THE PARTNER 3 TRIAL

PARTNER 3

Transcatheter or Surgical Aortic Valve Replacement in Low Risk Patients with Aortic Stenosis

Martin B. Leon, MD &
Michael J. Mack, MD
on behalf of the PARTNER 3 Trial Investigators

10 mins

Disclosures - Martin B. Leon, MD

TCTAP 2019; Seoul, Korea; April 27-30, 2019

Within the past 12 months, I or my spouse/partner have had a financial interest/arrangement or affiliation with the organization(s) listed below.

Financial Relationship	Company
• Research Support	Abbott, Boston Scientific, Edwards Lifesciences, Medtronic
• Consulting Fees*	Abbott, Boston Scientific, Gore, Medtronic, Meril Life Sciences
• Other	Edwards Lifesciences**

*Medical or scientific advisory board meetings

** Co-PI PARTNER 3 Trial; travel-related expenses only

Background (2)

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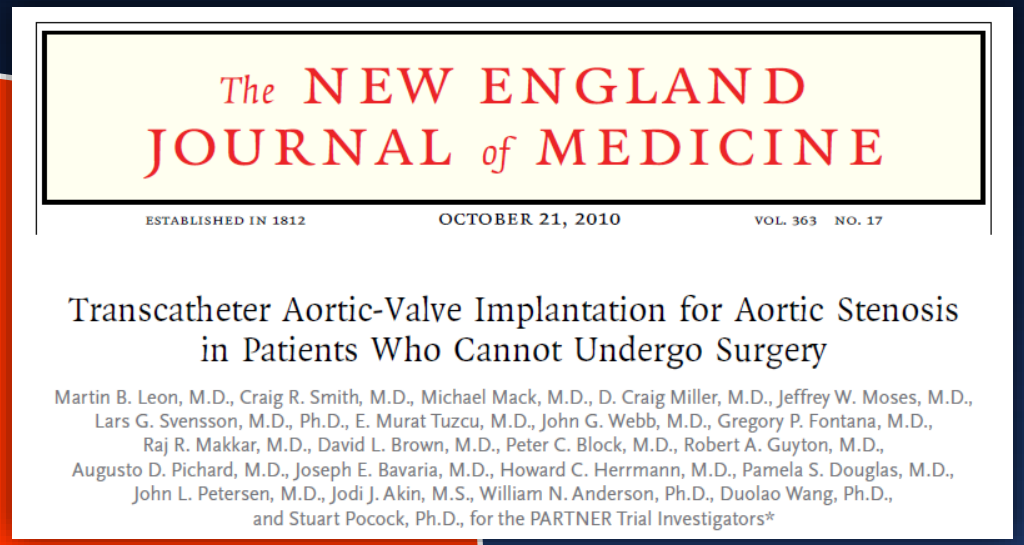
- RCT 1:1
- vs. Surgery
- N = 1000 pts

Low Risk

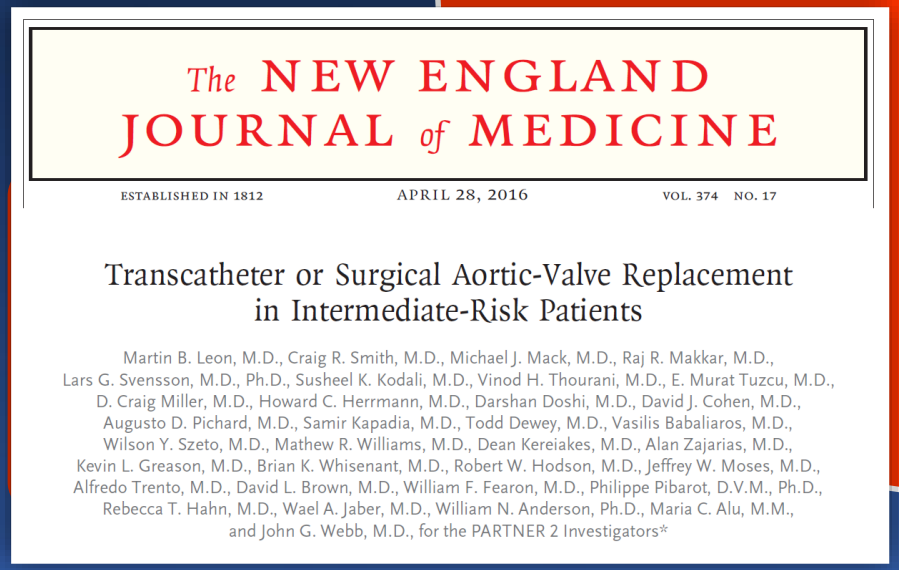


The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 OCTOBER 21, 2010 VOL. 363 NO. 17

Transcatheter Aortic-Valve Implantation for Aortic Stenosis in Patients Who Cannot Undergo Surgery

Martin B. Leon, M.D., Craig R. Smith, M.D., Michael Mack, M.D., D. Craig Miller, M.D., Jeffrey W. Moses, M.D., Lars G. Svensson, M.D., Ph.D., E. Murat Tuzcu, M.D., John G. Webb, M.D., Gregory P. Fontana, M.D., Raj R. Makkar, M.D., David L. Brown, M.D., Peter C. Block, M.D., Robert A. Guyton, M.D., Augusto D. Pichard, M.D., Joseph E. Bavaria, M.D., Howard C. Herrmann, M.D., Pamela S. Douglas, M.D., John L. Petersen, M.D., Jodi J. Akin, M.S., William N. Anderson, Ph.D., Duolao Wang, Ph.D., and Stuart Pocock, Ph.D., for the PARTNER Trial Investigators*



The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 APRIL 28, 2016 VOL. 374 NO. 17

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

Martin B. Leon, M.D., Craig R. Smith, M.D., Michael J. Mack, M.D., Raj R. Makkar, M.D., Lars G. Svensson, M.D., Ph.D., Susheel K. Kodali, M.D., Vinod H. Thourani, M.D., E. Murat Tuzcu, M.D., D. Craig Miller, M.D., Howard C. Herrmann, M.D., Darshan Doshi, M.D., David J. Cohen, M.D., Augusto D. Pichard, M.D., Samir Kapadia, M.D., Todd Dewey, M.D., Vasilis Babaliaros, M.D., Wilson Y. Szeto, M.D., Mathew R. Williams, M.D., Dean Kereiakes, M.D., Alan Zajarias, M.D., Kevin L. Greason, M.D., Brian K. Whisenant, M.D., Robert W. Hodson, M.D., Jeffrey W. Moses, M.D., Alfredo Trento, M.D., David L. Brown, M.D., William F. Fearon, M.D., Philippe Pibarot, D.V.M., Ph.D., Rebecca T. Hahn, M.D., Wael A. Jaber, M.D., William N. Anderson, Ph.D., Maria C. Alu, M.M., and John G. Webb, M.D., for the PARTNER 2 Investigators*

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 JUNE 9, 2011 VOL. 364 NO. 23

Transcatheter and Surgical Aortic-Valve Replacement in High-Risk Patients

Craig R. Smith, M.D., Martin B. Leon, M.D., Michael J. Mack, M.D., D. Craig Miller, M.D., Jeffrey W. Moses, M.D., Lars G. Svensson, M.D., Ph.D., E. Murat Tuzcu, M.D., John G. Webb, M.D., Gregory P. Fontana, M.D., Raj R. Makkar, M.D., Mathew Williams, M.D., Todd Dewey, M.D., Samir Kapadia, M.D., Vasilis Babaliaros, M.D., Vinod H. Thourani, M.D., Paul Corso, M.D., Augusto D. Pichard, M.D., Joseph E. Bavaria, M.D., Howard C. Herrmann, M.D., Jodi J. Akin, M.S., William N. Anderson, Ph.D., Duolao Wang, Ph.D., and Stuart J. Pocock, Ph.D., for the PARTNER Trial Investigators*

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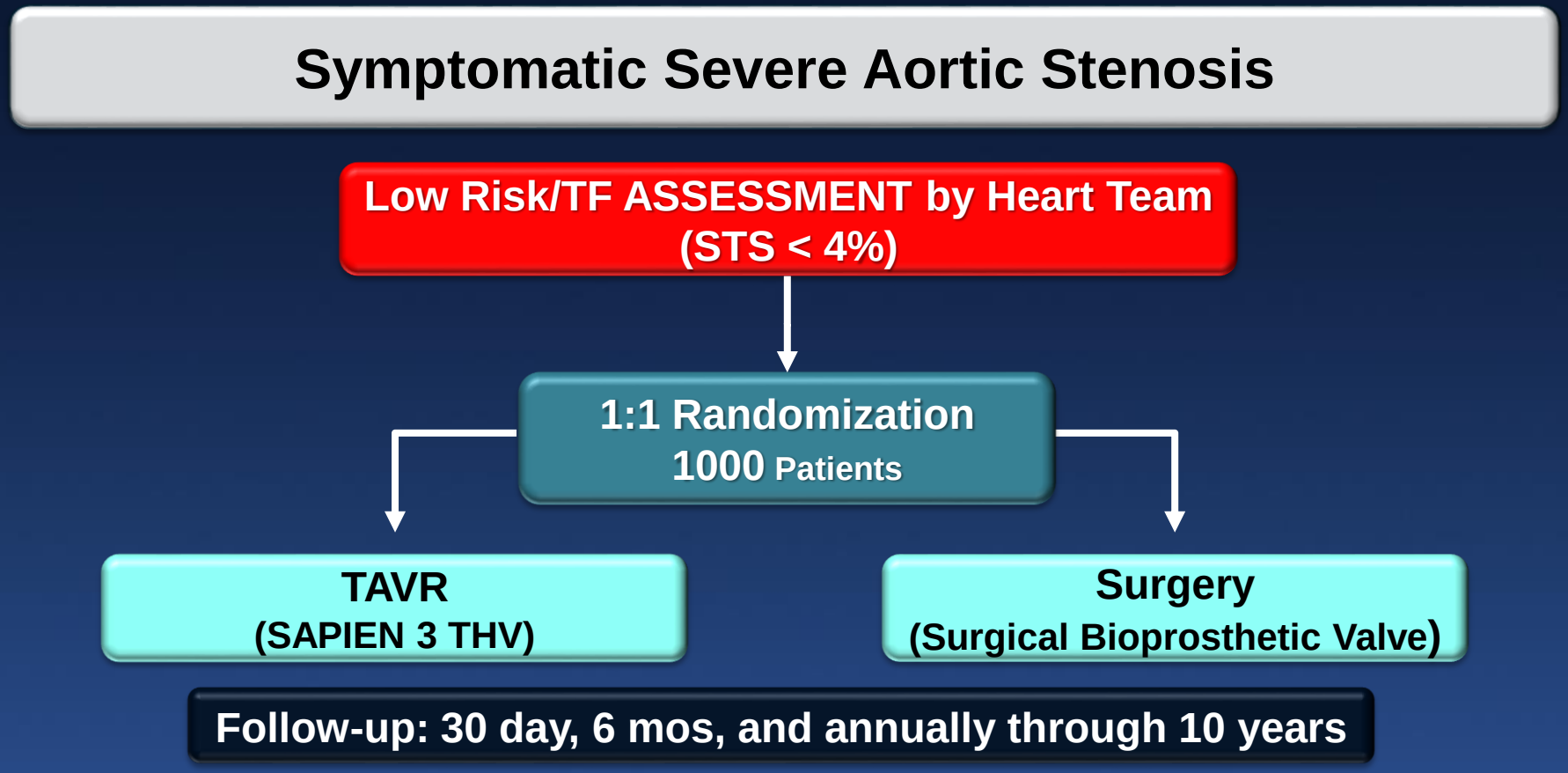
PARTNER 3 Study Design



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

PARTNER 3 Clinical Sites

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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 valvar 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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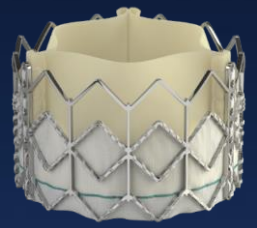
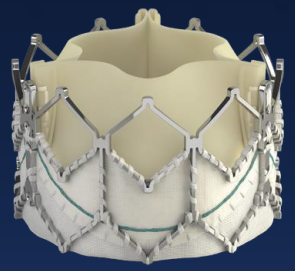
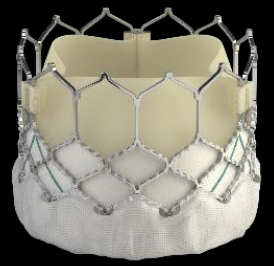
SAPIEN Valve Evolution

	SAPIEN	SAPIEN XT	SAPIEN 3
Valve Technology			
Sheath Compatibility			
Available Valve Sizes			
FDA Approval of Valve:	**PARTNER 1** 2011	**PARTNER 2** 2014	**PARTNER 3** 2015

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Primary Endpoint

- **Non-hierarchical composite of all-cause mortality, all strokes, or CV re-hospitalization at 1 year**
  - Primary analysis was non-inferiority, followed by superiority
  - Analysis cohort was the ‘as-treated’ (AT) population, defined as all randomized patients in whom the procedure was initiated.
  - Multiple sensitivity analyses performed

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Statistical Methods

- **Non-inferiority Testing for Primary Endpoint**
  - Upper bound of the 95% CI for the risk difference (TAVR-surgery) less than the pre-specified non-inferiority margin of 6%
- **Superiority Testing for Primary Endpoint**
  - If non-inferiority hypothesis met, superiority testing performed using a 2-sided alpha 0.05
- **Superiority Testing for Secondary Endpoints**
  - 1) Pre-specified in hierarchical order with multiplicity adjustments and 2) all others (P-values hypothesis generating)

Study Flow and Follow-Up

1520 patients with severe symptomatic AS at low surgical risk consented between March 25, 2016 and October 26, 2017 at 71 sites in the US, Canada, Japan, ANZ

Excluded from Randomization N=520

- Anatomic exclusions (n=308)
- Clinical exclusions (n=89)
- Other exclusions (n=38)
- Incomplete screening (n=85)

Eligible for Enrollment and Randomized N=1000 at 71 sites

TAVR N=503

Surgery N=497

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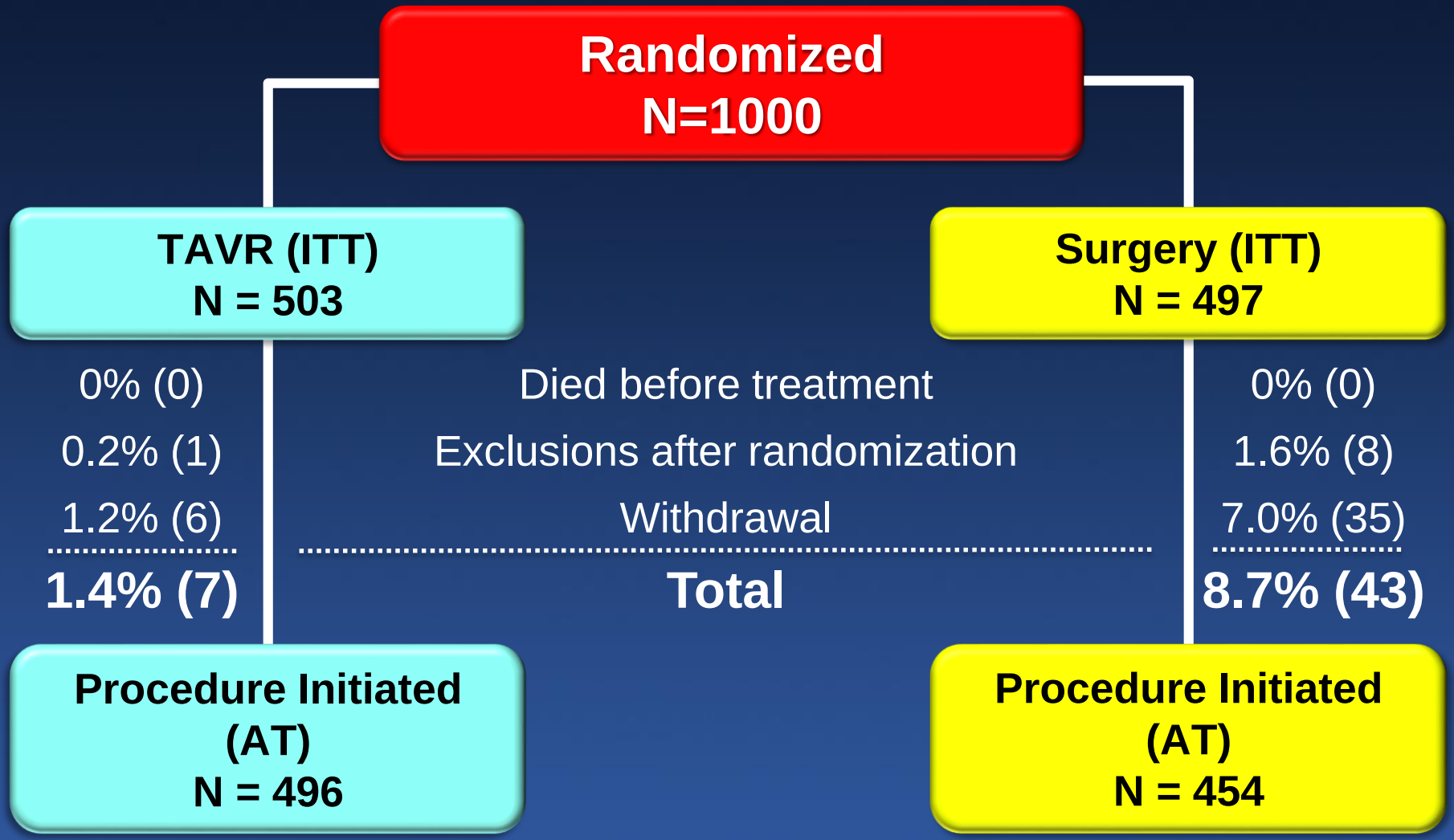
Study Populations

ITT to AT Patient Cohorts



Baseline Patient Characteristics

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% or mean ± SD

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%

*p = 0.01

Procedural & Hospital Findings

% or mean ± SD

Variable	TAVR (N=496)	Surgery (N=454)	P-value
Conscious Sedation	65.1%	NA	NA
Procedure Time (min)	58.6 ± 36.5	208.3 ± 62.2	<0.001
Fluoroscopy Time (min)	13.9 ± 7.1	NA	NA
Aortic Cross-Clamp Time (min)	NA	74.3 ± 27.8	NA
Total CPB Time (min)	NA	97.7 ± 33.8	NA
Median ICU Stay (days)	2.0	3.0	<0.001
Median Total LOS (days)	3.0	7.0	<0.001
Discharge to Home/Self-care	96.0%	73.1%	<0.001
Concomitant Procedures	7.9%	26.4%	<0.001

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Procedural Complications

In-Hospital

% or mean ± SD

Complication	TAVR (N=496)	Surgery (N=454)	P-value
In-hospital Death	0.4% (2)	0.9% (4)	0.43
≥ 2 Transcatheter Valves Implanted*	0.2% (1)	NA	NA
Valve Embolization	0	NA	NA
Aortic Dissection	0	NA	NA
Annular Rupture	0.2% (1)	NA	NA
Ventricular Perforation	0.2% (1)	0.4% (2)	0.61
Coronary Obstruction	0.2% (1)	0.4% (2)	0.61
Access Site Infections	0.4% (2)	1.3% (6)	0.16

*Valve-in-valve

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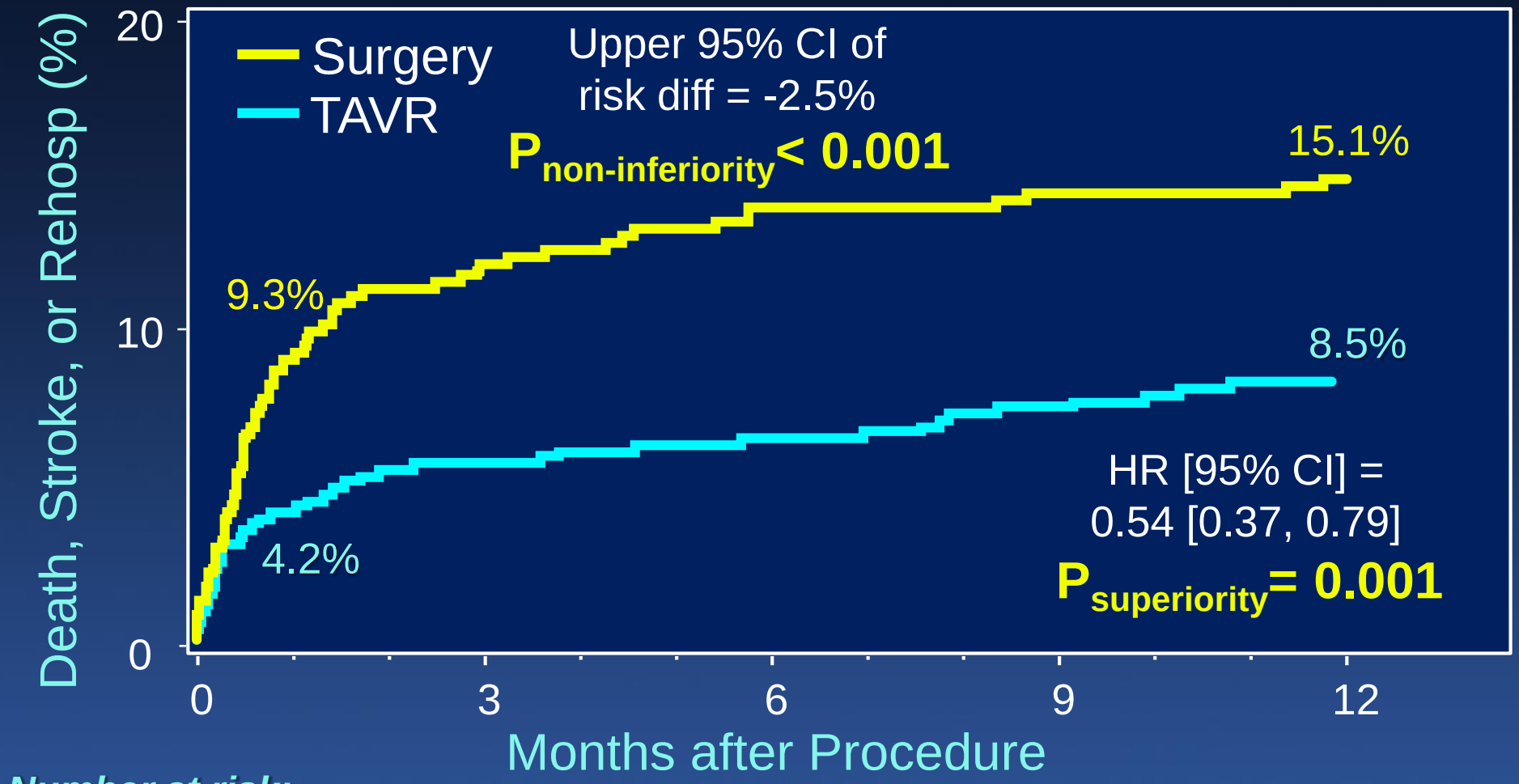
Primary Endpoint



Number at risk:

Surgery	**454**	**408**	**390**	**381**	**377**	**374**
TAVR	**496**	**475**	**467**	**462**	**456**	**451**

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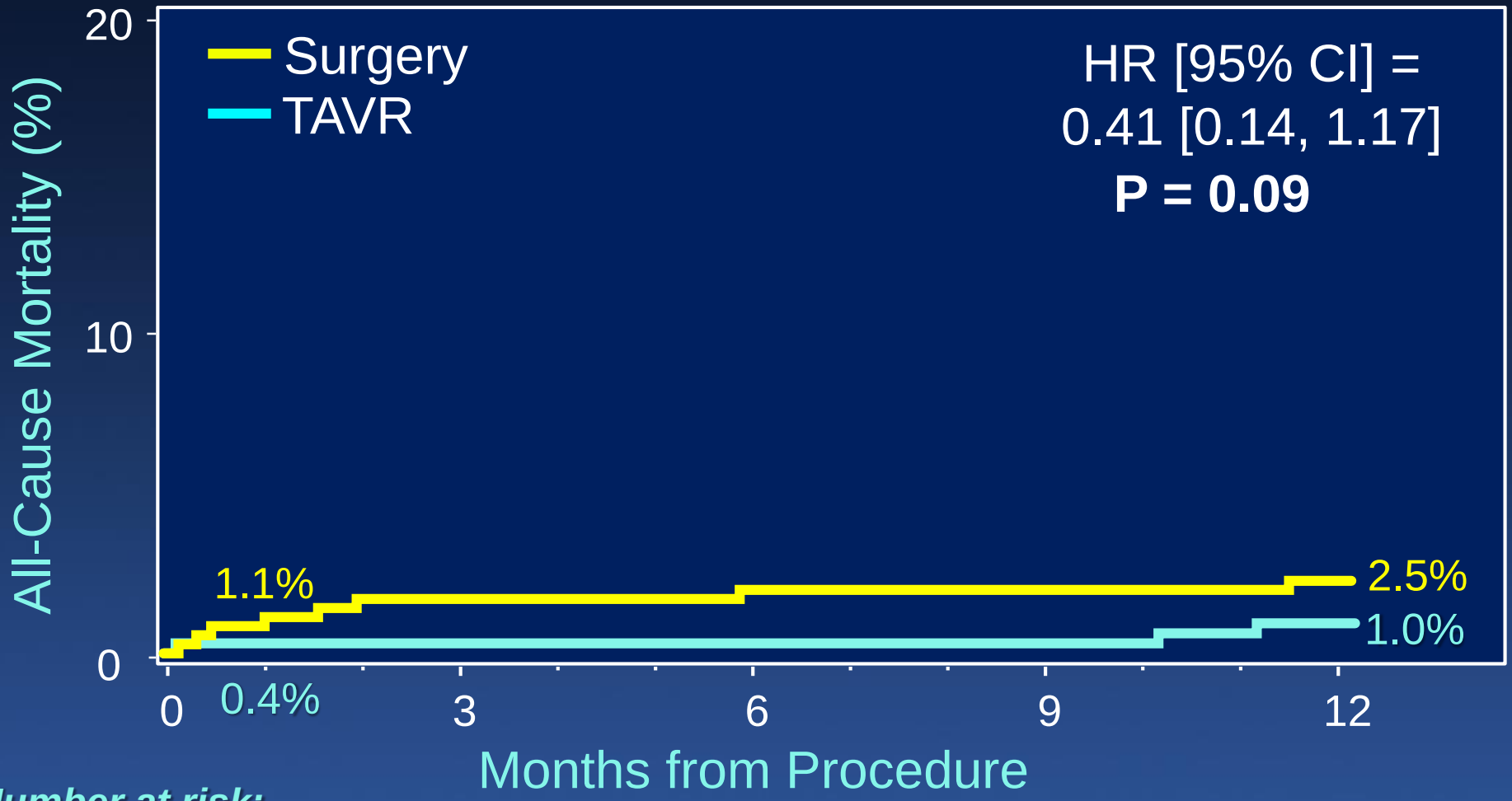
All-Cause Mortality



Number at risk:

Surgery	**454**	**445**	**438**	**433**	**431**	**427**
TAVR	**496**	**494**	**494**	**493**	**492**	**488**

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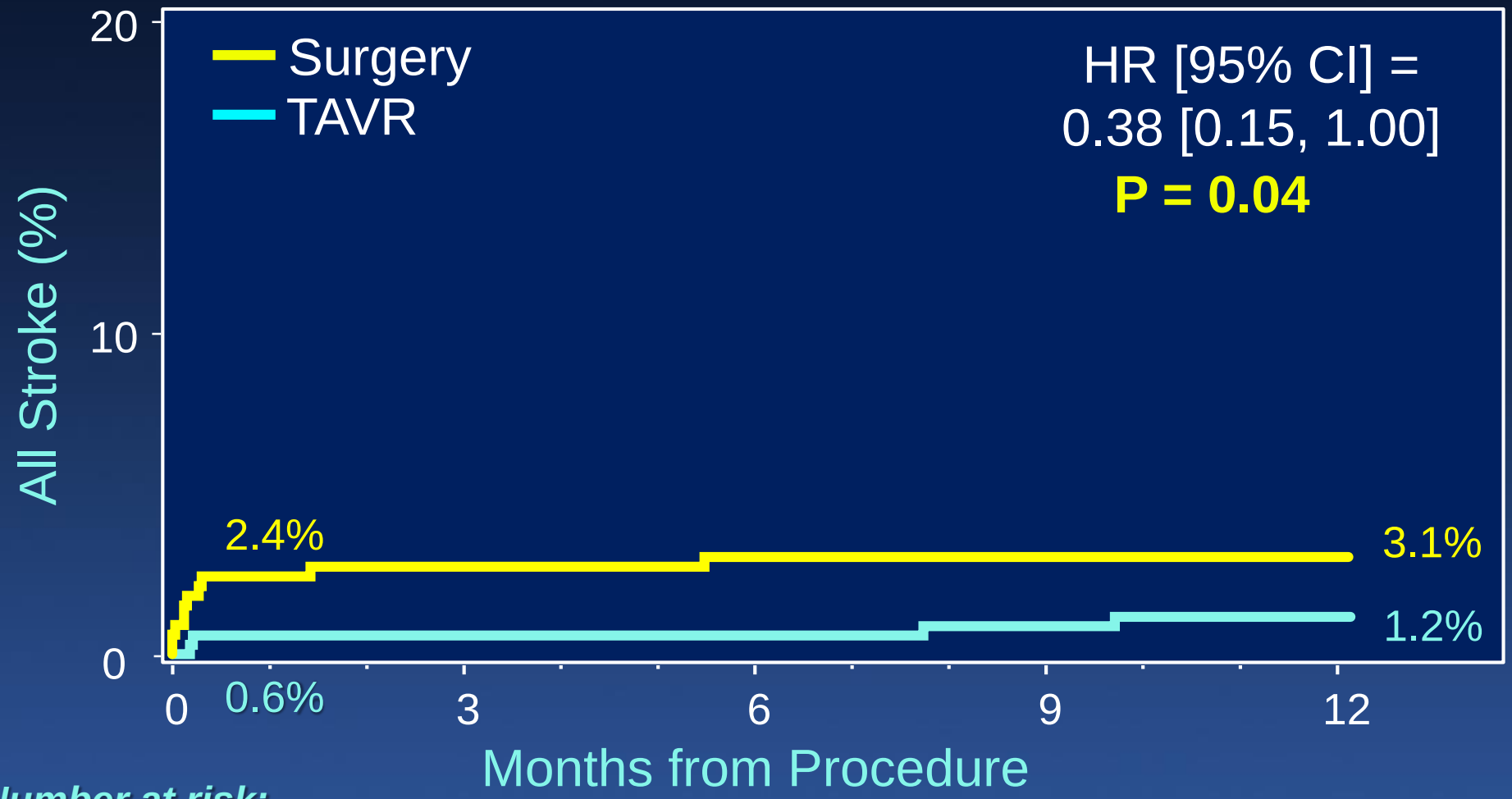
All Stroke



Number at risk:

Surgery	**454**	**435**	**427**	**423**	**421**	**417**
TAVR	**496**	**491**	**491**	**489**	**487**	**484**

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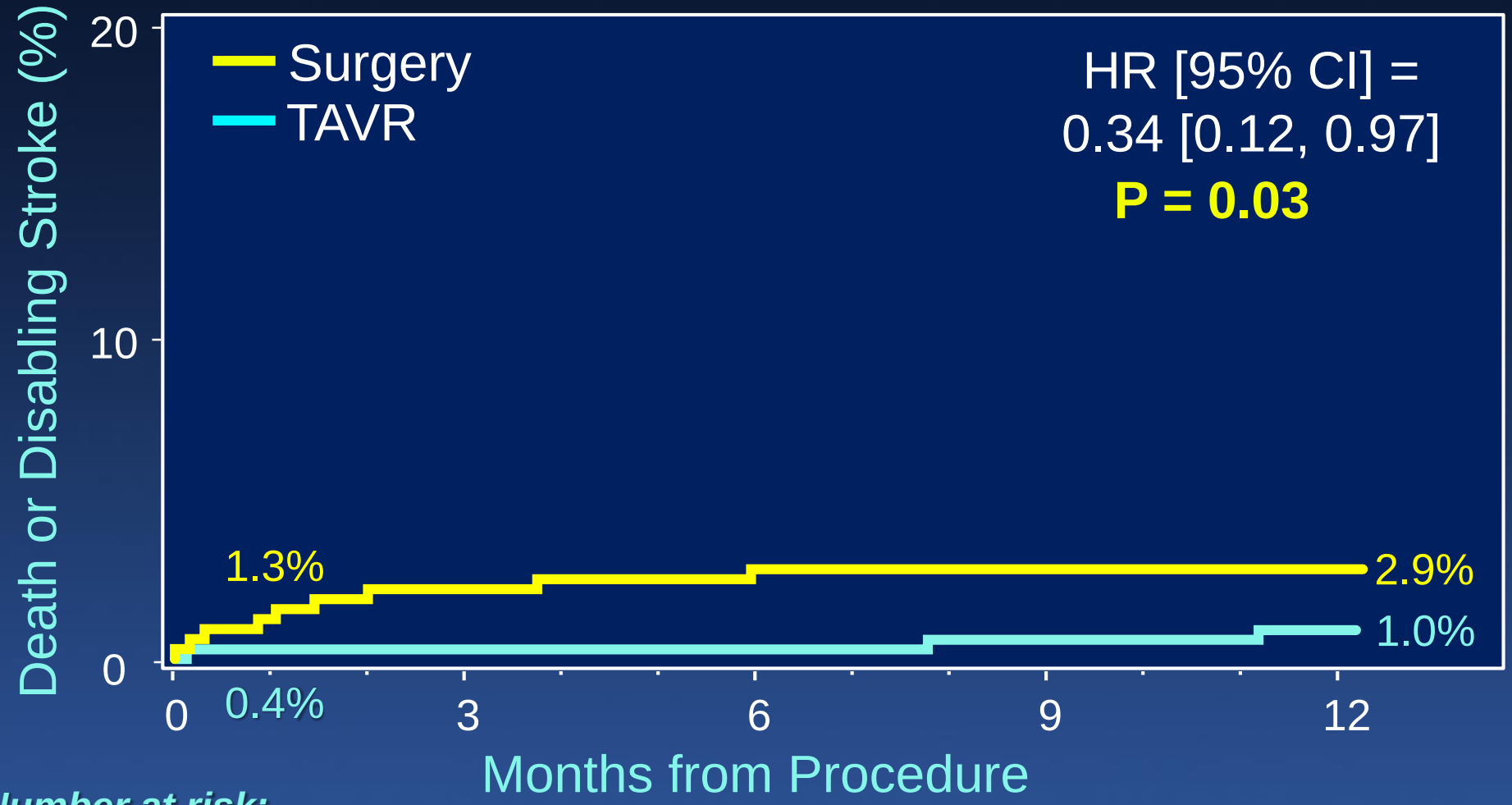
Death or Disabling Stroke



Number at risk:

Surgery	**454**	**444**	**436**	**432**	**430**	**426**
TAVR	**496**	**494**	**494**	**493**	**491**	**488**

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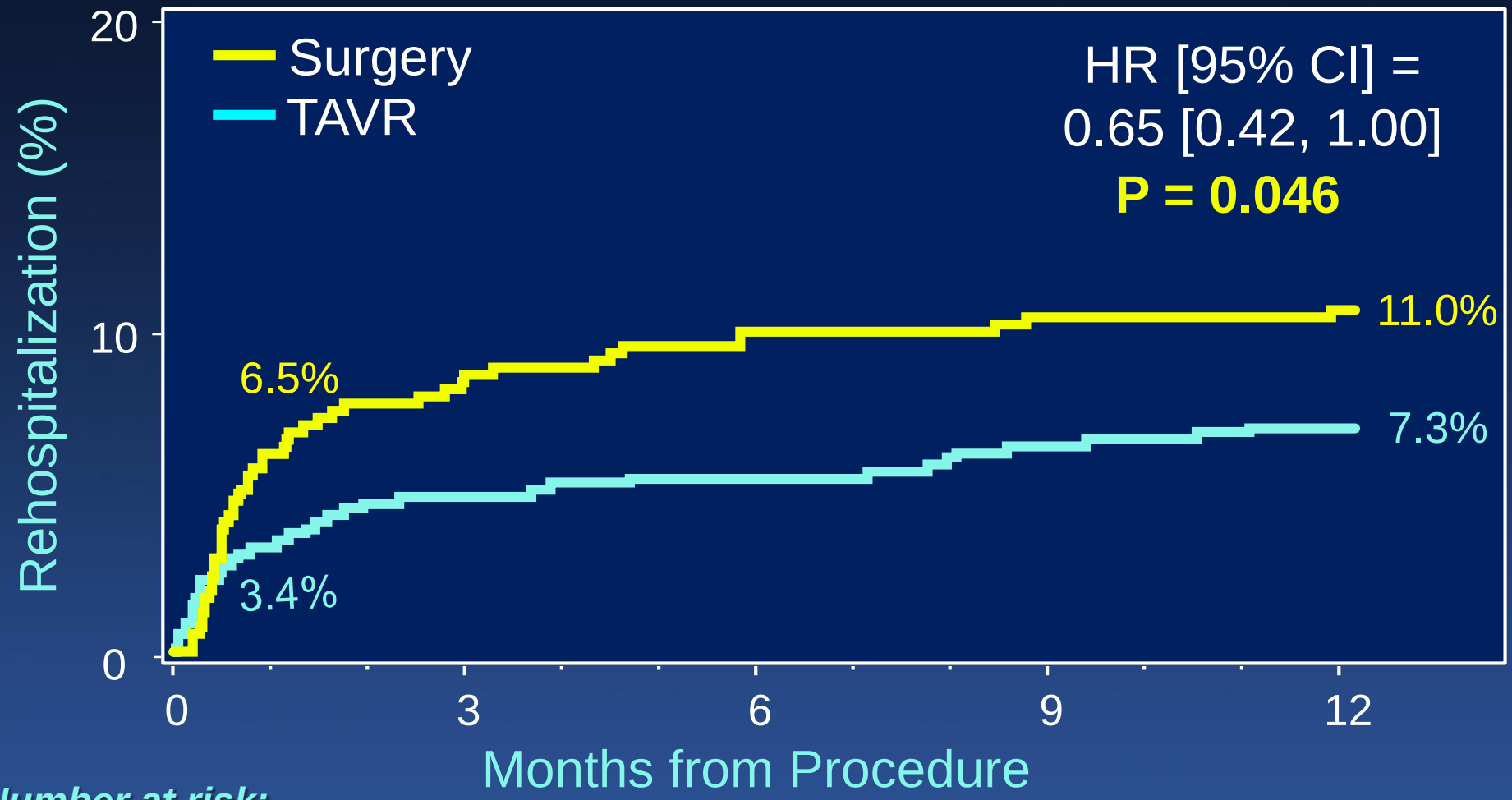
Rehospitalization

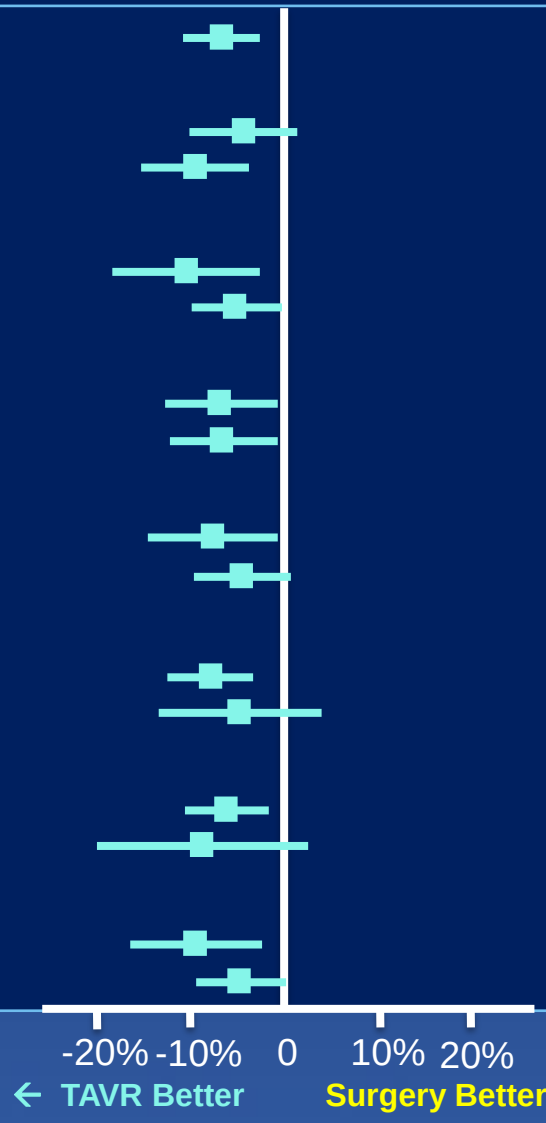


Number at risk:

Surgery	**454**	**416**	**399**	**389**	**385**	**382**
TAVR	**496**	**477**	**469**	**465**	**459**	**453**

Primary Endpoint - Subgroup Analysis

Subgroup	TAVR	Surgery	Diff [95% CI]	P-value*
Overall	**8.5**	**15.1**	**-6.6 [-10.8, -2.5]**	
Age				
≤ 74 (n=516)	10.6	14.9	-4.3 [-10.1, 1.5]	**0.21**
> 74 (n=434)	5.8	15.3	-9.5 [-15.3, -3.7]	
Sex				
Female (n=292)	8.1	18.5	-10.4 [-18.3, -2.5]	**0.27**
Male (n=658)	8.7	13.8	-5.1 [-9.9, -0.3]	
STS Score				
≤ 1.8 (n=464)	9.1	15.7	-6.7 [-12.6, -0.7]	**0.98**
> 1.8 (n=486)	8.0	14.5	-6.5 [-12.2, -0.8]	
LV Ejection Fraction				
≤ 65 (n=384)	9.6	17.2	-7.6 [-14.5, -0.7]	**0.48**
> 65 (n=524)	8.0	12.4	-4.4 [-9.6, 0.7]	
NYHA Class				
I/II (n=687)	6.8	14.5	-7.8 [-12.4, -3.2]	**0.54**
III/IV (n=263)	12.3	16.9	-4.7 [-13.5, 4.1]	
Atrial Fibrillation				
No (n=786)	7.9	14.0	-6.1 [-10.5, -1.7]	**0.67**
Yes (n=163)	11.6	20.3	-8.7 [-19.9, 2.5]	
KCCQ Overall Summary Score				
≤ 70 (n=407)	10.5	19.9	-9.4 [-16.5, -2.4]	**0.27**
> 70 (n=536)	6.5	11.2	-4.6 [-9.4, 0.2]	



Event rates are KM estimates (%)

* P-value is for interaction

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Pre-specified Secondary Endpoints

Subject to Multiplicity Adjustment

Order of Testing	Endpoint	TAVR (N=496)	Surgery (N=454)	Treatment Effect [95% CI]	P-value
1	New onset atrial fibrillation at 30 days	5.0%	39.5%	0.10 [0.06, 0.16]	
2	Length of index hospitalization (days)	3.0 (2.0, 3.0)	7.0 (6.0, 8.0)	-4.0 [-4.0, -3.0]	
3	All-cause death, all stroke, or rehospitalizations at 1 year	8.5%	15.1%	0.54 [0.37, 0.79]	
4	Death, KCCQ < 45 or KCCQ decrease from baseline ≥ 10 points at 30 days	3.9%	30.6%	-26.7% [-31.4%, -22.1%]	
5	Death or all stroke at 30 days	1.0%	3.3%	0.30 [0.11, 0.83]	
6	All stroke at 30 days	0.6%	2.4%	0.25 [0.07, 0.88]	

* P-value is Log-Rank test for items 1, 3, 5 and 6; P-value is Wilcoxon Rank-Sum Test for item 2; P-value is Fisher's Exact test for item 4

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Pre-specified Secondary Endpoints

Subject to Multiplicity Adjustment

Order of Testing	Endpoint	TAVR (N=496)	Surgery (N=454)	Treatment Effect [95% CI]	P-value
1	New onset atrial fibrillation at 30 days	5.0%	39.5%	0.10 [0.06, 0.16]	<0.001
2	Length of index hospitalization (days)	3.0 (2.0, 3.0)	7.0 (6.0, 8.0)	-4.0 [-4.0, -3.0]	<0.001
3	All-cause death, all stroke, or rehospitalizations at 1 year	8.5%	15.1%	0.54 [0.37, 0.79]	0.001
4	Death, KCCQ < 45 or KCCQ decrease from baseline ≥ 10 points at 30 days	3.9%	30.6%	-26.7% [-31.4%, -22.1%]	<0.001
5	Death or all stroke at 30 days	1.0%	3.3%	0.30 [0.11, 0.83]	0.01
6	All stroke at 30 days	0.6%	2.4%	0.25 [0.07, 0.88]	0.02

* P-value is Log-Rank test for items 1, 3, 5 and 6; P-value is Wilcoxon Rank-Sum Test for item 2; P-value is Fisher's Exact test for item 4

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Other Secondary Endpoints

Outcomes % (no. of pts)	30 Days			1 Year		
	TAVR (N=496)	Surgery (N=454)	P-value	TAVR (N=496)	Surgery (N=454)	P-value
Bleeding - Life-threat/Major	3.6% (18)	24.5% (111)	<0.001	7.7% (38)	25.9% (117)	<0.001
Major Vascular Complics	2.2% (11)	1.5% (7)	0.45	2.8% (14)	1.5% (7)	0.19
AKI - stage 2 or 3*	0.4% (2)	1.8% (8)	0.05	0.4% (2)	1.8% (8)	0.05
New PPM (incl baseline)	6.5% (32)	4.0% (18)	0.09	7.3% (36)	5.4% (24)	0.21
New LBBB	22.0% (106)	8.0% (35)	<0.001	23.7% (114)	8.0% (35)	<0.001
Coronary Obstruction	0.2% (1)	0.7% (3)	0.28	0.2% (1)	0.7% (3)	0.28
AV Re-intervention	0% (0)	0% (0)	NA	0.6% (3)	0.5% (2)	0.76
Endocarditis	0% (0)	0.2% (1)	0.29	0.2% (1)	0.5% (2)	0.49
Asymp Valve Thrombosis	0.2% (1)	0% (0)	0.34	1.0% (5)	0.2% (1)	0.13

Event rates are KM estimates (%) and p-values are based on Log-Rank test

* Event rates are incidence rates and p-value is Fisher's Exact test

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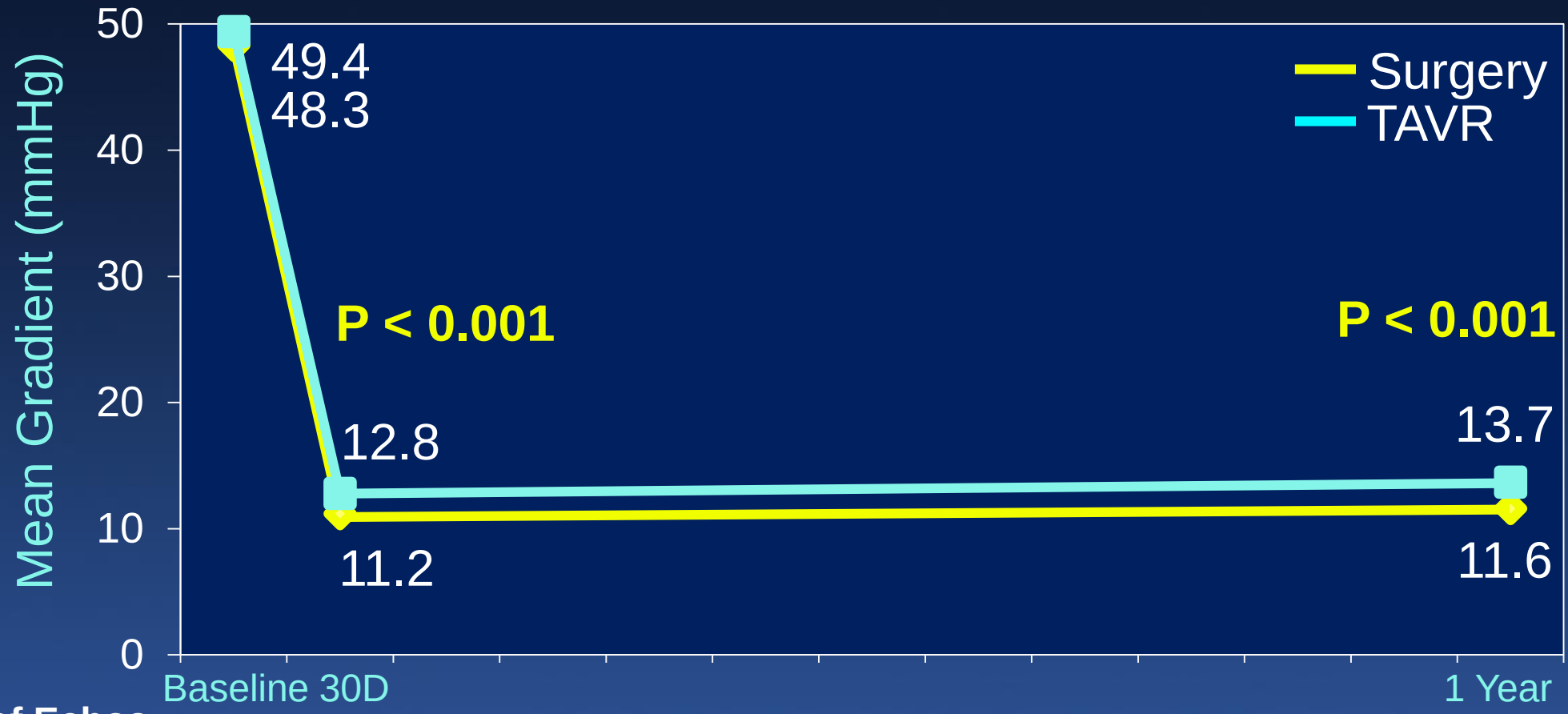
Echocardiography Findings

Mean Gradient



No. of Echos			
Surgery	441	426	390
TAVR	483	490	469

P-values are based on the ANCOVA for TAVR vs Surgery adjusted by baseline.

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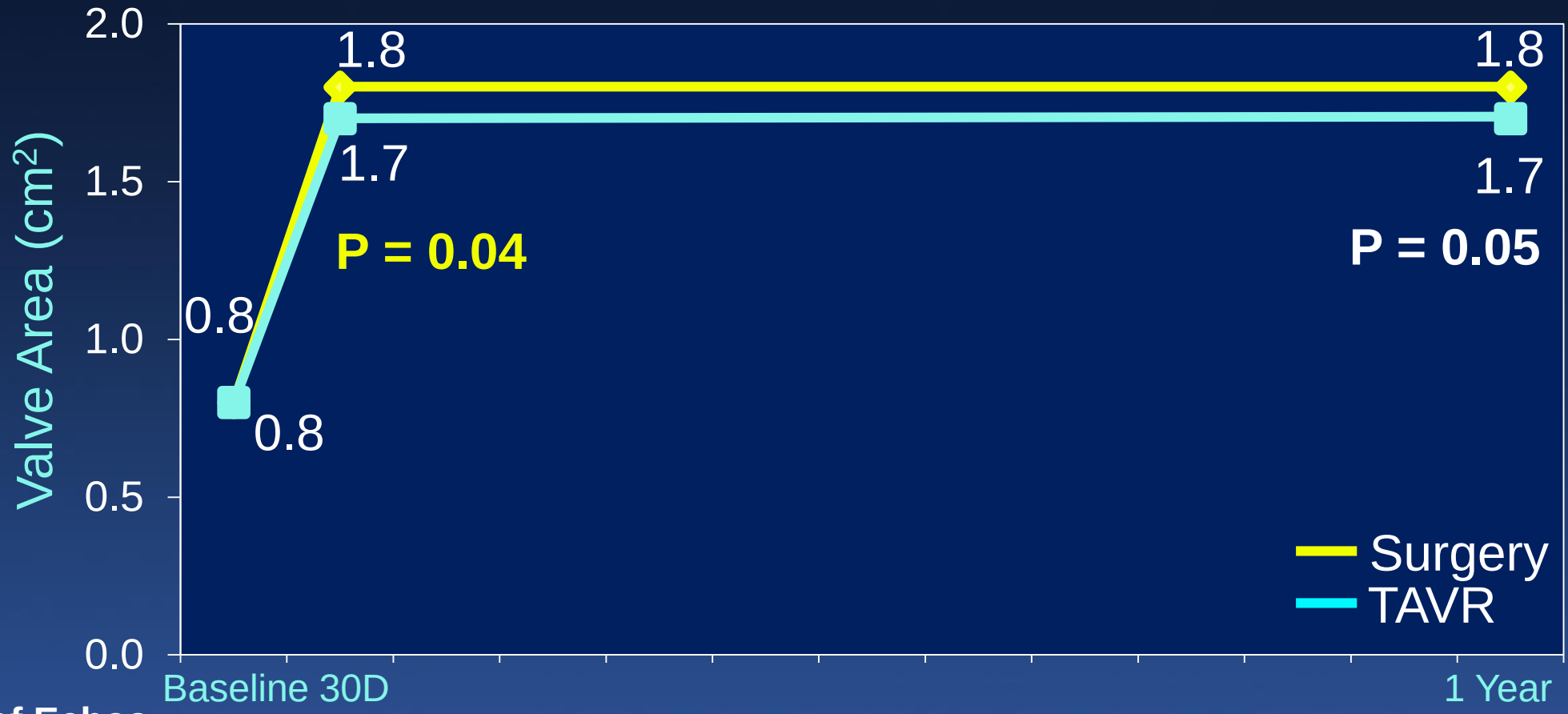
Echocardiography Findings

Aortic Valve Area



No. of Echos			
Surgery	**423**	**395**	**371**
TAVR	**458**	**470**	**446**

P-values are based on the ANCOVA for TAVR vs Surgery adjusted by baseline.

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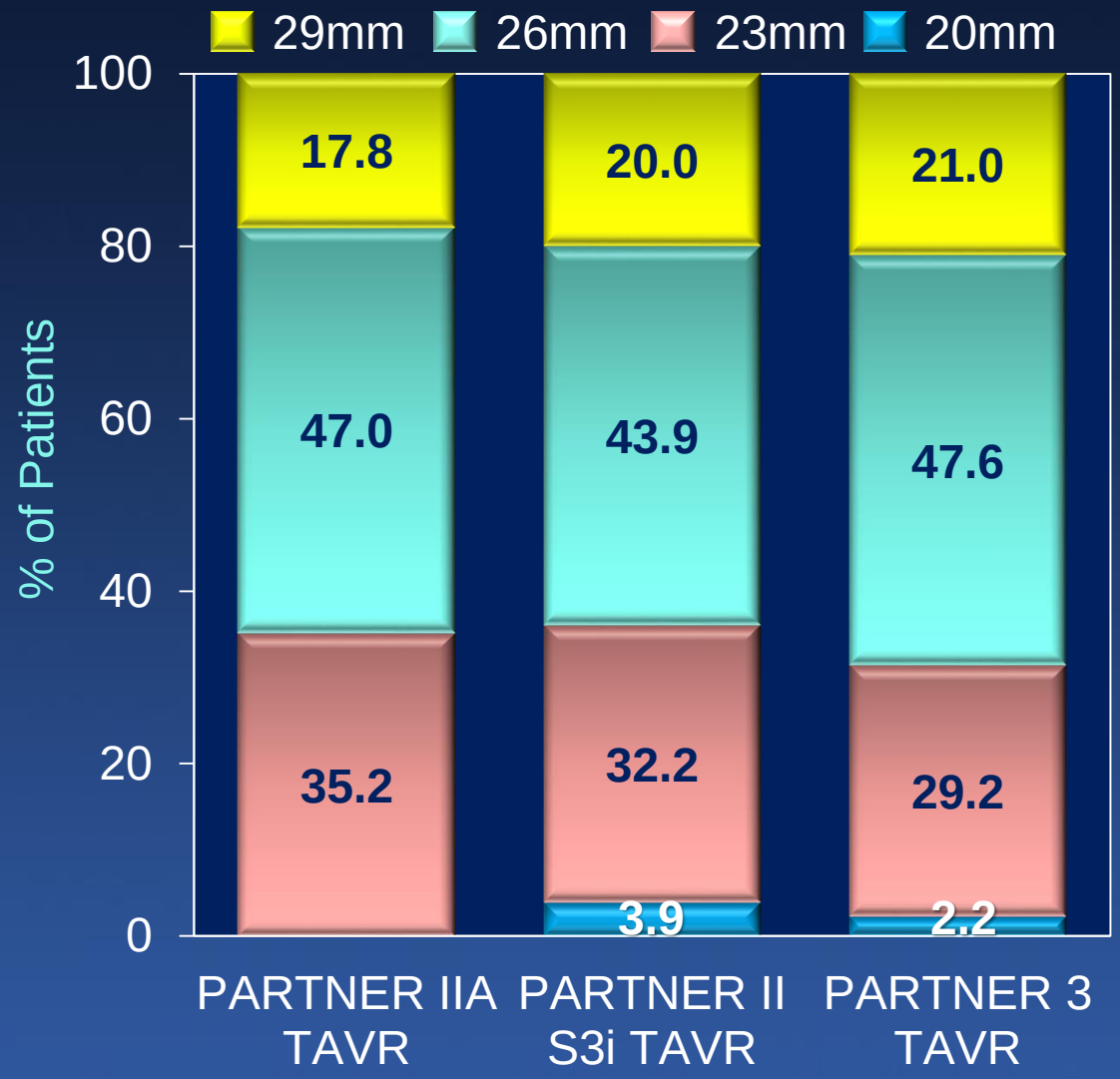
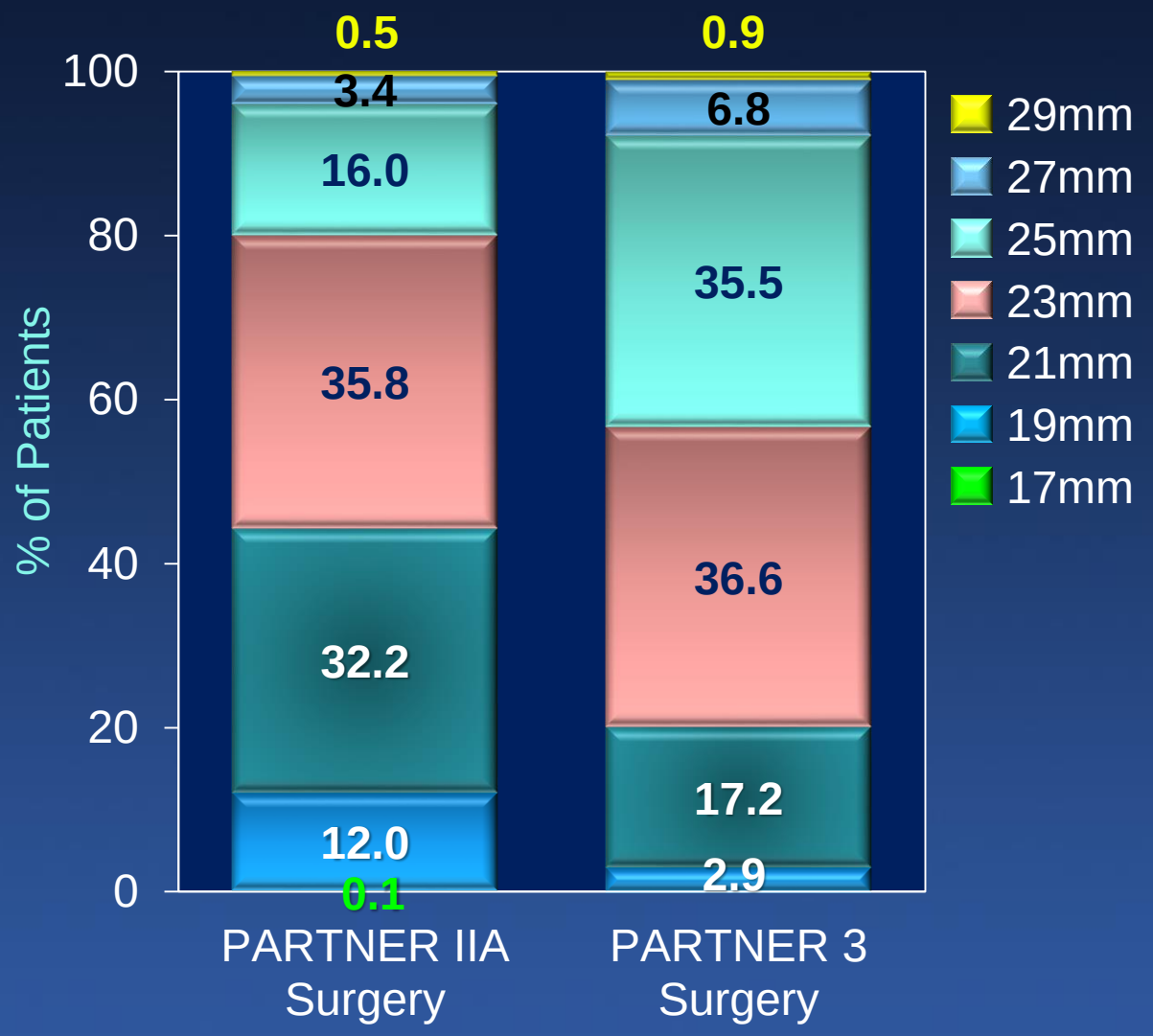
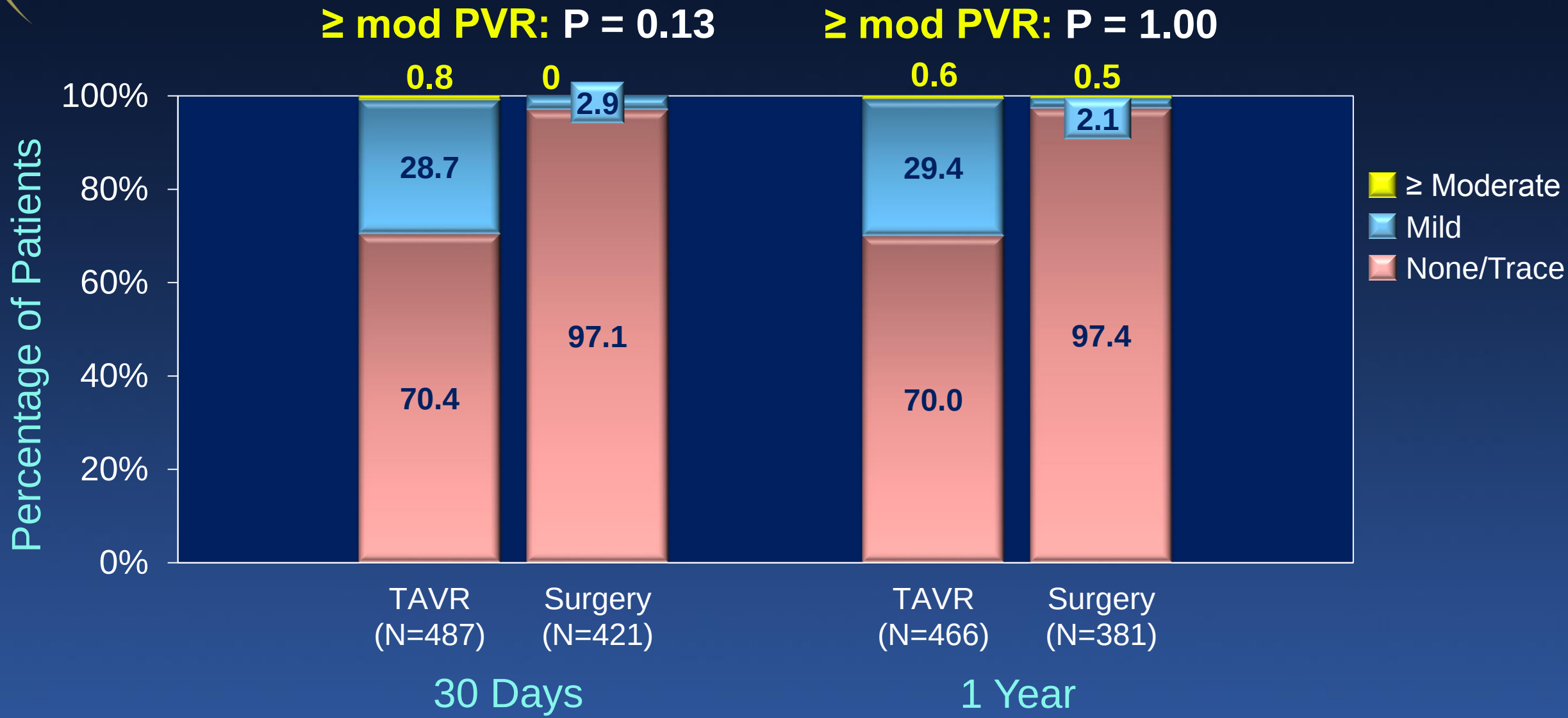
Valve Size Distribution





Paravalvular Regurgitation



P-values are based on the Wilcoxon rank-sum test.

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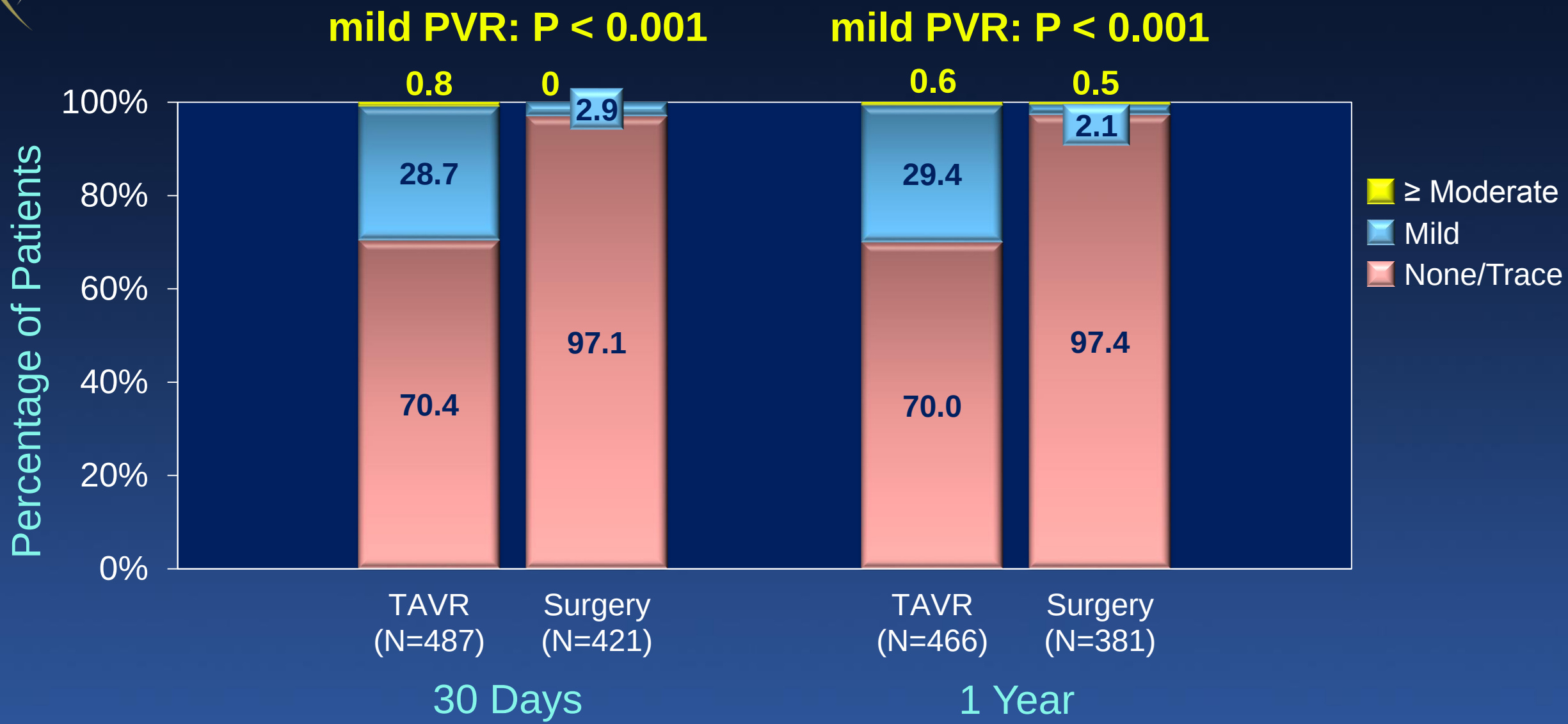
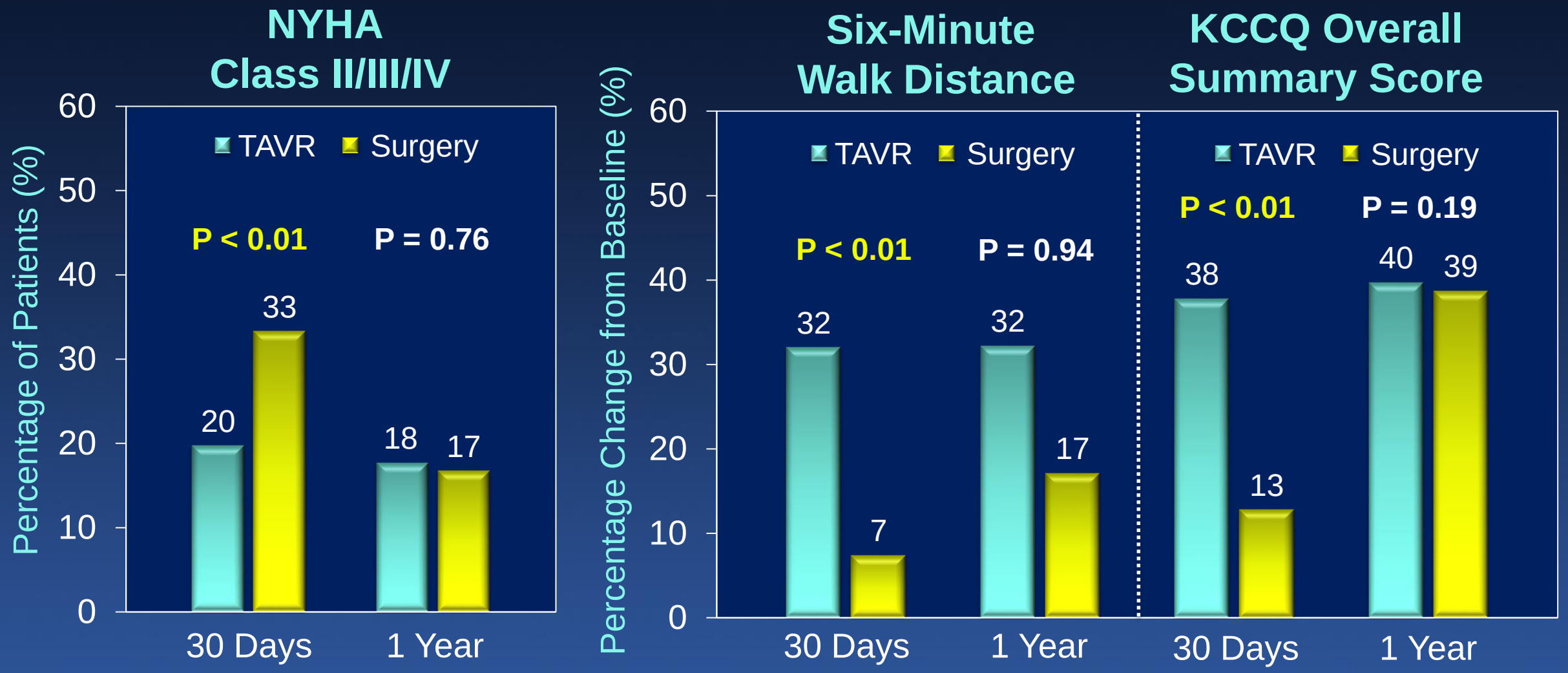
Paravalvular Regurgitation



P-values are based on the Wilcoxon rank-sum test.

THE PARTNER 3 TRIAL

Functional Assessments



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

P-values are based on the ANCOVA for TAVR vs Surgery adjusted by baseline.

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Conclusions (1)

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

- Significantly reduced the primary endpoint of death, stroke, or rehospitalization by 46% at 1-year.
  - Components of the primary endpoint favored TAVR, both at 30 days and 1 year
  - Multiple sensitivity analyses confirmed robustness of the primary endpoint findings

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Conclusions (2)

- Secondary endpoints adjusted for multiple comparisons indicated that TAVR reduced new-onset AF, index hospitalization days, and a measure of poor treatment outcome (death or low KCCQ score at 30 days).
- Other secondary endpoint analyses also showed reduced bleeding after TAVR and no differences in the need for new permanent pacemakers, major vascular complications, coronary obstruction, and mod-severe PVR.
- Some secondary endpoints favored surgery, including reduced new LBBB, reduced mild PVR, and lower aortic valve gradients.

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Conclusions (3)

- TAVR had more rapid post-procedure improvement in patient-oriented functional indices, including NYHA class, 6-minute walking distance, and KCCQ scores.

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Clinical Implications

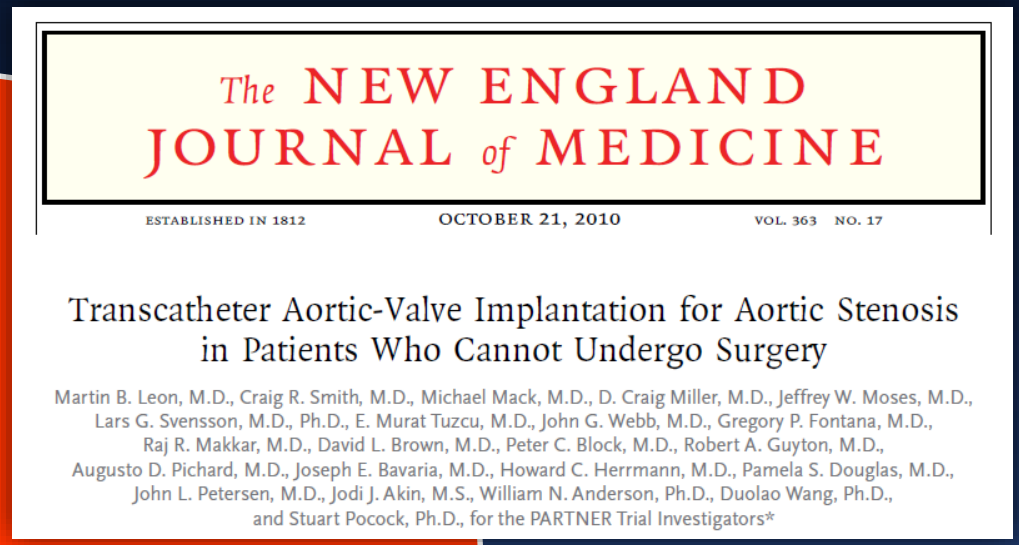
- *Based upon these findings, TAVR, through 1-year, should be considered the preferred therapy in low surgical risk aortic stenosis patients!*
- *PARTNER randomized trials over the past 12 years, clearly indicate that the relative value of TAVR compared with surgery is independent of surgical risk profiles.*
- *The choice of TAVR vs. surgery in aortic stenosis patients should be a shared-decision making process, respecting patient preferences, understanding knowledge gaps (esp. in younger patients), and considering clinical and anatomic factors.*

The PARTNER 3 Trial

The NEW ENGLAND JOURNAL of MEDICINE

Transcatheter Aortic-Valve Replacement with a Balloon-Expandable Valve in Low-Risk Patients

M.J. Mack, M.B. Leon, V.H. Thourani, R. Makkar, S.K. Kodali, M. Russo, S.R. Kapadia, S.C. Malaisrie, D.J. Cohen, P. Pibarot, J. Leipsic, R.T. Hahn, P. Blanke, M.R. Williams, J.M. McCabe, D.L. Brown, V. Babaliaros, S. Goldman, W.Y. Szeto, P. Genereux, A. Pershad, S.J. Pocock, M.C. Alu, J.G. Webb, and C.R. Smith, for the PARTNER 3 Investigators*

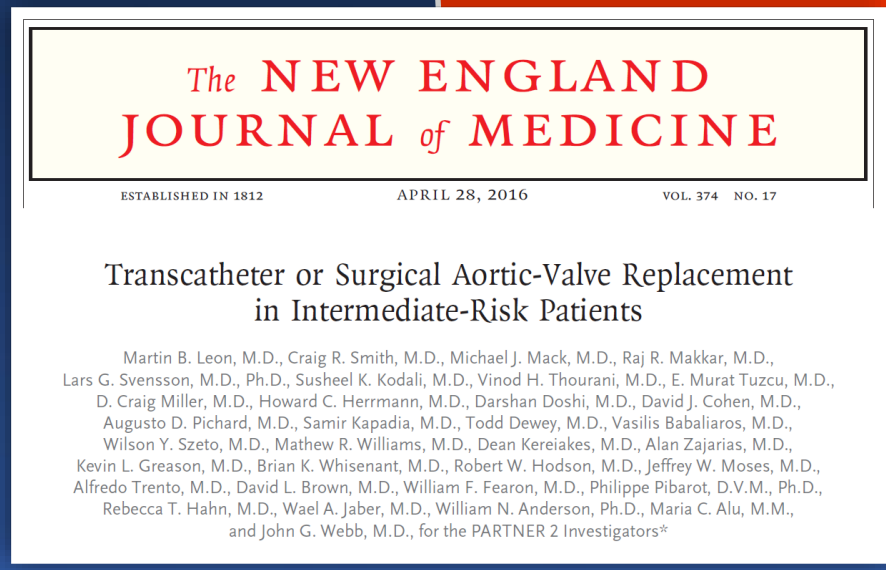


The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 OCTOBER 21, 2010 VOL. 363 NO. 17

Transcatheter Aortic-Valve Implantation for Aortic Stenosis in Patients Who Cannot Undergo Surgery

Martin B. Leon, M.D., Craig R. Smith, M.D., Michael Mack, M.D., D. Craig Miller, M.D., Jeffrey W. Moses, M.D., Lars G. Svensson, M.D., Ph.D., E. Murat Tuzcu, M.D., John G. Webb, M.D., Gregory P. Fontana, M.D., Raj R. Makkar, M.D., David L. Brown, M.D., Peter C. Block, M.D., Robert A. Guyton, M.D., Augusto D. Pichard, M.D., Joseph E. Bavaria, M.D., Howard C. Herrmann, M.D., Pamela S. Douglas, M.D., John L. Petersen, M.D., Jodi J. Akin, M.S., William N. Anderson, Ph.D., Duolao Wang, Ph.D., and Stuart Pocock, Ph.D., for the PARTNER Trial Investigators*



The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 APRIL 28, 2016 VOL. 374 NO. 17

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

Martin B. Leon, M.D., Craig R. Smith, M.D., Michael J. Mack, M.D., Raj R. Makkar, M.D., Lars G. Svensson, M.D., Ph.D., Susheel K. Kodali, M.D., Vinod H. Thourani, M.D., E. Murat Tuzcu, M.D., D. Craig Miller, M.D., Howard C. Herrmann, M.D., Darshan Doshi, M.D., David J. Cohen, M.D., Augusto D. Pichard, M.D., Samir Kapadia, M.D., Todd Dewey, M.D., Vasilis Babaliaros, M.D., Wilson Y. Szeto, M.D., Mathew R. Williams, M.D., Dean Kereiakes, M.D., Alan Zajarias, M.D., Kevin L. Greason, M.D., Brian K. Whisenant, M.D., Robert W. Hodson, M.D., Jeffrey W. Moses, M.D., Alfredo Trento, M.D., David L. Brown, M.D., William F. Fearon, M.D., Philippe Pibarot, D.V.M., Ph.D., Rebecca T. Hahn, M.D., Wael A. Jaber, M.D., William N. Anderson, Ph.D., Maria C. Alu, M.M., and John G. Webb, M.D., for the PARTNER 2 Investigators*

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 JUNE 9, 2011 VOL. 364 NO. 23

Transcatheter and Surgical Aortic-Valve Replacement in High-Risk Patients

Craig R. Smith, M.D., Martin B. Leon, M.D., Michael J. Mack, M.D., D. Craig Miller, M.D., Jeffrey W. Moses, M.D., Lars G. Svensson, M.D., Ph.D., E. Murat Tuzcu, M.D., John G. Webb, M.D., Gregory P. Fontana, M.D., Raj R. Makkar, M.D., Mathew Williams, M.D., Todd Dewey, M.D., Samir Kapadia, M.D., Vasilis Babaliaros, M.D., Vinod H. Thourani, M.D., Paul Corso, M.D., Augusto D. Pichard, M.D., Joseph E. Bavaria, M.D., Howard C. Herrmann, M.D., Jodi J. Akin, M.S., William N. Anderson, Ph.D., Duolao Wang, Ph.D., and Stuart J. Pocock, Ph.D., for the PARTNER Trial Investigators*