

# Primary Results From the Evolut Low Risk Trial

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For the Evolut Low Risk Trial Investigators

# Disclosure Statement of Financial Interests

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

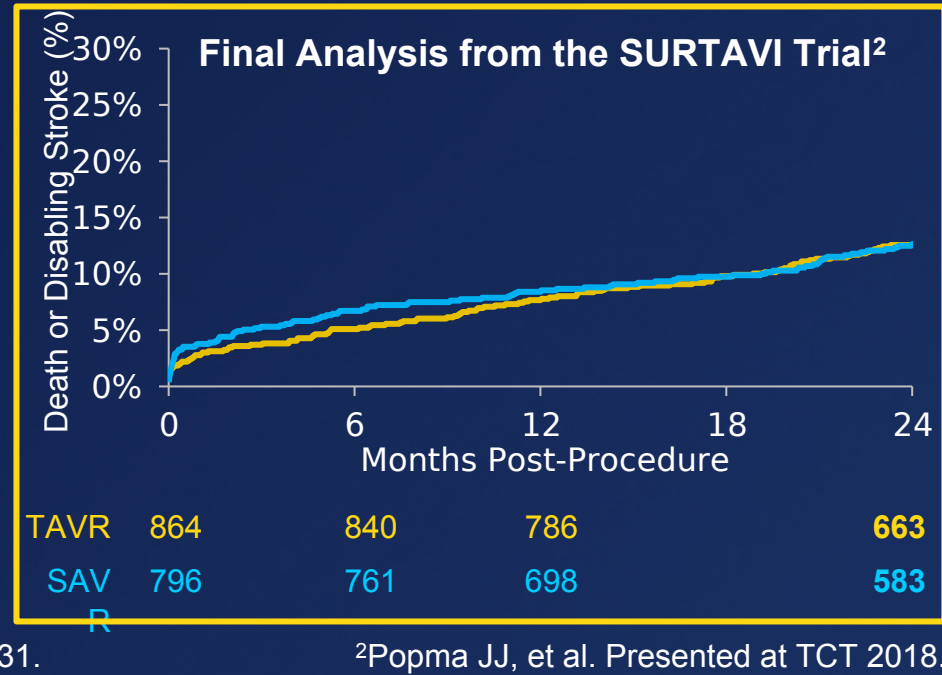
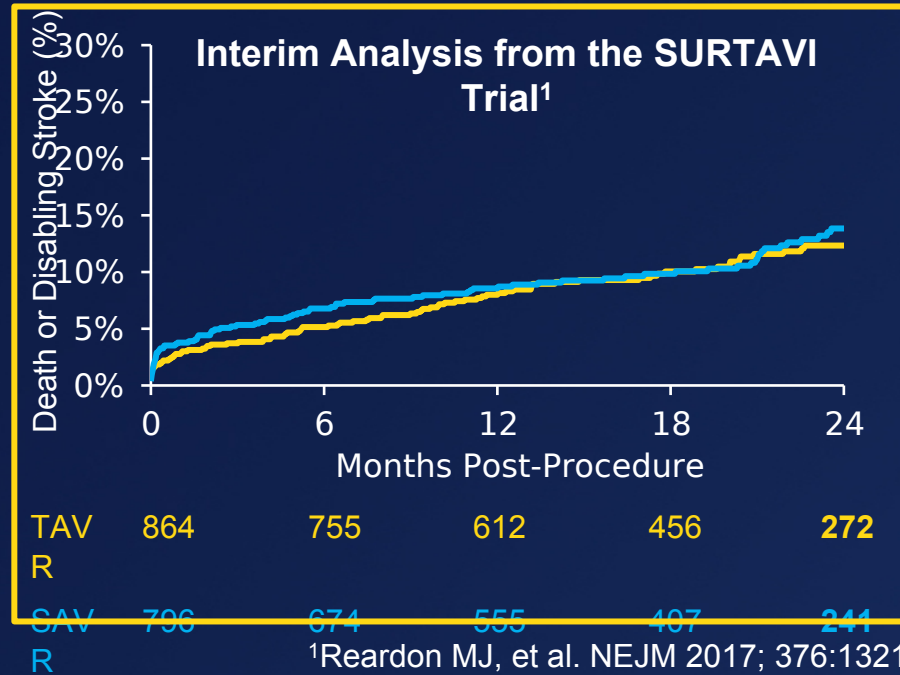
- We performed a series of randomized controlled trials in patients with severe aortic stenosis across a spectrum of surgical risk.
- In high-risk patients, TAVR was superior to SAVR for the primary endpoint to 2 years<sup>1</sup> and similar at 5 years<sup>2</sup>



<sup>1</sup>Reardon et al. J Am Coll Cardiol 2015; 66: 113-21; <sup>2</sup>Gleason, et al. J Am Coll Cardiol 2018; 72:

# Background

- 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.



# Objective

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

**Principal 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

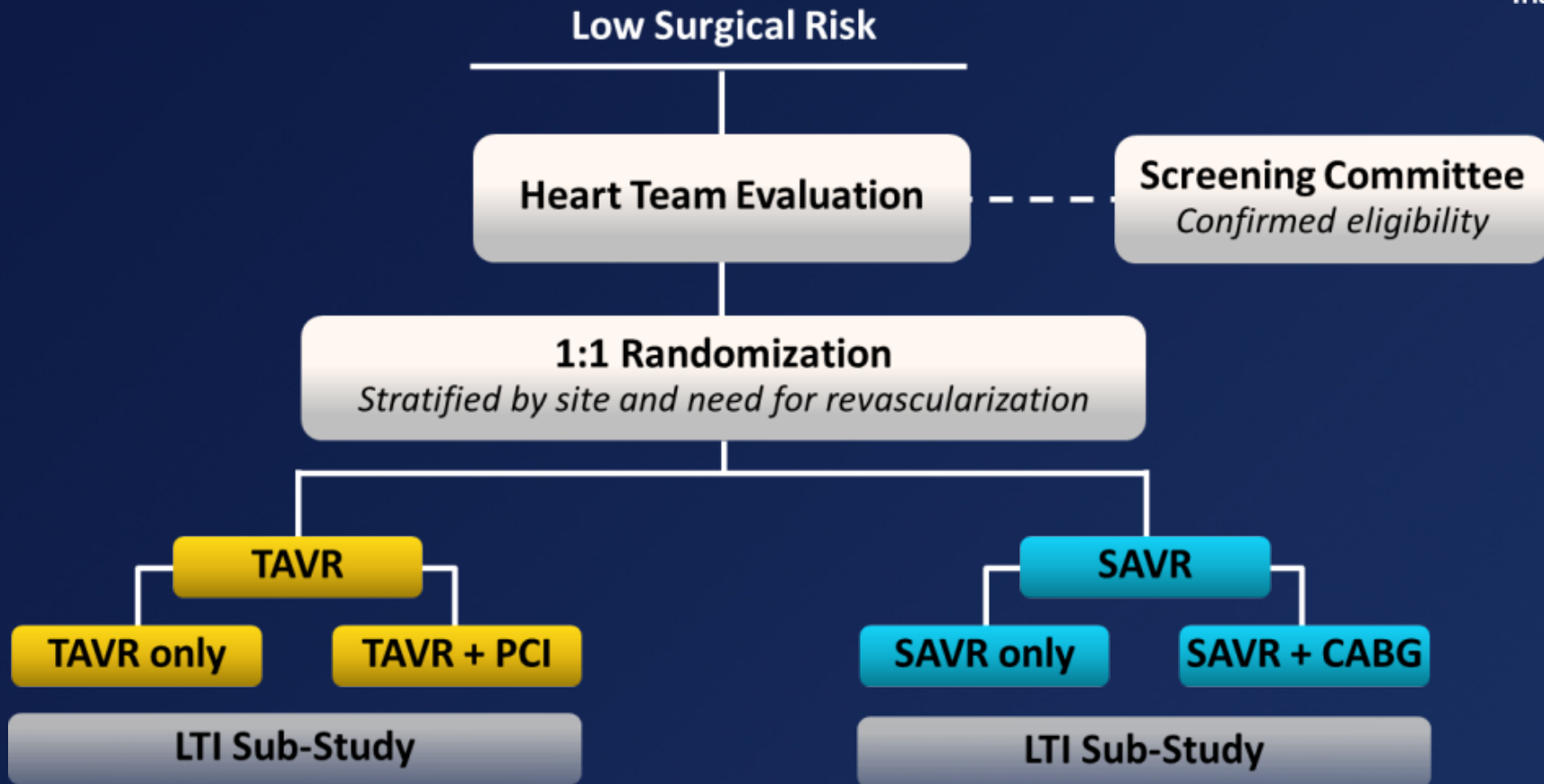
**Sponsor:** Medtronic



# Australia, Canada, Europe, Japan and New Zealand



# Study Design



# Study Endpoints

## Primary Safety and Effectiveness Endpoint All-cause mortality or disabling stroke at 2 years

### Hierarchical Powered Secondary Endpoints

#### Noninferiority

- 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

#### Superiority

- 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

# Key Inclusion Criteria

## Symptomatic severe AS<sup>1</sup>:

- Aortic valve area  $\leq 1.0$  cm<sup>2</sup> (or aortic valve area index  $< 0.6$  cm<sup>2</sup>/m<sup>2</sup>), **OR** mean gradient  $\geq 40$  mmHg **OR** Vmax  $\geq 4$  m/sec at rest

## Asymptomatic very severe AS<sup>1</sup>:

- Aortic valve area  $\leq 1.0$  cm<sup>2</sup> (or aortic valve area index  $< 0.6$  cm<sup>2</sup>/m<sup>2</sup>), **AND** Vmax  $\geq 5$  m/sec or mean gradient  $\geq 60$  mmHg at rest
- Aortic valve area of  $\leq 1.0$  cm<sup>2</sup> (or aortic valve area index of  $\leq 0.6$  cm<sup>2</sup>/m<sup>2</sup>), **AND** a mean gradient  $\geq 40$  mmHg or Vmax  $\geq 4.0$  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  $\leq 1.0$  cm<sup>2</sup> (or aortic valve area index of  $\leq 0.6$  cm<sup>2</sup>/m<sup>2</sup>), **AND** mean gradient  $\geq 40$  mmHg, **OR** Vmax  $\geq 4.0$  m/sec by transthoracic echocardiography at rest, **AND** LVEF  $< 50\%$ .

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

<sup>1</sup>Nishimura RA, et al. Circulation. 2014;129:2440-92.

# Key Exclusion Criteria

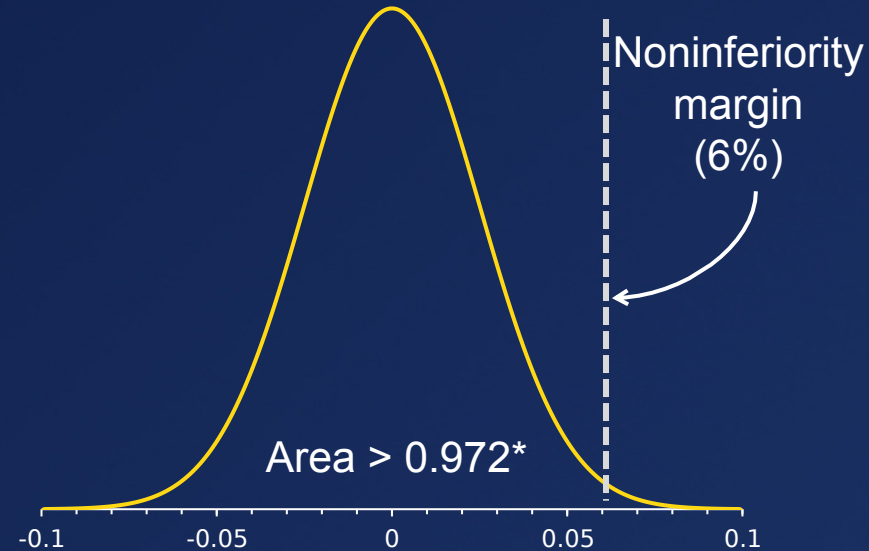
- Contraindication for placement of a bioprosthetic valve
- Multivessel coronary artery disease with SYNTAX score >22
- Bicuspid aortic valve verified by imaging
- Hypersensitivity or contraindication to all anticoagulation/ antiplatelet regimens
- Any PCI or peripheral intervention within 30 days prior 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*

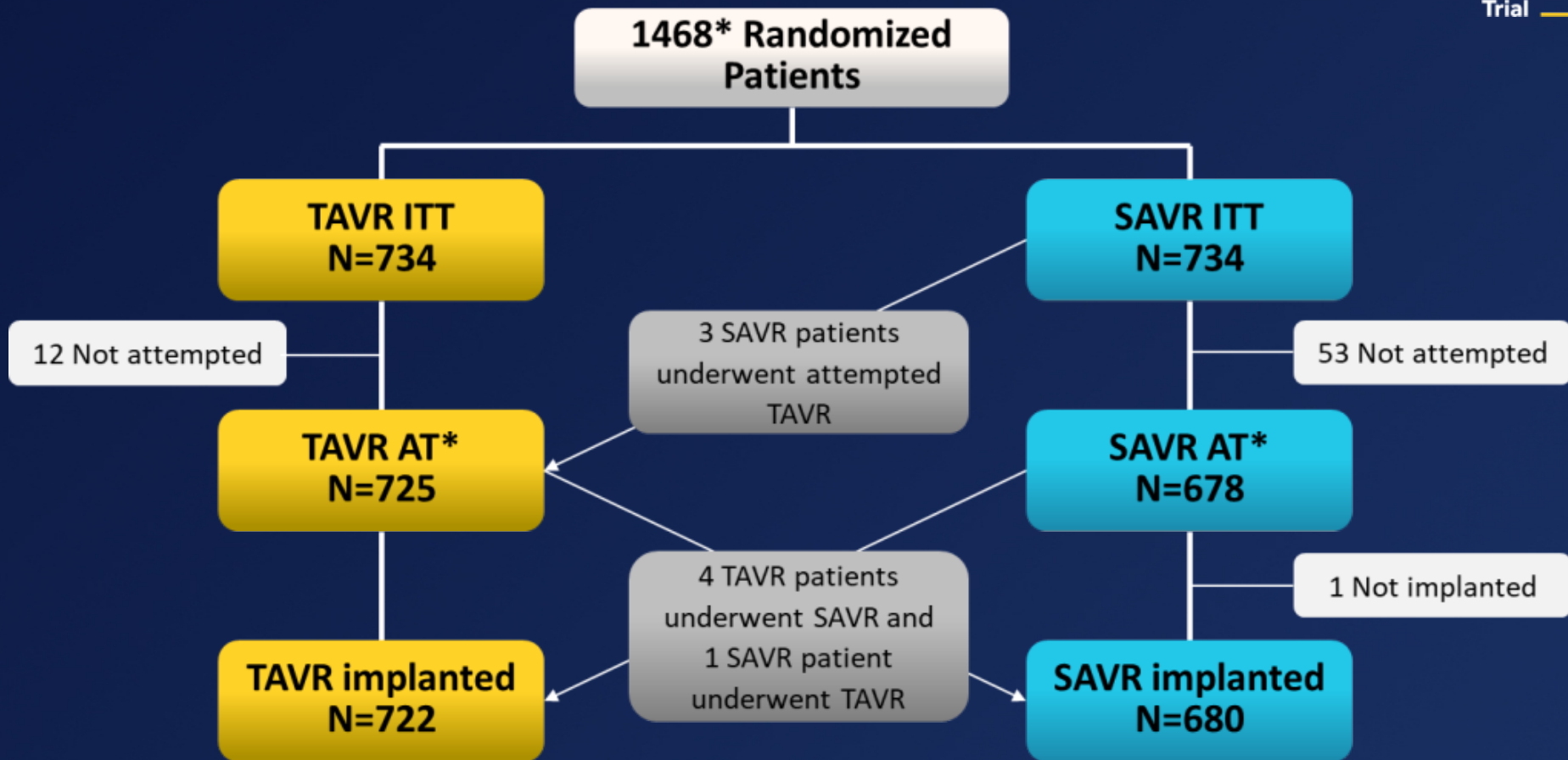
- This was a randomized, multinational, noninferiority trial.
- The Bayesian adaptive design prespecified an “early-win” interim analysis when 850 patients reached 1-year follow-up.
- The estimated sample size was 1200 patients.
- The 2-year primary analysis cohort comprised all patients with an attempted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

Posterior Distribution of the Difference  
(TAVR rate – SAVR rate)



\*Selected to maintain  $\alpha < 0.05$

# Patient Flow



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

# Study Timeline and Valves Studied



Primary Endpoint Assessment Dec. 27, 2018



## Vascular access

- § 99% transfemoral
- § 0.6% subclavian
- § 0.4% direct aortic

CoreValve 31 =  
3.6%

Evolut R = 74.1%

Evolut PRO =  
22.3%

\*For this analysis

# RESULTS

# Baseline Characteristics

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 <sup>2</sup>	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

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 <sup>2</sup>	0.8 ± 0.2	0.8 ± 0.2
Left ventricular ejection fraction, %	61.7 ± 7.9	61.9 ± 7.7

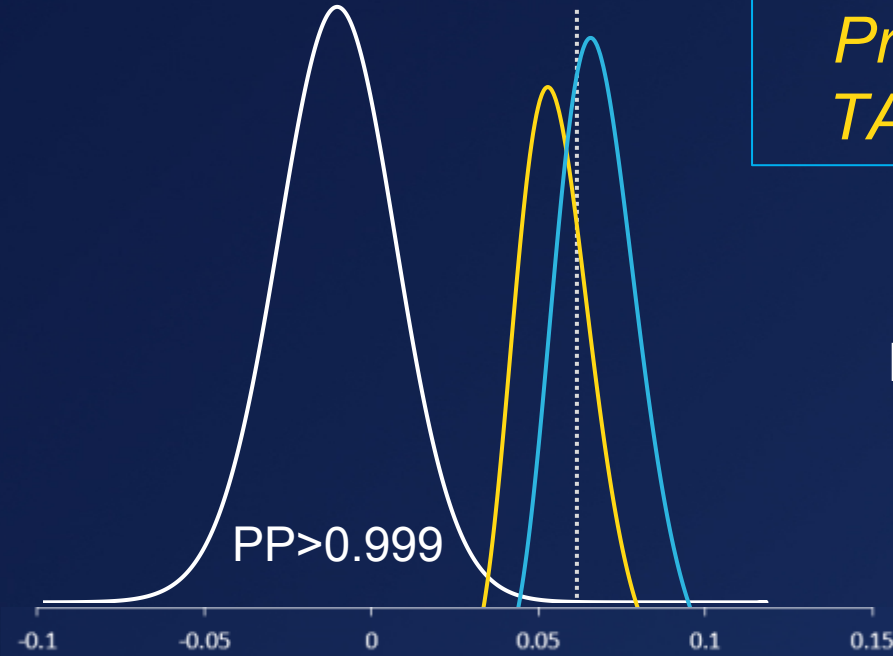
There are no significant differences between groups.

# TAVR Procedural Data

%	TAVR (N=724)
General anesthesia	56.9
Iliofemoral access	99.0
Emboic 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



*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% BCIs; -4.9, 2.1)

# Hierarchical Secondary Endpoints

All Noninferiority and Superiority Endpoints Met

	TAVR	SAVR	Difference TAVR–SAVR (90% BCI)	Posterior Probability	
<b>Noninferiority (margin)</b>					
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 <sup>2</sup> )	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	✓
<b>Superiority</b>					
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 <sup>2</sup>	2.3 ± 0.7	2.0 ± 0.6	0.3 (0.2, 0.4)	> 0.999	✓
Mean KCCQ change (30 Days–	20.0 ± 21.1	9.1 ± 22.3	10.9 (8.6,	> 0.999	✓

# Clinical Outcomes at 30 Days

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

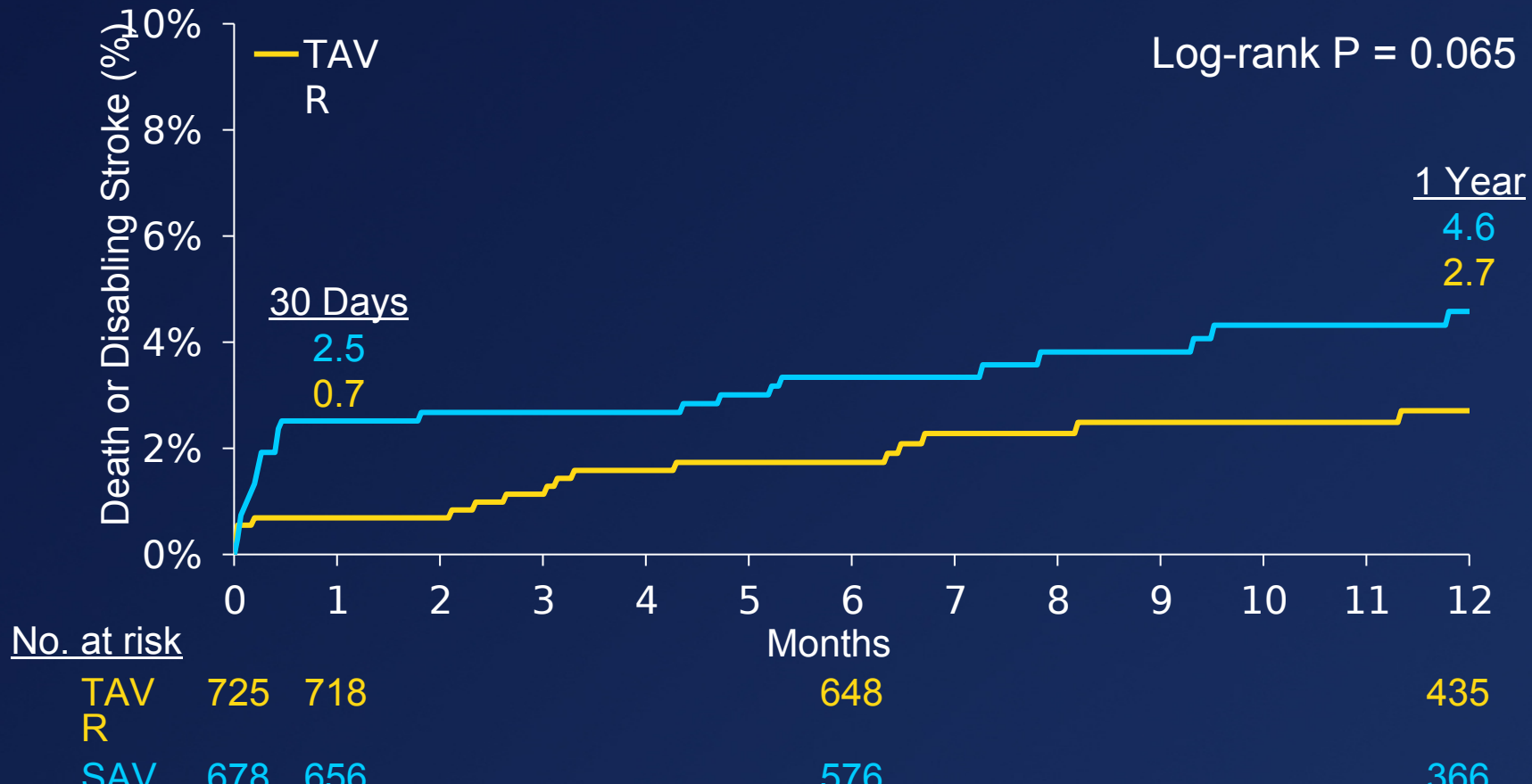
# Clinical Outcomes at 1 Year

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)
<b>Disabling stroke*</b>	<b>0.8</b>	<b>2.4</b>	<b>(-3.1, -0.3)</b>
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)
<b>Heart failure hospitalization*</b>	<b>3.2</b>	<b>6.5</b>	<b>(-5.9, -1.0)</b>

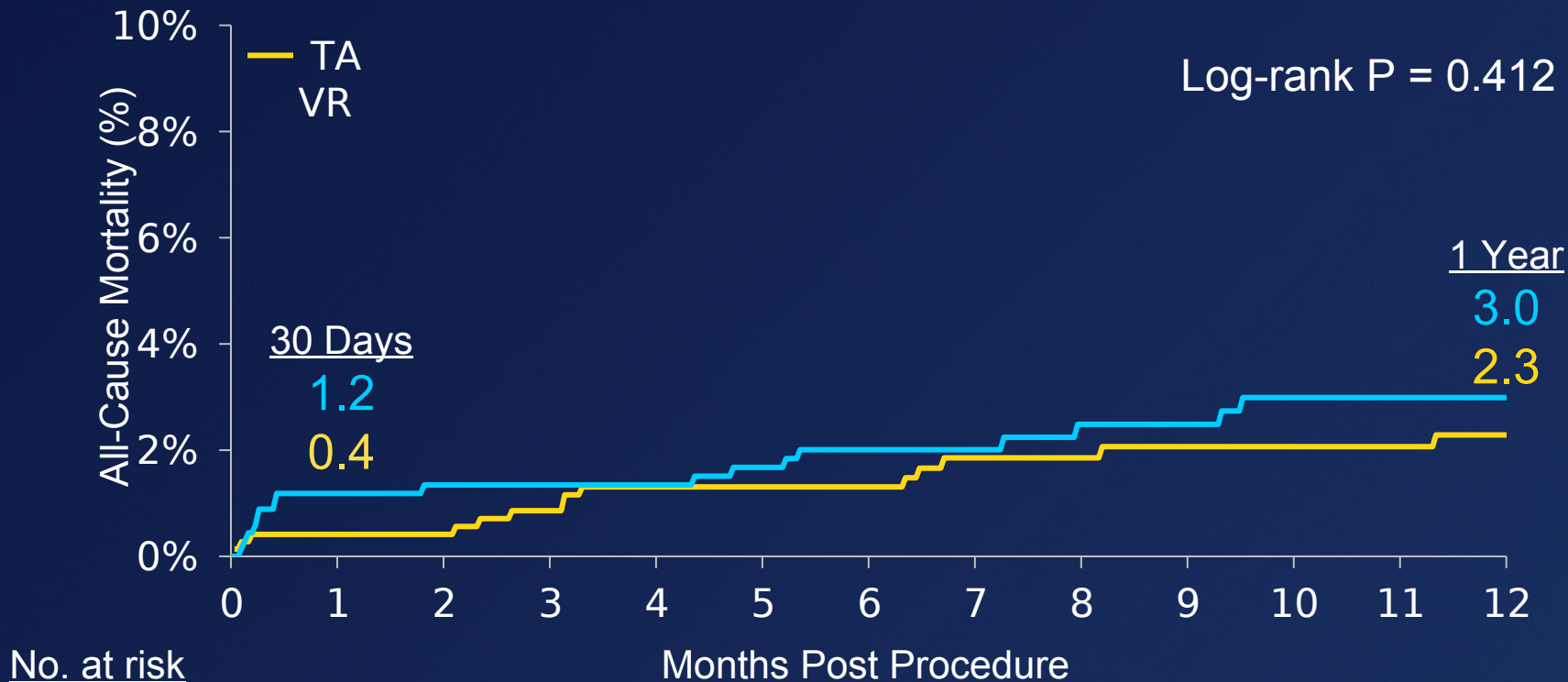
\* Significantly favors TAVR

BCI = Bayesian credible interval

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



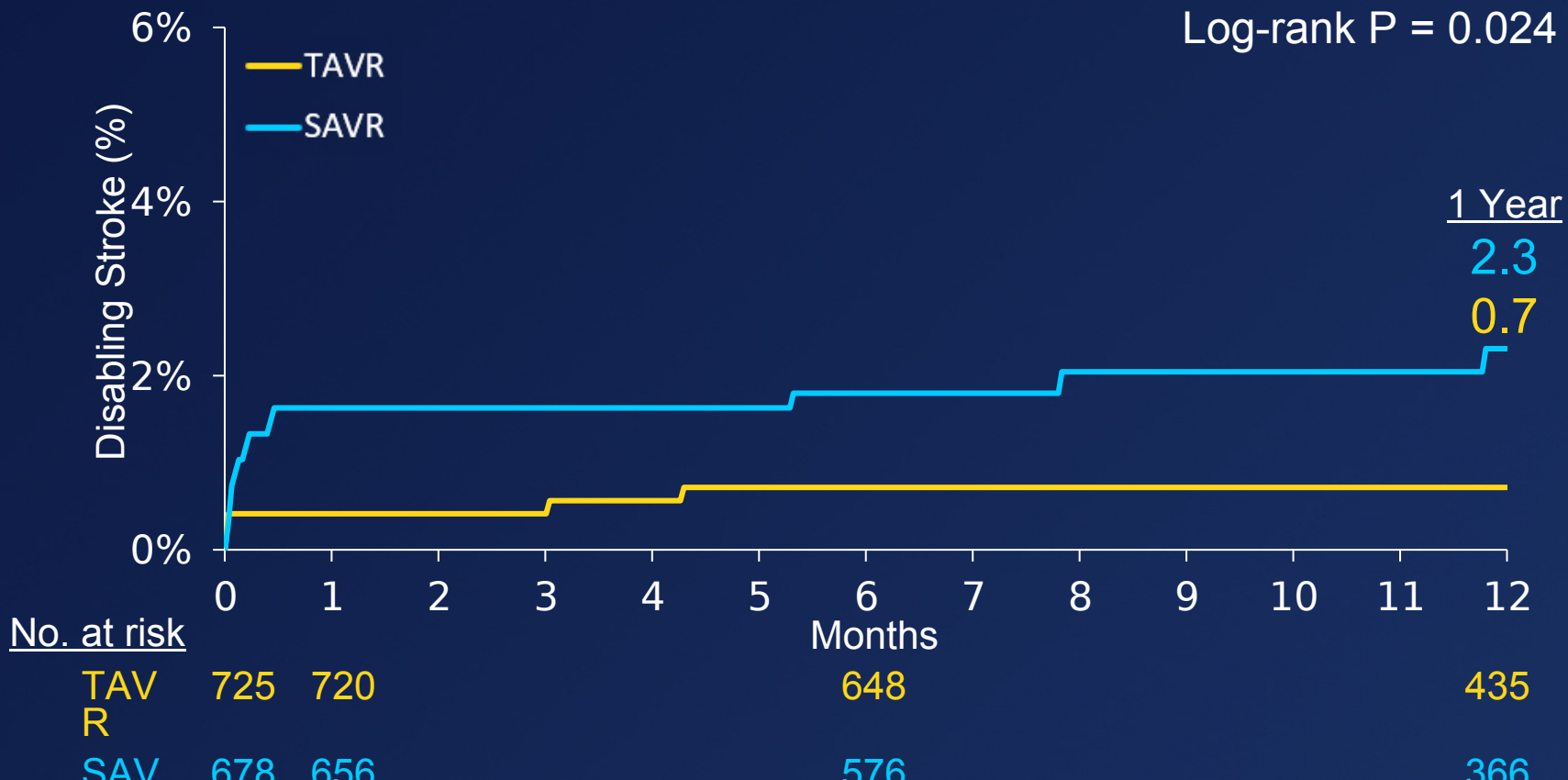
# K-M Rates of All-Cause Mortality at 1 Year



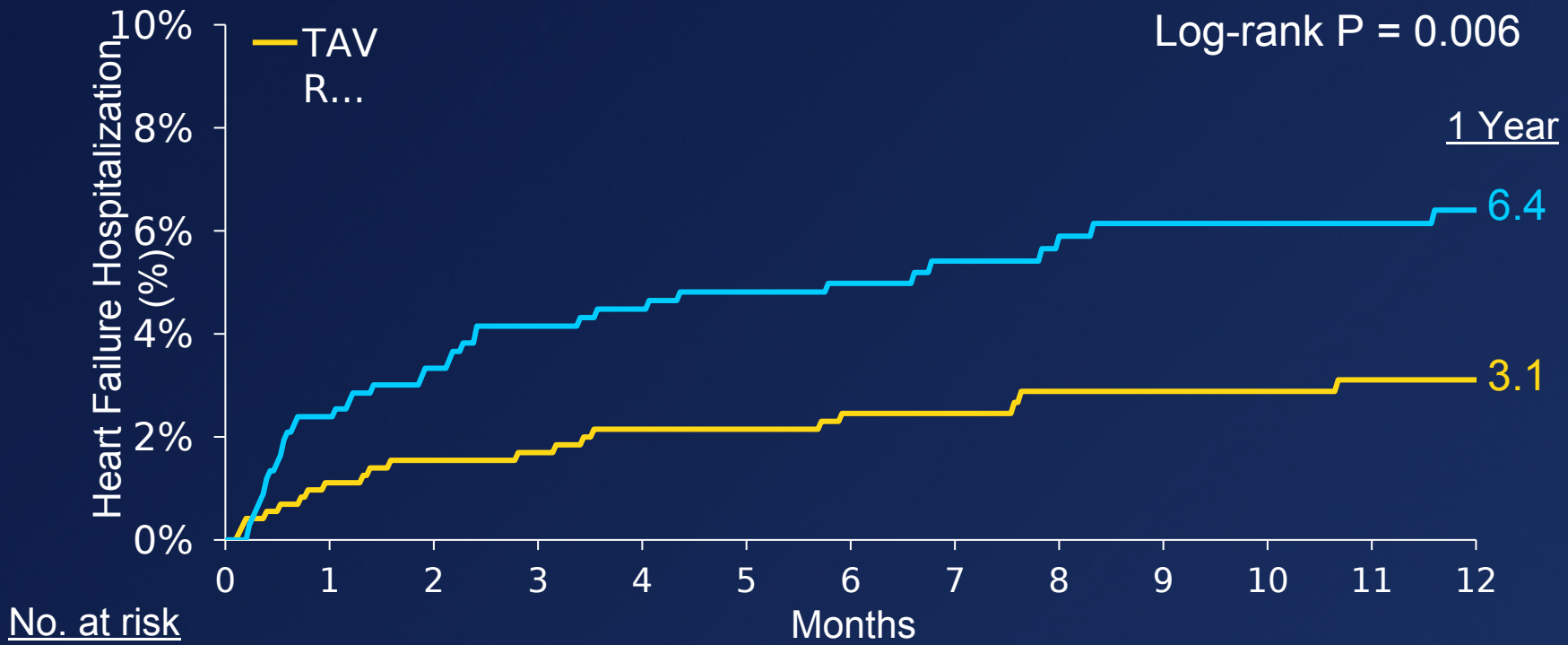
No. at risk

	0	1	2	3	4	5	6	7	8	9	10	11	12
TAVR	725	720					651						435
SAVR	678	665					583						373

# K-M Disabling Stroke at 1 Year



# K-M Heart Failure Hospitalization at 1 Year

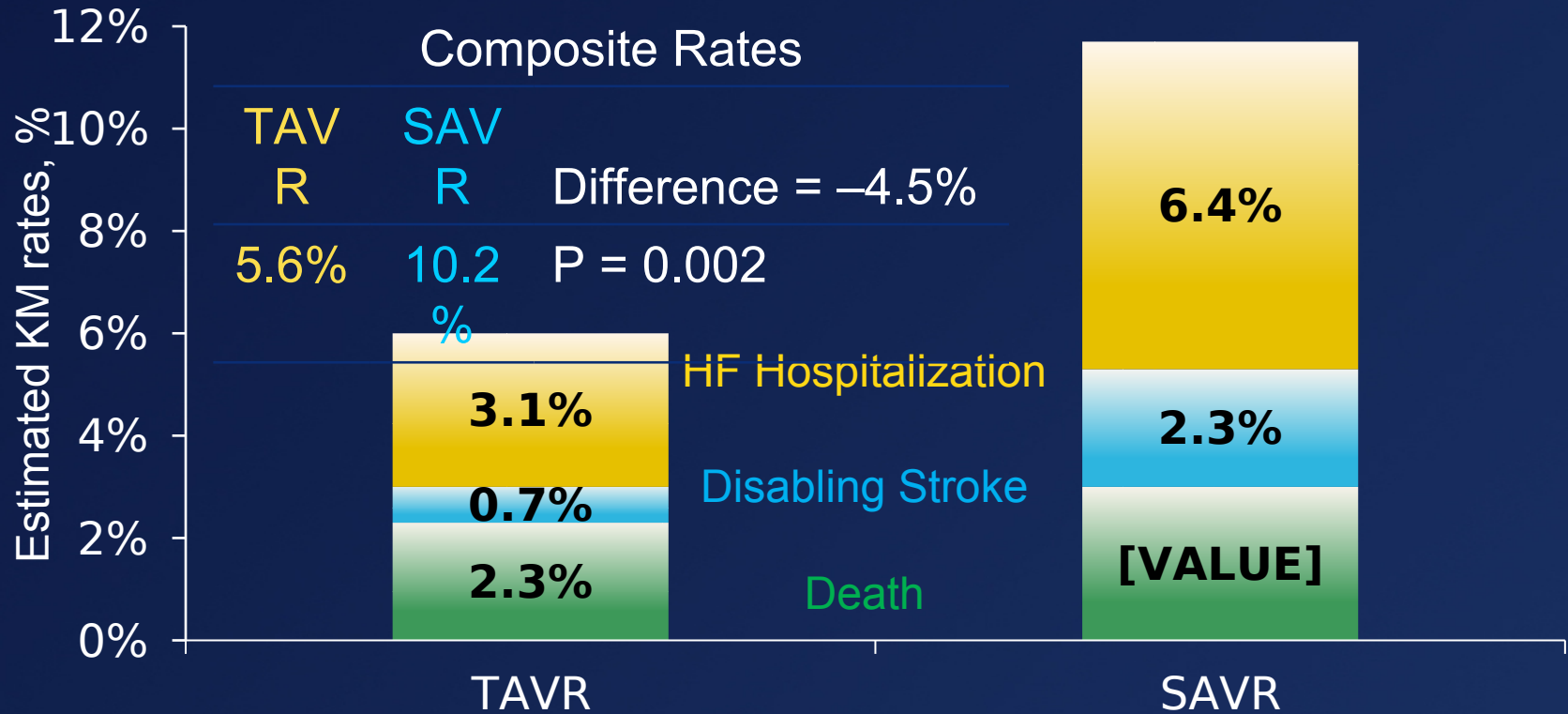


TAV	725	712	636	420
R...				

SAV	678	649	561	358
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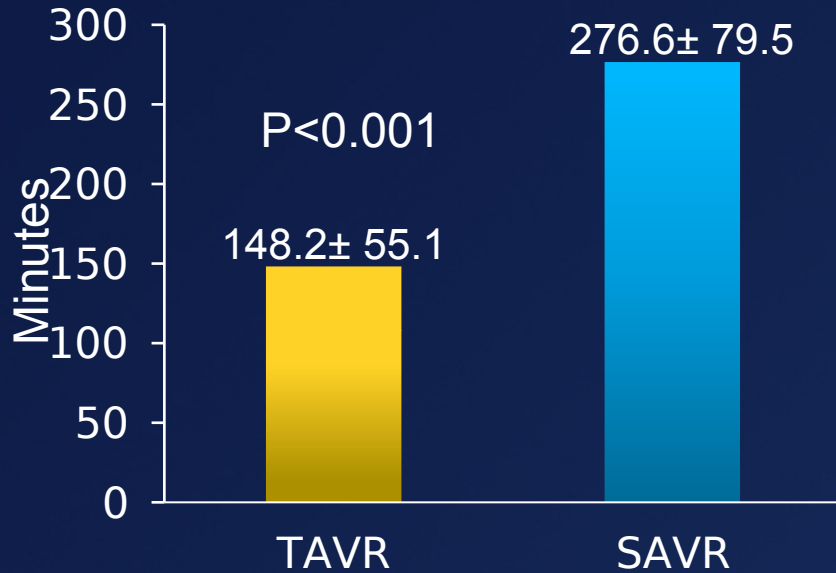
# Clinical Implications

Death, Disabling Stroke and Heart Failure Hospitalizations to 1 Year

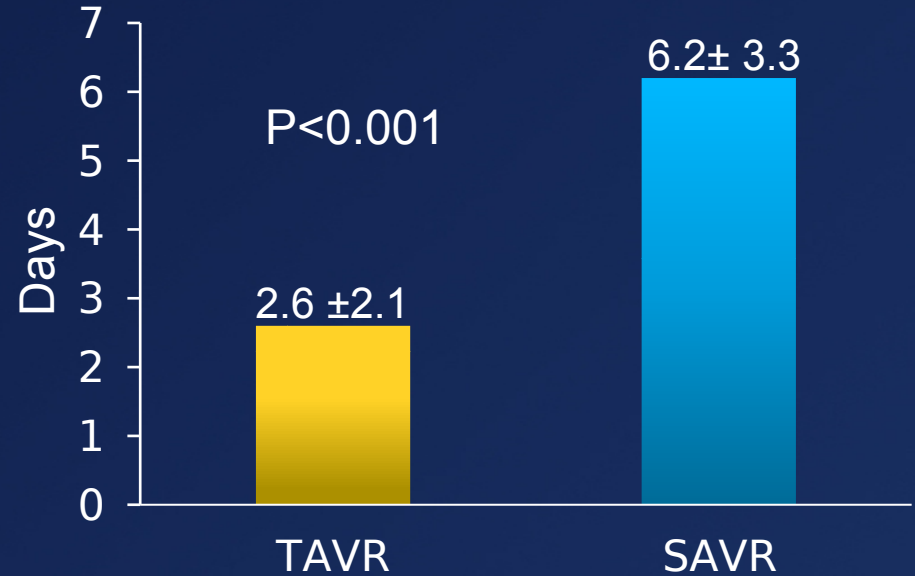


# Procedural Time and Length of Stay

## Time in Cath Lab or OR

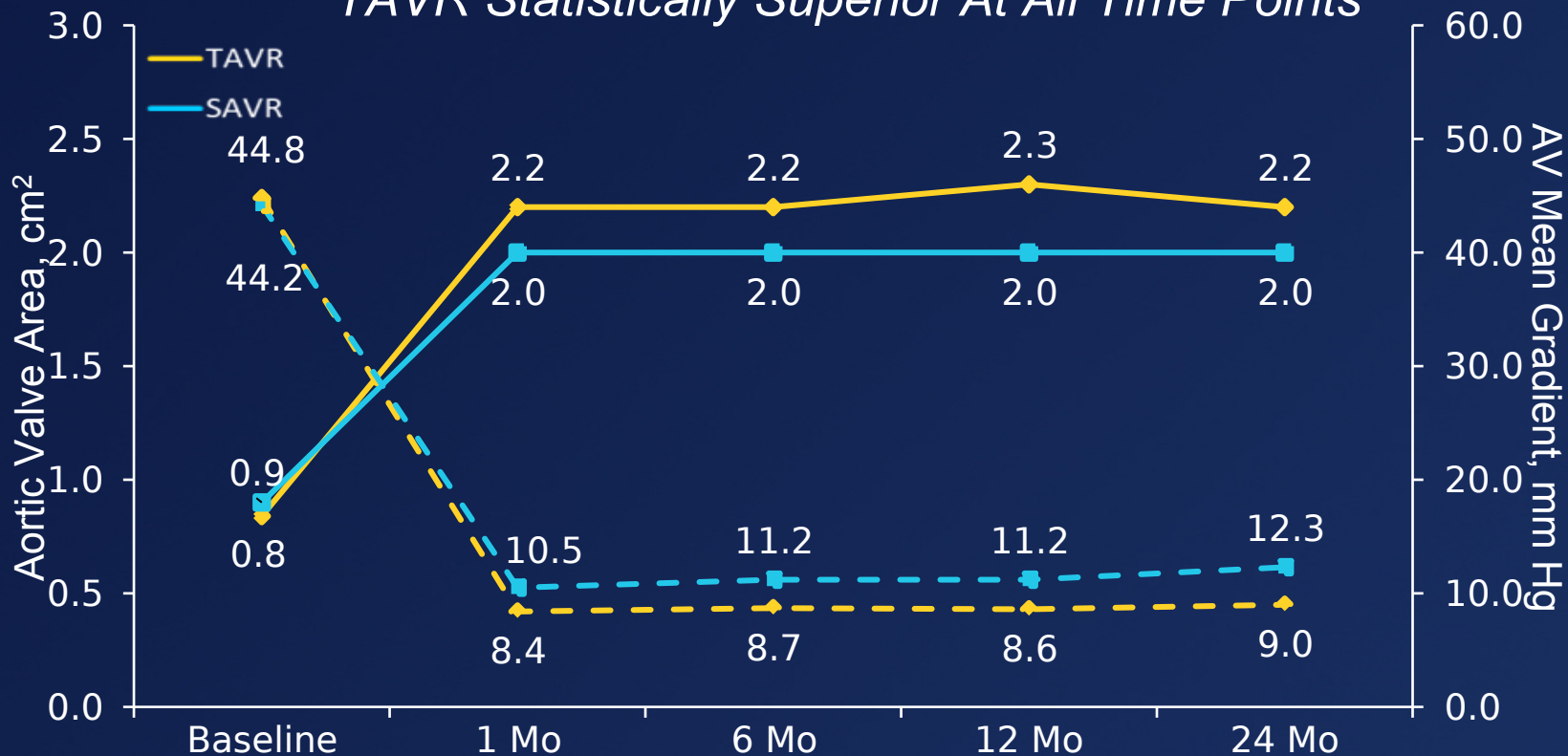


## Hospital Length of Stay

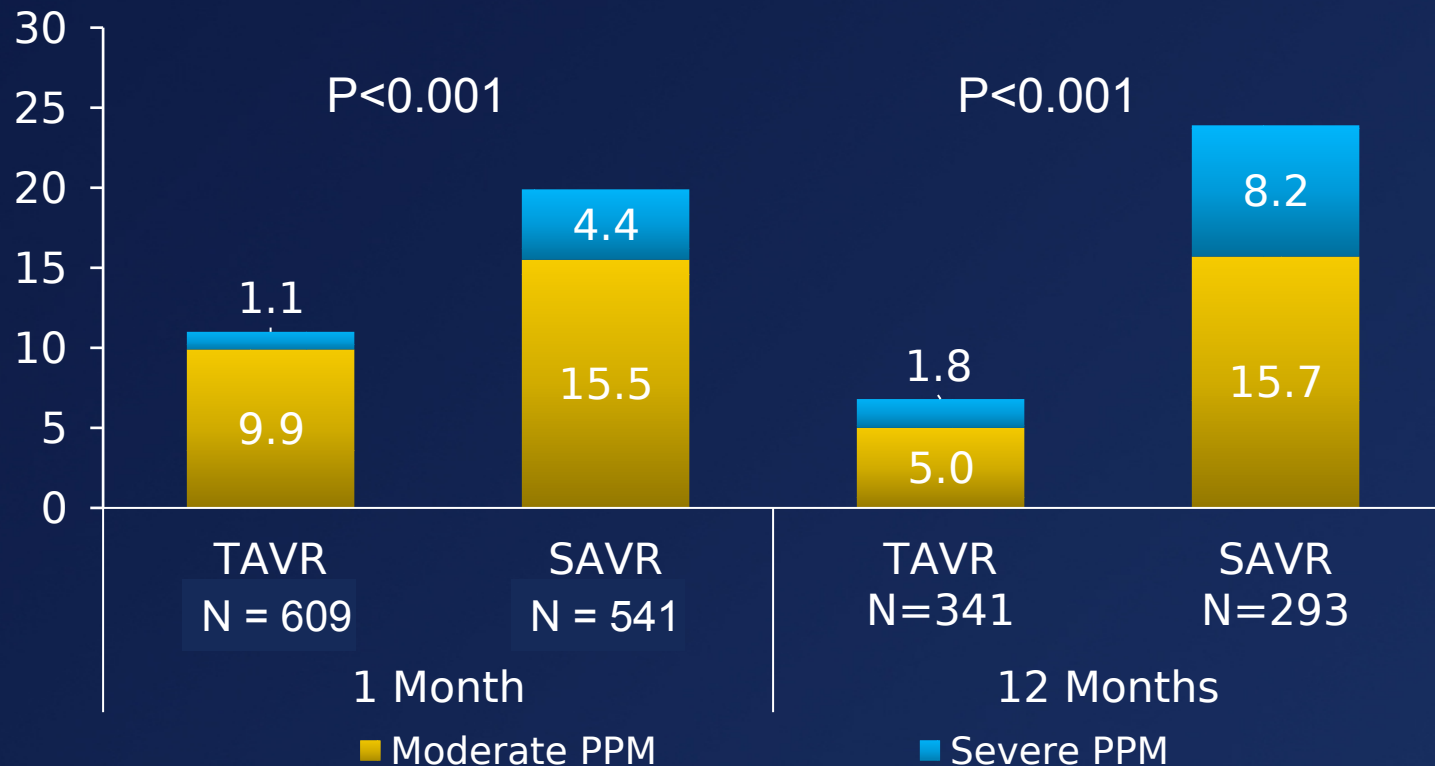


# Valve Hemodynamics

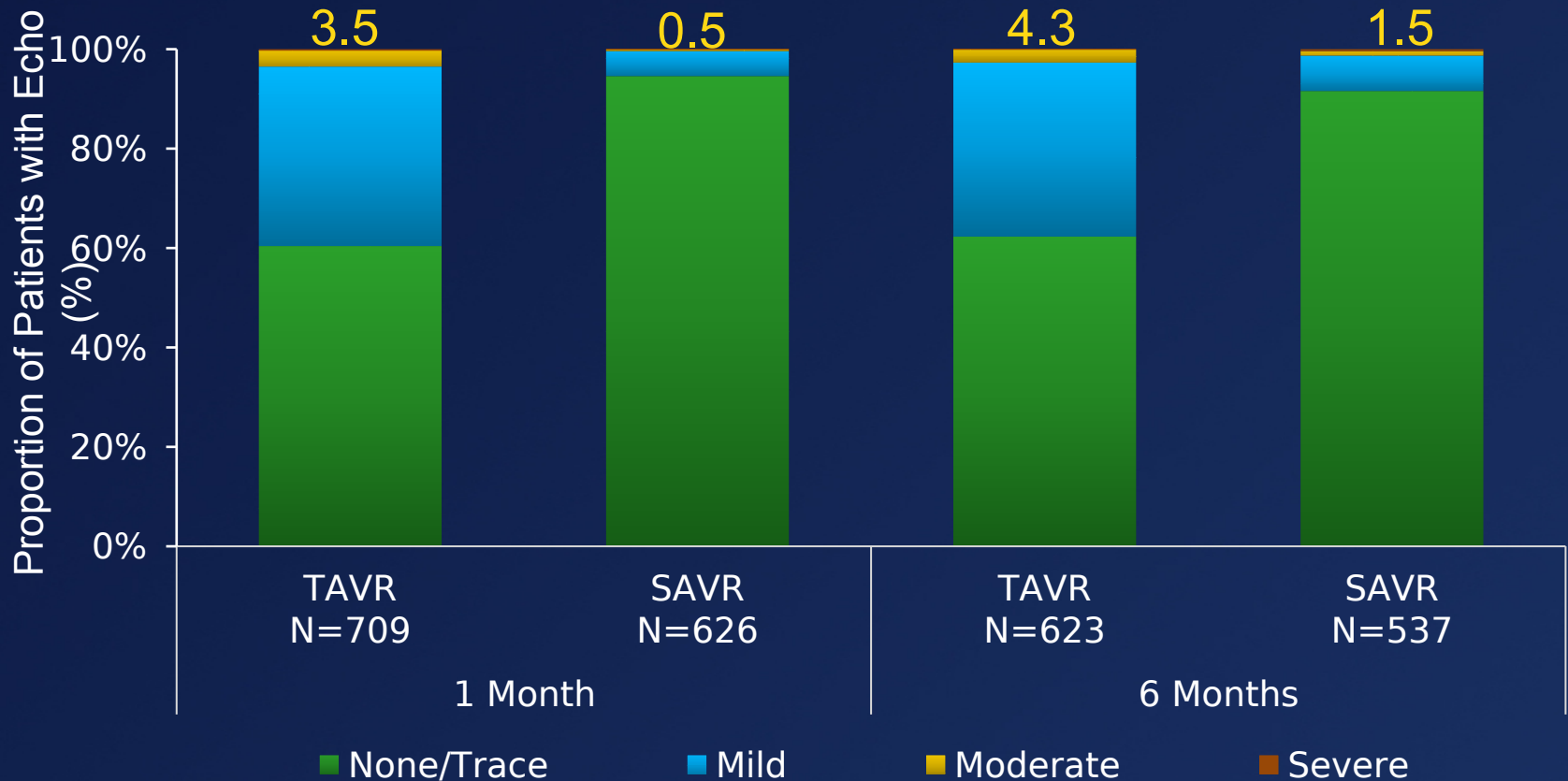
*TAVR Statistically Superior At All Time Points*



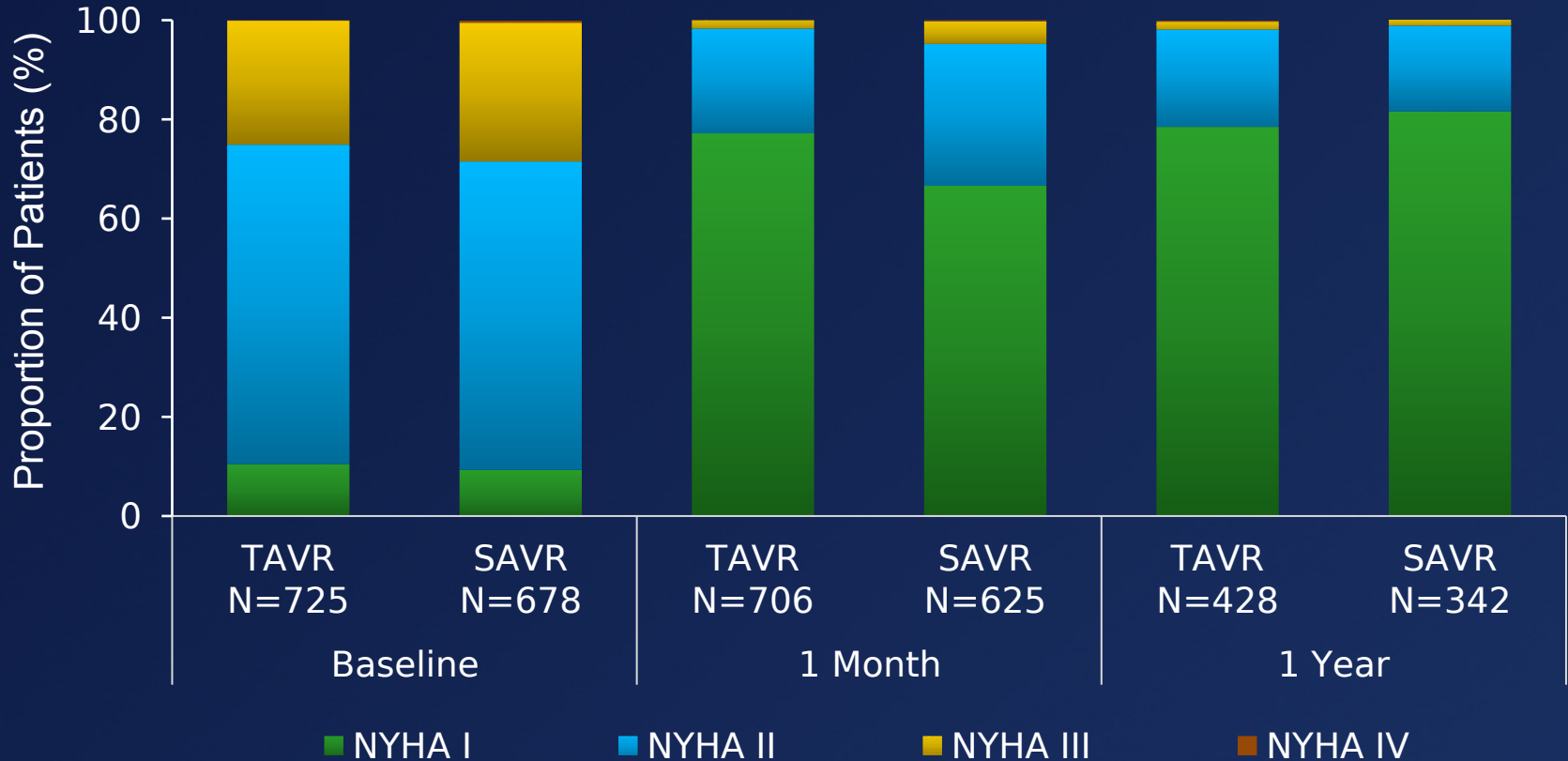
# Prosthesis-Patient Mismatch



# Total Aortic Valve Regurgitation

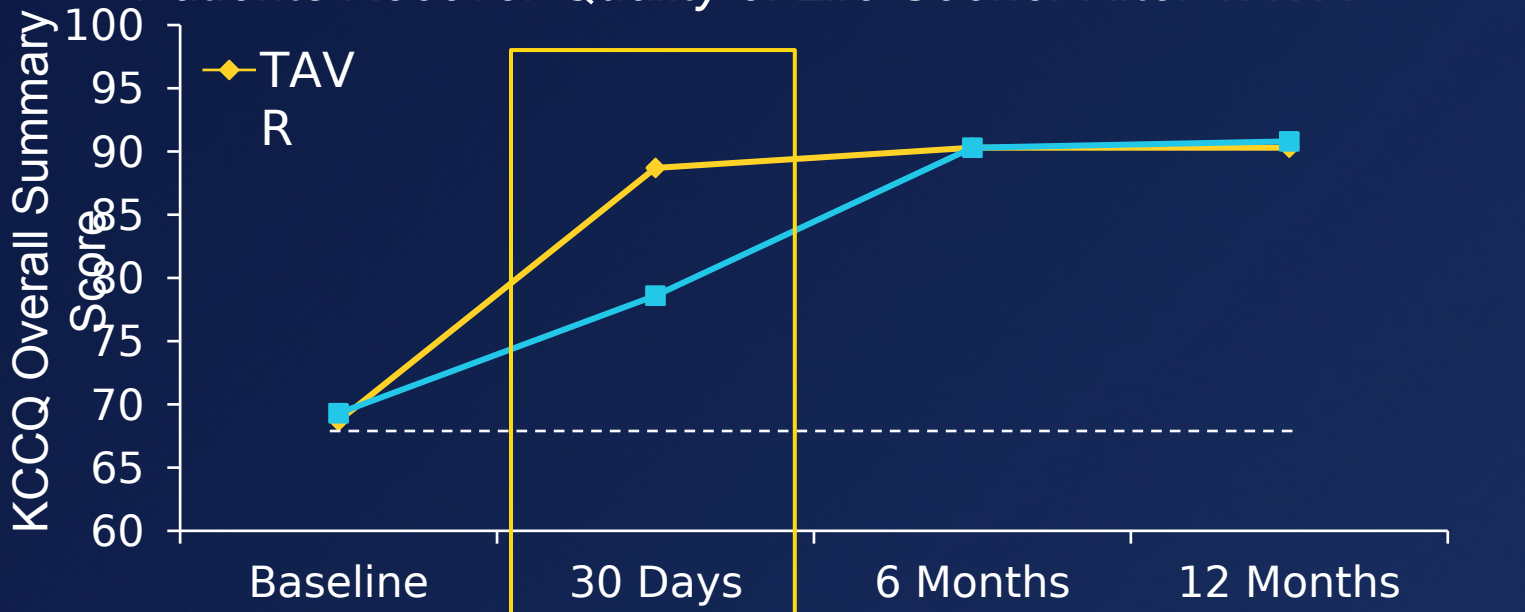


# NYHA Functional Class



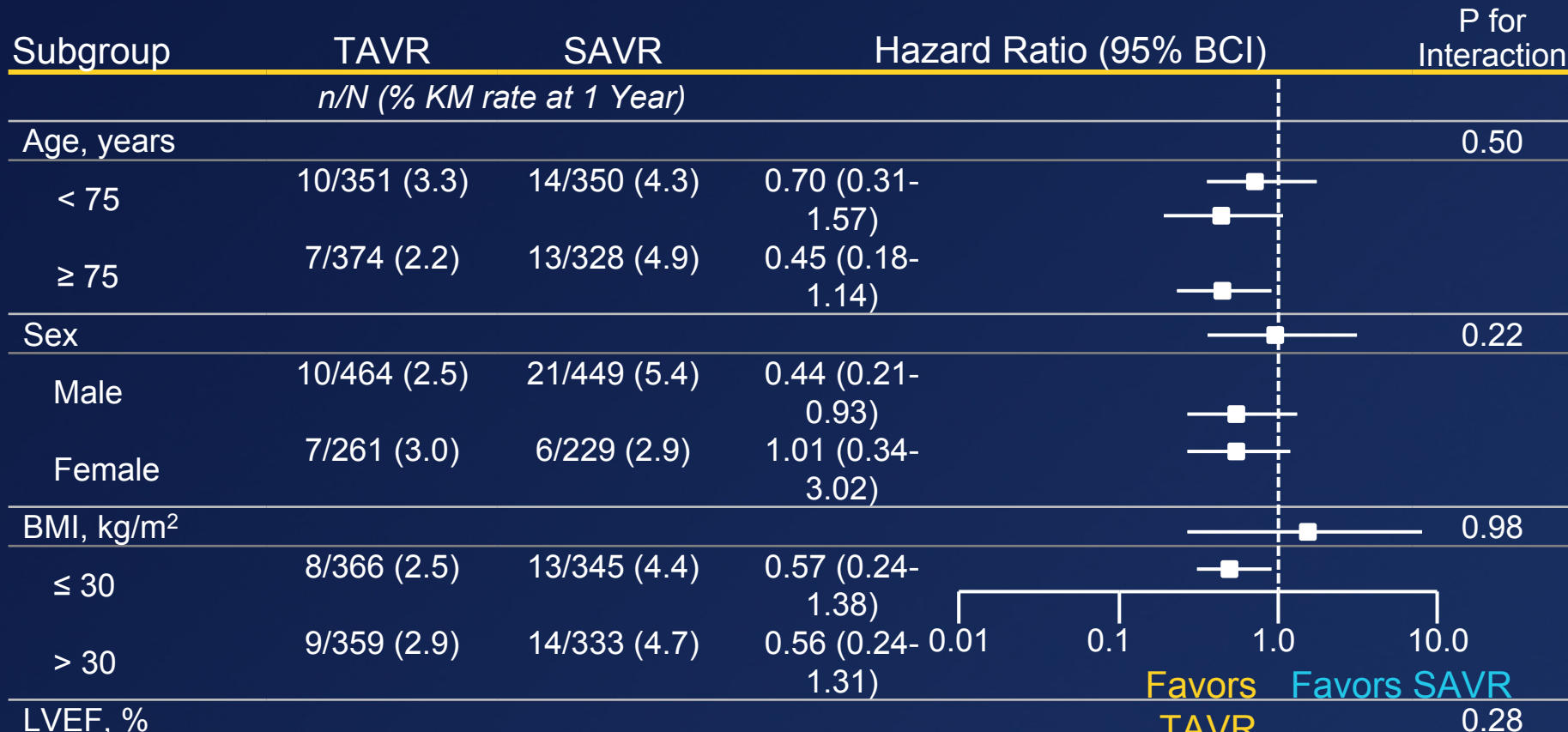
# KCCQ Summary Score

*Patients Recover Quality of Life Sooner After TAVR*

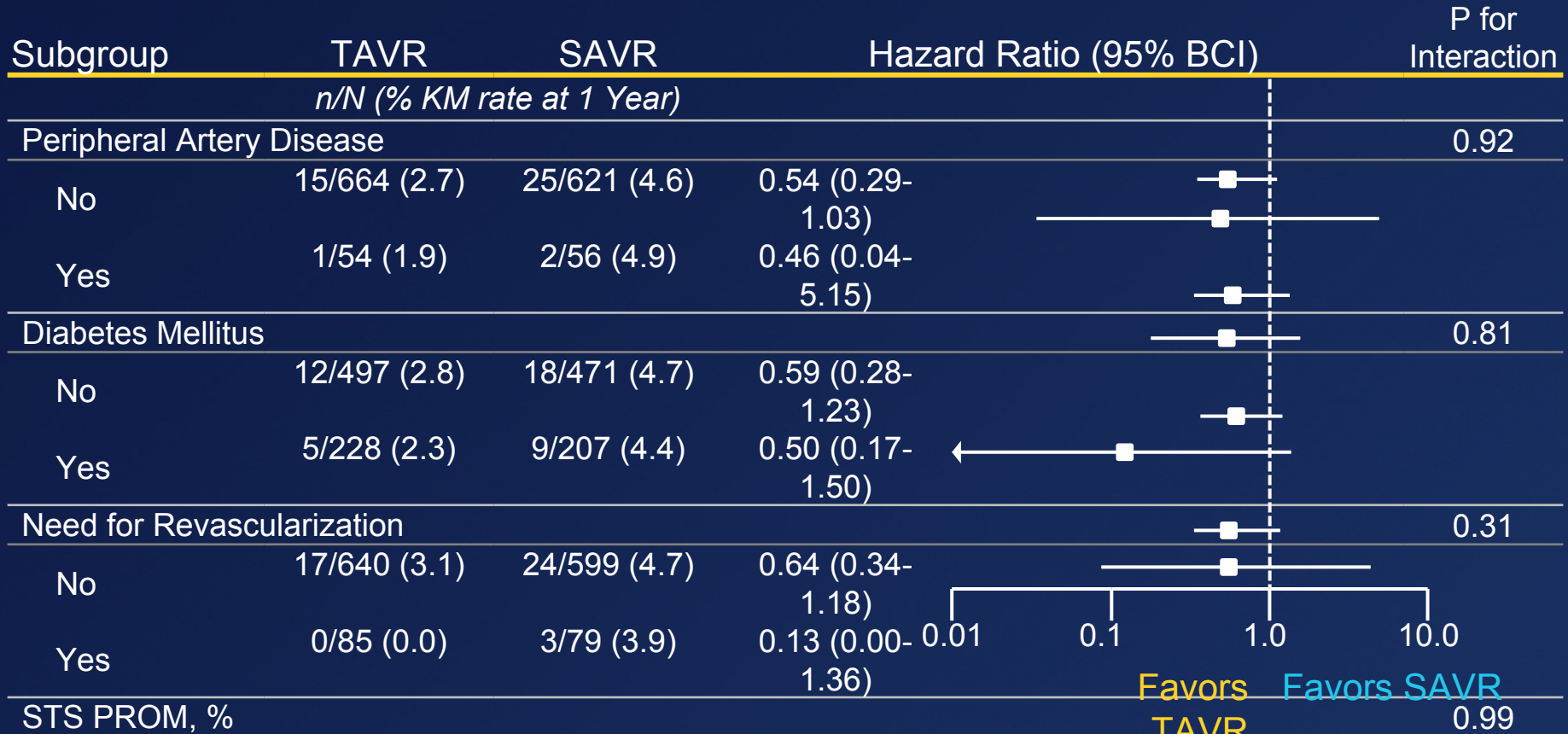


	30 Days	6 Months	12 Months
	Change from Baseline		
TAVR	20.0 ± 21.1	21.9 ± 21.2	22.2 ± 20.3
SAVR	9.1 ± 22.3	20.5 ± 20.5	20.9 ± 20.9
95% BCI for difference	(8.6, 13.2)	(-1.0, 3.8)	(-1.6, 4.3)

# Subgroup Analysis for Death or Disabling Stroke at 1 Year



# Subgroup Analysis for Death or Disabling Stroke at 1 Year



# Summary

- TAVR with self-expanding supra-annular valves was noninferior to surgery for the primary endpoint of death or disabling stroke at 2 years 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, larger EOAs and less PPM.

# Conclusion

TAVR may be a preferred strategy to surgery in patients with severe aortic stenosis at low risk of surgical mortality.



The NEW ENGLAND  
JOURNAL of MEDICINE

Evolut™  
Low Risk  
Trial

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.,  
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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\*

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