A CRITICAL ASSESSMENT OF VALVE PERFORMANCE AND OUTCOMES IN PATIENTS AT LOW RISK FOR SURGERY

UC202407811 EN

NOTE:

The following information and content is intended to be an educational resource to help support heart teams in their training, planning for, and conducting of the procedure and patient needs. These materials and resources are in no way intended to replace the independent medical judgment of a trained and licensed physician with respect to any patient needs or circumstances. The physician is solely responsible for all decisions and medical judgments relating to the treatment of their patient. Please see the complete Instructions for Use for products discussed or demonstrated, including all product indications, contraindications, precautions, warnings, and adverse events.

SECTION 1:

PATIENTS ENROLLED IN THE EVOLUT LOW RISK CLINICAL TRIAL

THE ROLE OF THE LOCAL HEART TEAM

EVOLUT LOW RISK RCT – DEEP DIVE

OBJECTIVES

- To describe the “state of the art” of TAVR in 2016 when the Low-Risk Trials began
- To discuss the outcome priorities for low surgical risk patients compared to intermediate and high surgical risk patients
- To consider weighing valve selection with patient life expectancy and subsequent lifetime management
- To review the role of the local heart team in selecting patients for the Evolut Low Risk trial
- To provide insight into current local heart team decision making based on the 2020 ACC/AHA Guidelines

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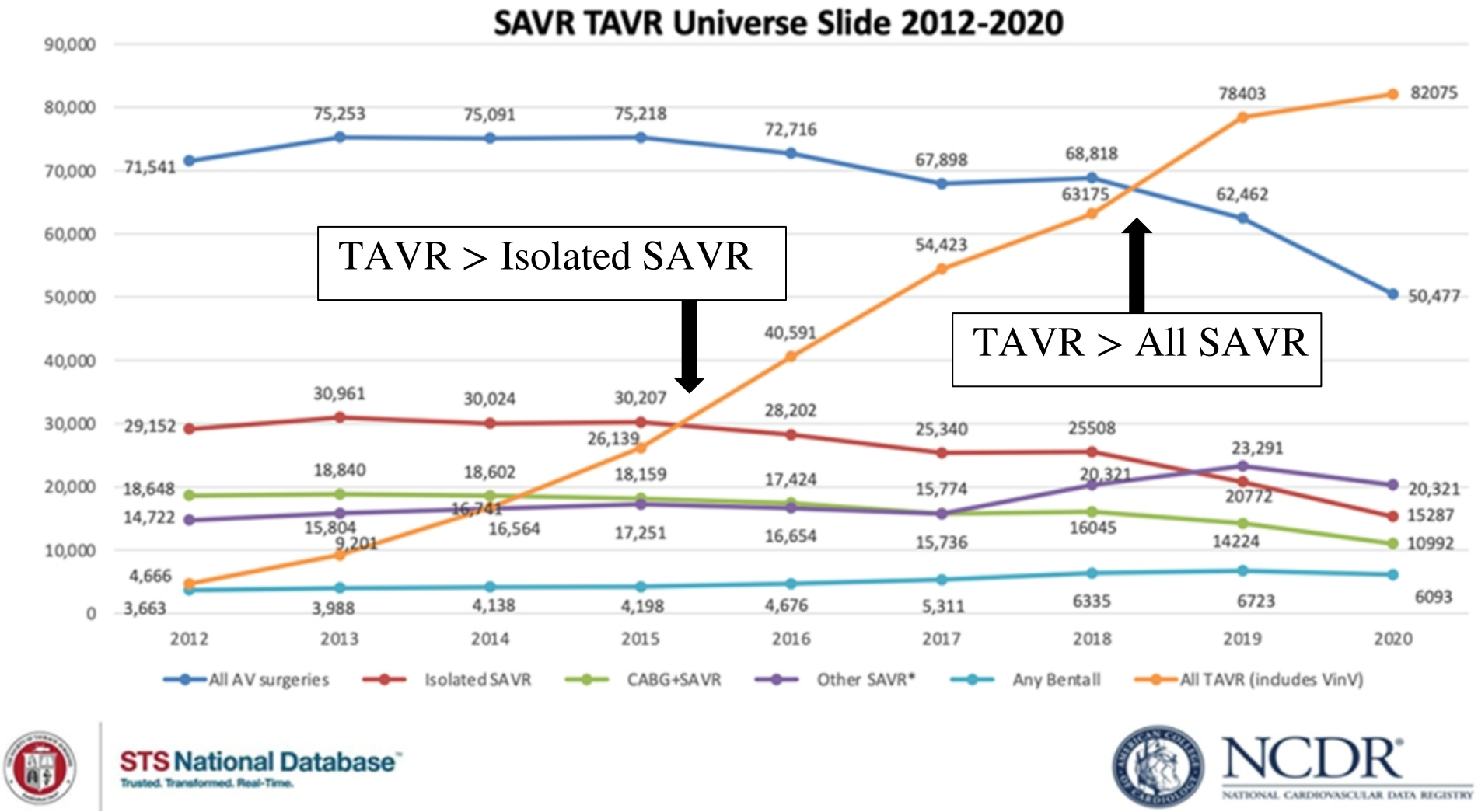
2016-2017 TAVR AND SURGICAL AVR VOLUMES

FEWER TAVRS THAN SURGERIES



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Bavaria EACTS 2021

EVOLUT LR RCT – DEEP DIVE

THE EVOLUT™ TAVR LOW RISK HEART TEAM IN 2016

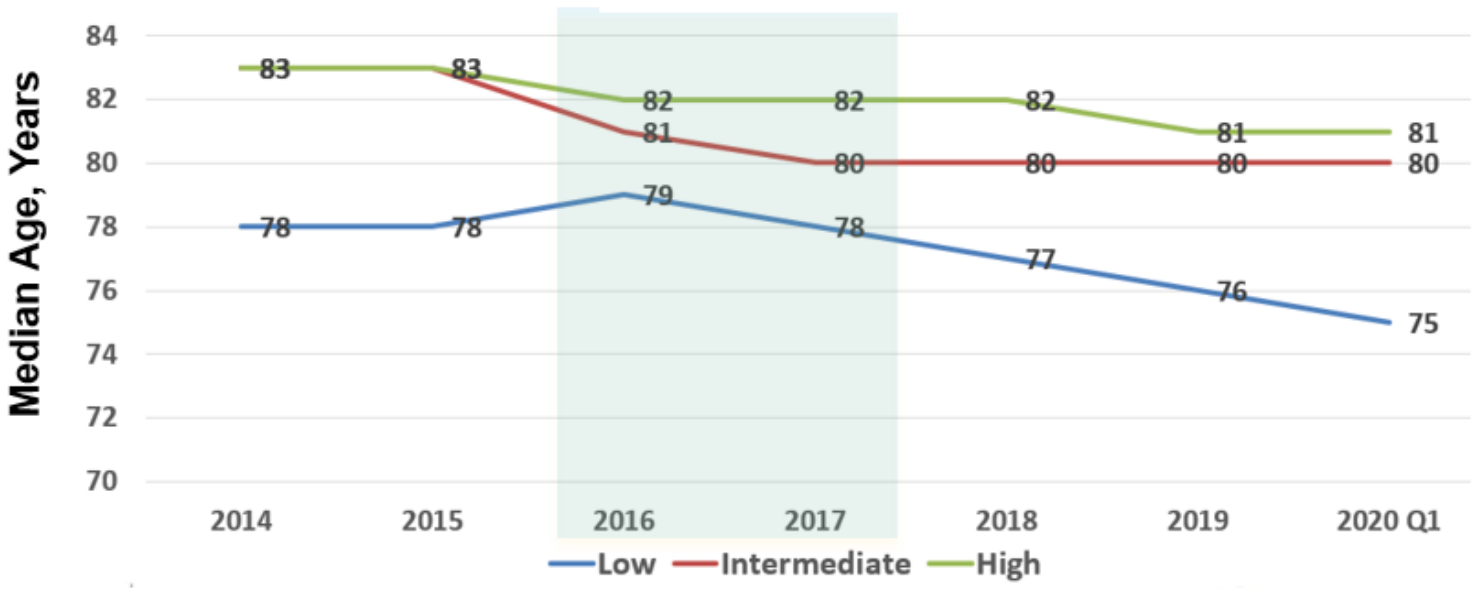
Heart Team

Structural Cardiologists
Heart Surgeon
Primary Provider
Patient Values and Preferences

COR	LOE	
1	C-EO	Patients with severe VHD should be evaluated by a Multidisciplinary Heart Valve Team (MDT) when intervention is considered
2a	C-LD	Consultation with or referral to a Primary or Comprehensive Heart Valve Center is reasonable when treatment options are being discussed for 1) asymptomatic patients with severe VHD, 2) patients who may benefit from valve repair versus valve replacement, or 3) patients with multiple comorbidities for whom valve intervention is considered

Nishimura Circ 2014;19:e521 - e643.
Figure from Otto JACC 2021;:e25-e197.

Median age for Low Risk TAVR patients in 2016-2017 was 78-79 years old [1,2]



[1] Carroll JD et al. JACC 2020;76:2492-516

[2]STS/ACC TVT Registry database.
With permission from ACC/STS

EVOLUT LOW RISK TRIAL: DEEP DIVE

Different Long-Term Priorities For Low-Risk Patients

PROCEDURAL SUCCESS METRICS

- Mortality & Stroke
- Quality of Life
- Conduction Disturbance (PPI)

ER/HR/IR + Low Risk

	ER/HR/IR	Low Risk
AGE	80+	70-80, CAD
ANATOMY	Tri-leaflet	More Bicuspid
ACTIVITY	Low	High(er)

LIFETIME MANAGEMENT METRICS

- Valve Performance
- Durability > Life Expectancy
- Coronary Access (PCI) & TAV-in-TAV

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EVOLUT LOW RISK HEART TEAM STRATEGY

PATIENT SELECTION COMMITTEE OVERSIGHT

Low Risk Patient Considerations

"Eligible patients had severe aortic-valve stenosis with suitable anatomy for TAVR or surgery and no more than a predicted 3% risk of death by 30 days with surgery, **as assessed by members of the local heart team** ."

Popma NEJM 2019; 380:1706-1715

EV Exclusion Rate

1723 – 255 = 1468 **(14.8%)**

Excluded from randomization (n=255)

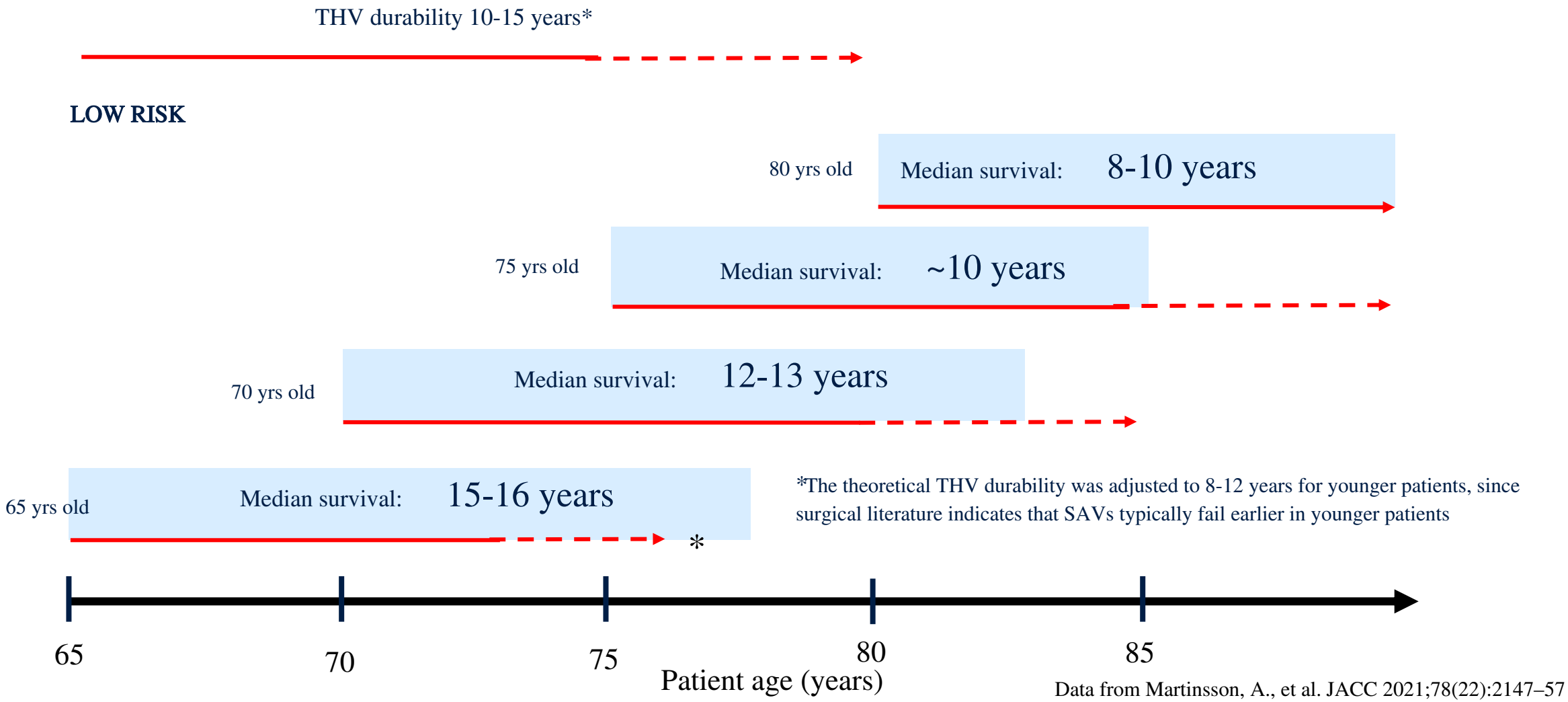
- Disapproved by Screening (n=231)
- Withdrawal (n=15)
- Did not meet I/E criteria (n=4)
- Other (n=5)

Top 5 Reasons for Rejection at Screening

- Bicuspid or unicuspid valve (n=138, 59.7%);
- Aortic root dimensions outside sizing guidelines (n=60, 26.0%)
- Other reasons (n=20, 8.7%).
- Prohibitive LVOT calcification (n=18, 7.8%)
- Predicted risk outside of the protocol criteria (N=6, 2.6%)
- Patients may have multiple reasons for disapproval

LIFETIME MANAGEMENT OF PATIENTS UNDERGOING TAVR

HYPOTHETICAL EXAMPLES FOR MATCHING LIFE EXPECTANCY WITH VALVE PERFORMANCE



*The theoretical THV durability was adjusted to 8-12 years for younger patients, since surgical literature indicates that SAVs typically fail earlier in younger patients

Data from Martinsson, A., et al. JACC 2021;78(22):2147–57

TAKE HOME MESSAGES

ACC-STS Society Guidelines

SAVR-TAVR: Low Risk Age 65-80 years

Otto JACC 2021 Feb 2;77(4):e25-e197.

- We performed our Evolut randomized clinical trial in patients who were mostly in their 70s and were deemed "low risk" for surgery by the local heart team
- Our study relied on surgical and heart team expertise in selecting patients suitable for either surgery or Evolut based on their clinical experience -- t he Screening Committee tried not to intervene in patient selection leading to a more "real world" low risk study
- Heart Team meetings today include:
  - § Potential role of surgical annular enlargement
  - § CT Scan Planning for SAVR and TAVR
  - § Patient preferences
  - § Balancing AVR strategy with life expectancy
  - § Referral to Heart Team with diagnosis of aortic stenosis

SECTION 2:

CLINICAL IMPACT OF BIOPROSTHETIC VALVE PERFORMANCE

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EVOLUT LOW RISK RCT – DEEP DIVE

OBJECTIVES

- To describe the impact of valve performance after surgical aortic valve replacement and its relationship to clinical outcomes
- To discuss the impact of severe PPM on clinical outcomes after TAVR
- To outline to differences in structural valve performance between surgical and transcatheter therapy, and the impact of SVD on clinical outcomes
- To outline to differences in bioprosthetic valve dysfunction between surgical and transcatheter therapy, and the impact of BVD on clinical outcomes
- To discuss the implications of valve performance in patients treated with balloon expandable and self-expanding, supra-annular Evolut THV

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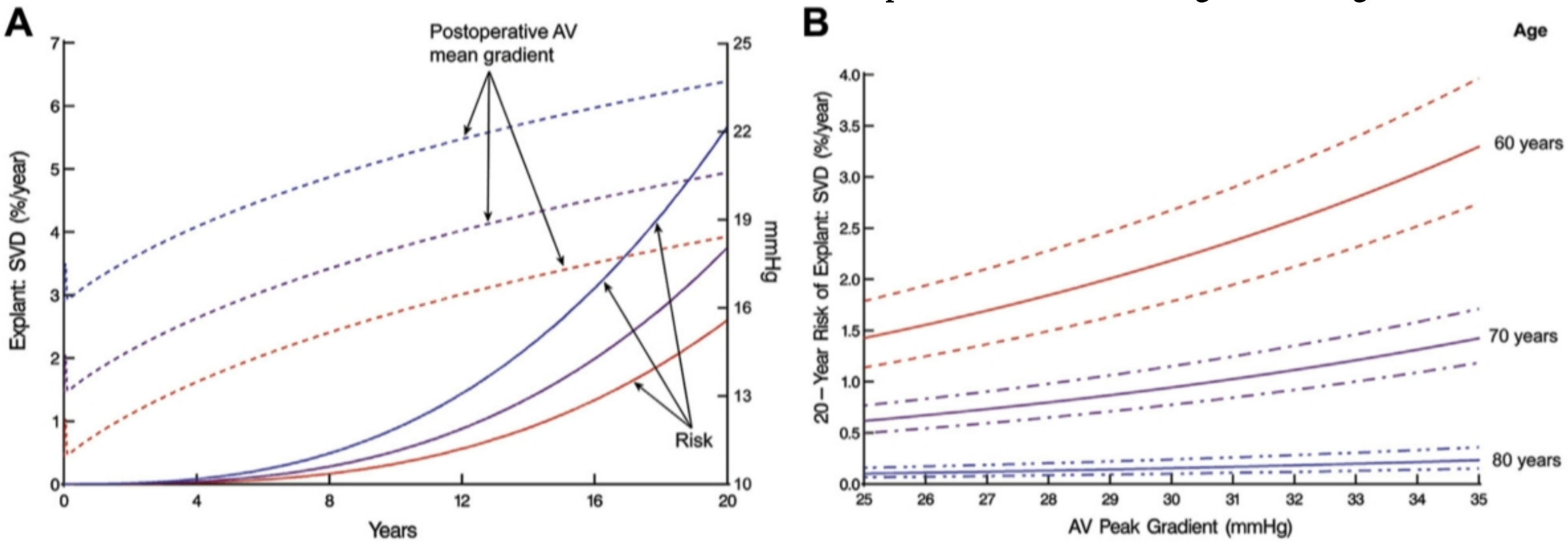
EVOLUT LOW RISK TRIAL – DEEP DIVE

354 SURGICAL EXPLANTS IN 12,569 PATIENTS AFTER SURGICAL AVR

Higher residual gradients increased risk for explant

Higher risk for explant in younger patients, particular those with a higher residual gradient



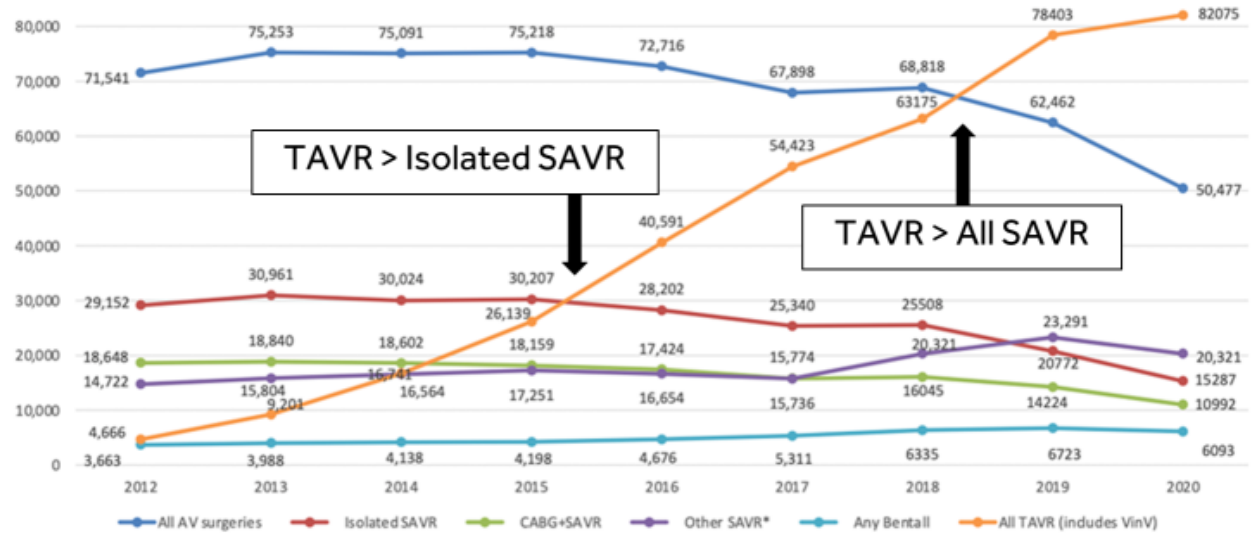
Explantation for structural valve deterioration (SVD) and postoperative mean transvalvular pressure gradient. (A) Unadjusted relationship between instantaneous risk of explant owing to SVD (left vertical axis) and temporal trend of mean postoperative aortic valve (AV) mean gradient (right vertical axis). Solid lines represent risk of explant for SVD; dashed lines represent 3 patient-specific profiles of postoperative AV mean gradient. Blue lines (top) represent the trend for a patient whose profile is at the 85th percentile. Purple lines (middle) represent the trend for a patient whose profile is at the 50th percentile. Red lines (bottom) represent the trend for a patient whose profile is at the 15th percentile. (B) Explant owing to SVD by 20 years (left vertical axis) according to postoperative AV peak gradient and age at implantation, with dashed lines representing 68% confidence bands.

Johnston DR, et al. Ann Thorac Surg 2015: 99(4): 1239-1247.

2016-2017 TAVR AND SURGICAL AVR VOLUMES

FEWER TAVRS THAN SURGERIES

More TAVRs were performed than isolated surgical AVR BUT not the total surgical AVRs



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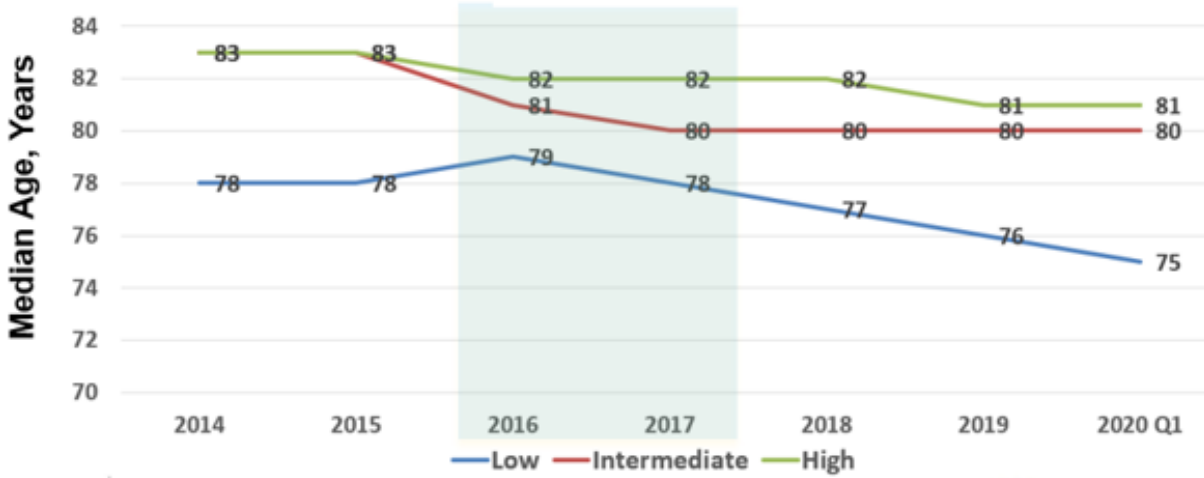
Median age for Low Risk TAVR patients in 2016-2017 was 78-79 years old [1,2]



[1] Carroll JD et al. JACC 2020;76:2492-516

[2]STS/ACC TVT Registry database.
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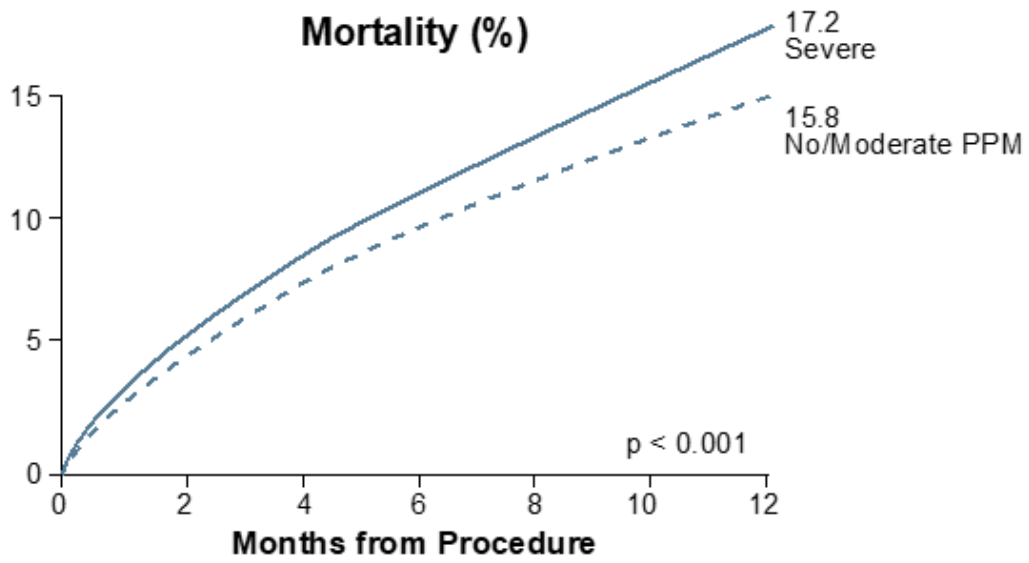
EVOLUT LOW RISK RCT – DEEP DIVE

Impact of Severe Prosthesis Patient Mismatch after TAVR

- 62,125 patient enrolled in TVT Registry between 2014-2017
- PPM predictors: Small (≤23-mm diameter) valve prosthesis, valve-in-valve procedure, larger BSA, female sex, younger patients

Severe PPM was associated with higher 1-year mortality[1]



Severe PPM leads to a 12% increase in HF rehospitalization

Association of PPM with HF Hospitalization at One-Year				
	Unadjusted Hazard Ratio (95% CI)	p-value	Adjusted Hazard Ratio (95% CI)	p-value
Severe vs. Not Severe	1.22 (1.11–1.33)	< 0.001	1.12 (1.02–1.24)	0.017
Moderate vs. None	1.08 (1.00–1.15)	0.036	1.02 (0.95–1.10)	0.567
Severe vs. None	1.24 (1.13–1.37)	< 0.001	1.13 (1.03–1.25)	0.014

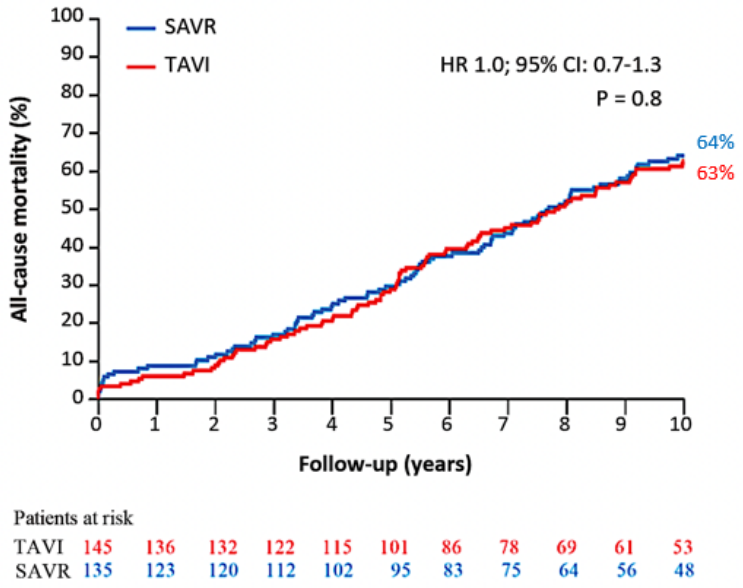
[1] Herrmann HC, et al. *JACC*. 2018;72:2701-2711.

EVOLUT LOW RISK RCT – DEEP DIVE

NOTION "ALL COMERS" TRIAL | 10 YEAR RESULTS

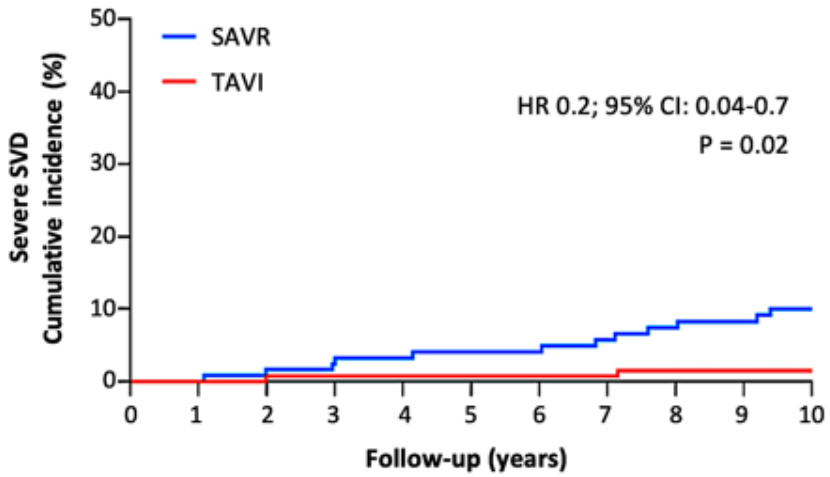
Long-term data are limited in "all comer" lower risk patients. In the NOTION 10-year with an average age of ~79, 37% of TAVI patients survived 10 years – the rates of valve degeneration, as assessed by various measures of severe structural valve deterioration (SVD) and severe bioprosthetic valve dysfunction (BVD), were significantly lower in the patients treated with the 1st generation CoreValve compared with surgery [1]

All-cause mortality



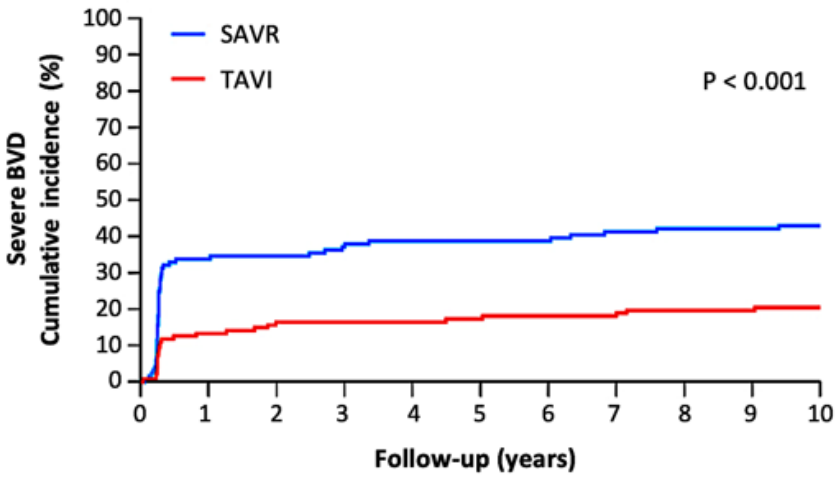
Patients at risk											
TAVI	145	136	132	122	115	101	86	78	69	61	53
SAVR	135	123	120	112	102	95	83	75	64	56	48

Severe SVD



Patients at risk											
TAVI	134	132	129	118	109	96	82	73	62	51	40
SAVR	123	122	119	110	100	91	79	70	58	50	39

Severe BVD



Patients at risk											
TAVI	127	108	102	95	91	79	69	62	53	46	40
SAVR	121	80	79	74	68	65	58	50	42	37	33

[1]de Backer et al The Notion Trial London Valves 2023, London, with permission.

EVOLUT LOW RISK RCT – DEEP DIVE

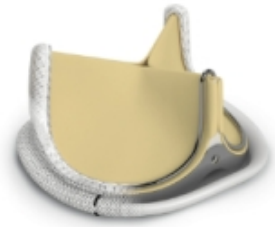
SUSTAINED REDUCTIONS IN GRADIENTS IN RCTS

Consistently Better Hemodynamics with THV

- CoreValve High Risk (Gleason)
- CoreV alve Intermediate Risk (van Miegham)
- Evolut Low Risk (Forrest JACC 2023)

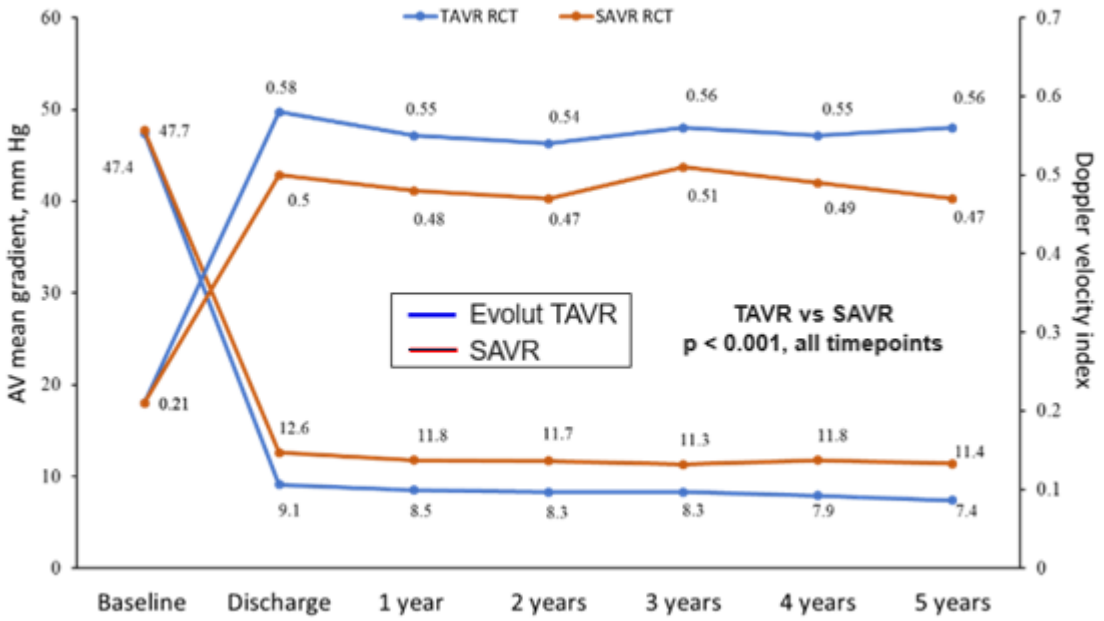
Evolut

Versus



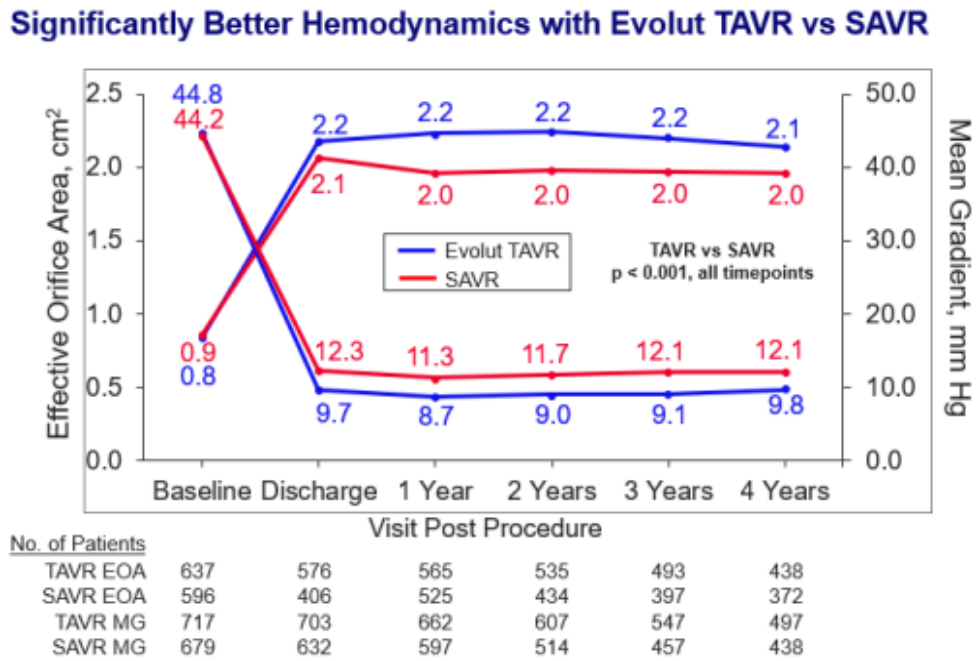
Surgery

Intermediate and High Risk RCTs



O-Hair et al TCT 2019

Evolut Low Risk RCT (N=1414)



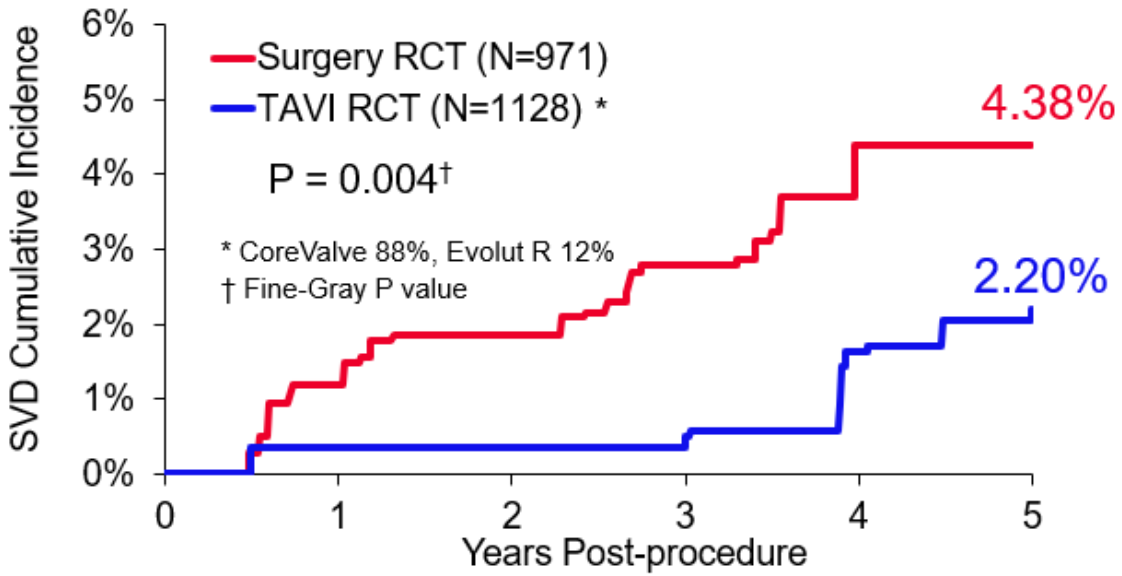
Reardon et al TCT 2023 LBCT October 24, 2023 San Francisco, CA

EVOLUT LOW RISK RCT – DEEP DIVE

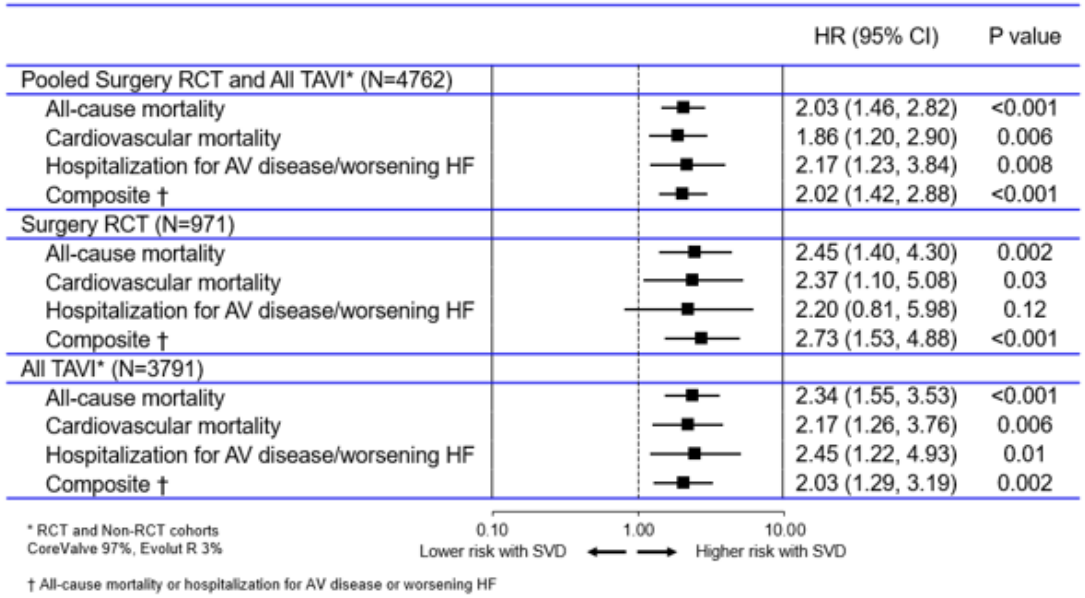
STRUCTURAL VALVE DETERIORATION : CORE VALVE/EVOLUT TAVR V. SURGERY

- Our prior randomized studies of high- and intermediate-risk patients have demonstrated lower rates of SVD in patients undergoing CoreValve/Evolut TAVR compared with surgery at 5 years [1]
- SVD was associated with a two-fold risk for death, cardiovascular death, or rehospitalization in all AVR [1]

Significantly Less SVD with CoreValve/Evolut TAVR



SVD Predicts 5-Year Mortality

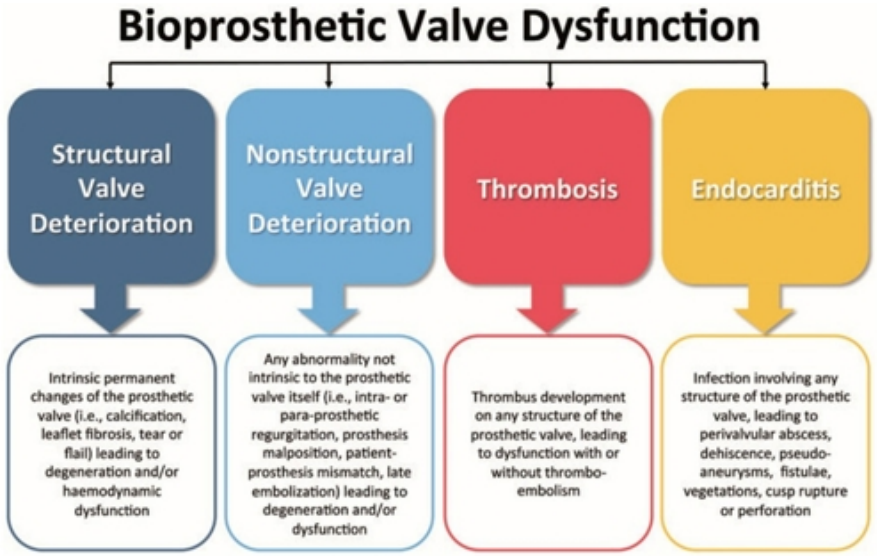


1. O-Hair et al JAMA Cardiol. 2023 Feb 1;8(2):111-119.

EVOLUT LOW RISK RCT – DEEP DIVE

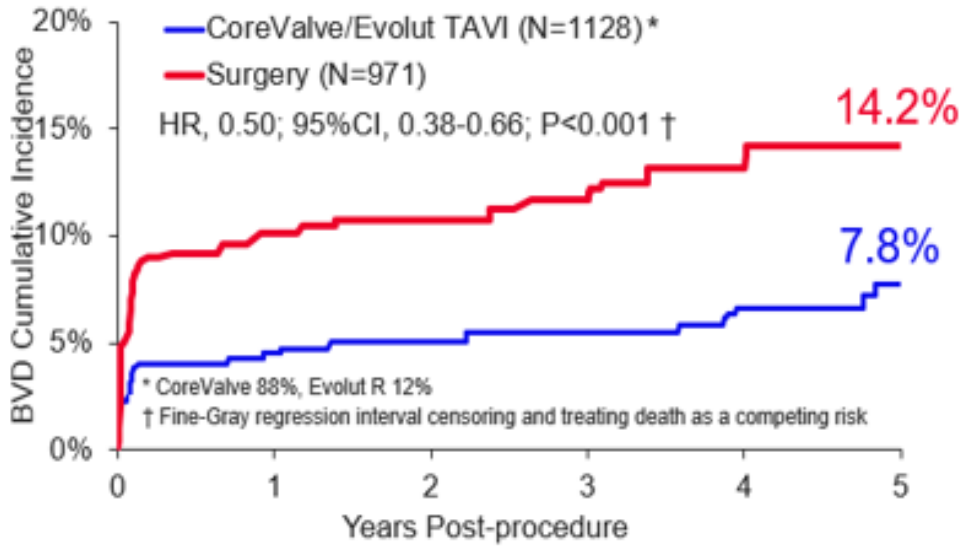
VALVE PERFORMANCE AND CLINICAL OUTCOME

- Our prior randomized studies showed lower rates of bioprosthetic valve dysfunction at 5 years, which is an indicator of valve performance, and includes SVD, non SVD (severe PPM or PVL), thrombosis or endocarditis
- Bioprosthetic valve dysfunction was associated with an approximately 50% increased risk for death, cardiovascular death, or rehospitalization in all AVR at 5 years [1,2]



Capodanno et al. Eur Heart J. 2017 Dec 1;38(45):3382-3390.

Significantly Less BVD with CoreValve/Evolut TAVR



Worse Clinical Outcomes with BVD

	HR (95% CI)	P value
Pooled Surgery RCT and All CoreValve/Evolut TAVI (N=4762)		
All-cause mortality	1.49 (1.31, 1.71)	<0.001
Cardiovascular mortality	1.68 (1.43, 1.99)	<0.001
Hospitalization for valve disease/worsening HF	1.34 (1.10, 1.63)	0.003
Composite	1.40 (1.23, 1.60)	<0.001
Surgery RCT (N=971)		
All-cause mortality	1.58 (1.15, 2.19)	0.005
Cardiovascular mortality	2.14 (1.44, 3.18)	<0.001
Hospitalization for valve disease/worsening HF	1.67 (1.11, 2.51)	0.01
Composite	1.51 (1.12, 2.02)	0.007
All CoreValve/Evolut TAVI (N=3791)		
All-cause mortality	1.55 (1.34, 1.80)	<0.001
Cardiovascular mortality	1.70 (1.41, 2.04)	<0.001
Hospitalization for valve disease/worsening HF	1.31 (1.05, 1.64)	0.02
Composite	1.44 (1.25, 1.67)	<0.001

Lower risk to patients with BVD 0.10 ← 1.00 → 10.00 *Higher risk to patients with BVD*

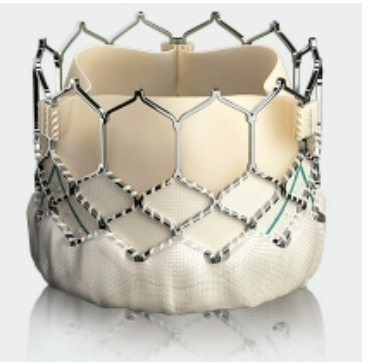
EVOLUT LOW RISK RCT – DEEP DIVE

THV Performance With Exercise

10 Patients Rest and Stress CMR After TAVI

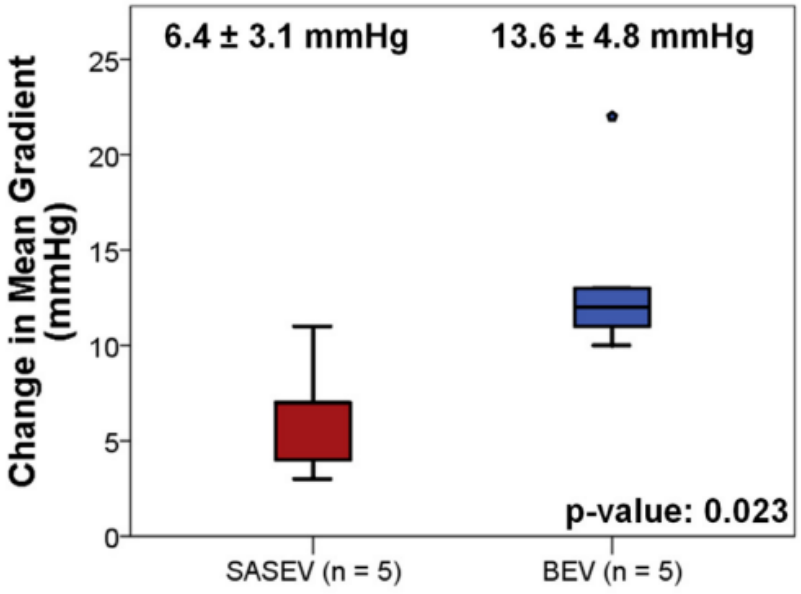
Evolut

Versus



Sapien 3

Augmentation in Mean Gradient from Rest to Stress



Association of Valve Type With Stress Induced Change in V_{Max}

Clinical Marker	β*	P-value
Age	-0.024	0.903
Resting Ejection Fraction	0.708	0.043
Gender	0.419	0.216
BMI	0.132	0.580
STS Score	-1.335	0.016
SASEV vs. BEV	1.158	0.008

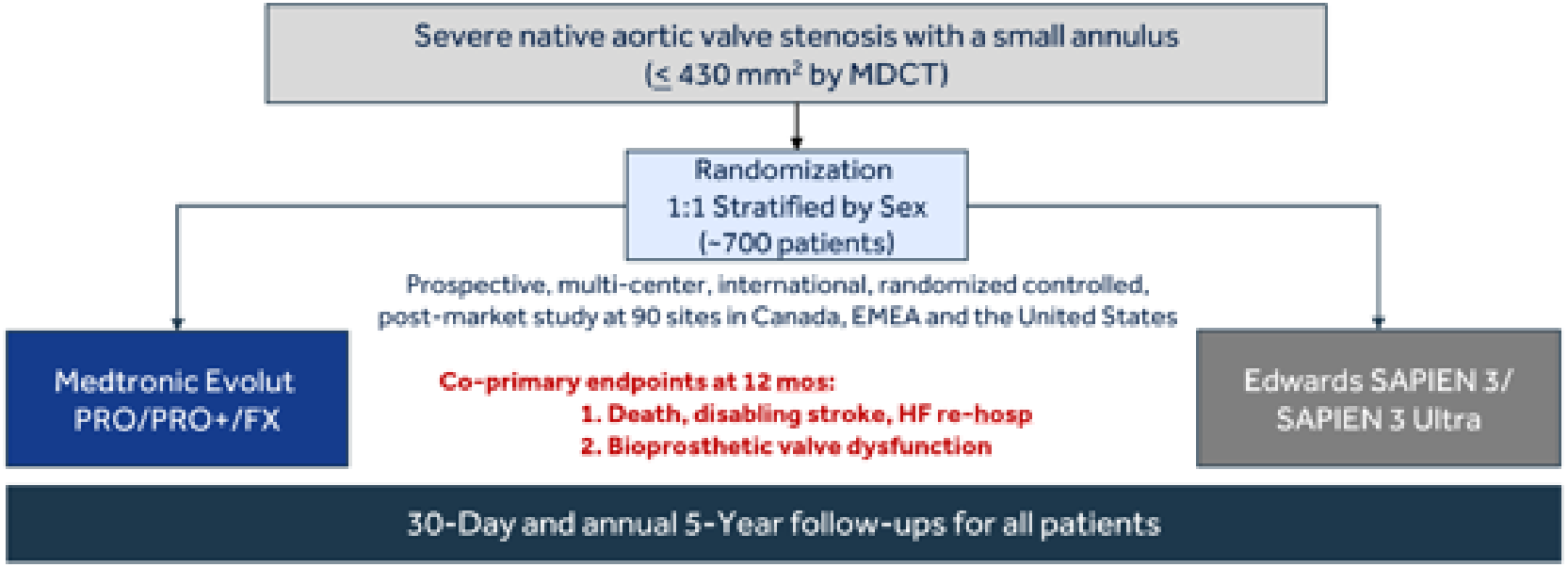
*Standardized coefficients obtained from multivariate linear regression model with R^2 = 0.955 and p-value = 0.04 indicating significance of the model using the above predictors

Attizzani GF, et al. Am J Cardiol. 2022 Sep 1;178:169-171 .

EVOLUT LOW RISK RCT – DEEP DIVE

THE SMART TRIAL – COMPARISON OF BIOPROSTHETIC VALVE DYSFUNCTION

TRIAL UPDATES: SMART (SMall Annuli Randomized To evolut or sapien)



Enrollment Completed

Powered Secondary Endpoints

1. Mean grad/EOA (continuous) at 12 mos
2. Hemo SVD at 12 mos
3. BVD in the female subjects at 12 months
4. Mod/severe PPM at 30 days

EVOLUT LOW RISK RCT – DEEP DIVE

TAKE HOME MESSAGES

- Higher post surgical aortic valve gradients are associated with higher surgical explant rates – correlation with severe prosthesis patient mismatch and mortality has also been shown after TAVR
- The CoreValve clinical studies found lower rates of early bioprosthetic valve dysfunction and later structural valve deterioration in patients undergoing CoreValve TAVR compared with surgery.
- The development of bioprosthetic valve dysfunction and SVD have both been associated with higher rates of all cause mortality, cardiovascular mortality, and re-hospitalization
- Randomized studies with Sapien 3 and Evolut TAVR are ongoing

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SECTION 3

HIGH LEVEL RESULTS OF THE EVOLUT LOW RISK RANDOMIZED CLINICAL TRIAL

EVOLUT LOW RISK RCT – DEEP DIVE

OBJECTIVES

- To discuss the differences in valve design in patients treated with surgery or Evolut TAV in the Evolut Low Risk study
- To describe the patients who were enrolled in the Evolut Low Risk Study
- To review the 4-year primary endpoint of all-cause mortality or disabling stroke, and its components in patients treated with Evolut or surgery
- To compare the hemodynamic results and valve performance in patients treated with Evolut TAV or surgery, including the occurrence of paravalvular regurgitation
- To discuss the clinical implications of the Evolut Low Risk Trial

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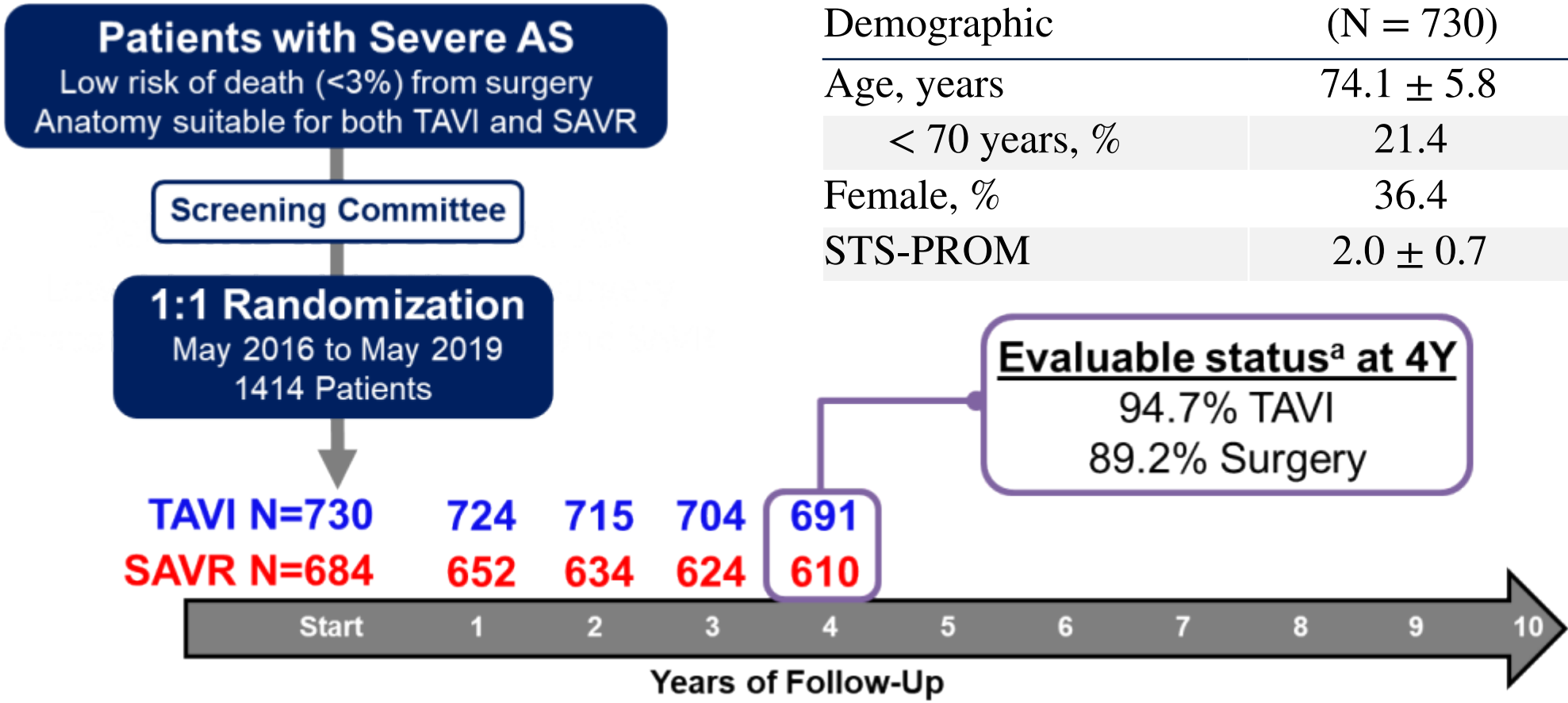
EVOLUT LOW RISK RCT – DEEP DIVE

EVOLUT LOW RISK TRIAL | 4-YEAR RESULTS



Demographic	Evolut TAVR (N = 730)	SAVR (N = 684)
Age, years	74.1 ± 5.8	73.7 ± 5.9
< 70 years, %	21.4	24.0
Female, %	36.4	34.1
STS-PROM	2.0 ± 0.7	1.9 ± 0.7

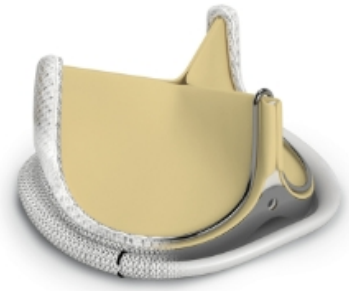
[a]Evaluable status was calculated as the number of patients expected after withdrawal and loss to follow-up and included death as known status for each time point.

Reardon et al TCT 2023 LBCT October 24, 2023 San Francisco, CA

EVOLUT LOW RISK RCT – DEEP DIVE

SURGICAL VALVE TYPES AVAILABLE IN 2016

Surgical Bioprosthetic Valves



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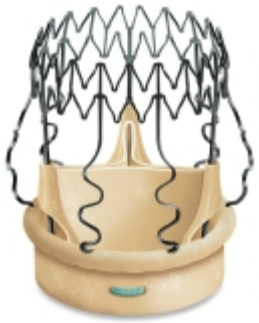
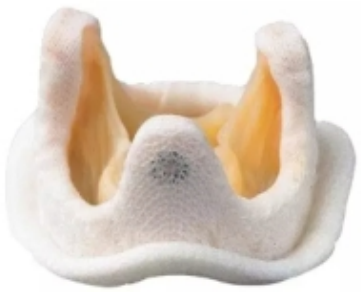
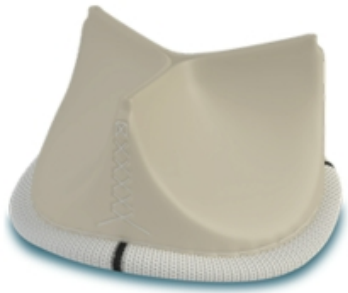


Perceval

Intuity



Mosaic



Trifecta

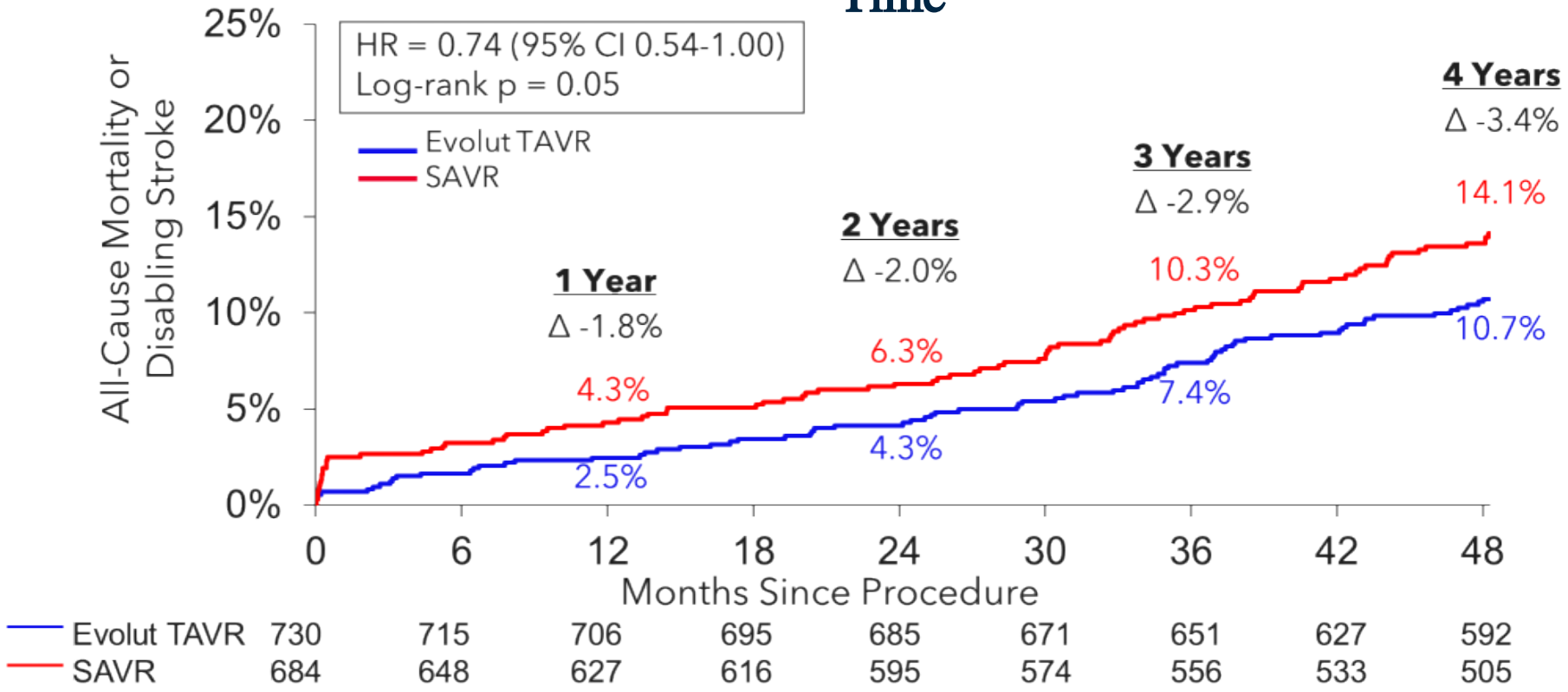
Versus

Evolut Self Expanding Supra Annular THV

EVOLUT LOW RISK RCT – DEEP DIVE

PRIMARY ENDPOINT: ALL-CAUSE MORTALITY OR DISABLING STROKE

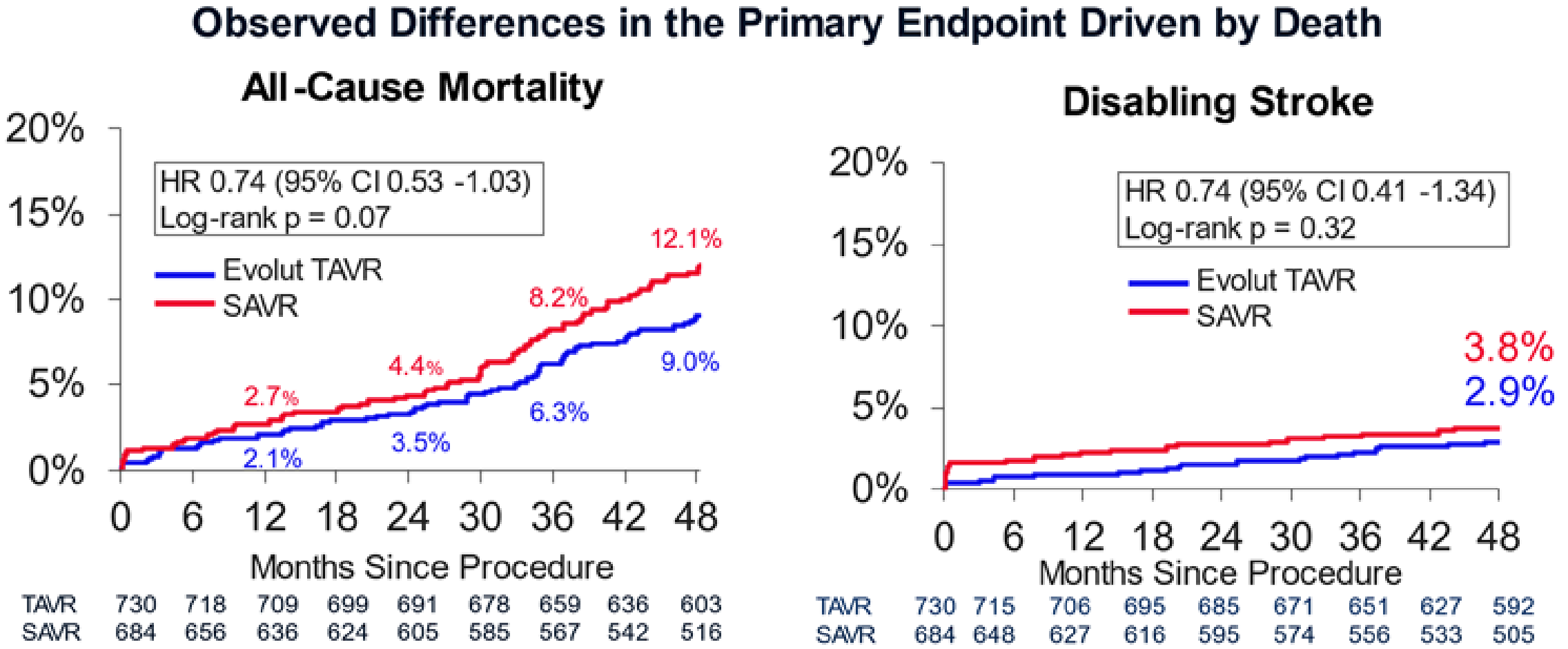
26% Relative Reduction in Hazard for Death or Disabling Stroke (p = 0.05) with Evolut TAVR vs SAVR and the Curves Continue to Separate Over Time



Reardon et al TCT 2023 LBCT October 24, 2023 San Francisco, CA

EVOLUT LOW RISK RCT – DEEP DIVE

All-Cause Mortality and Disabling Stroke

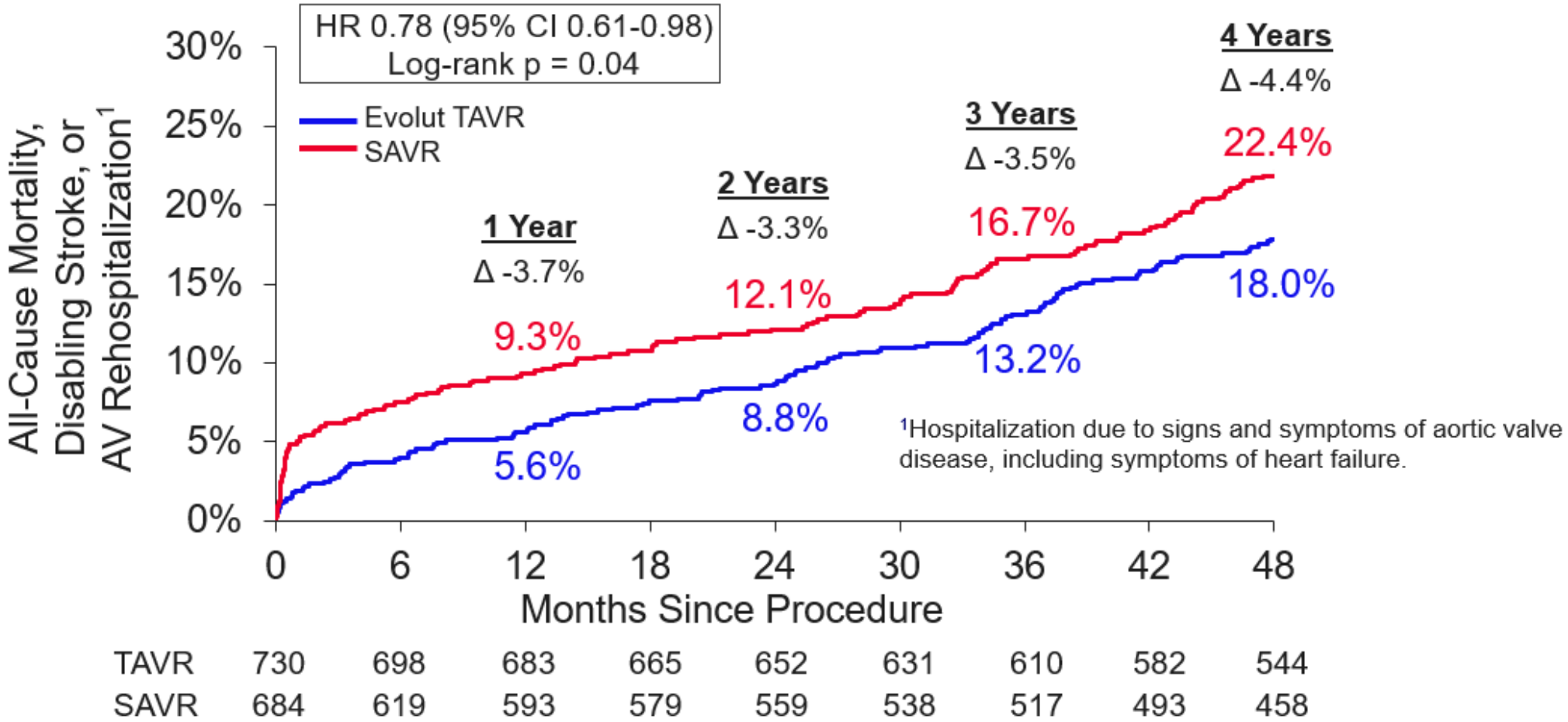


Reardon et al TCT 2023 LBCT October 24, 2023 San Francisco, CA

EVOLUT LOW RISK RCT – DEEP DIVE

All-Cause Mortality, Disabling Stroke or AV Rehospitalization

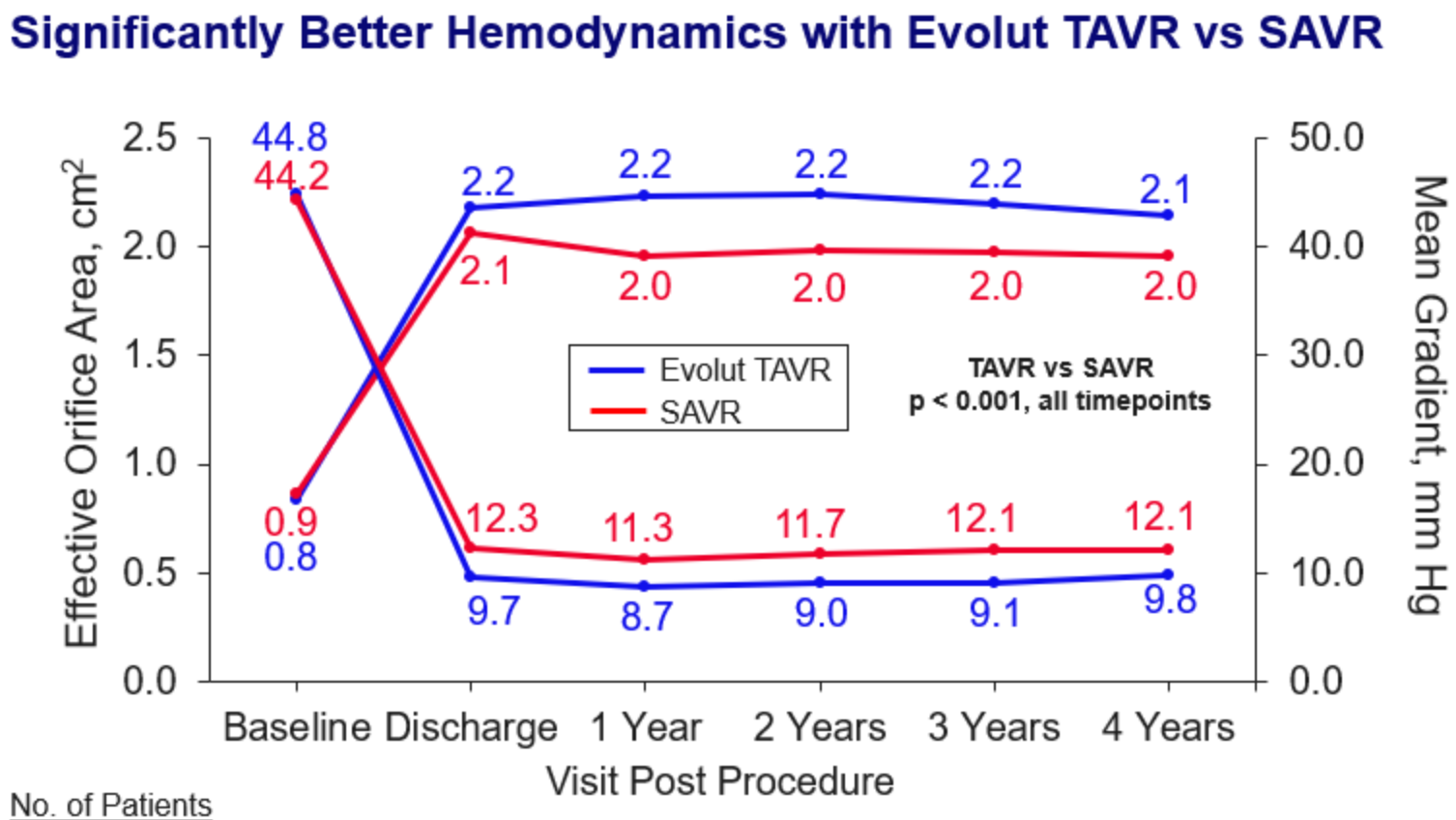
Significantly Lower Rate with Evolut TAVR vs SAVR



Reardon et al TCT 2023 LBCT October 24, 2023 San Francisco, CA

EVOLUT LOW RISK RCT – DEEP DIVE

COMPARATIVE HEMODYNAMICS



No. of Patients						
TAVR EOA	637	576	565	535	493	438
SAVR EOA	596	406	525	434	397	372
TAVR MG	717	703	662	607	547	497
SAVR MG	679	632	597	514	457	438

Reardon et al TCT 2023 LBCT October 24, 2023 San Francisco, CA

EVOLUT LOW RISK RCT – DEEP DIVE

BIOPROSTHETIC VALVE PERFORMANCE AT 4 YEARS

Significantly Less Mean Gradient ≥ 20 mmHg and Severe PPM With Evolut TAVR vs Surgery

Parameter	Evolut TAVI	SAVR	P Value
Mean gradient ≥ 20 mm Hg[a]	**4.0 (20/497)**	**8.9 (39/438)**	**0.002**
Severe PVR[a], %	0.0 (0/496)	0.0 (0/426)	N/A
Severe PPM (VARC-3)[a], %	**1.1 (7/611)**	**3.5 (19/549)**	**0.008**
Valve endocarditis[b], %	0.9 (6)	2.2 (13)	0.06
Clinical or subclinical valve thrombosis[b], %	0.7 (5)	0.6 (4)	0.84
Clinical thrombosis, %	0.3 (2)	0.2 (1)	0.61
Subclinical thrombosis, %	0.4 (3)	0.5 (3)	0.91

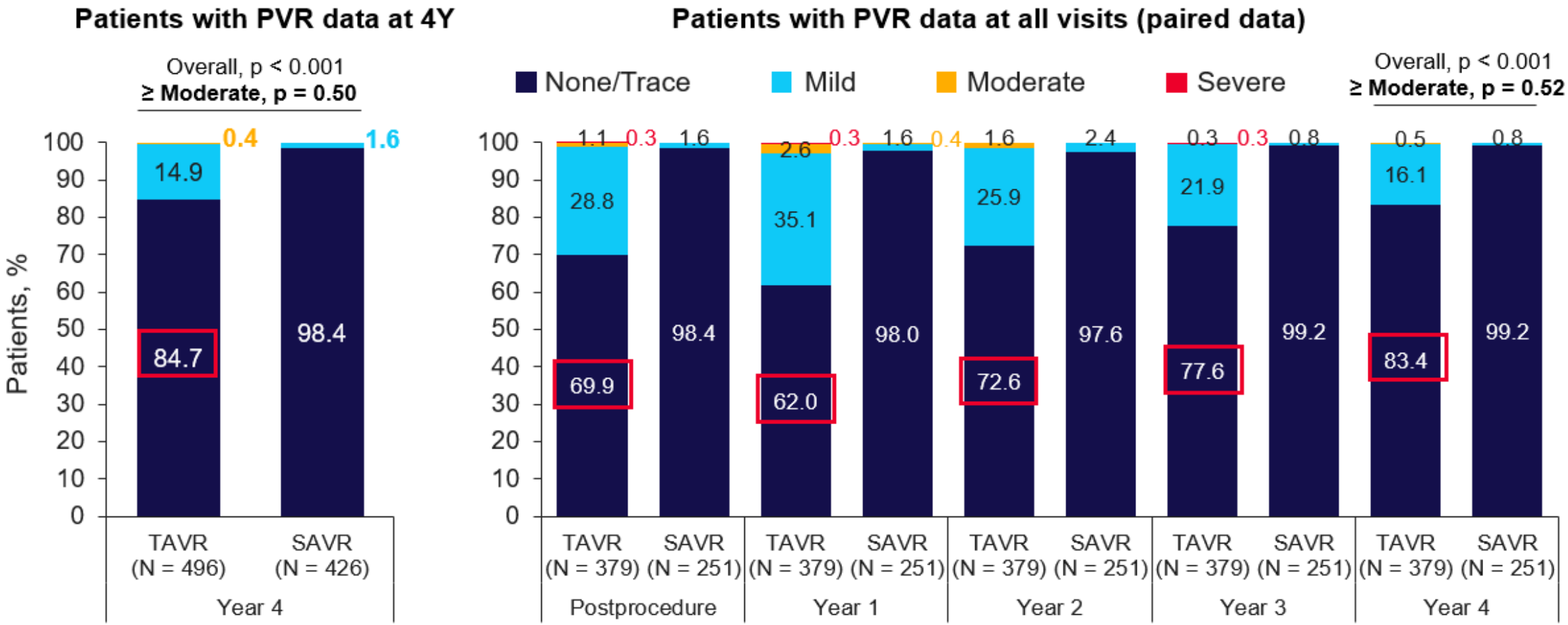
[a]Non-cumulative data based on the 4-year (MG, PVR) or 30-day (PPM) echo, reported as proportion % (n), and compared by chi-square test. [b]Cumulative rates reported as Kaplan-Meier estimates % (n) and compared by log-rank test.
MG = mean gradient; PPM = patient-prosthesis mismatch; PVR = paravalvular regurgitation

Reardon et al TCT 2023 LBCT October 24, 2023 San Francisco, CA

EVOLUT LOW RISK RCT – DEEP DIVE

PARAVALVULAR REGURGITATION

No Difference Between Groups in Moderate or Greater PVR



Reardon et al TCT 2023 LBCT October 24, 2023 San Francisco, CA

EVOLUT LOW RISK RCT – DEEP DIVE

CONSIDERATIONS

The Evolut Low Risk Trial has several important considerations

- Patients enrolled in the Evolut Low Risk study were on the higher end of the spectrum of "low risk" patients owing to the minimal number of exclusions by the national Screening Committee
- Patients enrolled in Evolut LR had an average age of 74 years – and approximately 23% of patients were under 70 years of age – comparative outcomes in much younger patients will require additional study
- The surgical operator proficiency and surgical valve selection and sizing were "best in class" surgery – but annular enlargement was performed in < 5% of patients. The effect of larger surgical valve sizing with annular enlargement will require additional study
- This report provides an analysis of hard clinical endpoints 4 years after AVR. Patients will be followed for 10 years to determine whether there is additional Divergence of the clinical outcome curves
- The higher pacemaker rate in this study has been lowered to < 10% at 30 days in the TVT Registry with refinement in the procedural technique [1]

[1]Harvey JE et al. presented at TVT 2022, Chicago, IL.

EVOLUT LOW RISK RCT – DEEP DIVE

SUMMARY

- TAVR patients in the Evolut Low Risk trial continue to show durable outcomes for the primary endpoint and significantly better hemodynamics than SAVR through 4 years
- 26% relative reduction in hazard for death or disabling stroke ($p = 0.05$) with Evolut TAVR compared to SAVR at 4 years and the curves continue to Diverge over time
- Significantly lower mean gradients and higher EOAs with Evolut TAVR vs SAVR at all follow-up timepoints
- 85% of Evolut TAVR patients had none/trace PVR and there was no difference between groups in moderate or greater PVR (0.4% vs 0.0%, $p = 0.50$)
- Indicators of valve performance, including high gradients at 4 years, severe PPM, and endocarditis overall favored TAVR, with similarly low thrombosis rates in both groups

EVOLUT LOW RISK RCT – DEEP DIVE

Clinical Implications

In low-risk patients, the Evolut platform is a preferred THV due to valve performance and associated excellent clinical outcomes:

- Evolut has reported lower rates of death or disabling stroke versus state-of-the-art surgery that are Diverging each year to 4 years [1]
- Evolut shows superior hemodynamics over SAVR at all time points tested [1]
- Evolut has shown significantly lower rates of structural valve deterioration, which result in lower death and hospitalization for AV or HF at 5 years [2]
- Evolut has shown significantly better valve performance, which also improves late clinical outcomes [3,4]

1. Forrest JK, et al. *J Am Coll Cardiol* . 2023; ePub Oct 24. 2. O'Hair D, et al . *JAMA Cardiol*. 2023 Feb 1;8(2):111-119. 3. Yakubov SJ. 5-Year Incidence of Bioprosthetic Valve Dysfunction in Patients Randomized to Surgery or TAVI: Insights from the US CoreValve Pivotal and SURTAVI Trials. Presented at: CRT 2023, Washington, D.C. 4. Van Mieghem N. 5-Year Bioprosthetic Valve Dysfunction after Surgery or Self-Expanding TAVI. Presented at: EuroPCR 2023, Paris, France.

SECTION 4:

UNDERSTANDING EARLY AND LATE MORTALITY IN THE LOW RISK RANDOMIZED TRIALS

Any data from multiple studies presented side-by-side in this deck are intended to provide an overview of published data and are not intended nor appropriate for cross-study comparisons of different valves or patient cohorts

EVOLUT LOW RISK RCT – DEEP DIVE

OBJECTIVES

- To review the difference in the two low risk trials with respect to primary endpoints and patient flow after consent
- To describe the concomitant surgical procedural, valve types, and valve sizes in the two low risk randomized studies
- To report the 30-day and 1-year surgical outcomes in the low risk randomized trials
- To compare the late surgic al outcomes in the low risk randomized trials
- To emphasize the importance comparison of surgical trials with age matched controls adjusted for risk

UC202407811 EN

EVOLUT LOW RISK RCT – DEEP DIVE

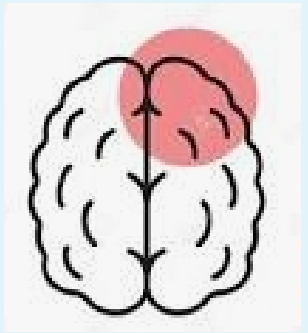
Different Primary Endpoints

Mack MJ, et al. N Engl J Med. 2019 May 2;380(18):1695-1705

Forrest JK, et al. J Am Coll Cardiol. 2022 Mar 8;79(9):882-896

Primary Endpoints

Death

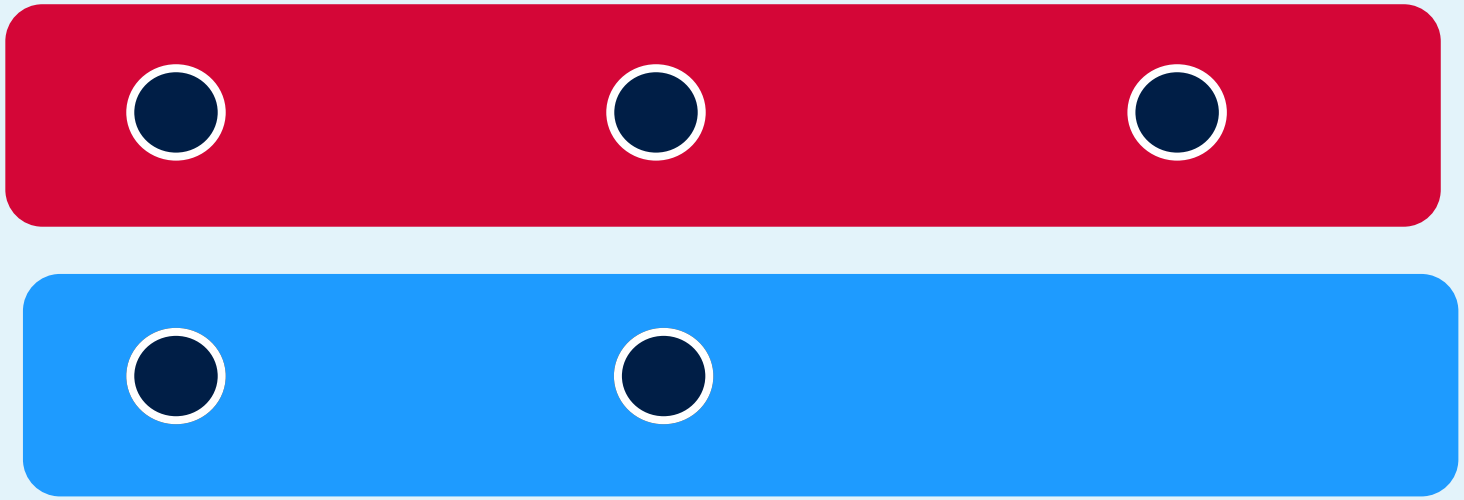


Stroke

Rehospitalization

PARTNER 3
As Treated – 950 patients
1 Year Endpoint
Follow-up: TAVR, 99%, SAVR, 97%

EVOLUT LOW RISK
As Treated – 1414 patients
2 Year Endpoint
Follow-up: TAVR, 97%, SAVR, 92%



EVOLUT LOW RISK RCT – DEEP DIVE

Differences Between Partner 3 and Evolut Low Risk

Partner 3 Mack NEJM 2019 Supplement

P3 "excluded patients with poor transfemoral access, bicuspid aortic valves, **or other anatomical or clinical factors that increased the risk of complications associated with either TAVR or surgery** "

P3 Exclusion Rate

1520 – 520 excluded = 1000 **(34.2%)**

Excluded from randomization (n=520)

- Anatomic exclusion criteria (n=308, 59.2%)
- Medical exclusion criteria (n=89, 17.1%)
- Other exclusion criteria (n=38, 7.3%)
- Incomplete screening (n=85, 16.3%)

Top 5 Reasons for Rejection by Case Review Committee

- Severe LVOT Calcium – 38%*
- Adverse Aortic Root (includes small sinus of Valsalva and/or small, calcified sinotubular junction) – 17%
- Poor TF Access – 7%
- Anomalous Coronary – 5%
- High risk of prosthesis patient mismatch – 5%*

*Not exclusion criteria

Evolut LR Popma NEJM 2019 Supplement

"EV used local heart team assessment of suitability for either surgery or TAVR"

EV Exclusion Rate

1723 – 255 excluded = 1468 **(14.8%)**

Excluded from randomization (n=255)

- Disapproved by Screening (n=231, 90.6%)
- Withdrawal (n=15, 5.9%)
- Did not meet I/E criteria (n=4, 1.6%)
- Other (n=5, 2.0%)

Top 5 Reasons for Rejection by Screening Committee

- Bicuspid or unicuspid valve (n=138, 59.7%);
- Aortic root dimensions outside sizing guidelines (n=60, 26.0%)
- Other reasons (n=20, 8.7%).
- Prohibitive LVOT calcification (n=18, 7.8%)
- Predicted risk outside of the protocol criteria (N=6, 2.6%)
- Patients may have multiple reasons for disapproval

EVOLUT LOW RISK RCT – DEEP DIVE

EVOLUT LOW RISK SUB RANDOMIZATION TO AVR-CABG OR TAVR-PCI

PARTNER 3	N=454
Concomitant procedures	**26.4%**
Root enlargement	4.6%
CABG	12.8%
MAZE	4.8%
LAA ligation	9.5%
Ascending aorta replacement	0.2%
Septal myomectomy	0.9%
Aortic endarterectomy	0.9%
Mitral replacement/repair	1.3%
Tricuspid replacement/repair	0.9%
Other	0.2%

Evolut Low Risk	N=678
Concomitant procedures	**26.3%**
Aortic root enlargement	1.6%
CABG	13.6%
Atrial fibrillation treatment	3.5%
LAA closure	6.2%
PFO closure	0.7%
Mitral valve repair	0.6%
Other	5.0%

Popma JP, et al. NEJM 2019. Supplemental data.

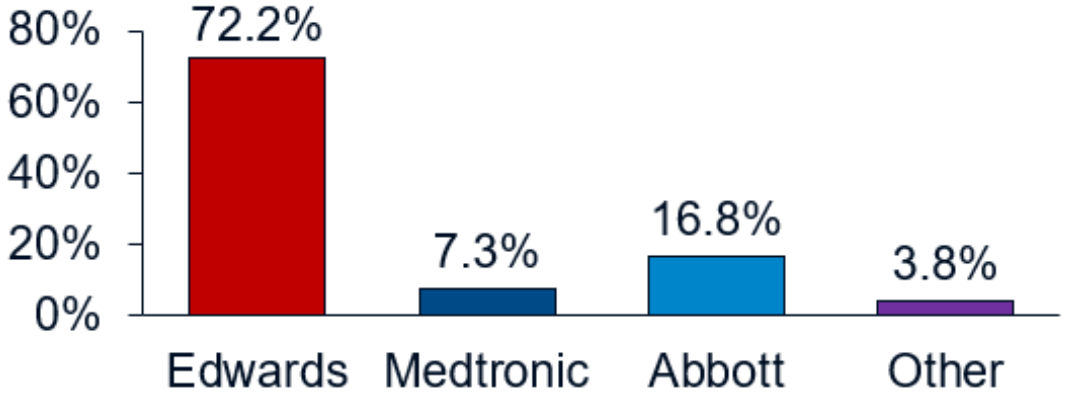
Mack MJ, et al. NEJM 2019. Supplemental data.

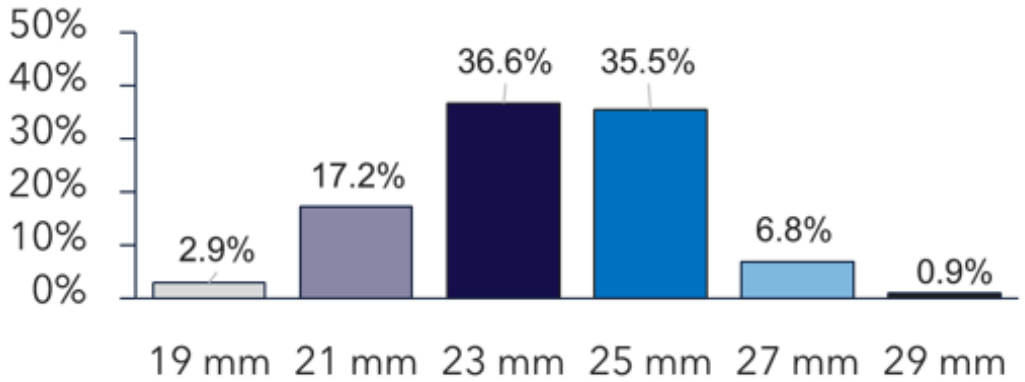
EVOLUT LOW RISK RCT – DEEP DIVE

SURGICAL VALVE DISTRIBUTION BY MANUFACTURER AND SIZE

PARTNER 3 Surgical Valves[1]

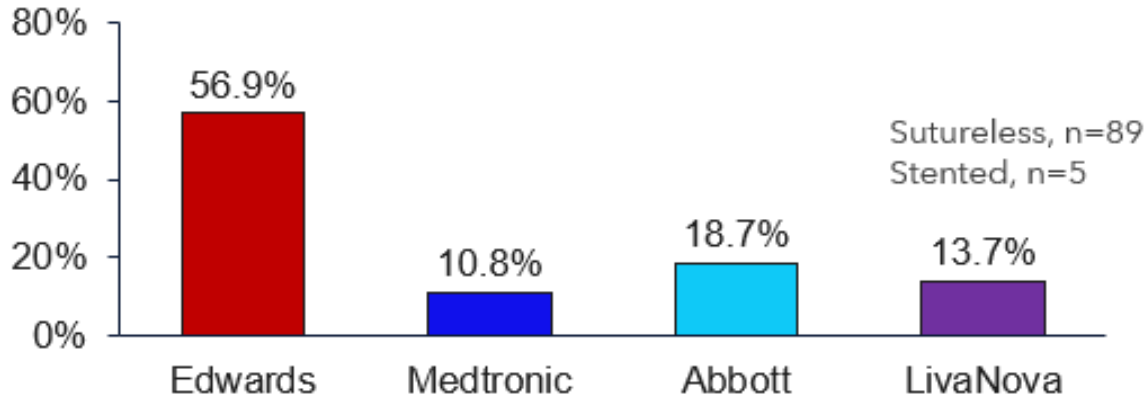
Mean STS Score	30-day Mortality	O/E Ratio
1.9%	1.1	0.58

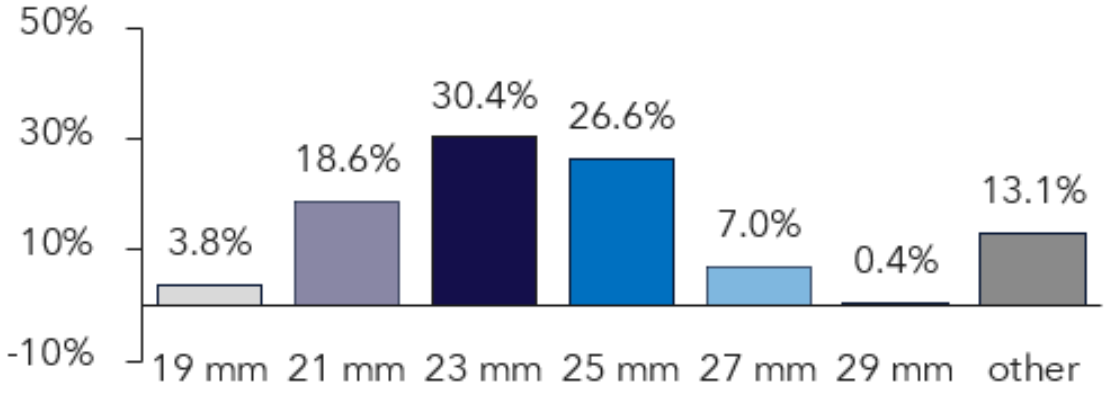




Evolut Low Risk Surgical Valves[2]

Mean STS Score	30-day Mortality	O/E Ratio
1.9%	1.2	0.63





[1]Mack MJ, et al. NEJM 2019. Supplemental data. [2]Popma JJ et al. NEJM 2019. Supplemental data; Reardon et al TCT LBCT 2023

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EVOLUT LOW RISK RCT – DEEP DIVE

One Year Hemodynamic Outcomes

	1-Year Echo	PARTNER 3 [1]	Evolut Low Risk [2,3]
Surgical Arm	EOA	1.8 cm ^{2}	2.0 cm ^{2}
	Mean gradient	11.6 mm Hg	11.3 mm Hg
	None/trace total aortic regurgitation	93.8%	90.9%
	Mild total AR	5.7%	7.6%
	Moderate total AR	0.5%	1.5%
	Severe PPM †	6.3%	8.2%

†Defined as:

	Moderate	Severe
Indexed effective orifice area (cm2/m2) for BMI <30 kg/m2	0.85–0.65 cm2/m2	< 0.65 cm2/m2

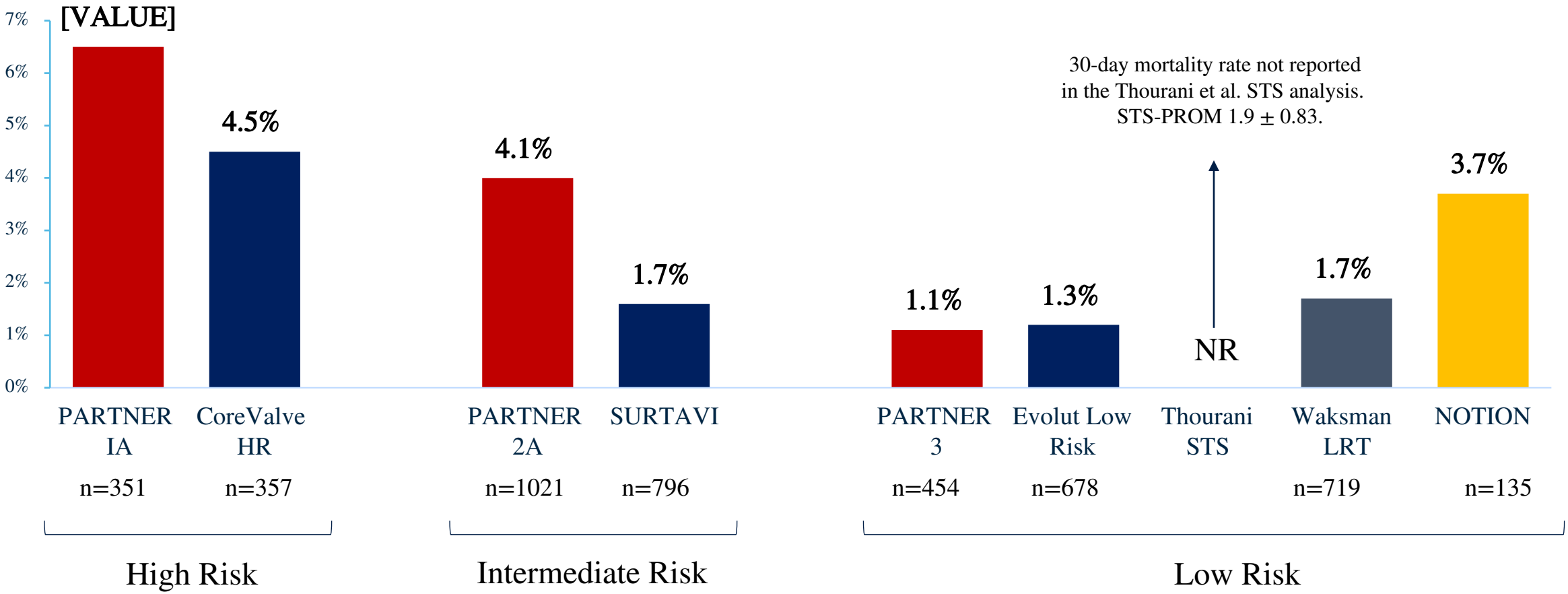
[1] Mack NEJM 2019, supplemental data

[2] Popma JP, et al. NEJM 2019. Supplemental data.

[3] Forrest, et al. JACC 2022.

EVOLUT LOW RISK RCT – DEEP DIVE

30 Day All Cause Mortality in Surgical Arms



Smith et al. NEJM 2011. P1A. ITT population.

Adams et al. NEJM 2014. AT population.

Leon et al. NEJM 2016. ITT population.

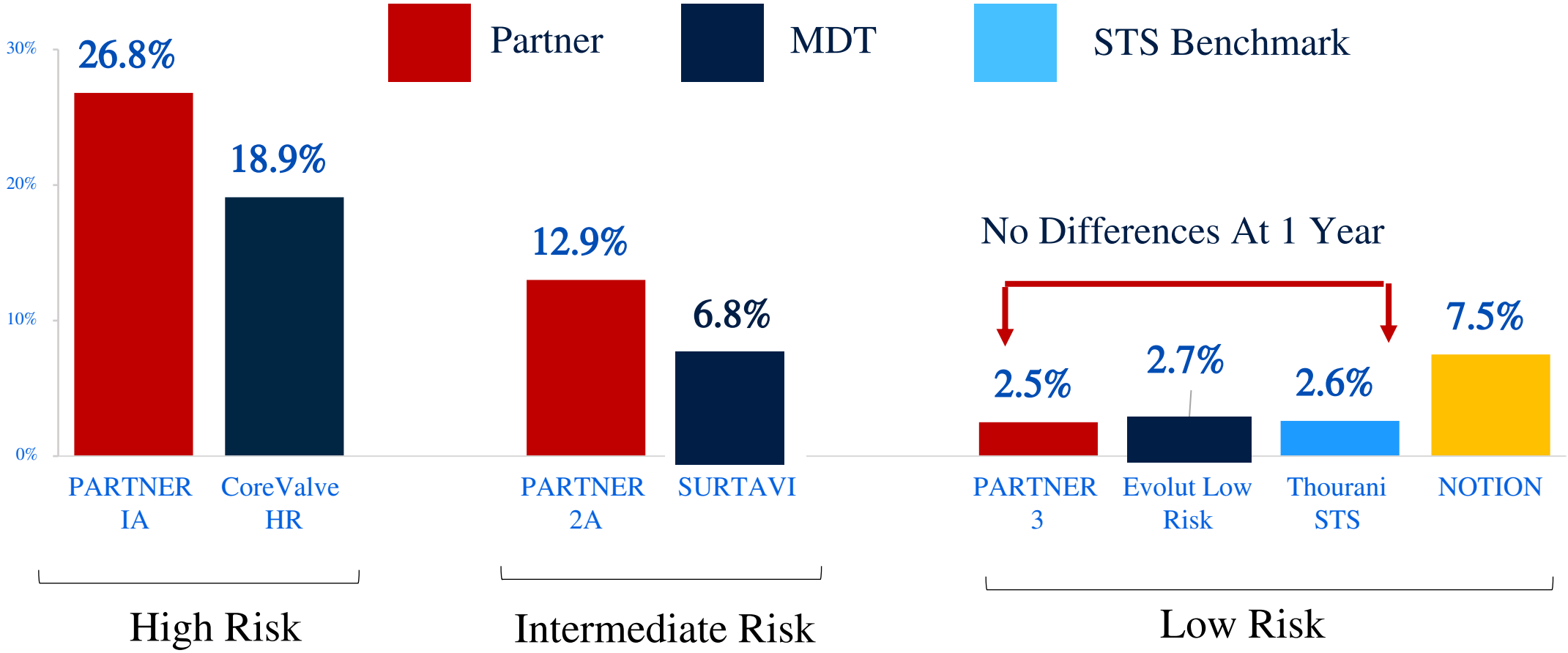
Reardon et al. NEJM 2017. Modified ITT population.

Mack et al. NEJM 2019. P3; Popma NEJM 2019. Bayesian 30-day rate.

Waksman et al. JACC 2018; Thyregod et al. JACC 2015 .

EVOLUT LOW RISK RCT – DEEP DIVE

One Year All Cause Mortality in Surgical Arms



Mack, et al. Lancet 2015. P1A. - ITT population.

Gleason, et al. JACC 2018. CV HR - AT

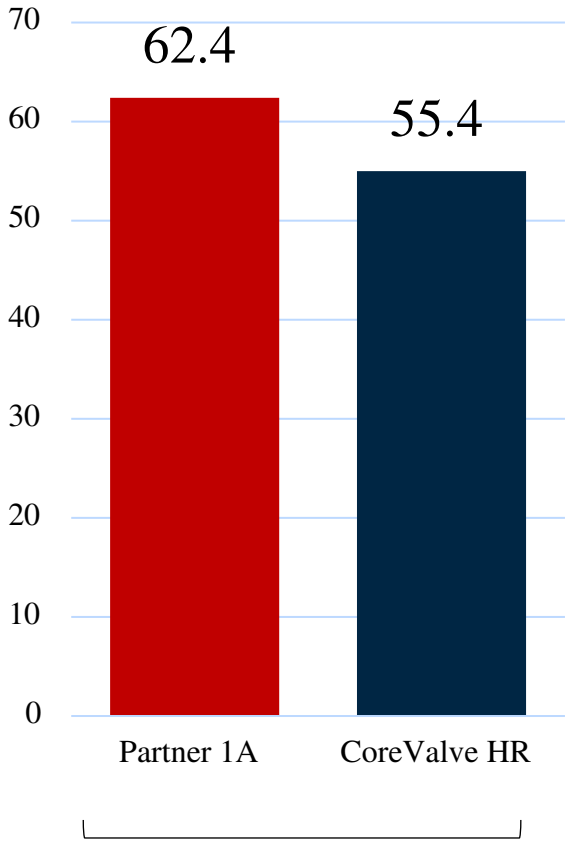
Leon et al. NEJM 2016. ITT

Reardon NEJM 2017

Mack et al. NEJM 2019. P3 supplement; Reardon TCT LBC2023; Forrest et al. JACC 2023; Thourani et al. Ann Thor Surg 2023. STS analysis Thyregod et al. JACC. 2015. NOTION

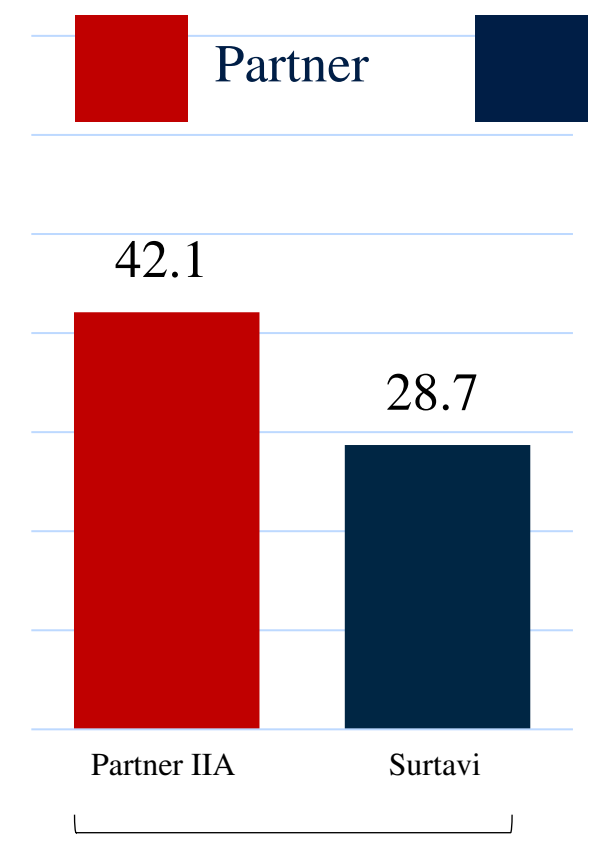
EVOLUT LOW RISK RCT – DEEP DIVE

All Cause Mortality in Surgical Arms



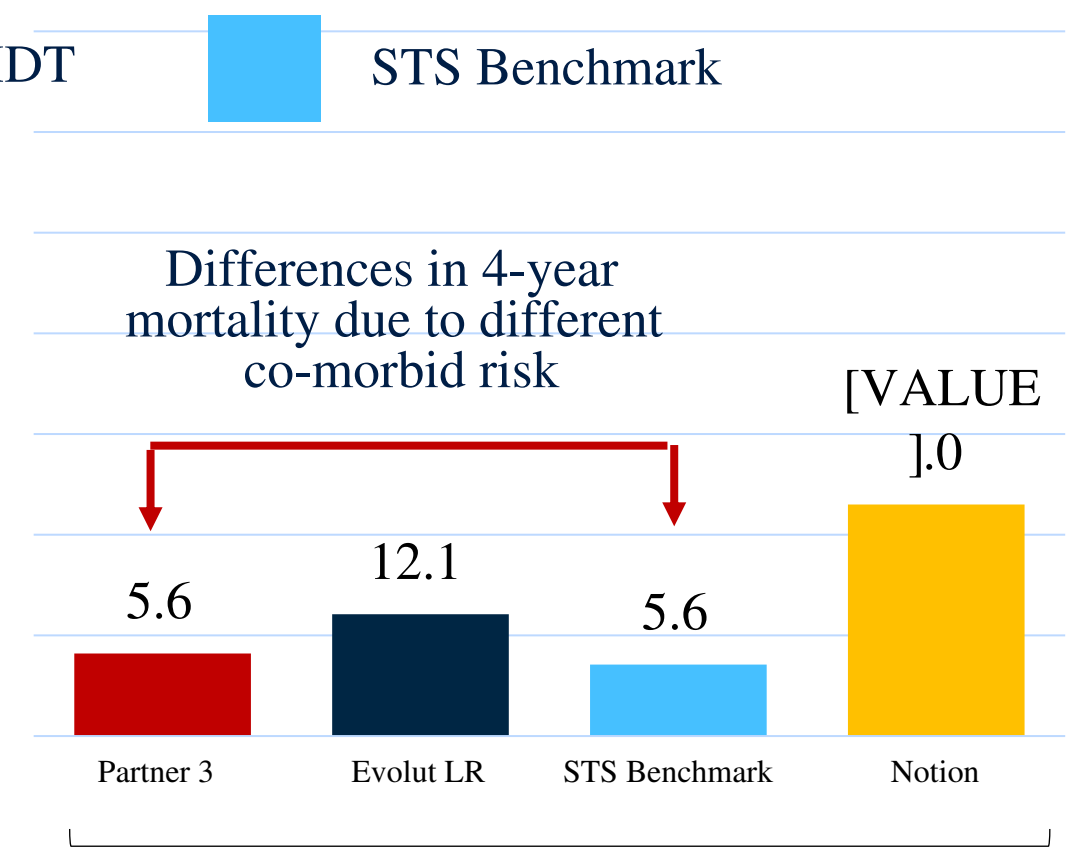
5 Year High Risk

Mack, et al. Lancet 2015. P1A. - ITT population
Gleason, et al. JACC 2018. CV - AT population.



5 Year Intermediate Risk

Makkar, et al. NEJM 2020. Rates - ITT
Van Mieghem, et al. JAMA 2022. mITT



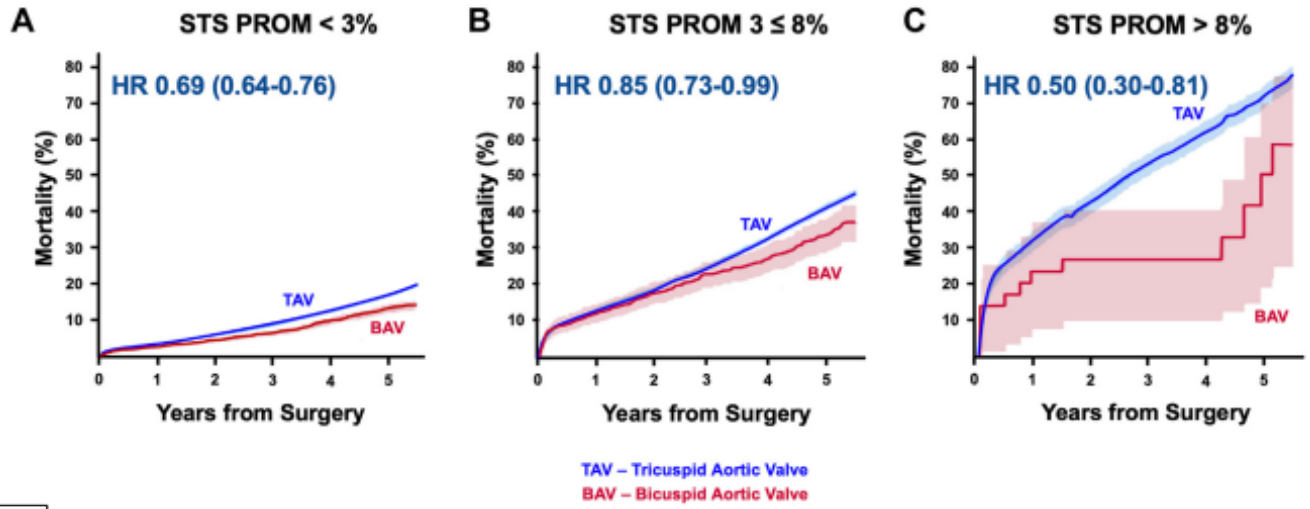
4 Year Low Risk

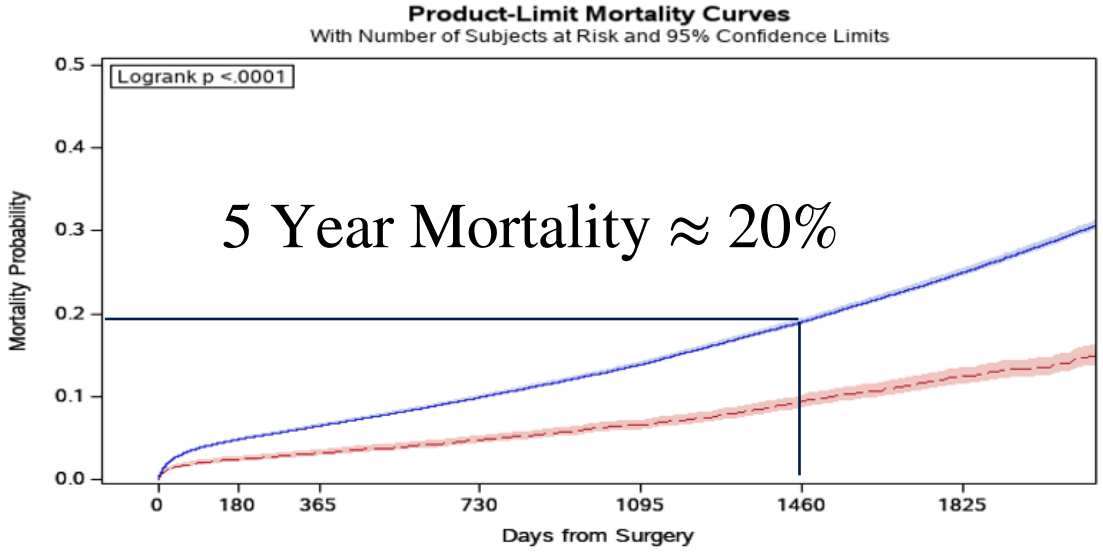
Leon et al. TCT 2023 PARTNER 3 ; Forrest et al. JACC 2023. Evolut Low Risk
Thourani et al. Ann Thor Surg 2023. STS analysis; Sondergaard et al. EuroPCR 2017

EVOLUT LOW RISK RCT – DEEP DIVE

Late Outcome is Influenced By Co-Morbidities

- STS report of 65,687 patients at 1146 US sites were analysis for tricuspid and bicuspid morphology
- Linked with CMS for long-term (5 year) mortality (62.1% matched to CMS)
- Late mortality related to STS PROM





- Tricuspid Aortic Valve Replacement
- Average Age, 75 years
- STS PROM 1.8%

Hirji Ann Thorac Surg 2023;116:1222-1232

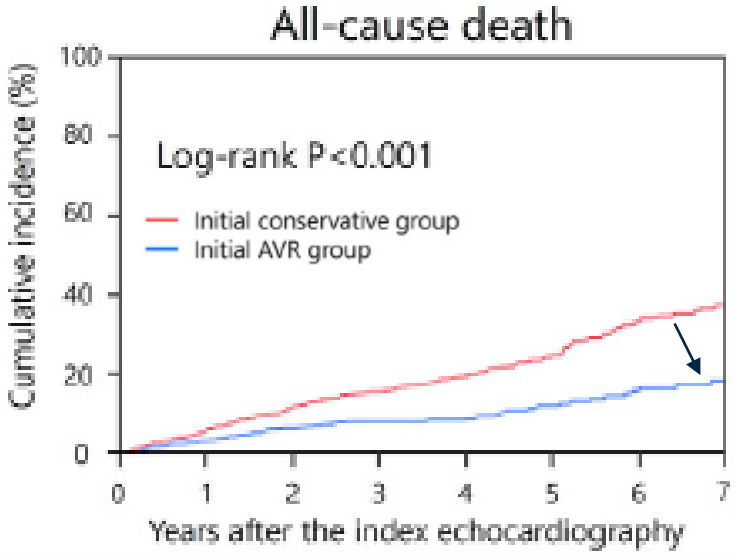
EVOLUT LOW RISK RCT – DEEP DIVE

JAPANESE SURGICAL AVR OUTCOMES BY STS RISK AND AGE

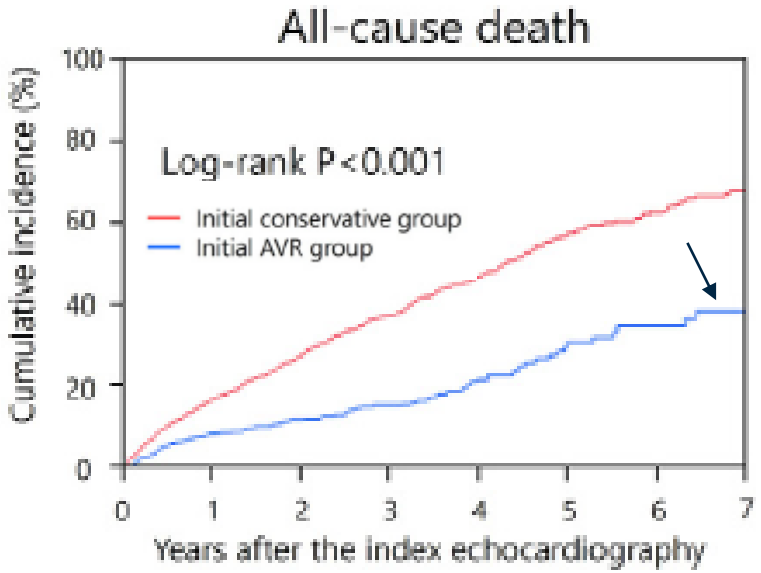
METHODS : Among 1197 patients with severe AS enrolled in the CURRENT registry undergoing surgical aortic valve replacement, 647 patients were low surgical risk, 433 were intermediate surgical risk, and 117 were high surgical risk. The expected survival of the general Japanese population was obtained from the Statistics Bureau of Japan.

CONCLUSIONS : The median follow-up was 3.7 years. **The observed mortality in low-risk patients was comparable to the expected mortality across all the age-groups,** while intermediate-risk patients aged <75 years, and high-risk patients across all age-groups had higher mortality compared with the expected mortality.

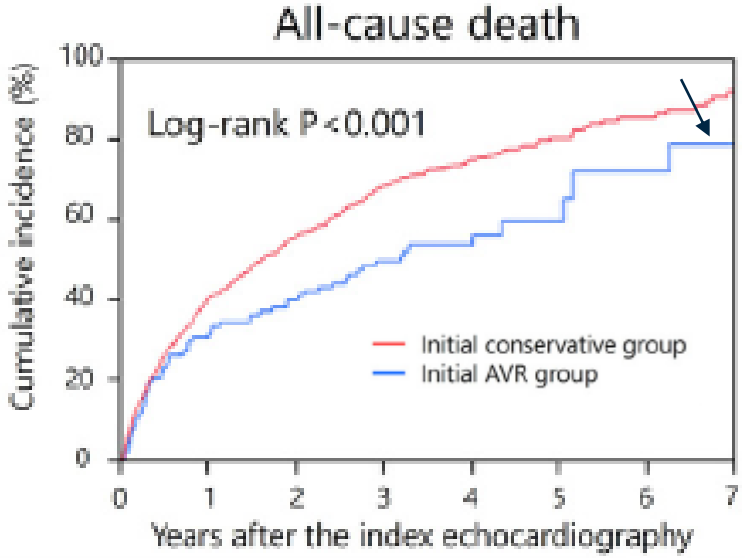
STS score <3%



STS score 3-8%



STS score >8%

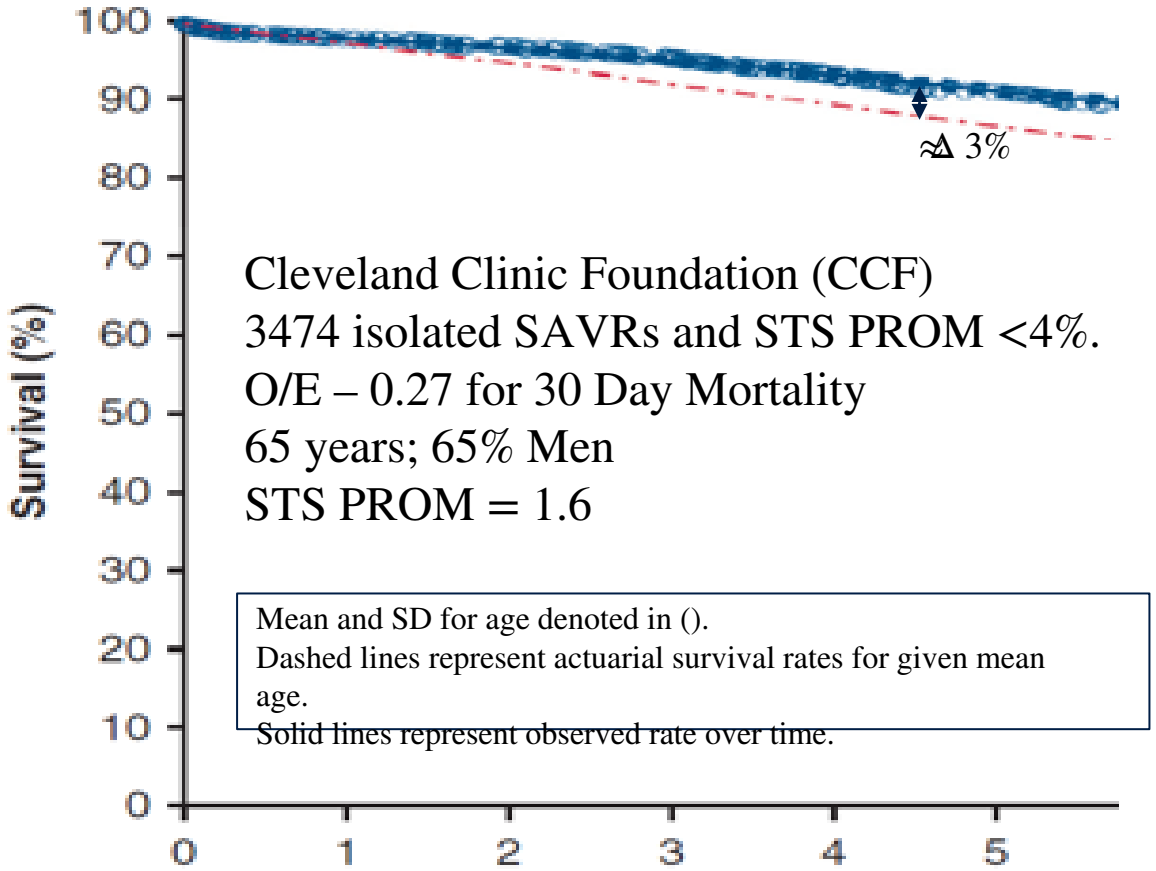


Taniguchi Ann Thorac Surg 2023;116:1195-204

EVOLUT LR RCT – DEEP DIVE

COMPARISONS WITH AGE MATCHED CONTROL WITH CCF AND EVOLUT LOW RISK

Modest Improvement over Age Matched

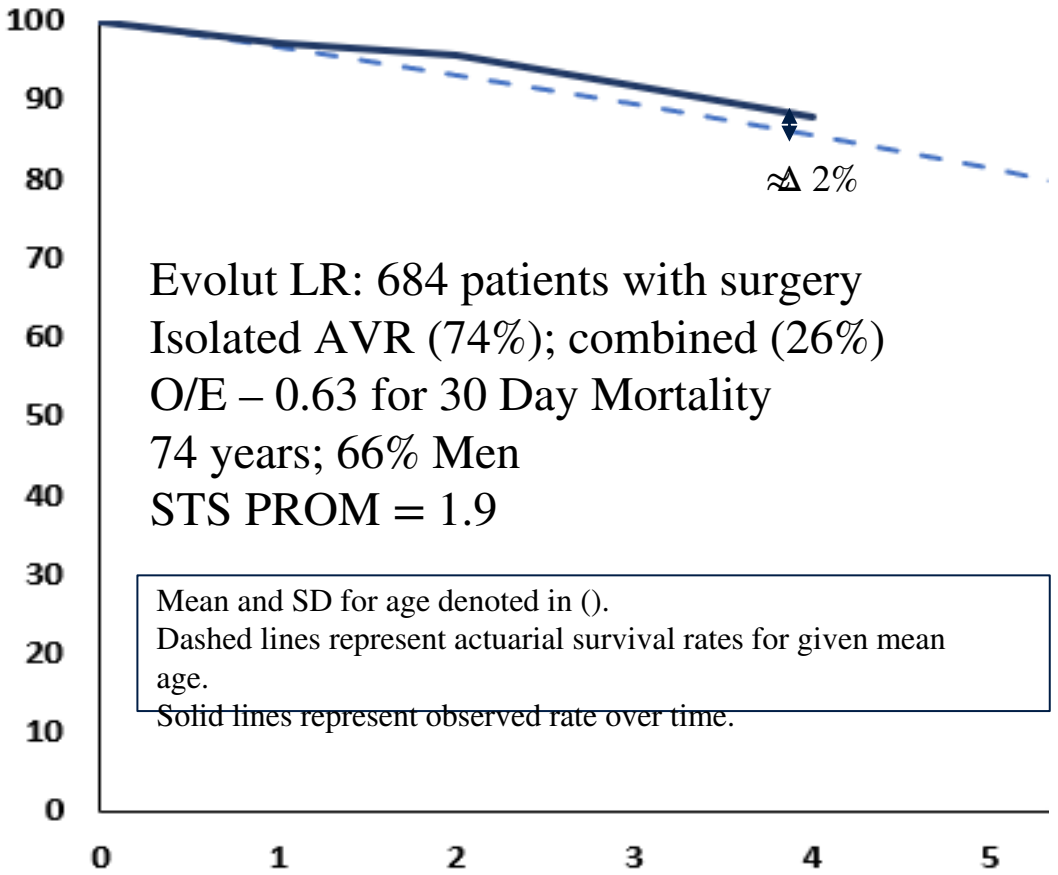


Cleveland Clinic Foundation (CCF)
3474 isolated SAVRs and STS PROM <4%.
O/E – 0.27 for 30 Day Mortality
65 years; 65% Men
STS PROM = 1.6

Mean and SD for age denoted in ().
Dashed lines represent actuarial survival rates for given mean age.
Solid lines represent observed rate over time.

Johnston et al J Thorac Cardiovasc Surg 2023;165:591-604

Modest Improvement over Age Matched



Evolut LR: 684 patients with surgery
Isolated AVR (74%); combined (26%)
O/E – 0.63 for 30 Day Mortality
74 years; 66% Men
STS PROM = 1.9

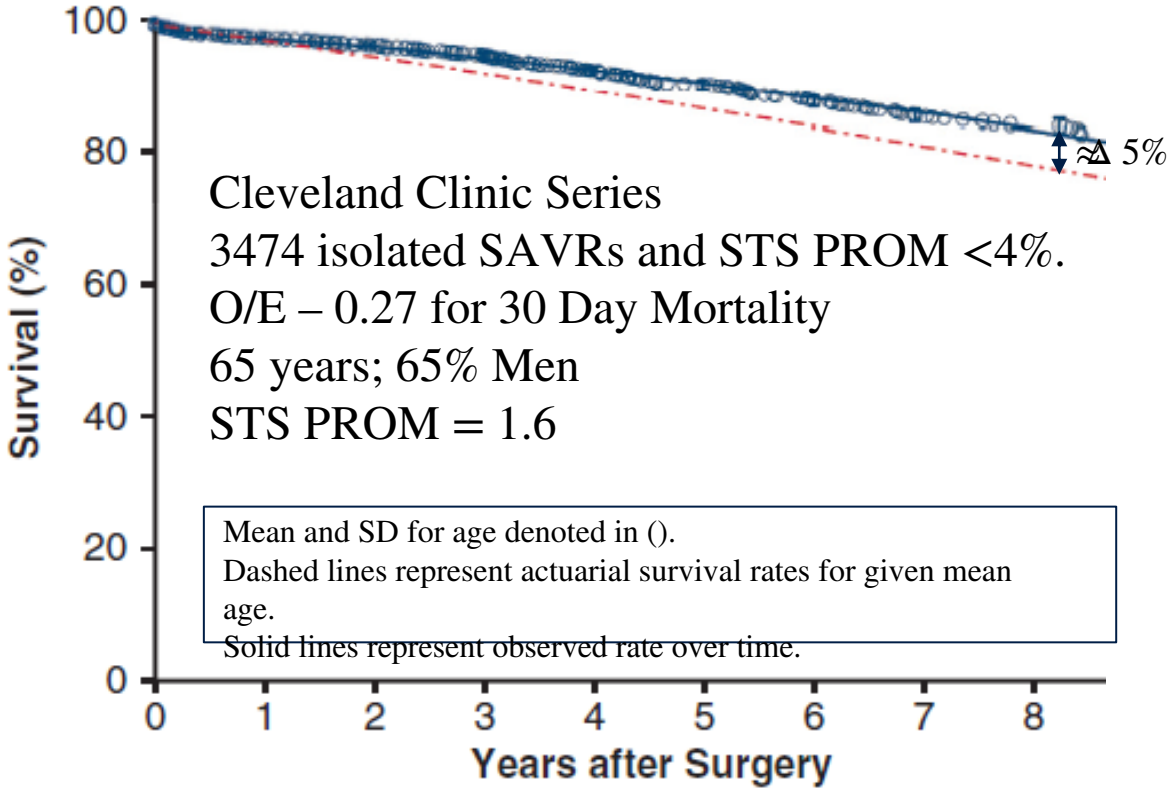
Mean and SD for age denoted in ().
Dashed lines represent actuarial survival rates for given mean age.
Solid lines represent observed rate over time.

Reardon TCT LBCT October 23, 2014
Human Mortality Database. https:// www.mortality.org . Downloaded 2023;

EVOLUT LR RCT – DEEP DIVE

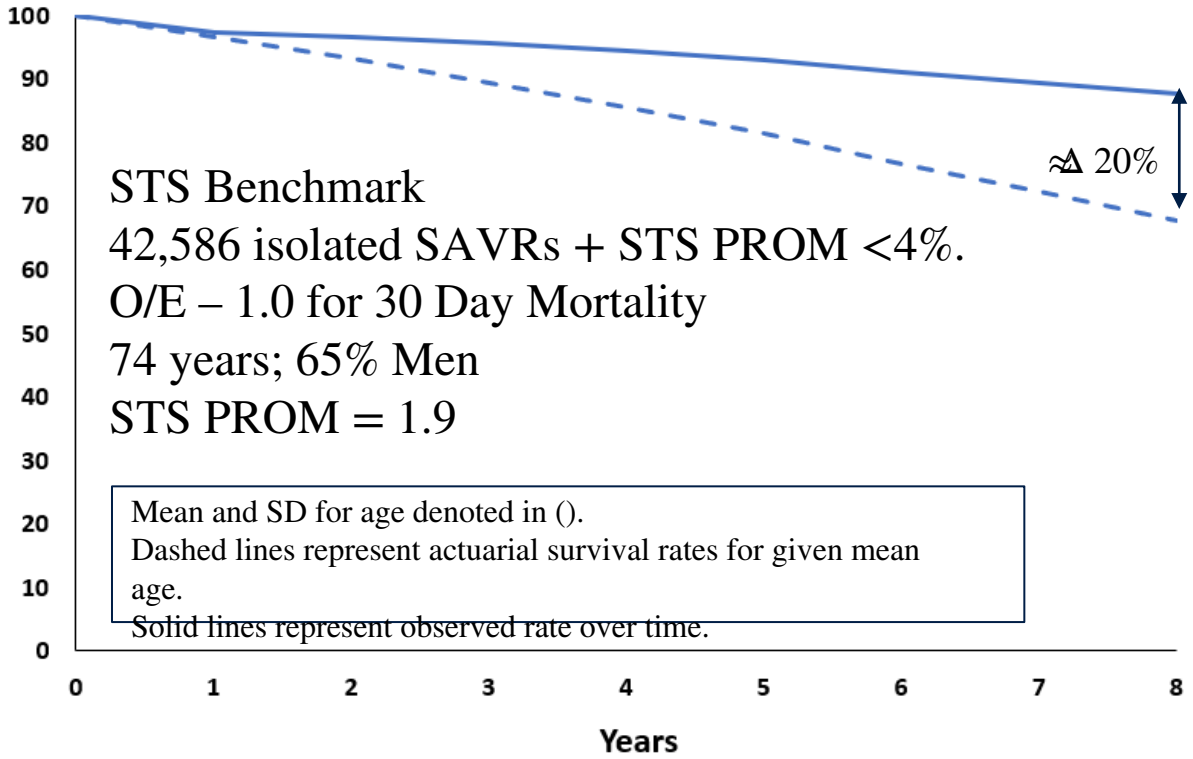
COMPARISONS WITH AGE MATCHED CONTROL WITH CCF AND STS BENCHMARK

Modest Improvement over Age Matched



Johnston et al J Thorac Cardiovasc Surg 2023;165:591-604

Marked Improvement over Age Matched



Thourani Annals Thoracic Surgery 2023 epublication
Human Mortality Database. https:// www.mortality.org . Downloaded 2023;

EVOLUT LOW RISK RCT – DEEP DIVE

TAKE HOME MESSAGES

- Despite more frequent exclusion after consent in the Partner 3 Trial than the Evolut Low Risk study, the 30 day- and 1-year surgical outcomes were similar in the two studies. Observed to expected ratio were similar in both studies.
- The use of concomitant procedures, valve sizing, and valve types were similar in the two studies. Annu lar enlargement was uncommon (< 5%) in both studies.
- Echocardiographic findings at one year suggested similar surgical valve performance in both studies.
- The 4-year Evolut Low Risk surgical mortality rates matched age adjusted mortality rates, comparable with other low risk surgical studies.
- Because of minimal exclusions after consent in the Evolut Low Risk study, recruitment of patients supports an "all comer" approach to low risk patients.

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SECTION 5:

ADDRESSING LIFETIME MANAGEMENTS IN LOW-RISK PATIENTS UNDERGOING TAVR

EVOLUT LOW RISK RCT – DEEP DIVE

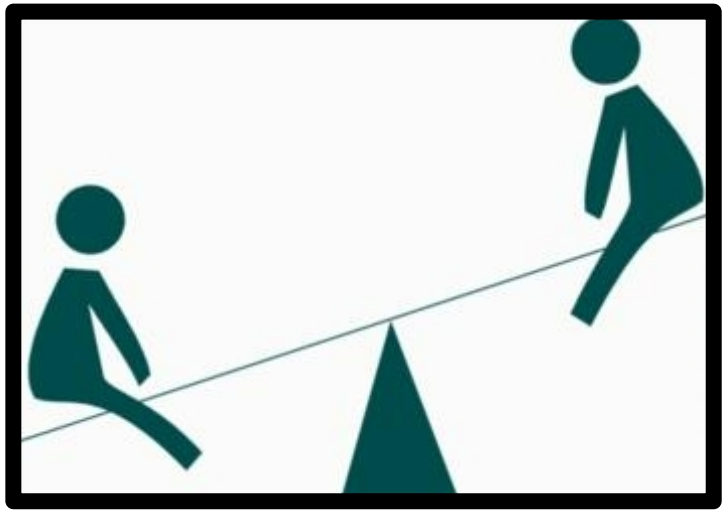
OBJECTIVES

- To understand the impact of the Evolut FX TAV on procedural predictability, deployment symmetry, and commissural alignment
- To review the recent result with cusp overlap technique and new pacemaker implant need and to discuss conduction system care pathways after TAVR
- To review contemporary data on coronary angiography after Evolut FX TAV implantation
- To discuss recent procedural updates on the use of balloon expandable TAVR for Evolut TAV failure due to stenosis or insufficiency

UC202407811 EN

Planning for Lifetime Management

Durability
Valve Performance
Leaflet Thrombosis

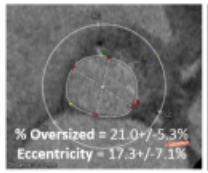


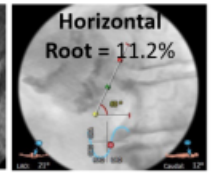
Ease of Use
Pacemaker Need
Coronary Access
BE for SE Failure

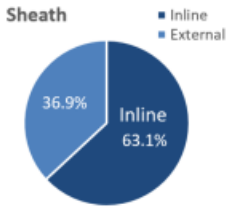
EVOLUT LOW RISK RCT – DEEP DIVE

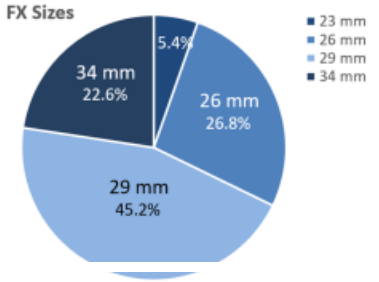
Initial Evolut Fx Multicenter Results

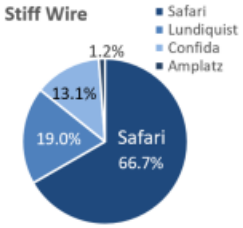
EVOLUT FX
INITIAL MULTICENTER RESULTS





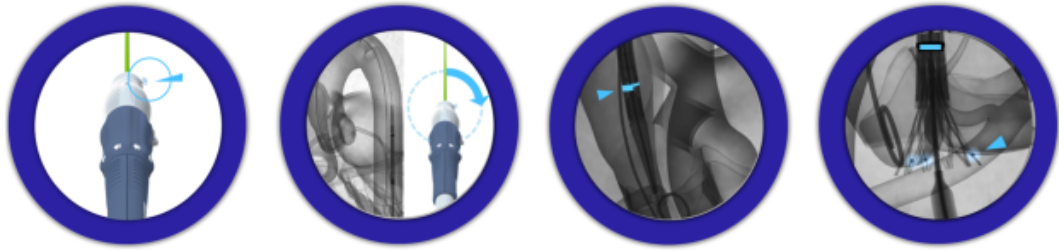






Procedural Characteristics	N=168
Valve-in-Valve - TAV-in-SAV - TAV-in-TAV (failed BEV)	18 (10.7%) 16 (9.5%) 2 (1.2%)
Transfemoral: Right	144 (85.7%)
Conscious Sedation	157 (93.5%)
Pre Dilatation	88 (52.4%)
Post Dilatation	25 (14.9%)
Sentinel Use	39 (23.2%)
Device Recapture / Reposition	48 (28.6%)
IV Contrast Use	83+/-42 mL
2nd Valve Required	1 (0.6%)

EVOLUT FX
INITIAL MULTICENTER RESULTS



1
Insert delivery system with flush port oriented at 3 o'clock

99.4%
3 o'clock @ insertion

2
Check flush port & "Hat" marker orientation in LAO in descending

98.2%
3 o'clock in descending "Hat" at outer curve / center back
Need to rotate catheter to get "Hat" to optimal position: 3.0%

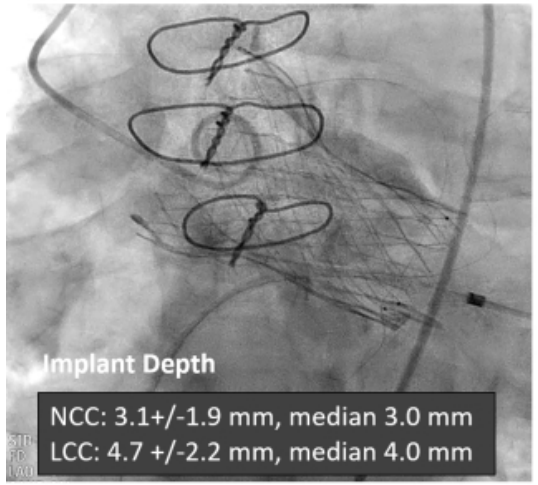
3
Verify "Hat" marker position at/near center front in cusp overlap

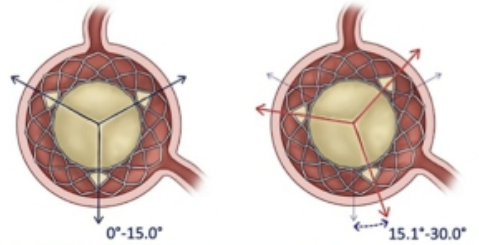
98.2%
"Hat" at center front / outer curve at annulus

4
Visualize FX dot marker orientation in cusp overlap view

- 2 left, 1 right 88.7%
- Evenly spaced 4.2%
- 2 right, 1 left 7.1%

EVOLUT FX
INITIAL MULTICENTER RESULTS





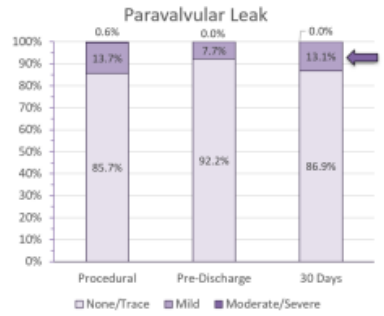
95.8%
Commissures aligned

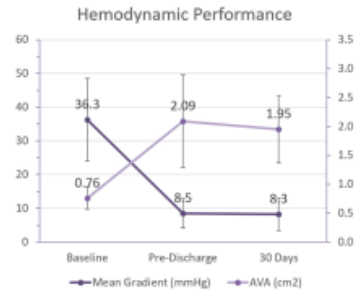
EVOLUT FX
INITIAL MULTICENTER RESULTS

- 'Hat' marker position at center front at cusp overlap view in >93% of cases
- Commissural alignment achieved in 95.8% of cases
- Improved trackability, more symmetric final deployment
- Low LBBB / reasonable pacemaker rates with early experience
- No moderate/severe and only 13.1% mild paravalvular leak at 30 days
- Excellent hemodynamics similar to prior Evolut systems

30-Day Outcomes	Evolut FX, N=168
Death	2 (1.2%)
Stroke	3 (1.8%)
Major Vascular Complication	2 (1.2%)
New LBBB	29 (19.0%)
Permanent Pacemaker* - 34 mm FX - Excluding prior RBBB (N=9) - Excluding prior RBBB + 34mm FX (N=14)	23 (15.0%) 7 (18.4%) **14 (9.7%)** **9 (6.5%)**

*prior pacemaker excluded, no association with learning curve or no Lundiquist wire use



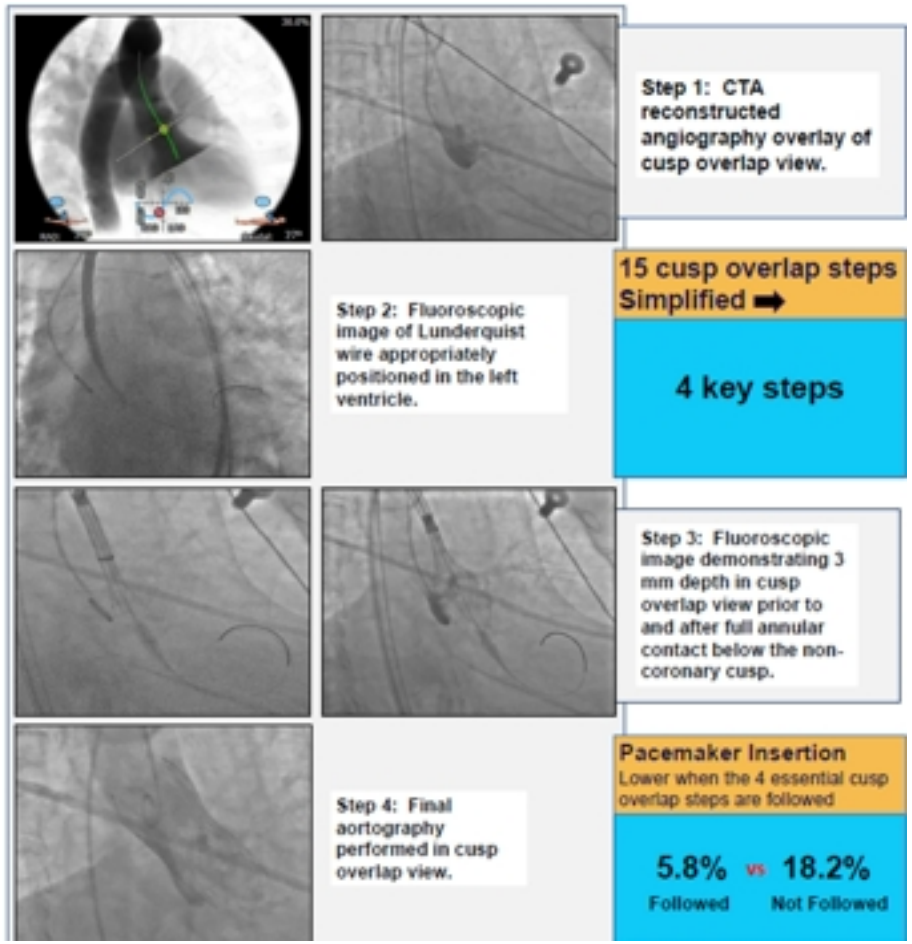


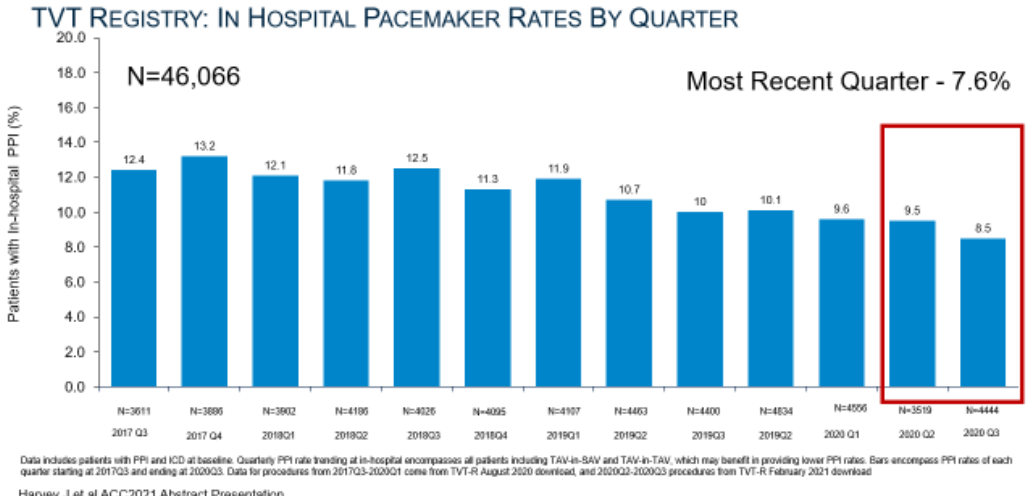
Zaid et al. JACC Interv 2023.

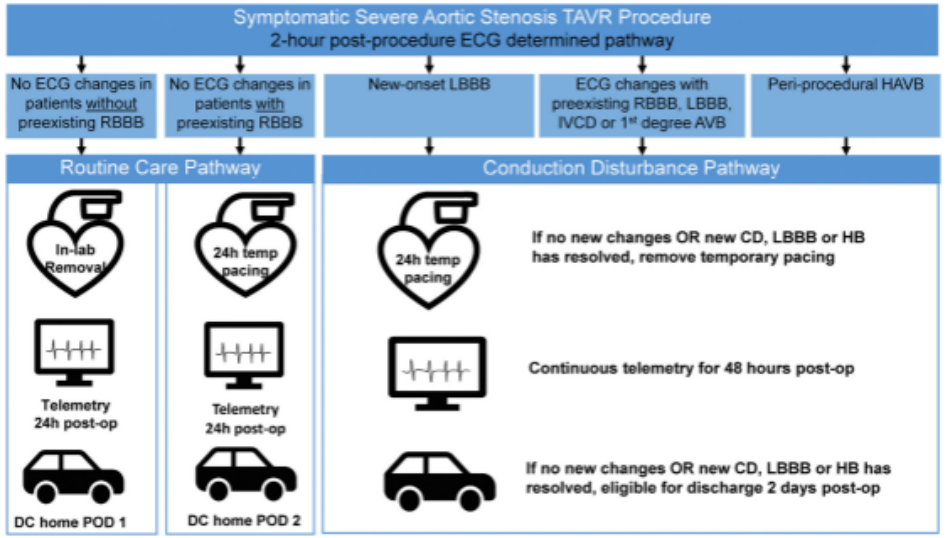
EVOLUT LOW RISK RCT – DEEP DIVE

Cusp Overlap Technique and Conduction Abnormalities

COT -- Reduced PPI







Grubb JSCAI 2023, epub prior to print

EVOLUT LOW RISK RCT – DEEP DIVE

COMMISSURAL POST ORIENTATION

Favorable Alignment

Potential Considerations

- Better hemodynamics
- Reduced thrombogenicity
- Coronary access
- Future leaflet management options

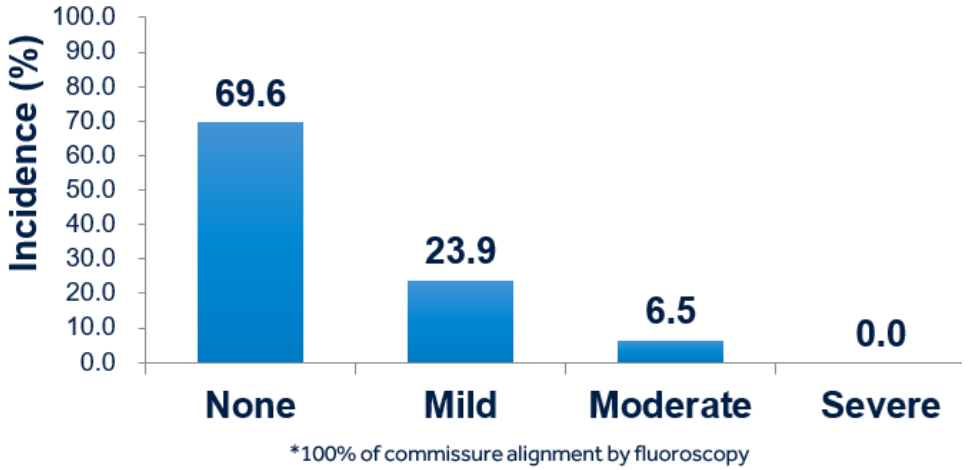
Source: Rogers T. Small Annuli Symposium. Presented at TCT Connect 2020.

*Commissural misalignment shown to affect hemodynamics and thrombogenicity in balloon-expanding valves. Rasplicher et al. JACC 2022

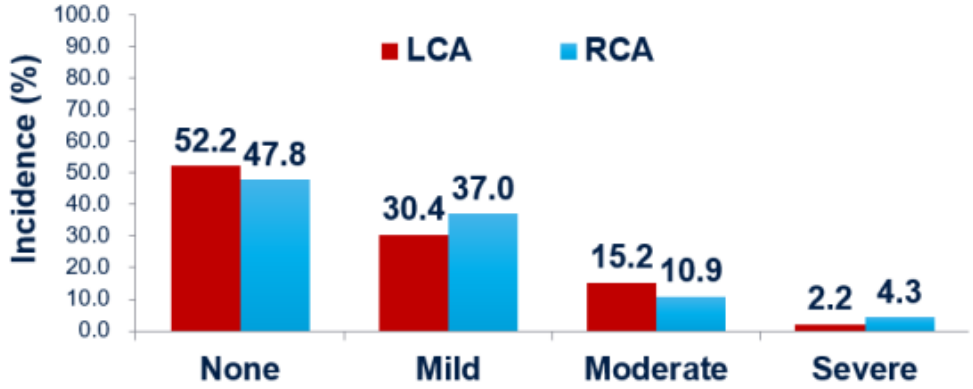
EVOLUT LOW RISK RCT – DEEP DIVE

CORONARY IMAGING WITH EVOLUT FX

Commissural Misalignment (CT Based)

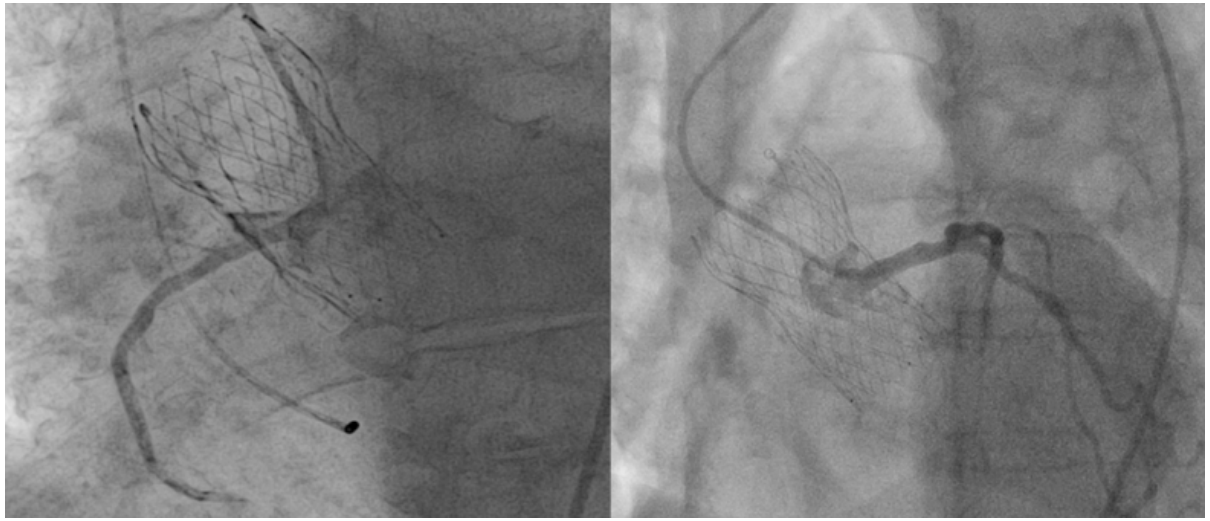


Coronary Misalignment (CT Based)

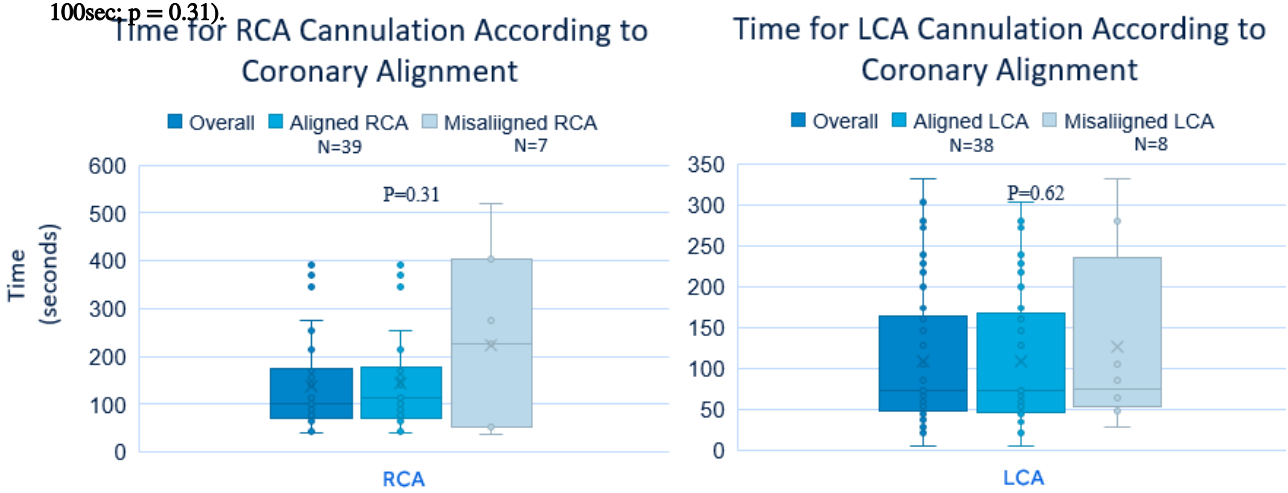


Attizzani et al TCT2023 Coronary Access

50/50 (100%) Diagnostic Imaging for Both Coronaries

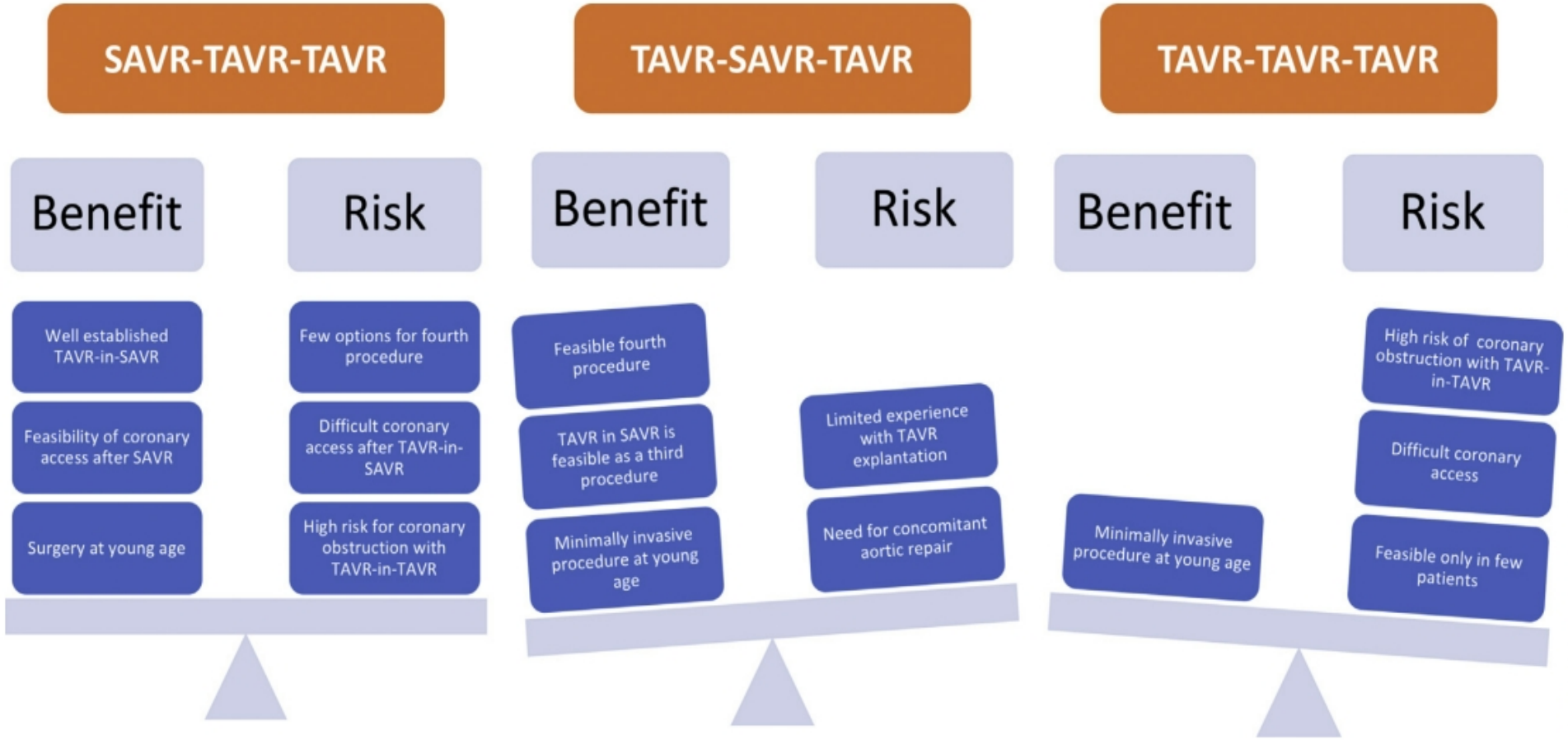


Coronary misaligned vs. aligned groups (LCA 126 ± 114 vs. 109 ± 83 sec, p = 0.62; RCA 224 ± 189 vs. 143 ± 100sec; p = 0.31).



EVOLUT LOW RISK RCT – DEEP DIVE

THEORETICAL SEQUENCES OF AVR DURING THE LIFETIME MANAGEMENT

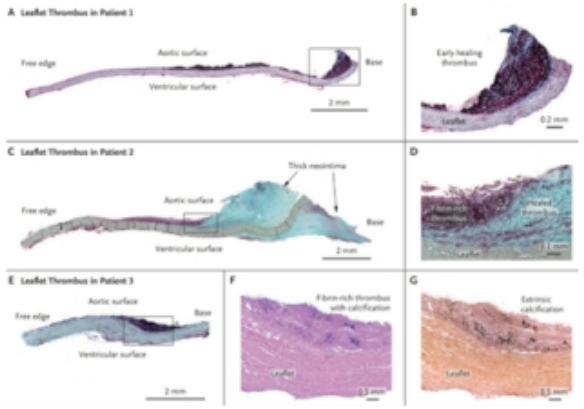


Yerasi, C. et al. J Am Coll Cardiol Intv. 2021;14(11):1169–80.

Evolut THV for THV failures has not been approved for clinical use by the USA FDA and is off label. Medtronic does not promote or recommend the use of Evolut THV for THV failures.

EVOLUT LOW RISK RCT – DEEP DIVE

PATHOLOGY LEADING TO TAVR DEGENERATION

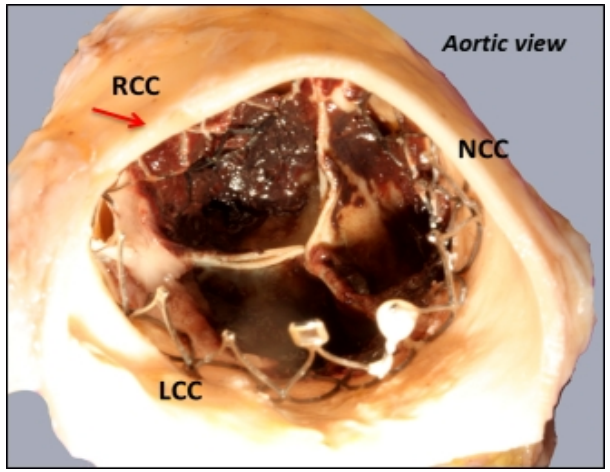


Yahagi et al N Engl J Med 2020; 383(2): e8.

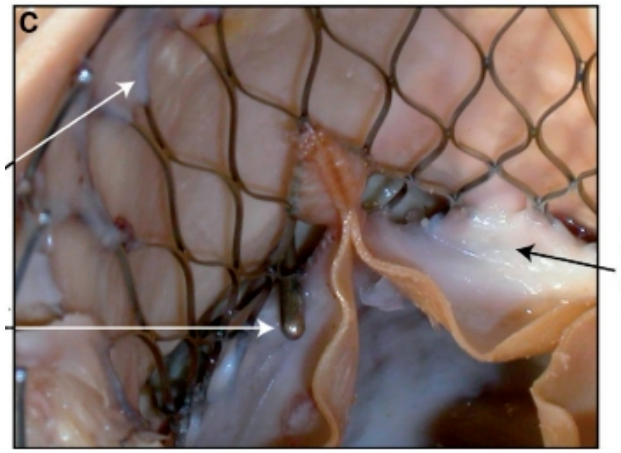
There are multiple mechanisms that can lead to valve failure. Early thrombus may be an important nidus for later structural valve deterioration

Calcification [1]

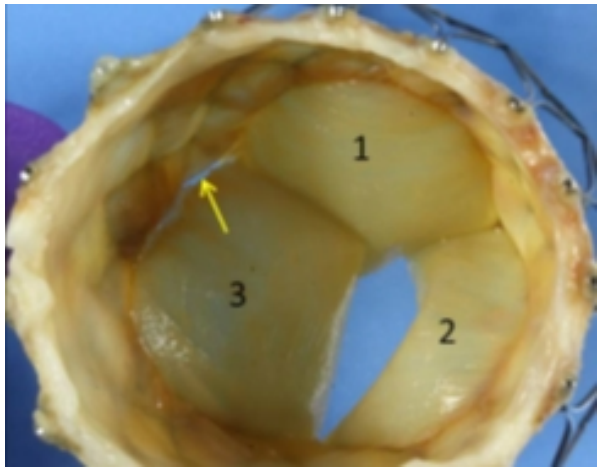
Thrombus [2]



Pannus [3]



Leaflet Tear [4]

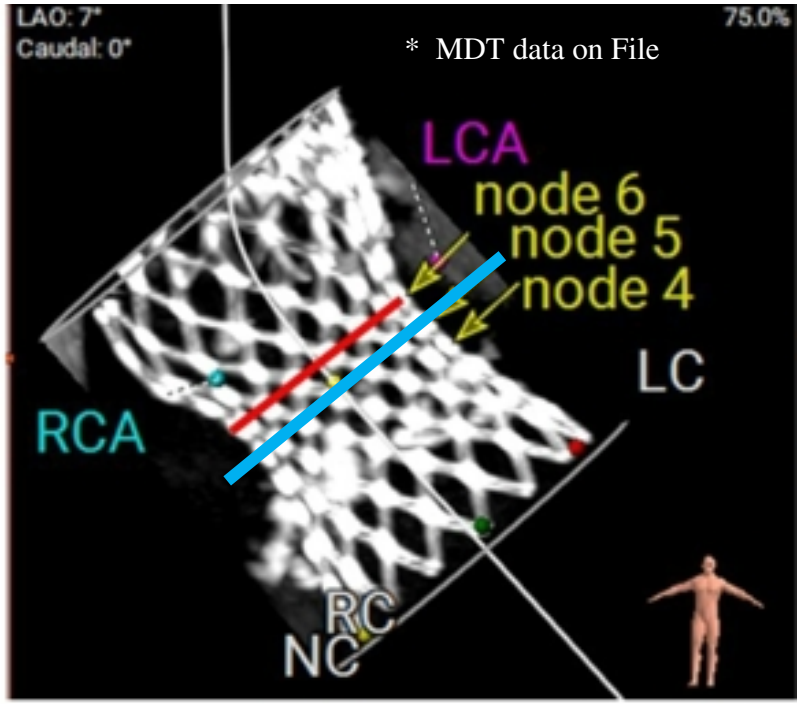


1. Ong et al. Eur Heart J 2012. 2. De Marchena E et al. JACC Cardiovasc Interv 2015. 3. Noble S et al. EuroInterv 2009; [4] MDT Internal Data

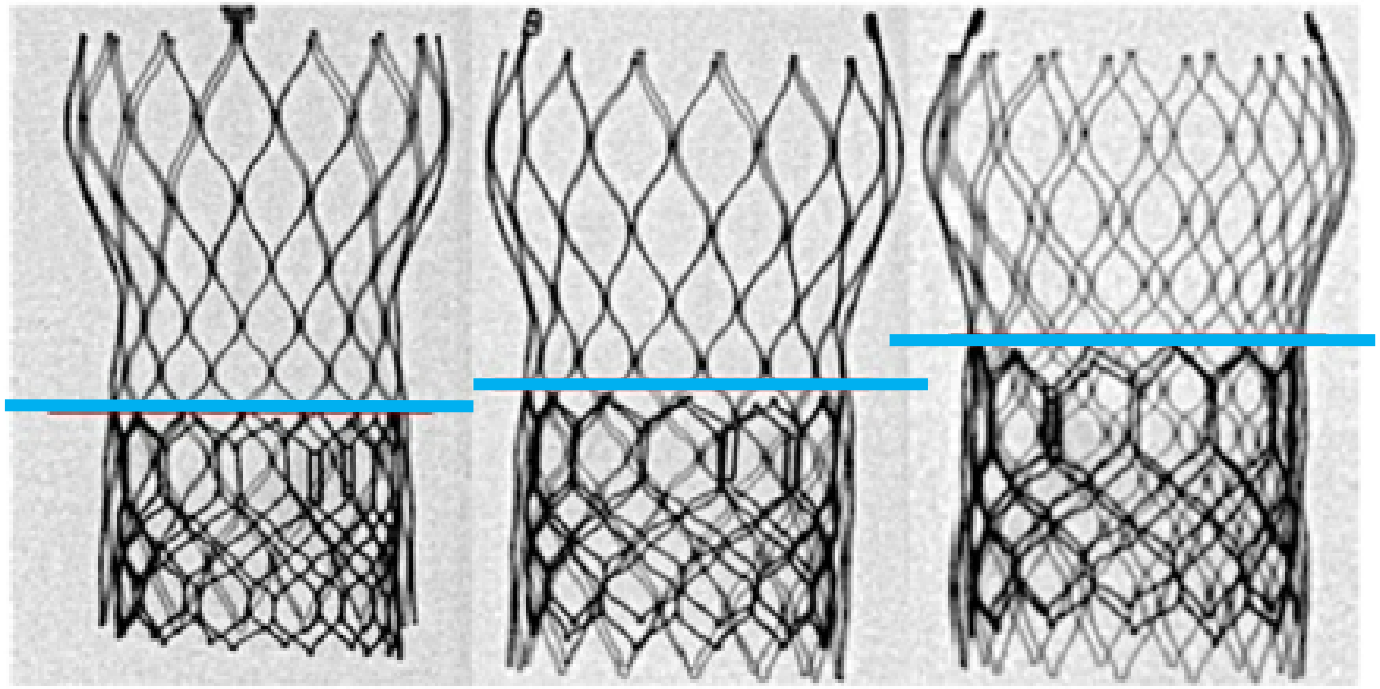
EVOLUT LOW RISK RCT – DEEP DIVE

REDO TAVR WITH SAPIEN 3 IN EVOLUT THV

Based on the planned implantation height of the second BE-TAV, one can determine the anticipated **neoskirt height => risk plane** and estimate the neoskirt-to-coronary distance and neoskirt-to-STJ distance.



Coronary markers are at the inferior aspect of coronary arteries



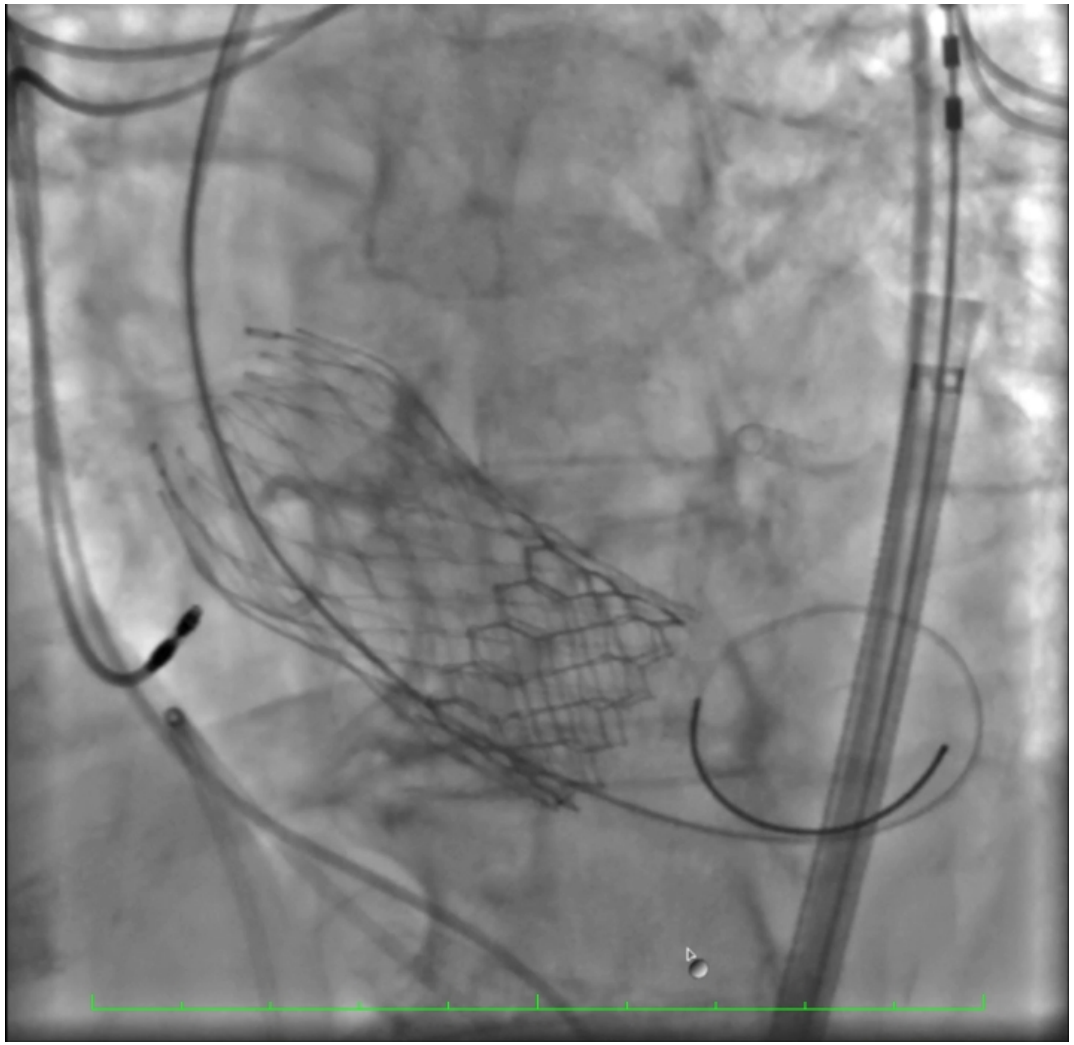
Coronary Risk Plane THV Risk Plane

Left Image: Medtronic, data on file

Tarantini et al AJC 2023, epub prior to print

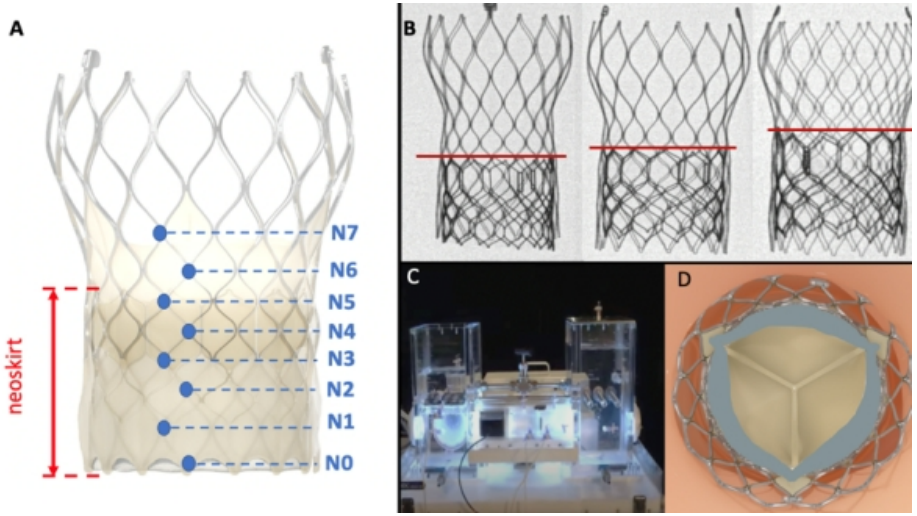
EVOLUT LOW RISK RCT – DEEP DIVE

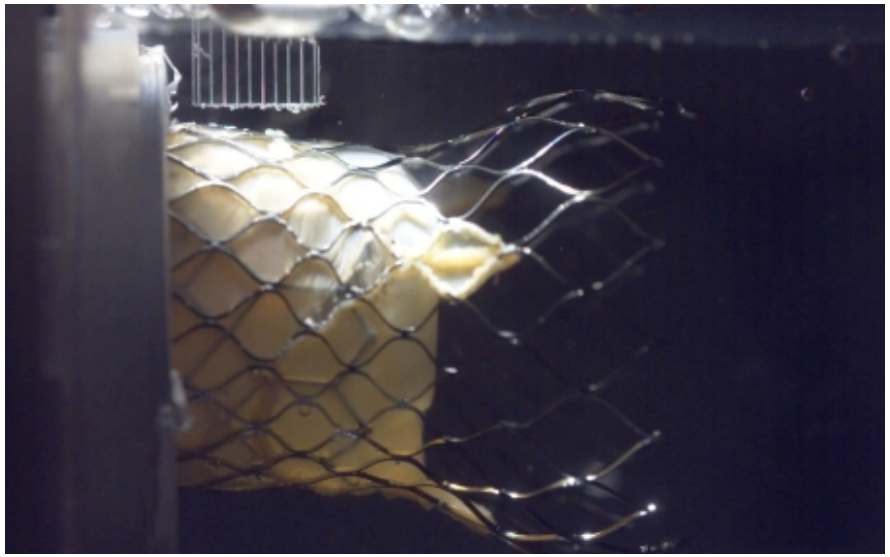
SAPIEN FUNCTION AFTER NODE 4 IMPLANT



Courtesy of Michael Caskey, MD

In vitro testing of Sapien valve function using ISO standard assessing stenosis and regurgitation





Akodad JACC CV 2021

EVOLUT LOW RISK RCT – DEEP DIVE

SAPIEN FOR THV FAILURE

348,338 patients underwent TAVR with Edwards balloon-expandable valves

11/09/2011 – 9/30/2022

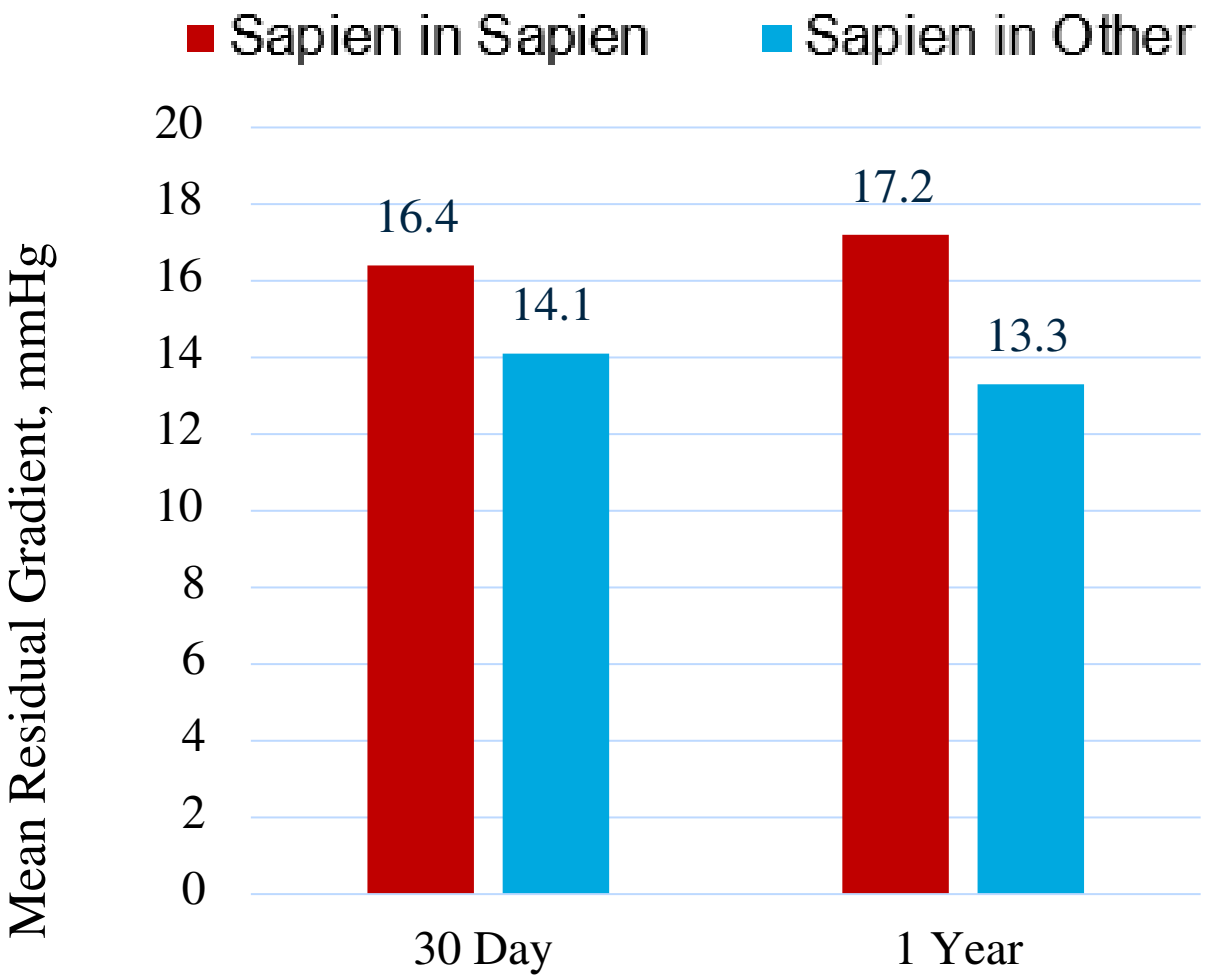
Redo TAVR

n = 1216

Redo-TAVR of Edwards Index THV	Redo-TAVR of Non-Edwards Index THV
n = 475	*n = 741*

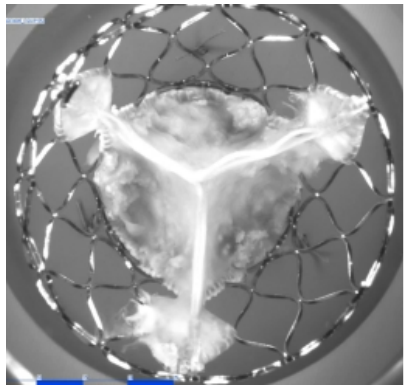
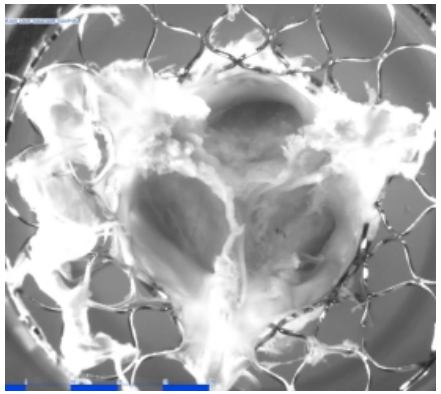
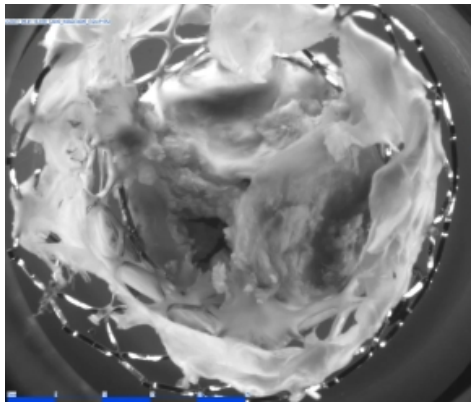
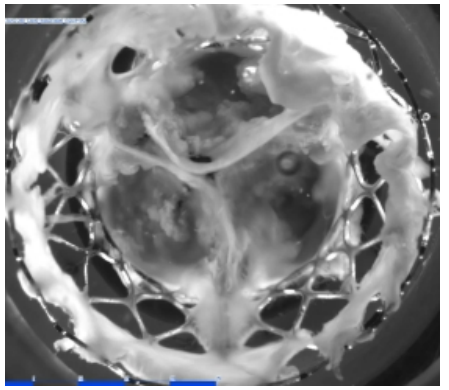
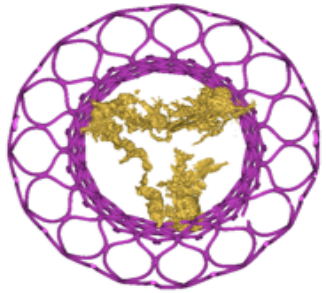
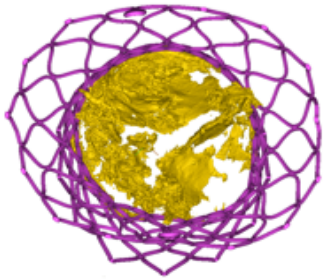
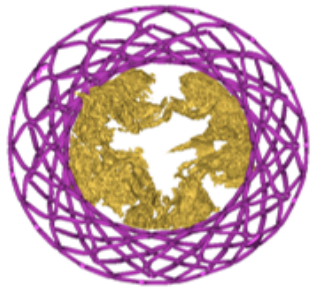
Makkar et al LBCT EuroPCR2023

Mean Residual Gradients



EVOLUT LOW RISK RCT – DEEP DIVE

SAPIEN NODE 5 IMPLANTS IN STENOTIC EVOLUT FAILURES

	23mm Evolut R	29mm CoreValve	29mm Evolut PRO	34mm Evolut R
				
EOA (cm ^{2})	0.82	1.10	0.85	0.66
Mean Gradient (mmHg)	56.3	32.7	41.4	76.6
				
Calcium volume (mm^3)	77.9	246.8	448.5	603.0

All TAV explants were stenotic before Redo-TAVR

Frame

Calcium

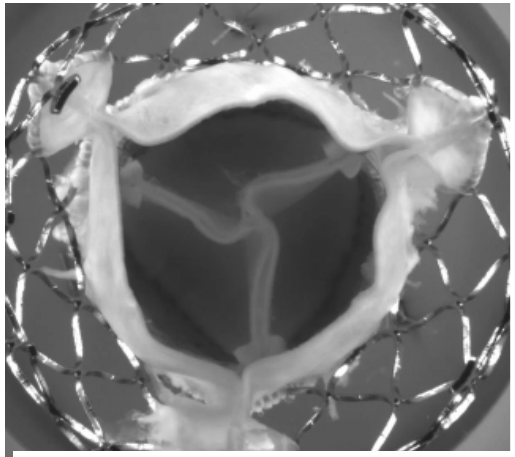
Sellers et al TCT2023 Abstract

Sellers et al TCT2023 Abstract

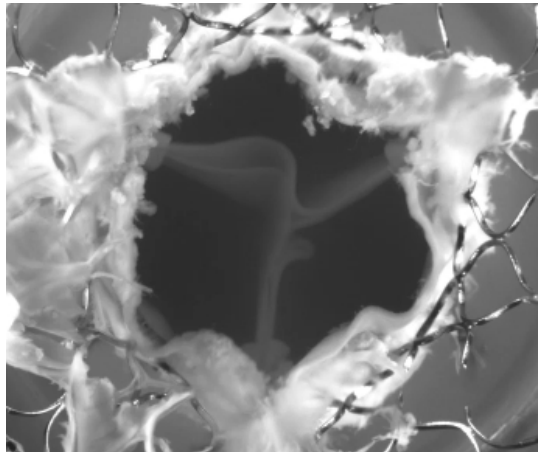
EVOLUT LOW RISK RCT – DEEP DIVE

ADEQUATE SAPIEN 3 HEMODYNAMIC PERFORMANCE AND VALVE FUNCTION

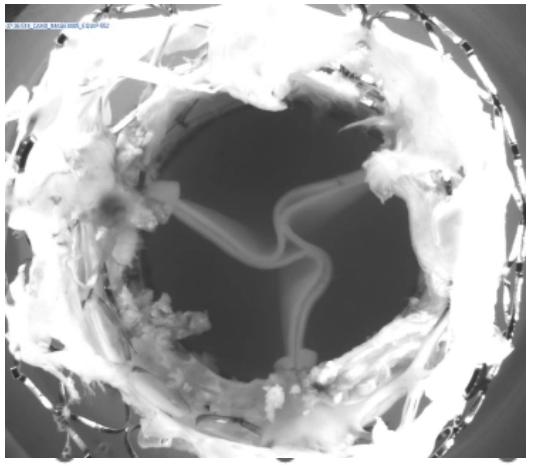
20mm Sapien 3 in 23mm Evolut R



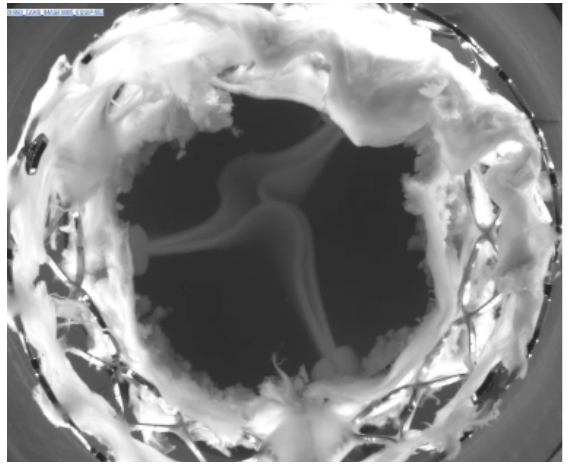
26mm Sapien 3 in 29mm CoreValve



26mm Sapien 3 in 29mm Evolut PRO



29mm Sapien 3 in 34mm Evolut R



	EOA (cm^2)			Mean Gradient (mmHg)		Peak Velocity (m/s)		Regurgitant Fraction (%)
	Pre Redo-TAVR	Post Redo-TAVR	ISO accepted	Pre Redo-TAVR	Post Redo-TAVR	Pre Redo-TAVR	Post Redo-TAVR	Post Redo-TAVR
20mm S3 in 23mm Evolut R	0.82	1.17	0.95	56.3	28.5	5.0	3.4	7.9
26mm S3 in 29mm CoreValve	1.10	2.16	1.60	32.7	9.5	3.8	1.9	18.9
26mm S3 in 29mm Evolut PRO	0.85	2.07	1.60	41.4	10.2	4.6	1.9	12.3
29mm S3 in 34mm Evolut R	0.66	2.54	2.10	76.6	6.9	6.2	1.6	25.8 *

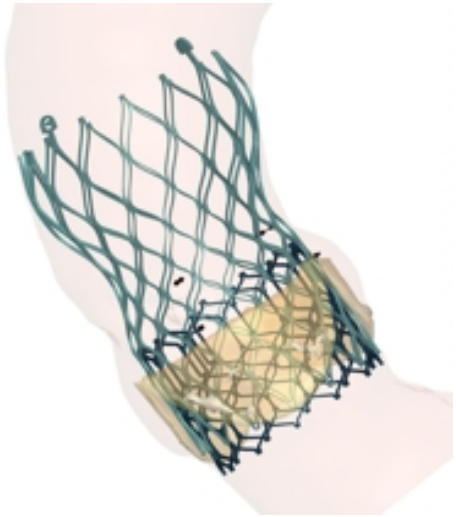
Sellers et al TCT2023 Abstract

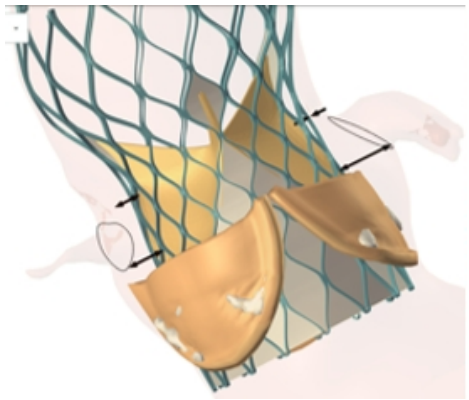
* ISO accepted: <20% (additional studies on-going)

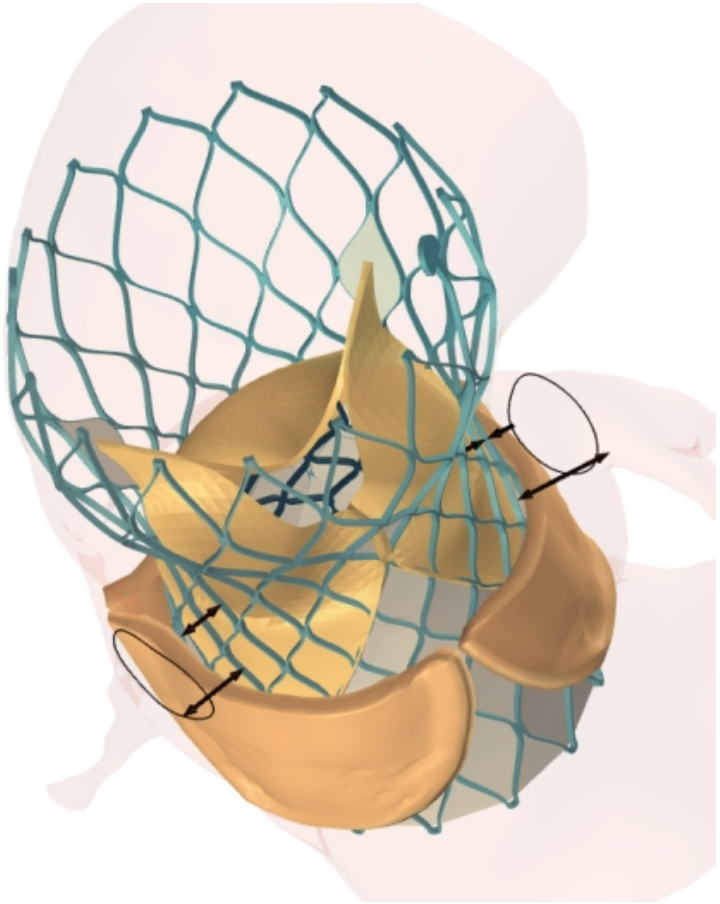
EVOLUT LOW RISK RCT – DEEP DIVE

ADVANCED CASE PLANNING WITH FEOPS SIMULATION

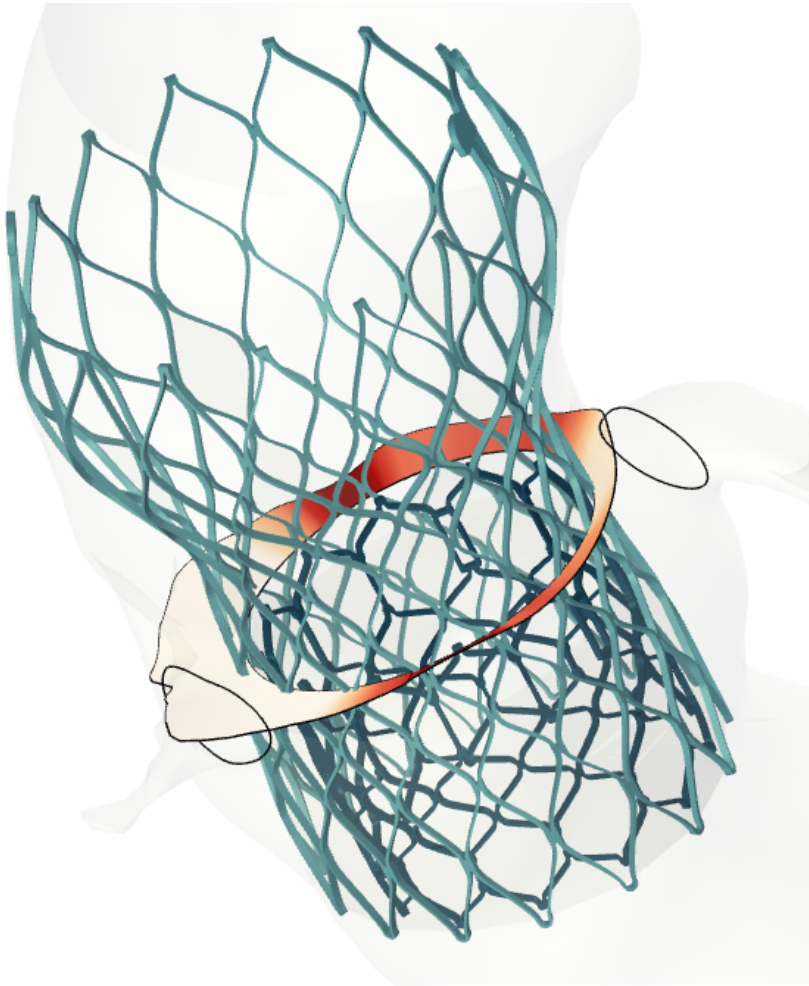
Courtesy of Feops







3D analysis of coronary access (red color = gap < 2mm)



Leaflet overhang
Impact of commissural alignment

EVOLUT LOW RISK RCT – DEEP DIVE

Take Home Messages

- Design iterations with the next generation Evolut FX have improved catheter delivery, deployment symmetry, and commissural alignment
- Improved procedure methods with the cusp overlap technique have reduced conduction system abnormalities and the need for new permanent pacemaker placement
- Commissural alignment has improved the feasibility of coronary angiography after Evolut FX TAVR
- Treatment of Evolut failures with an appropriately positioned balloon expandable valve to preserve coronary perfusion has been used without adverse on the balloon expandable value function or residual gradients due to leaflet overhang.
- Pre-TAVR case planning may be useful in planning for the first valve implant

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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 cm2 or aortic valve area index ≤ 0.6 cm2/m2, 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 cm2 or aortic valve area index ≤ 0.6 cm2/m2, 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/mm3), thrombocytopenia (platelet count < 50,000 cells/mm3), 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™

710 Medtronic Parkway
Minneapolis, MN 55432-5604
USA

Toll-free: 800.328.2518
Tel: +1.763.514.4000

medtronic.com

LifeLine
CardioVascular Technical Support
Toll-free: 877.526.7890
Tel: +1.763.526.7890
rs.structuralheart@medtronic.com