



Medtronic

Engineering the extraordinary

Four-year outcomes from the Evolut Low Risk Trial

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On behalf of the Evolut Low Risk Trial Investigators

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EVOLUT LOW RISK TRIAL | 4 YEAR RESULTS

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Statistical Analyses: Medtronic

Sponsor: Medtronic

EVOLUT LOW RISK TRIAL | 4 YEAR RESULTS

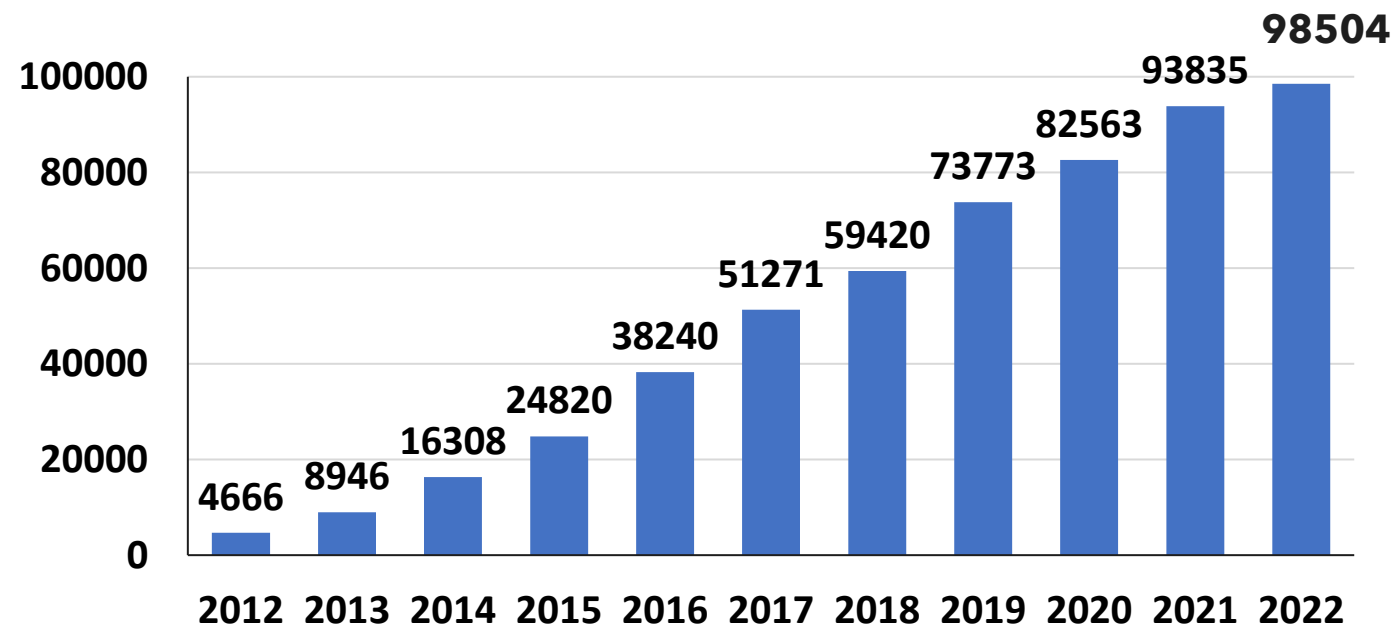


Background

Increasing Number of TAVR Procedures in Younger Lower Risk Patients

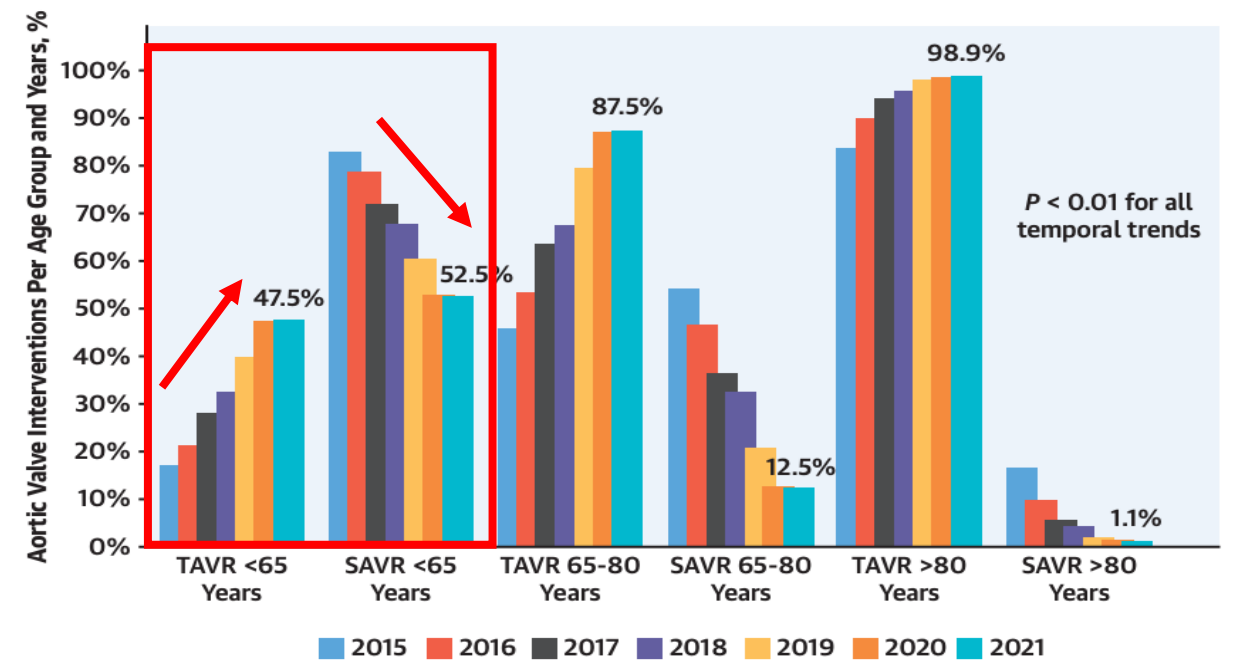
Trends in transcatheter and surgical aortic valve replacement (TAVR and SAVR) in the U.S. show yearly increases in the overall number of TAVR procedures and significant growth in TAVR utilization among younger adults with aortic stenosis.^{1,2}

Commercial TAVR procedures in the U.S.



¹STS/ACC TVT Registry database.

TAVR and SAVR procedures by age group in the U.S.



²Sharma T, et al., *J Am Coll Cardiol.* 2023;80(2):2054-2056. Republished with permission from Elsevier Inc.

EVOLUT LOW RISK TRIAL | 4 YEAR RESULTS

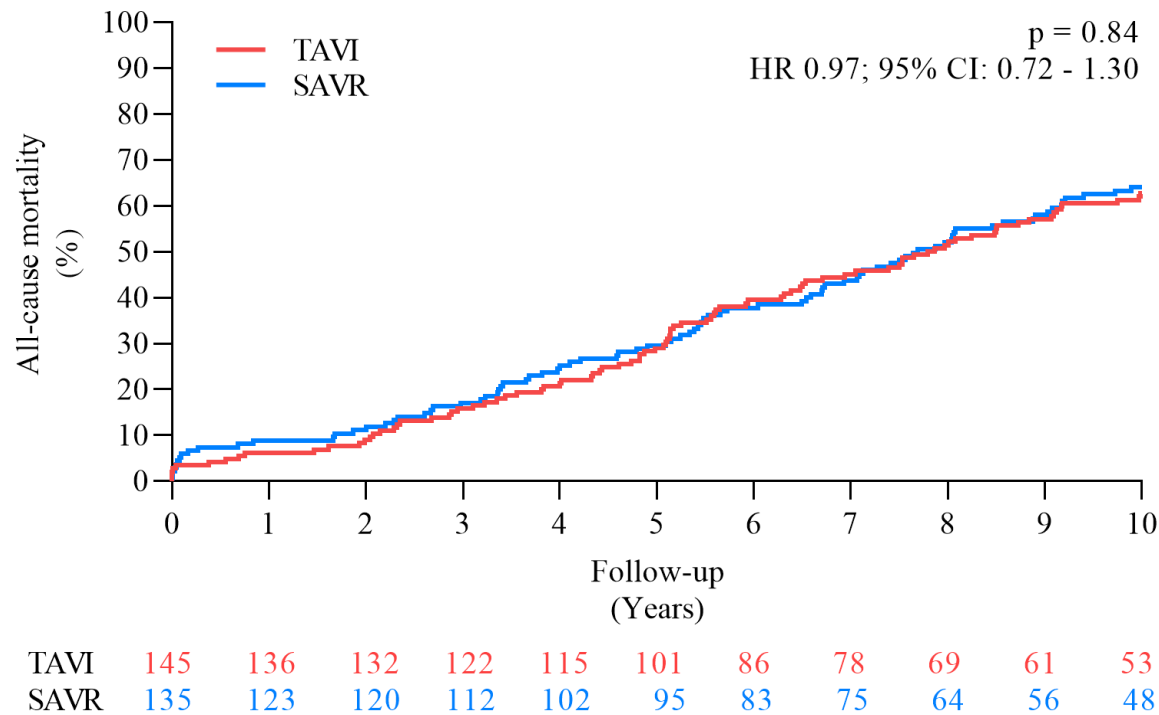


Background

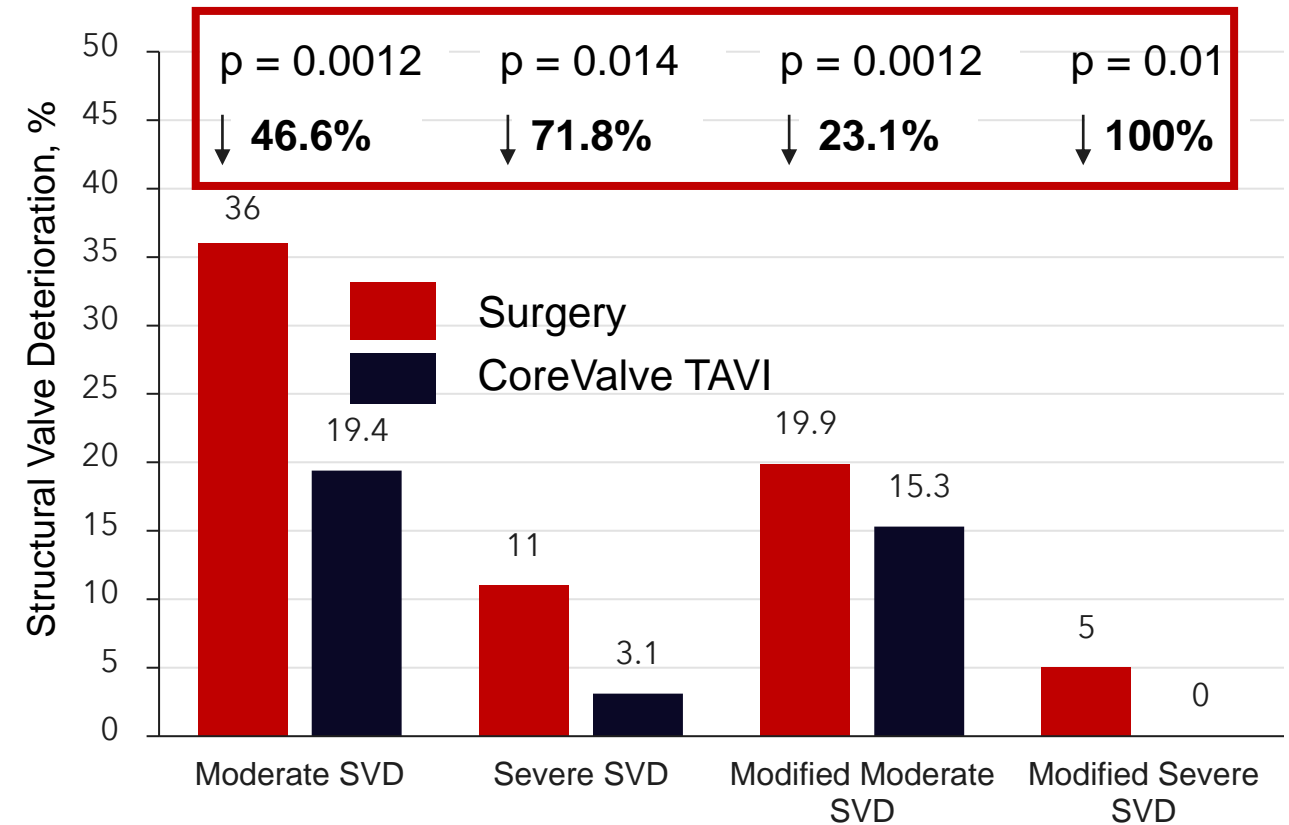
NOTION 10-Year: Less SVD with CoreValve TAVR vs SAVR

Long-term data are limited in “all comer” lower risk patients. In the NOTION 10-year, 37% of patients survived 10 years – the rates of valve degeneration, as assessed by various measures of structural valve deterioration, were significantly lower in the patients treated with the 1st generation CoreValve compared with surgery¹

NOTION 10Y: All-cause mortality



Structural Valve Deterioration



EVOLUT LOW RISK TRIAL | 4 YEAR RESULTS

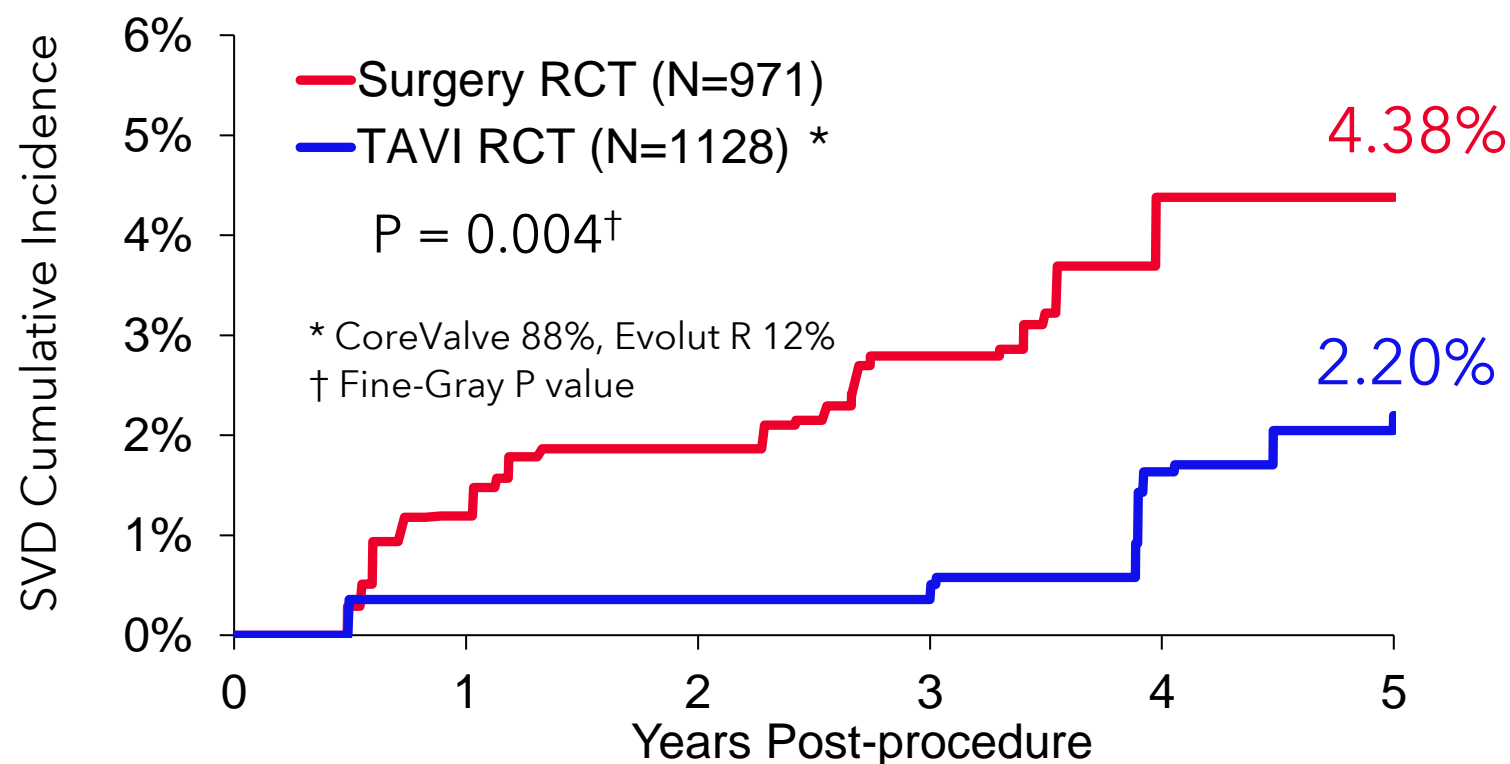


Background

SVD Is Associated with Worse Clinical Outcomes

- Our prior randomized studies of high- and intermediate-risk patients have demonstrated lower rates of SVD in patients undergoing CoreValve TAVR compared with surgery at 5 years¹
- SVD was associated with a two-fold risk for death, cardiovascular death, or rehospitalization in all AVR¹

Significantly Less SVD with CoreValve/Evolut TAVR



SVD Predicts 5-Year Mortality

	HR (95% CI)	P value
Pooled Surgery RCT and All TAVI* (N=4762)		
All-cause mortality	2.03 (1.46, 2.82)	<0.001
Cardiovascular mortality	1.86 (1.20, 2.90)	0.006
Hospitalization for AV disease/worsening HF	2.17 (1.23, 3.84)	0.008
Composite †	2.02 (1.42, 2.88)	<0.001
Surgery RCT (N=971)		
All-cause mortality	2.45 (1.40, 4.30)	0.002
Cardiovascular mortality	2.37 (1.10, 5.08)	0.03
Hospitalization for AV disease/worsening HF	2.20 (0.81, 5.98)	0.12
Composite †	2.73 (1.53, 4.88)	<0.001
All TAVI* (N=3791)		
All-cause mortality	2.34 (1.55, 3.53)	<0.001
Cardiovascular mortality	2.17 (1.26, 3.76)	0.006
Hospitalization for AV disease/worsening HF	2.45 (1.22, 4.93)	0.01
Composite †	2.03 (1.29, 3.19)	0.002

* RCT and Non-RCT cohorts
CoreValve 97%, Evolut R 3%

0.10 1.00 10.00
Lower risk with SVD ← → Higher risk with SVD

† All-cause mortality or hospitalization for AV disease or worsening HF

EVOLUT LOW RISK TRIAL | 4 YEAR RESULTS

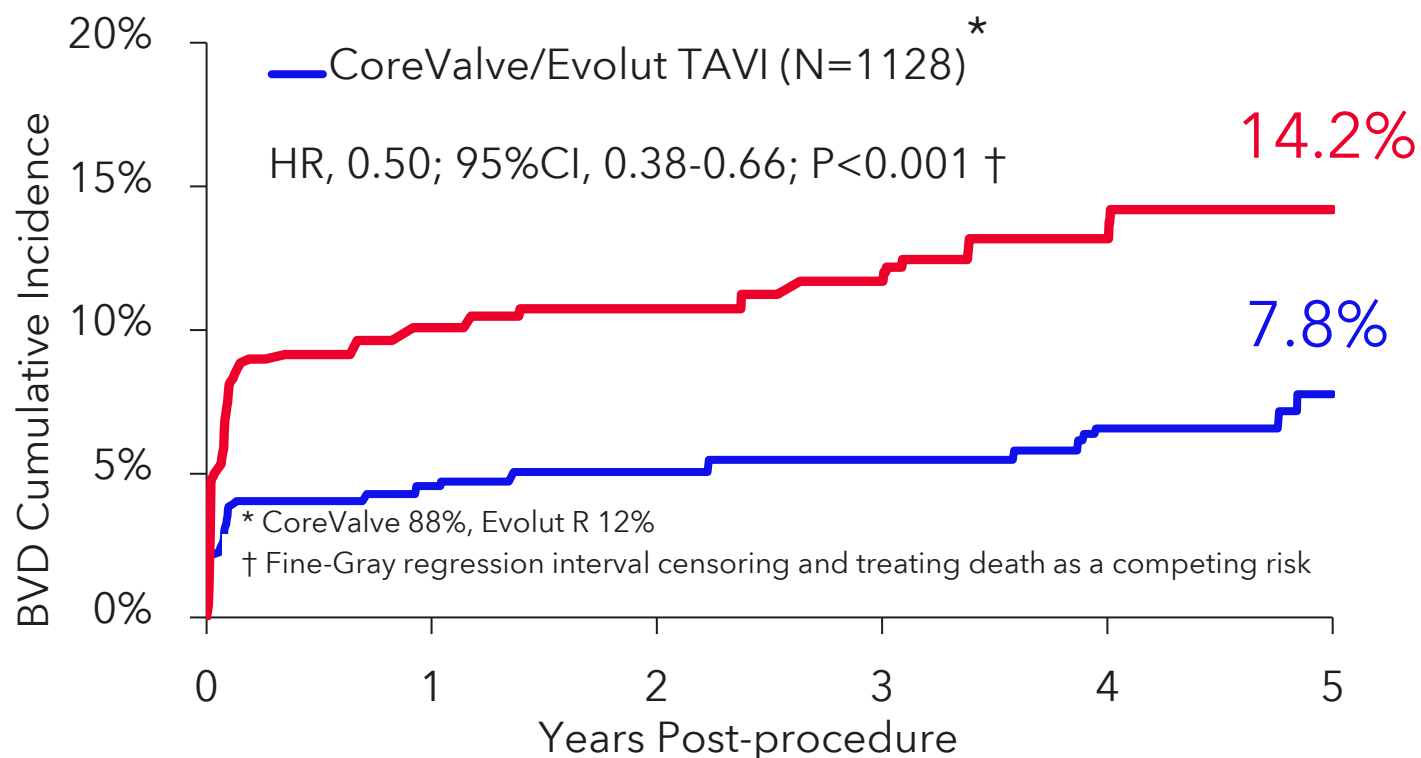


Background

Valve Performance Is Associated with Clinical Outcomes

- Our prior randomized studies of high and intermediate risk patients have demonstrated superior valve performance, as determined by lower rates of bioprosthetic valve dysfunction, in patients undergoing CoreValve TAVR compared with surgery at 5 years^{1,2}
- 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}

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



Need For Close Follow-up of the Low Risk Population

Reporting results more frequently in the low risk population will help establish the relationship between valve performance and clinical outcomes and to inform the heart teams on treatment options.

EVOLUT LOW RISK TRIAL | 4 YEAR RESULTS

Objective

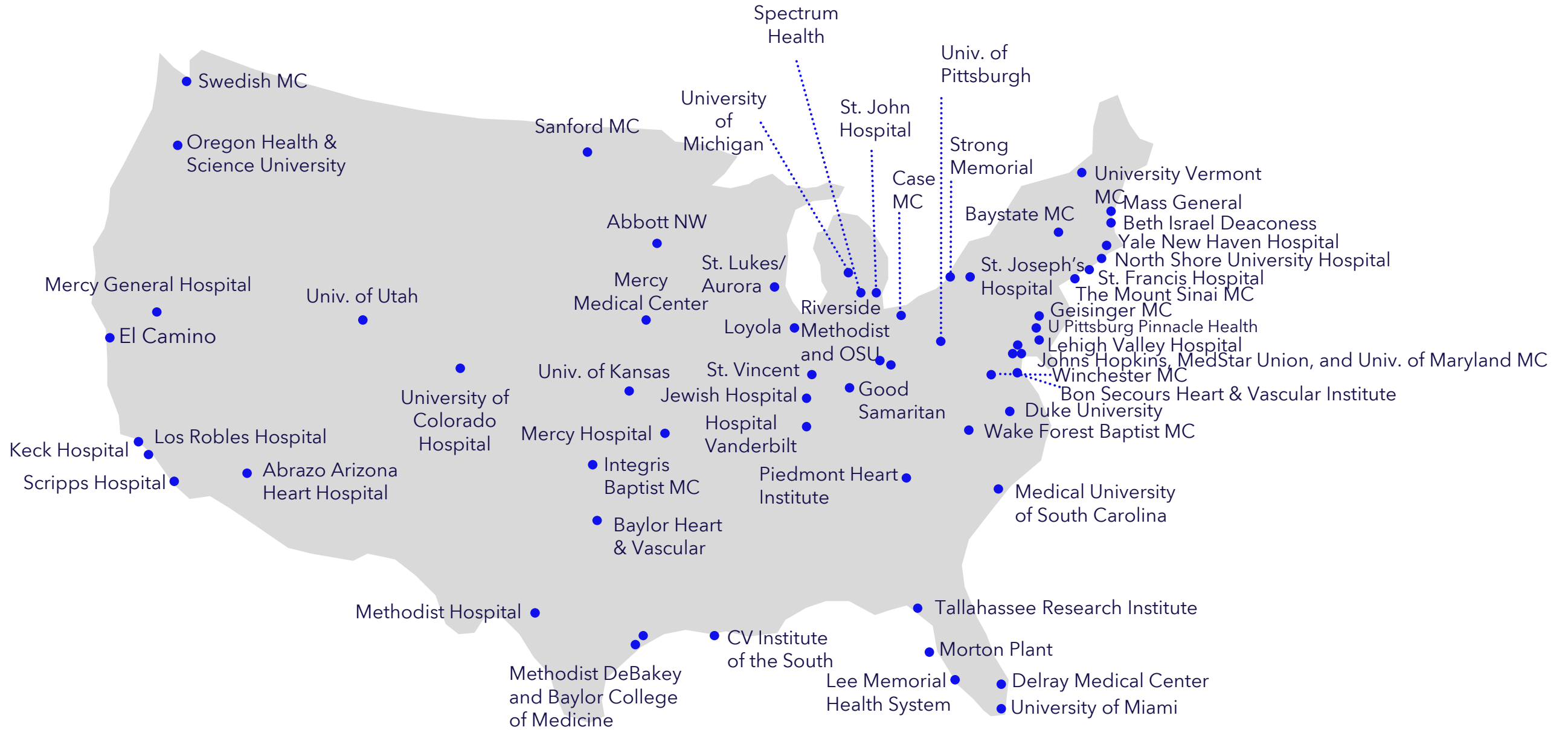


To evaluate 4-year clinical and hemodynamic outcomes with TAVR vs SAVR in patients from the Evolut Low Risk trial

EVOLUT LOW RISK TRIAL | 4 YEAR RESULTS



US Study Sites (N = 61)

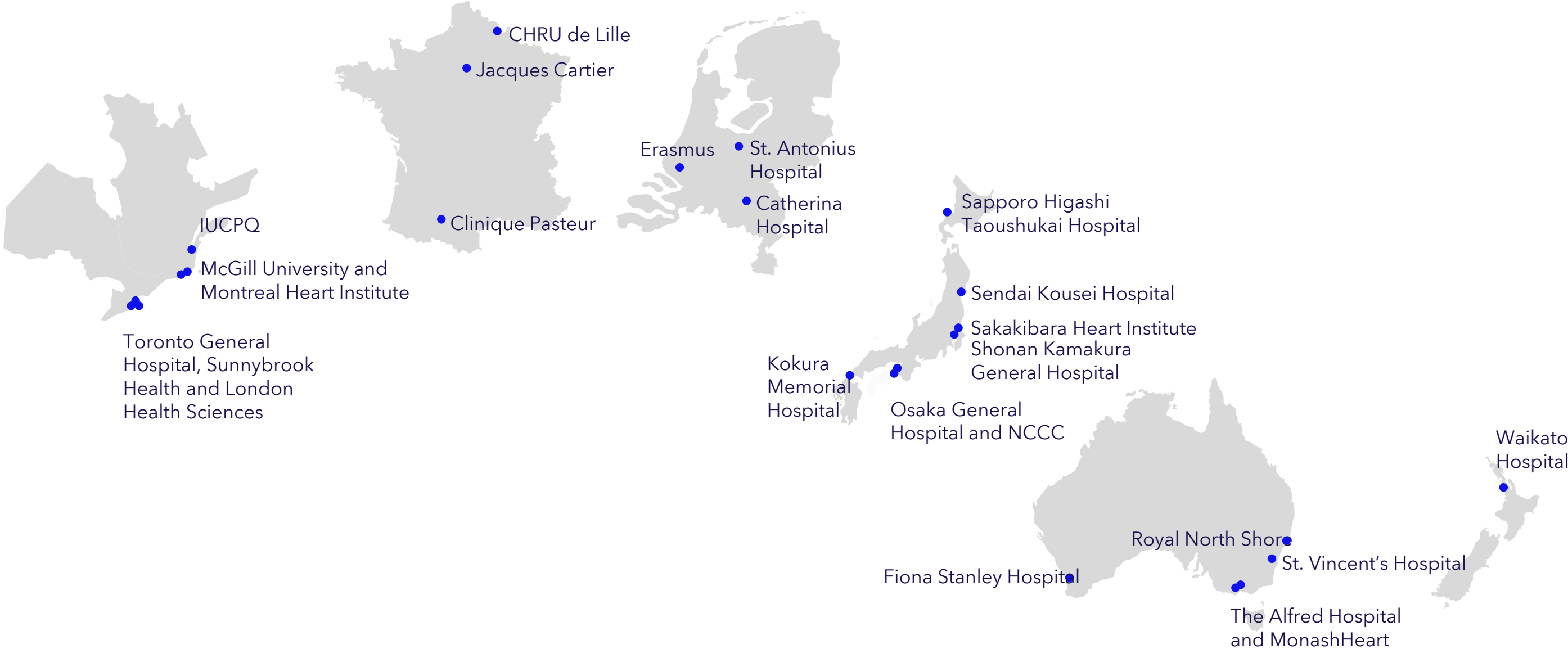


EVOLUT LOW RISK TRIAL | 4 YEAR RESULTS



International Sites

Canada, Europe, Japan, Australia, New Zealand (N = 25)



EVOLUT LOW RISK TRIAL | 4 YEAR RESULTS



Study Design

Patients with Severe AS
 Low risk of death (<3%) from surgery
 Anatomy suitable for both TAVR and SAVR

Screening Committee
 Confirmed eligibility

1:1 Randomization
 May 2016 to May 2019
 1414 Patients

Clinical Events Committee
Echo Core Laboratory

Evaluable status^a at 4Y
 94.7% TAVR
 89.2% Surgery



^aEvaluable 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.



EVOLUT LOW RISK TRIAL | 4 YEAR RESULTS



Baseline Characteristics

No Significant Difference Between Treatment Groups

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
NYHA class III/IV, %	24.9	28.2
Hypertension, %	84.8	82.6
Chronic lung disease (COPD), %	15.1	18.0
Previous CABG, %	2.5	2.0
Previous PCI, %	14.1	12.9
Atrial fibrillation/atrial flutter, %	15.4	14.4
Pre-existing permanent pacemaker or defibrillator, %	3.3	3.8
Left ventricular ejection fraction, %	61.7 ± 7.9	61.9 ± 7.7

EVOLUT LOW RISK TRIAL | 4 YEAR RESULTS



Bioprosthetic Valve performance at 4 Years

Significantly Less Mean Gradient \geq 20 mmHg and Severe PPM With Evolut vs Surgery

Parameter	Evolut TAVR	SAVR	P Value
Mean gradient \geq 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

^aNon-cumulative data based on the 4-year (MG, PVR) or 30-day (PPM) echo, reported as proportion % (n), and compared by chi-square test.

^bCumulative rates reported as Kaplan-Meier estimates % (n) and compared by log-rank test.

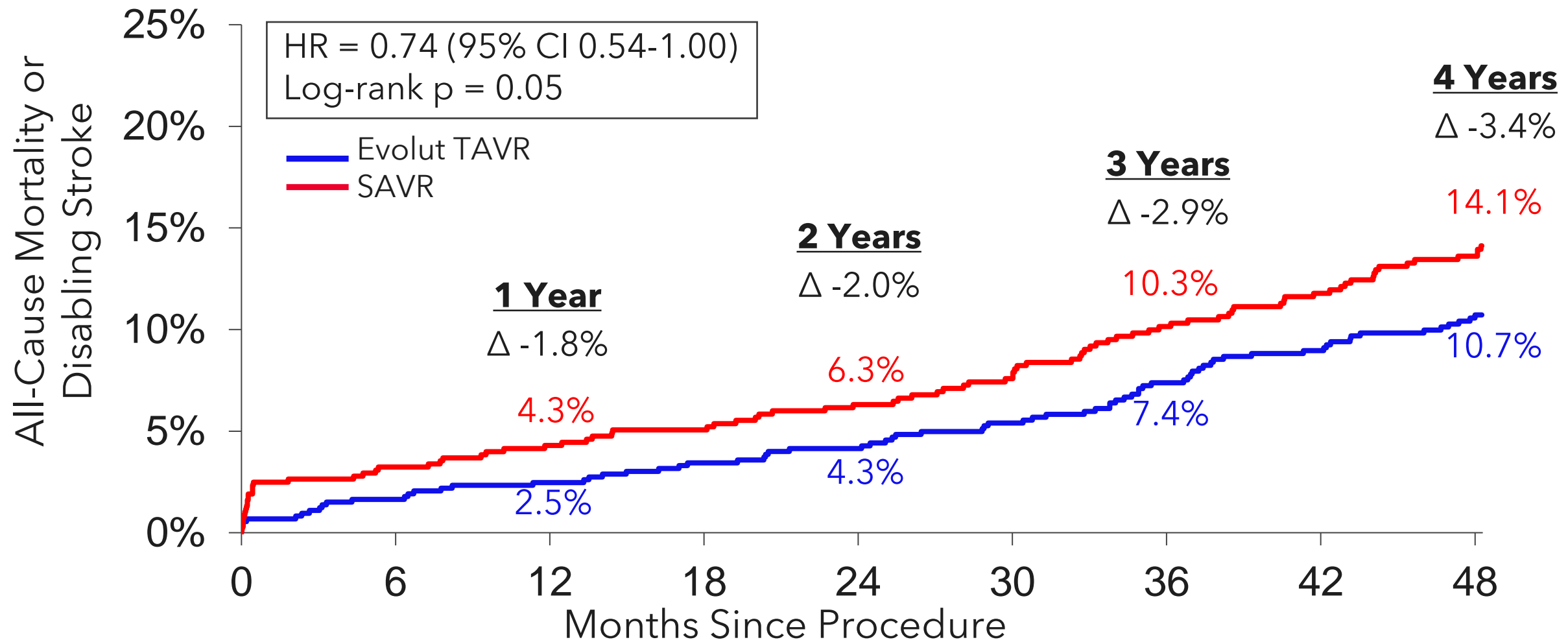
MG = mean gradient; PPM = patient-prosthesis mismatch; PVR = paravalvular regurgitation

EVOLUT LOW RISK TRIAL | 4 YEAR RESULTS



Primary Endpoint: All-Cause Mortality and 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



— Evolut TAVR	730	715	706	695	685	671	651	627	592
— SAVR	684	648	627	616	595	574	556	533	505

Medtronic

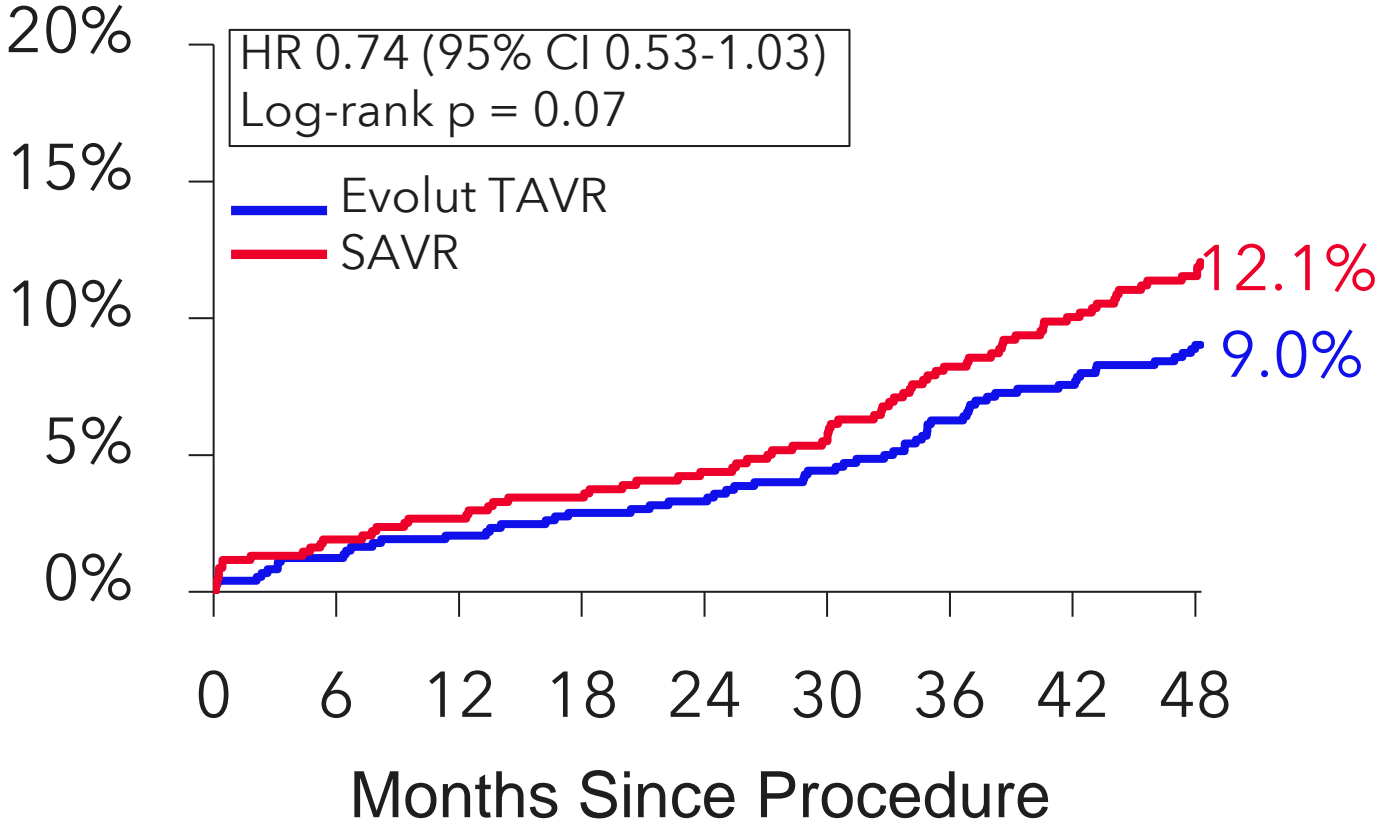
EVOLUT LOW RISK TRIAL | 4 YEAR RESULTS



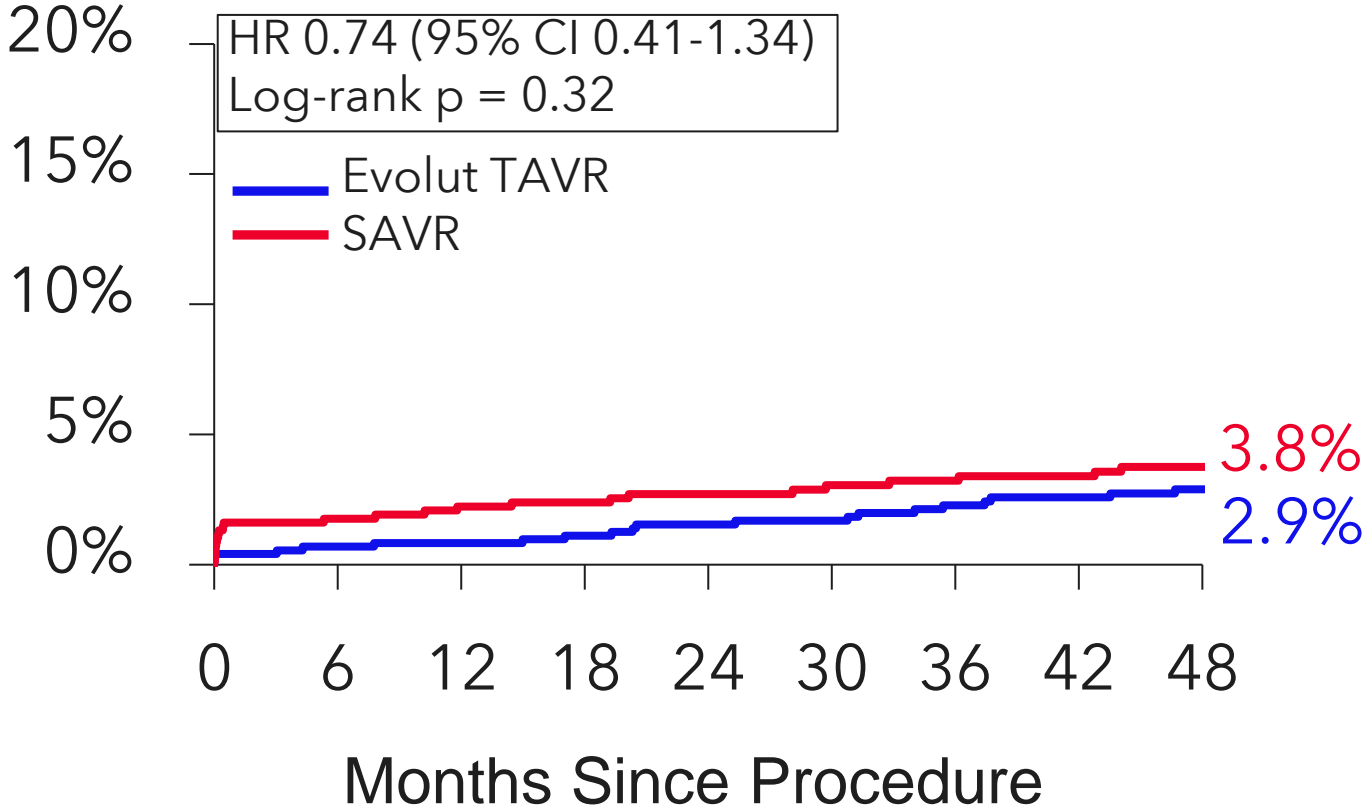
All-Cause Mortality and Disabling Stroke

Observed Differences in the Primary Endpoint Driven by Death

All-Cause Mortality



Disabling Stroke



TAVR	730	718	709	699	691	678	659	636	603
SAVR	684	656	636	624	605	585	567	542	516

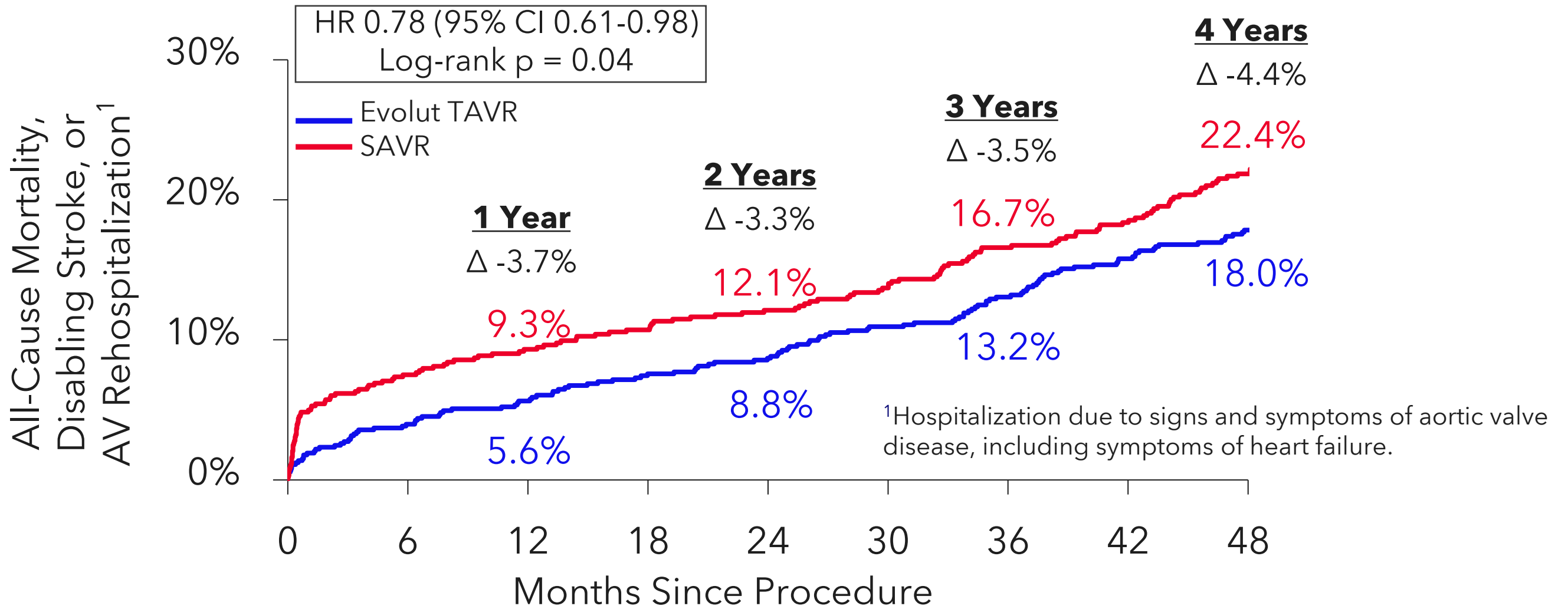
TAVR	730	715	706	695	685	671	651	627	592
SAVR	684	648	627	616	595	574	556	533	505

EVOLUT LOW RISK TRIAL | 4 YEAR RESULTS



All-Cause Mortality, Disabling Stroke or AV Rehospitalization

Significantly Lower Rate with Evolut TAVR vs SAVR



TAVR	730	698	683	665	652	631	610	582	544
SAVR	684	619	593	579	559	538	517	493	458

EVOLUT LOW RISK TRIAL | 4 YEAR RESULTS



Secondary Endpoints at 4 Years

Secondary Endpoint	Evolut TAVR	SAVR	P Value
All-cause mortality, %	9.0 (64)	12.1 (76)	0.07
Cardiovascular mortality, %	5.3 (37)	7.3 (46)	0.12
Disabling stroke, %	2.9 (20)	3.8 (24)	0.32
AV hospitalization ^a , %	10.3 (71)	12.1 (75)	0.27
All-cause mortality, disabling stroke, or AV rehospitalization	18.0 (128)	22.4 (144)	0.04
Myocardial infarction, %	4.8 (33)	2.6 (17)	0.06
Permanent pacemaker implant ^b , %	24.6 (171)	9.9 (62)	<0.001
Permanent pacemaker implant ^c , %	23.8 (171)	9.7 (63)	<0.001
Atrial fibrillation, %	14.0 (100)	40.8 (276)	<0.001
Reintervention, %	1.3 (9)	1.7 (10)	0.63

Data are reported as Kaplan-Meier estimate % (n) and compared by log-rank p value. ^aHospitalization due to signs and symptoms of aortic valve disease, including symptoms of heart failure. ^bPatients with pacemaker or ICD at baseline are not included. ^cPatients with pacemaker or ICD at baseline are included.

EVOLUT LOW RISK TRIAL | 4 YEAR RESULTS

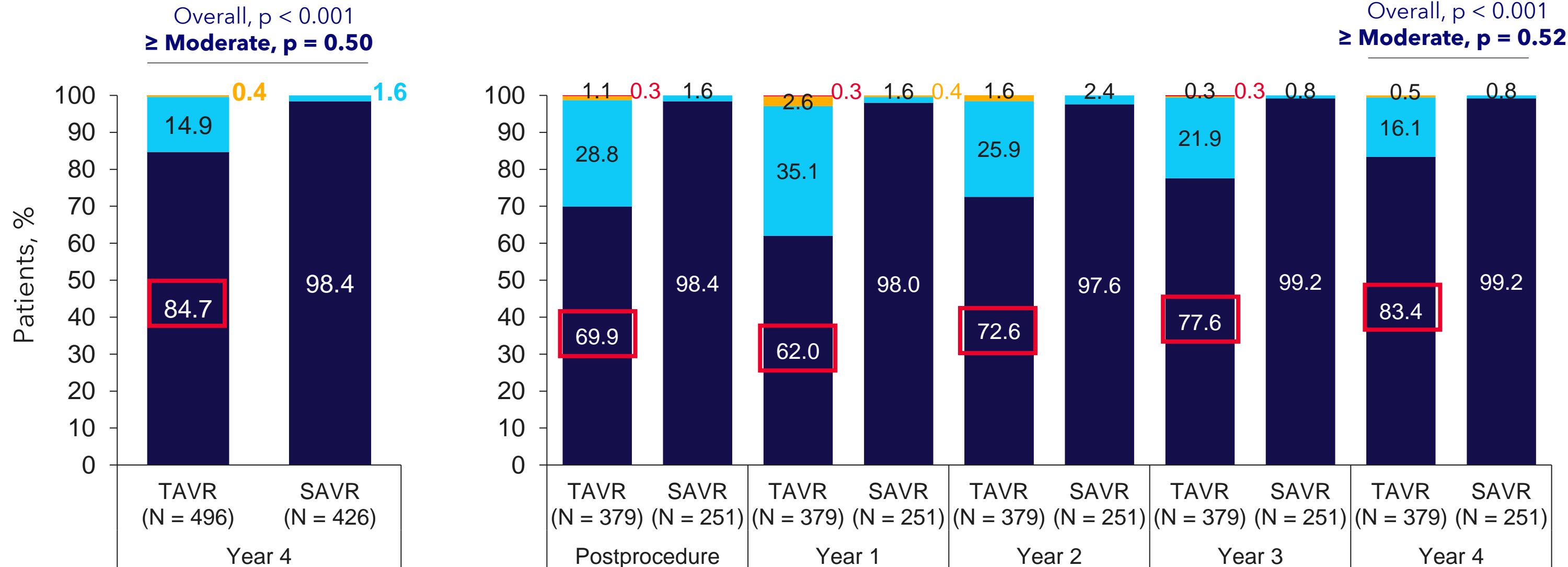


Paravalvular regurgitation

No Difference Between Groups in Moderate or Greater PVR

Patients with PVR data at 4Y

Patients with PVR data at all visits (paired data)

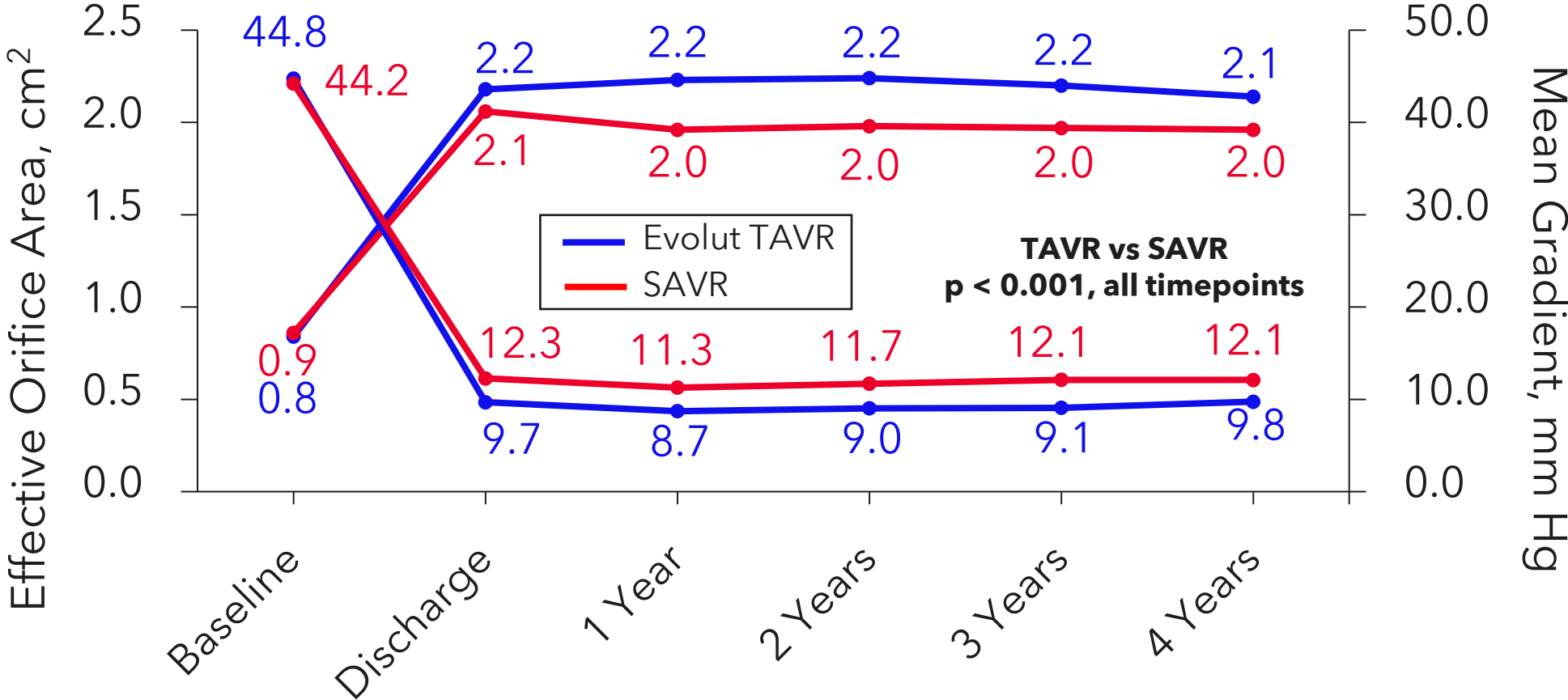


EVOLUT LOW RISK TRIAL | 4 YEAR RESULTS



Comparative Hemodynamics

Significantly Better Hemodynamics with Evolut TAVR vs SAVR



TAVR vs SAVR
p < 0.001, all timepoints

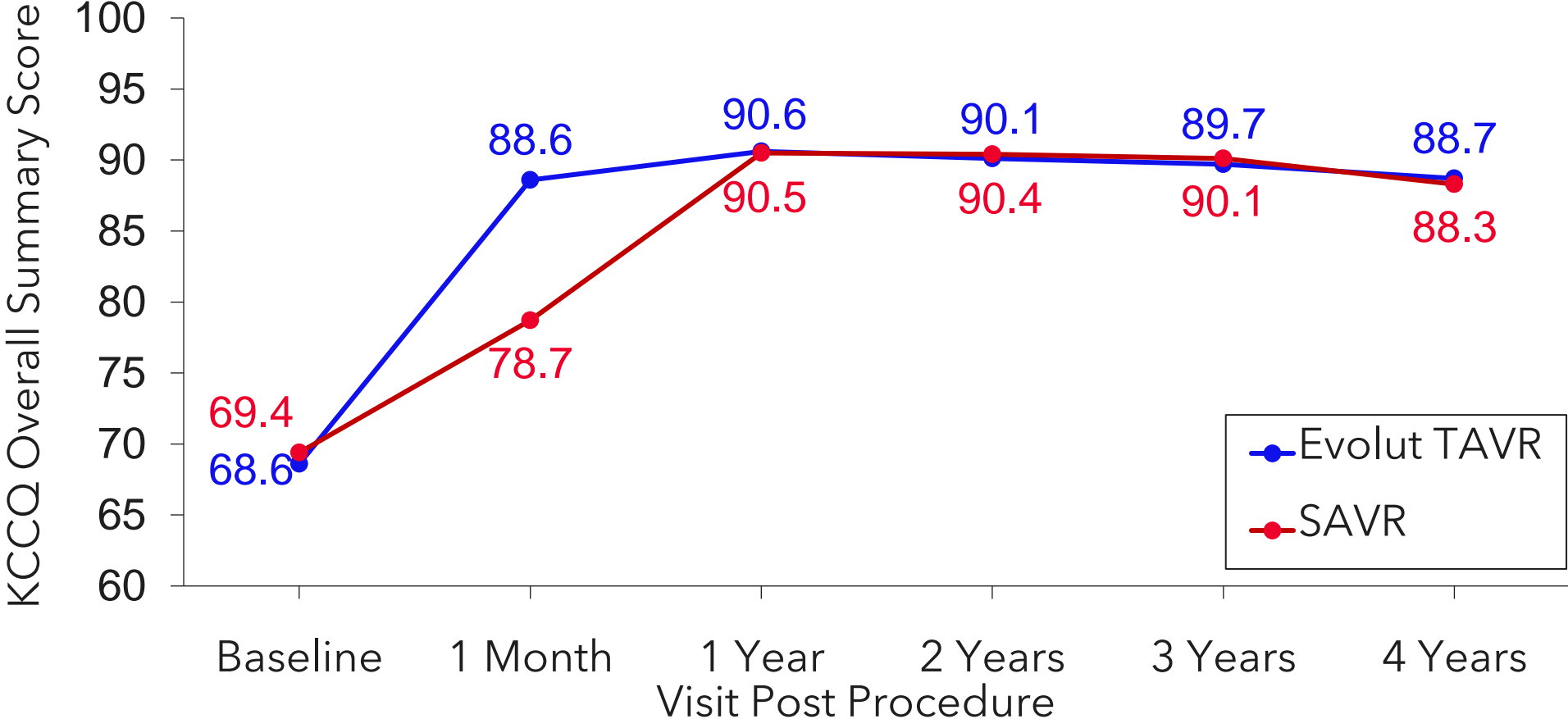
No. of Patients	Visit Post Procedure					
TAVR EOA	637	576	565	535	493	438
SAVR EOA	596	406	525	434	397	372
TAVR MG	717	703	662	607	547	497
SAVR MG	679	632	597	514	457	438

EVOLUT LOW RISK TRIAL | 4 YEAR RESULTS



KCCQ Overall Summary Score

Sustained Improvement from Baseline in QoL Through 4 Years



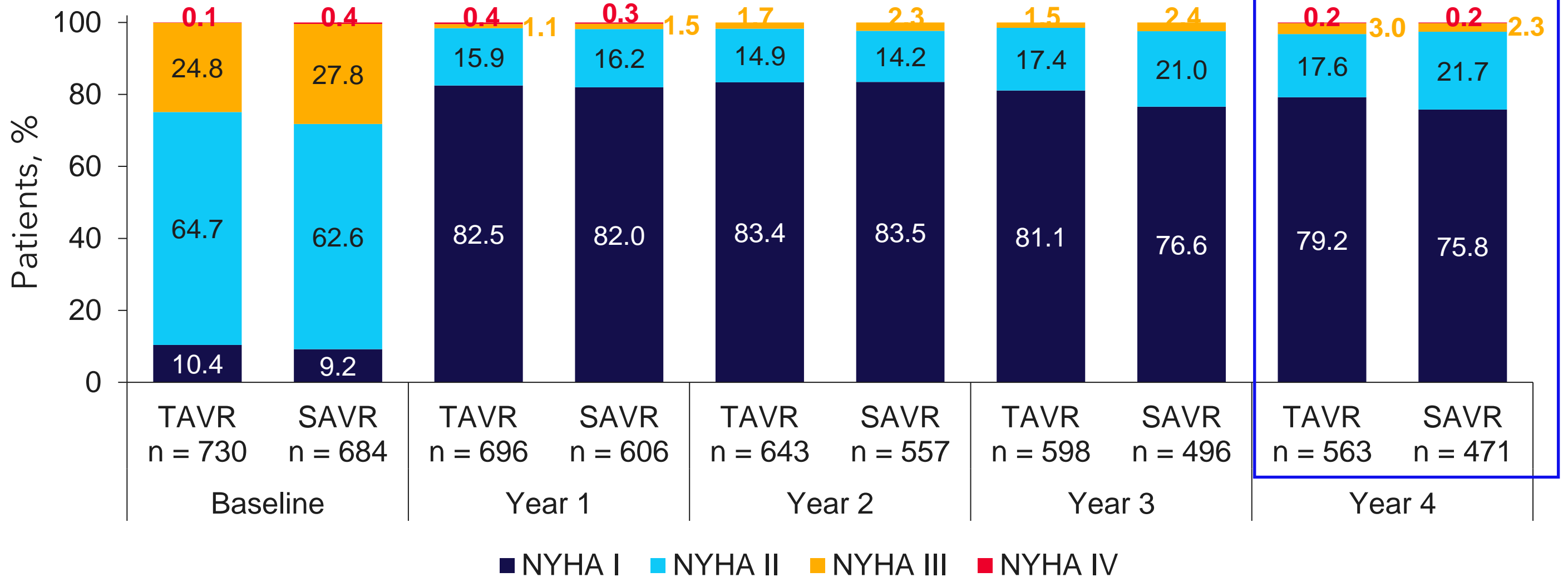
Change from Baseline		1 Month	1 Year	2 Years	3 Years	4 Years
Evolut TAVR		20.0 ± 21.1	21.6 ± 20.6	20.9 ± 20.8	20.1 ± 20.6	19.3 ± 20.7
SAVR		9.2 ± 22.3	20.7 ± 20.3	20.0 ± 20.0	19.3 ± 21.1	17.3 ± 20.9
P Value		<0.001	0.42	0.44	0.53	0.13

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NYHA Classification by Visit

Sustained Improvement in Functional Status at 4 Years



EVOLUT LOW RISK TRIAL | 4 YEAR RESULTS



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 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 technique¹

EVOLUT LOW RISK TRIAL | 4 YEAR RESULTS



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% versus 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 TRIAL | 4 YEAR RESULTS

Clinical Implications



In low risk patients,
the Evolut platform is
the THV of first
choice 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 years¹

Evolut shows better hemodynamics over SAVR at all time points tested¹

Evolut has shown significantly lower rates of structural valve deterioration, which result in lower death and hospitalization for AV or HF at 5 years²

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.

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4 Year Results in JACC

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Letters

RESEARCH LETTER

4-Year Outcomes of Patients With Aortic Stenosis in the Evolut Low Risk Trial

A recent 3-year analysis of the Medtronic Evolut Transcatheter Aortic Valve Replacement in Low Risk Patients trial (NCT02701283) demonstrated sustained valve performance and durable benefits for all-cause mortality or disabling stroke compared to aortic valve replacement (TAVR vs SAVR) in surgical-risk patients with severe aortic stenosis. Close follow-up of the low-risk patients is warranted given the limited intermediate-term data currently available to inform treatment decisions in these patients. We report the 4-year outcomes of the Evolut Low Risk trial.

The Evolut Low Risk study design has been described.¹ Patients underwent aortic valve replacement with a supra-annular CoreValve/Edwards S3 (Medtronic) or a surgical bioprosthesis from June 2012 to May 2019 and are being followed up. The primary endpoint of the Evolut Low Risk trial is the composite of all-cause mortality or disabling stroke through 2 years,² with annual reporting of this outcome prespecified in the study protocol. Additional endpoints in this 4-year analysis include safety events and quality of life, as determined by echocardiography. Outcomes were reported as Kaplan-Meier survival curves, compared by log-rank test. Endpoints were based on echocardiographic assessment. The study was approved by the Institutional Review Boards at each site, and all patients gave informed consent.

Of 730 TAVR and 684 SAVR patients who underwent attempted implantation, 4 were unable for 94.7% of TAVR patients and 7 were lost to follow-up, 1 for 99.2% of SAVR patients (610/684; 60 were lost to follow-up). At baseline, patients had a mean age of 74 years in both treatment arms and mean Society of Thoracic Surgeons Predicted Risk of Mortality scores of 2.0 in the TAVR group and 1.9 in the SAVR group. There were no significant baseline differences between groups.¹

The primary endpoint of all-cause mortality or disabling stroke at 4 years was 10.7% (76) in the TAVR group and 14.1% (90) in the SAVR group (HR: 0.74; 95% CI: 0.54-1.00; P = 0.05), representing a 26% relative reduction in the hazard for death or disabling stroke with TAVR compared with SAVR. The absolute difference between treatment arms for the primary endpoint continued to increase over time: -1.8% at 1 year, -2.0% at 2 years, -2.9% at 3 years, and -3.4% at 4 years (Figure 1). Rates of the primary endpoint components were 9.0% (64) vs 12.1% (76) (P = 0.07) for all-cause mortality and 2.9% (20) vs 3.8% (24) (P = 0.32) for disabling stroke with TAVR vs SAVR, respectively. The composite of all-cause mortality, disabling stroke, or aortic valve rehospitalization was significantly lower with TAVR compared with SAVR (18.0% [128] vs 22.4% [144]; HR: 0.78; 95% CI 0.61-0.98; P = 0.04). Aortic valve rehospitalization was 10.3% (71) with TAVR vs 12.1% (75) with SAVR (P = 0.27). New permanent pacemaker implantation was significantly higher in the TAVR group (24.6% [171] vs 9.9% [62]; P < 0.001). Indicators of valve performance including aortic valve reintervention (1.3% [9] TAVR vs 1.7% [10] SAVR; P = 0.63), clinical or subclinical valve thrombosis (0.7% [5] TAVR vs 0.6% [4] SAVR; P = 0.84), and valve endocarditis (0.9% [6]

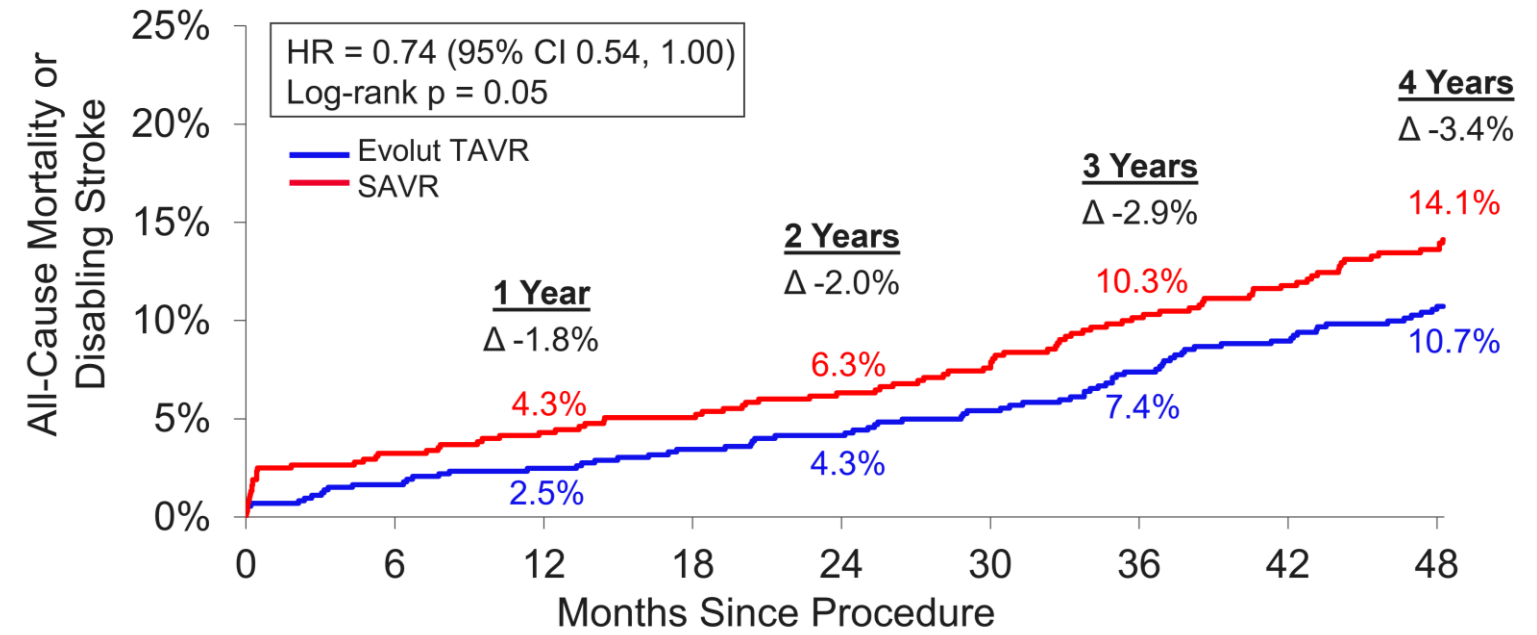
Published Today in JACC

What is the clinical question being addressed?
What are the 4-year outcomes of patients randomized to TAVR vs SAVR in the Evolut Low Risk Trial?

What is the main finding?
There was a 26% reduction (P = 0.05) in all-cause mortality or disabling stroke with TAVR vs SAVR, and the difference expanded over time.

COR 568 BTD ■ JACC 2023 ■ 19 October 2023 ■ 10:47 am ■

Primary Endpoint: All-Cause Mortality or Disabling Stroke

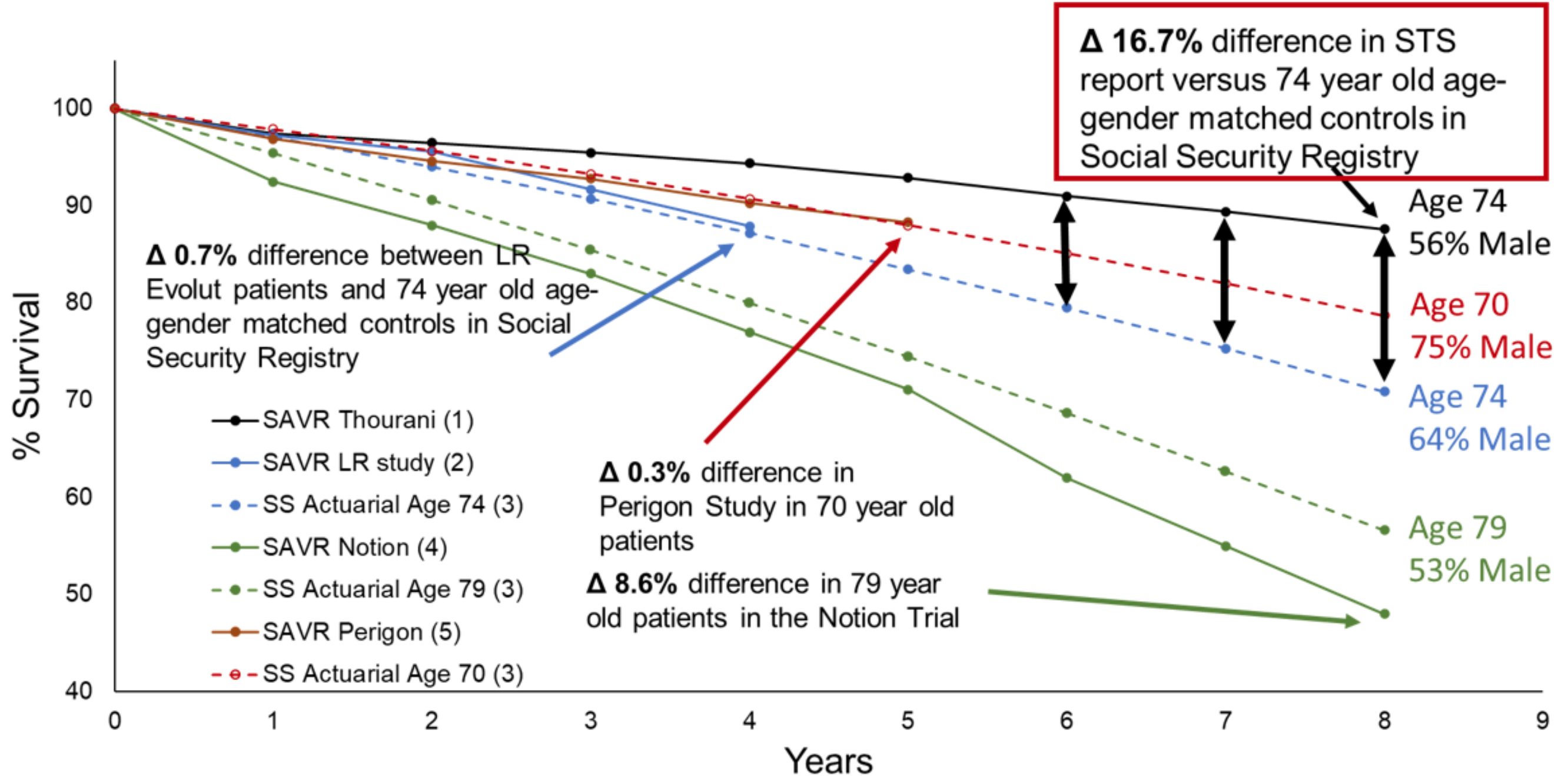


Evolut TAVR	730	715	706	695	685	671	651	627	592
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Back Up

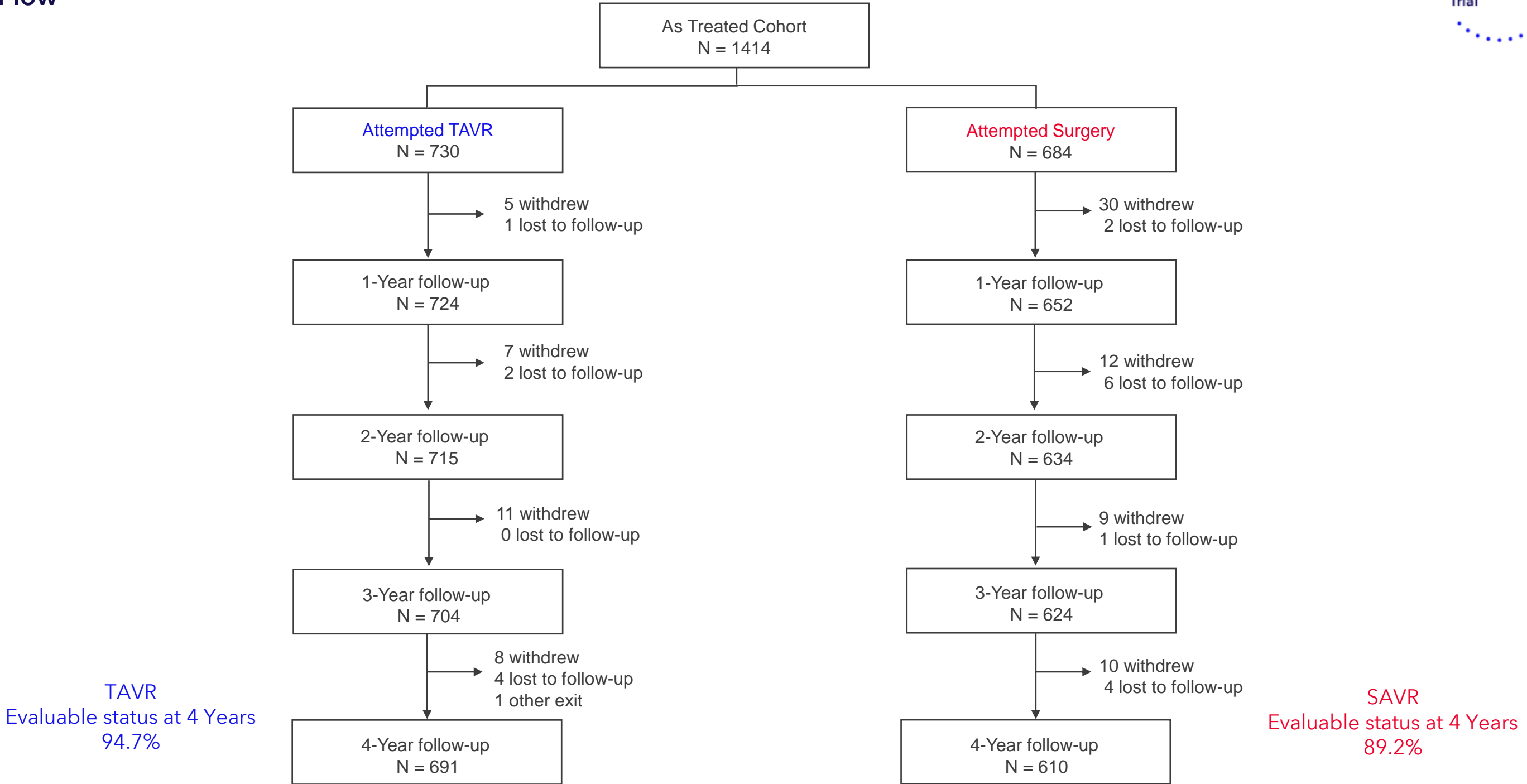
SURGICAL CURVES FROM SAVR STUDIES VS AGE-MATCHED SS ACTUARIAL RATES



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Patient Flow



EVOLUT LOW RISK TRIAL | 4 YEAR RESULTS



Comparisons of the Evolut LR and PARTNER III studies



Evolut R = 73% Evolut PRO = 23.4% CoreValve 31 mm = 3.6%	TAVR product used	S3 = 100%
56.9% Edwards, 10.8% Medtronic, 18.7% Abbott, and 13.7% LivaNova	SAVR product used	72.2% Edwards, 7.3% Medtronic, 16.8% Abbott, 3.8% Other
Low risk assessment by heart team < 3% mortality at 30 days (a heart team considers factors beyond STS score)	Risk definition	Low risk assessment by heart team and STS PROM < 4%
All-cause mortality OR disabling stroke at 2Y	Primary endpoint	All-cause mortality, all stroke, OR rehospitalization at 1Y
Bayesian approach with interim analysis when 850 patients evaluable for 12-month follow-up	Statistical technique	Standard frequentist approach with no interim analysis
Native aortic annulus < 18 mm or > 30 mm AND bicuspid	Anatomical exclusion criteria	Native aortic annulus size unsuitable for sizes 20, 23, 26, and 29 mm THV based on 3D imaging AND bicuspid
231 (14%) patients disapproved by screening committee	Screening Committee Exclusion	520 (34%) patients excluded from randomization
Bicuspid or unicuspid anatomy (n = 138), aortic root dimensions (n = 60)	Top reasons for exclusions	Severe LVOT calcium (~200 patients), aortic root dimensions (~88 patients), and poor TF access (~26 patients) ³

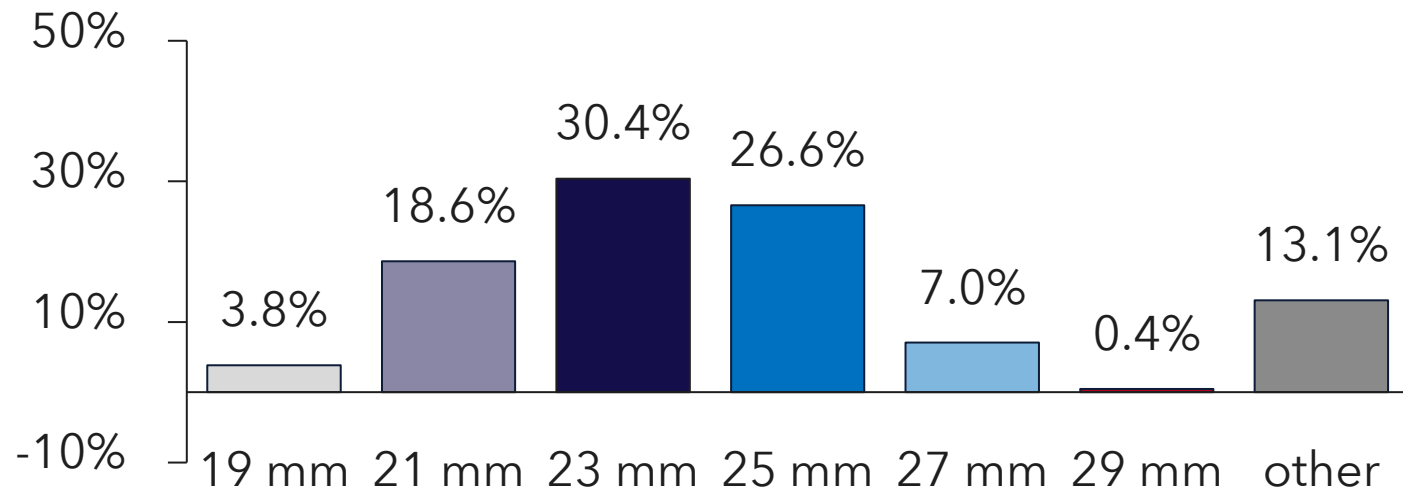
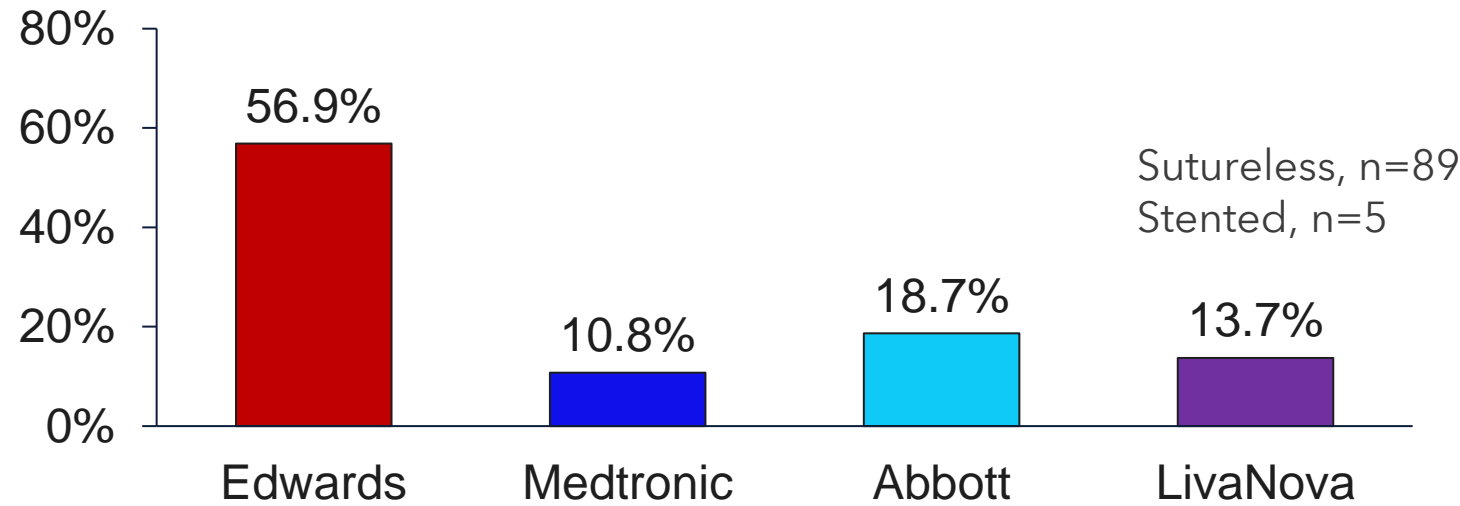
EVOLUT LOW RISK TRIAL | 4 YEAR RESULTS

Comparisons Of Surgical Valves and Sizing



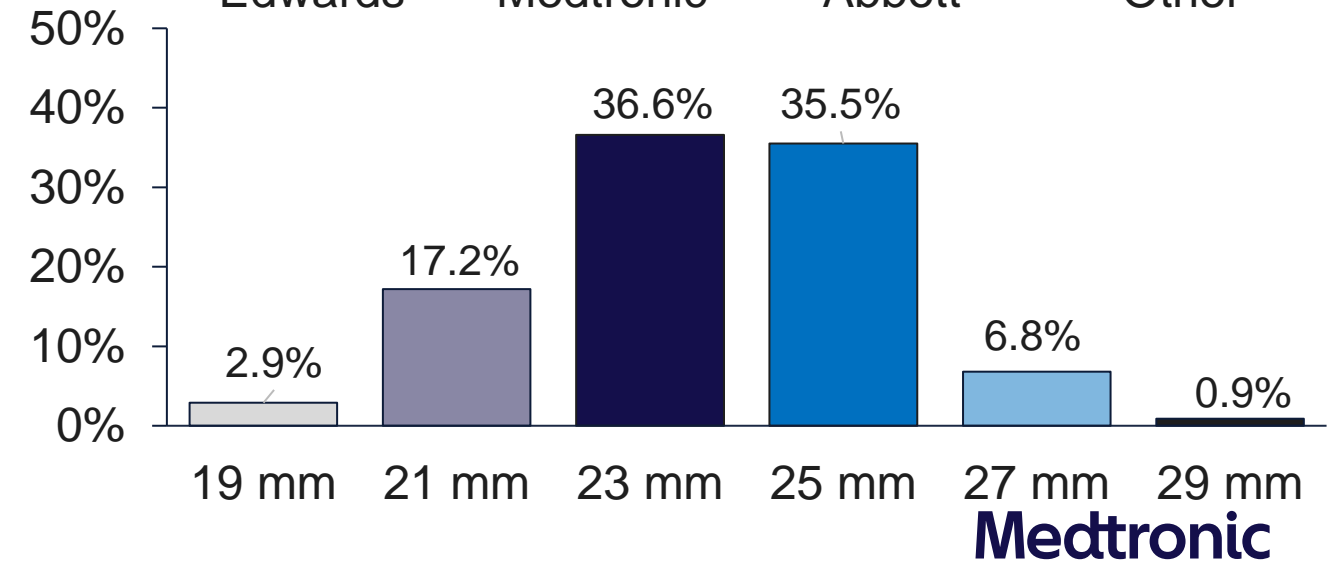
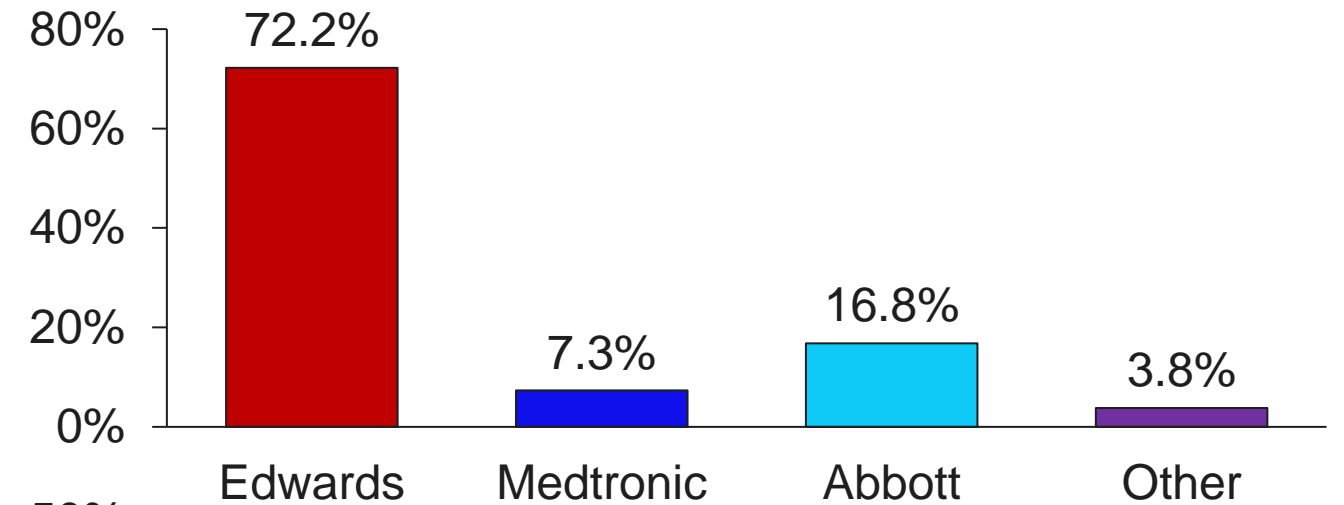
Evolut Low Risk Surgical Valves¹

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



PARTNER 3 Surgical Valves²

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



30 Reardon et al. Four-year outcomes from the Evolut Low Risk Trial | October 24, 2023 | TCT 2023 Conference

1. Data on file. 2. Leon MB, et al. *J. Am Coll Cardiol.* March 9, 2021;77(9):1149-1161.

EVOLUT LOW RISK TRIAL | 4 YEAR RESULTS

Comparison of 1-Year Surgical Outcomes

Surgical Arm	1-Year Echo	Evolut Low Risk Surgical Arm ¹	PARTNER 3 Surgical Arm ²
	EOA	2.0 cm ²	1.8 cm ²
	Mean gradient	11.2 mm Hg	11.6 mm Hg
	None/trace total aortic regurgitation	90.9%	93.8%
	Mild total AR	7.6%	5.7%
	Moderate total AR	1.5%	0.5%
	Severe PPM ^{†*}	3.5%	6.3%

¹Popma JP, et al. NEJM 2019. Supplemental data. Bayesian rates. ²Mack MJ, et al. NEJM 2019. Supplemental data.

*Medtronic data on file.

†Defined as:
 Indexed effective orifice area (cm²/m²) for BMI <30 kg/m² Moderate Severe
 0.85–0.65 cm²/m² < 0.65 cm²/m²
 Indexed effective orifice area (cm²/m²) for BMI >30 kg/m² 0.70–0.55 cm²/m² < 0.55 cm²/m²

EVOLUT LOW RISK TRIAL

Definitions of SVD from O'Hair et al JAMA Cardiol

Primary endpoint - moderate or greater hemodynamic SVD: Moderate SVD was defined as (1) hemodynamic valve deterioration (HVD) showing an increase in mean aortic gradient of 10 mm Hg or greater from discharge or 30-day echocardiography to last available echocardiography with a final mean gradient of 20 mm Hg or greater or (2) new occurrence or increase of 1 grade or more of intraprosthetic AR resulting in moderate or severe AR.

VARC-3 SVD: Moderate SVD was defined as hemodynamic valve deterioration (HVD) showing an increase in mean aortic gradient ≥ 10 mmHg from discharge/30-day echo to last available echo with a final mean gradient ≥ 20 mmHg and with a concomitant decrease in EOA ≥ 0.3 cm² or $\geq 25\%$ and/or decrease in DVI ≥ 0.1 or $\geq 20\%$ from discharge/30-day echo to last available echo, OR new occurrence or increase of ≥ 1 grade of intraprosthetic aortic regurgitation (AR) resulting in \geq moderate regurgitation. Severe SVD was defined as HVD showing an increase in mean gradient ≥ 20 mmHg from discharge/30-day echo to last available echo with a final mean gradient ≥ 30 mmHg and with a concomitant decrease in EOA ≥ 0.6 cm² or $\geq 50\%$ and/or decrease in DVI ≥ 0.2 or $\geq 40\%$ from discharge/30-day echo to last available echo, OR new occurrence or increase of ≥ 2 grades of intraprosthetic AR resulting in severe regurgitation.¹

HVD: Related to bioprosthetic stenosis and defined as an increase in mean aortic gradient ≥ 10 mmHg from discharge/30-day echo to last available echo, OR aortic valve reintervention for stenosis > 30 days post-procedure.^{2,3}

¹Généreux P, et al. J Am Coll Card. 2021. ²Vemulapalli S, et al. Am Heart J. 2018;195:1-13. ³O'Hair D, et al. J Am Coll Card. 2021;77(18_Supplement_1):904-904.

EVOLUT LOW RISK TRIAL

Thank You to Our Top Implanting Clinical Sites and Investigators

Clinical Site	Surgeon	Interventional Cardiologist
Abbott Northwestern Hospital - Minneapolis Heart Institute, Minnesota	Judah Askew, Robert Saeid Farivar*	Paul Sorajja
Abrazo Arizona Heart Hospital, Phoenix, Arizona	Merick Kirshner	Timothy Byrne
Aurora/St Luke's Hospital, Milwaukee, Wisconsin	Daniel O'Hair*	Tanvir Bajwa
Houston Methodist DeBakey Heart & Vascular Center, Houston, Texas	Michael Reardon	Neal Kleiman
Icahn School of Medicine at Mount Sinai, New York, New York	David Adams	Samin Sharma
Lee Memorial Health System, Fort Myers, Florida	Michael DeFrain, Brian Hummel*	Murali Muppala
London Health Sciences Centre - University Campus, Ontario, Canada	Michael Chu, Bob Kiaii*	Rodrigo Bagur
Massachusetts General Hospital, Boston, Massachusetts	Serguei Melnitchouk, Arminster Jassar*	Ignacio Inglessis
MedStar Union Memorial Hospital, Baltimore, Maryland	Michael Fiocco*	John Wang, Amish Sura*
Mercy Medical Center - Iowa Heart, Des Moines, Iowa	Bart Jensen	Atul Chawla
Morton Plant Hospital, Clearwater, Florida	Joshua Rovin	Douglas Spriggs*
Northwell, Manhasset, New York	Rick Esposito*	Bruce Rutkin
OhioHealth Riverside Methodist Hospital, Columbus, Ohio	Daniel Watson*	Steven Yakubov
Oregon Health & Science University Hospital, Portland, Oregon	Howard Song	Firas Zahr

Medtronic

*Study PI at the time of valve implantation

EVOLUT LOW RISK TRIAL

Thank You to Our Top Implanting Clinical Sites and Investigators

Clinical Site	Surgeon	Interventional Cardiologist
Piedmont Heart Institute, Atlanta, Georgia	James Kauten*	Vivek Rajagopal
Saint Francis Hospital, Roslyn, New York	Newell Robinson	George Petrossian
Saint Joseph's Hospital Health Center, Liverpool, New York	Zhadong Zhou	Ayman Iskander, Ronald Caputo*
Bon Secours Heart & Vascular Institute, Richmond, Virginia	Mark Bladergroen, Marc Katz*	Scott Lim*
Scripps Memorial Hospital, La Jolla, California	Jeffrey Tyner	Paul Teirstein
Spectrum Health Hospitals, Grand Rapids, Michigan	Stephane Leung, John Heiser*	William Merhi
Tallahassee Memorial Hospital, Tallahassee, Florida	Julian Hurt*	Thomas Noel
The University of Kansas Hospital, Kansas City, Kansas	George Zorn	Peter Tadros
University Hospitals Cleveland Medical Center, Cleveland, Ohio	Alan Markowitz	Guilherme Attizzani
University of Pittsburgh Medical Center Pinnacle, Harrisburg, Pennsylvania	Mubashir Mumtaz	Hemal Gada
University of Michigan Health System - University Hospital, Ann Arbor, Michigan	G. Michael Deeb	Stanley Chetcuti
Winchester Medical Center, Winchester, Virginia	Basel Ramlawi	

*Study PI at the time of valve implantation

Medtronic

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 \geq 8% or at a \geq 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 \leq 1.0 cm² or aortic valve area index \leq 0.6 cm²/m², a mean aortic valve gradient \geq 40 mm Hg, or a peak aortic-jet velocity \geq 4.0 m/s; (2) symptomatic severe low-flow, low-gradient aortic stenosis – aortic valve area \leq 1.0 cm² or aortic valve area index \leq 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 \geq 5 mm when using models ENVEOR-US/D-EVPROP2329US/D-EVOLUTFX-2329 or \geq 5.5 mm when using model ENVEOR-N-US or \geq 6 mm when using models D-EVPROP34US/D-EVOLUTFX-34, or patients must present with an ascending aortic (direct aortic) access site \geq 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 \geq 5.5 mm when using models ENVEOR-L-US/D-EVPROP2329US/D-EVOLUTFX-2329 or \geq 6 mm when using model ENVEOR-N-US or \geq 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 \geq 2 of these factors are present, consider an alternative access route to prevent vascular complications. Limited clinical data are available for transcatheter aortic valve replacement in patients with a congenital bicuspid aortic valve who are deemed to be at low surgical risk. Anatomical characteristics should be considered when using the valve in this population. In addition, patient age should be considered as long-term durability of the valve has not been established. During Use If a misload is detected during fluoroscopic inspection, do not attempt to reload the bioprosthesis. Discard the entire system. Inflow crown overlap that has not ended before the 4th node within the capsule increases the risk of an infold upon deployment in constrained anatomies, particularly with moderate-severe levels of calcification and/or bicuspid condition. Do not attempt to direct load the valve. After the procedure, administer appropriate antibiotic prophylaxis as needed for patients at risk for prosthetic valve infection and endocarditis. After the procedure, administer anticoagulation and/or antiplatelet therapy per physician/clinical judgment. Excessive contrast media may cause renal failure. Prior to the procedure, measure the patient's creatinine level. During the procedure, monitor contrast media usage. Conduct the procedure under fluoroscopy. Fluoroscopic procedures are associated with the risk of radiation damage to the skin, which may be painful, disfiguring, and long-term. The safety and efficacy of a CoreValve Evolut R, Evolut PRO+, or Evolut FX bioprosthesis implanted within a transcatheter bioprosthesis have not been demonstrated.

Potential adverse events

Potential risks associated with the implantation of the CoreValve Evolut R, Evolut PRO+, or Evolut FX transcatheter aortic valve may include, but are not limited to, the following: • death • myocardial infarction, cardiac arrest, cardiogenic shock, or cardiac tamponade • coronary occlusion, obstruction, or vessel spasm (including acute coronary closure) • cardiovascular injury (including rupture, perforation, tissue erosion, or dissection of vessels, ascending aorta trauma, ventricle, myocardium, or valvular structures that may

require intervention) • emergent surgical or transcatheter intervention (e.g., coronary artery bypass, heart valve replacement, valve explant, percutaneous coronary intervention [PCI], balloon valvuloplasty) • prosthetic valve dysfunction (regurgitation or stenosis) due to fracture; bending (out-of-round configuration) of the valve frame; underexpansion of the valve frame; calcification; pannus; leaflet wear, tear, prolapse, or retraction; poor valve coaptation; suture breaks or disruption; leaks; mal-sizing (prosthesis-patient mismatch); malposition (either too high or too low)/malplacement • prosthetic valve migration/embolization • prosthetic valve endocarditis • prosthetic valve thrombosis • delivery catheter system malfunction resulting in the need for additional recrossing of the aortic valve and prolonged procedural time delivery catheter system component migration/embolization • stroke (ischemic or hemorrhagic), transient ischemic attack (TIA), or other neurological deficits • individual organ (e.g., cardiac, respiratory, renal [including acute kidney failure]) or multi-organ insufficiency or failure • major or minor bleeding that may require transfusion or intervention (including life-threatening or disabling bleeding) • vascular access-related complications (e.g., dissection, perforation, pain, bleeding, hematoma, pseudoaneurysm,

irreversible nerve injury, compartment syndrome, arteriovenous fistula, or stenosis) • mitral valve regurgitation or injury • conduction system disturbances (e.g., atrioventricular node block, left bundle-branch block, asystole), which may require a permanent pacemaker infection (including septicemia) • hypotension or hypertension • hemolysis • peripheral ischemia • General surgical risks applicable to transcatheter aortic valve implantation: • bowel ischemia • abnormal lab values (including electrolyte imbalance) • allergic reaction to antiplatelet agents, contrast medium, or anesthesia • exposure to radiation through fluoroscopy and angiography • permanent disability.

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

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

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

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