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SURTAVI Step by Step: Moving Forward to Low Risk and Younger Patients

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Physician Name	Company/Relationship
Speaker Bureau/Advisory Board:	Medtronic: C, SB, AB, OF LivaNova: C, SB, AB Highlife: AB, SB Boston Scientific: C, SB, AB Millipede: SB, C Pipeline: SB,C
Equity Interest:	InSeal Medical: E, AB, Valtech: E, SB, Claret: E, AB Shockwave: E, AB Valve Medical: E, AB Mitra/Trialign E, AB, SB

Key

G – Grant and or Research Support E – Equity Interests S – Salary, AB – Advisory Board

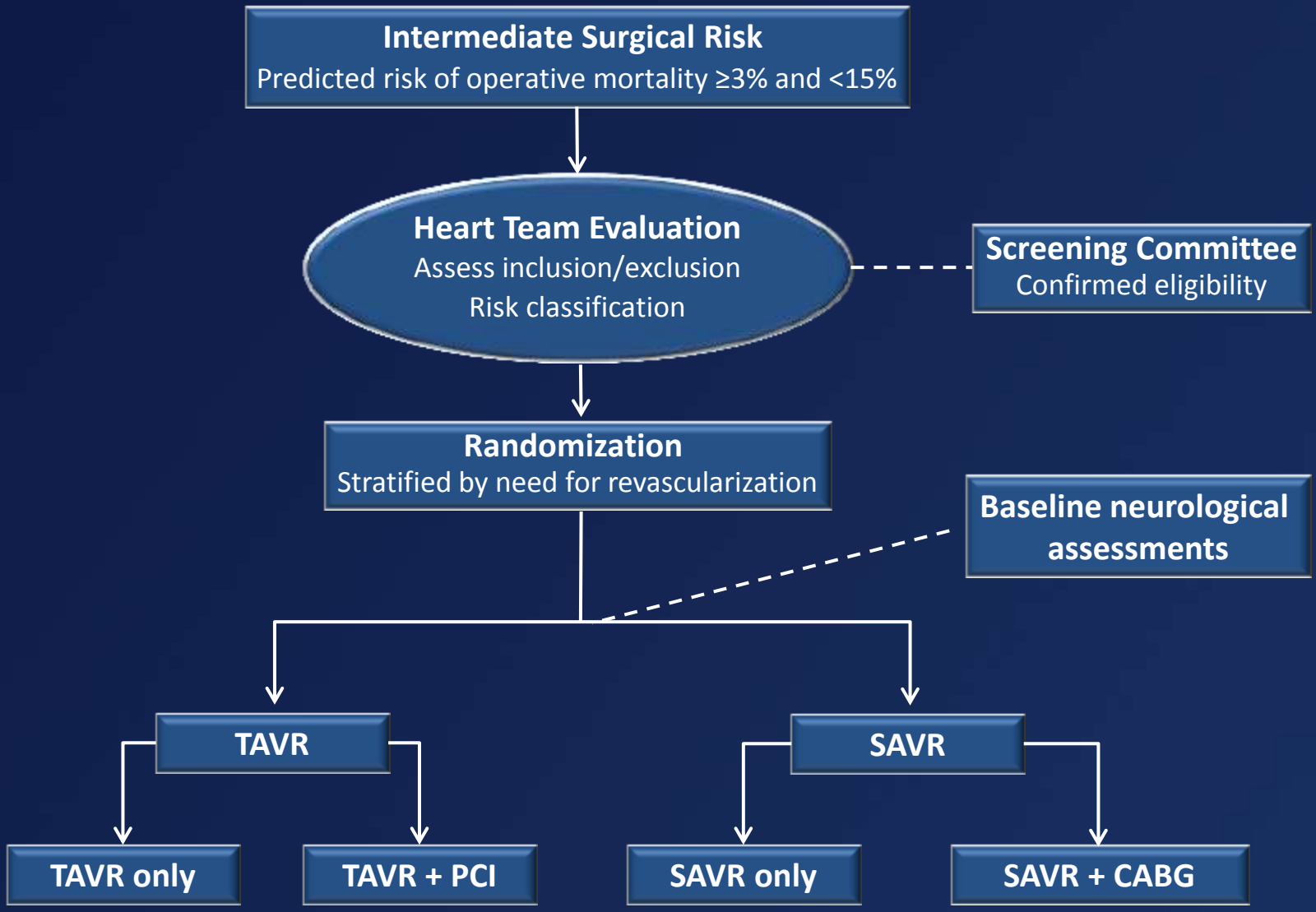
C – Consulting fees, Honoraria R – Royalty Income I – Intellectual Property Rights

SB – Speaker's Bureau O – Ownership OF – Other Financial Benefits '

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

Participating Sites
United States

65 sites in the United States

Study Timeline

2012 2013 2014 2015 *April* 2016

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)

16% second generation valves

Key Inclusion Criteria

- ***Severe aortic valve stenosis*** defined by an initial aortic ***valve area of ≤1.0 cm²*** 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.

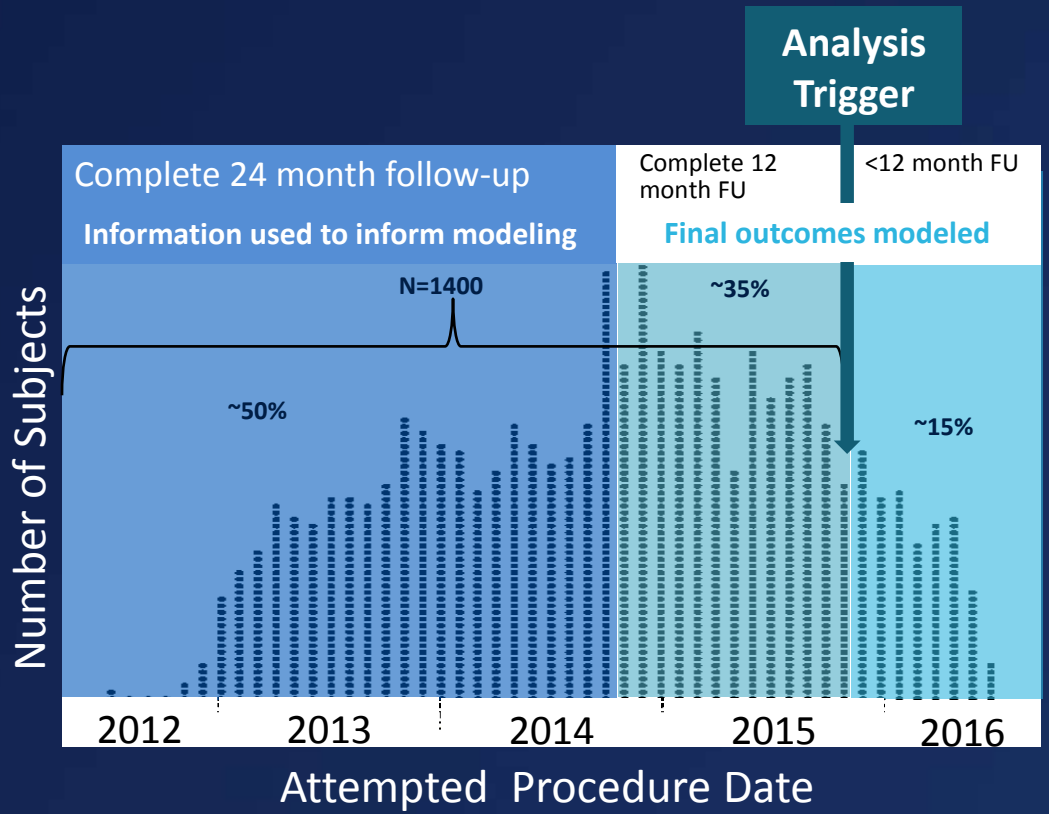
- Life-threatening or disabling bleeding was defined using BARC criteria.

Statistical Methods

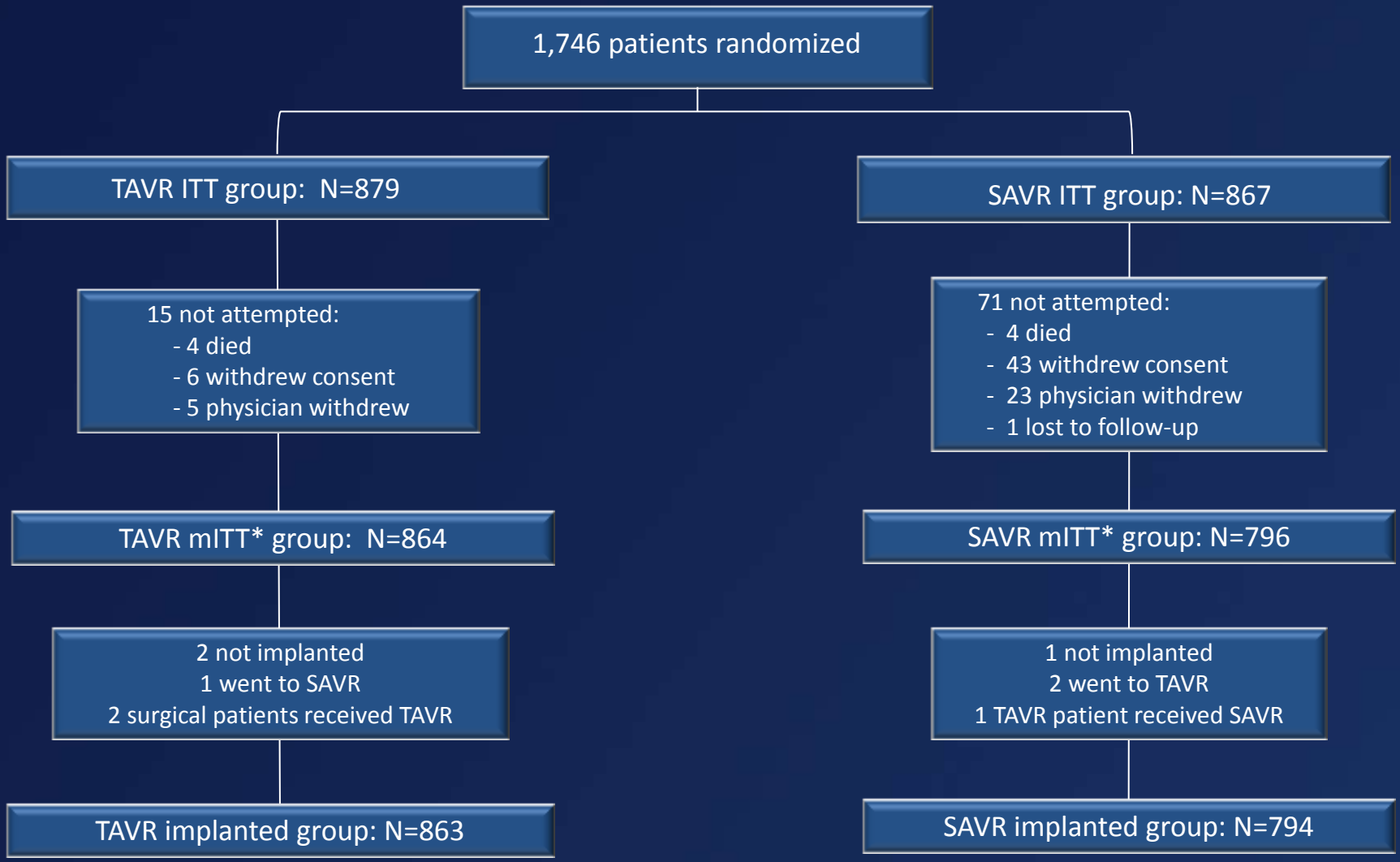
- The SURTAVI trial utilized a novel Bayesian statistical methodology.
- The primary objective of the trial was to show that TAVR is noninferior to SAVR for all-cause mortality or disabling stroke at 24 months with a noninferiority margin of 0.07.
- The sample size of 1600 attempted implants assumed 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.



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*

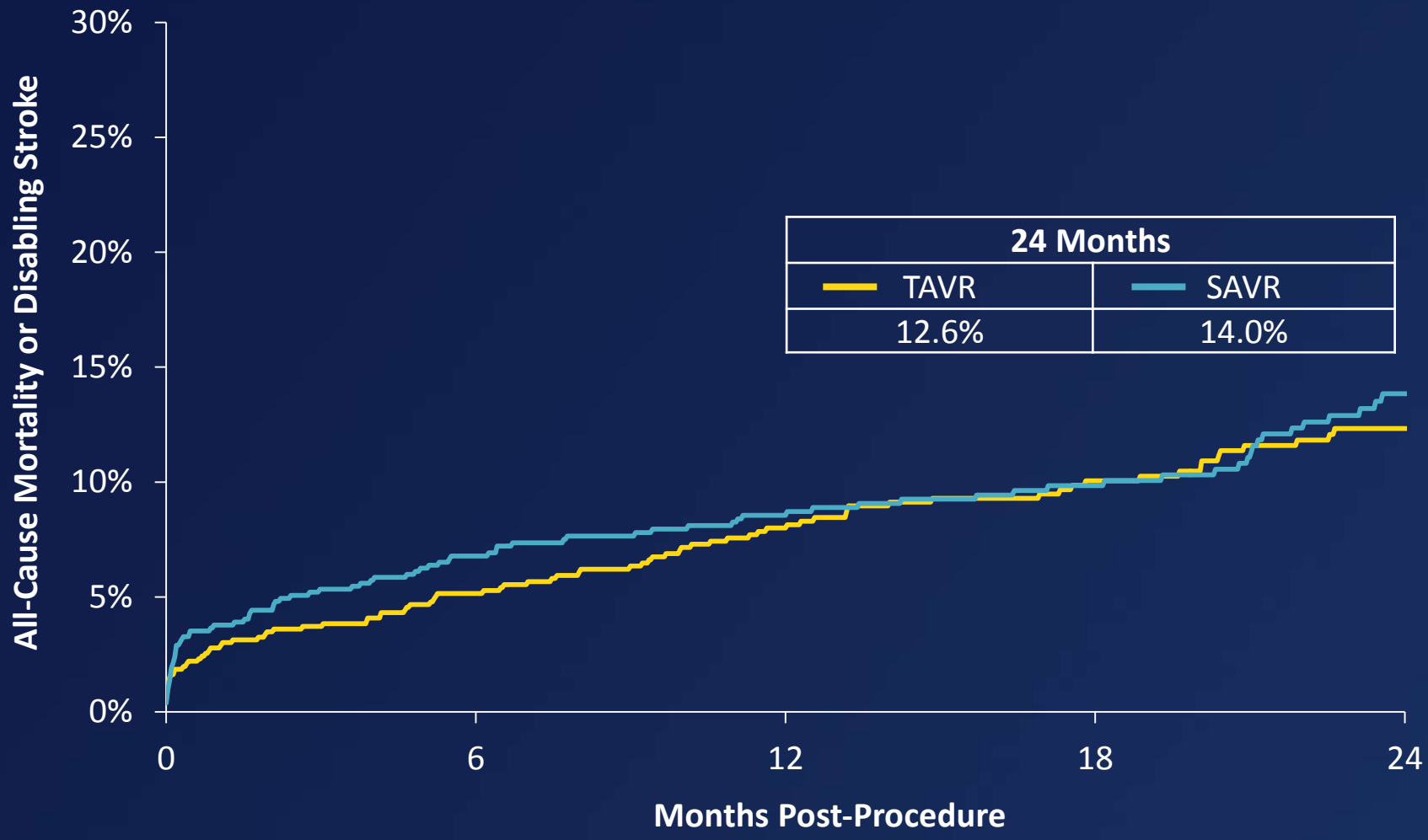
n (%) or mean ± SD	TAVR (N=864)	SAVR (N=796)
Body mass index <21 kg/m^2	20 (2.3)	21 (2.6)
Falls in past 6 months	102 (11.8)	101 (12.7)
5 meter gait speed >6 s	428 (51.8)	403 (52.9)
6 minute walk test (meters)	254.1 ± 115.8	260.9 ± 117.9
Grip strength below threshold	519 (62.5)	490 (63.1)
Does not live 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

CoreValve SURTAVI Trial

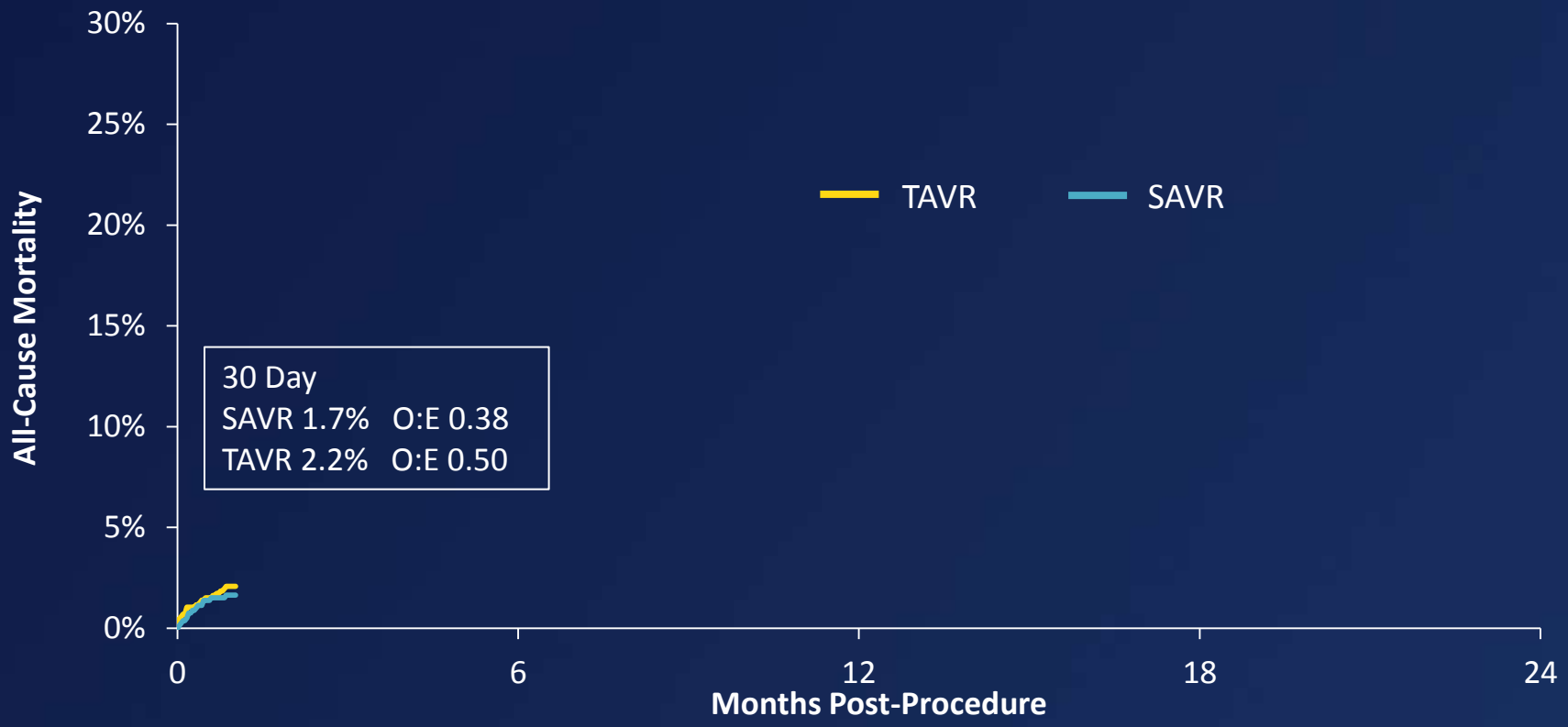


No. at Risk

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

All-Cause Mortality

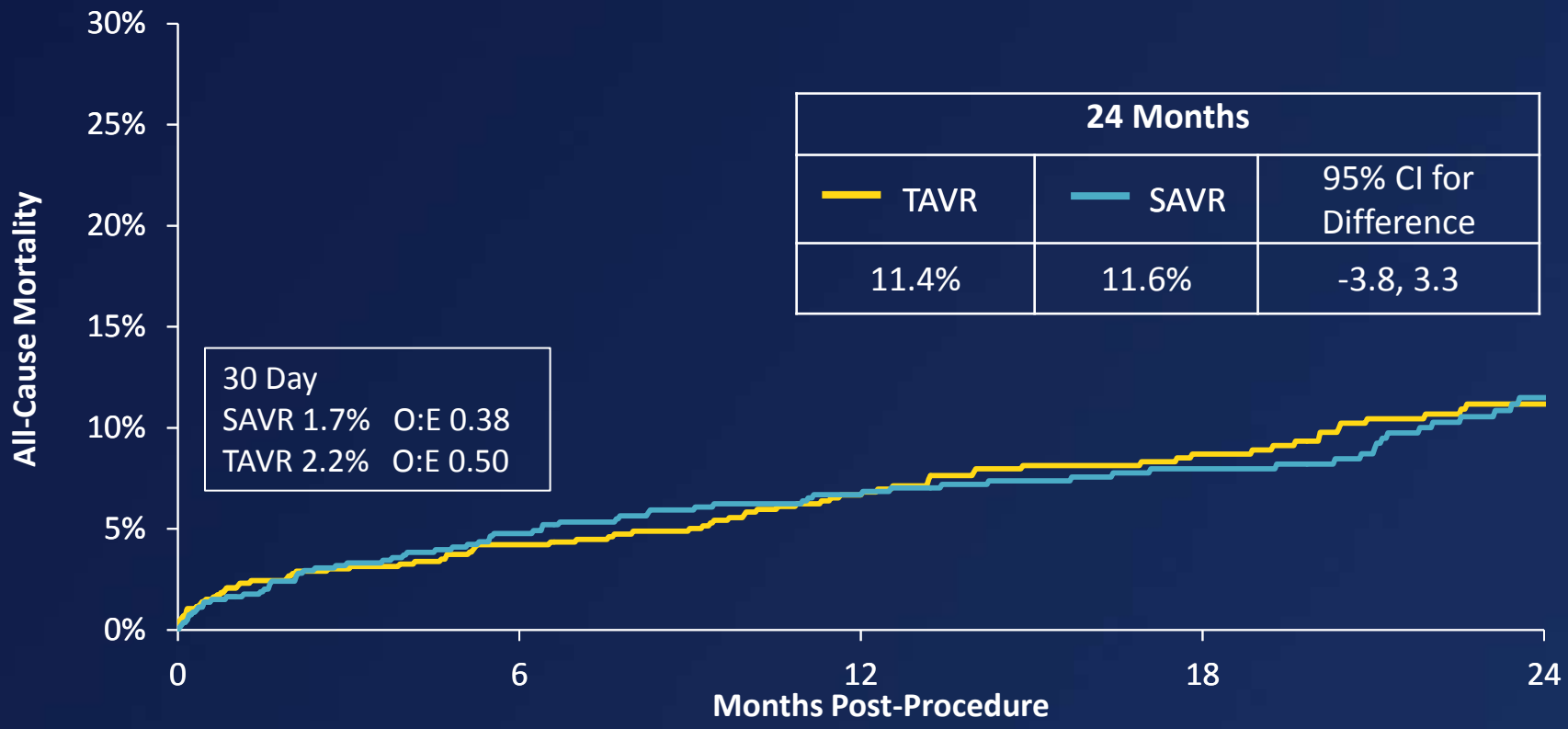
CoreValve SURTAVI Trial



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

All-Cause Mortality

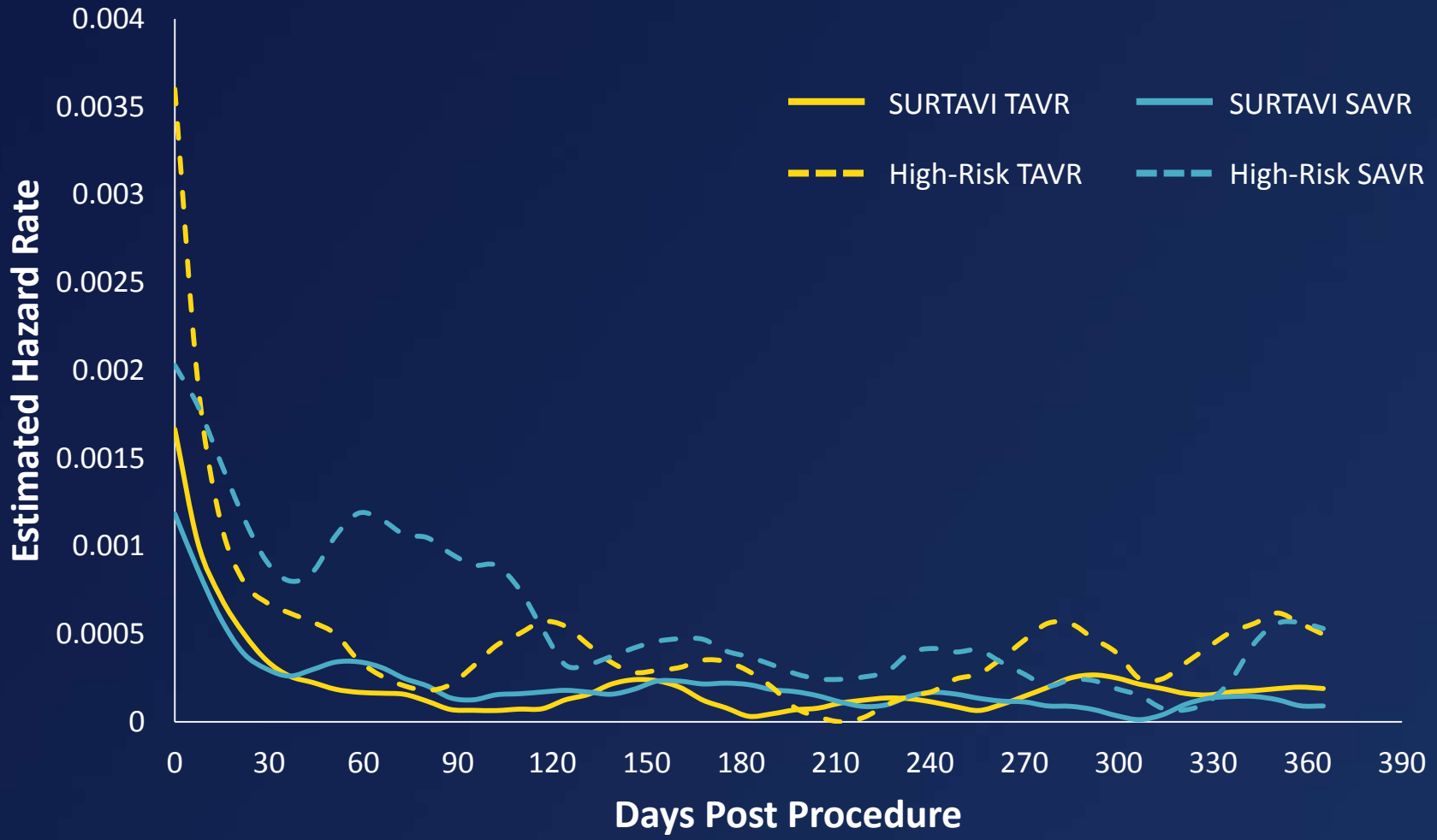
CoreValve SURTAVI Trial



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

Instantaneous Hazard of Mortality

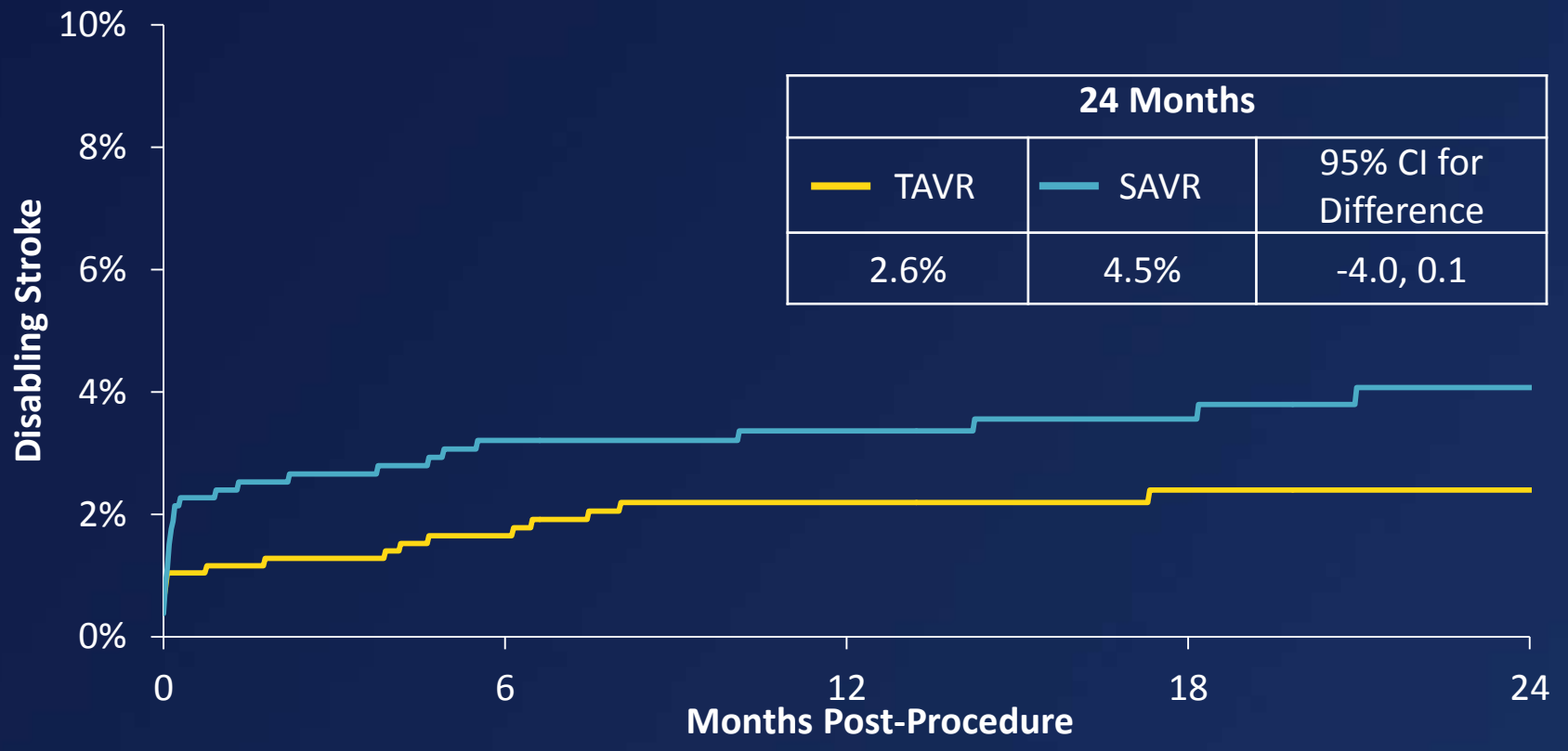
CoreValve SURTAVI Trial



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

Disabling Stroke

CoreValve SURTAVI Trial



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)

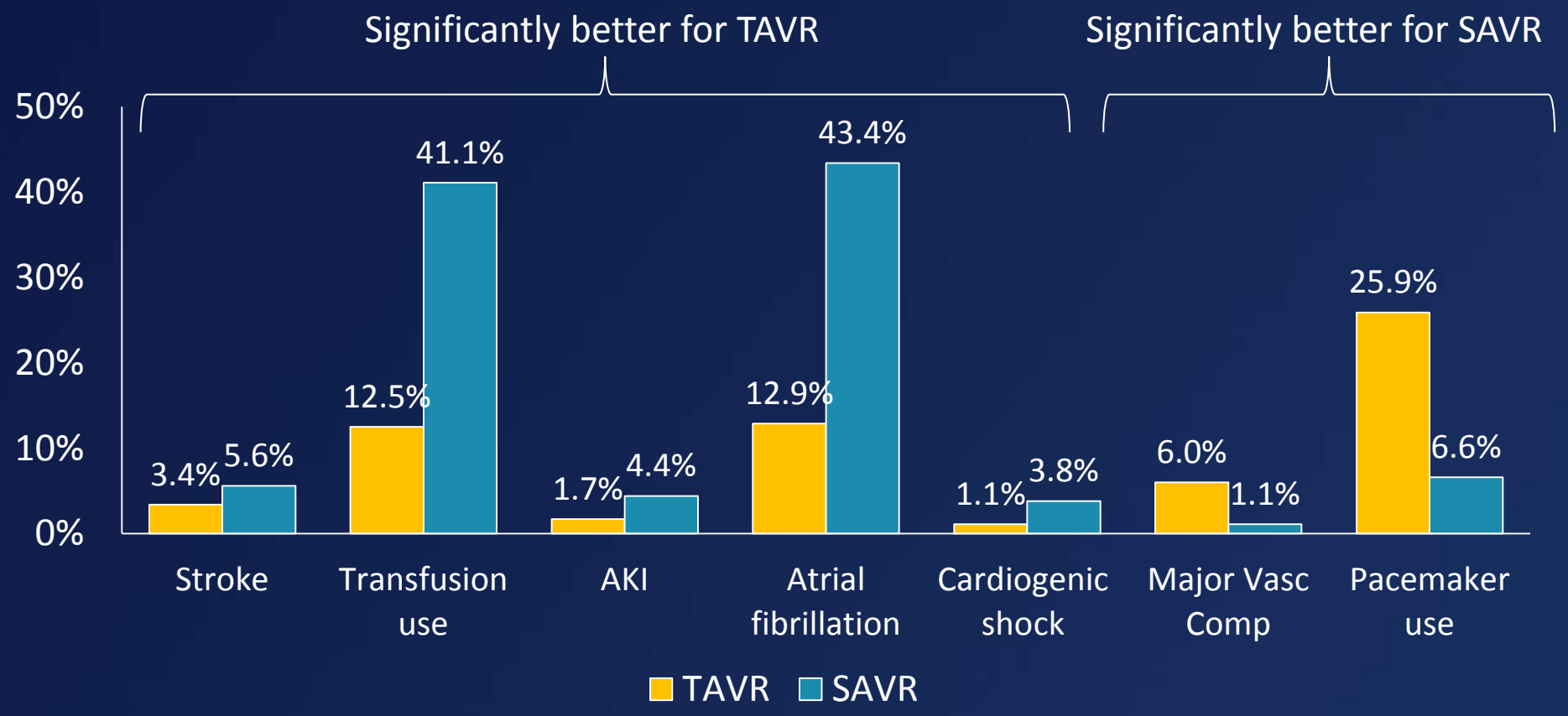
30-Day Safety and Procedure-related Complications

	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

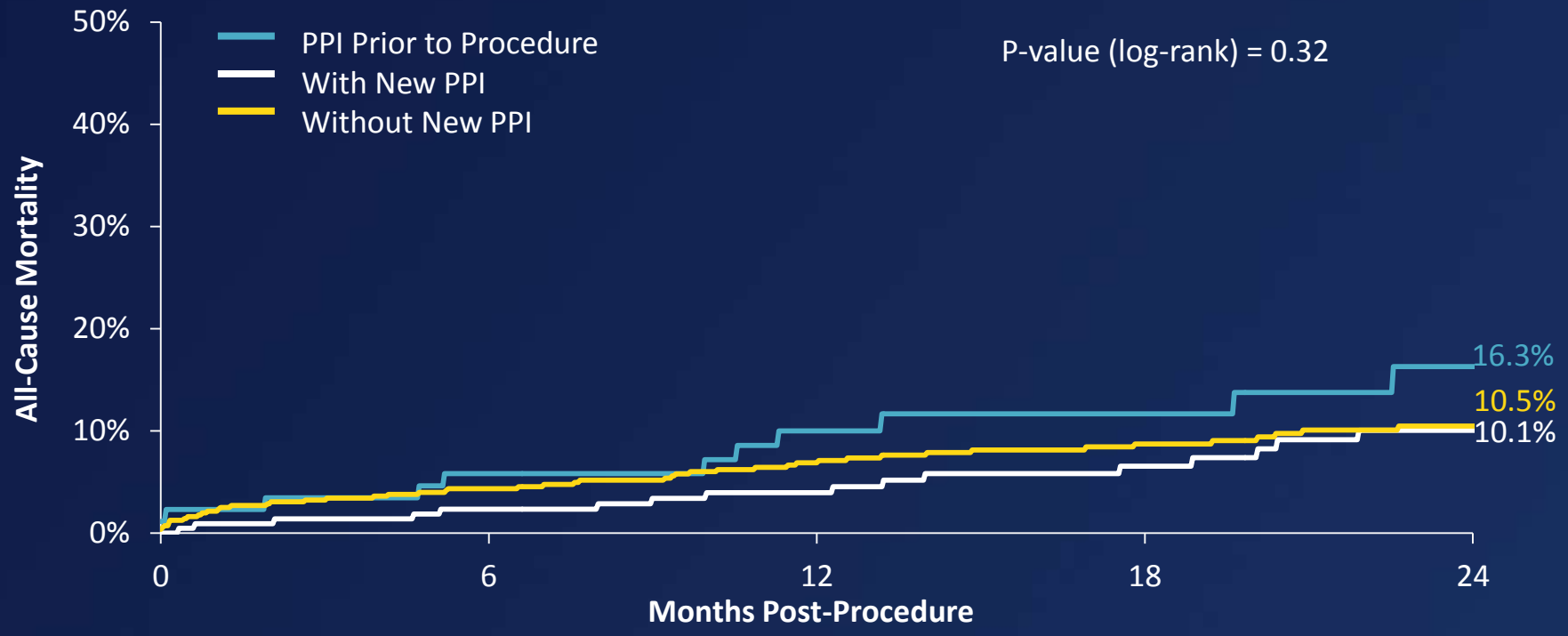
30 Day Safety Outcomes

CoreValve SURTAVI Trial



All-Cause Mortality by Pacemaker Implantation

CoreValve SURTAVI Trial



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* 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

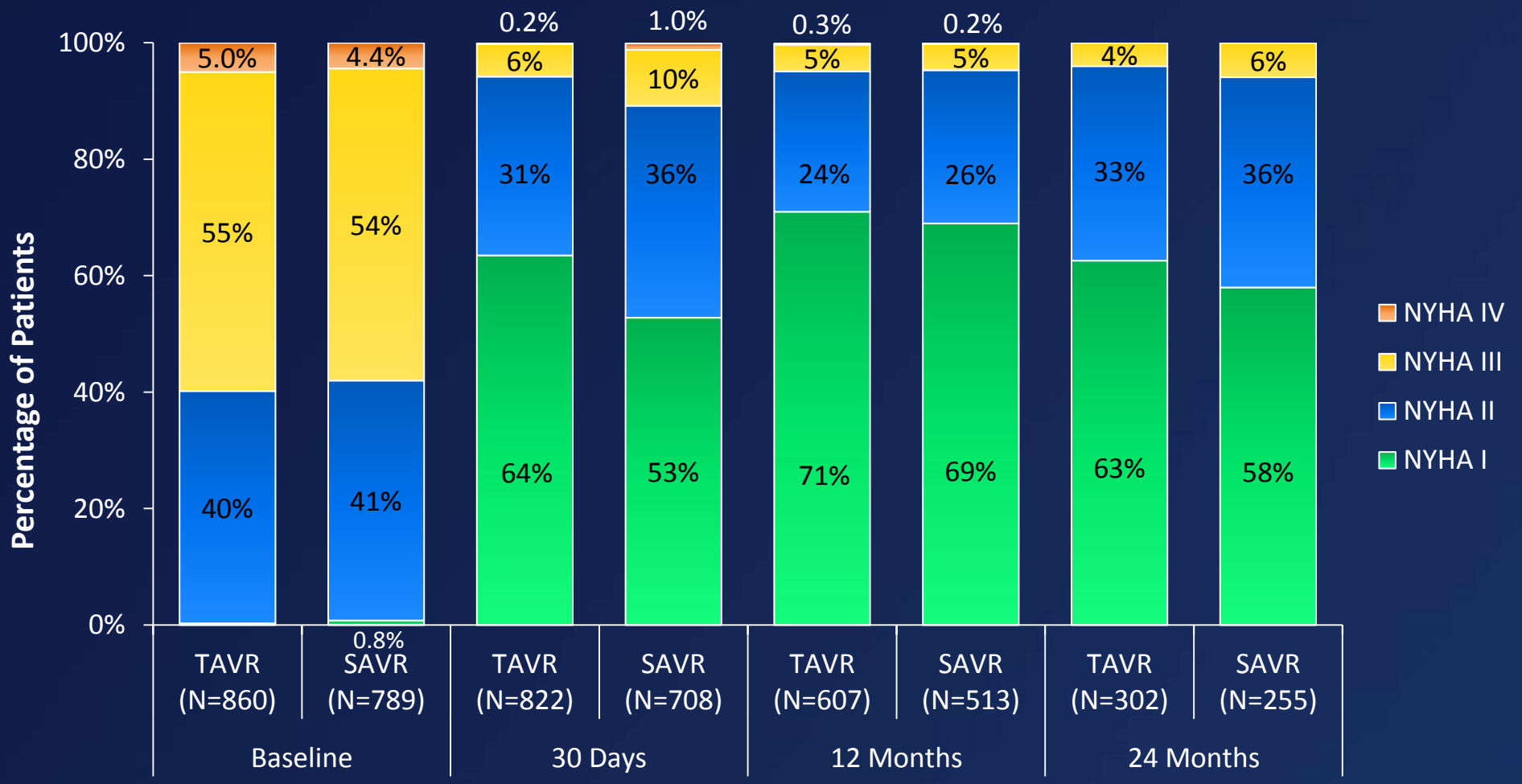
Hemodynamics*

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

*Core lab adjudicated

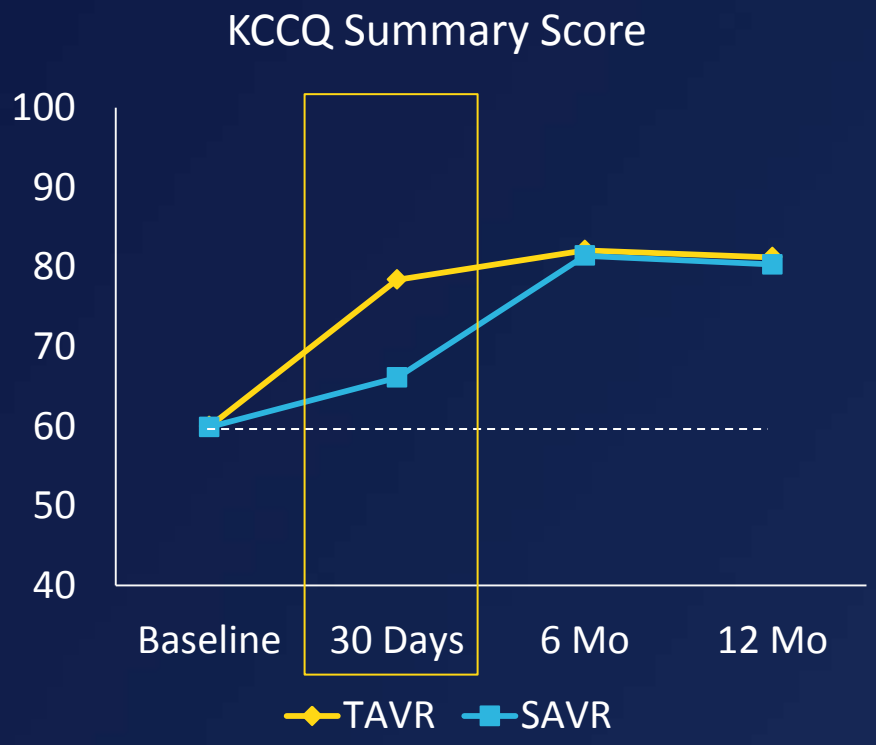
NYHA Functional Class

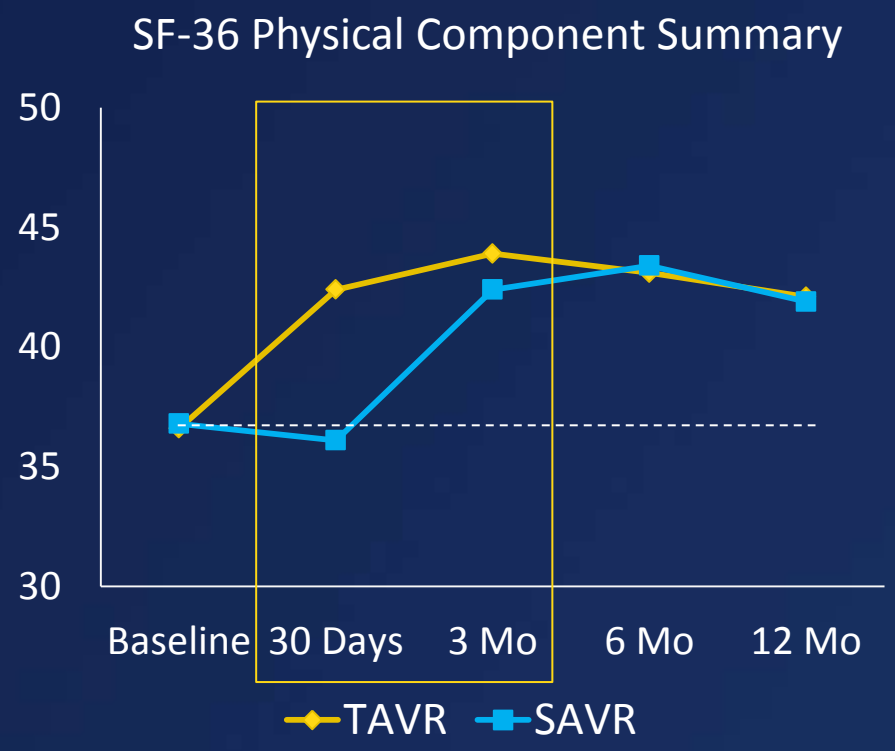
CoreValve SURTAVI Trial



Quality of Life

Patients recover quality of life sooner after TAVR than SAVR





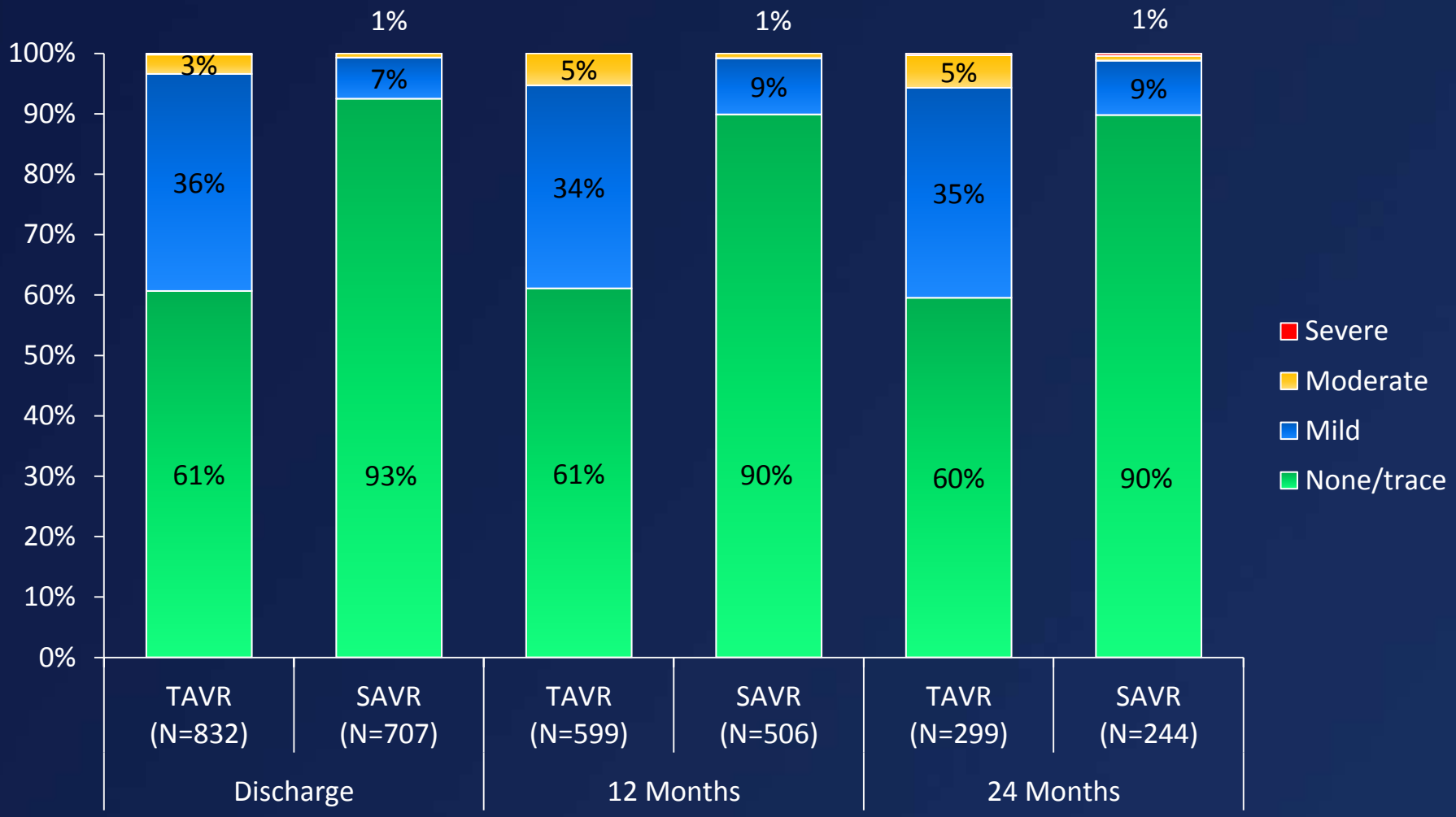
Length of Hospital Stay

TAVR patients had significantly fewer days in the ICU and in hospital

Mean ± SD	TAVR	SAVR	95% CI for difference
Length of index procedure hospital stay, days	(n=863) 5.75 ± 4.85	(n=795) 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)

Total Aortic Regurgitation*

CoreValve SURTAVI Trial

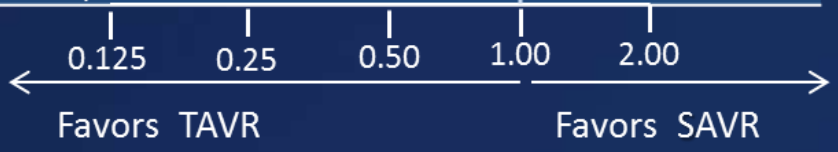


* Implanted population, core lab adjudicated

All-Cause Mortality or Disabling Stroke at 12 Months

CoreValve SURTAVI Trial

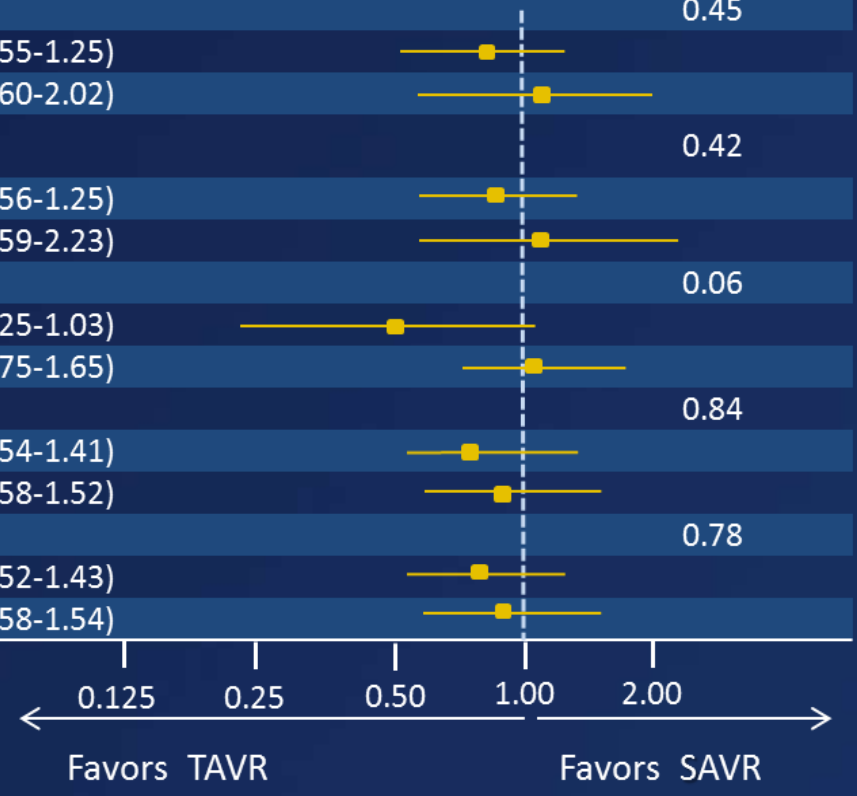
Subgroup	TAVR	SAVR	Hazard Ratios (95% CI)	P for Interaction
	n/N (KM rate at 12 months)			
Age				0.82
<80	22/352 (6.6)	21/330 (6.8)	0.96 (0.53-1.74)	
≥80	44/512 (9.2)	45/466 (10.0)	0.88 (0.58-1.33)	
Gender				0.73
Male	42/498 (9.0)	38/438 (9.2)	0.94 (0.61-1.47)	
Female	24/366 (6.9)	28/358 (8.2)	0.83 (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

CoreValve SURTAVI Trial

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