Transcatheter or Surgical Aortic Valve Replacement in Intermediate Risk Patients with Aortic Stenosis:
Final Results from the PARTNER 2A Trial

Craig R. Smith, MD
on behalf of the PARTNER Trial Investigators

ACC 2016 | Chicago | April 2, 2016

THE PARTNER II TRIAL

Presenter Disclosure Information for PARTNER 2A at ACC

Chicago, IL; April 2, 2016

Craig R. Smith, MD

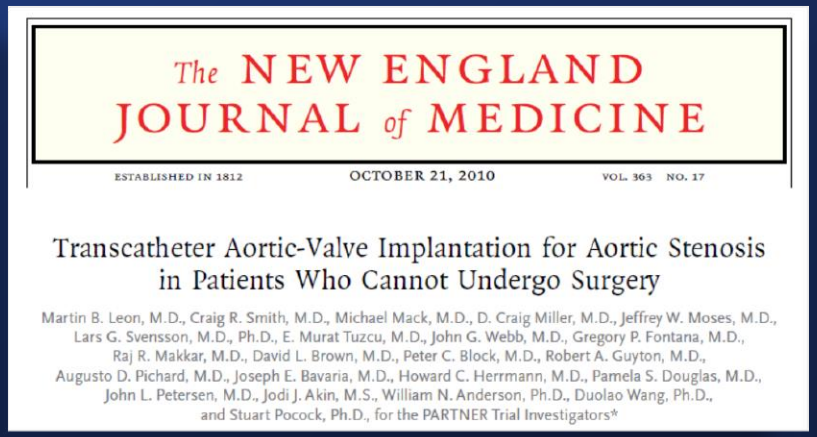
PARTNER Trial sponsor (Edwards LifeSciences) reimburses customary travel and other expenses

THE PARTNER TRIAL

Background (1)

THE PARTNER II TRIAL

- In PARTNER 1, transcatheter aortic valve replacement (TAVR) was superior to standard therapy in patients with symptomatic severe aortic stenosis who were not candidates for surgery AND was equivalent to surgery in high-risk patients.



The NEW ENGLAND JOURNAL of MEDICINE

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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

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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*

Background (2)

THE PARTNER II TRIAL

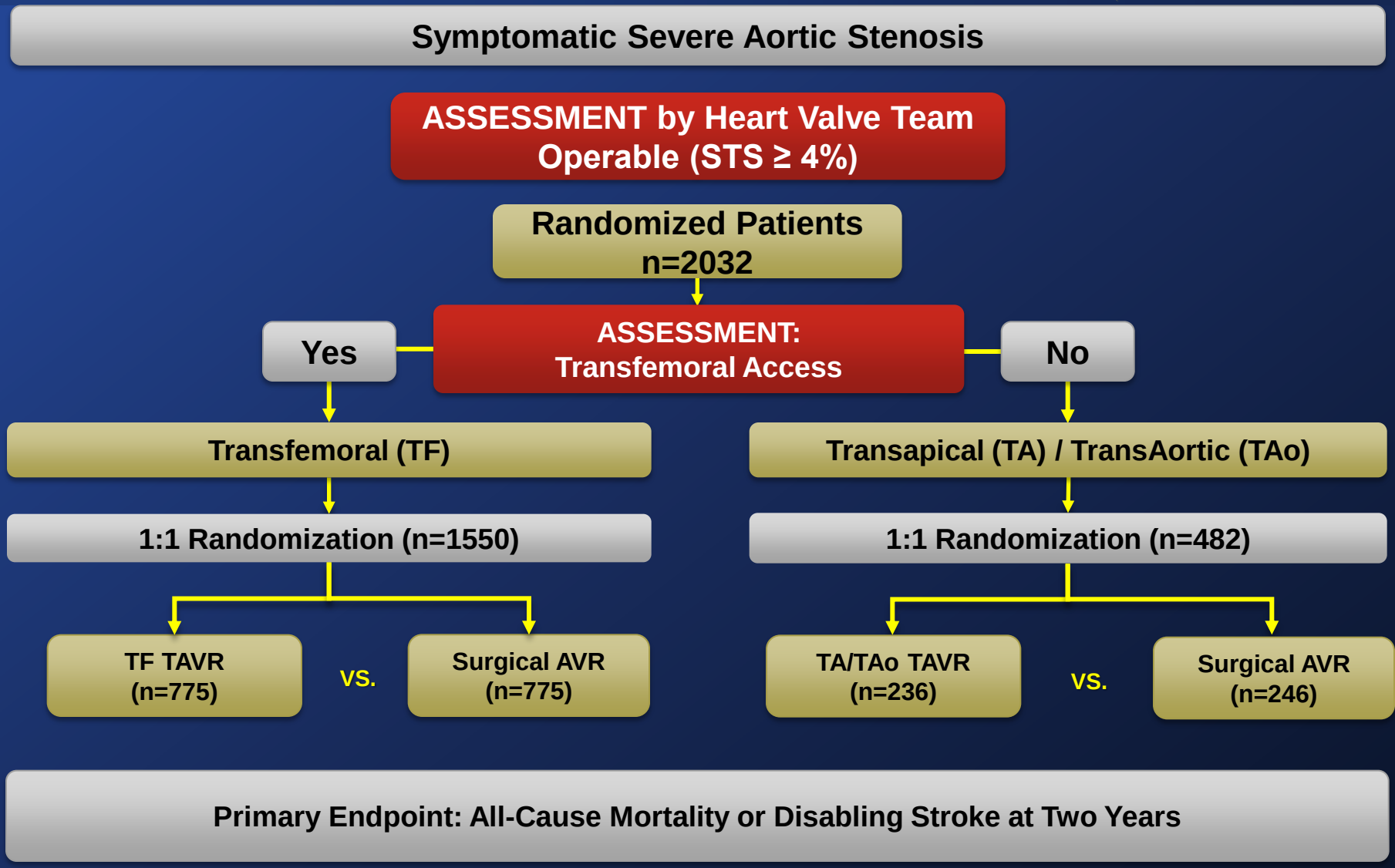
- However, early operator experiences using first generation TAVR systems resulted in frequent peri-procedural complications.
- Lower profile second generation TAVR systems have been associated with improved clinical outcomes.
- Recently, there has been a worldwide trend to extend TAVR therapy to lower-risk patients, but rigorous evidence-based medicine validation is lacking.

Purpose

THE PARTNER II TRIAL

To compare the safety and effectiveness of the second generation SAPIEN XT TAVR system with conventional surgery in *intermediate-risk* patients using rigorous clinical trial methodologies.

The PARTNER 2A Trial
Study Design



The PARTNER 2A Trial
Participating Sites

THE PARTNER II TRIAL

2032 Randomized Pts
55 US & 2 Canadian Sites

The PARTNER 2A Trial
Top Enrolling Sites

THE PARTNER II TRIAL

Columbia University New York, NY Susheel Kodali & Mathew Williams	**206**	**Mayo Clinic** Rochester, MN Verghese Mathew & Kevin Greason	**53**
Cedars-Sinai Medical Center Los Angeles, CA Raj Makkar & Alfredo Trento	**205**	**Baylor Heart Hospital** Plano, TX William Brinkman & David Brown	**52**
Emory University Atlanta, GA Vinod Thourani & Vasilis Babaliaros	**149**	**Providence Heart & Vascular Institute** Portland, OR Robert Hodson & Jeffrey Swanson	**52**
University of Pennsylvania Philadelphia, PA Howard Herrmann & Joseph Bavaria	**82**	**The Christ Hospital** Cincinnati, OH Dean Kereiakes & Thomas Ivey	**49**
Medical City Dallas Dallas, TX Bruce Bowers & Todd Dewey	**75**	**Intermountain Medical Ctr.** Murray, UT Brian Whisenant & Kent Jones	**49**
Barnes Jewish / Washington University St. Louis, MO Alan Zajarias & Hersh Maniar	**68**	**University of Virginia** Charlottesville, VA Irving Kron & Scott Lim	**48**
Washington Hospital Center Washington, DC Augusto Pichard & Paul Corso	**57**	**Scripps Green Hospital** La Jolla, CA Paul Teirstein & Scot Brewster	**42**
Stanford University Palo Alto, CA Craig Miller & Alan Yeung	**53**	**Brigham Women's Hospital** Boston, MA Ralph Bolman, III & Frederick G. Welt	**41**

The PARTNER 2A Trial
Study Administration

Co-Principal Investigators

Martin B. Leon, Craig R. Smith
Columbia University Medical Ctr, NYC

Executive Committee

Martin B. Leon, Michael Mack, D. Craig Miller, Jeffrey W. Moses, Craig R. Smith, Lars G. Svensson, E. Murat Tuzcu, John G. Webb

Data & Safety Monitoring Board

Chairman: Joseph P. Carrozza
Caritas, St. Elizabeth Med Ctr, Boston

Members: Blase Carabello, Andrew Wechsler, Eric Peterson
Neurology: K. Michael Welch

Clinical Events Committee

Chairman: Venu Menon
Cleveland Clinic, C5 Research

Echo Core Laboratory

Chairman: Wael A. Jaber
Cleveland Clinic, C5 Research

Quality of Life and Cost-Effectiveness

Chairman: David J. Cohen
Mid America Heart Institute, Kansas City

Independent Biostatistical Core Laboratory

Melissa Nichols
Cardiovascular Research Foundation, NYC

Eugene Blackstone
Cleveland Clinic, Cleveland, OH

Publications Office

Co-Located at Columbia-CRF and Cleveland Clinic: Director – Maria Alu

Sponsor

Edwards Lifesciences

Inclusion Criteria

THE PARTNER II TRIAL

- *Severe AS:* Echo-derived AVA < 0.8 cm^2 (*or* AVA index < 0.5 cm^2/m^2) and mean AVG > 40 mm Hg *or* peak jet velocity > 4.0 m/s
- *Cardiac Symptoms:* NYHA Functional Class ≥ II
- *Intermediate Risk:*
  1. Determined by the multi-disciplinary Heart Team
  2. Using a guideline STS ≥ 4%, and
  3. Adjudicated by case review committee

Key Exclusion Criteria

THE PARTNER II TRIAL

Anatomic:

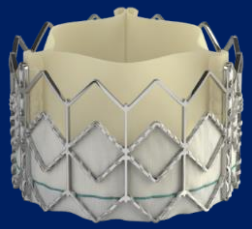
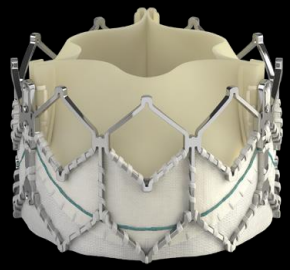
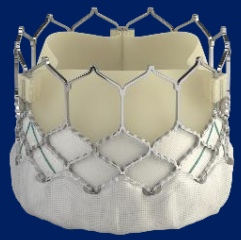
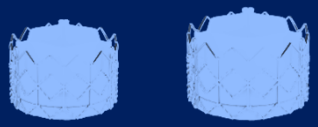
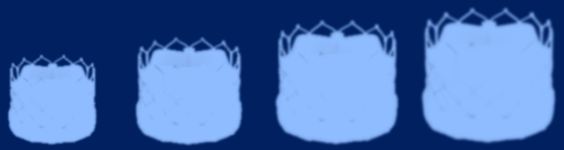
- Aortic annulus diameter < 18 mm or > 27 mm (echo or CT)
- Bicuspid AV or predominant AR (> 3+)
- Severe LV dysfunction (LVEF < 20%)
- Untreated CAD requiring revascularization with either unprotected LM coronary disease or Syntax score > 32
- Pre-existing surgical valve in any position

Clinical:

- Serum Cr > 3.0 mg/dL or dialysis dependent
- Acute MI within 1 month
- CVA or TIA within 6 months
- Hemodynamic instability
- Life expectancy < 24 months

PARTNER SAPIEN Platforms
Device Evolution

THE PARTNER II TRIAL

	SAPIEN	SAPIEN XT	SAPIEN 3
Valve Technology			
Sheath Compatibility			
Available Valve Sizes	 23 mm 26 mm	 23mm 26mm 29mm*	 20 mm 23 mm 26 mm 29 mm

*First Implant Oct 30, 2012

Primary Endpoint

THE PARTNER II TRIAL

- Non-hierarchical composite of *all-cause mortality or disabling stroke* at two years*
- Intention-to-treat population is the primary analysis;
  - As-Treated (AT) population also a pre-specified, powered analysis
  - Transfemoral (TF) subgroup pre-specified
- All patients followed for at least 2 years
- Event rates by Kaplan-Meier estimates

* Disabling stroke = CEC adjudicated stroke by a neurologist with a modified Rankin score of 2 or greater at 90-day evaluation

Other Important Endpoints

VARC 2 Definitions

THE PARTNER II TRIAL

Safety

- Cardiac mortality
- Major vascular complications
- All strokes and TIAs
- Repeat hospitalizations
- Peri-procedural MIs
- Acute kidney injury
- Life-threatening or disabling bleeding
- New permanent pacemakers
- New onset atrial fibrillation
- Repeat AV intervention
- Endocarditis

Efficacy

- NYHA class
- QOL instruments
- 6-minute walk test
- Days alive out-of-hospital
- ICU and index hospital LOS

Echo Valve Performance

- Mean AV gradient
- Effective orifice area (and index)
- LV function (ejection fraction)
- Paravalvular regurgitation (PVR)

Statistical Analysis Plan

THE PARTNER II TRIAL

- *Primary hypothesis* is non-inferiority of test (SAPIEN XT) vs. control (surgery) for all-cause mortality or disabling stroke at 2 years (non-hierarchical)
- *Non-inferiority ratio:* 1.20
- *One-sided alpha:* 0.025
- *Assumptions* (for 1:1 randomization)
  - Event rate: 30% in both trial arms
  - Power: 80%
- *Sample size:* 1744 patients (adjusted to 2,000 patients to account for lost to follow-up and other trial contingencies)

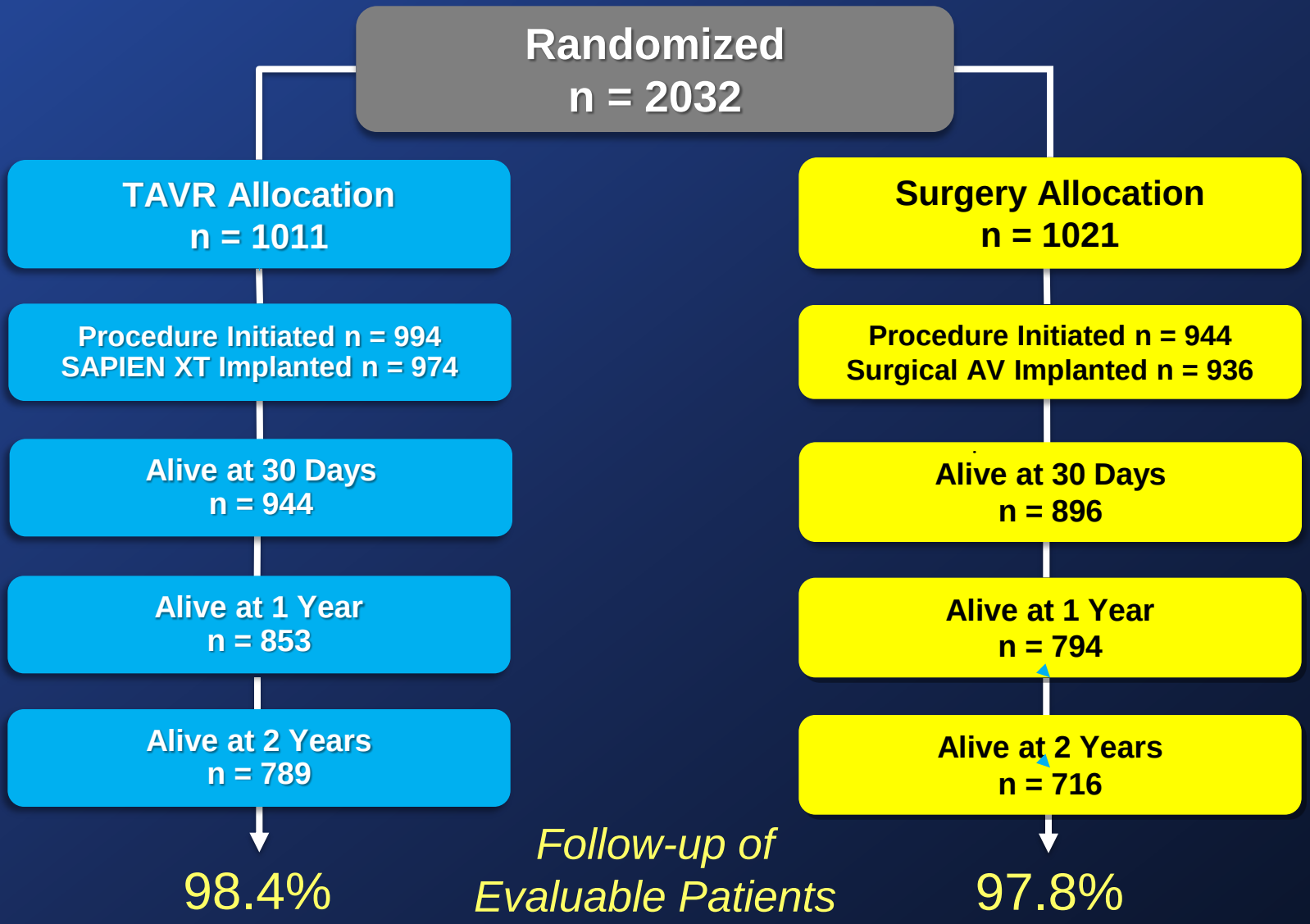
Study Methodology

THE PARTNER II TRIAL

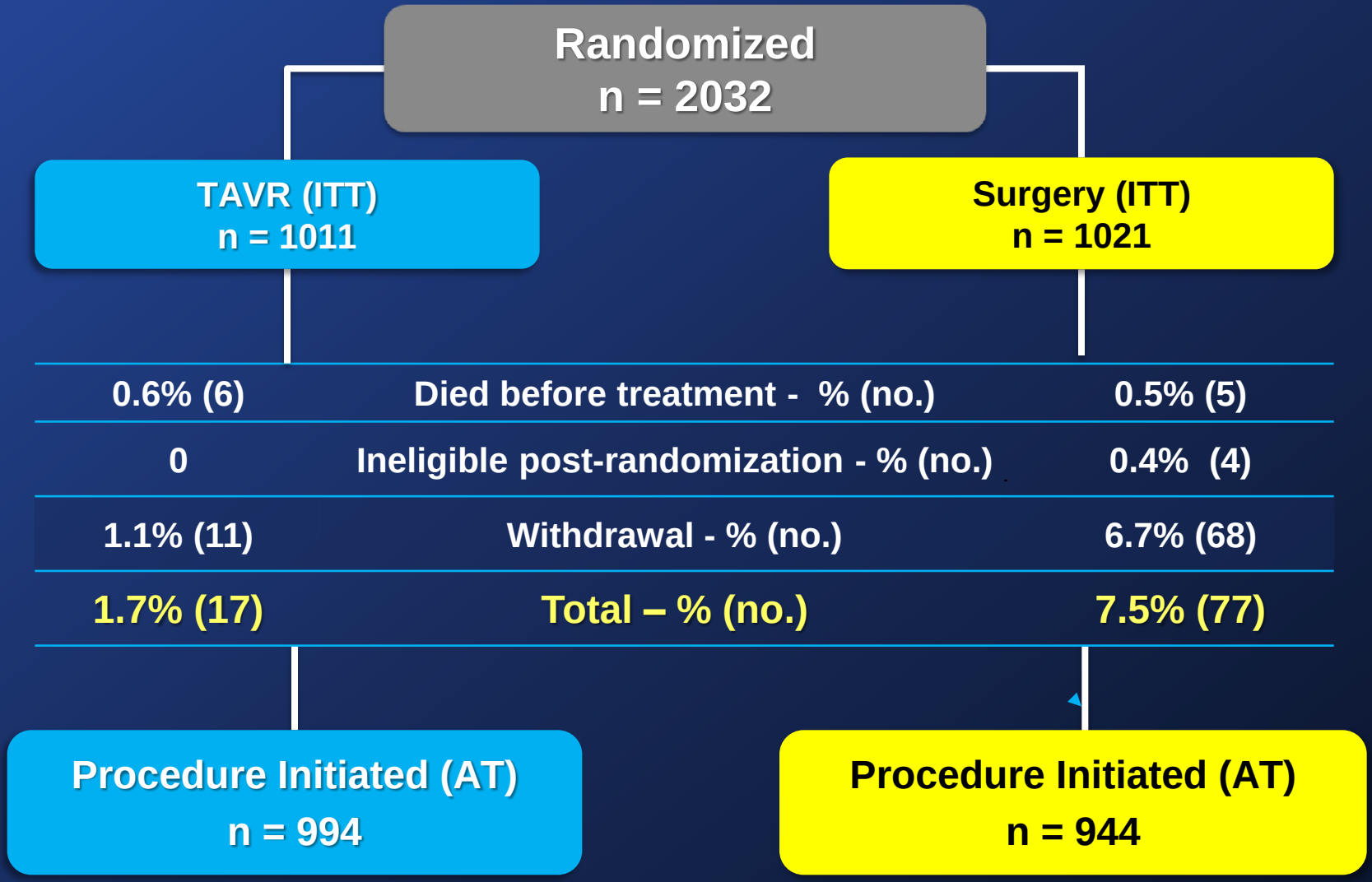
- Every patient reviewed (including imaging studies) by multi-disciplinary Heart Team AND case review committee
- Systematic assessment by neurologists before and after index procedures for ascertainment of neurologic events
- MDCT evaluation of annulus dimensions recommended but not consistently applied
- In patients with CAD requiring revascularization: treatment (PCI or CABG) allowed (unless unprotected left main disease or Syntax score > 32) at the discretion of the Heart Team
- 100% CEC adjudication of all major clinical events (VARC 2 definitions whenever possible)

Study Flow
Vital Status

THE PARTNER II TRIAL



Study Populations
ITT to AT Patient Dropouts



Study Populations
AT to VI Procedural Events

THE PARTNER II TRIAL

TAVR Procedure Initiated (AT) n = 994		Surgery Procedure Initiated (AT) n = 944	
12	Aborted procedures	5	Aborted procedures
	8 imaging findings, 2 access failure, 2 procedure complications		5 excessive Ao calcium
7	Conversion to open	1	Conversion to BAV
	3 valve embolization, 3 annulus rupture, 1 RV perforation		1 severe hypotension
1	Ineligible for TAVR	2	Not treated as assigned
20	Total	8	Total
TAVR Implant (VI) n = 974		**Surgical Implant (VI) n = 936**	

Baseline Patient Characteristics
Demographics and Vascular Disease

THE PARTNER II TRIAL

Characteristic	TAVR (n = 1011)	Surgery (n = 1021)	p-value
Age - yrs	81.5 ± 6.7	81.7 ± 6.7	0.63
Male - %	54.2	54.8	0.79
STS Score - %	5.8 ± 2.1	5.8 ± 1.9	0.29
NYHA Class III or IV - %	77.3	76.1	0.53
CAD - %	69.2	66.5	0.20
Prior CABG - %	23.6	25.6	0.33
Cerebrovascular Disease - %	32.1	31.0	0.60
PVD - %	27.9	32.9	0.02

Baseline Patient Characteristics
Other Co-morbidities

THE PARTNER II TRIAL

Characteristic (%)	TAVR (n = 1011)	Surgery (n = 1021)	p-value
Diabetes	37.7	34.2	0.11
COPD – Any	31.8	30.0	0.48
O_2 dependent	3.4	3.1	0.64
Creatinine > 2 mg/dL	5.0	5.2	0.92
Atrial Fibrillation	31.0	35.2	0.05
Permanent Pacemaker	11.7	12.0	0.84
Frailty (15 ft walk > 7 s)	44.4	46.4	0.43
Liver Disease	1.9	2.5	0.37

Baseline Patient Characteristics
Echocardiography Findings

THE PARTNER II TRIAL

Characteristic	TAVR (n = 1011)	Surgery (n = 1021)	p-value
Aortic Valve Area - cm^2	0.70 ± 0.2	0.69 ± 0.2	0.06
Mean Gradient - mmHg	44.9 ± 13.4	44.6 ± 12.5	0.82
LV Ejection Fraction - %	56.2 ± 10.8	55.3 ± 11.9	0.48
LV Mass Index - g/m^2	119.8 ± 31.5	120.6 ± 32.6	0.74
Mod-Severe MR - %	16.8	19.1	0.22
Aortic Regurgitation - %			0.52
Mild	40.6%	42.5%	
Mod-Severe	11.2%	12.0%	

Mean ± SD

Procedural Characteristics (AT)

THE PARTNER II TRIAL

Characteristic	TAVR (n = 994)	Surgery (n = 944)	p-value
Anesthesia Time (min)	207	333	< 0.001
Procedure Time (min)	103	237	< 0.001
Fluoroscopy Time (min)	20	NA	NA
Aortic Cross-clamp Time (min)	NA	75	NA
Total CPB Time (min)	NA	104	NA
Median ICU Stay (days)	2.0 [2, 4]	4.0 [3, 6]	< 0.001
Median Total Length of Stay (days)	6.0 [4, 9]	9.0 [8, 14]	< 0.001

Median [IQR]

Procedural Complications (AT)

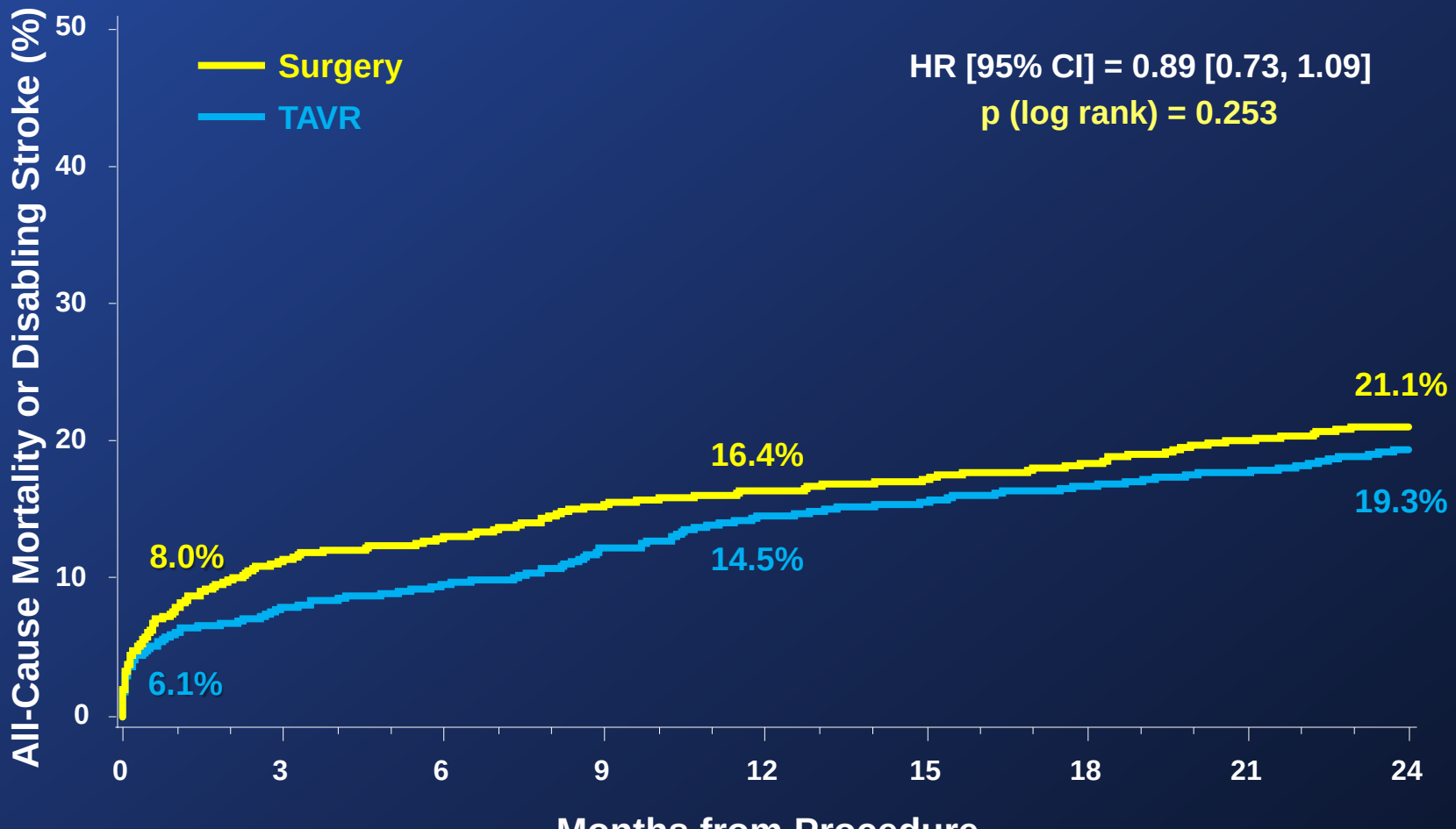
THE PARTNER II TRIAL

Complication	TAVR (n = 994)	Surgery (n = 944)
Procedural deaths (0-3 days)	12 (1.2%)	10 (1.1%)
≥ 2 transcatheter valves*	26 (2.6%)	NA
Valve embolization	10 (1.0%)	NA
Annular rupture	3 (0.3%)	NA
Coronary obstruction	4 (0.4%)	6 (0.6%)
Access site infections	15 (1.2%)	12 (1.3%)

* Valve-in-valve (22) or with valve embolization (4)

Primary Endpoint (ITT)
All-cause Mortality or Disabling Stroke

THE PARTNER II TRIAL



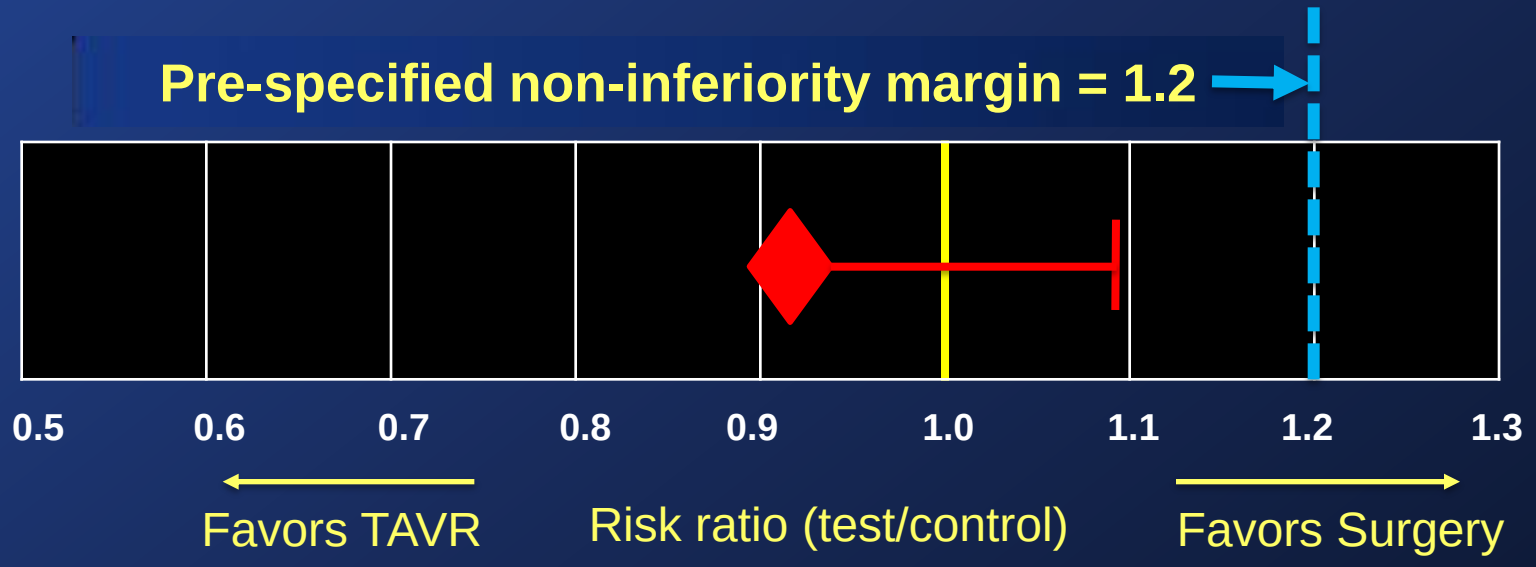
Number at risk:									
Surgery	1021	838	812	783	770	747	735	717	695
TAVR	1011	918	901	870	842	825	811	801	774

Primary Endpoint (ITT)
All-cause Mortality or Disabling Stroke

THE PARTNER II TRIAL

TAVR	SAVR		
n = 1011	n = 1021	Relative Risk Ratio	0.92
19.3%	21.1%	Upper 1-sided 97.5%CI	1.09

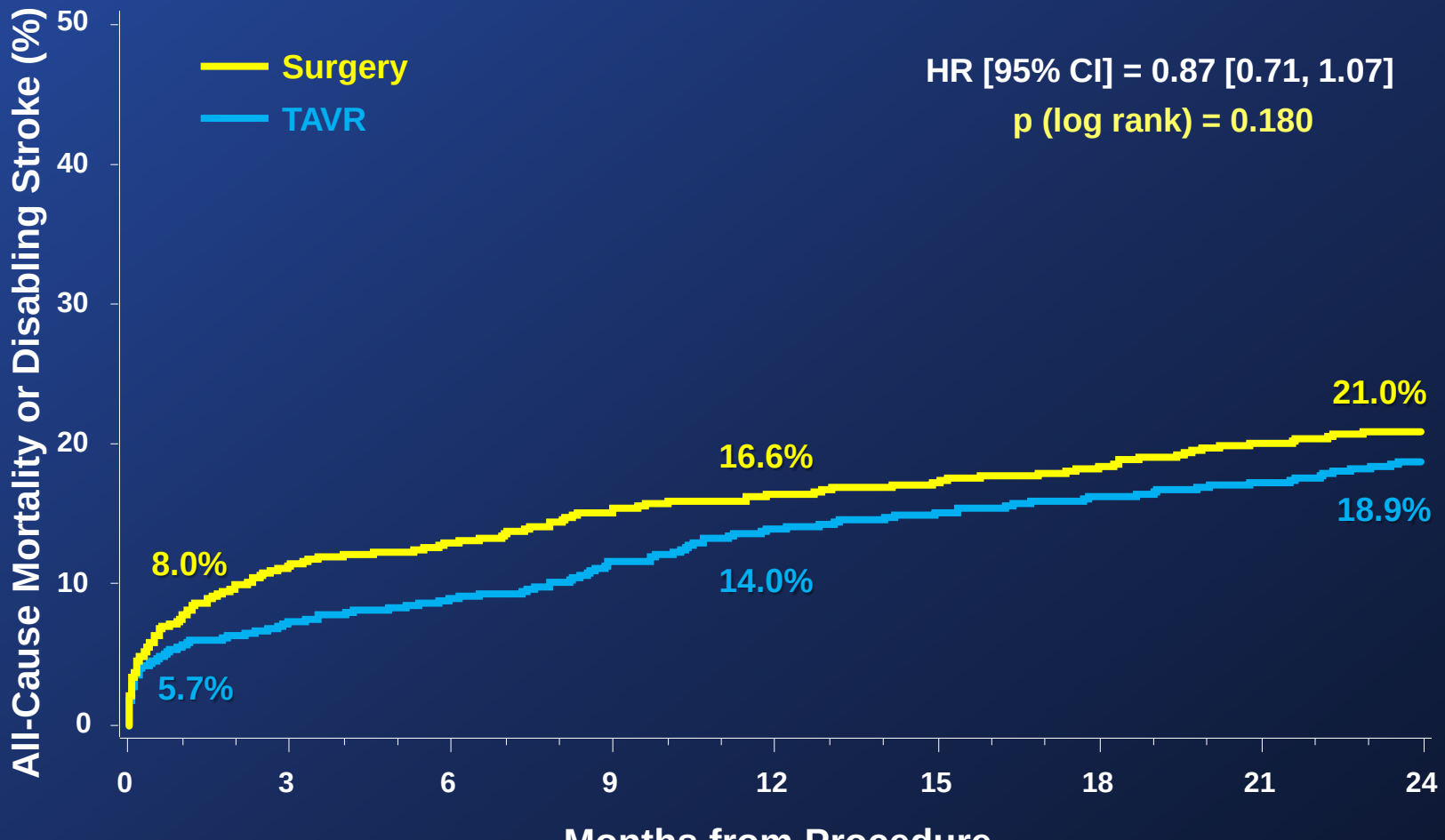
Non-Inferiority p-value = 0.001



Primary Non-Inferiority Endpoint Met

Primary Endpoint (AT)
All-cause Mortality or Disabling Stroke

THE PARTNER II TRIAL

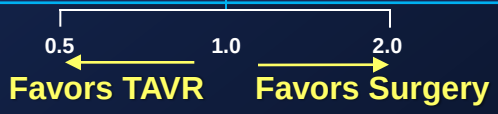


Number at risk:									
Surgery	944	826	807	779	766	743	731	715	694
TAVR	994	917	900	870	842	825	811	801	774

Primary Endpoint
Subgroup Analysis

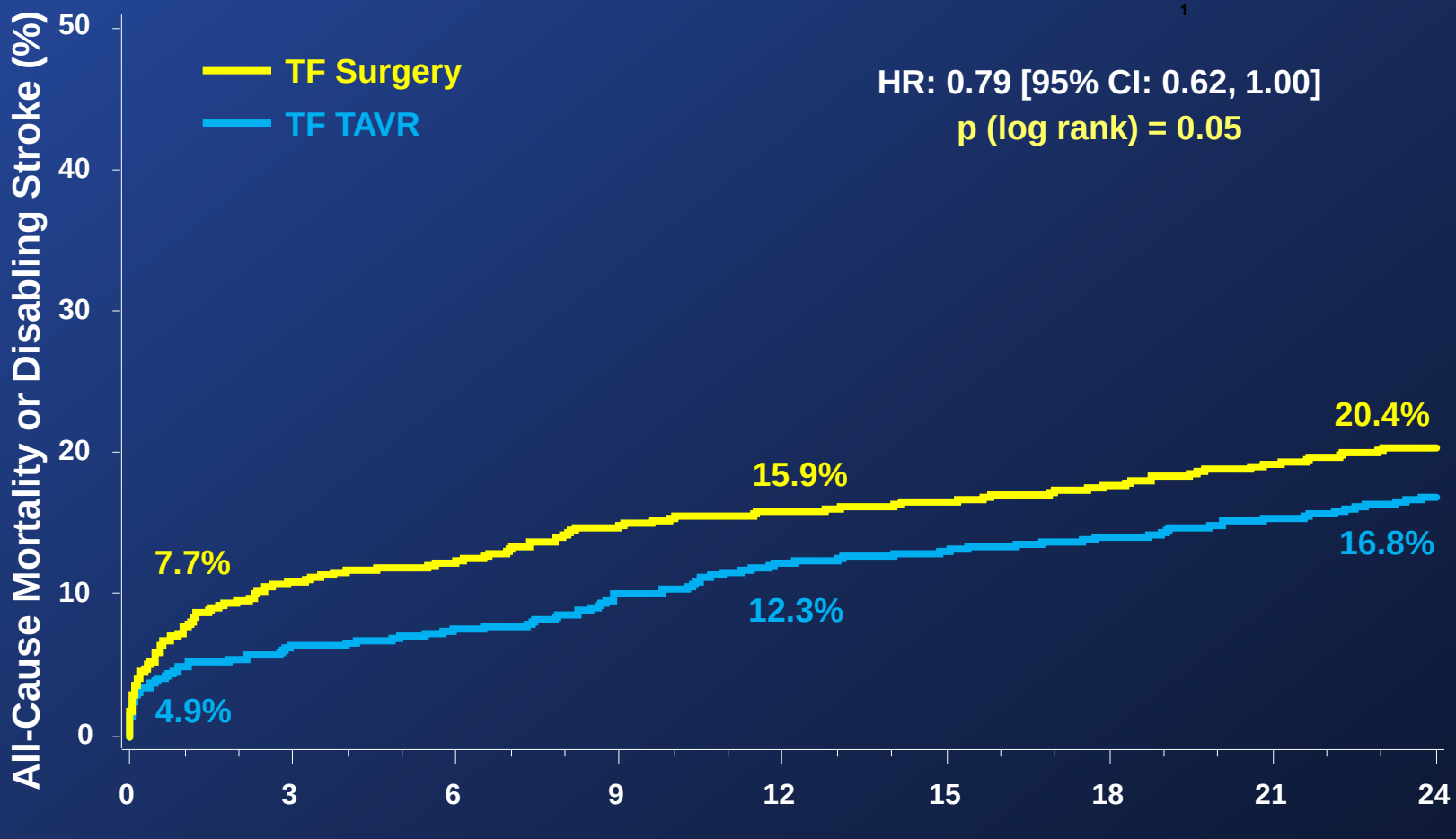
THE PARTNER II TRIAL

Subgroup	TAVR (%) n = 1011	AVR (%) n = 1021	Hazard Ratio (95% CI)	HR (95% CI)	p-value for interaction
Overall	19.3	21.1		0.89 [0.73-1.09]	
Age					0.96
< 85	18.0	19.5		0.90 [0.69-1.17]	
≥ 85	21.5	23.6		0.89 [0.65-1.20]	
Sex					0.37
Female	16.9	20.3		0.81 [0.59-1.10]	
Male	21.4	21.7		0.96 [0.74-1.25]	
STS Score					0.60
≤ 5	15.8	18.4		0.84 [0.61-1.16]	
> 5	22.4	23.1		0.94 [0.73-1.21]	
LV Ejection Fraction					0.27
≤ 55	19.1	21.5		0.84 [0.56-1.25]	
> 55	20.1	18.0		1.11 [0.81-1.53]	
Mod or Severe Mitral Regurgitation					0.53
No	17.8	20.3		0.85 [0.67-1.08]	
Yes	25.9	24.4		1.00 [0.64-1.57]	
Previous CABG					0.69
No	20.6	22.2		0.91 [0.73-1.13]	
Yes	15.3	18.0		0.82 [0.53-1.27]	
Peripheral Vascular Disease					0.47
No	18.2	20.7		0.85 [0.67-1.09]	
Yes	22.3	22.0		0.99 [0.71-1.40]	
15 Foot Walk Test					0.43
≤ 7 secs	17.7	20.9		0.82 [0.62-1.09]	
> 7 secs	20.7	20.8		0.97 [0.71-1.31]	
Access Route					0.06
Transfemoral	16.8	20.4		0.79 [0.62-1.00]	
Transthoracic	27.7	23.4		1.21 [0.84-1.74]	



TF Primary Endpoint (ITT)
All-cause Mortality or Disabling Stroke

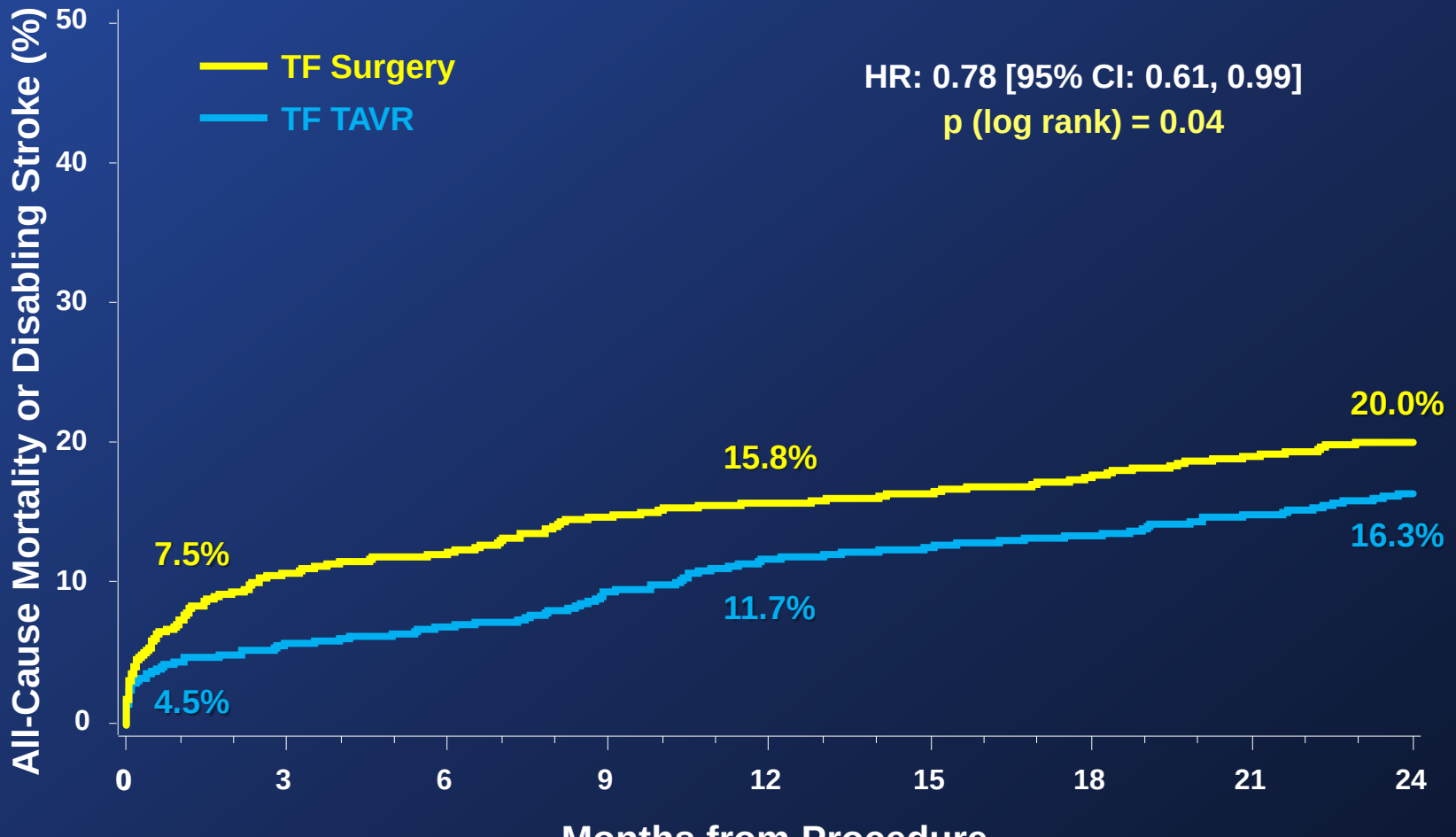
THE PARTNER II TRIAL



Number at risk:									
TF Surgery	775	643	628	604	595	577	569	557	538
TF TAVR	775	718	709	685	663	652	644	634	612

TF Primary Endpoint (AT)
All-cause Mortality or Disabling Stroke

THE PARTNER II TRIAL



Number at risk:									
TF Surgery	722	636	624	600	591	573	565	555	537
TF TAVR	762	717	708	685	663	652	644	634	612

Primary Endpoint Events (ITT)
At 30 Days and 2 Years

THE PARTNER II TRIAL

Events (%)	30 Days			2 Years		
	TAVR (n = 1011)	Surgery (n = 1021)	p-value*	TAVR (n = 1011)	Surgery (n = 1021)	p-value*
Death (all-cause) and Stroke (disabling)	6.1	8.0	0.11	19.3	21.1	0.33
Death						
All-cause	3.9	4.1	0.78	16.7	18.0	0.45
Cardiovascular	3.3	3.2	0.92	10.1	11.3	0.38
Neurological Events						
All Stroke	5.5	6.1	0.57	9.5	8.9	0.67
Disabling Stroke	3.2	4.3	0.20	6.2	6.4	0.83
TIA	0.9	0.4	0.17	3.7	2.3	0.09

*Event rates are KM estimates, p-values are point in time

Other Clinical Endpoints (ITT)
At 30 Days and 2 Years

THE PARTNER II TRIAL

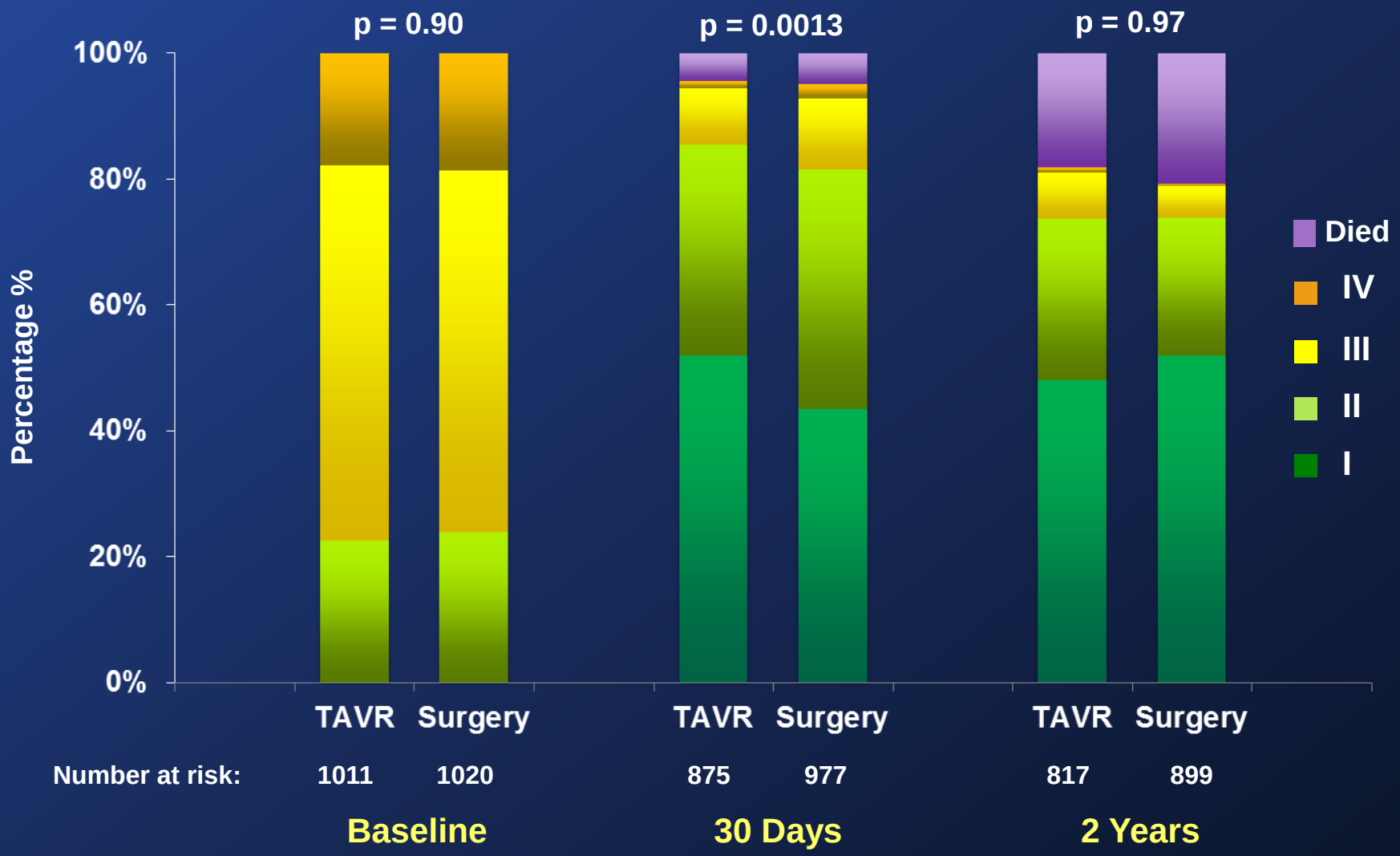
Events (%)	30 Days			2 Years		
	TAVR (n = 1011)	Surgery (n = 1021)	p-value*	TAVR (n = 1011)	Surgery (n = 1021)	p-value*
Rehospitalization	6.5	6.5	0.99	19.6	17.3	0.22
MI	1.2	1.9	0.22	3.6	4.1	0.56
Major Vascular Complications	7.9	5.0	0.008	8.6	5.5	0.006
Life-Threatening / Disabling Bleeding	10.4	43.4	<0.001	17.3	47.0	<0.001
AKI (Stage III)	1.3	3.1	0.006	3.8	6.2	0.02
New Atrial Fibrillation	9.1	26.4	<0.001	11.3	29.3	<0.001
New Permanent Pacemaker	8.5	6.9	0.17	11.8	10.3	0.29
Re-intervention	0.4	0.0	0.05	1.4	0.6	0.09
Endocarditis	0.0	0.0	NA	1.2	0.7	0.22

*Event rates are KM estimates, p-values are point in time

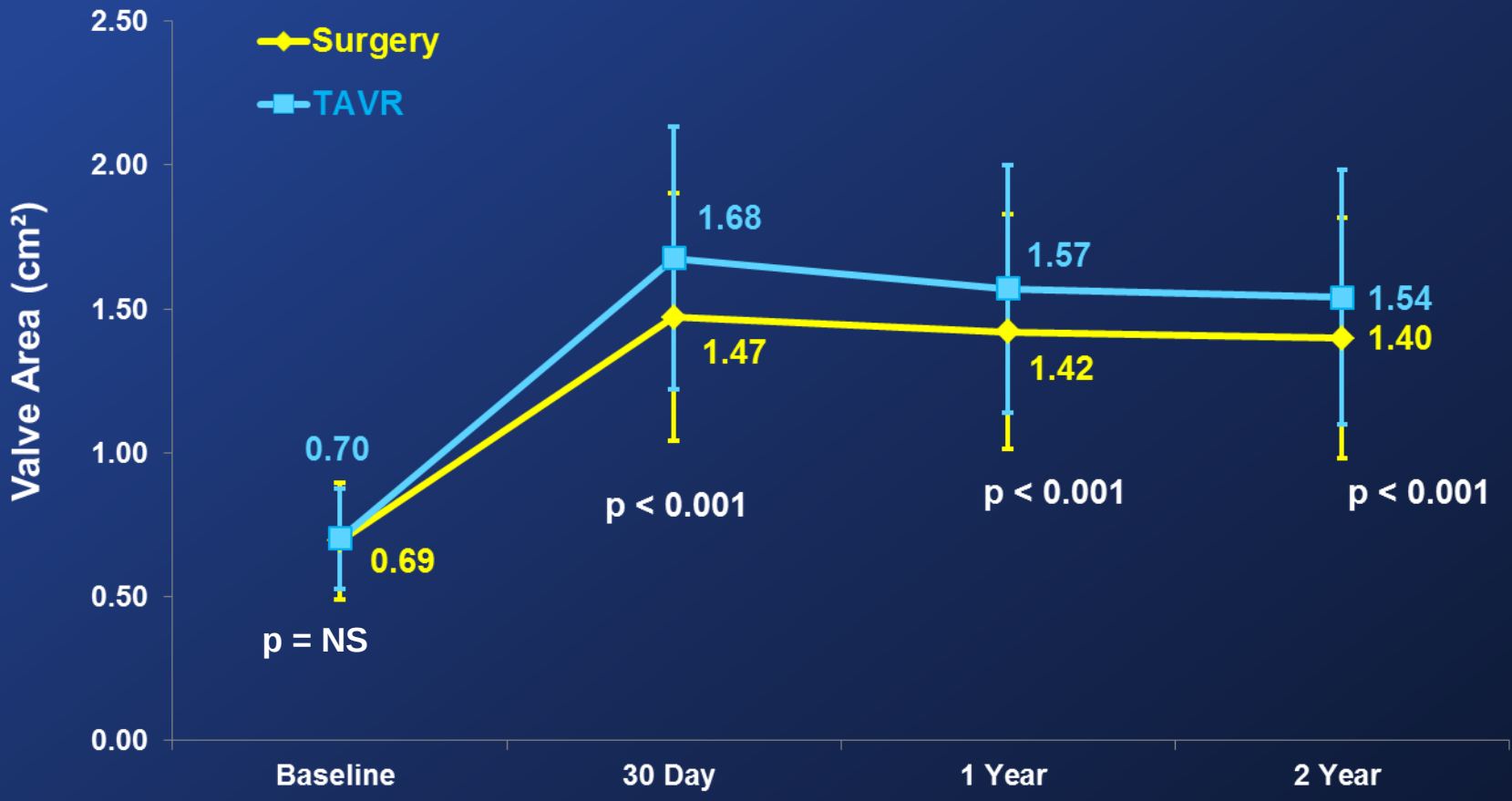
NYHA Class (ITT)
All Patients

THE PARTNER II TRIAL

All p < 0.001 for change from baseline to each time point



Echocardiography Findings (VI)
Aortic Valve Area

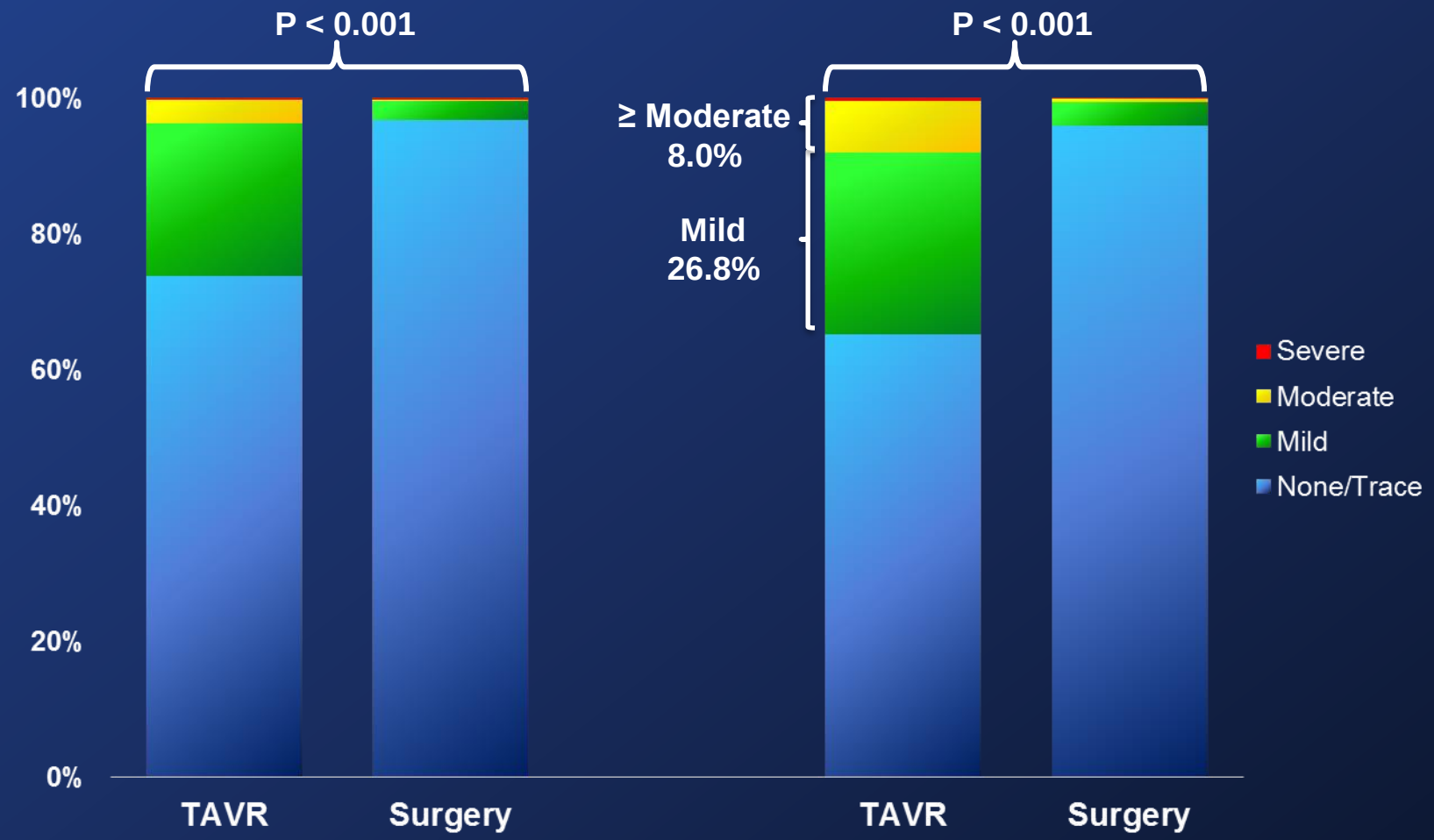


No. of Echos				
Surgery	861	727	590	488
TAVR	899	829	695	567

Error bars represent ± Standard Deviation

Paravalvular Regurgitation (VI)
3-Class Grading Scheme

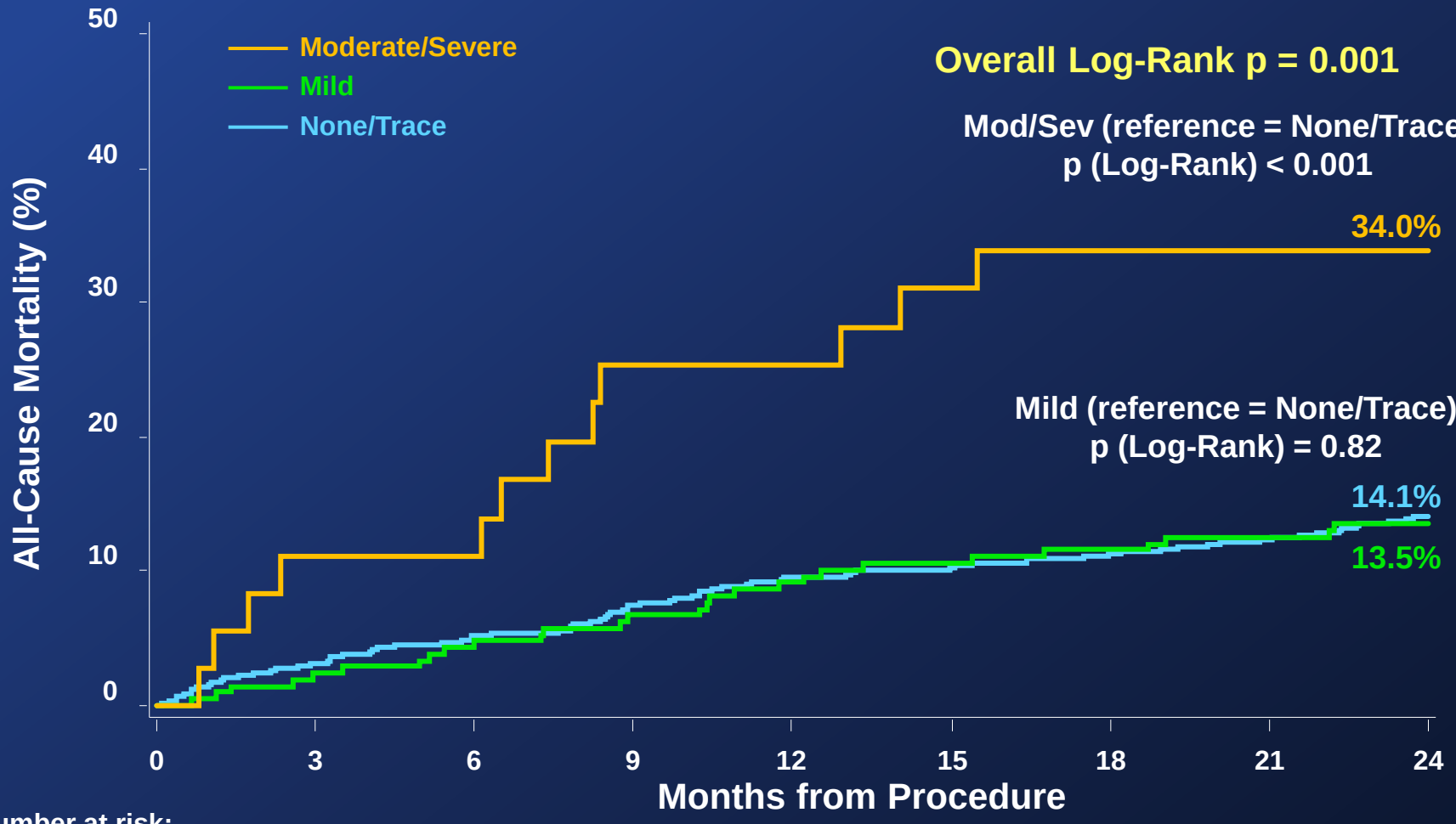
THE PARTNER II TRIAL



No. of echos	30 Days	2 Years
TAVR	872	600
Surgery	757	514

Severity of PVR at 30 Days and All-cause Mortality at 2 Years (VI)

THE PARTNER II TRIAL



Number at risk:

Moderate/Sev	36	32	32	26	26	24	22	22	21
Mild	210	204	199	194	188	184	182	180	175
None/Trace	701	678	664	647	628	621	612	605	585

The PARTNER 2A Trial
Conclusions (1)

THE PARTNER II TRIAL

In intermediate-risk patients with symptomatic severe aortic stenosis, results from the PARTNER 2A trial demonstrated that...

- TAVR using SAPIEN XT and surgery were similar (non-inferior) for the primary endpoint (all-cause mortality or disabling stroke) at 2 years.
- In the transfemoral subgroup (76% of patients), TAVR using SAPIEN XT significantly reduced all-cause mortality or disabling stroke vs. surgery (ITT: $p = 0.05$, AT: $p = 0.04$).

The PARTNER 2A Trial
Conclusions (2)

- Other clinical outcomes:
  - TAVR reduced AKI, severe bleeding, new AF, and LOS
  - Surgery reduced vascular complications and PVR
- The SAPIEN XT valve significantly increased echo AVA compared to surgery.
- In the SAPIEN XT TAVR cohort, moderate or severe PVR, but not mild PVR, was associated with increased mortality at 2 years.

The PARTNER 2A Trial
Clinical Implications

THE PARTNER II TRIAL

- *The results from PARTNER 2A support the use of TAVR as an alternative to surgery in intermediate risk patients, similar to those included in this trial.*
- In patients who are candidates for transfemoral access, TAVR may result in additional clinical advantages.
- Long-term durability assessments of transcatheter bioprosthetic valves are still lacking and extrapolation of these findings to low-risk patients requires further clinical trial validation.