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Five-year Clinical And Echocardiographic Outcomes From The PARTNER 3 Low-risk Randomized Trial

Martin B. Leon, MD &
Michael J. Mack, MD

on behalf of the PARTNER 3 Trial Investigators

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Disclosures: Martin B. Leon, 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
• Institutional Research Support (Columbia University)	Abbott, Boston Scientific, Edwards Lifesciences, Medtronic
• Consulting Fees	Anteris, Foldax
• Other	Alta, Ancora, Cathworks, Croivalve, East End Medical, Medinol, Pi-cardia, SoloPace, Valve Medical, XenterMD

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Background

- The PARTNER 3 trial, comparing TAVR vs. Surgery in low surgical risk patients with severe symptomatic AS, showed superior or similar primary endpoint clinical outcomes (death, stroke, and rehospitalization) at 1 and 2 years.
- Since the majority of AS patients treated with Surgery have low surgical risk profiles and are younger, the 5-year outcomes from PARTNER 3 are essential to inform patient-centered therapy for initial and subsequent aortic valve procedures.

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Purpose

To report the clinical and echocardiographic outcomes of the PARTNER 3 Trial at *5 years* for low-risk patients with severe symptomatic aortic stenosis treated with balloon-expandable, SAPIEN 3 TAVR 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 day, 6 mos, and annually through 10 years

PRIMARY ENDPOINT AT 1 YEAR:
Non-hierarchical composite of all-cause death, all stroke, or rehospitalization (valve-, procedure-, or HF-related)

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Statistical Considerations

For 5-year Follow-up

- Endpoints and definitions meant to evaluate safety and effectiveness at 1 year were supplemented to assess late bioprosthetic valve performance and clinical outcomes at 5 years.
- An extension SAP was created with a pre-specified hierarchical composite endpoint analysis that would be more clinically meaningful for 5-year follow-up.
- Valve thrombosis and bioprosthetic valve failure were defined according to VARC-3.

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Five-year Primary Endpoints

Primary Endpoint 1

- **Non-hierarchical composite** of all-cause death, all stroke, or rehospitalization* (time to first event)
- Assessed as the KM rate difference at 5 years
- Also depicted as a hazard ratio (HR)
  - *Odds ratios were calculated for any clinical outcomes that showed evidence of non-proportionality of hazards for time-to-event analyses*

Primary Endpoint 2

- **Hierarchical composite** of all-cause death, disabling stroke, non-disabling stroke, and rehospitalization* days
- Assessed using the *win ratio* method

**Rehosp defined as valve-, procedure-, or HF-related*

Patient Disposition to 5 Years

Randomized: N = 1000

Allocated to TAVR
N = 503

Did not receive allocated intervention (n=7)
- Died before treatment: 0
- Exclusion criteria found after randomization: 1
- Withdrew: 6

Procedure Initiated (AT)
N = 496

1 Withdrawal

1-year follow up
N = 99.8% (495/496)

11 Withdrawals
15 Lost to f/u

5-year follow up
N = 94.6% (469/496)

Allocated to Surgery
N = 497

Did not receive allocated intervention (n=43)
- Died before treatment: 0
- Exclusion criteria found after randomization: 8
- Withdrew: 35

Procedure Initiated (AT)
N = 454

11 Withdrawals
1 Lost to f/u

1-year follow up
N = 97.4% (442/454)

31 Withdrawals
10 Lost to f/u

5-year follow up
N = 88.3% (401/454)

Total

18 withdrawals
16 Lost to f/u

Total

77 withdrawals
11 Lost to f/u

91.6% of patients available for primary endpoint analysis at 5 years

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Baseline Characteristics

% or mean ± SD

Demographics & Vascular Disease	TAVR (N=496)	Surgery (N=454)	Other Comorbidities	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%

*$P = 0.01$

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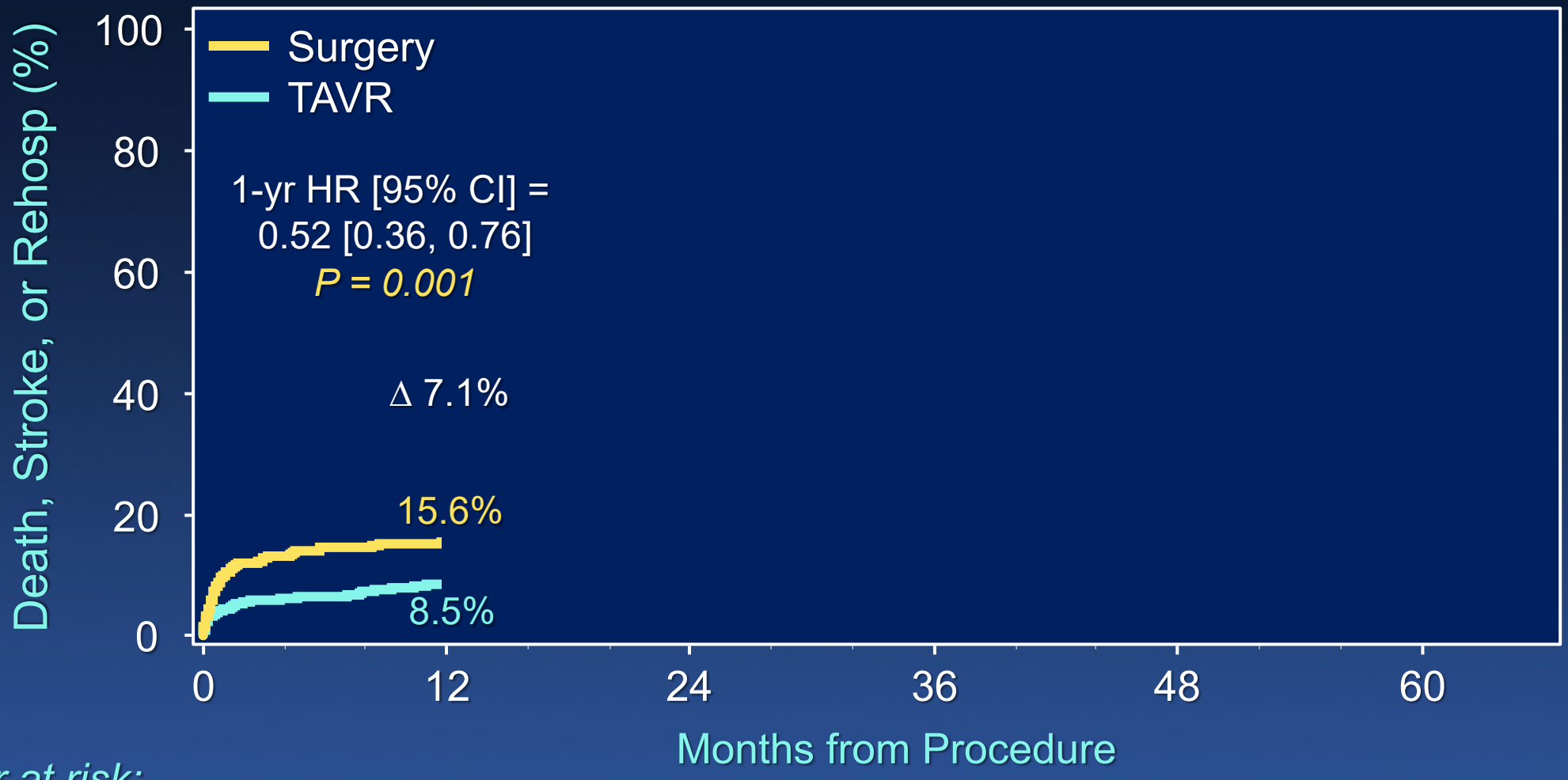
Primary Endpoint 1



Number at risk:

TAVR	496	453	434	415	391	353
Surgery	454	372	349	328	309	276

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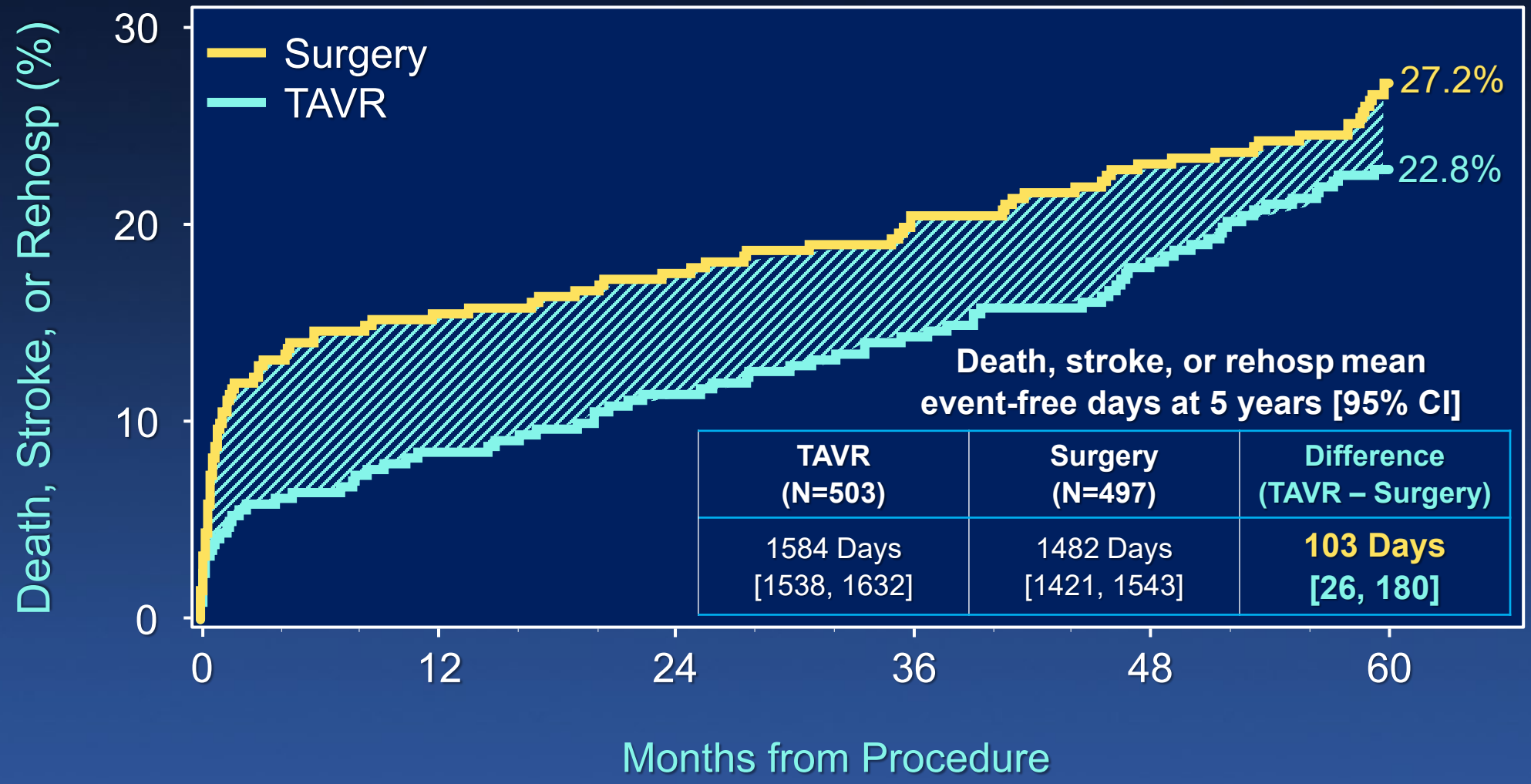
Restricted Mean Event-free Survival Time (Days)



Death, stroke, or rehosp mean event-free days at 5 years [95% CI]

TAVR (N=503)	Surgery (N=497)	Difference (TAVR – Surgery)
1584 Days [1538, 1632]	1482 Days [1421, 1543]	**103 Days [26, 180]**

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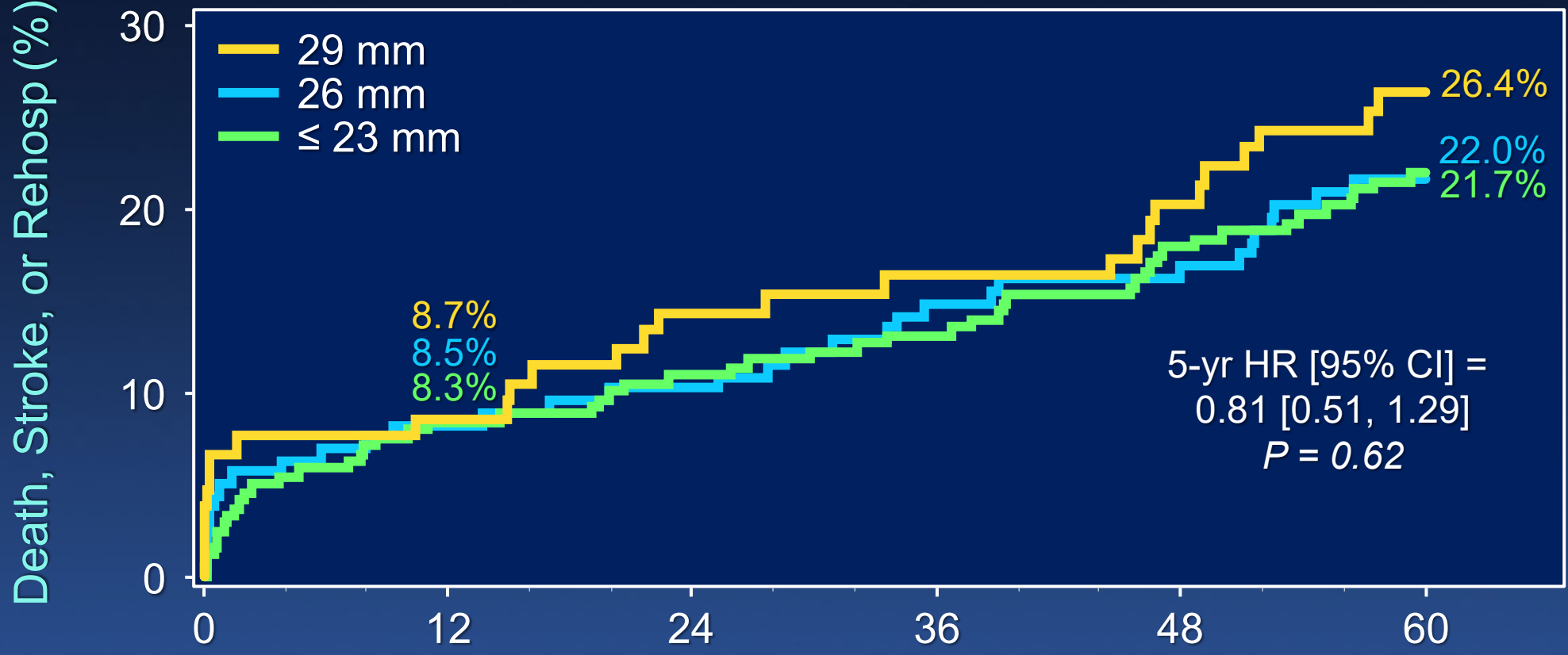
Primary Endpoint 1

By Valve Size – TAVR



Number at risk:

≤ 23 mm	156	142	137	129	125	108
26 mm	236	216	208	201	186	172
29 mm	104	95	89	85	80	73

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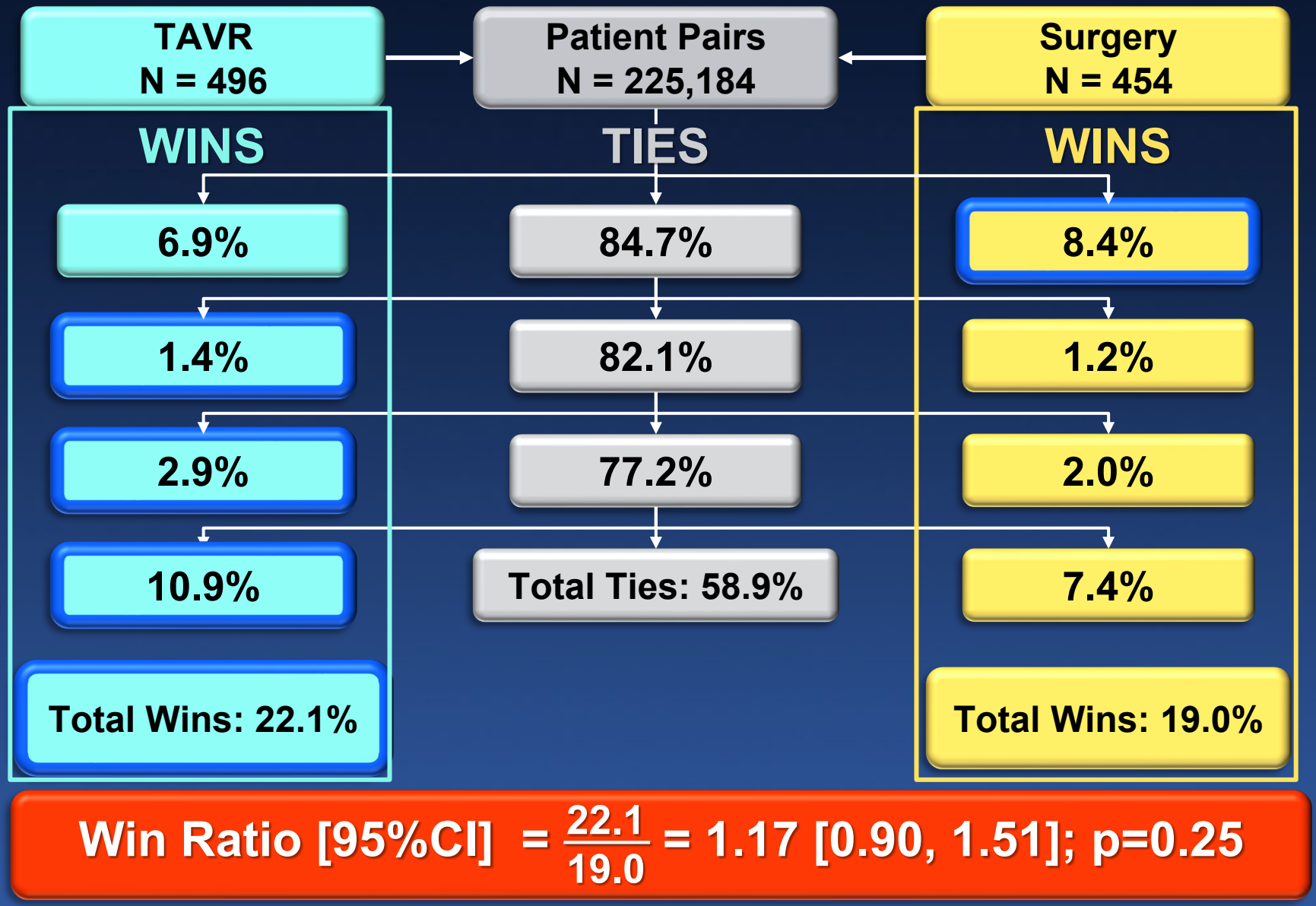
Primary Endpoint 2

Hierarchical Components:

1. All-cause Death
2. Disabling Stroke
3. Non-disabling Stroke
4. Rehospitalization Days
   (valve-, procedure-, or HF-related)



Win Ratio [95%CI] = $\frac{22.1}{19.0}$ = 1.17 [0.90, 1.51]; p=0.25

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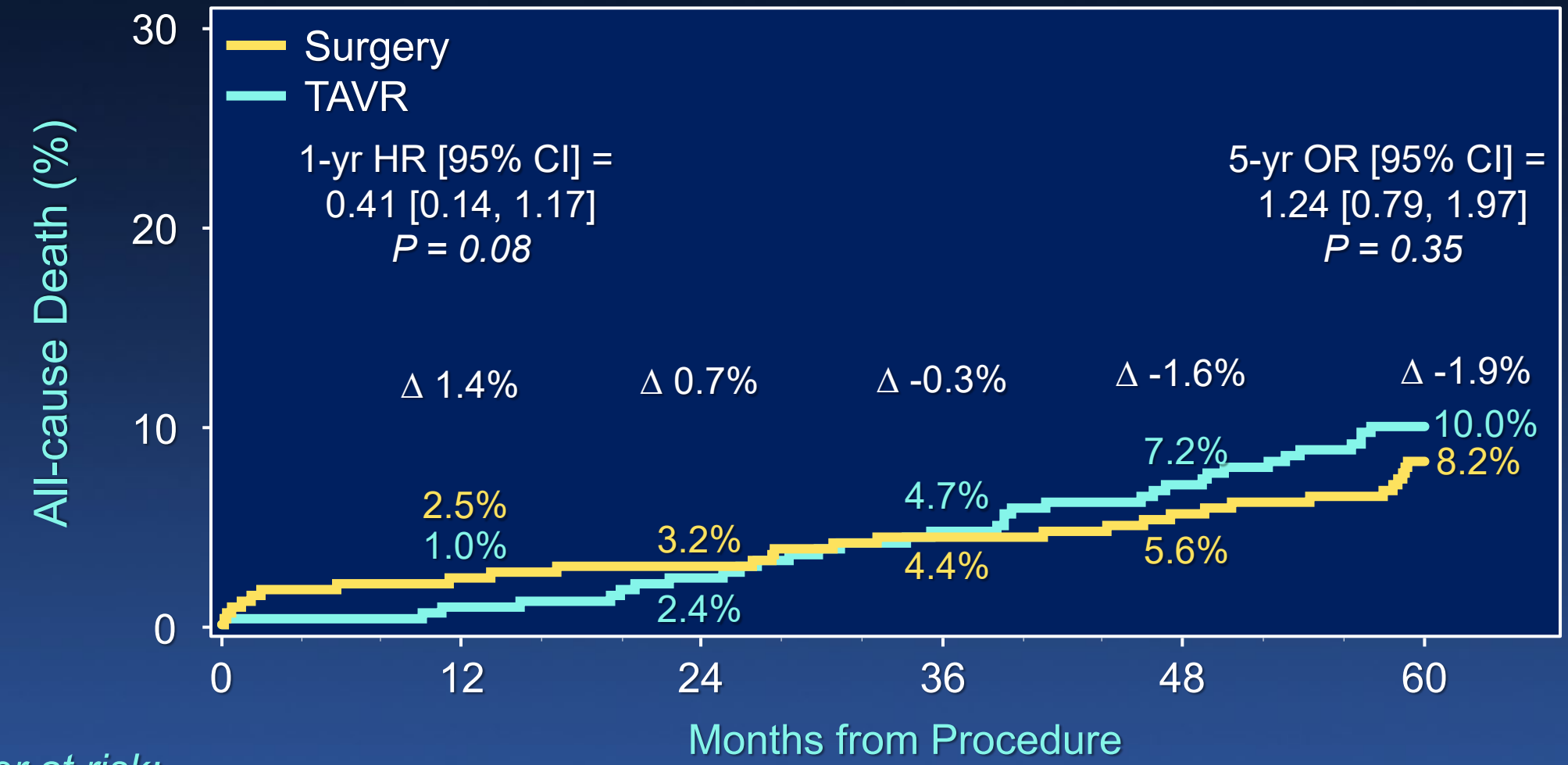
All-cause Death



Number at risk:

TAVR	496	490	478	460	438	405
Surgery	454	427	409	394	379	346

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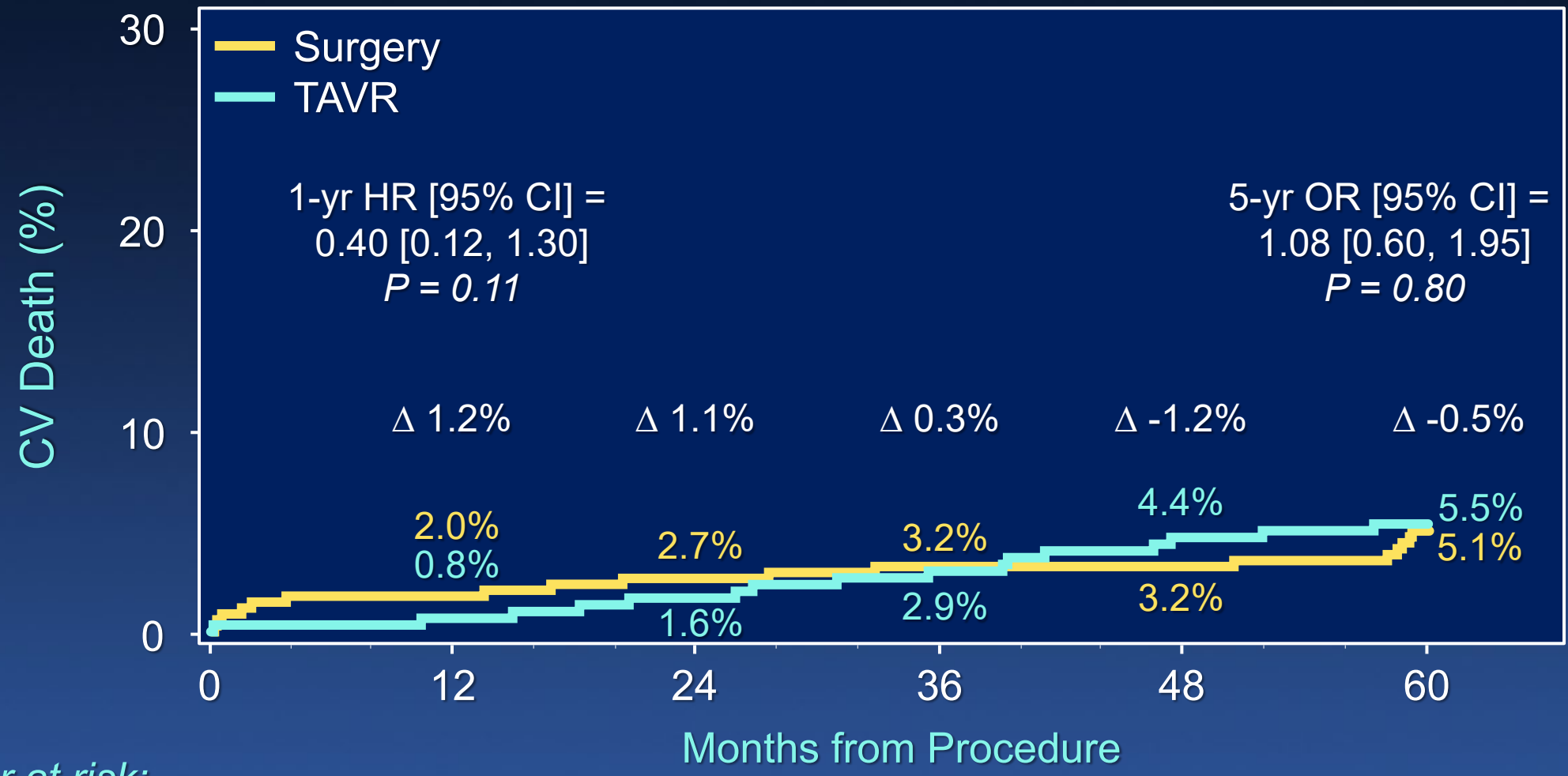
CV Death



Number at risk:

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Causes of Death 0-5 Years

CV Causes

Cause, No. of pts	TAVR	Surgery
Cardiac Cause	**8**	**9**
Acute MI	0	2
Cardiac Arrest	2	1
Cardiogenic Shock	0	1
CHF	2	3
Endocarditis	0	1
Sudden Cardiac Death	4	1
Non-coronary Vascular Conditions	**11**	**6**
Procedure-related	2	2
Stroke	3	4
Traumatic Head Injury from Fall	6	0
Unknown	**7**	**6**
Totals	**26**	**21**

Non-CV Causes

Cause, No. of pts	TAVR	Surgery
Cancer	9	5
COVID-19	3	1
Cirrhosis	1	0
MVA	1	1
Parkinson's Disease	0	1
Respiratory Failure*	3	4
Sepsis	4	1
Suicide	1	0
Totals	**22**	**13**

*Due to chronic respiratory disease or pneumonia

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CV Causes

Cause, No. of pts	TAVR	Surgery
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Traumatic Head Injury from Fall	**6**	**0**
Unknown	**7**	**6**
Totals	**26**	**21**

Non-CV Causes

Cause, No. of pts	TAVR	Surgery
Cancer	**9**	**5**
COVID-19	**3**	**1**
Cirrhosis	1	0
MVA	1	1
Parkinson's Disease	0	1
Respiratory Failure*	3	4
Sepsis	**4**	**1**
Suicide	1	0
Totals	**22**	**13**

*Due to chronic respiratory disease or pneumonia

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Vital Status Sweep Methods

For 5-year Follow-up

- To improve completeness of follow-up, a vital status (alive or dead) sweep was performed by sites (patient/family phone calls) and using publicly available data.
- Of 95 patients identified, vital status was obtained in 66 additional patients; TAVR = 21 and Surgery = 45; 18/21 TAVR patients and 38/45 Surgery patients were alive at 5 years.
- Overall, vital status was known for 98.0% with TAVR and 97.1% with Surgery.

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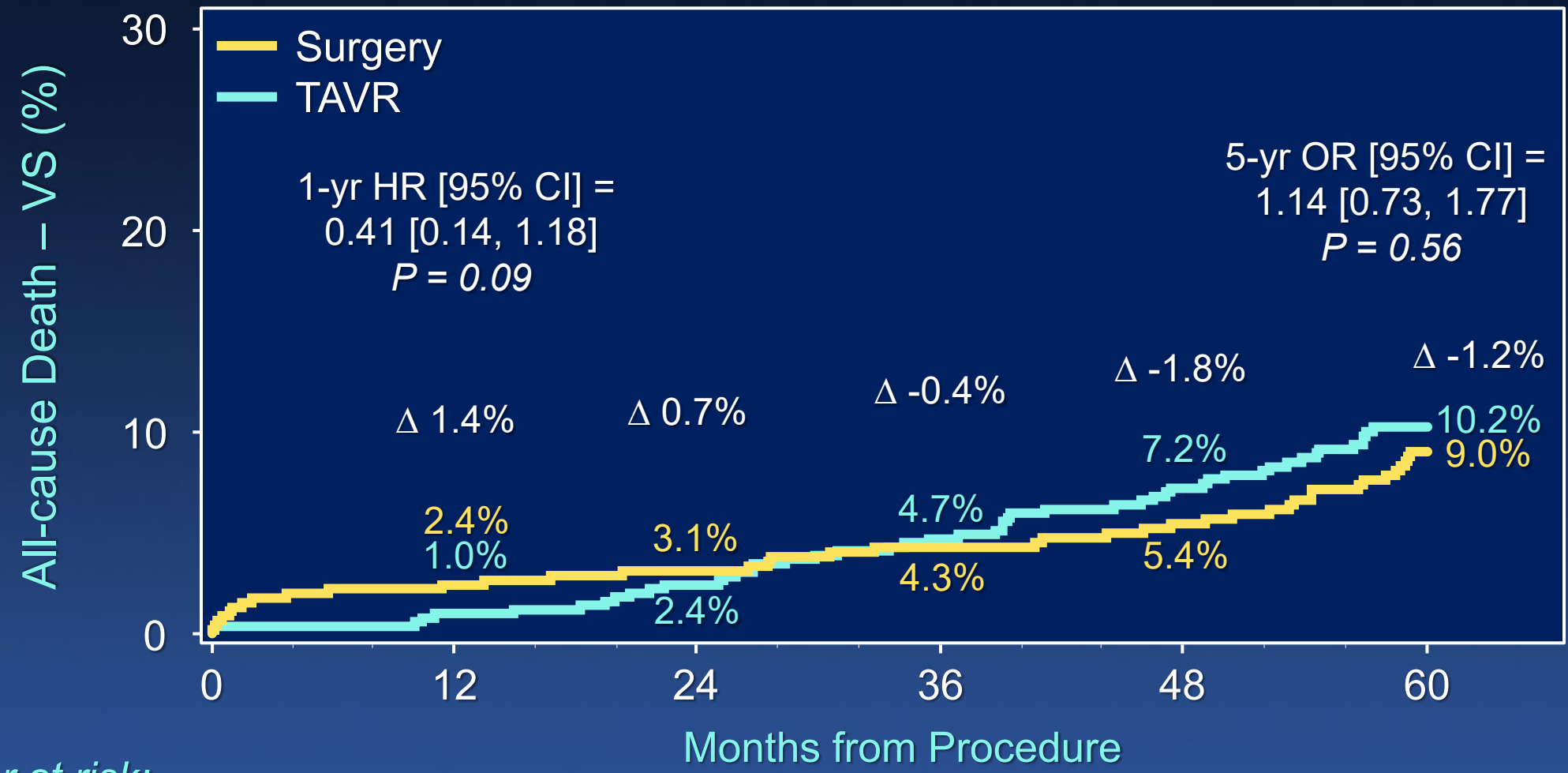
Vital Status Sweep



Number at risk:

TAVR	496	490	479	463	445	415
Surgery	454	435	424	413	404	378

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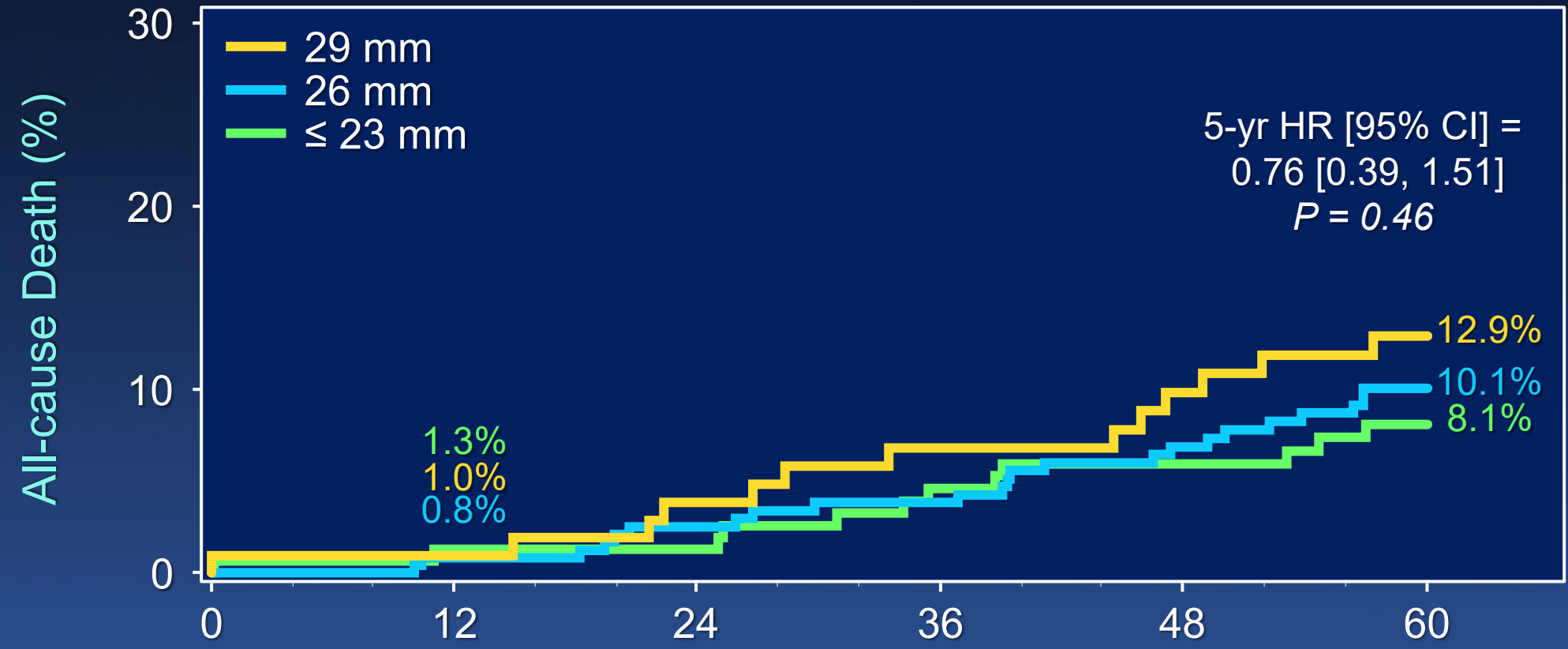
All-cause Death
By Valve Size – TAVR



Number at risk:

≤ 23 mm	156	153	150	143	139	125
26 mm	236	234	228	223	210	196
29 mm	104	103	100	94	89	84

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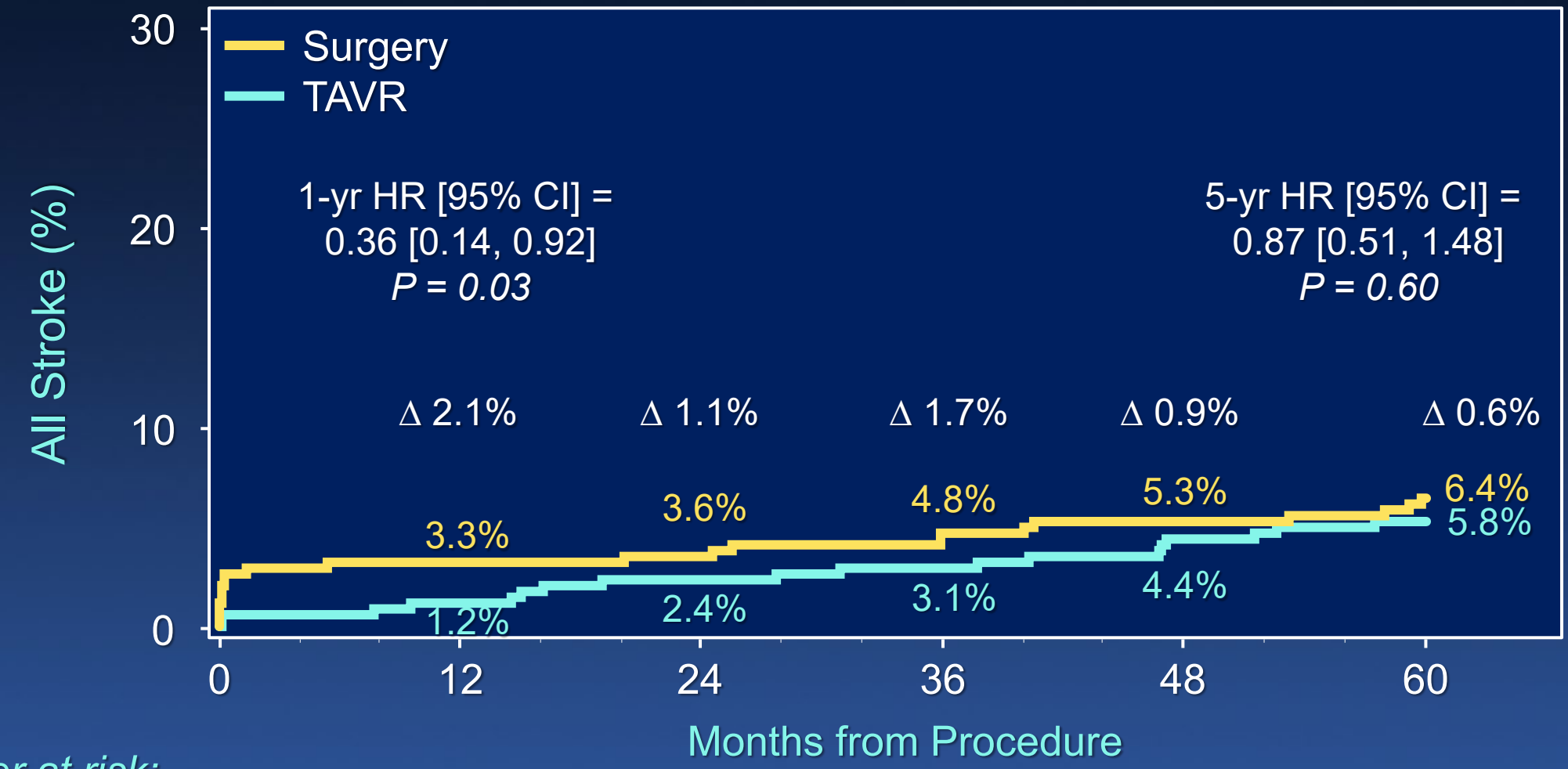
All Stroke



Number at risk:

TAVR	496	486	468	450	428	391
Surgery	454	416	397	378	361	329

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Stroke Types

KM Rate (No. of pts) or no. of pts

Endpoint	0 – 5 Years	
	TAVR	Surgery
All Stroke	**5.8% (27)***	**6.4% (27)**
Disabling	**2.9% (13)***	**2.7% (11)**
Ischemic	10	8
Hemorrhagic	3	3
Non-disabling	**3.2% (15)***	**3.7% (16)**
Ischemic	14	13
Hemorrhagic	1	1
Undetermined	0	2

*3 patients in the TAVR arm had multiple strokes

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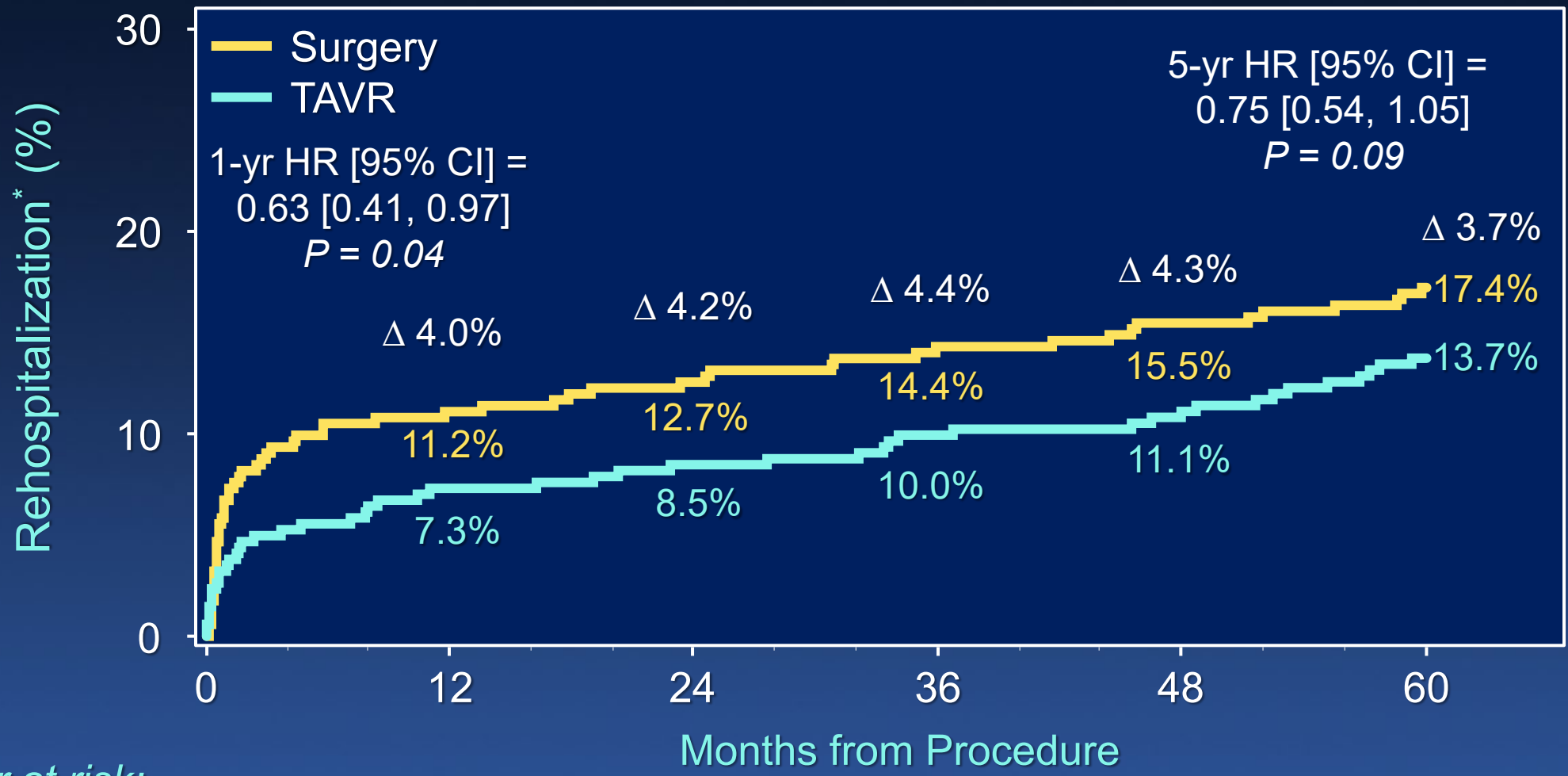
Rehospitalization*



Number at risk:

TAVR	496	455	439	419	396	361
Surgery	454	381	359	339	321	289

*Rehosp defined as valve-, procedure-, or HF-related

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Additional Clinical Endpoints

KM% (No. of patients)

Endpoints	0 – 5 Years			
	TAVR	Surgery	HR [95% CI]	*P-value*
Aortic valve reintervention	2.6% (12)	3.0% (12)	0.86 [0.39, 1.92]	0.72
Endocarditis	1.3% (6)	2.0% (8)	0.65 [0.23, 1.87]	0.42
Valve thrombosis (VARC-3)	2.5% (12)	0.2% (1)	10.52 [1.37, 80.93]	< 0.01
New-onset atrial fibrillation*	13.7% (55)	42.4% (155)	0.25 [0.19, 0.34]	< 0.0001
New pacemaker	13.5% (63)	10.4% (43)	1.33 [0.90, 1.96]	0.15
MI*	2.1% (10)	4.4% (18)	0.48 [0.22, 1.05]	0.06
Serious bleeding*	10.2% (49)	14.8% (64)	0.65 [0.45, 0.95]	0.02
Revascularization*	3.7% (17)	6.0% (25)	0.59 [0.32, 1.09]	0.09

*Site-reported values (not CEC-adjudicated to 5 years)

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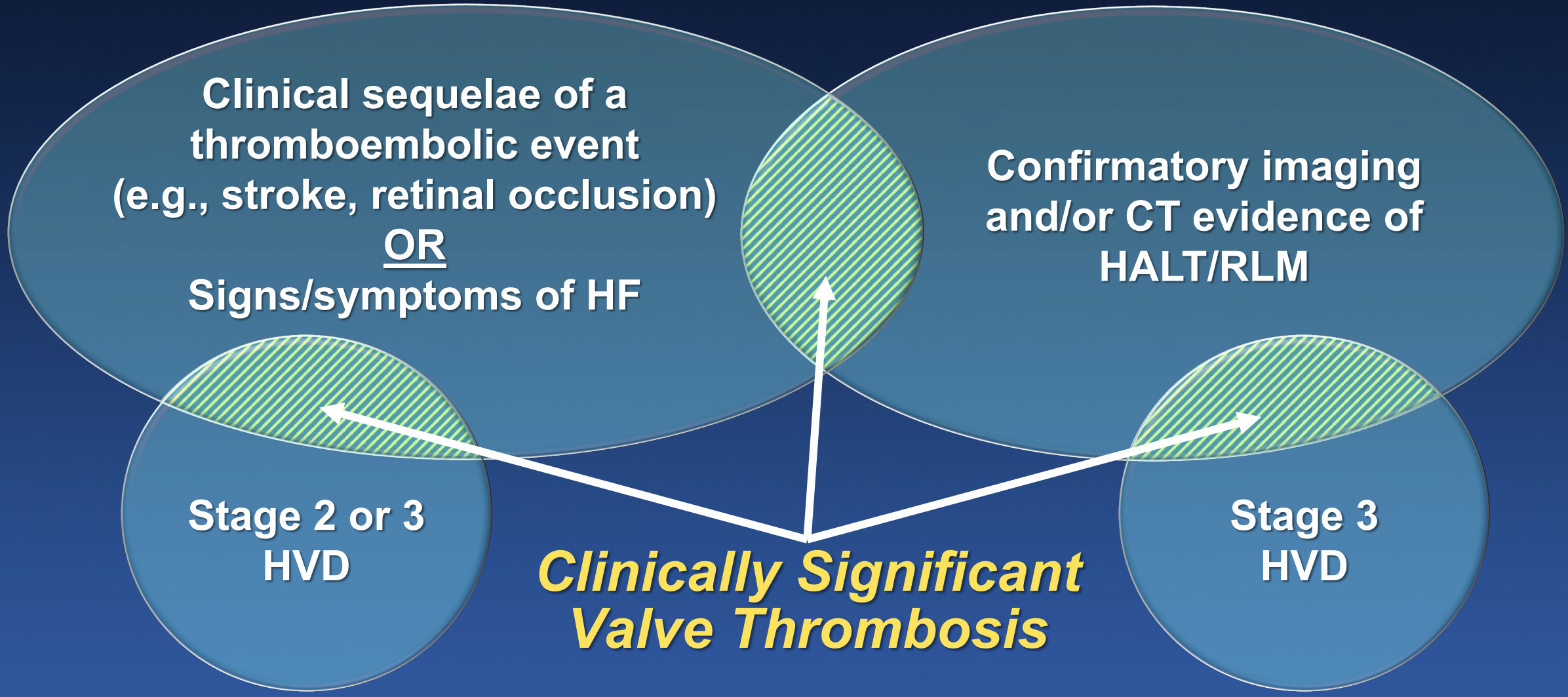
VARC-3 Definitions

Clinically Significant Valve Thrombosis



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Valve Thrombosis

No. of patients

Clinically Significant Valve Thrombosis	0 – 5 Years	
	TAVR	Surgery
Valve Thrombosis Events*	**13 events in 12 pts†**	**1 event in 1 pt**
Clinical Sequelae Related to Thrombosis		
Death	0	0
Stroke (all ischemic)	3	0
Disabling	1	0
Non-disabling	2	0
Stage 2 or 3 HVD	8	0
Occurred after 1 year	11†	1
Resolved with Anticoagulation	7	0

*All patients had confirmatory imaging

†1 patient had 2 events; the first occurred POD 40, the second POD 371 (both Stage 1 HVD)

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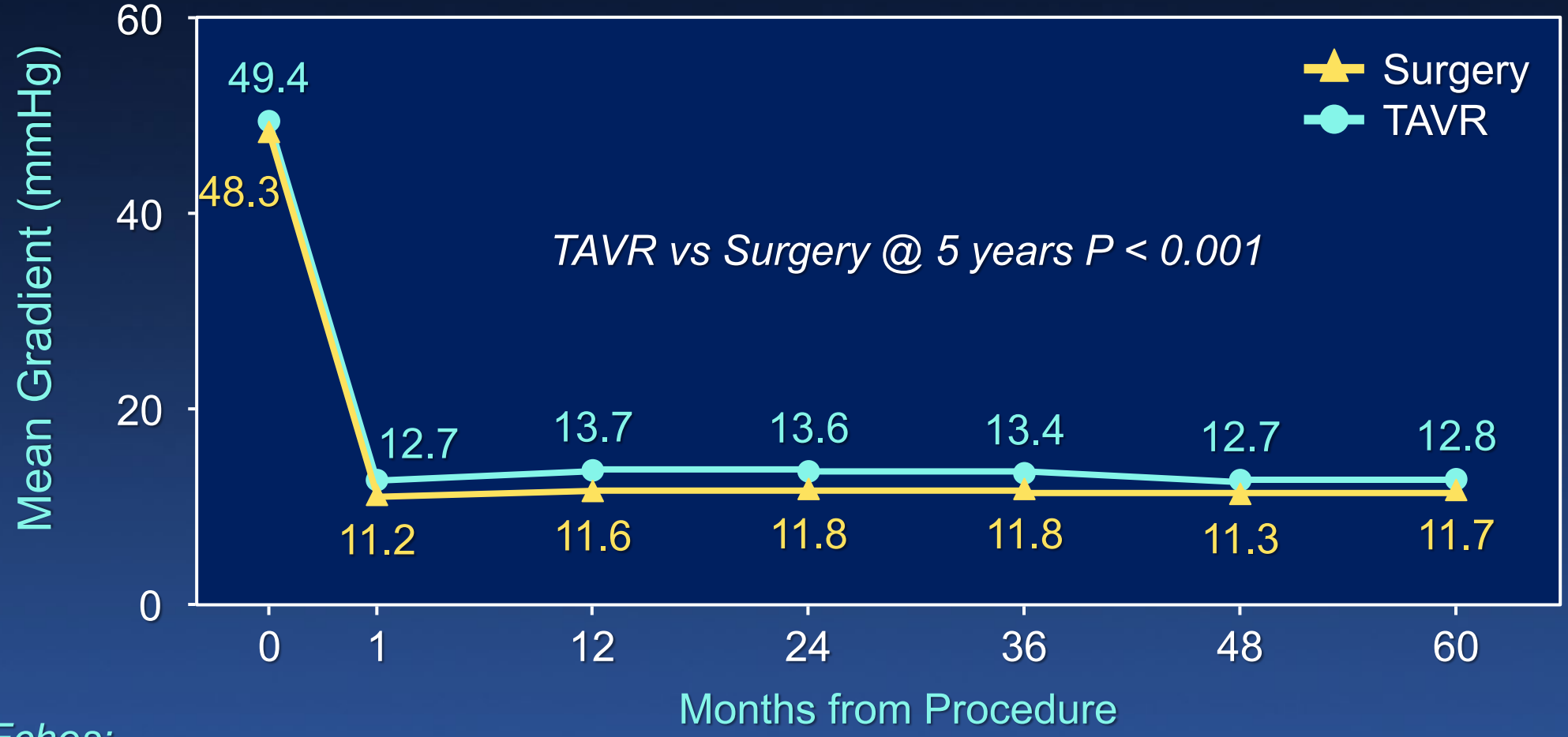
Valve Hemodynamics

Mean Gradient



No. of Echos:

TAVR	483	492	474	437	372	348	329
Surgery	442	432	391	360	304	305	282

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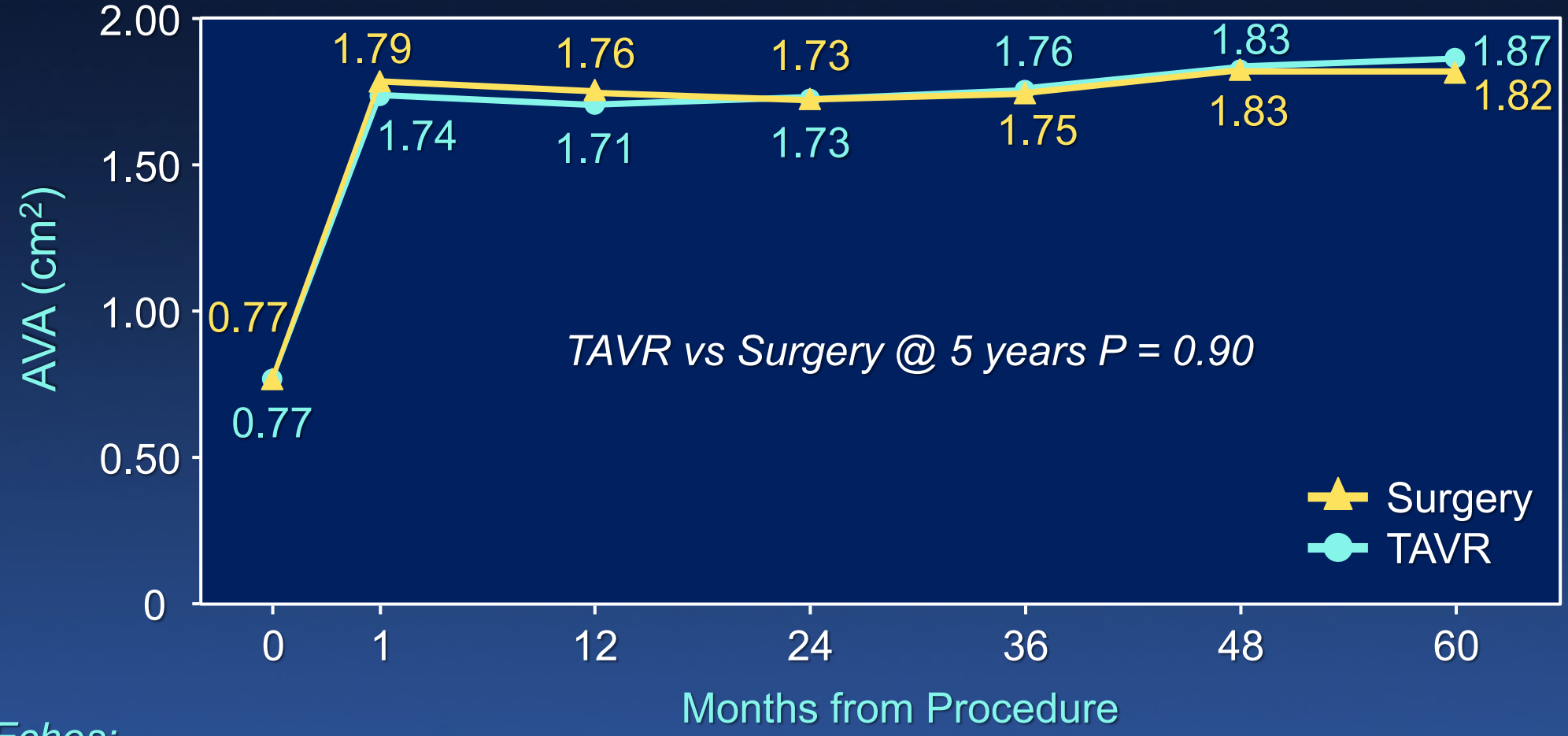
Valve Hemodynamics

Aortic Valve Area



No. of Echos:

TAVR	458	482	450	416	347	334	320
Surgery	424	415	371	342	289	295	275

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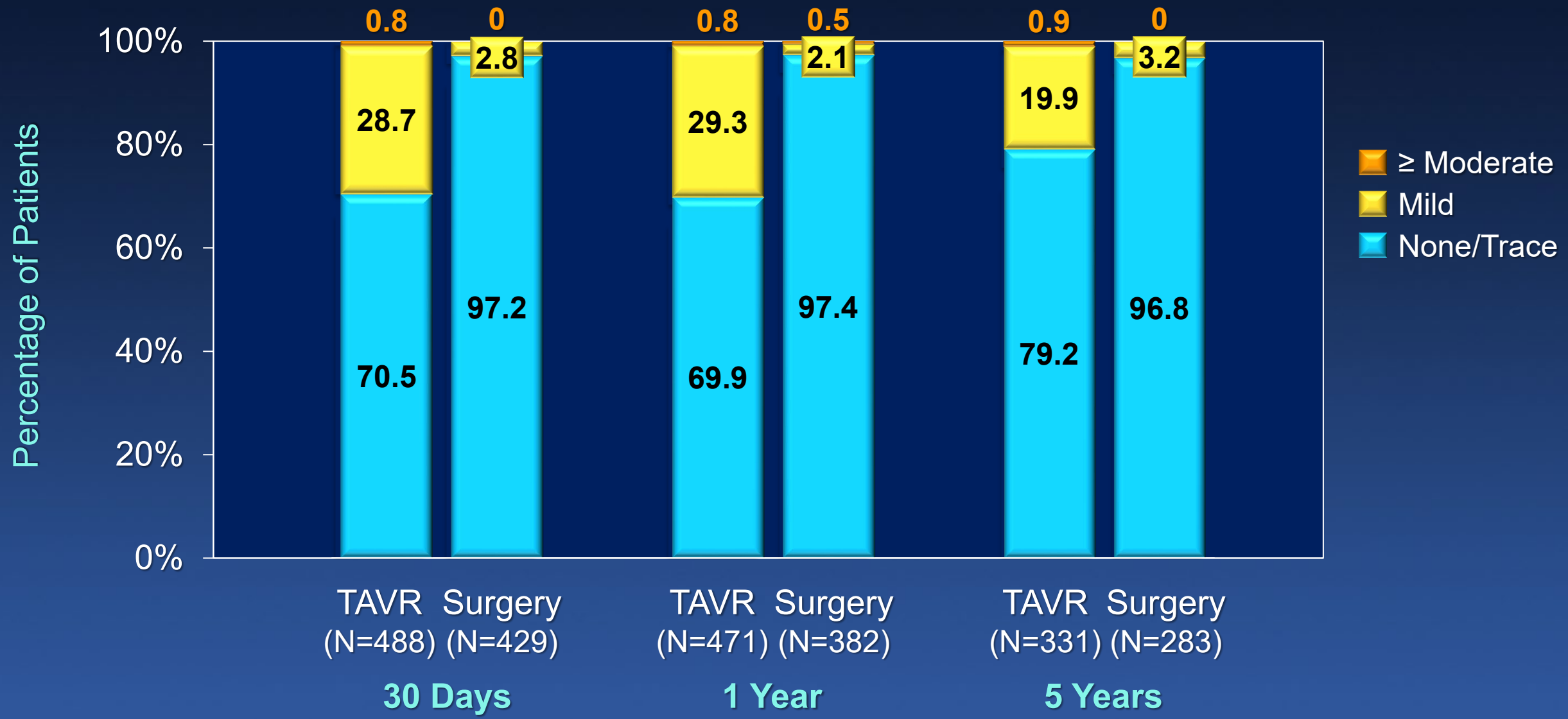
Paravalvular Regurgitation

≥ mild P < 0.001 at all time points



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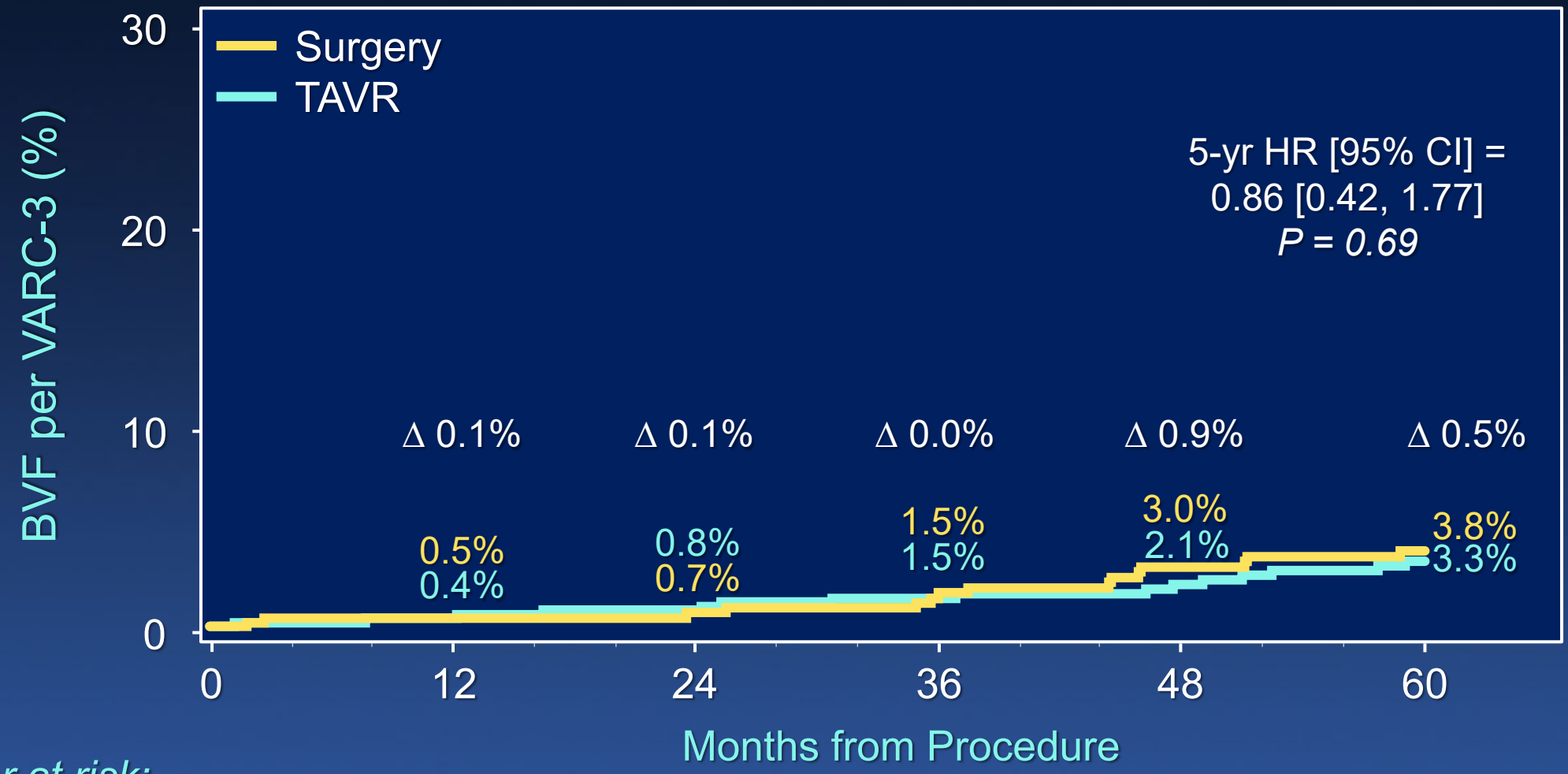
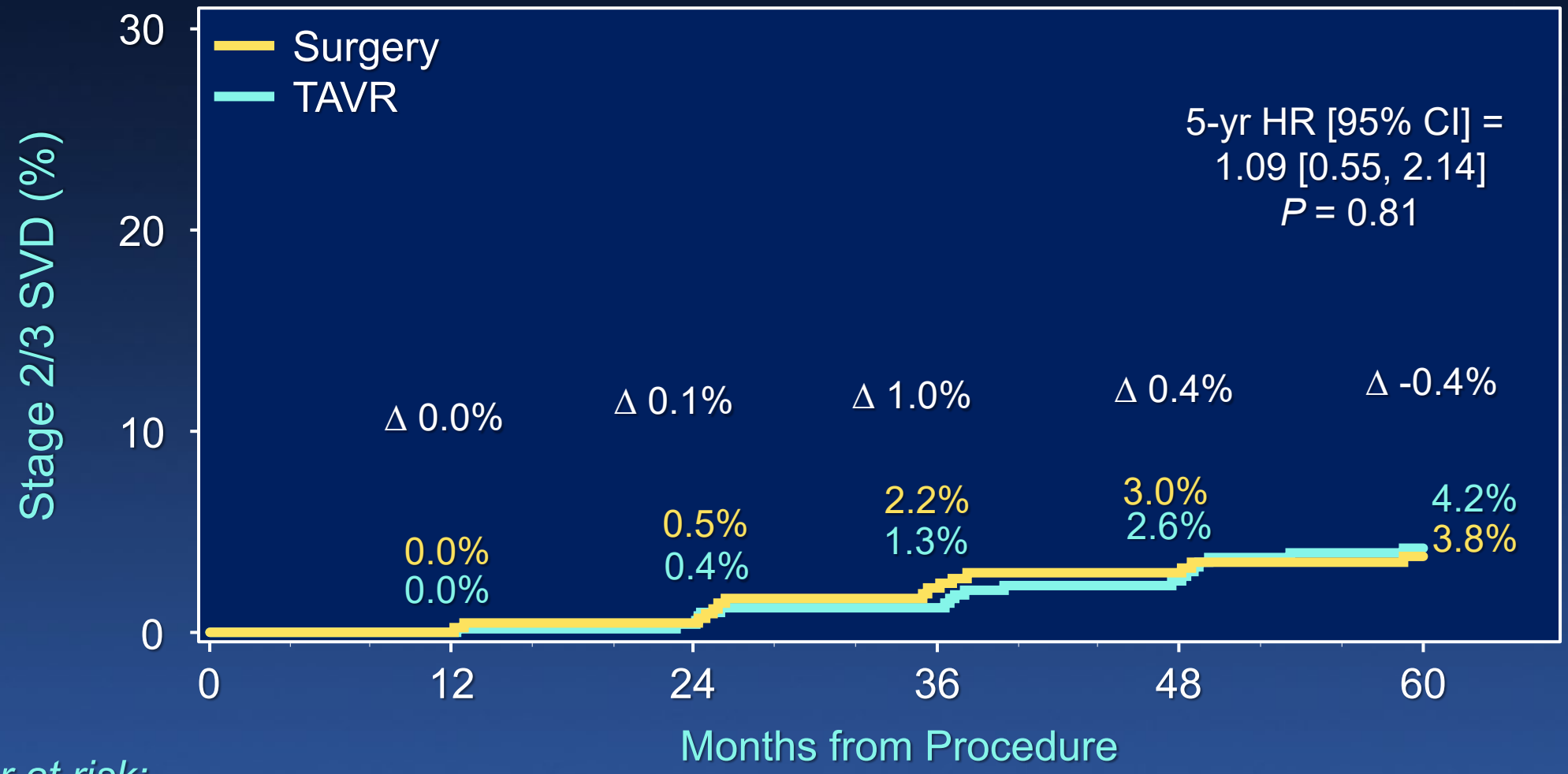
BVF to 5 Years (VARC-3)



Number at risk:

TAVR	496	489	475	454	430	392
Surgery	454	426	407	390	369	334

THE PARTNER 3 TRIAL Stage 2/3 SVD to 5 Years (VARC 3)



Number at risk:

TAVR	496	490	476	454	428	387
Surgery	454	426	407	385	366	332

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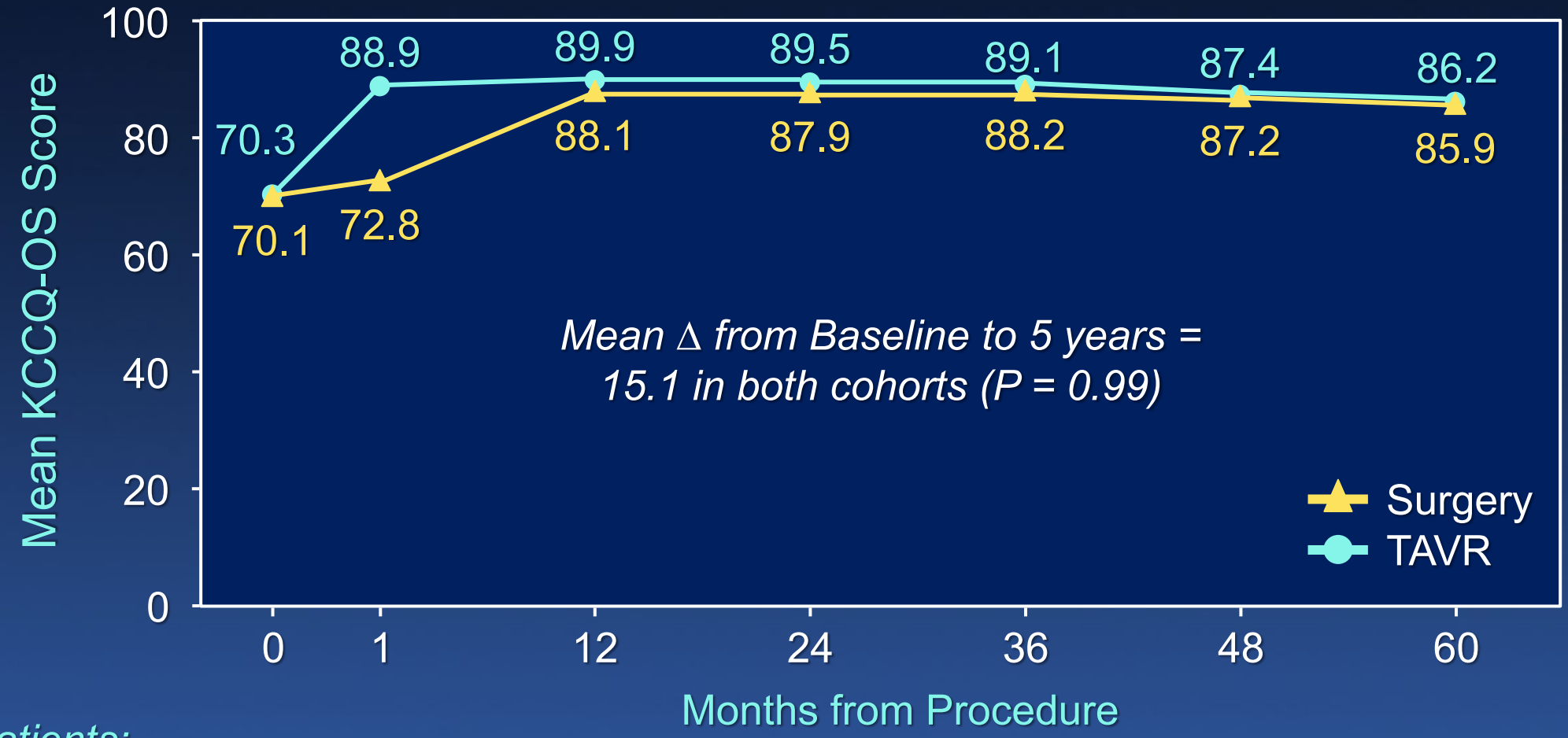
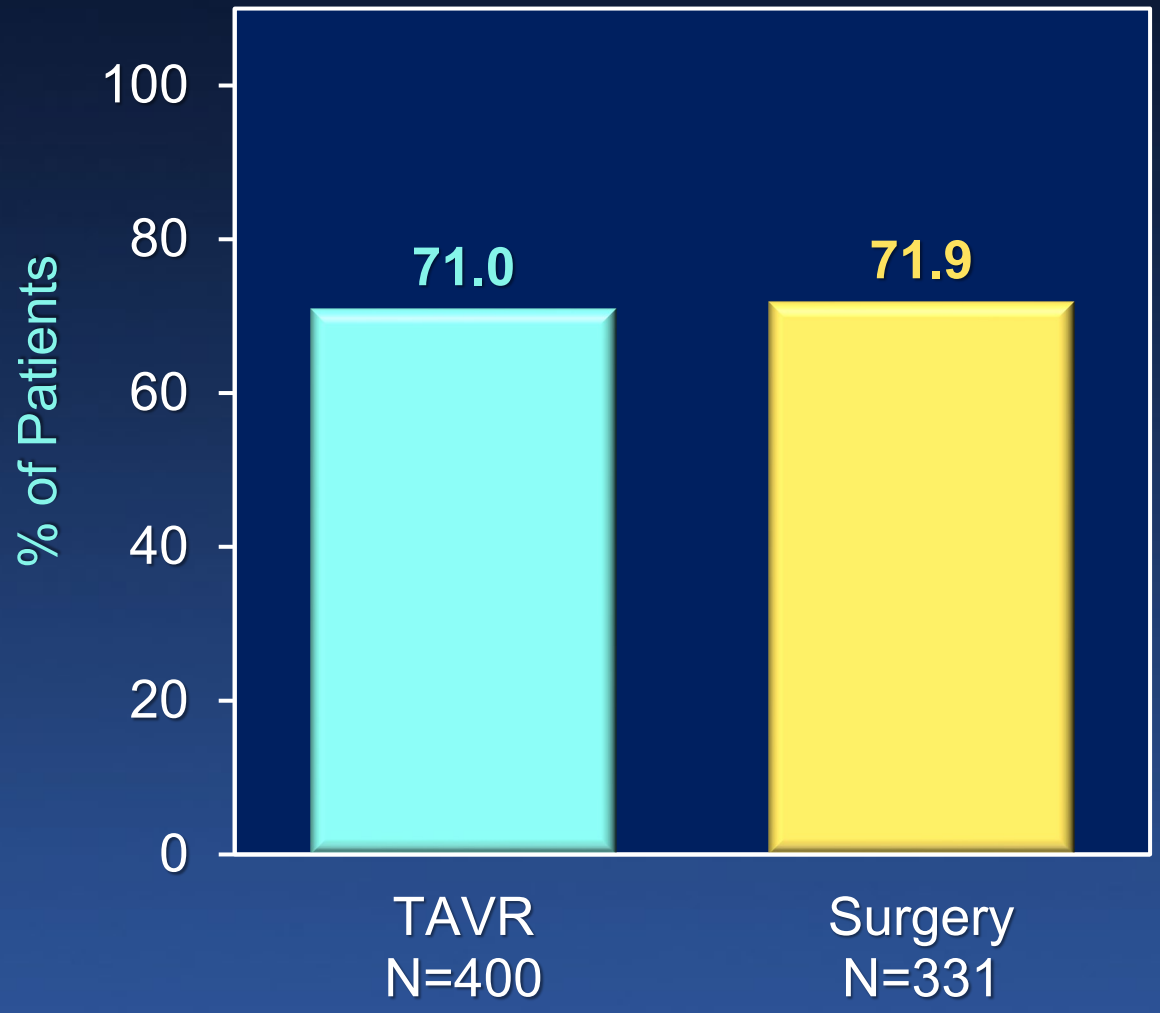
Mean KCCQ-OS Score



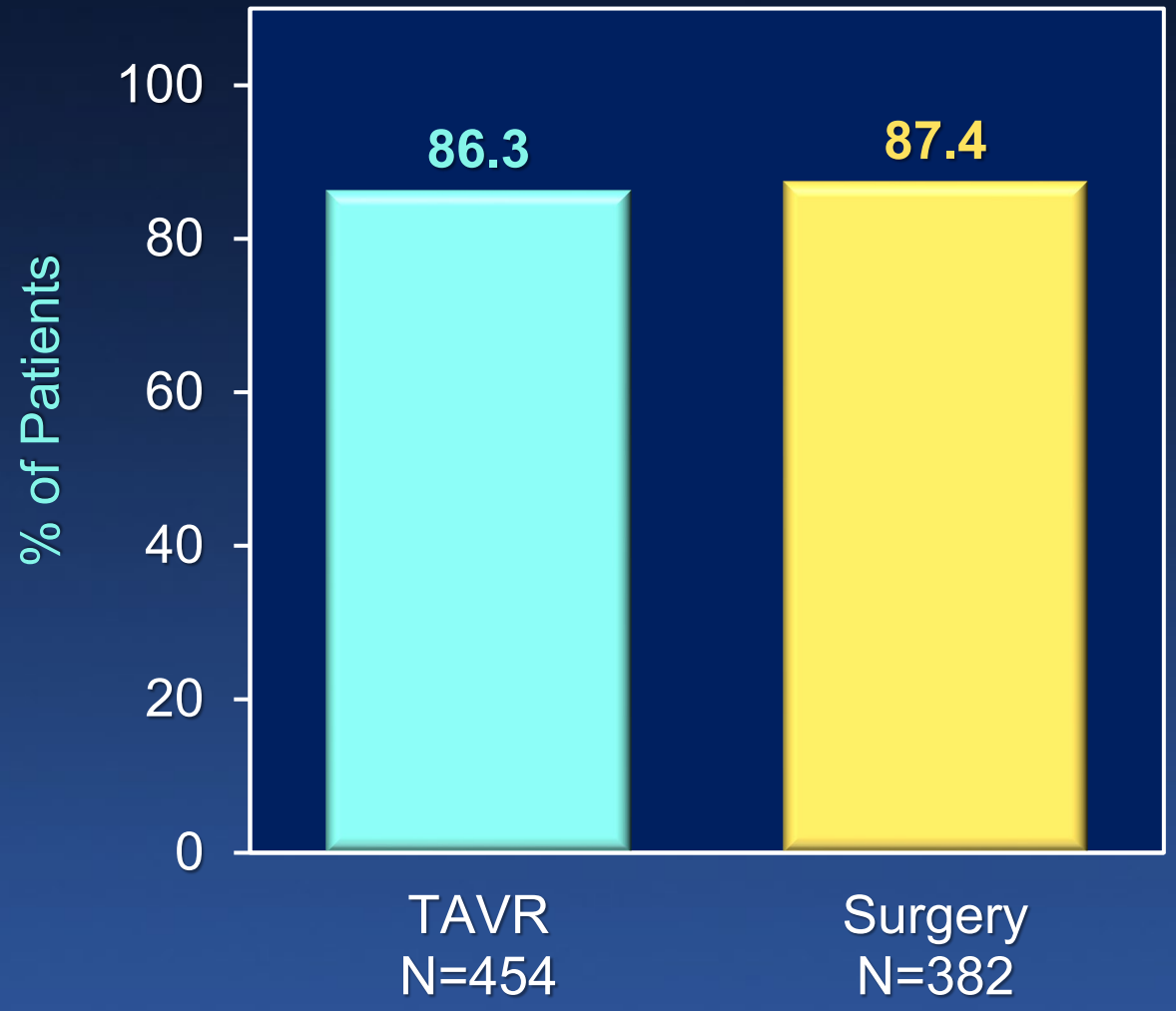
No. of Patients:

TAVR	493	491	481	444	406	381	354
Surgery	448	433	403	367	340	321	301

QOL and Valve Durability at 5 Years



Alive with a KCCQ Score > 75



Alive with a Durable Valve (no BVF)

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Conclusions (1)

In low-risk severe symptomatic AS patients, treated with either SAPIEN 3 TAVR or Surgery, over 5 years follow-up:

- **BOTH** TAVR and Surgery were associated with similar and low clinical event rates (CV death ~1%/yr, all stroke ~1%/yr, and CV rehospitalization ~3%/yr).
- Differences in the primary composite endpoint rate, which favored TAVR at 1-year, were attenuated after 5 years (Δ 7.1% to Δ 4.3%).
- Other important endpoints were either similar for both therapies (new PM and reintervention), favored TAVR (new AF and serious bleeding), or favored Surgery (mild PVR and valve thrombosis).

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Conclusions (2)

- The improvements in antegrade valve hemodynamics were maintained for both therapies at 5 years.
- VARC-3 bioprosthetic valve failure and SVD were similar and infrequent with both therapies (BVF - TAVR 3.3% and Surgery 3.8%; SVD - TAVR 4.2% and Surgery 3.8%), encouraging signs for favorable valve durability; 10-year follow-up is planned.
- Marked 1-year improvements in patient-reported outcomes (esp. KCCQ scores) were maintained and similar for both therapies.

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Clinical Implications

The 5-year follow-up findings from the PARTNER 3 trial reaffirm the clinical and echocardiographic benefits of SAPIEN 3 TAVR as a meaningful alternative to surgical therapy for low-risk severe, symptomatic AS patients!

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Just Published in NEJM!

The NEW ENGLAND JOURNAL of MEDICINE

Transcatheter Aortic-Valve Replacement in Low-Risk Patients at Five Years

Michael J. Mack, M.D., Martin B. Leon, M.D., Vinod H. Thourani, M.D., Philippe Pibarot, D.V.M., Ph.D., Rebecca T. Hahn, M.D., Philippe Genereux, M.D., Susheel K. Kodali, M.D., Samir R. Kapadia, M.D., David J. Cohen, M.D., Stuart J. Pocock, Ph.D., Michael Lu, Ph.D., Roseann White, Ph.D., Molly Szerlip, M.D., Julien Ternacle, M.D., S. Chris Malaisrie, M.D., Howard C. Herrmann, M.D., Wilson Y. Szeto, M.D., Mark J. Russo, M.D., Vasilis Babaliaros, M.D., Craig R. Smith, M.D., Philipp Blanke, M.D., John G. Webb, M.D., and Raj Makkar, M.D., for the PARTNER 3 Investigators*

Thank you!

To all the Investigators, Heart Teams, and especially, the 10,000 participating Patients, for 15 years of PARTNER!

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See you at the Echo LBCT and the Deep-Dive PARTNER 3 Symposium

2:00pm	**Five-year Echocardiographic Outcomes from the PARTNER 3 Low-risk Randomized Trial** Rebecca T. Hahn
3:30pm	**Perspectives on Mortality in the PARTNER 3 5-Year Study** Vinod H. Thourani
3:45pm	**Important Secondary Endpoints from the PARTNER 3 5-Year Study** Raj Makkar
4:00 pm	**An Echo Deep Dive of the PARTNER 3 5-Year Study** Philippe Pibarot
4:15 pm	**Importance of Patient Reported Outcomes** David J. Cohen