8th Annual Emirates Cardiac Society Conference

ACC Middle East Conference 2017

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Implications of Current TAVR Trials with Focus on Intermediate Risk

Michael J. Reardon, M.D.
Professor of Cardiothoracic Surgery
Allison Family Distinguish Chair of Cardiovascular Research
Houston Methodist DeBakey Heart & Vascular Center

ACC Middle East Conference 2017

COI

Steering committees

CoreValve

Evolut R

SurTAVI

Reprise III

National Surgical PI

SurTAVI

Reprise III

Evolut R low risk trial

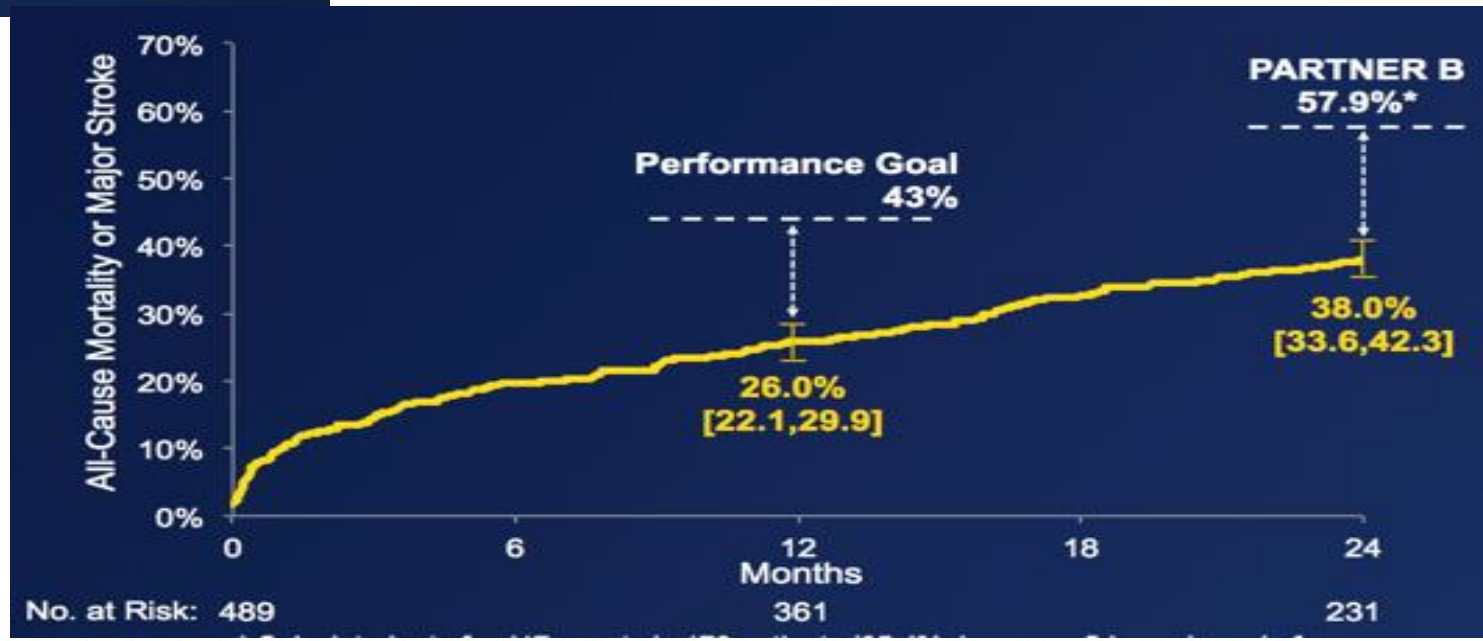
Reprise IV

DONE

CoreValve Extreme Risk

PARTNER IB

DONE



Extreme Risk

ACC Middle East Conference 2017

2017 AHA/ACC Focused Update of the 2014 AHA/ACC Guideline for the Management of Patients With Valvular Heart Disease

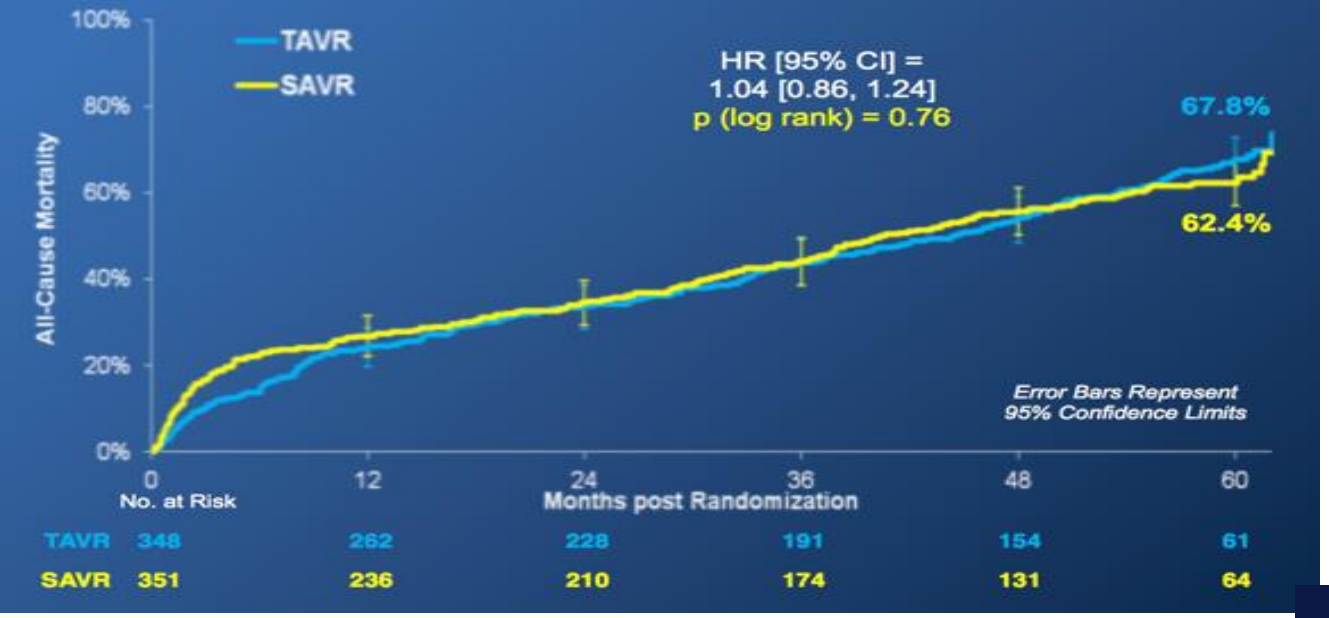
A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines

Developed in Collaboration With the American Association for Thoracic Surgery, American Society of Echocardiography, Society for Cardiovascular Angiography and Interventions, Society of Cardiovascular Anesthesiologists, and Society of Thoracic Surgeons

I	A	**TAVR is recommended for symptomatic patients with severe AS (Stage D) and a prohibitive risk for surgical AVR who have a predicted post-TAVR survival greater than 12 months (58-61).**	**MODIFIED: LOE updated from B to A.** Longer-term follow-up from RCTs and additional observational studies has demonstrated the benefit of TAVR in patients with a prohibitive surgical risk.
See Online Data Supplements 5 and 9 (Updated From 2014 VHD Guideline)			

Nishimura RA, Otto CM, Bonow RO, Carabello BA, Erwin JP 3rd, Fleisher LA, Jneid H, Mack MJ, McLeod CJ, O'Gara PT, Rigolin VH, Sundt TM 3rd, Thompson A, 2017 AHA/ACC Focused Update of the 2014 AHA/ACC Guideline for the Management of Patients With Valvular Heart Disease: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. J Am Coll Cardiol. 2017 Mar 10.

Extreme Risk



PARTNER IA

DONE

DONE

CoreValve High Risk

High Risk

ACC Middle East Conference 2017

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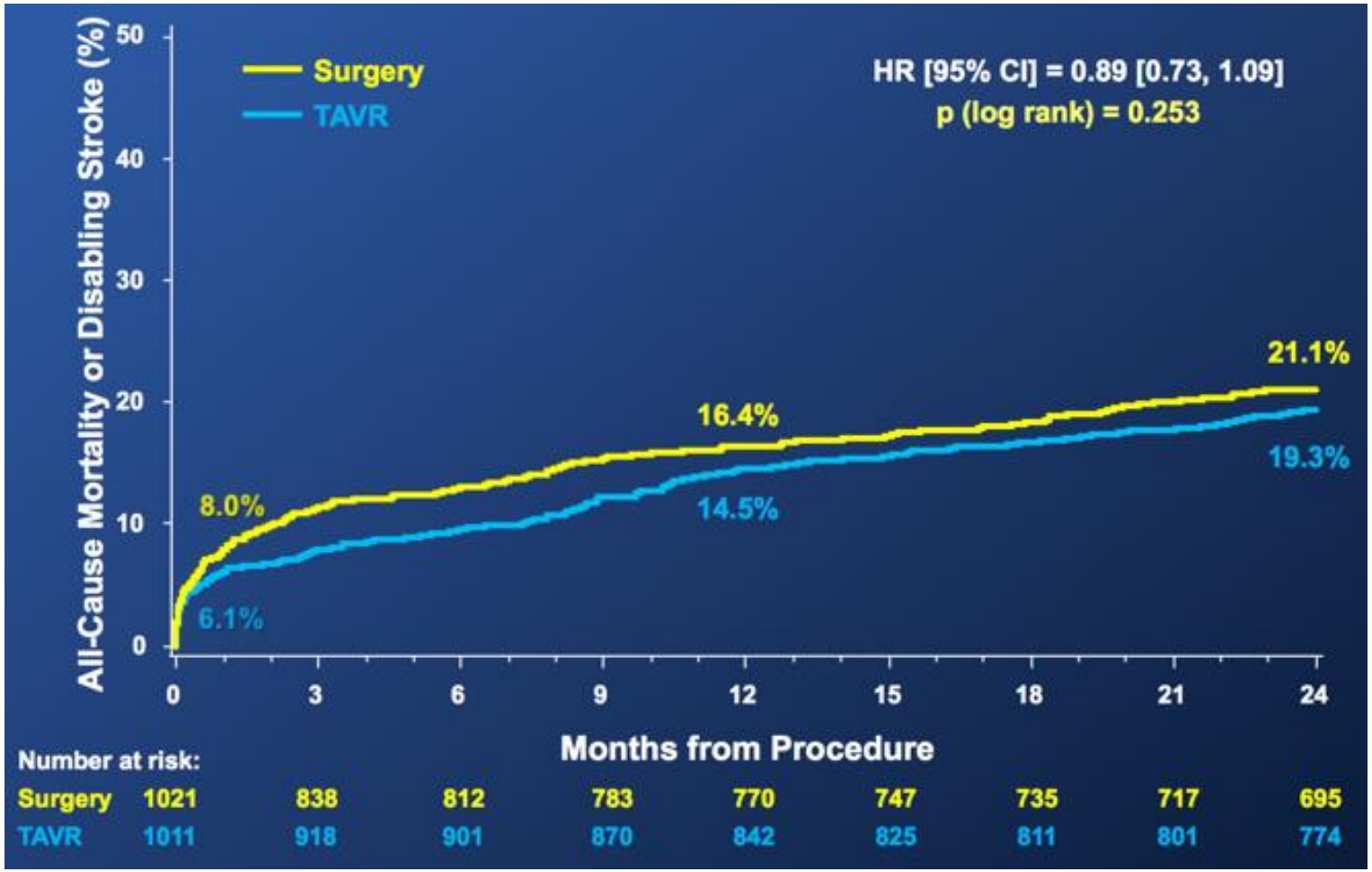
I	A	**Surgical AVR or TAVR is recommended for symptomatic patients with severe AS (Stage D) and high risk for surgical AVR, depending on patient-specific procedural risks, values, and preferences (49-51).**	**MODIFIED: COR updated from IIa to I, LOE updated from B to A.** Longer-term follow-up and additional RCTs have demonstrated that TAVR is equivalent to surgical AVR for severe symptomatic AS when
See Online Data Supplement 9 (Updated From 2014 VHD Guideline)			

Nishimura RA, Otto CM, Bonow RO, Carabello BA, Erwin JP 3rd, Fleisher LA, Jneid H, Mack MJ, McLeod CJ, O'Gara PT, Rigolin VH, Sundt TM 3rd, Thompson A, 2017 AHA/ACC Focused Update of the 2014 AHA/ACC Guideline for the Management of Patients With Valvular Heart Disease: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. J Am Coll Cardiol. 2017 Mar 10.

High Risk



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PARTNER IIA

Intermediate Risk

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Developed in Collaboration With the American Association for Thoracic Surgery, American Society of Echocardiography, Society for Cardiovascular Angiography and Interventions, Society of Cardiovascular Anesthesiologists, and Society of Thoracic Surgeons

IIa	B-R
See Online Data Supplements 5 and 9 (Updated From 2014 VHD Guideline)	

TAVR is a reasonable alternative to surgical AVR for symptomatic patients with severe AS (Stage D) and an intermediate surgical risk, depending on patient-specific procedural risks, values, and preferences (62-65).

NEW: New RCT showed noninferiority of TAVR to surgical AVR in symptomatic patients with severe AS at intermediate surgical risk.

Nishimura RA, Otto CM, Bonow RO, Carabello BA, Erwin JP 3rd, Fleisher LA, Jneid H, Mack MJ, McLeod CJ, O'Gara PT, Rigolin VH, Sundt TM 3rd, Thompson A, 2017 AHA/ACC Focused Update of the 2014 AHA/ACC Guideline for the Management of Patients With Valvular Heart Disease: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. J Am Coll Cardiol. 2017 Mar 10.

Intermediate Risk

Transcatheter Aortic Valve Replacement with a Self-Expanding Prosthesis or Surgical Aortic Valve Replacement in Intermediate-Risk Patients: First Results from the SURTAVI Clinical Trial

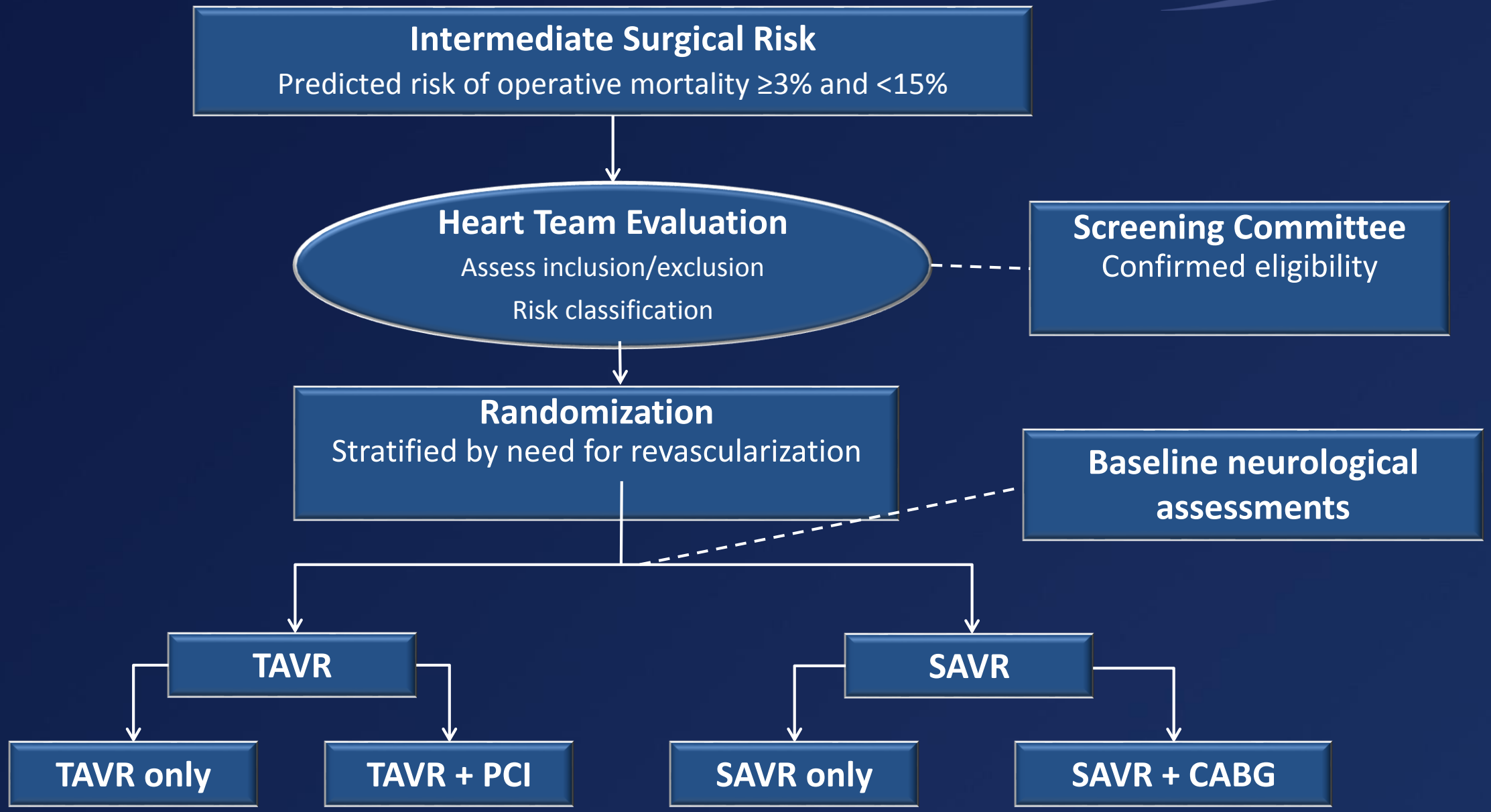
Michael J. Reardon, MD

For the SURTAVI Investigators

Objective

To assess the safety and efficacy of TAVR with the self-expanding valve vs. surgical AVR in patients with symptomatic, severe aortic stenosis at intermediate surgical risk

Trial Design



Study Endpoints

Primary endpoint

All-cause mortality or disabling stroke at 24 months

Key secondary endpoints

Safety:

- All-cause mortality
- All stroke
- Aortic valve reintervention
- Major vascular complications
- Life-threatening or major bleeding
- Pacemaker implantation
- Major adverse cardiovascular and cerebrovascular events (MACCE)

Efficacy:

- Mean gradient
- EOA
- Moderate/severe AR

Quality of life:

- KCCQ

Participating Sites – Canada and Europe

Montreal Heart Institute
Montreal, Quebec

Toronto General Hospital
Toronto, Ontario

McGill Univ Health Center/Glen Hosp
Montreal, Quebec

London Health Sciences Center
London, Ontario

Sunnybrook Health Sciences Centre
Toronto, Ontario

5 sites in Canada

17 sites in Europe

Erasmus Medical Center
Rotterdam, Netherlands

Glenfield Hospital
Leicester, UK

Amphia Hospital
Breda, Netherlands

Medisch Centrum Leeuwarden
Leeuwarden, Netherlands

Karolinska University Hospital
Stockholm, Sweden

Rigshospitalet
Copenhagen, Denmark

Leeds General Infirmary
Leeds, UK

St. George's Hospital
London, UK

St. Antonius Ziekenhuis
Nieuwegein, Netherlands

University Hospital
Bonn, Germany

Royal Sussex County Hospital
Brighton, UK

German Heart Center
Munich, Germany

Hospital Universitario Central de Asturias
Oviedo, Spain

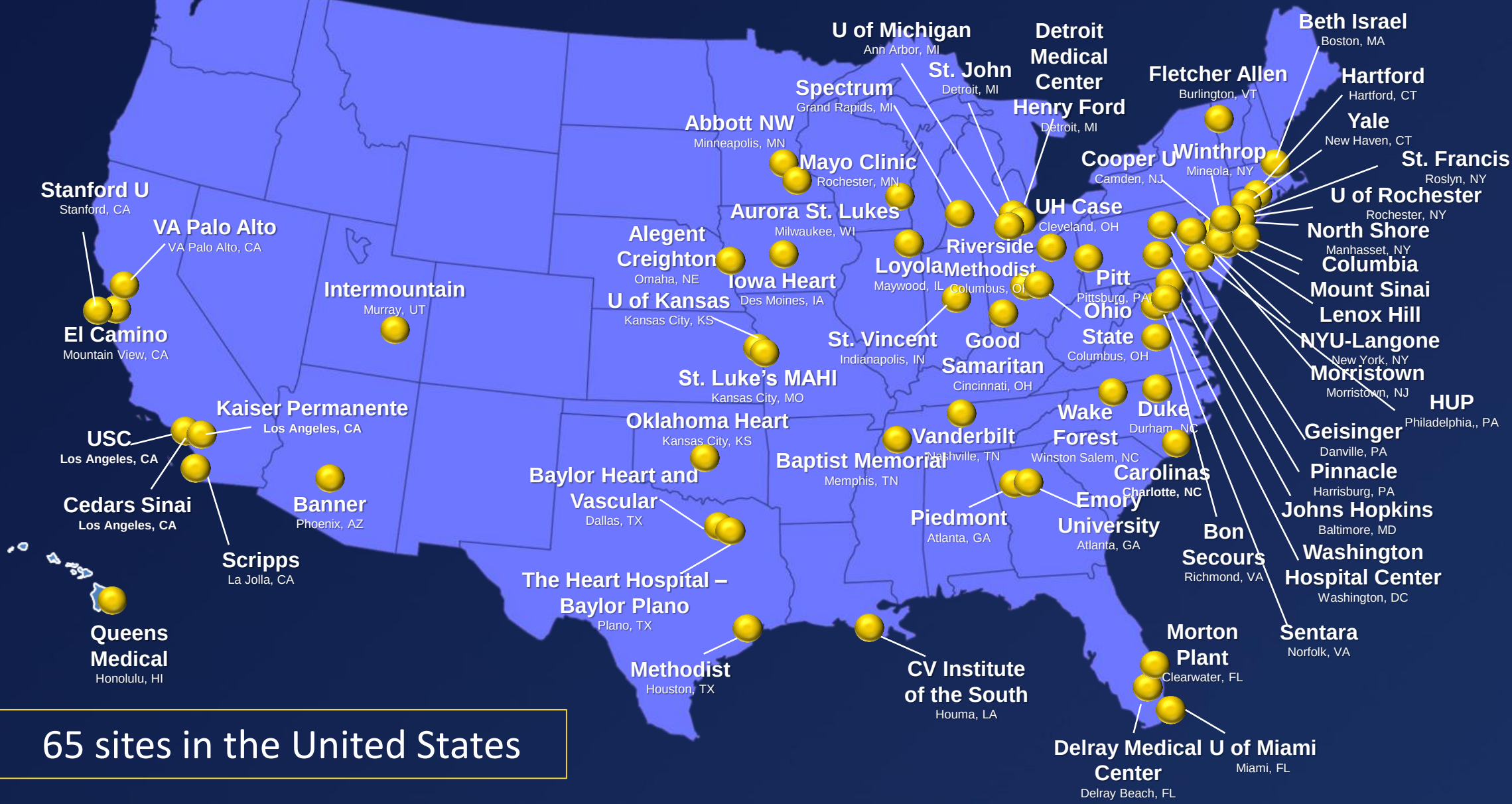
Heart Centre - Bad Krozingen
Bad Krozingen, Germany

Universitatsspital Zurich
Zurich, Switzerland

Inselspital - Universitatsspital Bern
Bern, Switzerland

Hospital Universitario Virgen de la Victoria
Malaga, Spain

Participating Sites – United States



65 sites in the United States

Study Timeline

2012 2013 2014 2015 2016 *April*

First patient enrolled
June 19, 2012

Enrollment completed
June 30, 2016

CoreValve: 23, 26 and 29 mm (US)

Evolut R (US)

CoreValve: 23, 26 and 29 mm (CAN, EU)

Primary endpoint assessment
Dec 2016

CoreValve: 31 mm (US, CAN, EU)

CoreValve (n=724)

94% TF
4% DA
2% SCA

Evolut R (n=139)

Key Inclusion Criteria

- Severe aortic valve stenosis defined by an initial aortic valve area of ≤1.0 cm^2 or aortic valve area index <0.6 cm^2/m^2, AND a mean gradient >40 mmHg or Vmax >4 m/sec, at rest or with dobutamine provocation in patients with a LVEF <55%, or Doppler velocity index <0.25 by resting echocardiogram
- Heart team agreement that predicted 30-day surgical mortality risk is ≥3% and <15% based on STS PROM and overall clinical status including frailty, disability and comorbidity factors
- NYHA functional class II or greater

Key Exclusion Criteria

- Contraindication for placement of a bioprosthetic valve
- A known hypersensitivity or contraindication to all anticoagulation/ antiplatelet regimens
- Any PCI or peripheral intervention within 30 days of randomization
- Symptomatic carotid or vertebral artery disease or successful treatment of carotid stenosis within six weeks of randomization
- Recent cerebrovascular accident or transient ischemic attack
- Acute MI within 30 days
- Multivessel CAD with Syntax score >22
- Severe liver, lung or renal disease
- Unsuitable anatomy including native aortic annulus <18 mm or >29 mm
- Severe mitral or tricuspid regurgitation
- Congenital bicuspid or unicuspid valve verified by echo

Definitions

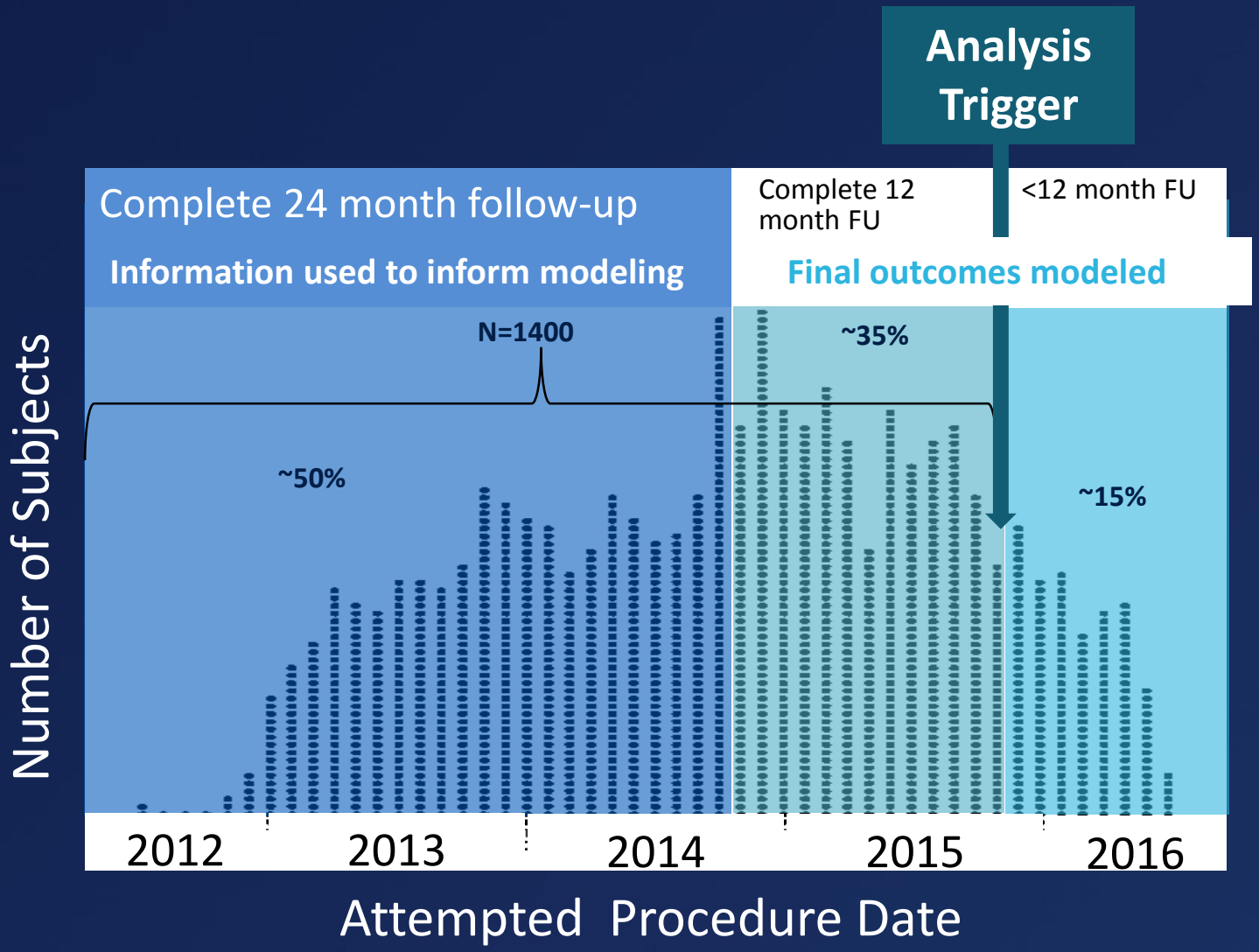
- Stroke assessment
  - All the patients were seen by a trained neurologist or stroke specialist at baseline.
  - Follow-up neurological assessments were done at discharge, 30 days, 6, 12, 18 and 24 months.
  - Neurologic events were adjudicated by a neurologist on the CEC.
  - Stroke was defined according to the VARC-2 criteria.
  - Disabling stroke was defined as a modified Rankin score of ≥2 at 90 days and an increase in at least 1 mRS category.
- Life-threatening or disabling bleeding was defined using BARC criteria.

Statistical Methods

- The SURTAVI trial utilized a novel Bayesian statistical methodology.
- The primary objective of the trial was to show that TAVR is noninferior to SAVR for all-cause mortality or disabling stroke at 24 months with a noninferiority margin of 0.07.
- The sample size of 1600 attempted implants assumed a 17% incidence of the primary endpoint in surgery patients.
- The primary and secondary endpoints were evaluated in the modified intention-to-treat (mITT) population.

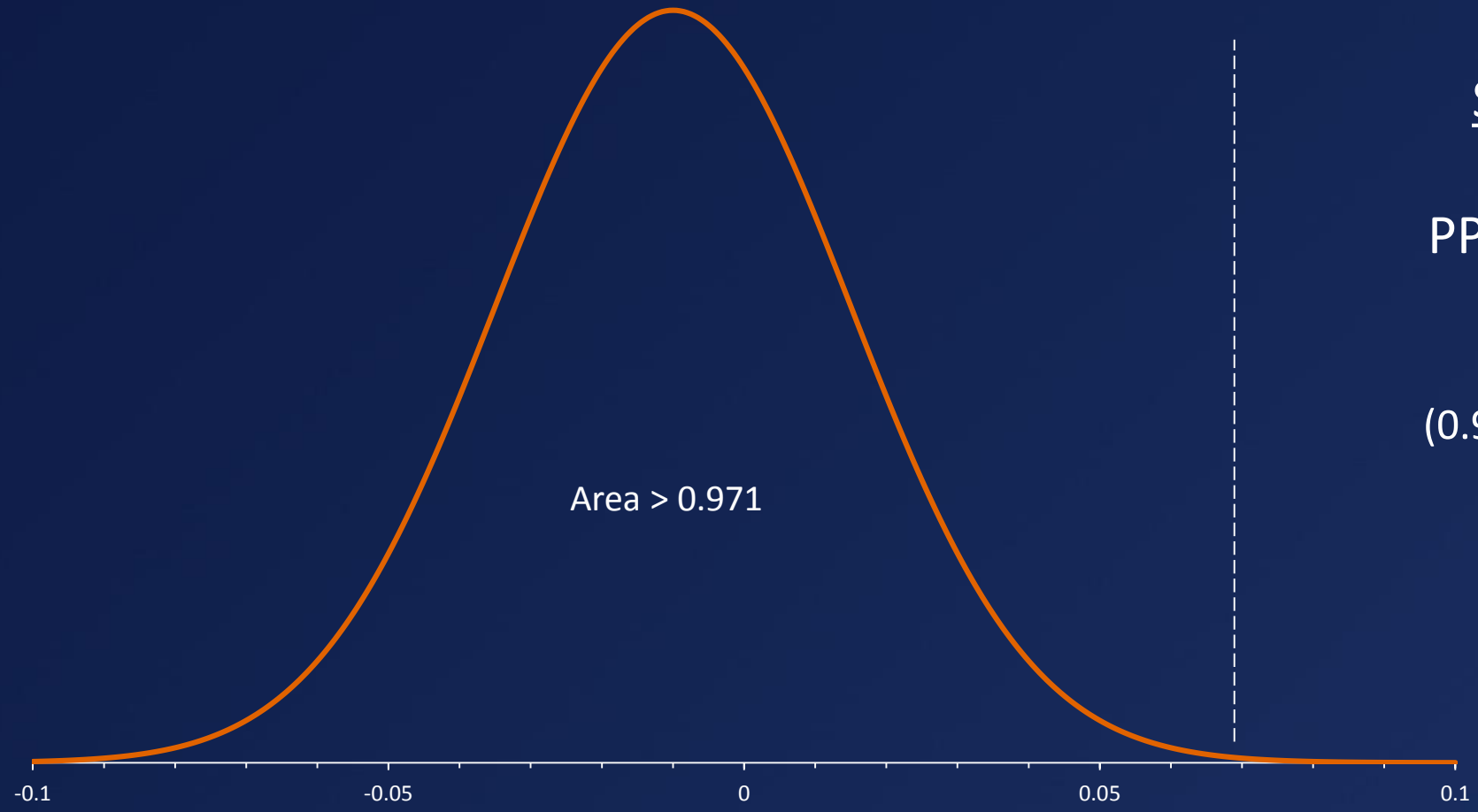
Bayesian Analysis of the 24-Month Primary Endpoint

- A pre-specified interim analysis occurred when 1400 patients reached 12-month follow-up.
- Observed 24-month outcomes were used to inform modeling.
- Subjects who had not reached 24-month follow-up had their outcomes imputed using their last known event status.
- Combining imputed and observed data, the posterior distribution of the difference in 24-month event rates was calculated.



Standard of Success for Noninferiority of the Primary Endpoint

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



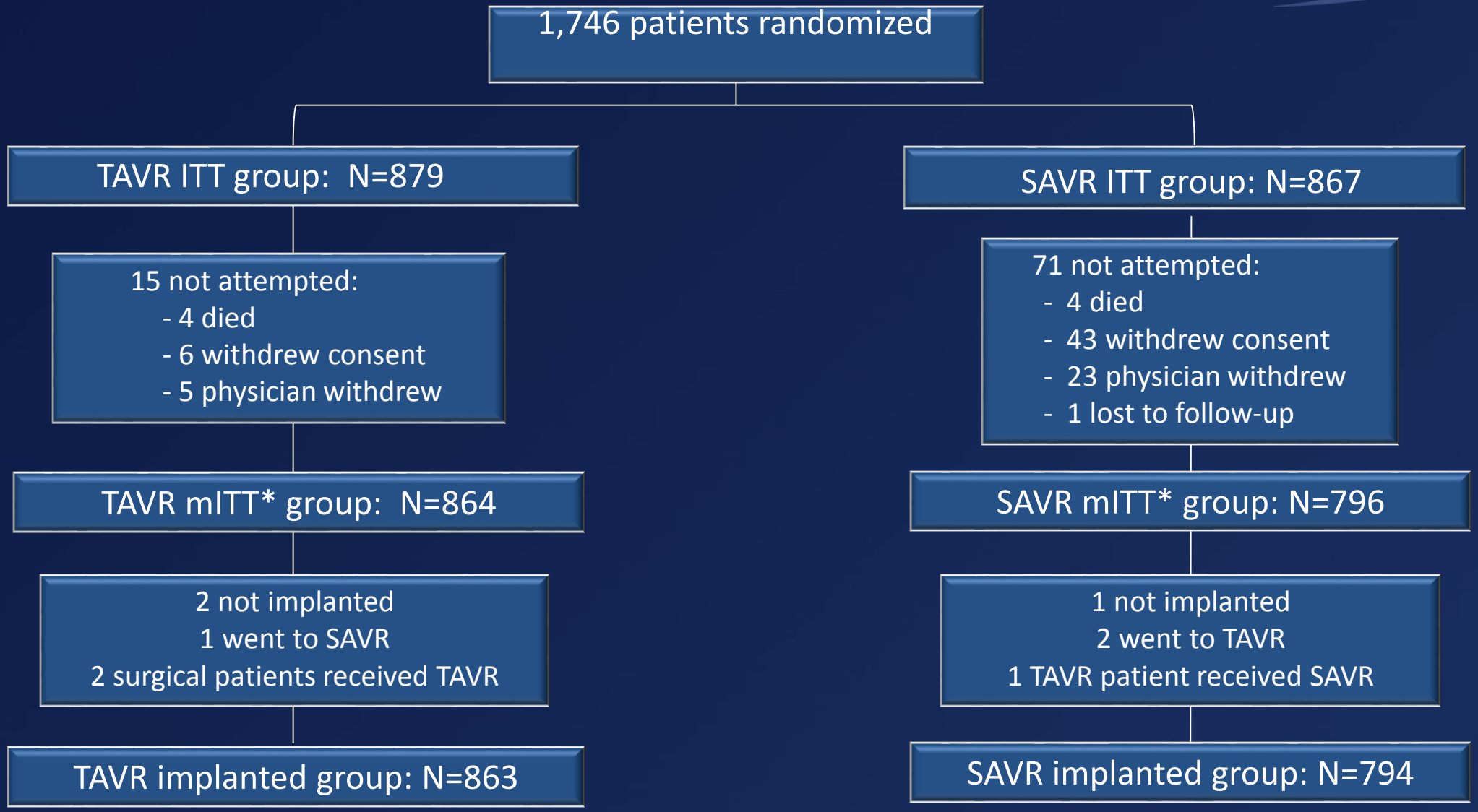
Standard of Success:

$PP(\pi_T - \pi_C < 0.07) > 0.971$

(0.971 chosen to keep $\alpha \leq 0.05$)

PP = Posterior Probability; π_T = TAVR rate; π_C = SAVR rate

Patient Flow



*The modified intention-to-treat (mITT) population includes all subjects with an attempted procedure

Baseline Characteristics*

n (%) or mean ± SD	TAVR (N=864)	SAVR (N=796)
Age, years	79.9 ± 6.2	79.7 ± 6.1
Male sex	498 (57.6)	438 (55.0)
Body surface area, m^2	1.9 ± 0.2	1.9 ± 0.2
STS PROM, %	4.4 ± 1.5	4.5 ± 1.6
Logistic EuroSCORE, %	11.9 ± 7.6	11.6 ± 8.0
Diabetes mellitus	295 (34.1)	277 (34.8)
Serum creatinine >2 mg/dl	14 (1.6)	17 (2.1)
Prior stroke	57 (6.6)	57 (7.2)
Prior TIA	58 (6.7)	46 (5.8)
Peripheral vascular disease	266 (30.8)	238 (29.9)
Permanent pacemaker	84 (9.7)	72 (9.0)

*mITT population; no significant difference in any baseline characteristics

Baseline Cardiac Risk Factors*

n (%)	TAVR (N=864)	SAVR (N=796)
Coronary artery disease	541 (62.6)	511 (64.2)
Prior CABG	138 (16.0)	137 (17.2)
Prior PCI	184 (21.3)	169 (21.2)
Prior myocardial infarction	125 (14.5)	111 (13.9)
Congestive heart failure	824 (95.4)	769 (96.6)
History of arrhythmia	275 (31.8)	250 (31.4)
Atrial fibrillation	243 (28.1)	211 (26.5)
NYHA Class III/IV	520 (60.2)	463 (58.2)

*mITT population; no significant difference in any baseline characteristics

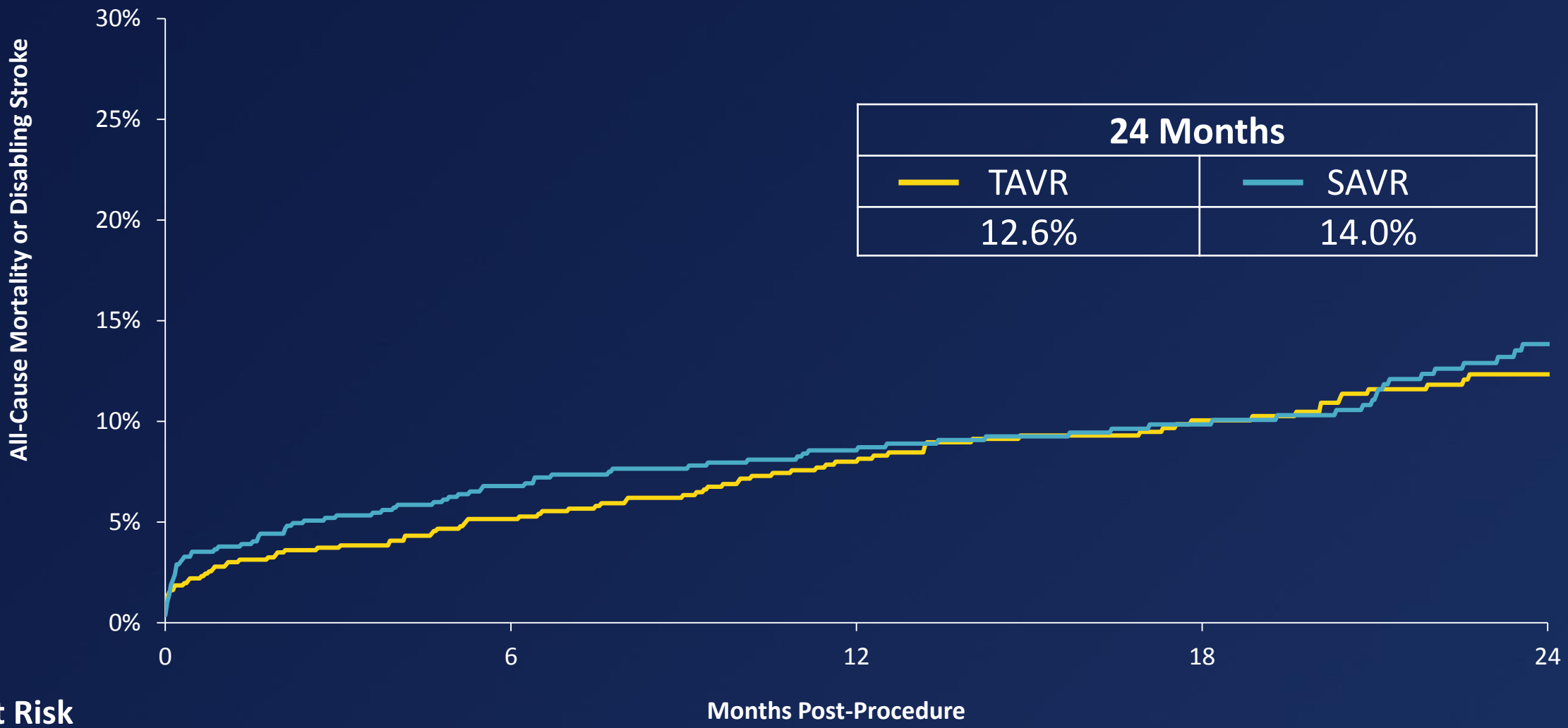
Baseline Frailty, Disabilities and Comorbidities*

n (%) or mean ± SD	TAVR (N=864)	SAVR (N=796)
Body mass index <21 kg/m^2	20 (2.3)	21 (2.6)
Falls in past 6 months	102 (11.8)	101 (12.7)
5 meter gait speed >6 s	428 (51.8)	403 (52.9)
6 minute walk test (meters)	254.1 ± 115.8	260.9 ± 117.9
Grip strength below threshold	519 (62.5)	490 (63.1)
Does not live independently	18 (2.1)	22 (2.8)
Chronic lung disease (mod/severe)	115 (13.3)	106 (13.3)
Home oxygen	18 (2.1)	21 (2.6)
Cirrhosis of the liver	4 (0.5)	5 (0.6)
Immunosuppressive therapy	64 (7.4)	68 (8.5)

*mITT population; no significant difference in any baseline characteristics

RESULTS

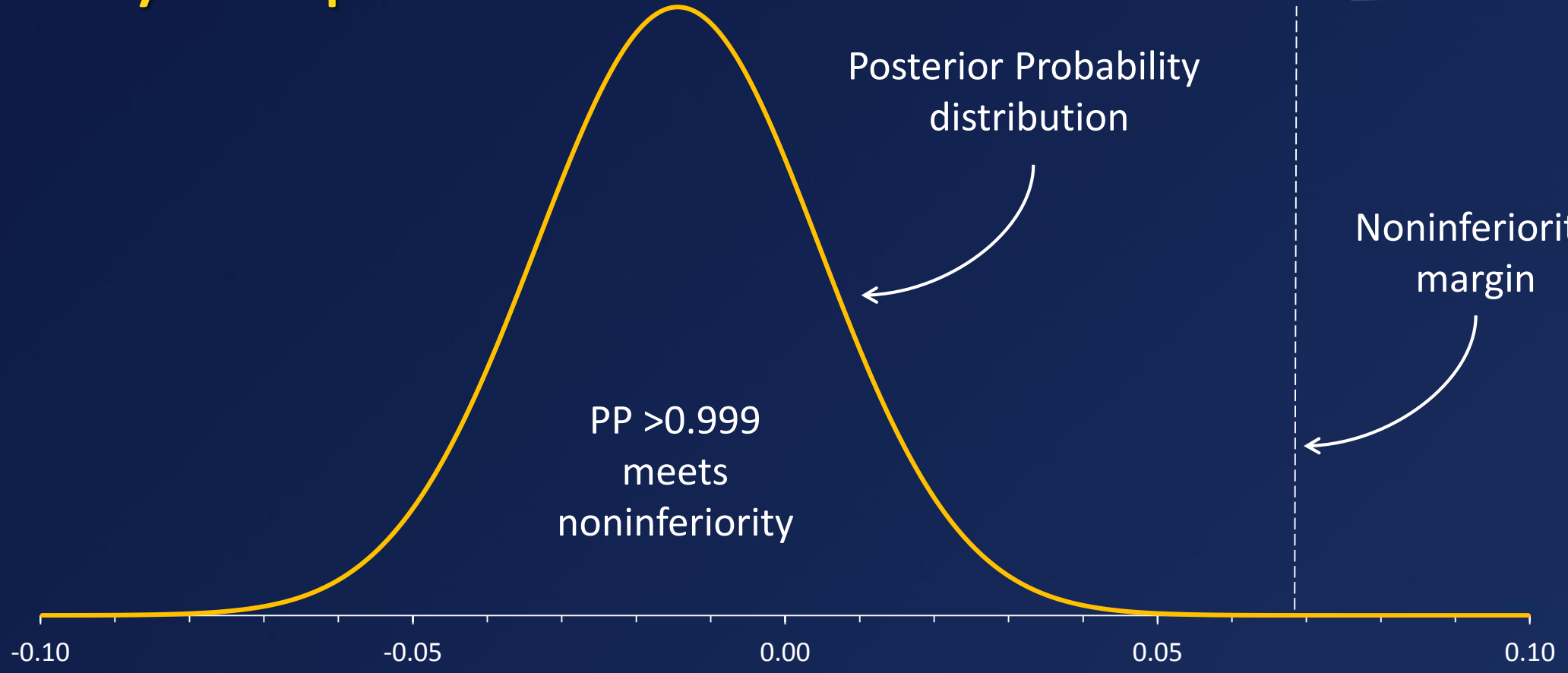
All-Cause Mortality or Disabling Stroke



No. at Risk

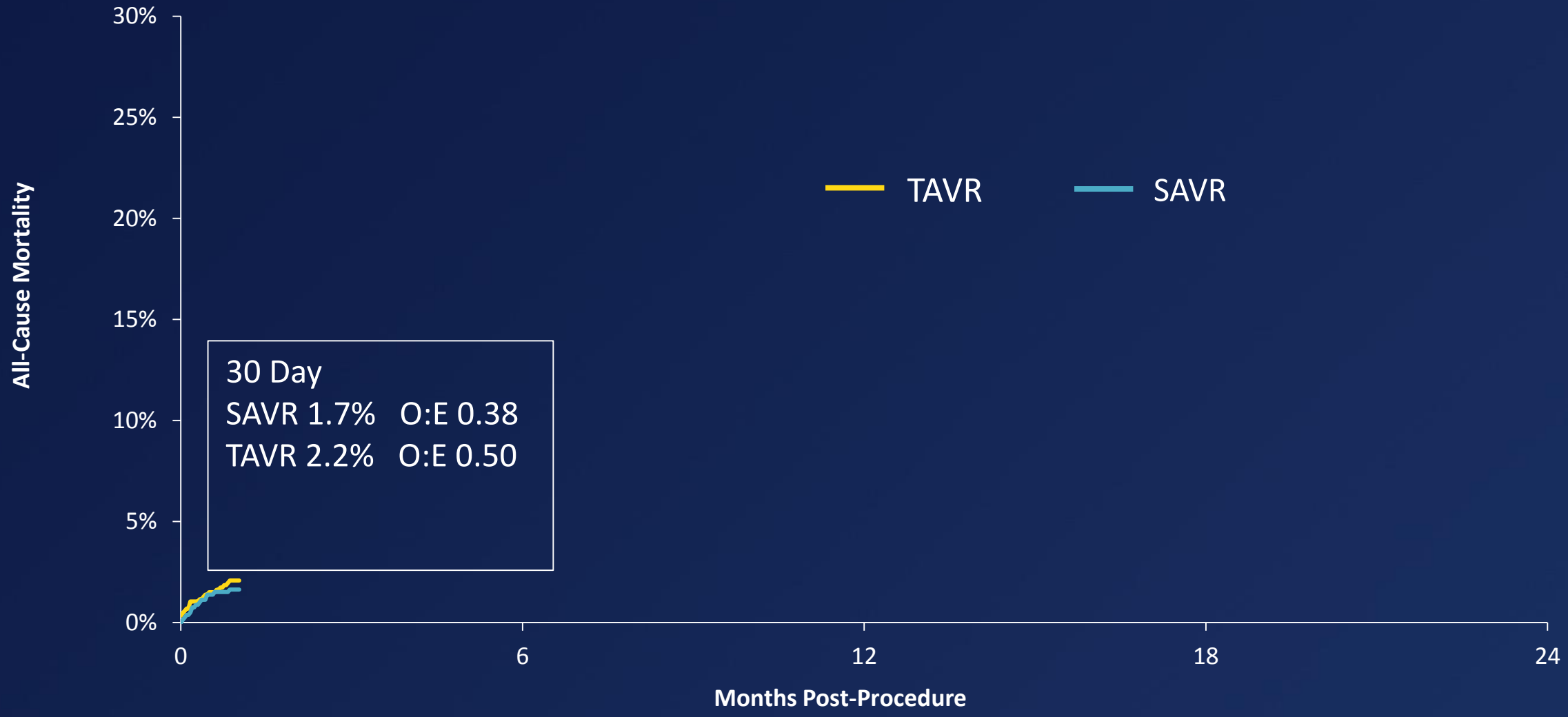
SAVR	796	674	555	407	241
TAVR	864	755	612	456	272

Primary Endpoint



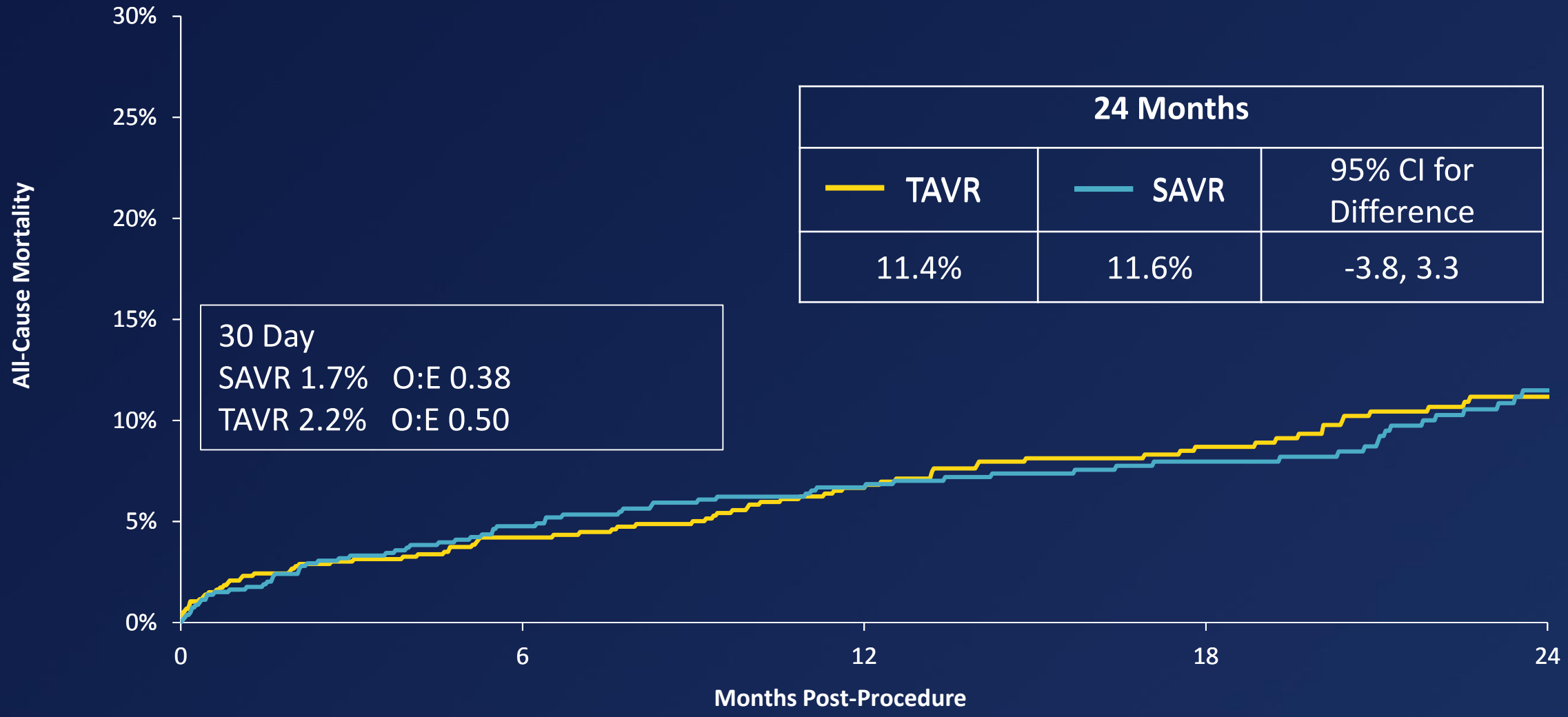
TAVR (95% CI)	SAVR (95% CI)	Difference (95% CI)
12.6% (10.2%, 15.3%)	14.0% (11.4%, 17.0%)	–1.4% (–5.2%, 2.3%)

All-Cause Mortality



No. at Risk					
SAVR	796	690	569	414	249
TAVR	864	762	621	465	280

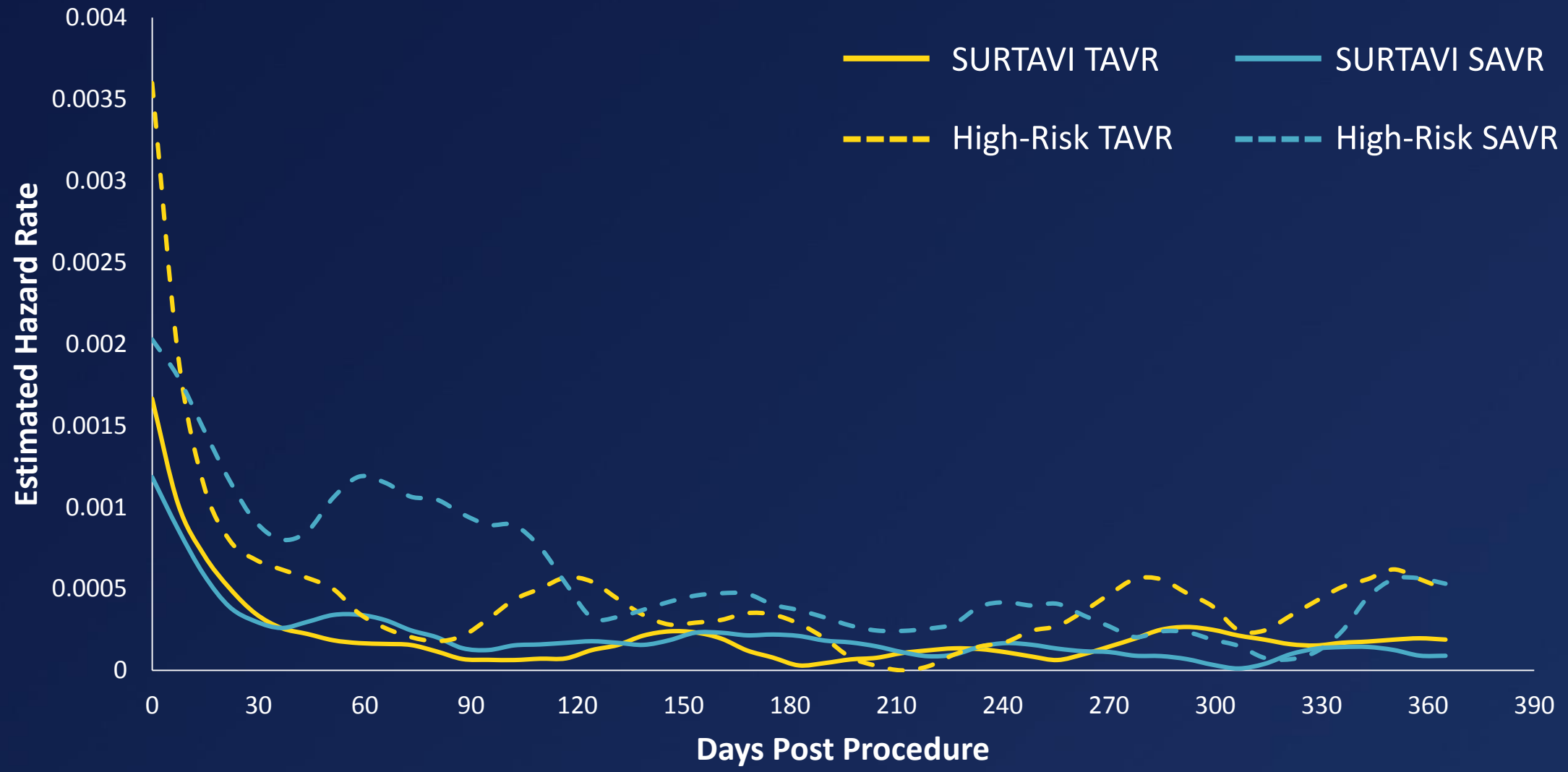
All-Cause Mortality



24 Months		
TAVR	SAVR	95% CI for Difference
11.4%	11.6%	-3.8, 3.3

No. at Risk					
SAVR	796	690	569	414	249
TAVR	864	762	621	465	280

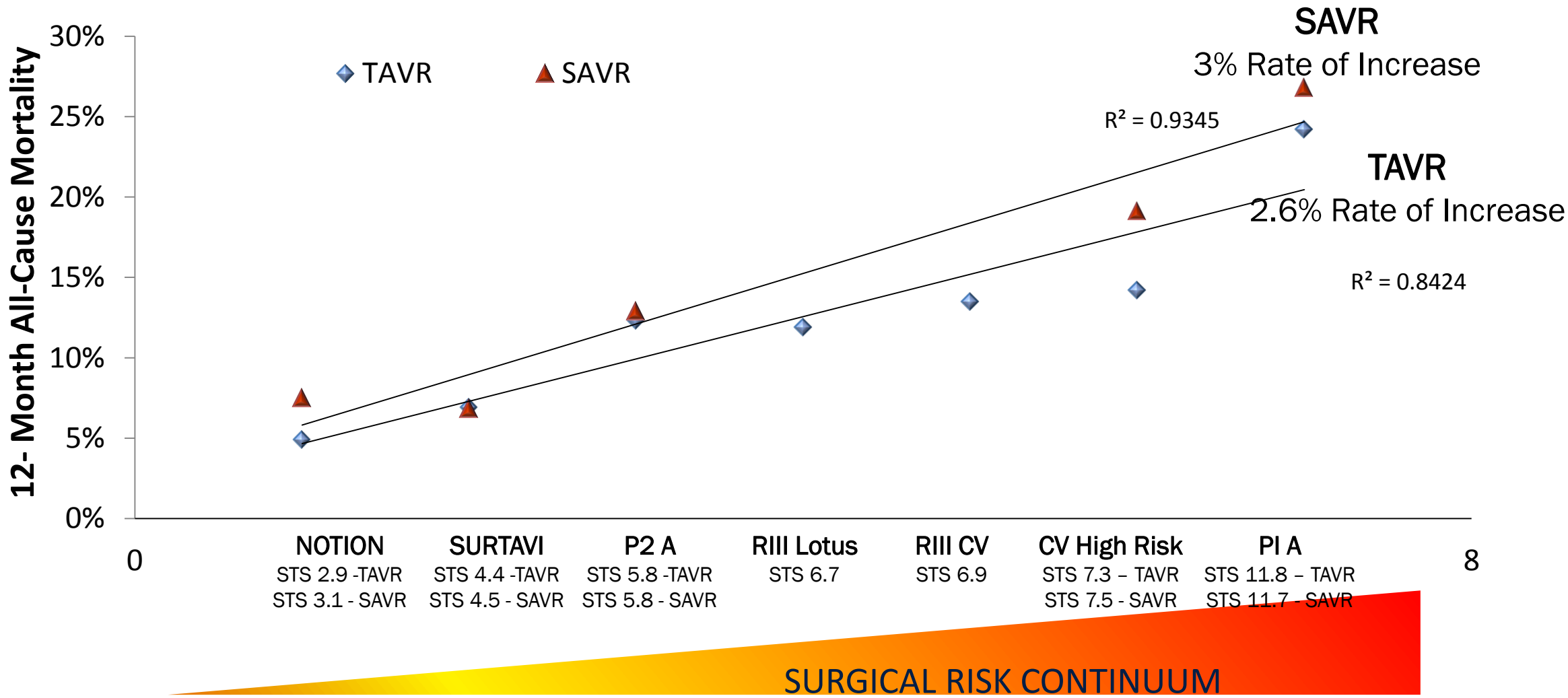
Instantaneous Hazard of Mortality



Guadiani V. Deeb GM, Popma JJ, et al. J Thorac Cardiovasc Surg 2017.

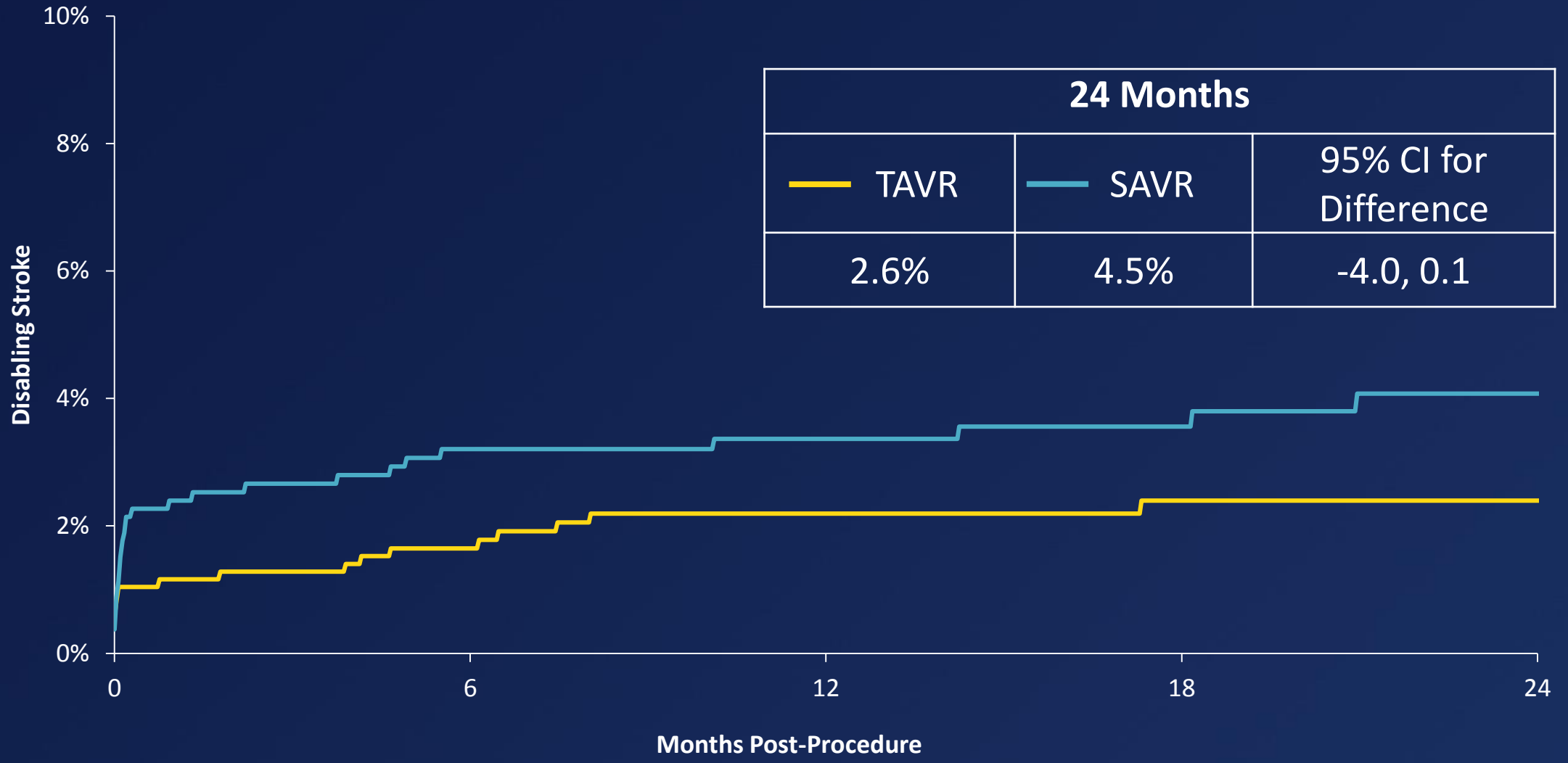
1-YEAR ALL-CAUSE MORTALITY BY STS SCORE

HOUSTON Methodist DEBAKEY HEART & VASCULAR CENTER



NOTION: Thyregold, JACC 2015. SURTAVI: Reardon, NEJM 2017. PARTNER 2A: Leon, NEJM 2016. REPRISE III: Feldman, PCR 2017. CoreValve High Risk: Adams, NEJM 2014. PARTNER 1A: Smith, NEJM 2011. The Lotus™ Valve System / LOTUS Edge™ Valve System may only be used in countries where it is approved for use. The Lotus™ Valve System / LOTUS Edge™ Valve System is not available for sale

Disabling Stroke



24 Months		
TAVR	SAVR	95% CI for Difference
2.6%	4.5%	-4.0, 0.1

No. at Risk

SAVR	796	674	555	407	241
TAVR	864	755	612	456	272

Procedural Characteristics

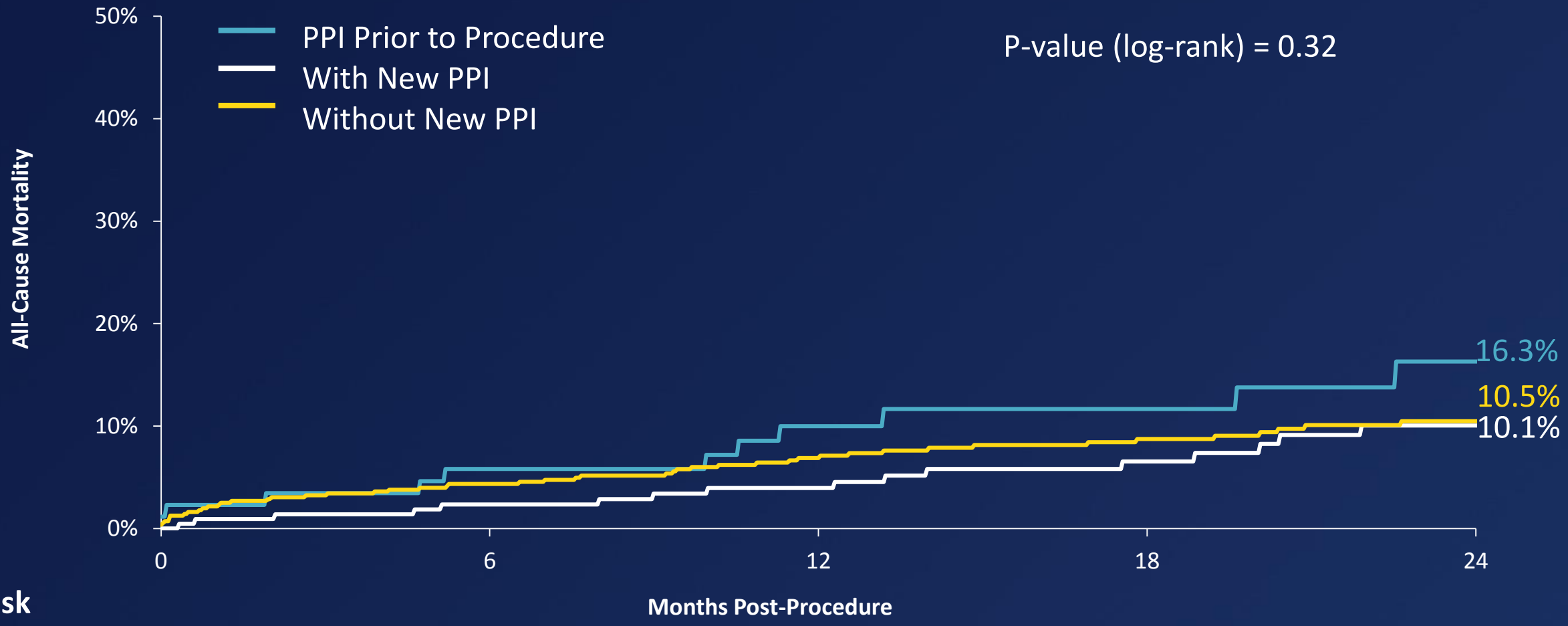
Characteristic, mean ± SD	TAVR (n=864)	SAVR (n=796)	95% CI for difference
Procedure time, min	52.3 ± 32.7	203.7 ± 69.1	(-156.7, -146.1)
Total time in cath lab or OR, min	190.8 ± 61.3	295.5 ± 81.6	(-111.7, -97.6)
Aortic cross-clamp time, min	NA	74.3 ± 30.4	NA
CPB time, min	NA	97.8 ± 39.3	NA
Length of index procedure hospital stay, days	5.75 ± 4.85	9.75 ± 8.03	(-4.65, -3.36)
Length of ICU stay, hours	(n=767) 48.6 ± 44.0	(n=778) 70.4 ± 96.2	(-29.3, -14.3)

30-Day Safety and Procedure-related Complications

	TAVR (N=864)	SAVR (N=796)	95% CI for Difference
All-cause mortality or disabling stroke	2.8	3.9	-2.8, 0.7
All-cause mortality	2.2	1.7	-0.9, 1.8
Disabling stroke	1.2	2.5	-2.6, 0.1
All stroke	3.4	5.6	-4.2, -0.2
Overt life-threatening or major bleeding	12.2	9.3	-0.1, 5.9
Transfusion of PRBCs* - n (%)			
0 units	756 (87.5)	469 (58.9)	24.4, 32.5
2 – 4 units	48 (5.6)	136 (17.1)	-14.5, -8.5
≥ 4 units	31 (3.6)	101 (12.7)	-11.7, -6.5
Acute kidney injury, stage 2-3	1.7	4.4	-4.4, -1.0
Major vascular complication	6.0	1.1	3.2, 6.7
Cardiac perforation	1.7	0.9	-0.2, 2.0
Cardiogenic shock	1.1	3.8	-4.2, -1.1
Permanent pacemaker implant	25.9	6.6	15.9, 22.7
Atrial fibrillation	12.9	43.4	-34.7, -26.4

*Percentage rates, all others are Bayesian rates

All-Cause Mortality by Pacemaker Implantation



No. at Risk					
PPI Prior	87	74	59	46	28
With New PPI	217	198	164	121	56
Without New PPI	559	491	400	300	197

Clinical Outcomes* at 12 and 24 Months

	12 Months			24 Months		
	TAVR	SAVR	95% CI for Difference	TAVR	SAVR	95% CI for Difference
All-cause mortality or disabling stroke	8.1	8.8	-3.5, 2.1	12.6	14.0	-5.2, 2.3
All-cause mortality	6.7	6.8	-2.7, 2.4	11.4	11.6	-3.8, 3.3
All stroke	5.4	6 .9	-3.9, 0.9	6.2	8.4	-5.0, 0.4
Disabling stroke	2.2	3.6	-3.1, 0.4	2.6	4.5	-4.0, 0.1
TIA	3.2	2.0	-0.4, 2.8	4.3	3.1	-0.9, 3.2
Myocardial infarction	2.0	1.6	-0.9, 1.8	2.8	2.2	-1.1, 2.4
Aortic valve re-intervention	2.1	0.5	0.4, 2.7	2.8	0.7	0.7, 3.5
Aortic valve hospitalization	8.5	7.6	-1.8, 3.6	13.2	9.7	0.1, 7.0
MACCE	13.2	12.8	-2.9, 3.7	18.6	18.6	-4.2, 4.2

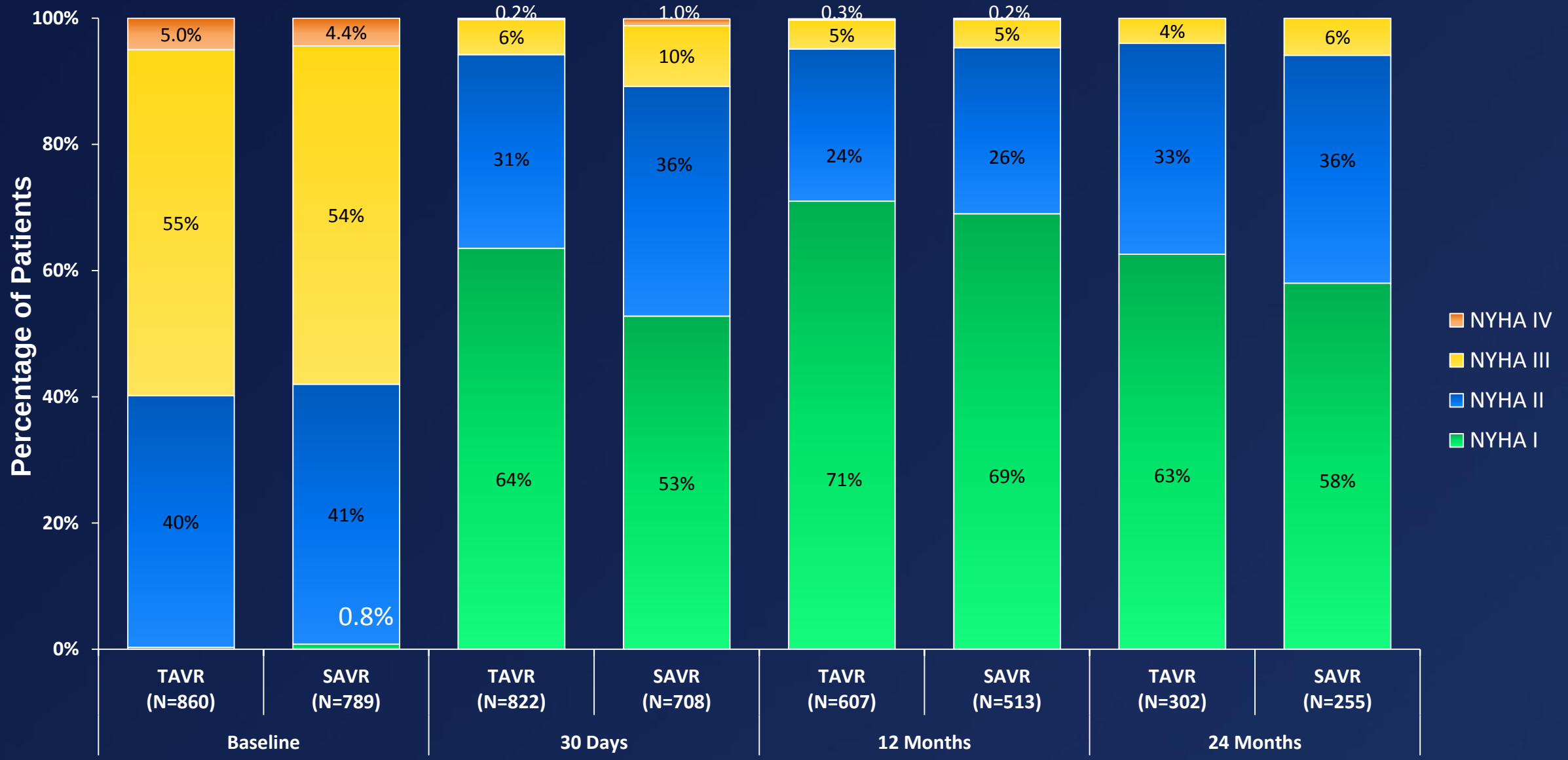
*All are reported as Bayesian rates

Hemodynamics*

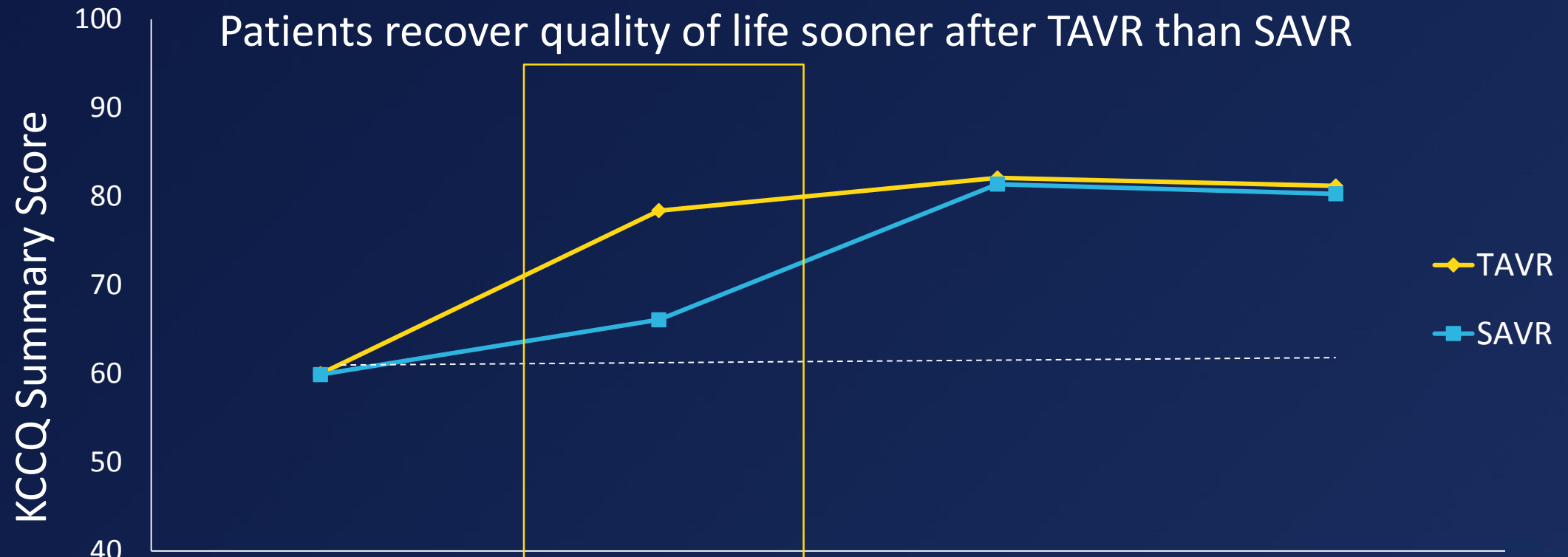
TAVR had significantly better valve performance over SAVR at all follow-up visits

*Core lab adjudicated

NYHA Functional Class

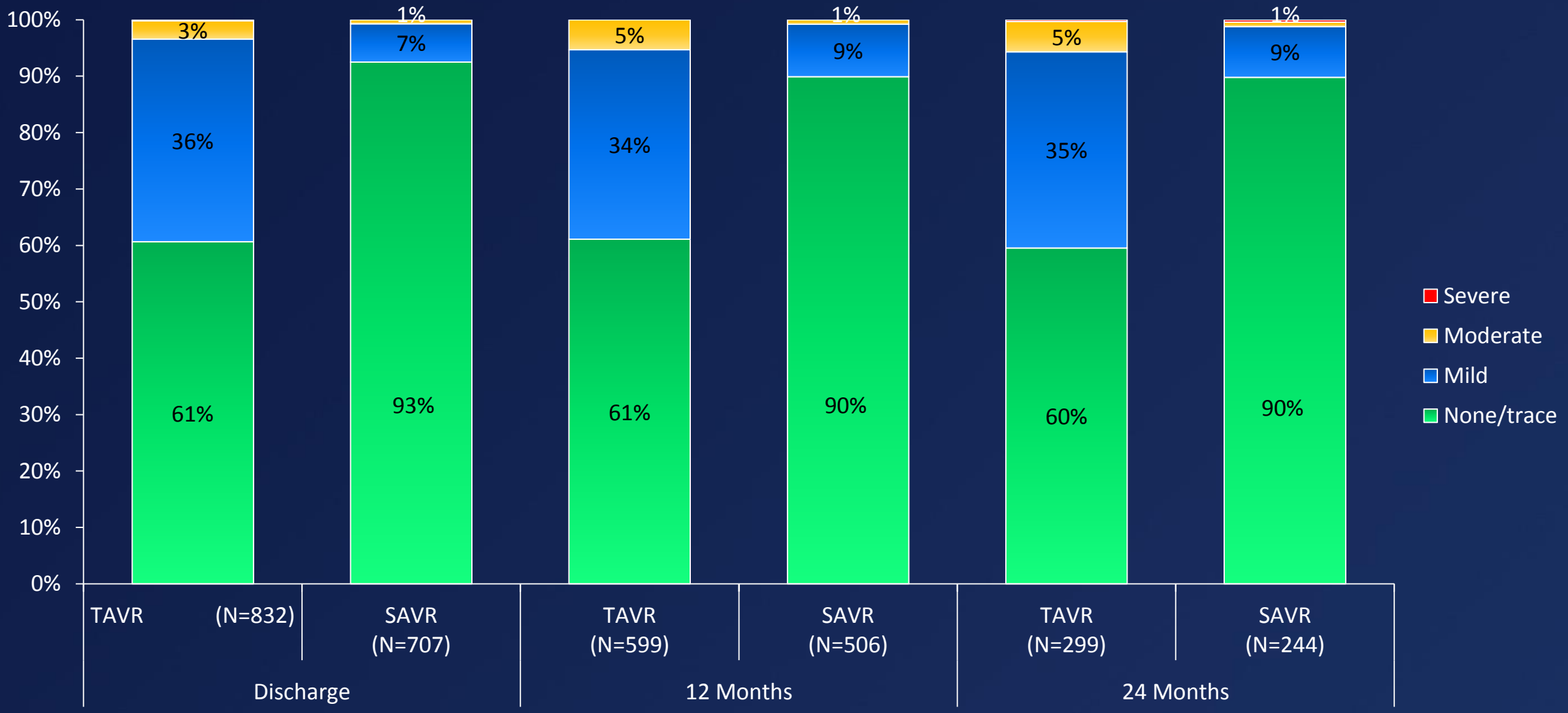


KCCQ Summary Score Over Time



	Change from Baseline		
TAVR	18.4 ± 22.8	21.8 ± 22.3	20.9 ± 22.2
SAVR	5.9 ± 27.0	21.3 ± 22.3	20.6 ± 22.2
95% CI for difference	(10.0, 15.1)	(-1.9, 2.8)	(-2.2, 2.9)

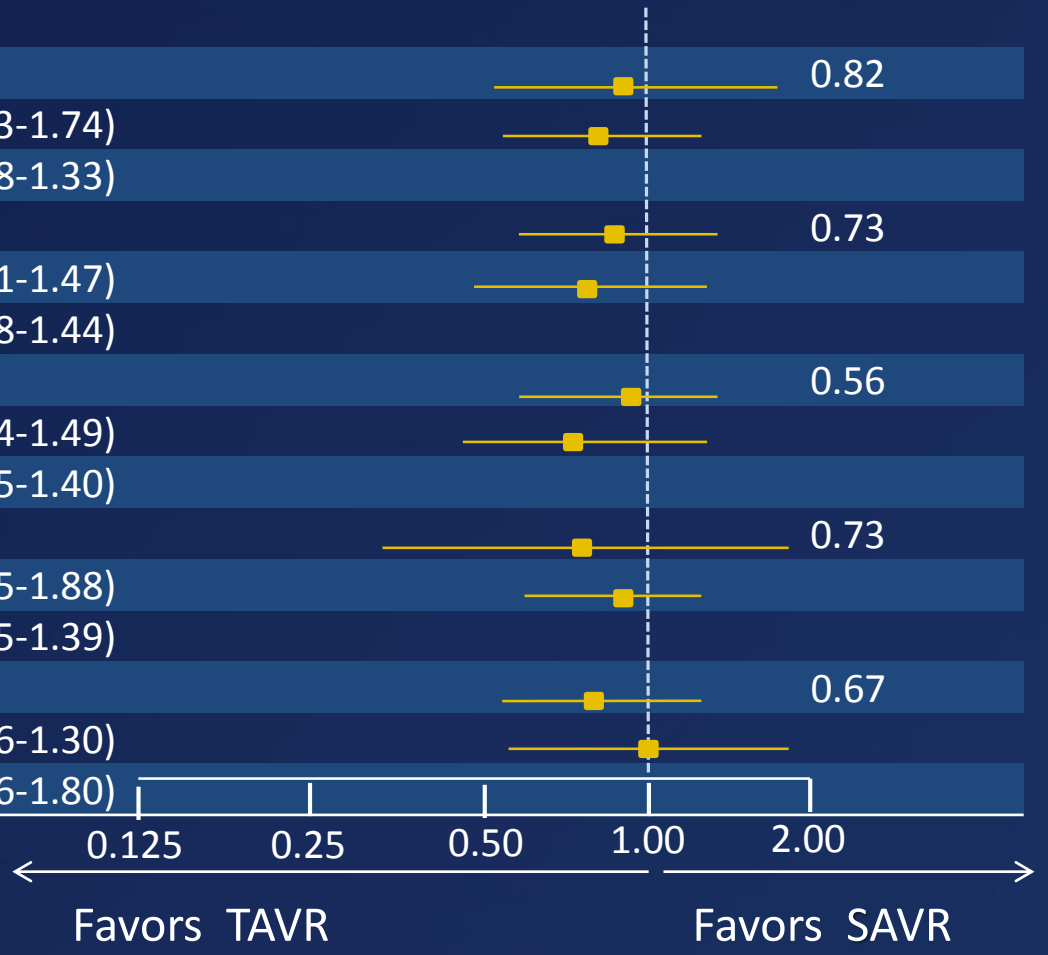
Total Aortic Regurgitation*



* Implanted population, core lab adjudicated

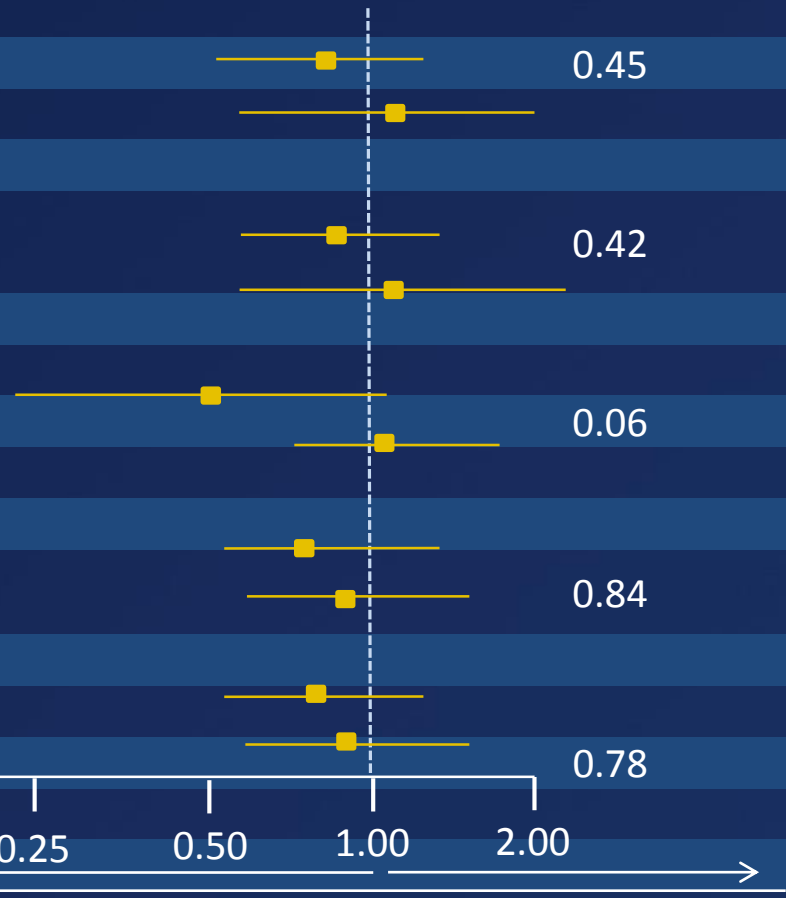
All-Cause Mortality or Disabling Stroke at 12 Months

Subgroup	TAVR	SAVR	Hazard Ratios (95% CI)	P for Interaction
	n/N (KM rate at 12 months)			
Age				0.82
<80	22/352 (6.6)	21/330 (6.8)	0.96 (0.53-1.74)	
≥80	44/512 (9.2)	45/466 (10.0)	0.88 (0.58-1.33)	
Gender				0.73
Male	42/498 (9.0)	38/438 (9.2)	0.94 (0.61-1.47)	
Female	24/366 (6.9)	28/358 (8.2)	0.83 (0.48-1.44)	
BMI				0.56
≤30	44/527 (8.8)	41/486 (8.8)	0.98 (0.64-1.49)	
>30	22/337 (7.1)	25/310 (8.6)	0.79 (0.45-1.40)	
LVEF				0.73
≤50	10/131 (8.0)	12/133 (9.3)	0.81 (0.35-1.88)	
>50	56/732 (8.2)	52/657 (8.3)	0.95 (0.65-1.39)	
PVD				0.67
No	42/598 (7.6)	45/558 (8.5)	0.86 (0.56-1.30)	
Yes	24/266 (9.4)	21/238 (9.3)	1.00 (0.56-1.80)	



All-Cause Mortality or Disabling Stroke at 12 Months

Subgroup	TAVR	SAVR	Hazard Ratios (95% CI)	P for Interaction
	n/N (KM rate at 12 months)			
Diabetes				0.45
No	43/569 (8.0)	47/519 (9.5)	0.83 (0.55-1.25)	
Yes	23/295 (8.3)	19/277 (7.3)	1.10 (0.60-2.02)	
Revascularization				0.42
No	47/695 (7.3)	50/633 (8.3)	0.84 (0.56-1.25)	
Yes	19/169 (11.7)	16/163 (10.3)	1.15 (0.59-2.23)	
STS				0.06
<4	12/345 (3.8)	20/299 (7.2)	0.50 (0.25-1.03)	
≥4	54/519 (10.8)	46/497 (9.5)	1.11 (0.75-1.65)	
Logistic EuroSCORE				0.84
<10	31/429 (7.8)	35/432 (8.7)	0.87 (0.54-1.41)	
≥10	35/435 (8.5)	31/363 (8.8)	0.93 (0.58-1.52)	
5 m gait speed				0.78
≤6 sec	29/399 (7.9)	30/359 (9.0)	0.86 (0.52-1.43)	
>6 sec	33/428 (8.2)	32/403 (8.1)	0.95 (0.58-1.54)	



Summary

- SURTAVI met its primary endpoint demonstrating that TAVR with a self-expanding CoreValve or Evolut R bioprosthesis is noninferior to SAVR for all-cause mortality or disabling stroke at 24 months.

Summary

- TAVR had significantly less 30 day stroke, AKI, atrial fibrillation and transfusion use and a superior quality of life at 30 days.
- TAVR resulted in significantly improved AV hemodynamics with lower mean gradients and larger aortic valve areas than SAVR through 24 months.
- SAVR had less residual aortic regurgitation, major vascular complications and fewer new pacemakers.
- Need for a new pacemaker after TAVR was not associated with increased mortality.

Conclusion

In SURTAVI, TAVR with the self-expanding valve was safe and effective treatment for patients with symptomatic severe AS at intermediate risk for surgical mortality

IMPLICATIONS

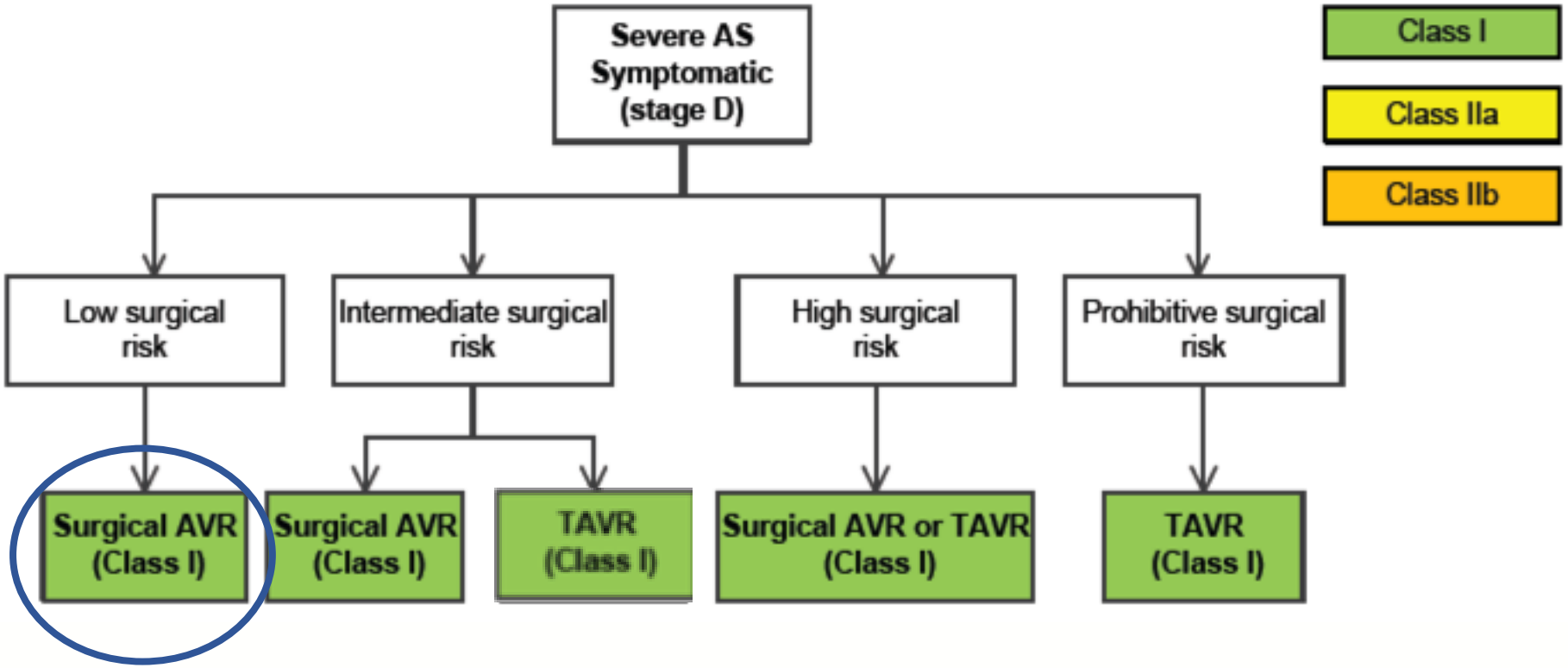
The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Surgical or Transcatheter Aortic-Valve Replacement in Intermediate-Risk Patients

M.J. Reardon, N.M. Van Mieghem, J.J. Popma, N.S. Kleiman, L. Søndergaard, M. Mumtaz, D.H. Adams, G.M. Deeb, B. Maini, H. Gada, S. Chetcuti, T. Gleason, J. Heiser, R. Lange, W. Merhi, J.K. Oh, P.S. Olsen, N. Piazza, M. Williams, S. Windecker, S.J. Yakubov, E. Grube, R. Makkar, J.S. Lee, J. Conte, E. Vang, H. Nguyen, Y. Chang, A.S. Mugglin, P.W.J.C. Serruys, and A.P. Kappetein, for the SURTAVI Investigators*

2017 Guidelines



With SURTAVI Data

PARTNER 3

Low Risk, Symptomatic AS

STS <4

Age >65 years

RCT- TAVR vs SAVR

1,228 patients

Nested Registries-3

50 Sites

One year Composite Endpoint

- Death
- Stroke
- Rehospitalization

4D CT Imaging Substudy -400 patients

CoreValve Evolut R

Low Risk Symptomatic AS

STS < 3

No Age Floor

RCT – TAVR vs. SAVR

1,200 patients

80 sites

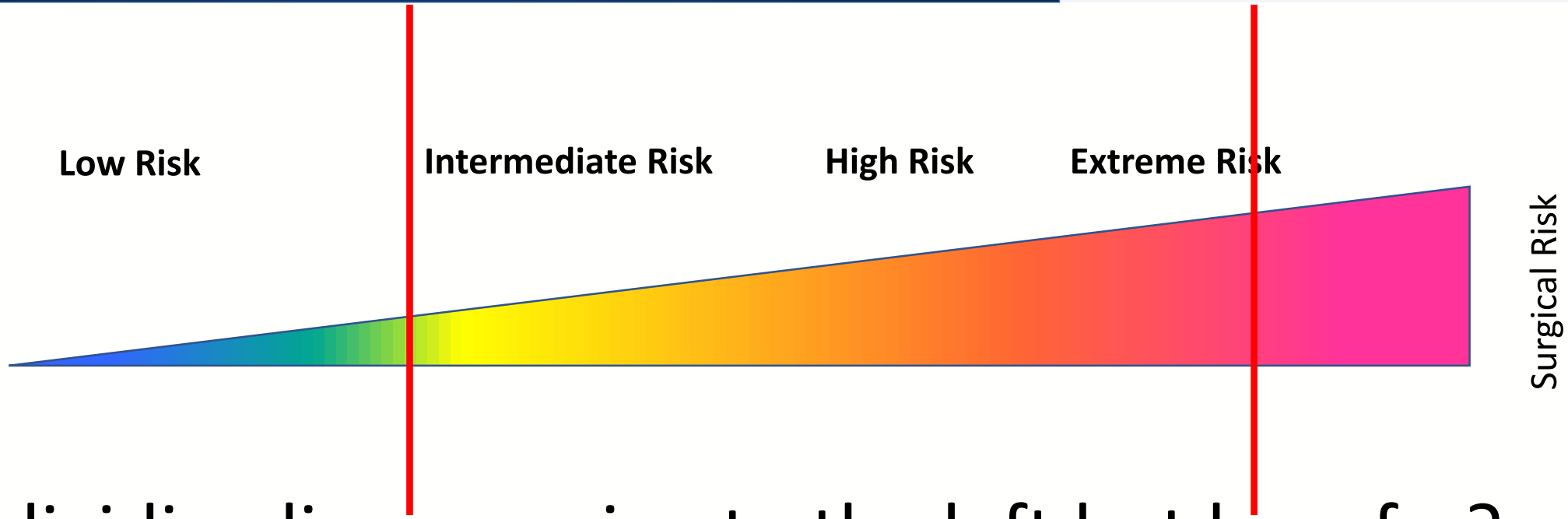
Two Year Endpoint

- Death
- Disabling Stroke
- Adaptive Design

4D CT Imaging Study- 400 Patients

IMPLICATIONS OF TRIALS

HOUSTON Methodist DEBAKEY HEART & VASCULAR CENTER



Both dividing lines moving to the left but how far?

Durablity

Thank You

HOUSTON Methodist
DEBAKEY HEART & VASCULAR CENTER