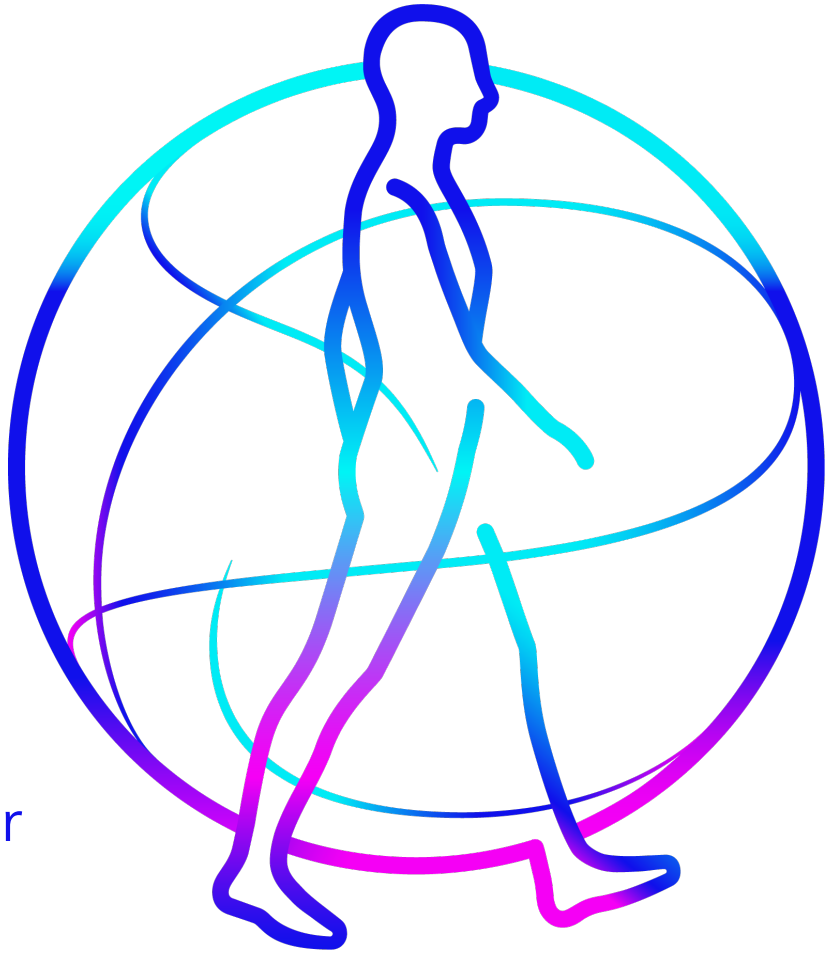
Medtronic
Engineering the extraordinary

WELCOME

Bioprosthetic Valve Dysfunction
A closer look



Featuring:

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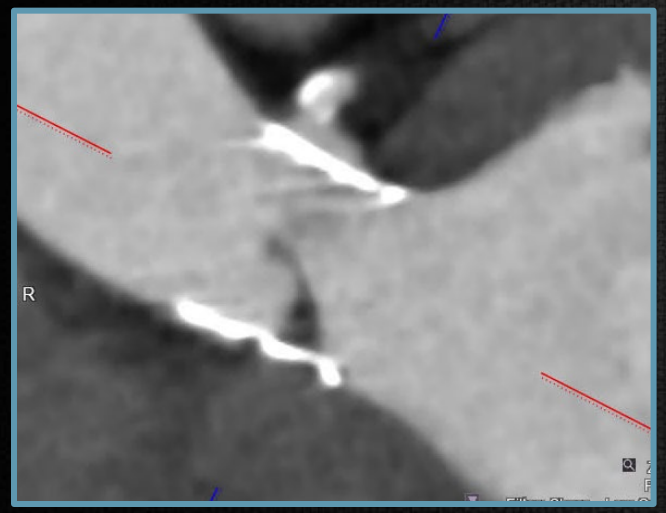
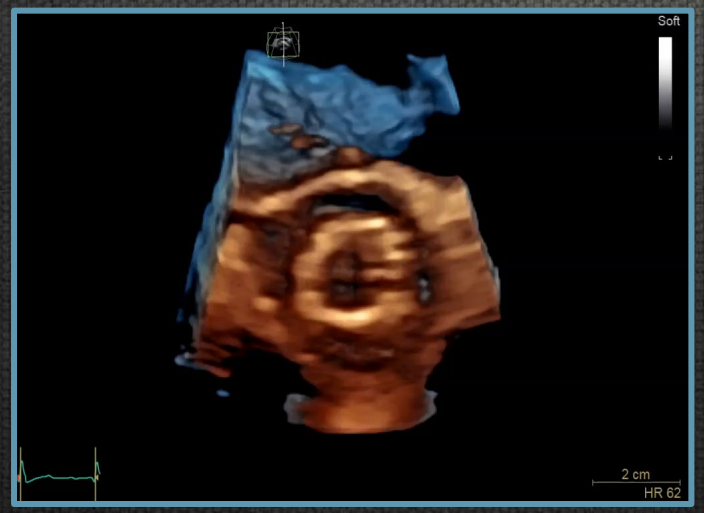
UC202406043 EN October 2023

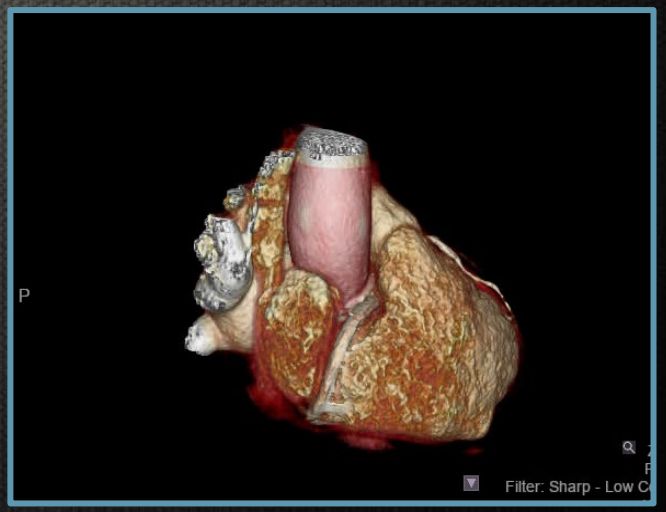
Originally Recorded Thursday, September 14th 6:00 p.m. CST

Bioprosthetic Valve Dysfunction

Webinar







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(VARC) Valve Academic Research Consortium

Collection of TAVR data from multiple sources and research trials

- GOAL: Standardize definitions of aortic valve replacements
- VARC 2011, VARC-2 2012, VARC-3 2021

GOAL of VARC-3 Update

- Define secondary endpoints for long term outcomes with patient-centric focus
  - Rehospitalization
  - Bioprosthetic valve dysfunction and failure
    - Stages of deterioration
    - Leaflet thickening and reduced motion
    - Valve thrombus
  - Patient reported outcomes

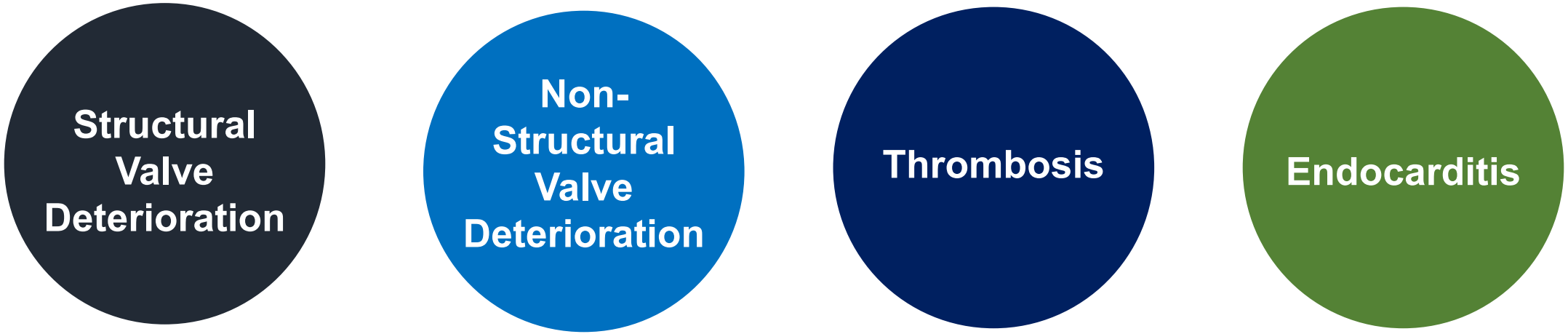
Bioprosthetic Valve Dysfunction

Definitions

Bioprosthetic Valve Dysfunction

- Structural Valve Deterioration
- Non-Structural Valve Deterioration
- Endocarditis
- Thrombosis

Staging of Bioprosthetic Valve Dysfunction



Stages of Deterioration

STAGE 1
Morphological valve deterioration

Evidence of structural valve deterioration, non-structural valve dysfunction (other than Paravalvular regurgitation or prothesis-patient mismatch) , thrombosis, or endocarditis without significant hemodynamic changes.

STAGE 2
Moderate hemodynamic deterioration

Increase in mean transvalvular gradient ≥ 10 mmHg resulting in mean gradient ≥ 20mmHg with concomitant decrease in EOA ≥0.3 cm² or ≥ 25% and/or decrease in Doppler velocity index > 0.1 or ≥ 20% compared to echo assessment performed 1 to 3 months post-procedure.

Or

New occurrence or increase of ≥1 grade of intraprosthetic AR resulting in ≥ moderate AR

STAGE 3
Severe hemodynamic deterioration

Increase in mean transvalvular gradient ≥ 20 mmHg resulting in mean gradient ≥ 30mmHg with concomitant decrease in EOA ≥0.6 cm² or ≥ 50% and/or decrease in Doppler velocity index > 0.2 or ≥ 40% compared to echo assessment performed 1 to 3 months post-procedure.

Or

New occurrence or increase of ≥2 grade of intraprosthetic AR resulting in ≥ moderate AR

Genereux P, et al. Valve Academic Research Consortium 3: Updated Endpoint Definitions for Aortic Valve Clinical Research. *JACC*. 2021;77(21):2717-2746.

ECHO – INITIAL MODALITY OF CHOICE

ACC GUIDELINES

- TAVR:
  - 30 DAY TTE
  - ANNUAL TTE
- SAVR:
  - BASELINE TTE
  - 5 YEAR TTE
  - 10 YEAR TTE
  - ANNUALLY

VARC-3 TAVR AND SAVR

- BASELINE TTE
- ANNUAL TTE

Imaging Evaluation of Prosthetic Valve Dysfunction

2D TTE

First line Imaging

(+) Hemodynamics

(+) Leaflet motion

Limited for morphological Evaluation

Acoustic Shadowing

Other Limitations: Body Habitus, Emphysema, Pericardial Effusion

Better for Mitral > Aortic

TEE/3D TEE

Superior to 2D TTE for id PV dysfunction

3D TEE Can Differentiate between vegetation vs pannus

Cinefluoroscopy

limited to mechanical valves

Cardiac CTA

3D with excellent spatial resolution

Enables anatomic and leaflet motion assessment

Can differentiate between pannus and thrombus

Cardiac CMR

Limited by artifacts

Hemodynamic assessment of Regurgitation

Know Your Data!

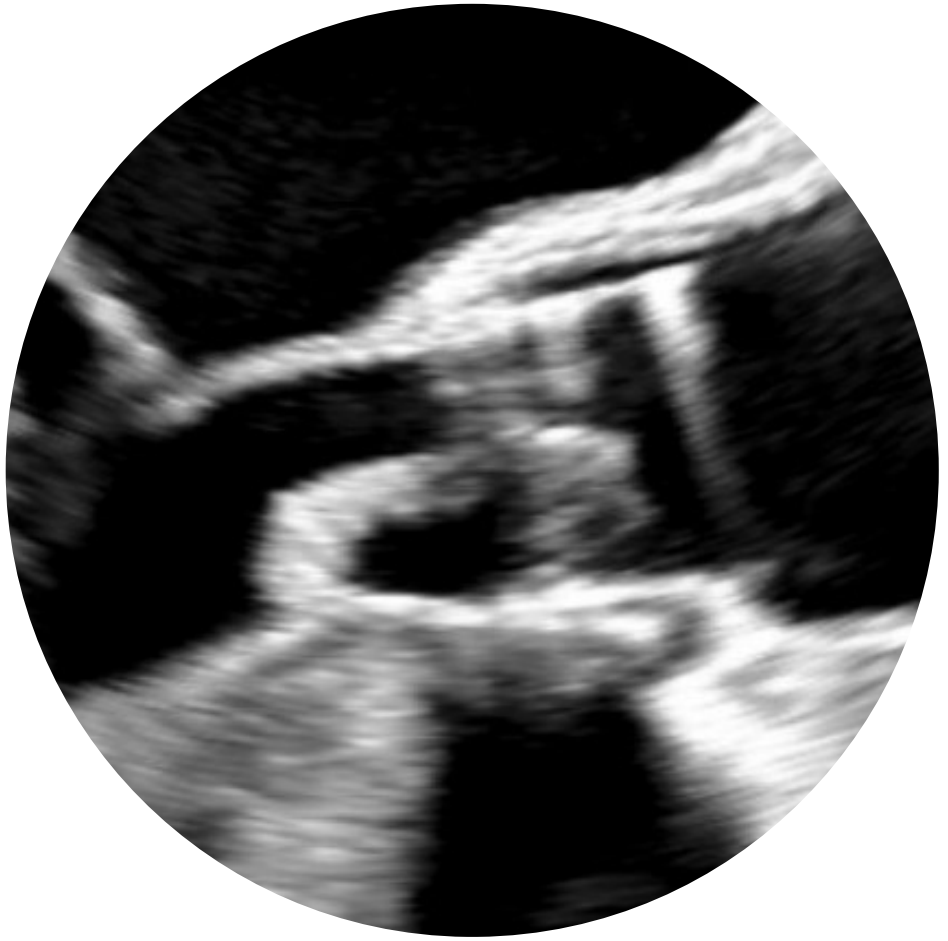
- TVT mandates a 30 day and 1 year TTE
- Valve Team should be evaluating this data
  - Monitor for changes early
  - If mean gradient is increasing → investigate!
    - CT heart structure → eval for HALT
    - TEE
    - Oral anticoagulation
    - Repeat TTE 3-6 month
- Lifetime planning for TAVR valve aging

Types of Prosthetic Valve Dysfunction

Endocarditis

Prosthetic Valve Endocarditis

- Key Features:
  - Recent infection (or procedure)
    - Fevers, rigors, leukocytosis
    - Bacteremia
  - Septic emboli → abscesses
  - Can happen at any time
  - AI > AS
- TEE test of choice, ID and CV surgery consult



HALT / Thrombus

Acronyms & Definitions

HALT (Hypo-Attenuated Leaflet Thickening)

- “Subclinical leaflet thickening”

RLM (Restricted Leaflet Motion)

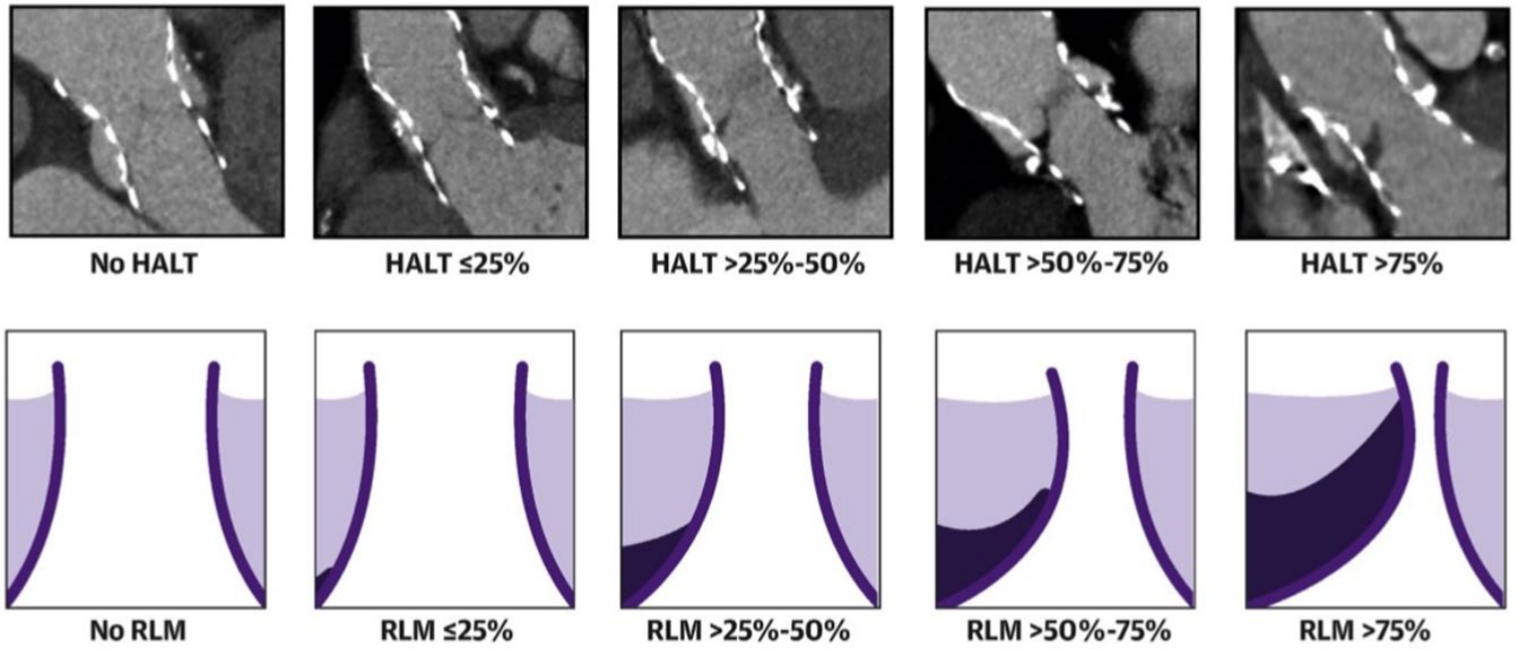
- Or HAM (hypoattenuation affecting motion) if > 50%

Clinical Thrombus

1. Clinical event from thrombus (TIA, CVA…) + HALT
2. Worsening valve deterioration Stage III + HALT
   - VARC3: Increase in mG by 20mmHg leading to a mG > 30mmHg AND decrease in EOA > 0.6cm2 AND/OR decrease in velocity index by > 40% compared to postoperative ECHO

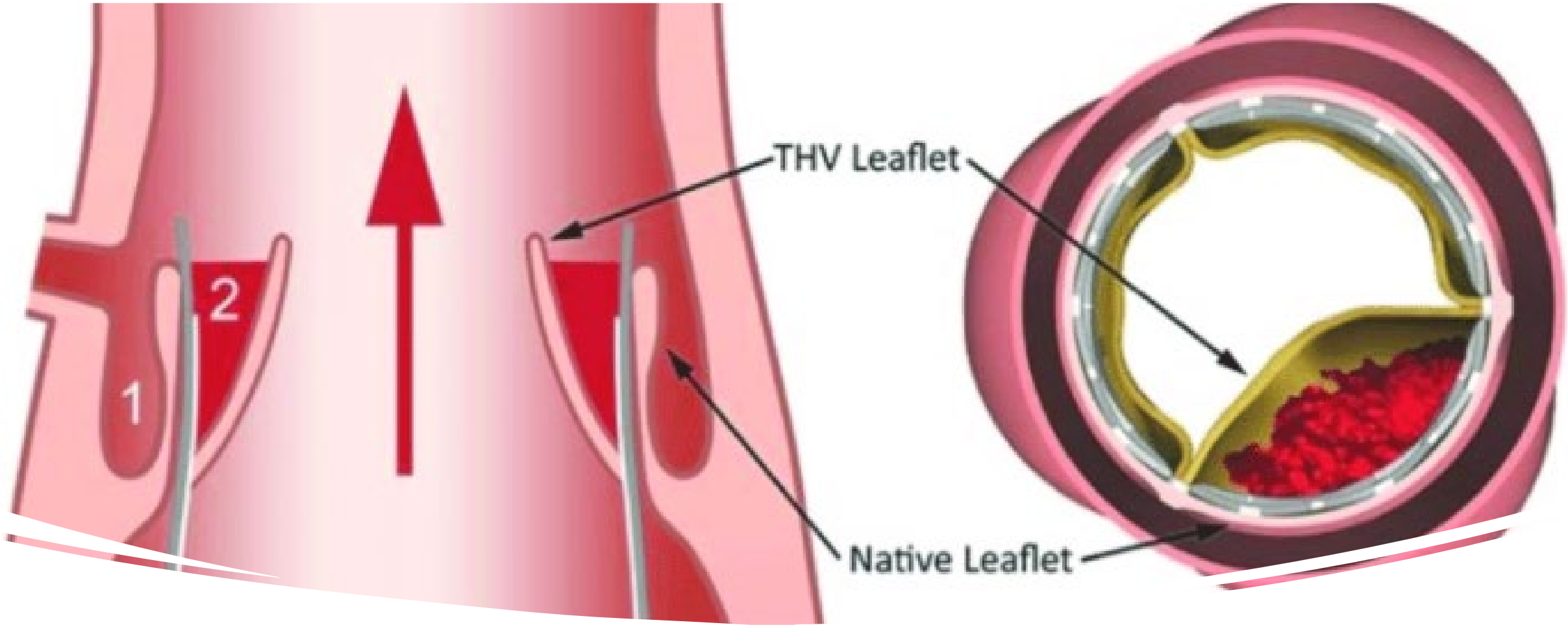
HALT

- CT Scan is Test of Choice (can also see on TEE)
  - Usually in “meniscal” pattern
  - Thick at base and thinner at coaptation points



RISK FACTORS for HALT

- Under expansion of Valve Stent
- Larger neo-sinuses or large prosthesis
- Men
- Intra-annular > Supra-annular valves
- Paravalvular Regurgitation
- Patient Co-Morbidities
  - CKD, DMII, CHF, AF, chronic anemia, tobacco abuse…



Neo-Sinus

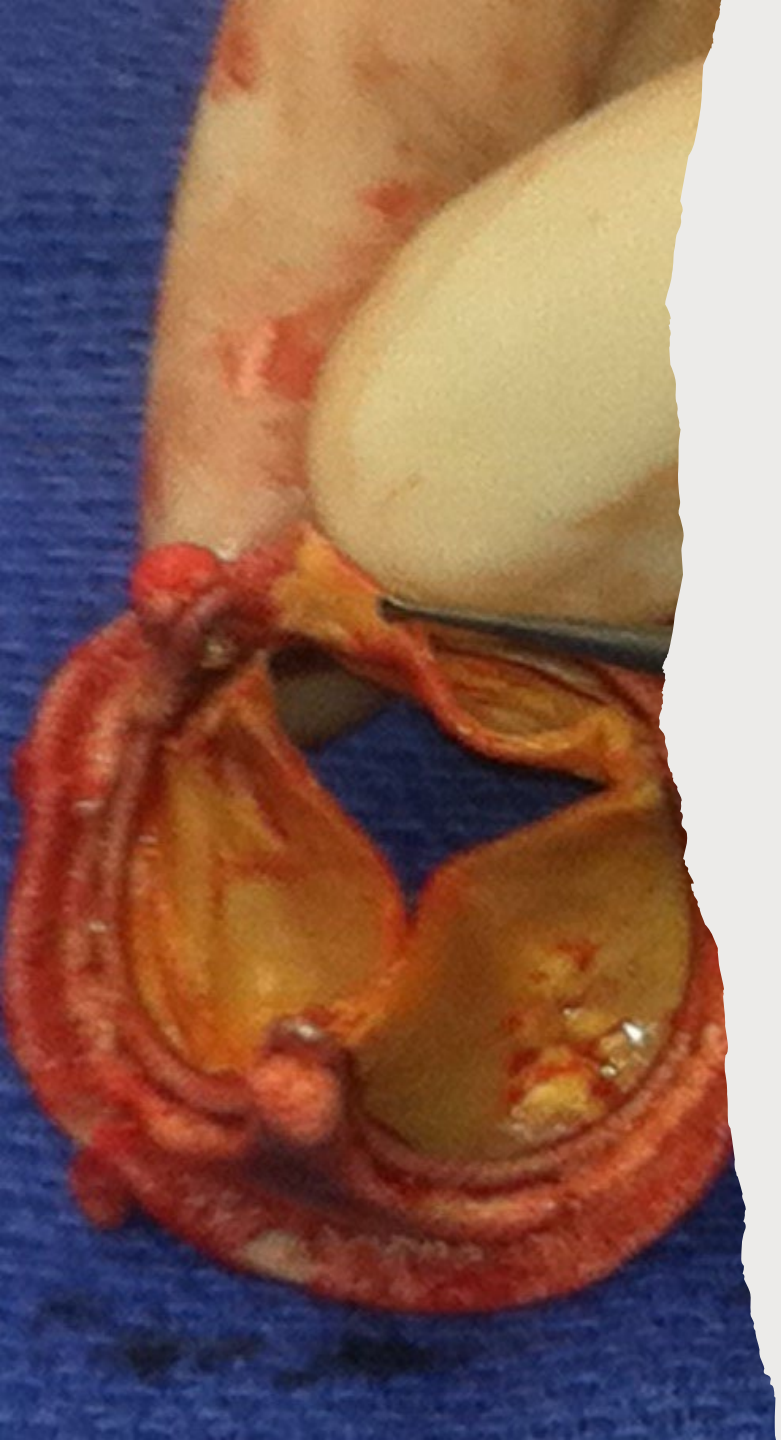
Source: Midha P., et al. The Fluid Mechanics of Transcatheter Heart Valve Leaflet Thrombosis in the Neosinus. Circulation. 24 October 2017

Structural Valve Deterioration (SVD)

Structural Valve Degeneration (SVD)

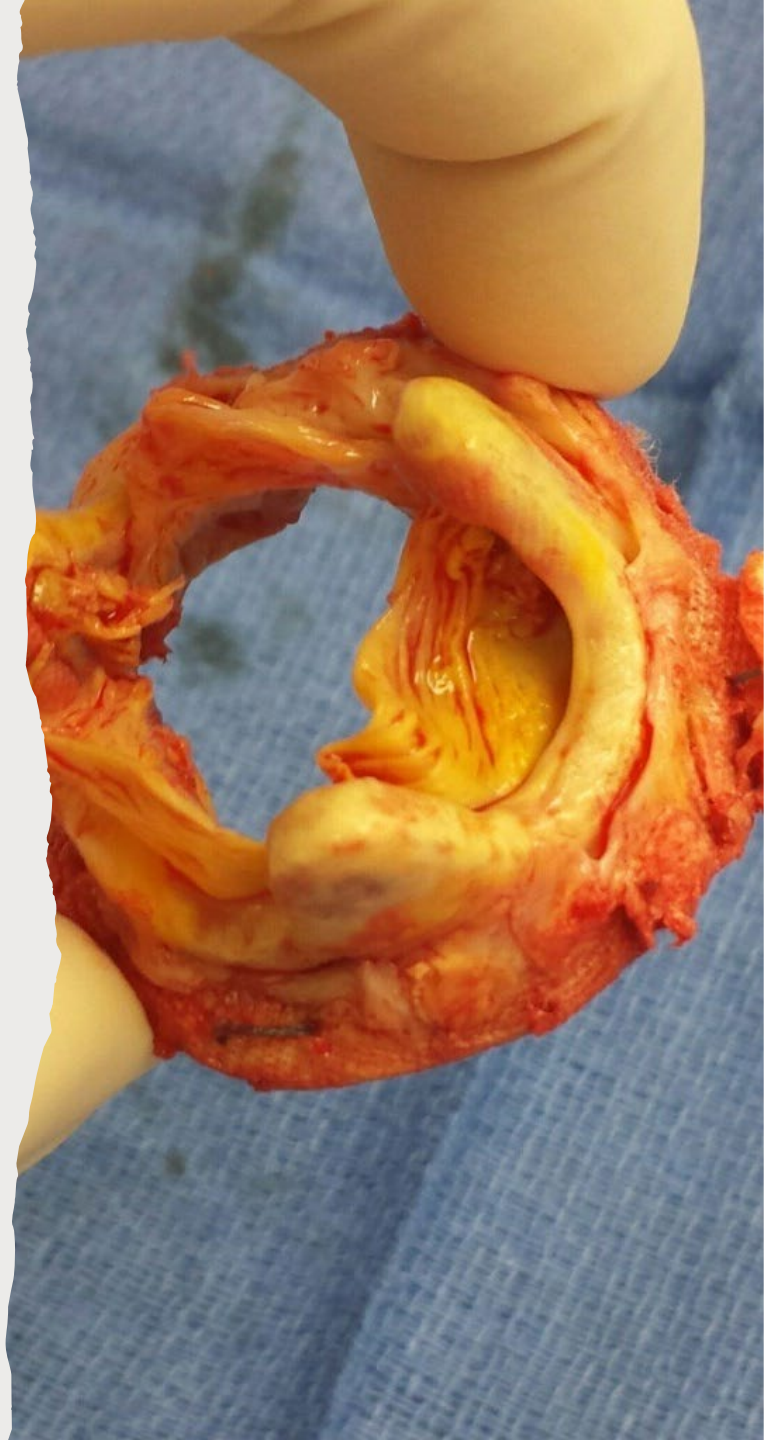
- Irreversible changes to the valve

- Effects on the structure of the valve
  - Torn leaflets
  - Calcifications
  - Strut deformation



Structural Valve Degeneration

- Older valve (8+ years)
- AI / AS or mixed
- Calcified leaflets
- Torn leaflets



Non Structural Valve Deterioration (NSVD)

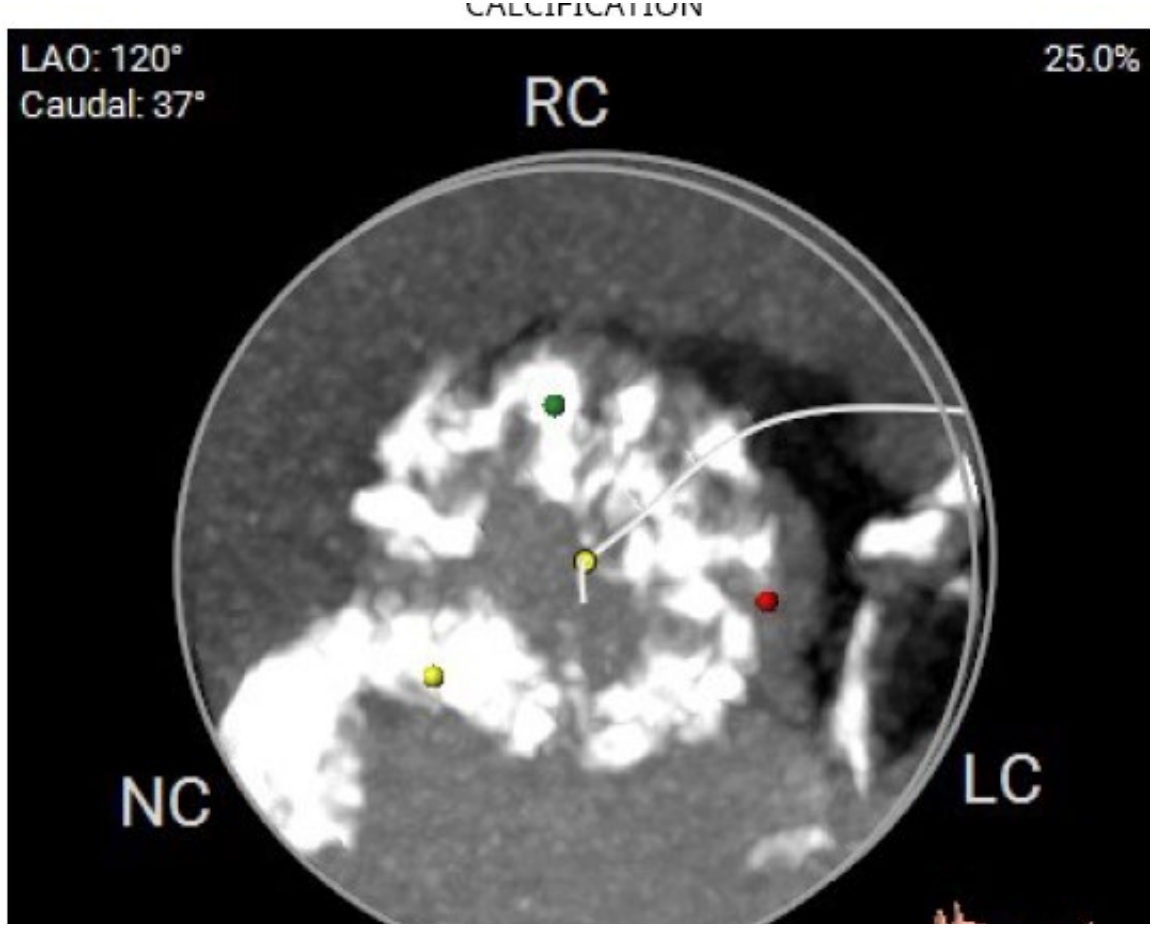
Non-Structural Valve Degeneration (NSVD)

- Valve is normal, other issues causing valve to ‘malfunction’
  - Paravalvular leak (PVL)
  - Patient Prosthesis Mismatch (PPM)
  - Poor placement / embolization
  - Leaflet entrapment (pannus / suture)

Non-Structural Valve Degeneration (NSVD)

- Poorly expanded TAVR
- Malpositioned valve
- PPM : Small annulus / Large patient

- Look for:
  - AS or AI
  - Higher gradients immediately post op
  - Restricted leaflet motion
  - Non-circular valve or deeply implanted valve



Patient Prosthesis Mismatch

Definition, Management, Diagnosis

Patient Prosthesis Mismatch (PPM)

- EOA of valve is too small for body size
- Predict by using Hemodynamic Reference Values (Available for all valve types)

- Presentation:
  - Higher gradients immediately post op
  - Seen in Morbidly obese or small annular size patient
  - Valve leaflets functioning normally
  - Seen in valve-in-valve more commonly than native

- Why is it important:
  - Less LV remodeling
  - More CHF events
  - Higher rates of MI, CVA and death

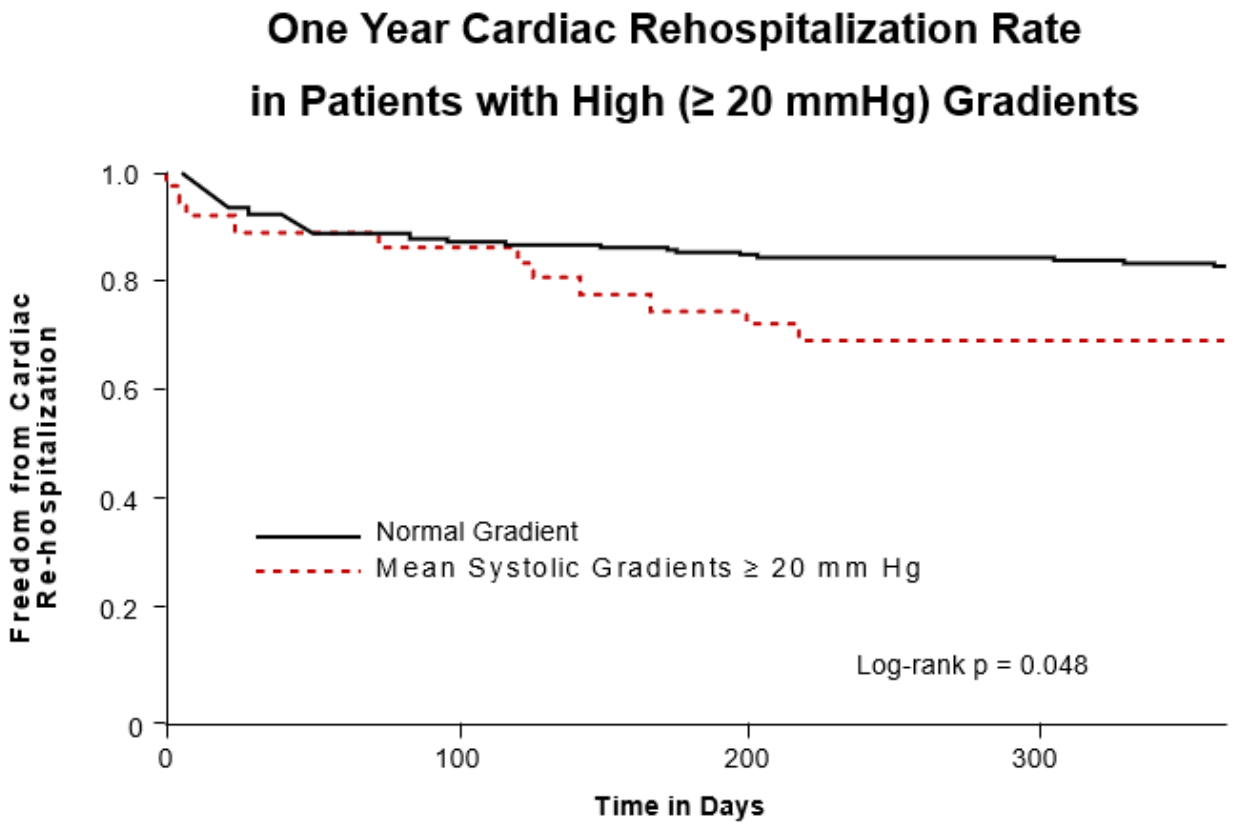
Patient Prosthesis Mismatch (PPM)

- High (> 20 mmHg) mean gradients and/or residual patient prosthetic mismatch are associated with:
  - More frequent rehospitalizations at 1 year
  - Higher late mortality
    - Severe PPM associated with 1 year mortality in SE and BE TAVR

High Gradients & Rehospitalization

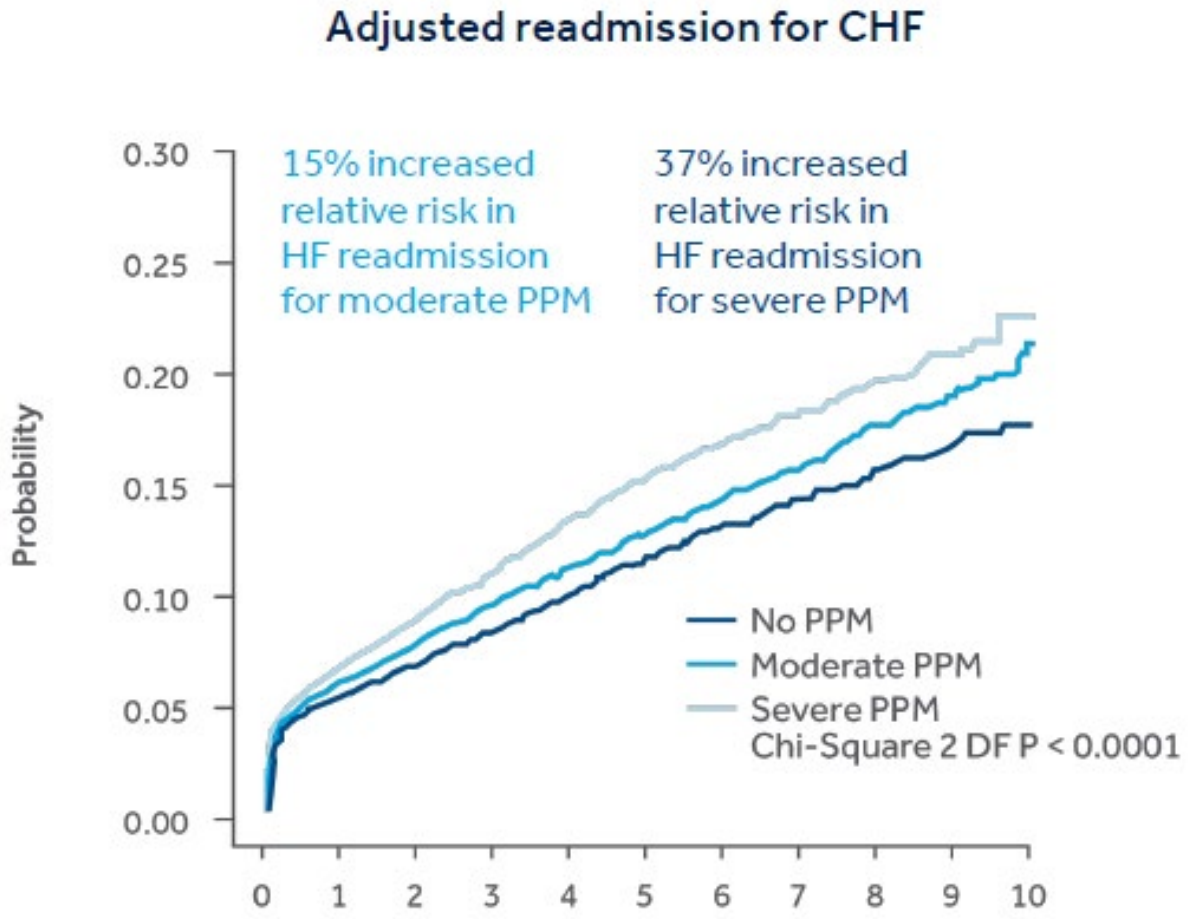
Baseline Characteristics

	Mean Systolic Gradient ≥ 20 mm Hg (n = 36)	Normal Gradient (n = 388)	p-value
Age, mean ± SD (years)	77.8 ± 7.8	81.0 ± 8.2	0.02
Women	19 (53%)	158 (41%)	0.16
BMI, mean ± SD (kg/m^2)	33.2 ± 9.2	29.6 ± 6.6	0.03
Hypertensive	32 (89%)	348 (90%)	0.88
Valve Size			
20 mm	2 (5%)	1 (0.3%)	< 0.0001
23 mm	16 (46%)	91 (24%)	
26 mm	16 (46%)	190 (50%)	
29 mm	0 (0%)	59 (16%)	
31 mm	1 (3%)	36 (10%)	



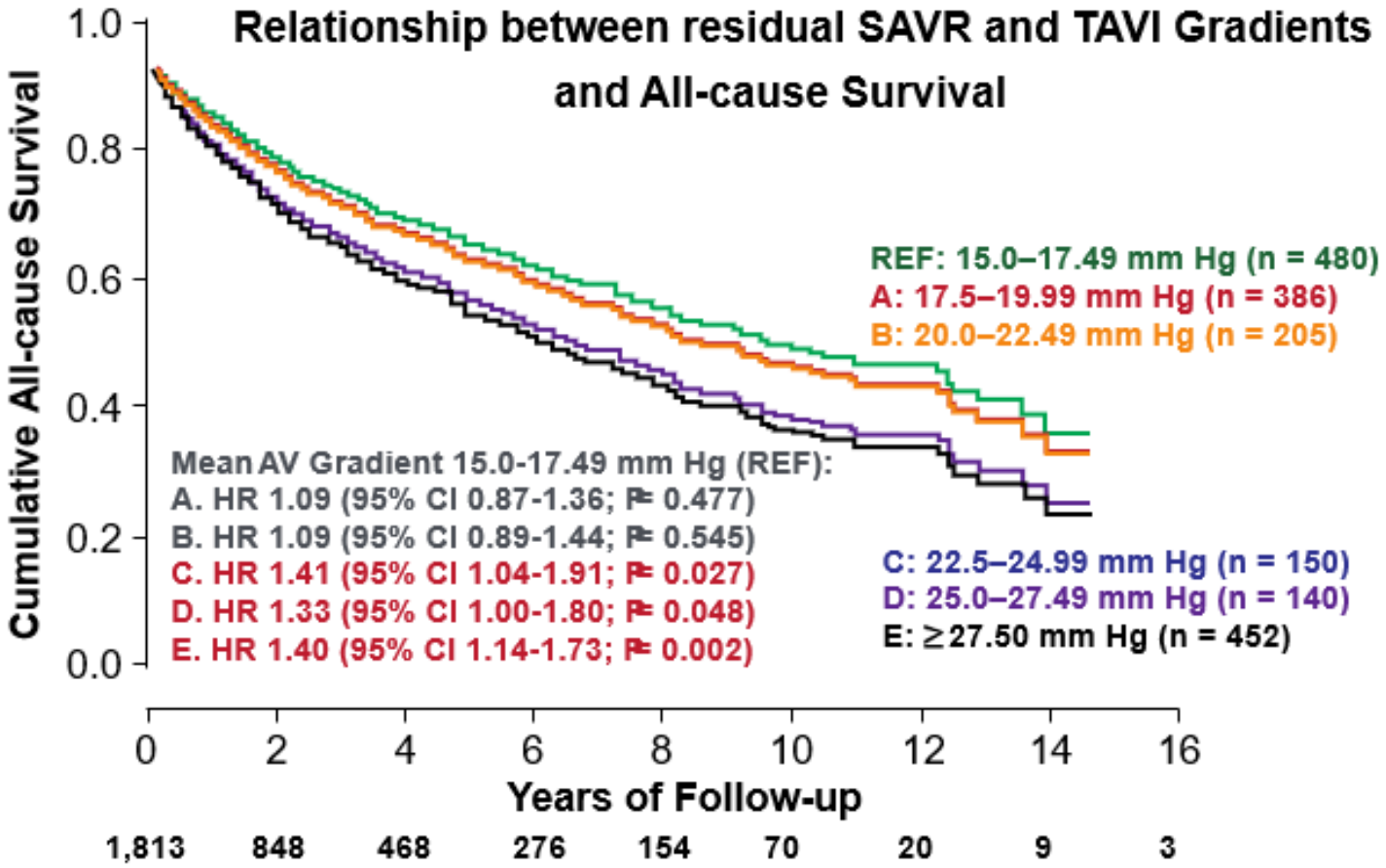
Source: Anand V, et al., *Am J Cardiol.* 2020;125:941-947.

PPM and Readmission



Fallon JM, et al. *Ann Thorac Surg*. 2018;106:14-22.

Australian Echocardiographic Registry

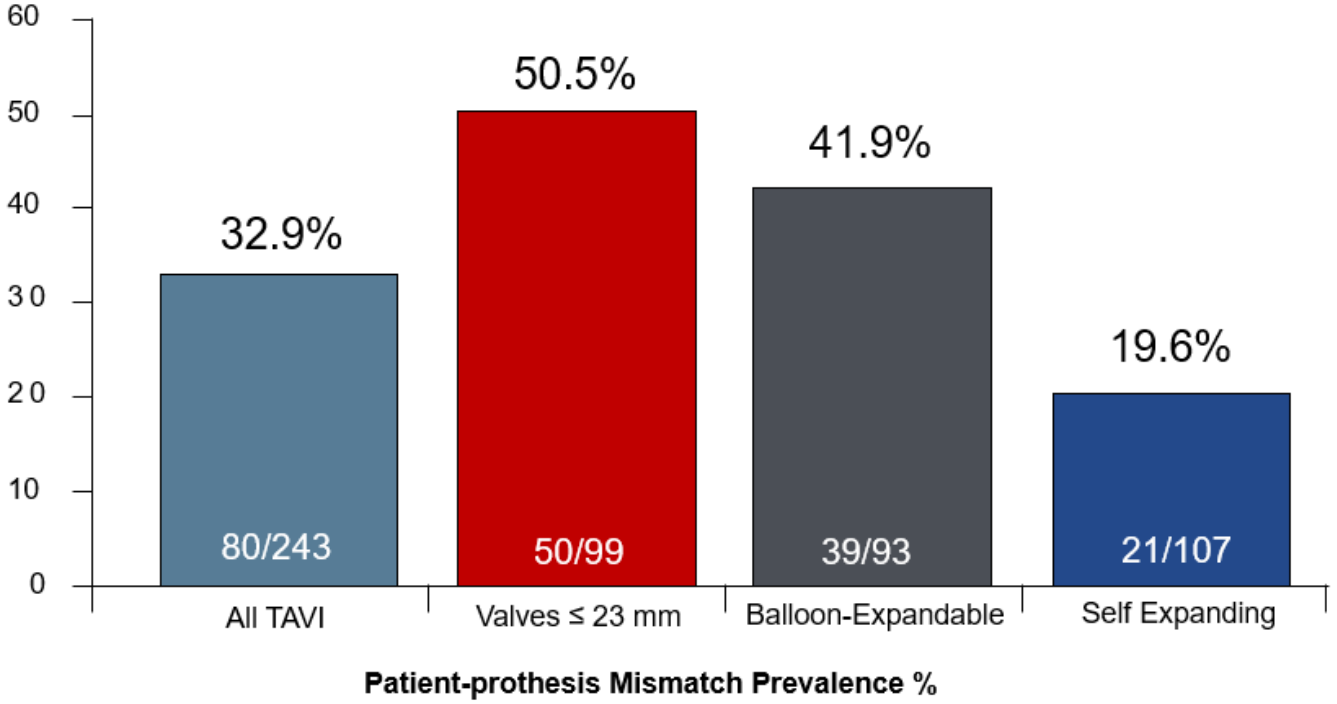


Playford D, et al., *J Am Soc Echocardiogr*. 2020;33:1077-1086.e1.

Predictors of PPM in Women

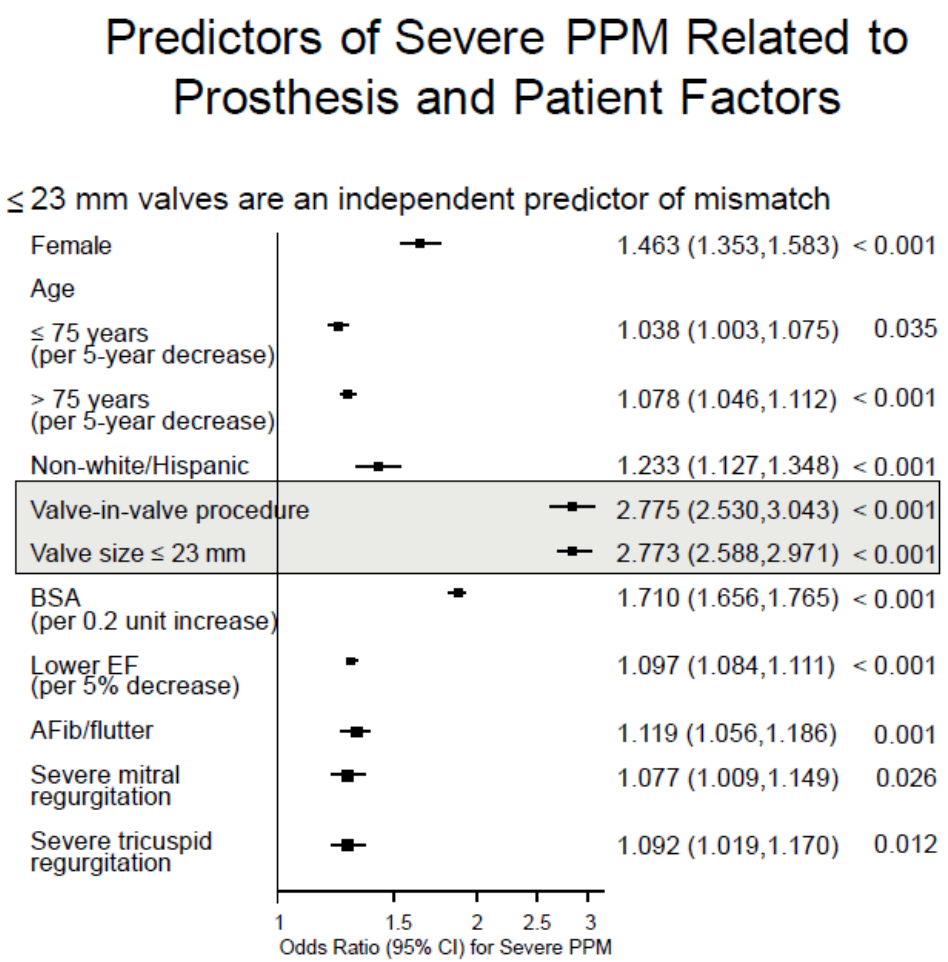
Women's International TAVI (Win-TAVI) Registry

Balloon-expandable transcatheter heart valves (THV) include all the Edwards valves (S3, XT) and self-expanding THV all the Medtronic iterations (CoreValve and Evolut R).



Source: Panoulas VF, et al., *Catheter Cardiovasc Interv.* 2021;97:516-526.

PPM Predictions



Source: Herrmann HC, et al. *JACC*. 2018;72:2701-2711.

The NOTION TRIAL

10 year follow up

NOTION Trial (Nordic Aortic Valve Intervention)

- Severe Aortic Stenosis
- Low surgical risk randomized to TAVR (1st generation CoreValve) vs SAVR
  - 280 patients

- Now 10 Year Data!
- Presented at the European Society of Cardiology

NOTION SVD at 10 years

Presentation by Dr. Jorgensen at ESC Congress at Amsterdam 2023
8/28/2023

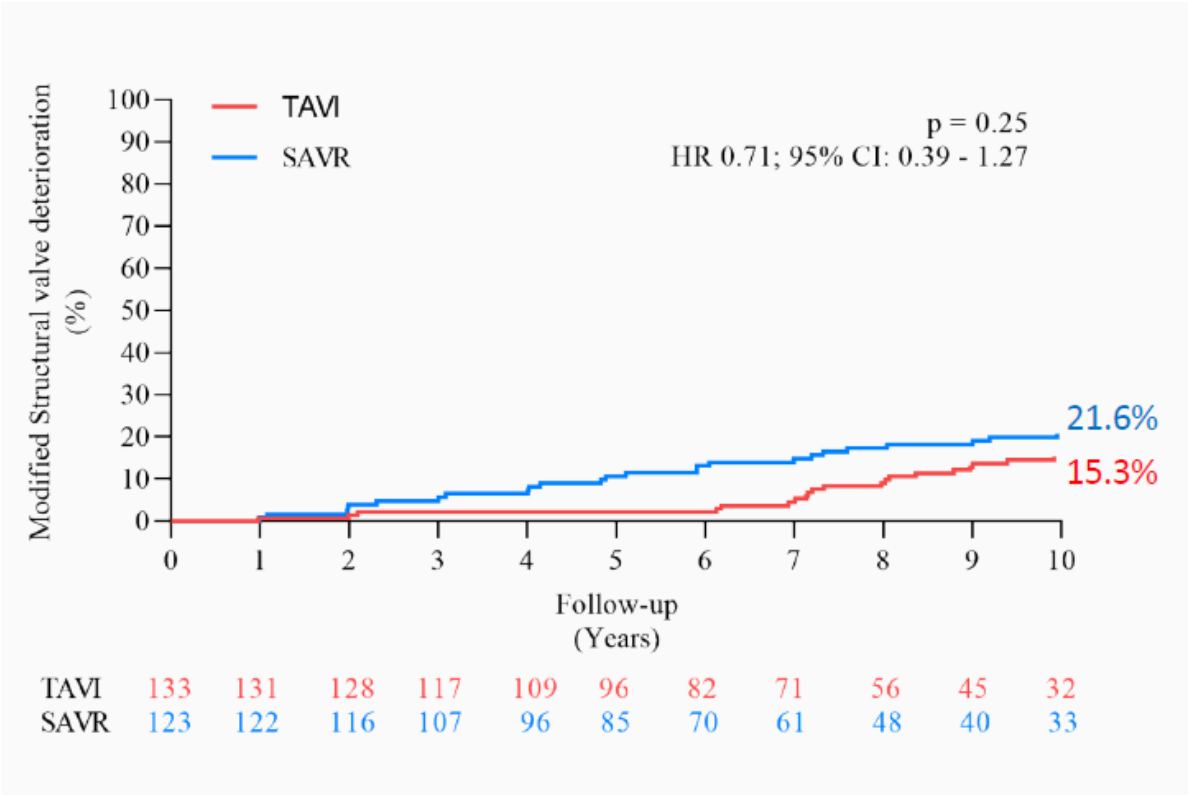
Modified SVD Criteria

mG > 20 mmHg AND

mG > 10 mmHg from 3 months

OR

Moderate-severe transvalvular AI



Bioprosthetic Valve Dysfunction

Presentation by Dr. Jorgensen at ESC Congress at Amsterdam 2023
8/28/2023

	TAVI (n = 130)	SAVR (n = 121)	p-value
Bioprosthetic valve dysfunction	67.8	81.2	0.007
Structural valve deterioation	20.2	37.7	0.0008
Non-structural valve deterioration	59.2	70.6	0.030
- Paravalvular leakage	25.4	2.5	<0.0001
- Patient-Prosthesis mismatch	48.9	69.8	0.0008
Clinical valve thrombosis	0	0	-
Endocarditis	7.2	7.4	0.95

Bioprosthetic Valve Failure

Presentation by Dr. Jorgensen at ESC Congress at Amsterdam 2023
8/28/2023

Valve-related death

Death caused by BVD or sudden unexplained death following diagnosis of BVD

Aortic valve re-intervention

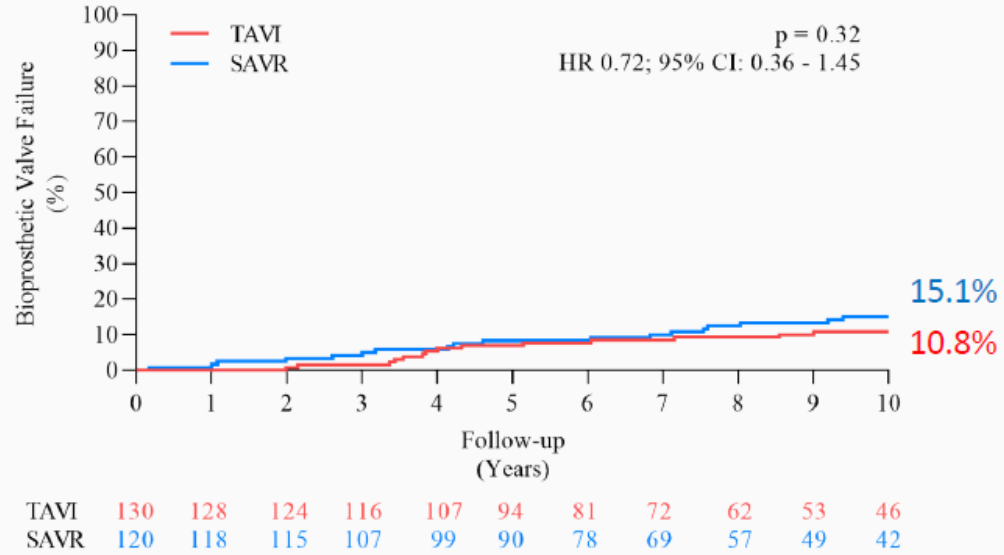
TAVI or SAVR following diagnosis of BVD

Severe hemodynamic structural valve deterioration

Mean gradient ≥40 mmHg *OR*

Mean gradient ≥20 mmHg change from 3 months *OR*

Severe AR (new or worsening from discharge)



	TAVI	SAVR	p-value
- Valve Death	5.0	3.7	0.60
- Severe SVD	3.1	11.0	0.014
- Aortic Valve Re-intervention	4.3	2.2	0.33

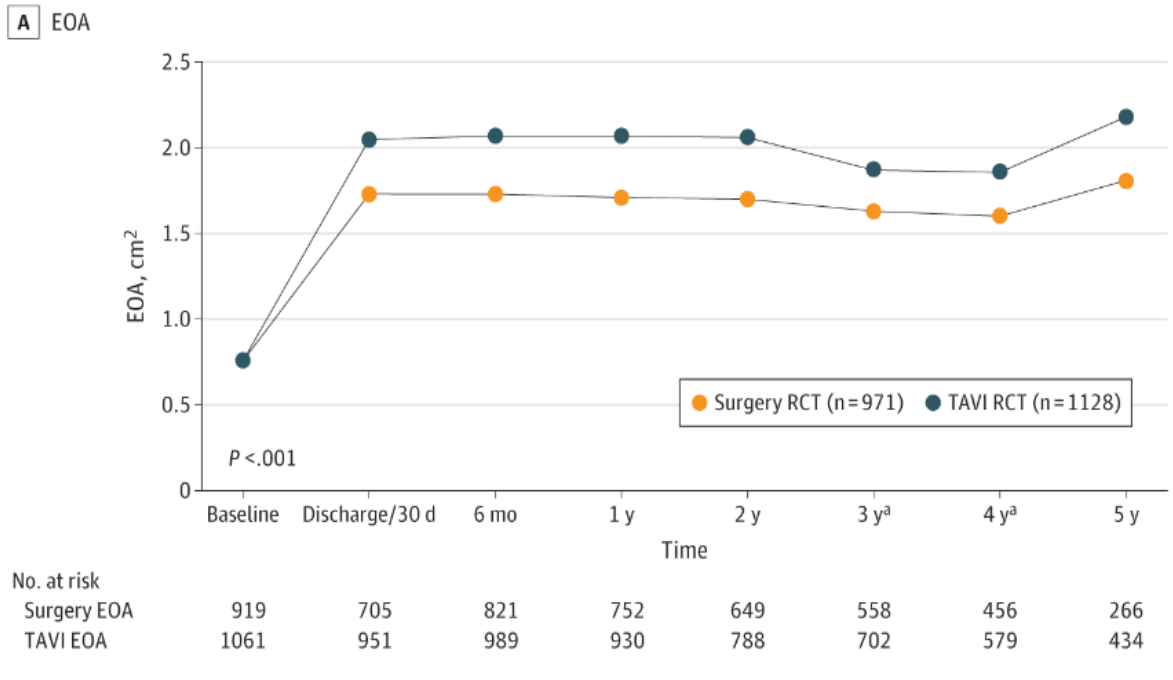
NOTION Summary

- **10 year** for low risk SAVR patients
  - Lower risk of SVD by 1st generation CoreValve TAVR than SAVR
  - Diverging Valve Failure Rates
  - (Similar all-cause mortality, CVA, and MI)

SVD in Evolut vs SAVR in intermediate to High Risk

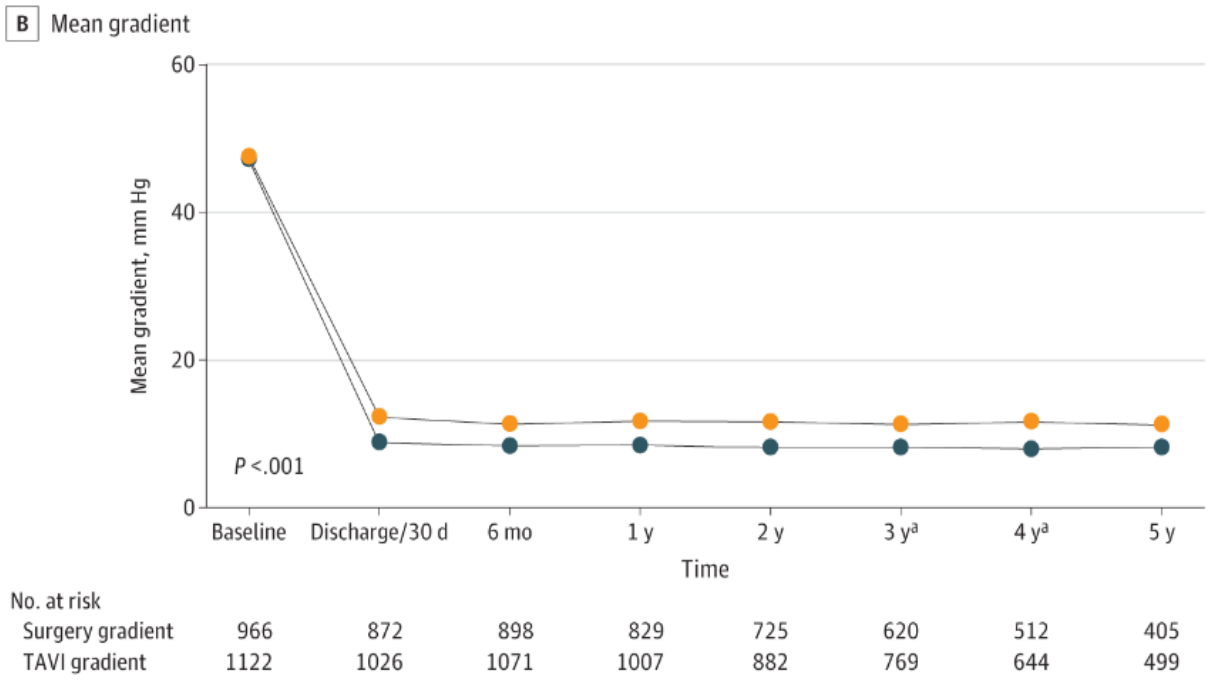
JAMA Cardiology. 2023 Feb 1;8(2):111-119.

Hemodynamics in Patients Randomized to Surgery or Transcatheter Aortic Valve Implantation (TAVI)



No. at risk

Surgery EOA	919	705	821	752	649	558	456	266
TAVI EOA	1061	951	989	930	788	702	579	434



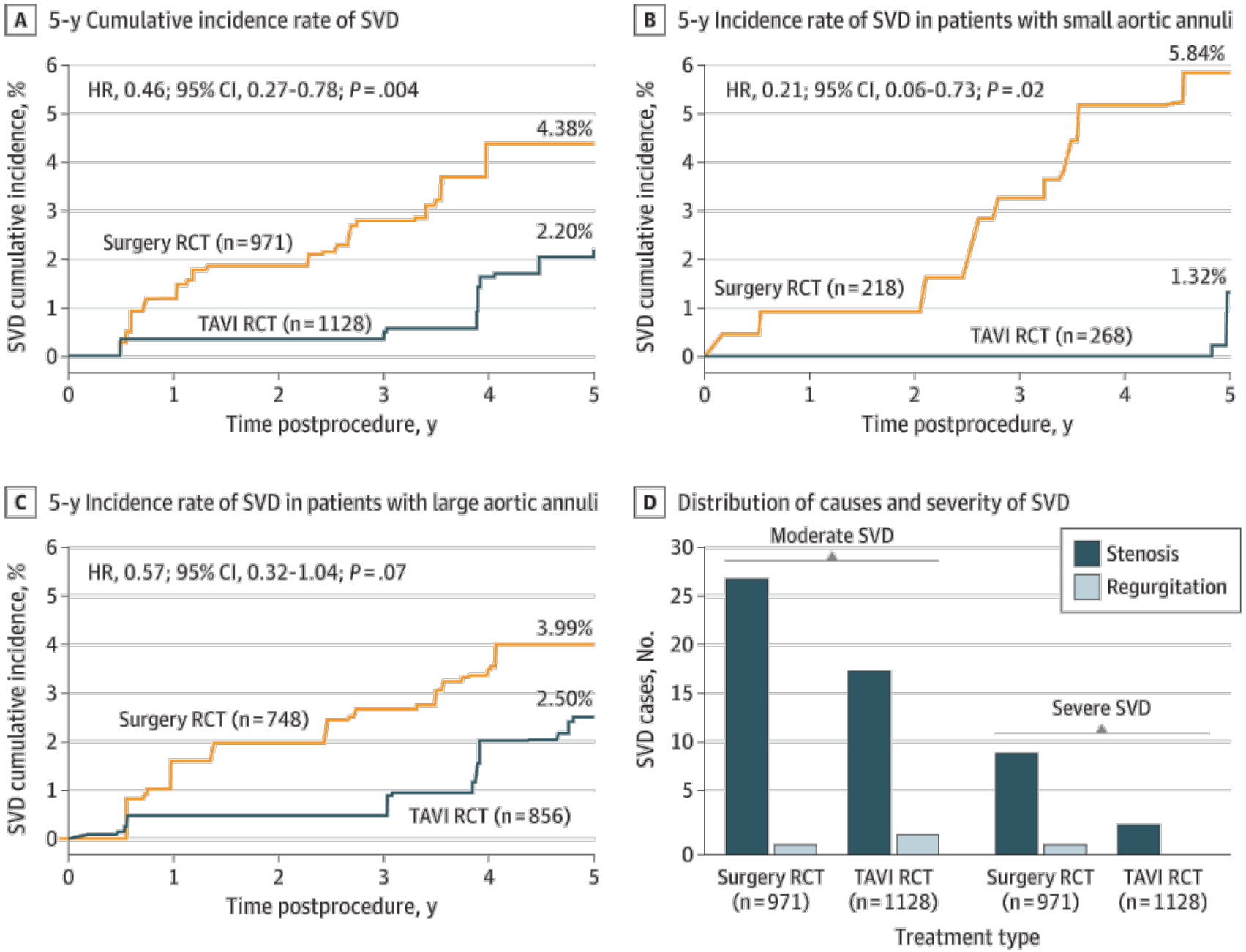
No. at risk

Surgery gradient	966	872	898	829	725	620	512	405
TAVI gradient	1122	1026	1071	1007	882	769	644	499

Effective orifice area (EOA) and mean gradient hemodynamic trends through 5 years. Patients in the TAVI group had significantly larger EOA and significantly lower mean gradient than patients in the surgery group at all time points after the procedure. RCT indicates randomized clinical trial.

*Change from Core Laboratory to site-reported echocardiographic readings.

JAMA Cardiol. 2023: 8(2):111-119

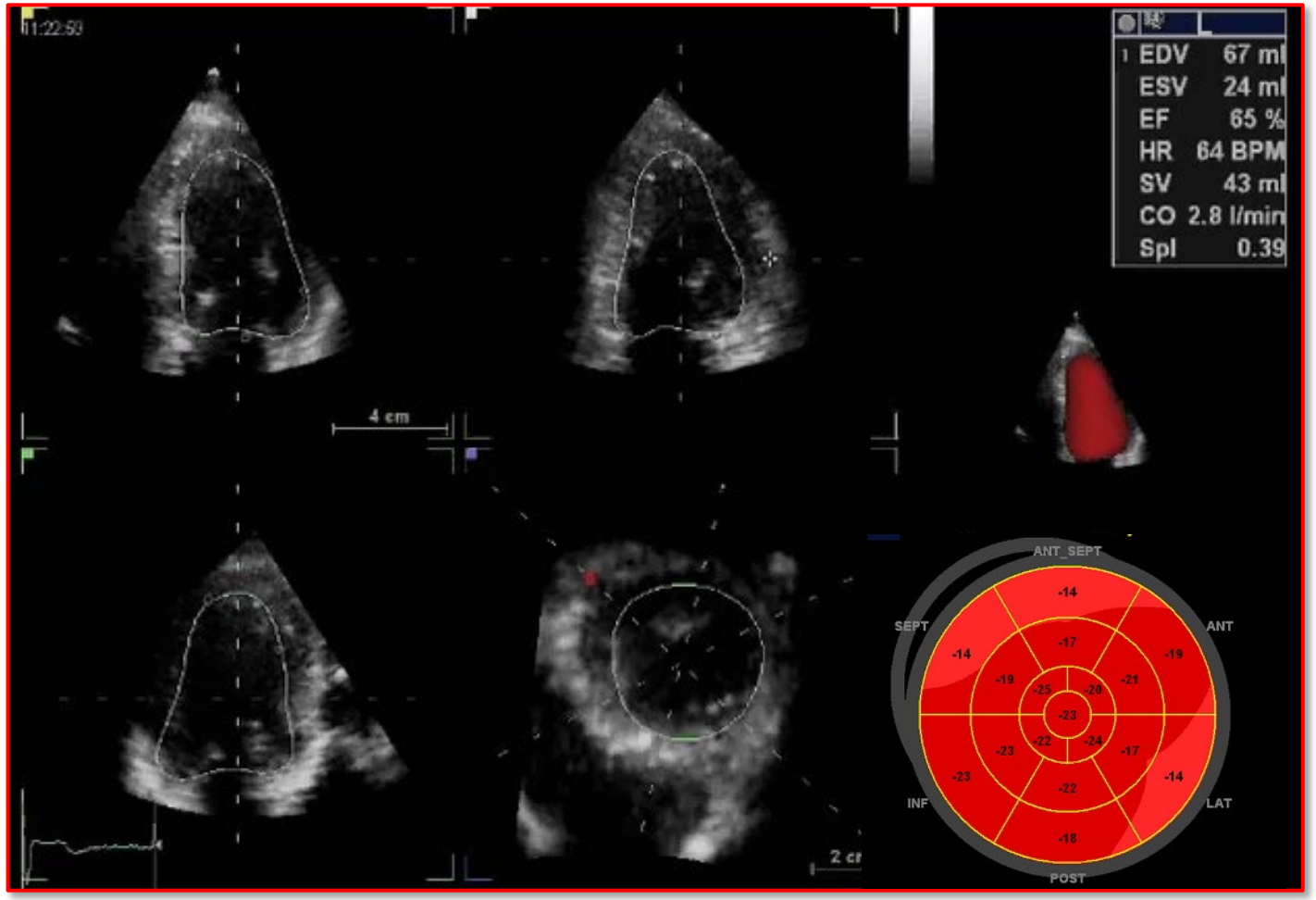


JAMA Cardiol. 2023: 8(2):111-119

CASES

CASE #1

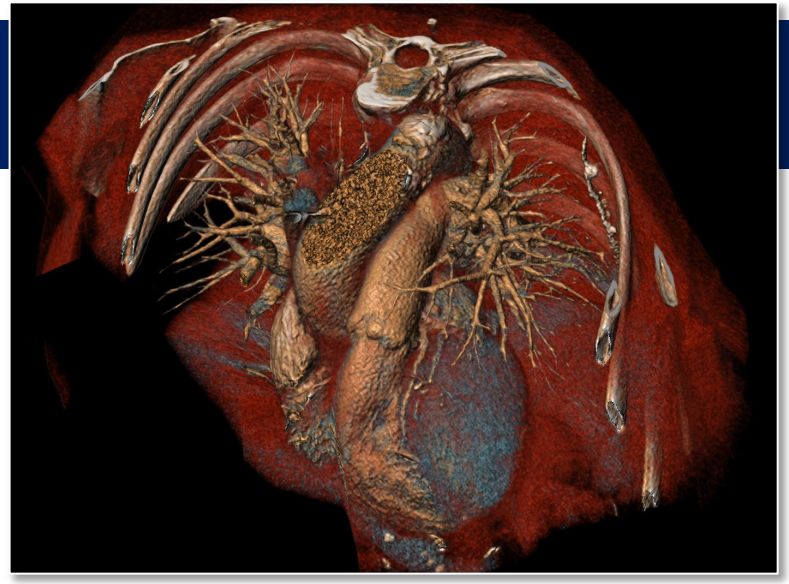
75-year-old woman with severe aortic stenosis

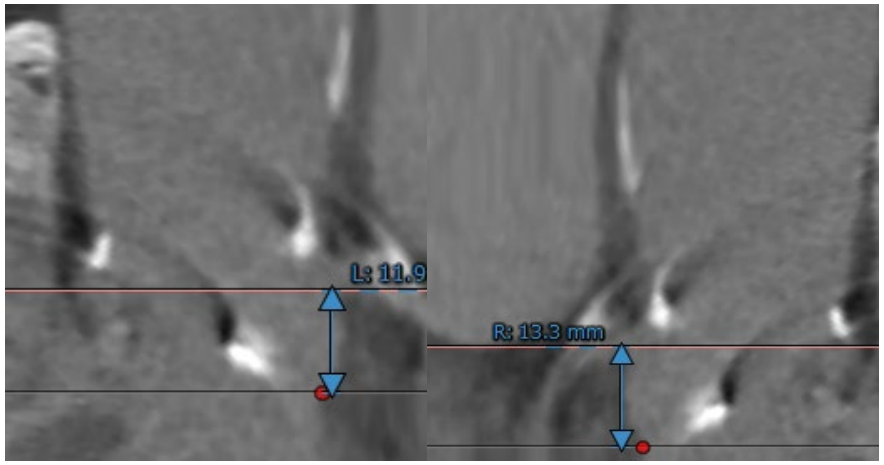


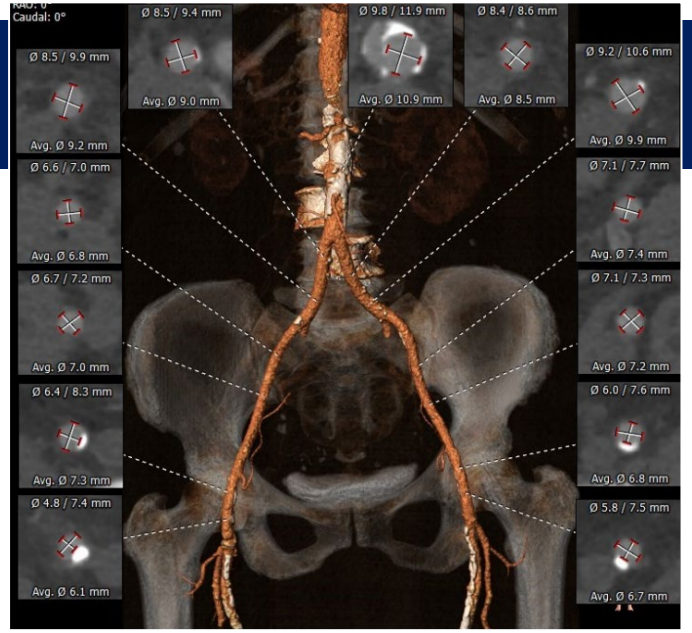
Severe Calcific Aortic Stenosis:
Peak Velocity 4.3 m/sec
mean gradient 40 mmHg
AVA 0.95 cm2

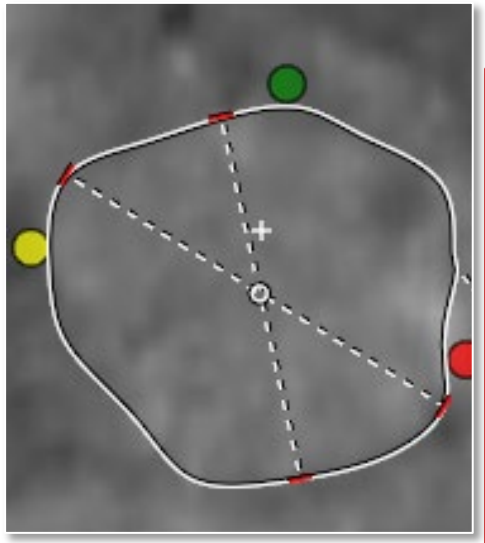
LVEF 65%
Mildly abnormal Strain = -19.7%
Grade 1 diastolic dysfunction

CARDIAC CT



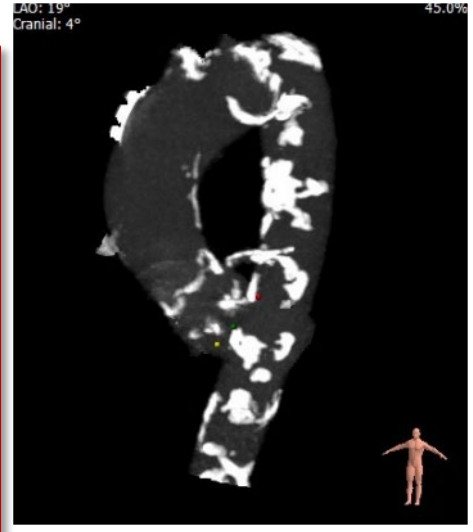






Calcified Trileaflet Aortic Valve Calcium Score = 1676
Aortic Annulus Perimeter = 61.3 mm (Area = 269.2 mm2)
Mean SOV diameter = 26.4 mm, Height =17.9 mm
ST Junction Calcium, no LVOT calcium

Coronary Heights – LCA = 11.9 mm, RCA 13.3 mm
No femoral access issues
Calcified dissection in descending abdominal Aorta



Risk Model and Variables – STS Adult Cardiac Surgery Database Version 2.81

RISK SCORES

About the STS Risk Calculator

Procedure: AV Replacement

Risk of Mortality: 3.7%
Morbidity or Mortality: 18.4%
Long Length of Stay: 9.2%
Short Length of Stay: 25.2%
Permanent Stroke: 2.2%
Prolonged Ventilation: 11.4%
DSW Infection: 0.10%
Renal Failure: 2.5%
Reoperation: 4.9%

Surgical Risk:

LOW

Evolut™ Hemodynamic Reference Values[1]

Annular Diameter (mm)	≤ 22.3	> 22.3 to ≤ 23.2	> 23.2 to ≤ 24.7	> 24.7 to ≤ 26.2	> 26.2 to ≤ 30.2
Diameter Derived Annular Area (mm²)	≤ 391	391-423	423-479	479-539	539-716
EOA Ref Data (cm²)	1.66 ± 0.42 (n = 53)	1.82 ± 0.43 (n = 38)	1.98 ± 0.56 (n = 62)	1.98 ± 0.59 (n = 49)	2.56 ± 0.77 (n = 53)

Patient BSA (m²)					
1.3	1.28	1.40	1.52	1.52	1.97
1.4	1.19	1.30	1.41	1.41	1.83
1.5	1.11	1.21	1.32	1.32	1.71
1.6	1.04	1.14	1.24	1.24	1.60
1.7	0.98	1.07	1.16	1.16	1.51
1.8	0.92	1.01	1.10	1.10	1.42
1.9	0.87	0.96	1.04	1.04	1.35
2	0.83	0.91	0.99	0.99	1.28
2.1	0.79	0.87	0.94	0.94	1.22
2.2	0.75	0.83	0.90	0.90	1.16
2.3	0.72	0.79	0.86	0.86	1.11
2.4	0.69	0.76	0.83	0.83	1.07
2.5	0.66	0.73	0.79	0.79	1.02
2.6	0.64	0.70	0.76	0.76	0.98
2.7	0.61	0.67	0.73	0.73	0.95
2.8	0.59	0.65	0.71	0.71	0.91

In Vivo Indexed Effective Orifice Area (iEOA)

Sapien 3™* Hemodynamic Reference Values[1]

Area Derived Annular Diameter (mm)	≤ 22.1	> 22.2 to ≤ 23.64	> 23.64 to ≤ 24.9	> 24.9 to ≤ 26.2	> 26.2 to ≤ 29.4
Annular Area (mm²)	248-384	385-439	440-488	489-537	538-678
EOA Ref Data (cm²)	1.41 ± 0.27 (n = 189)	1.58 ± 0.33 (n = 191)	1.73 ± 0.36 (n = 192)	1.79 ± 0.35 (n = 191)	1.91 ± 0.42 (n = 188)

Patient BSA (m²)					
1.3	1.08	1.22	1.33	1.38	1.47
1.4	1.01	1.13	1.24	1.28	1.36
1.5	0.94	1.05	1.15	1.19	1.27
1.6	0.88	0.99	1.08	1.12	1.19
1.7	0.83	0.93	1.02	1.05	1.12
1.8	0.78	0.88	0.96	0.99	1.06
1.9	0.74	0.83	0.91	0.94	1.01
2	0.71	0.79	0.87	0.90	0.96
2.1	0.67	0.75	0.82	0.85	0.91
2.2	0.64	0.72	0.79	0.81	0.87
2.3	0.61	0.69	0.75	0.78	0.83
2.4	0.59	0.66	0.72	0.75	0.80
2.5	0.56	0.63	0.69	0.72	0.76
2.6	0.54	0.61	0.67	0.69	0.73
2.7	0.52	0.59	0.64	0.66	0.71
2.8	0.50	0.56	0.62	0.64	0.68

In Vivo Indexed Effective Orifice Area (iEOA)

The analysis provided above assesses data from separate clinical studies. These charts are not intended to be a direct comparison of these devices as there is no head-to-head clinical study, but rather are intended to illustrate an analysis of similar trials. Multiple factors, including the use of different echo corelabs, contribute to clinical study outcomes and need to be considered in making any assessments across different studies. Where measurements are derived, conversions assume circularity.

References

[1] Hahn RT, Leipsic J, Douglas PS, et al. Comprehensive Echocardiographic Assessment of Normal Transcatheter Valve Function. *JACC Cardiovasc Imaging*. Published online June 8, 2018.

[2] Kappetein AP, Head SJ, Généreux P, et al. Updated standardized endpoint definitions for transcatheter aortic valve implantation: the Valve Academic Research Consortium-2 consensus document. *Eur Heart J*. October 2012;33(19):2403-2418.

Indexed Effective Orifice Area (iEOA) = EOA/BSA[2]

iEOA > 0.85 cm²/m²	mild
iEOA 0.85-0.65 cm²/m²	moderate
iEOA < 0.65 cm²/m²	severe

To Aid Patient-Prosthesis Matching[2]

- First determine patient's body surface area (BSA).
- Second, using the chart, select a valve size with iEOA > 0.85 to avoid moderate PPM.

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Further, Together

23 mm EVOLUT FX

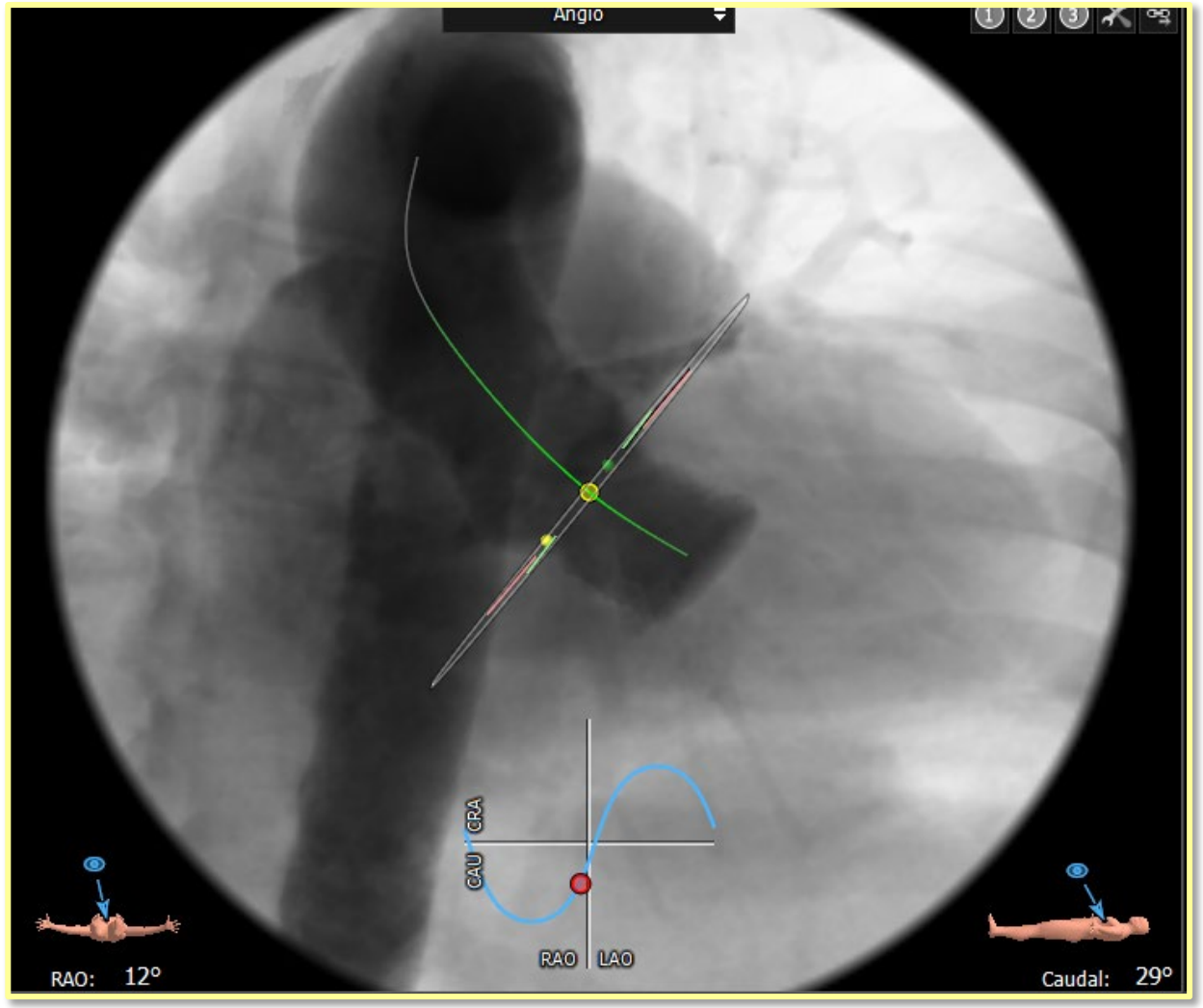
No patient-prosthesis mismatch

20 mm Sapien 3

Predicted moderate patient-prosthesis mismatch

PROCEDURE

Cusp Overlap View (projected from CT)

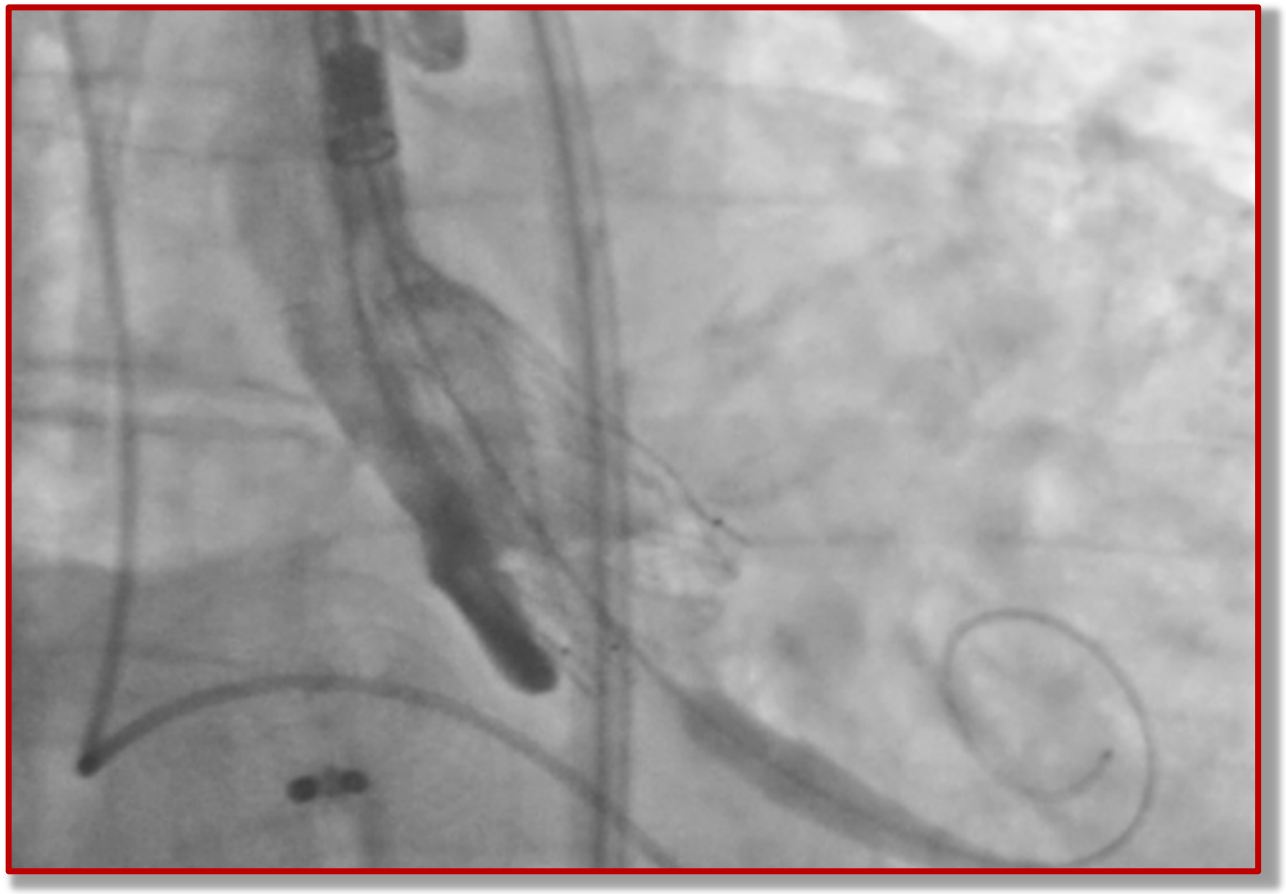


RAO 10, CAU 30

Non-coronary cusp isolated (lowest point of annulus)

Right and Left Coronary cusps overlap

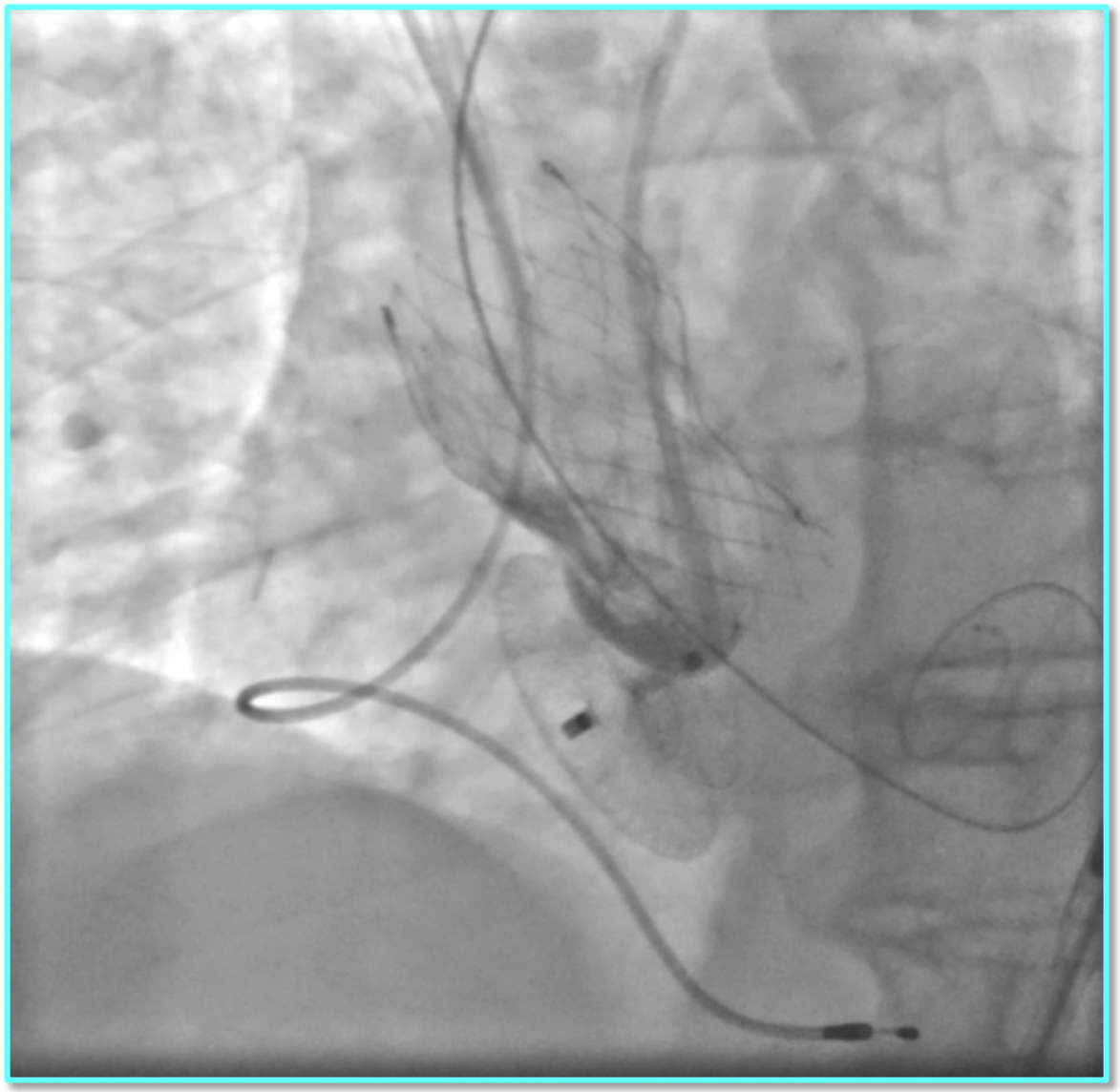
Deployment in Cusp Overlap



80% Deployment

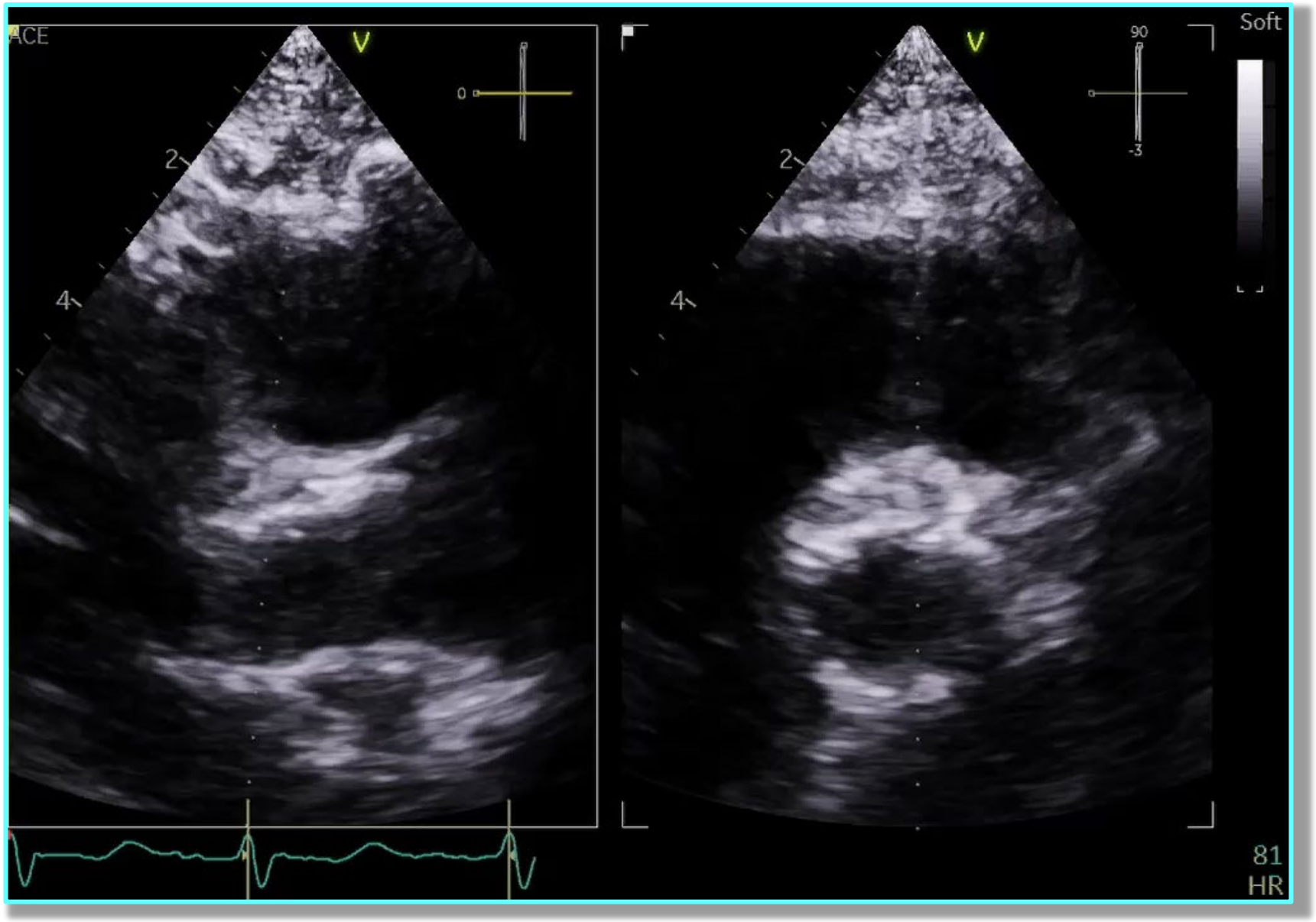
Orient to LAO 33 for final deployment

Deployment in Cusp Overlap



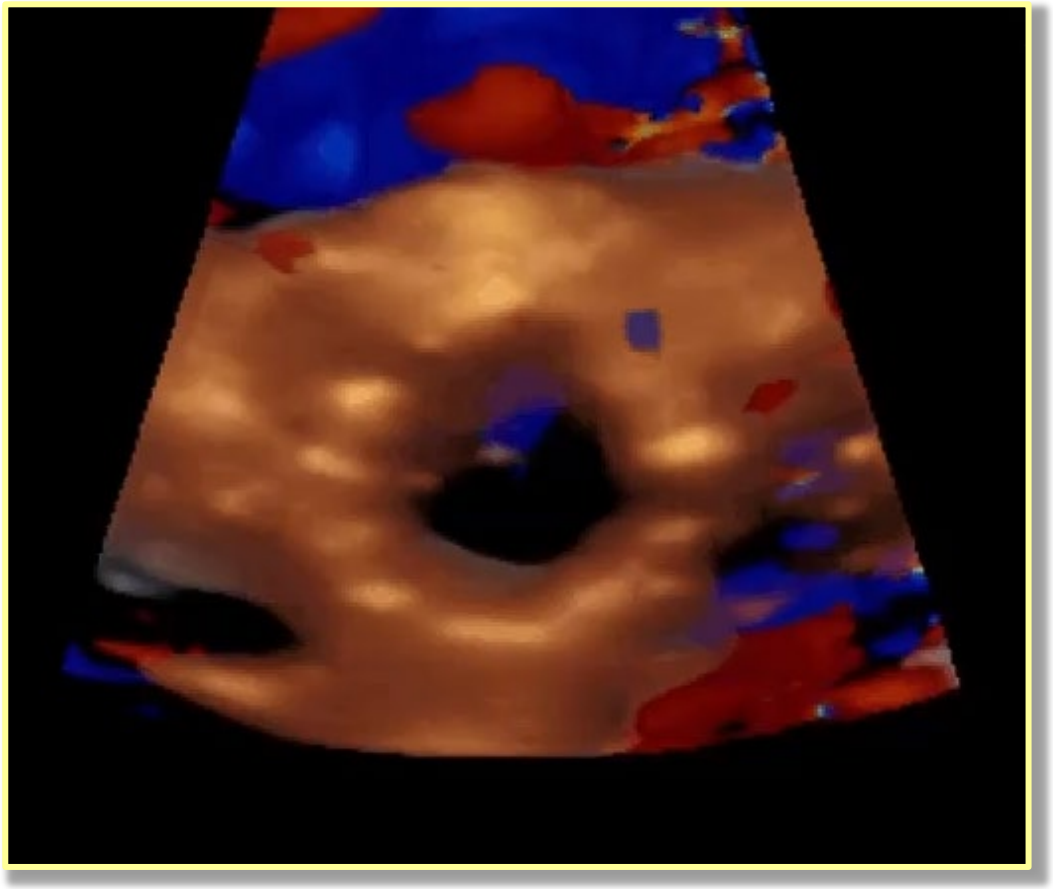
No requirement for pacing after deployment

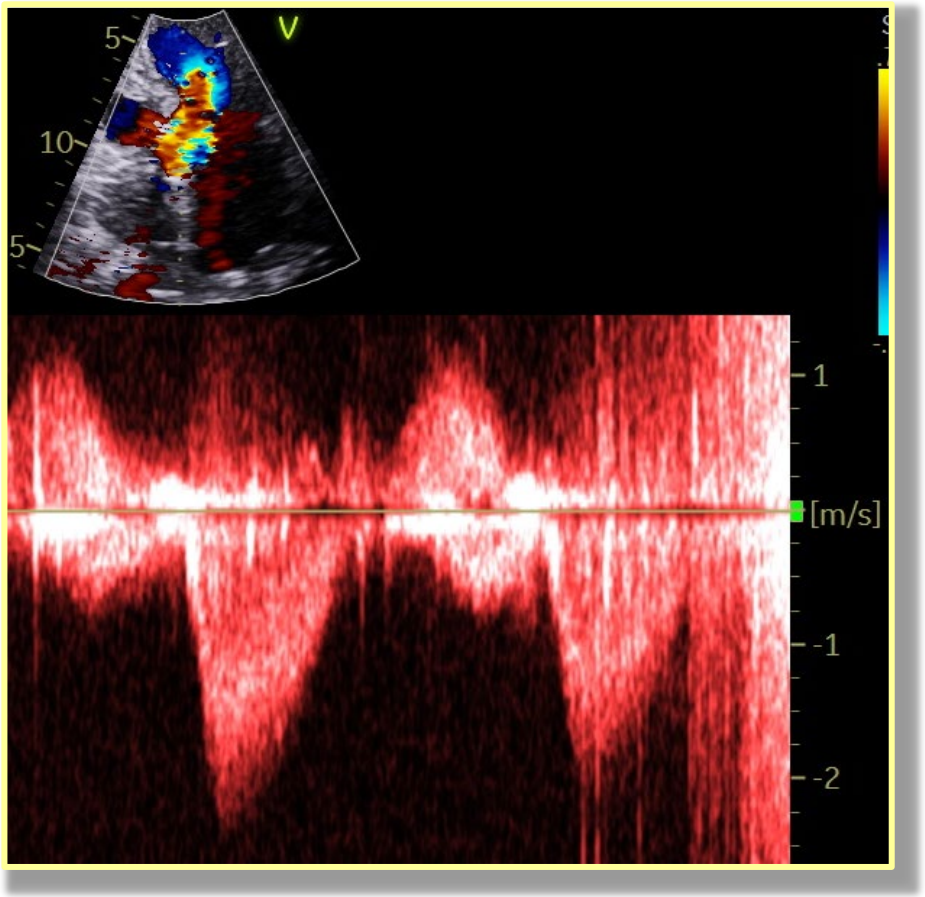
Procedural Echo



FINAL RESULT:

No paravalvular regurgitation
Mean gradient = 10 mmHg, AVA 2.1 cm2





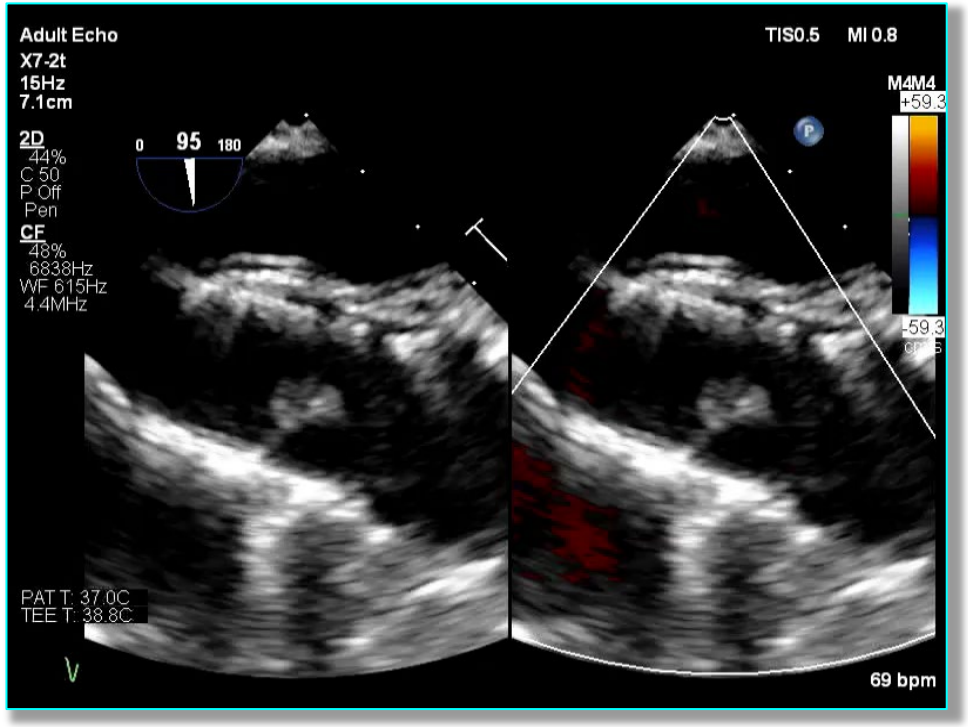
SLMC Prevention of PPM

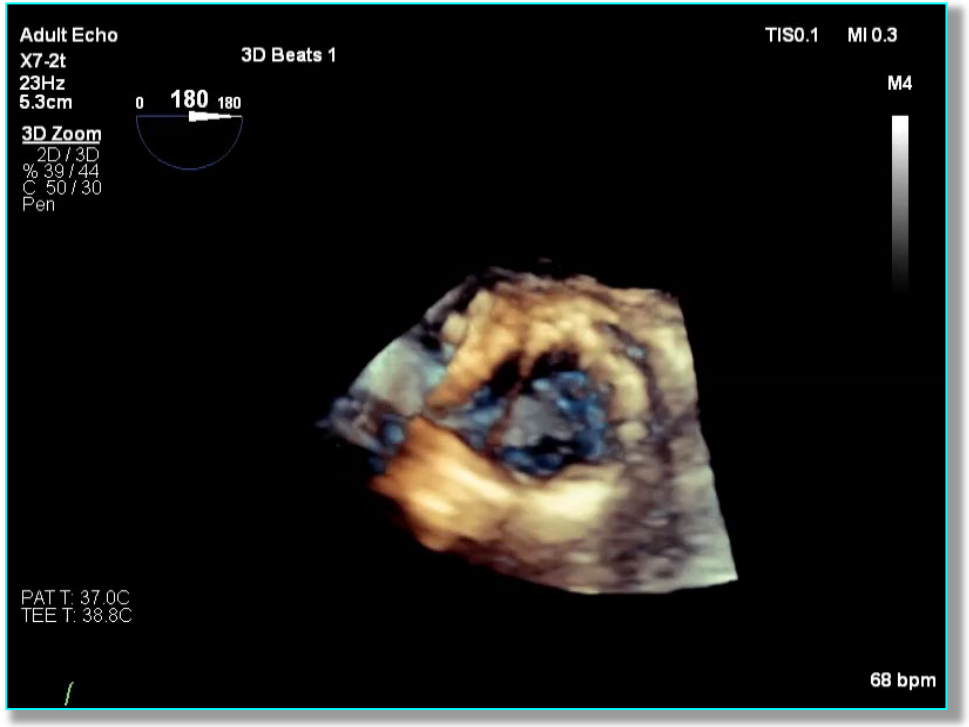
- TAVR CT
  - Small annulus or predicted PPM
    - Evolut TAVR
    - Root enlargement?
  - Avoid using < 23 TAVR Valve
- All ViV get Evolut

Case #2

90-year-old woman who underwent TAVI

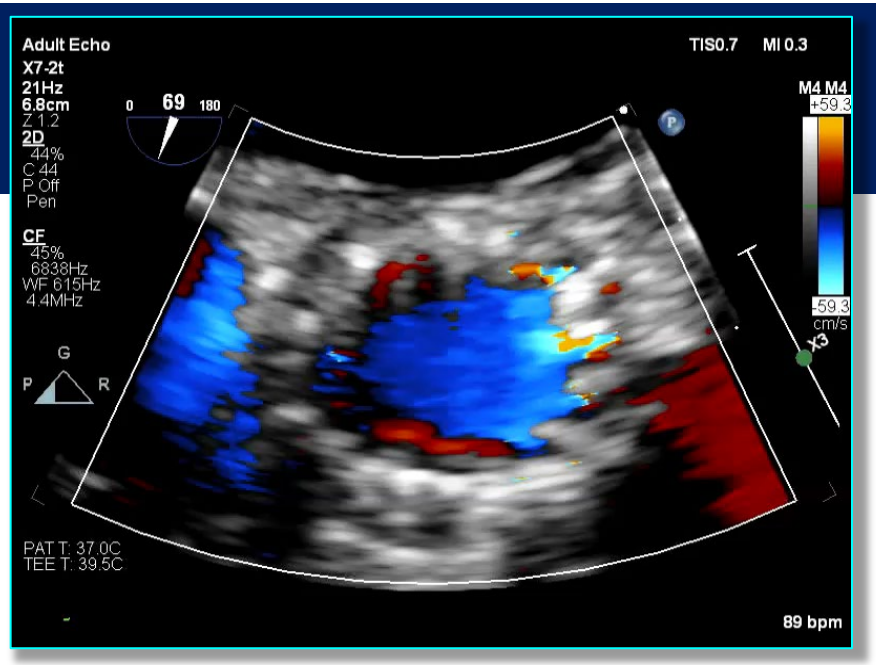
- **2018 - 29 mm Evolut R (High surgical risk)**
- **9 months later - *Enterococcas feacilis bacteremia***

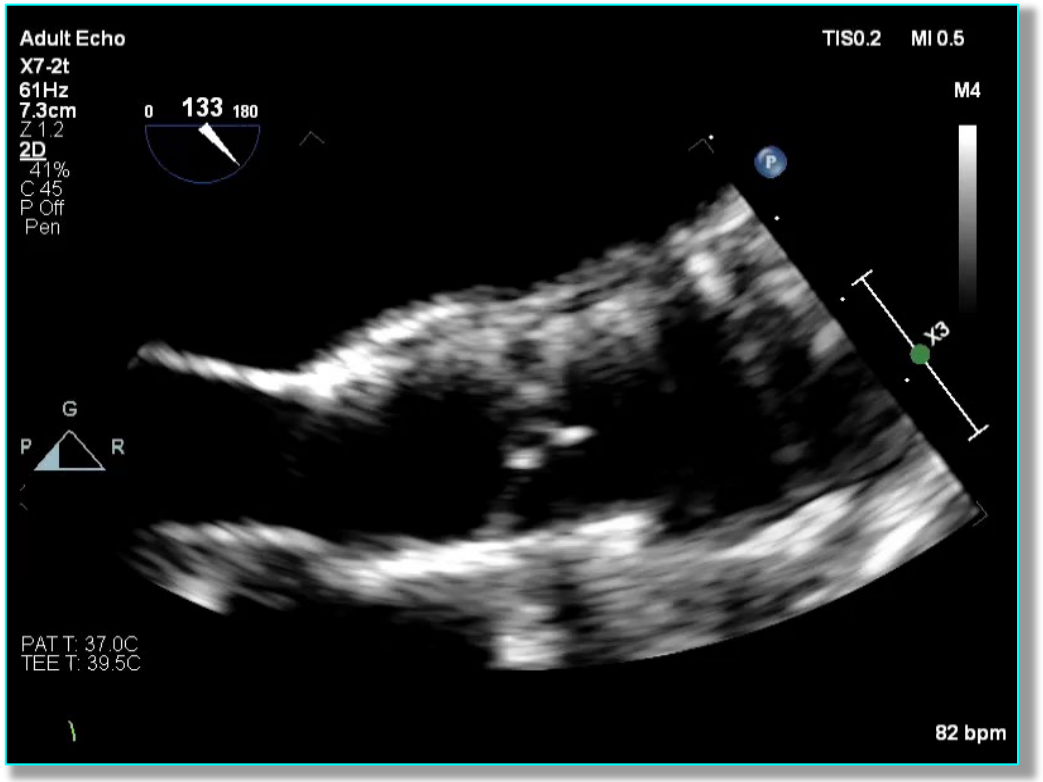


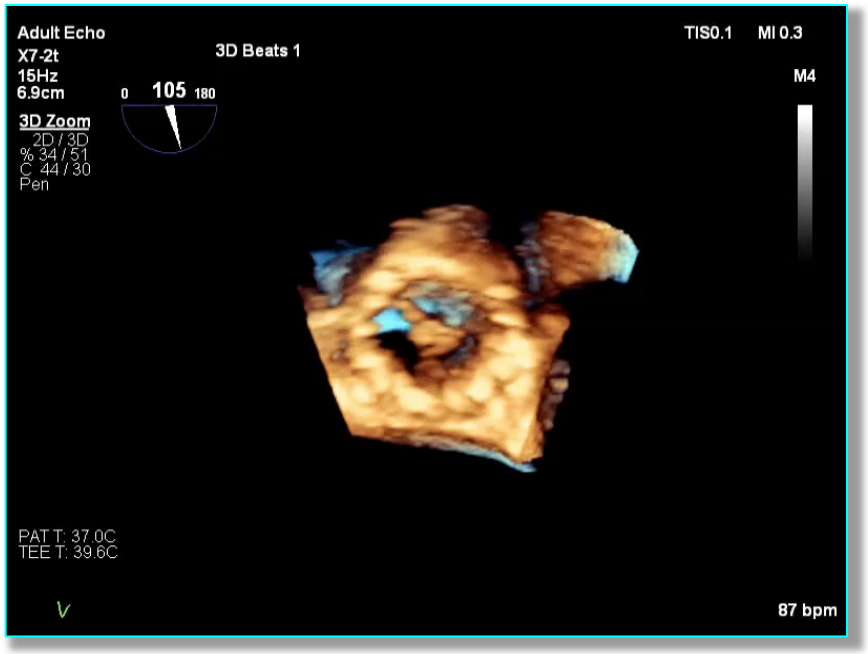


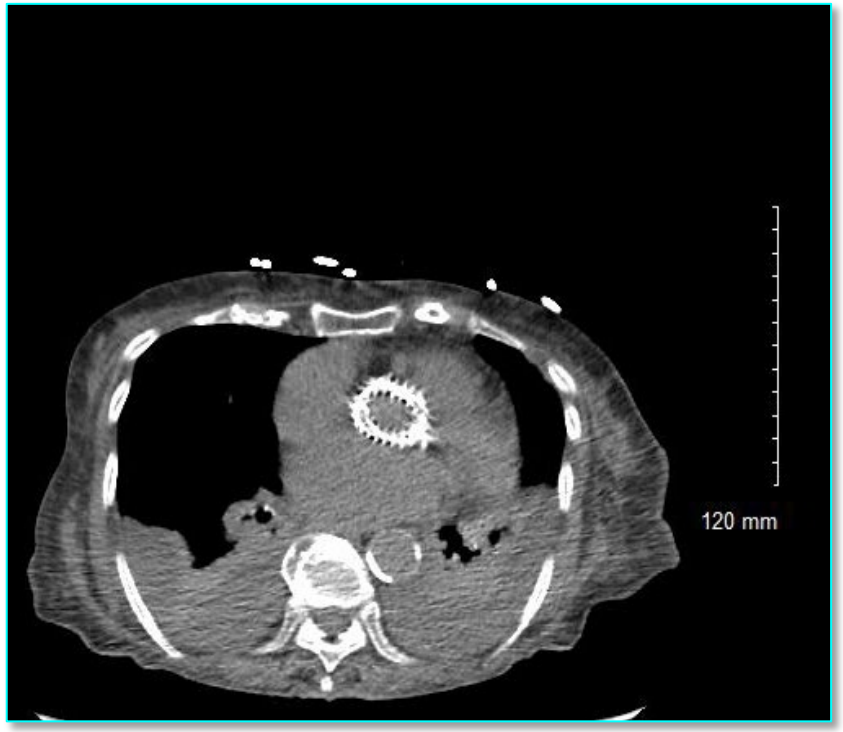
TAVI Endocarditis

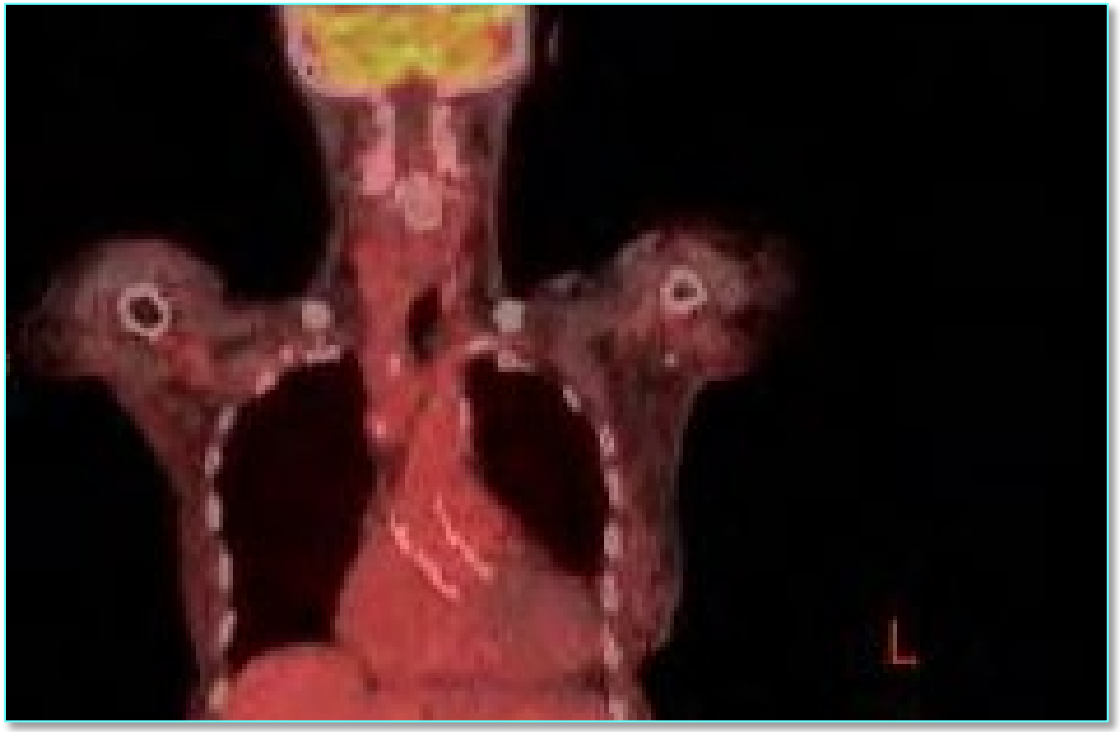
- 6 weeks of IV antibiotics
- 2 months later – Repeat TEE











- **PET/CT:**
  No active infection in the TAVI
  Patient declined further work-up

- **2022:**
  Doing well, living independently

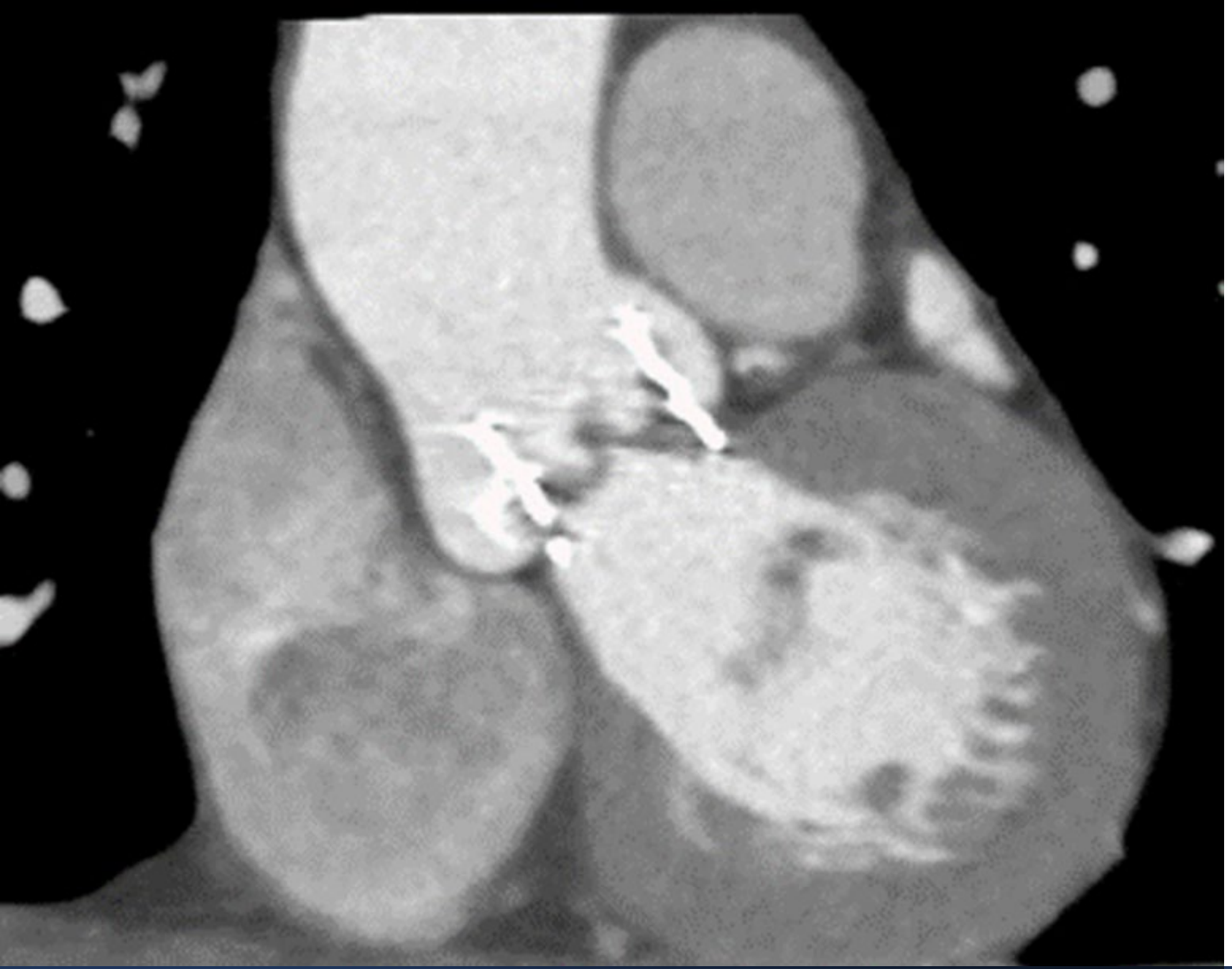
Case #3

Patient

- 63 year old
- PMHx Hepatitis C, liver cirrhosis c ascites, current ETOH abuse, thrombocytopenia (plts 50,000s), NIDDM, anxiety and depression, esophageal varices, obesity (BMI 40), CKD3, Hx ETOH seizure
- Severe symptomatic aortic stenosis, mild CAD
  - AVA 0.8, mG 41, pV 4.0 EF 41.
- Deemed intermediate risk of SAVR
  - STS 1.8%
  - Mayo 30 day Mortality risk: 3.0%

TAVR

- Underwent an IF TAVR #26 Sapien 2020, junctional rhythm improved to NSR and DC'd on POD#2
  - POD#1 TTE: mG 6
  - 1 Month TTE: mG 11
  - 1 year TTE: mG 28 – ordered a 6 month follow up TTE
    - After discussion with high risk for OAC, repeat TTE in 6 months
  - 1.5 year TTE: mG 58 – ordered a 4D CT heart structure



CT scan

The valve is well seated. Leaflets are thickened. At the base of the left and right cusps there are areas of hypoattenuation (average Hounsfield unit 60-80 HU) consistent with HALT. 4D cine images demonstrate restricted leaflet motion in midsystole (30% phase).

HALT Treatment

- Patient with ETOH cirrhosis and platelet count of 40-50k
- Eliquis 5mg po BID
  - ASA 81mg QOD

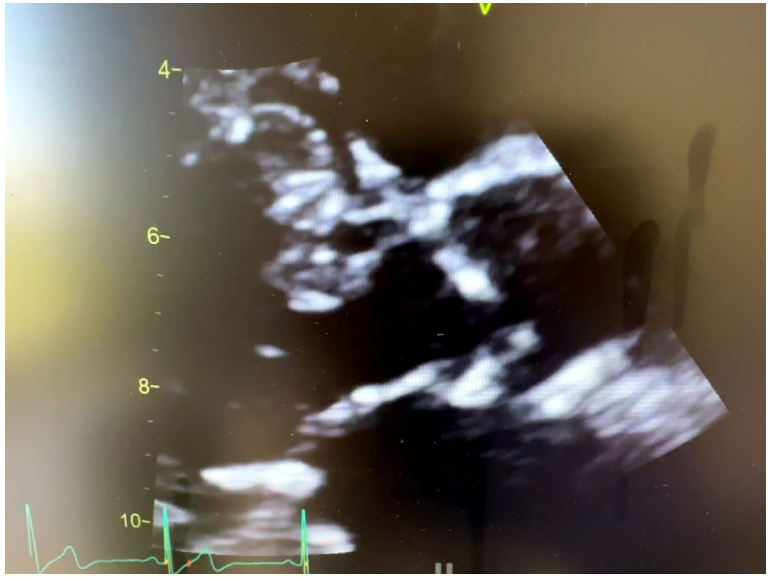
Follow Up

- TTE 3 months later after OAC mG 26
- TTE 6 months later mG 13 – reduced to Eliquis 2.5mg

What to do if you suspect HALT or Thrombus?

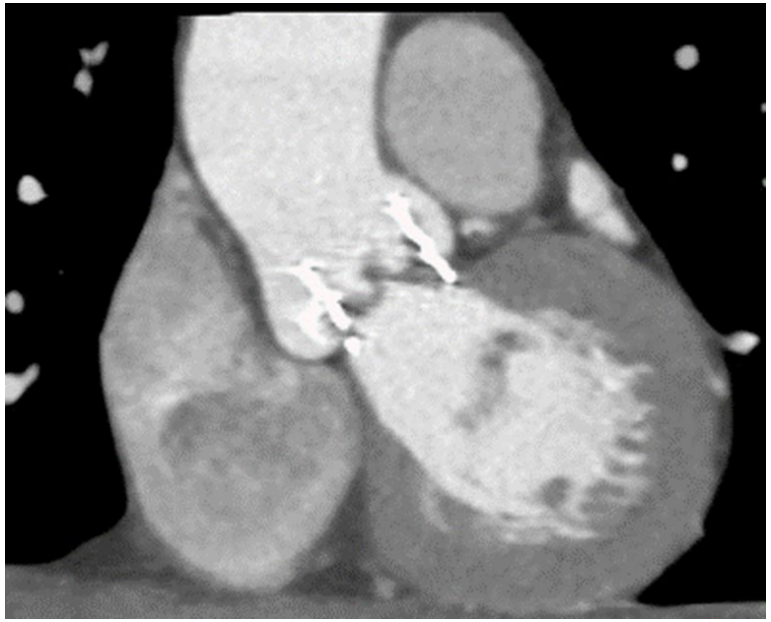
Step One

- Make sure ECHO mG accurate
  - Repeat the study?
  - LVOT obstruction: Septal hypertrophy? SAM?
    - Now holding BB p TAVR → revealing more LVOT gradient?



Step Two

- MDCT (multidetector computed tomography)
  - CT heart structure “4D”



Step Three

- TEE
  - If unable to do CT secondary to CKD
  - Eval LVOT and valve function

Risks of Halt

- Majority of the time – HALT (and RLM) does NOT result in higher mean gradients
- Unsure of long-term complications
  - Reduced durability of valve?
- No significant increase in death, MI
- Increased risk of TIA or CVA

Treatment

- If CT + for HALT
  - Warfarin for 3 months then re-evaluate with TTE
    - (We have used NOAC)
  - Continue AC until thrombus resolved and valve functioning improves
    - Repeat TTE 3 months

- Retrospective trials show that half regress without treatment

SUMMARY

Summary

- Monitor your valves! Planned interventions rather than emergent
- Pick the right valve for the right patient
  - SAVR (bioprosthetic vs mechanical) vs TAVR
  - Self-expandable valve has better EOA and gradients, particularly in small annuli
- Initial valve hemodynamics affect long-term durability and patient outcomes
- Even small increases in mean gradient matter
- Self-expandable valve has better SVD rates than SAVR at 10 years

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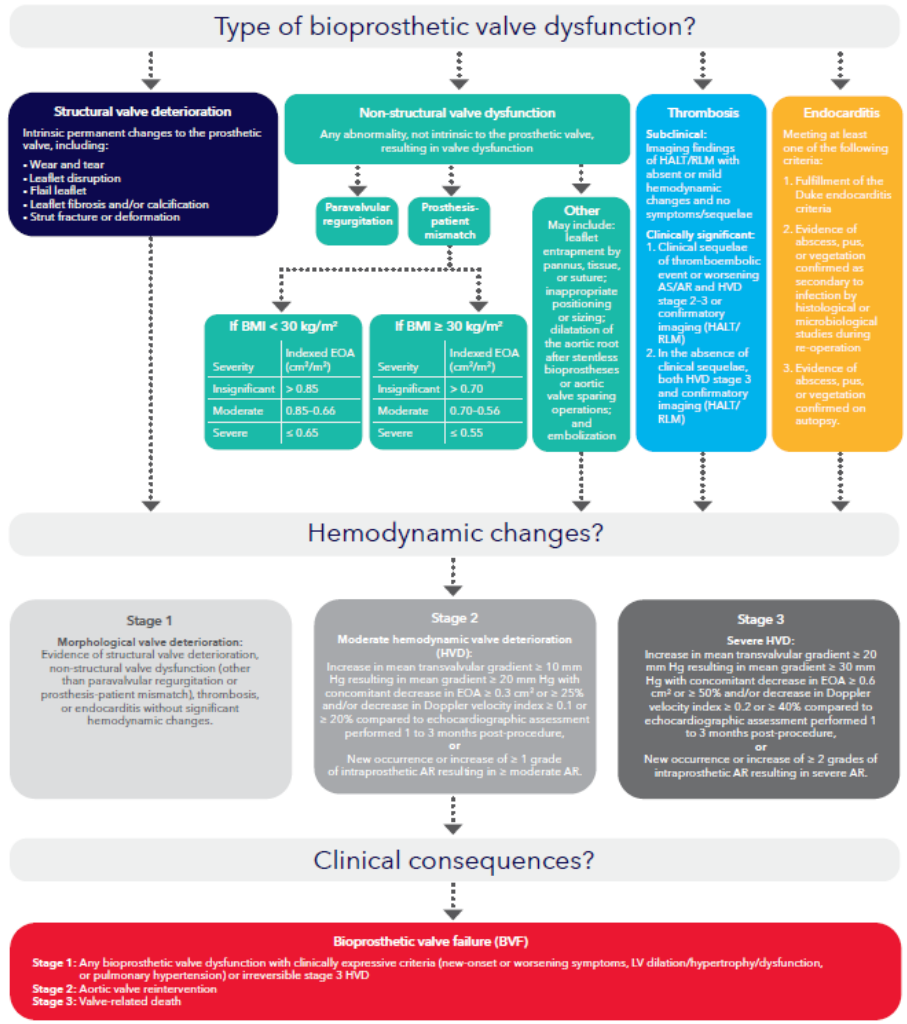
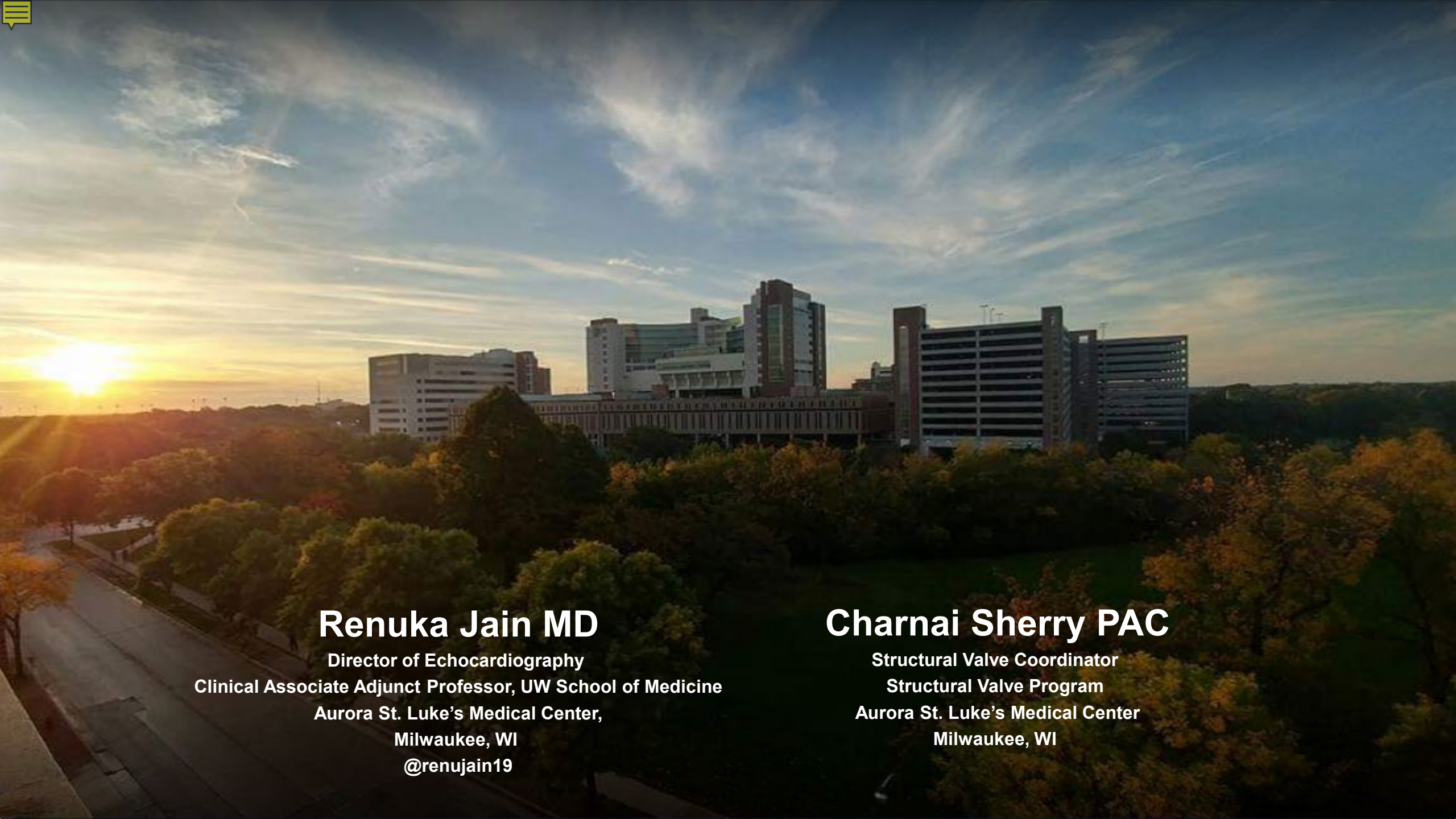
VARC-3 bioprosthetic valve dysfunction[1]





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THANK YOU

Q & A

Please type your questions in the Q&A

Complete the Survey via
QR code or Link in CHAT

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Indications

The Medtronic CoreValve™ Evolut™ R, Evolut™ PRO+, and Evolut™ FX Systems are indicated for relief of aortic stenosis in patients with symptomatic heart disease due to severe native calcific aortic stenosis who are judged by a heart team, including a cardiac surgeon, to be appropriate for the transcatheter heart valve replacement therapy.

The Medtronic CoreValve Evolut R, Evolut PRO+, and Evolut FX Systems are indicated for use in patients with symptomatic heart disease due to failure (stenosed, insufficient, or combined) of a surgical bioprosthetic aortic valve who are judged by a heart team, including a cardiac surgeon, to be at high or greater risk for open surgical therapy (e.g., STS predicted risk of operative mortality score ≥ 8% or at a ≥ 15% risk of mortality at 30 days).

Contraindications

The CoreValve Evolut R, Evolut PRO+, and Evolut FX Systems are contraindicated in patients who cannot tolerate Nitinol (titanium or nickel), gold (for Evolut FX Systems alone), an anticoagulation/antiplatelet regimen, or who have active bacterial endocarditis or other active infections.

Warnings

General Implantation of the CoreValve Evolut R, Evolut PRO+, and Evolut FX Systems should be performed only by physicians who have received Medtronic CoreValve Evolut R, Evolut PRO+, or Evolut FX training. This procedure should only be performed where emergency aortic valve surgery can be performed promptly. Mechanical failure of the delivery catheter system and/or accessories may result in patient complications. *Transcatheter aortic valve (bioprosthesis)* Accelerated deterioration due to calcific degeneration of the bioprostheses may occur in: children, adolescents, or young adults; patients with altered calcium metabolism (e.g., chronic renal failure or hyperthyroidism).

Precautions

General Clinical long-term durability has not been established for the bioprosthesis. Evaluate bioprosthesis performance as needed during patient follow-up. The safety and effectiveness of the CoreValve Evolut R, Evolut PRO+, and Evolut FX Systems have not been evaluated in the pediatric population. The safety and effectiveness of the bioprostheses for aortic valve replacement have not been evaluated in the following patient populations: Patients who do not meet the criteria for symptomatic severe native aortic stenosis as defined: (1) symptomatic severe high-gradient aortic stenosis – aortic valve area ≤ 1.0 cm^2 or aortic valve area index ≤ 0.6 cm^2/m^2, a mean aortic valve gradient ≥ 40 mm Hg, or a peak aortic-jet velocity ≥ 4.0 m/s; (2) symptomatic severe low-flow, low-gradient aortic stenosis – aortic valve area ≤ 1.0 cm^2 or aortic valve area index ≤ 0.6 cm^2/m^2, a mean aortic valve gradient < 40 mm Hg, and a peak aortic-jet velocity < 4.0 m/s; with untreated, clinically significant coronary artery disease requiring revascularization; with a preexisting prosthetic heart valve with a rigid support structure in either the mitral or pulmonic position if either the preexisting prosthetic heart valve could affect the implantation or function of the bioprosthesis or the implantation of the bioprosthesis could affect the function of the preexisting prosthetic heart valve; patients with liver failure (Child-Pugh Class C); with cardiogenic shock manifested by low cardiac output, vasopressor dependence, or mechanical hemodynamic support; patients who are pregnant or breastfeeding. The safety and effectiveness of a CoreValve Evolut R, Evolut PRO+, or Evolut FX bioprosthesis implanted within a failed preexisting transcatheter bioprosthesis have not been demonstrated. Implanting a CoreValve Evolut R, Evolut PRO+, or Evolut FX bioprosthesis in a degenerated surgical bioprosthetic valve (transcatheter aortic valve in surgical aortic valve [TAV-in-SAV]) should be avoided in the following conditions: The degenerated surgical bioprosthetic valve presents with: a significant concomitant paravalvular leak (between the prosthesis and the native annulus), is not securely fixed in the native annulus, or is not structurally intact (e.g., wire form frame fracture); partially detached leaflet that in the aortic position may obstruct a coronary ostium; stent frame with a manufacturer-labeled inner diameter < 17 mm. The safety and effectiveness of the bioprostheses for aortic valve replacement have not been evaluated in patient populations presenting with the following: Blood dyscrasias as defined as leukopenia (WBC < 1,000 cells/mm^3), thrombocytopenia (platelet count < 50,000 cells/mm^3), history of bleeding diathesis or coagulopathy, or hypercoagulable states; congenital unicuspid valve; mixed aortic valve disease (aortic stenosis and aortic regurgitation with predominant aortic regurgitation [3-4+]); moderate to severe (3-4+) or severe (4+) mitral or severe (4+) tricuspid regurgitation; hypertrophic obstructive cardiomyopathy; new or untreated echocardiographic evidence of intracardiac mass, thrombus, or vegetation; native aortic annulus size < 18 mm or > 30 mm per the baseline diagnostic imaging or surgical bioprosthetic aortic annulus size < 17 mm or > 30 mm; transarterial access unable to accommodate an 18 Fr introducer sheath or the 14 Fr equivalent EnVeo InLine™ Sheath when using models ENVEOR-US/D-EVPROP2329US or Evolut FX Delivery Catheter System with InLine™ Sheath when using model D-EVOLUTFX-2329 or transarterial access unable to accommodate a 20 Fr introducer sheath or the 16 Fr equivalent EnVeo InLine Sheath when using model ENVEOR-N-US or transarterial access unable to accommodate a 22 Fr introducer sheath or the 18 Fr equivalent Evolut PRO+ InLine Sheath when using model D-EVPROP34US or Evolut FX Delivery Catheter System with InLine Sheath when using model D-EVOLUTFX-34; prohibitive left ventricular outflow tract calcification; sinus of Valsalva anatomy that would prevent adequate coronary perfusion; significant aortopathy requiring ascending aortic replacement; moderate to severe mitral stenosis; severe ventricular dysfunction with left ventricular ejection fraction (LVEF) < 20%; symptomatic carotid or vertebral artery disease; and severe basal septal hypertrophy with an outflow gradient.

Before Use Exposure to glutaraldehyde may cause irritation of the skin, eyes, nose, and throat. Avoid prolonged or repeated exposure to the vapors. Damage may result from forceful handling of the catheter. Prevent kinking of the catheter when removing it from the packaging. The bioprosthesis size must be appropriate to fit the patient's anatomy. Proper sizing of the devices is the responsibility of the physician. Refer to the Instructions for Use for available sizes. Failure to implant a device within the sizing matrix could lead to adverse effects such as those listed below. Patients must present with transarterial access vessel diameters of ≥ 5 mm when using models ENVEOR-US/D-EVPROP2329US/D-EVOLUTFX-2329 or ≥ 5.5 mm when using model ENVEOR-N-US or ≥ 6 mm when using models D-EVPROP34US/D-EVOLUTFX-34, or patients must present with an ascending aortic (direct aortic) access site ≥ 60 mm from the basal plane for both systems. Implantation of the bioprosthesis should be avoided in patients with aortic root angulation (angle between plane of aortic valve annulus and horizontal plane/vertebrae) of > 30° for right subclavian/axillary access or > 70° for femoral and left subclavian/axillary access. For subclavian access, patients with a patent left internal mammary artery (LIMA) graft must present with access vessel diameters that are either ≥ 5.5 mm when using models ENVEOR-L-US/D-EVPROP2329US/D-EVOLUTFX-2329 or ≥ 6 mm when using model ENVEOR-N-US or ≥ 6.5 mm when using models D-EVPROP34US/D-EVOLUTFX-34. Use caution when using the subclavian/axillary approach in patients with a patent LIMA graft or patent RIMA graft. For direct aortic access, ensure the access site and trajectory are free of patent RIMA or a preexisting patent RIMA graft. For transfemoral access, use caution in patients who present with multiplanar curvature of the aorta, acute angulation of the aortic arch, an ascending aortic aneurysm, or severe calcification in the aorta and/or vasculature. If ≥ 2 of these factors are present, consider an alternative access route to prevent vascular complications. Limited clinical data are available for transcatheter aortic valve replacement in patients with a congenital bicuspid aortic valve who are deemed to be at low surgical risk. Anatomical characteristics should be considered when using the valve in this population. In addition, patient age should be considered as long-term durability of the valve has not been established.

During Use If a misload is detected during fluoroscopic inspection, do not attempt to reload the bioprosthesis. Discard the entire system. Inflow crown overlap that has not ended before the 4th node within the capsule increases the risk of an infold upon deployment in constrained anatomies, particularly with moderate-severe levels of calcification and/or bicuspid condition. Do not attempt to direct load the valve. After the procedure, administer appropriate antibiotic prophylaxis as needed for patients at risk for prosthetic valve infection and endocarditis. After the procedure, administer anticoagulation and/or antiplatelet therapy per physician/clinical judgment. Excessive contrast media may cause renal failure. Prior to the procedure, measure the patient's creatinine level. During the procedure, monitor contrast media usage. Conduct the procedure under fluoroscopy. Fluoroscopic procedures are associated with the risk of radiation damage to the skin, which may be painful, disfiguring, and long-term. The safety and efficacy of a CoreValve Evolut R, Evolut PRO+, or Evolut FX bioprosthesis implanted within a transcatheter bioprosthesis have not been demonstrated.

Potential adverse events

Potential risks associated with the implantation of the CoreValve Evolut R, Evolut PRO+, or Evolut FX transcatheter aortic valve may include, but are not limited to, the following: • death • myocardial infarction, cardiac arrest, cardiogenic shock, or cardiac tamponade • coronary occlusion, obstruction, or vessel spasm (including acute coronary closure) • cardiovascular injury (including rupture, perforation, tissue erosion, or dissection of vessels, ascending aorta trauma, ventricle, myocardium, or valvular structures that may require intervention) • emergent surgical or transcatheter intervention (e.g., coronary artery bypass, heart valve replacement, valve explant, percutaneous coronary intervention [PCI], balloon valvuloplasty) • prosthetic valve dysfunction (regurgitation or stenosis) due to fracture; bending (out-of-round configuration) of the valve frame; underexpansion of the valve frame; calcification; pannus; leaflet wear, tear, prolapse, or retraction; poor valve coaptation; suture breaks or disruption; leaks; mal-sizing (prosthesis-patient mismatch); malposition (either too high or too low)/malplacement • prosthetic valve migration/embolization • prosthetic valve endocarditis • prosthetic valve thrombosis • delivery catheter system malfunction resulting in the need for additional recrossing of the aortic valve and prolonged procedural time delivery catheter system component migration/embolization • stroke (ischemic or hemorrhagic), transient ischemic attack (TIA), or other neurological deficits • individual organ (e.g., cardiac, respiratory, renal [including acute kidney failure]) or multi-organ insufficiency or failure • major or minor bleeding that may require transfusion or intervention (including life-threatening or disabling bleeding) • vascular access-related complications (e.g., dissection, perforation, pain, bleeding, hematoma, pseudoaneurysm, irreversible nerve injury, compartment syndrome, arteriovenous fistula, or stenosis) • mitral valve regurgitation or injury • conduction system disturbances (e.g., atrioventricular node block, left bundle-branch block, asystole), which may require a permanent pacemaker infection (including septicemia) • hypotension or hypertension • hemolysis • peripheral ischemia • General surgical risks applicable to transcatheter aortic valve implantation: • bowel ischemia • abnormal lab values (including electrolyte imbalance) • allergic reaction to antiplatelet agents, contrast medium, or anesthesia • exposure to radiation through fluoroscopy and angiography • permanent disability.

Please reference the CoreValve Evolut R, Evolut PRO+, and Evolut FX Instructions for Use for more information regarding indications, warnings, precautions, and potential adverse events.

Caution: Federal Law (USA) restricts these devices to the sale by or on the order of a physician.

The commercial name of the Evolut™ R device is Medtronic CoreValve™ Evolut™ R System, the commercial name of the Evolut™ PRO+ device is Medtronic Evolut™ PRO+ System, and the commercial name of the Evolut™ FX device is Medtronic Evolut™ FX System.

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