

MHIF FEATURED STUDY: ATTR CM

OPEN and ENROLLING: EPIC message to Research MHIF Patient Referral

CONDITION: Transthyretin-Mediated Amyloid Cardiomyopathy	PI: Mosi Bennett, MD	RESEARCH CONTACTS: Sarah Schwager Sarah.Schwager@allina.com 612-863-6257 Jane Fox Jane.Fox@allina.com 612-863-6289	SPONSOR: Ionis Pharmaceuticals
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DESCRIPTION: A Phase 3 Global, Double-Blind, Randomized, Placebo-Controlled Study to Evaluate the Efficacy and Safety of ION-682884 in Patients with Transthyretin-Mediated Amyloid Cardiomyopathy

ION-682884 vs. placebo administered by subcutaneous injection once every 4 weeks in patients with ATTR-CM receiving available background therapy. ION-682884 is a ligand-conjugated antisense drug designed to reduce the production of transthyretin to treat all types of TTR amyloidosis.

CRITERIA LIST/ QUALIFICATIONS:

Inclusion

- Amyloid deposits in cardiac or non-cardiac tissue
- Medical history of HF secondary to hereditary or wild-type ATTR-CM

Exclusion

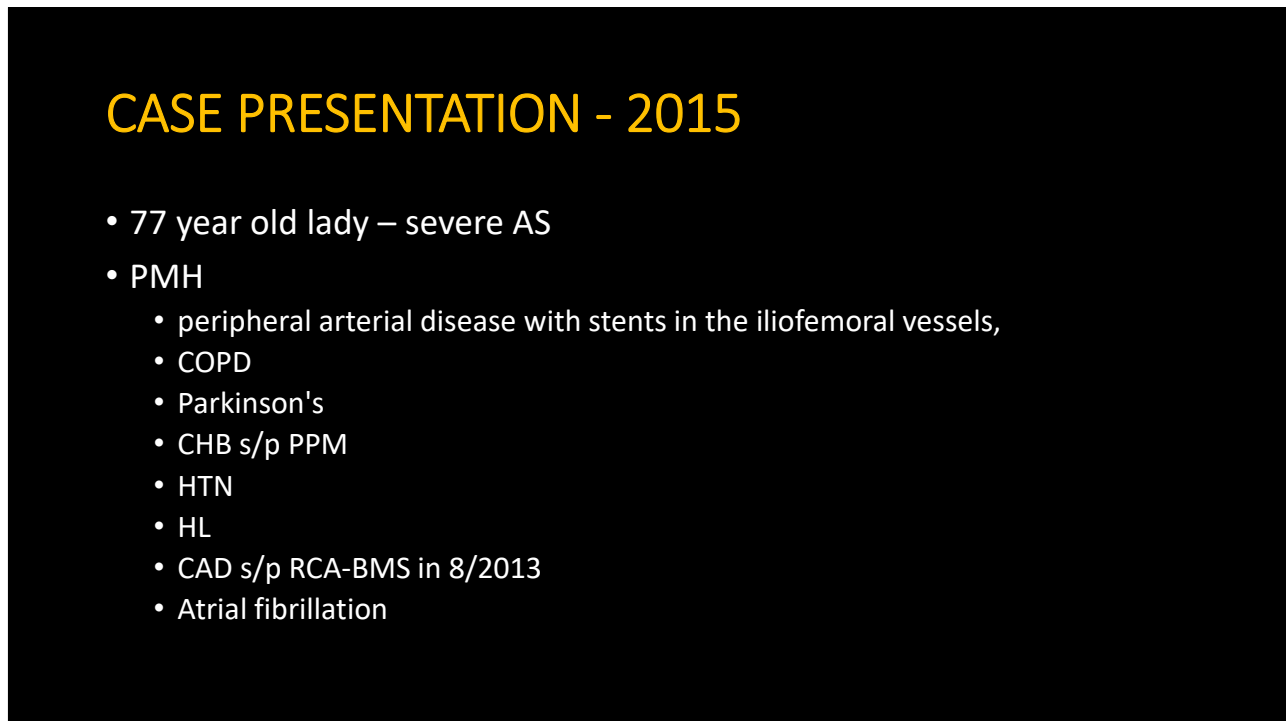
- Cardiomyopathy not primarily caused by ATTR-CM
- Significant co-morbidities
- Current treatment with inotersen, patisiran, diflunisal, doxycycline, non-dihydropyridine calcium-channel blocker

HOPE
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 **Minneapolis
Heart Institute
Foundation**
Creating a world without heart and vascular disease



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ECHO CARDIOGRAM 2015

- The aortic valve is tricuspid- calcified and sclerotic, moderate to severe stenosis and mild regurgitation.
- Peak velocity is 3.4 m/second, mean gradient is 28 mm Hg, valve area is 0.84 cm squared, and dimensionless index is 0.23
- **Dobutamine Stress Echo 2015**
- The aortic valve is calcified, severe aortic stenosis. AVA is 0.7cm² at rest. With dobutamine, Vmax increases to 4.2-4.3 m/sec.

3

2015 TAVR – TRANSAORTIC



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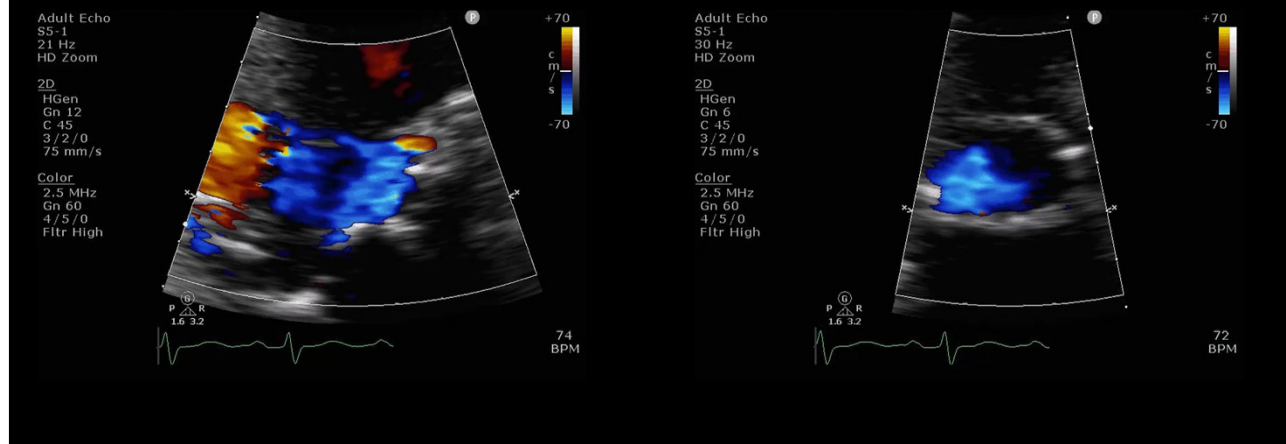
POST PROCEDURE ECHO

- 23 mm SapienXT bioprosthesis in the aortic position with mean gradient of 11.6 mmHg, dimensionless index of 0.54, EOA of 1.5 cm², and mild anteromedial paravalvular regurgitation.

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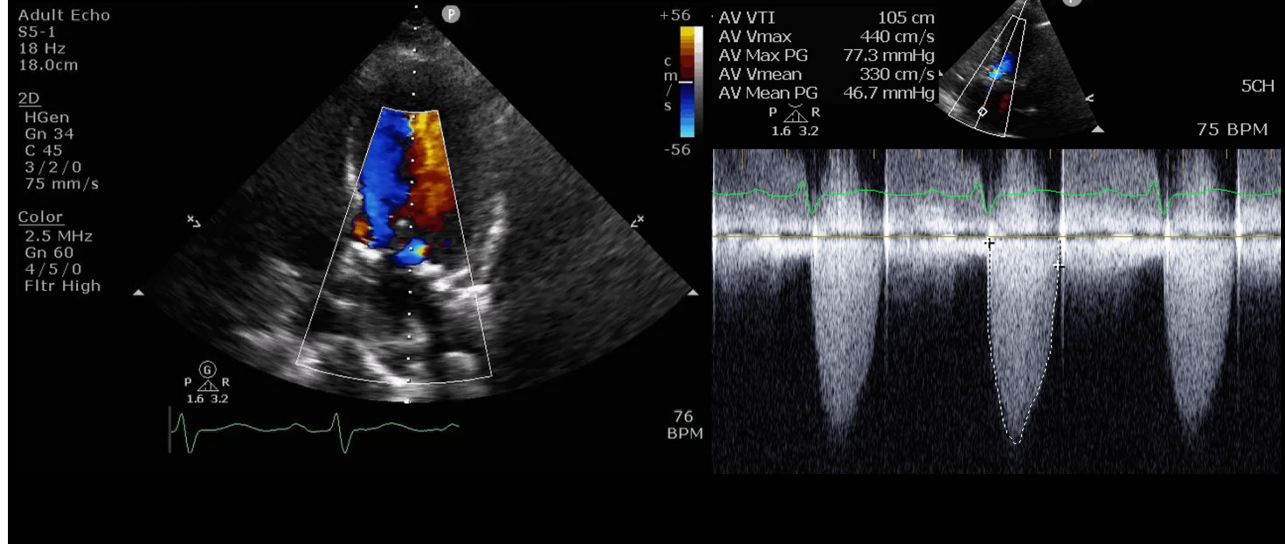
CASE PRESENTATION - 2020

- Developed symptoms of HF



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CASE PRESENTATION - 2020



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WHAT TO DO NOW?!

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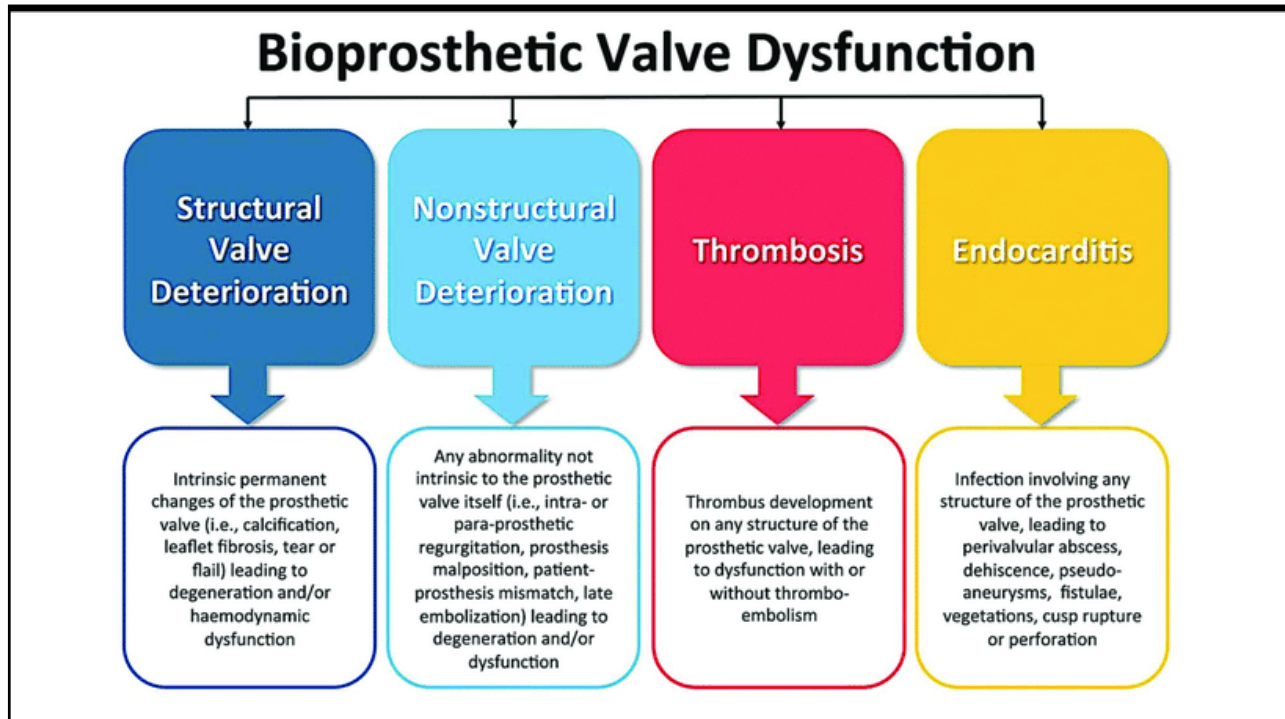
OBJECTIVE

- Background on longevity of these valves and mechanism of deterioration
- Management of TAVR failure – Surgery vs Redo TAVR
- Limitation of TAVR in TAVR
- Bench testing
- Coronary protection: Chimney stent and Basilica

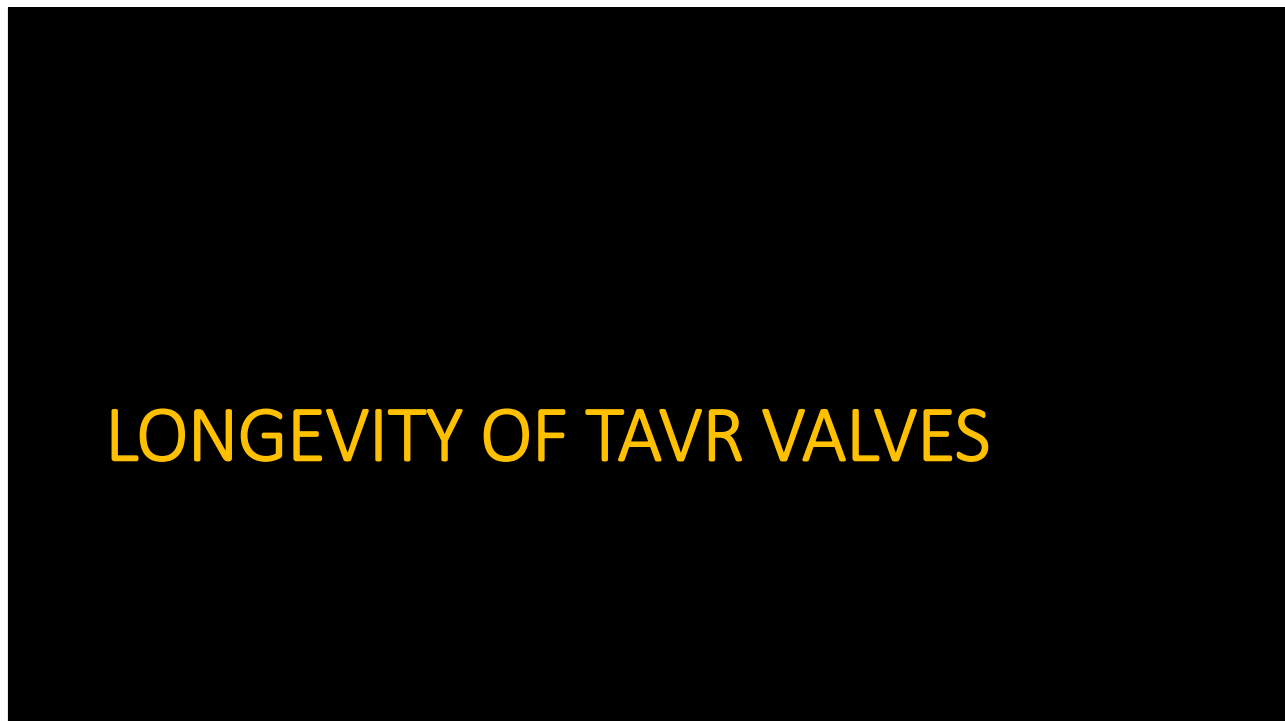
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MECHANISM OF TAVR FAILURE

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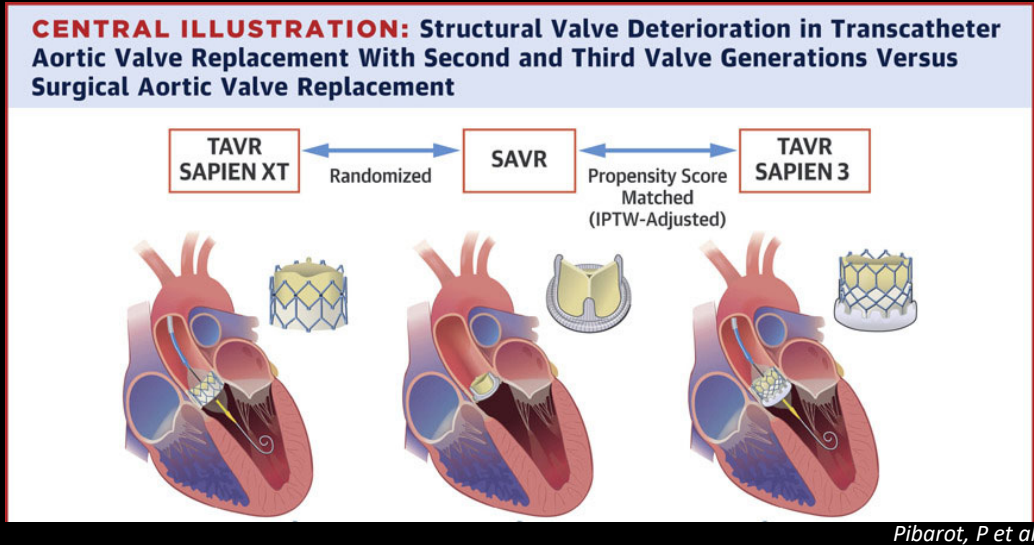


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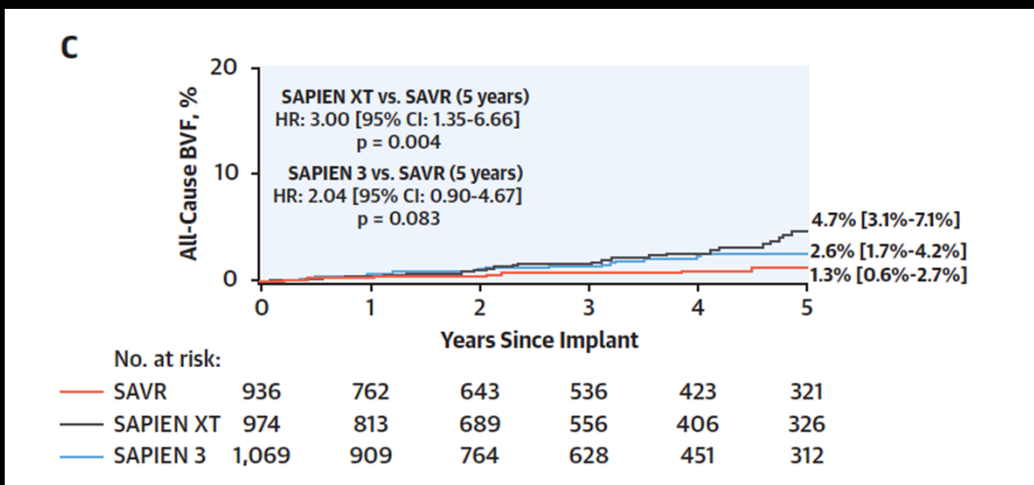


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VALVE DETERIORATION – TAVR VS SAVR



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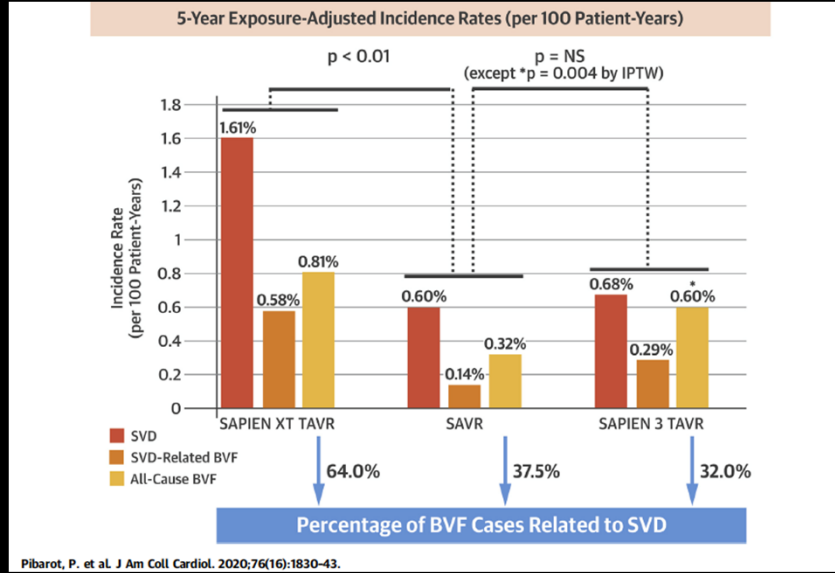


Bioprosthetic Valve Failure:

- 1) Valve dysfunction with clinically expressive criteria or irreversible stage 3 (severe) hemodynamic valve deterioration;
 - 2) Valve reintervention
 - 3) Valve-related death
- Pibarot, P et al, JACC 2020*

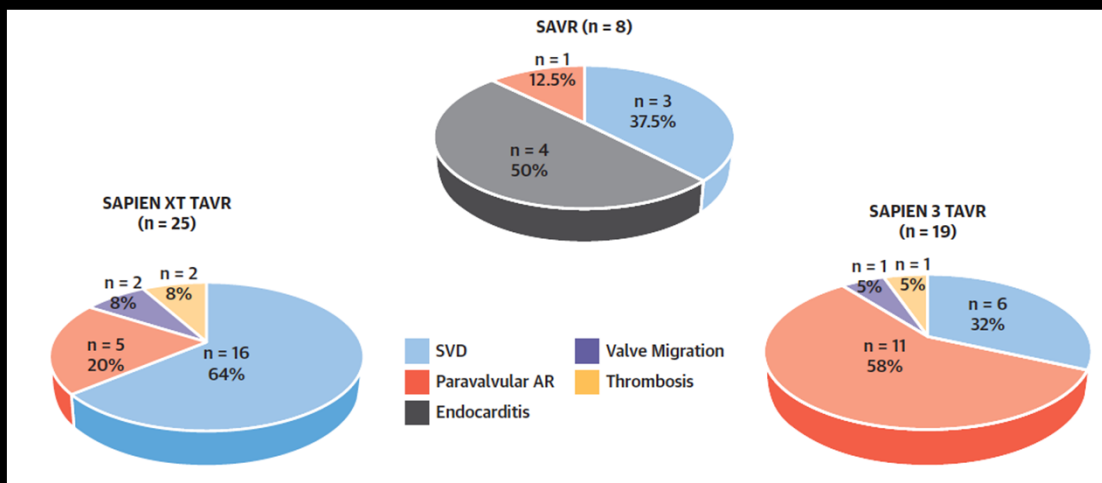
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VALVE DETERIORATION – TAVR VS SAVR



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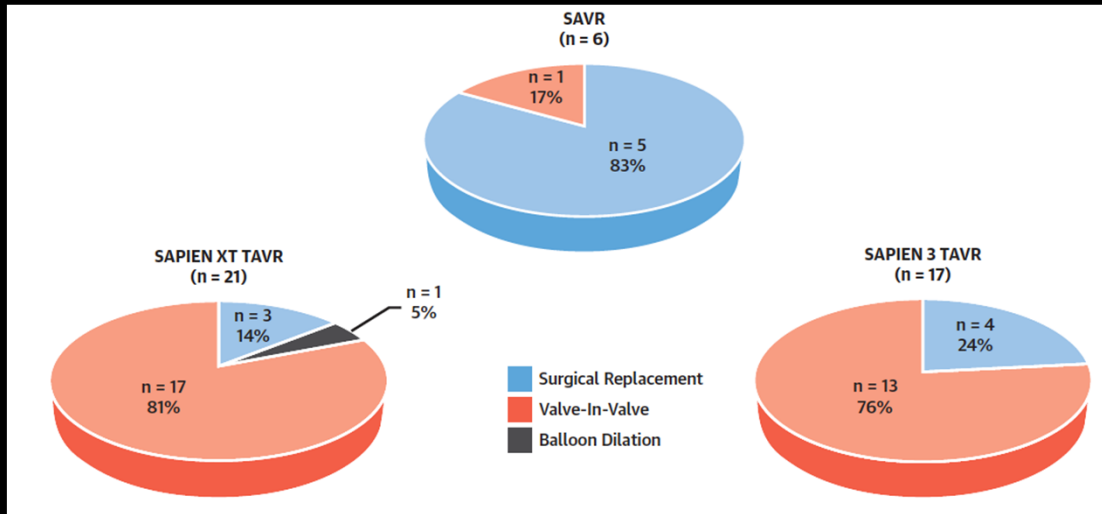
CAUSES OF VALVE FAILURE



Pibarot, P et al, JACC 2020

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TYPE OF VALVE REINTERVENTION



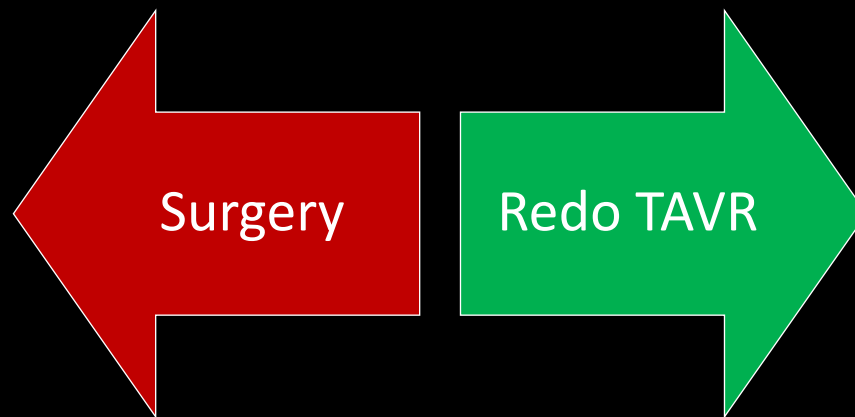
Pibarot, P et al, JACC 2020

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MANAGEMENT OF FAILING TAVRS

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MANAGEMENT OF FAILING TAVRS



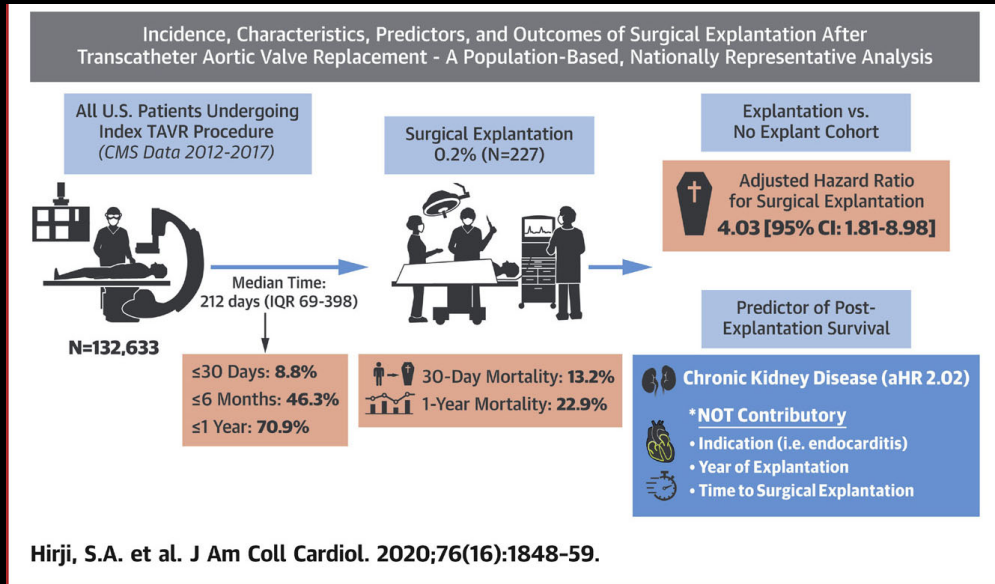
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TAVR EXPLANT CONSIDERATION

- Overall mortality of SAVR after TAVR remains ~10%
- Meticulous surgical technique is required in these commonly intermediate to high-risk surgical patients
- May need root replacement if the valve was implanted > 1 year (Thorani) , particularly in Evolut

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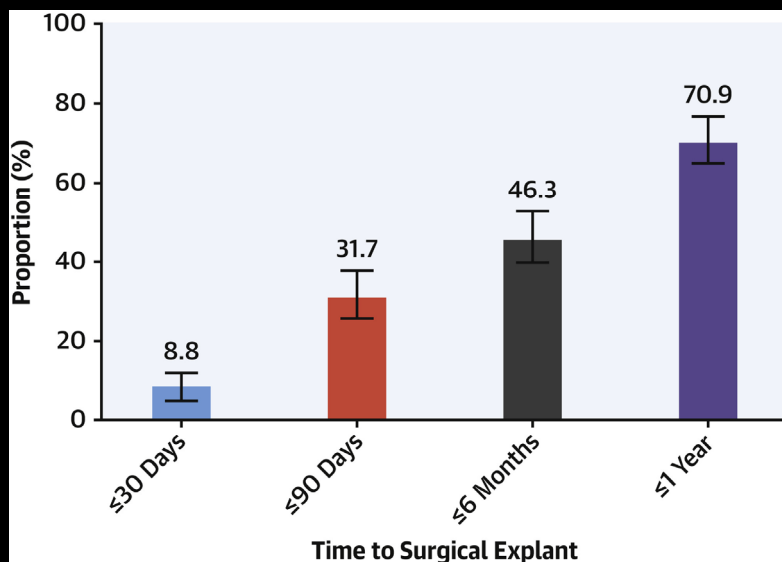
TAVR EXPLANT REGISTRY



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TAVR EXPLANT REGISTRY

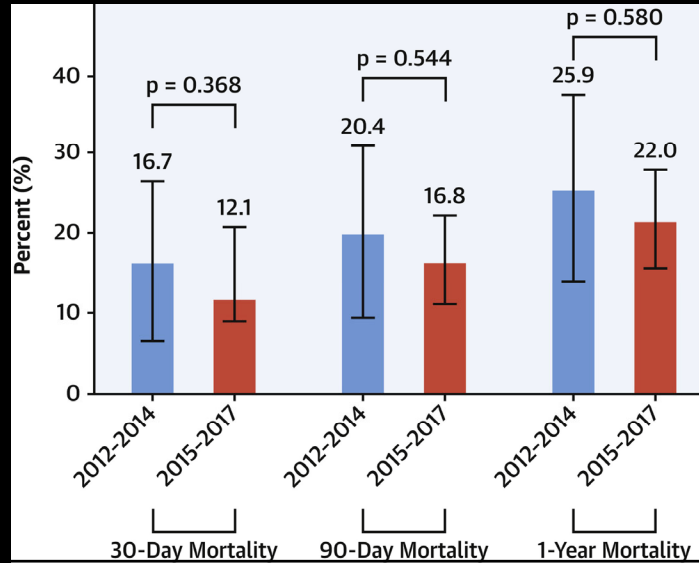
- Indication for the explant:**
- Endocarditis 20.7%
 - Bioprosthetic failure 79.3%



Hirji et al, JACC 2020

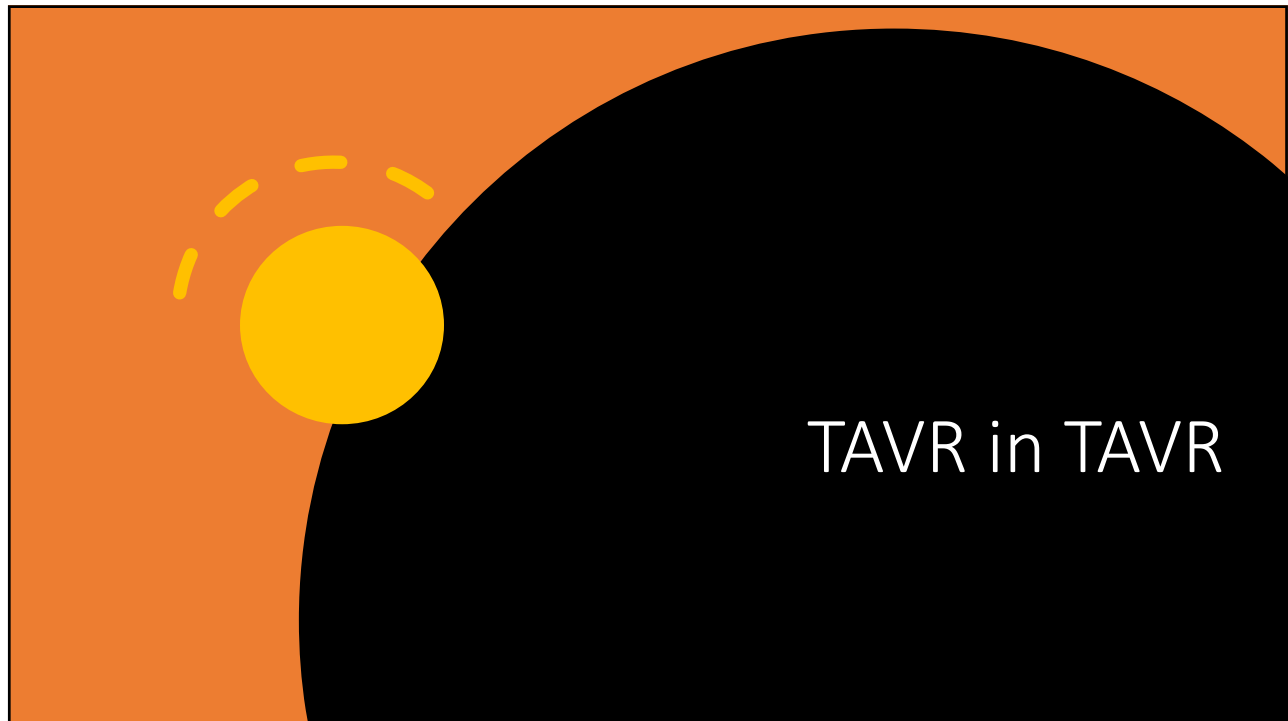
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TAVR EXPLANT REGISTRY



Hirji et al, JACC 2020

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CONCERNS ABOUT REDO TAVR

- Unknown Safety / Mortality
- Challenging Coronary Access
- Coronary Obstruction
- Patient Prosthesis Mismatch
- Uncertainty Valve choice / sizing / positioning

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OUTCOMES OF TAVR IN TAVR



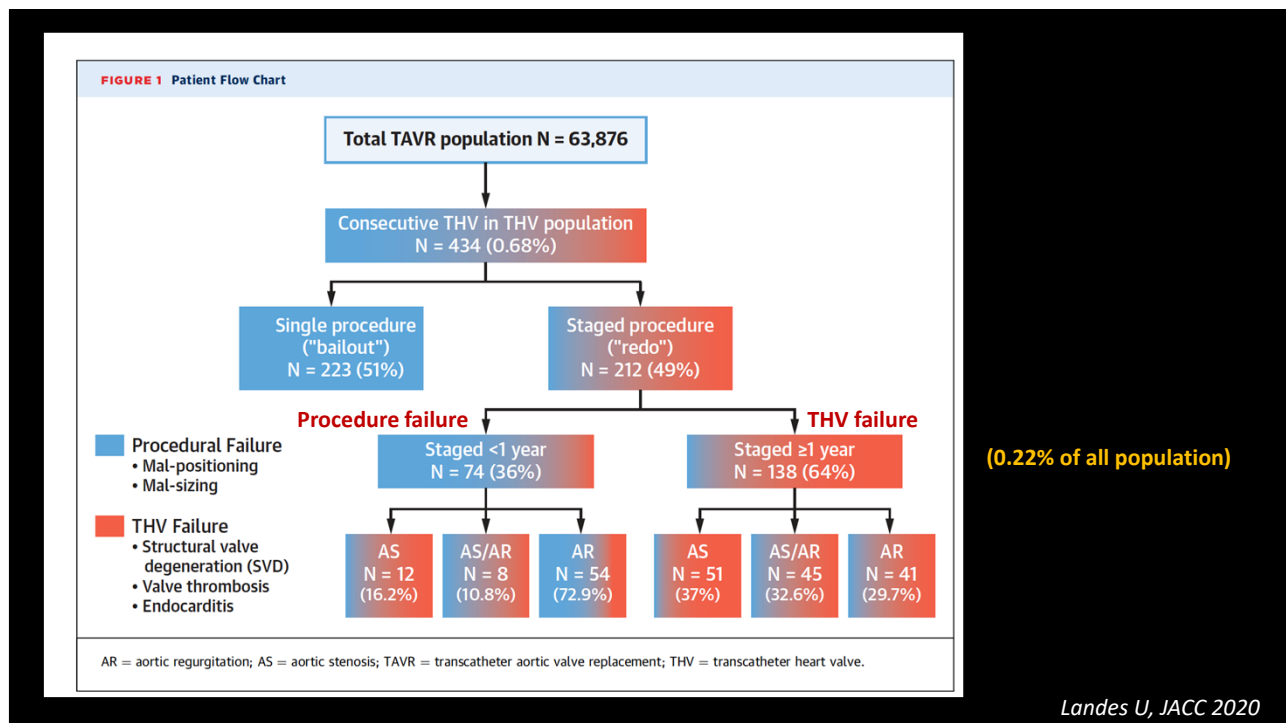
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REDO TAVR REGISTRY

- The Redo-TAVR registry collected data on consecutive patients who underwent redo-TAVR at 37 centers
- Patients were classified as:
 - Probable TAVR failure (procedure related; <1 year of index TAVR)
 - Probable THV failure (Prosthesis related; >1 year of index TAVR)

Landes U, JACC 2020

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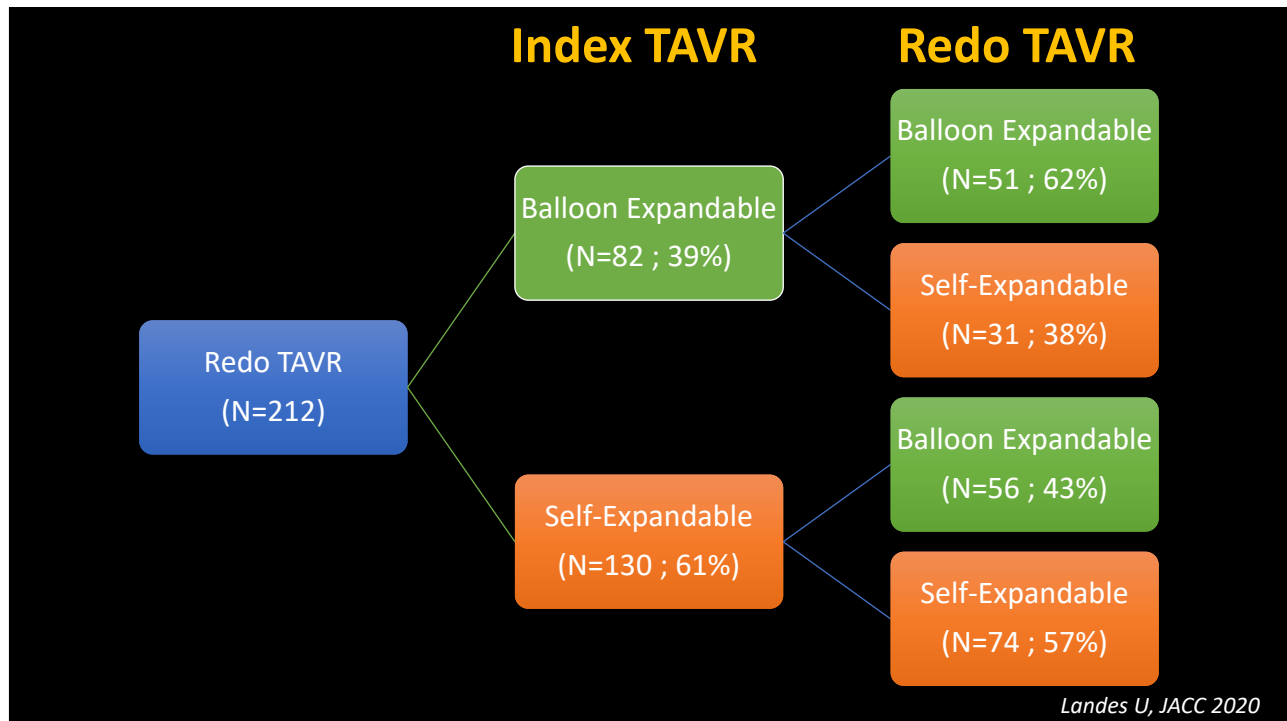
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REDO TAVR REGISTRY

- Median follow-up (post redo-TAVR) was 15 (3 to 36) months
- Similar model was used in 60% of the patients
 - Corevalve (37%)
 - Sapien XT (24%)

Landes U, JACC 2020

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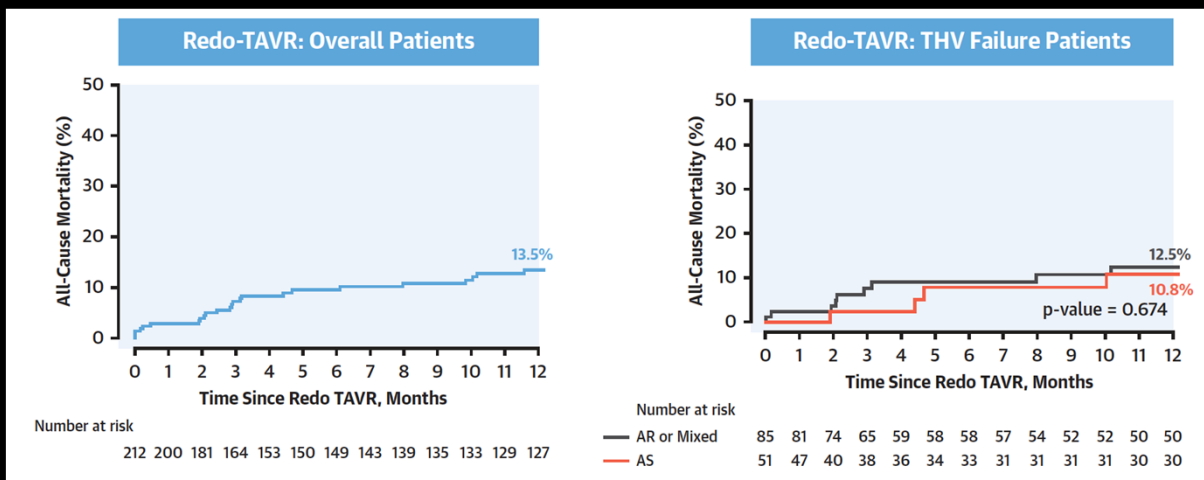
SIZING FOR REDO TAVR

1st THV (mm)	2nd THV (mm)						
	20	23	25	26	27	29	31
20	1	0	0	0	0	0	0
23	0	36	0	11	0	0	0
24	0	1	0	1	0	0	0
25	0	4	0	3	0	0	0
26	0	5	1	46	2	8	0
27	1	1	0	6	0	3	1
29	0	1	1	13	0	35	2
31	0	0	0	1	0	9	6
34	0	0	0	2	0	6	0

Landes U, JACC 2020

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REDO TAVR OUTCOMES

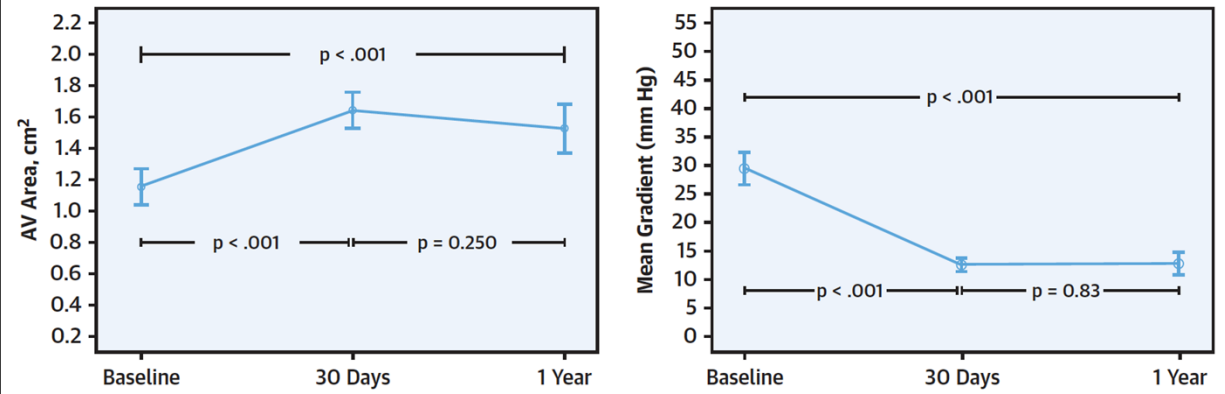


Median follow-up time was 447 (95 to 1,091) days

Landes U, JACC 2020

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REDO TAVR VALVE PERFORMANCE

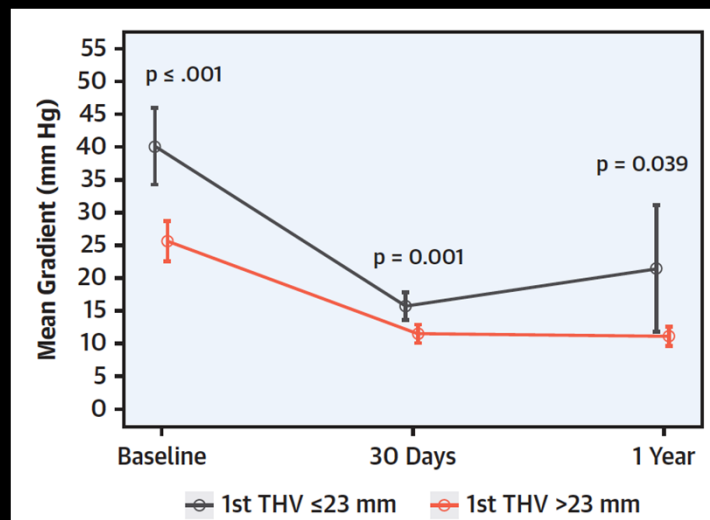


- Transvalvular gradients decreased markedly with a mean of 12.6 +/- 7.5 mm Hg
- Index TAVR residual gradient was 11.1 mmHg

Landes U, JACC 2020

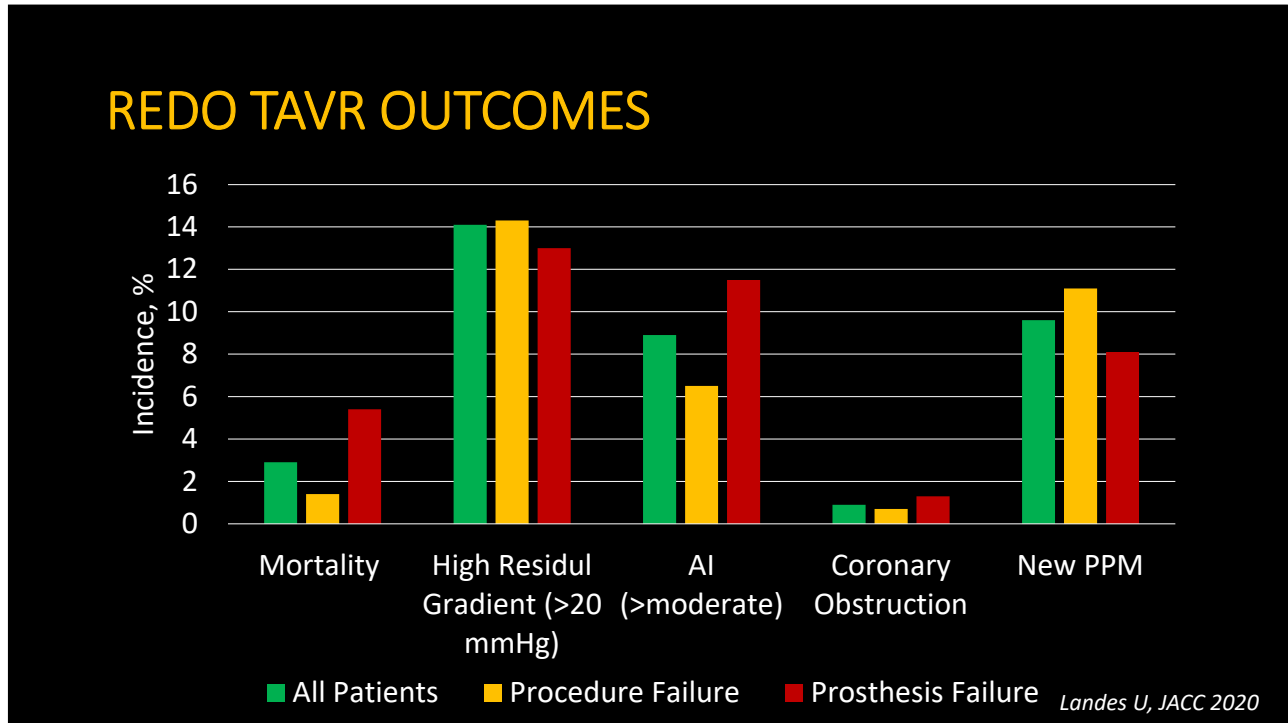
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REDO TAVR VALVE PERFORMANCE

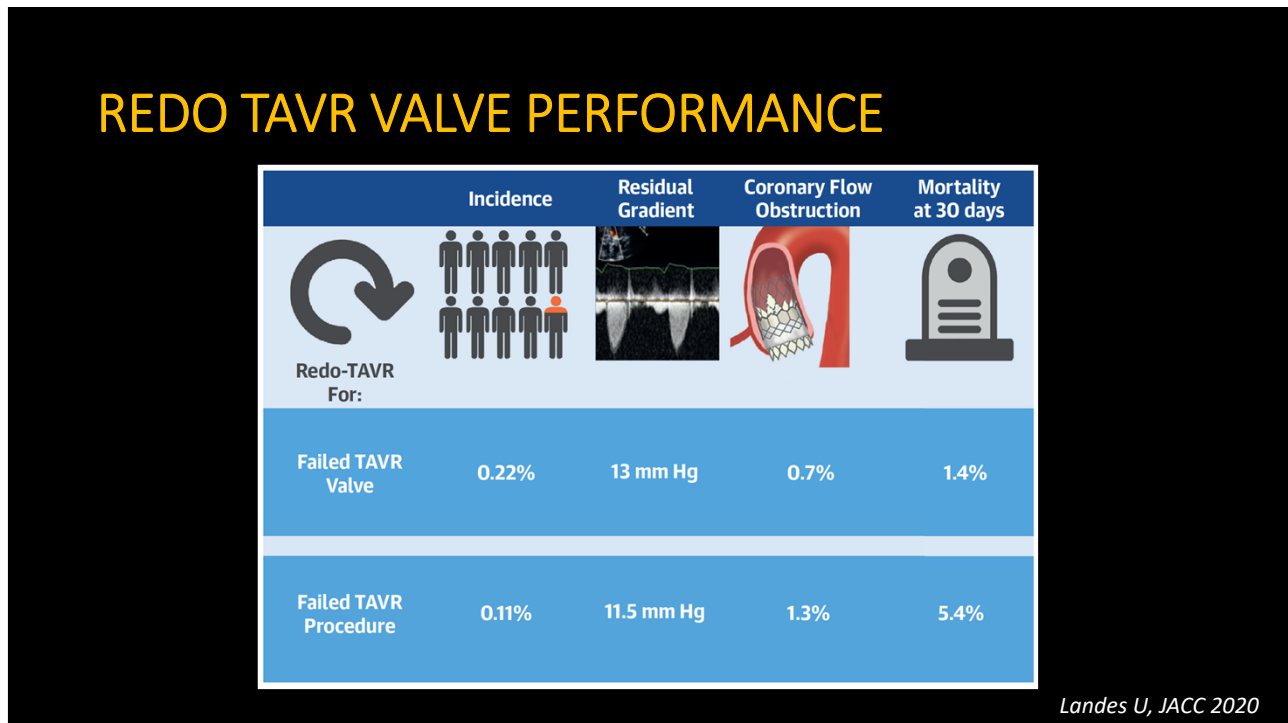


Landes U, JACC 2020

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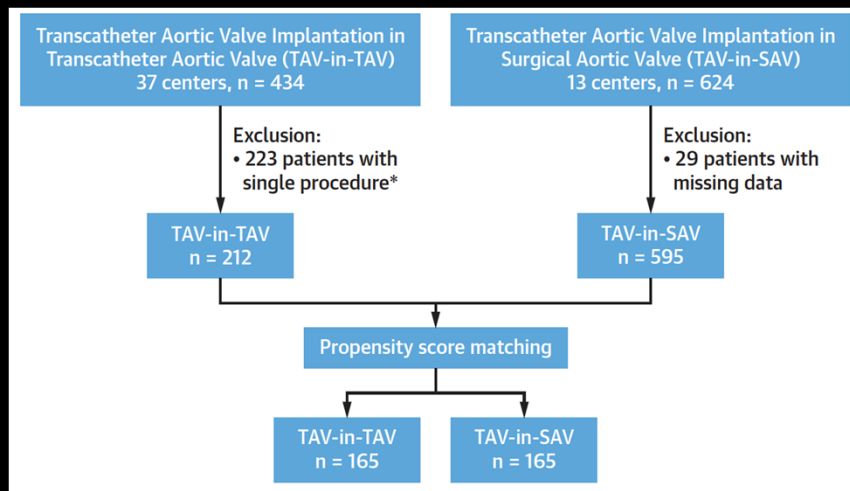


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HOW DOES THAT COMPARE TO TAVR IN SAVR?

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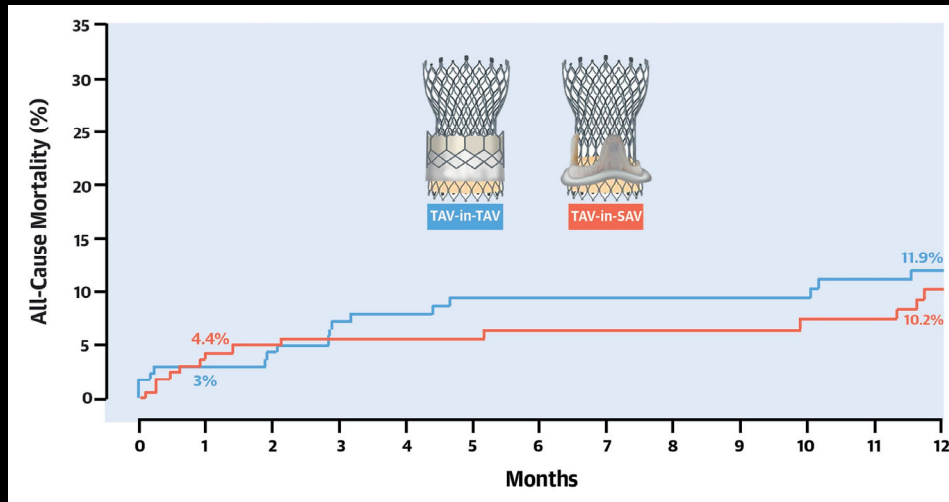
REDO TAVR VS TAVR IN SAVR



Landes U, JACC 2021

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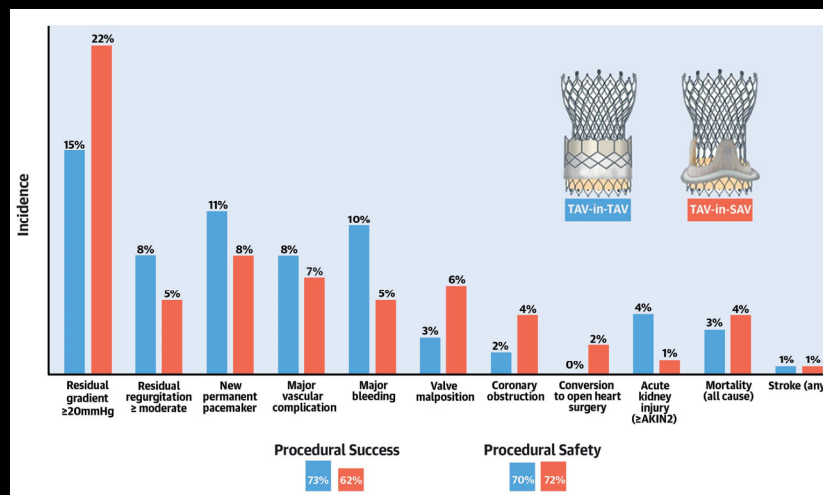
REDO TAVR VS TAVR IN SAVR



Landes U, JACC 2021

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REDO TAVR VS TAVR IN SAVR



Landes U, JACC 2021

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**CONCLUSION: TAVR IN TAVR
APPEARS TO BE SAFE!**
IS THAT THE FULL STORY?!

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LIMITATIONS OF REDO TAVR REGISTRY





- The denominator is missing
- Only low risk patients are offered TAVR in TAVR
- What about patients who have TAVR dysfunction and were not candidate for redo TAVR?

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TAVR IN TAVR PLANNING

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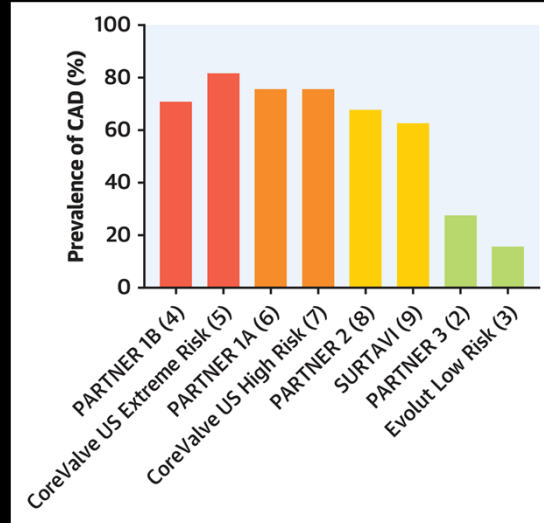
TAVR IN TAVR
IS AN ART

-  MAINTAIN CORONARY PERFUSION
-  MAINTAIN CORONARY ACCESS
-  CHOOSING/POSITIONING THE SECOND VALVE
-  AVOID PATIENT PROSTHESIS MISMATCH

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CAD IN TAVR PATIENTS IN CLINICAL TRIALS

- About 50% of TAVR patients have CAD
- 11% have LM disease
- 50% have LAD disease
- About 10% will present with ACS within 2 years
- Success rate of PCI is only 90% in those with Corevalve



Kleinman NS, et al CRT 2019.

Vilalta V, et al, JACCI Intv 2018;11:2523-33

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Screening and Procedural Considerations

Original THV Design	Original THV Characteristics	Anatomy	Failure Mode
Type	THV position in native anatomy	Coronary Access	PVL – malposition / calcification / size
Size	Expansion shape and ID/OD	Calcifications	Denegation – stenosis vs regurgitation
Frame design	Commissure Alignment	Sinus / VTC	Leaflet thrombosis
Leaflet Attachment		STJ diameter and Sinus Heights Room to expand original THV	

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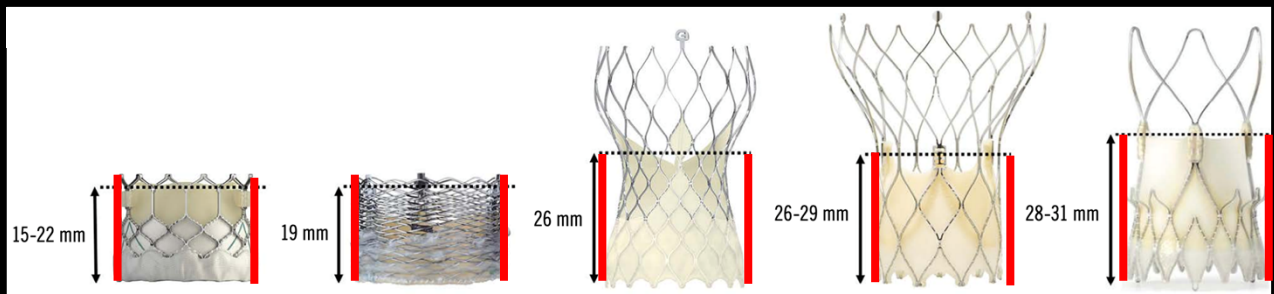
KEY TERMINOLOGY

- **Commissure** – Leaflet outflow attachment
- **Valve To Coronary:** distance measured from the valve to coronary ostia
- **Risk Plane**
- **Valve To Aorta (VTA) or Valve To STJ:** Distance between the valve stent frame to the aorta or STJ

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RISK PLANE

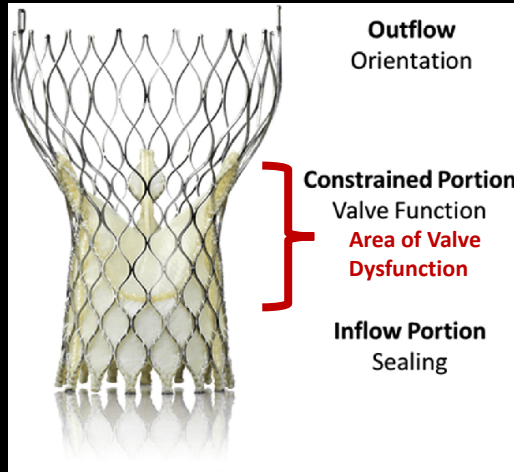
- Level at which the stent frame of the first THV will be covered after the leaflets are displaced vertically with the implantation of the second THV



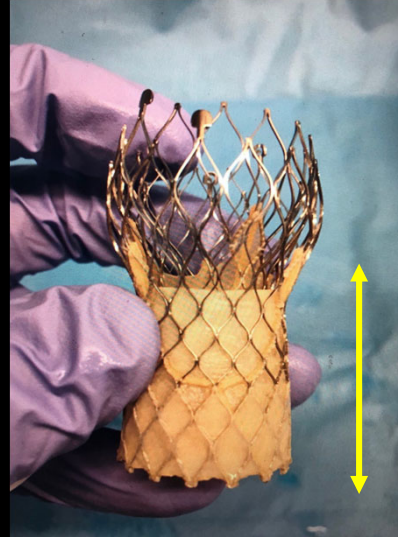
THV in THV → Large covered stent!

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SAPIEN IN EVOLUT

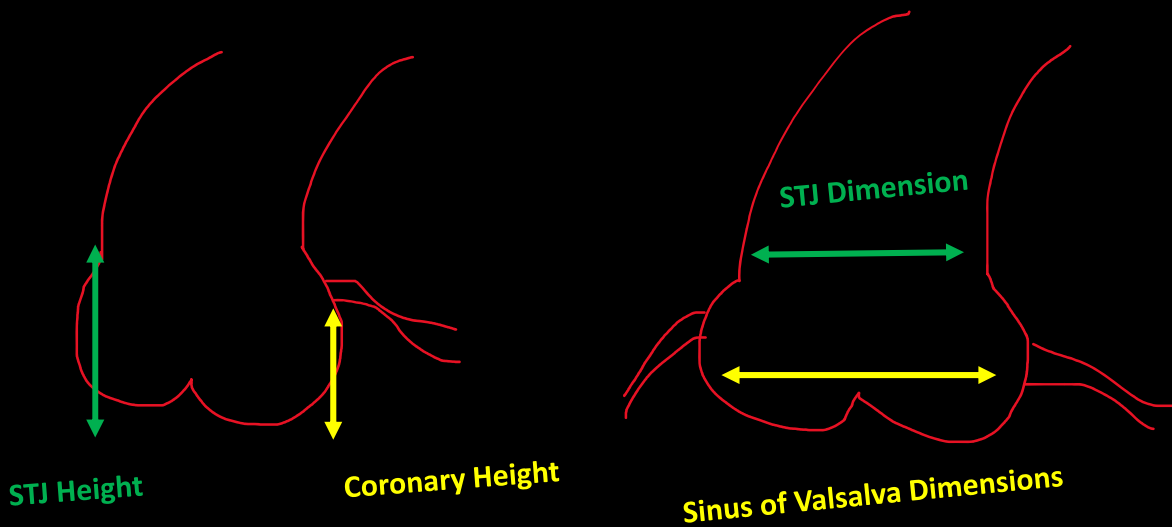


Need to be covered by the new valve



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PATIENT RELATED FACTORS



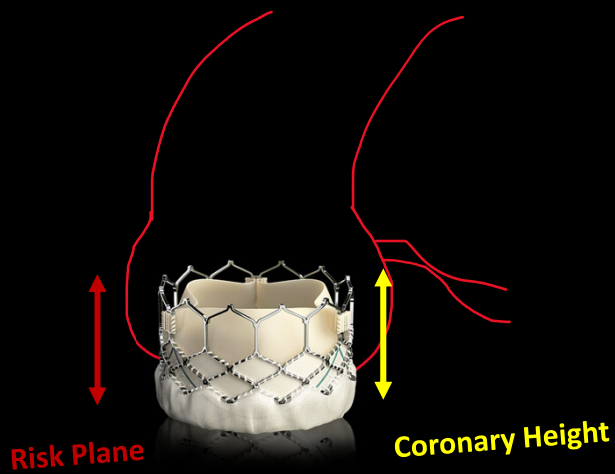
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VALVE – PATIENT INTERPLAY

Possible scenarios

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VALVE PATIENT INTERPLAY – SCENARIO #1



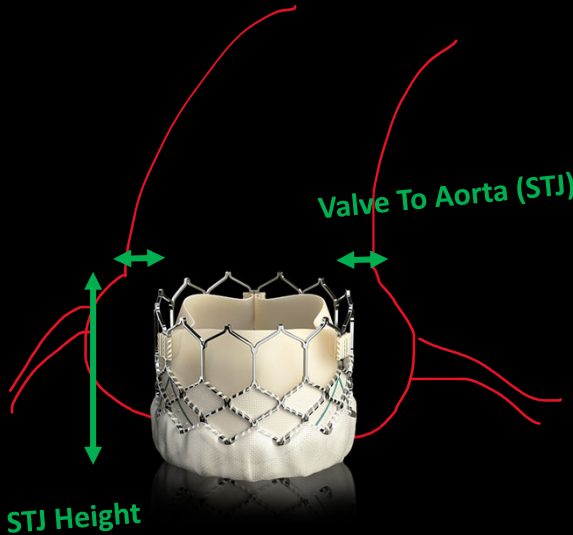
Coronary Artery ABOVE
Risk Plane



THV in THV is likely
feasible

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VALVE PATIENT INTERPLAY – SCENARIO #2



Coronary Artery **BELLOW** Risk Plane



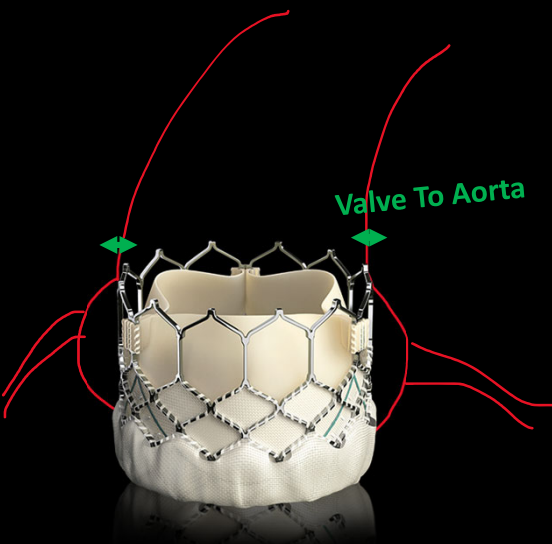
Large VTA distance / Valve Bellow STJ



THV in THV is likely feasible

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VALVE PATIENT INTERPLAY – SCENARIO #3



Coronary Artery **BELLOW** Risk Plane



Small VTA distance



Sinus Sequestration!
THV in THV is likely NOT feasible

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PLANNING SECOND VALVE

VIRTUAL CT ANALYSIS

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Feasibility of Coronary Access and Aortic Valve Reintervention in Low-Risk TAVR Patients



Toby Rogers, MD, PhD,^{a,b} Benjamin C. Gre
Paige Craig, MPH,^a Christian Shults, MD,^d
John Goncalves, MD,^h Robert Levitt, MD,ⁱ
David Butzel, MD,^m Scott Buchanan, MD,ⁿ
Federico Asch, MD,^g Hector M. Garcia-Garc
Ron Waksman, MD^o

Risk of Coronary Obstruction and Feasibility of Coronary Access After Repeat Transcatheter Aortic Valve Replacement With the Self-Expanding Evolut Valve

A Computed Tomography Simulation Study

Brian J. Forrestal, MBBS; Brian C. Case, MD; Charan Yerasi, MD; Corey Shea, MS; Rebecca Torguson, MPH;
Clayton Zhang, MD, MSc, PhD; David M. Teitelbaum, MD; Scott Ali, MBBS; Lowell F. Satler, MD;
; Jaffar M. Khan, MD, PhD; Jaffar M. Khan, MD, PhD; Jaffar M. Khan, MD, PhD; Jaffar M. Khan, MD, PhD;

JACC: CARDIOVASCULAR INTERVENTIONS
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VOL. 13, NO. 22, 2020

Risk of Coronary Obstruction Due to Sinus Sequestration in Redo Transcatheter Aortic Valve Replacement



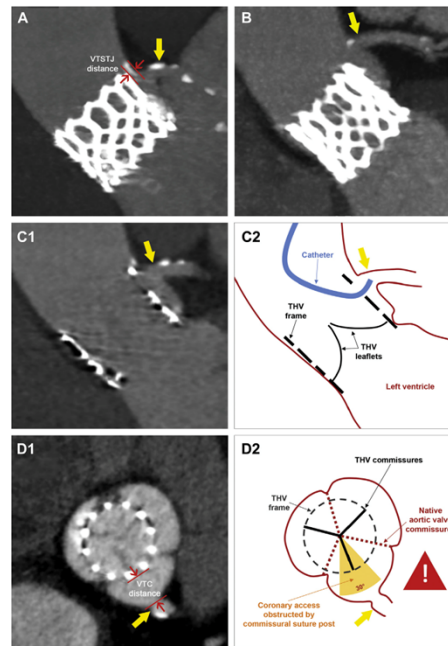
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LOW RISK TRIAL

- Sapien valve
- Enrolled 200 subjects
- 137 subjects had 30-day CTA + adequate image quality for analysis
- Age: mean 74 years
- Comprehensive CTA assessment

Rogers, T, et al, JACC Intv 2020

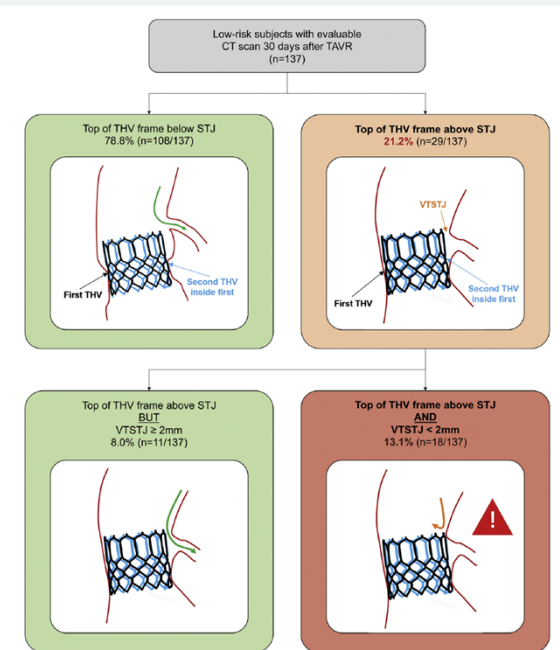
CENTRAL ILLUSTRATION Aortic Root Anatomies After TAVR with a Balloon-Expandable Valve



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

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FIGURE 2 Feasibility of Future TAVR-in-TAVR



STJ = sinotubular junction; TAVR = transcatheter aortic valve replacement; VTSTJ = valve-to-sinotubular junction distance; other abbreviations as in Figure 1.

13% of the patient will NOT be a candidate for TAVR in TAVR

Rogers, T, et al, JACC Intv 2020

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THE COREVALVE EVOLUT PRO PROSPECTIVE REGISTRY (EPROMPT; NCT03423459)

- 81 patients had Evolut/ Corevalve
- CTA was performed 30 days after TAVR

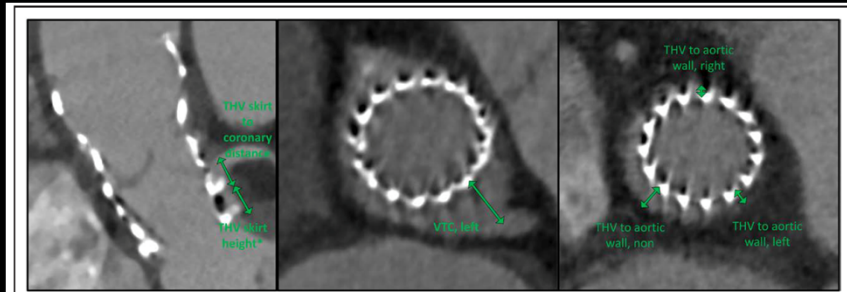


Figure 2. Computed tomographic images with measurements used to calculate the risk of obstruction and feasibility of coronary access.

Forrestal, et al, CIRC Intv 2020

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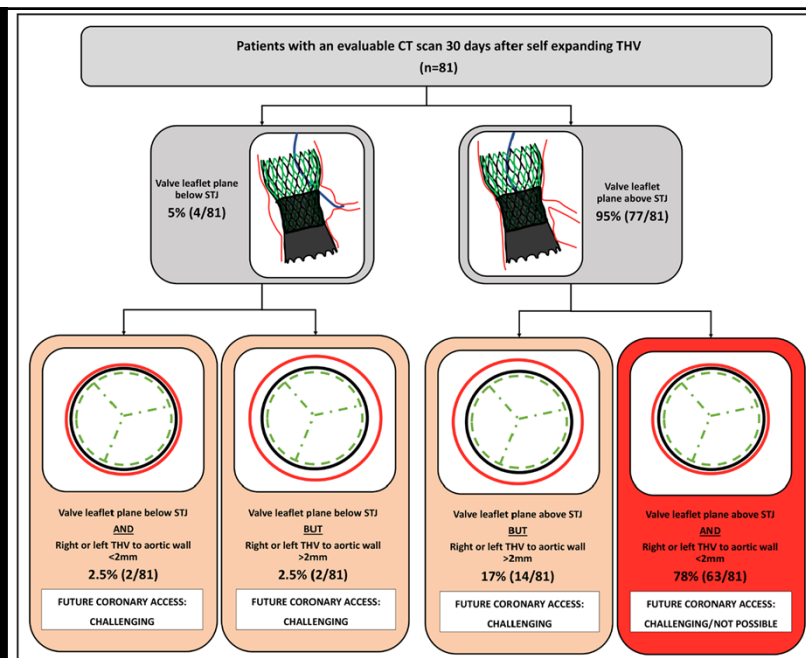
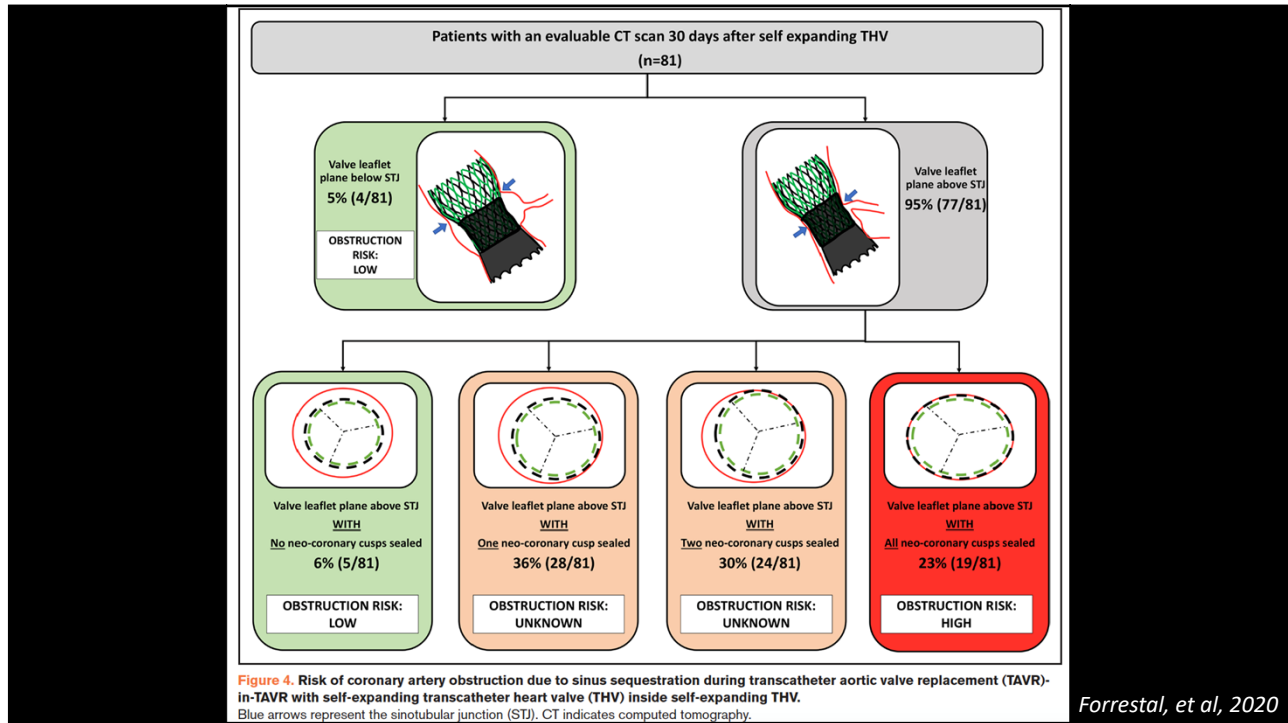


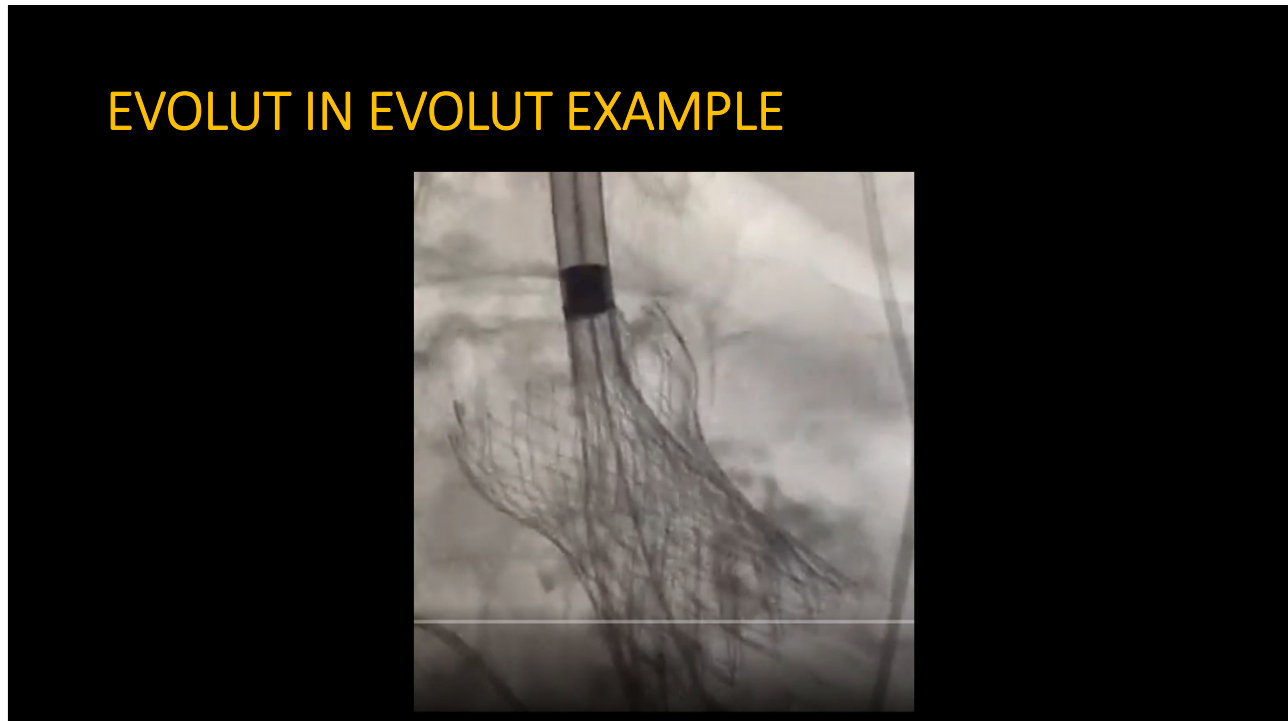
Figure 5. Feasibility of future coronary access after transcatheter aortic valve replacement (TAVR)-in-TAVR with self-expanding transcatheter heart valve (THV) inside self-expanding THV. CT indicates computed tomography; and STJ, sinotubular junction.

Forrestal, et al, 2020

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THE COREVALVE EVOLUT PRO PROSPECTIVE REGISTRY (EPROMPT; NCT03423459)

WHAT THE STUDY ADDS

Our computed tomography–based simulation predicts the following:

- There is a risk of coronary obstruction due to sinus sequestration after TAVR-in-TAVR with an Evolut PRO or Evolut PRO+ transcatheter heart valve in up to **1 in 4 patients**.
- Future coronary access is likely to be **not possible**, or exceedingly challenging, in up to **4 of 5 patients** after TAVR-in-TAVR.

Forrestal, et al, CIRC Intv 2020

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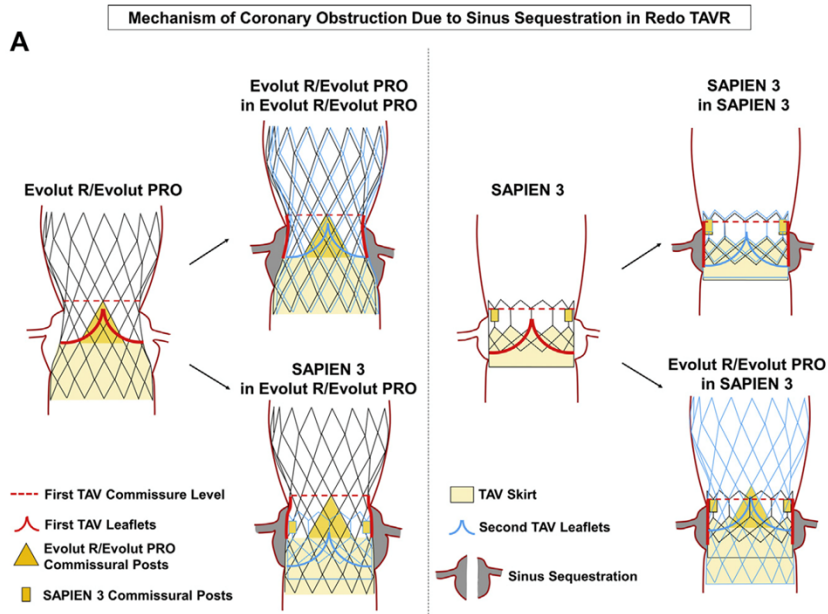
THE RESOLVE REGISTRY (CEDARS-SINAI)

- **Virtual analysis of Post-TAVR CT**
 - 66 patients → Evolut R or Evolut PRO
 - 345 patients → Sapien S3
- **Sinus Sequestration:**
 - Prior TAV commissure level was above sinotubular junction (STJ)
 - The distance between TAV and STJ was <2.0 mm in each coronary sinus

Makkar, et al, JACC Intv 2020

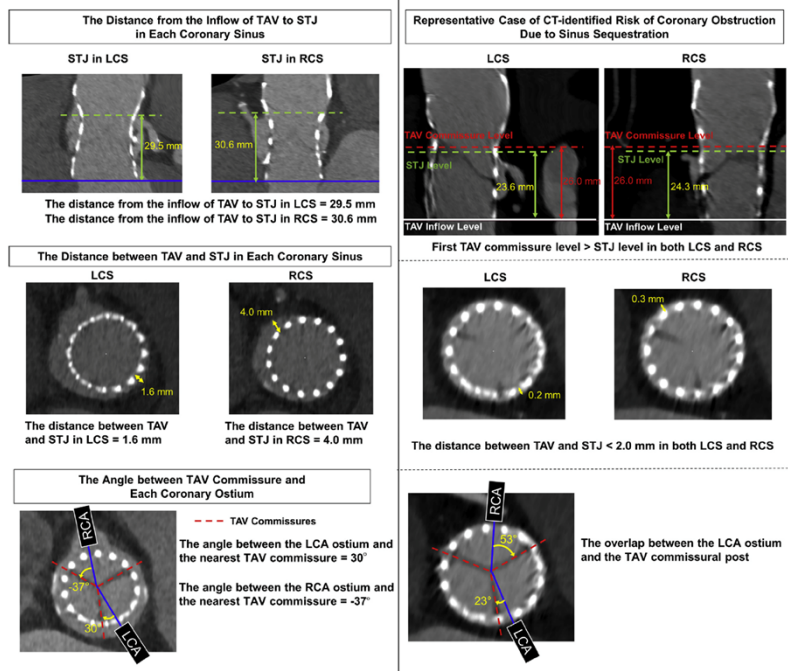
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FIGURE 1 Mechanism of Coronary Obstruction Due to Sinus Sequestration in Redo TAVR and Definition of the CT-Identified Risk



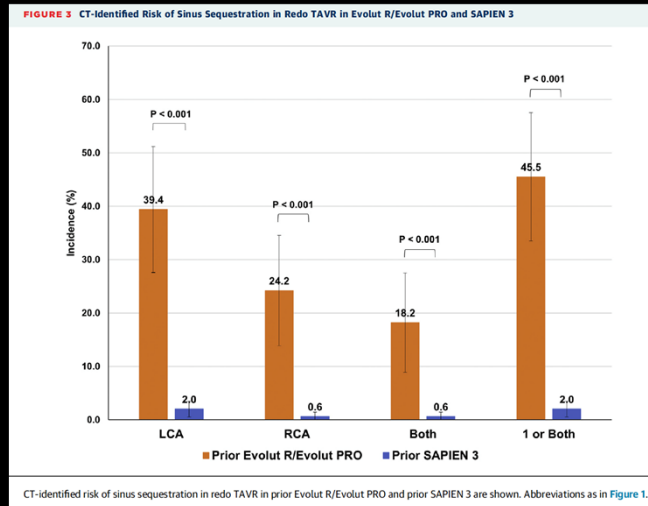
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FIGURE 2 CT Measurements



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The RESOLVE Registry (Cedars-Sinai)



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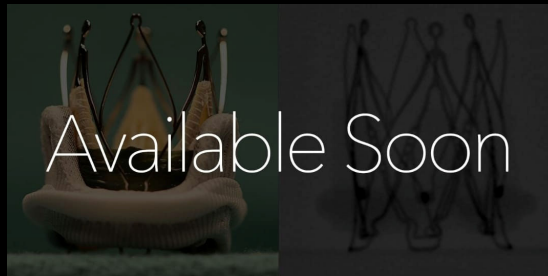
PLANNING FEASIBLE PATIENTS

REMAINS A CHALLENGE

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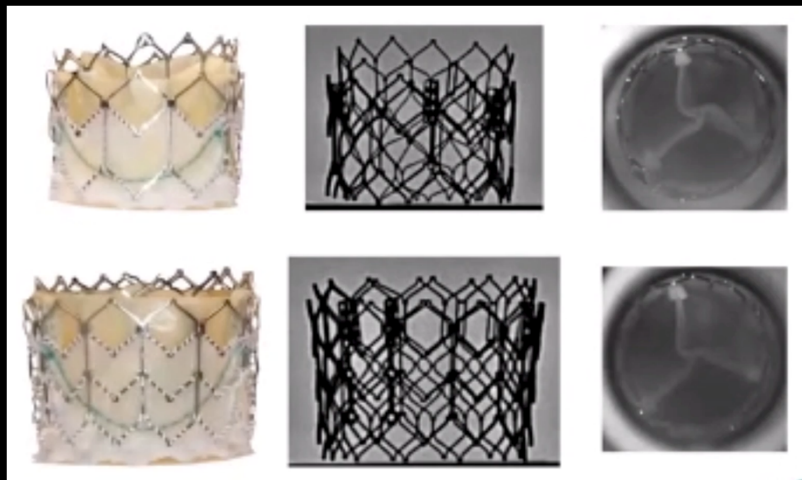
VALVE SIZING – MANY UNKNOWNNS

- Same index valve size if using the same brand?
 - 1st valve expansion
- Should we size based on native anulus?
- Should we use ViV APP?



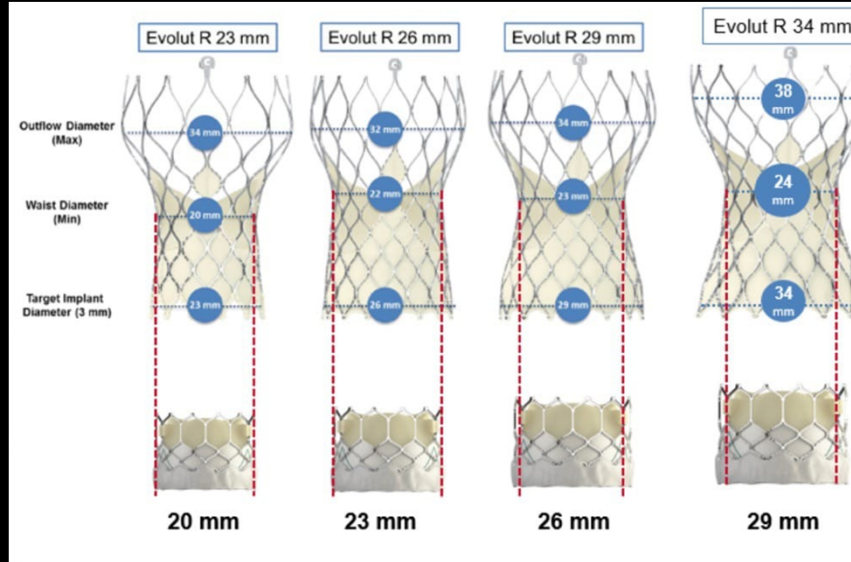
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VALVE SIZING – AVOID PINWHEELING



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VALVE SIZING



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VALVE SIZING

- No data available for valve sizing for Accurate Neo, Medtronic, or Portico valve

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Valve Positioning

- Very limited data
- More straight forward when using same brand
- More challenging when then index valve is self expandable

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REPEAT TAVR AND IMPLICATIONS FOR THV PERFORMANCE: INSIGHTS FROM BENCH TESTING

Index Valve



2nd Valve

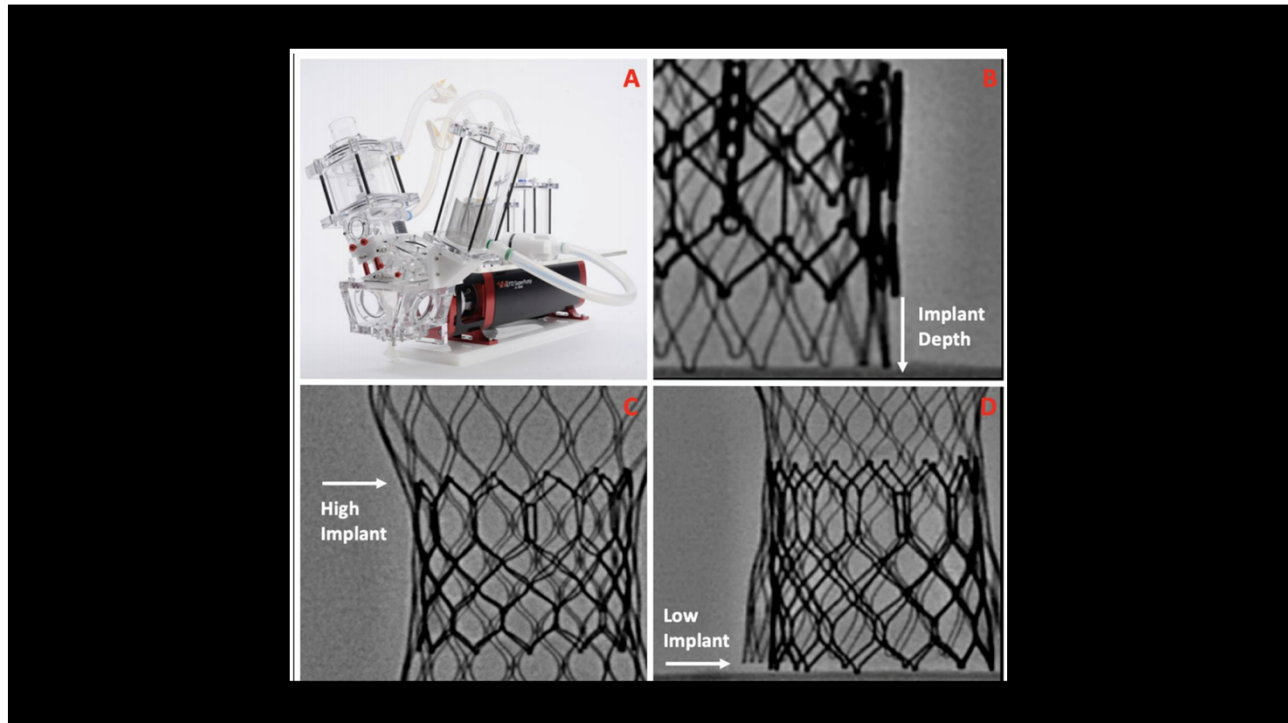
Sapien 3, Evolut Pro, Acurate neo, Allegra, and Portico

Outcome

Hydrodynamic function was evaluated using a pulse duplicator
Multimodality imaging was performed

Sathanathan et al. Eurointervention 2021

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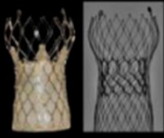
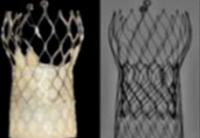
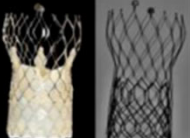
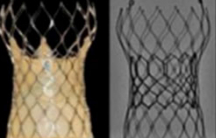



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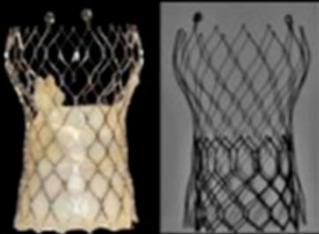
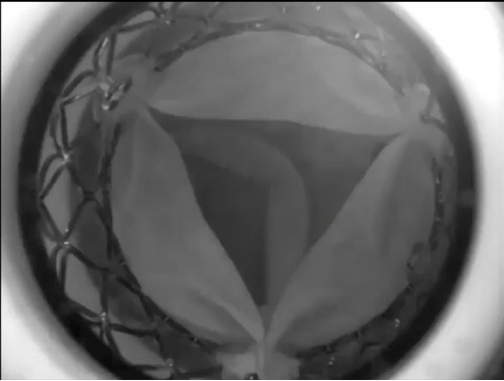
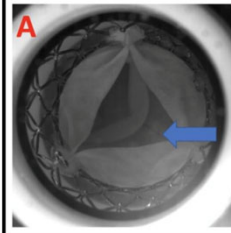
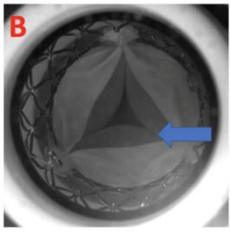
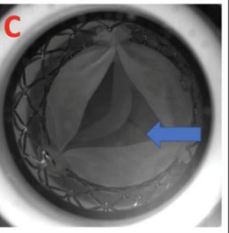
Index Valve 23 mm Sapien XT

<p>MG: 9.2mmHg EOA: 2.1cm² RF: 18.7%</p>	<p>26mm Evolut +4mm</p> <p>MG: 6.1mmHg EOA: 2.7cm² RF: 5.3%</p>	<p>Small ACURATE +4mm</p> <p>MG: 5.6mmHg EOA: 2.7cm² RF: 10.3%</p>	<p>23mm Allegra +4mm</p> <p>MG: 9.6mmHg EOA: 2.1cm² RF: 8.0%</p>	<p>25mm Portico +4mm</p> <p>MG: 8.8mmHg EOA: 2.1cm² RF: 9.5%</p>
<p>23mm Sapien 3</p> <p>MG: 9.2mmHg EOA: 2.1cm² RF: 18.7%</p>	<p>26mm Evolut 0mm</p> <p>MG: 5.6mmHg EOA: 2.3cm² RF: 6.9%</p>	<p>Small ACURATE 0mm</p> <p>MG: 7.8mmHg EOA: 2.4cm² RF: 10.2%</p>	<p>23mm Allegra 0mm</p> <p>MG: 8.0mmHg EOA: 2.2cm² RF: 7.6%</p>	<p>25mm Portico 0mm</p> <p>MG: 9.6mmHg EOA: 2.1cm² RF: 1%</p>
	<p>26mm Evolut -4mm</p> <p>MG: 8.0mmHg EOA: 2.7cm² RF: 4.6%</p>	<p>Small ACURATE -4mm</p> <p>MG: 11.1mmHg EOA: 1.9cm² RF: 14.4%</p>	<p>23mm Allegra -4mm</p> <p>MG: 9.8mmHg EOA: 2.0cm² RF: 8.8%</p>	<p>25mm Portico -4mm</p> <p>MG: 9.6mmHg EOA: 2.0cm² RF: 10%</p>

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EVOLUT 23		EVOLUT 26		EVOLUT 29	
20mm Sapien 3 High	23mm Sapien 3 High	23mm Sapien 3 Low	23mm Sapien 3 High	26mm Sapien 3 Low	
					
20mm S3 <u>Nominal volume</u> Embolized	23mm S3 <u>Nominal volume</u> Embolized	MG: 5.6mmHg EOA: 2.8cm ² RF: 26.2%	23mm S3 <u>Nominal volume</u> Embolized	MG: 4.8mmHg EOA: 3.0cm ² RF: 25.9%	
20mm S3 +1cc MG: 11.5mmHg EOA: 1.8cm ² RF: 17.6%	23mm S3 +1cc MG: 4.3mmHg EOA: 3.3cm ² RF: 6.0%		23mm S3 +1cc MG: 6.6mmHg EOA: 2.6cm ² RF: 18.9%		

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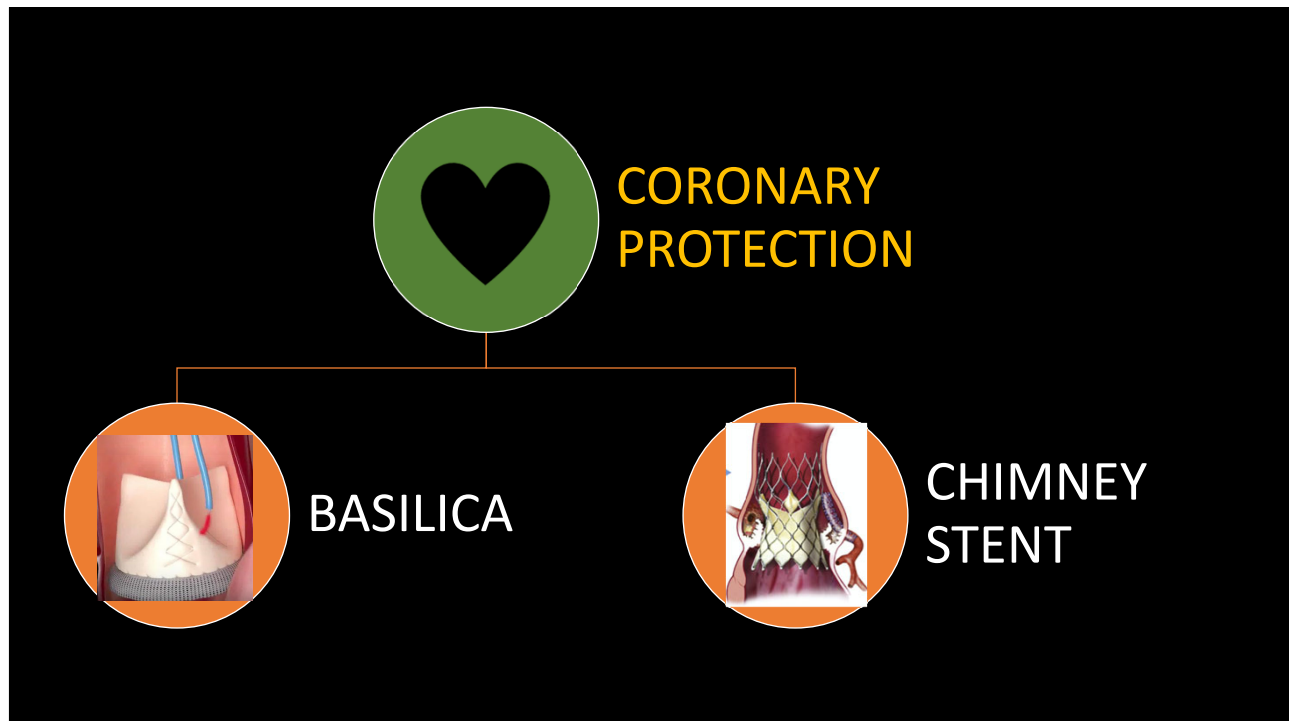
26mm Sapien 3 Low			
MG: 4.8mmHg EOA: 3.0cm ² RF: 25.9%			
			

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WHAT ABOUT HIGH RISK PATIENTS?

ROLE OF CORONARY PROTECTION!

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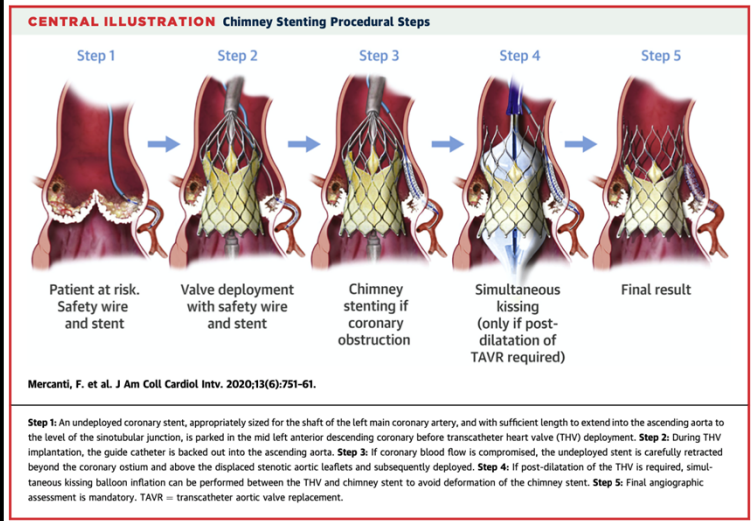
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CHIMNEY STENTING

TABLE 5 30-Day Clinical Outcomes (N = 60)

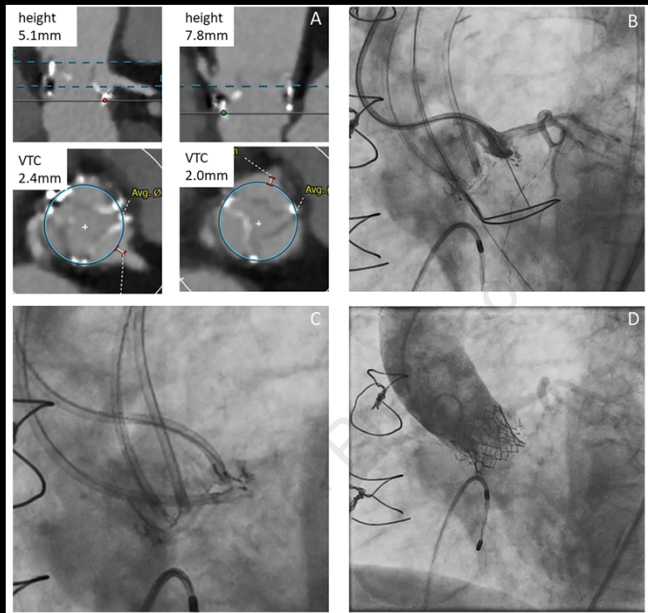
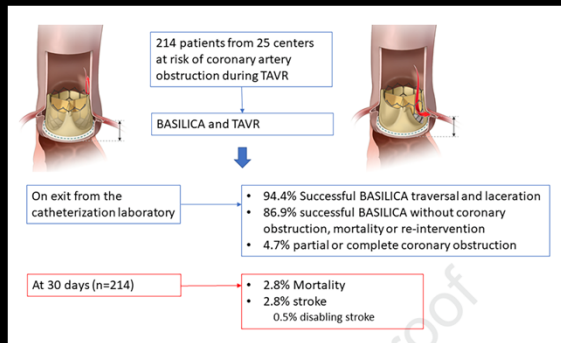
	Total (N = 60)	CAO		p Value	Coronary Protection		p Value
		ICA0 (n = 35)	eCAO (n = 25)		Present (n = 44)	Absent (n = 16)	
Procedural death	3 (5.0)	0 (0.0)	3 (12.0)	0.07	0 (0.0)	3 (18.75)	0.02
30-day death	3 (5.0)	0 (0.0)	3 (12.0)	0.07	0 (0.0)	3 (18.75)	0.02
MI	13 (21.6)	0 (0.0)	13 (52.0)	<0.01	6 (13.6)	7 (43.8)	0.03
Cardiogenic shock	14 (23.3)	1 (2.9)	13 (52.0)	<0.01	4 (9.1)	10 (62.5)	<0.01
Stroke	1 (1.7)	0 (0.0)	1 (4.0)	—	0 (0.0)	1 (6.2)	—
Major vascular complication	2 (3.4)	1 (2.9)	1 (4.0)	0.7	2 (4.5)	0 (0.0)	0.5
Life-threatening bleeding	1 (1.7)	0 (0.0)	1 (4.0)	—	0 (0.0)	1 (6.2)	—
AKI grade 3	3 (5.0)	1 (2.9)	2 (8.0)	0.4	1 (2.3)	2 (12.5)	0.15

Values are n (%).
 AKI = acute kidney injury; eCAO = established coronary artery occlusion; ICAO = impending coronary artery occlusion; MI = myocardial infarction.



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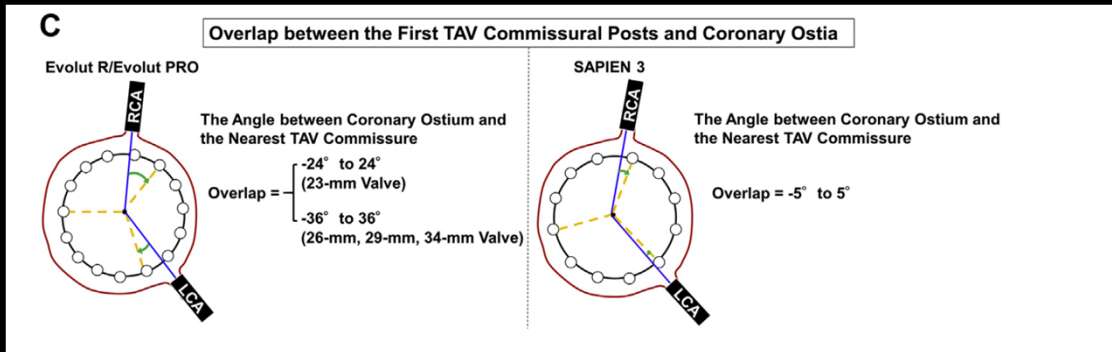
BASILICA



Khan, JACC-Interventional 3/2021

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COMMISSURES, SKIRTS AND BASILICA



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BASILICA IN TAVR IN TAVR

- Splay Angles and slit width
 - Sapien XT & Lotus > Sapien 3 and Evolut R

We believe that BASILICA may NOT reliably prevent coronary obstruction for TAVR in-TAVR, especially when the predicted mechanism of obstruction is sinus of Valsalva effacement

FIGURE 1 Splay Characteristics After Benchtop BASILICA and TAVR-in-TAVR in 4 Common TAVR Devices



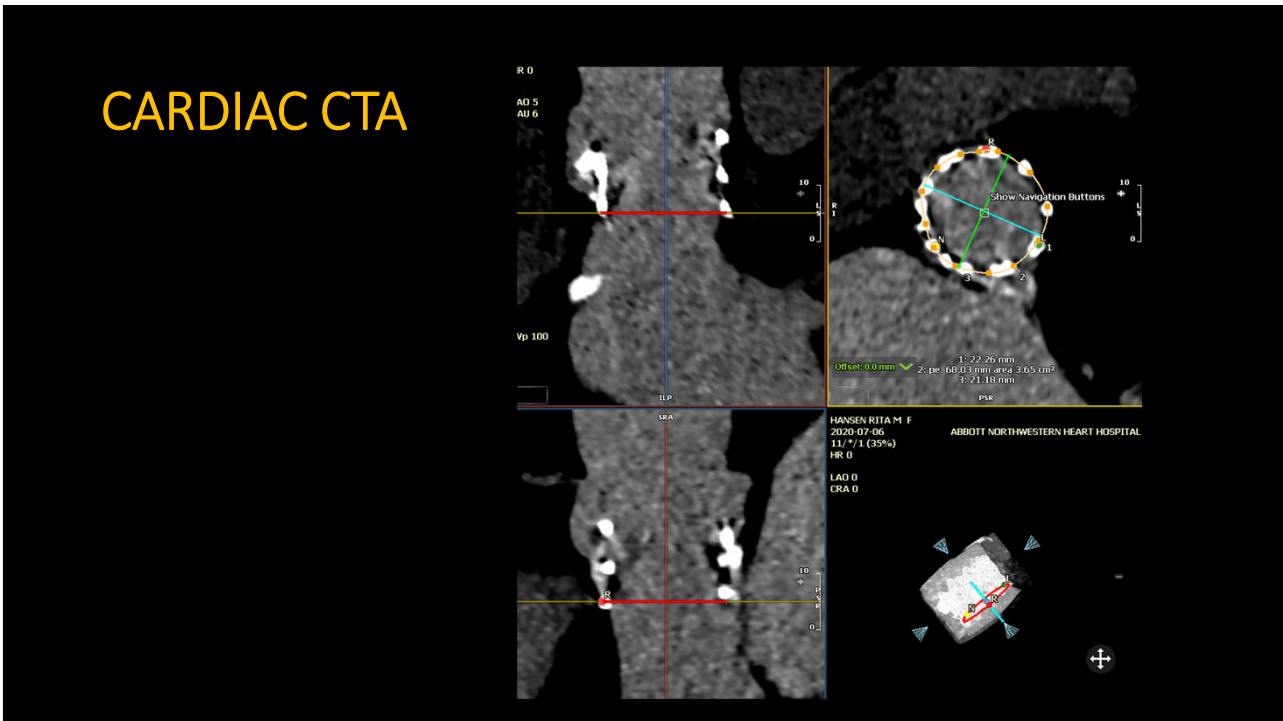
Degenerated Valve	Splay Angle (degrees, min/max)	Slit width maximum (mm)	Slit height (mm)	Splay area free of TAVR skirt (mm ²)
Evolut R implanted in prior TAVR				
Sapien 3 23mm	11	3	14	12
Evolut R 23mm	16 / 52	7	12	29
Sapien XT 23mm	34	6	9	26
Lotus 25mm	59	10	10	37
Sapien 3 implanted in prior TAVR				
Sapien 3 23mm	22	6	14	32
Evolut R 23mm	19 / 34	6	12	33
Sapien XT 23mm	49	8	9	30
Lotus 25mm	56	11	11	41

The orifices created by BASILICA-splayed leaflets are depicted in red. TAVR = transcatheter aortic valve replacement.

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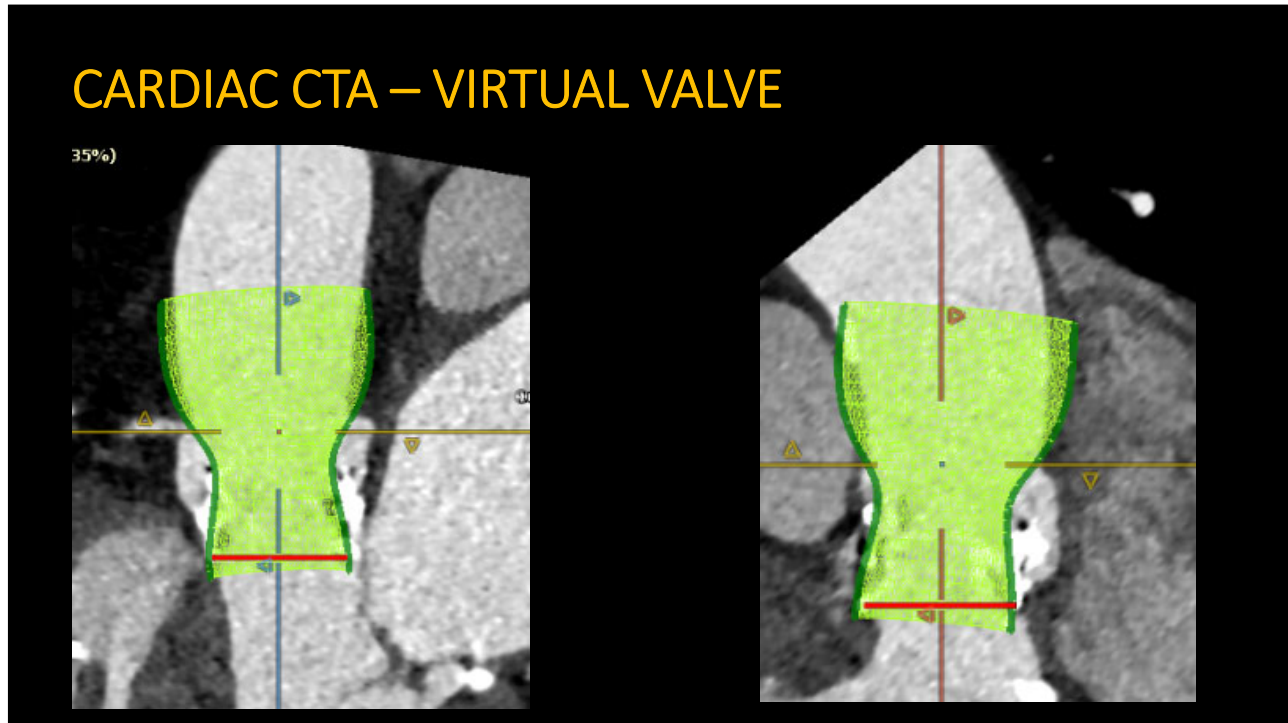


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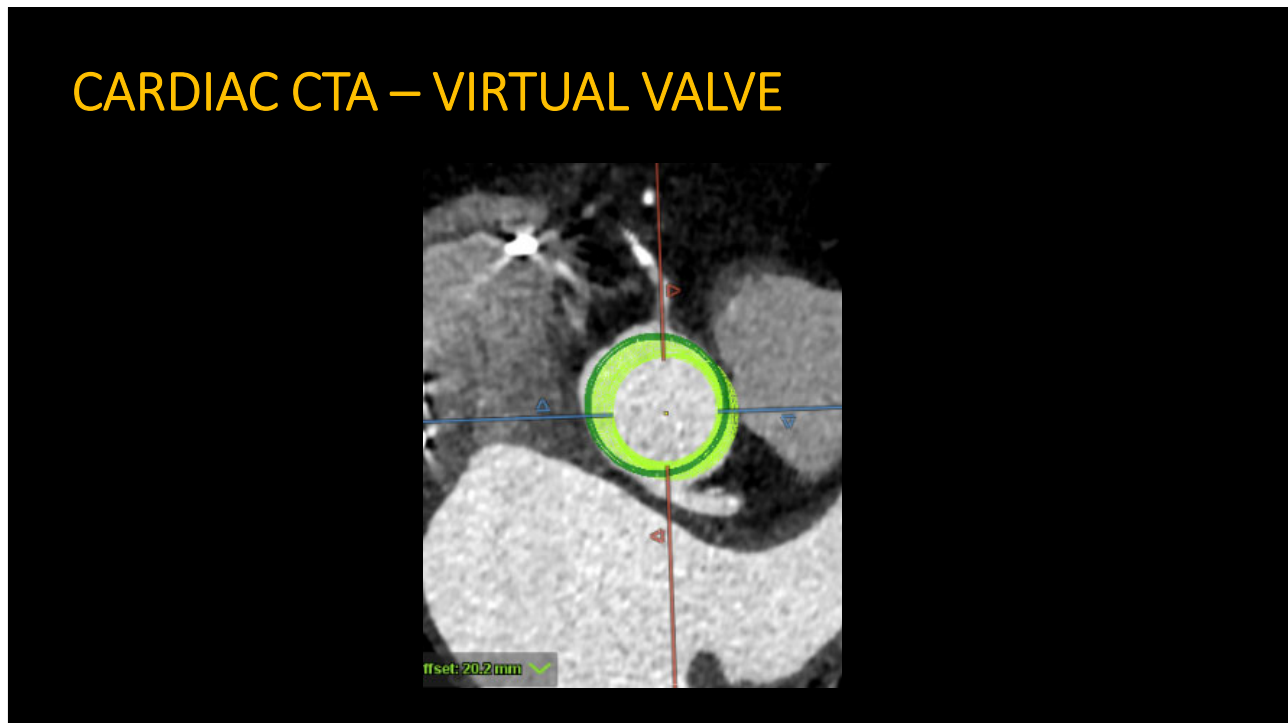
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CARDIAC CTA – VIRTUAL VALVE



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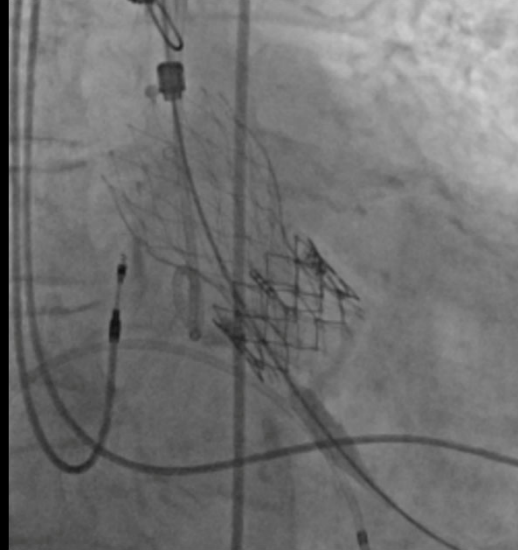
CARDIAC CTA – VIRTUAL VALVE



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TAVR 2020 – EVOLUT PRO 23 MM

- TTE next day:
 - Mean gradient 16-17 mmHg
 - Mild PVL

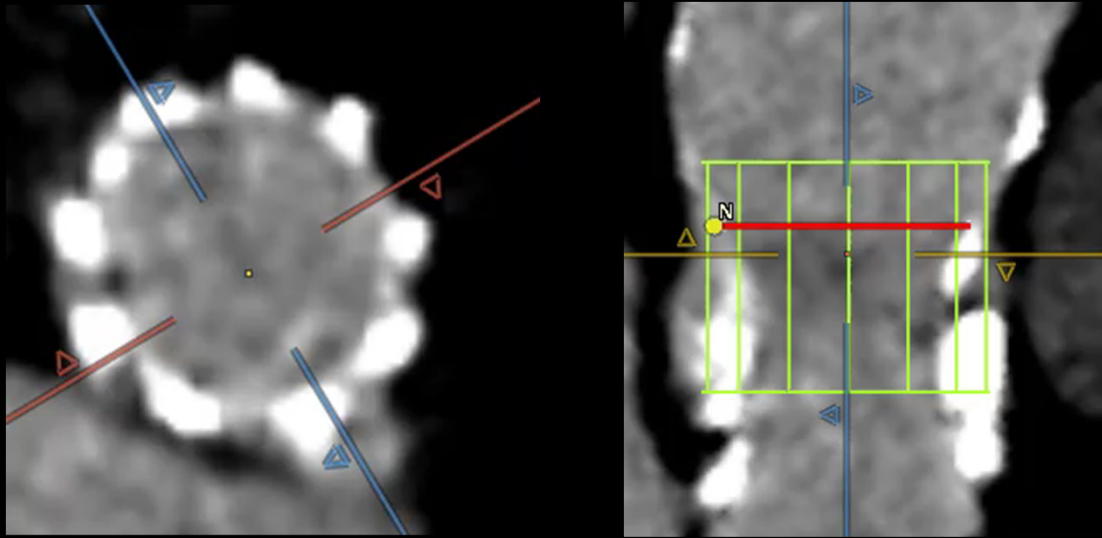


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LETS GO TO THE FUTURE!

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PLANNING 3rd VALVE



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CONCLUSION

- TAVR is TAVR is feasible in selected patients
- Specific consideration 1st THV selection and positioning is important in allowing future TAVR in TAVR
- Coronary protection techniques might be helpful, but still limited

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