A Randomized Evaluation of the SAPIEN XT Transcatheter Valve System in Patients with Aortic Stenosis Who Are Not Candidates for Surgery: PARTNER II, Inoperable Cohort

Martin B. Leon, MD
on behalf of The PARTNER Trial Investigators

ACC 2013 | San Francisco | March 10, 2013

THE PARTNER II TRIAL

Disclosure Statement of Financial Interest

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 Lifesciences, Medtronic
• Consulting Fees/Honoraria	• None
• Major Stock Shareholder/Equity	• Sadra, Claret, Valve Medical, Apica

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Background (1)

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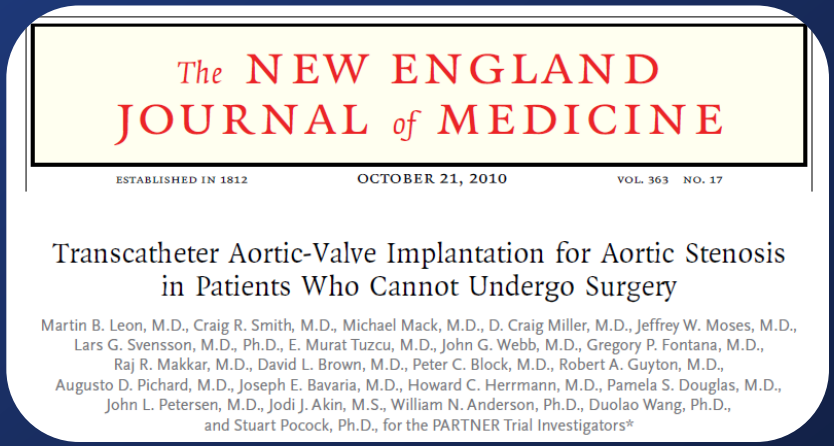
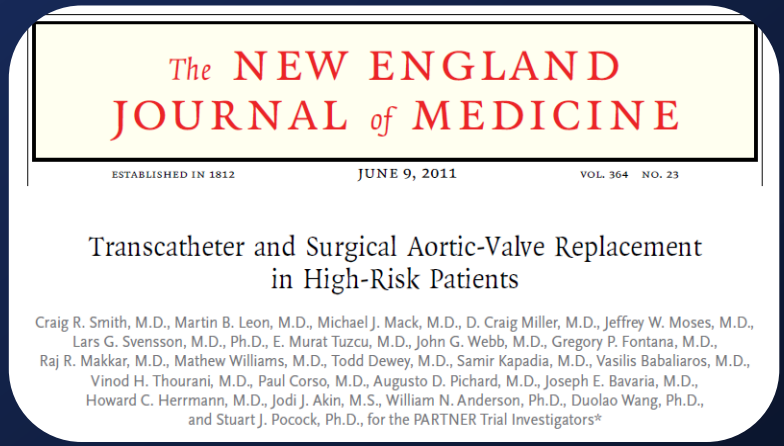
- In the PARTNER I randomized trials, patients with symptomatic severe aortic stenosis, treated using the balloon-expandable SAPIEN transcatheter heart valve system, had reduced mortality compared with standard therapy in patients who could not undergo surgery ("inoperable") and had similar mortality compared to surgical AVR in patients who were at high-risk for surgery.





Background (2)

THE PARTNER II TRIAL

- However, SAPIEN was associated with peri-procedural complications, including strokes, vascular events, and paravalvular regurgitation.

- The new lower-profile SAPIEN XT, currently in general clinical use around the world, incorporates important enhancements to the valve support frame, the valve leaflet geometry, and the delivery system which may be associated with improved clinical outcomes.

Purpose of PARTNER II
Inoperable Cohort

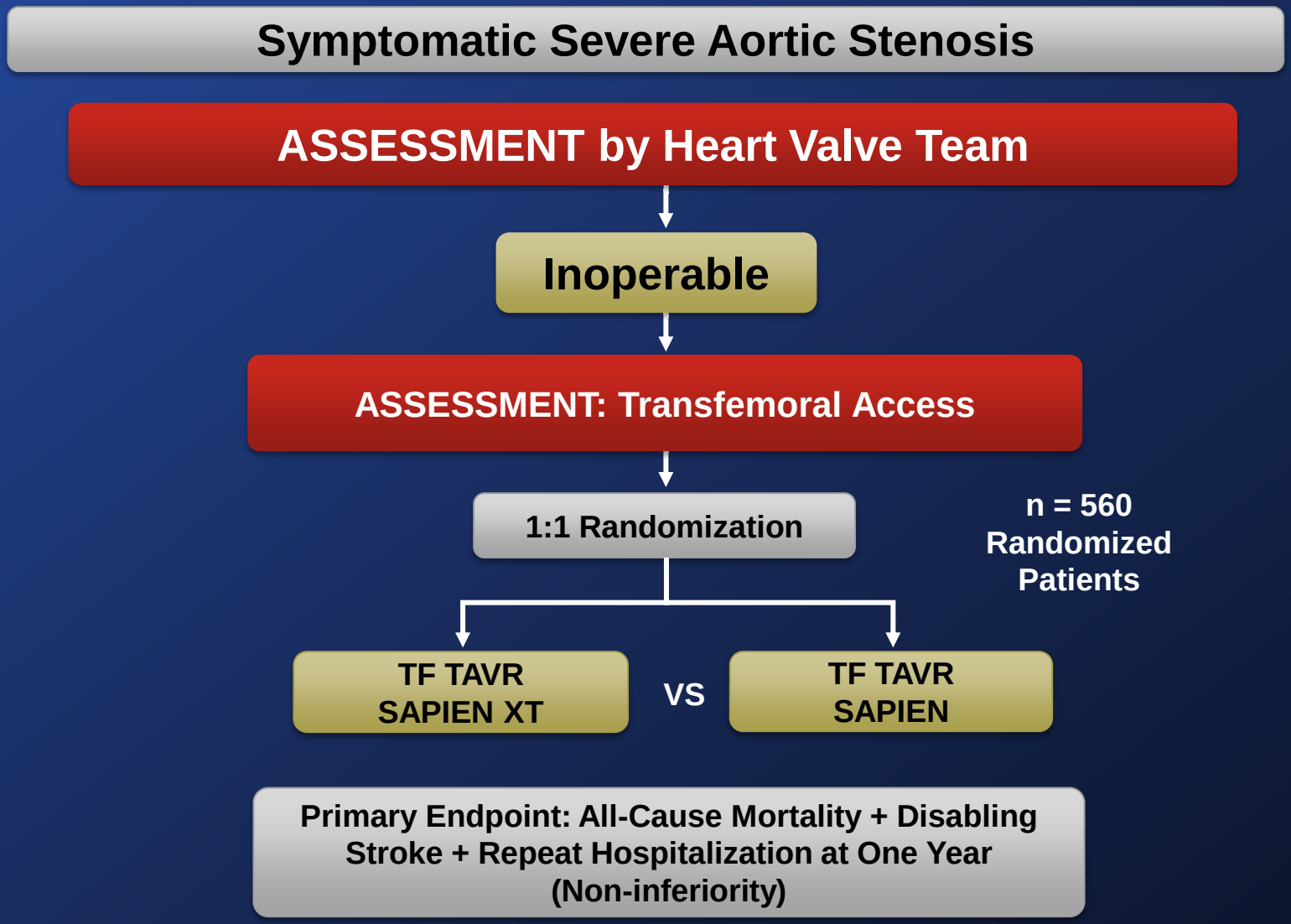
- To compare the safety and effectiveness of the new SAPIEN XT versus the FDA-approved SAPIEN in a randomized controlled trial for patients with symptomatic severe aortic stenosis who cannot have surgery (“inoperable”).

- To apply rigorous clinical trial methodologies including systematic serial neurologic assessments and VARC 2 definitions* for clinical outcomes.

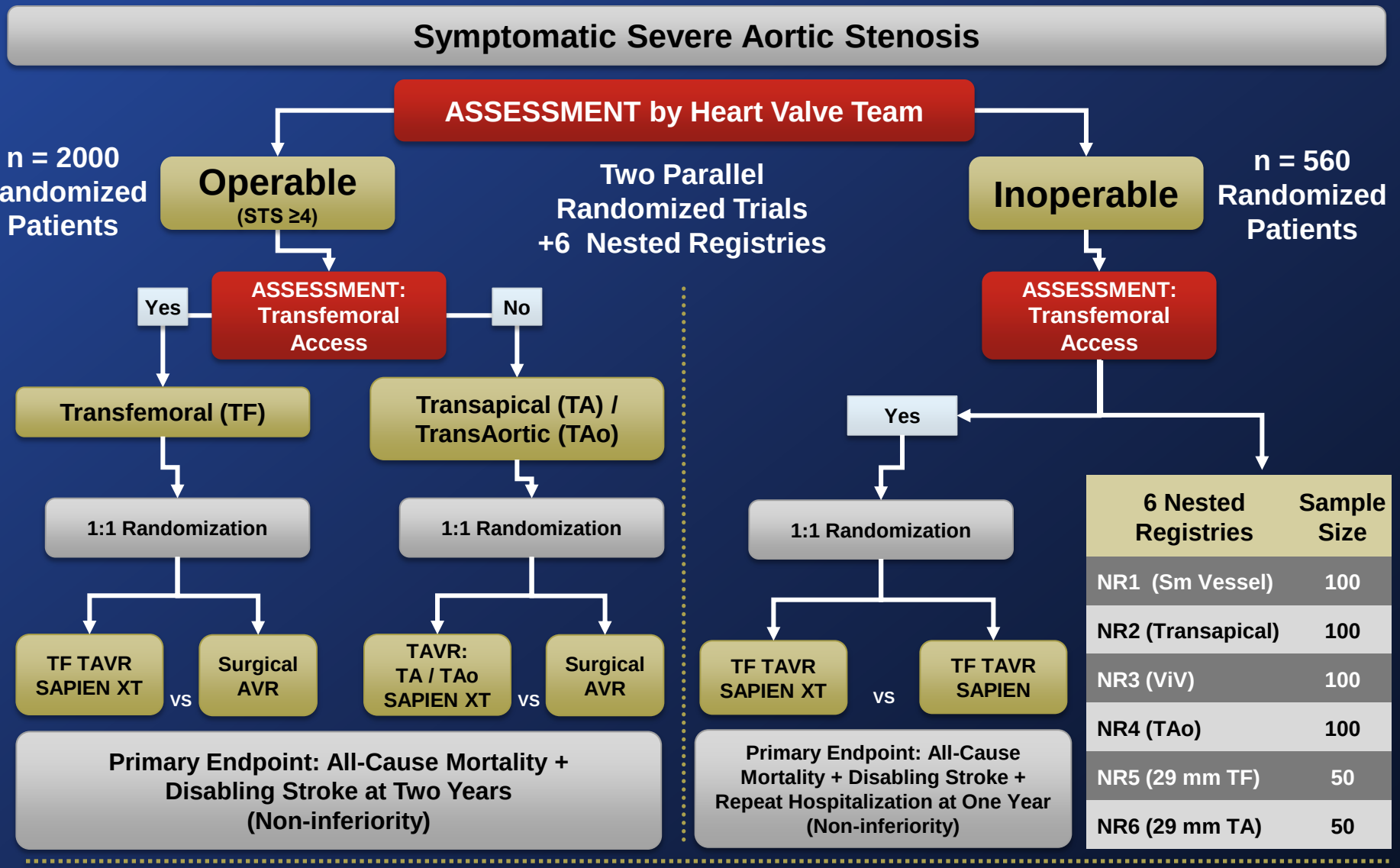
* Kappetein AP, et al. J Am Coll Cardiol 2012;60:1438-54

The PARTNER II Inoperable Cohort

Study Design



The PARTNER II Trial
Study Design



6 Nested Registries	Sample Size
NR1 (Sm Vessel)	100
NR2 (Transapical)	100
NR3 (ViV)	100
NR4 (TAo)	100
NR5 (29 mm TF)	50
NR6 (29 mm TA)	50

Primary Endpoint

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- A non-hierarchical composite of all-cause mortality, disabling stroke*, and re-hospitalization for symptoms of aortic stenosis and/or complications of the valve procedure.

- Intention-to-treat population, all patients followed for at least one year, non-inferiority trial arm comparison.

* Disabling stroke = CEC adjudicated stroke event 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

- Cardiovascular mortality
- Major vascular complications
- All strokes and TIAs
- Peri-procedural Mis
- Acute kidney injury
- Life-threatening or disabling bleeding
- No. of transfusions
- New permanent pacemakers
- New onset atrial fibrillation
- ≥ 2 THV implants
- Repeat 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 and peak AV gradient
- Effective orifice area (and index)
- LV function (ejection fraction)
- Paravalvular and total AR
- Structural valve deterioration

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

- *"Inoperable":* Risk of death or serious irreversible morbidity as assessed by a cardiologist and two surgeons must exceed 50%

Key Exclusion Criteria

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Anatomic:

- Aortic annulus diameter (echo measurement) < 18 mm or > 25 mm
- Iliac-femoral anatomy precluding safe sheath insertion (vessel size ≥7 mm diameter)
- Severe LV dysfunction (LVEF < 20%)
- Untreated CAD requiring revascularization

Clinical:

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

Edwards SAPIEN vs SAPIEN XT Transcatheter Heart Valves

THE PARTNER II TRIAL

NEW FRAME GEOMETRY
- Less metal content
- Lower crimp profile

NEW FRAME MATERIAL
- Cobalt-chromium
- Greater tensile and yield strength

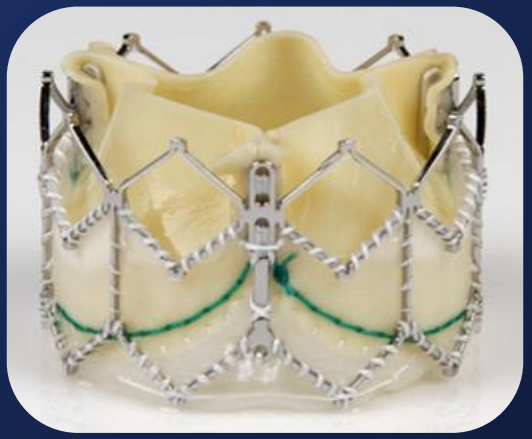
NEW LEAFLET GEOMETRY
- Partially closed

SAPIEN THV

Stainless Steel

SAPIEN XT THV

Cobalt-chromium



RetroFlex 3

NovaFlex

Sheath Size Comparison

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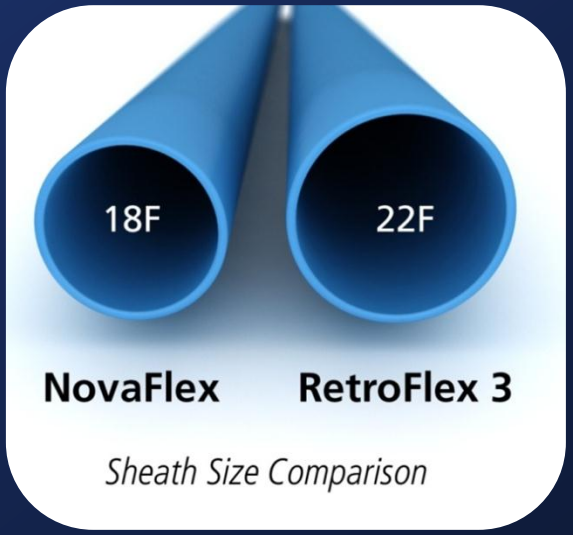
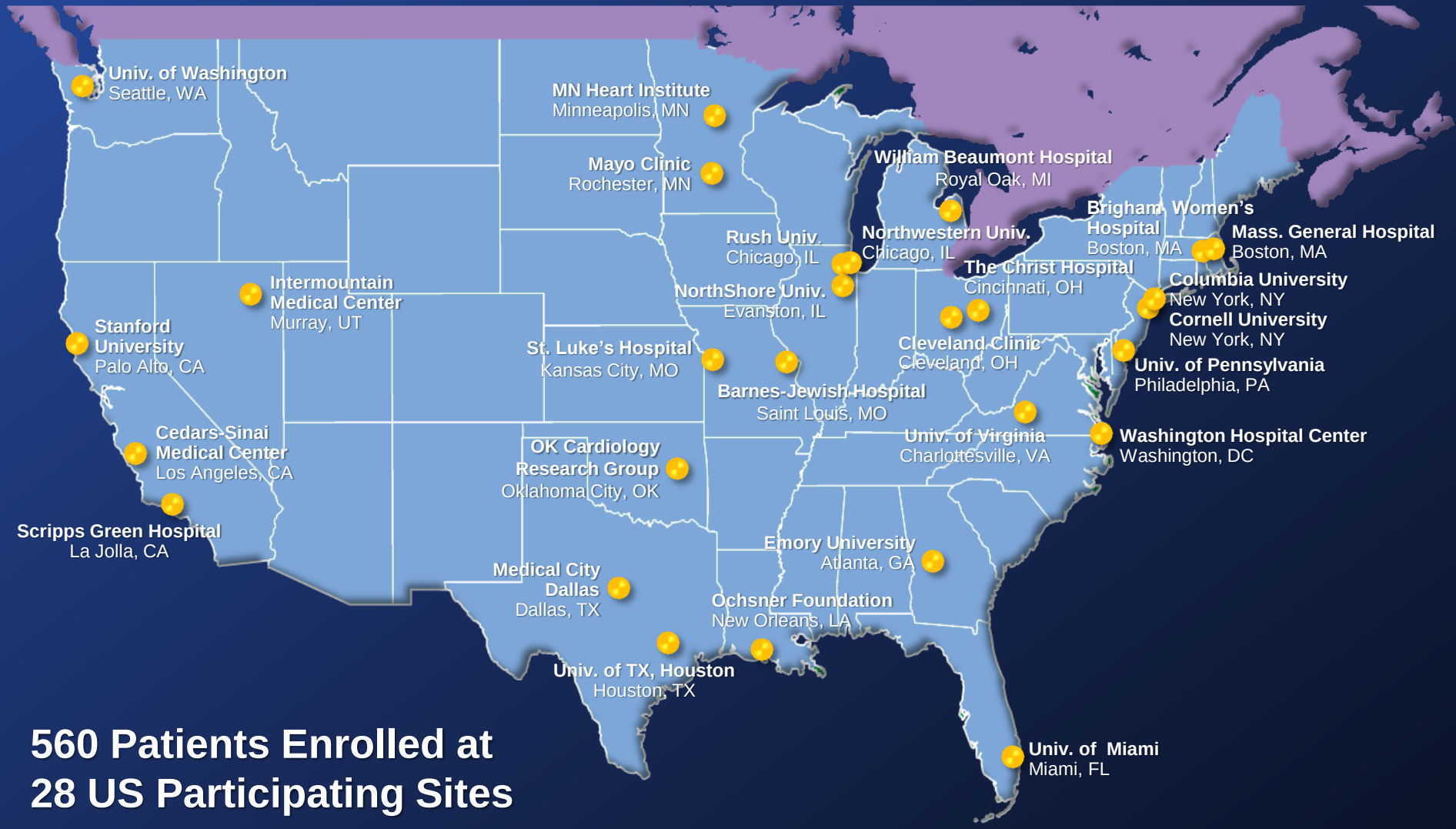
Valve	Valve Size	Sheath ID	Sheath OD	Minimum Vessel Diameter
SAPIEN THV	23mm	22F	25F (8.4mm)	7.0mm
SAPIEN XT THV	23mm	18F	22F (7.2mm)	6.0mm
SAPIEN THV	26mm	24F	28F (9.2mm)	8.0mm
SAPIEN XT THV	26mm	19F	23F (7.5mm)	6.5mm



33% reduction in CSA

The PARTNER II Inoperable Cohort
Participating Sites

THE PARTNER II TRIAL



560 Patients Enrolled at
28 US Participating Sites

PARTNER II Inoperable Cohort
Enrollment by Site (1 of 2)

THE PARTNER II TRIAL

Cedars-Sinai Medical Ctr.	Los Angeles, CA Wen Cheng & Raj Makkar	**87**
Columbia University	New York, NY Susheel Kodali & Mathew Williams	**75**
Emory University	Atlanta, GA Vasilis Babaliaros & Vinod Thourani	**58**
University of Pennsylvania	Philadelphia, PA Joseph Bavaria & Howard Herrmann	**56**
Washington Hospital Ctr.	Washington, DC Paul Corso & Augusto Pichard	**37**
Medical City Dallas	Dallas, TX David Brown & Todd Dewey	**33**
Cleveland Clinic	Cleveland, OH Lars Svensson & Murat Tuzcu	**25**
OK Cardiology Research	Oklahoma City, OK Mark Bodenhamer & Mohammad Ghani	**19**
Intermountain Medical Ctr.	Murray, UT Kent Jones & Brian Whisenant	**18**
Ochsner Hospital	New Orleans, LA Stephen Ramee & Patrick Parrino	**17**
Barnes-Jewish Hospital	Saint Louis, MO Hersh Maniar, Jr. & Alan Zajarias	**16**
The Christ Hospital	Cincinnati, OH Tom Ivey & Dean Kereiakes	**15**
Cornell University	New York, NY Karl Krieger & Chiu Wong	**13**
Stanford University	Palo Alto, CA Craig Miller & Alan Yeung	**12**
Mayo Clinic	Rochester, MN Kevin Greason & Verghese Mathew	**10**
Scripps Green Hospital	La Jolla, CA Scot Brewster & Paul Teirstein	**9**

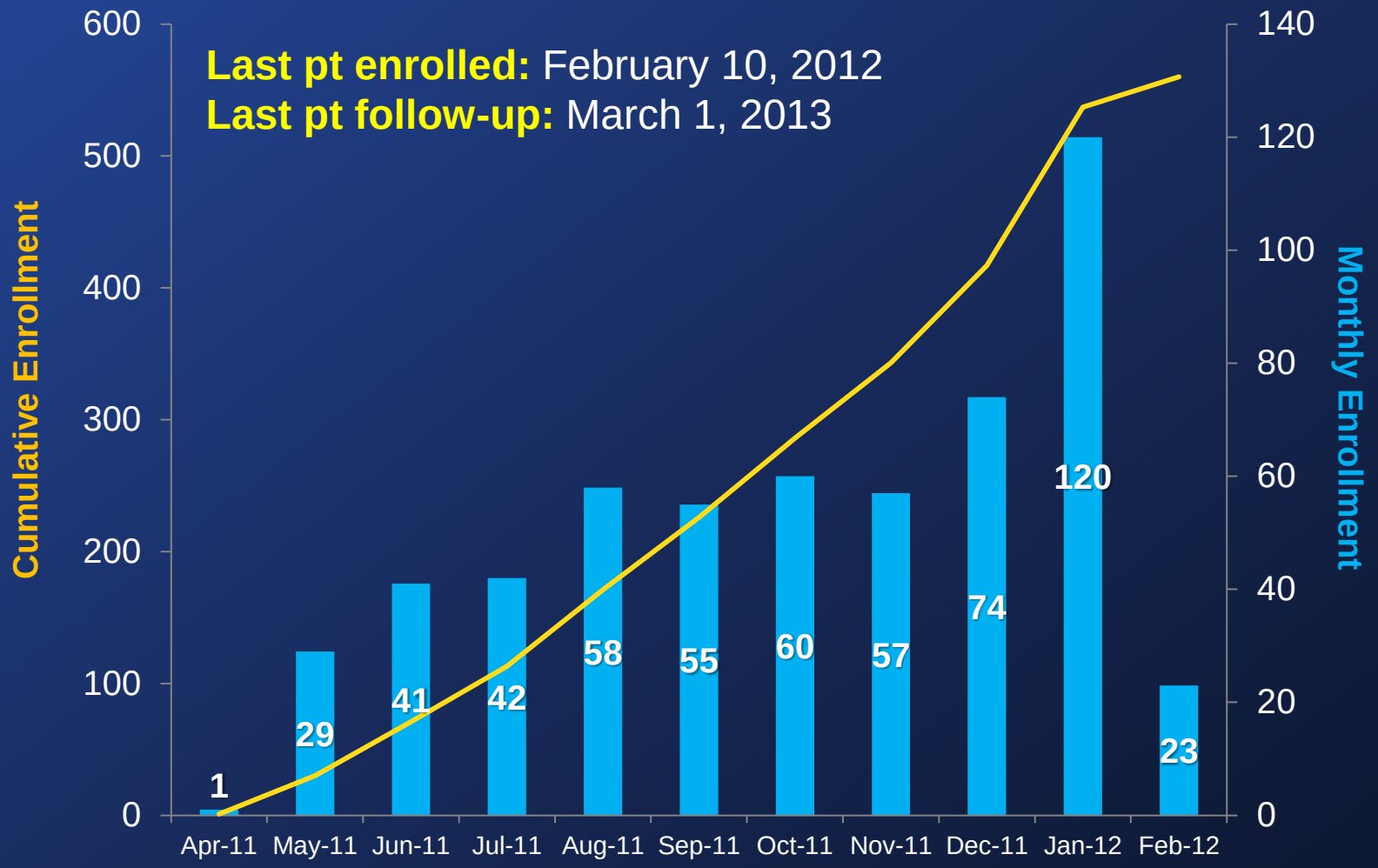
PARTNER II Inoperable Cohort
Enrollment by Site (2 of 2)

THE PARTNER II TRIAL

University of Miami		
Miami, FL		9
Alan Heldman & Donald B. Williams		
University of Virginia		
Charlottesville, VA		9
Irving Kron & Scott Lim		
NorthShore University		
Evanston, IL		8
Ted Feldman & Paul Pearson		
Rush University		
Chicago, IL		8
Zyiad M. Hijazi & Robert March		
Minneapolis Heart Institute		
Minneapolis, MN		7
Vibhu Kshettry & Wesley Pedersen		
St. Luke's Hospital (MAHI)		
Kansas City, MO		4
Michael Borkon & Adnan Chhatriwalla		
University of Washington		
Seattle, WA		4
Mark Reisman & Edward Verrier		
Brigham Women's Hospital		
Boston, MA		3
Ralph Bolman, III & Frederick G. Welt		
William Beaumont Hospital		
Royal Oak, MI		3
George Hanzel & Francis Shannon		
Northwestern University		
Chicago, IL		2
Charles Davidson & Chris Malaisrie		
University of Texas, Houston		
Houston, TX		2
Anthony Estrera & Richard Smalling		
Massachusetts General Hospital		
Boston, MA		1
Igor Palacios & Gus Vlahakes		

PARTNER II Inoperable Cohort
Enrollment Cadence

THE PARTNER II TRIAL



Study Administration

THE PARTNER II TRIAL

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
Neurology: Thomas Brott

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Caritas, St. Elizabeth Med Ctr, Boston

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Cleveland Clinic, C5 Research

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Mid America Heart Institute, Kansas City

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Helen Parise
Cardiovascular Research Foundation, NYC

Eugene Blackstone
Cleveland Clinic Foundation, Cleveland, OH

Publications Committee

Co-Located at: Columbia-CRF and Cleveland Clinic Foundation

Sponsor

Edwards Lifesciences: Jodi J. Akin

Study Methodology

THE PARTNER II TRIAL

- Every case reviewed by web-based conference call before enrollment
- All patients followed for at least one year
- Primary analysis performed by intention-to-treat (ITT), although as-treated (AT) analyses performed when appropriate
- Event rates as Kaplan-Meier estimates
- Composite analyses pre-specified
- 100% data monitoring of clinical events
- All 30-day events CEC adjudicated (>99%)
- 1-year primary endpoint events = CEC adjudicated (89%)

Baseline Patient Characteristics:
Demographics (ITT)

THE PARTNER II TRIAL

Characteristic	SAPIEN (n=276)		SAPIEN XT (n=284)		p-value
	n		n		
Age - yrs (mean ± SD)	276	84.6 ± 8.6	284	84.0 ± 8.7	0.44
Male (%)	142	51.4%	141	49.6%	0.67
BMI - kg/m^2 (mean ± SD)	275	27.4 ± 6.2	283	28.1 ± 7.3	0.42
STS Score (mean ± SD)	276	11.0 ± 5.7	284	10.3 ± 5.4	0.15
NYHA Class III or IV (%)	265	96.0%	275	96.8%	0.65

Baseline Patient Characteristics:
Vasculopathy (ITT)

THE PARTNER II TRIAL

Characteristic	SAPIEN (n=276)		SAPIEN XT (n=284)		
	n	%	n	%	p-value
CAD	186	67.4	186	65.5	0.66
Previous MI	58	21.0	55	19.4	0.67
Previous CABG	72	26.1	76	26.8	0.92
Previous PCI	100	36.2	90	31.7	0.28
Previous CVA	35	12.7	31	10.9	0.60
Previous TIA	30	10.9	24	8.5	0.39
Periph vasc disease	75	27.2	88	31.0	0.35

Baseline Patient Characteristics:
Other Co-morbidities (ITT)

THE PARTNER II TRIAL

Characteristic	SAPIEN (n=276)		SAPIEN XT (n=284)		
	n	%	n	%	p-value
Diabetes	100	36.2	102	35.9	0.99
COPD - Any	72	26.1	84	29.6	0.40
COPD - O_2 dependent	43	15.6	38	13.4	0.47
CKD - creat. ≥ 2mg/dL	33	12.0	31	10.9	0.79
Cancer Hx	99	35.9	100	35.2	0.93
Previous BAV	55	19.9	51	18.0	0.59
Atrial fibrillation	112	40.6	104	36.6	0.34
Permanent pacemaker	47	17.0	59	20.8	0.28

Baseline Patient Characteristics:
Inoperable Co-morbidities (ITT)

THE PARTNER II TRIAL

Characteristic	SAPIEN (n=276)		SAPIEN XT (n=284)		
	n	%	n	%	p-value
COPD - Inoperable	22	8.0	28	9.9	0.46
Dementia	12	4.3	22	7.7	0.11
Liver disease	13	4.7	12	4.2	0.84
Porcelain aorta	11	4.0	19	6.7	0.19
Chest wall radiation	9	3.3	13	4.6	0.52
Chest wall deformity	10	3.6	10	3.5	0.99
Frailty	166	60.1	168	59.2	0.86
Pulmonary HTN	57	20.7	72	25.4	0.19

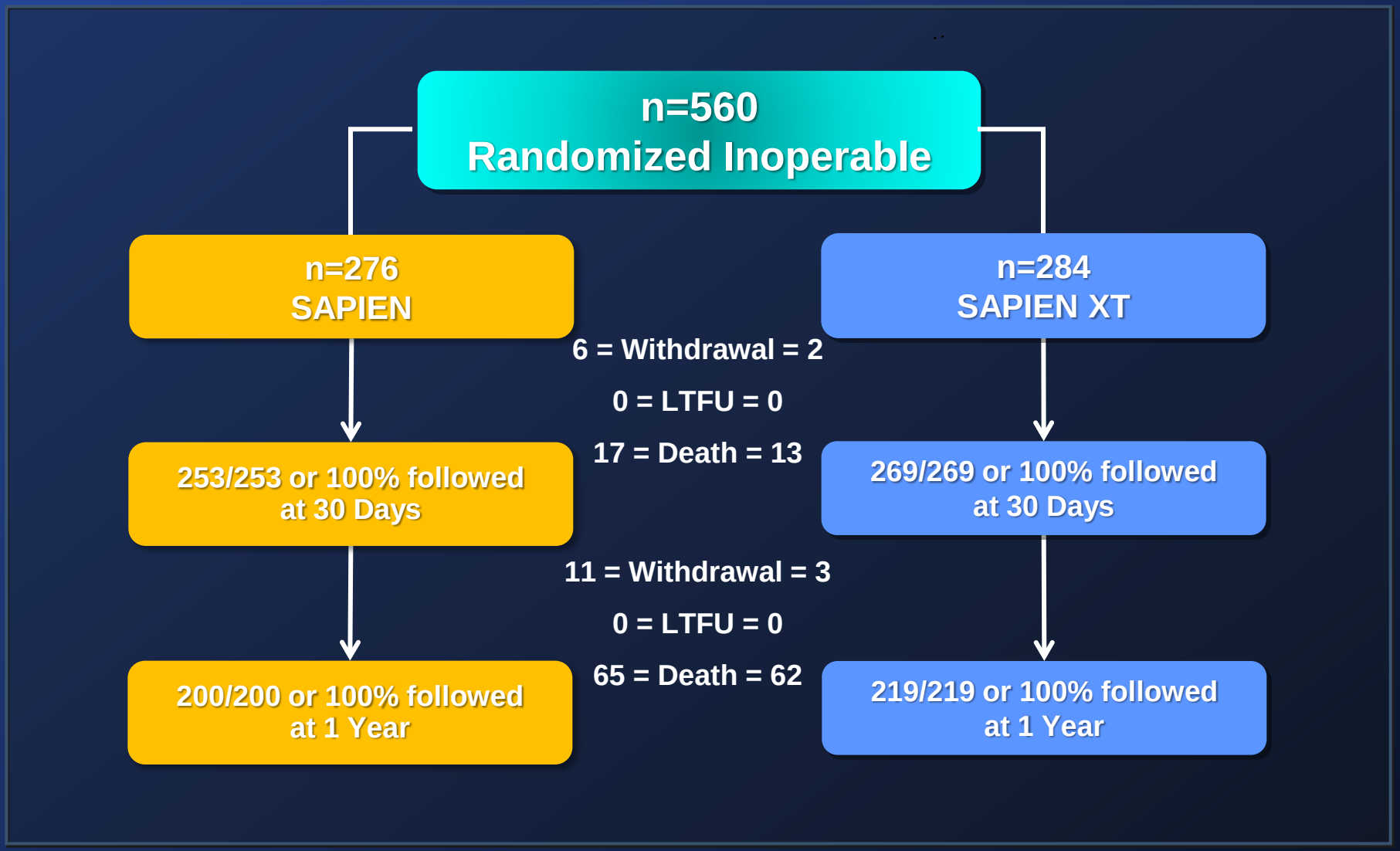
Baseline Echocardiography (Valve Implant)

THE PARTNER II TRIAL

Characteristic	SAPIEN (n=263)		SAPIEN XT (n=280)		p-value
	n		n		
AV area - cm^2 (mean ± SD)	229	0.6 ± 0.2	256	0.6 ± 0.2	0.59
AV gradient - mmHg (mean ± SD)	237	45.5 ± 14.4	263	45.2 ± 14.0	0.85
LV ejection fraction (%)	178	53.0 ± 13.7	197	52.4 ± 13.4	0.68
Mod-severe MR (%)	72	31.3	71	28.1	0.49

Study Flow – Inoperable
Vital Status

THE PARTNER II TRIAL



Procedural Factors (AT)

THE PARTNER II TRIAL

Events	SAPIEN (n=271)		SAPIEN XT (n=282)		
	n		n		p-value
Procedure time (mins)	271	109.6 ± 57.2	282	101.0 ± 43.2	0.18
Anesthesia time (mins)	266	212.0 ± 75.7	277	197.6 ± 60.8	0.02
≥ 2 valves implanted	10	3.7	3	1.1	0.05
Valve embolization	0	0	0	0	NA
Aborted procedure	8	3.0	2	0.7	0.06
Aortic rupture	2	0.7	1	0.4	0.62
Aortic dissection	1	0.4	1	0.4	0.99
IABP during procedure	6	2.2	1	0.4	0.06
Cardiopulmonary Bypass	5	1.8	5	1.8	0.99

Primary Endpoint Events:
At 30 Days (ITT)

THE PARTNER II TRIAL

Events	SAPIEN (n=276)		SAPIEN XT (n=284)		
	n	%	n	%	p-value*
Death:					
All-Cause	14	5.1	10	3.5	0.36
Cardiovascular	9	3.3	5	1.8	0.26
Stroke:					
Disabling	8	3.0	9	3.2	0.85
All	11	4.1	12	4.3	0.88
All + TIA	13	4.8	12	4.3	0.78
Death (all-cause) and Stroke (disabling)	19	6.9	18	6.4	0.80
Re-hospitalizations	27	10.2	32	11.6	0.59
Death (all-cause),Stroke (disabling), and Re-hosp	42	15.3	48	17.0	0.60

*p-values are KM - Log Rank

Other Clinical Outcomes:
At 30 Days (ITT)

THE PARTNER II TRIAL

Events	SAPIEN (n=276)		SAPIEN XT (n=284)		
	n	%	n	%	p-value
MI	2	0.7	5	1.8	0.27
AKI	38	14.2	37	13.3	0.78
New Permanent Pacemaker	16	5.9	18	6.4	0.78
Re-intervention	8	2.9	7	2.5	0.75
Endocarditis	0	0	0	0	NA

Vascular and Bleeding Events:
At 30 Days (AT)

THE PARTNER II TRIAL

	SAPIEN (n=271)		SAPIEN XT (n=282)		
Events	**n**	**%**	**n**	**%**	**p-value**
Vascular:					
Major	42	15.5	27	9.6	0.04
Minor	20	7.4	14	5.0	0.23
Bleeding:					
Disabling	34	12.6	22	7.8	0.06
Major	44	16.4	44	15.7	0.84
Patients with transfusions	80	29.5	73	25.9	0.40

Vascular Complication Categories:
At 30 Days (AT)

THE PARTNER II TRIAL

	SAPIEN (n=271)		SAPIEN XT (n=282)		
Events	n	%	n	%	p-value
Perforation	13	4.8	2	0.4	0.003
Dissection	25	9.2	12	4.3	0.03
Hematoma	16	5.9	10	3.6	0.23

All-Cause Mortality (ITT)

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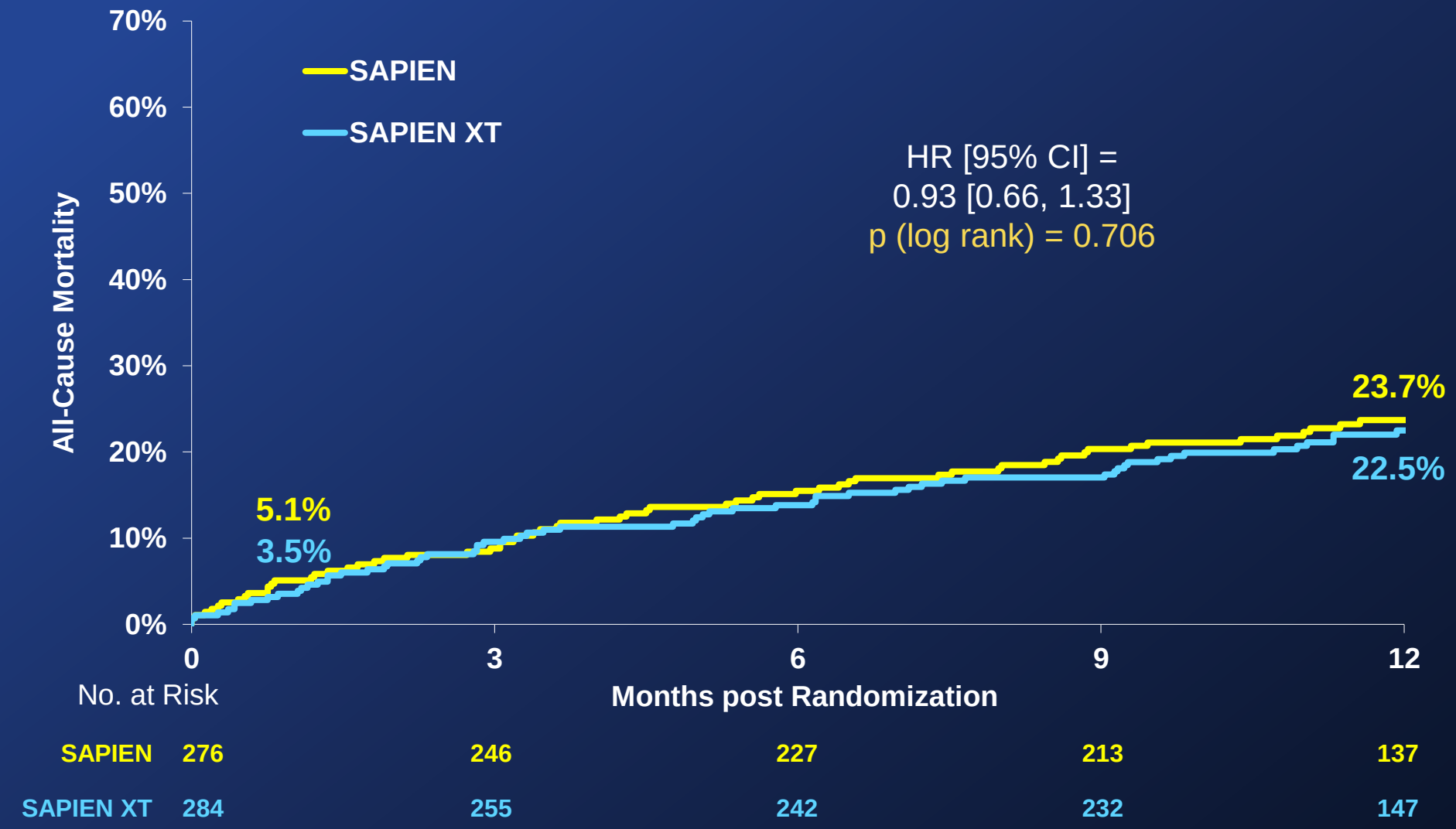

No. at Risk

SAPIEN	276	246	227	213	137
SAPIEN XT	284	255	242	232	147

Disabling Stroke (ITT)

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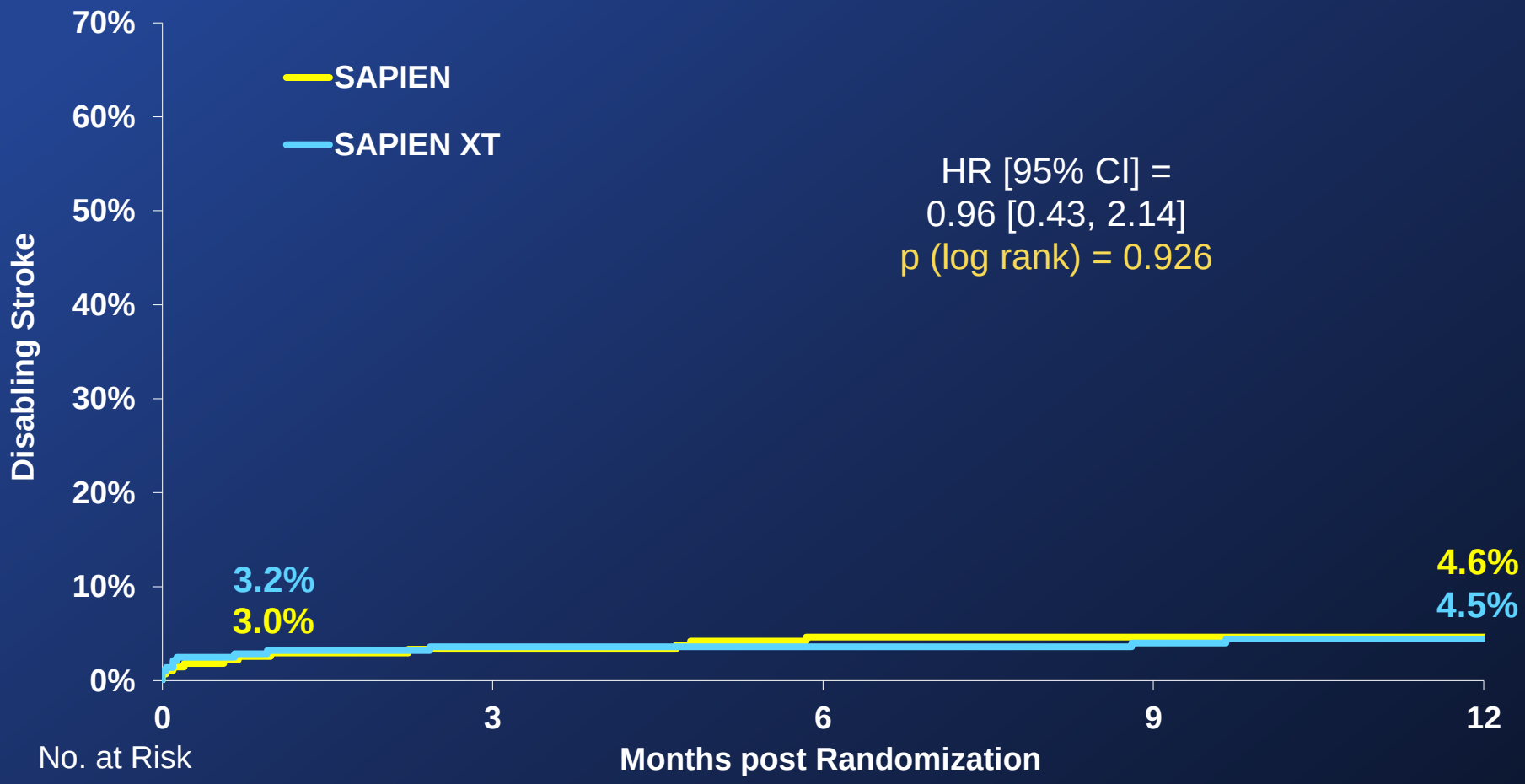
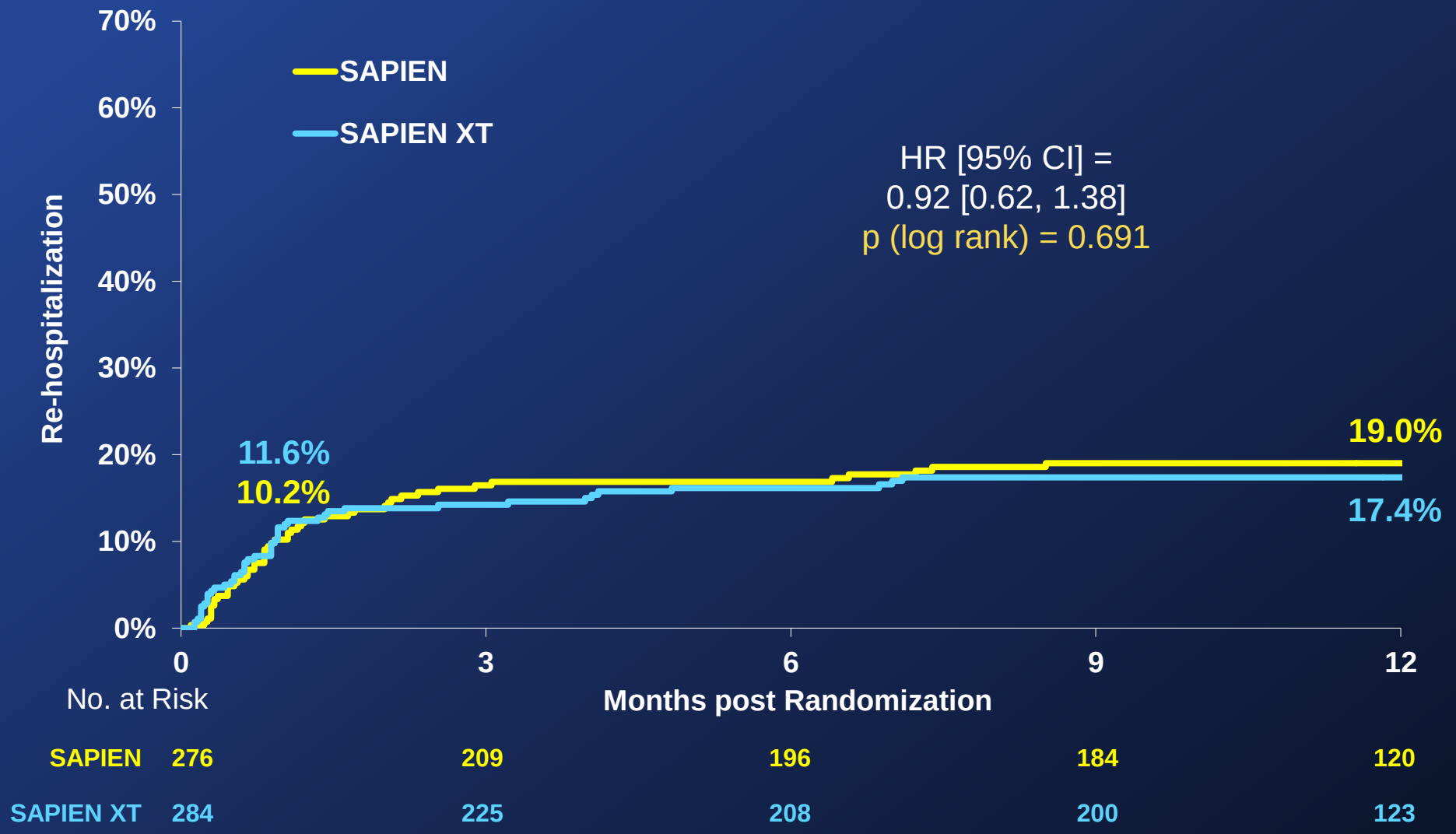


No. at Risk

SAPIEN	276	241	223	209	134
SAPIEN XT	284	250	238	227	145

Re-hospitalization (ITT)

THE PARTNER II TRIAL

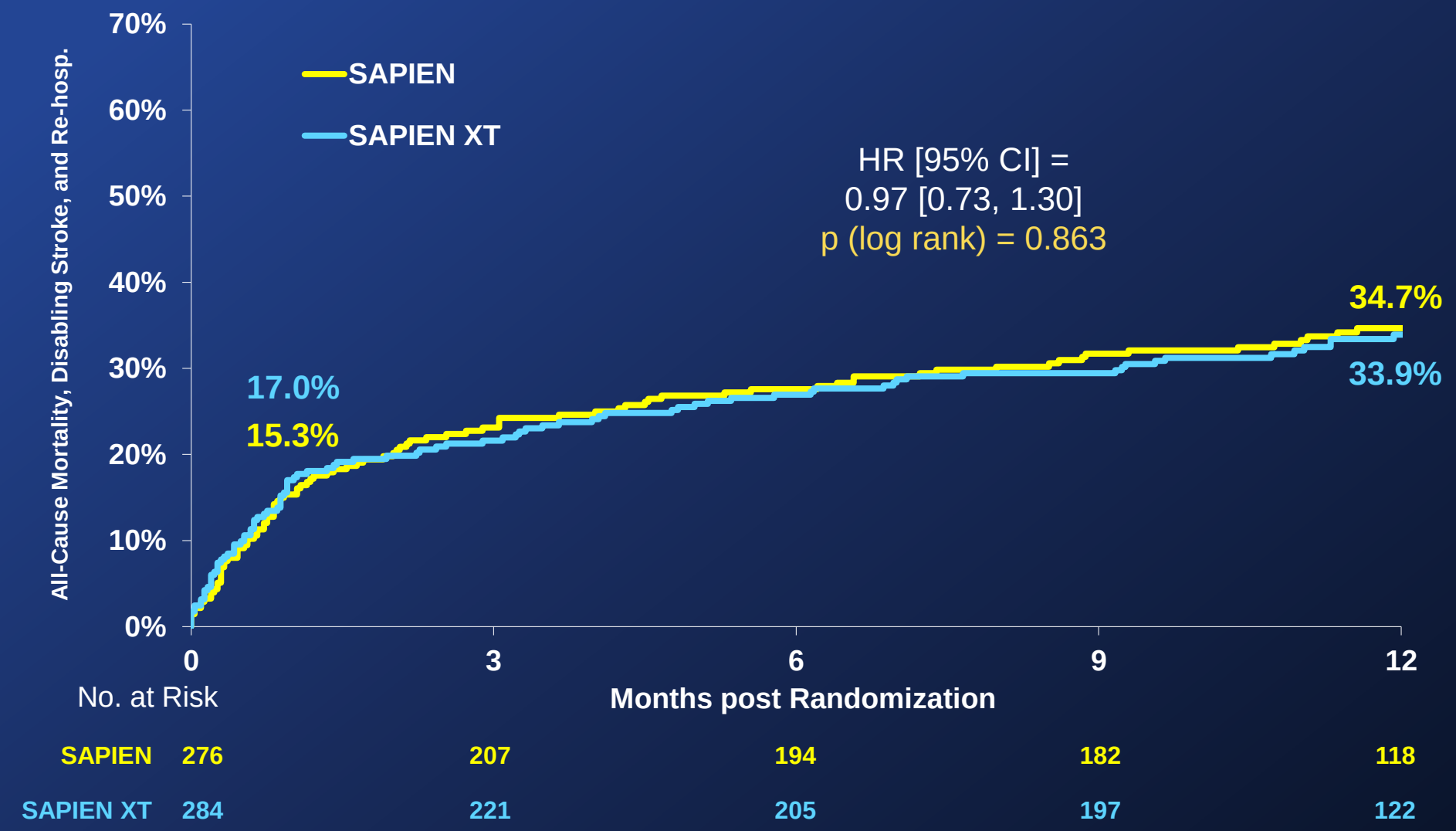


No. at Risk

SAPIEN	276	209	196	184	120
SAPIEN XT	284	225	208	200	123

All-Cause Mortality, Disabling Stroke, and Re-hospitalization (ITT)

THE PARTNER II TRIAL

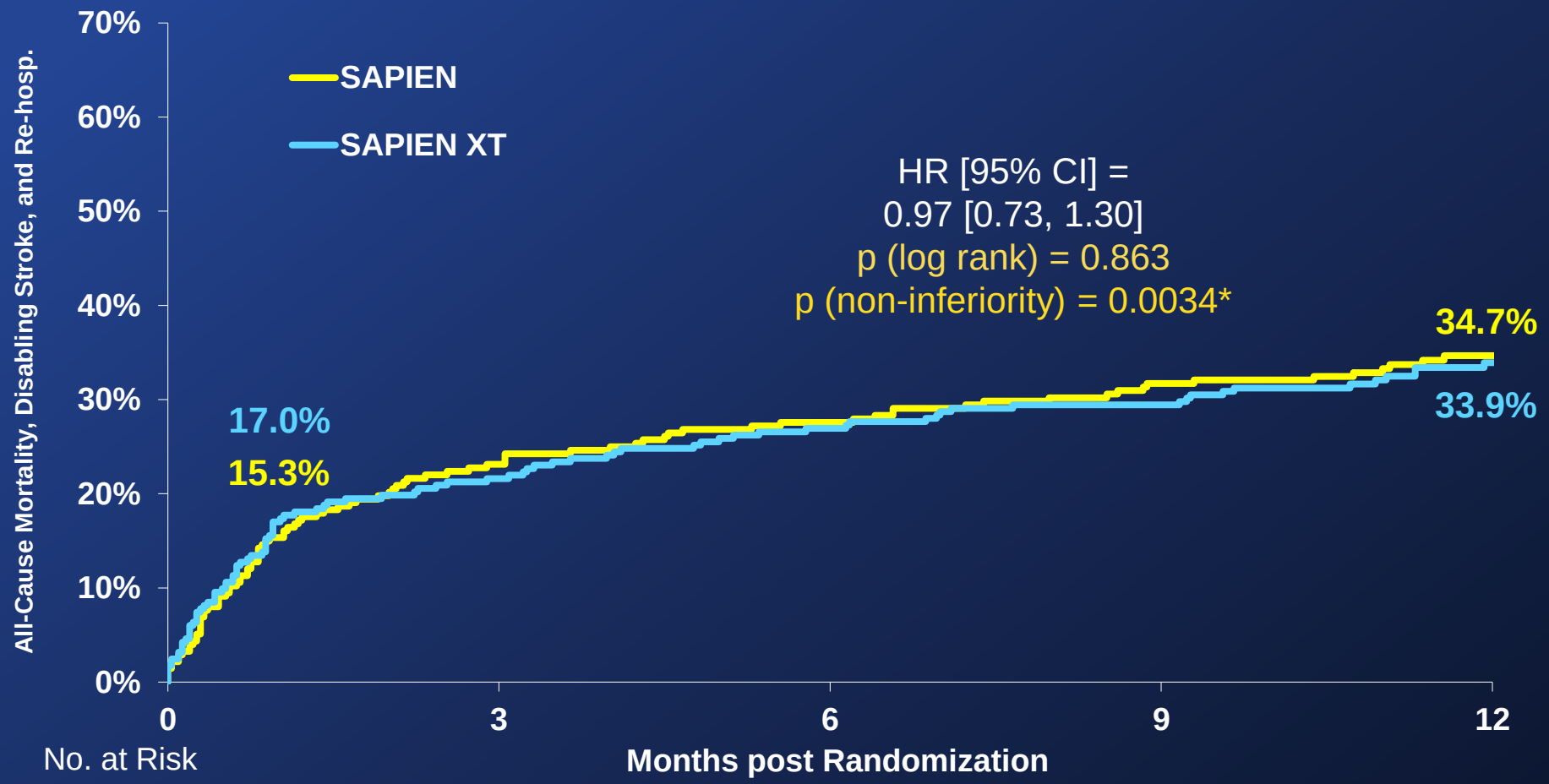


No. at Risk

SAPIEN	276	207	194	182	118
SAPIEN XT	284	221	205	197	122

All-Cause Mortality, Disabling Stroke, and Re-hospitalization (ITT)

THE PARTNER II TRIAL

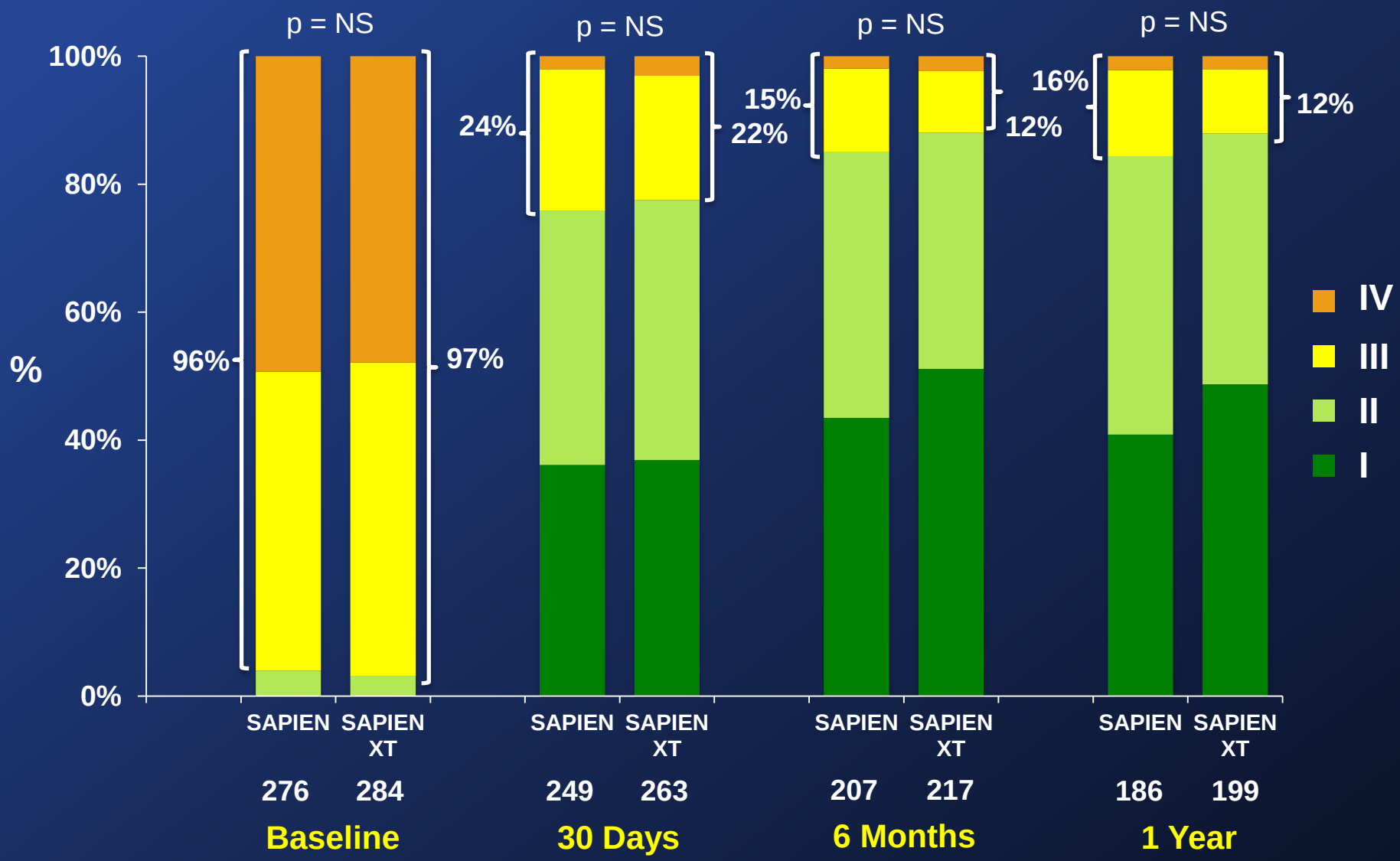


No. at Risk

SAPIEN	276	207	194	182	118
SAPIEN XT	284	221	205	197	122

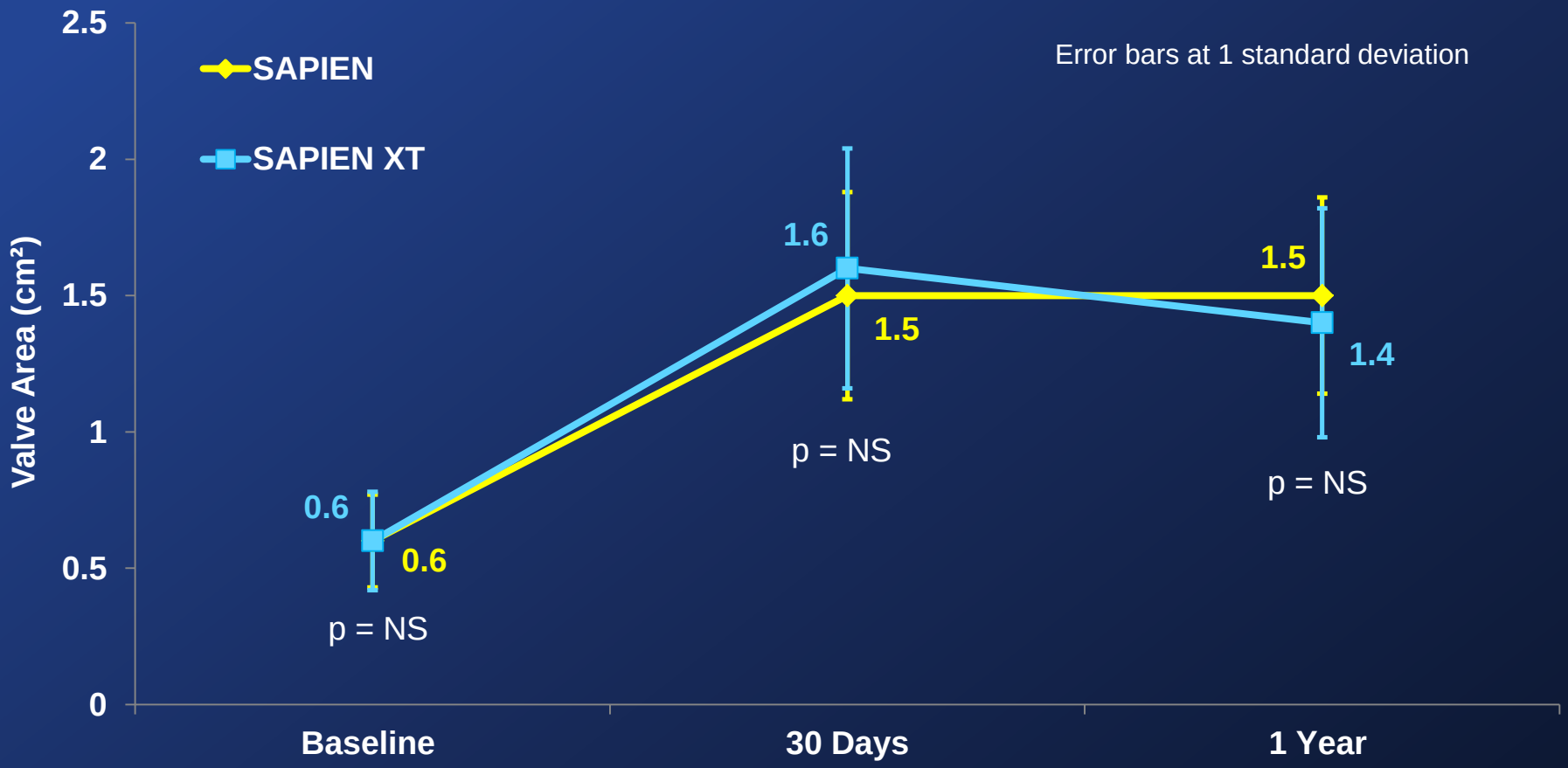
*Preliminary based upon 100% CEC adjudication at 30 days and 89% CEC adjudication at 1 year.

NYHA Class Survivors (ITT)



Echocardiographic Findings:
Aortic Valve Area (AT, Valve Implanted)

THE PARTNER II TRIAL

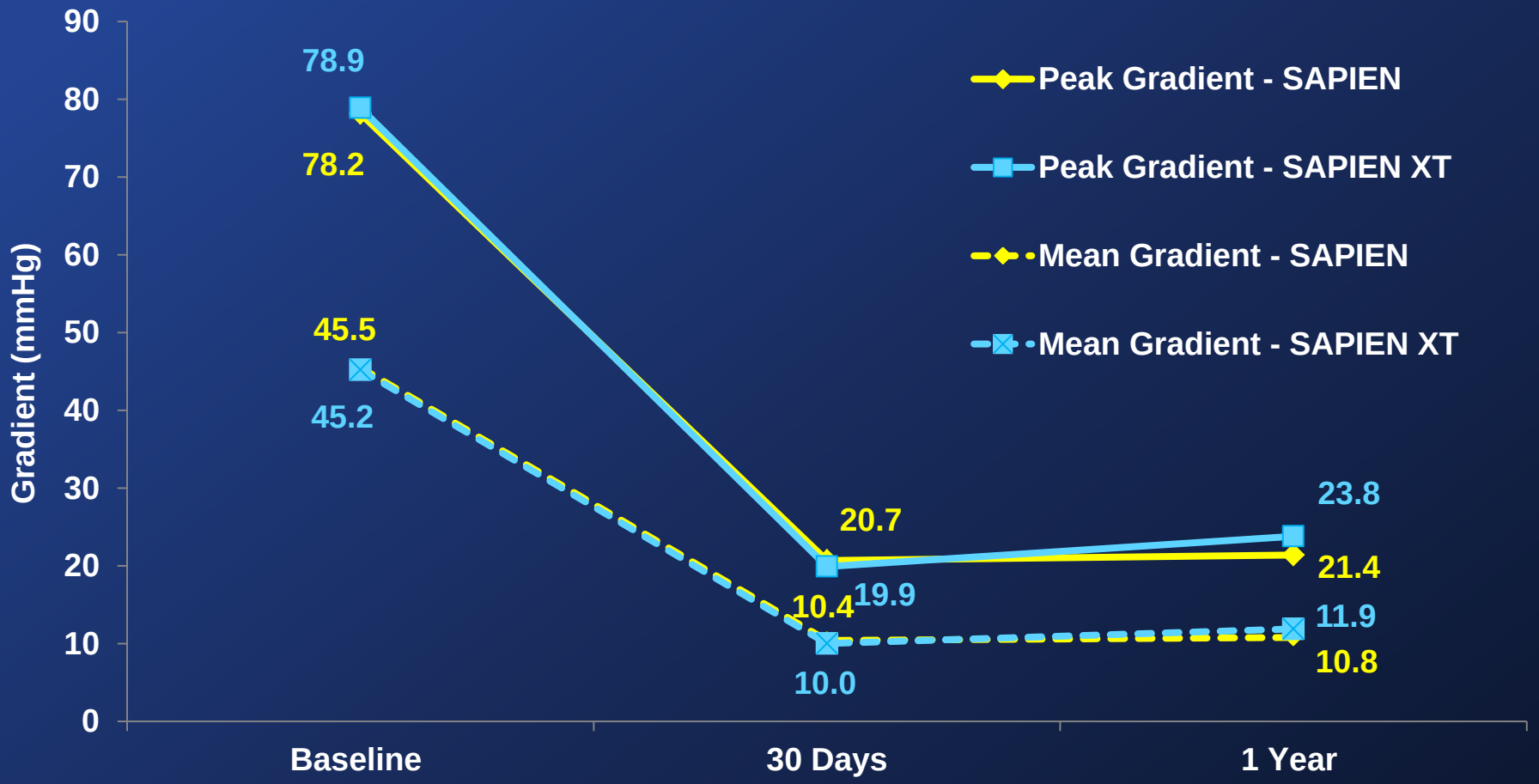


No. of Echos

SAPIEN	229	215	112
SAPIEN XT	256	233	117

Echocardiographic Findings:
Mean & Peak Gradients (AT, Valve Implant)

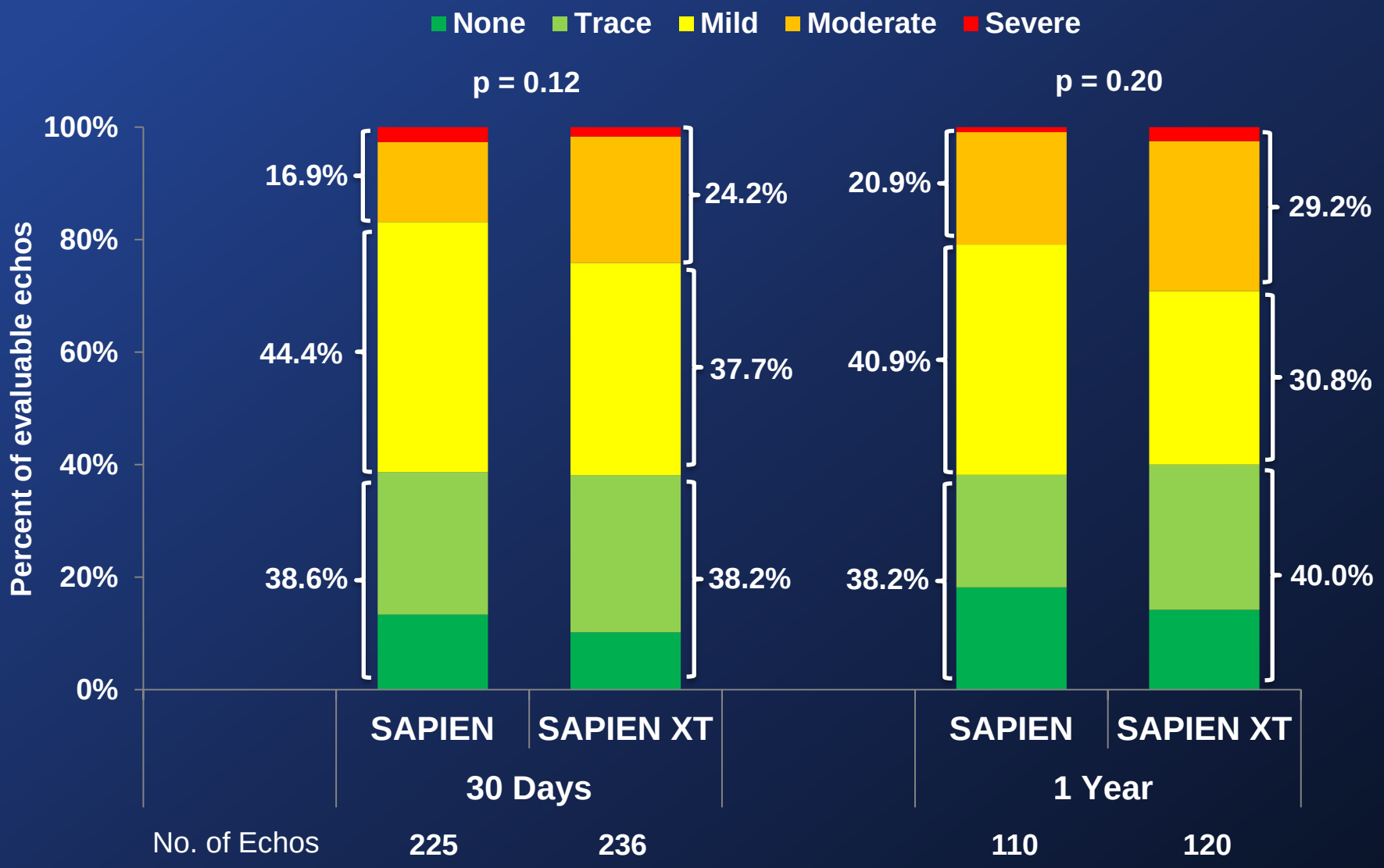
THE PARTNER II TRIAL



No. of Echos			
SAPIEN	237	224	113
SAPIEN XT	263	237	118

Paravalvular Aortic Regurgitation (AT, Valve Implant)

THE PARTNER II TRIAL



Conclusions (1)

THE PARTNER II TRIAL

In the inoperable cohort of the PARTNER II trial, comparing the SAPIEN versus the SAPIEN XT THV systems…

- During the TAVR procedure,
  - SAPIENT XT treatment was associated with reductions in anesthesia time ($p = 0.02$), multiple valve implants ($p = 0.05$), aborted procedures ($p = 0.06$), and the need for IABP hemodynamic support ($p = 0.06$).

Conclusions (2)

THE PARTNER II TRIAL

In the inoperable cohort of the PARTNER II trial, comparing the SAPIEN versus the SAPIEN XT THV systems…

- At 30 days,
  - All-cause mortality and disabling strokes were similar (Mortality: SAPIEN 5.1% vs. SAPIEN XT 3.5%; Strokes: SAPIEN 3.0% vs. SAPIEN XT 3.2%)
  - Major vascular complications were reduced after SAPIENT XT (from 15.5% to 9.6%, p = 0.04), including perforations, dissections, and hematomas
  - All other clinical endpoints were similar

Conclusions (3)

THE PARTNER II TRIAL

In the inoperable cohort of the PARTNER II trial, comparing the SAPIEN versus the SAPIEN XT THV systems…

- At 1 year,
  - All-cause mortality, disabling strokes, and re-hospitalizations were similar, including the non-hierarchical composite primary endpoint (SAPIEN XT 33.9% vs. SAPIEN 34.7%, non-inferiority p-value = 0.0034)
  - Improvement in NYHA class was similar
  - Echo valve performance (EOA and gradients) was similar

Implications

THE PARTNER II TRIAL

In the inoperable cohort of The PARTNER II Trial, the new lower profile SAPIEN XT THV system was associated with…

- Improved procedural outcomes
- Similar low 30-day mortality and strokes
- Reduced vascular complications
- Similar 1-year major clinical events and valve performance

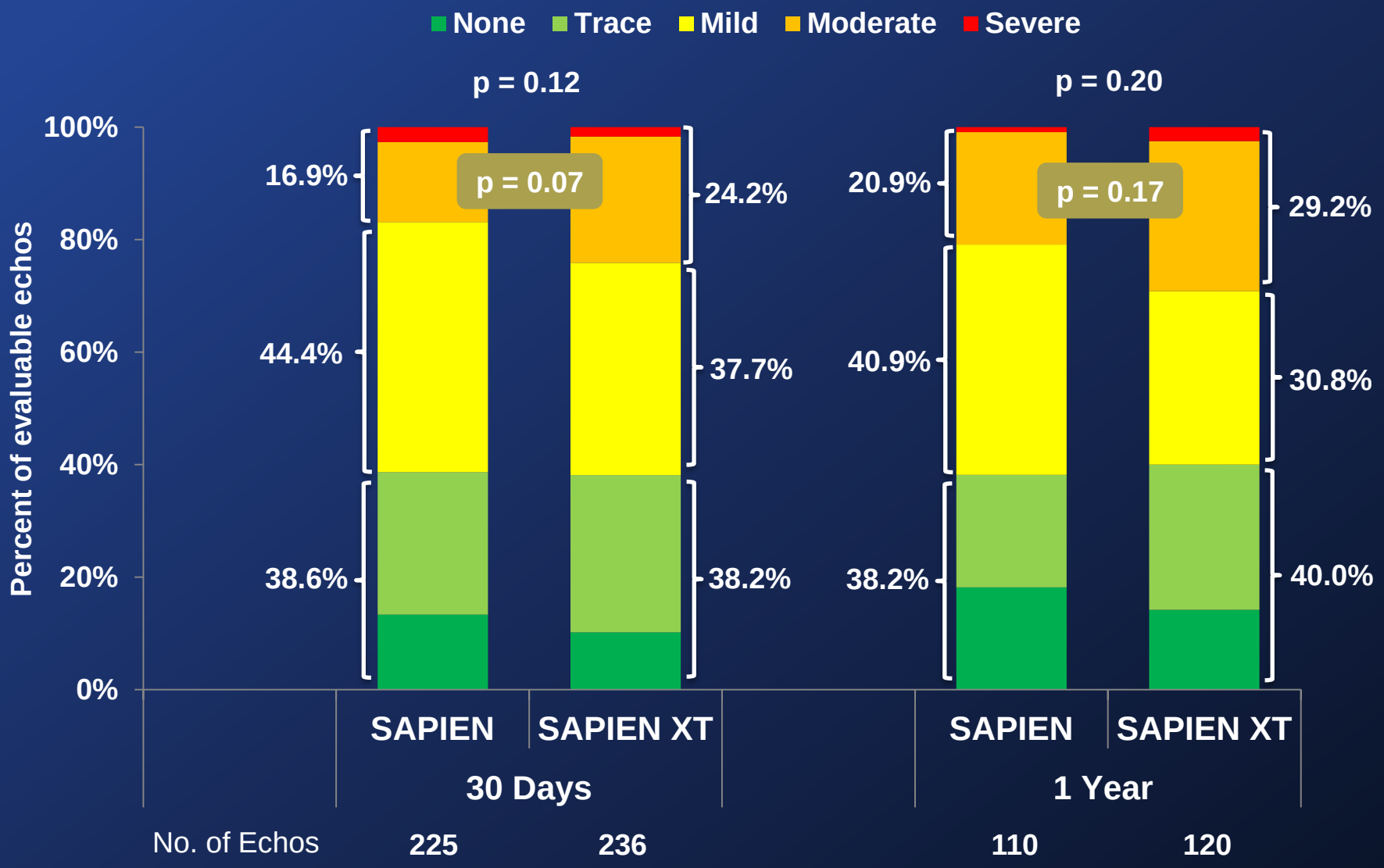
Therefore, SAPIEN XT represents a worthwhile advance with incremental clinical value and is the preferred balloon-expandable THV system.

BACK-UP SLIDES

THE PARTNER II TRIAL

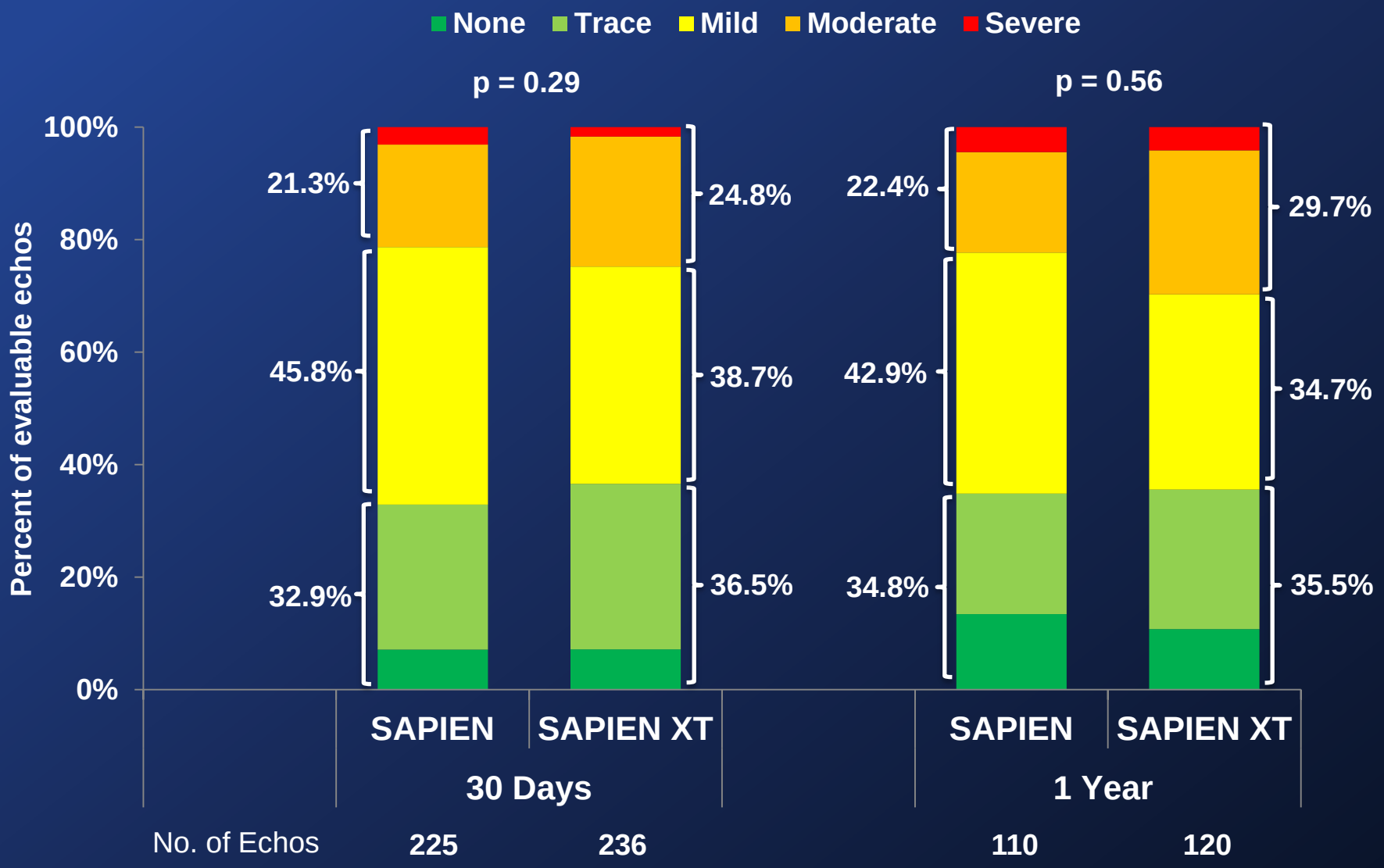
Paravalvular Aortic Regurgitation (AT, Valve Implant)

THE PARTNER II TRIAL



Total Aortic Regurgitation (AT, Valve Implant)

THE PARTNER II TRIAL



Primary Endpoint Events:
At 1 Year (ITT)

THE PARTNER II TRIAL

Events	SAPIEN (n=276)		SAPIEN XT (n=284)		
	n	%	n	%	p-value*
Death:					
All-Cause	63	23.7	62	22.5	0.71
Cardiovascular	39	15.1	32	12.0	0.30
Stroke:					
Disabling	12	4.6	12	4.5	0.93
All	15	5.7	16	5.9	0.93
All + TIA	18	6.9	16	5.9	0.65
Death (all-cause) and Stroke (disabling)	67	25.2	64	23.2	0.59
Re-hospitalizations	49	19.0	47	17.4	0.69
Death (all-cause), Stroke (disabling), and Re-hospitalizations	93	34.7	94	33.9	0.86

*p-values are KM - Log Rank

Primary Endpoint Events:
At 30 Days (AT)

THE PARTNER II TRIAL

Events	SAPIEN (n=271)		SAPIEN XT (n=282)		
	n	%	n	%	p-value*
Death:					
All-Cause	12	4.5	10	3.5	0.59
Cardiovascular	7	2.6	5	1.8	0.51
Stroke:					
Disabling	8	3.0	9	3.2	0.87
All	11	4.1	12	4.3	0.91
All + TIA	13	4.9	12	4.3	0.76
Death (all-cause) and Stroke (disabling)	17	6.3	18	6.4	0.97
Re-hospitalizations	27	10.3	32	11.6	0.63
Death (all-cause),Stroke (disabling), and Re-hosp	40	14.8	48	17.0	0.49

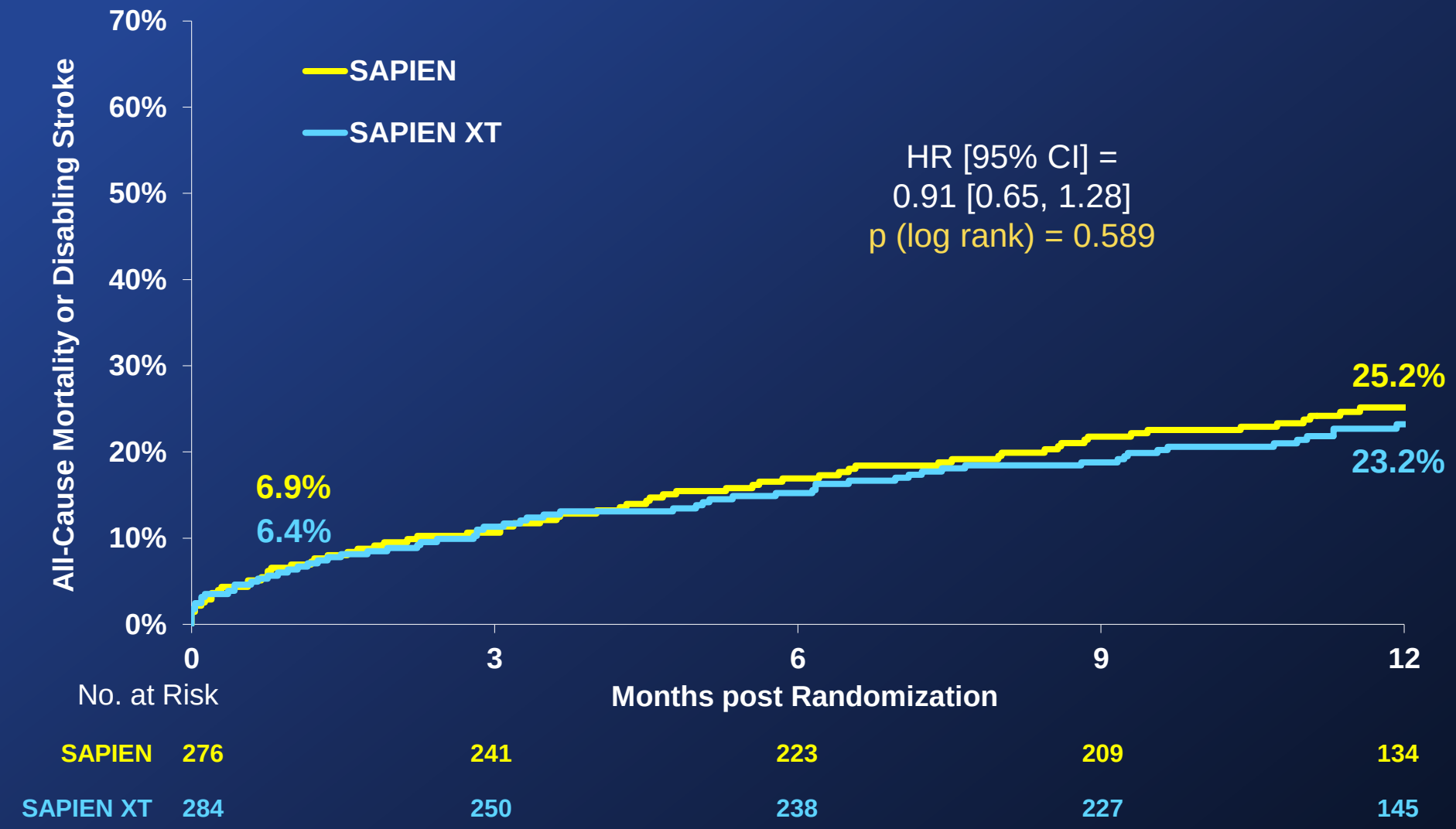
*p-values are KM - Log Rank

Statistical Analysis Plan

- Primary hypothesis is non-inferiority of test (SAPIEN XT) vs. control (SAPIEN) for all-cause mortality + disabling stroke + re-hospitalization at 1 year (non-hierarchical)
- **Non-inferiority ratio:** 1.35
- **One-sided alpha:** 0.025
- **Hypothesis testing:** upper bound of the 95% CI of the ratio of the primary endpoint (KM estimates test/control) < 1.35
- Assumptions (for 1:1 randomization)
  - Event rate: 43.6% in both trial arms
  - Power: 80%
- **Sample size:** 458 patients (adjusted to 500 patients to account for lost to follow-up and other trial contingencies)

All-Cause Mortality or Disabling Stroke (ITT)

THE PARTNER II TRIAL

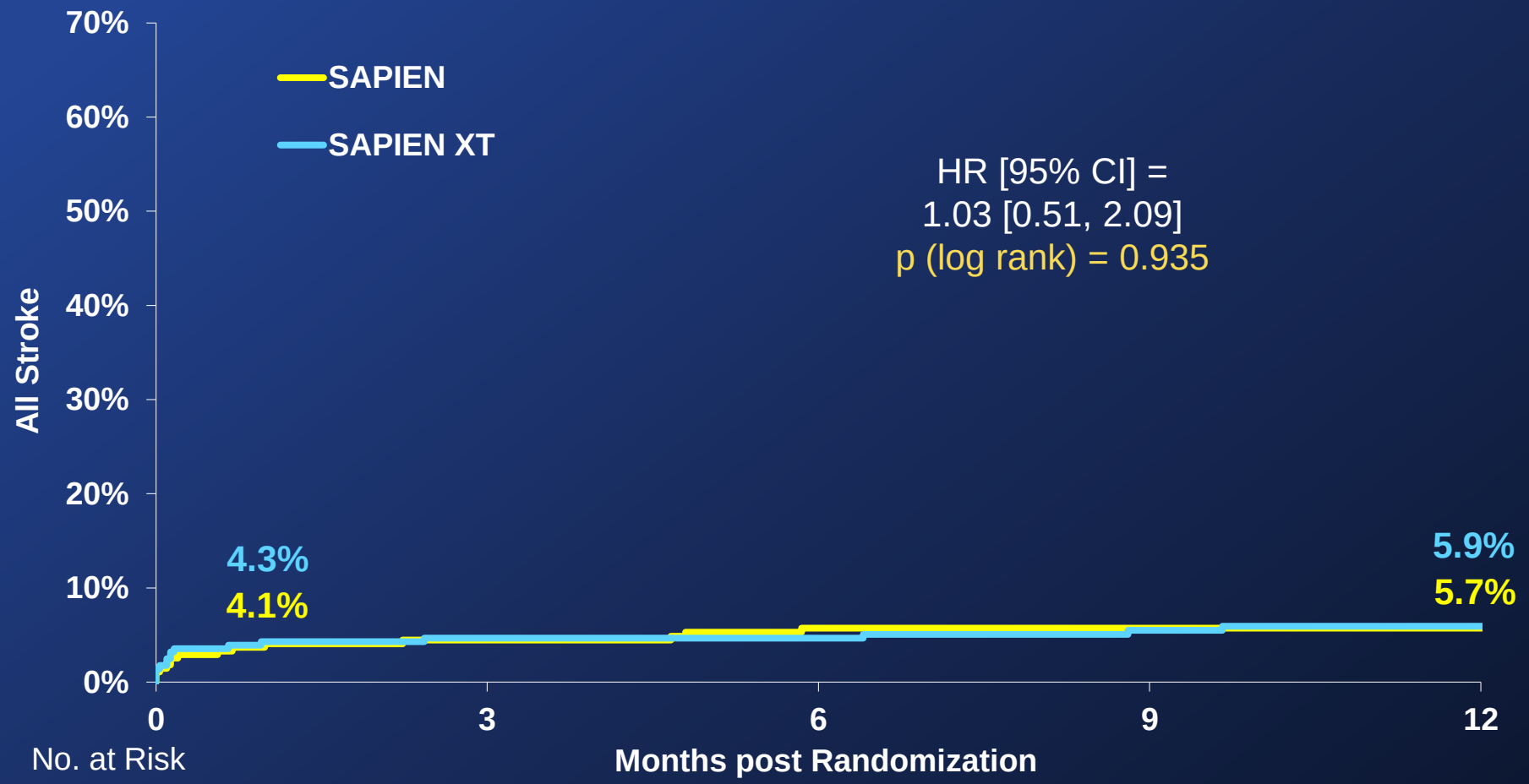


No. at Risk

SAPIEN	276	241	223	209	134
SAPIEN XT	284	250	238	227	145

All Stroke (ITT)

THE PARTNER II TRIAL



No. at Risk

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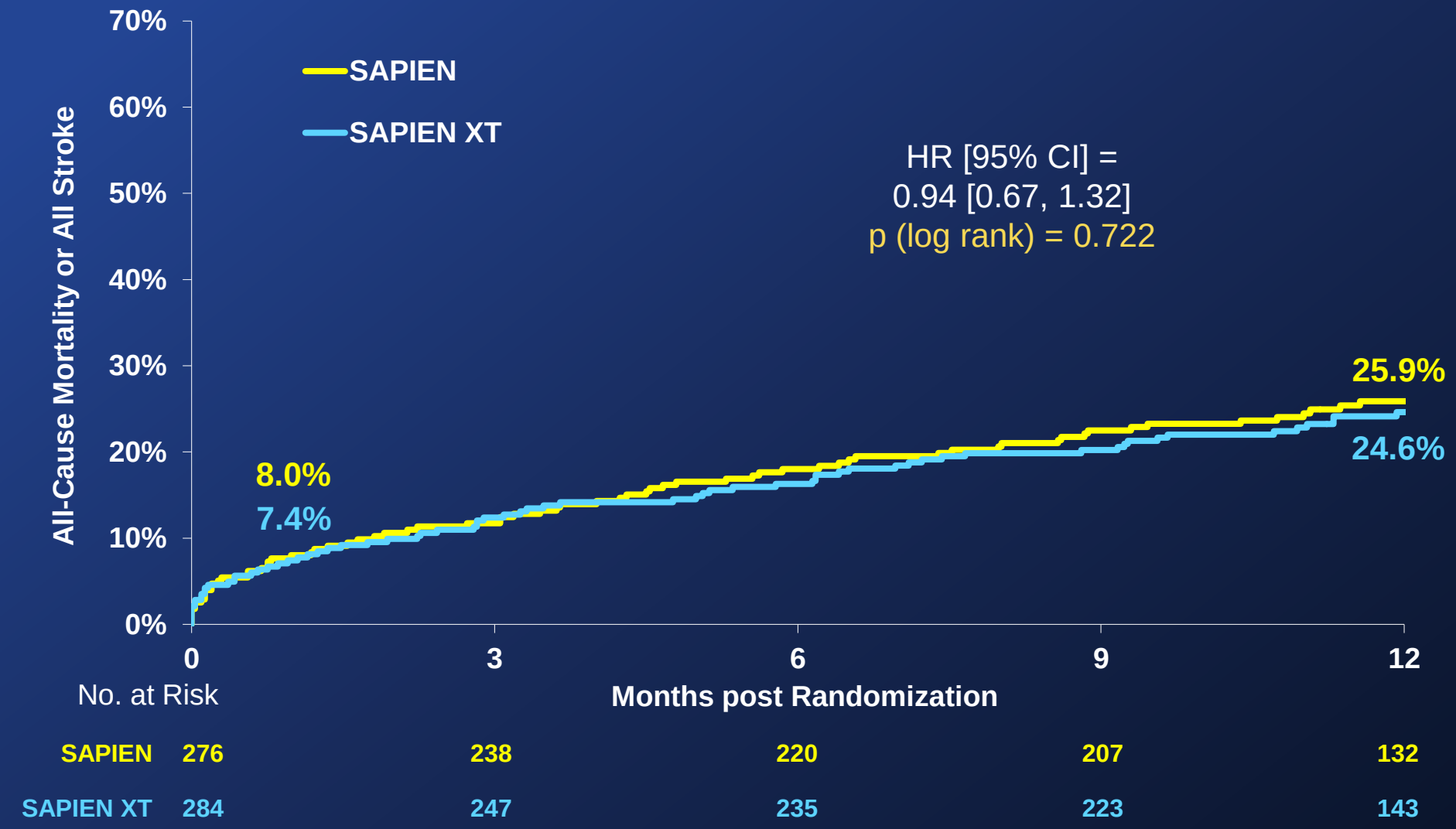
SAPIEN XT	284	247	235	223	143

All-Cause Mortality or All Stroke (ITT)

THE PARTNER II TRIAL



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