

Four-Year Outcomes from the Evolut Low Risk Trial

Michael J. Reardon, MD

Methodist DeBakey Heart and Vascular Center, Houston, TX

On behalf of the Evolut Low Risk Trial Investigators

Disclosure of Relevant Financial Relationships



Within the prior 24 months, I have had a relevant financial relationship with a company producing, marketing, selling, re-selling, or distributing healthcare products used by or on patients:

Nature of Financial Relationship

Grant/Research Support

Ineligible Company

Abbott, Boston Scientific, WL Gore Medical, and Medtronic

All relevant financial relationships have been mitigated.

Faculty disclosure information can be found on the app

EVOLUT LOW RISK TRIAL | 4 YEAR RESULTS

STUDY ADMINISTRATION

Evolut™
Low Risk
Trial

Principal Investigators



Michael Reardon, MD
Methodist DeBakey
Heart and Vascular Center



John Forrest, MD
Yale University
School of Medicine

Executive Committee



Michael Reardon, MD
Methodist DeBakey
Heart and Vascular Center



John Forrest, MD
Yale University
School of Medicine



G. Michael Deeb, MD
University of Michigan
Health Systems



Steven Yakubov, MD
OhioHealth Riverside
Methodist Hospital

Steering Committee

David Adams, Stanley Chetcuti,
G. Michael Deeb, John Forrest,
John Heiser, William Merhi,
Mubashir Mumtaz, Daniel O'Hair,
Jon Resar, Joshua Rovin,
Michael Reardon, Paul Teirstein,
Steven Yakubov, George Zorn

Screening Committee: Michael Reardon, G. Michael Deeb,
Steven Yakubov, Robert Stoler, Thomas Gleason

Echo Core Laboratory: Mayo Clinic

Clinical Events Committee: BAIM Institute

CT Core Laboratory: St. Paul's Hospital

Statistical Analyses: Medtronic

Sponsor: Medtronic

EVOLUT LOW RISK TRIAL | 4 YEAR RESULTS

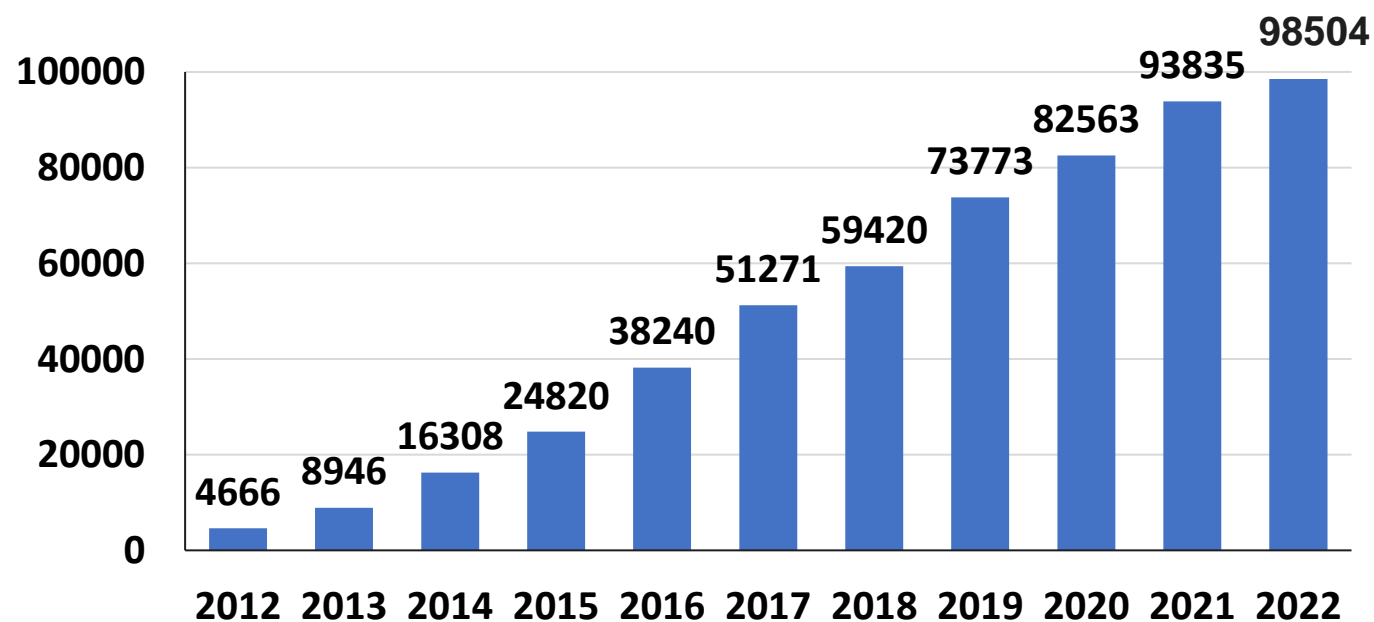


BACKGROUND

Increasing Number of TAVR Procedures in Younger Lower Risk Patients

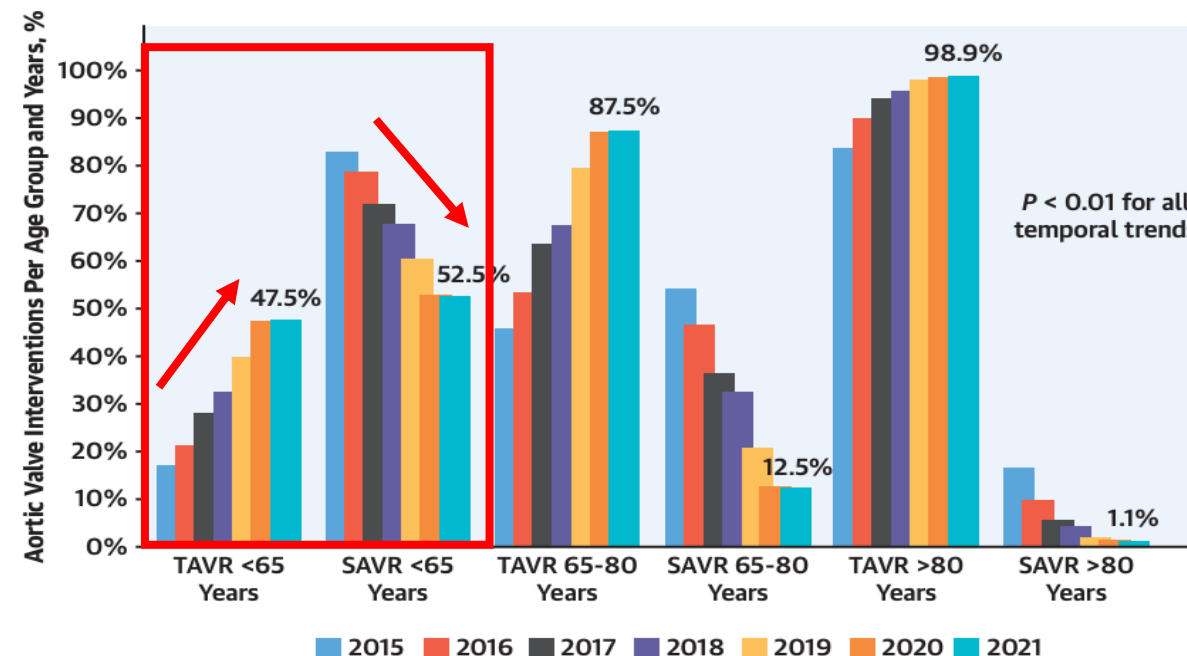
Trends in transcatheter and surgical aortic valve replacement (TAVR and SAVR) in the U.S. show yearly increases in the overall number of TAVR procedures and significant growth in TAVR utilization among younger adults with aortic stenosis.^{1,2}

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

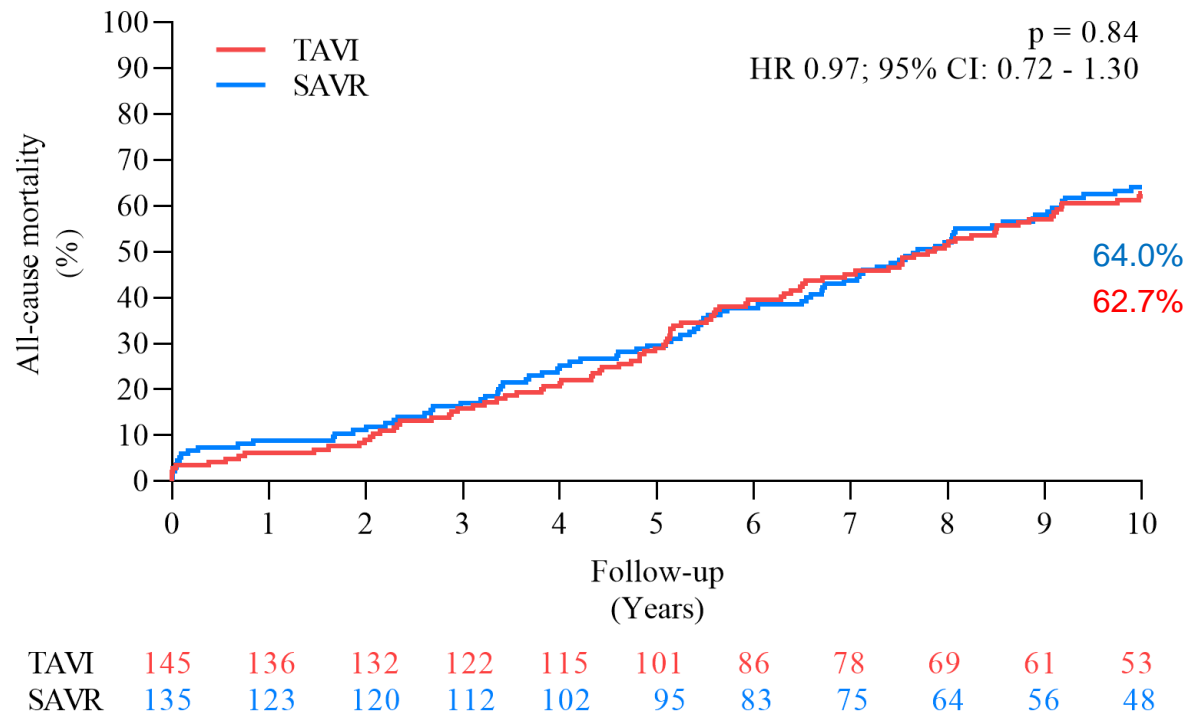


BACKGROUND

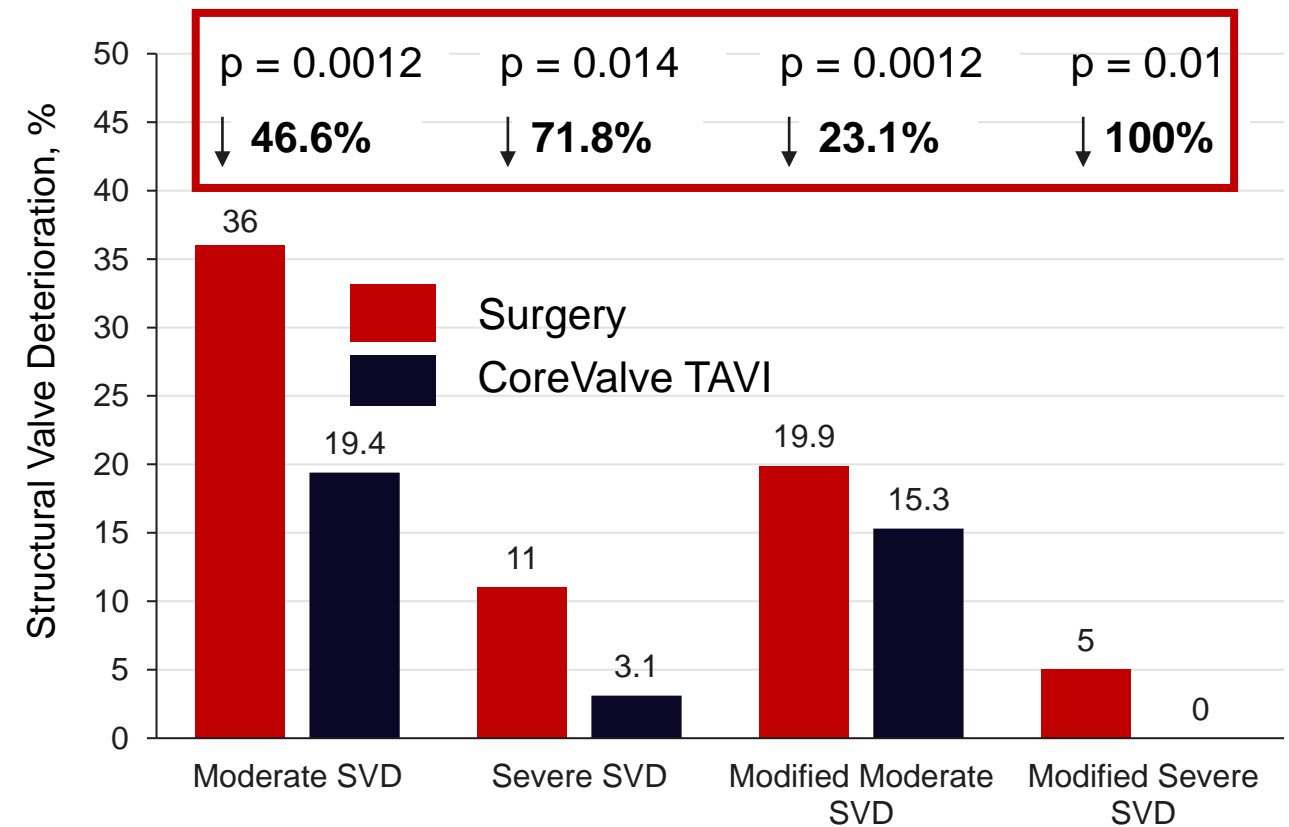
NOTION 10-Year: Less SVD with CoreValve TAVR vs SAVR

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



¹Jørgensen TH, et al. The Notion Trial ESC LBCT 2023, Amsterdam, Netherlands, with permission.

EVOLUT LOW RISK TRIAL | 4 YEAR RESULTS

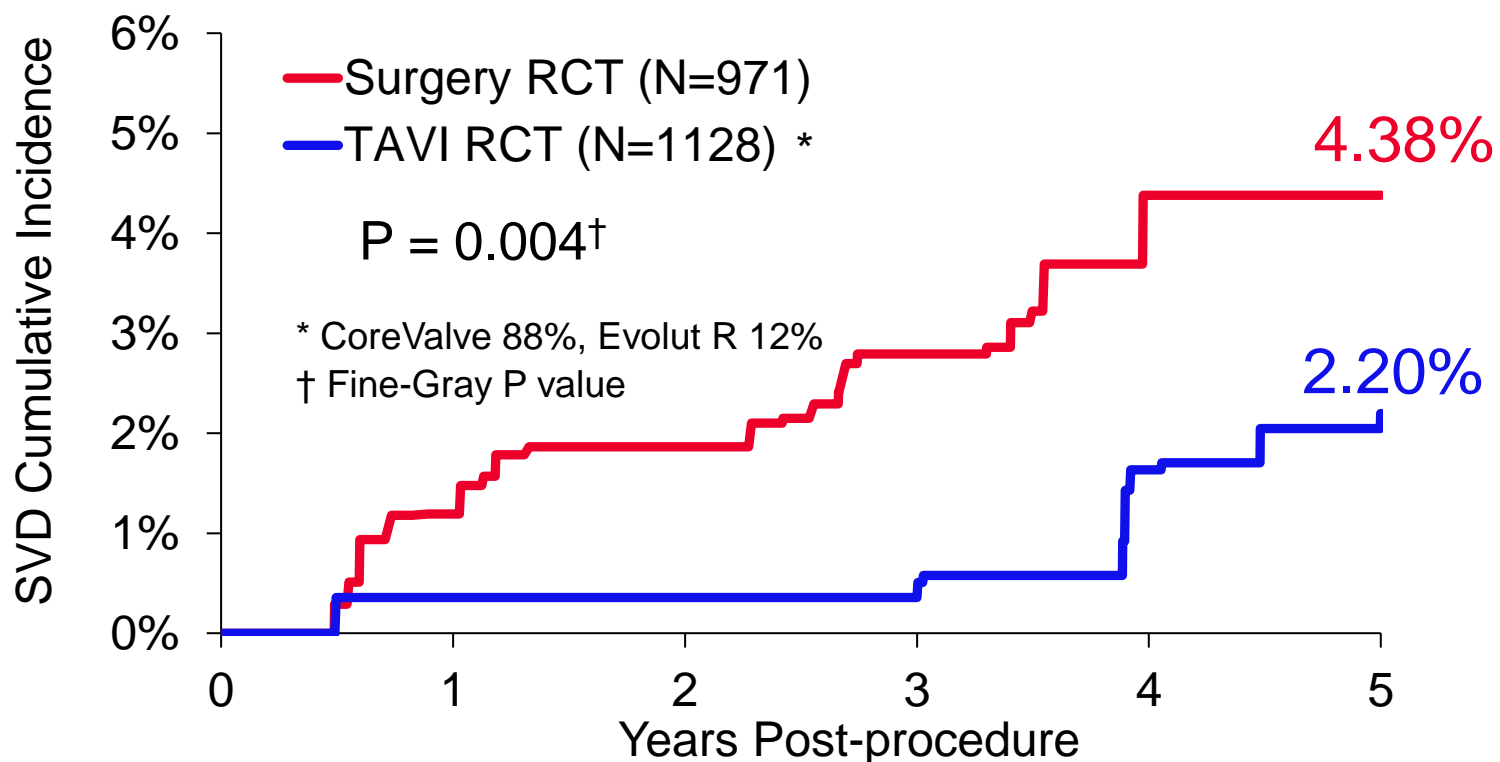


BACKGROUND

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

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

EVOLUT LOW RISK TRIAL | 4 YEAR RESULTS

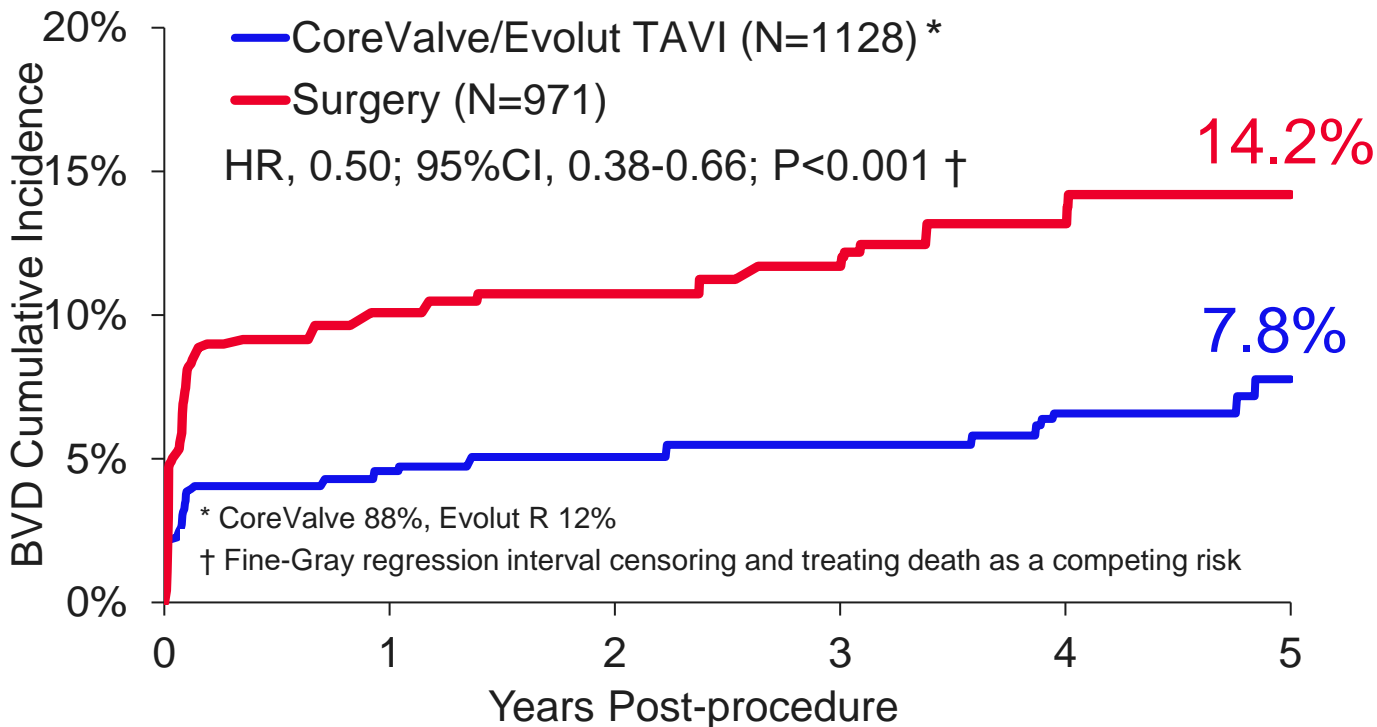


BACKGROUND

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 Composite	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 Composite	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 Composite	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

¹Yakubov SJ. et al CRT 2023 LBCT, Washington, D.C. ²Van Mieghem N et al EuroPCR 2023, Paris, France

EVOLUT LOW RISK TRIAL | 4 YEAR RESULTS

BACKGROUND



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



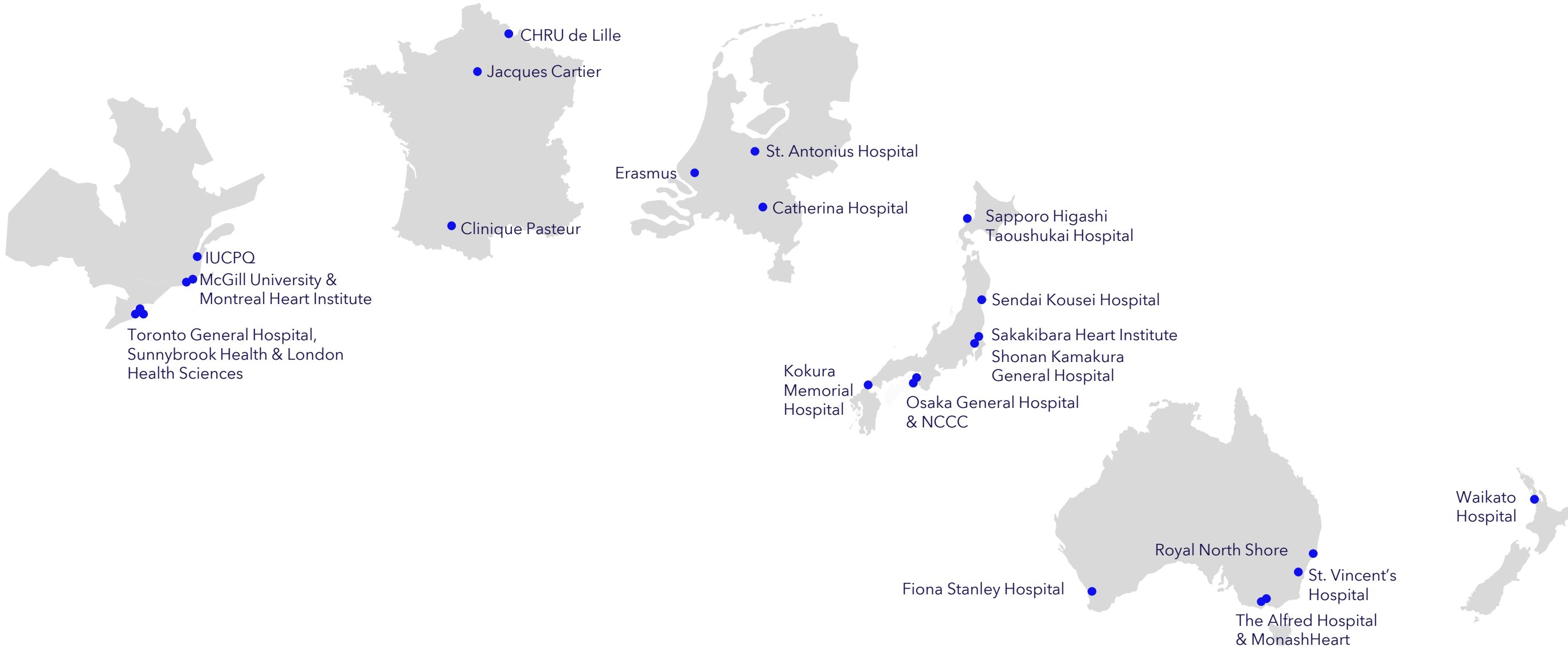
To evaluate 4-year clinical and hemodynamic outcomes with TAVR vs SAVR in patients from the Evolut Low Risk trial

EVOLUT LOW RISK TRIAL | 4 YEAR RESULTS



INTERNATIONAL SITES

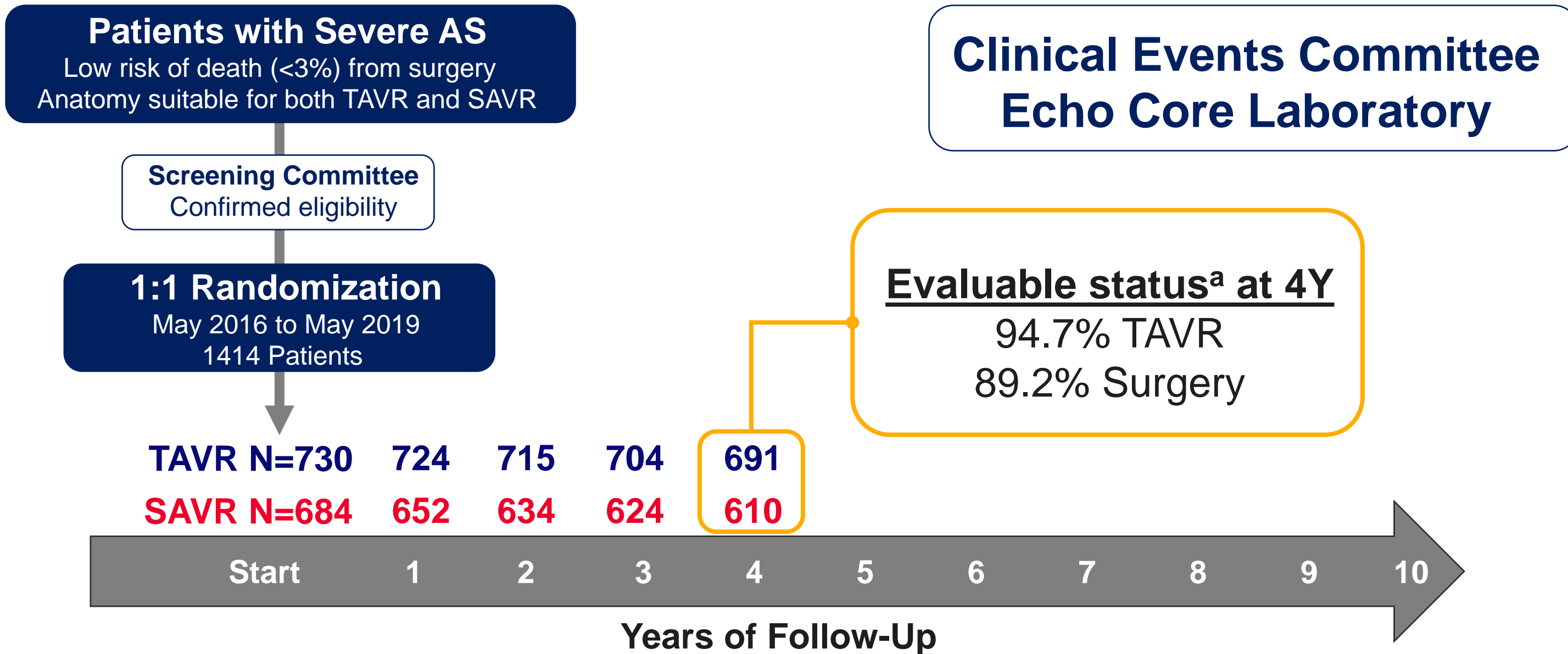
CANADA, EUROPE, JAPAN, AUSTRALIA, NEW ZEALAND (N = 25)



EVOLUT LOW RISK TRIAL | 4 YEAR RESULTS



STUDY DESIGN



^aEvaluatable 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 ≥ 20 mmHg and Severe PPM With Evolut vs Surgery

Parameter	Evolut TAVR	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

^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.

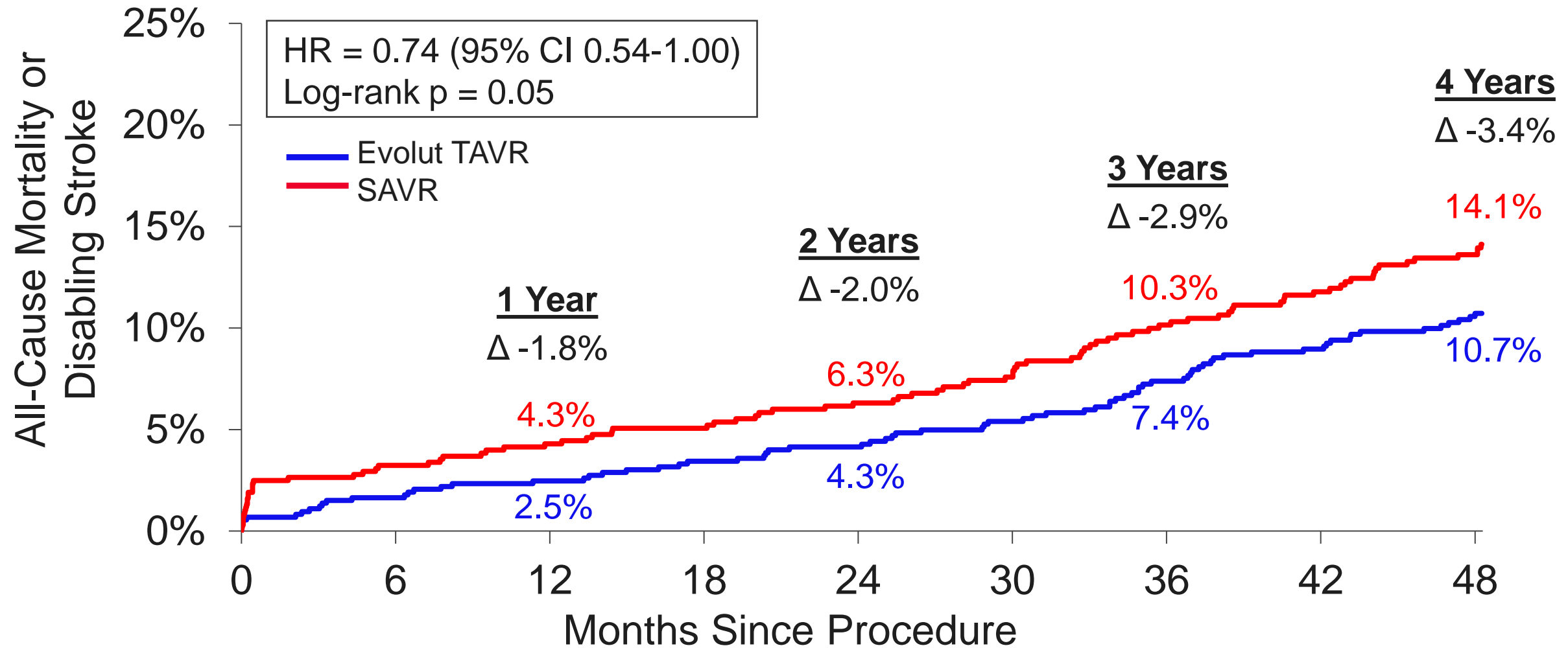
MG = mean gradient; PPM = patient-prosthesis mismatch; PVR = paravalvular regurgitation

EVOLUT LOW RISK TRIAL | 4 YEAR RESULTS



PRIMARY ENDPOINT: ALL-CAUSE MORTALITY 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



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

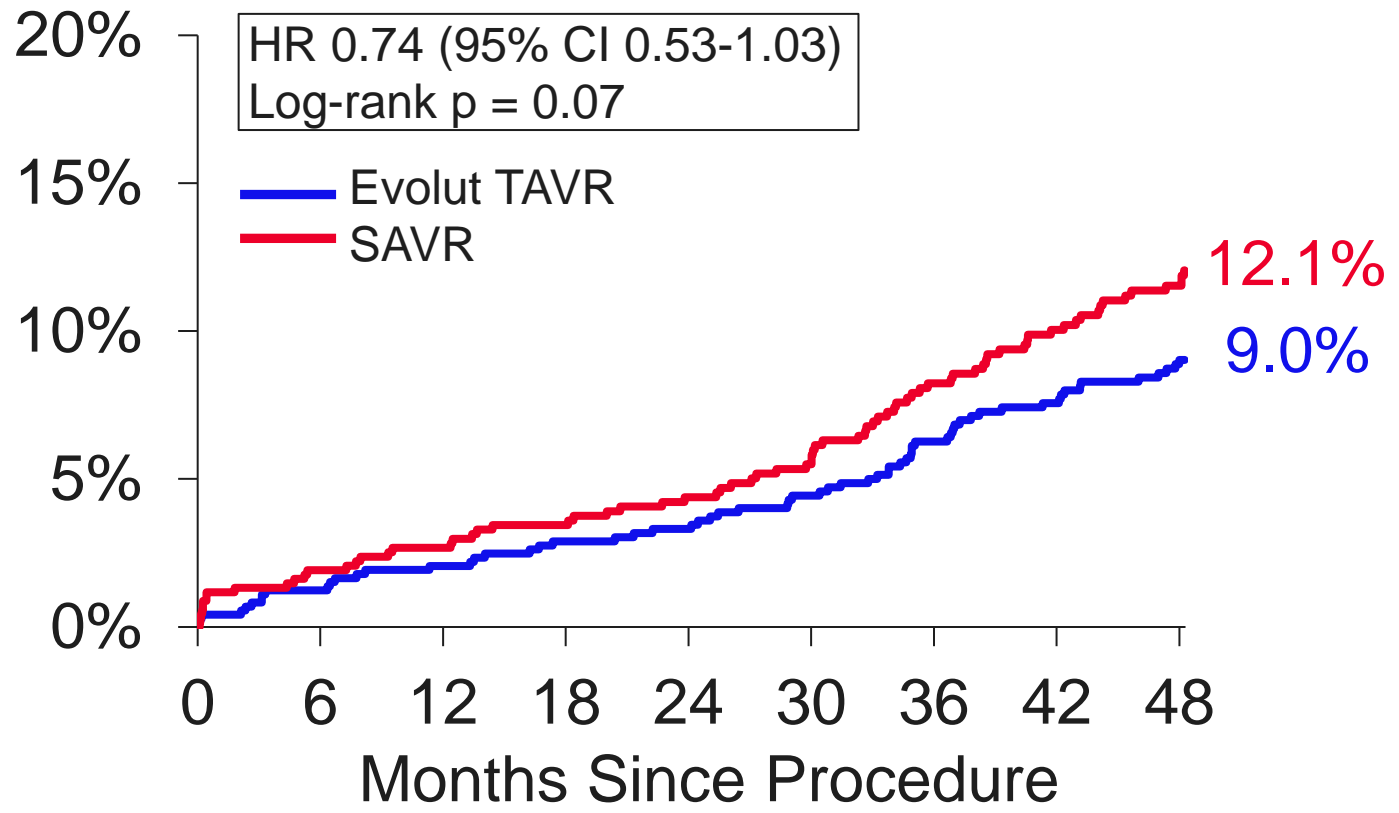
EVOLUT LOW RISK TRIAL | 4 YEAR RESULTS



ALL-CAUSE MORTALITY AND DISABLING STROKE

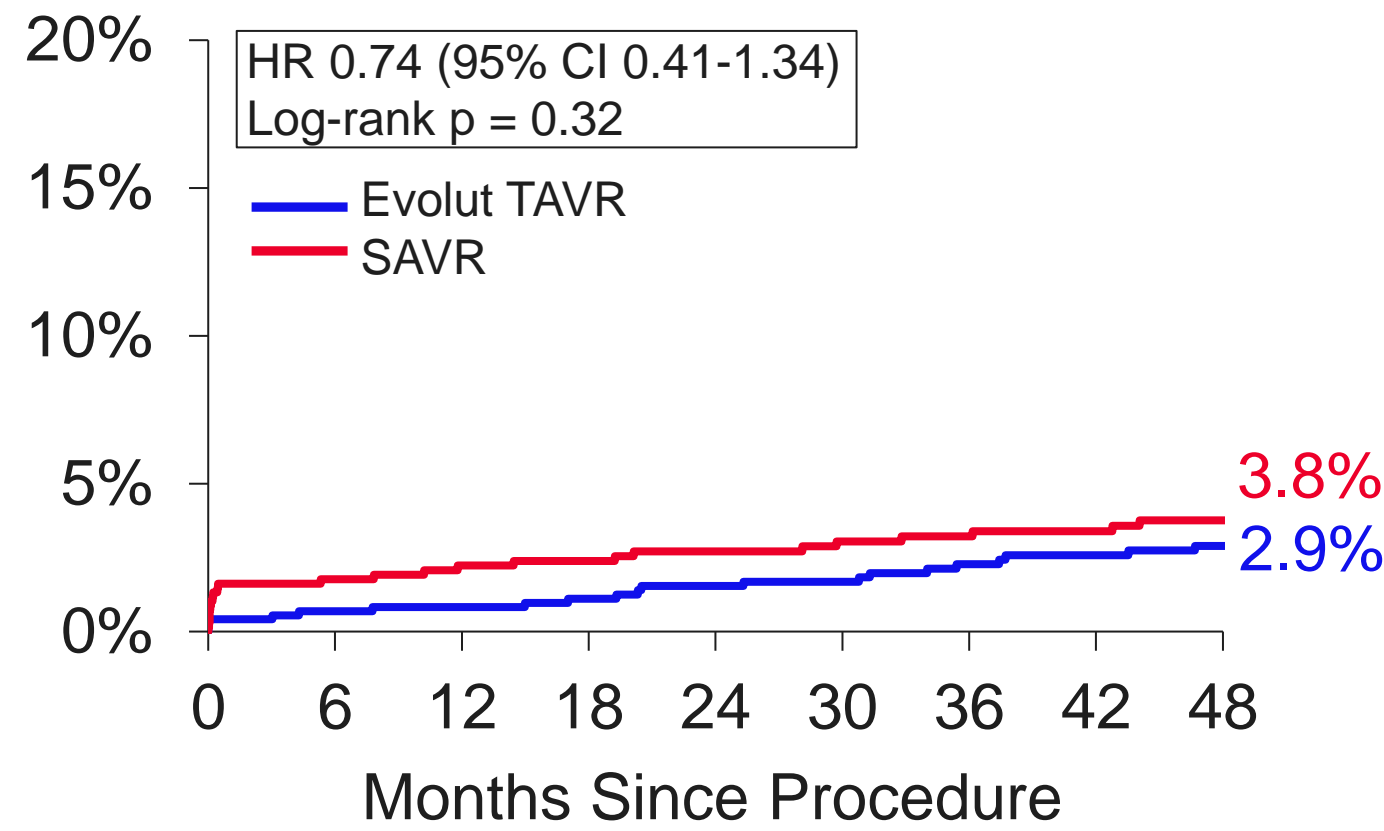
Observed Differences in the Primary Endpoint Driven by Death

All-Cause Mortality



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

Disabling Stroke



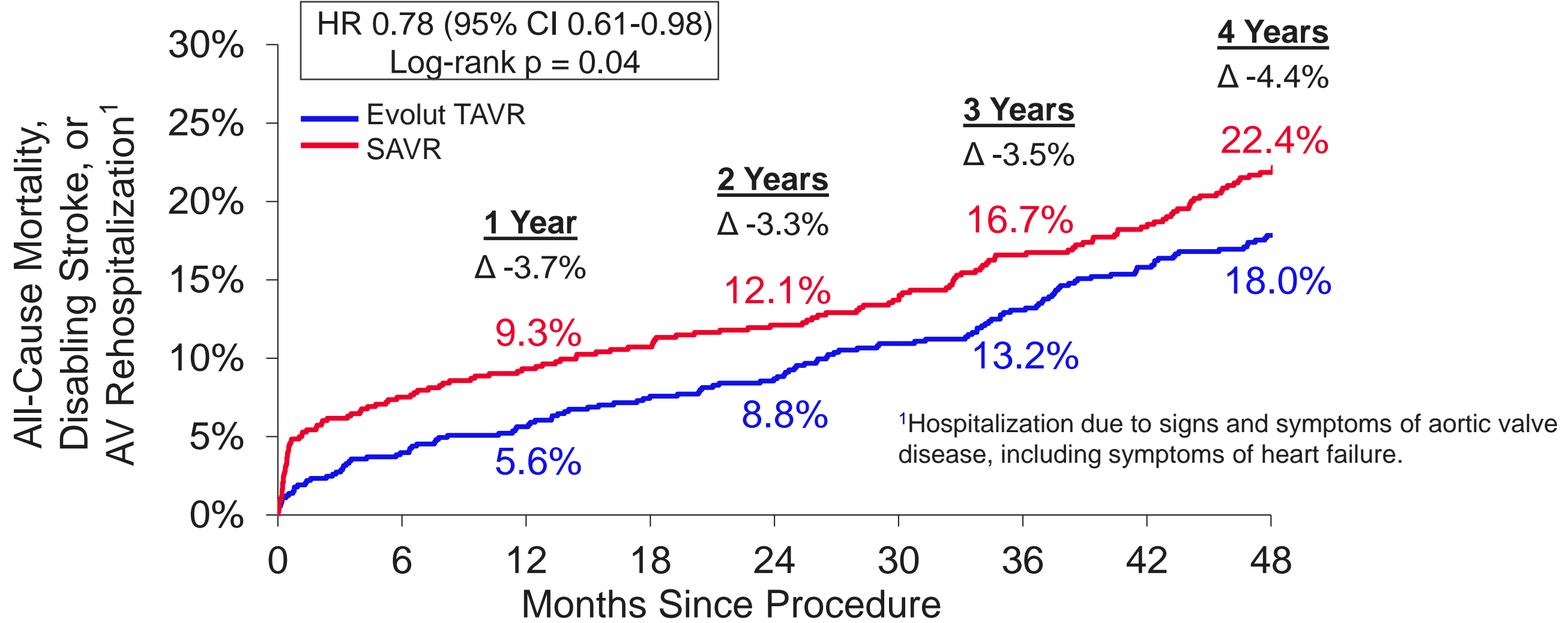
TAVR	730	715	706	695	685	671	651	627	592
SAVR	684	648	627	616	595	574	556	533	505

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

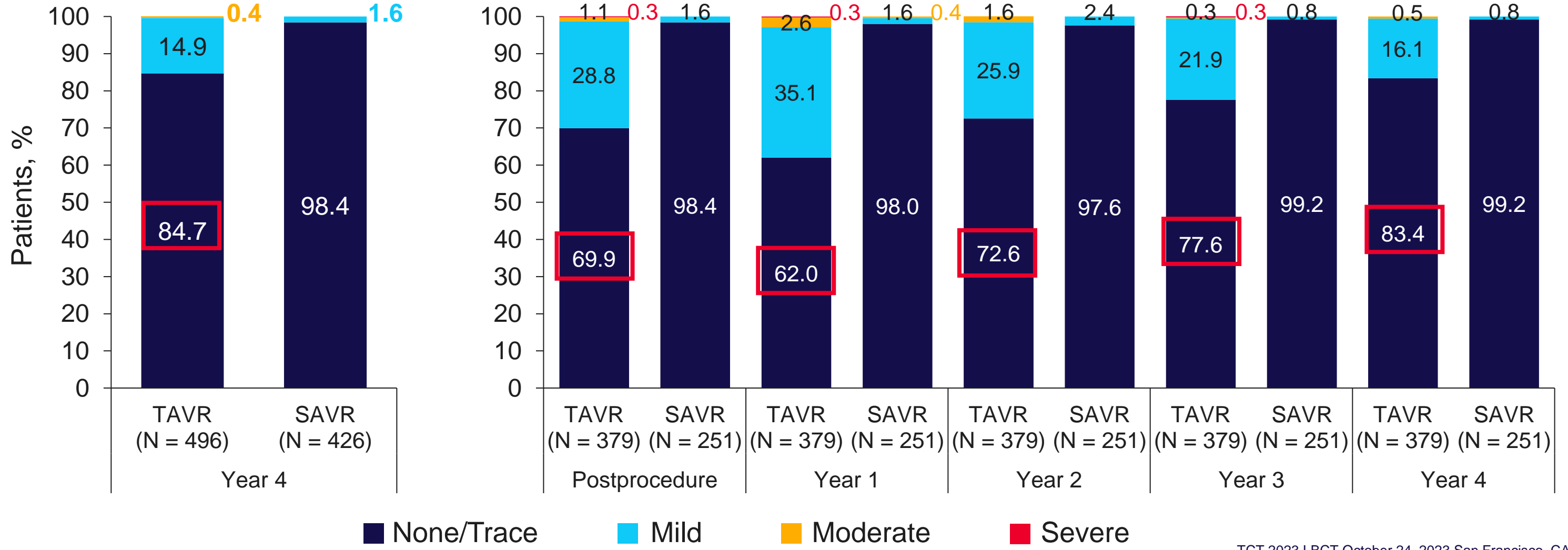
No Difference Between Groups in Moderate or Greater PVR

Patients with PVR data at 4Y

Patients with PVR data at all visits (paired data)

Overall, $p < 0.001$
 \geq Moderate, $p = 0.50$

Overall, $p < 0.001$
 \geq Moderate, $p = 0.52$

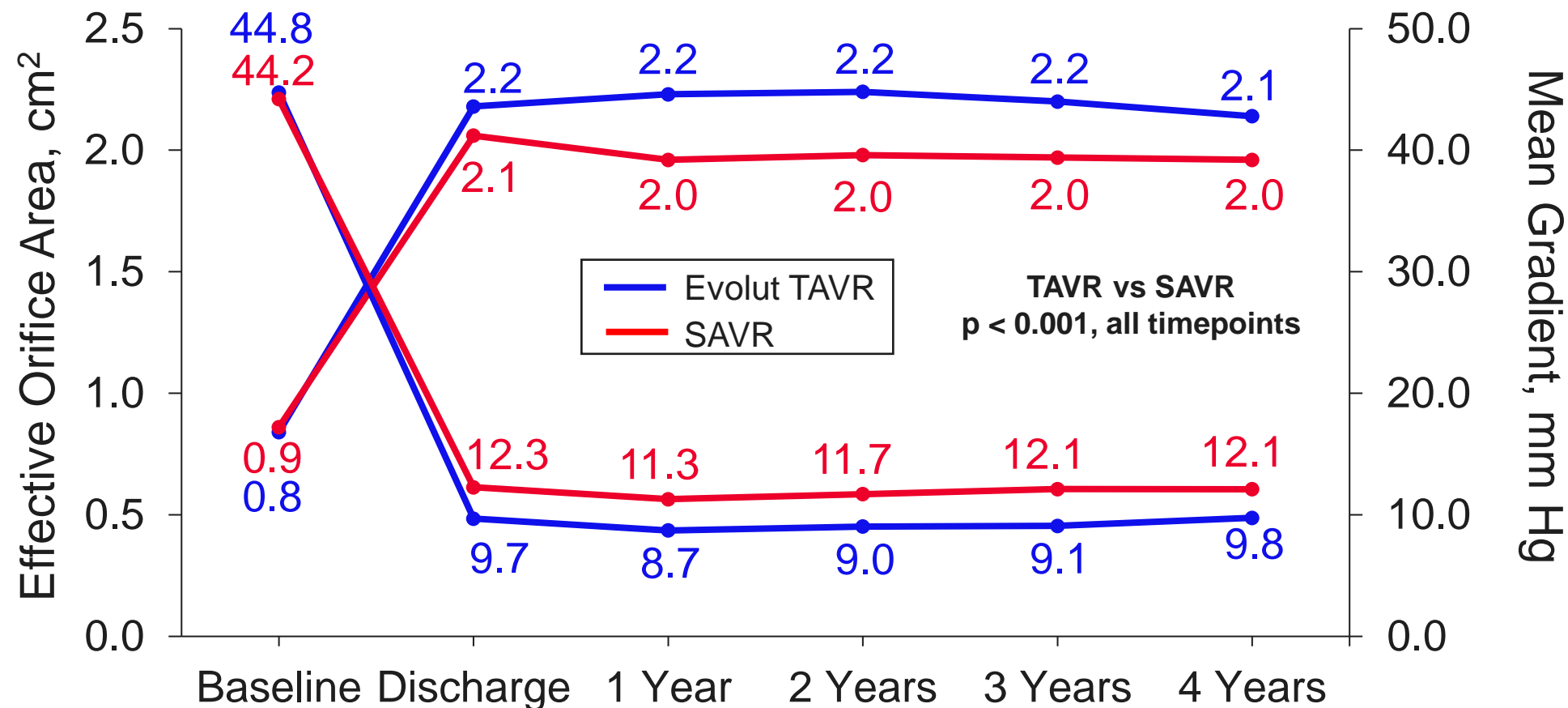


EVOLUT LOW RISK TRIAL | 4 YEAR RESULTS



COMPARATIVE HEMODYNAMICS

Significantly Better Hemodynamics with Evolut TAVR vs SAVR



No. of Patients

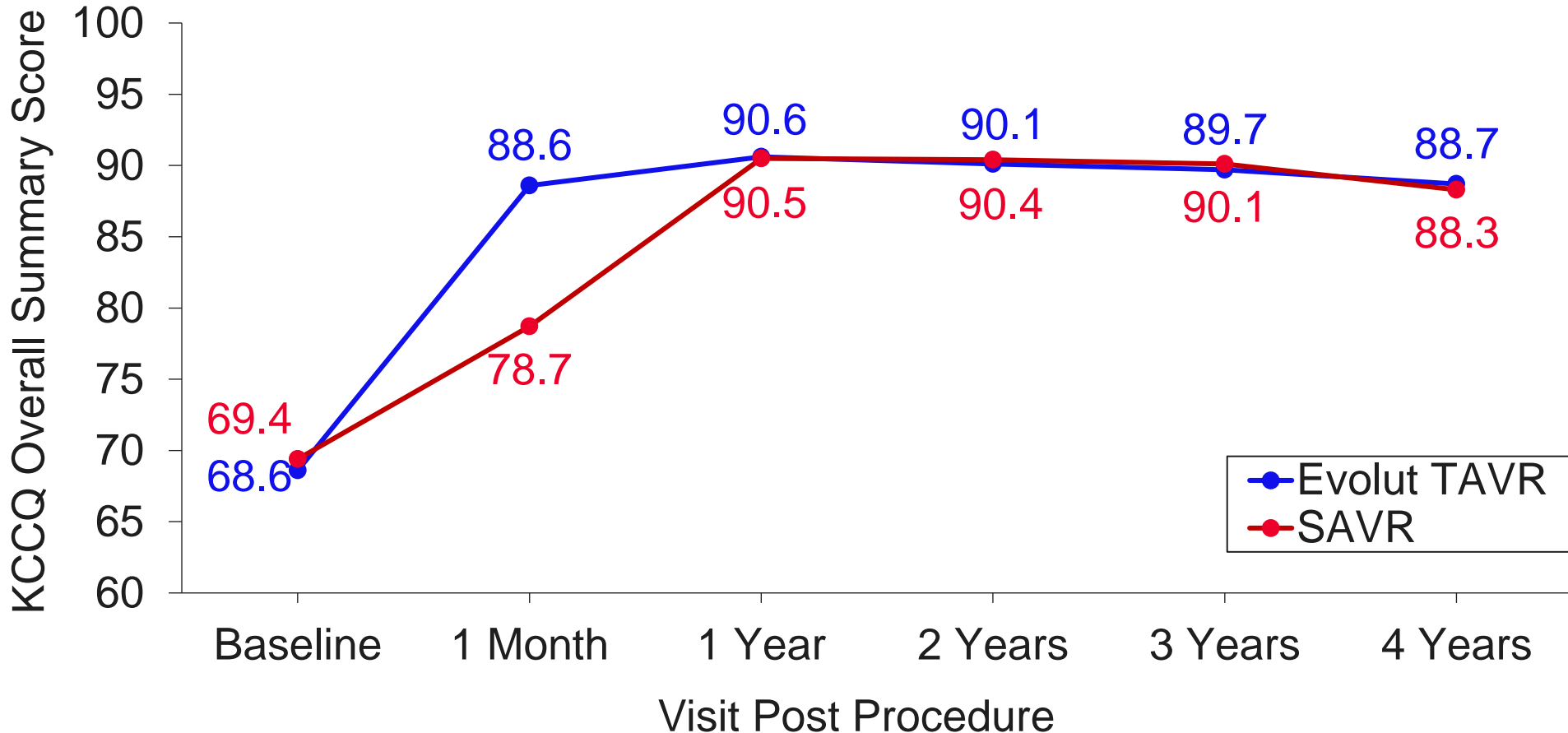
TAVR EOA	637	576	565	535	493	438
SAVR EOA	596	406	525	434	397	372
TAVR MG	717	703	662	607	547	497
SAVR MG	679	632	597	514	457	438

EVOLUT LOW RISK TRIAL | 4 YEAR RESULTS



KCCQ OVERALL SUMMARY SCORE

Sustained Improvement from Baseline in QoL Through 4 Years



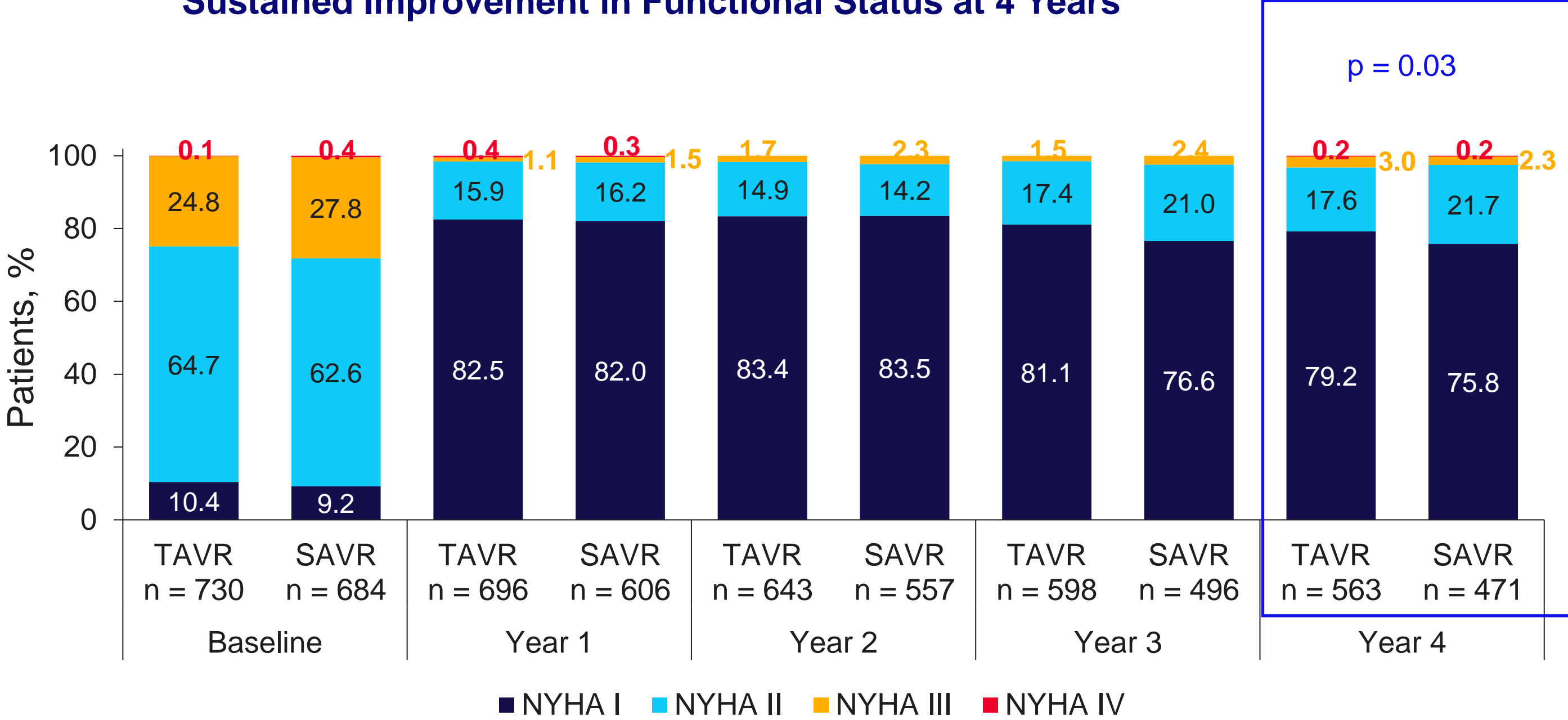
Change from Baseline		1 Month	1 Year	2 Years	3 Years	4 Years
Evolut TAVR		20.0 ± 21.1	21.6 ± 20.6	20.9 ± 20.8	20.1 ± 20.6	19.3 ± 20.7
SAVR		9.2 ± 22.3	20.7 ± 20.3	20.0 ± 20.0	19.3 ± 21.1	17.3 ± 20.9
P Value		<0.001	0.42	0.44	0.53	0.13

EVOLUT LOW RISK TRIAL | 4 YEAR RESULTS



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 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 technique¹

¹Harvey JE et al. TVT 2022, Chicago, IL.

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% 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 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 superior 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.

EVOLUT LOW RISK TRIAL

4 YEAR RESULTS IN JACC

Evolut™
Low Risk
Trial

ARTICLE IN PRESS

JOURNAL OF THE AMERICAN COLLEGE OF CARDIOLOGY

VOL. ■, NO. ■, 2023
ISSN 0735-1097/\$36.00

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 in expanding transcatheter compared with surgical aortic valve replacement (TAVR vs surgical-risk patients with severe aortic stenosis. Close follow-up of the low-risk trial is warranted given the limited information currently available in these patients. We report the 4-year outcomes of the Evolut Low Risk trial.

The Evolut Low Risk study design and results have been described.¹ Patients who underwent aortic valve replacement with either supra-annular CoreValve/Edwards S3 (Edwards Lifesciences) or a surgical bioprosthesis from June 2016 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 outcomes as determined by echocardiography. Outcomes were reported as Kaplan-Meier survival curves, compared by log-rank test. Endpoints were based on echocardiographic laboratory assessment. The study was approved by the Institutional Review Boards at each site, and all patients gave informed consent.

Of 730 TAVR, 684 SAVR patients completed implantation. Four-year follow-up was achieved for 94.7% of TAVR patients (695) and 89.2% of SAVR patients (616/684; 60 patients, 14 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]

What is the clinical question being addressed?

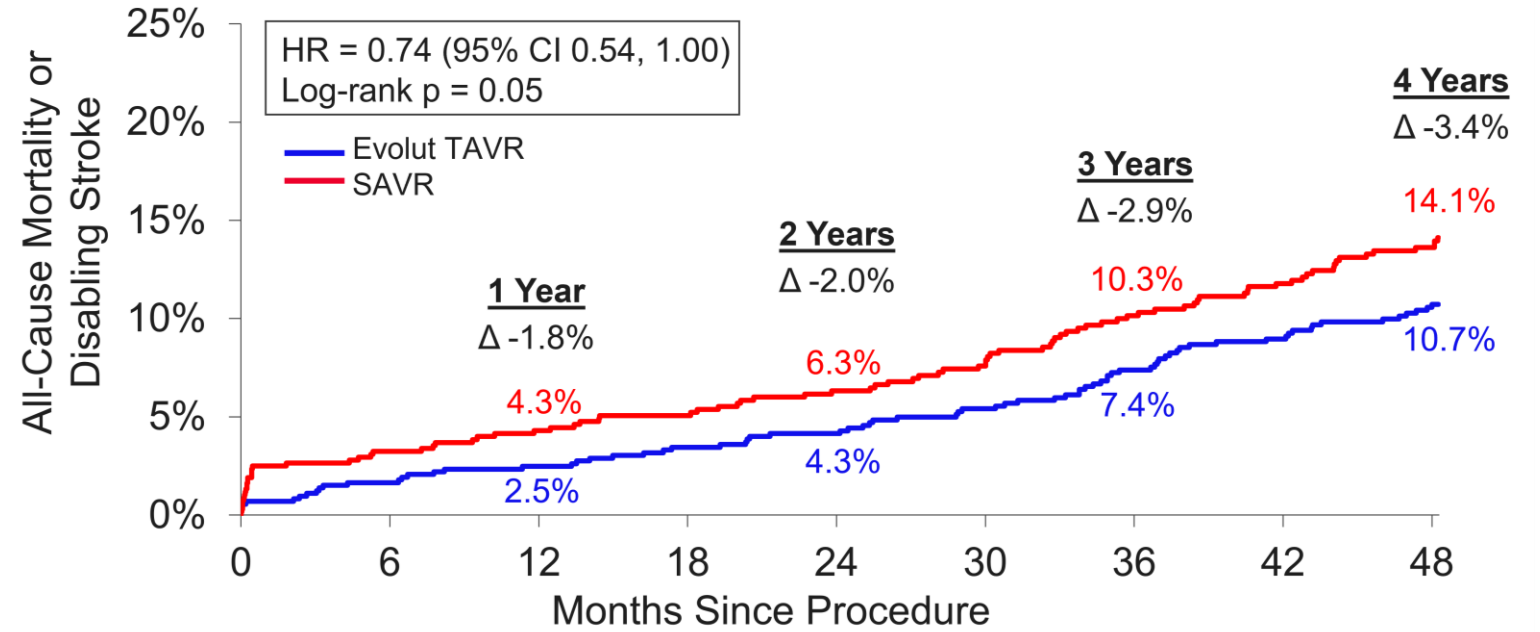
What are the 4-year outcomes of patients randomized to TAVR vs SAVR in the Evolut Low Risk Trial?

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.

Published Today in JACC

Primary Endpoint: All-Cause Mortality or Disabling Stroke



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

