

# *SAPIEN 3*

## *Clinical Update*

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21<sup>st</sup> CardioVascular Summit

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13 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

# SAPIEN 3 Clinical Update

## System Summary

# Evolution of Balloon-Expandable Transcatheter Valves



Cribier-Edwards

2002



SAPIEN

2006



SAPIEN XT

2009



SAPIEN 3

2013



24F



22F



16F



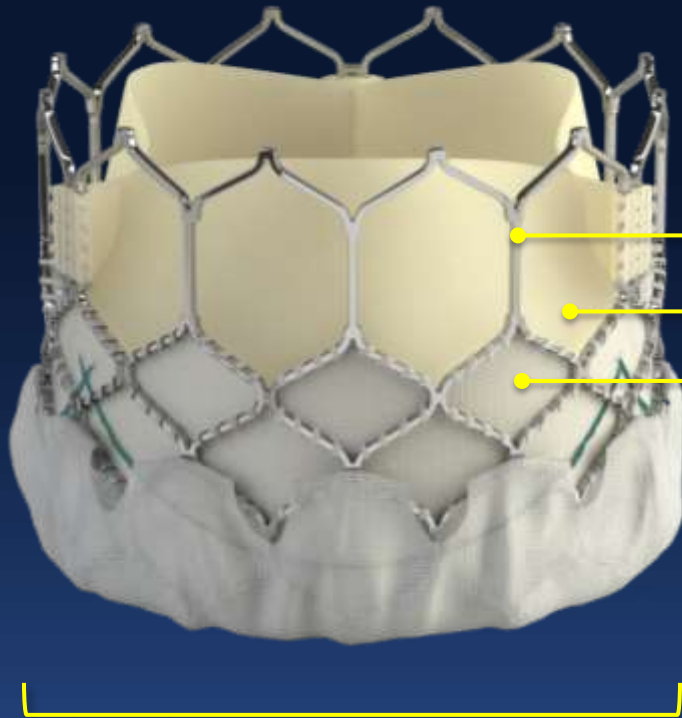
14F

\* Sheath compatibility for a 23 mm valve

# SAPIEN 3 THV

## Low frame height

- Respects the cardiac anatomy



## Frame design

- Enhanced frame geometry for low delivery profile
- High radial strength for circularity

## Bovine pericardial tissue

- Scalloped leaflet shape
- CE ThermaFix\* process is intended to minimize the risk of calcification

## Inner Skirt

- Polyethylene terephthalate (PET)

## Outer skirt

- PET outer skirt designed to reduce paravalvular leak

# SAPIEN 3 Sizing Guidelines



Specifications		20 mm	23 mm	26 mm	29 mm
Native Valve Annulus Size (CT)	Area				540–683 mm <sup>2</sup>
	Area Diameter				26.2–29.5 mm
Native Valve Annulus Size (TEE)		18–19 mm	19–22 mm	21–25 mm	24–28 mm

Borderline sizes = "Size UP"



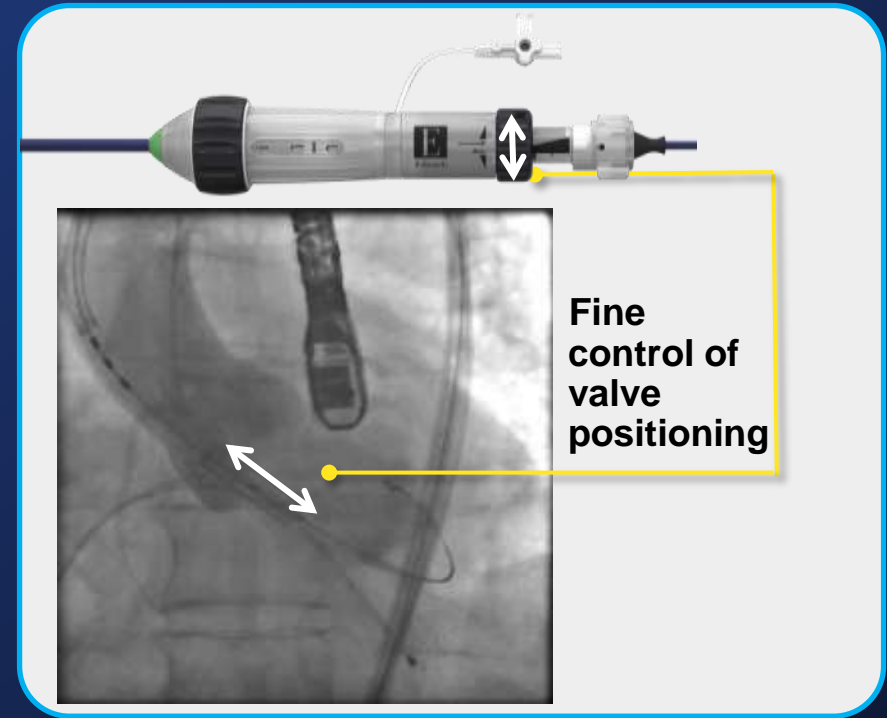
# SAPIEN 3 Commander Delivery System Distinguishing Features



- Improved coaxial alignment



- Accurate positioning



<b>SAPIEN 3 Valve Size</b>	<b>20 mm</b>	<b>23 mm</b>	<b>26 mm</b>	<b>29 mm</b>
<b>Expandable Sheath</b>	14F	14F	14F	16F
<b>Minimum Access Vessel Diameter</b>	5.5 mm	5.5 mm	5.5 mm	6.0 mm

# SAPIEN 3 Clinical Update

## Clinical Studies





## 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

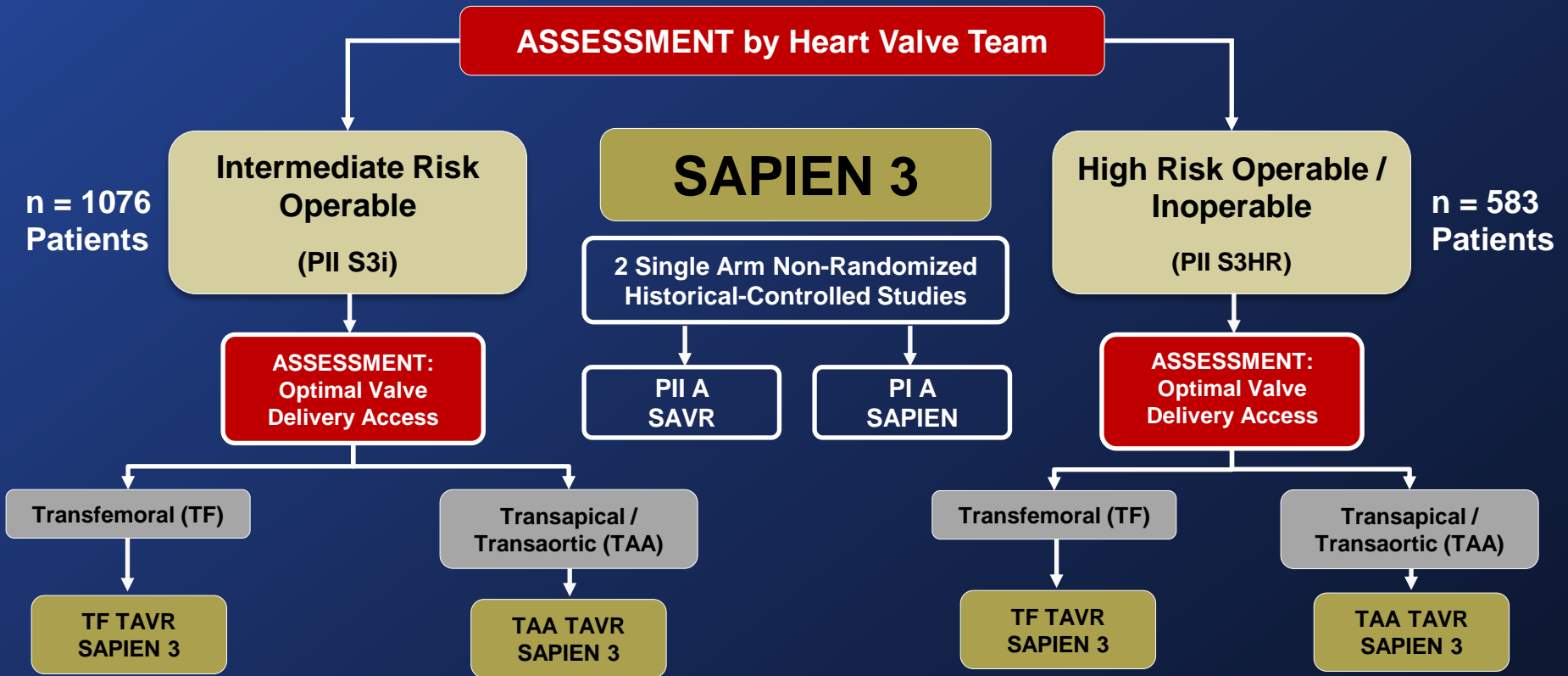


# The PARTNER II S3 Trial

## Study Design



Symptomatic Severe Aortic Stenosis



# Baseline Patient Characteristics

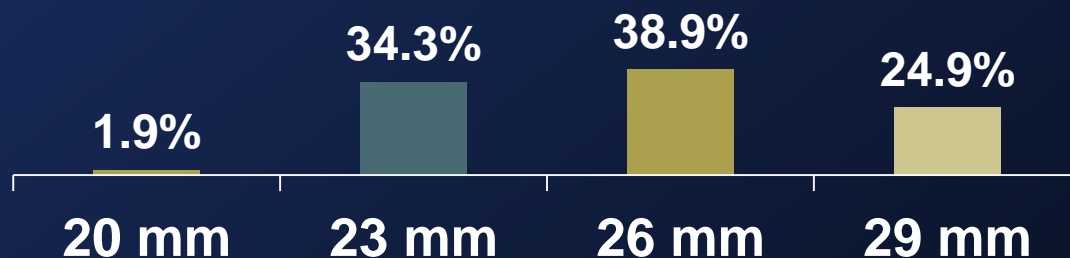
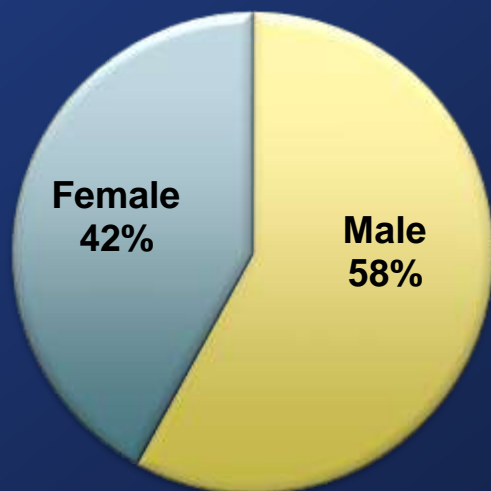
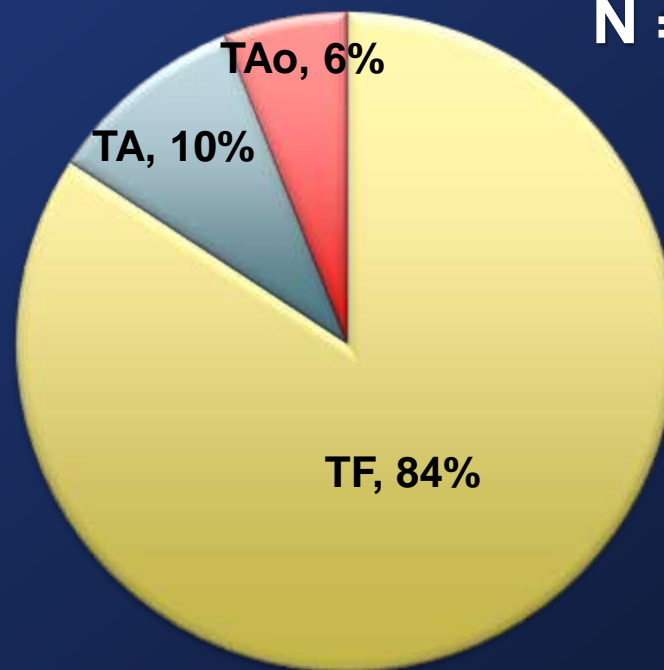
## S3HR Patients (n=583 at 29 sites)



Average STS =  
**8.6%**  
(Median 8.4%)

Average Age =  
**82.6yrs**

**N = 583**

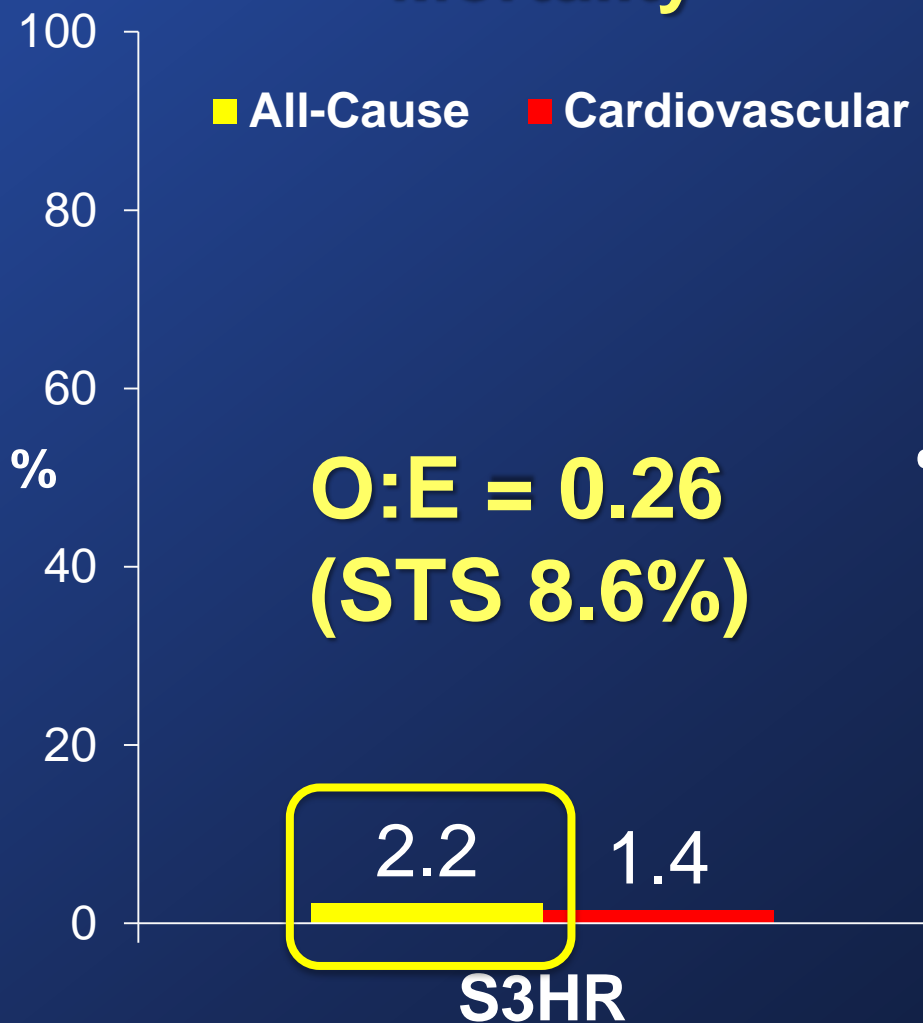


# Mortality and Stroke: S3HR

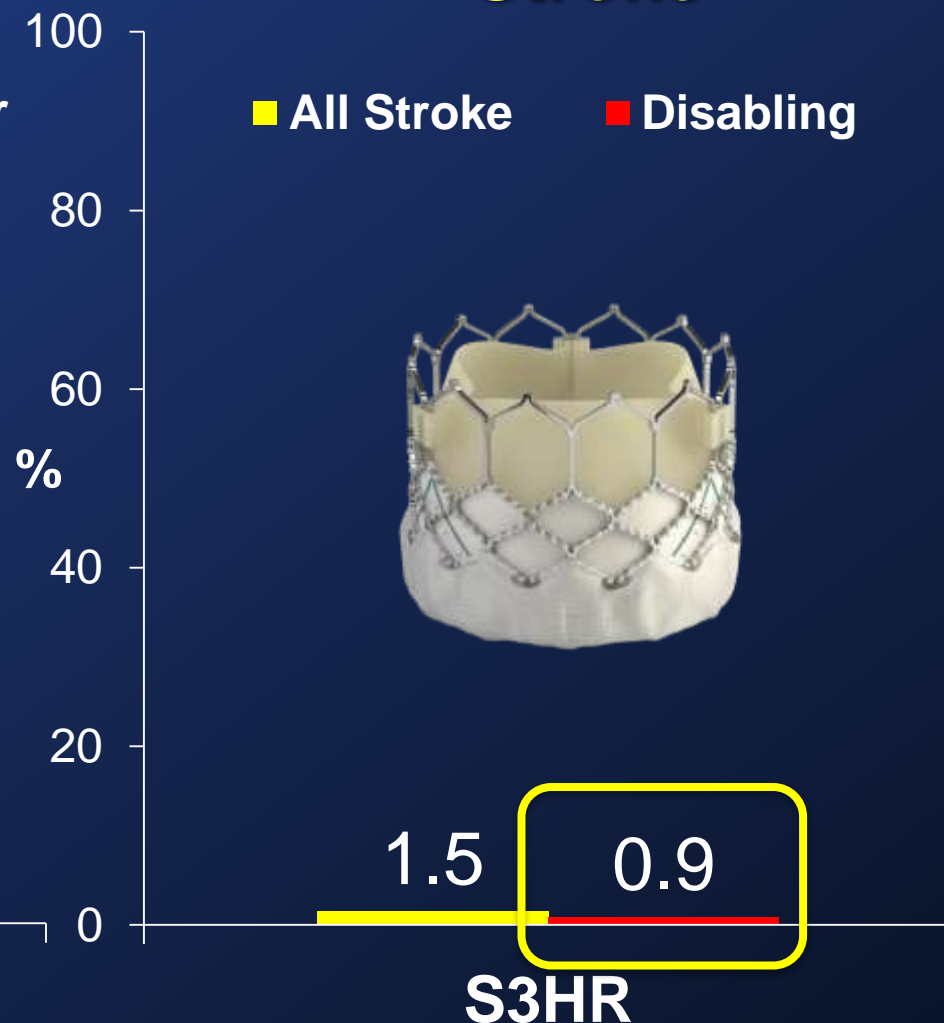
At 30 Days (As Treated Patients)



## Mortality



## Stroke



# Baseline Patient Characteristics

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



THE  
PARTNER II  
TRIAL

Average STS =

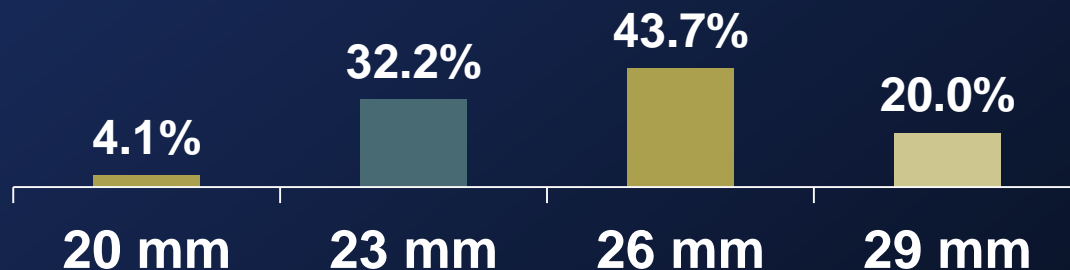
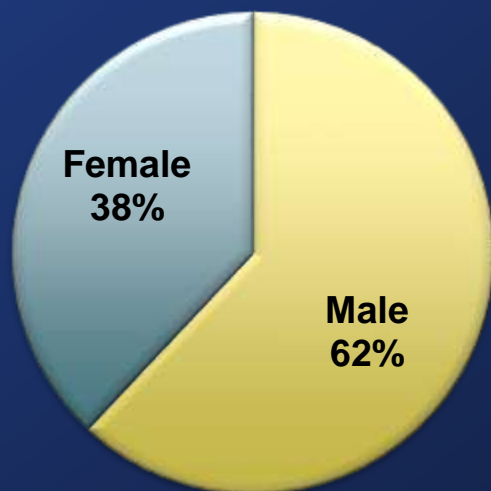
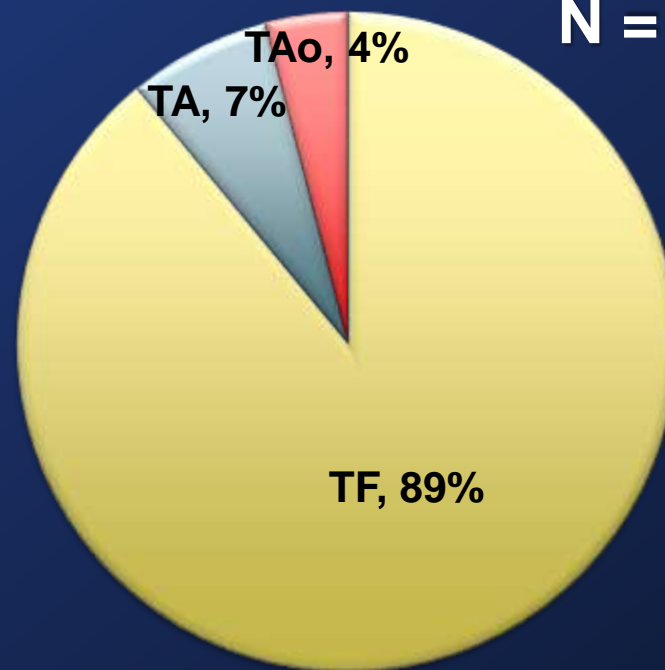
**5.3%**

(Median 5.2%)

Average Age =

**81.9yrs**

N = 1076

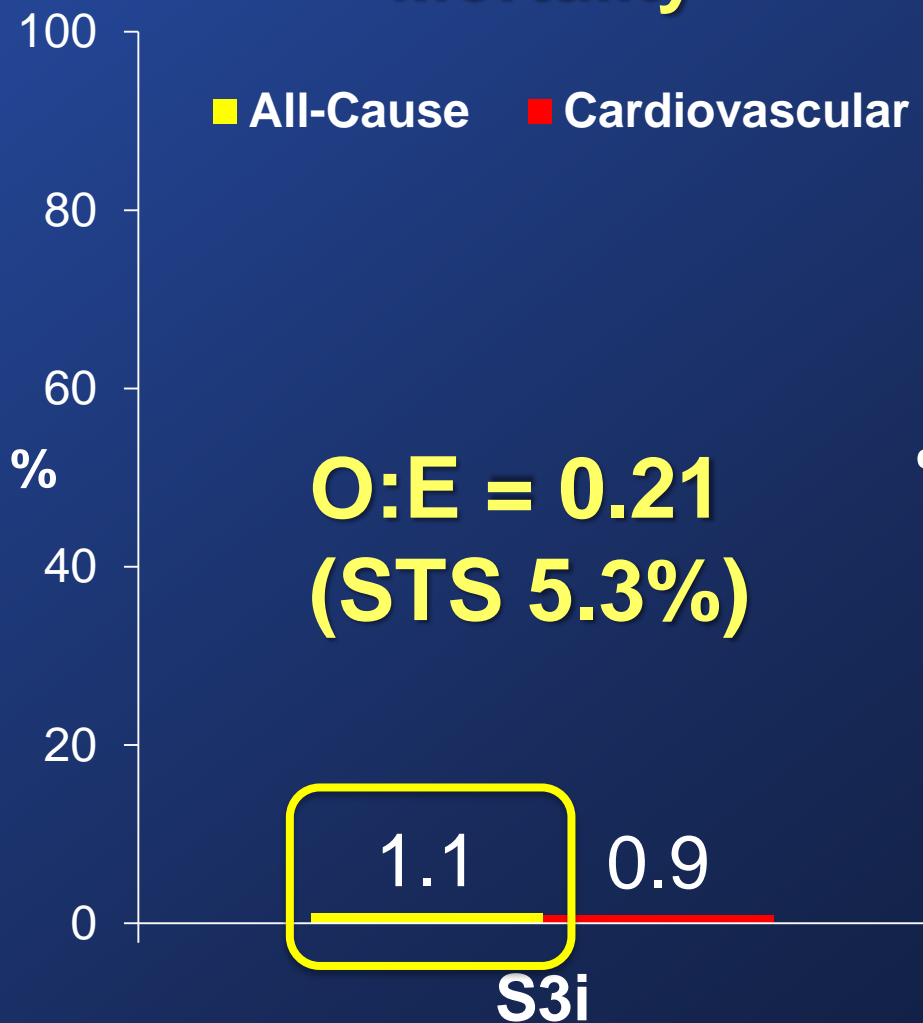


# Mortality and Stroke: S3i

## At 30 Days (As Treated Patients)



### Mortality



### Stroke



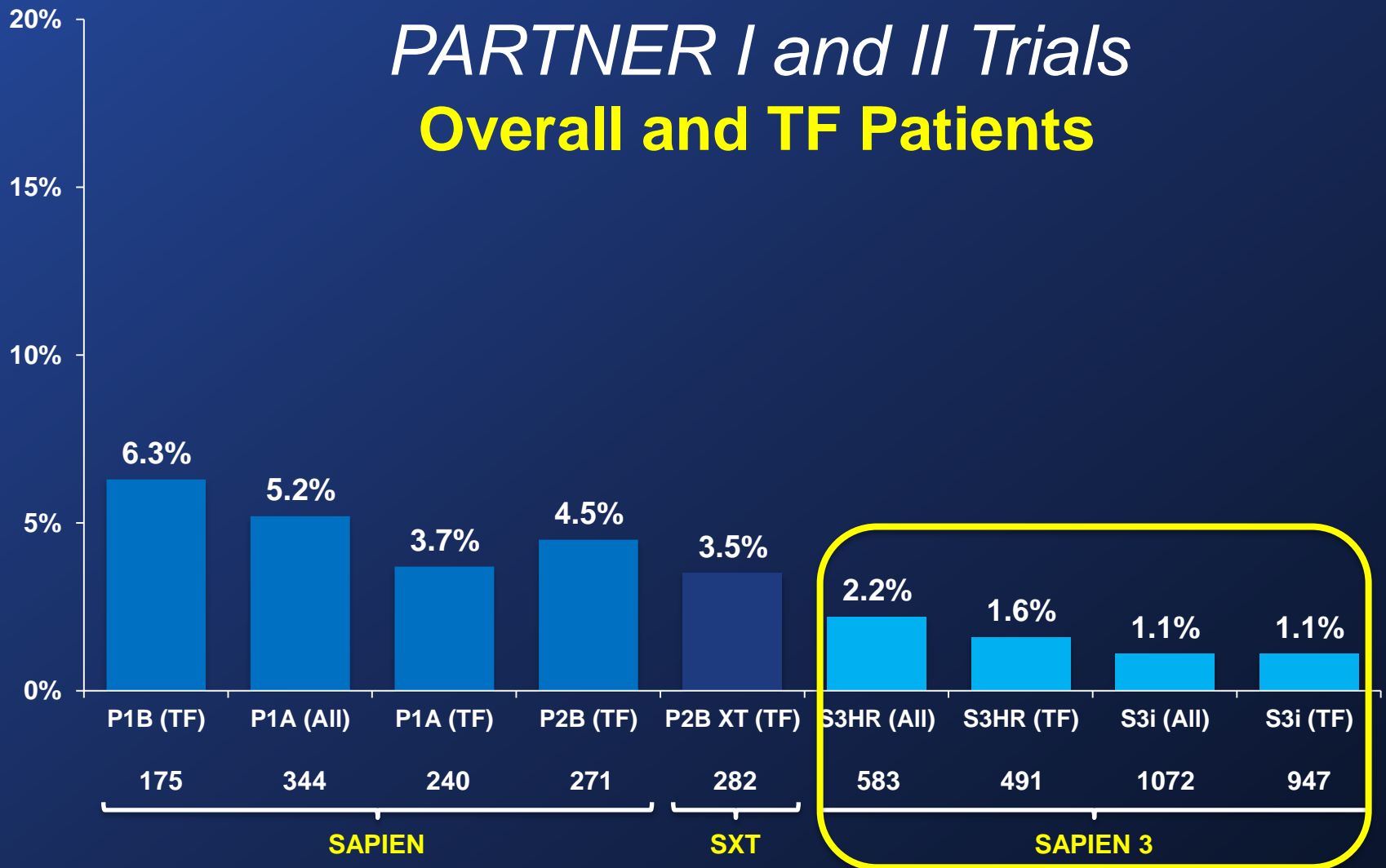
# All-Cause Mortality at 30 Days

## Edwards SAPIEN Valves



### *PARTNER I and II Trials*

## Overall and TF Patients

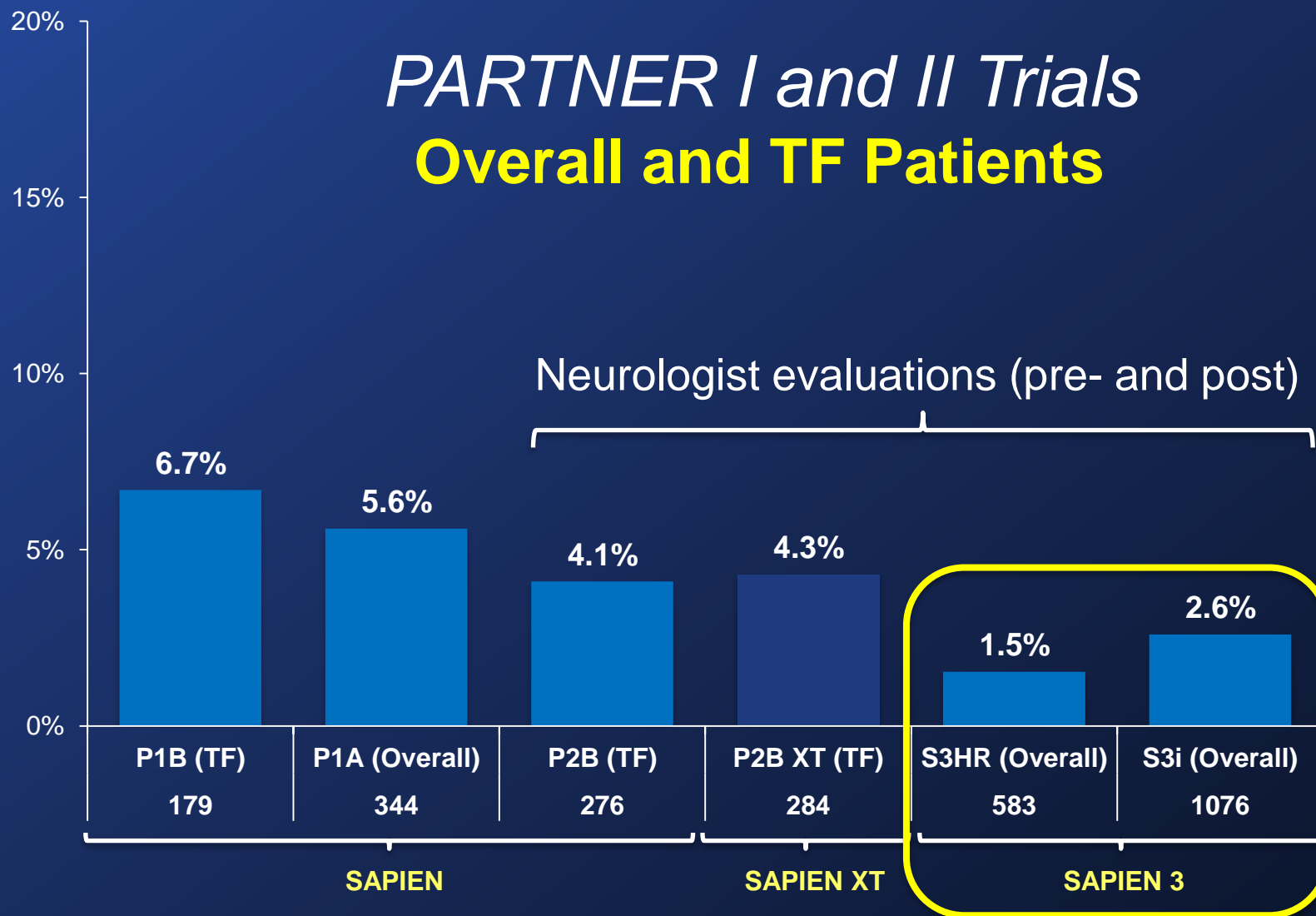


# All Strokes at 30 Days

## Edwards SAPIEN Valves

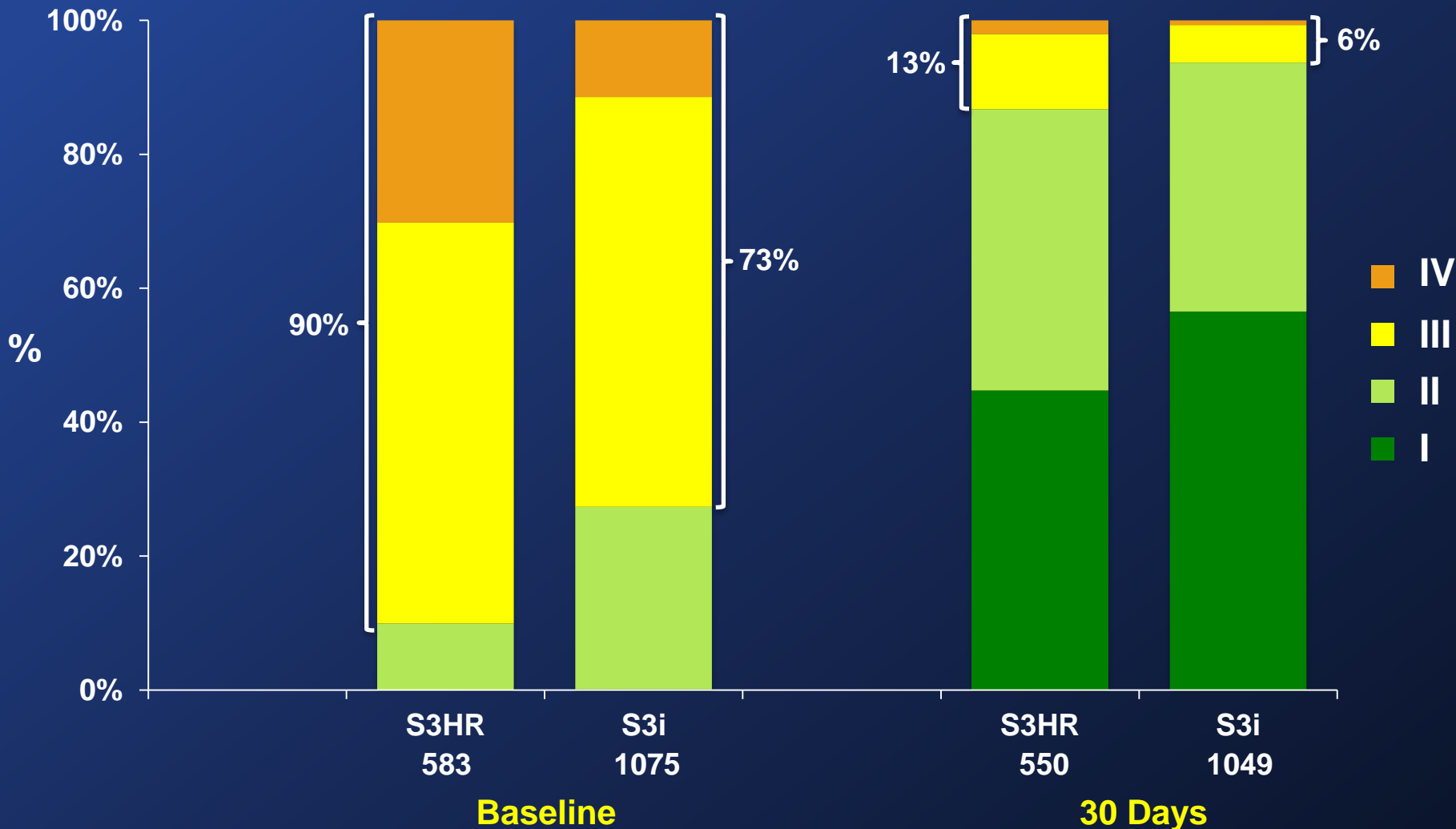


### *PARTNER I and II Trials* **Overall and TF Patients**





# NYHA Functional Class At 30 Days (As Treated Patients)



# S3HR & S3i: Other Outcomes

## Procedure

## Other Clinical Events At 30 Days (As Treated Patients)



Events (%)	S3HR	S3HR	S3HR	S3i	S3i	S3i
	Overall (n=583)	TF (n=491)	TA/TAo (n=92)	Overall (n=1076)	TF (n=951)	TA/TAo (n=125)
Major Vascular Comps.	5.0	5.3	3.3	5.6	5.9	3.2
Bleeding - Life Threatening	6.3	5.5	10.9	5.4	4.4	12.9
Annular Rupture	0.3	0.2	1.1	0.2	0.2	0
Myocardial Infarctions	0.5	0.4	1.1	0.3	0.3	0
Coronary Obstruction	0.2	0	1.1	0.4	0.4	0
Acute Kidney Injury	1.0	0.8	2.2	0.5	0.3	1.6
New Permanent Pacemaker	13.0	13.2	12.0	10.1	10.4	7.2
Aortic Valve Re-intervention	1.0	0.8	2.2	0.7	0.8	0
Endocarditis	0.2	0.2	0	0.1	0.1	0

Post-Dilatation

>1 Valve Impl

Valve Emboliz

IABP During P

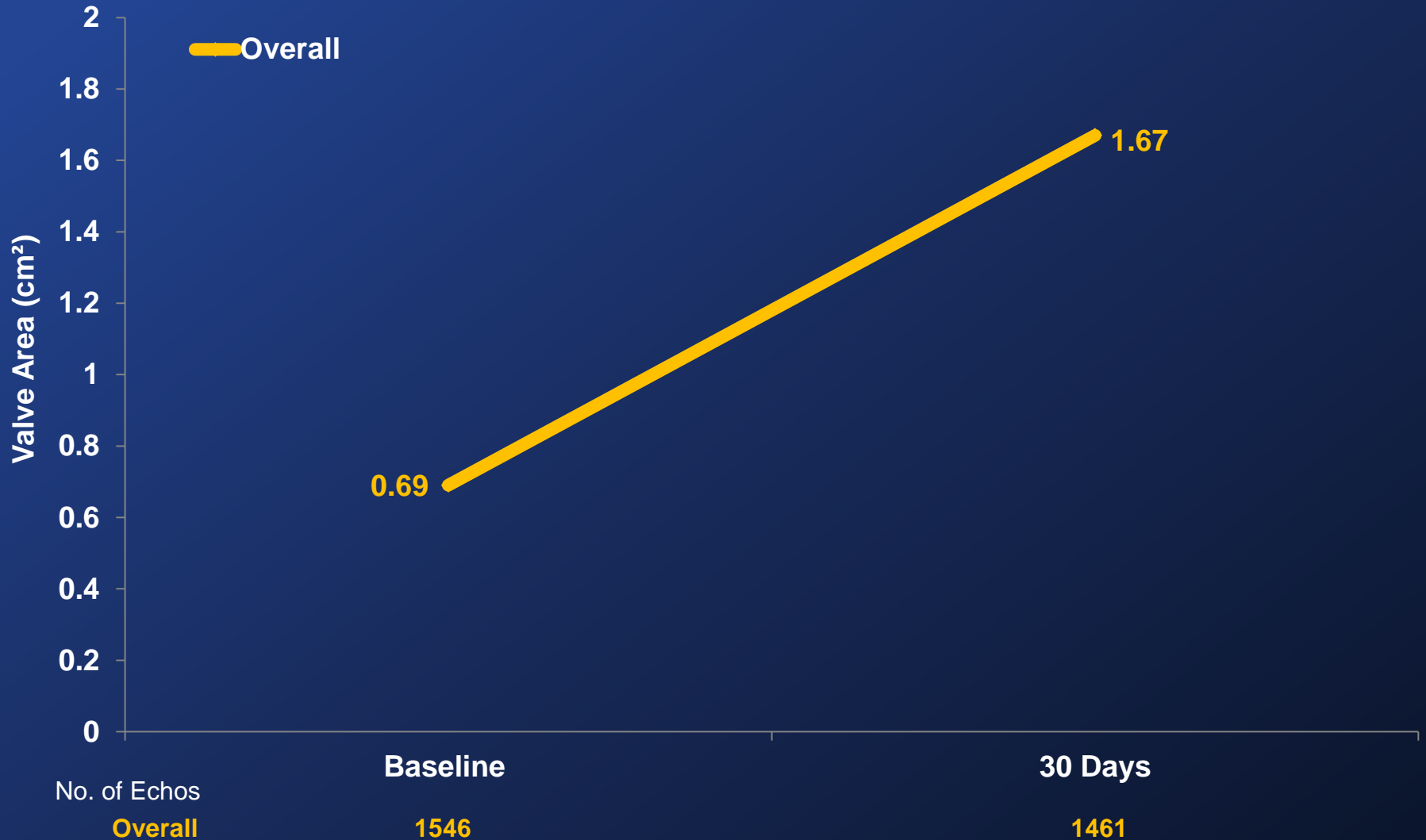
Cardiopulmor

Conscious Se

Median LOS

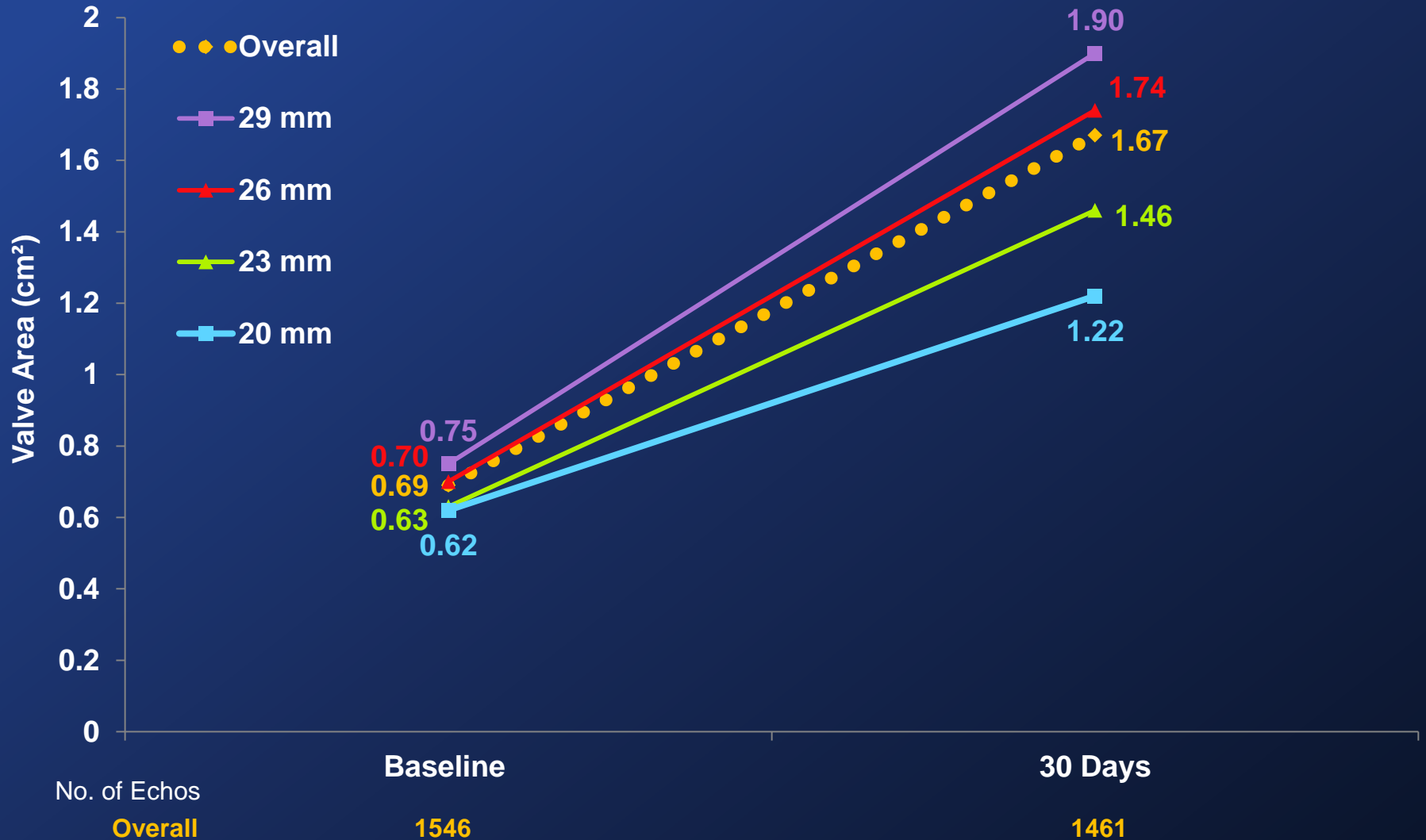
# Echo Findings: S3HR & S3i

## Aortic Valve Area (Valve Implant Patients)



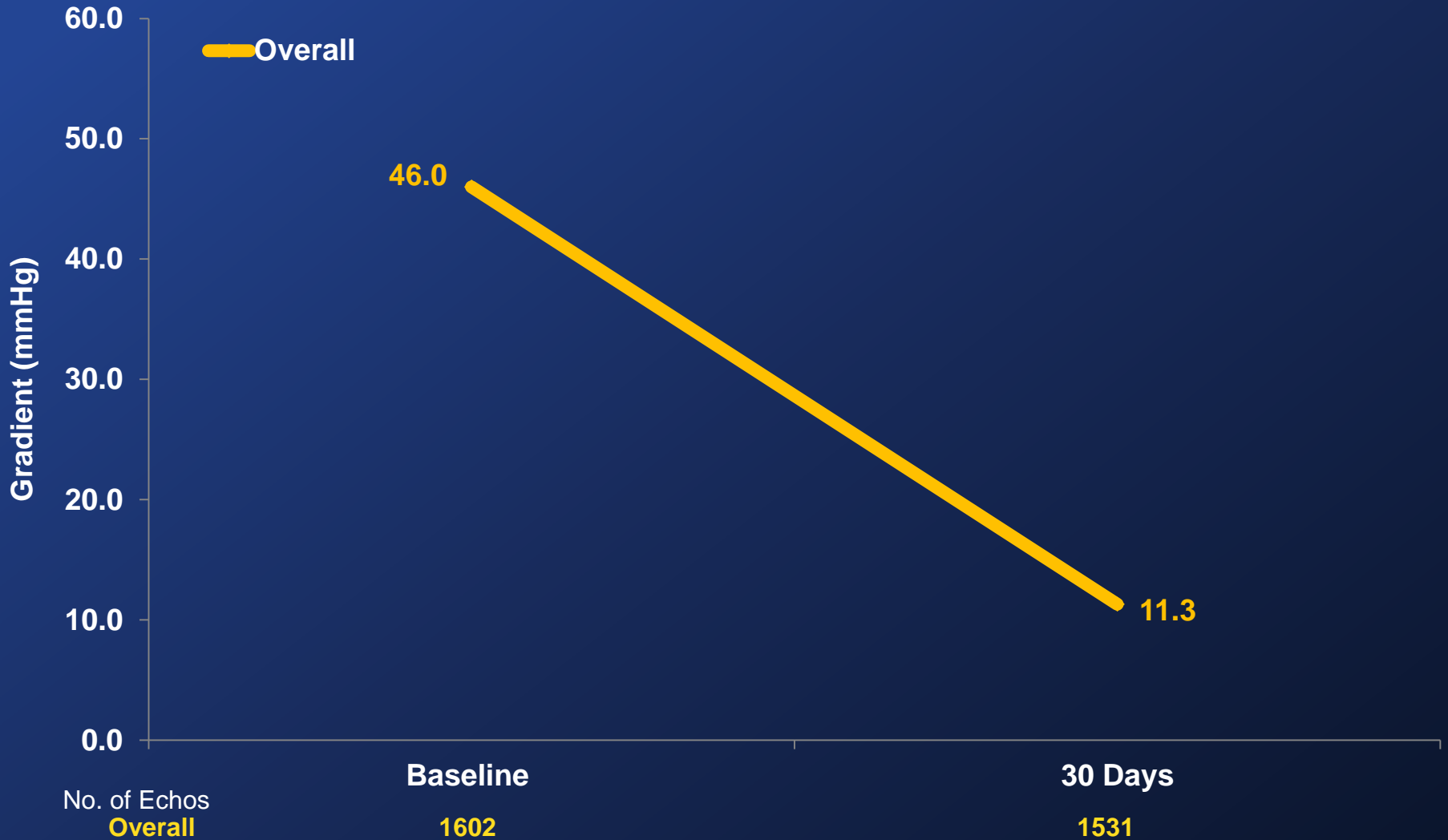
# Echo Findings: S3HR & S3i

## Aortic Valve Area (Valve Implant Patients)



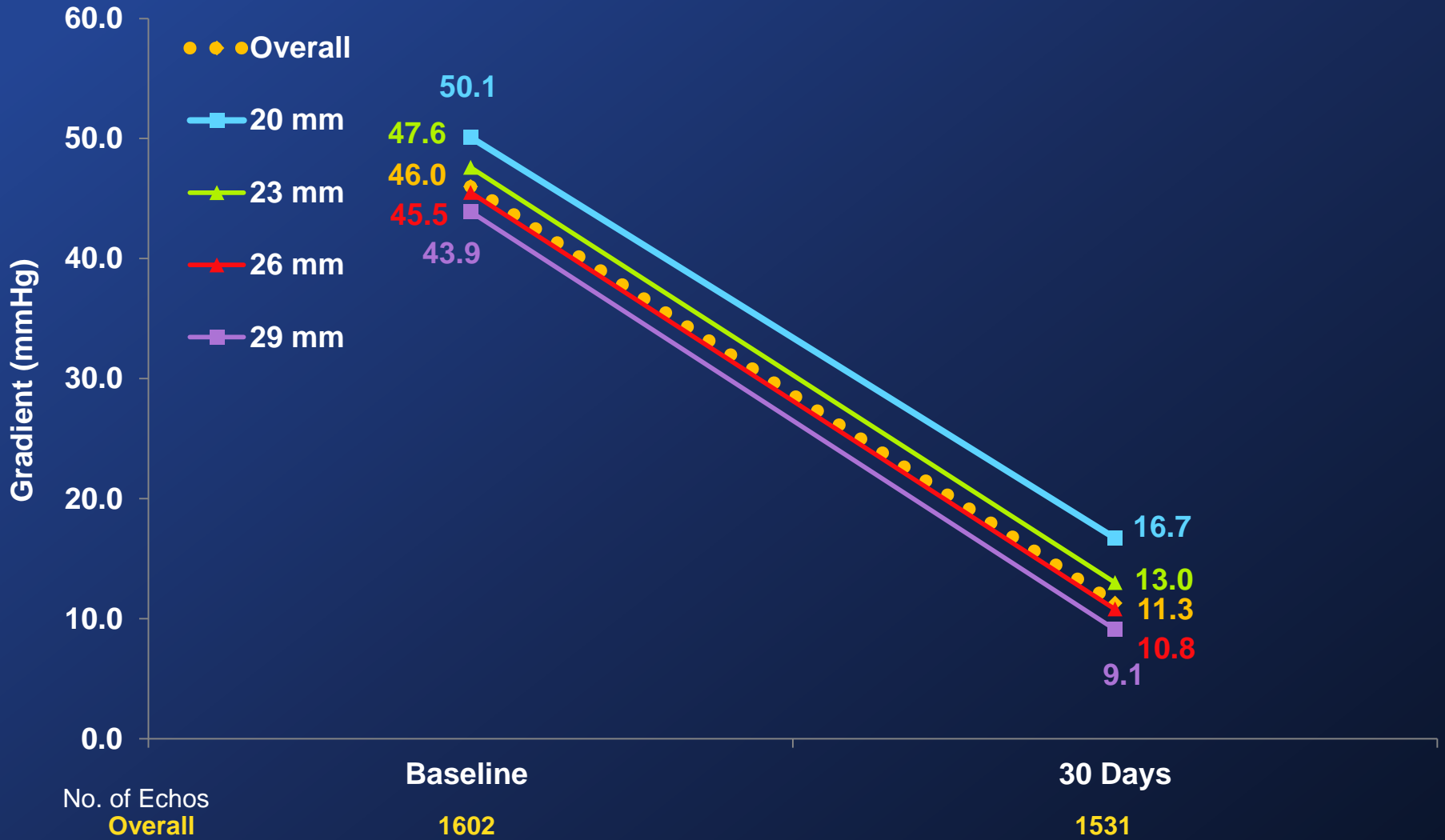
# Echo Findings: S3HR & S3i

## Mean Gradients (Valve Implant Patients)

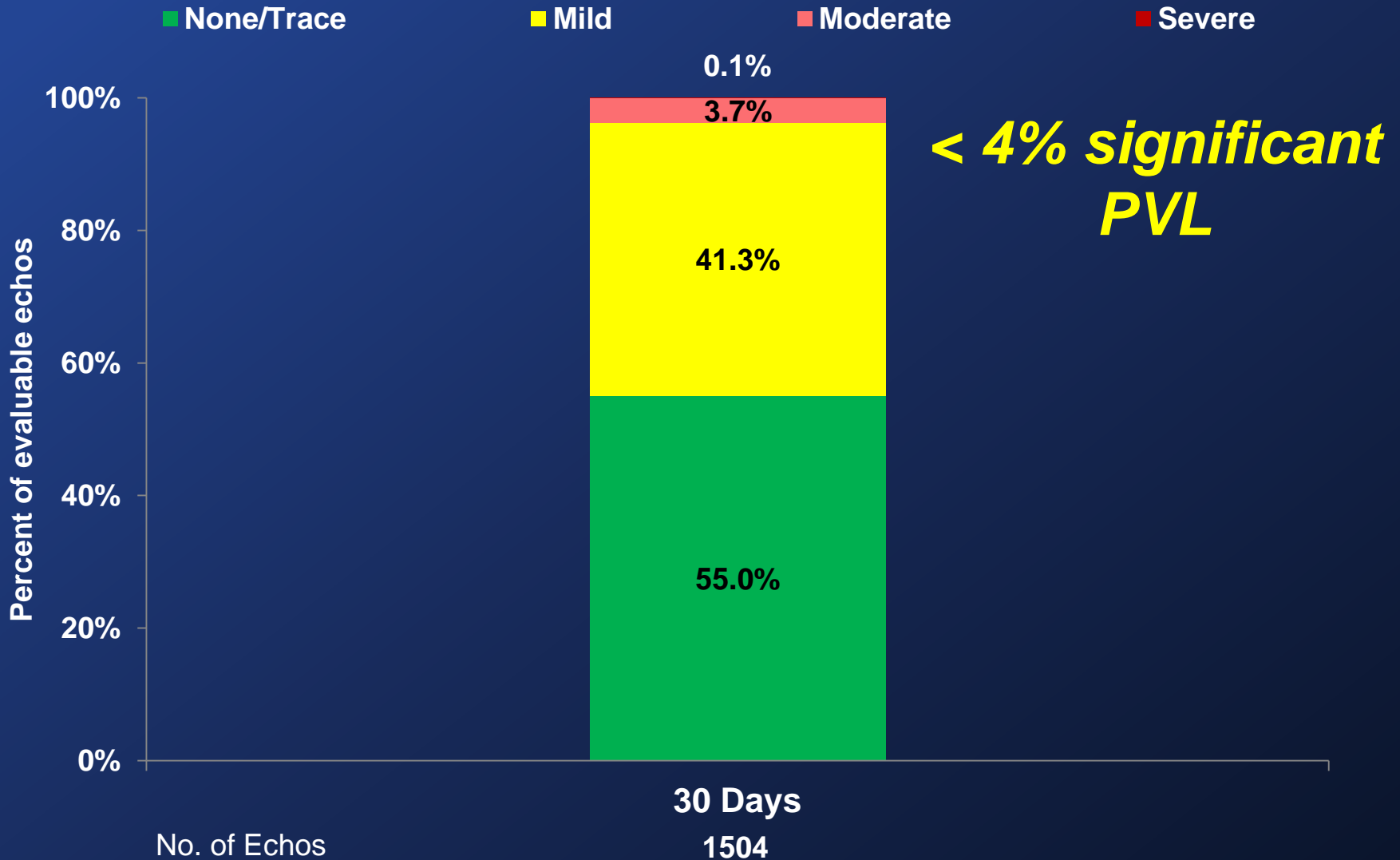


# Echo Findings: S3HR & S3i

## Mean Gradients (Valve Implant Patients)



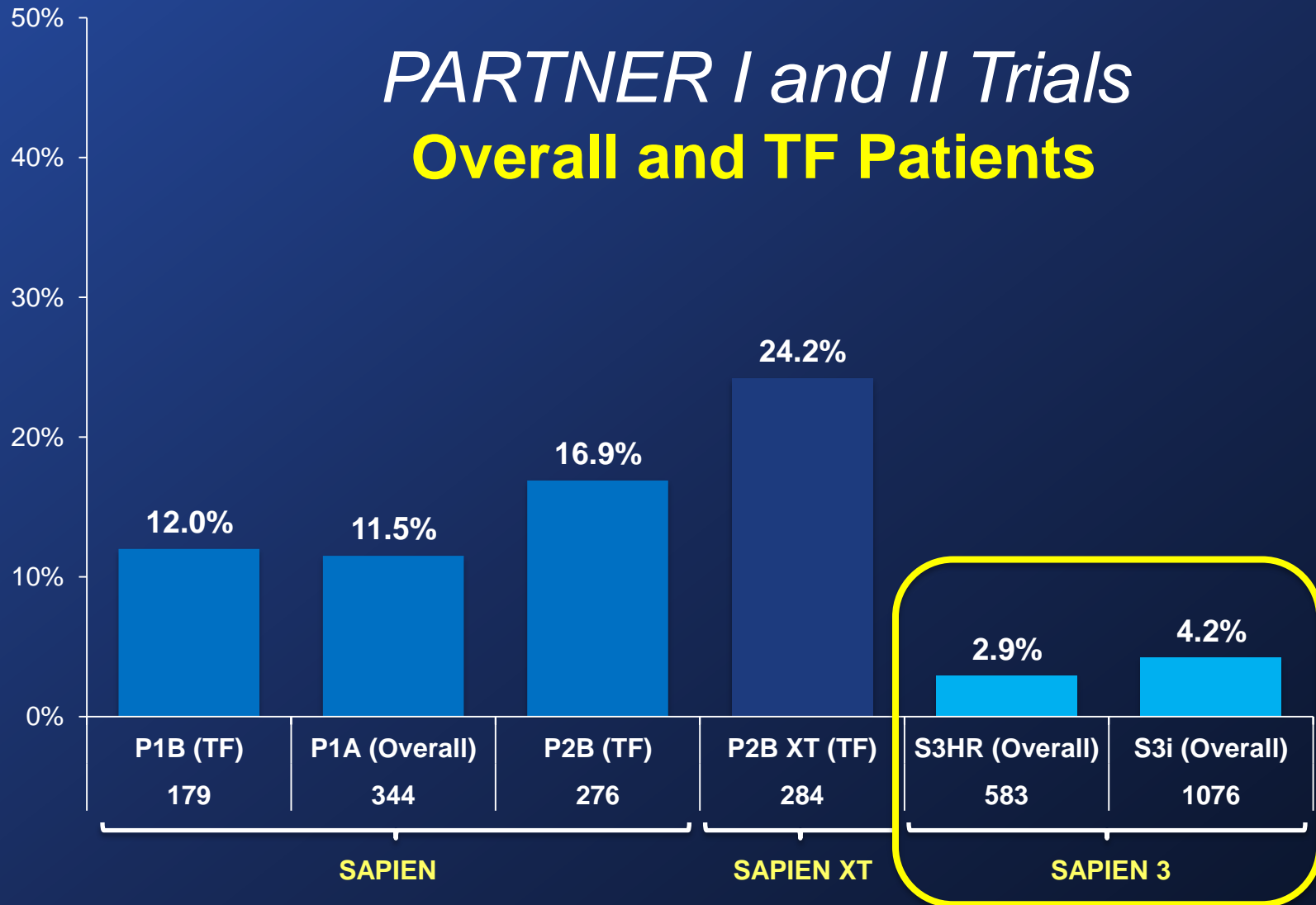
# Paravalvular Leak: S3HR & S3i (Valve Implant Patients)



# Moderate/Severe PVL at 30 Days Edwards SAPIEN Valves



## *PARTNER I and II Trials* Overall and TF Patients



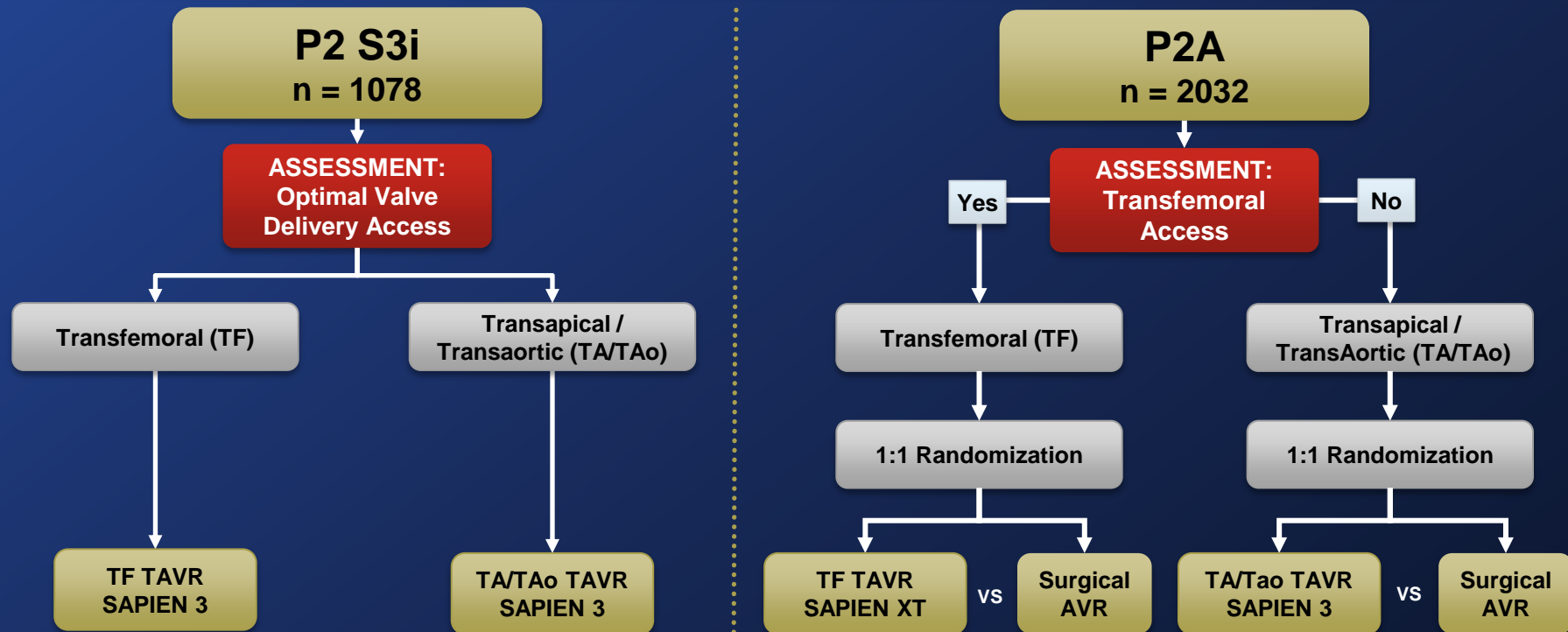


# The PARTNER 2A and S3i Trials Study Design



Intermediate Risk Symptomatic Severe Aortic Stenosis

Intermediate Risk ASSESSMENT by Heart Valve Team

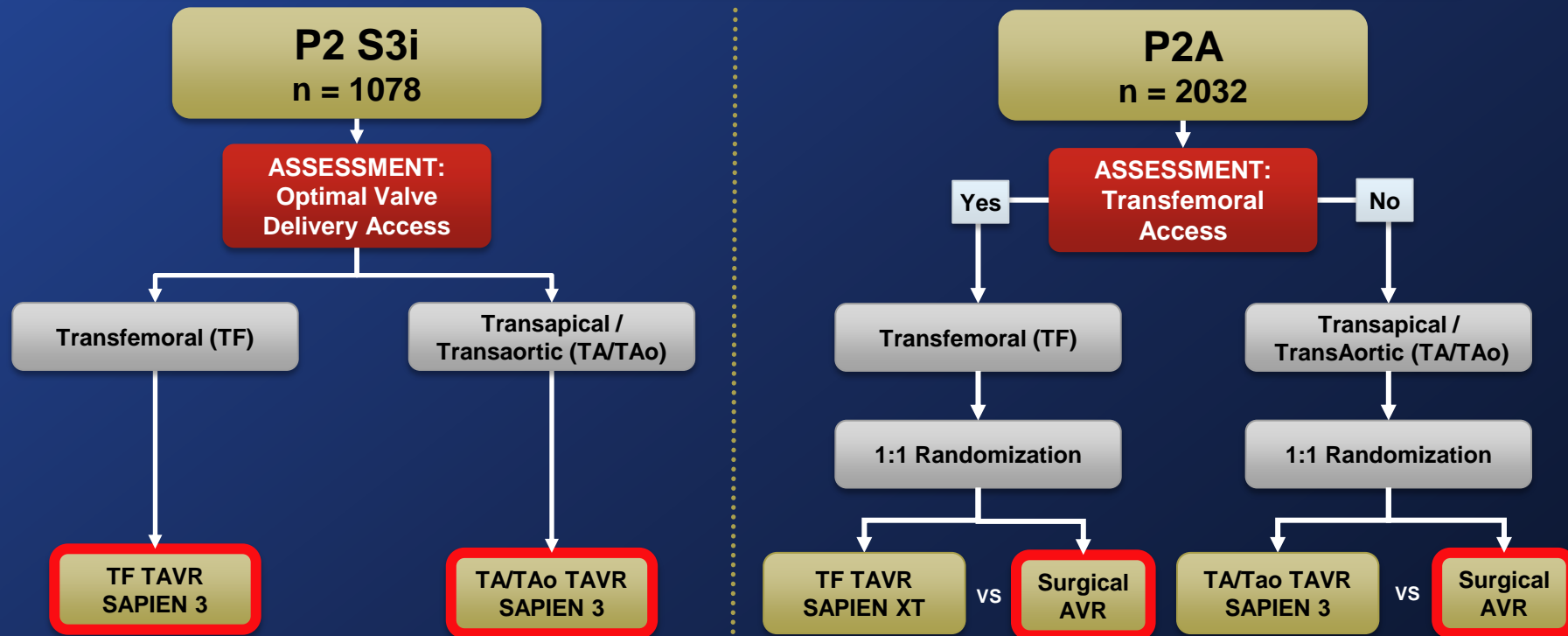


# The PARTNER 2A and S3i Trials Study Design



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]

# 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

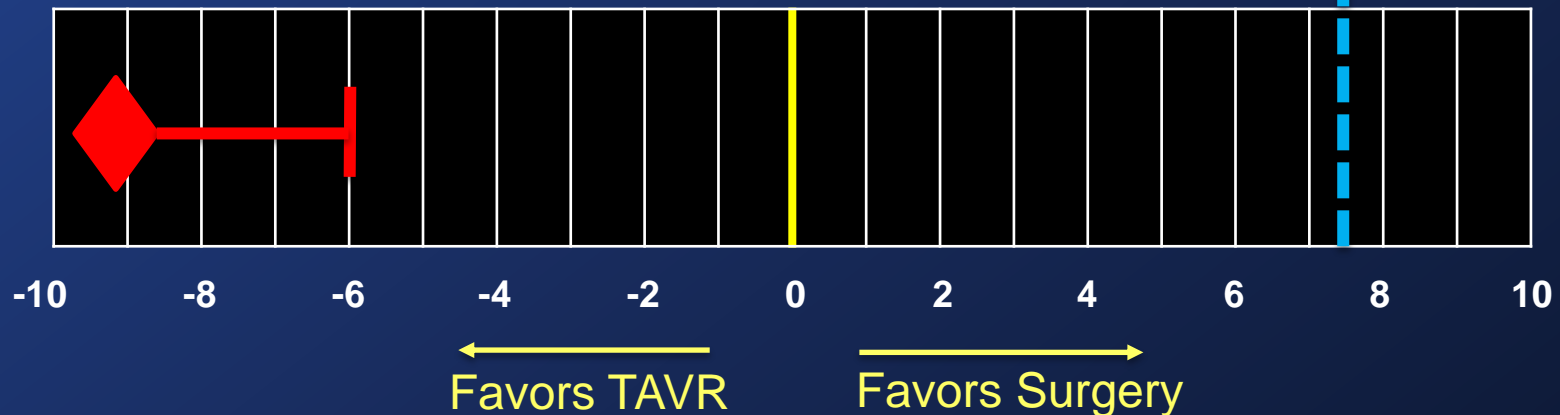
Death, Stroke, or AR  $\geq$  Mod at 1 Year (VI)



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

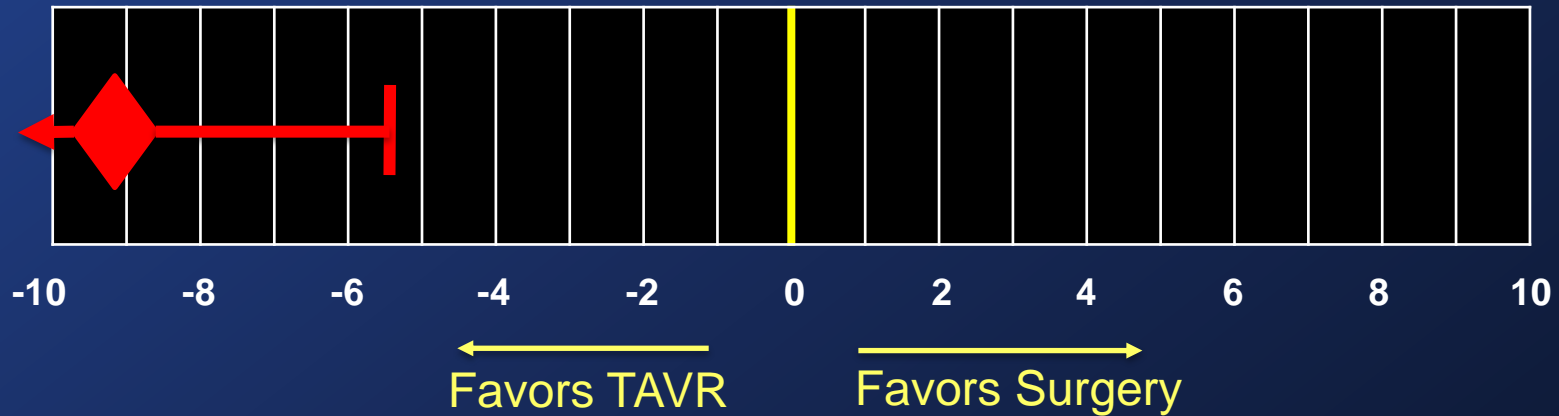
# Primary Endpoint - Superiority

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)

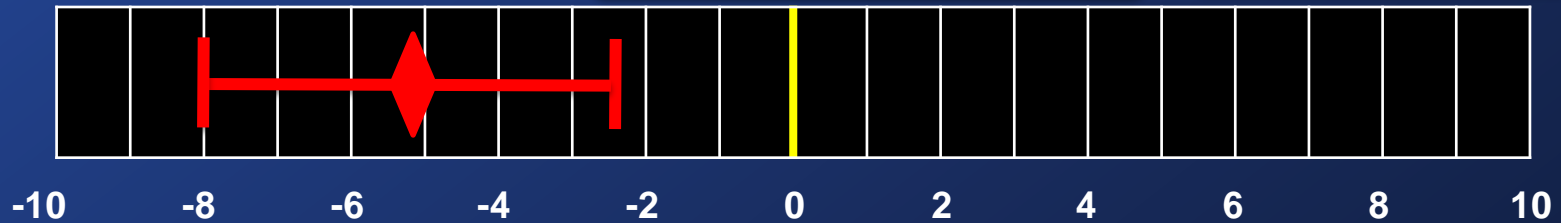


← Favors TAVR      Favors Surgery →

### Mortality

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

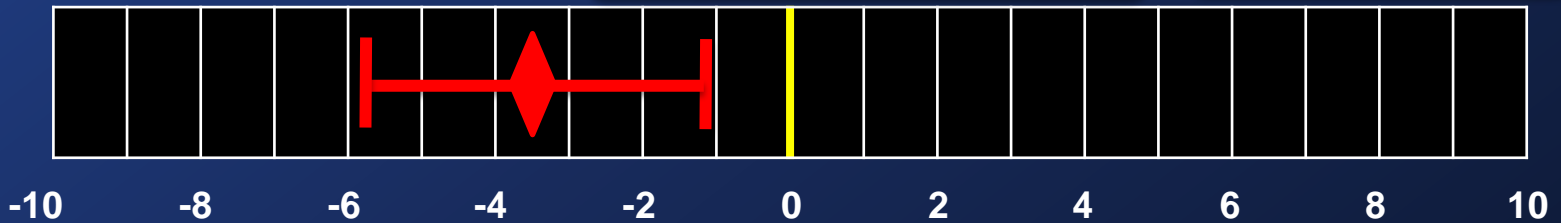
Superiority Testing  
p-value < 0.001



### Stroke

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

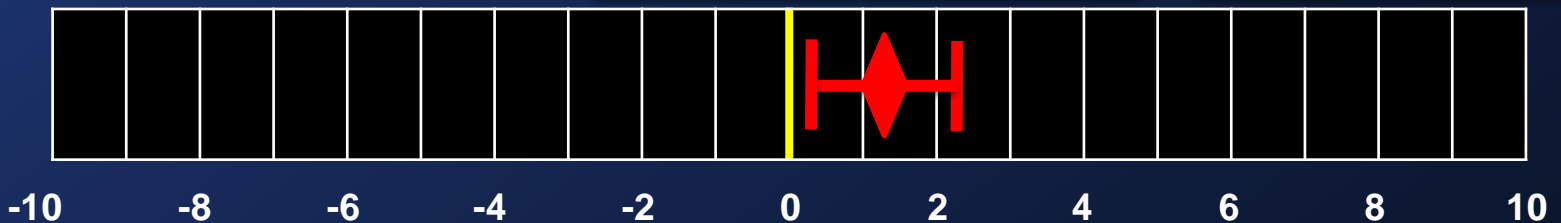
Superiority Testing  
p-value = 0.004



### AR ≥ Moderate

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

Superiority Testing  
p-value = 0.0149





# Unadjusted Clinical Events

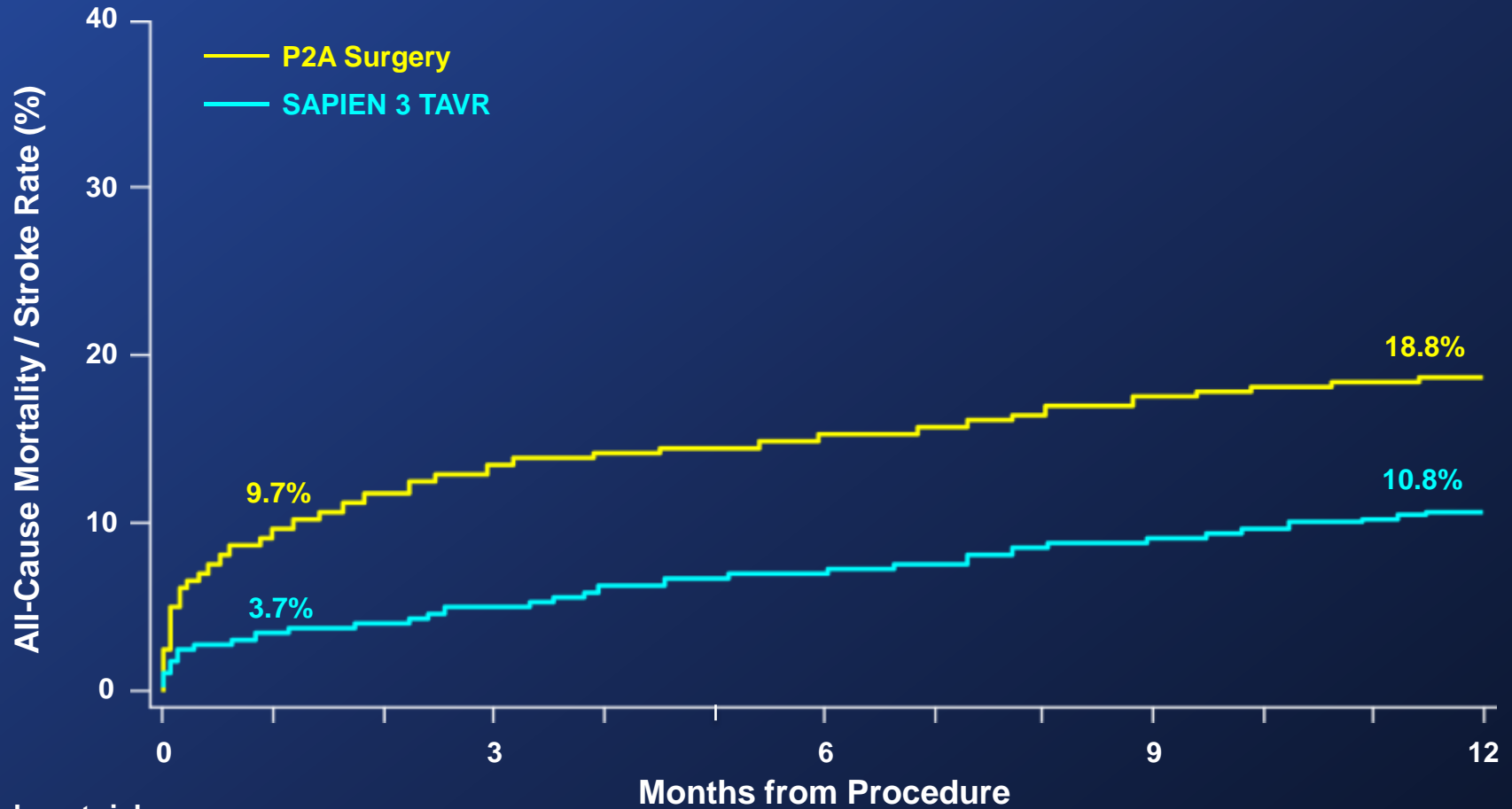
## At 30 Days and 1 Year (AT)



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)

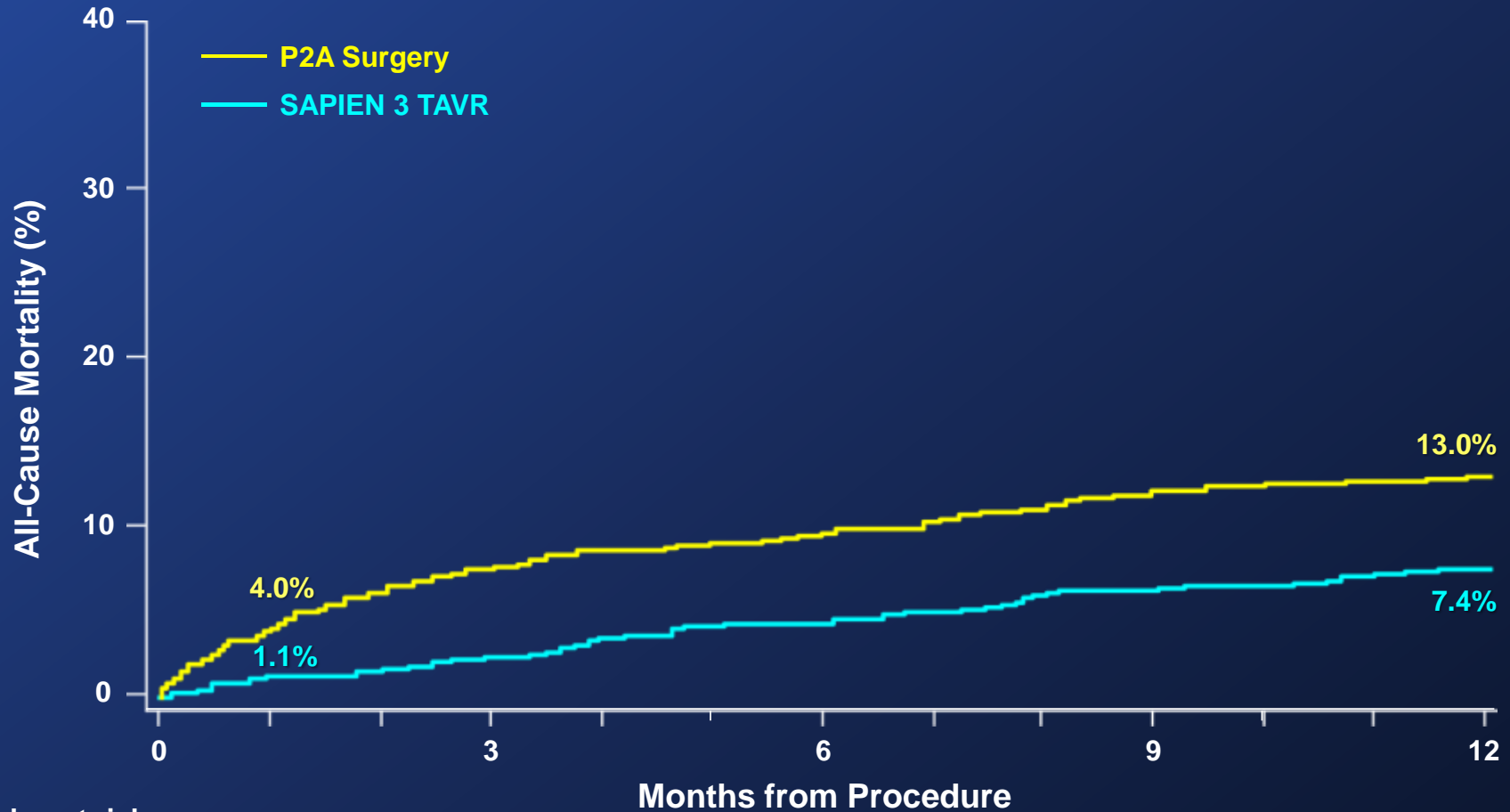


Number at risk:

	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**

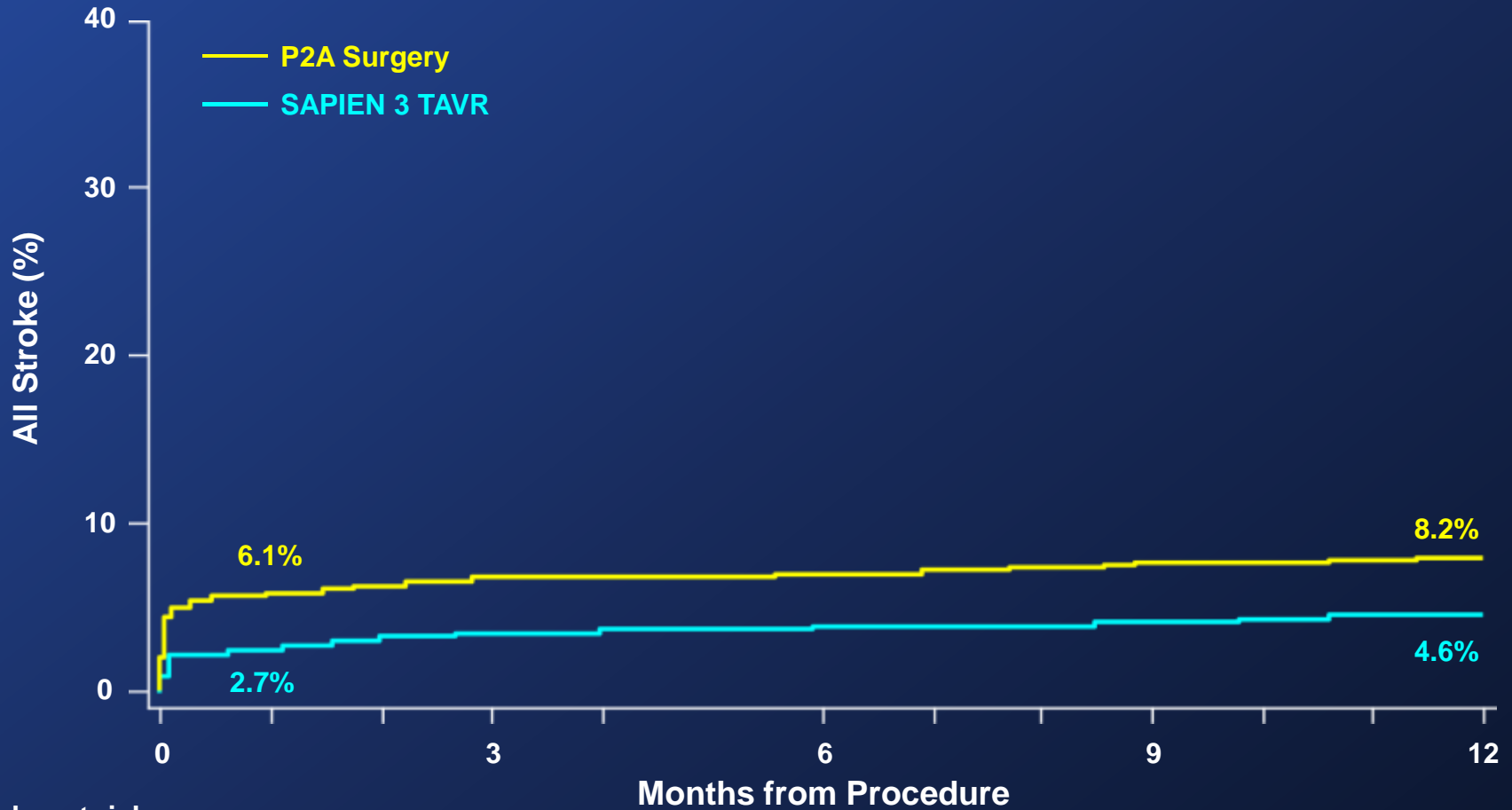
**836**  
**1017**

**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**

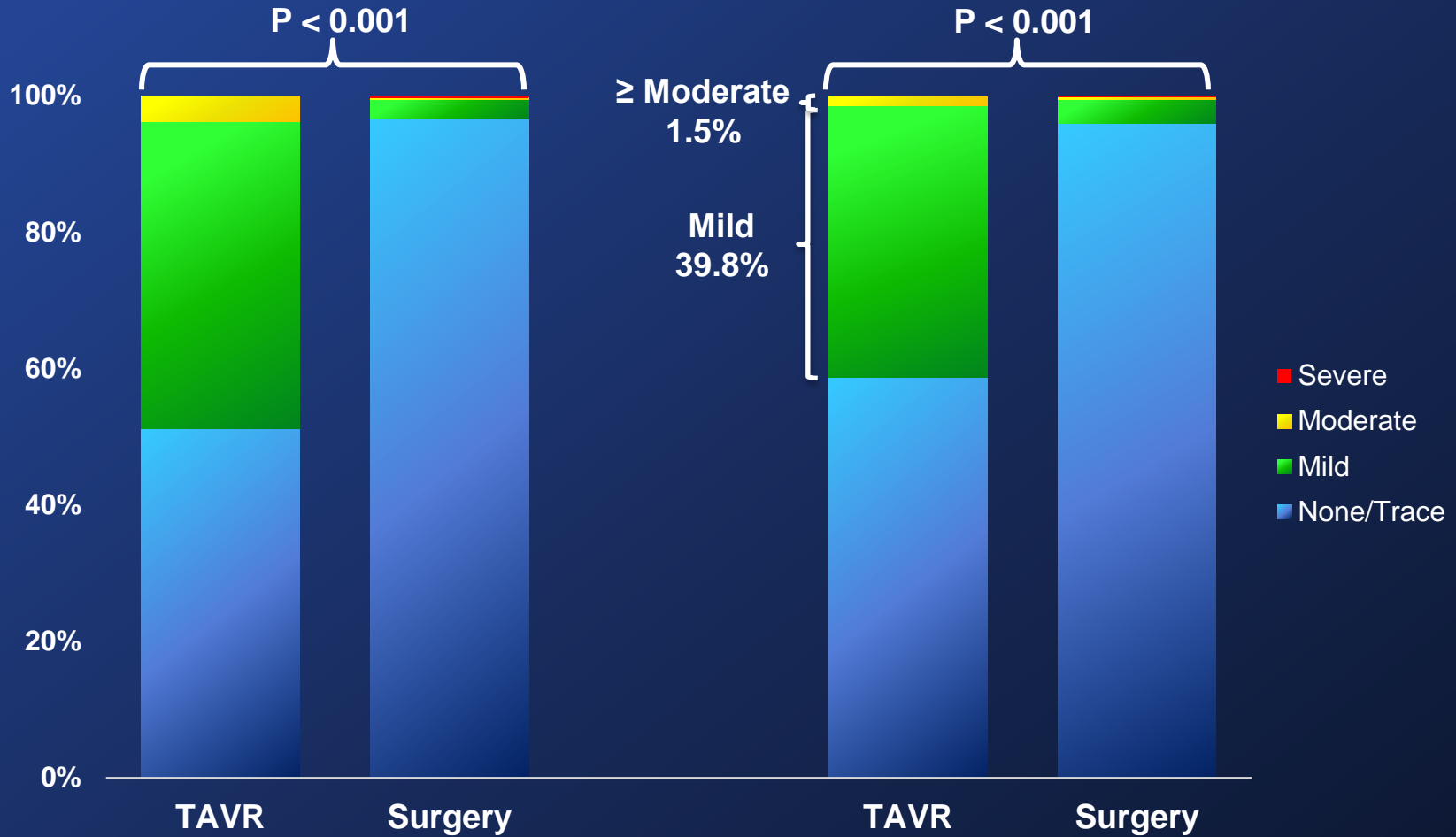
# Other Unadjusted Clinical Outcomes

## 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 Trial

## The Lancet On-line



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



*Vinod H Thourani, Susheel Kodali, Raj R Makkar, Howard C Hermann, 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*

**Special thanks to the PARTNER sites,  
the patients, the clinical research teams,  
and the manuscript writing group!**

# P2A and S3i Perspectives

## Key findings



### Surgery better

- Reduced vascular complications
- Less PVR

### TAVR better

- Reduced mortality and reduced strokes (esp. TF and with S3)
- Reduced ICU and hospital LOS
- Reduced AKI, severe bleeding, and new onset AF
- Improved valve hemodynamics (AVA and gradients)
- Better early recovery: 30-day QOL (NYHA class) and 6-minute walk test
- Increased days alive out-of-hospital (thru 2 years)



# The PARTNER 2A and S3i Trial

## Clinical Implications



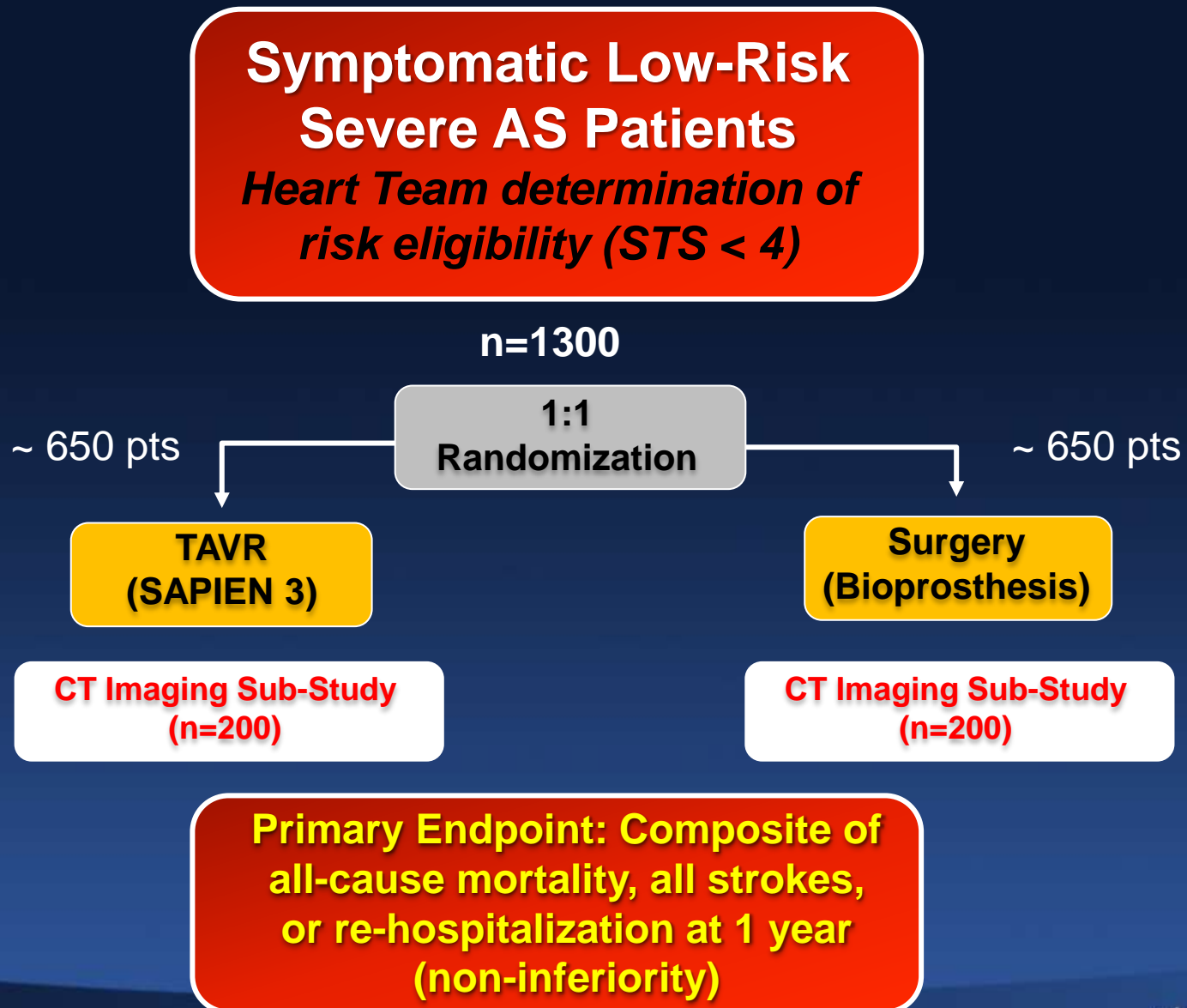
- The results from the PARTNER 2A randomized trial and the S3i propensity score analysis in > 3,100 intermediate-risk patients with severe aortic stenosis, provide strong evidence that SAPIEN 3 TAVR when compared with surgery improves clinical outcomes and is the preferred therapy!

# Expanding Clinical Indications

## *A TAVR Crossroads?*

- Bioprosthetic valve failure (aortic and mitral)
- Intermediate and low-risk patients
- Low-flow, low-gradient AS
- Bicuspid AV disease
- AS + concomitant disease (CAD, MR, AF)
- Severe asymptomatic AS
- Moderate AS + CHF
- High-risk AR

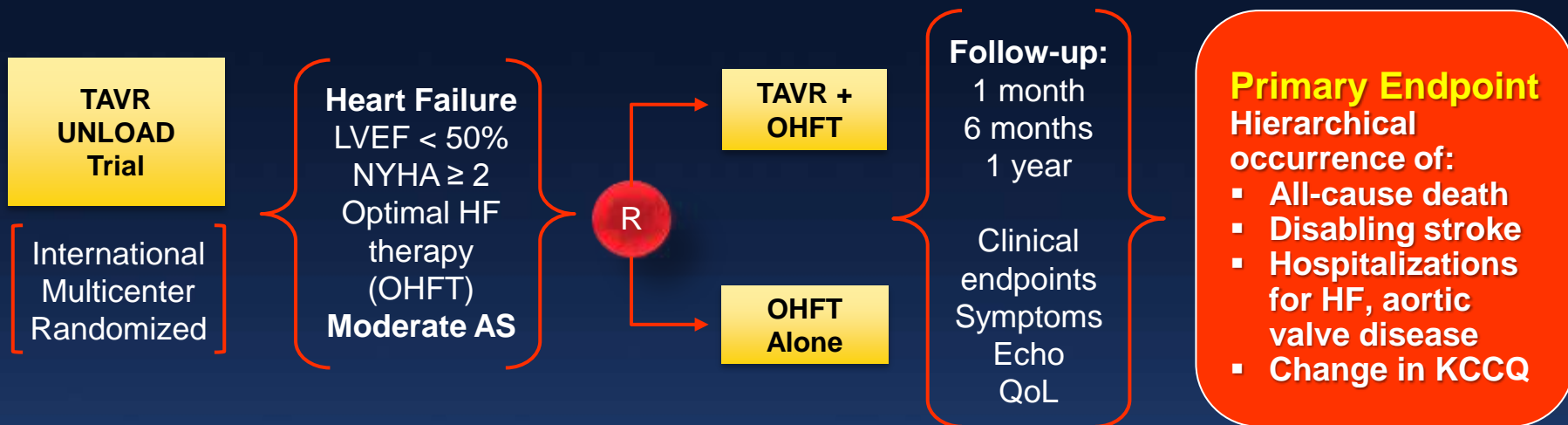
# PARTNER 3 Low Risk Trial



# TAVR - UNLOAD Trial Design

## Moderate AS + HF

(600 patients, 1:1 randomized)

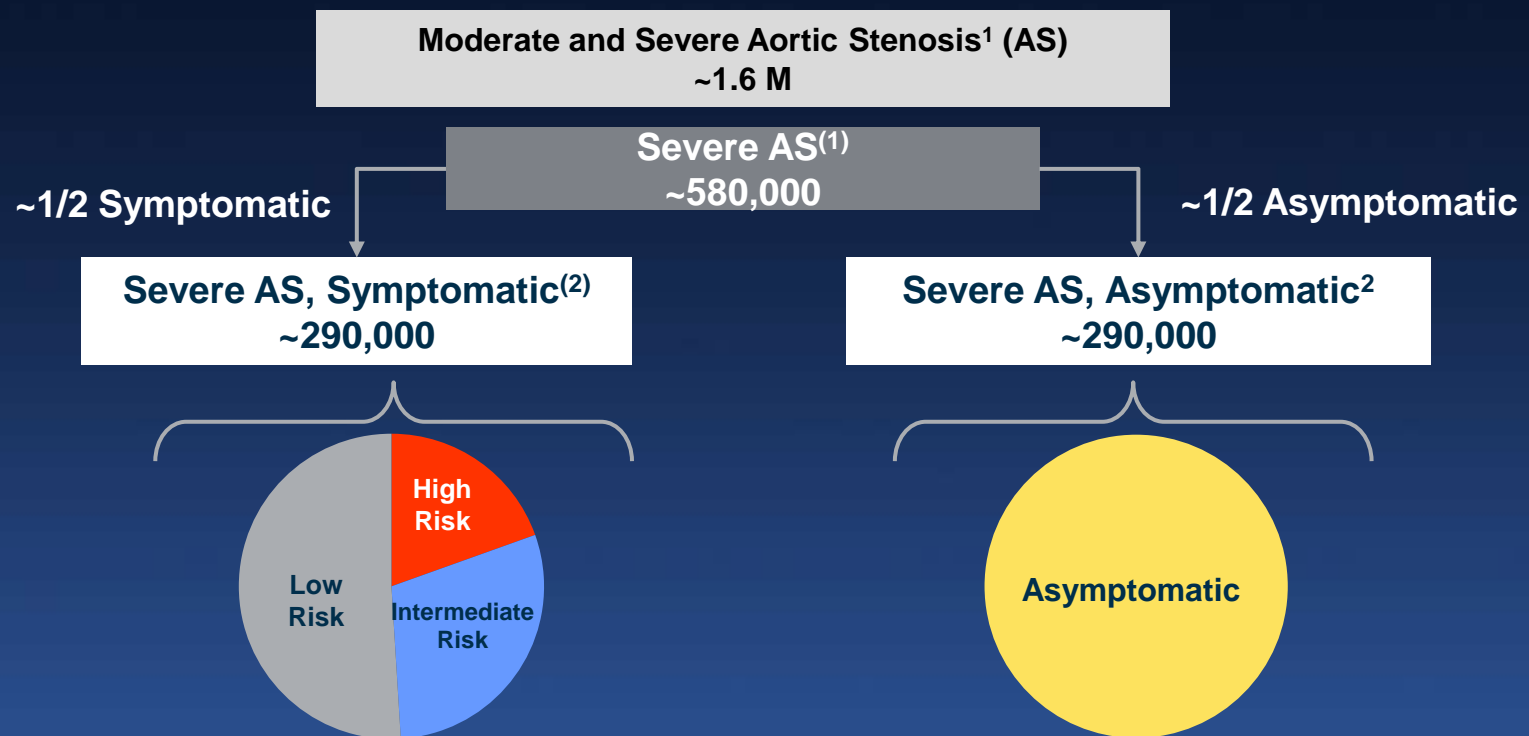


Reduced AFTERLOAD  
Improved LV systolic and diastolic function

# Severe Aortic Stenosis in Asymptomatic Patients

## *EARLY TAVR Trial*

### *2015 Total U.S. Population*



1. Nkomo 2006, Iivanainen 1996, Aronow 1991, Bach 2007
2. Freed 2010, Lung 2007, Pellikka 2005; Brown 2008 (n=622)

# Expanded TAVR Clinical Indications

## *A Transformative Technology at the Crossroads?*

