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Building Evidence for Treating Lower Risk Patients: Recent Updates from Evolut R Technology and Evidence

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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

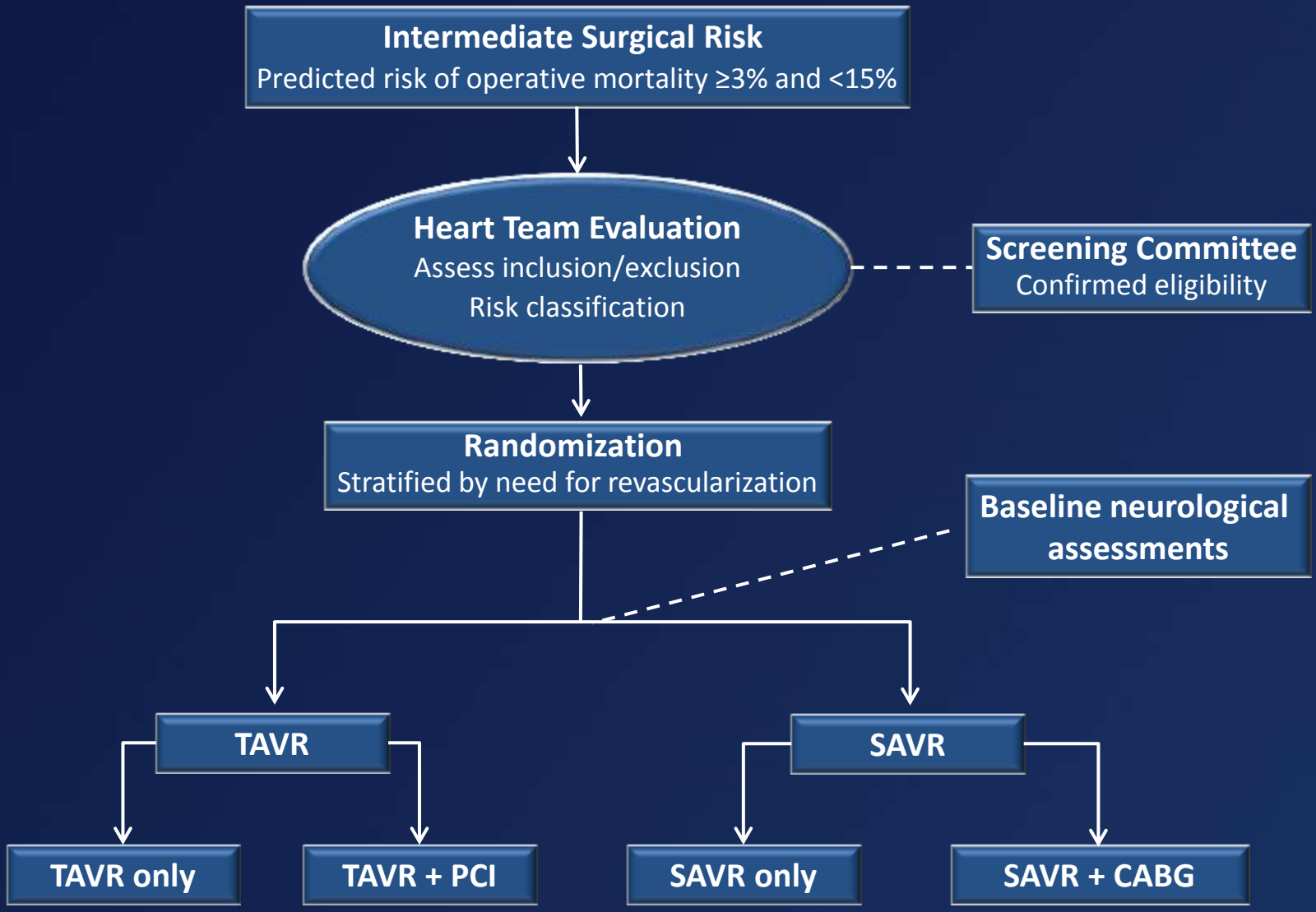
Michael Reardon MD,

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

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

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.

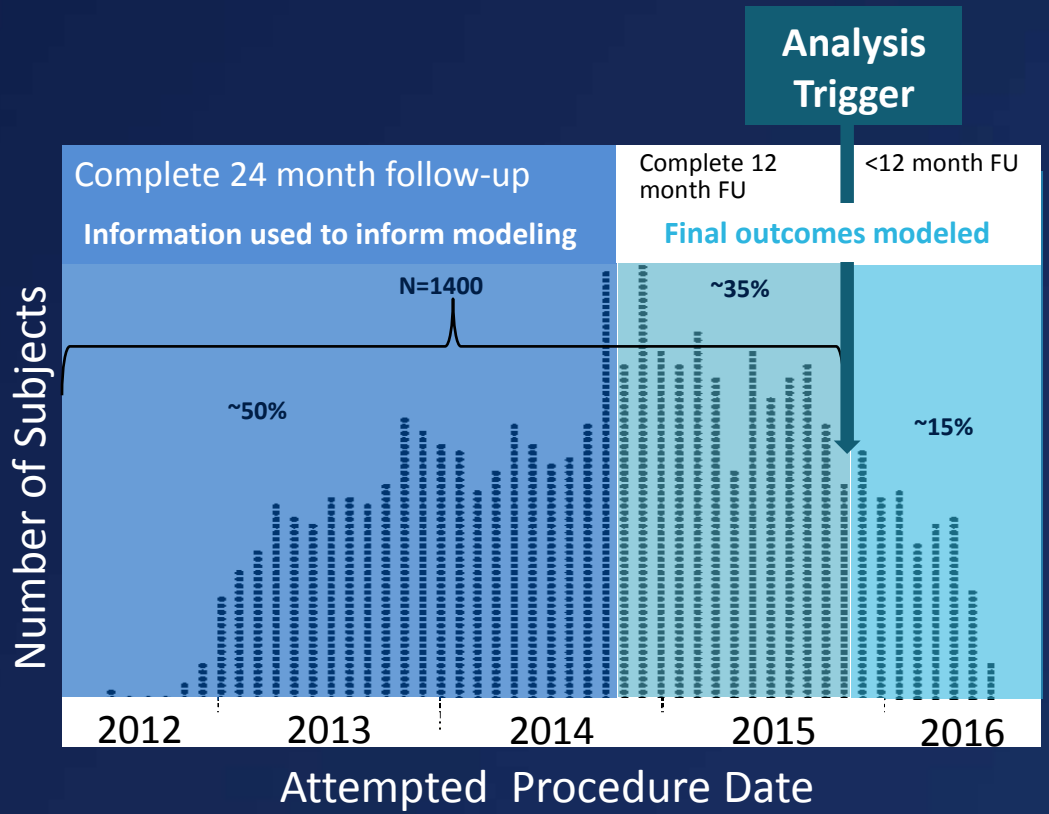
- Life-threatening or disabling bleeding was defined using BARC criteria.

Statistical Methods

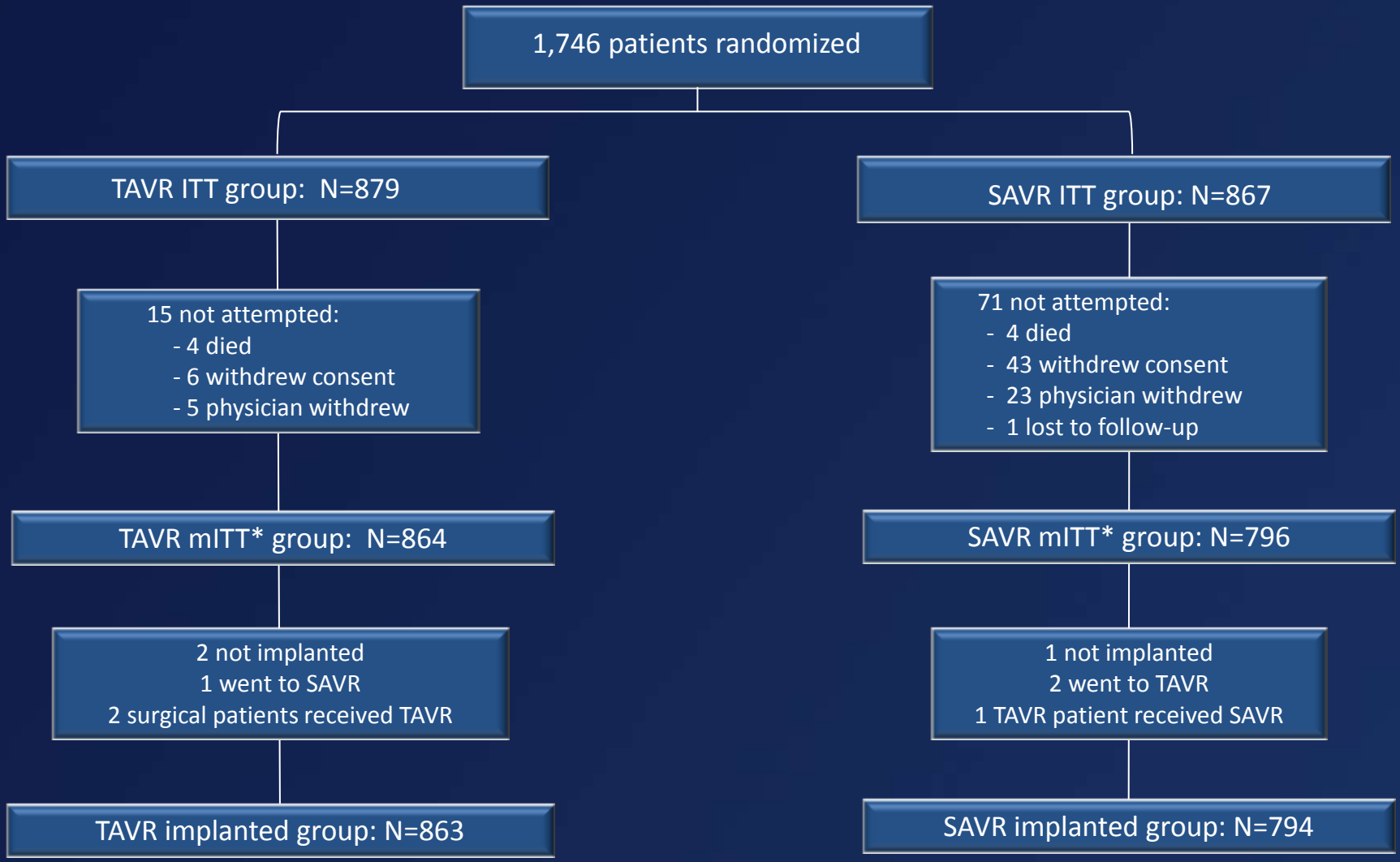
- The SURTAVI trial utilized a novel Bayesian statistical methodology.
- The primary objective of the trial was to show that TAVR is noninferior to SAVR for all-cause mortality or disabling stroke at 24 months with a noninferiority margin of 0.07.
- The sample size of 1600 attempted implants assumed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

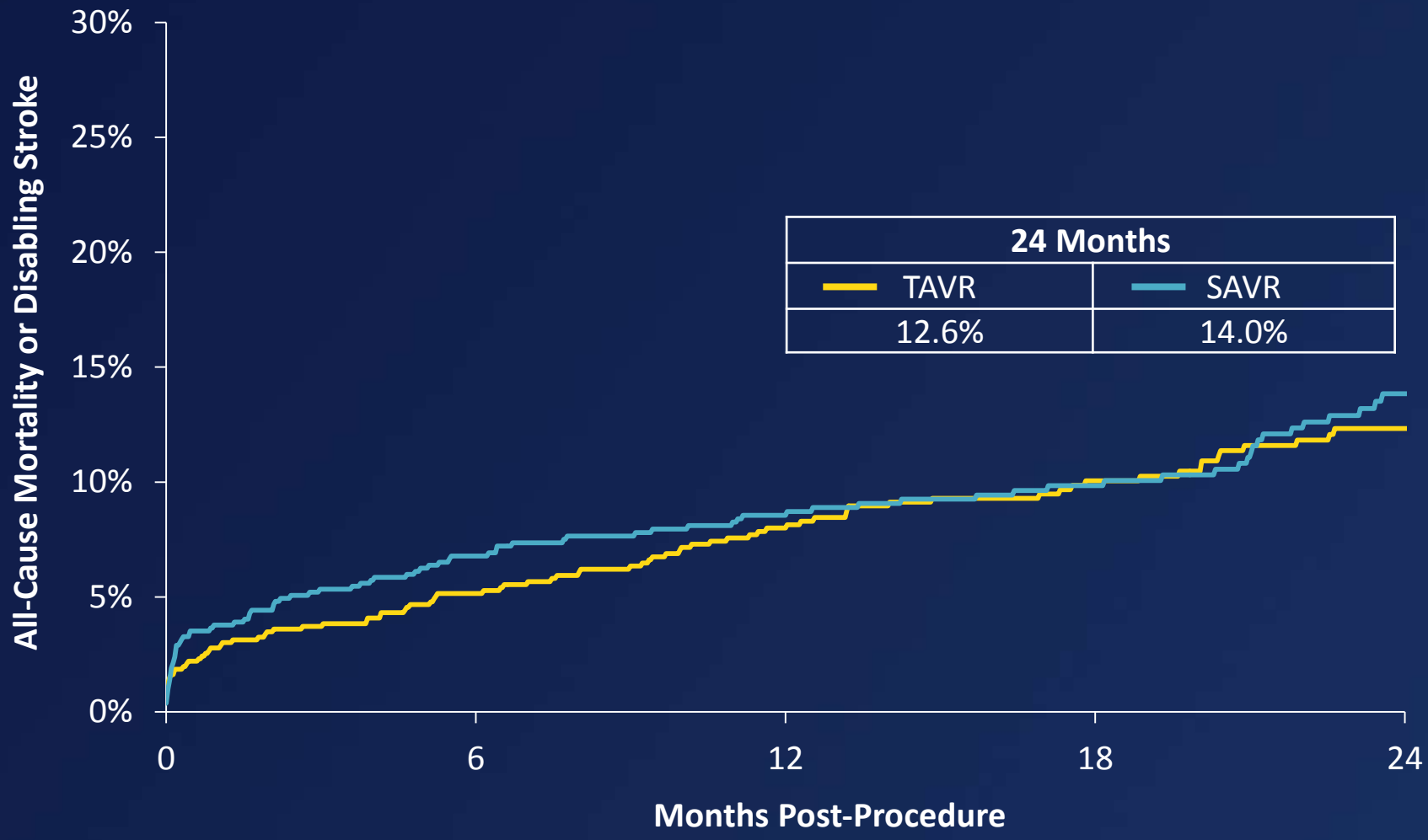
n (%) or mean ± SD	TAVR (N=864)	SAVR (N=796)
Body mass index <21 kg/m^2	20 (2.3)	21 (2.6)
Falls in past 6 months	102 (11.8)	101 (12.7)
5 meter gait speed >6 s	428 (51.8)	403 (52.9)
6 minute walk test (meters)	254.1 ± 115.8	260.9 ± 117.9
Grip strength below threshold	519 (62.5)	490 (63.1)
Does not live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

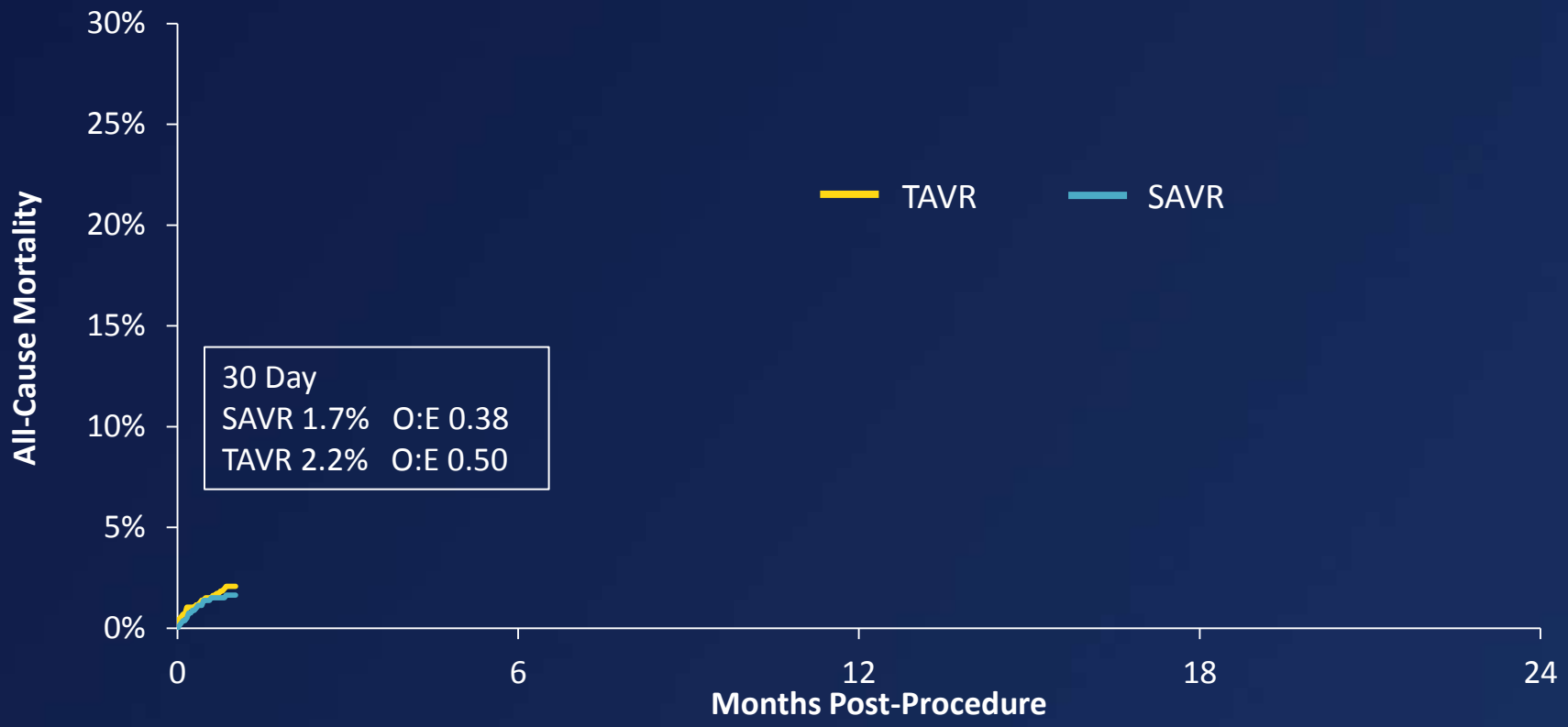


No. at Risk

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

All-Cause Mortality

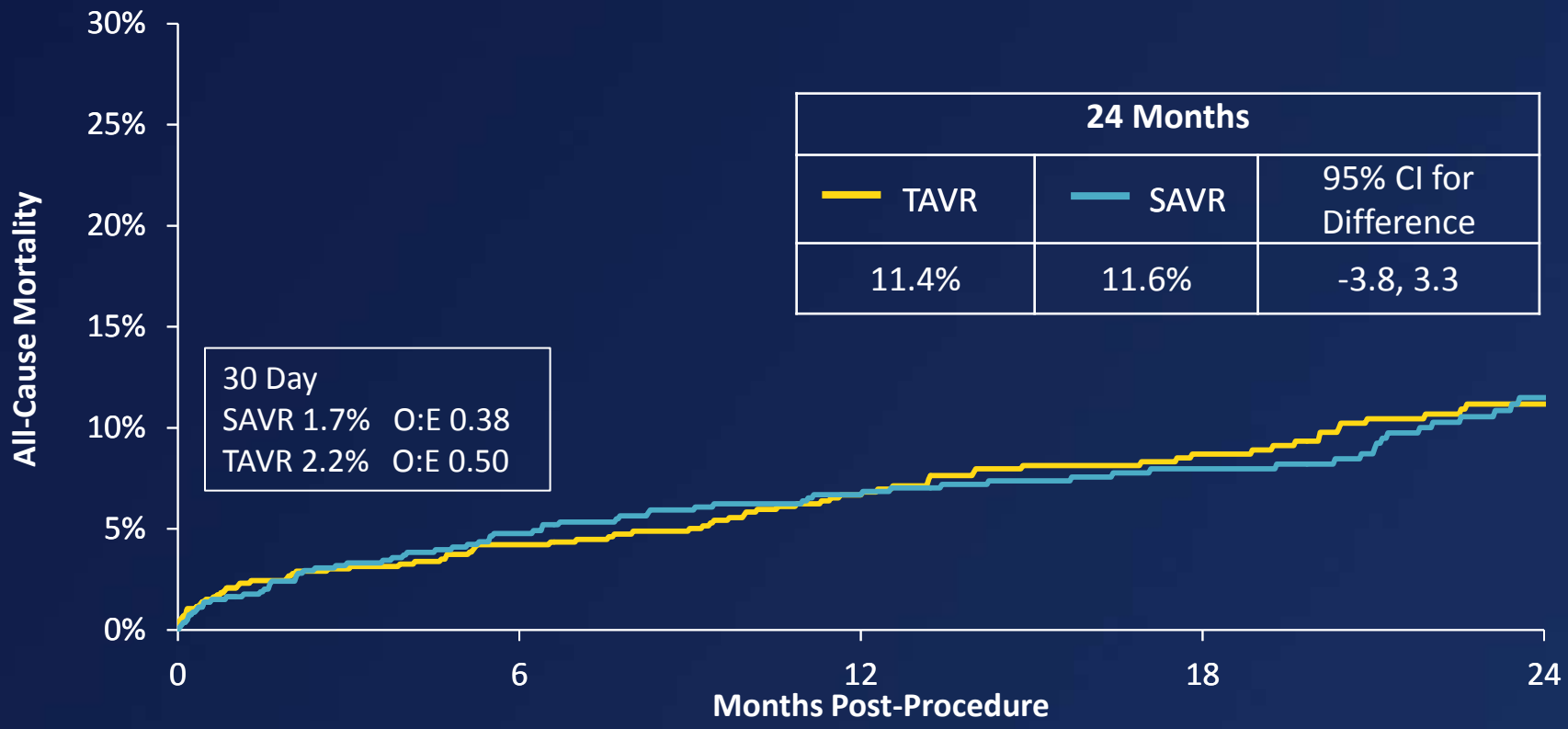
CoreValve SURTAVI Trial



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
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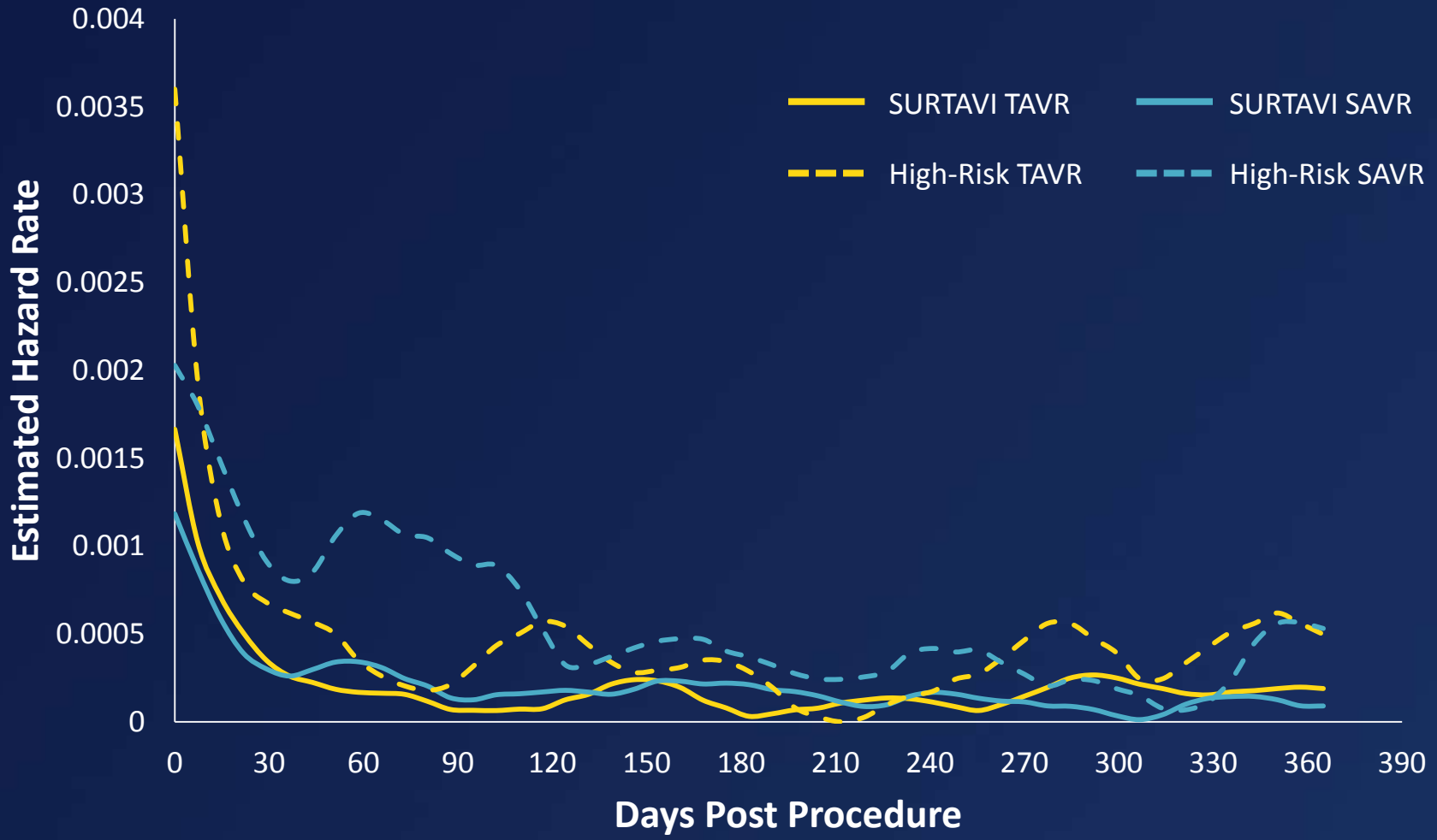
Instantaneous Hazard of Mortality

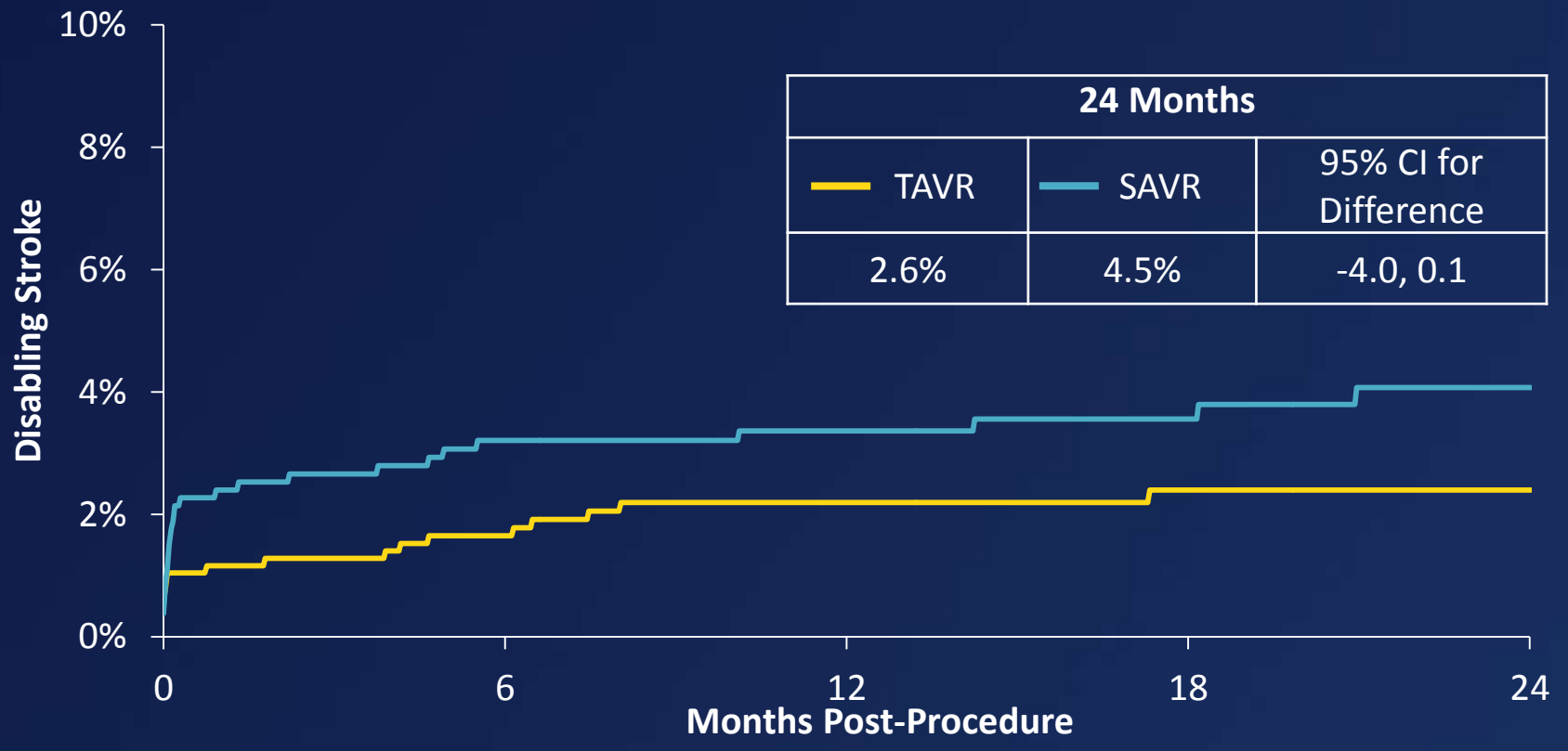
CoreValve SURTAVI Trial



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

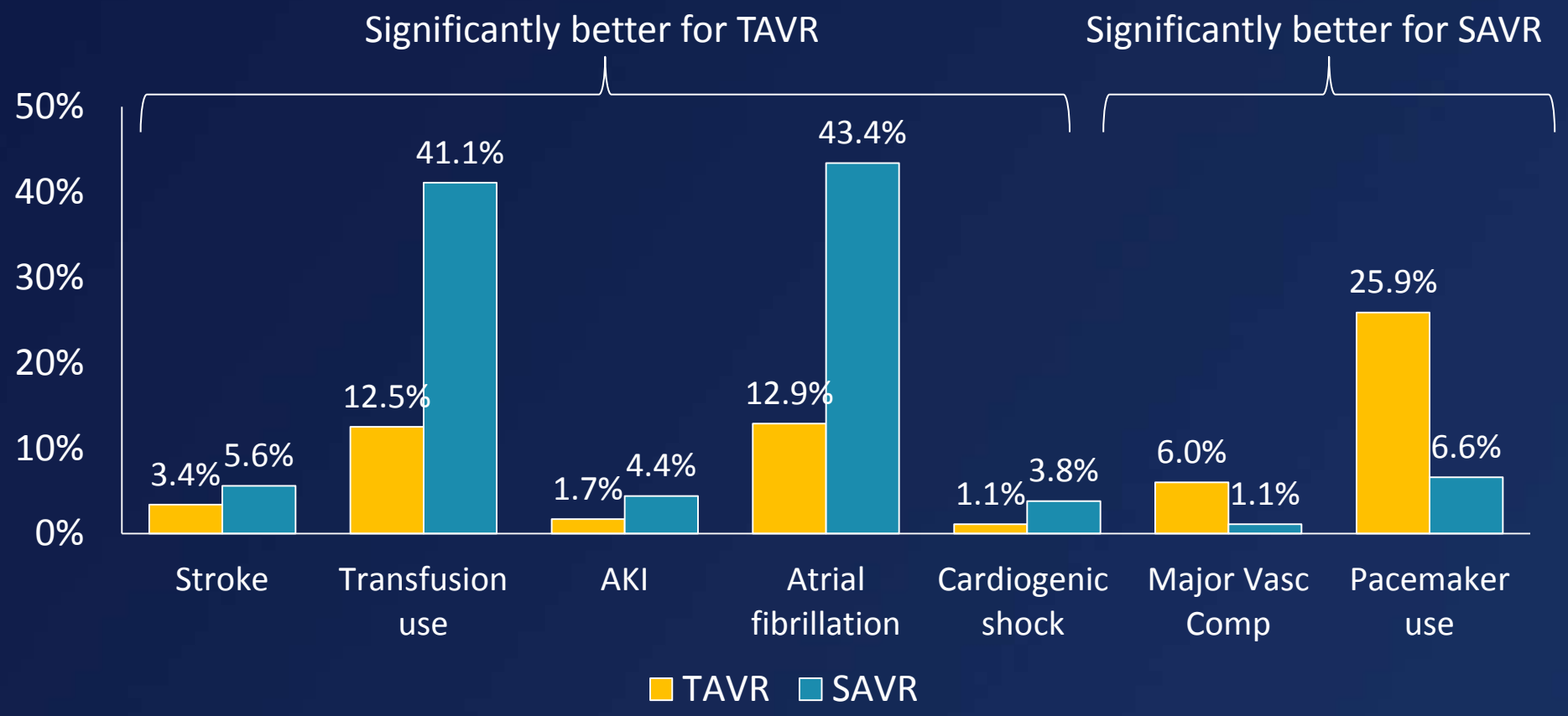
30-Day Safety and Procedure-related Complications

	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

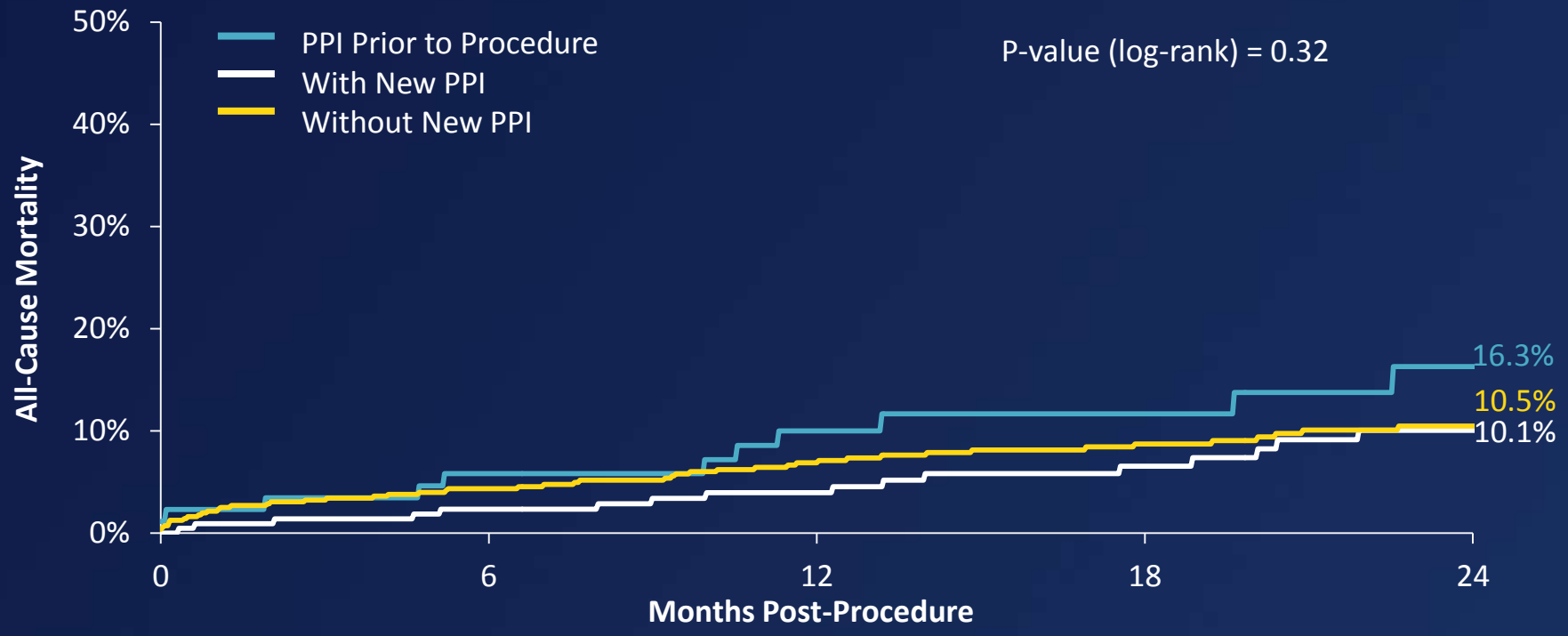
30 Day Safety Outcomes

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

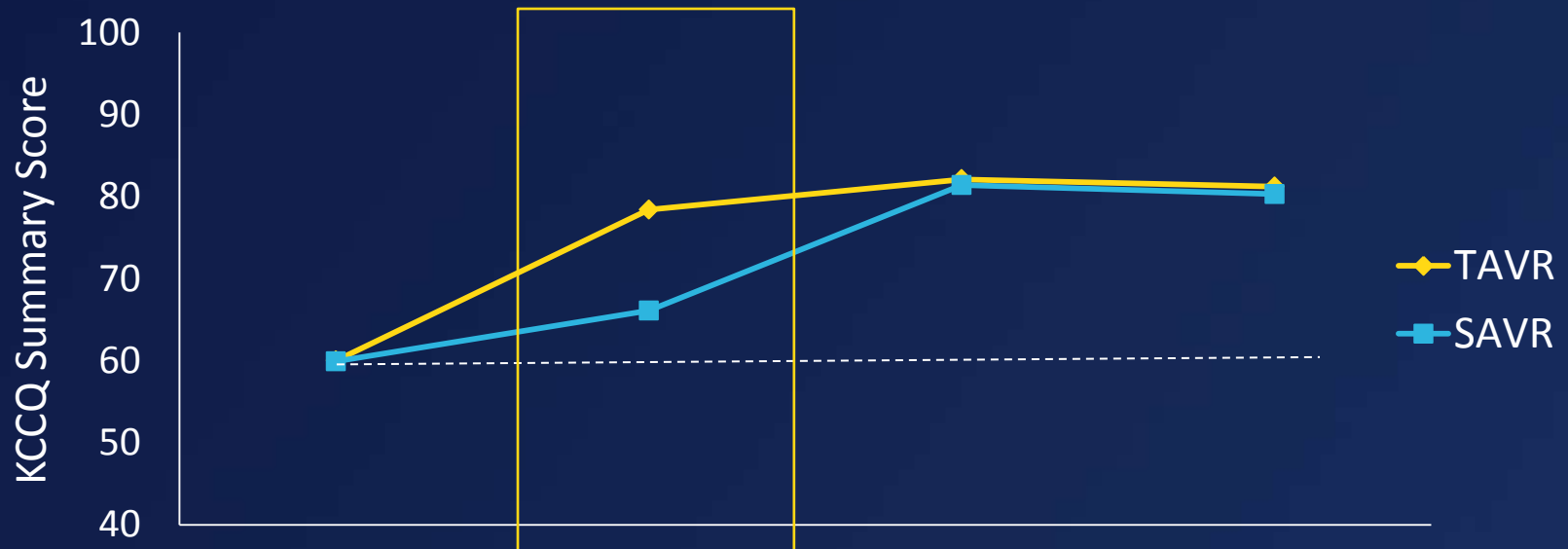
Hemodynamics*

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

*Core lab adjudicated

KCCQ Summary Score Over Time

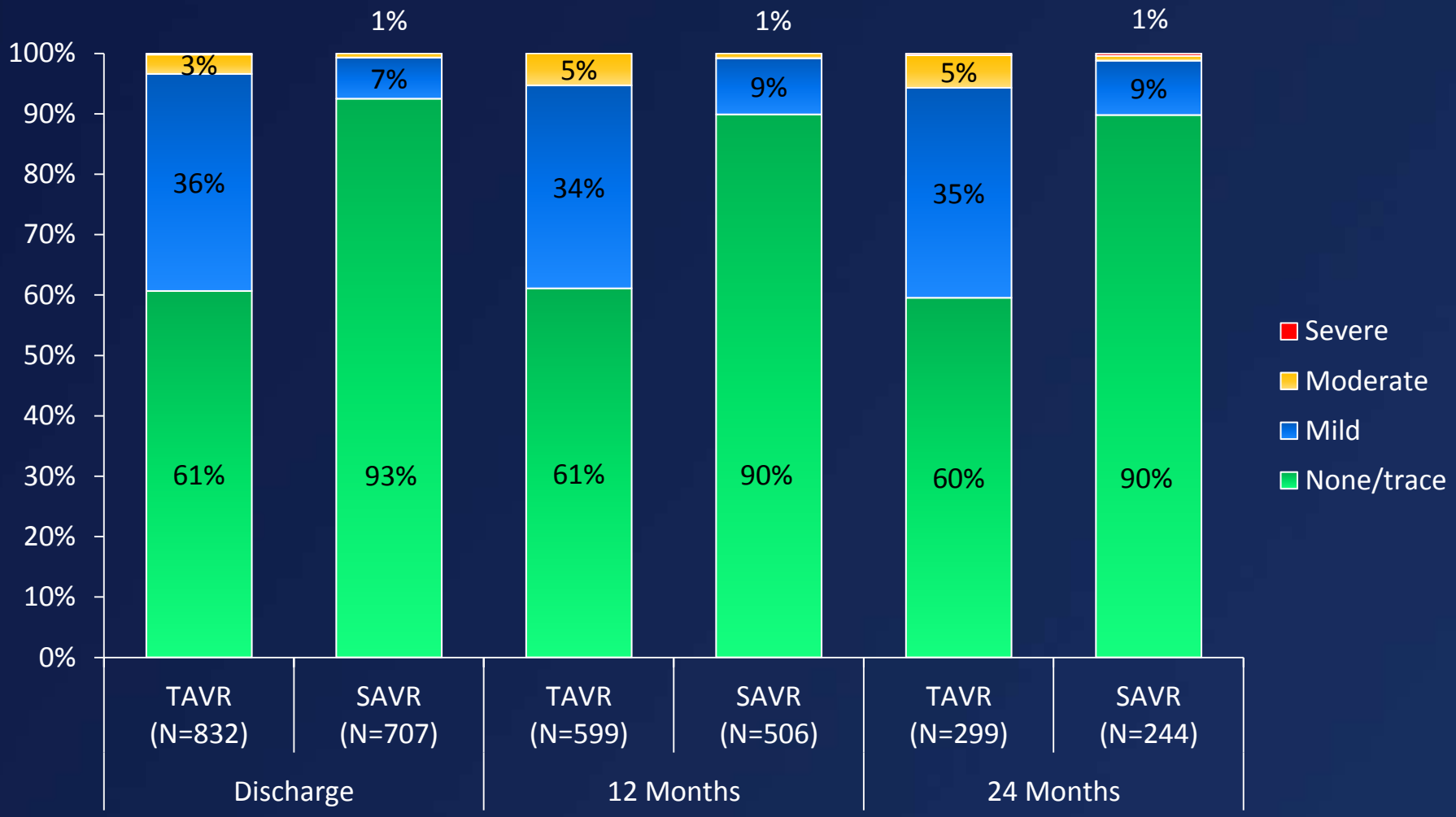
Patients recover quality of life sooner after TAVR than SAVR



	Baseline	30 Days	6 Months	12 Months
		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*

CoreValve SURTAVI Trial



* Implanted population, core lab adjudicated

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.

30-Day Safety and Echocardiographic Outcomes Following Transcatheter Aortic Valve Replacement with the Self-Expanding Repositionable Evolut PRO System

John K. Forrest, MD, For the Evolut PRO US Clinical Study Investigators

The Evolut PRO is the Next Generation Evolut R Valve

Evolut R

Porcine pericardial wrap on lower 1.5 rows of inflow cells

Evolut PRO

Evolut PRO Study Methods

- The Evolut PRO Study is a 60-patient prospective, multicenter, controlled, non-randomized single-arm study at 8 US centers.
- The 2 primary safety endpoints were all-cause mortality and disabling stroke at 30 days.
- The primary efficacy endpoint was the percentage of patients with none or trace aortic regurgitation at 30 days.
- An independent Echocardiographic Core Laboratory (Mayo Clinic, Rochester, MN) was used to adjudicate all echocardiographic assessments.

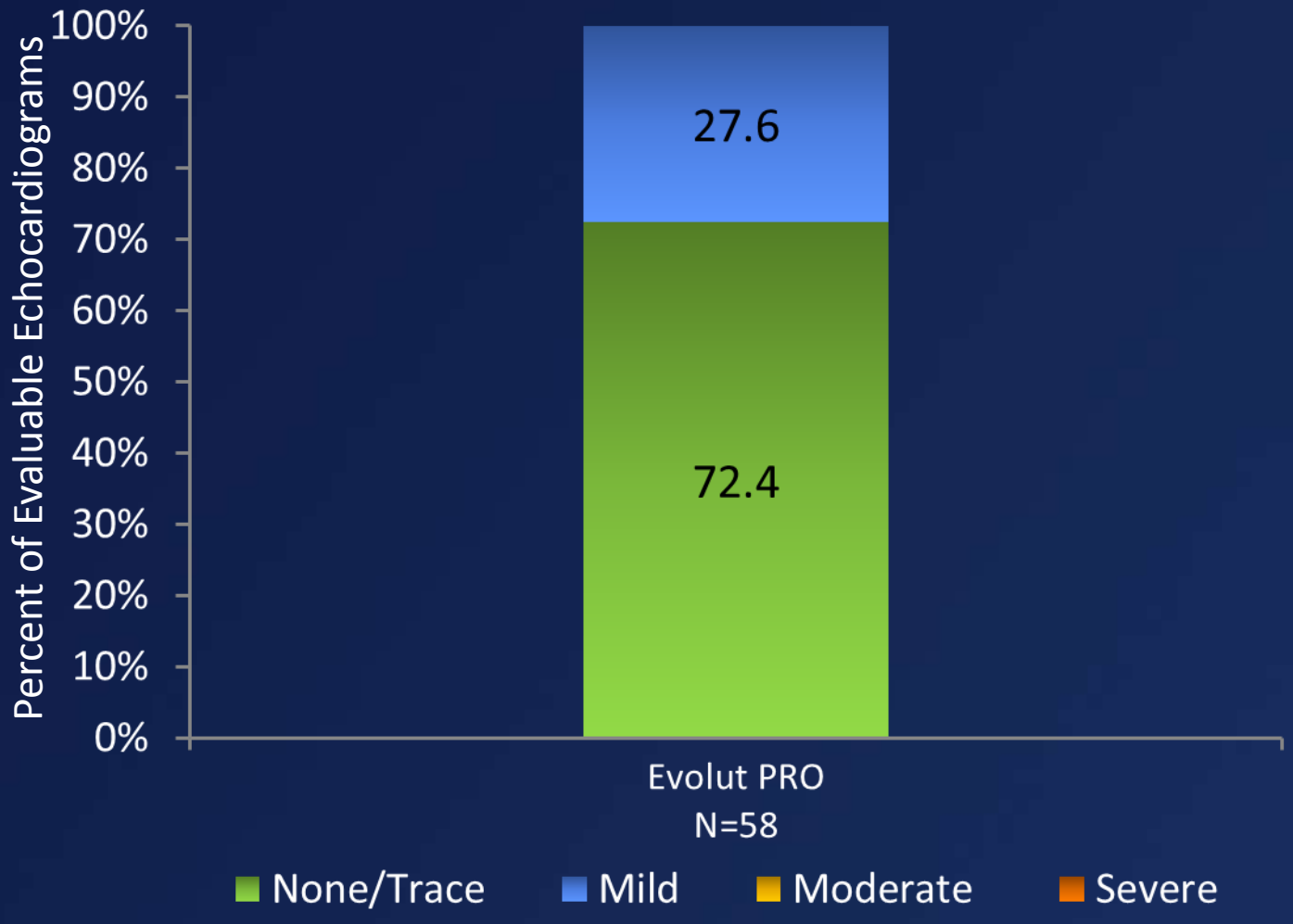
Evolut PRO Baseline Characteristics

Characteristic, mean ± SD or %	N=60
Age, years	83.3 ± 7.2
Female	65.0
BSA, m^2	1.8 ± 0.2
STS – PROM, %	6.4 ± 3.9
NYHA Class III or IV	70.0
Peripheral vascular disease	43.3
Atrial fibrillation / atrial flutter	18.6
Diabetes mellitus	43.3
Severe aortic calcification	20.5
LV ejection fraction, %	58.9 ± 12.4
Pre-existing pacemaker	15.0

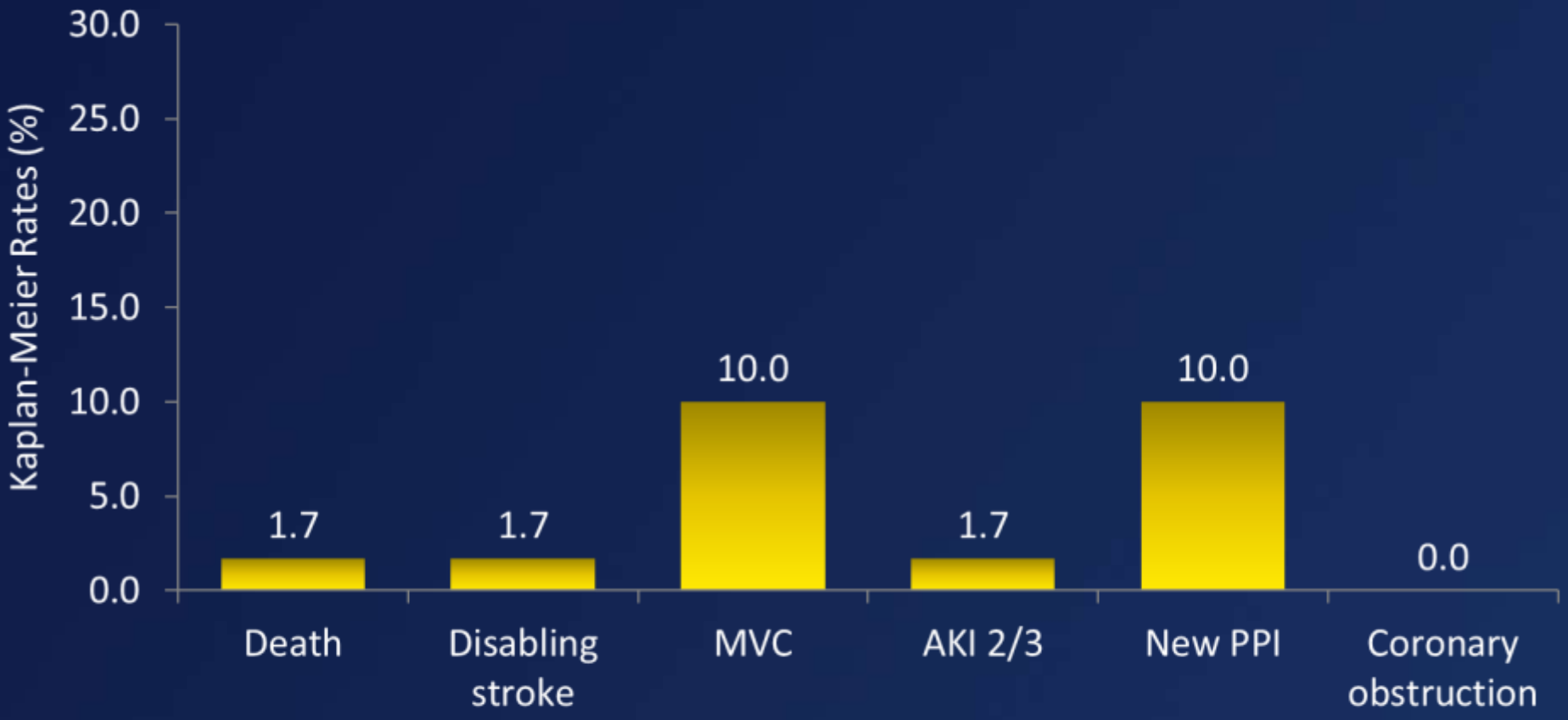
Evolut PRO Procedural Outcomes

Characteristic, % or mean ± SD	N = 60
General anesthesia	58.3
Iliofemoral access approach	98.3
Valve Size Implanted	
26 mm	40.0
29 mm	60.0
Pre-TAVR balloon dilation	51.7
Post-implant balloon dilation	26.7
Percentage of patients repositioned	35.0
Average implant depth, mm	4.3 ± 1.6

Evolut PRO Aortic Regurgitation at 30 Days

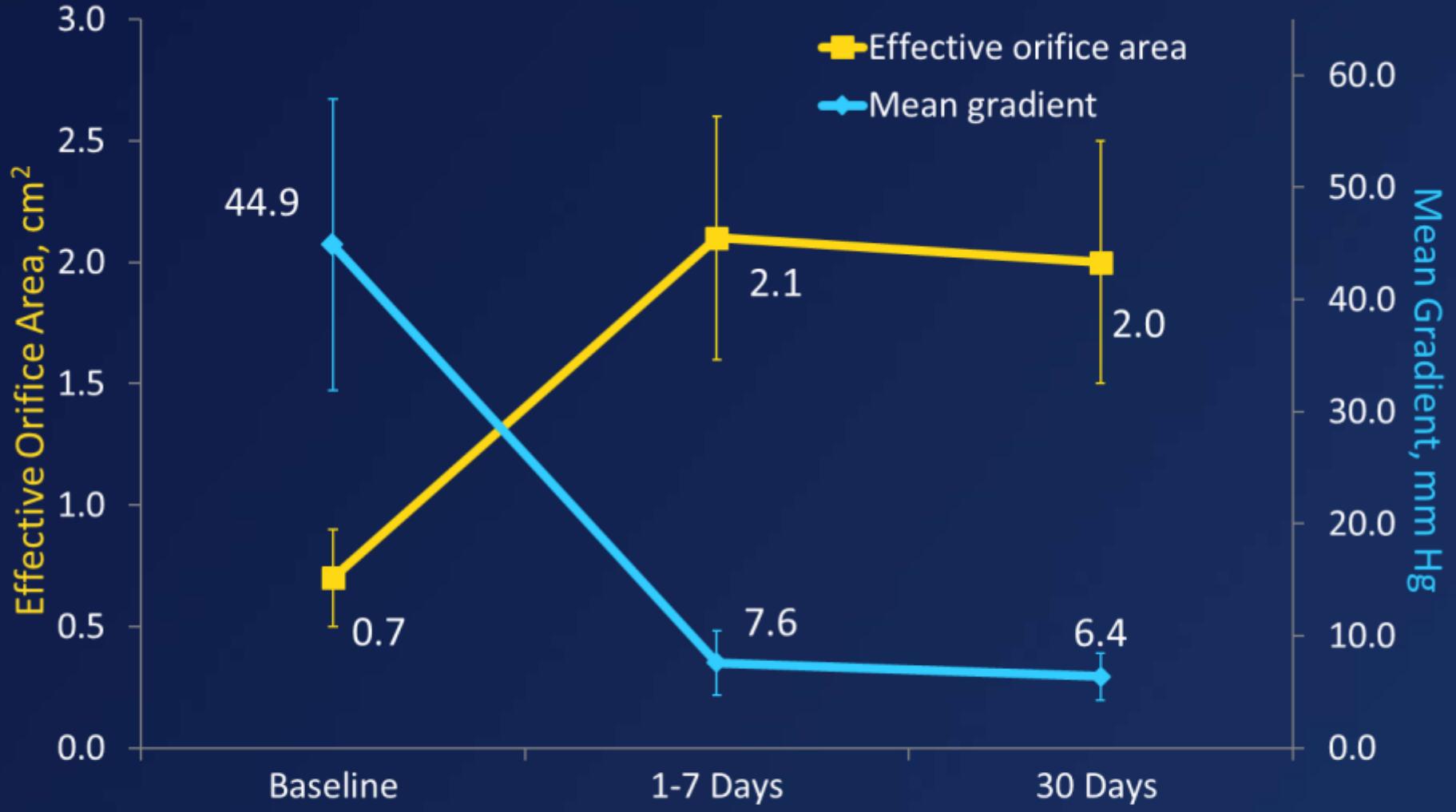


Evolut PRO Safety Outcomes at 30 Days



AKI, acute kidney injury; MVC, major vascular complication; PPI, permanent pacemaker implantation.

Evolut PRO Valve Performance

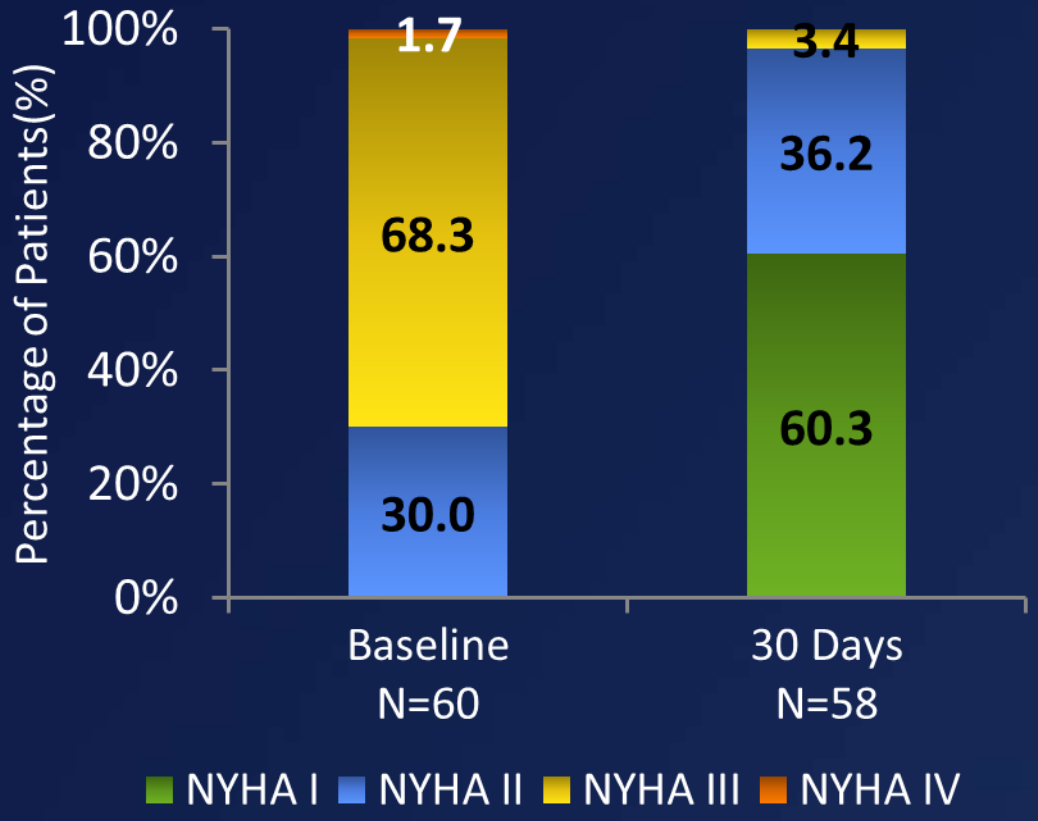


	Baseline	1-7 Days	30 Days
Gradient	59	57	55
EOA	57	49	47

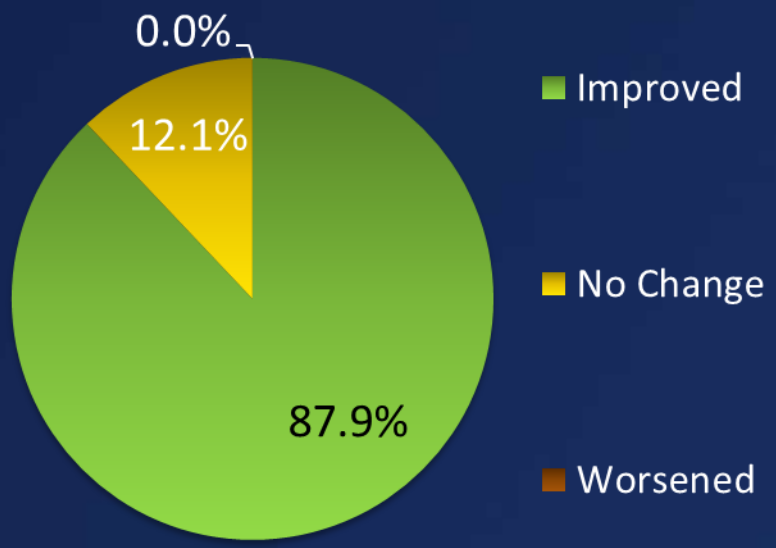
Evolut PRO ACC.17

Error bars are standard deviations.

Evolut PRO New York Heart Association



87.9% of Survivors Improved NYHA Class at 30 Days



Evolut PRO Clinical Summary

- The majority of patients (72.4%) implanted with the Evolut PRO valve had none or trace regurgitation at 30 days. The rest of the patients had mild aortic regurgitation (27.6%).
- There were no patients with more than mild aortic regurgitation at 30 days.
- The valve demonstrated excellent hemodynamics with a new permanent pacemaker rate of 10% at 30 days.