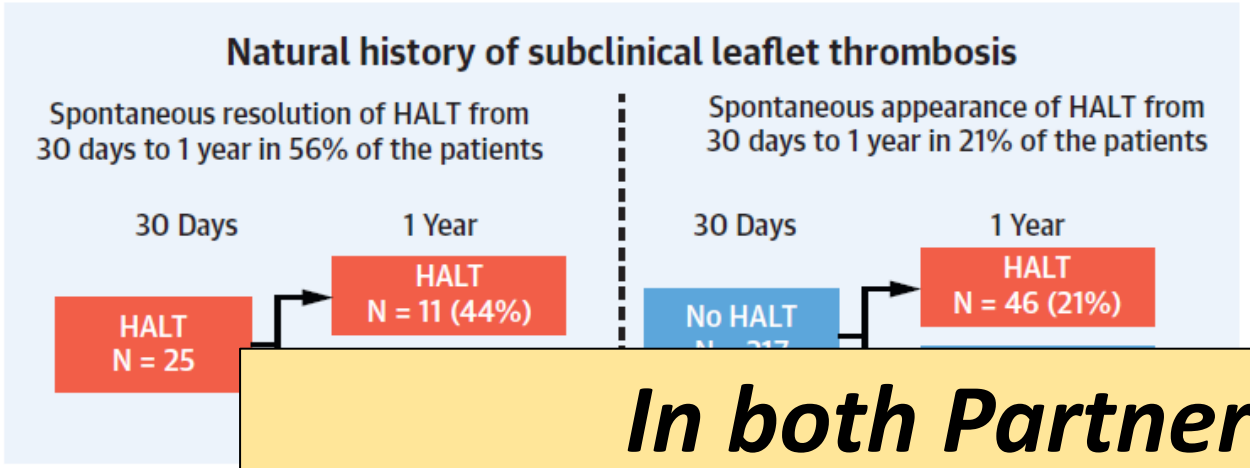
- Dynamic change over time
- Extent of HALT had no impact on mean Gradient in Low Risk trials

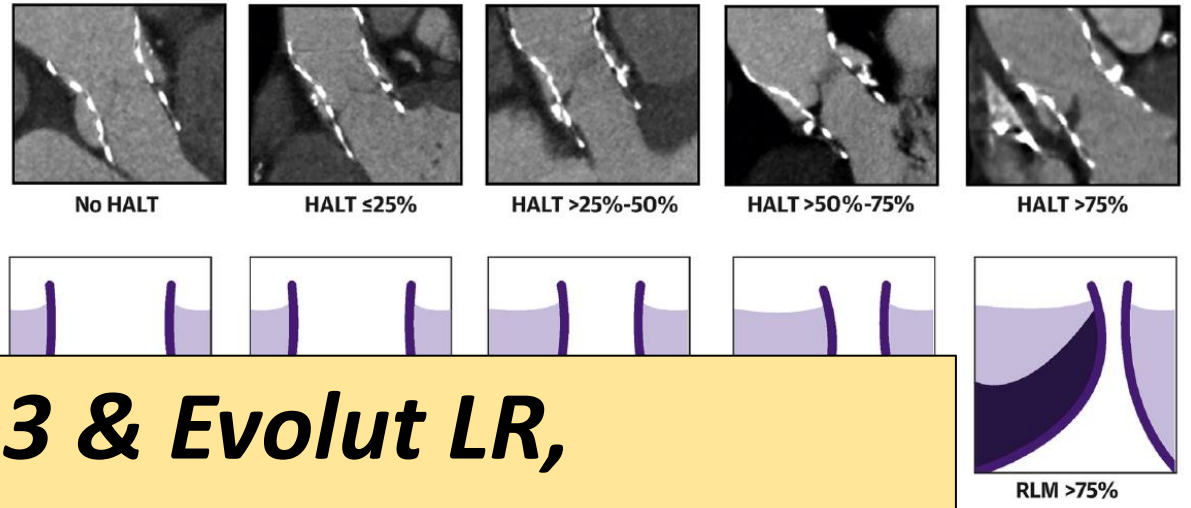
- Leaflet integrity & SVD
- Cerebro-embolic events

Blanke JACC 2020;75:2430–42. Makkar, JACC 2020;75:3003–15

TAVR Durability

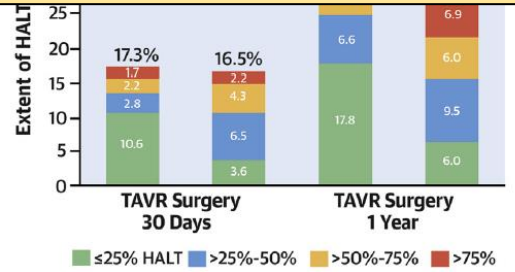
DOES HALT AND RELM AFFECT DURABILITY?





In both Partner 3 & Evolut LR, HALT did NOT result in hemodynamic changes

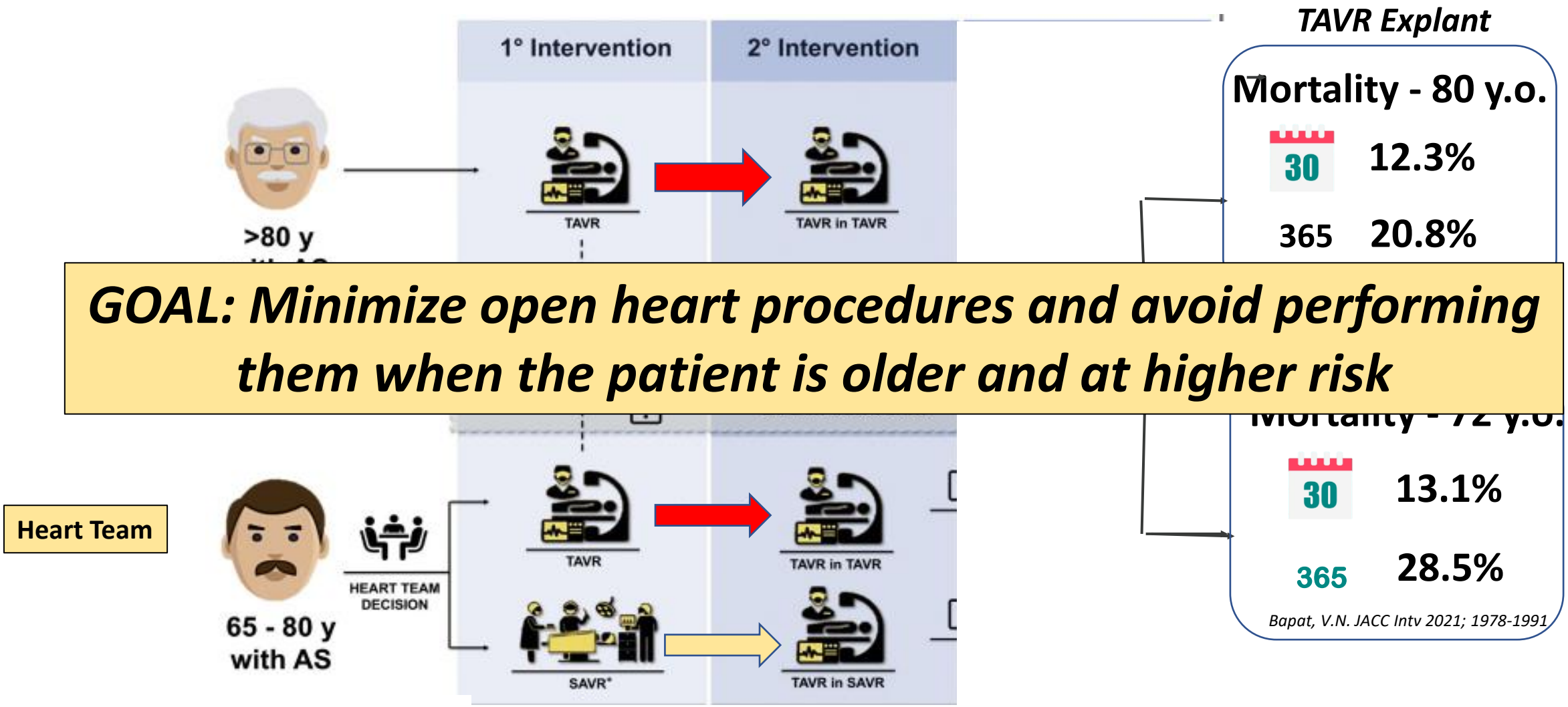
Makkar et al. JACC 2020



Holmes et al. Circulation 2017

Lifetime management in patients undergoing AVR

Planning for future Interventions!

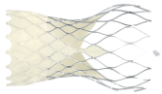


GOAL: Minimize open heart procedures and avoid performing them when the patient is older and at higher risk

Tarantini G. J Am Coll Cardiol Intv. 2021, 14 (15) 1717–1726

CONCEPT # 1: 2nd Intervention Choice

First Intervention
SAVR



First Intervention
TAVR

«TAVR will be likely the most frequent 2nd intervention in a lifetime strategy of a patient»

30 **7-8%**

365 **10-11%**

JACC 2020; 4;76(5):489-499.
EuroIntervention 2022;17:1227-1237.

30 **2-3%**

365 **5-6%**

JACC Intv. 2021;14(2):211–20
EuroIntervention 2022;17:1227-1237.

with Ao. Root replacement)

30 **12-13%**

365 **21-29%**

Percy ED et al., JACC Intv 2021, Vol 14 N 15

30 **6%**

365 **20%**

Percy ED et al., JACC Intv 2021, Vol 14 N 15

CONCEPT # 2 : 1st THV choice MATTERS

Time

First Intervention

Second Intervention

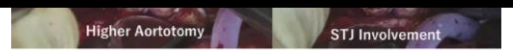
TAVR EXPLANT with ASC AORTA REPLACEMENT

CORONARY IMPAIRMENT

« TAVR repeatability» might be as important as leaflet durability»

Valve Type 2

VALVE DURABILITY: ? >8 y



p=0.009

18%

Fukuhara S. Ann Thorac Surg. 2022;113:138-145

p=0.12

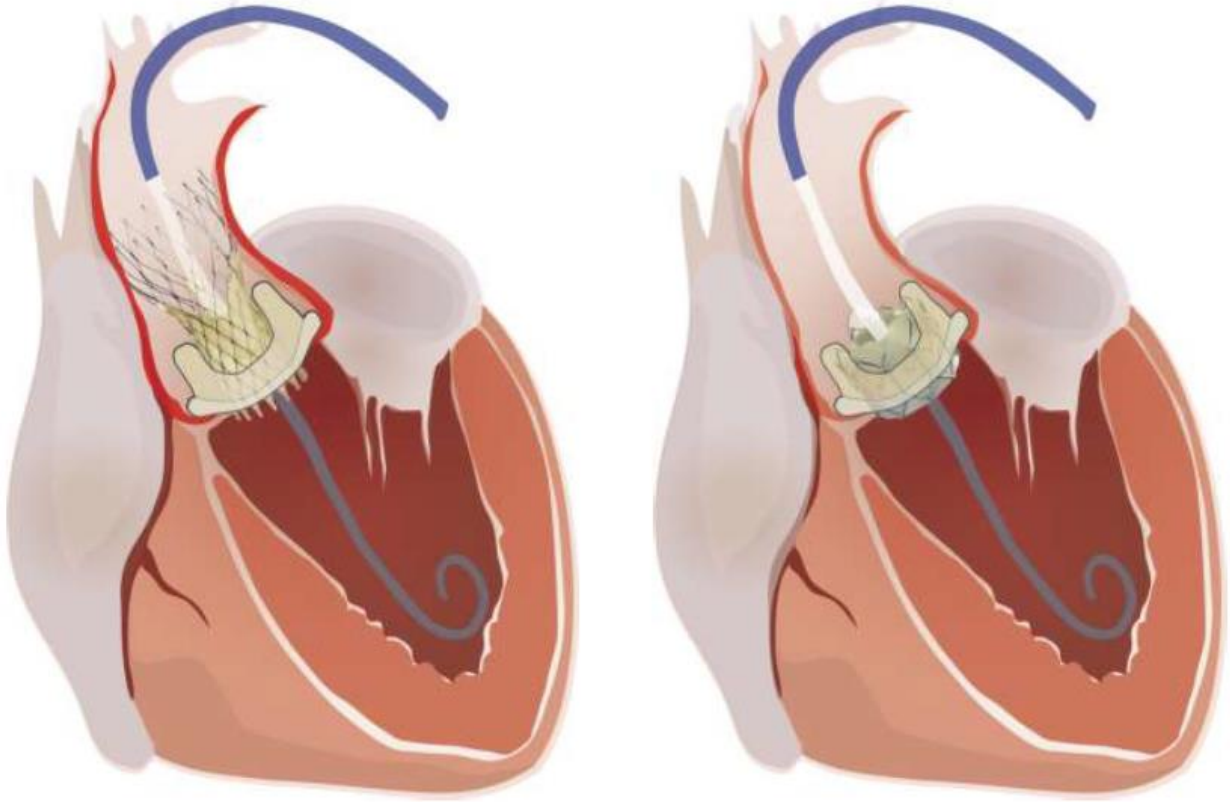
27% *(CT analysis)*

De Becker Ole et al. JACC Int 2020 13 (21) 2528–2538

TAVR I Lifetime Management

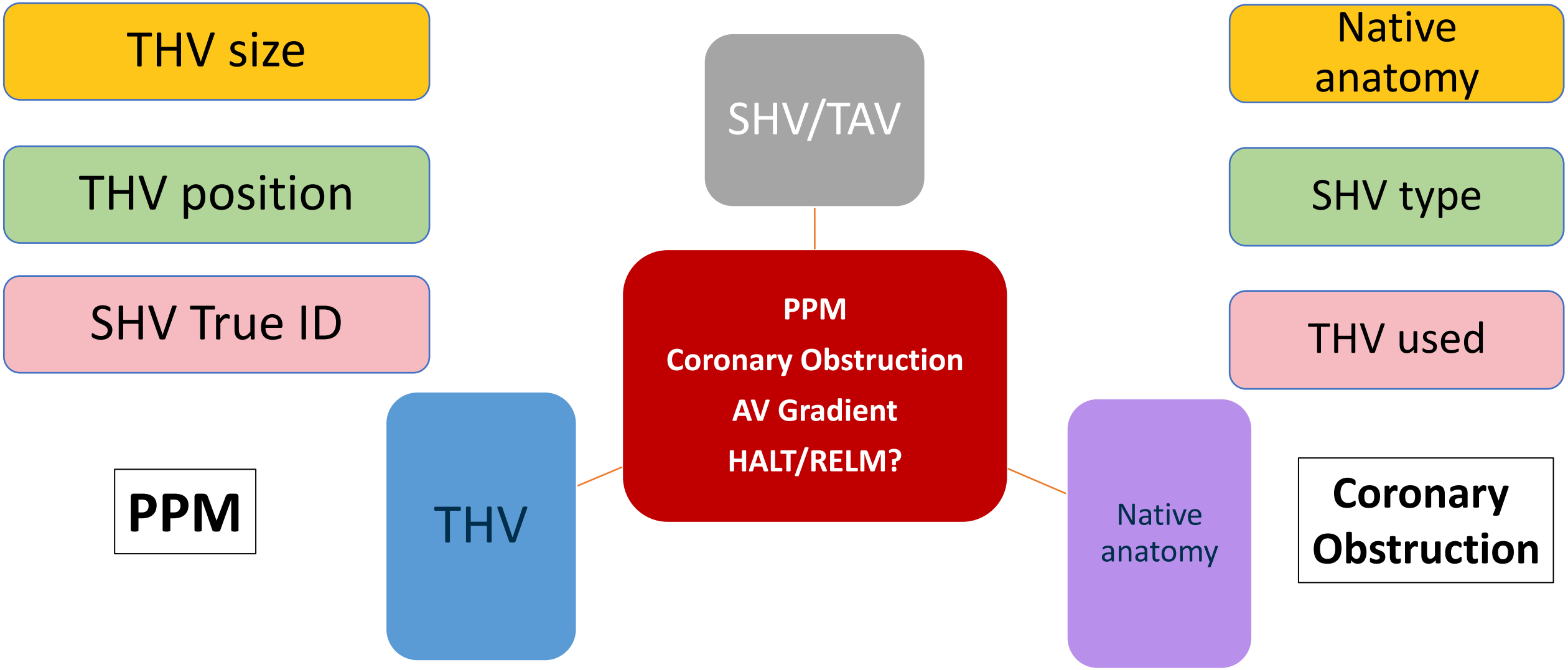
TAV-in-SAV and TAV-in-TAV

A less invasive approach for failed bioprosthesis



[1]Kapadia. Presented at Scottsdale Interventional Forum 2017

Main Concerns with V-in-V Aortic

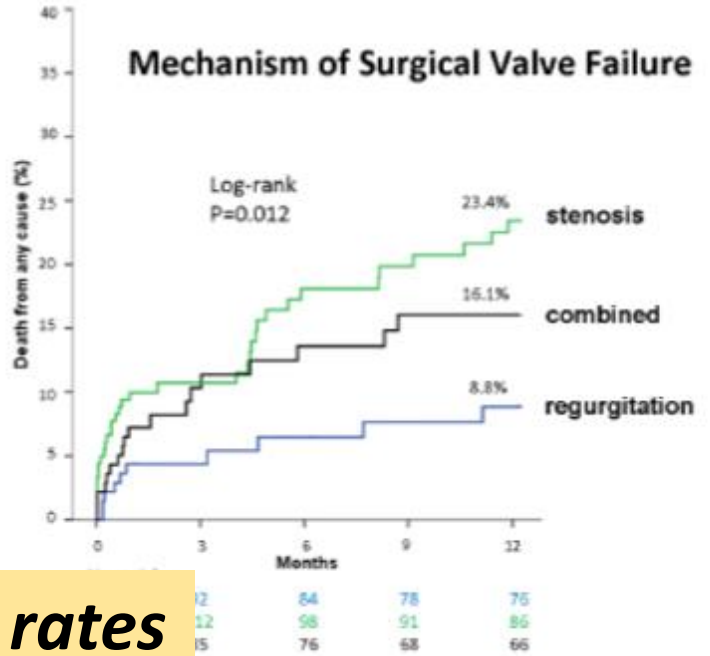


TAVR FOR SURGICAL VALVE FAILURE

UNTOWARD PROGNOSTIC IMPACT OF RESIDUAL PPM

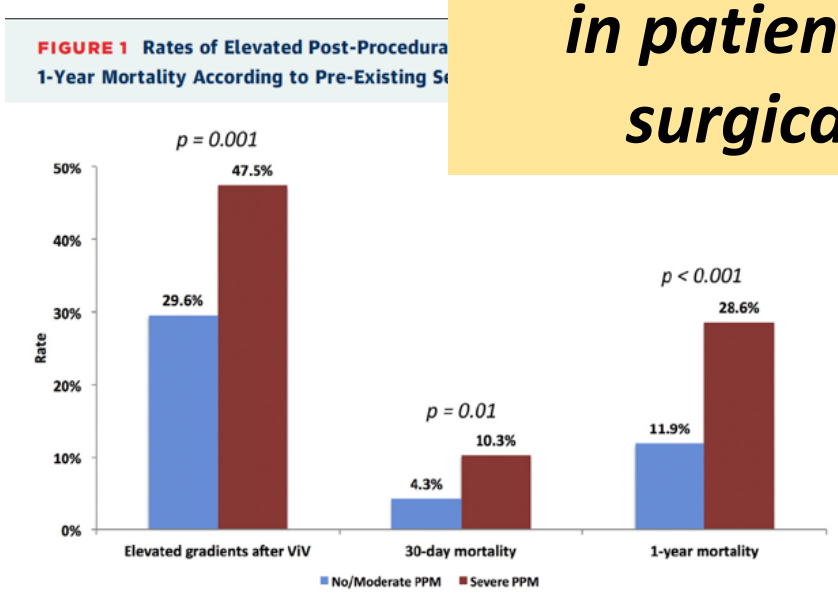
A significant portion of AVR patients have small surgical valves.

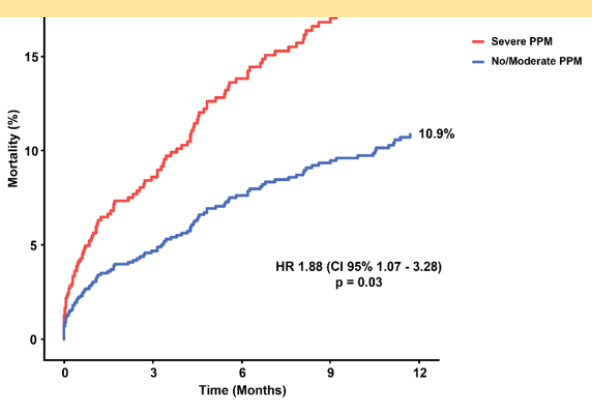
	VIVA Trial (n=202)	TVT Registry (n=1,150) U.S. patients	VIVID Registry (n=1,168) Global patients
SAV label size			
≤21 mm	41.3%	26.2%	30.5%
>21 and <25 mm	32.8%	24.8%	38.3%
≥25 mm	25.9%	24.3%	31.3%
Unknown	NA	24.5%	NA

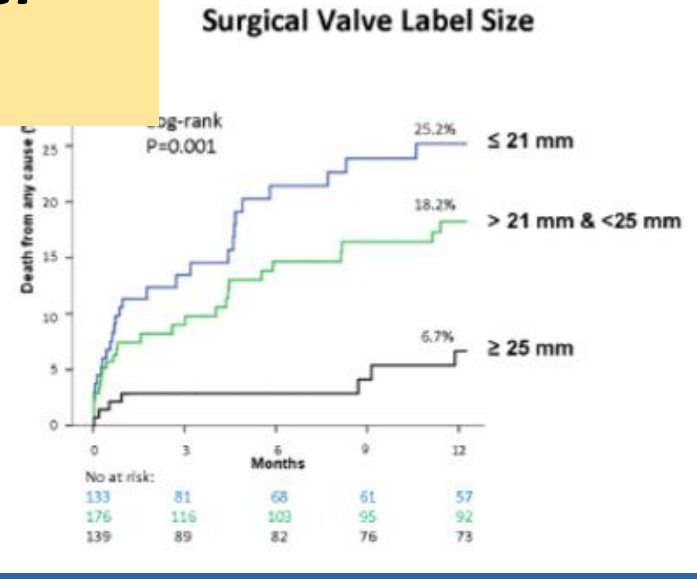


Tuzcu et al., J Am Coll Cardiol. 201

Multiple series show higher mortality rates in patients undergoing TAV in smaller surgical valves with residual PPM







Pibarot P, et al. VIVID Registry JACC Int 2017

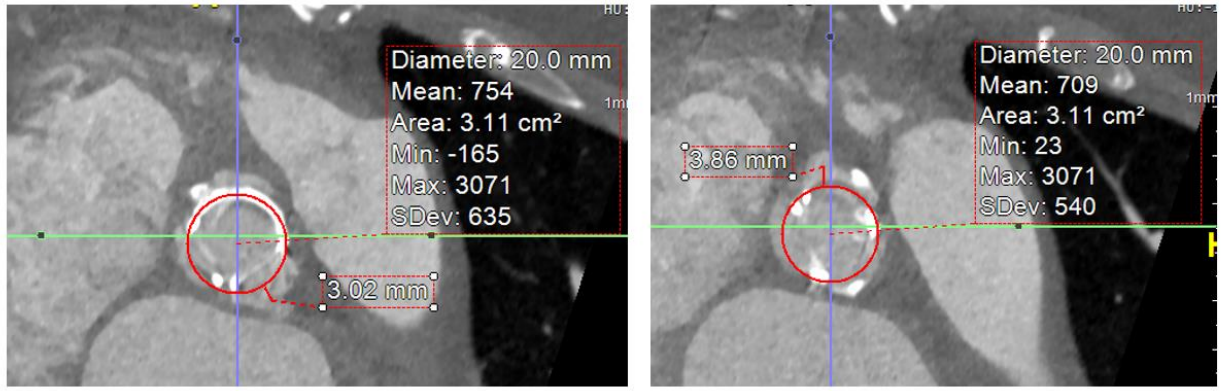
Pibarot P, et al. VIVID Registry JACC Int 2017

Dvir, et al. JAMA. 2014; 312(2):162-170

TAVR FOR SURGICAL VALVE FAILURE

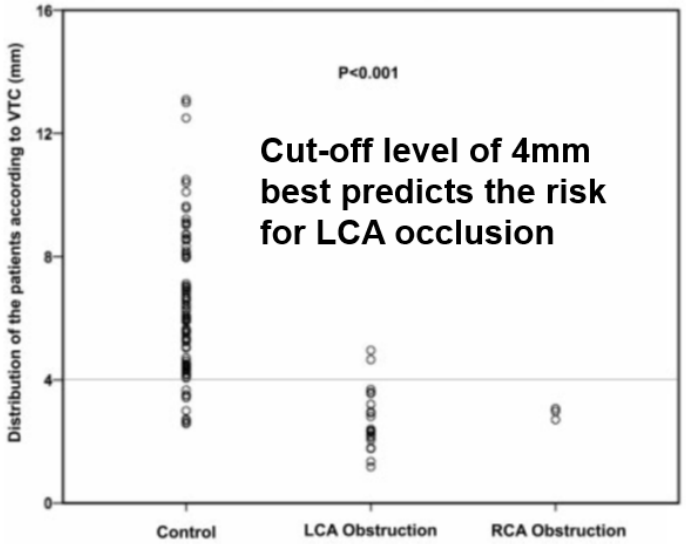
RISK FOR CORONARY OCCLUSION

Risk of Coronary Obstruction?



Chhatriwalla TCT 2022 presentation

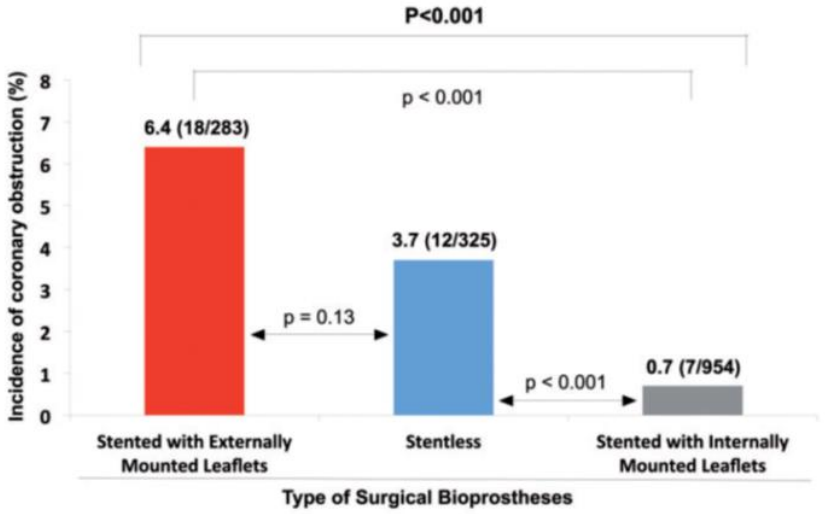
VTC and coronary obstruction post ViV



Ribeiro et al. EHJ 2018

VIVID registry: 1621 ViV cases, 37 (2.3%) coronary obstruction

	Univariable OR (95% CI)	*P*-value	Multivariable model OR (95% CI)	*P*-value
Model for the overall population (*n* = 1612)				
CABG to the left system	0.36 (0.13–1.03)	0.056	0.38 (0.13–1.09)	0.07
STS-PROM	1.03 (0.99–1.06)	0.068	1.02 (0.99–1.05)	0.21
Post-dilatation	2.05 (0.92–4.56)	0.080	1.82 (0.8–4.14)	0.15
Stented with external mounted leaflet or stentless bioprosthesis	7.07 (3.09–16.2)	<0.001	7.67 (3.14–18.7)	<0.001
Model for the computed tomography cohort (*n* = 110)				
VTC[a]	0.18 (0.08–0.39)	<0.001	0.22 (0.09–0.51)	<0.001
Sinus of Valsalva mean diameter	0.70 (0.58–0.83)	<0.001	0.95 (0.72–1.25)	0.71
Stented with external mounted leaflet or stentless bioprosthesis	4.90 (1.51–15.9)	0.008	4.30 (0.85–21.7)	0.08



Ribeiro et al. EHJ 2018

Ribeiro et al. EHJ 2018

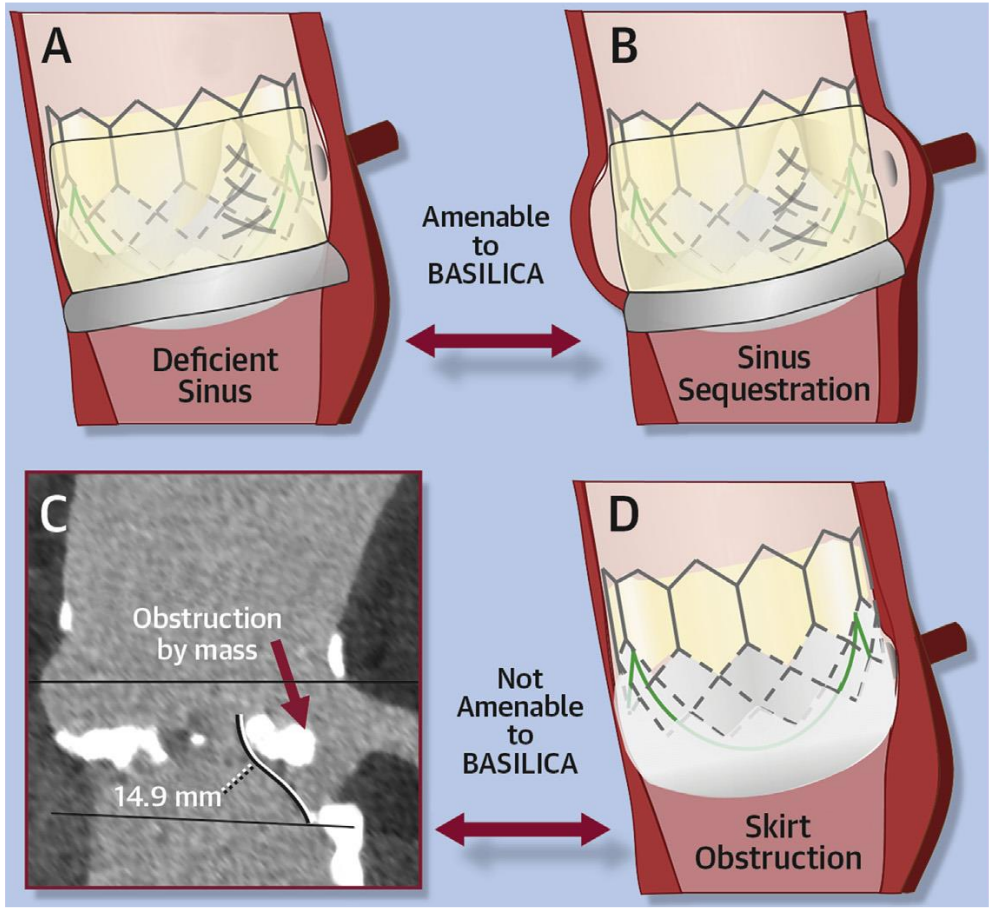
TAVR for Transcatheter Valve Failure

Considerations When Coronary Sequestration May Occur

Basilica Procedure

Amenable to BASILICA

Non- Amenable to BASILICA

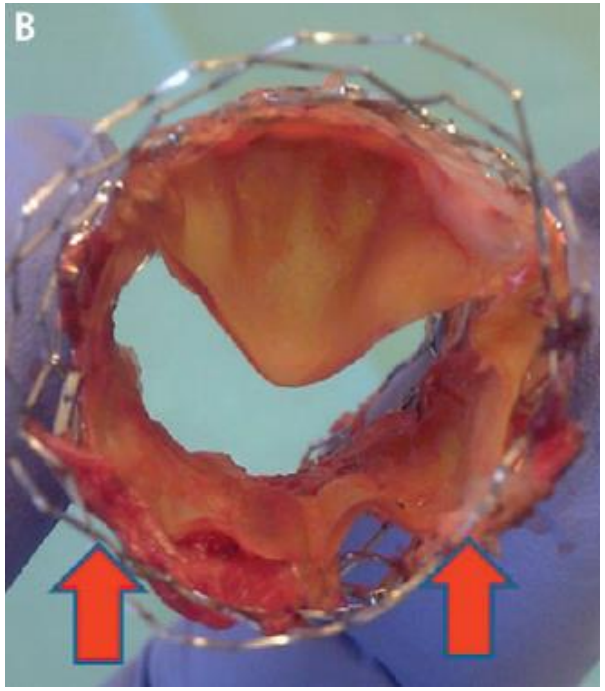


Lifetime Management

Key Concerns

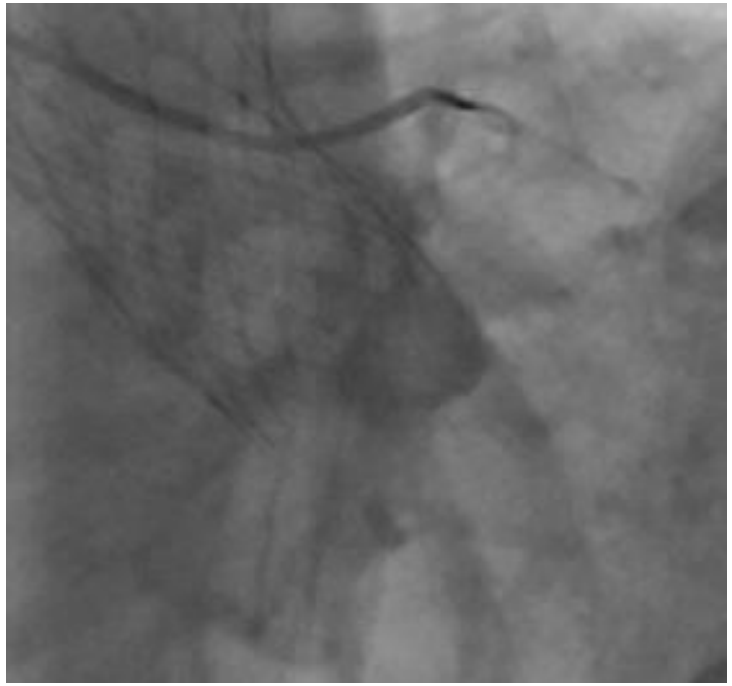
Failed TAVs

Redo TAVR or surgical revision will be required for a subset of patients

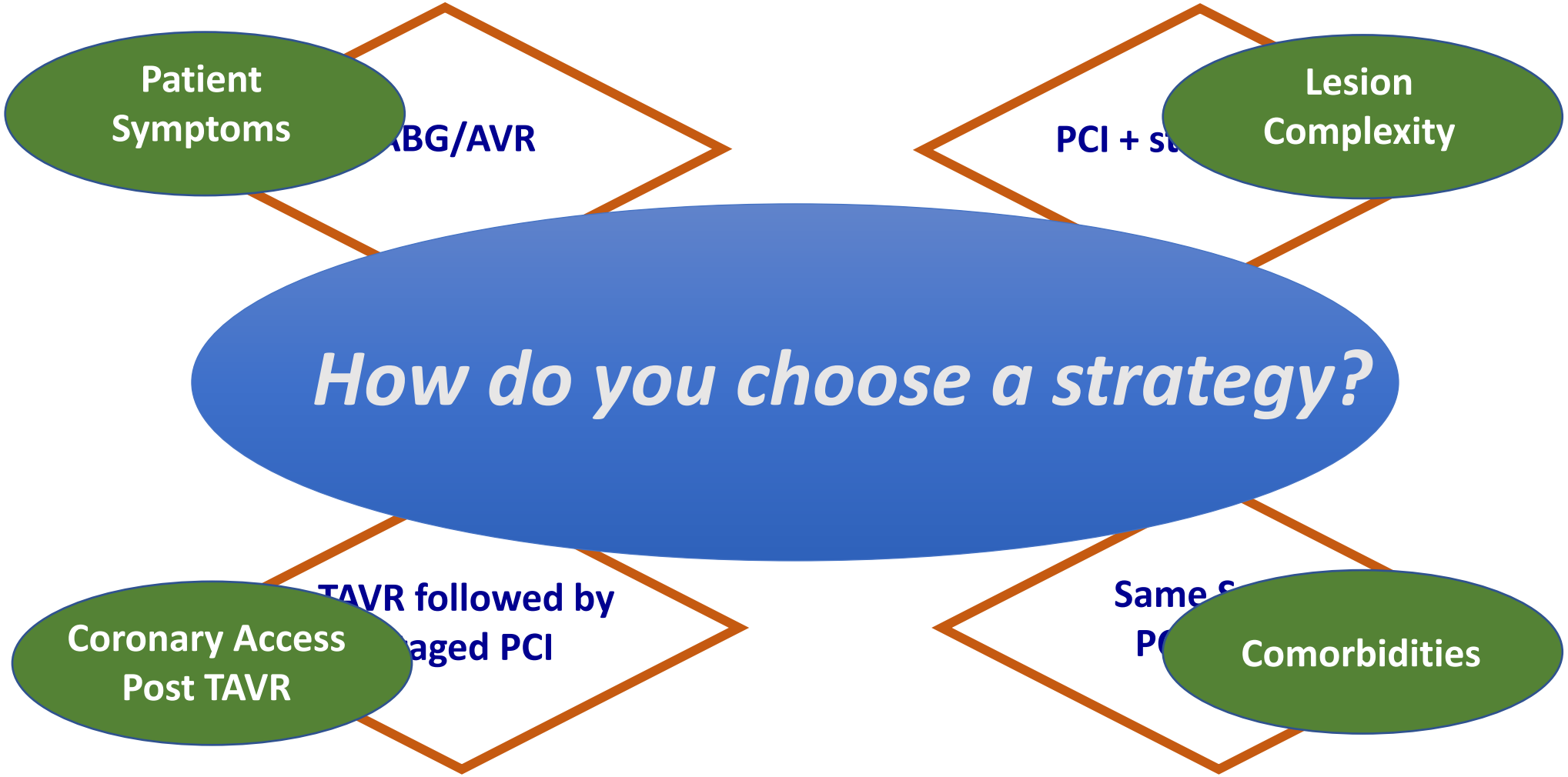


Coronary Artery Disease

Strategies to manage CAD post TAVR will be needed

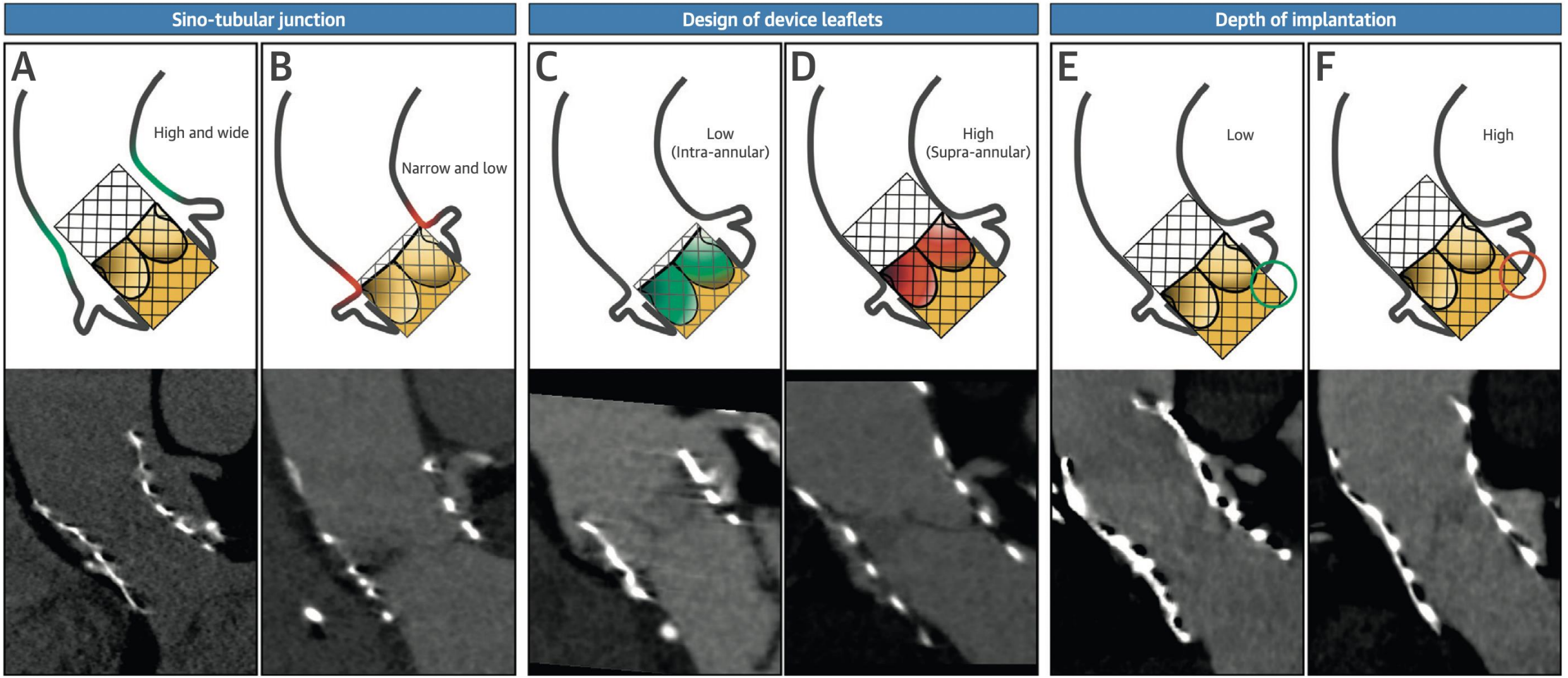


Approach to CAD in Patients undergoing TAVR



Planning for Future Coronary Access

Anatomic and Device features allowing coronary access

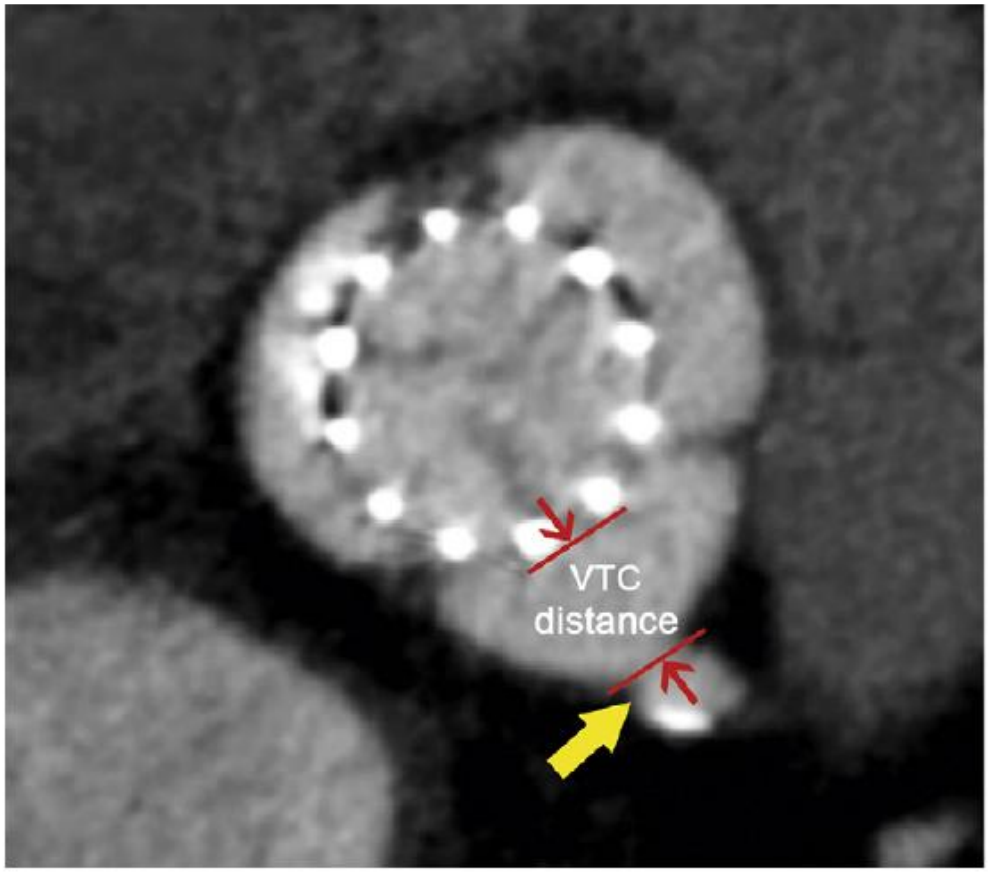


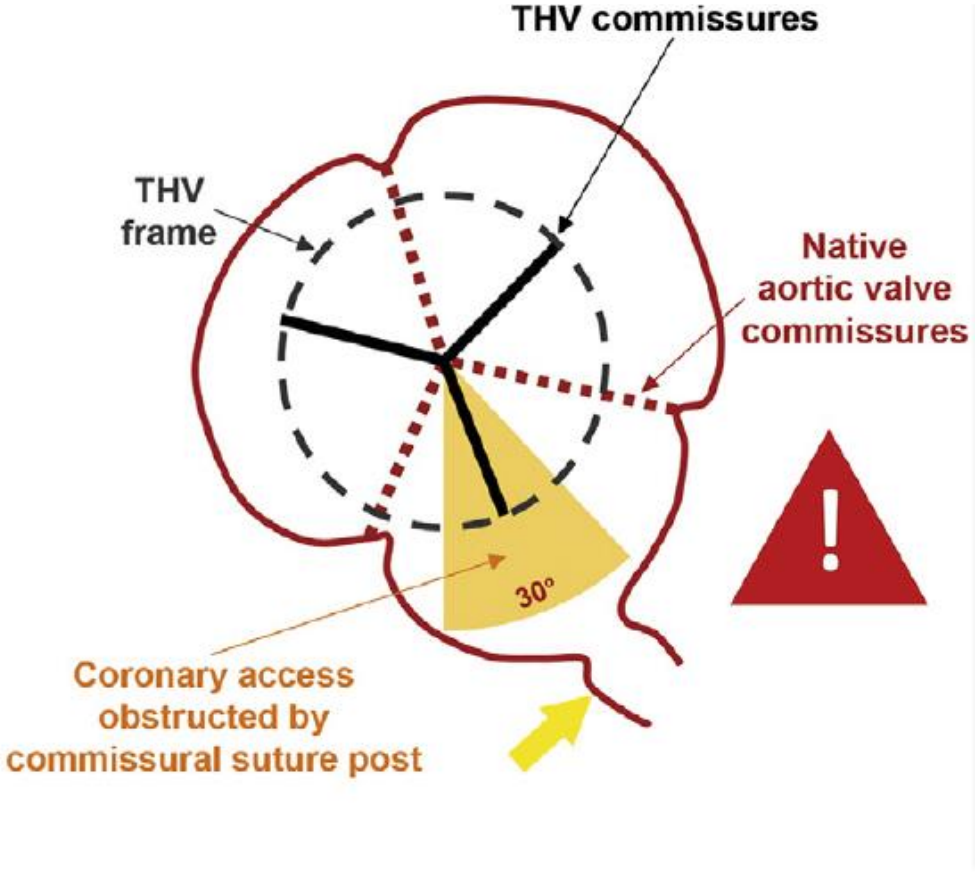
Buzzatti N et al. JACC Cardiovasc Imaging 2020;13(2 Pt 1):508–15.

Planning for Future Coronary Access

Commissural Alignment

Stent post and commissural alignment between the native aortic valve and transcatheter valve is a procedural modification that may help ease future coronary access.

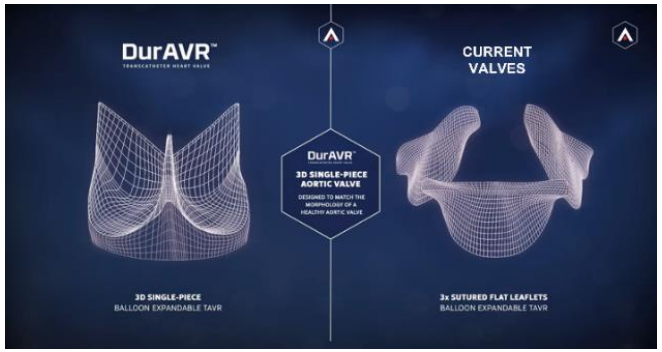


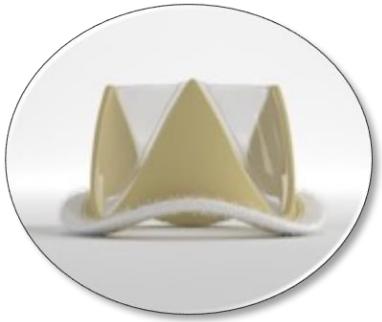


Rogers, T. et al. J Am Coll Cardiol Intv. 2020;13(6):726-35.

Bioprosthetic Valves
“The Future”

Aortic Valve Therapies: New Technologies





It's all about the leaflets and material science innovation!

- **Anteris DurAVR transcatheter valve**
  - Single piece 3D shape
- **Foldax TRIA heart valve**
  - Polymer Leaflets &Robotic Manufactoring

ALTERNATIVE VALVE DESIGNS

ANTERIS DURAVR™ BIOPROSTETHIC

DurAVR THV: A biomimetic design shaped for native performance

Native-like shaped valve

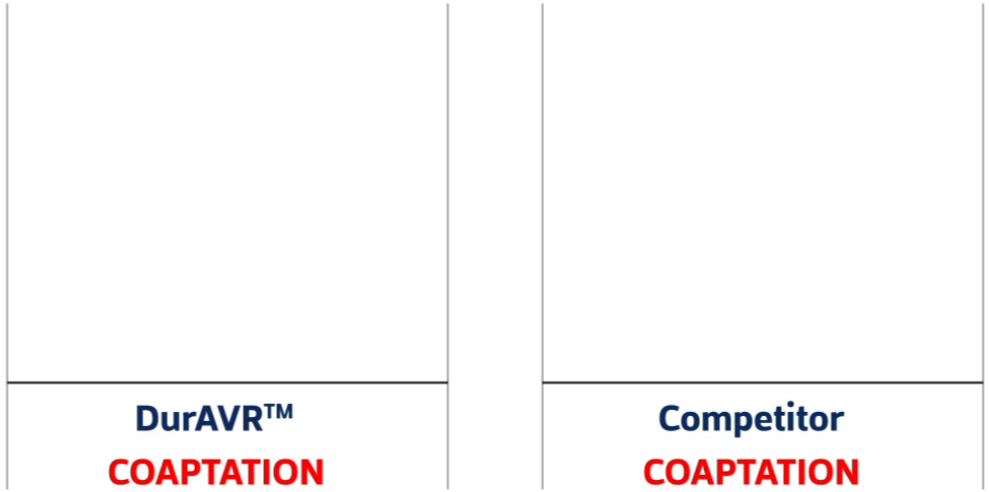
ADAPT® Anti-Calcification Tissue Engineering Process

PVL skirt

Large open cells for coronary access

Single-piece leaflet design

Balloon-expandable delivery With Commissure alignment

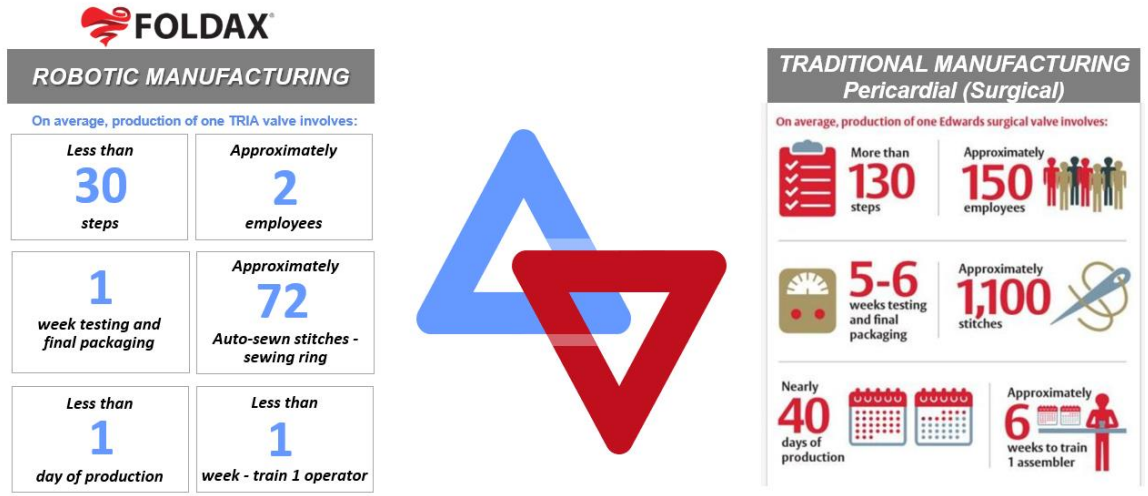


Meduri et al TCT2022 presentation

ADVANCED LEAFLET TECHNOLOGY

ROBOTIC VALVE MANUFACTURING / FOLDAX

Automated and Personalized to CT



- Superior durability
  - -No rejection, calcification
  - -Strong polymer leaflets
- Superior hemodynamics
  - -Thinner, more pliable leaflet
- No long-term anticoagulation
- Precision manufacturing
  - -complete robotic manufacturing
- Potential lifetime valve

Matched ID and Nominal Size

Valve Size	25 Inspiris	25 Tria
Stent Inside Diameter	24 mm	25 mm
Total Height	16 mm	16.5 mm
Cuff Outside Diameter	32 mm	34 mm

TAVR Prototypes

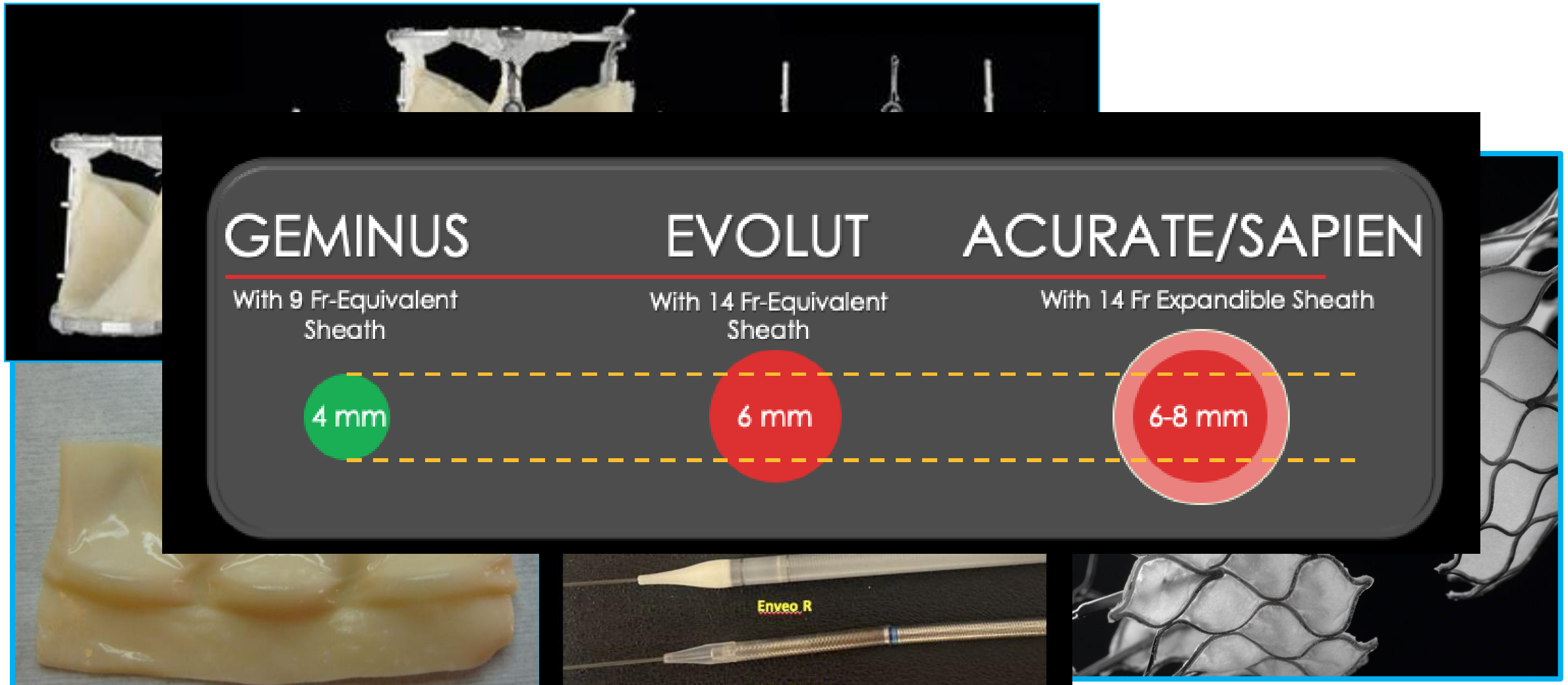
The Valve Medical Xemed™ Modular TAVR System

Valve Module

Assembled device

Anchor Module

Valve Medical ultra-low Profile Xemed TAVR System



FIH Patient #1

31/05/2023

Rabin Medical Center, Petakh-Tikva, Israel

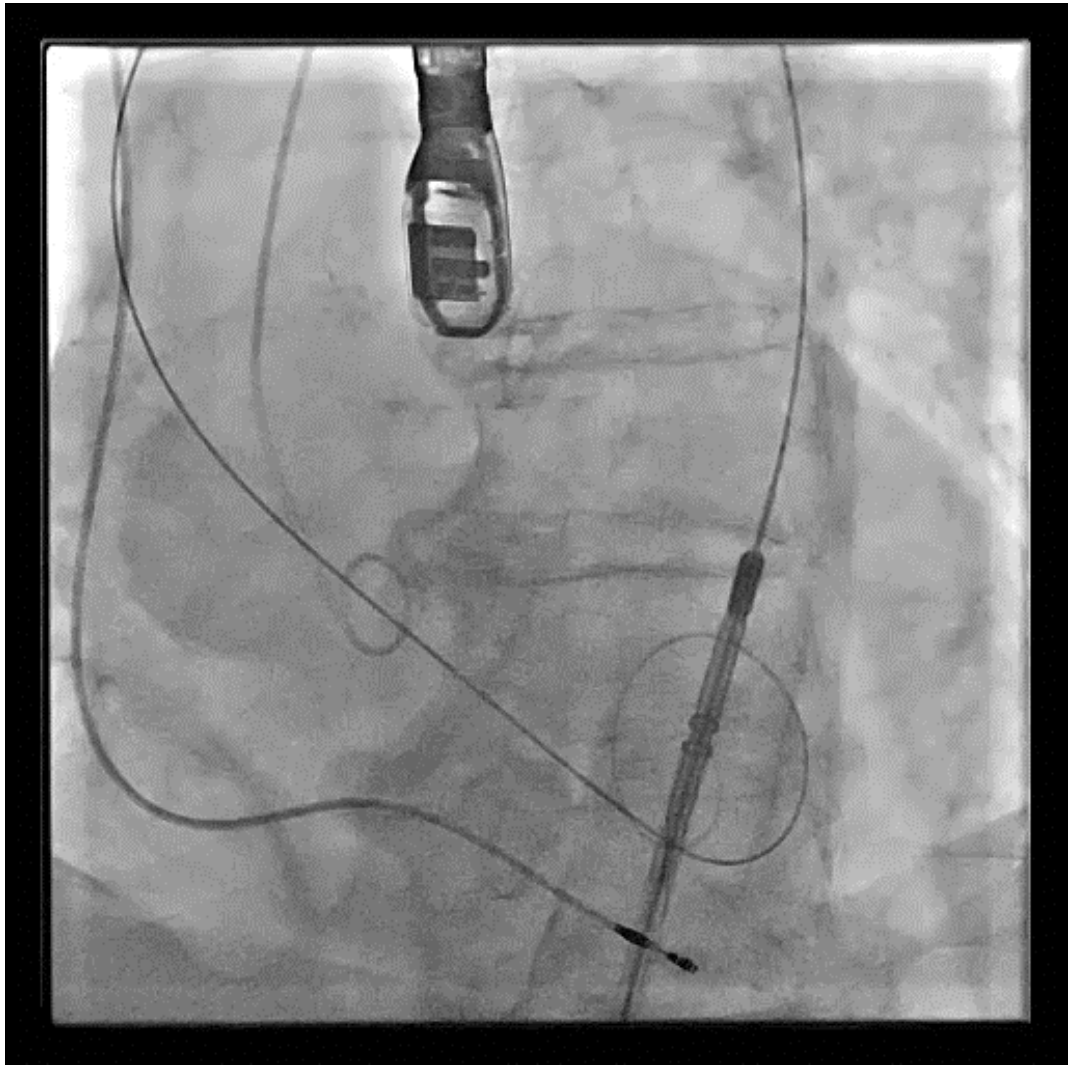
Primary Operators*:*

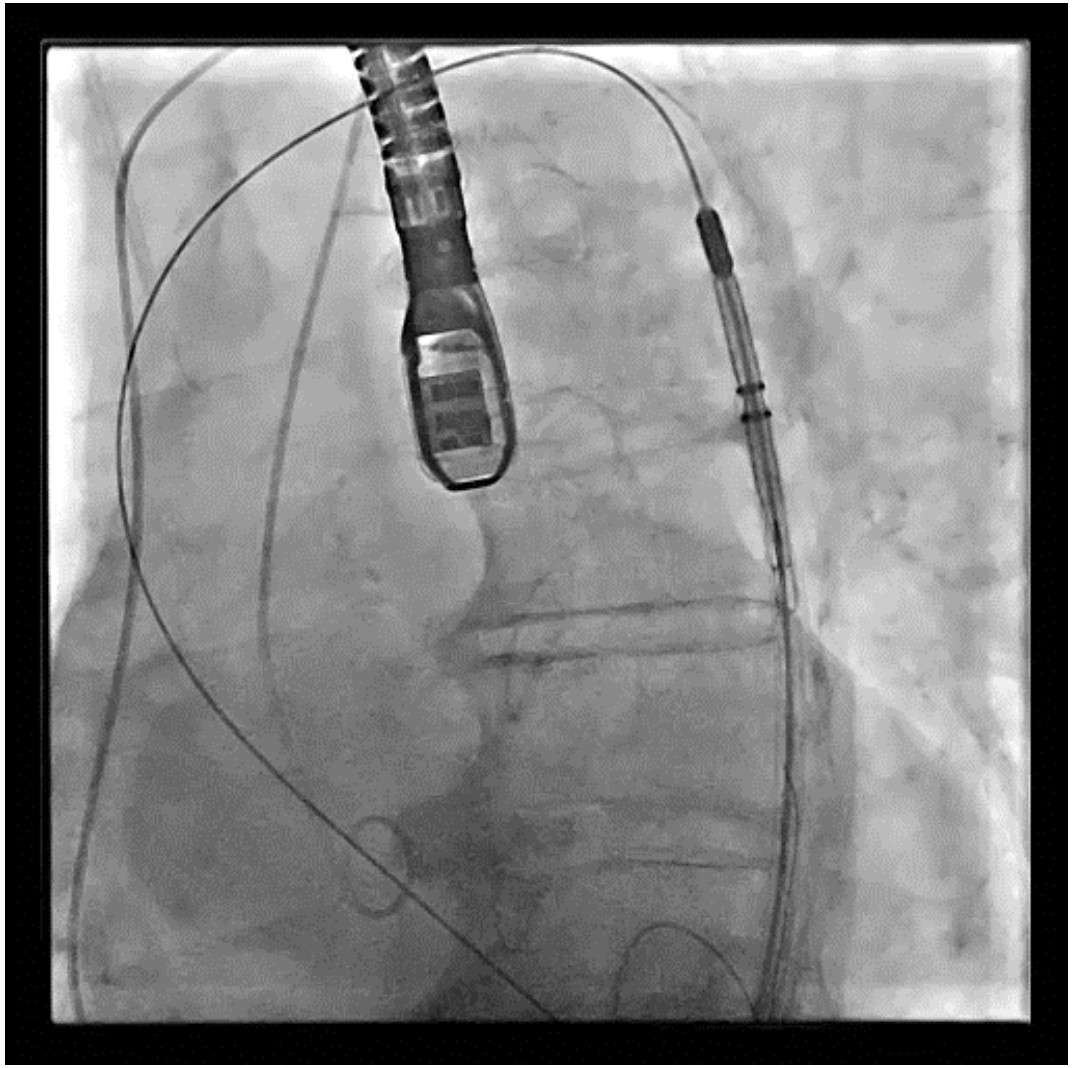
Prof. Ran Kornowski

Prof. Hana Vaknin Assa

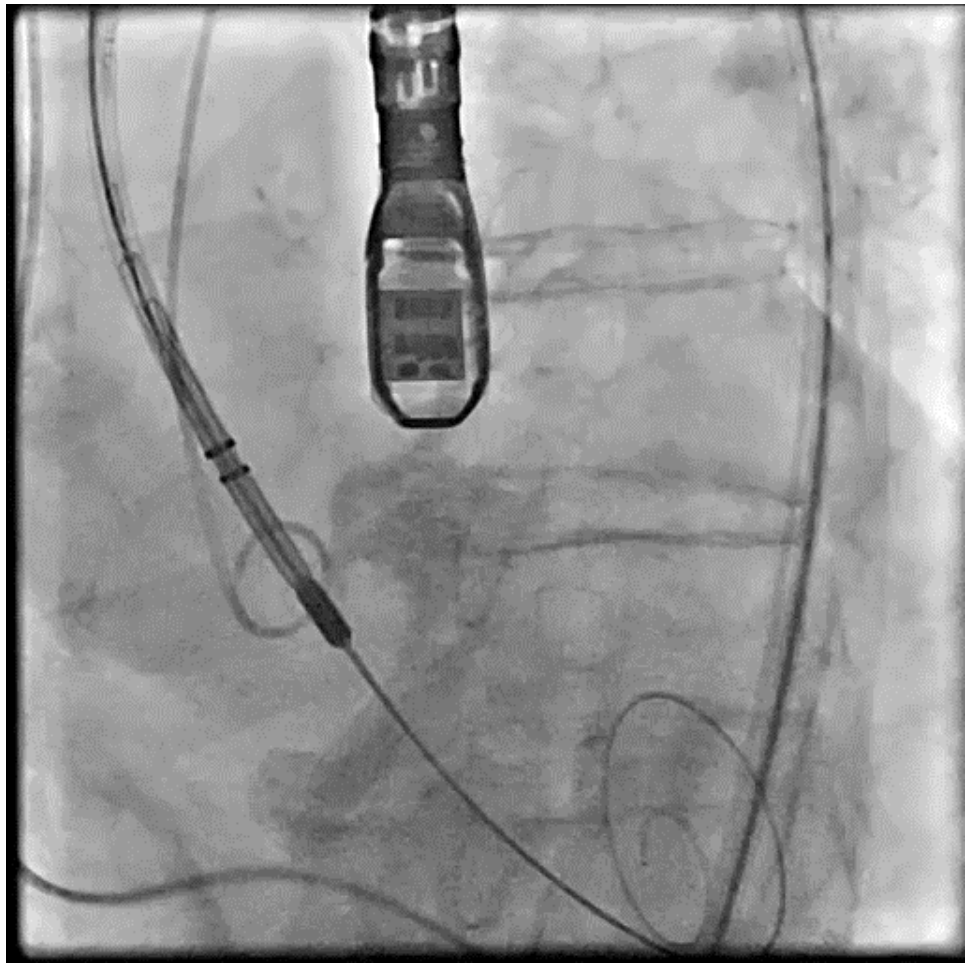
Prof. Guy Witberg

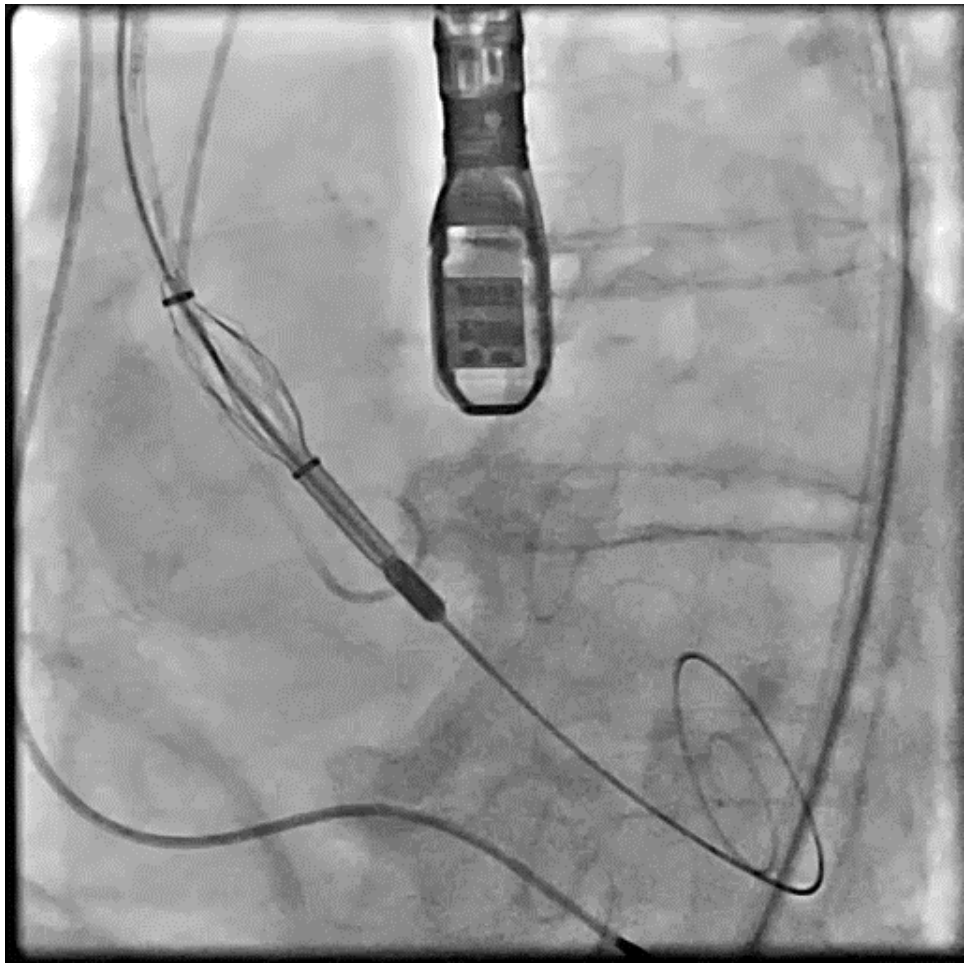
Valve Delivery



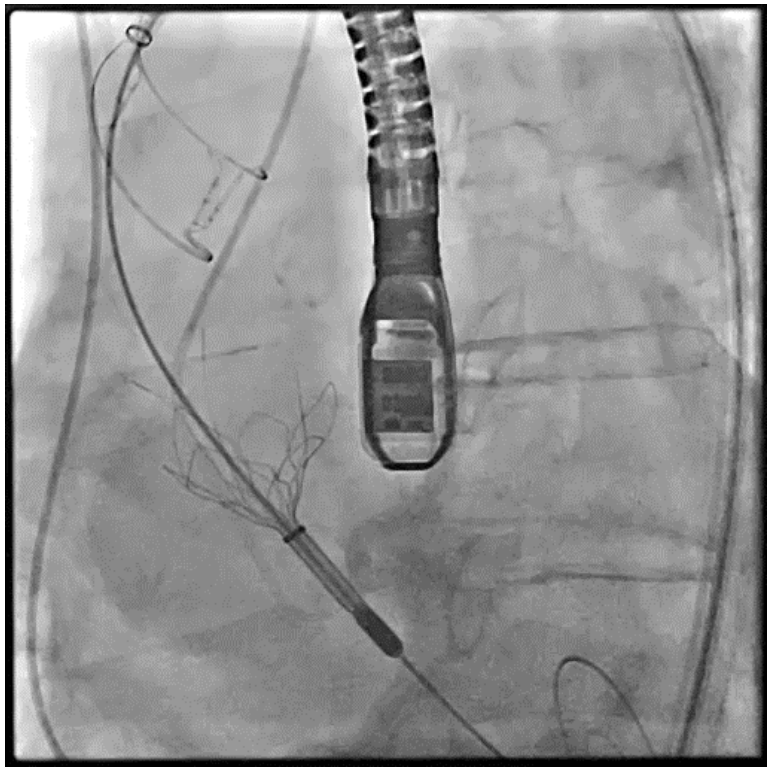


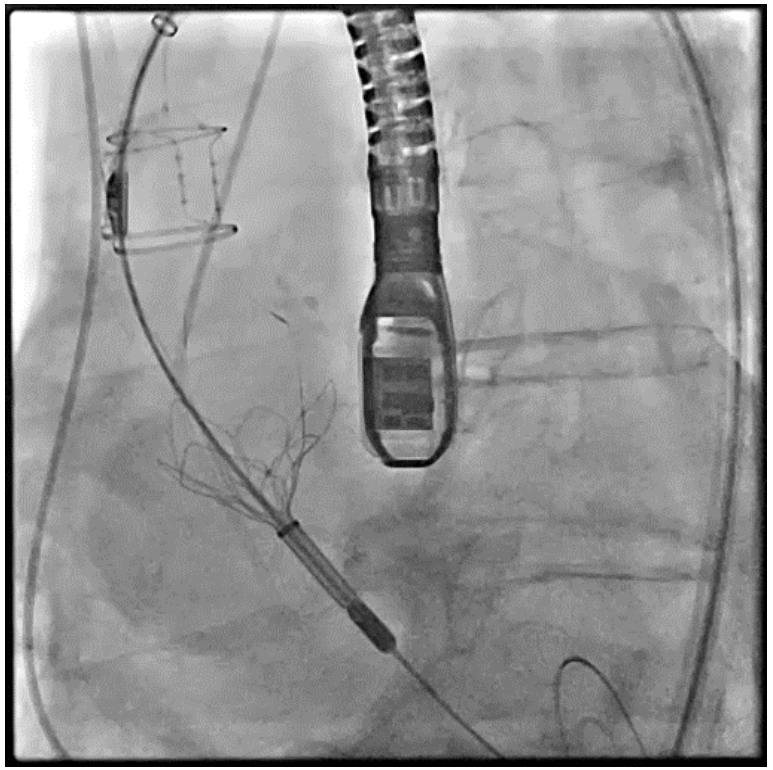
Upper Frame Deployment (Anchor module)

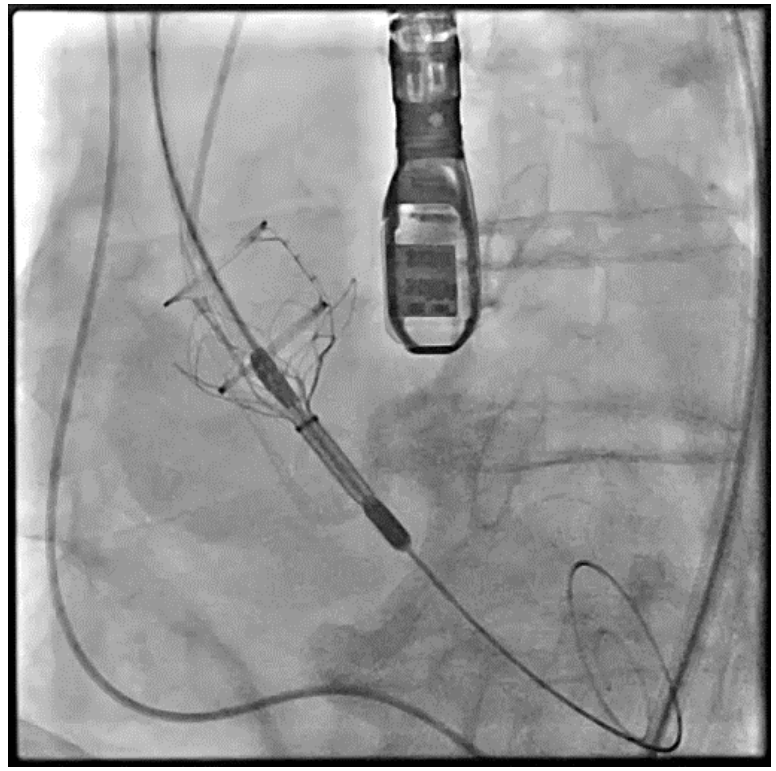




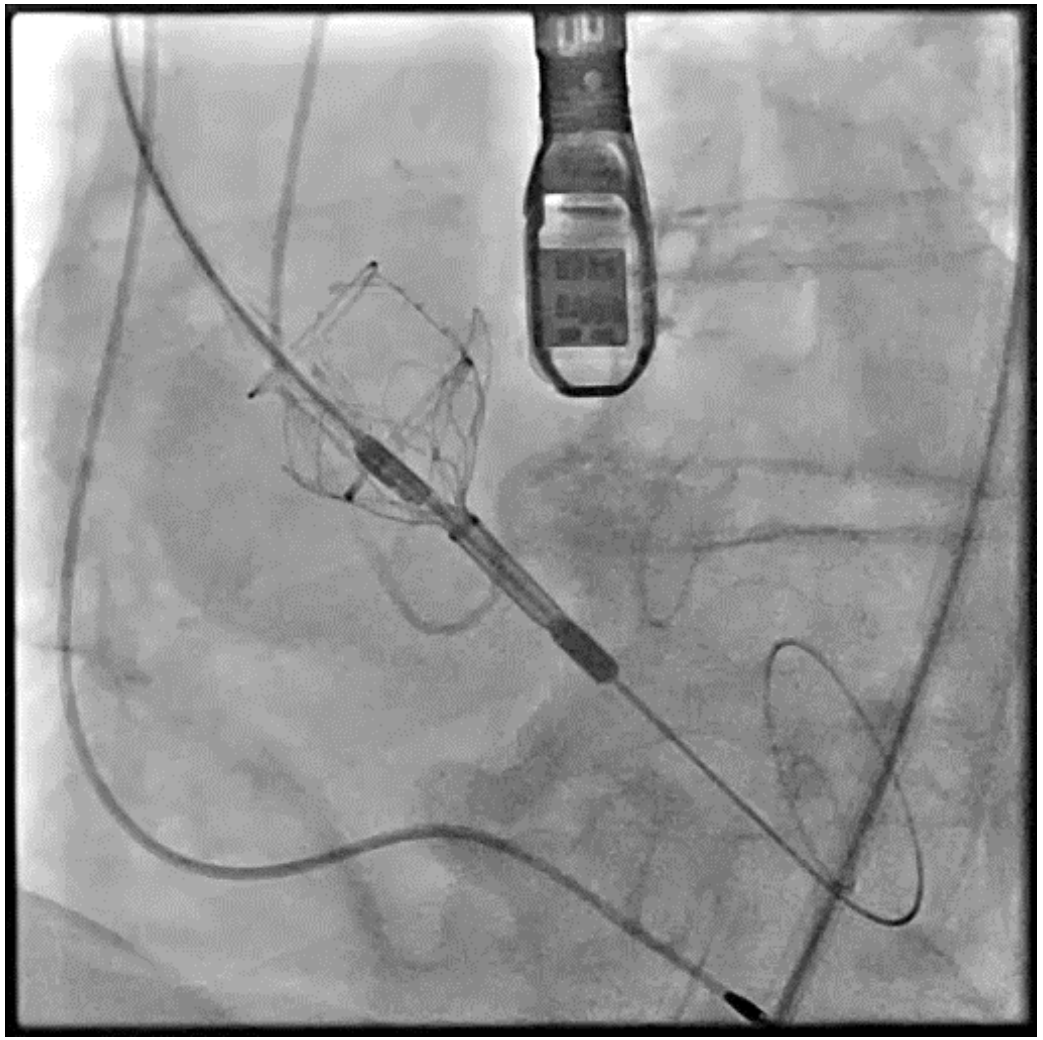
Valve Module Pre-Docking

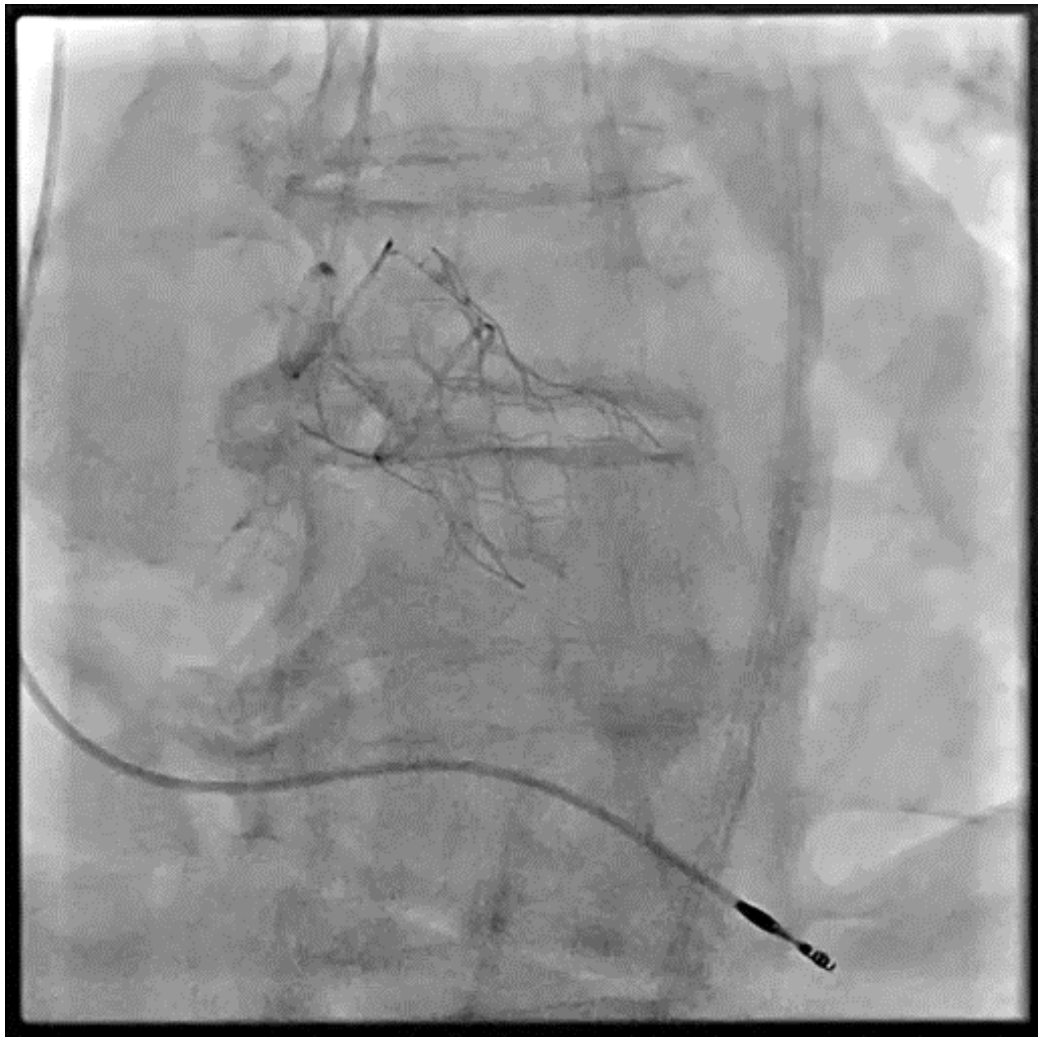






Implantation





Ran Kornowski and Team, Rabin Medical Center

The Evolution of Heart Valves

The promise…

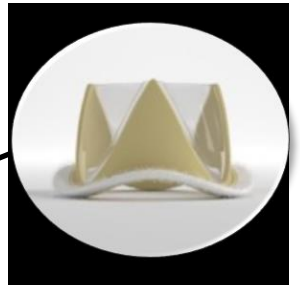
Non living

Mechanical valves

Bioprosthetic valves

Synthetic permanent Polymer

1960



One valve for life!

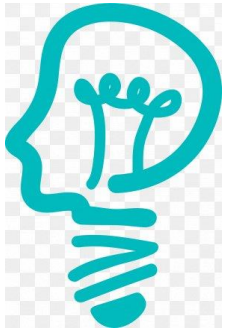
Living

2020

Regenerative material/tissue engineered valve

Finally,
What can we learn from the TAVR Success to future Trends in Structural Heart Disease?

- **Interventional Cardiology has been driven by technology innovations and by better understanding the CV diseases.**
- **It is the individuals with strong conviction, vision, risk taking and resilience, teaming with technology innovators who have been driving forward new therapies and challenging the IC community with out-of-the-box ideas.**




THANK YOU AND
BE SAFE!