THE PARTNER 3 TRIAL

Two-year Clinical and Echocardiographic Outcomes from the PARTNER 3 Low-risk Randomized Trial

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Martin B. Leon, MD
on behalf of the PARTNER 3 Trial Investigators

Disclosures - Michael J. Mack, MD

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Within the past 36 months, I or my spouse/partner has had a financial interest/arrangement or affiliation with the organization(s) listed below.

Financial Relationship	Company
• Research Support	Abbott, Edwards Lifesciences, Gore, Medtronic
• Consulting Fees	None
• Trial Co-PI or Study Chair (Travel expenses only, for trial activities)	Abbott, Edwards Lifesciences, Medtronic

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Background

- Previous PARTNER trials have shown that TAVR was superior to standard therapy in extreme-risk patients and non-inferior to surgery in high- and intermediate-risk patients with aortic stenosis.
- Results from the PARTNER 3 Trial in low-risk patients demonstrated superiority for TAVR vs. surgery for the primary endpoint of death, stroke, or rehospitalization at 1 year.

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Purpose

To report the clinical and echocardiographic outcomes of the PARTNER 3 Trial at *2 years* for low-risk patients with severe symptomatic aortic stenosis treated with the SAPIEN 3 TAVR system vs. surgery

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PARTNER 3 Study Design

Symptomatic Severe Aortic Stenosis

Low Risk/TF ASSESSMENT by Heart Team
(STS < 4%)

1:1 Randomization
1000 Patients

TAVR
(SAPIEN 3 THV)

Surgery
(Surgical Bioprosthetic Valve)

Follow-up: 30 days, 6 mos, and annually through 10 years

PRIMARY ENDPOINT:
Composite of all-cause mortality, stroke, or CV re-hospitalization at 1 year post-procedure

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Key Inclusion Criteria

Severe Calcific Aortic Stenosis

- AVA ≤ 1.0 cm^2 or AVA index ≤ 0.6 cm^2/m^2
- Jet velocity ≥ 4.0 m/s or mean gradient ≥ 40 mmHg, AND
  - NYHA Functional Class ≥ 2, OR
  - Abnormal exercise test with severe SOB, abnormal BP response, or arrhythmia, OR
  - Asymptomatic with LVEF < 50%

Low Surgical Risk

- Determined by multi-disciplinary heart team
- STS < 4%
- Adjudicated by case review board

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Key Exclusion Criteria

Anatomic

- Aortic annulus diameter < 16 mm or > 28 mm (3D imaging)
- Bicuspid valve (CT imaging)
- Severe AR (> 3+) or MR (> 3+)
- Severe LV dysfunction (LVEF < 30%)
- Severe calcification of aortic valvular complex (esp. LVOT)
- Vascular anatomy not suitable for safe femoral access
- Complex CAD: ULM, Syntax score > 32, or not amenable for PCI
- Low coronary takeoff (high risk for obstruction)

Clinical

- Acute MI within 1 month
- Stroke or TIA within 90 days
- Renal insufficiency (eGFR < 30 ml/min) and/or renal replacement Rx
- Hemodynamic or respiratory instability
- Frailty (objective assessment; > 2/4+ metrics)

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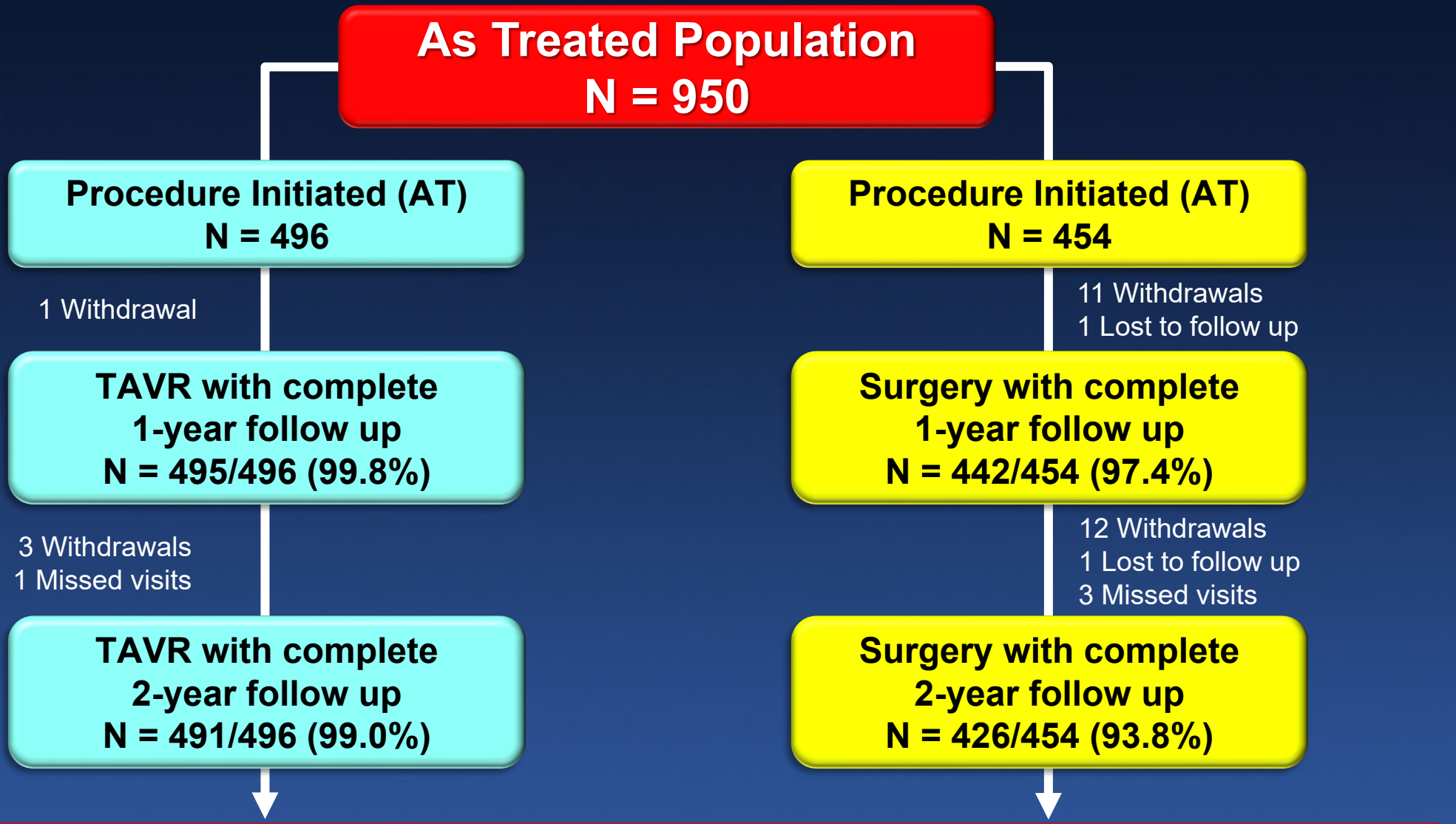
Patient Disposition to 2 Years



96.5% Available for Primary Endpoint Analysis at 2 Years

Baseline Patient Characteristics

Demographics & Vascular Disease	TAVR (N=496)	Surgery (N=454)	Other Co-Morbidities	TAVR (N=496)	Surgery (N=454)
Age (years)	73.3 ± 5.8	73.6 ± 6.1	Diabetes	31.3%	30.2%
Male	67.5%	71.1%	COPD (any)	5.1%	6.2%
BMI – kg/m^2	30.7 ± 5.5	30.3 ± 5.1	Pulmonary Hypertension	4.6%	5.3%
STS Score	1.9 ± 0.7	1.9 ± 0.6	Creatinine > 2mg/dL	0.2%	0.2%
NYHA Class III or IV*	31.3%	23.8%	Frailty (overall; > 2/4+)	0	0
Coronary Disease	27.7%	28.0%	Atrial Fibrillation (h/o)	15.7%	18.8%
Prior CABG	3.0%	1.8%	Permanent Pacemaker	2.4%	2.9%
Prior CVA	3.4%	5.1%	Left Bundle Branch Block	3.0%	3.3%
Peripheral Vascular Disease	6.9%	7.3%	Right Bundle Branch Block	10.3%	13.7%

% or mean ± SD
*P = 0.01

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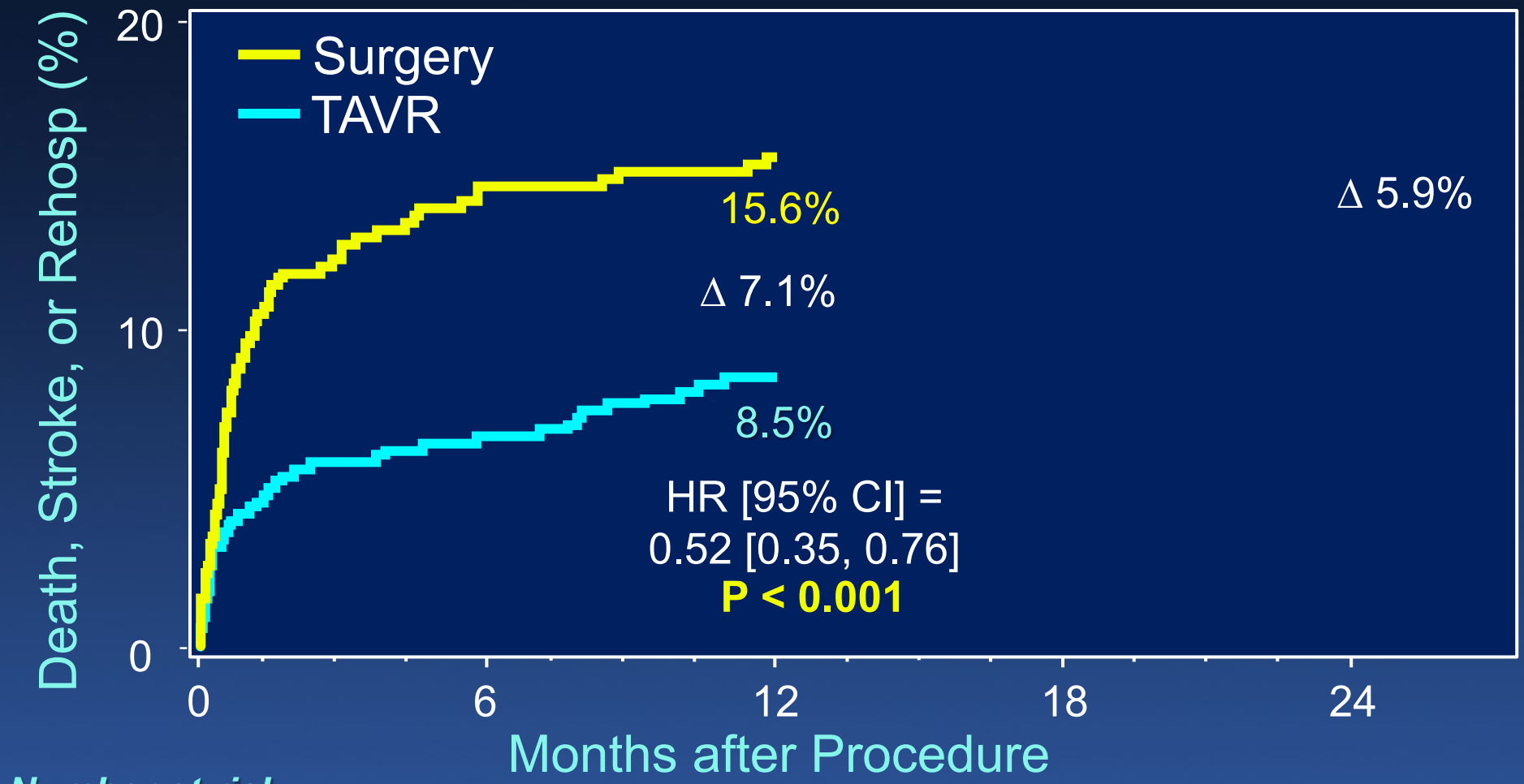
Primary Endpoint



Number at risk:

Surgery	**454**	**378**	**370**	**352**	**339**
TAVR	**496**	**462**	**452**	**436**	**422**

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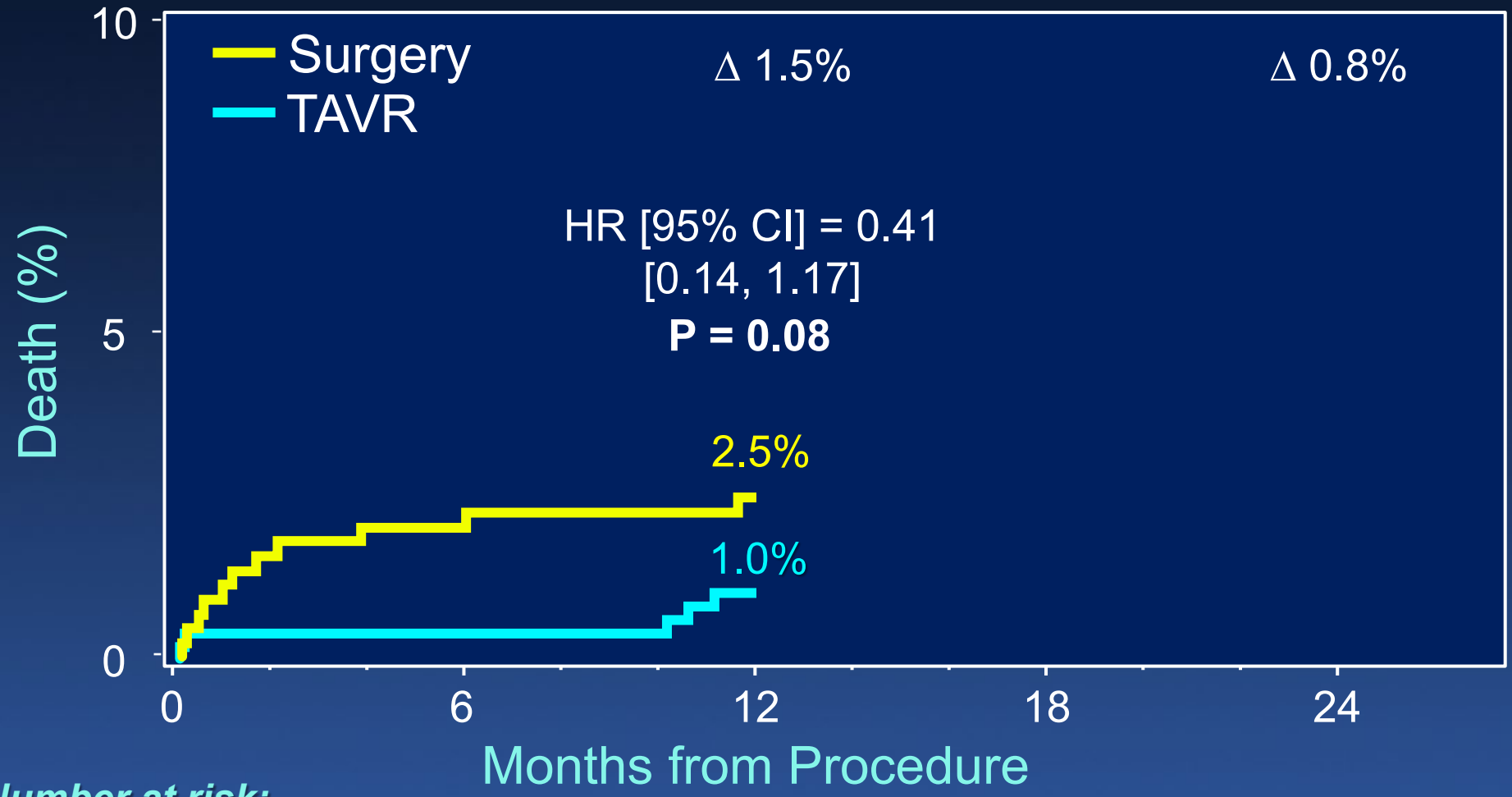
Death



Number at risk:

Surgery	**454**	**432**	**425**	**408**	**397**
TAVR	**496**	**493**	**489**	**477**	**466**

Causes of Death (Year 1 to 2)

TAVR

POD	Cause of death	Age
452	Sudden cardiac death	82
553	Fatal intracranial bleed secondary to fall	78
592	Unknown	72
628	Cardiac arrest secondary to complications of hip surgery	79
607	Cancer	72
657	Suicide	60
679	Sepsis	81

Surgery

POD	Cause of death	Age
408	Heart failure	76
615	Unknown	84
510	Unknown	73

Light blue rows indicate CV-death; dark blue rows are non-CV death

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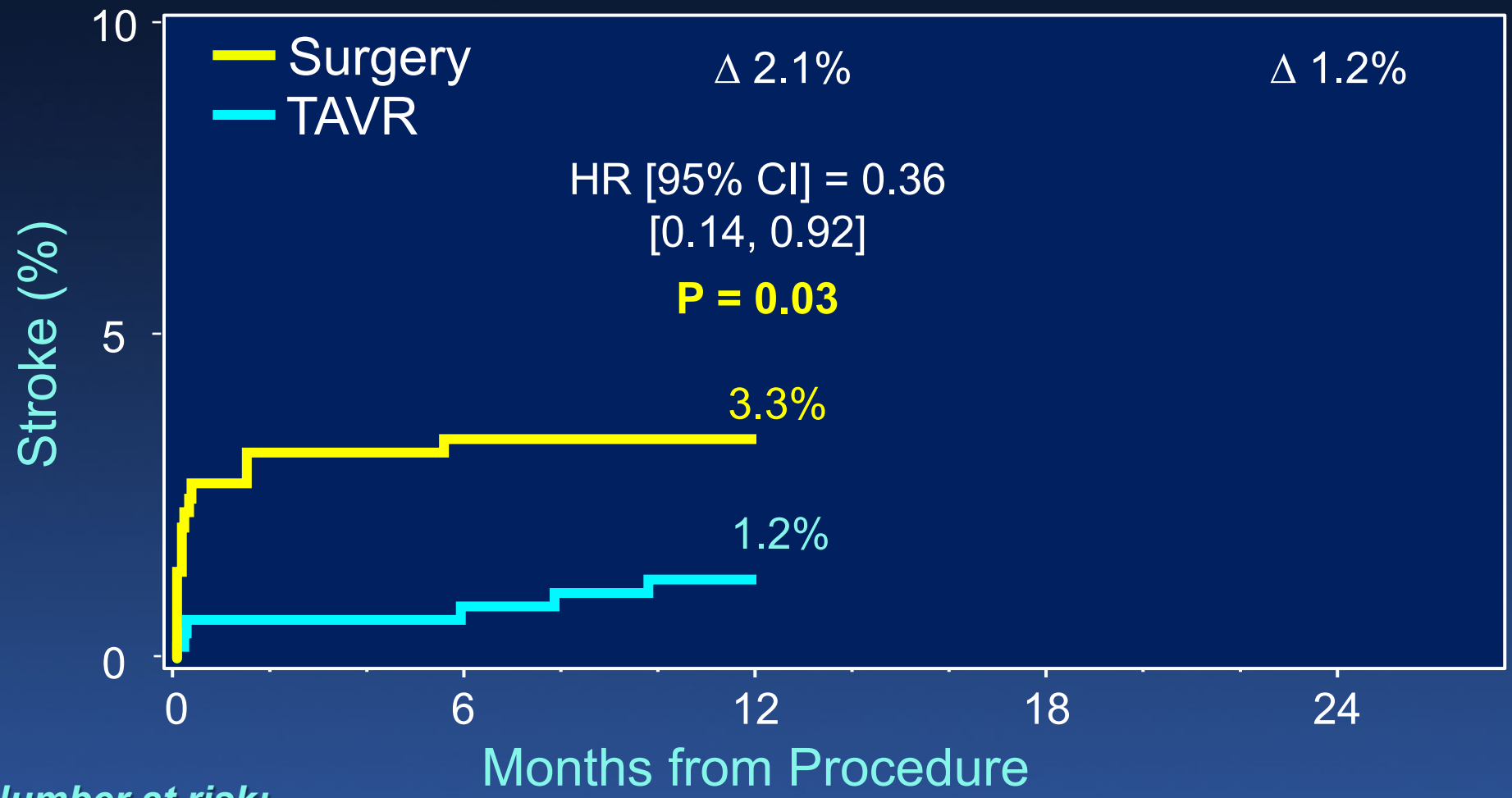
Stroke



Number at risk:

Surgery	**454**	**421**	**414**	**398**	**386**
TAVR	**496**	**489**	**485**	**468**	**456**

Stroke Events (Year 1 to 2)

TAVR

POD	Event Description	Age
442	L-sided weakness, CT & MRI pos; mRS 2 @90d	83
492	Aphasia, MRI pos; valve explanted (thrombosis)	68
578	L-sided weakness, MRI pos; mRS 4 @ 30d	69
376	R-sided weakness; mRS 1 @ 90d	76
456	Dysarthria, confusion; CT neg; mRS 0 @ 30d	84
518	Visual disturbances, CT neg @ time of event; KCCQ showed no disability @ f/u	71

Surgery

POD	Event Description	Age
612	RUE weakness, CT neg/MRI pos mRS 1 @ 90d.	69

Light blue rows indicate a disabling stroke; dark blue rows are non-disabling

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Stroke Events (Year 1 to 2)

REFERENCE

- There were 6 new stroke events in TAVR and 1 in surgery from years 1 to 2
- All 7 strokes from year 1 to 2 were ischemic
  - The 1 stroke event in the surgery arm was non-disabling
  - Of the 6 strokes in the TAVR group, 3 were disabling:
    - 2 had AFib (one pre-existing, one new onset)
    - 2 had valve thrombosis
    - 1 was on anticoagulation (Xarelto) for pre-existing AFib

Disabling Stroke	Atrial Fibrillation	Anti-Coagulation	Valve Thrombosis
#1	Yes (Prior)	Yes	Yes
#2	Yes (New Onset)	No	No
#3	No	No	Yes

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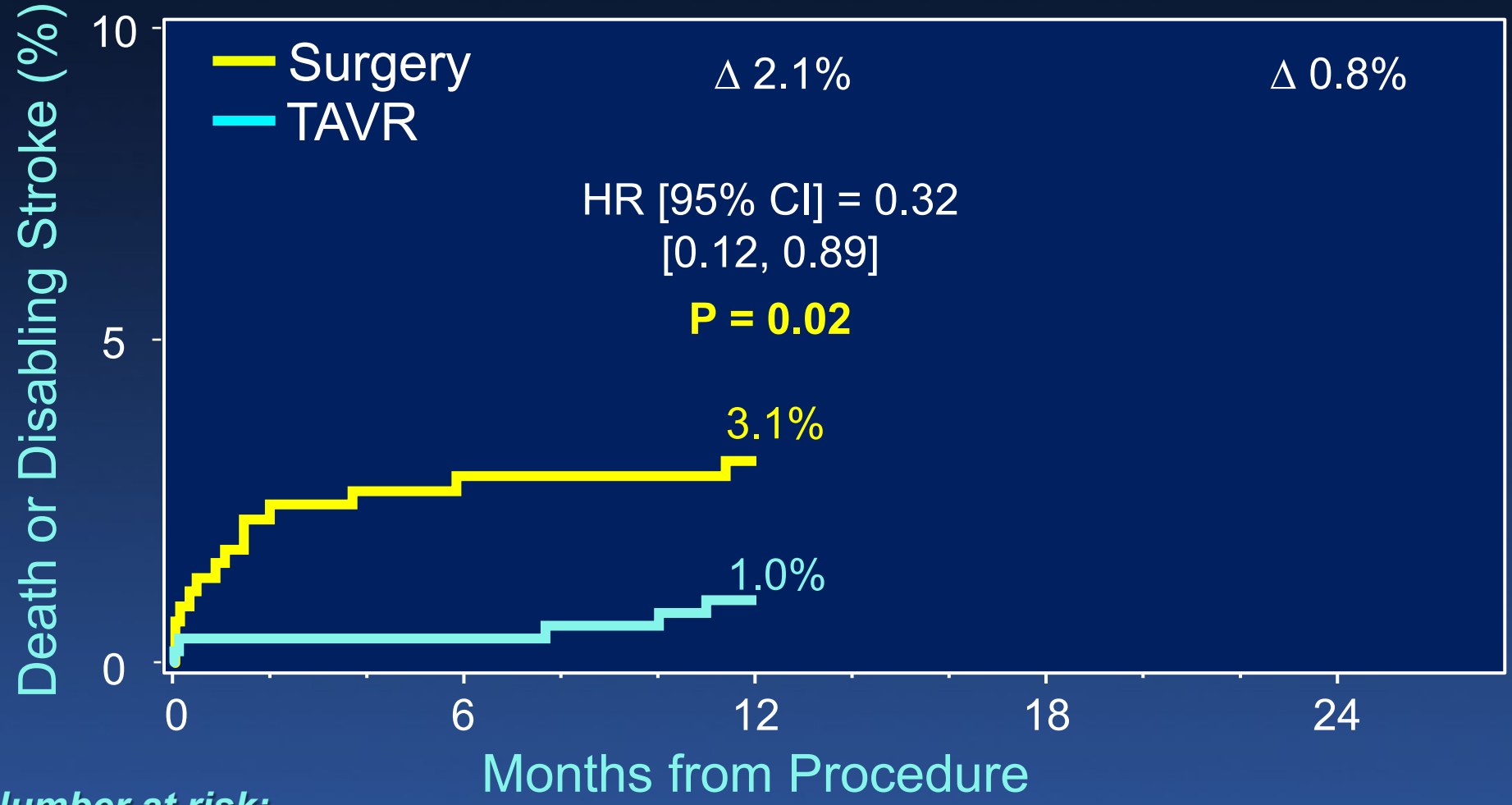
Death or Disabling Stroke



Number at risk:

Surgery	**454**	**430**	**423**	**406**	**395**
TAVR	**496**	**493**	**489**	**475**	**463**

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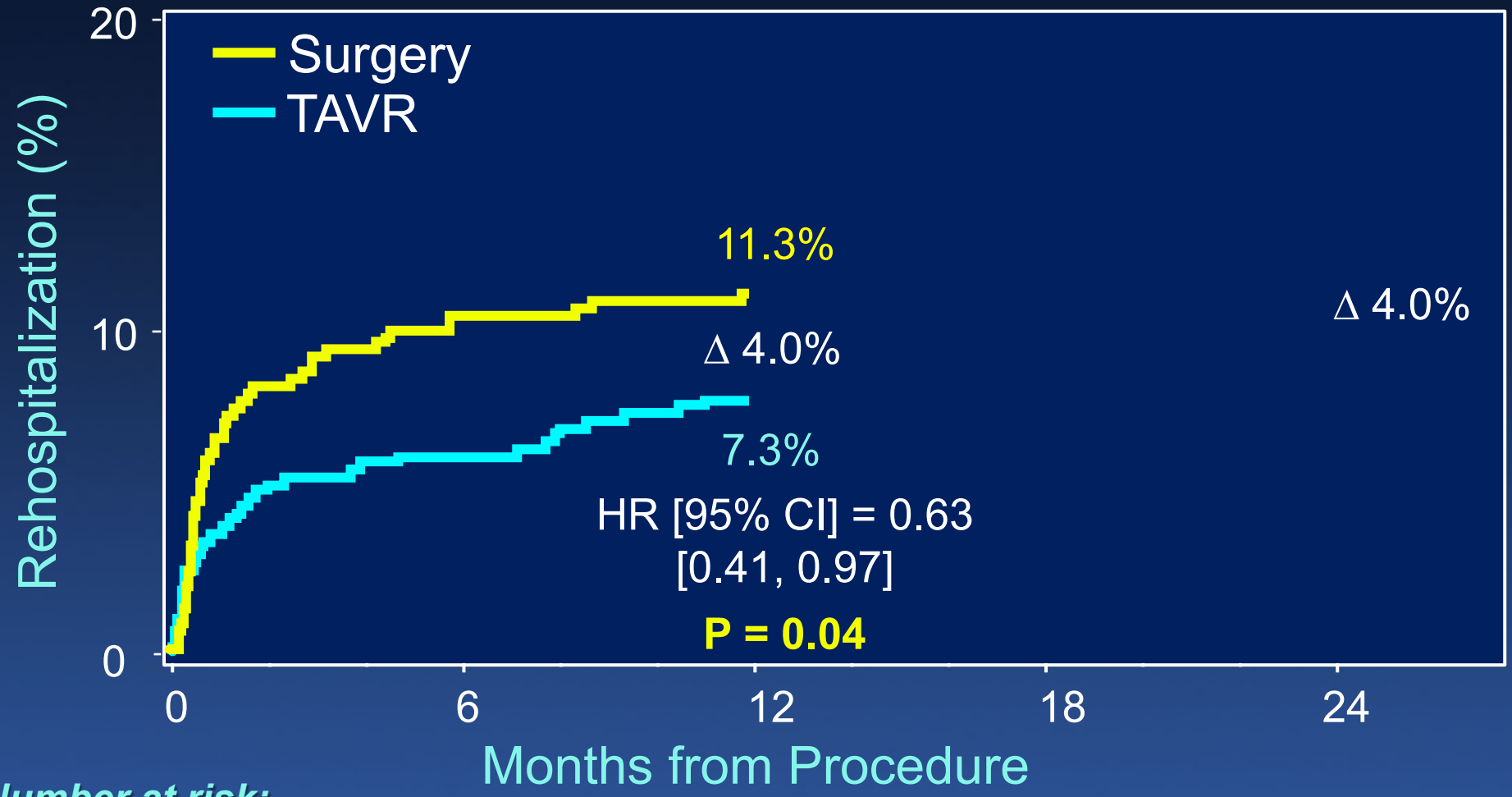
Rehospitalization



Number at risk:

Surgery	**454**	**387**	**379**	**360**	**348**
TAVR	**496**	**465**	**454**	**441**	**427**

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Causes of Rehospitalization

Year 1 to 2

Cause of Rehospitalization	TAVR (N=10)	Surgery (N=8)
CHF	60% (6)	75.0% (6)
CVA with Valve Thrombosis	20% (2)	0% (0)
Syncope	10% (1)	0% (0)
Bacteremia	10% (1)	0% (0)
Endocarditis	0% (0)	12.5% (1)
Permanent Pacemaker Implantation	0% (0)	12.5% (1)

Event rates are incidence [% (no. of subjects with event)]

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Secondary Endpoints

Outcomes	1 Year			2 Years		
	TAVR (N=496)	Surgery (N=454)	P-value	TAVR (N=496)	Surgery (N=454)	P-value
MI	1.2% (6)	2.2% (10)	0.23	1.8% (9)	2.7% (12)	0.36
New onset atrial fibrillation	7.2% (30)	40.9% (150)	< 0.001	7.9% (33)	41.8% (153)	< 0.001
New PPM (incl baseline)	7.3% (36)	5.4% (24)	0.21	8.5% (42)	6.3% (28)	0.19
New LBBB	23.9% (115)	8.0% (35)	< 0.001	24.4% (117)	9.4% (41)	< 0.001
Coronary Obstruction	0.2% (1)	0.7% (3)	0.28	0.2% (1)	0.7% (3)	0.28
AV Re-intervention	0.6% (3)	0.5% (2)	0.76	0.8% (4)	0.9% (4)	0.85
Endocarditis	0.2% (1)	0.5% (2)	0.49	0.2% (1)	0.9% (4)	0.13
Valve Thrombosis*	1.0% (5)	0.2% (1)	0.13	2.6% (13)	0.7% (3)	0.02

Event rates are Kaplan-Meier estimate [% (no. of subjects with event)] and P-values are based on Log-Rank test

* Valve thrombosis according to VARC 2 definition [Thrombus associated with an implanted valve, interfering with valve function or warranting treatment (anticoagulation or explantation)]

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Valve Thrombosis to 2 Years

Outcomes	TAVR (N=496)	Surgery (N=454)	P-value
Valve Thrombosis	2.6% (13)	0.7% (3)	0.02
Mean Gradient > 20mmHg and ↑ > 10mmHg	53.8% (7)	0% (0)	
Mean Gradient > 20mmHg and ↑ < 10mmHg	30.7% (4)	100.0% (3)	
↑ transvalvular AR (mild) with no change in mean gradient	7.7% (1)	0% (0)	
CT findings with no change in hemodynamics	7.7% (1)	0% (0)	

CEC adjudicated valve thrombosis per VARC 2 (all patients received anticoagulation). Valve thrombosis events are Kaplan-Meier estimate [% (no. of subjects with event)] and P-value is based on Log-Rank test; all other event rates are incidence [% (no. of subjects with event)]

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Valve Thrombosis Clinical Events

Possibly Related to Valve Thrombosis				
Patient	**Treatment Arm**	**Timing of Valve Thrombosis**	**Timing of Clinical Event**	**Clinical Event**
1	TAVR	~18 months	~18 months	CVA
2	TAVR	12 months	19 months	CVA
3	TAVR	1 month	~4 months	Syncope
4	Surgery	12 months	21 months	TIA

Possibly Related to Anticoagulation				
Patient	**Treatment Arm**	**Timing of Valve Thrombosis**	**Timing of Clinical Event**	**Clinical Event**
1	TAVR	12 months	~24 months	Periorbital ecchymosis
2	TAVR	1 month	~2 months	Subdural hematoma

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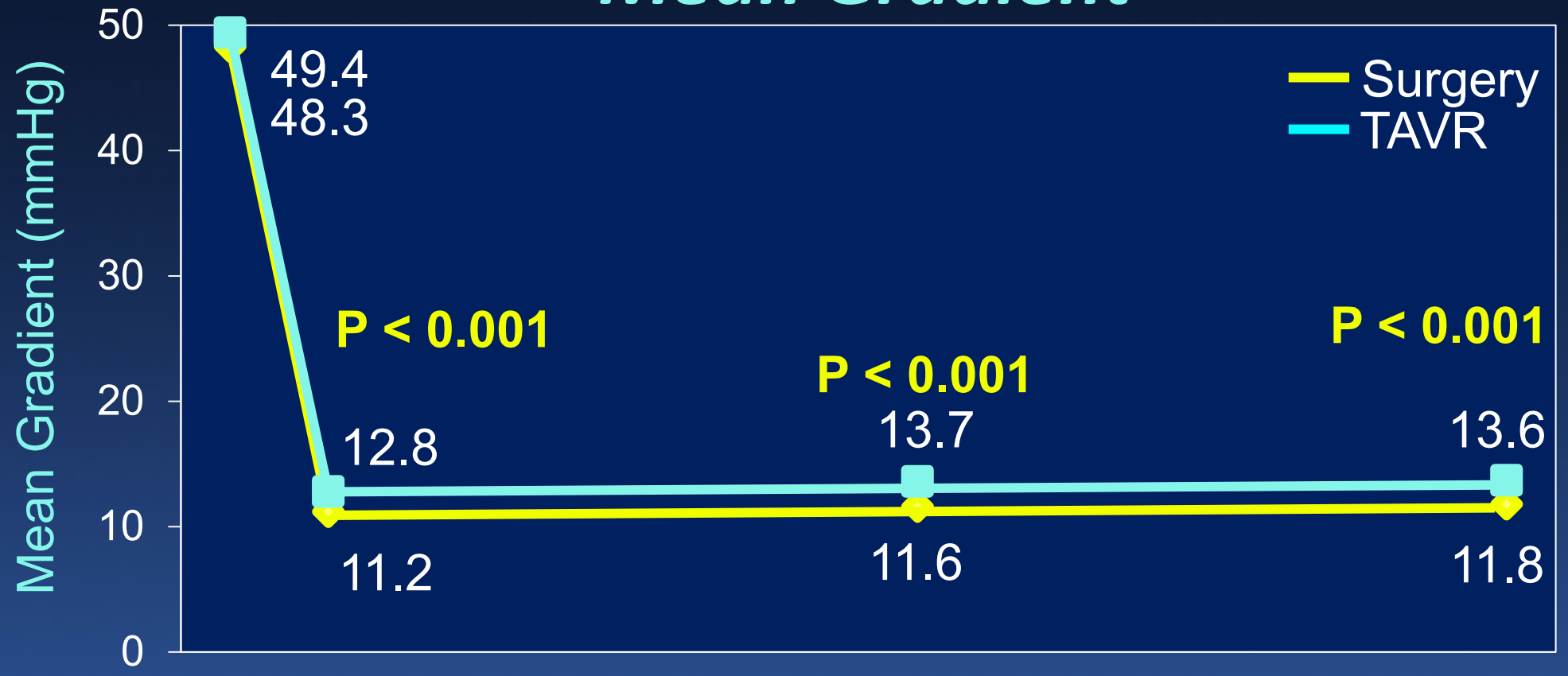
Echocardiography Findings

Mean Gradient



No. of Echos				
Surgery	441	426	391	355
TAVR	483	490	473	431

P-values are based on the ANCOVA, with baseline as a covariate

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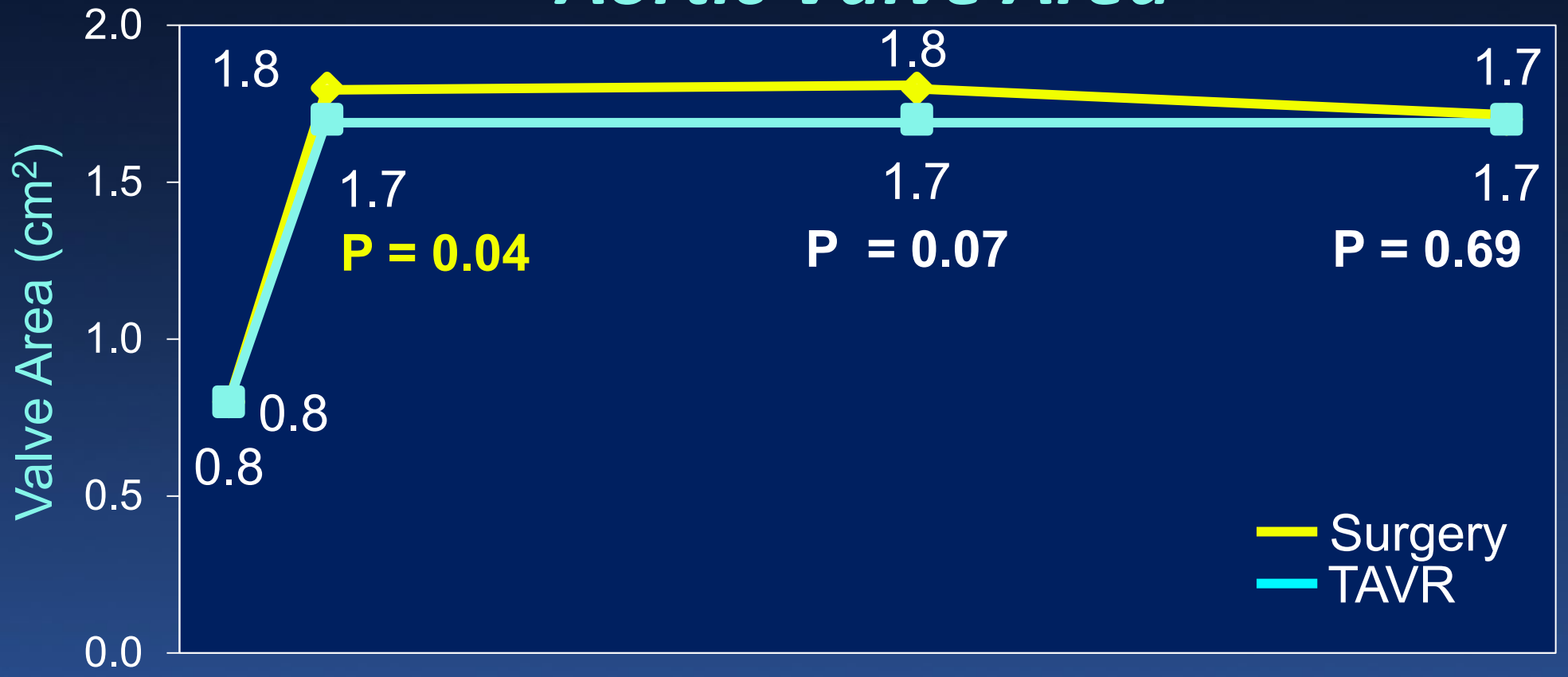
Echocardiography Findings

Aortic Valve Area



No. of Echos				
Surgery	441	395	371	339
TAVR	483	470	450	410

P-values are based on the ANCOVA, with baseline as a covariate

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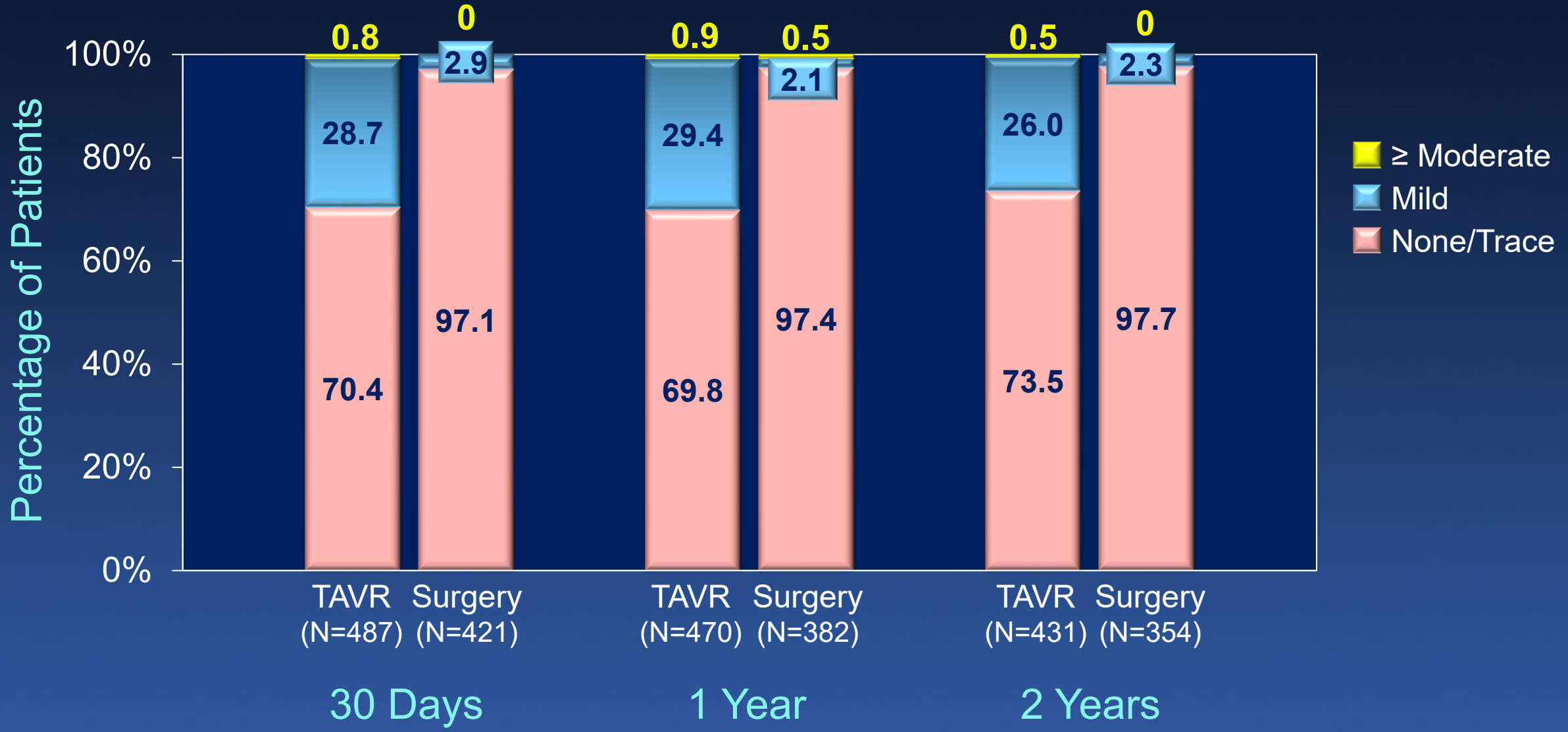
Paravalvular Regurgitation

≥ mod PVR: P = NS; ≥ mild PVR: P < 0.001 for all time points



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Study Limitations

- Results only apply to the enrolled AS population (e.g. bicuspid aortic valves, severe LVOT calcification, non-suitable for TF, and complex CAD excluded)
- Less follow-up data available in the surgical group due to greater patient withdrawal
- Valve thrombosis definitions by VARC 2 criteria are outdated and may be exaggerated by recent CT-imaging leaflet thickening studies
- Results reflect only 2-year outcomes; long-term assessment of structural valve deterioration is required
  - 10-year clinical and echocardiographic FU planned in all patients

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Conclusions (1)

In a defined population of severe symptomatic aortic stenosis patients who were at low surgical risk, TAVR (using the SAPIEN 3 valve) compared to surgery @ 2 years demonstrated:

- Reduced primary endpoint events (37% reduction in death, stroke or CV rehospitalization); BUT…
  - More death and stroke events in TAVR patients from 1 to 2 years; no significant differences @ 2 years
  - Reduced CV rehospitalizations favoring TAVR

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Conclusions (2)

- Increased valve thrombosis events in TAVR patients, esp. from 1 to 2 years
- Hemodynamic improvements and frequency of moderate or mild paravalvular regurgitation were unchanged between 1 and 2 years in both TAVR and surgery patients

Back-Up Slides

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Study Leadership

National Principal Investigators

- Martin B. Leon, MD, Columbia University Medical Center, New York, NY
- Michael J. Mack, MD, The Heart Hospital Baylor Plano, Plano, TX

Steering Committee

- Howard Herrmann, Samir Kapadia, Susheel Kodali, Martin B. Leon, Michael J. Mack, Raj Makkar, Craig R. Smith (chair), Wilson Szeto, Vinod Thourani, John Webb

Data & Safety Monitoring Board

- Cardiovascular Research Foundation, New York, NY; Joseph Carrozza, Jr., MD, chair

Clinical Events Committee

- Cardiovascular Research Foundation, New York, NY; Steven O. Marx, MD, chair

CT Core Laboratory

- The University of British Columbia; Jonathon Leipsic, MD, chair; Philipp Blanke, MD, chair

Echocardiographic Core Laboratory

- Quebec Heart & Lung Institute (Laval University); Philippe Pibarot, DVM PhD, chair
- Cardiovascular Research Foundation, New York, NY; Rebecca Hahn, MD, chair

Sponsor

- Edwards Lifesciences, Irvine, CA

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Study Methodology

- The primary endpoint was a non-hierarchical composite of all-cause mortality, all strokes, or CV rehospitalization at 1 year.
- Analysis cohort was the 'as-treated' (AT) population, defined as all randomized patients in whom the procedure was initiated.
- Baseline and 30-day neuro assessment in all patients; serial neurologist examinations and neuro-imaging for suspected neuro events.
- CEC adjudication of all primary endpoint events, valve thrombosis, endocarditis, and AV-reintervention to 2 years.
- 10-year clinical and echocardiography follow-up in all patients.

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Key Endpoint Definitions

- Valve Thrombosis (VARC 2)
  - Thrombus associated with an implanted valve, interfering with valve function or warranting treatment (anticoagulation or explantation)
- Hemodynamic Valve Deterioration - Stage 2 or 3 (VARC 3)*
  - ↑ mean gradient ≥ 10 or 20 mmHg with final mean gradient ≥ 20 or 30 mmHg AND: i) ↓ AVA ≥ 0.3 or 0.6 cm2 or ≥ 25 or 50%; OR ii) ↓ DVI ≥ 0.1 or 0.2 or ≥ 20 or 40%; AND/OR ≥ 1 or 2 grade new/worsening transvalvular AR with final grade ≥ mod or severe
- Bioprosthetic Valve Failure (VARC 3/EACTS-EAPCI)*
  - Re-intervention or death 2^{ry} to valve dysfunction OR Severe (Stage 3) HVD related to intrinsic permanent changes to the prosthetic valve

* HVD and BVF cases were adjudicated by a group of 3 experts

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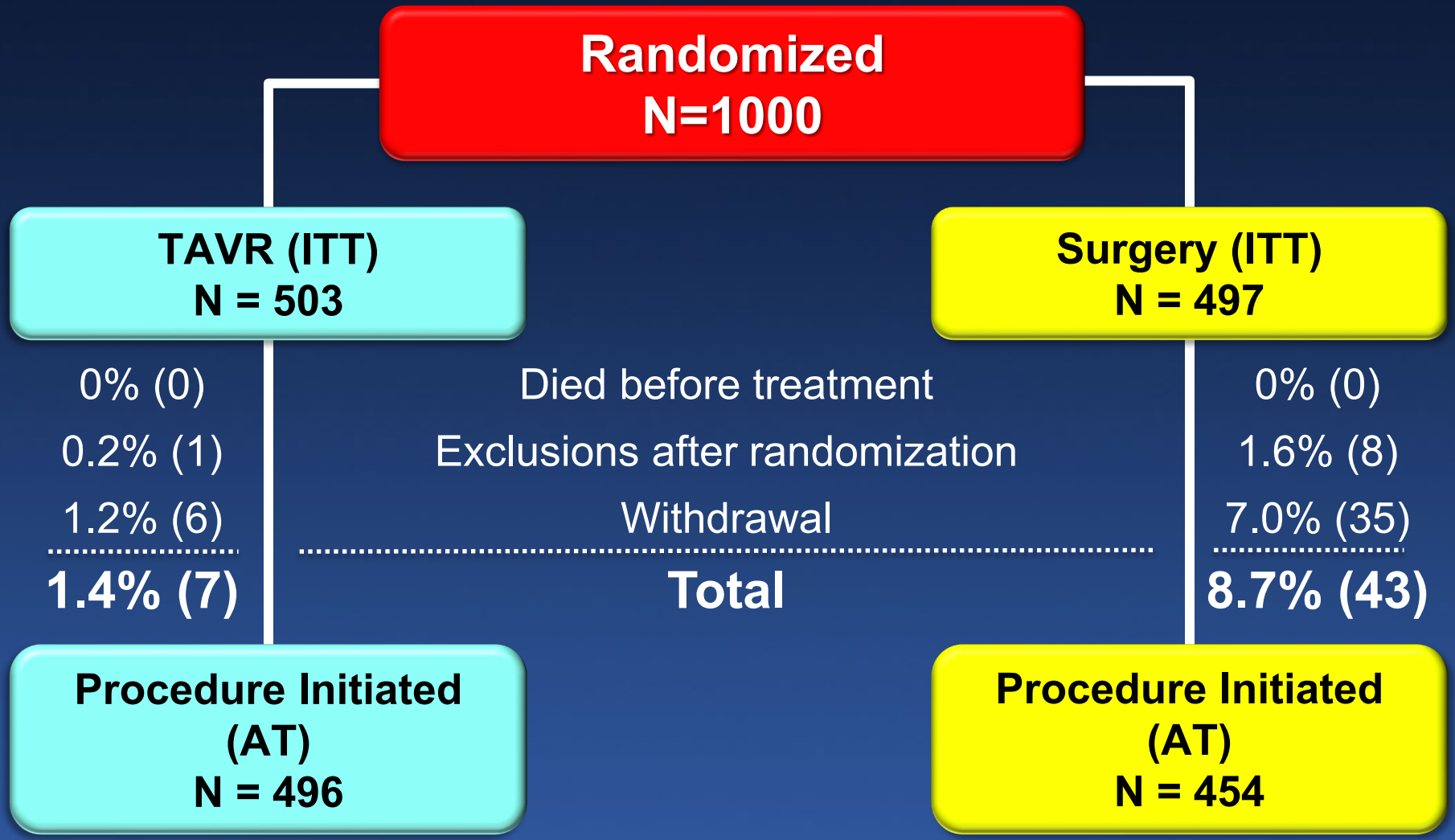
Study Populations

ITT to AT Patient Cohorts



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Primary Endpoint

As Treated Population

Endpoint	KM Rate at 1 Year				KM Rate at 2 Years			
	TAVR (N=496)	Surgery (N=454)	Hazard Ratio [95% CI]	P-value	TAVR (N=496)	Surgery (N=454)	Hazard Ratio [95% CI]	P-value
Death, stroke, and rehosp‡								

Event rates are Kaplan-Meier estimate [% (no. of subjects with event)] and P-values are based on Log-Rank test

‡ Rehospitalization (valve- or procedure-related and including heart failure)

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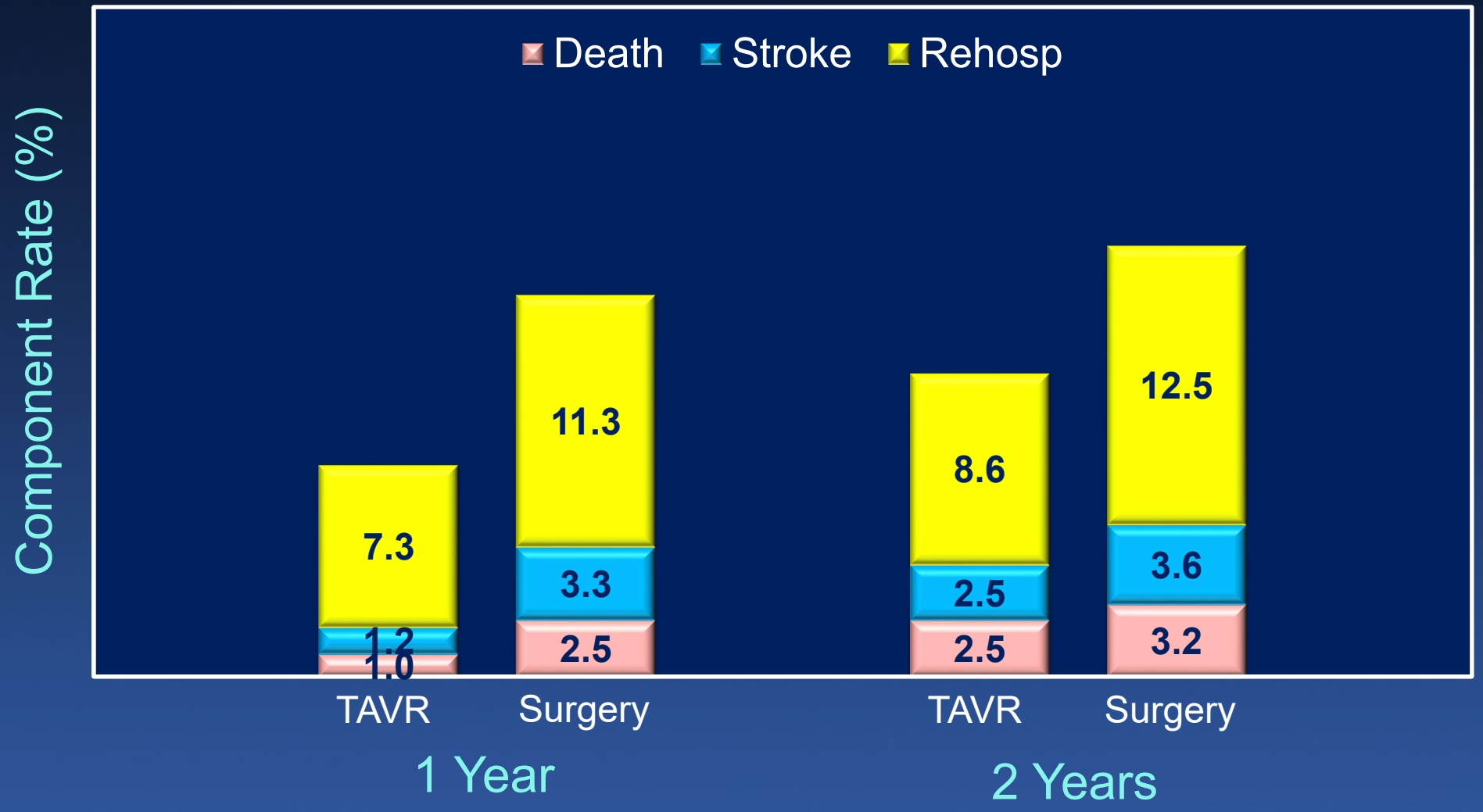
Component Rates of the Primary Endpoint



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Causes of Death (to 1 Year)

TAVR

POD	Cause of death	Age	Valve Size
0	Annulus rupture	64	29mm
3	LV perforation (intra-procedural)	83	23mm
318	Fatal Intracranial bleed secondary to fall following ViV procedure	74	26mm
335	Sudden cardiac death (PEA arrest)	68	23mm
305	Motor vehicle accident	78	26mm

Surgery

POD	Cause of death	Age	Valve Size
0	PEA arrest	80	19mm
4	PEA arrest	54	23mm
10	PEA arrest	61	21mm
14	Respiratory failure	68	21mm
31	Failure to wean from ECMO	69	25mm
47	Hemorrhagic stroke	84	23mm
59	Endocarditis	68	23mm
111	Acute MI	79	25mm
177	Stroke with subsequent pneumonia	73	25mm
25	Sepsis	70	25mm
346	Cancer	81	25mm

Light blue rows indicate CV-death; dark blue rows are non-CV death

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Stroke to 2 Years

Outcomes	TAVR (N=12)	Surgery (N=16)
All Stroke		
Disabling	66.7% (8)	31.3% (5)
Non-disabling	33.3% (4)	68.8% (11)
Timing of Stroke		
Peri-procedural (within 30 days)	25.0% (3)	75.0% (12)
Acute (≤ 24 hours)	8.3% (1)	37.5% (6)
Subacute (24 hours – 30 days)	16.7% (2)	37.5% (6)
Early (30 days – 1 year)	25.0% (3)	18.8% (3)
Late (> 1 year)	50.0% (6)	6.3% (1)
Type of Stroke		
Ischemic	100.0% (12)	68.8% (11)
Hemorrhagic	0% (0)	12.5% (2)*
Undetermined	0% (0)	18.8% (3)

Event rates are incidence [% (no. of subjects with event)]
*Both hemorrhagic strokes were fatal

Causes of Rehosp (Year 1 to 2)

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TAVR

POD	Event Description	Age	Valve Size
494	CVA w/ valve thrombosis	68	29
617	CHF	77	29
695	CHF	75	26
392	Syncope	75	20
604	CHF	69	23
578	CVA w/ valve thrombosis	69	26
439	Bacteremia	74	23
416	CHF	68	23
422	CHF	68	29
510	CHF	68	29

Surgery

POD	Event Description	Age	Valve Size
430	CHF	81	23
544	CHF	75	25
622	CHF	74	21
519	CHF	69	21
581	CHF/PVL w/ reintervention	81	25
413	CHB w/ PPM implantation	78	25
711	Endocarditis w/ reintervention	72	25
644	CHF	76	25

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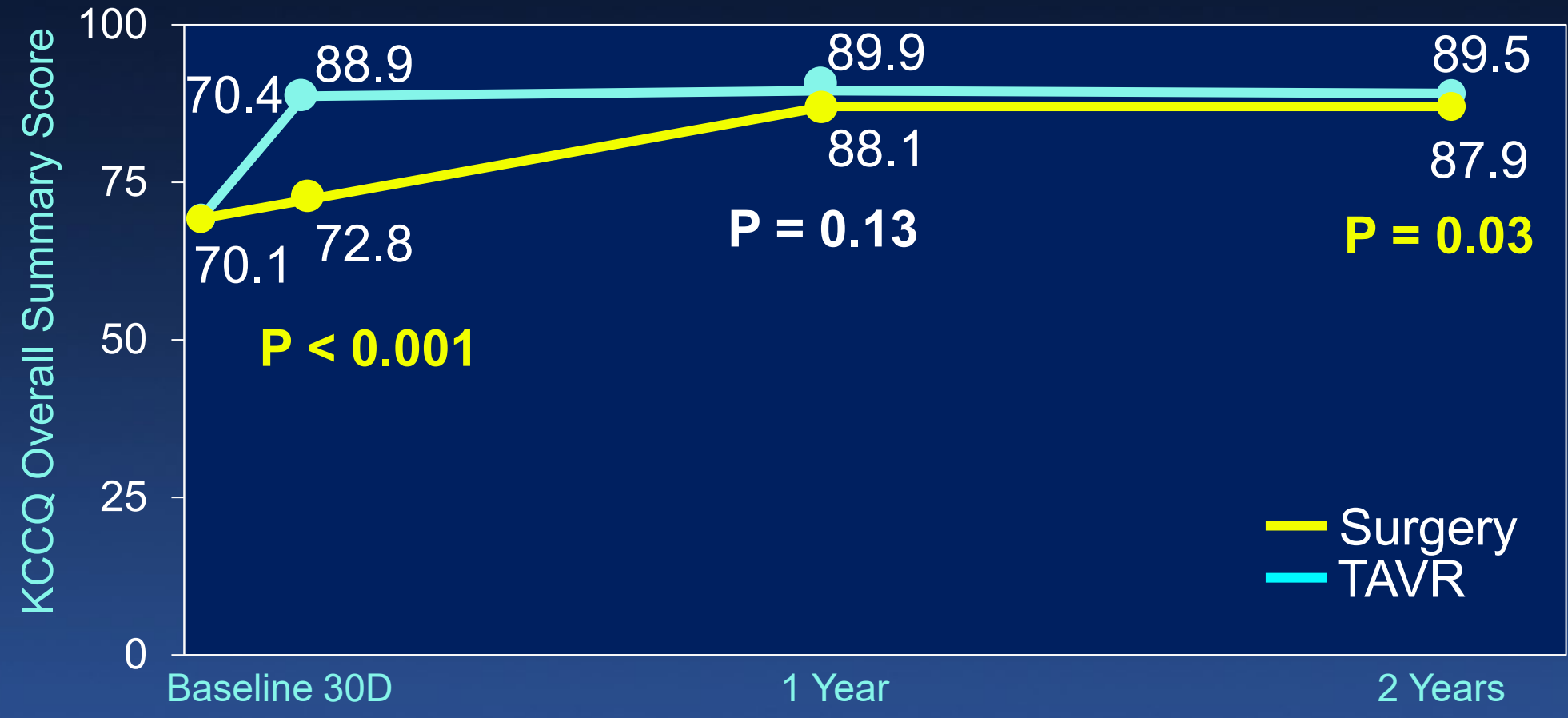
KCCQ Overall Summary Score



Surgery	**449**	**433**	**403**	**366**
TAVR	**494**	**492**	**482**	**444**

P-values are based on t-test and indicate change from baseline.

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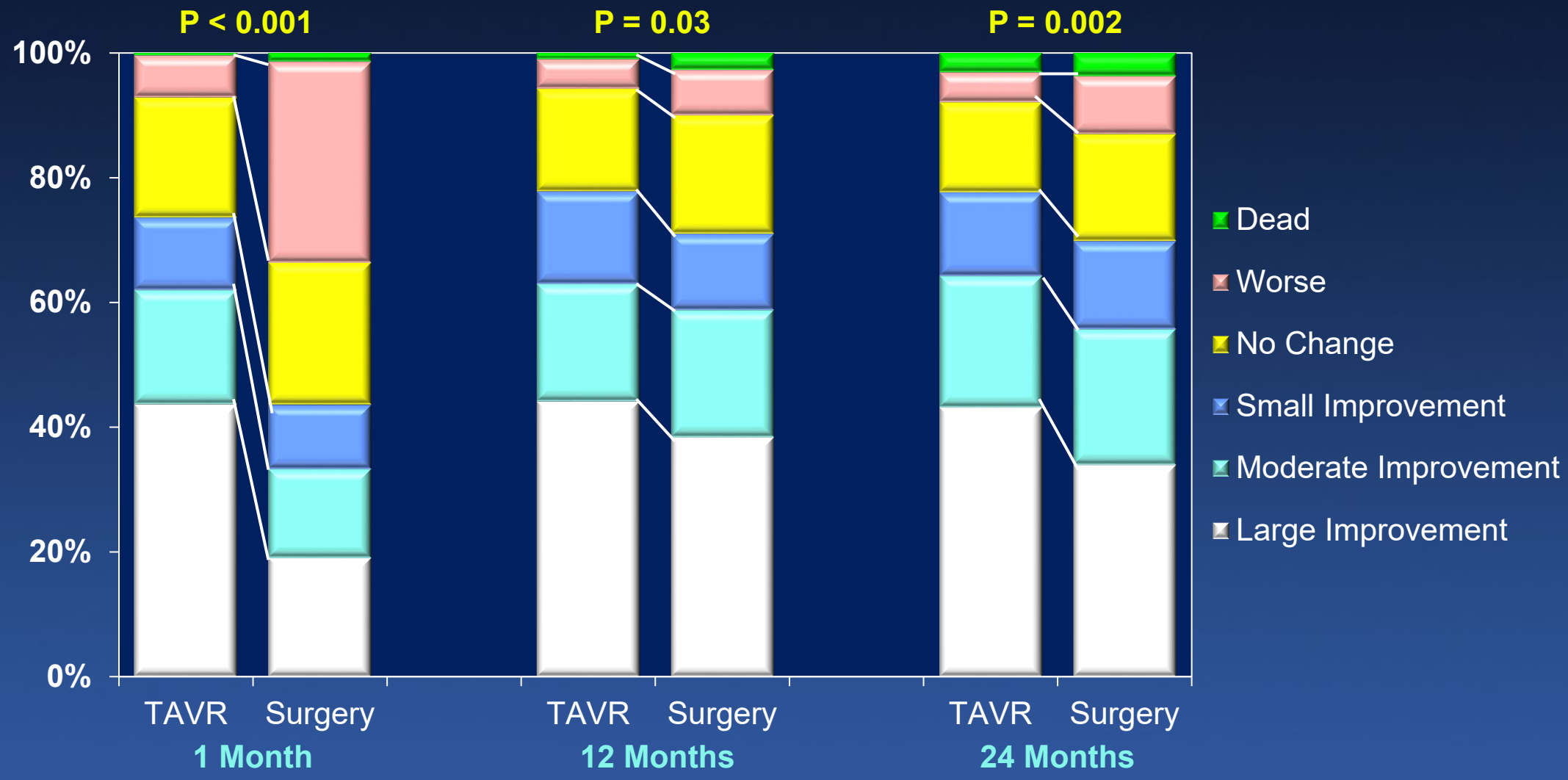
Categorical Analysis:

Survival and Health Status (KCCQ-OS) Combined



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Primary Endpoint Sensitivity Analyses to 2 years

Multiple Imputation

	TAVR (N=503)	Surgery (N=497)	HR	95% CI for the HR	P-value (sup)
No Imputation	11.5%	17.4%	0.63	[0.45, 0.88]	0.007
Missing at Random	11.6%	17.3%	0.67	[0.48, 0.94]	0.02
Informative Missing	11.5%	17.3%	0.67	[0.48, 0.94]	0.02

*95% CI based on the Greenwood standard error

WIN Ratio

No. of Total Pairs	No of TAVR Win	No. of Surgery Win	Win ratio for Primary Endpoint	95% CI* for the WR	P-value
454 X 496 = 225,184	36496	23020	1.59	[1.13, 2.23]	0.008

*95% CI and p-value is based on the Finkelstein and Schoenfeld approach

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Restricted Mean Survival Time

PMAAT Restricted at 2 years

Endpoint	Statistic in 730 days	TAVR [95% CI]	Surgery [95% CI]	Difference (TAVR – Surgery) [95% CI]	P-Value
Death, stroke, and rehosp‡	Mean primary endpoint-free time	670.13 [653.93, 686.32]	621.53 [598.66, 644.39]	48.60 [20.58, 76.62]	< 0.001
Death	Mean survival time	722.65 [717.49, 727.82]	712.43 [702.81, 722.04]	10.23 [-0.69, 21.15]	0.07
Stroke	Mean stroke-free time	719.46 [712.96, 725.97]	706.02 [694.21, 717.83]	13.44 [-0.04, 26.93]	0.05
Rehosp‡	Mean rehosp-free time	680.90 [665.83, 695.98]	652.29 [632.36, 672.21]	28.61 [3.63, 53.60]	0.02

Based on Restricted Mean Survival Time (RMST): Royston & Parmar, BMC Medical Research Methodology, 2013, 13-152

‡ Rehospitalization (valve- or procedure-related and including heart failure)

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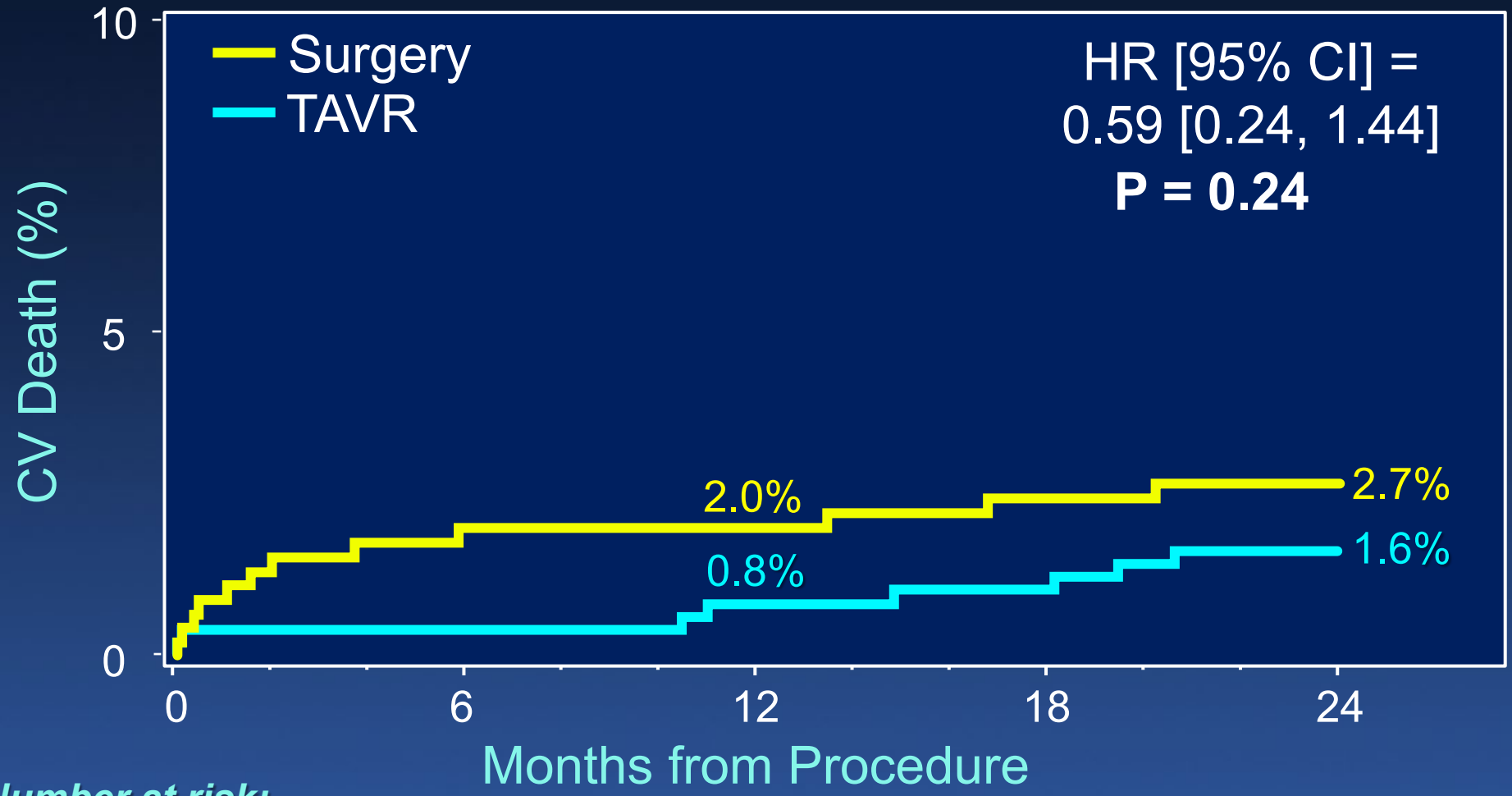
Cardiovascular Death

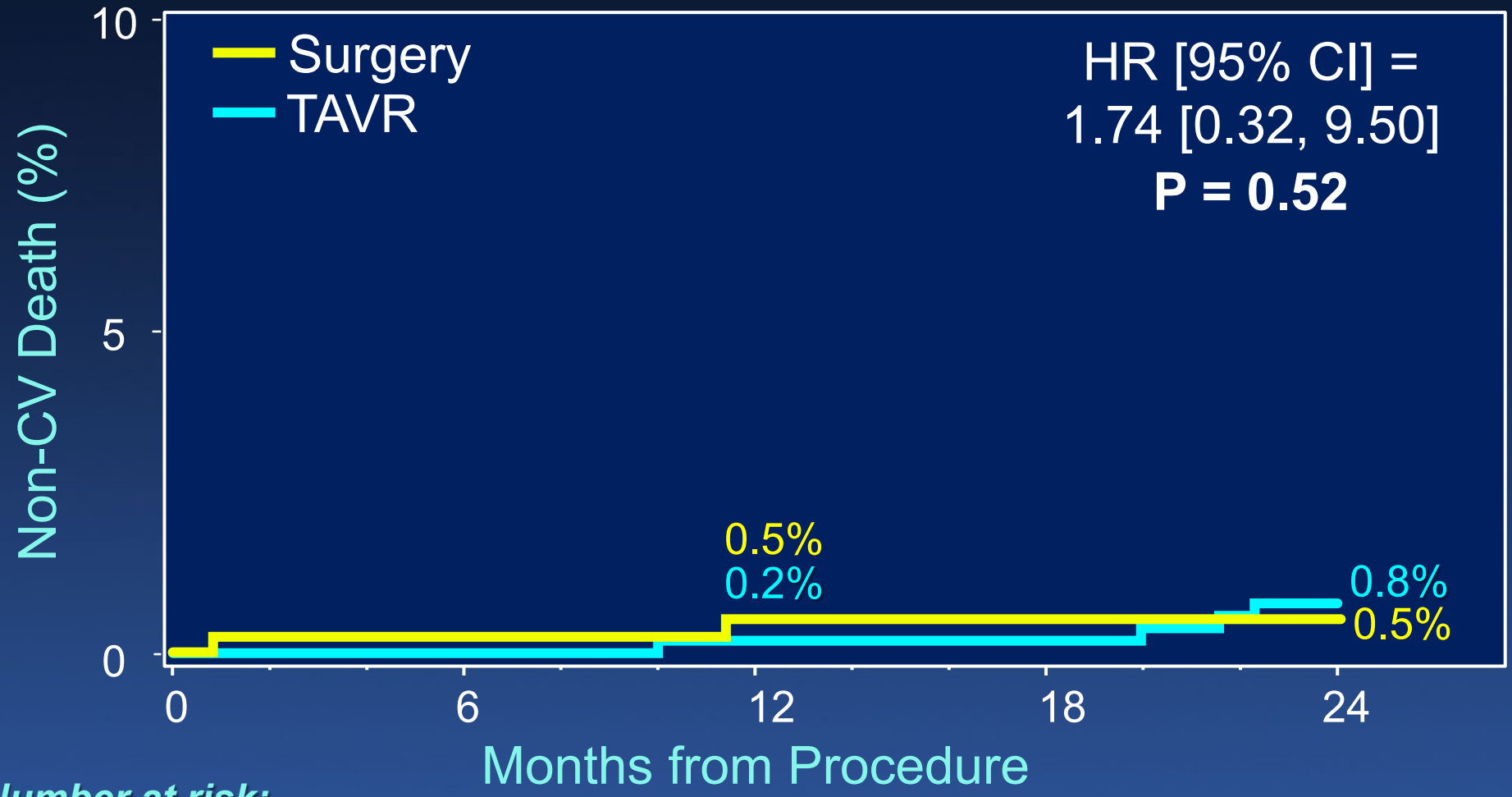


Number at risk:

Surgery	**454**	**432**	**425**	**408**	**397**
TAVR	**496**	**493**	**489**	**477**	**466**

THE PARTNER 3 TRIAL

Non-Cardiovascular Death



Number at risk:

Surgery	**454**	**432**	**425**	**408**	**397**
TAVR	**496**	**493**	**489**	**477**	**466**

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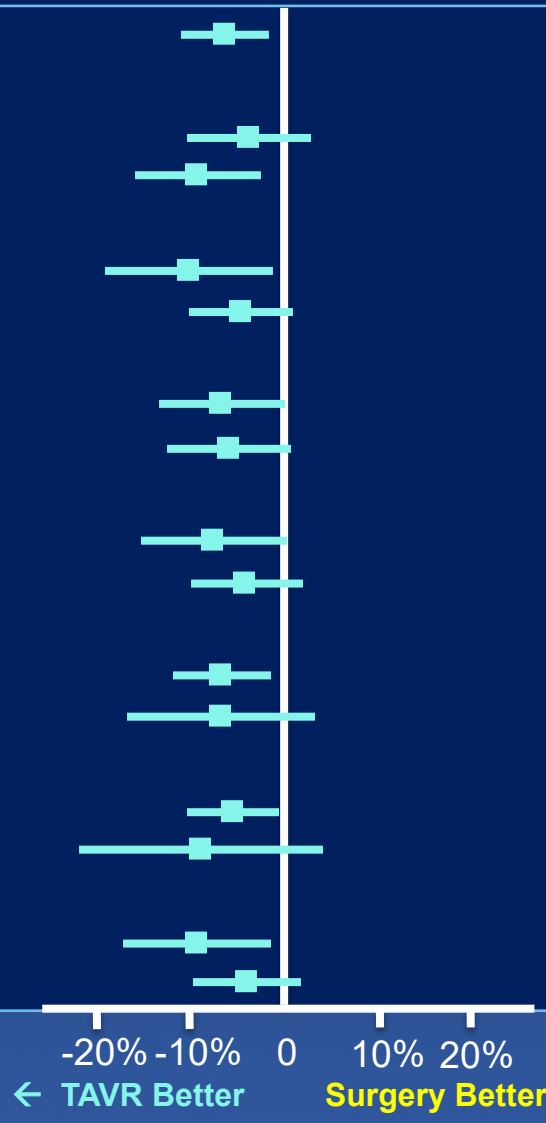
Primary Endpoint - Subgroup Analysis

Subgroup	TAVR	Surgery	Diff [95% CI]	P-value*
Overall	**11.6**	**17.5**	**-5.9 [-10.4, -1.4]**	
Age				
≤ 74 (n=516)	13.6	17.2	-3.5 [-9.8, 2.8]	**0.25**
> 74 (n=434)	9.1	17.8	-8.8 [-15.2, -2.3]	
Sex				
Female (n=292)	11.3	21.0	-9.7 [-18.3, -1.1]	**0.30**
Male (n=658)	11.7	16.1	-4.3 [-9.6, 1.0]	
STS Score				
≤ 1.8 (n=464)	11.3	17.5	-6.3 [-12.7, 0.2]	**0.88**
> 1.8 (n=486)	11.9	17.4	-5.5 [-11.9, 0.8]	
LV Ejection Fraction				
≤ 65 (n=384)	13.0	20.2	-7.2 [-14.7, 0.4]	**0.48**
> 65 (n=524)	10.7	14.5	-3.8 [-9.5, 2.0]	
NYHA Class				
I/II (n=687)	9.8	16.1	-6.3 [-11.3, -1.3]	**0.997**
III/IV (n=263)	15.5	21.9	-6.3 [-16.1, 3.4]	
Atrial Fibrillation				
No (n=786)	10.6	15.7	-5.1 [-9.9, -0.3]	**0.63**
Yes (n=163)	17.0	25.4	-8.4 [-21.0, 4.2]	
KCCQ Overall Summary Score				
≤ 70 (n=407)	13.4	22.2	-8.8 [-16.3, -1.3]	**0.28**
> 70 (n=536)	9.9	13.6	-3.7 [-9.2, 1.8]	

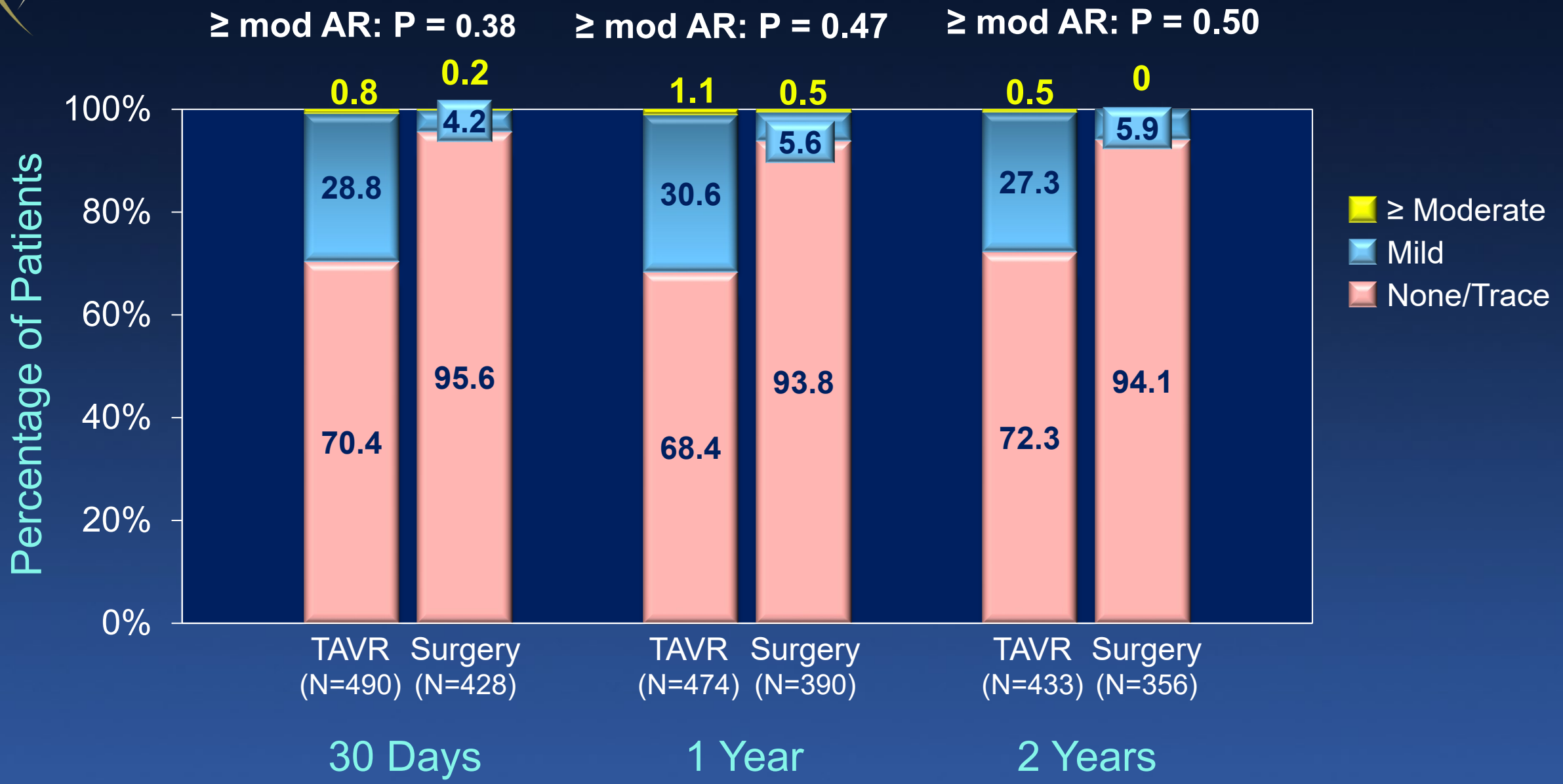


Event rates are KM estimates (%)

* P-value is for interaction

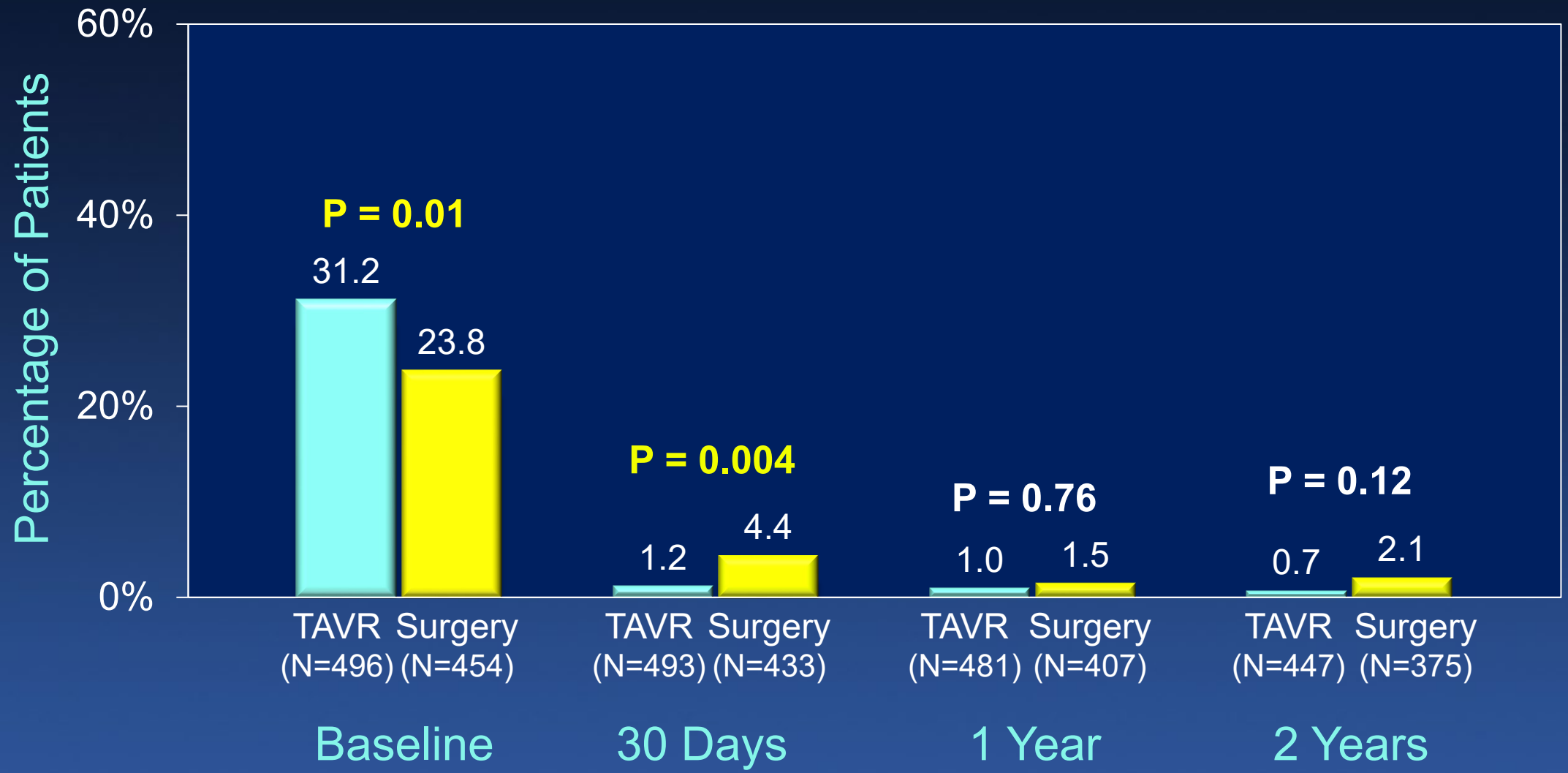
THE PARTNER 3 TRIAL

Total Aortic Regurgitation



THE PARTNER 3 TRIAL

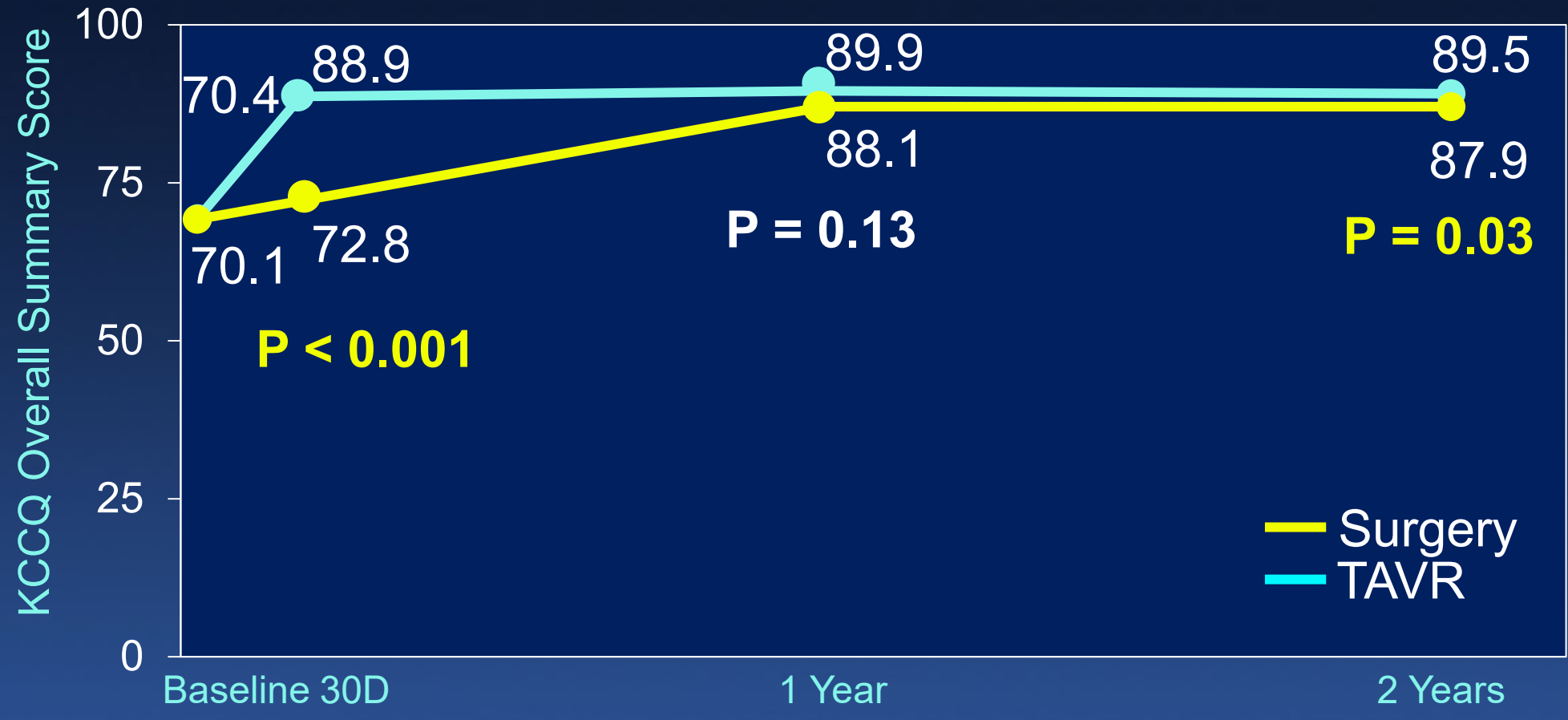
NYHA Class III/IV



P-values are based on Fisher's Exact test.

THE PARTNER 3 TRIAL

KCCQ Overall Summary Score



Surgery	**449**	**433**	**403**	**366**
TAVR	**494**	**492**	**482**	**444**

P-values are based on t-test and indicate change from baseline.