

# *PARTNER 2A - TAVR in Intermediate Risk Patients*

Martin B. Leon, MD

Columbia University Medical Center  
Cardiovascular Research Foundation  
New York City

21<sup>st</sup> CardioVascular Summit

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Coex, Seoul, Korea

12 mins

*April 27, 2016*

# Disclosure Statement of Financial Interest

## TCTAP 2016; Seoul, Korea; April 26-29, 2016

### Martin B. Leon, MD

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

Affiliation / Financial Relationship	Company
• Grant / Research Support	Abbott, Boston Scientific, Edwards Lifescience, Medtronic, St. Jude Medical
• Consulting Fees / Honoraria	Abbott, Boston Scientific, Medtronic, St. Jude Medical
• Shareholder / Equity	Claret, Coherex, Elixir, GDS, Medinol, Mitralign, Valve Medical

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

**Martin B. Leon, MD**

on behalf of the PARTNER Trial Investigators

ACC 2016 | Chicago | April 2, 2016



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TRIAL

# The PARTNER 2A Trial Study Design



**Symptomatic Severe Aortic Stenosis**

**ASSESSMENT by Heart Valve Team  
Operable (STS  $\geq$  4%)**

**Randomized Patients  
n = 2032**

**Yes**

**ASSESSMENT:  
Transfemoral Access**

**No**

**Transfemoral (TF)**

**Transapical (TA) / TransAortic (TAo)**

**1:1 Randomization (n = 1550)**

**1:1 Randomization (n = 482)**

**TF TAVR  
(n = 775)**

**vs.**

**Surgical AVR  
(n = 775)**

**TA/TAo TAVR  
(n = 236)**

**vs.**

**Surgical AVR  
(n = 246)**

**Primary Endpoint: All-Cause Mortality or Disabling Stroke at Two Years**

# The PARTNER 2A Trial

## Participating Sites



**2032 Randomized Pts**  
**55 US & 2 Canadian Sites**

# PARTNER SAPIEN Platforms

## Device Evolution

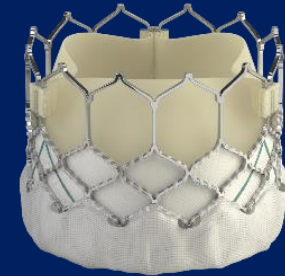
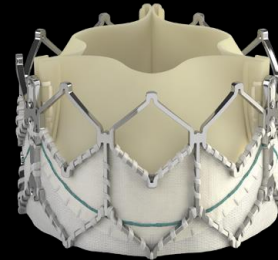
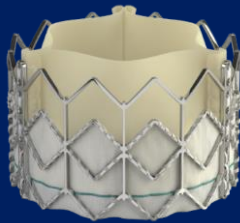


### SAPIEN

### SAPIEN XT

### SAPIEN 3

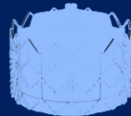
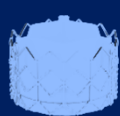
Valve Technology



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

# Baseline Patient Characteristics

## Demographics and Vascular Disease



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

# Procedural Characteristics (AT)



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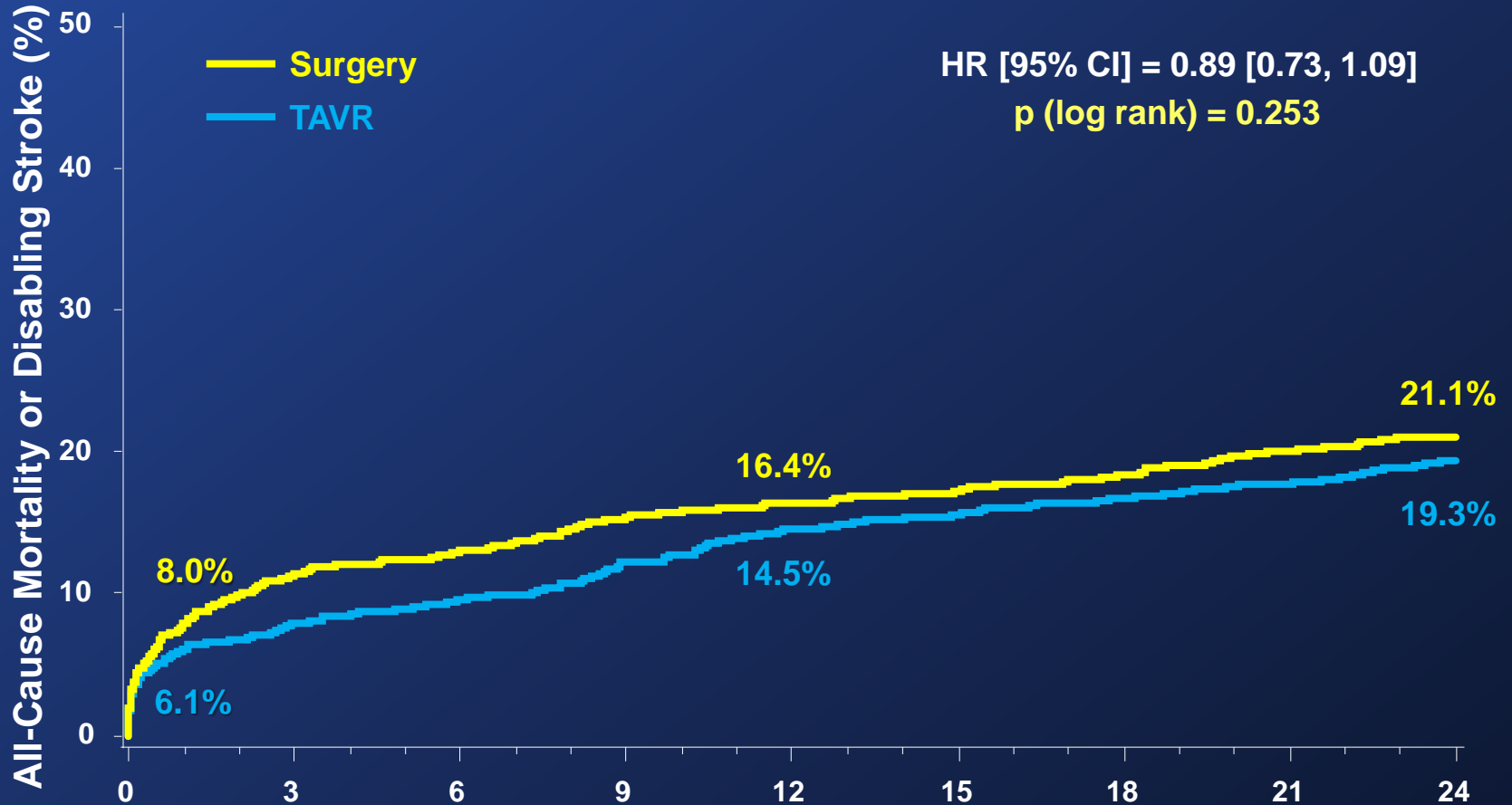
Characteristic	TAVR (n = 994)	Surgery (n = 944)	p-value
Anesthesia Time (min)	207	333	< 0.001
Procedure Time (min)	103	237	< 0.001
Fluoroscopy Time (min)	20	NA	NA
Aortic Cross-clamp Time (min)	NA	75	NA
Total CPB Time (min)	NA	104	NA
Median ICU Stay (days)	2.0 [2, 4]	4.0 [3, 6]	< 0.001
Median Total Length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

Median [IQR]



# Primary Endpoint (ITT)

## All-Cause Mortality or Disabling Stroke



Number at risk:

	0	3	6	9	12	15	18	21	24
Surgery	1021	838	812	783	770	747	735	717	695
TAVR	1011	918	901	870	842	825	811	801	774

Months from Procedure

# Primary Endpoint (ITT)

## All-cause Mortality or Disabling Stroke

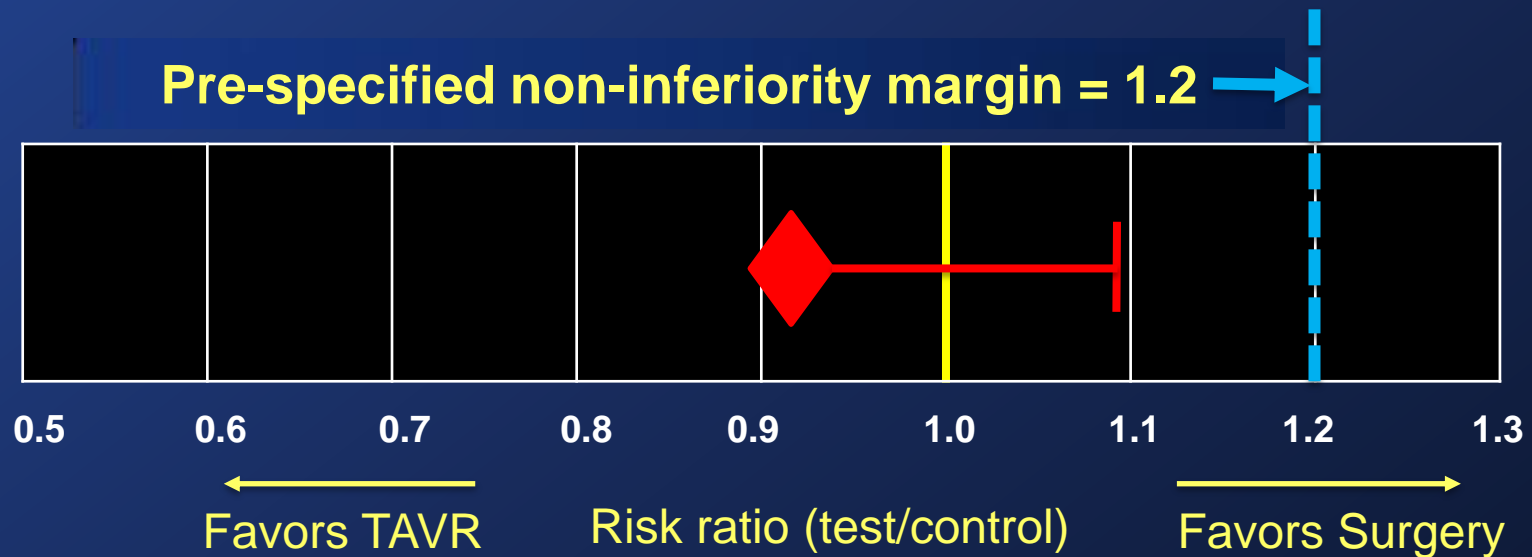


**TAVR**  
n = 1011  
19.3%

**SAVR**  
n = 1021  
21.1%

Relative Risk Ratio 0.92  
Upper 1-sided 97.5%CI 1.09

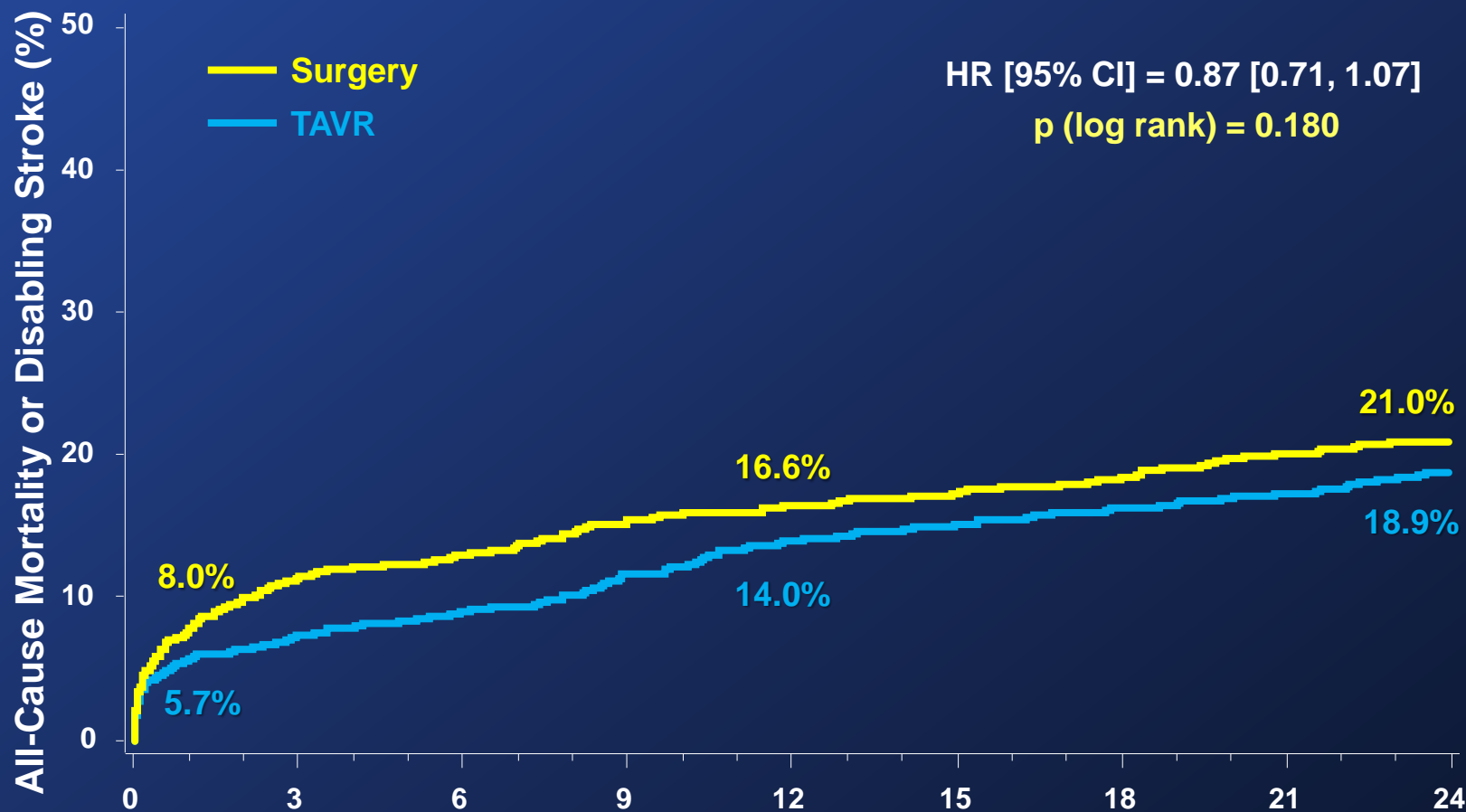
Non-Inferiority  
p-value = 0.001



**Primary Non-Inferiority Endpoint Met**

# Primary Endpoint (AT)

## All-Cause Mortality or Disabling Stroke



Number at risk:

	0	3	6	9	12	15	18	21	24
Surgery	944	826	807	779	766	743	731	715	694
TAVR	994	917	900	870	842	825	811	801	774

Months from Procedure

# Primary Endpoint Subgroup Analysis

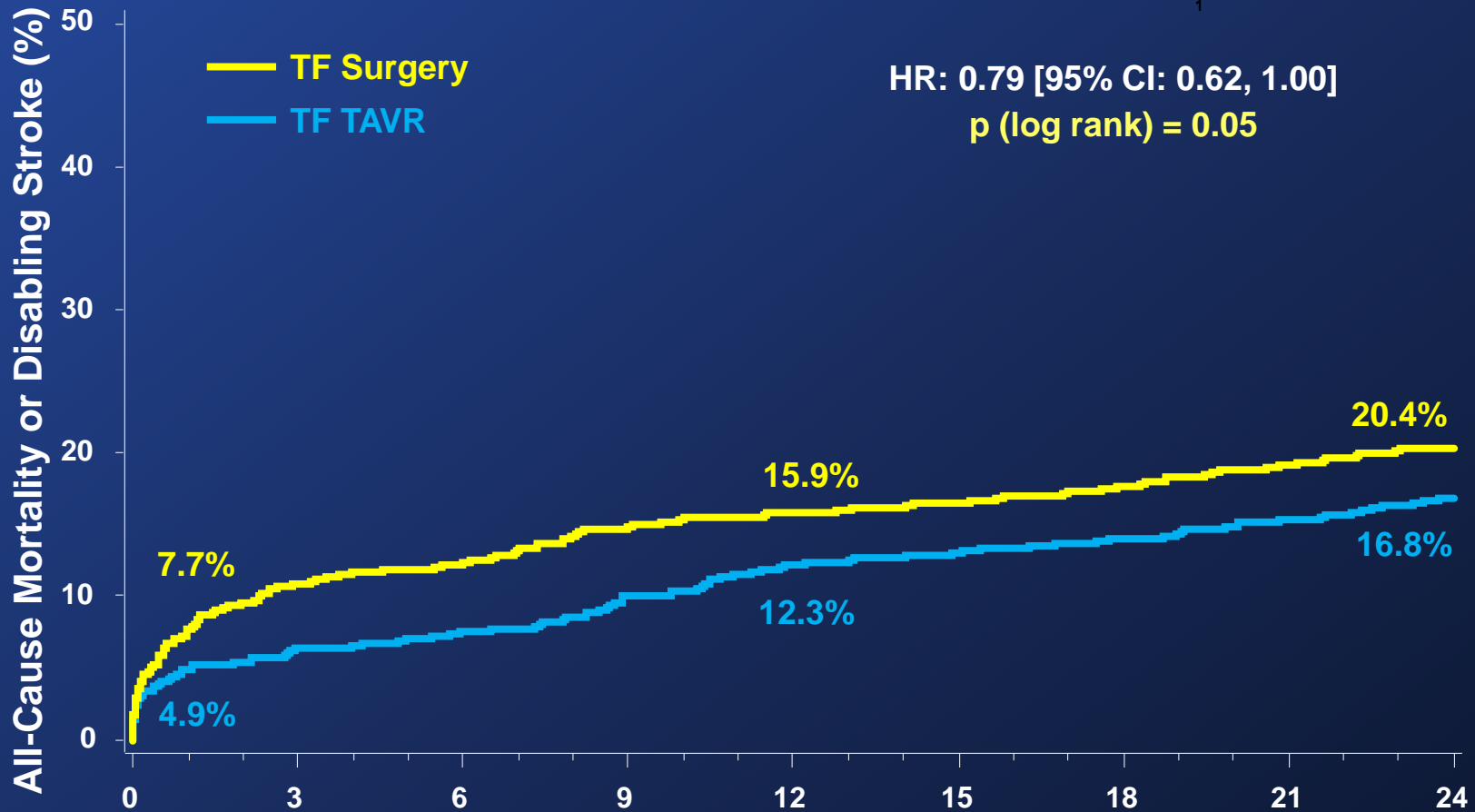


Subgroup	TAVR (%) n = 1011	AVR (%) n = 1021	Hazard Ratio (95% CI)	HR (95% CI)	p-value for interaction
<b>Overall</b>	19.3	21.1		0.89 [0.73-1.09]	
<b>Age</b>	18.0	19.5		0.90 [0.69-1.17]	<b>0.96</b>
< 85	21.5	23.6		0.89 [0.65-1.20]	
<b>Sex</b>	16.9	20.3		0.81 [0.59-1.10]	<b>0.37</b>
Female	21.4	21.7		0.96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



# TF Primary Endpoint (ITT)

## All-cause Mortality or Disabling Stroke



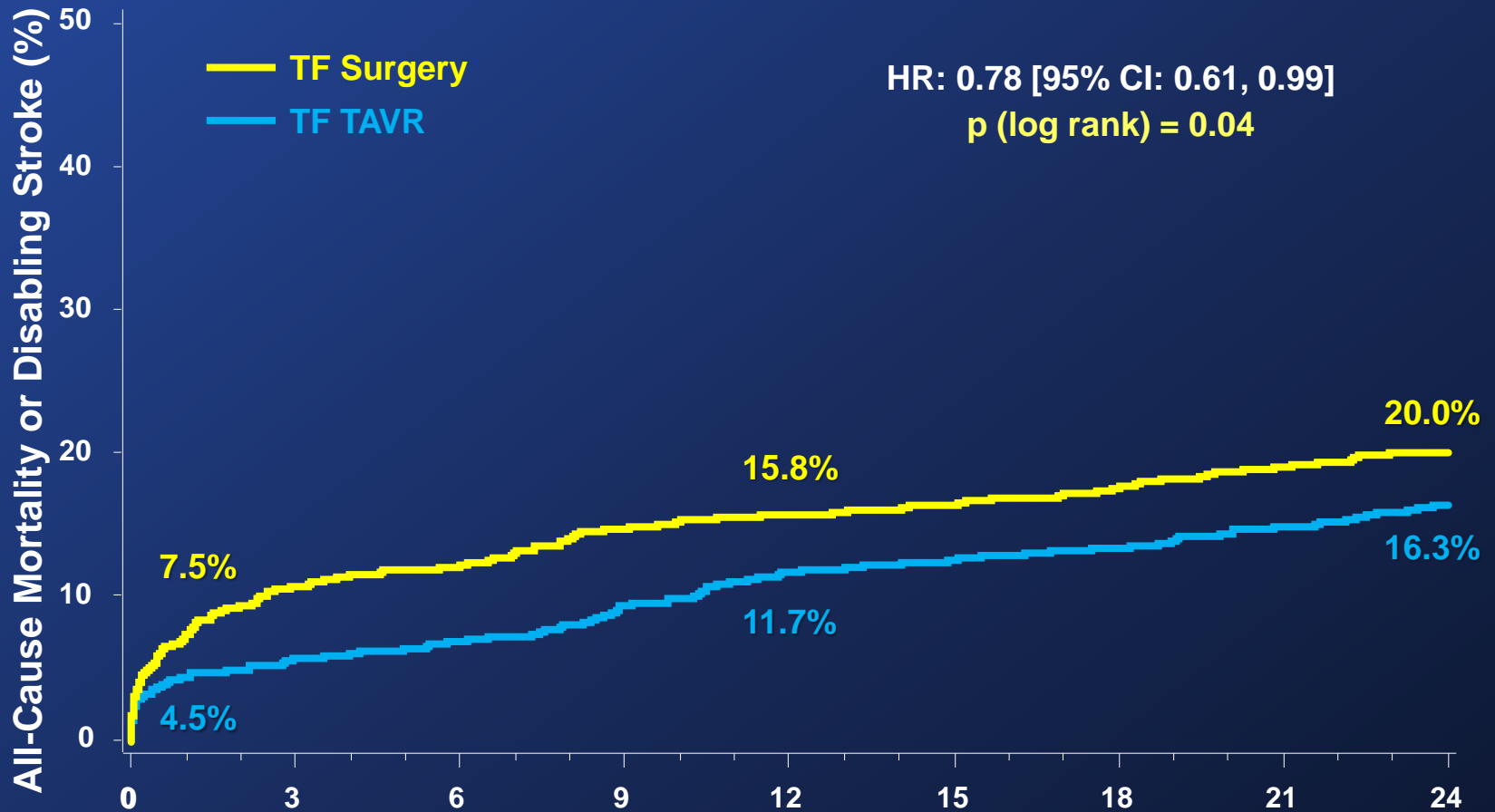
Number at risk:

	0	3	6	9	12	15	18	21	24
TF Surgery	775	643	628	604	595	577	569	557	538
TF TAVR	775	718	709	685	663	652	644	634	612

Months from Procedure

# TF Primary Endpoint (AT)

## All-Cause Mortality or Disabling Stroke



Number at risk:

	0	3	6	9	12	15	18	21	24
TF Surgery	722	636	624	600	591	573	565	555	537
TF TAVR	762	717	708	685	663	652	644	634	612

Months from Procedure

# Other Clinical Endpoints (ITT)

## At 30 Days and 2 Years

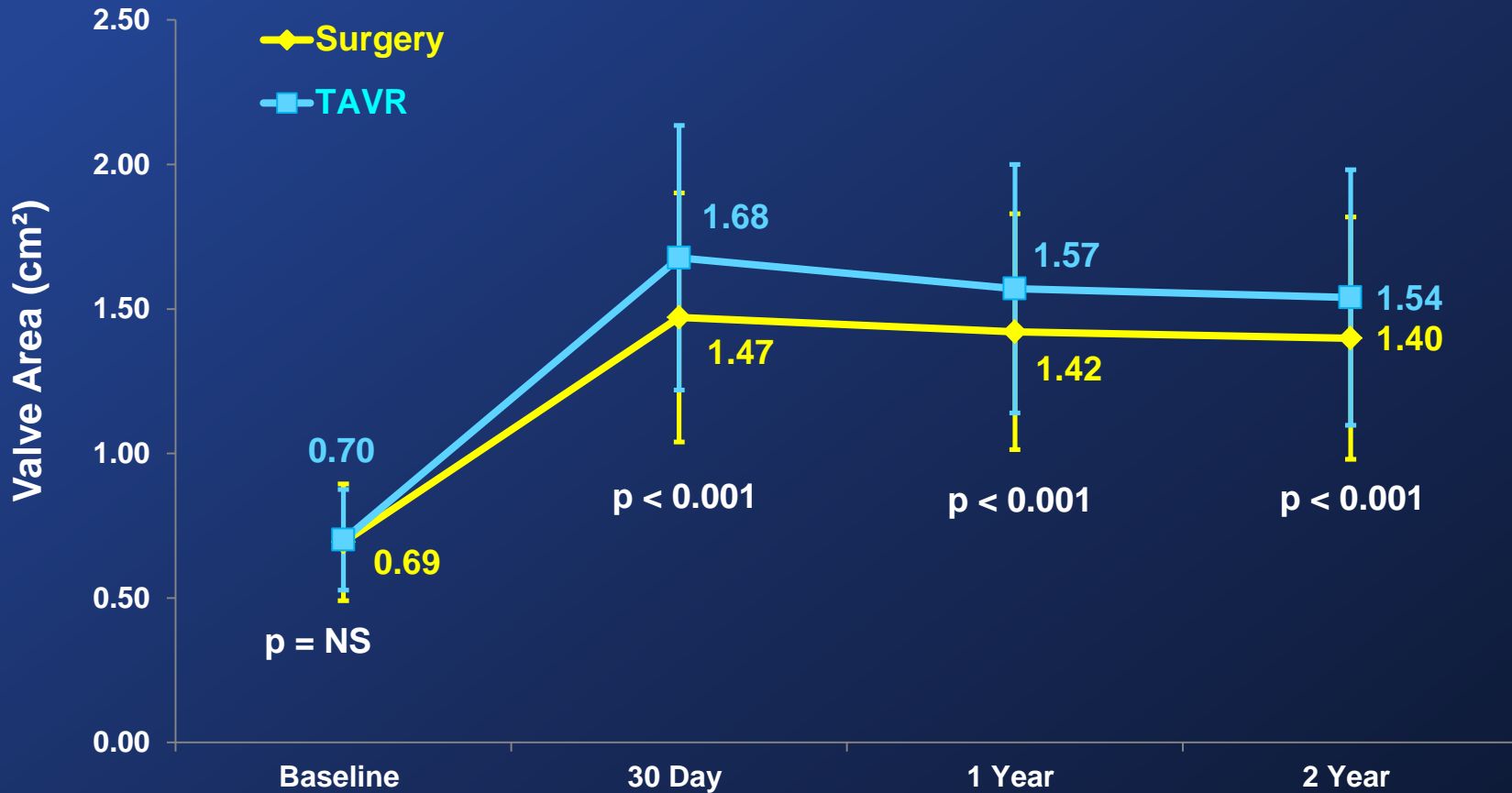


Events (%)	30 Days			2 Years		
	TAVR (n = 1011)	Surgery (n = 1021)	p-value*	TAVR (n = 1011)	Surgery (n = 1021)	p-value*
Rehospitalization	6.5	6.5	0.99	19.6	17.3	0.22
MI	1.2	1.9	0.22	3.6	4.1	0.56
Major Vascular Complications	7.9	5.0	0.008	8.6	5.5	0.006
Life-Threatening / Disabling Bleeding	10.4	43.4	<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	27.3	<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

# Echocardiography Findings (VI)

## Aortic Valve Area



No. of Echos

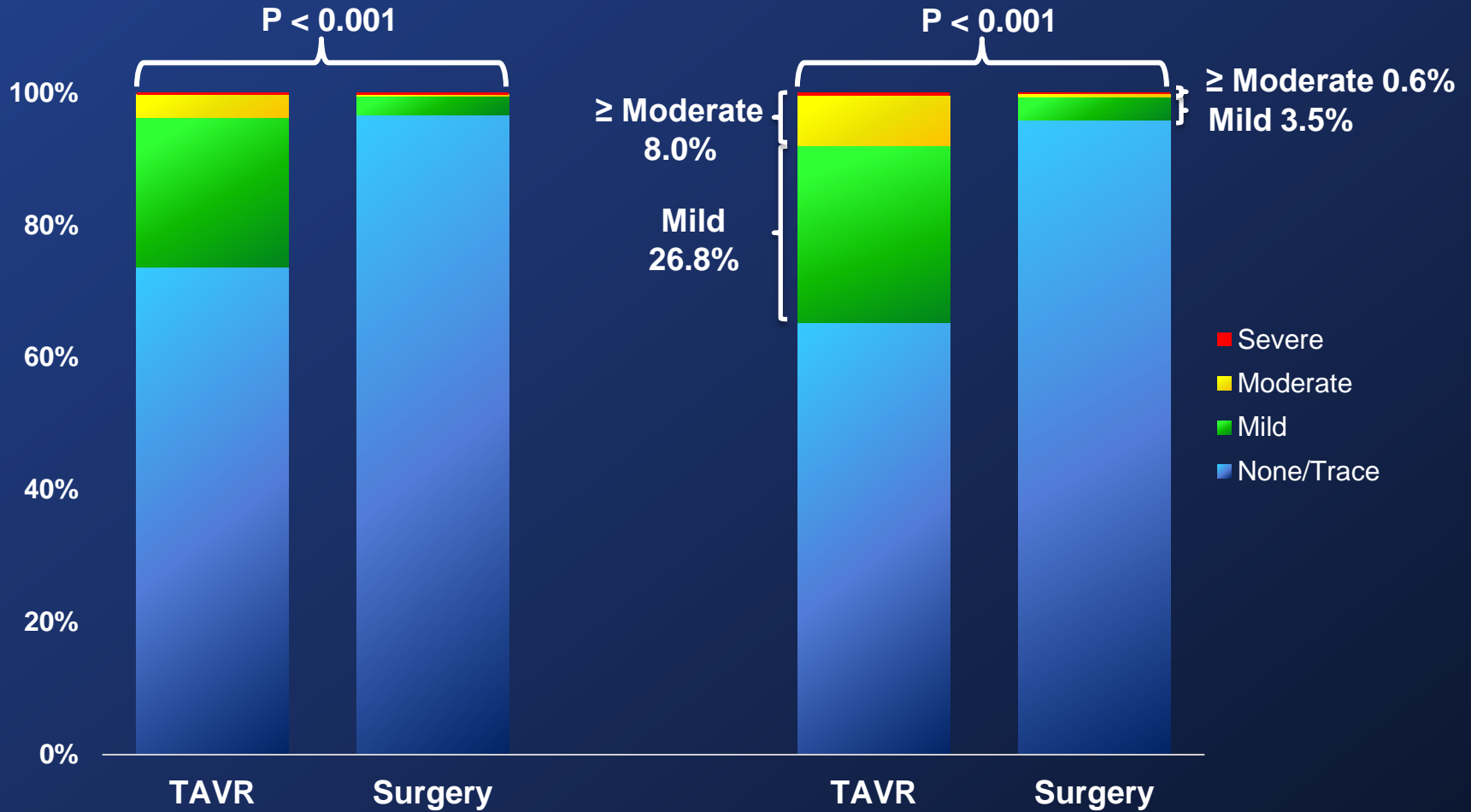
<b>Surgery</b>	<b>861</b>	<b>727</b>	<b>590</b>	<b>488</b>
<b>TAVR</b>	<b>899</b>	<b>829</b>	<b>695</b>	<b>567</b>

Error bars represent  $\pm$  Standard Deviation



# Paravalvular Regurgitation (VI)

## 3-Class Grading Scheme



No. of echos

30 Days

2 Years

TAVR

872

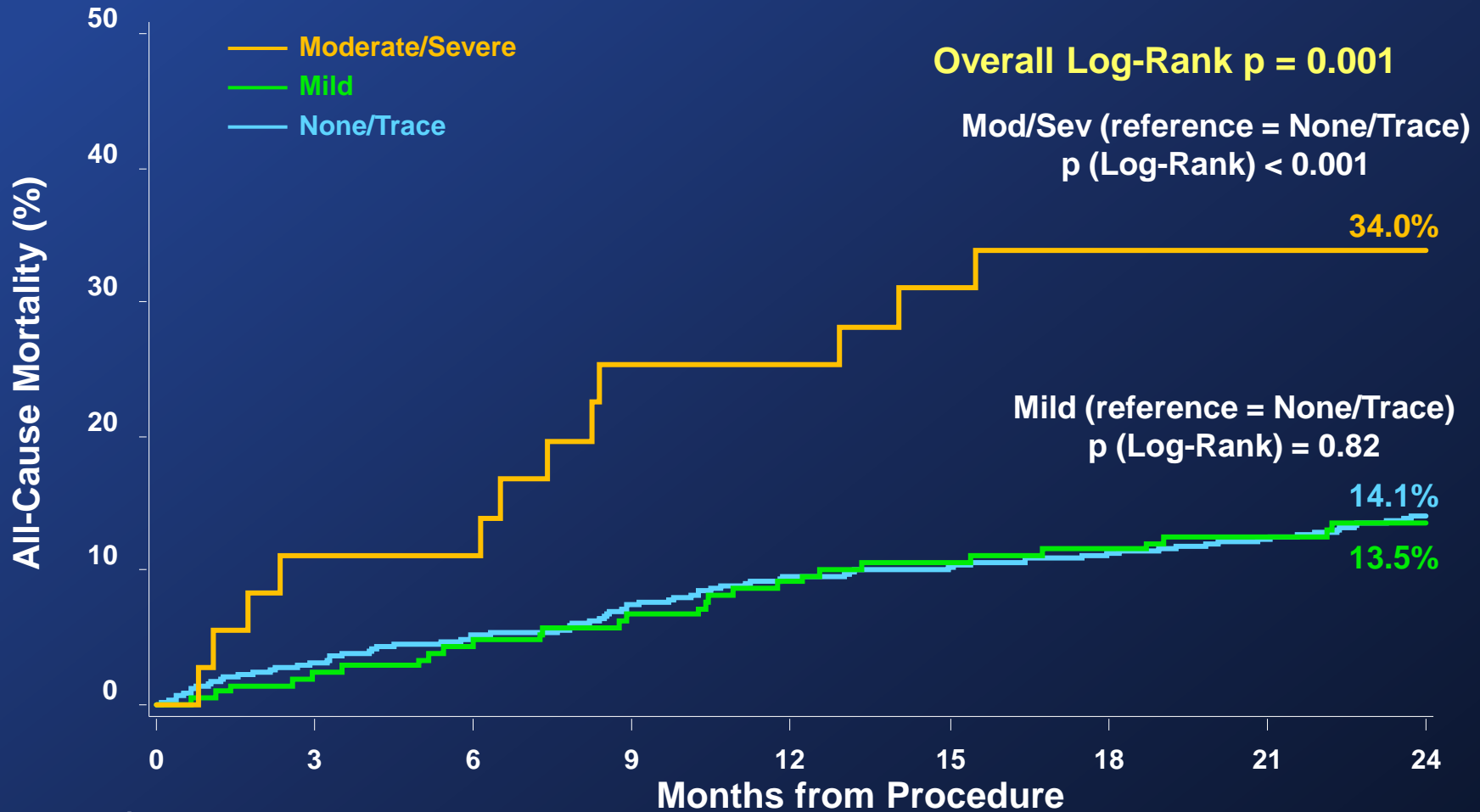
600

Surgery

757

514

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



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)



*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.

# SAPIEN Platforms in PARTNER

## Device Evolution

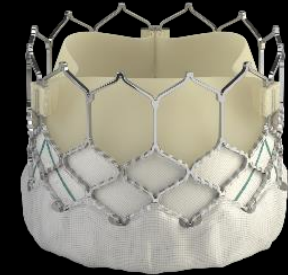
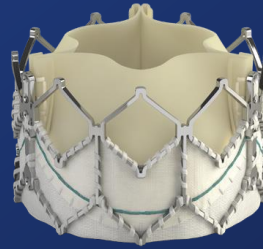
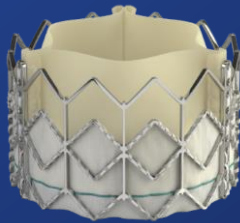


### SAPIEN

### SAPIEN XT

### SAPIEN 3

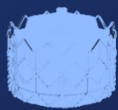
Valve Technology



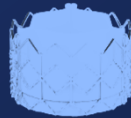
Sheath Compatibility



Available Valve Sizes



23 mm



26 mm



23 mm



26 mm



29 mm



20 mm



23 mm



26 mm



29 mm



## Early clinical and echocardiographic outcomes after **SAPIEN 3** transcatheter aortic valve replacement in inoperable, high-risk and intermediate-risk patients with aortic stenosis

Susheel Kodali<sup>1\*</sup>, Vinod H. Thourani<sup>2</sup>, Jonathon White<sup>1</sup>, S. Chris Malaisrie<sup>3</sup>, Scott Lim<sup>4</sup>, Kevin L. Greason<sup>5</sup>, Mathew Williams<sup>6</sup>, Mayra Guerrero<sup>7</sup>, Andrew C. Eisenhauer<sup>8,9</sup>, Samir Kapadia<sup>10</sup>, Dean J. Kereiakes<sup>11</sup>, Howard C. Herrmann<sup>12</sup>, Vasilis Babaliaros<sup>2</sup>, Wilson Y. Szeto<sup>12</sup>, Rebecca T. Hahn<sup>1</sup>, Philippe Pibarot<sup>13</sup>, Neil J. Weissman<sup>14</sup>, Jonathon Leipsic<sup>15</sup>, Philipp Blanke<sup>15</sup>, Brian K. Whisenant<sup>16</sup>, Rakesh M. Suri<sup>10</sup>, Raj R. Makkar<sup>17</sup>, Girma M. Ayele<sup>18</sup>, Lars G. Svensson<sup>10</sup>, John G. Webb<sup>15</sup>, Michael J. Mack<sup>19</sup>, Craig R. Smith<sup>1</sup>, and Martin B. Leon<sup>1</sup>

**Susheel Kodali, MD**

on behalf of The PARTNER Trial Investigators



# Baseline Patient Characteristics

## S3i Patients (n=1076 at 51 sites)



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Average STS =

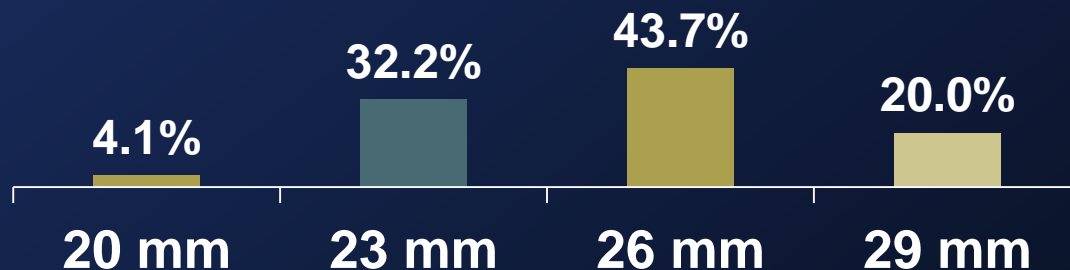
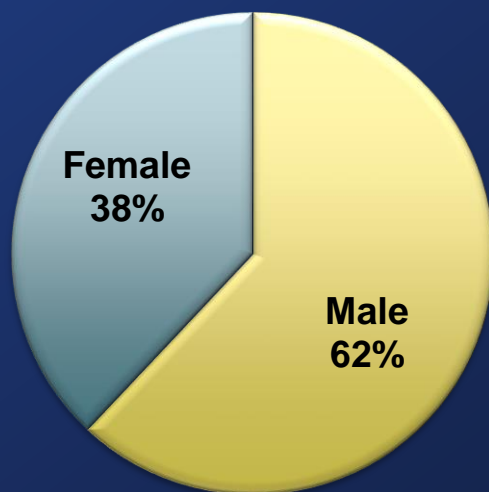
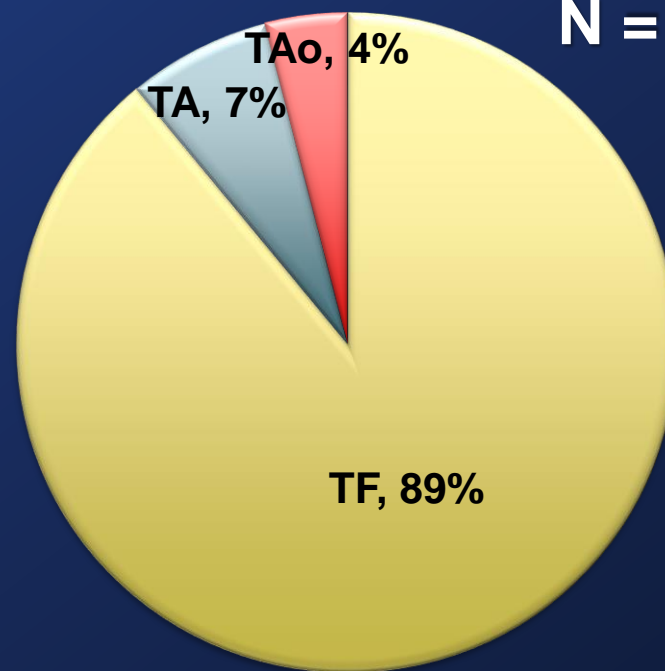
**5.3%**

(Median 5.2%)

Average Age =

**81.9yrs**

N = 1076

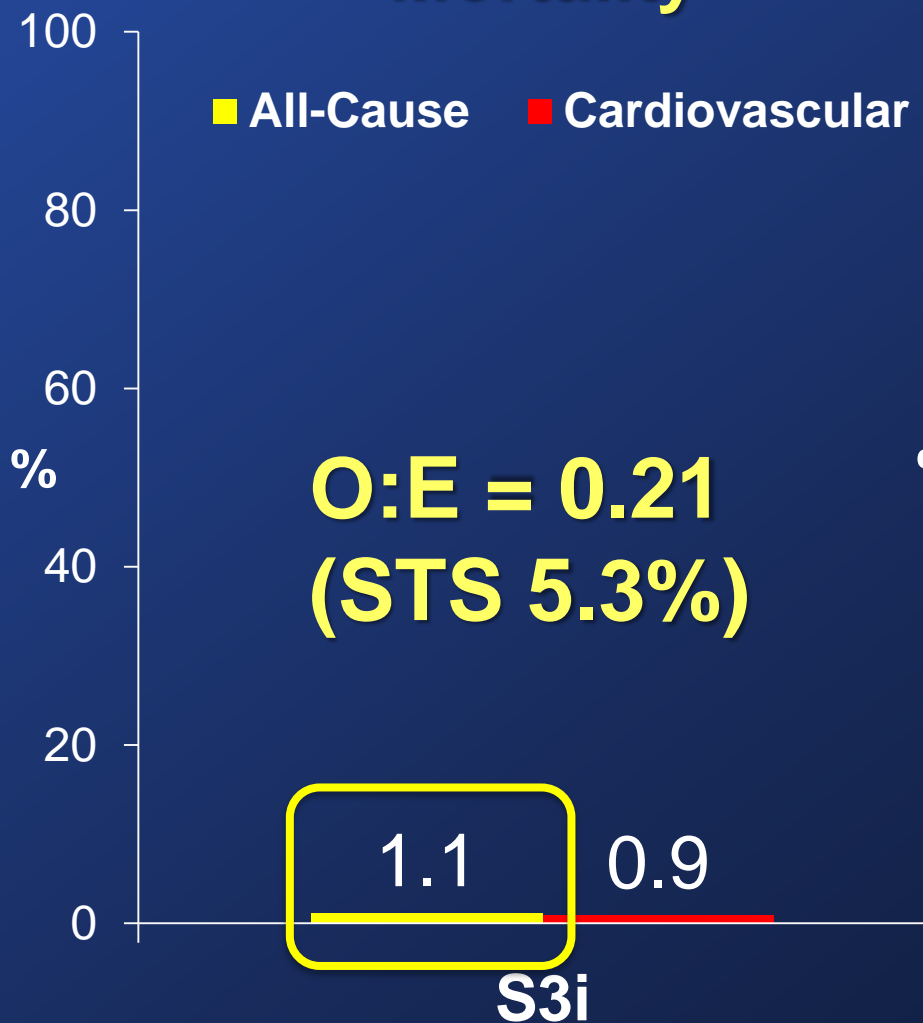


# Mortality and Stroke: S3i

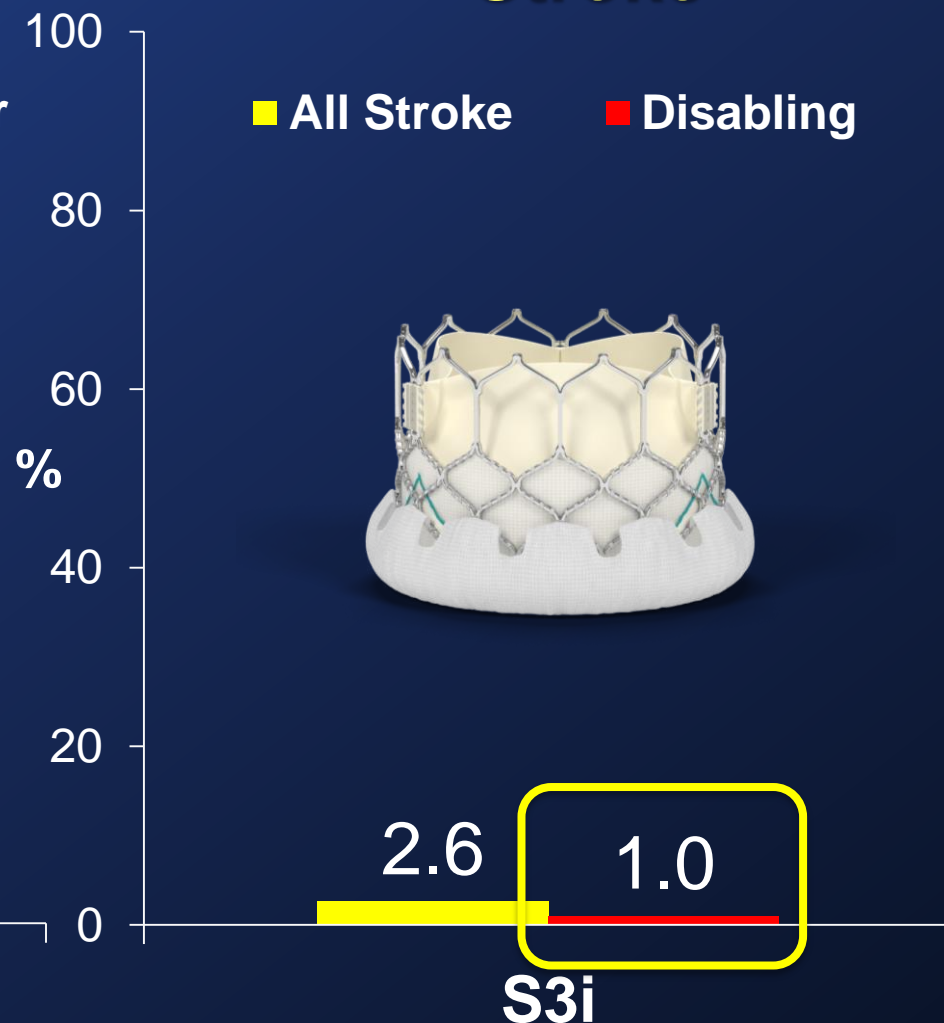
## At 30 Days (As Treated Patients)



### Mortality



### Stroke





**SAPIEN 3 Transcatheter Aortic Valve  
Replacement Compared with Surgery in  
Intermediate-Risk Patients:  
A Propensity Score Analysis**

**Vinod H. Thourani, MD**

on behalf of The PARTNER Trial Investigators

ACC 2016 | Chicago | April 3, 2016



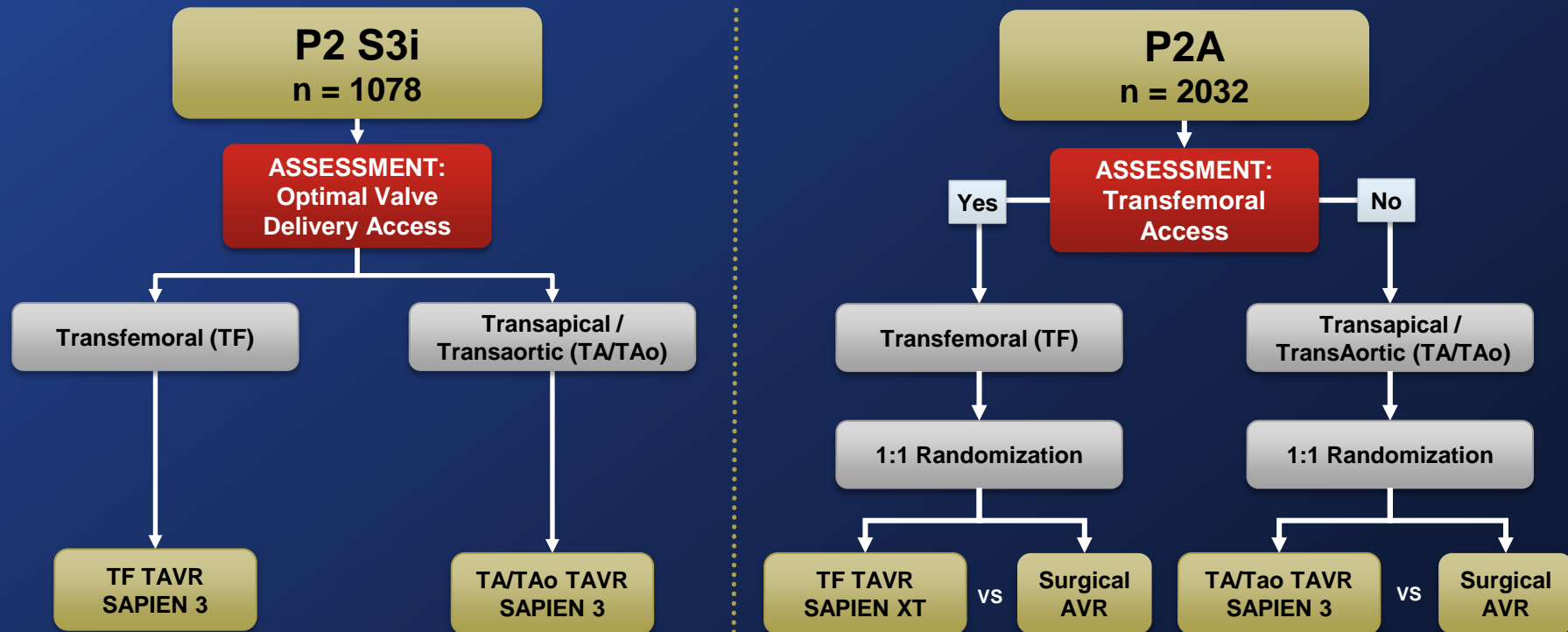
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TRIAL

# The PARTNER 2A and S3i Trials Study Design



Intermediate Risk Symptomatic Severe Aortic Stenosis

Intermediate Risk ASSESSMENT by Heart Valve Team

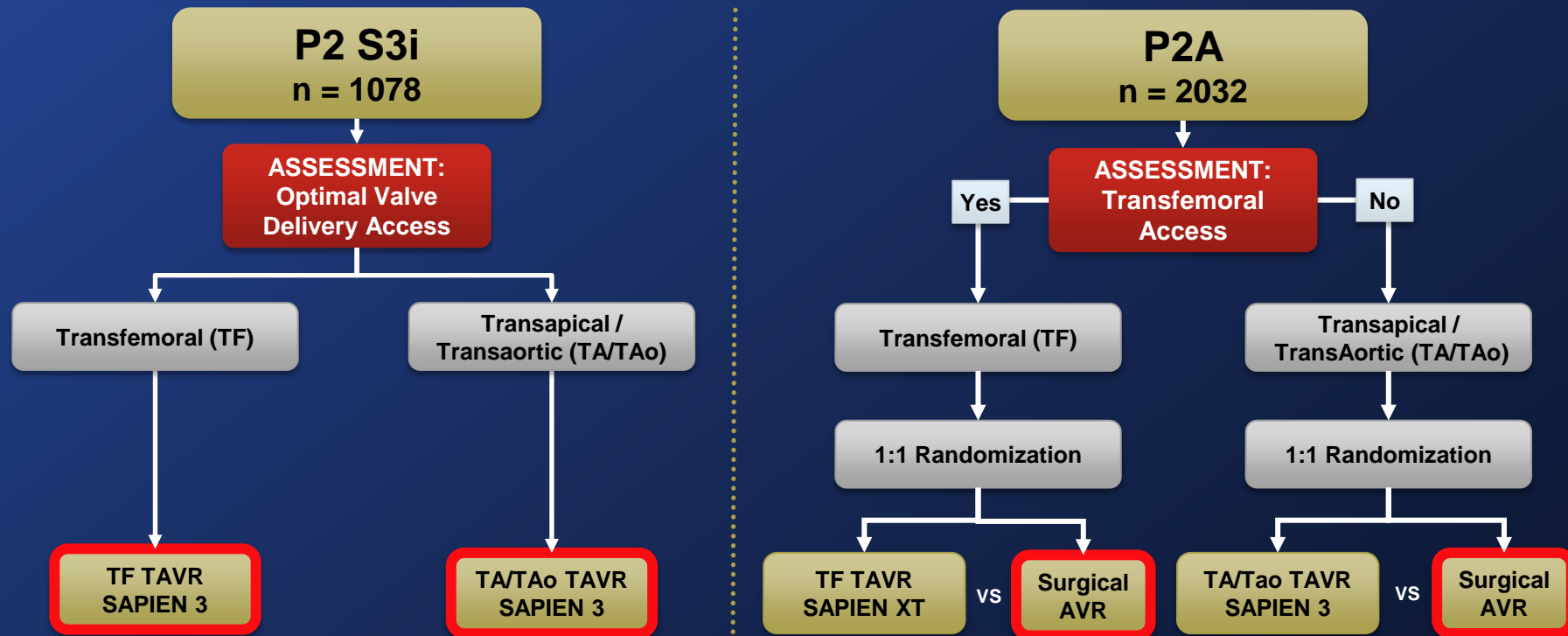


# The PARTNER 2A and S3i Trials Study Design



Intermediate Risk Symptomatic Severe Aortic Stenosis

Intermediate Risk ASSESSMENT by Heart Valve Team



Primary Endpoint: All-Cause Mortality, All Stroke, or Mod/Sev AR at One Year  
(Non-inferiority Propensity Score Analysis)

# Baseline Patient Characteristics

## Demographics (AT)



Characteristic	TAVR (n = 1077)	Surgery (n = 944)	p-value
Age - yrs	81.9 ± 6.6	81.6 ± 6.8	0.23
Male - %	61.7	55.0	0.002
BMI - kg/m <sup>2</sup>	28.7 ± 6.1	28.4 ± 6.2	0.32
Median STS Score - %	5.2 [4.3, 6.3]	5.4 [4.4, 6.7]	0.0002
NYHA Class III or IV - %	72.5	76.1	0.07

mean ± SD, median [IQR]

# Baseline Patient Characteristics

## Other Co-morbidities (AT)



<b>Characteristic (%)</b>	<b>TAVR (n = 1077)</b>	<b>Surgery (n = 944)</b>	<b>p-value</b>
<b>CAD</b>	<b>69.6</b>	<b>66.5</b>	<b>0.14</b>
<b>Previous CABG</b>	<b>27.9</b>	<b>25.7</b>	<b>0.27</b>
<b>Cerebrovascular Disease</b>	<b>9.0</b>	<b>10.3</b>	<b>0.36</b>
<b>PVD</b>	<b>28.2</b>	<b>32.2</b>	<b>0.05</b>
<b>COPD</b>	<b>30.0</b>	<b>30.2</b>	<b>0.92</b>
<b>Cr level &gt; 2 mg/dL</b>	<b>7.5</b>	<b>5.4</b>	<b>0.06</b>
<b>Atrial Fibrillation</b>	<b>36.0</b>	<b>34.9</b>	<b>0.61</b>
<b>Permanent Pacemaker</b>	<b>13.2</b>	<b>12.0</b>	<b>0.42</b>
<b>15 ft Walk Test &gt; 7s</b>	<b>41.3</b>	<b>45.7</b>	<b>0.06</b>

# Statistical Analysis Plan



- Pre-specified propensity score analysis of SAPIEN 3 TAVR vs. P2A surgery for the composite primary endpoint (all-cause mortality, all stroke, or total AR  $\geq$  moderate at 1 year).
- The analysis incorporated 22 pre-specified baseline characteristics that were factored through a logistic regression into a propensity score.
- Patient population was divided into quintiles based on propensity scores.
- Quintile stratification (unlike patient matching) allows for the use of data from all patients, minimizing selection bias.

# Quintile Propensity Score Analysis: Primary Endpoint



Surgery		TAVR			
# Patients	Mortality, Stroke, AR $\geq$ Mod	# Patients	Mortality, Stroke, AR $\geq$ Mod	Proportion Difference	Weighting
191	28.3%	138	13.8%	-14.5%	0.14
175	22.9%	171	9.9%	-12.9%	0.18
<b>147</b>	<b>19.7%</b>	<b>197</b>	<b>10.7%</b>	<b>-9.1%</b>	<b>0.20</b>
126	23.0%	219	14.6%	-8.4%	0.23
108	19.4%	238	15.1%	-4.3%	0.25

Overall weighted  
difference of proportions  
**- 9.2%**  
[-12.4%,-6.0%] two-sided 90% CI

# Primary Endpoint - Non-inferiority

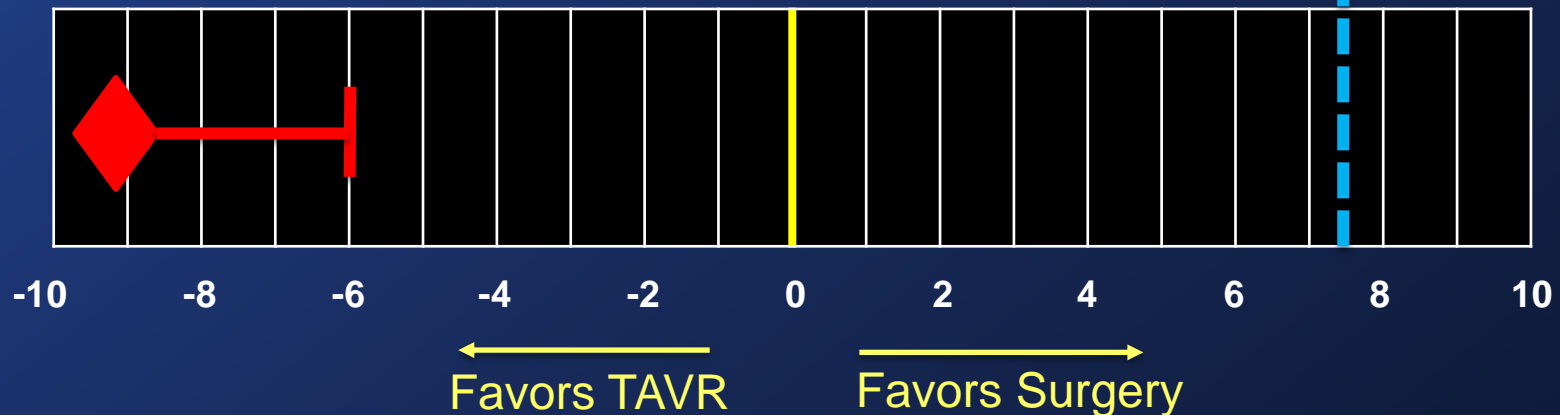
Death, Stroke, or AR  $\geq$  Mod at 1 Year (VI)



Weighted Difference -9.2%  
Upper 1-sided 95% CI -6.0%

Non-Inferiority  
p-value < 0.001

Pre-specified non-inferiority margin = 7.5%



**Primary Non-Inferiority Endpoint Met**



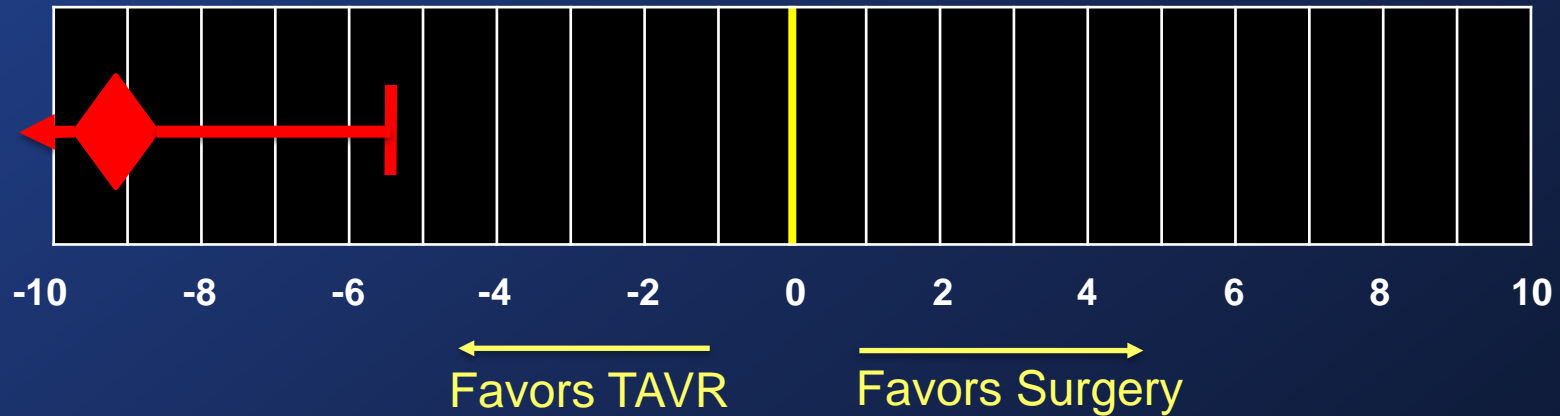
# Primary Endpoint - Superiority

Death, Stroke, or AR  $\geq$  Mod at 1 Year (VI)



Weighted Difference -9.2%  
Upper 2-sided 95% CI -5.4%

Superiority Testing  
p-value < 0.001



**Superiority Achieved**

# Superiority Analysis

## Components of Primary Endpoint (VI)



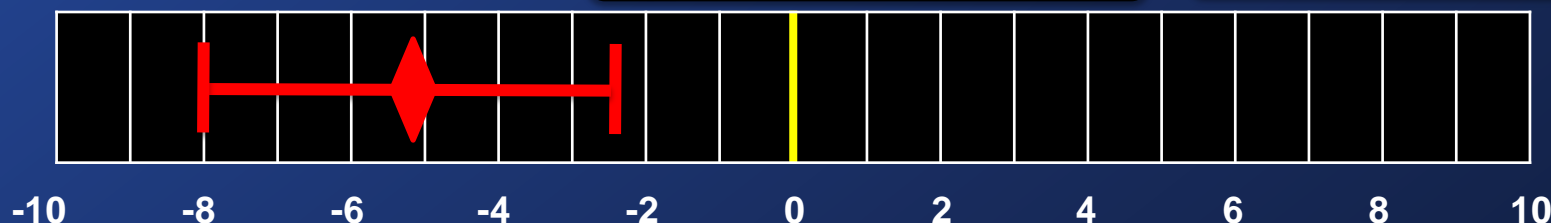
← Favors TAVR

→ Favors Surgery

### Mortality

Weighted Difference -5.2%  
Upper 2-sided 95% CI -2.4%

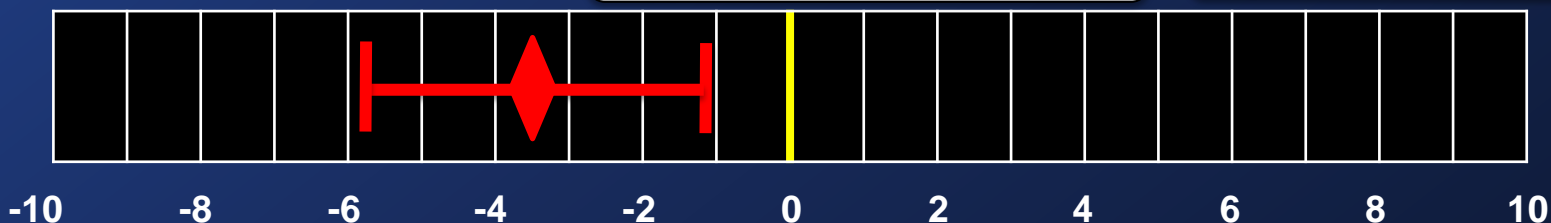
Superiority Testing  
p-value < 0.001



### Stroke

Weighted Difference -3.5%  
Upper 2-sided 95% CI -1.1%

Superiority Testing  
p-value = 0.004



### AR $\geq$ Moderate

Weighted Difference +1.2%  
Lower 2-sided 95% CI +0.2%

Superiority Testing  
p-value = 0.0149



# Unadjusted Clinical Events

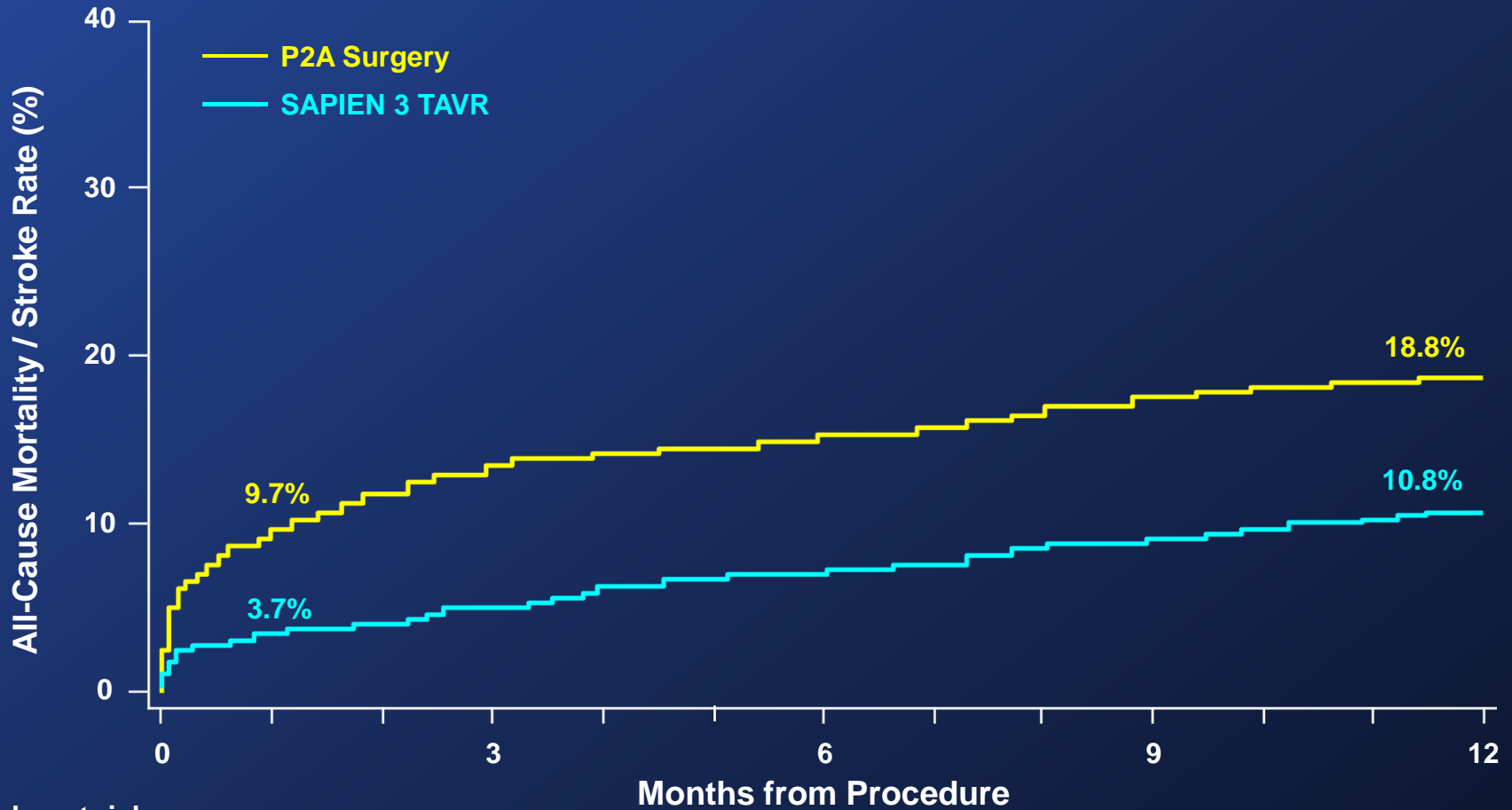
## At 30 Days and 1 Year (AT)



Events (%)	30 Days		1 Year	
	TAVR	Surgery	TAVR	Surgery
<b>Death</b>				
All-cause	1.1	4.0	7.4	13.0
Cardiovascular	0.9	3.1	4.5	8.1
<b>Neurological Events</b>				
Disabling Stroke	1.0	4.4	2.3	5.9
All Stroke	2.7	6.1	4.6	8.2
<b>All-cause Death and Disabling Stroke</b>	2.0	8.0	8.4	16.6

# Unadjusted Time-to-Event Analysis

## All-Cause Mortality and All Stroke (AT)

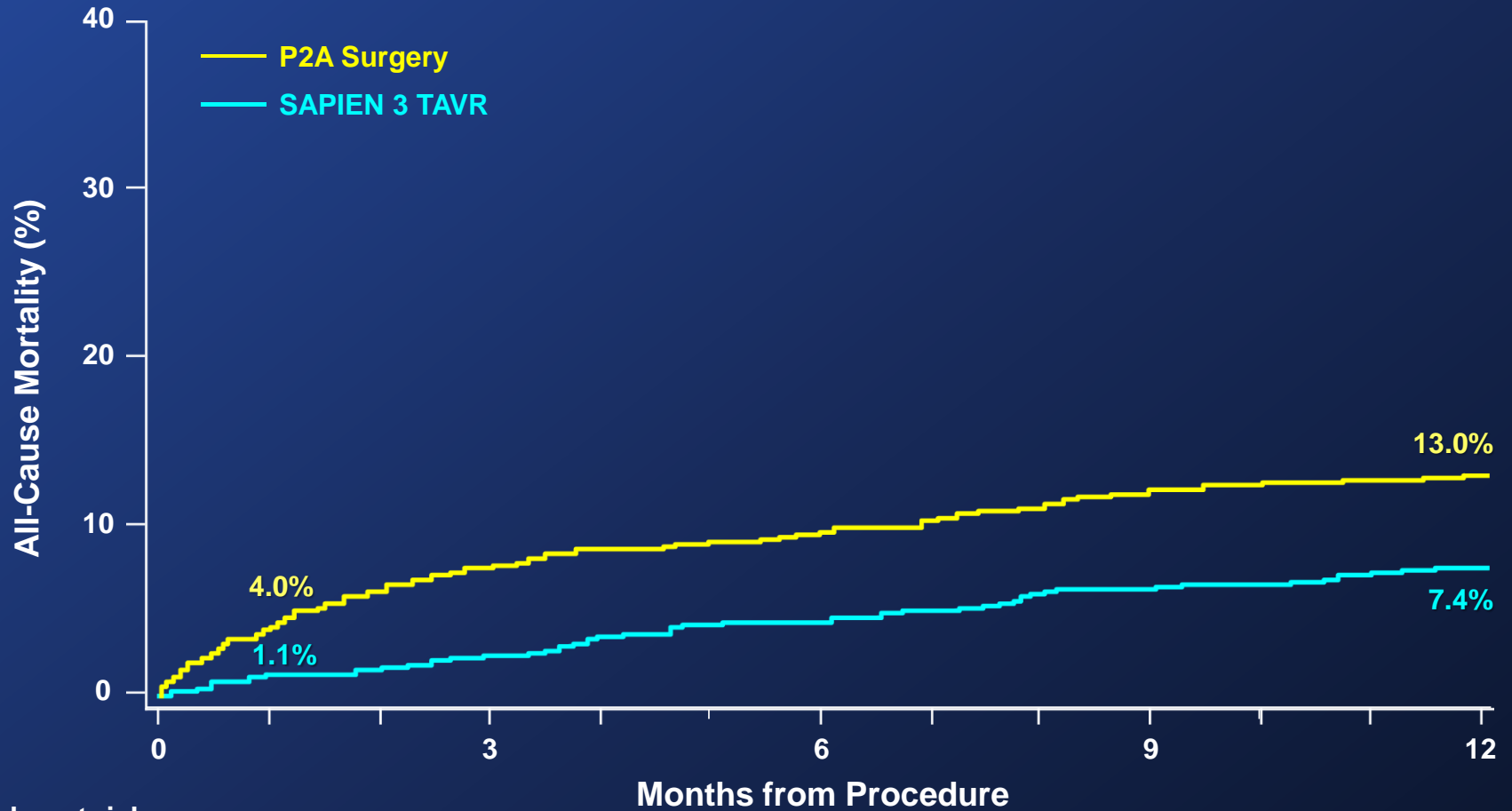


Number at risk:

	0	3	6	9	12
<b>P2A Surgery</b>	<b>944</b>	<b>805</b>	<b>786</b>	<b>757</b>	<b>743</b>
<b>S3 TAVR</b>	<b>1077</b>	<b>1012</b>	<b>987</b>	<b>962</b>	<b>930</b>

# Unadjusted Time-to-Event Analysis

## All-Cause Mortality (AT)



Number at risk:

P2A Surgery 944

S3 TAVR 1077

859

1043

836

1017

808

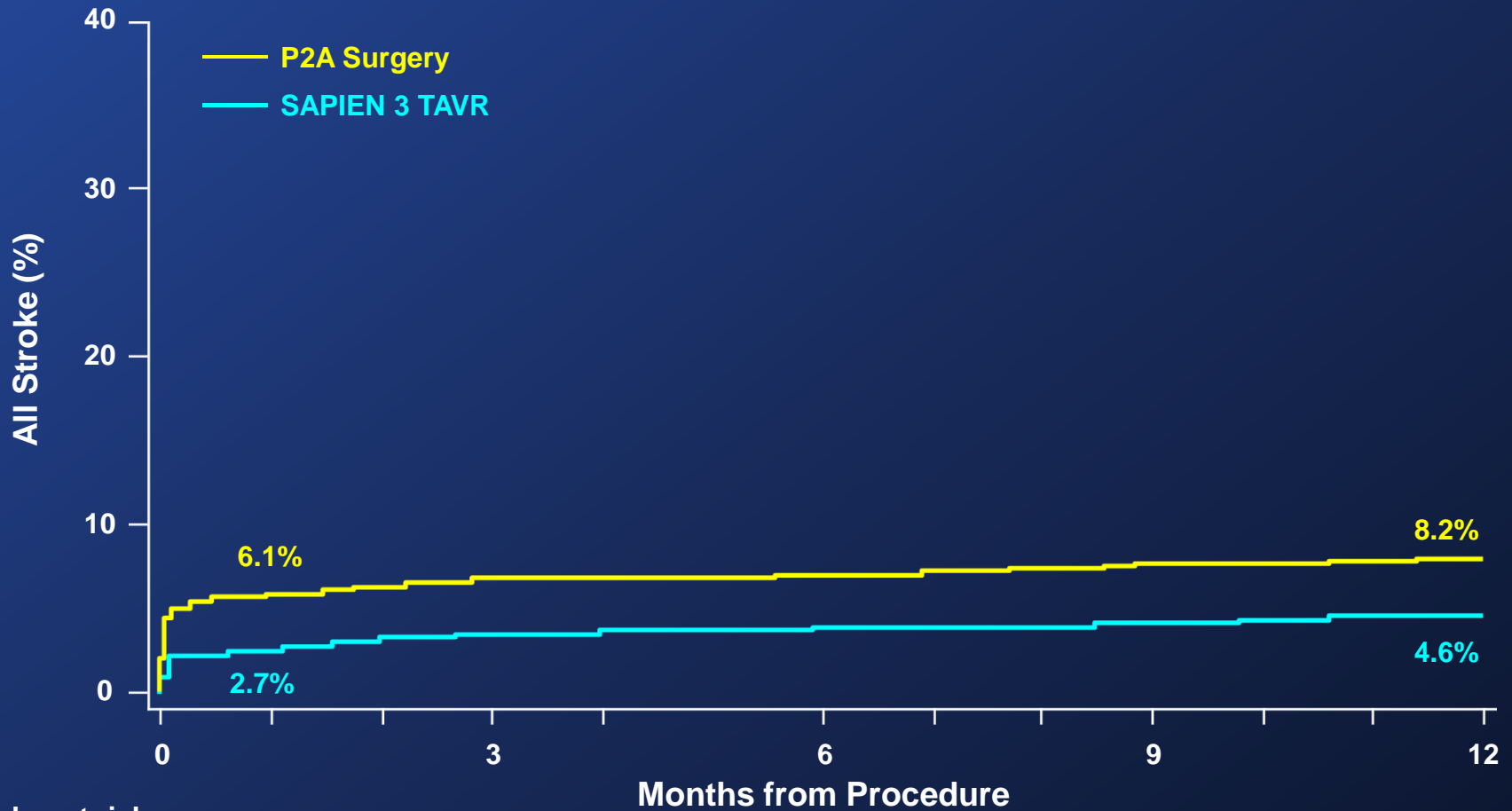
991

795

963

# Unadjusted Time-to-Event Analysis

## All Stroke (AT)



Number at risk:

**P2A Surgery** 944  
**S3 TAVR** 1077

**805**  
**1012**

**786**  
**987**

**757**  
**962**

**743**  
**930**

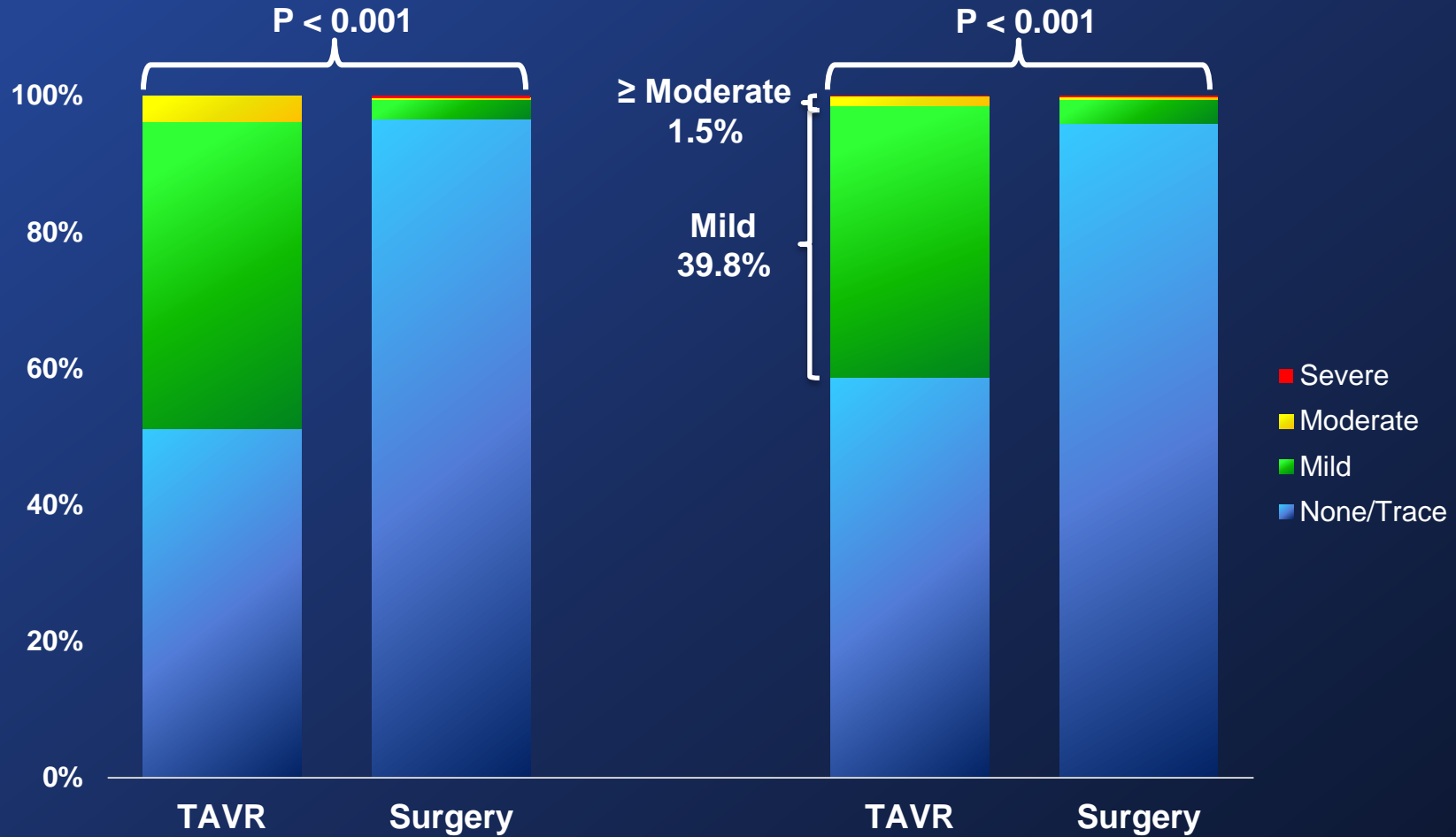
# Other Unadjusted Clinical Outcomes

## At 30 Days and 1 Year (AT)



Events (%)	30 Days		1 Year	
	TAVR (n = 1077)	Surgery (n = 944)	TAVR (n = 1077)	Surgery (n = 944)
Re-hospitalization	4.6	6.8	11.4	15.1
MI	0.3	1.9	1.8	3.1
Major Vascular Complication	6.1	5.4	---	---
AKI (Stage III)	0.5	3.3	---	---
Life-Threat/Disabling Bleeding	4.6	46.7	---	---
New Atrial Fibrillation	5.0	28.3	5.9	29.2
New Permanent Pacemaker	10.2	7.3	12.4	9.4
Re-intervention	0.1	0.0	0.6	0.5
Endocarditis	0.2	0.0	0.8	0.7

# Paravalvular Regurgitation 3-Class Grading Scheme (VI)



No. of echos

30 Days

1 Year

P2A Surgery

755

610

S3i TAVR

992

875



# The PARTNER 2A and S3i Trials

## Conclusions



- A propensity score analysis comparing SAPIEN 3 TAVR with surgery from PARTNER 2A in intermediate-risk patients at 1 year demonstrated:
  - Non-inferiority for the primary endpoint (composite of all-cause mortality, all stroke, or AR  $\geq$  moderate)
  - Superiority of SAPIEN 3 TAVR for the primary endpoint, all-cause mortality, and all stroke
  - Superiority of surgery for AR  $\geq$  moderate
- Time-to-event analyses indicated that the benefits of SAPIEN 3 TAVR occurred in the first few months, suggesting procedure-related effects

# The PARTNER 2A and S3i Trial

## Clinical Implications



- The results from the PARTNER 2A randomized trial and the S3i propensity score analysis in > 3,100 intermediate-risk patients with severe aortic stenosis, provide strong evidence that SAPIEN 3 TAVR when compared with surgery improves clinical outcomes and is the preferred therapy!

# The PARTNER 2A and S3i Trial

## The NEJM and Lancet On-line



The NEW ENGLAND  
JOURNAL of MEDICINE

ORIGINAL ARTICLE

### Transcatheter aortic valve replacement versus surgical valve replacement in intermediate-risk patients: a propensity score analysis



*Vinod H Hourani, Susheel Kodali, Raj R Makkar, Howard C Herrmann, Mathew Williams, Vasilis Babaliaros, Richard Smalling, Scott Lim, S Chris Malaisrie, Samir Kapadia, Wilson Y Szeto, Kevin L Greason, Dean Kereiakes, Gorav Ailawadi, Brian K Whisenant, Chandan Devireddy, Jonathon Leipsic, Rebecca T Hahn, Philippe Pibarot, Neil J Weissman, Wael A Jaber, David J Cohen, Rakesh Suri, E Murat Tuzcu, Lars G Svensson, John G Webb, Jeffrey W Moses, Michael J Mack, D Craig Miller, Craig R Smith, Maria C Alu, Rupa Parvataneni, Ralph B D'Agostino Jr, Martin B Leon*

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\*