Evolut™ Low Risk Trial

Primary Results From the Evolut Low Risk Trial

Michael J. Reardon, MD, FACC
Houston Methodist DeBakey Heart & Vascular Institute, Houston, TX
For the Evolut Low Risk Trial Investigators

Disclosure Statement of Financial Interests

Evolut™ Low Risk Trial

Within the past 12 months, I have had a financial interest/arrangement or affiliation with the organization(s) listed below.

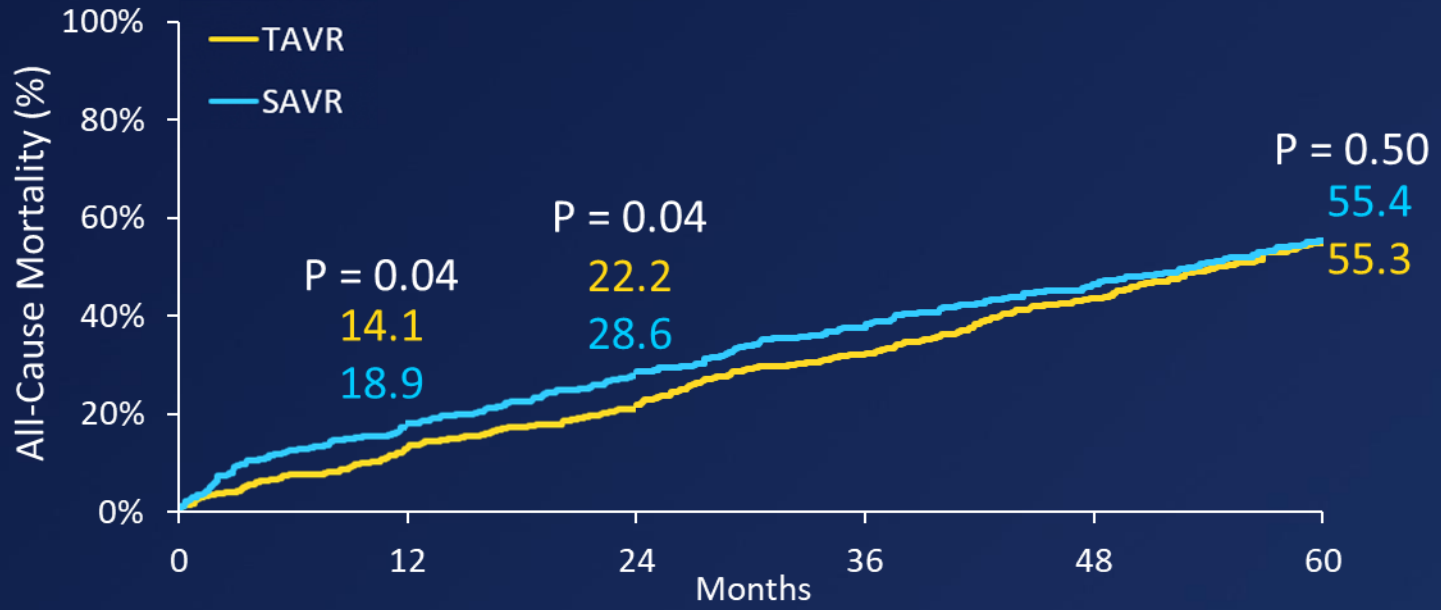
Financial Relationship	Company
Consultant (fees paid to institution)	Medtronic

Medtronic personnel performed all statistical analyses and assisted with the graphical display of the data presented.

Background

Evolut™ Low Risk Trial

- We performed a series of randomized controlled trials in patients with severe aortic stenosis across a spectrum of surgical risk.
- In high-risk patients, TAVR was superior to SAVR for the primary endpoint to 2 years[1] and similar at 5 years.[2]

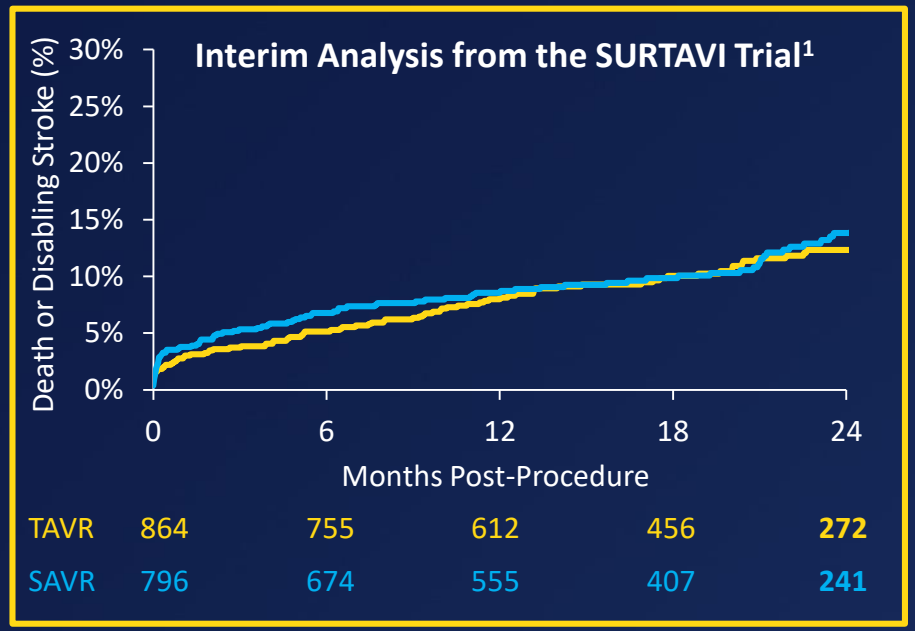


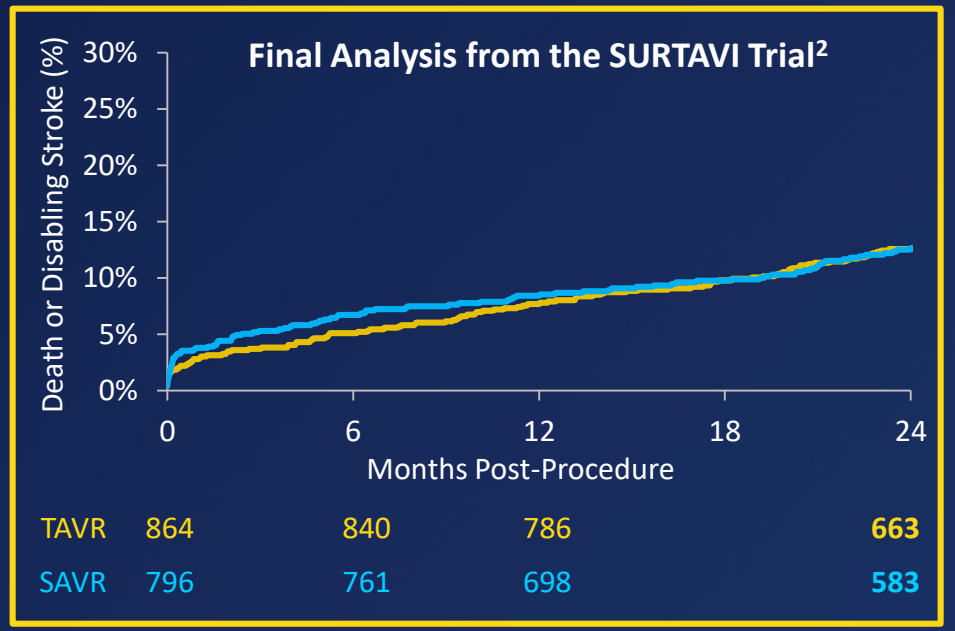
[1]Reardon et al. J Am Coll Cardiol 2015; 66: 113-21; [2]Gleason, et al. J Am Coll Cardiol 2018; 72: 2687-96.

Background

Evolut™ Low Risk Trial

- The SURTAVI intermediate risk trial showed noninferiority at interim analysis.
- The final analysis of the SURTAVI Trial confirmed the early Bayesian results, showing TAVR noninferior to SAVR.





[1]Reardon MJ, et al. NEJM 2017; 376:1321-31.

[2]Popma JJ, et al. Presented at TCT 2018.

Objective

Evolut™ Low Risk Trial

To assess the safety and efficacy of TAVR with the Evolut self-expanding supra-annular valve compared with surgical AVR in patients with a low predicted risk of 30-day surgical mortality.

Study Administration

Evolut™ Low Risk Trial

Principle Investigators: Jeffrey Popma, Michael Reardon

Executive Committee: Jeffrey Popma, Michael Reardon, G. Michael Deeb, Steven Yakubov

Steering Committee: David Adams, Stan Chetcuti, G. Michael Deeb, John Forrest, Thomas Gleason, John Heiser, William Mehri, Mubashir Mumtaz, Daniel O'Hair, Nicolo Piazza, Joshua Rovin, Michael Reardon, Paul Sorajja, Didier Tchétché, Paul Teirstein, Antony Walton, Steven Yakubov, George Zorn III

Screening Committee: G. Michael Deeb (Chair), Thomas Gleason, Jeffrey Popma, Michael Reardon, Steven Yakubov

Echo Core Laboratory: Jae Oh, Mayo Clinic, Rochester, MN

Data & Safety Monitoring Board: Baim Institute for Clinical Research; David Faxon (Chair), William Holman, John Lopez, Scott Kasner, John Orav

Clinical Events Committee: Baim Institute for Clinical Research; Claudia Hochberg (Chair), Cliff Berger, Torin Fitton, Sergio Waxman, Scott Bortman, Carey Kimmelstiel, David Grossman, Manish Chauhan, Jeffrey Veluz, Robert Rodriguez, Sanjay Samy, Gregory Smaroff, Jonathan Waks, Daniel Kramer

Statistical Design and Analyses: Andrew Mugglin, Paradigm Biostatistics, LLC

Sponsor: Medtronic

Participating Sites in the United States

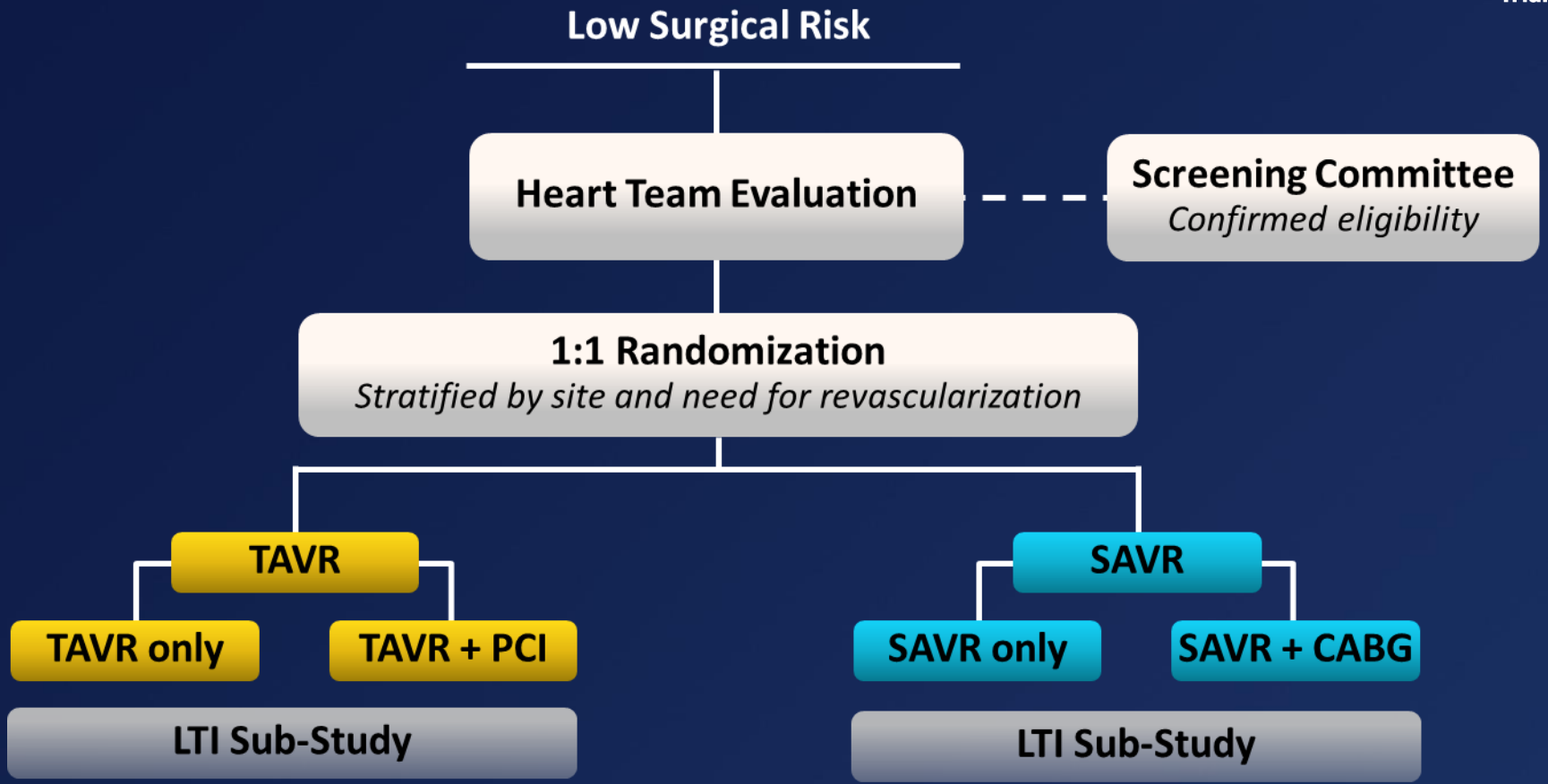
Evolut™ Low Risk Trial

Australia, Canada, Europe, Japan and New Zealand

Evolut™ Low Risk Trial

Study Design

Evolut™ Low Risk Trial



Study Endpoints

Evolut™ Low Risk Trial

Primary Safety and Effectiveness Endpoint

All-cause mortality or disabling stroke at 2 years

Hierarchical Powered Secondary Endpoints

<u>Noninferiority</u>

- Mean gradient at 1 year
- EOA at 1 year
- Change in NYHA class from baseline to 1 year
- Change in KCCQ score from baseline to 1 year

<u>Superiority</u>

- Mean gradient at 1 year
- EOA at 1 year
- Change in KCCQ score from baseline to 30 days

Other Secondary Endpoints

- 30-day safety composite of
  - All-cause mortality
  - Disabling stroke
  - Life-threatening bleeding
  - Major vascular complications
  - Stage 2 or 3 acute kidney injury
- New pacemaker implantation at 30 days
- Heart failure rehospitalizations at 1 year
- Aortic-valve reintervention at 1 year
- Moderate/severe AR at 1 year
- All stroke at 1 year
- Life-threatening bleeding at 1 year

Key Inclusion Criteria

Evolut™ Low Risk Trial

Symptomatic severe AS[1]:

- Aortic valve area ≤1.0 cm^2 (or aortic valve area index <0.6 cm^2/m^2), **OR** mean gradient ≥40 mmHg **OR** Vmax ≥4 m/sec at rest

Asymptomatic very severe AS[1]:

- Aortic valve area ≤1.0 cm^2 (or aortic valve area index <0.6 cm^2/m^2), **AND** Vmax ≥5 m/sec or mean gradient ≥ 60 mmHg at rest
- Aortic valve area of ≤1.0 cm^2 (or aortic valve area index of ≤0.6 cm^2/m^2), **AND** a mean gradient ≥40 mmHg or Vmax ≥4.0 m/sec by transthoracic echocardiography at rest, **AND** an exercise tolerance test that demonstrates limited exercise capacity, abnormal BP response, or arrhythmia
- Aortic valve area of ≤1.0 cm^2 (or aortic valve area index of ≤0.6 cm^2/m^2), **AND** mean gradient ≥40 mmHg, **OR** Vmax ≥4.0 m/sec by transthoracic echocardiography at rest, **AND** LVEF<50%.

A predicted risk of 30-day mortality <3% per multidisciplinary local heart team assessment.

[1]Nishimura RA, et al. Circulation. 2014;129:2440-92.

Key Exclusion Criteria

Evolut™ Low Risk Trial

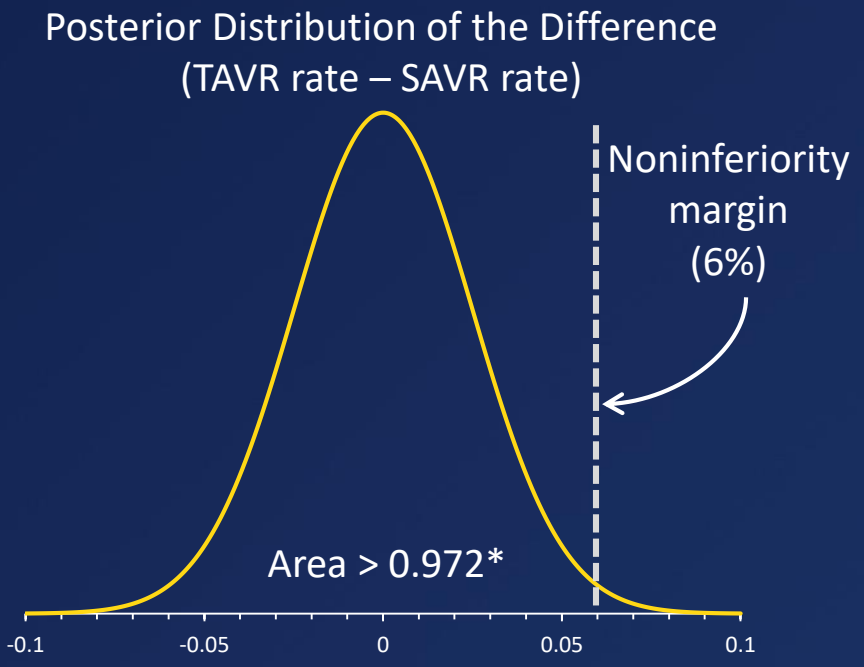
- Contraindication for placement of a bioprosthetic valve
- Multivessel coronary artery disease with SYNTAX score >22
- Bicuspid aortic valve verified by imaging
- Hypersensitivity or contraindication to all anticoagulation/ antiplatelet regimens
- Any PCI or peripheral intervention within 30 days prior to randomization
- Symptomatic carotid or vertebral artery disease or successful treatment of carotid stenosis within 10 weeks of Heart Team assessment
- Recent (within 2 months) cerebrovascular accident or transient ischemic attack
- Acute MI within 30 days
- Severe liver, lung or renal disease
- Unsuitable anatomy including native aortic annulus <18 mm or >30 mm
- Severe mitral or tricuspid regurgitation

Statistical Methods

Noninferiority Testing of the Primary Endpoint

Evolut™ Low Risk Trial

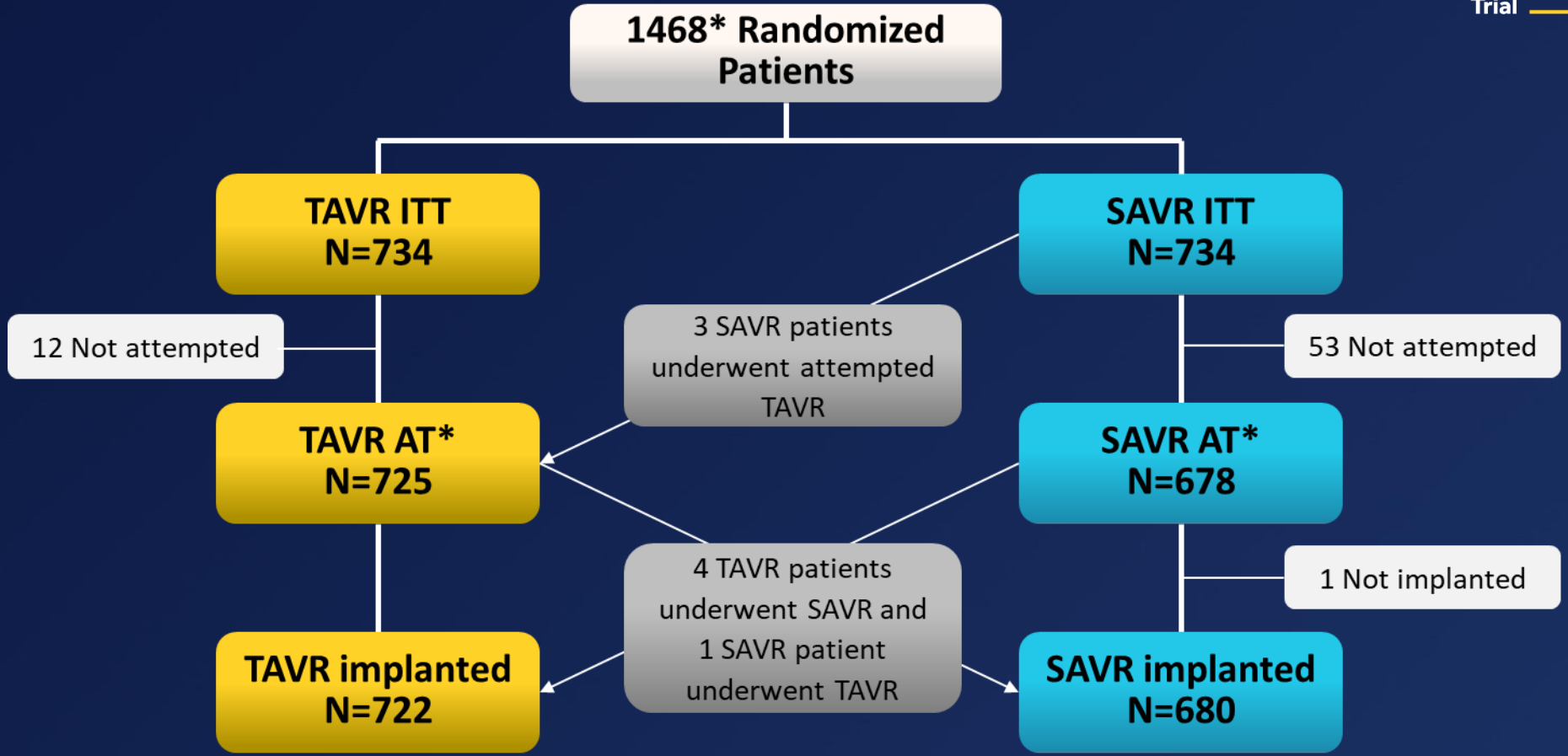
- This was a randomized, multinational, noninferiority trial.
- The Bayesian adaptive design prespecified an “early-win” interim analysis when 850 patients reached 1-year follow-up.
- The estimated sample size was 1200 patients.
- The 2-year primary analysis cohort comprised all patients with an attempted implant procedure (as-treated).
- The prespecified criteria for success was posterior probability >0.972.



*Selected to maintain α < 0.05

Patient Flow

Evolut™ Low Risk Trial



*Additional patients were randomized to permit completion of the LTI substudy and to enroll a Japanese cohort.

Study Timeline and Valves Studied

Evolut™ Low Risk Trial

2016	2017	2018

First Patient Randomized
Mar. 28, 2016

*Last Patient Randomized
Nov. 27, 2018

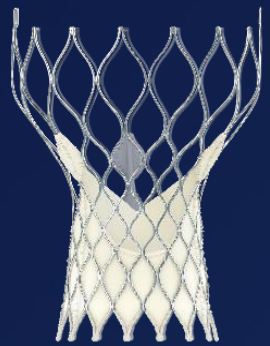
CoreValve 31 mm

Evolut R: 23, 26, 29

Added Evolut R 34 mm

Evolut PRO: 23, 26, 29 mm

Primary Endpoint Assessment
Dec. 27, 2018



CoreValve 31 = 3.6%	Evolut R = 74.1%	Evolut PRO = 22.3%

Vascular access
- 99% transfemoral
- 0.6% subclavian
- 0.4% direct aortic

*For this analysis

Evolut™
Low Risk
Trial

RESULTS

Baseline Characteristics

Evolut™ Low Risk Trial

Mean ± SD or %	TAVR (N=725)	SAVR (N=678)
Age, years	74.1 ± 5.8	73.6 ± 5.9
Female sex	36.0	33.8
Body surface area, m^2	2.0 ± 0.2	2.0 ± 0.2
STS PROM, %	1.9 ± 0.7	1.9 ± 0.7
NYHA Class III or IV	25.1	28.5
Hypertension	84.8	82.6
Chronic lung disease (COPD)	15.0	18.0
Cerebrovascular disease	10.2	11.8
Peripheral arterial disease	7.5	8.3

There are no significant differences between groups.

Baseline Cardiac Risk Factors

Evolut™ Low Risk Trial

Mean ± SD or %	TAVR (N=725)	SAVR (N=678)
SYNTAX Score	1.9 ± 3.7	2.1 ± 3.9
Permanent pacemaker, CRT or ICD	3.2	3.8
Prior CABG	2.5	2.1
Previous PCI	14.2	12.8
Previous myocardial infarction	6.6	4.9
Atrial fibrillation/flutter	15.4	14.5
Aortic valve gradient, mm Hg	47.0 ± 12.1	46.6 ± 12.2
Aortic Valve area, cm^2	0.8 ± 0.2	0.8 ± 0.2
Left ventricular ejection fraction, %	61.7 ± 7.9	61.9 ± 7.7

There are no significant differences between groups.

TAVR Procedural Data

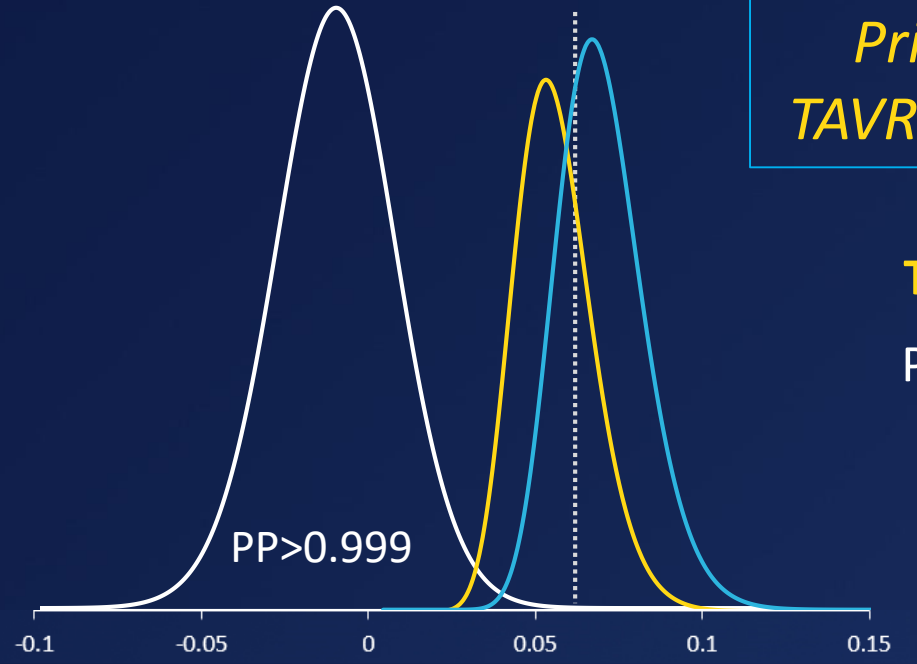
Evolut™ Low Risk Trial

%	TAVR (N=724)
General anesthesia	56.9
Iliofemoral access	99.0
Embolic protection device used	1.2
Pre-TAVR balloon dilation	34.9
Post-TAVR balloon dilation	31.3
More than 1 valve used	1.2
Partial or complete repositioning of the valve (Evolut/PRO only)	37.3
Staged or concomitant PCI performed	6.9

Primary Endpoint

All-Cause Mortality or Disabling Stroke at 2 Years

Evolut™ Low Risk Trial



Primary Endpoint Met
TAVR is noninferior to SAVR

TAVR 5.3% **SAVR 6.7%**

Posterior probability of noninferiority > 0.999

TAVR –SAVR difference = -1.4% (95% BCI; -4.9, 2.1)

Hierarchical Secondary Endpoints

All Noninferiority and Superiority Endpoints Met

Evolut™ Low Risk Trial

	TAVR	SAVR	Difference TAVR–SAVR	Posterior Probability
Noninferiority (margin)			(90% BCI)	
Mean gradient at 12 months (5 mmHg)	8.6 ± 3.7	11.2 ± 4.9	-2.6 (-3.1, -2.1)	> 0.999 ✓
Mean EOA at 12 months (0.1 cm^2)	2.3 ± 0.7	2.0 ± 0.6	0.3 (0.2, 0.4)	> 0.999 ✓
Mean NYHA class change (12 months –Baseline) (0.375)	0.9 ± 0.7	1.0 ± 0.7	-0.1 (-0.2, 0.0)	> 0.999 ✓
Mean KCCQ change (12 months –Baseline) (5)	22.2 ± 20.3	20.9 ± 21.0	1.3 (-1.2, 3.8)	> 0.999 ✓
Superiority			(95% BCI)	
Mean gradient at 12 months, mmHg	8.6 ± 3.7	11.2 ± 4.9	-2.6 (-3.2, -2.0)	> 0.999 ✓
Mean EOA at 12 months, cm^2	2.3 ± 0.7	2.0 ± 0.6	0.3 (0.2, 0.4)	> 0.999 ✓
Mean KCCQ change (30 Days–Baseline)	20.0 ± 21.1	9.1 ± 22.3	10.9 (8.6, 13.2)	> 0.999 ✓

Clinical Outcomes at 30 Days

Evolut™ Low Risk Trial

Bayesian rates as %	TAVR (N=725)	SAVR (N=678)	(95% BCI for Difference)
30-Day composite safety endpoint*	5.3	10.7	(-8.3, -2.6)
All-cause mortality	0.5	1.3	(-1.9, 0.2)
Disabling stroke*	0.5	1.7	(-2.4, -0.2)
Life-threatening or disabling bleeding*	2.4	7.5	(-7.5, -2.9)
Acute kidney injury, stage 2-3*	0.9	2.8	(-3.4, -0.5)
Major vascular complication	3.8	3.2	(-1.4, 2.5)
Atrial fibrillation*	7.7	35.4	(-31.8, -23.6)
Permanent pacemaker implant*	17.4	6.1	(8.0, 14.7)
All-cause mortality or disabling stroke*	0.8	2.6	(-3.2, -0.5)
All stroke	3.4	3.4	(-1.9, 1.9)
Aortic valve reintervention	0.4	0.4	(-0.8, 0.7)

* Significantly favors TAVR; * Significantly favors SAVR

BCI = Bayesian credible interval

Clinical Outcomes at 1 Year

Evolut™ Low Risk Trial

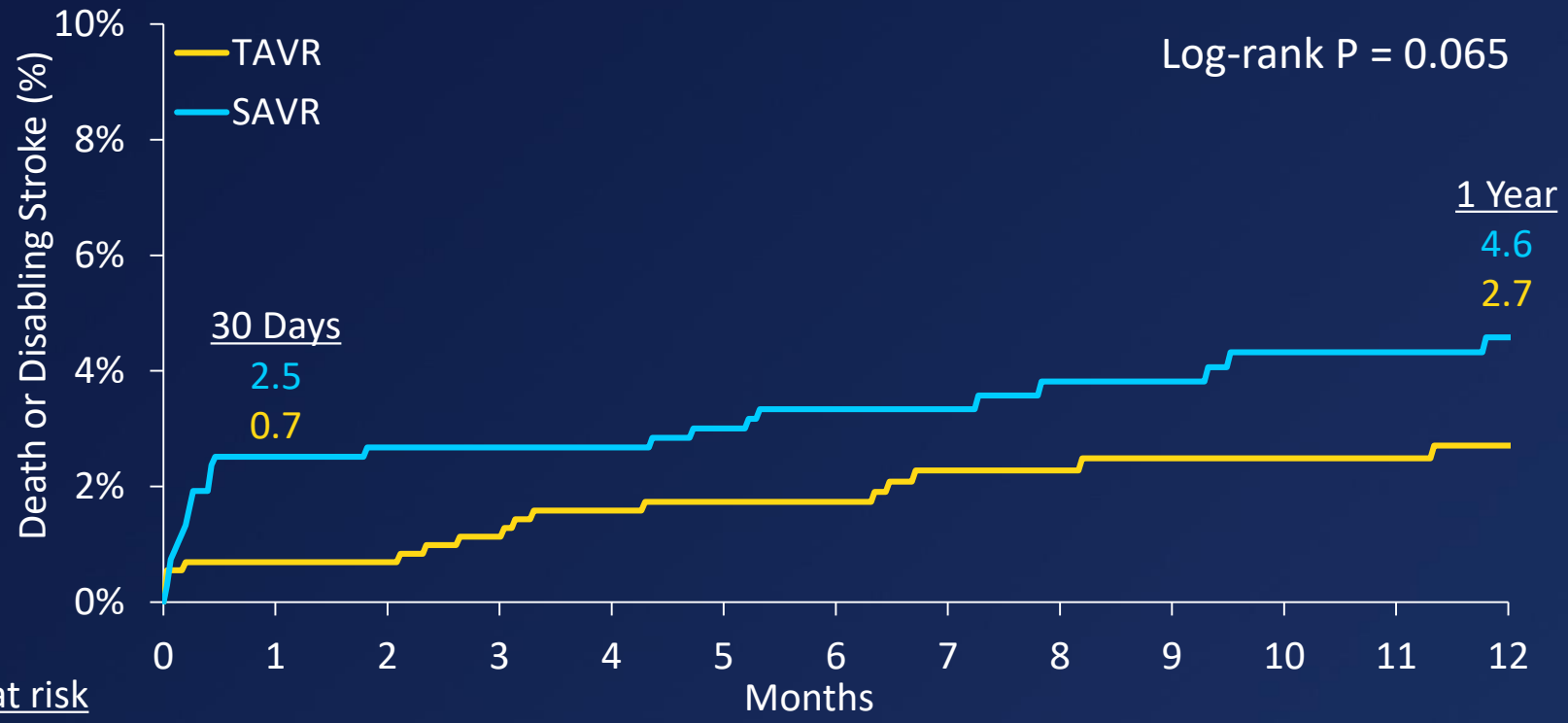
Bayesian rates as %	TAVR (N=725)	SAVR (N=678)	(95% BCI for Difference)
All-cause mortality or disabling stroke	2.9	4.6	(-4.0, 0.4)
All-cause mortality	2.4	3.0	(-2.6, 1.3)
Cardiovascular mortality	1.7	2.6	(-2.7, 0.7)
All stroke	4.1	4.3	(-2.4, 1.9)
Disabling stroke*	0.8	2.4	(-3.1, -0.3)
Transient ischemia attack	1.7	1.8	(-1.6, 1.3)
Myocardial infarction	1.7	1.6	(-1.3, 1.5)
Endocarditis	0.2	0.4	(-0.9, 0.5)
Valve thrombosis	0.2	0.3	(-0.9, 0.5)
Aortic valve reintervention	0.7	0.6	(-1.0, 0.9)
Heart failure hospitalization*	3.2	6.5	(-5.9, -1.0)

* Significantly favors TAVR

BCI = Bayesian credible interval

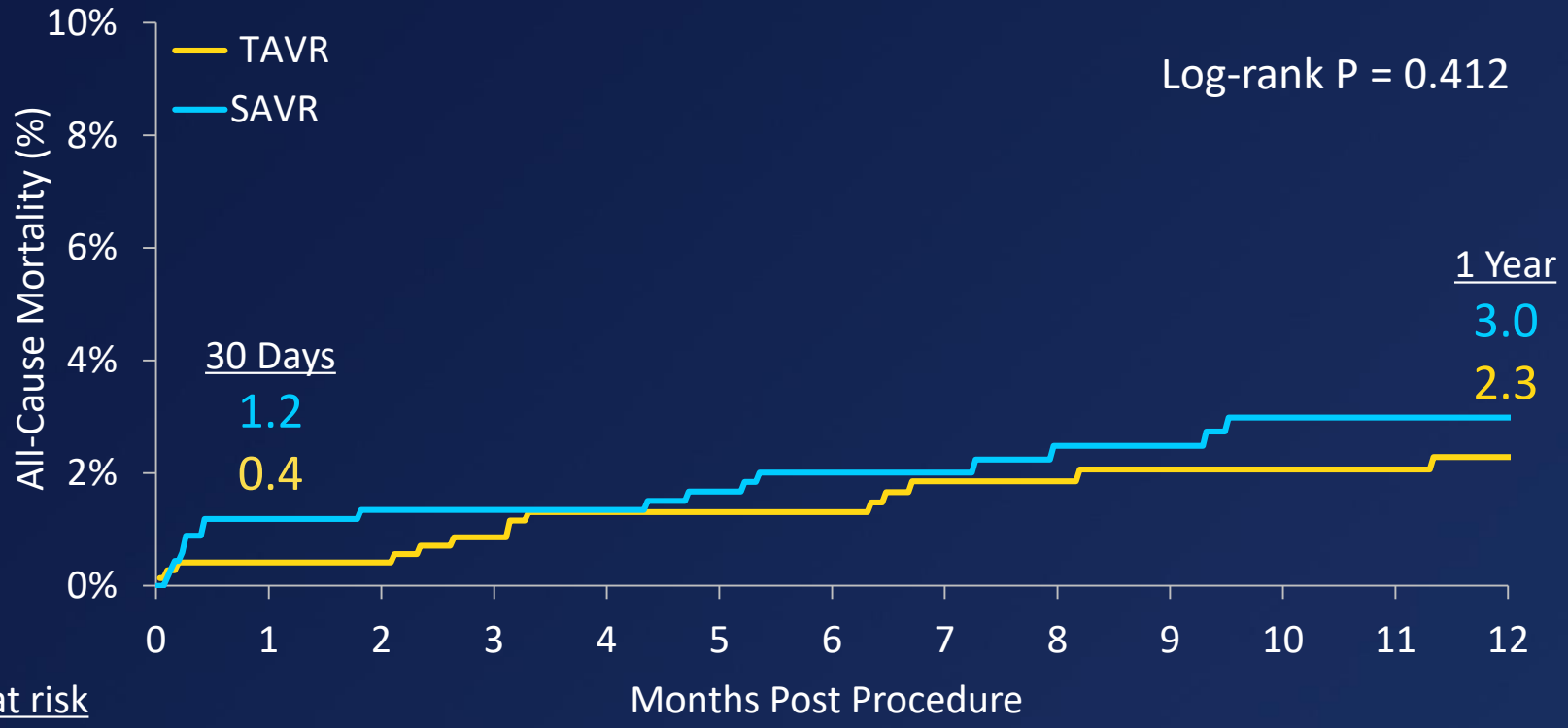
K-M All-Cause Mortality or Disabling Stroke at 1 Year

Evolut™ Low Risk Trial



K-M Rates of All-Cause Mortality at 1 Year

Evolut™ Low Risk Trial

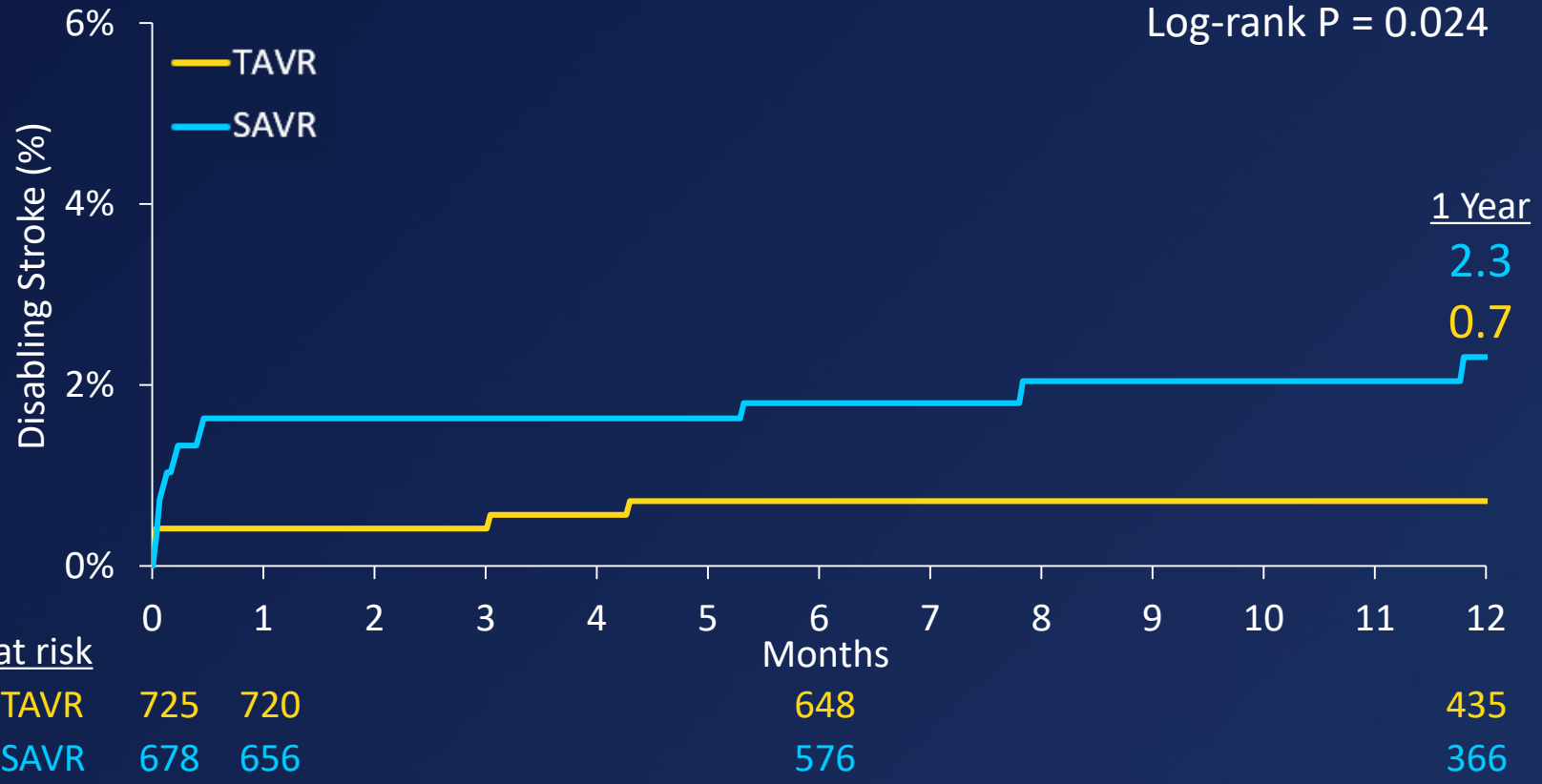


No. at risk

TAVR	725	720	651	435
SAVR	678	665	583	373

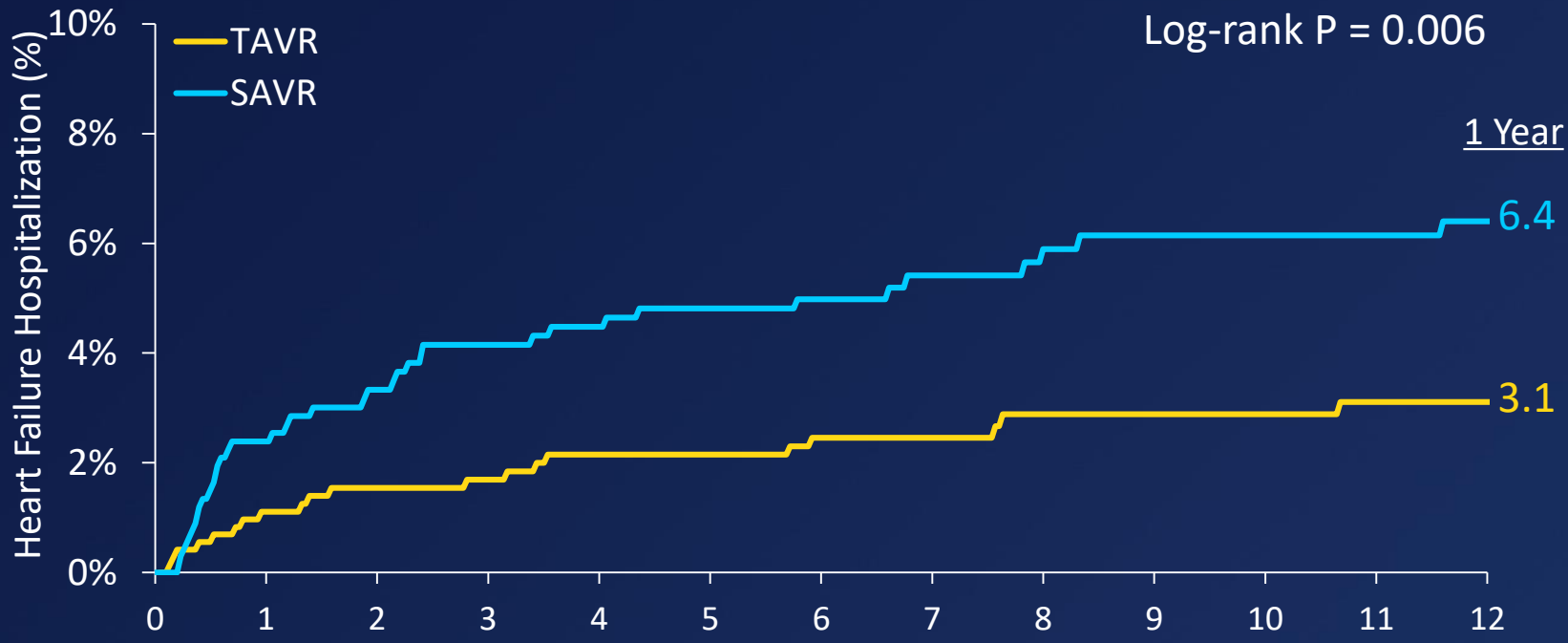
K-M Disabling Stroke at 1 Year

Evolut™ Low Risk Trial



K-M Heart Failure Hospitalization at 1 Year

Evolut™ Low Risk Trial

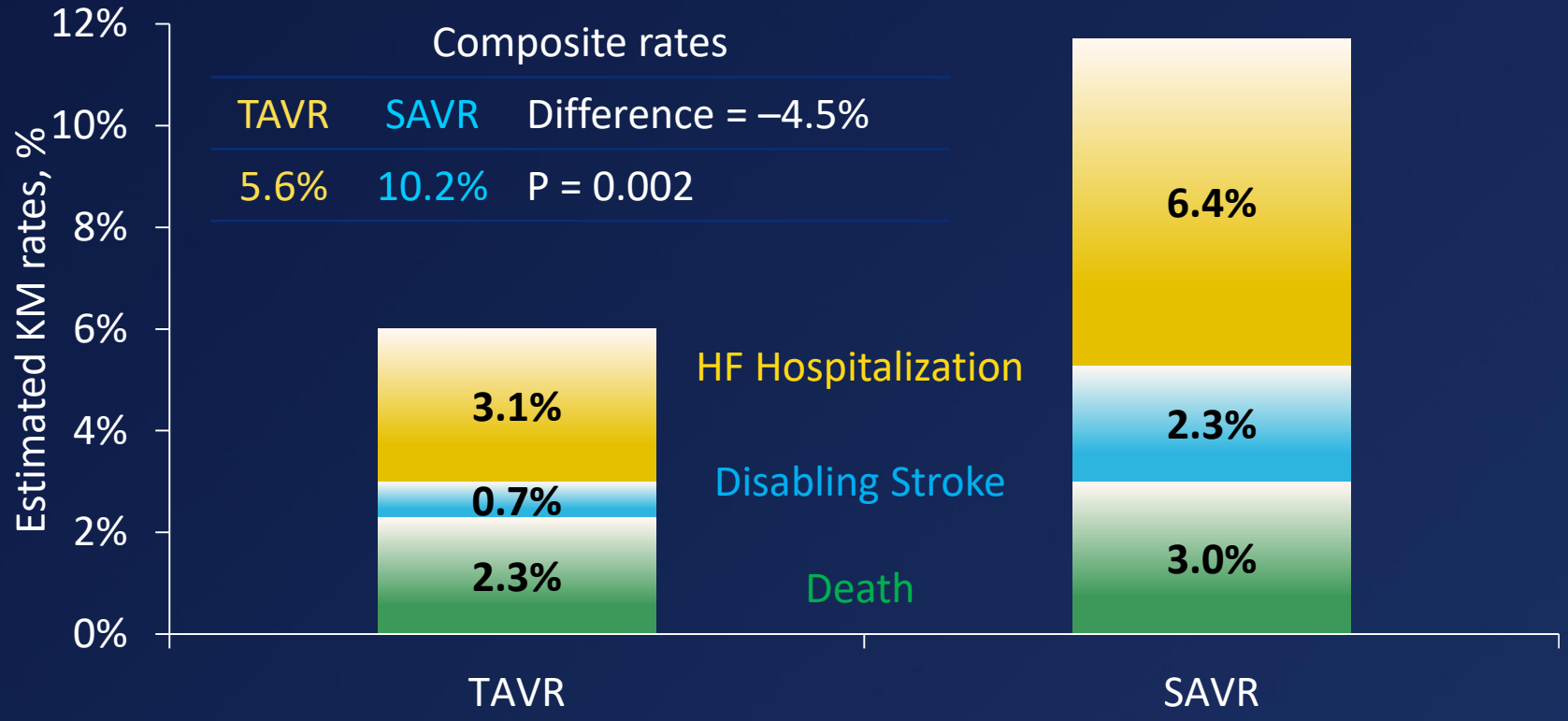


No. at risk					
TAVR	725	712	636		420
SAVR	678	649	561		358

Clinical Implications

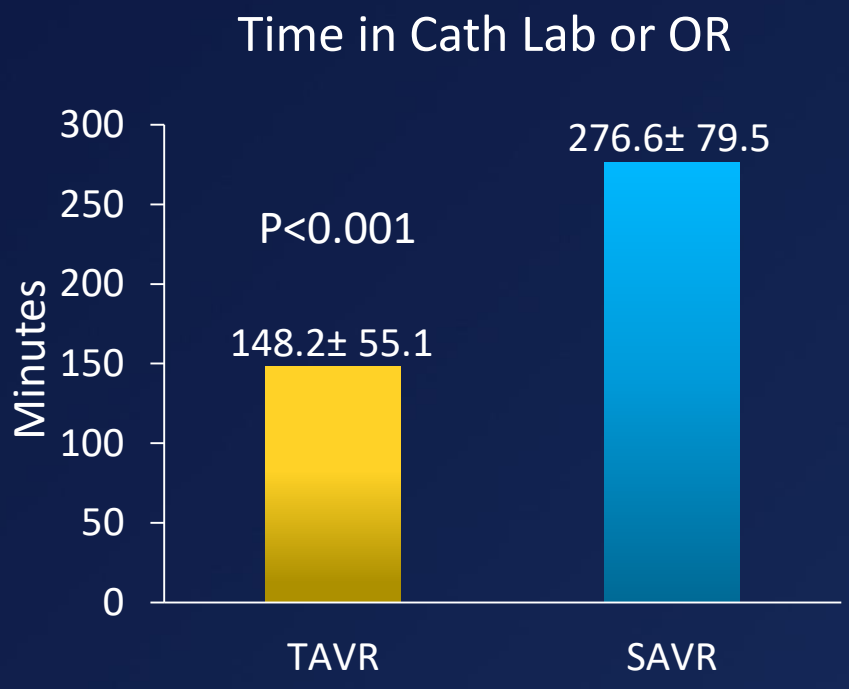
Death, Disabling Stroke and Heart Failure Hospitalizations to 1 Year

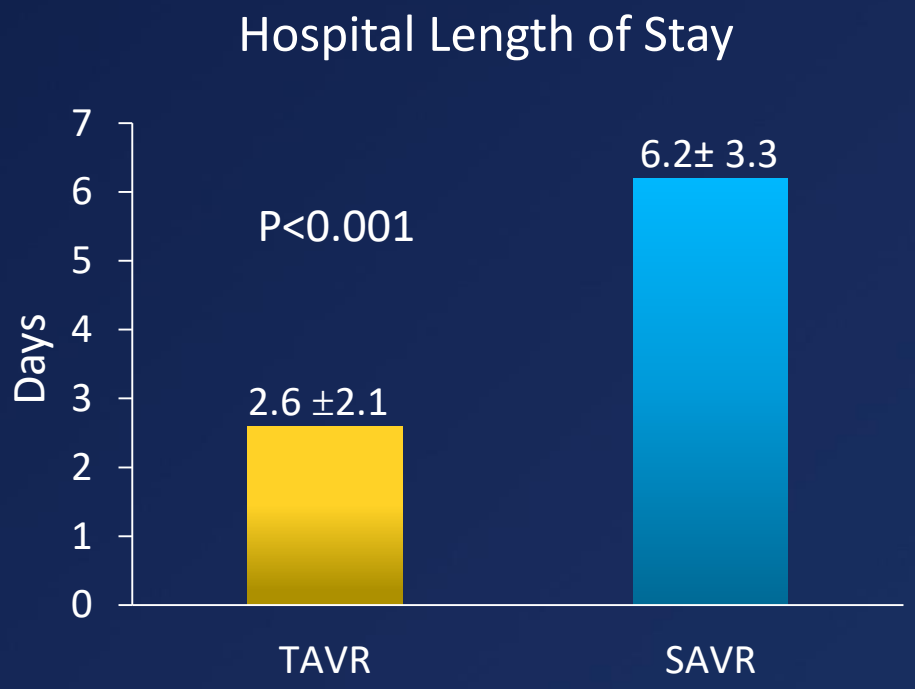
Evolut™ Low Risk Trial



Procedural Time and Length of Stay

Evolut™ Low Risk Trial

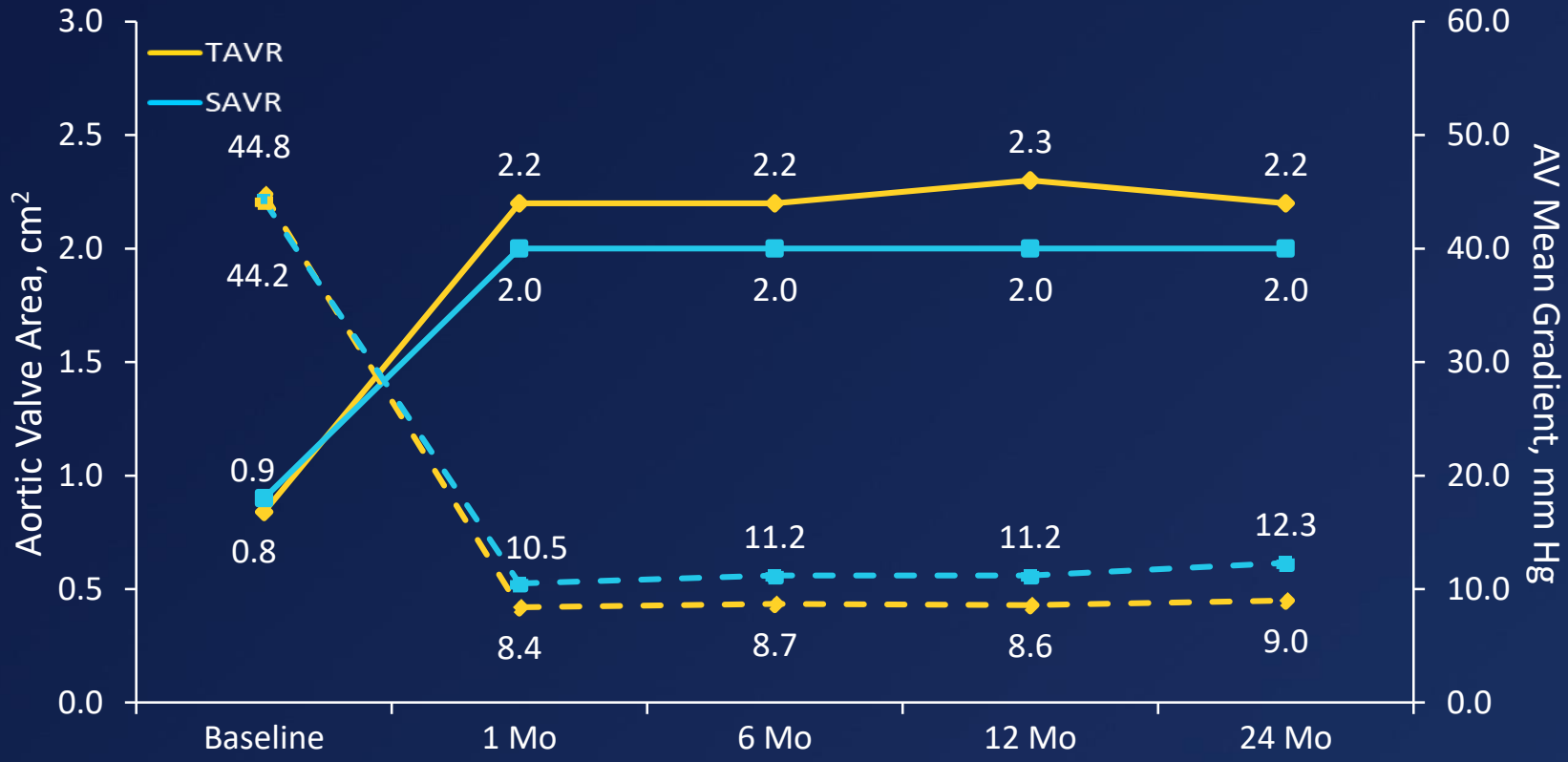




Valve Hemodynamics

TAVR had Significantly Better Valve Performance vs SAVR at all Follow-up Visits*

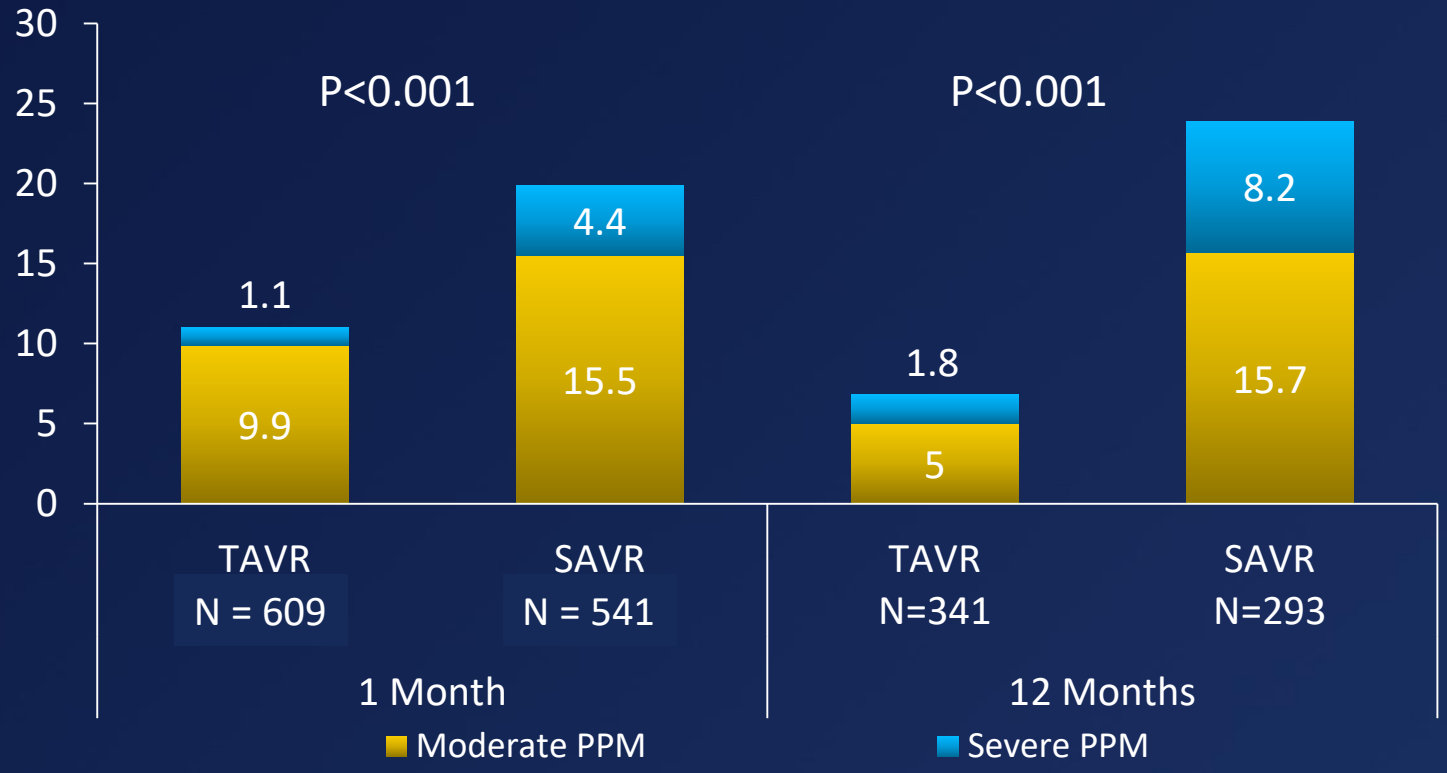
Evolut™ Low Risk Trial



Implanted population. Core lab assessments. * Statistically superior at all timepoints.

Prosthesis-Patient Mismatch

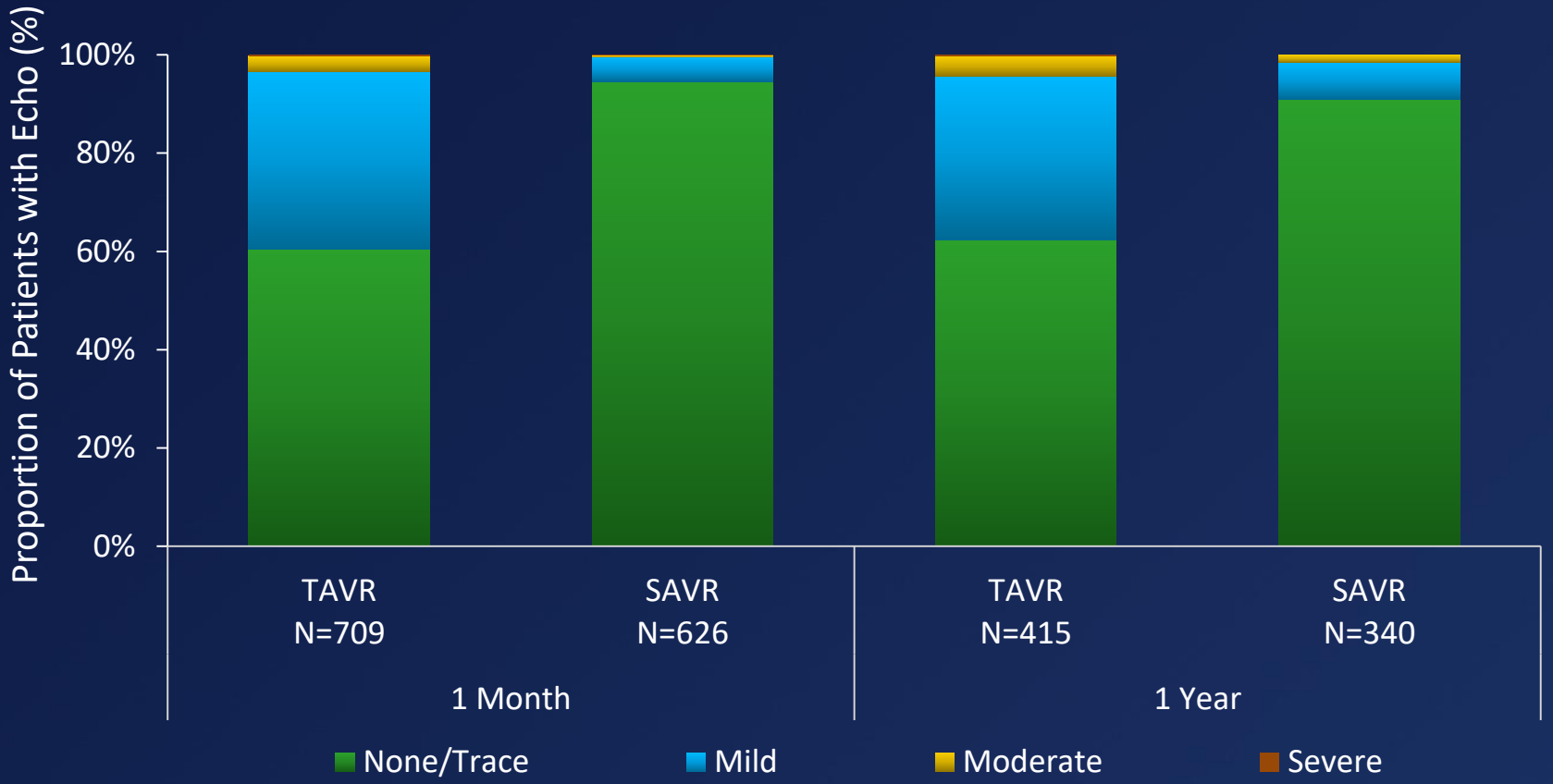
Evolut™ Low Risk Trial



Implant population. Core lab assessments.

Total Aortic Valve Regurgitation

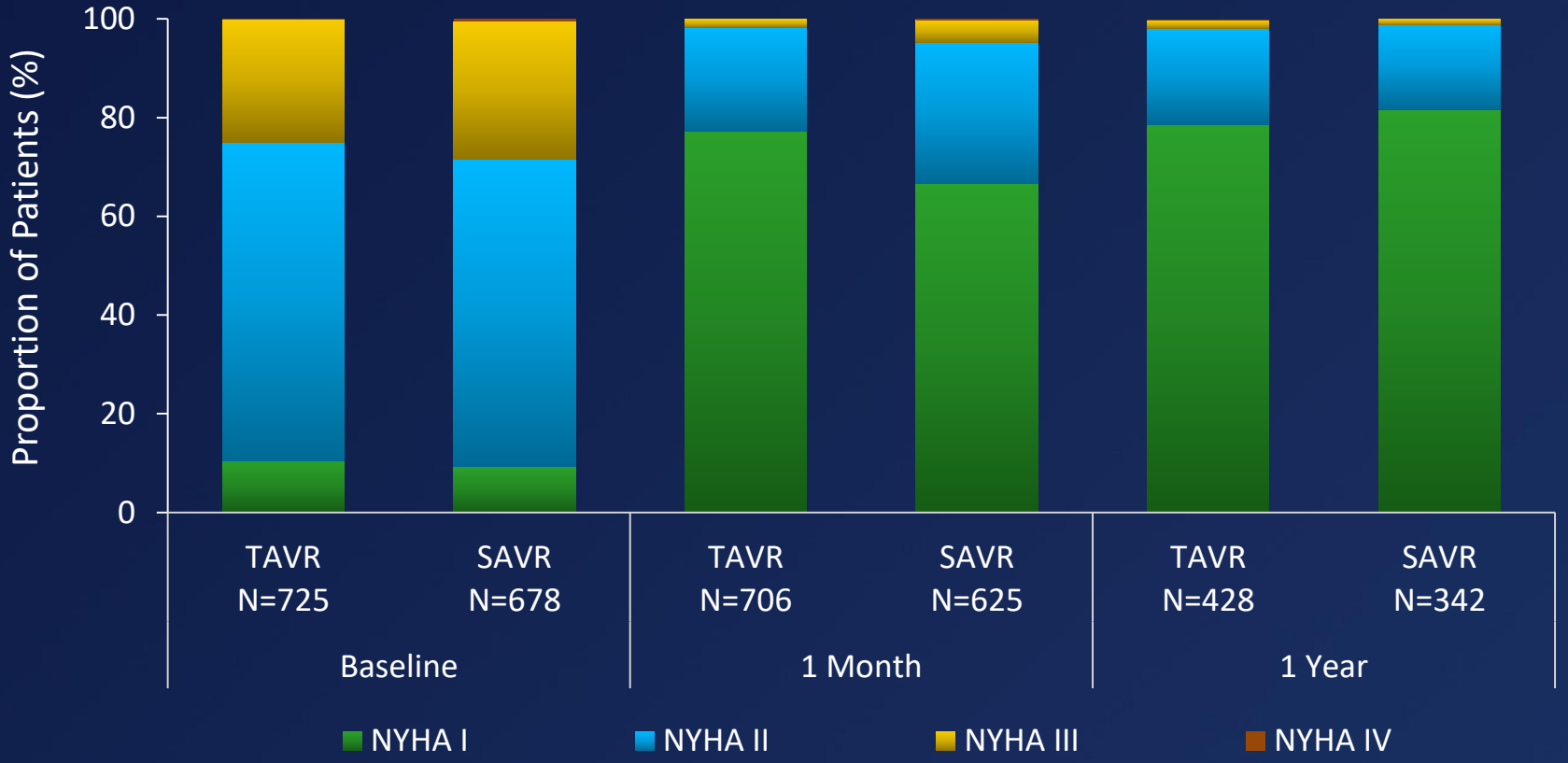
Evolut™ Low Risk Trial



Implant population. Core lab assessments.

NYHA Functional Class

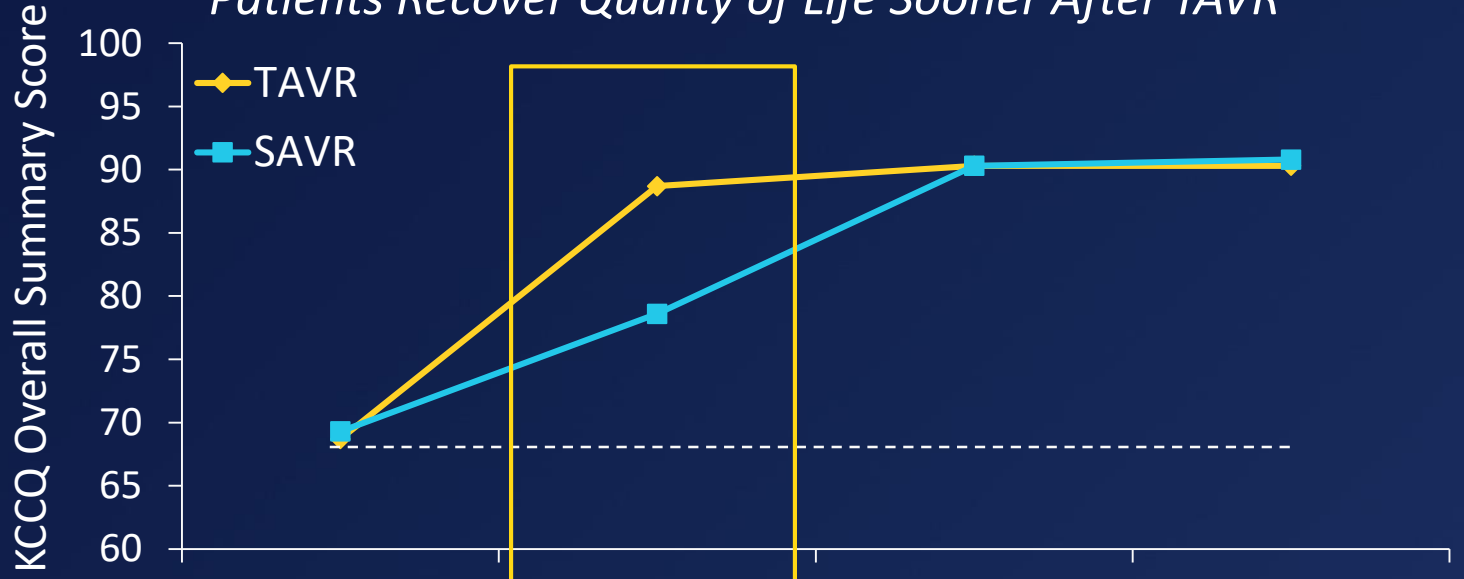
Evolut™ Low Risk Trial



KCCQ Summary Score

Evolut™ Low Risk Trial

Patients Recover Quality of Life Sooner After TAVR

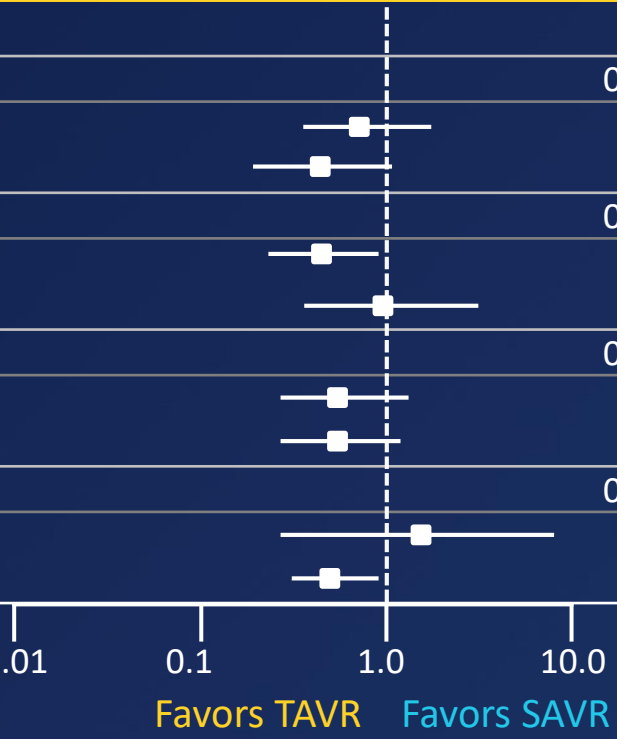


		Change from Baseline	
TAVR	20.0 ± 21.1	21.9 ± 21.2	22.2 ± 20.3
SAVR	9.1 ± 22.3	20.5 ± 20.5	20.9 ± 20.9
95% BCI for difference	(8.6, 13.2)	(-1.0, 3.8)	(-1.6, 4.3)

Subgroup Analysis for Death or Disabling Stroke at 1 Year

Evolut™ Low Risk Trial

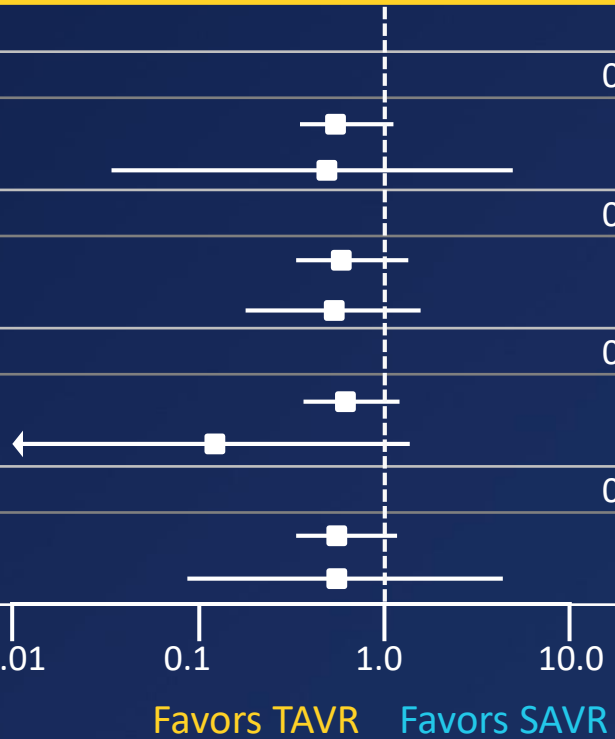
Subgroup	TAVR	SAVR	Hazard Ratio (95% BCI)	P for Interaction
	n/N (% KM rate at 1 Year)			
Age, years				0.50
< 75	10/351 (3.3)	14/350 (4.3)	0.70 (0.31-1.57)	
≥ 75	7/374 (2.2)	13/328 (4.9)	0.45 (0.18-1.14)	
Sex				0.22
Male	10/464 (2.5)	21/449 (5.4)	0.44 (0.21-0.93)	
Female	7/261 (3.0)	6/229 (2.9)	1.01 (0.34-3.02)	
BMI, kg/m^2				0.98
≤ 30	8/366 (2.5)	13/345 (4.4)	0.57 (0.24-1.38)	
> 30	9/359 (2.9)	14/333 (4.7)	0.56 (0.24-1.31)	
LVEF, %				0.28
≤ 50	3/56 (7.4)	2/56 (3.6)	1.44 (0.24-8.63)	
> 50	14/669 (2.3)	25/621 (4.6)	0.50 (0.26-0.97)	



Subgroup Analysis for Death or Disabling Stroke at 1 Year

Evolut™ Low Risk Trial

Subgroup	TAVR	SAVR	Hazard Ratio (95% BCI)	P for Interaction
	n/N (% KM rate at 1 Year)			
Peripheral Artery Disease				0.92
No	15/664 (2.7)	25/621 (4.6)	0.54 (0.29-1.03)	
Yes	1/54 (1.9)	2/56 (4.9)	0.46 (0.04-5.15)	
Diabetes Mellitus				0.81
No	12/497 (2.8)	18/471 (4.7)	0.59 (0.28-1.23)	
Yes	5/228 (2.3)	9/207 (4.4)	0.50 (0.17-1.50)	
Need for Revascularization				0.31
No	17/640 (3.1)	24/599 (4.7)	0.64 (0.34-1.18)	
Yes	0/85 (0.0)	3/79 (3.9)	0.13 (0.00-1.36)	
STS PROM, %				0.99
< 3	15/678 (2.5)	25/650 (4.4)	0.56 (0.29-1.06)	
≥ 3	2/47 (5.3)	2/28 (7.6)	0.55 (0.08-3.90)	



Summary

Evolut™ Low Risk Trial

- TAVR with self-expanding supra-annular valves was noninferior to surgery in patients with severe aortic stenosis at low surgical risk.
- At 30 days, TAVR showed a better safety and recovery profile than surgery, with less death or disabling stroke, less disabling stroke, shorter length of stay and better QOL while SAVR had fewer pacemakers implanted and less residual AR.
- At 1 year, both groups had excellent survival. TAVR showed fewer disabling strokes and heart failure rehospitalizations with superior hemodynamics manifest by lower gradients and larger EOAs.
- TAVR may be a preferred strategy to surgery in patients with severe aortic stenosis at low risk of surgical mortality.

Evolut™
Low Risk
Trial

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Transcatheter Aortic-Valve Replacement with a Self-Expanding Valve in Low-Risk Patients

Jeffrey J. Popma, M.D., G. Michael Deeb, M.D., Steven J. Yakubov, M.D., Mubashir Mumtaz, M.D., Hemal Gada, M.D., Daniel O'Hair, M.D., Tanvir Bajwa, M.D., John C. Heiser, M.D., William Merhi, D.O., Neal S. Kleiman, M.D., Judah Askew, M.D., Paul Sorajja, M.D., Joshua Rovin, M.D., Stanley J. Chetcuti, M.D., David H. Adams, M.D., Paul S. Teirstein, M.D., George L. Zorn, III, M.D., John K. Forrest, M.D., Didier Tchétché, M.D., Jon Resar, M.D., Antony Walton, M.D., Nicolo Piazza, M.D., Ph.D., Basel Ramlawi, M.D., Newell Robinson, M.D., George Petrossian, M.D., Thomas G. Gleason, M.D., Jae K. Oh, M.D., Michael J. Boulware, Ph.D., Hongyan Qiao, Ph.D., Andrew S. Mugglin, Ph.D., and Michael J. Reardon, M.D., for the Evolut Low Risk Trial Investigators*

Evolut™ Low Risk Trial

Thank you to the Evolut Low Risk patients, site personnel, investigators and sponsor for making this and our series of randomized trials possible