2013 Updates after Transcatheter or Surgical Aortic Valve Replacement in PARTENER Patients with Severe Aortic Stenosis

Gerald Yong MBBS (Hons) FRACP FSCAI
Interventional Cardiologist
Royal Perth Hospital
Western Australia

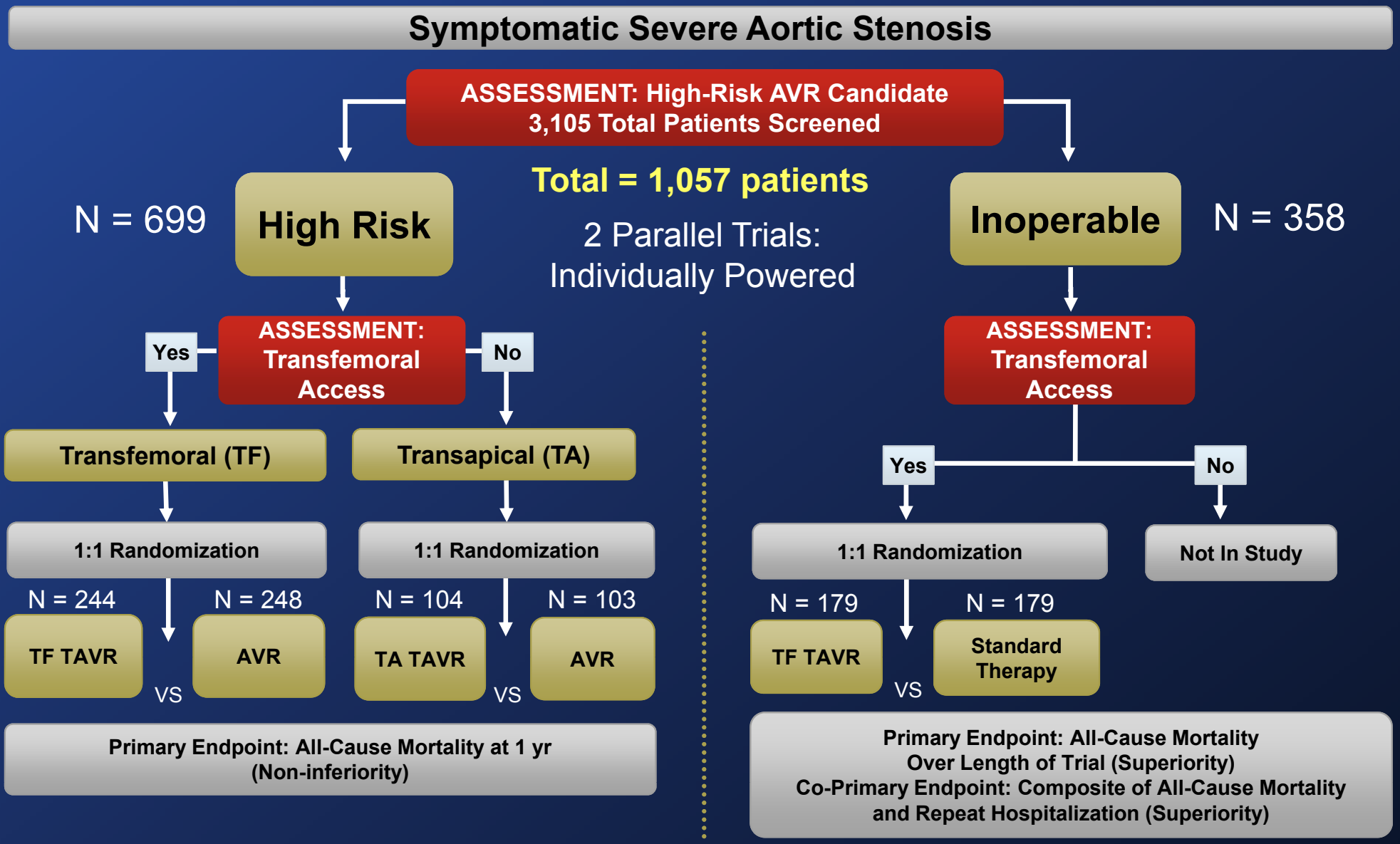
THE PARTNER TRIAL

Disclosure Statement of Financial Interest

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:	
Consulting Fees/Honoraria:	**Edwards Lifesciences (consultant & proctor)**
Major Stock Shareholder/Equity Interest:	
Royalty Income:	
Ownership/Founder:	
Salary:	
Intellectual Property Rights:	
Other Financial Benefit:	

PARTNER Study Design



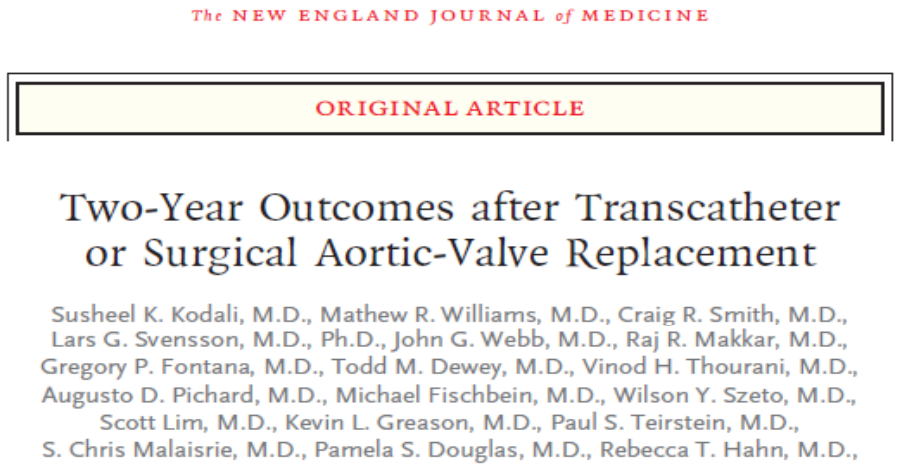
Publications in NEJM

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*



The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

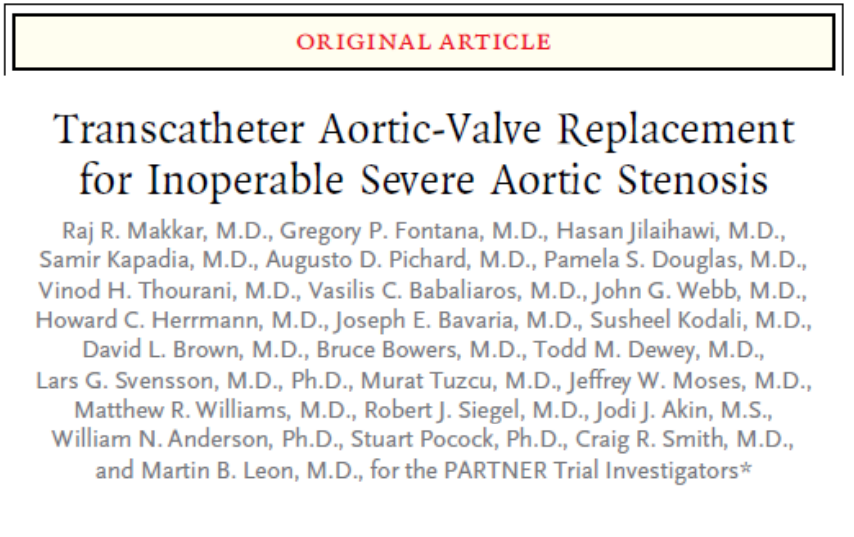
Two-Year Outcomes after Transcatheter or Surgical Aortic-Valve Replacement

Susheel K. Kodali, M.D., Mathew R. Williams, M.D., Craig R. Smith, M.D., Lars G. Svensson, M.D., Ph.D., John G. Webb, M.D., Raj R. Makkar, M.D., Gregory P. Fontana, M.D., Todd M. Dewey, M.D., Vinod H. Thourani, M.D., Augusto D. Pichard, M.D., Michael Fischbein, M.D., Wilson Y. Szeto, M.D., Scott Lim, M.D., Kevin L. Greason, M.D., Paul S. Teirstein, M.D., S. Chris Malaisrie, M.D., Pamela S. Douglas, M.D., Rebecca T. Hahn, M.D.,

The NEW ENGLAND JOURNAL of MEDICINE

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 C. 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*



ORIGINAL ARTICLE

Transcatheter Aortic-Valve Replacement for Inoperable Severe Aortic Stenosis

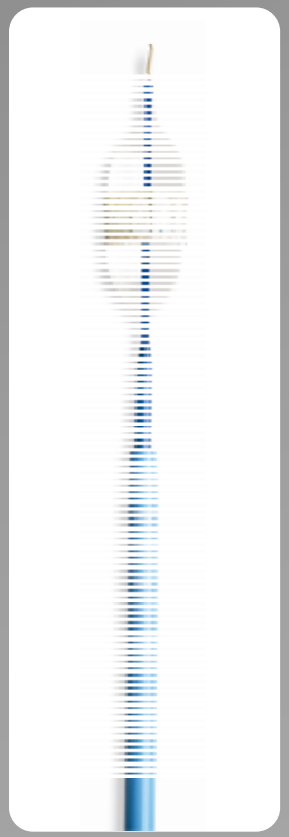
Raj R. Makkar, M.D., Gregory P. Fontana, M.D., Hasan Jilaihawi, M.D., Samir Kapadia, M.D., Augusto D. Pichard, M.D., Pamela S. Douglas, M.D., Vinod H. Thourani, M.D., Vasilis C. Babaliaros, M.D., John G. Webb, M.D., Howard C. Herrmann, M.D., Joseph E. Bavaria, M.D., Susheel Kodali, M.D., David L. Brown, M.D., Bruce Bowers, M.D., Todd M. Dewey, M.D., Lars G. Svensson, M.D., Ph.D., Murat Tuzcu, M.D., Jeffrey W. Moses, M.D., Matthew R. Williams, M.D., Robert J. Siegel, M.D., Jodi J. Akin, M.S., William N. Anderson, Ph.D., Stuart Pocock, Ph.D., Craig R. Smith, M.D., and Martin B. Leon, M.D., for the PARTNER Trial Investigators*

Study Devices

THE PARTNER TRIAL

Transfemoral

Transapical



Edwards SAPIEN THV
23 and 26 mm valves

RetroFlex
22 and 24 F sheaths

Ascendra
24 and 26 F sheaths

Enrolling Study Sites

THE PARTNER TRIAL

n = 699 patients
25 investigator sites
22 USA, 2 Canada, 1 Germany

PARTNER Study Design

THE PARTNER TRIAL

Symptomatic Severe Aortic Stenosis

ASSESSMENT: High-Risk AVR Candidate
3,105 Total Patients Screened

Total = 1,057 patients

2 Parallel Trials:
Individually Powered

Inoperable N = 358

ASSESSMENT: Transfemoral Access

Yes | **No**

1:1 Randomization

Not In Study

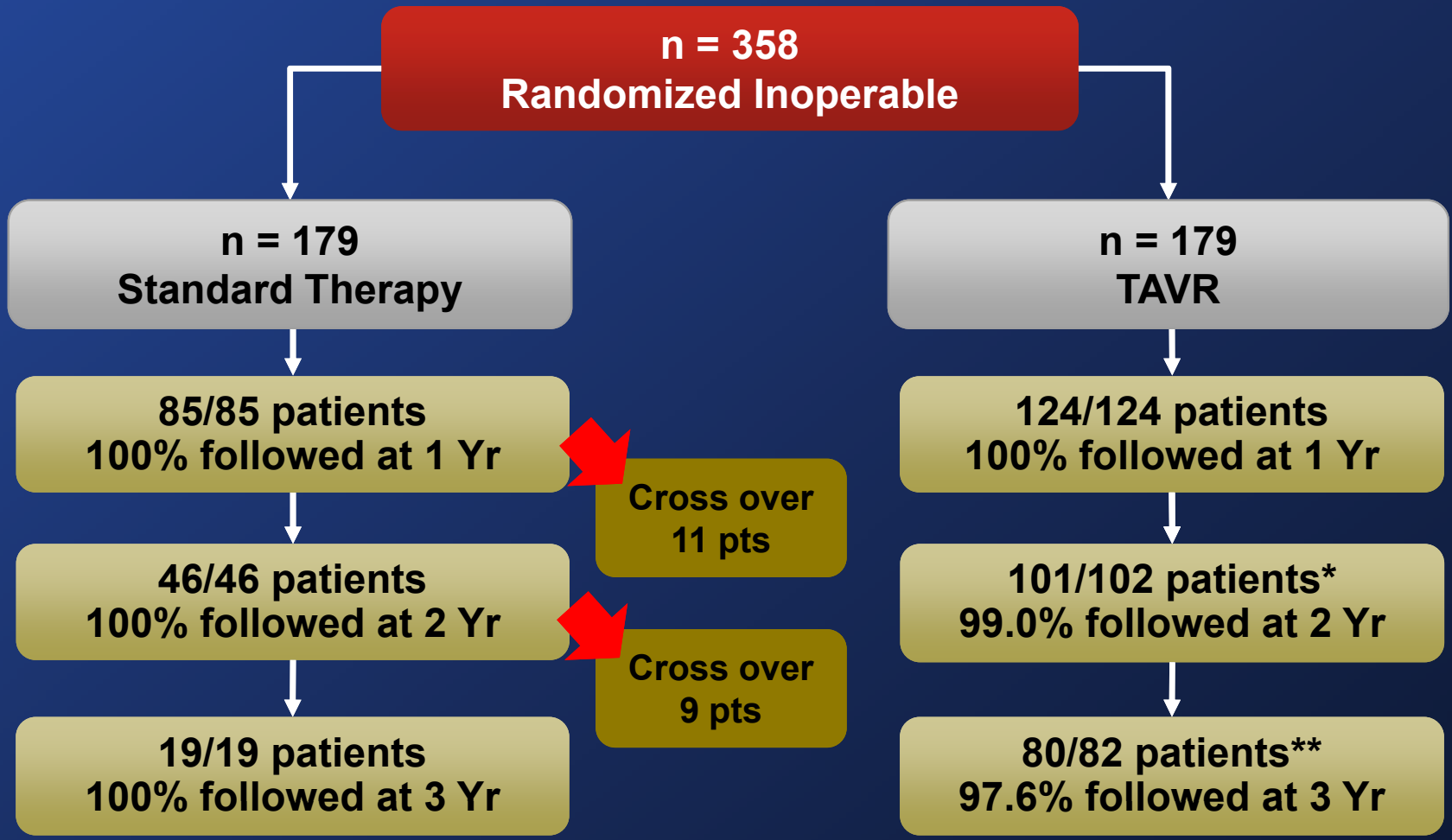
N = 179 **TF TAVR**

VS

N = 179 **Standard Therapy**

Primary Endpoint: All-Cause Mortality
Over Length of Trial (Superiority)
Co-Primary Endpoint: Composite of All-Cause Mortality and Repeat Hospitalization (Superiority)

Study Flow of 3-Year FU
Cohort B Inoperable Patients



- **One TAVR patient was alive and censored prior to the window*
- ***Two TAVR patients were alive and censored prior to the window (including the one in the same status at 2 years); one TAVR patient withdrew between 2 and 3 years*
- *No patients were lost to follow-up*

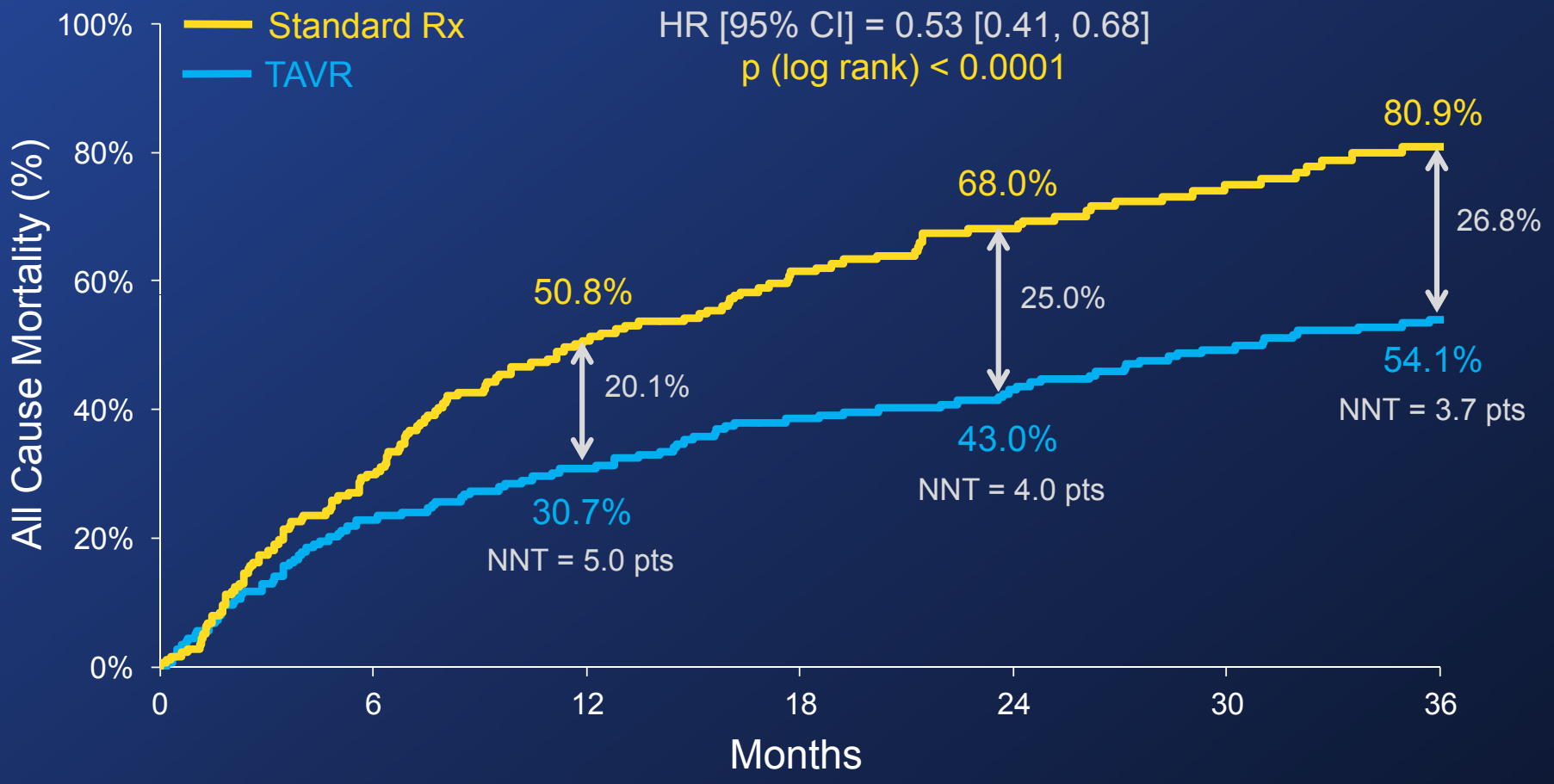
Samir R. Kapadia, MD in TCT 2012

Patient Characteristics (1)

Characteristic	*TAVR* *n = 179*	*Standard Rx* *n = 179*	*p value*
Age – yr	83.1 ± 8.6	83.2 ± 8.3	0.95
Male sex (%)	45.8	46.9	0.92
STS Score	11.2 ± 5.8	12.1 ± 6.1	0.14
NYHA			
I or II (%)	7.8	6.1	0.68
III or IV (%)	92.2	93.9	0.68
CAD (%)	67.6	74.3	0.20
Prior MI (%)	18.6	26.4	0.10
Prior CABG (%)	37.4	45.6	0.17
Prior PCI (%)	30.5	24.8	0.31
Prior BAV (%)	16.2	24.4	0.09
CVD (%)	27.4	27.5	1.00

Note: Same as previously presented at TCT 2010 and published in the NEJM manuscript.

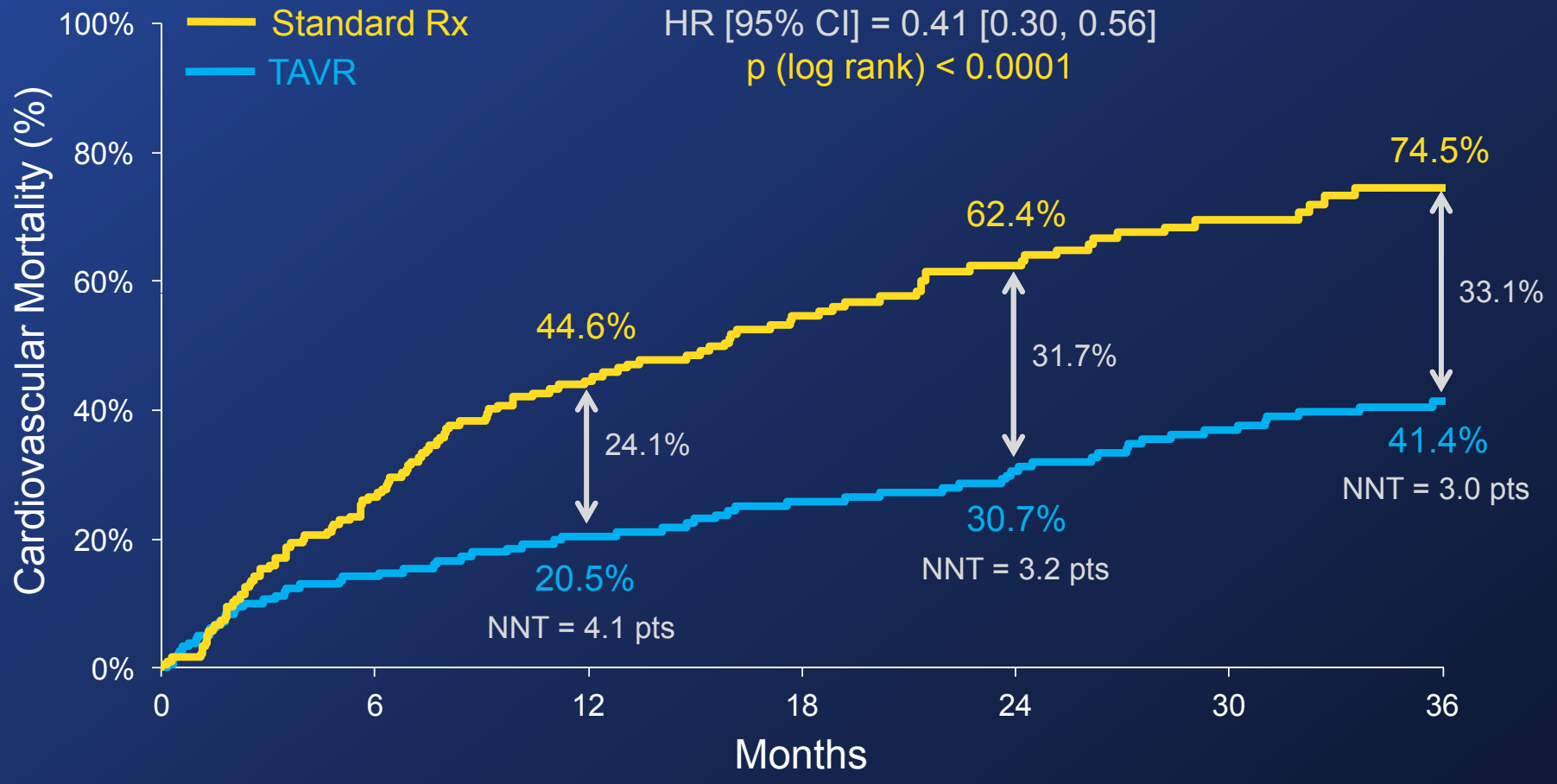
All Cause Mortality (ITT)
Crossover Patients Censored at Crossover



Numbers at Risk

Standard Rx	**179**	**121**	**85**	**62**	**46**	**27**	**17**
TAVR	**179**	**138**	**124**	**110**	**101**	**88**	**70**

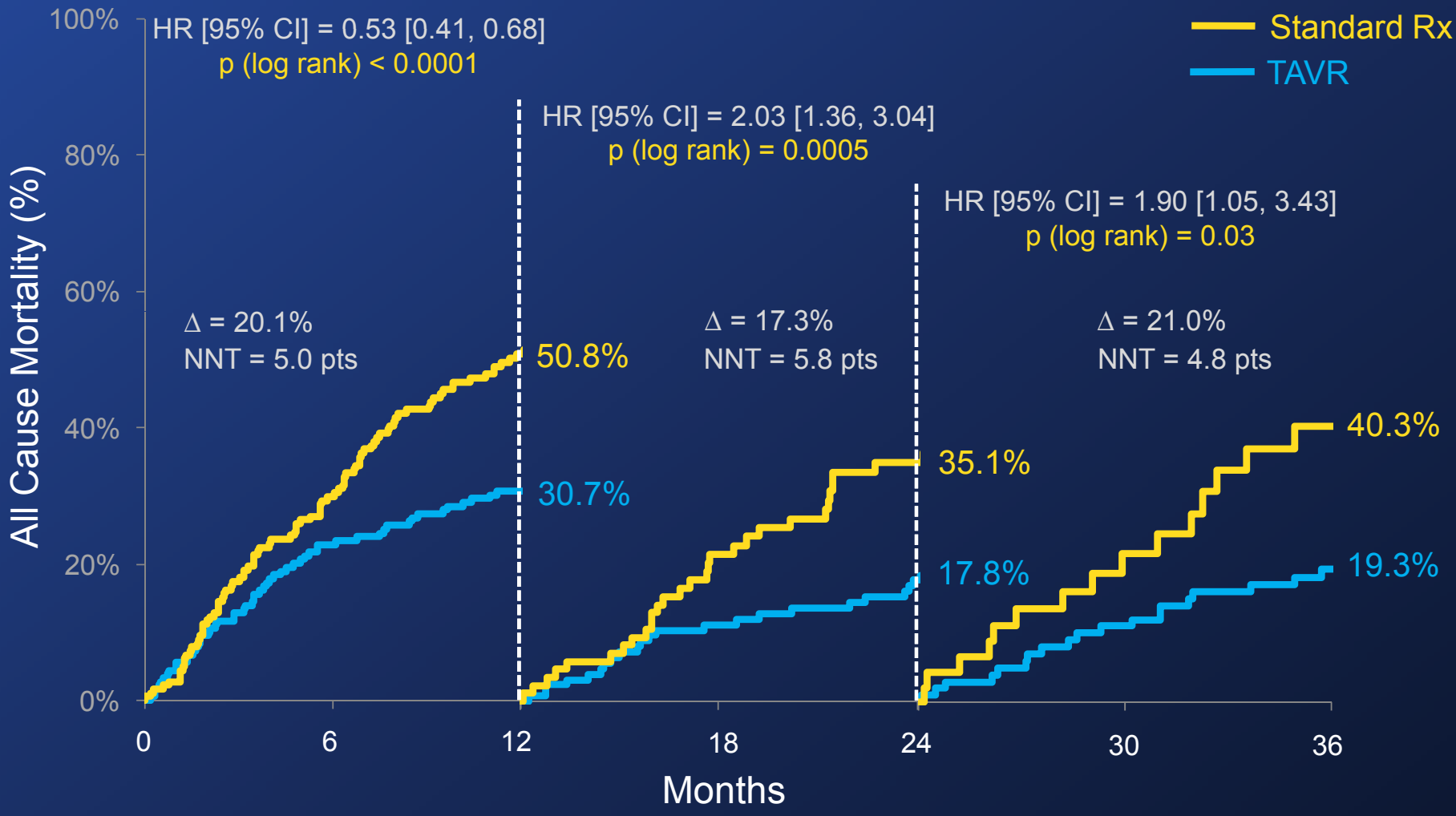
Cardiovascular Mortality (ITT)
Crossover Patients Censored at Crossover



Numbers at Risk

Standard Rx	**179**	**121**	**85**	**62**	**46**	**27**	**17**
TAVR	**179**	**138**	**124**	**110**	**101**	**88**	**70**

All Cause Mortality (ITT)
Landmark Analysis



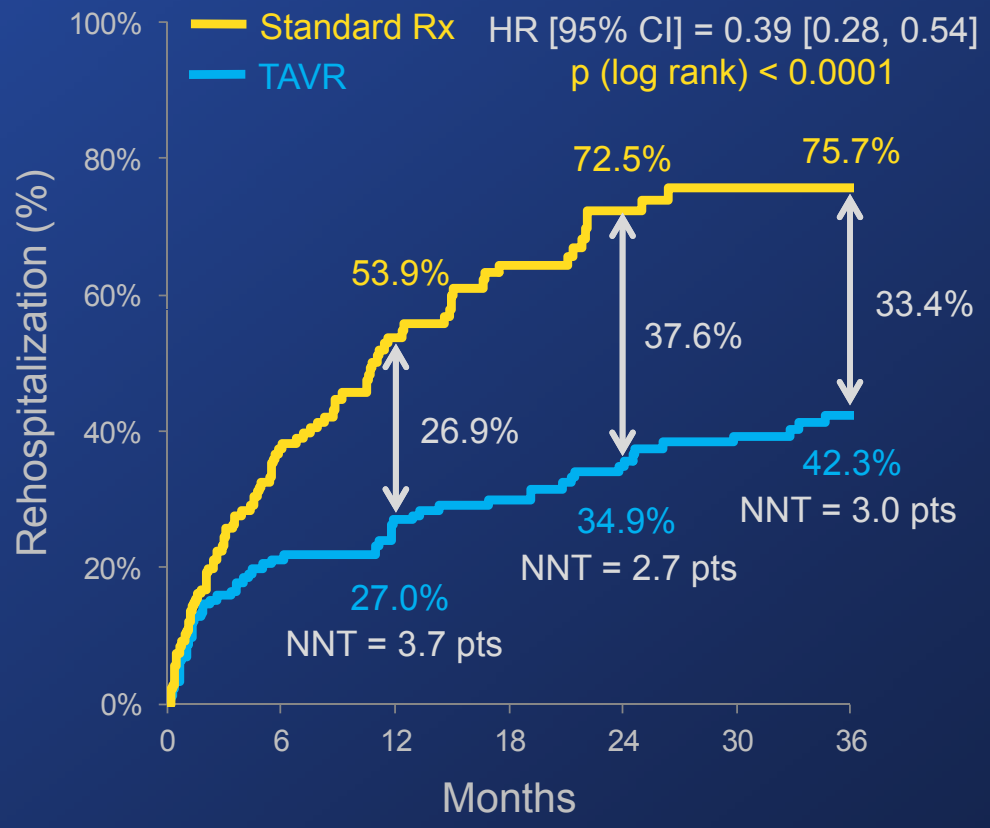
Numbers at Risk

Standard Rx	**179**	**121**	**85**	**62**	**46**	**27**	**17**
TAVR	**179**	**138**	**124**	**110**	**101**	**88**	**70**

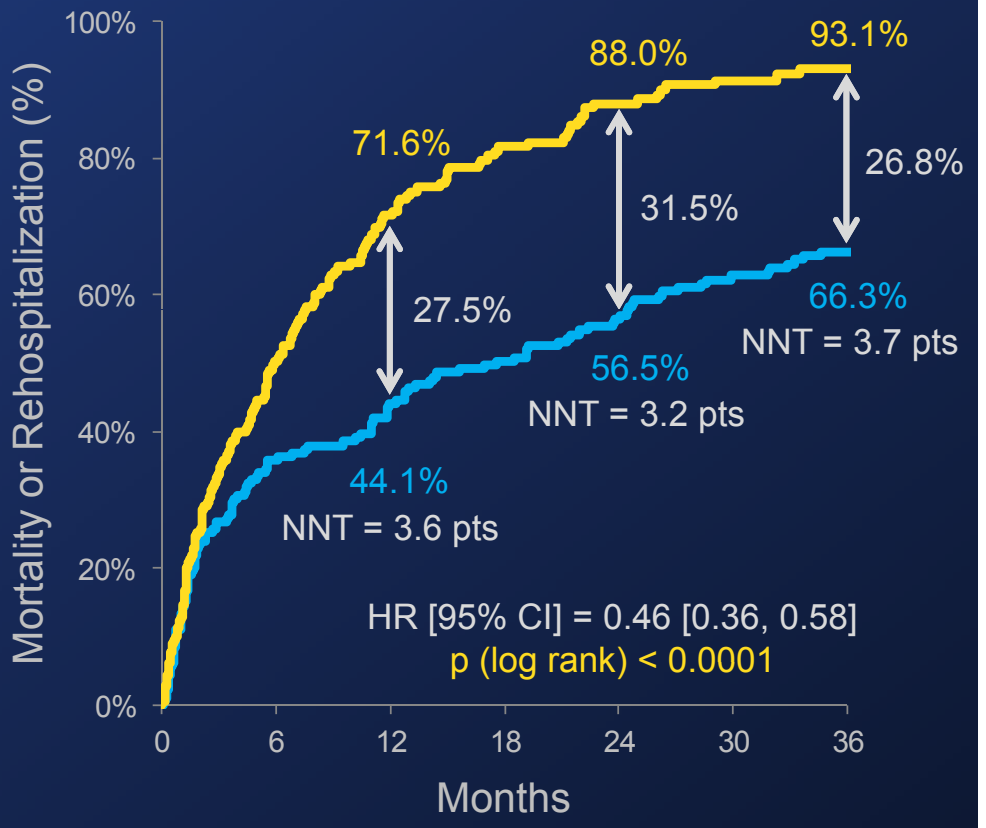
Repeat Hospitalization (ITT)

THE PARTNER TRIAL

Rehospitalization



Mortality or Rehospitalization

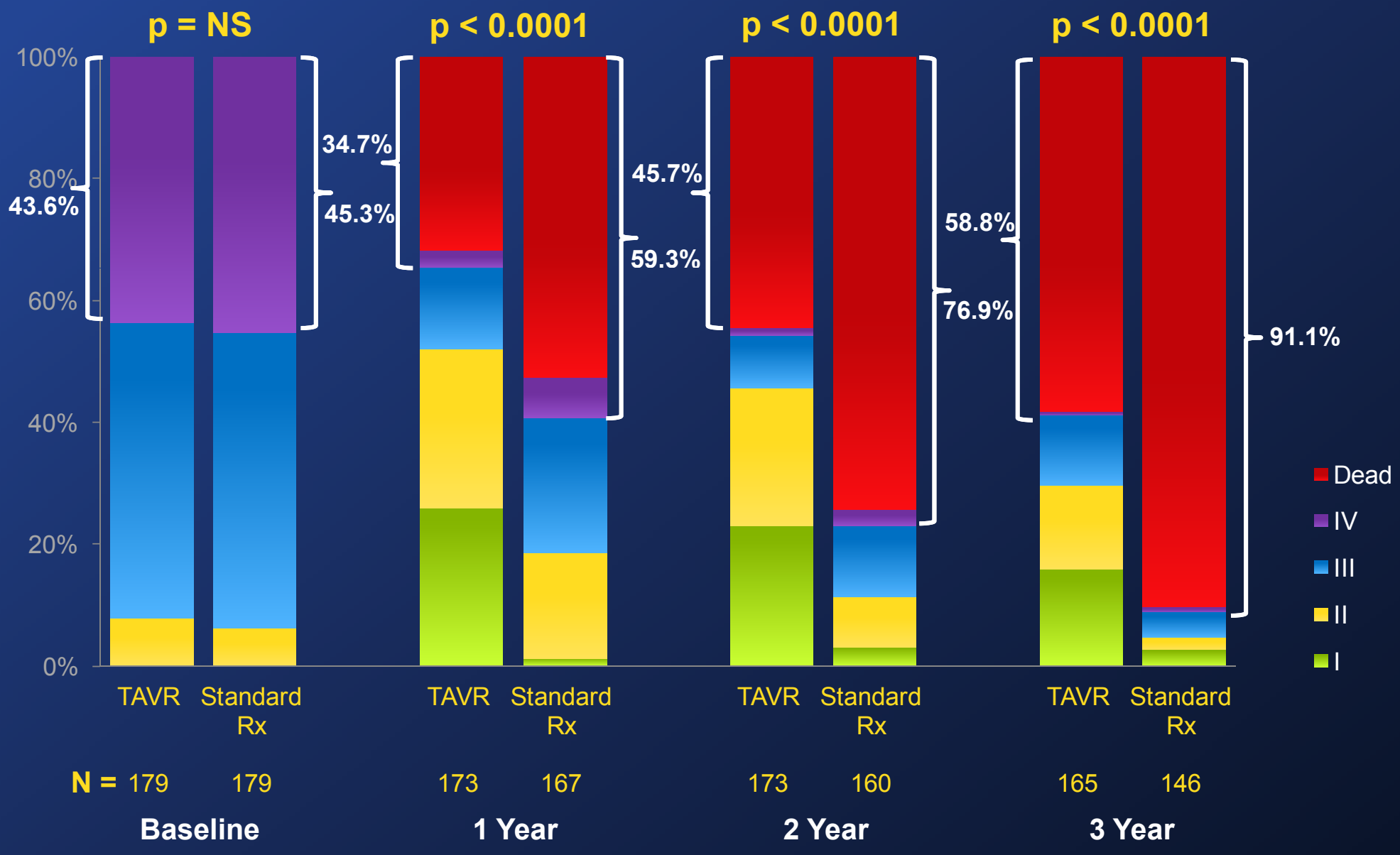


Days Alive Out of Hospital Median [IQR] **TAVR 944 [233-1096]** **Standard Rx 368 [147-1096]** **p <.0001**

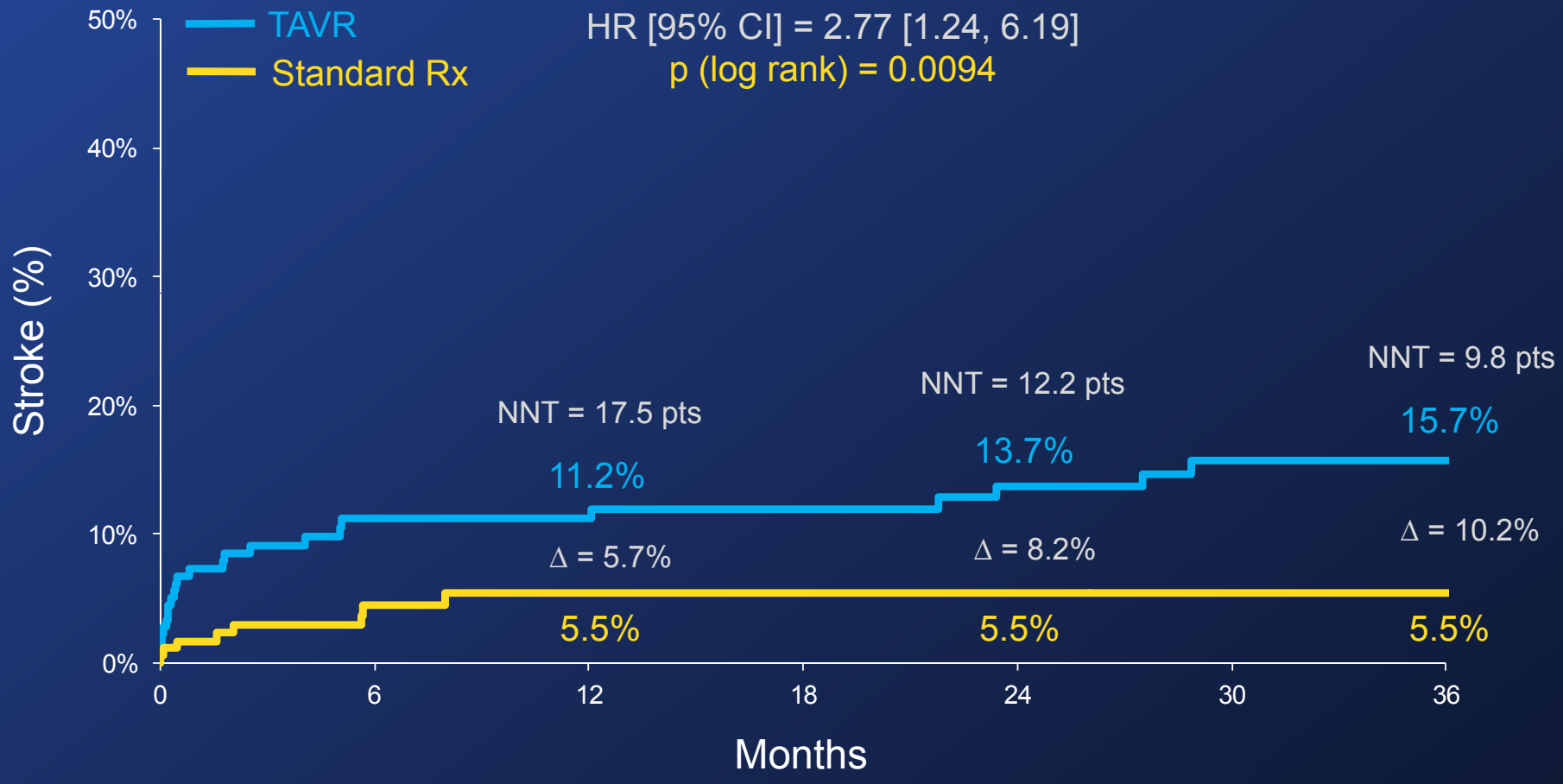
Numbers at Risk

Standard Rx	**179**	**86**	**49**	**30**	**19**	**11**	**7**	**179**	**86**	**49**	**30**	**19**	**11**	**7**
TAVR	**179**	**115**	**100**	**89**	**77**	**64**	**49**	**179**	**115**	**100**	**89**	**77**	**64**	**49**

NYHA Class Over Time (ITT)



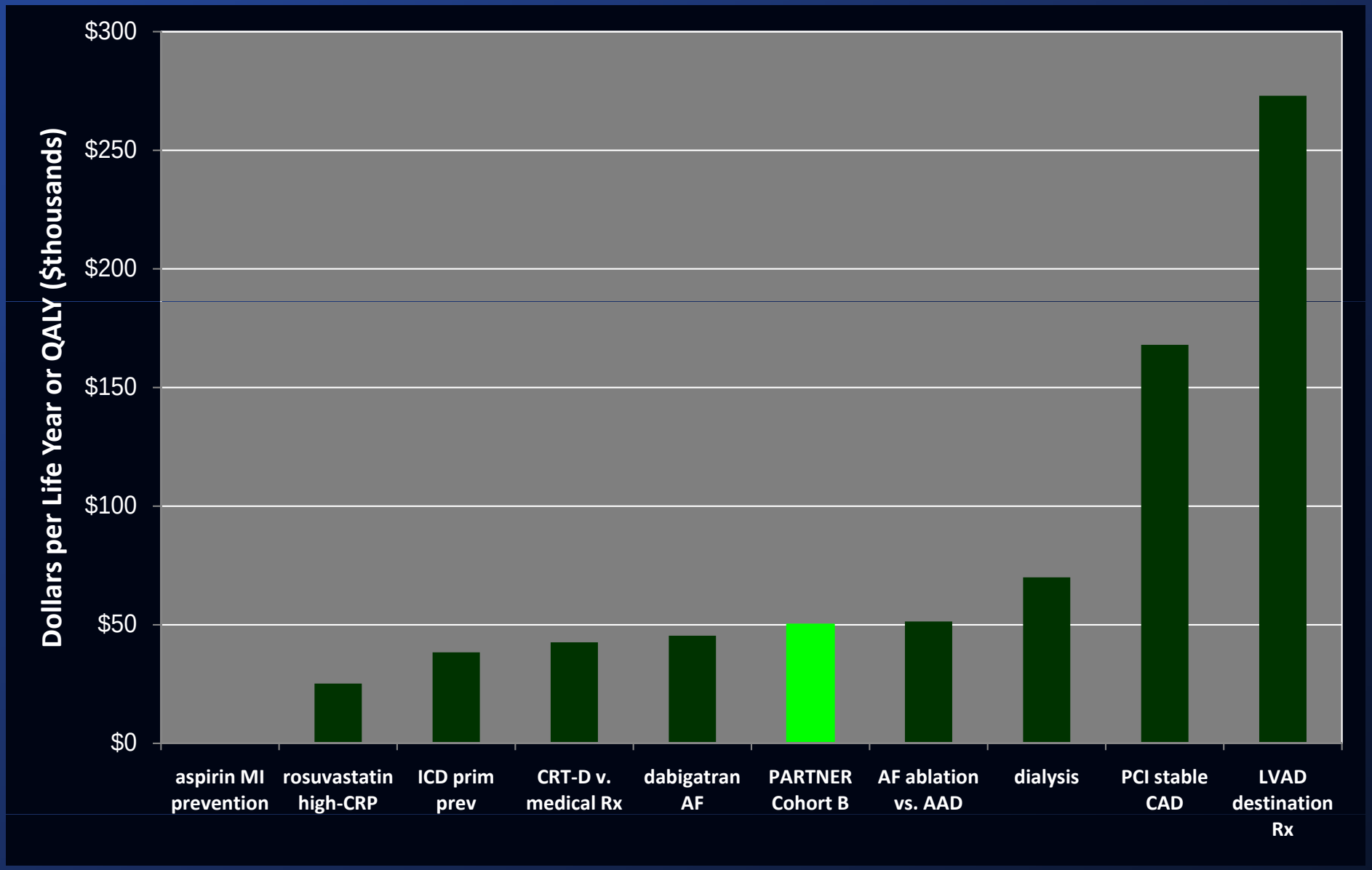
All Stroke (ITT)



Numbers at Risk

TAVR	**179**	**128**	**116**	**105**	**96**	**82**	**65**
Standard Rx	**179**	**118**	**84**	**62**	**46**	**27**	**17**

PARTNER Cohort B – Cost Effectiveness

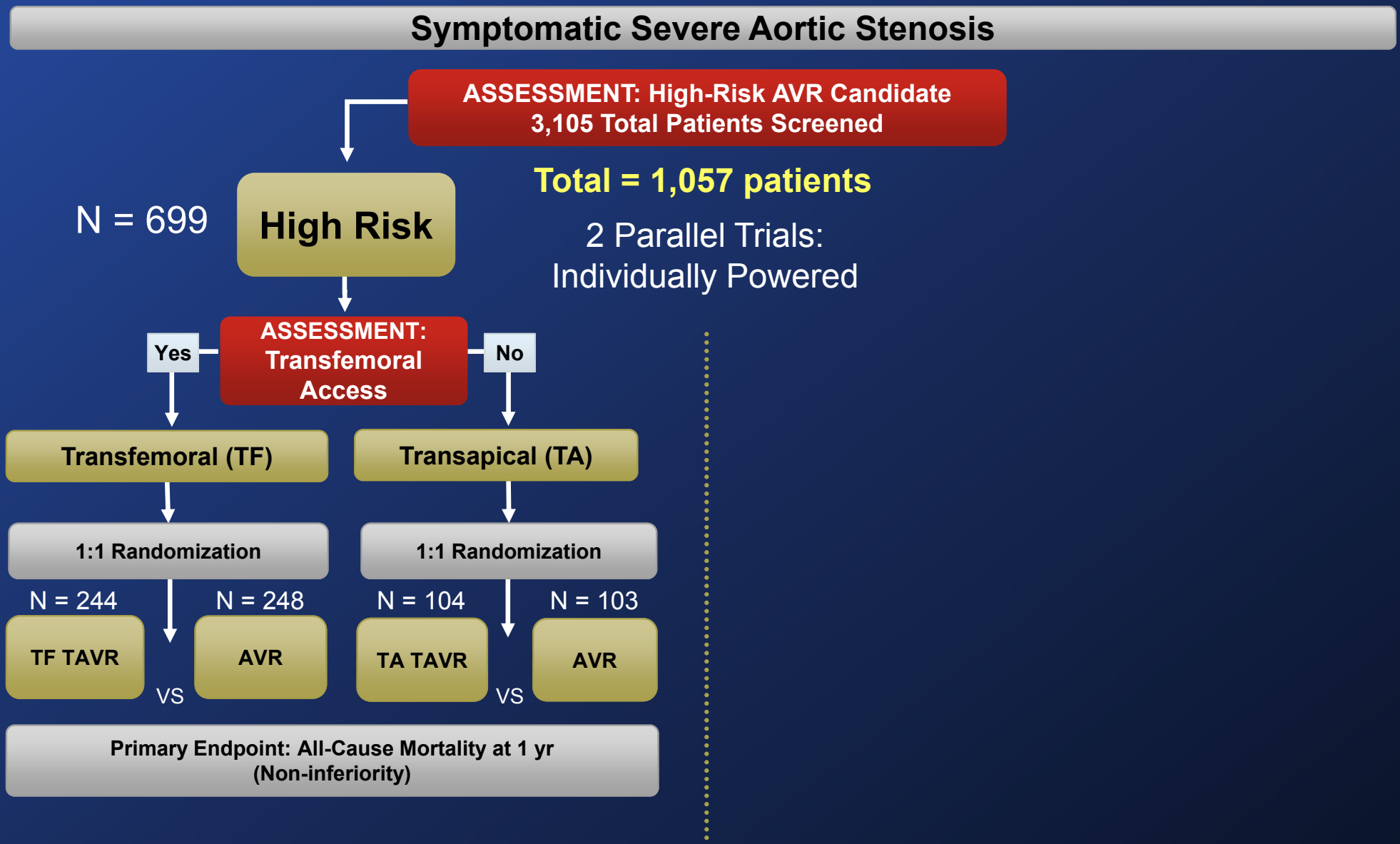


Reynolds, M. R., et al. *Circulation.* 2012;125:1102-9

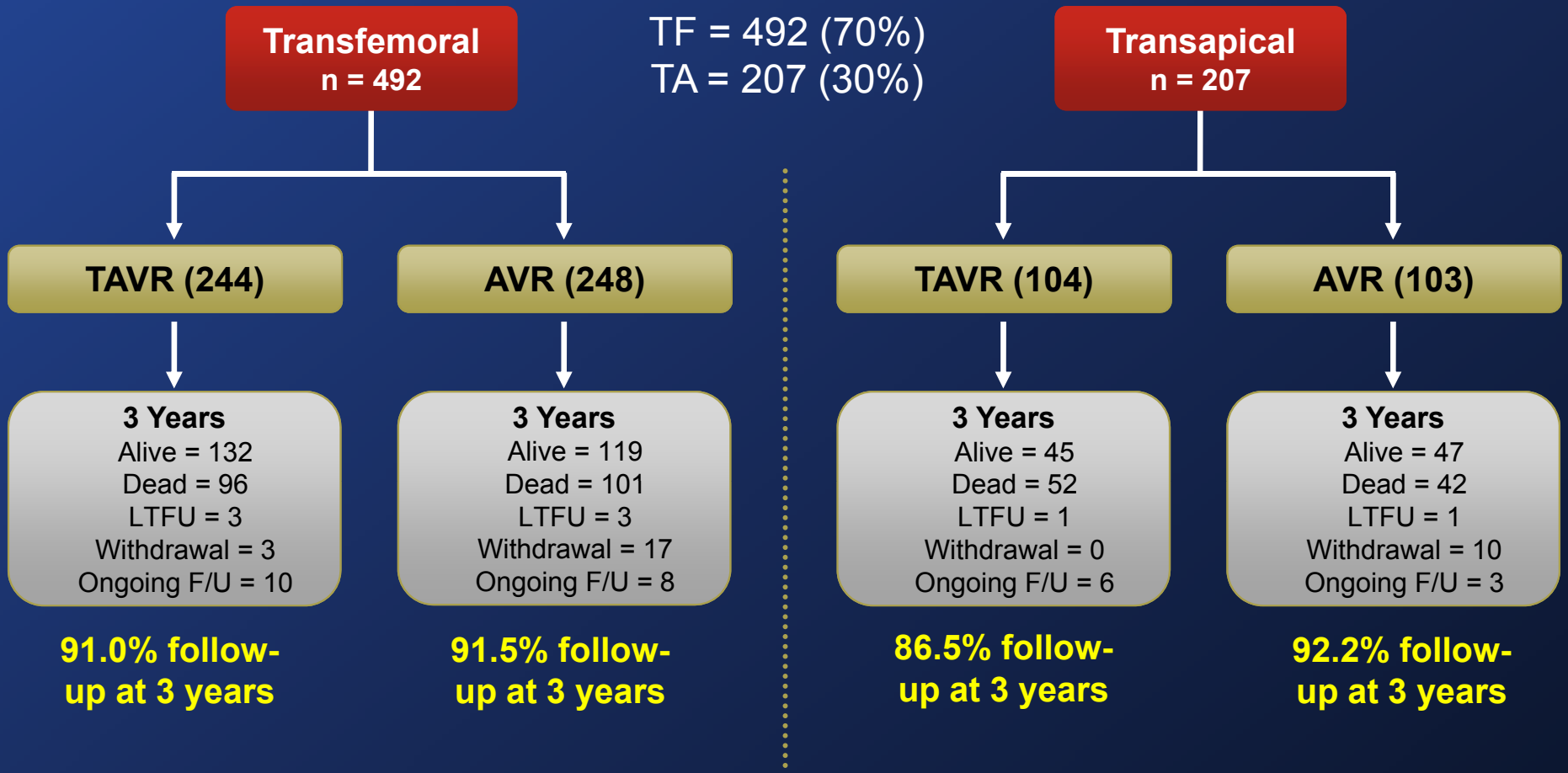
Clinical Implications

- Three year data continue to support the role of TAVR as the standard-of-care for symptomatic patients with aortic stenosis who are not surgical candidates.
- These data underscore the importance of patient selection before TAVR and the need for aggressive management of illnesses after TAVR.

PARTNER Study Design



Study Flow of 3-Year FU Cohort A High-Risk Patients

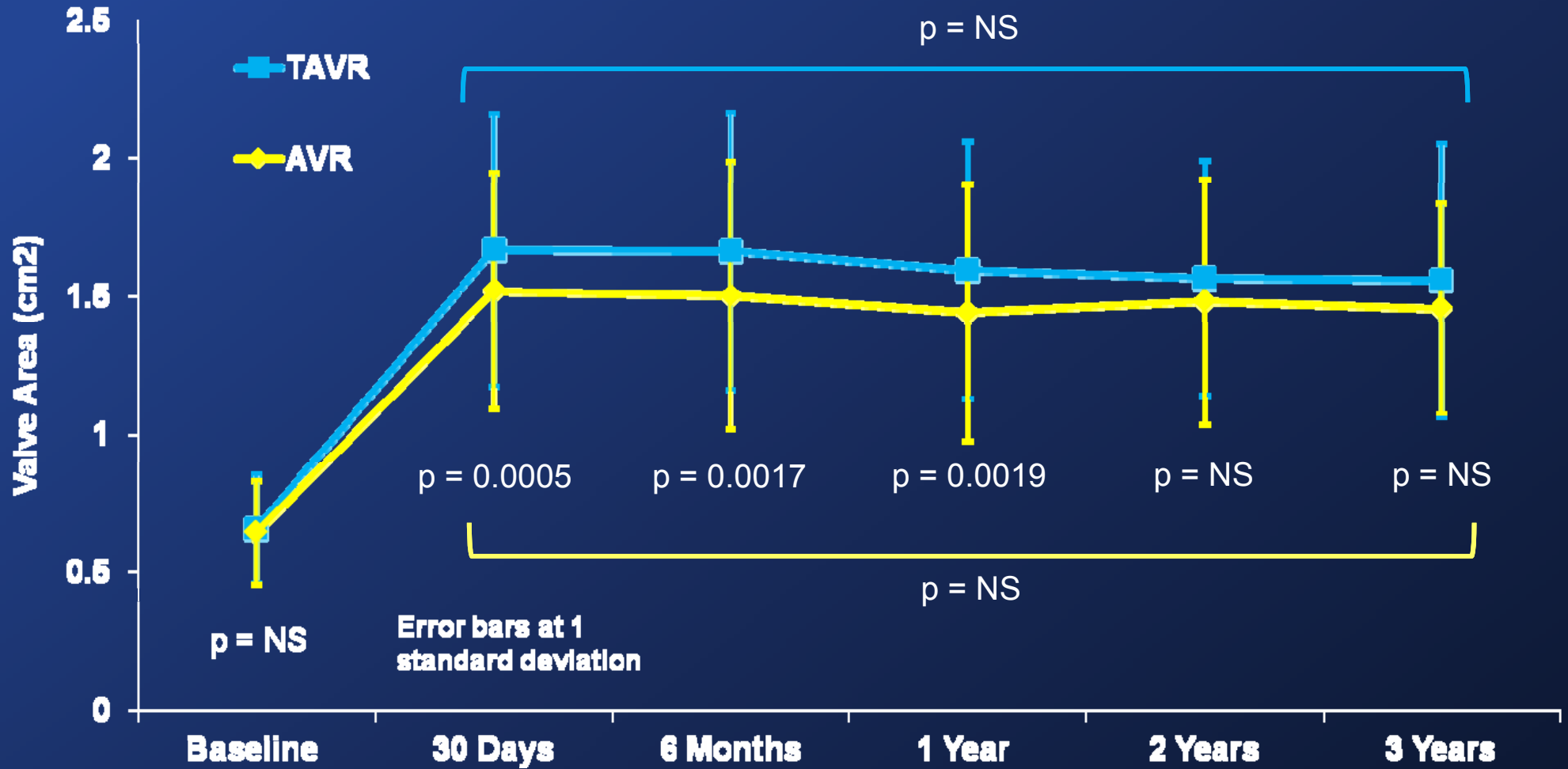


Vinod H. Thourani, MD in ACC 2013

Baseline Patient Characteristics
Demographics

	TAVR (n=348)		AVR (n=351)	
Characteristic	n		n	
Age – years (Mean ± SD)	348	83.6 ± 6.8	349	84.5 ± 6.4
Male	201	57.8%	198	56.7%
NYHA Class III or IV	328	94.3%	328	94.0%
Previous CABG	148	42.5	152	43.6
Cerebrovascular disease	96	29.4	87	26.8
Peripheral vascular disease	149	43.2	142	41.6
STS Score (Mean ± SD)	347	11.8 ± 3.3	349	11.7 ± 3.5

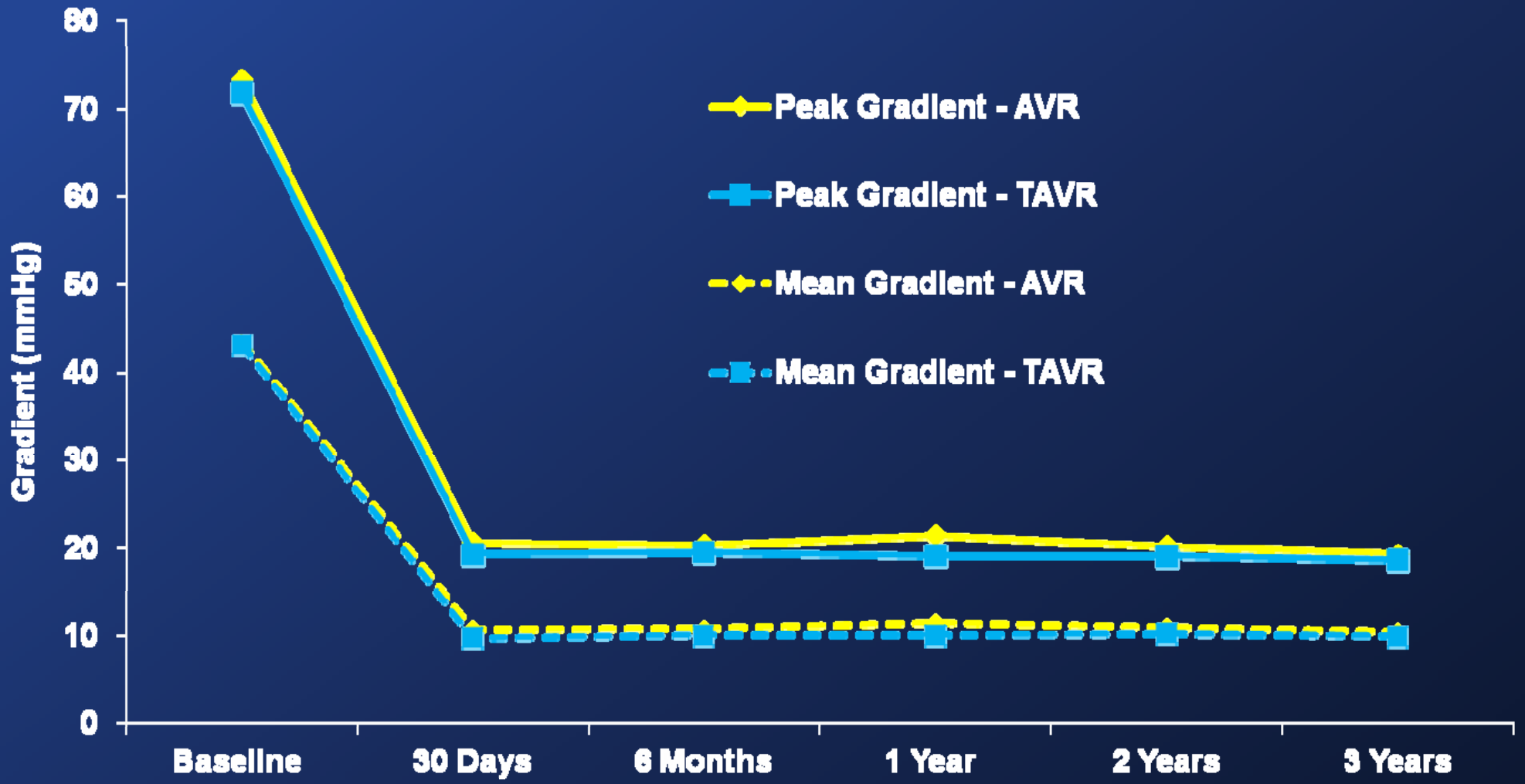
Echocardiographic Findings (AT)
Aortic Valve Area



No. of Echos

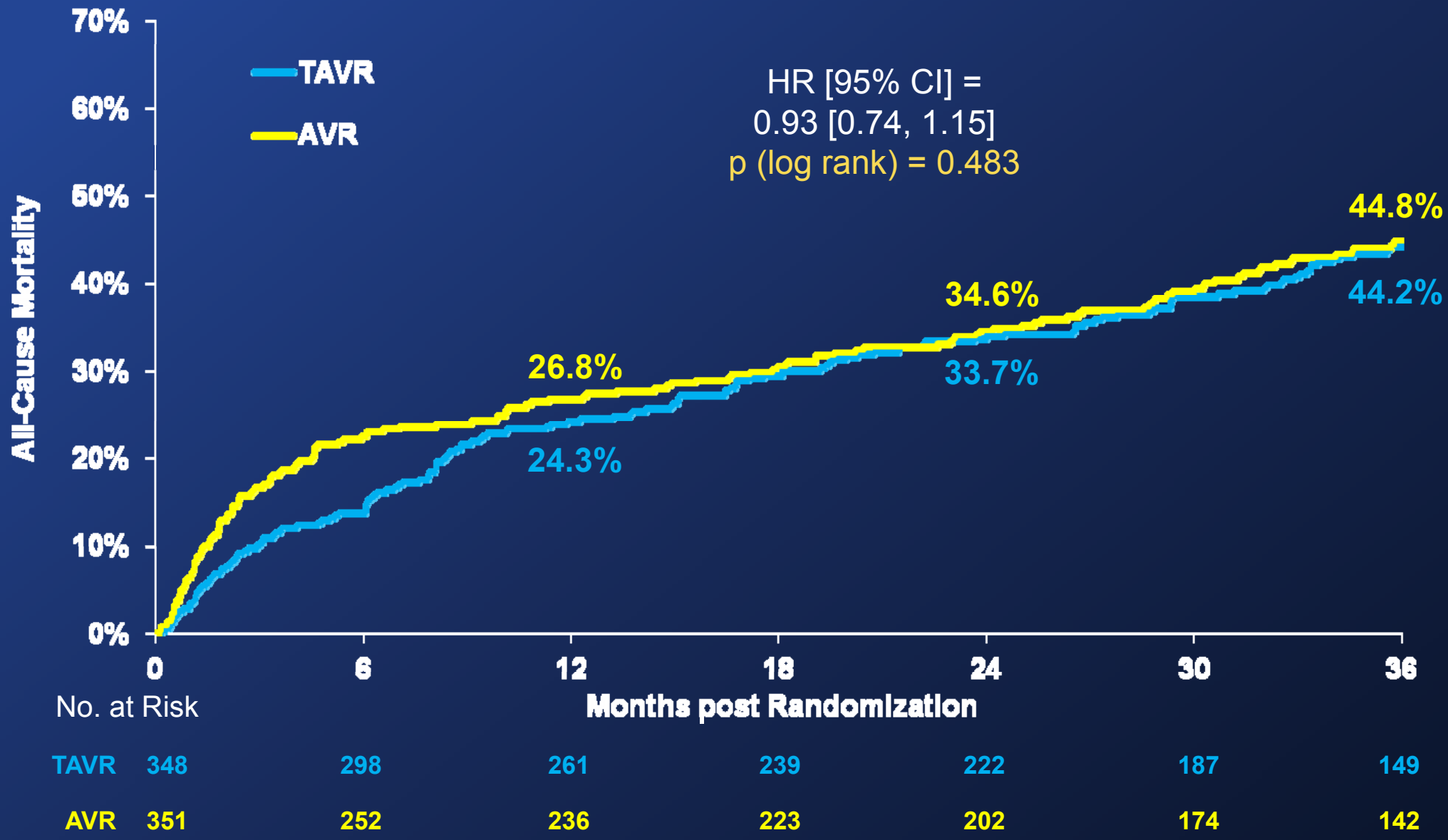
TAVR	304	271	223	211	150	88
AVR	294	226	163	154	121	70

Echocardiographic Findings (AT)
Mean & Peak Gradients



No. of Echos	Baseline	30 Days	6 Months	1 Year	2 Years	3 Years
TAVR	310	277	233	219	155	88
AVR	299	230	169	158	123	72

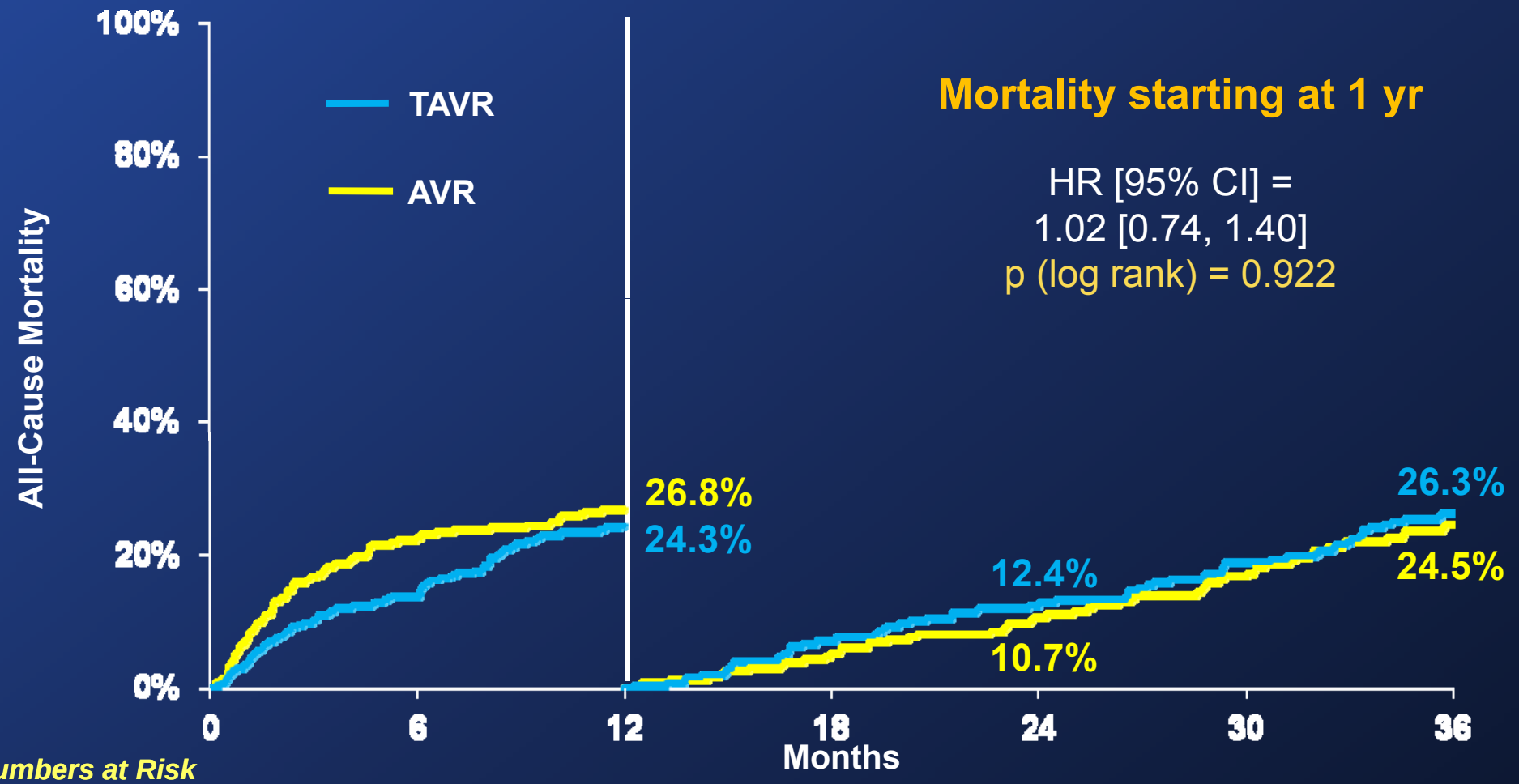
All-Cause Mortality (ITT)



No. at Risk

TAVR	348	298	261	239	222	187	149
AVR	351	252	236	223	202	174	142

All-Cause Mortality (ITT)
Landmark Analysis



Mortality starting at 1 yr

HR [95% CI] =
1.02 [0.74, 1.40]
p (log rank) = 0.922

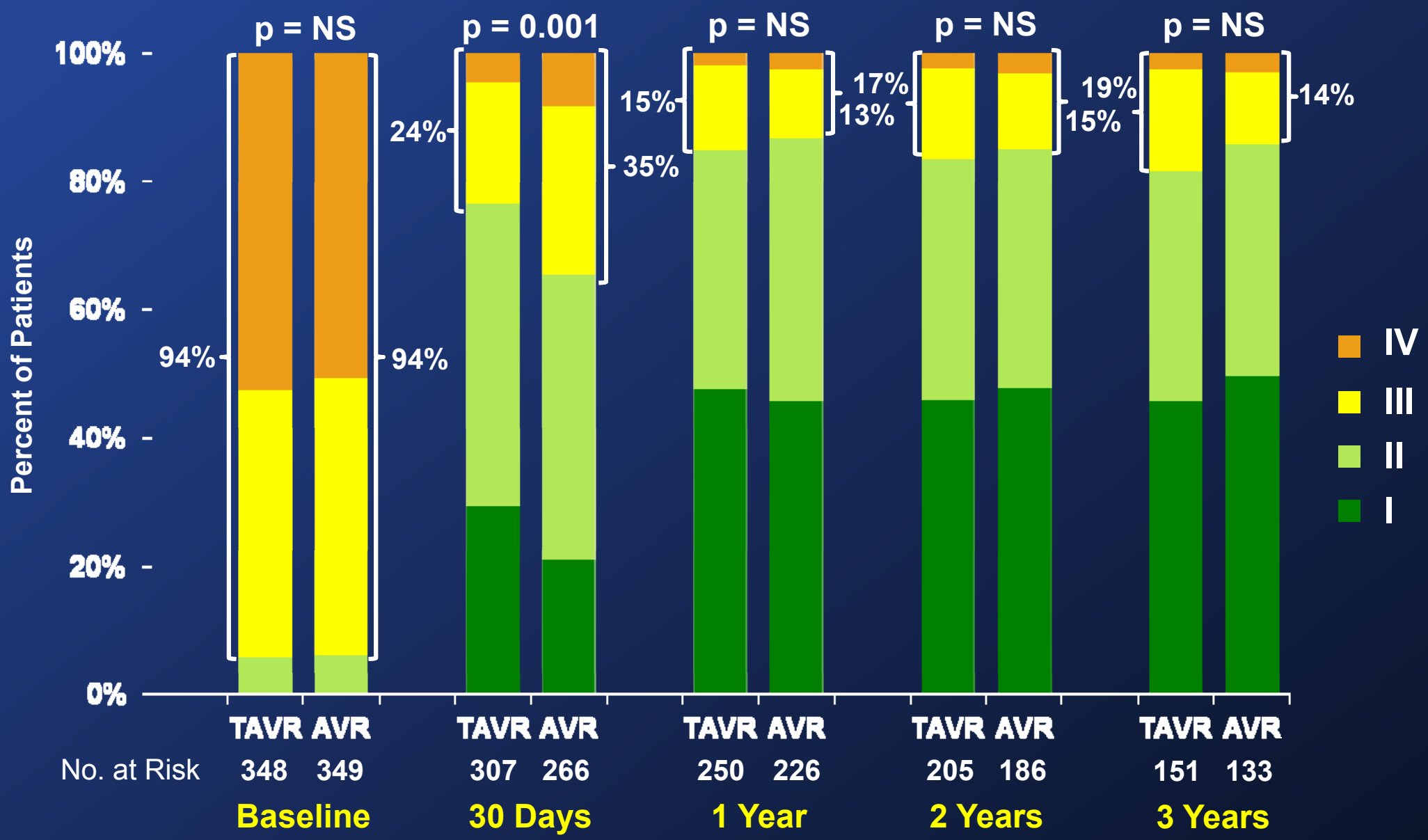
Numbers at Risk

TAVR	348	298	261	239	222	187	149
AVR	351	252	236	223	202	174	142

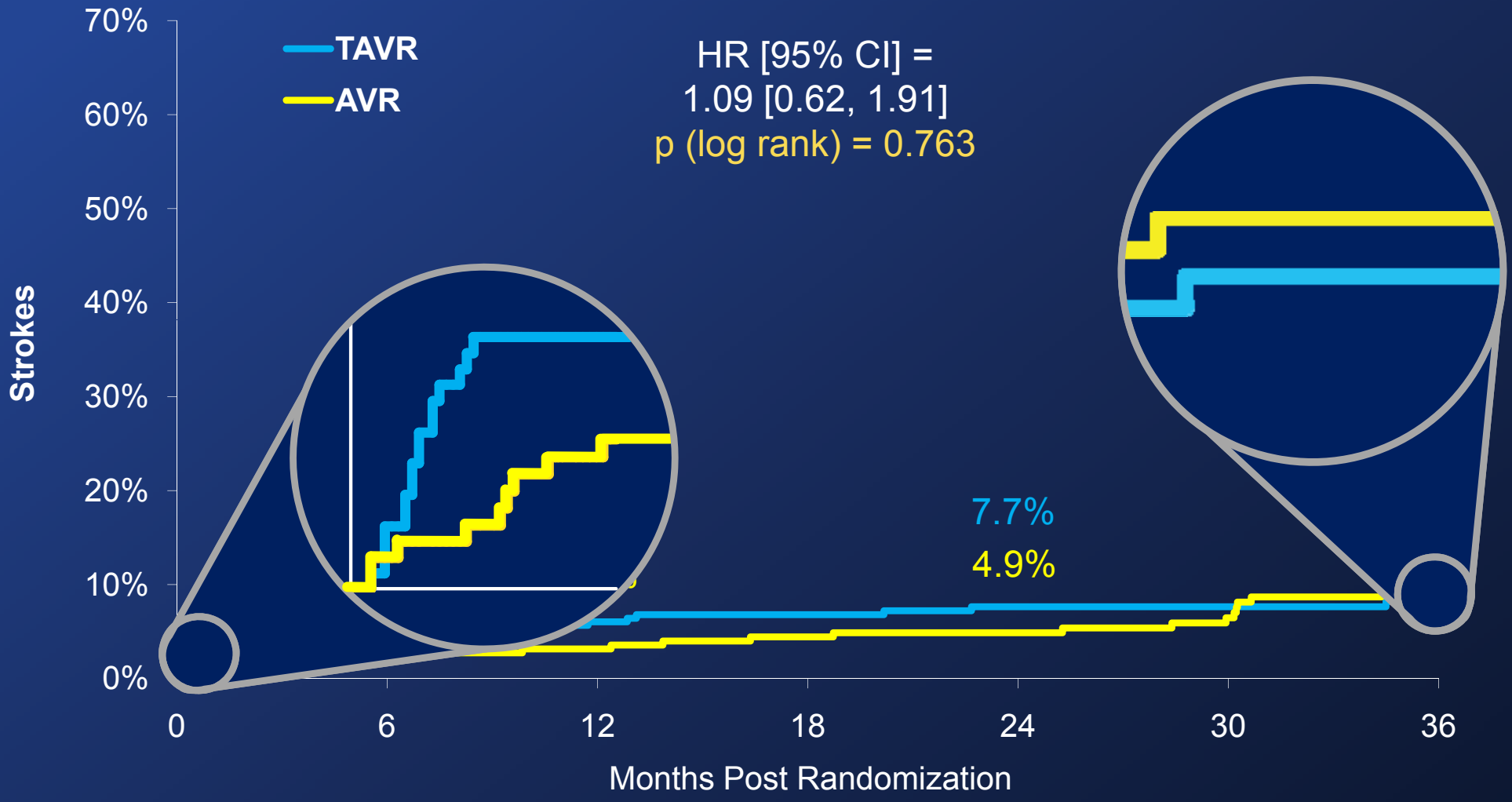
Multivariable Baseline Predictors of Mortality (ITT) – TAVR

TAVR	Hazard Ratio [95% CI]	p-value
Body Mass Index (lbs/in^2)	0.95 [0.92, 0.98]	0.0003
Atrial Fibrillation	1.62 [1.15, 2.27]	0.0056
Mean Gradient (Baseline)	0.98 [0.97, 0.99]	0.0033
Liver Disease	2.39 [1.11, 5.14]	0.0254
Renal Disease (CR ≥ 2)	1.61 [1.11, 2.35]	0.0131

NYHA Class Survivors (ITT)



PARTNER A – Major / Minor Srtoke (ITT)



No. at Risk

TAVR	348	287	250	228	211	176	139
AVR	351	246	230	217	197	169	139

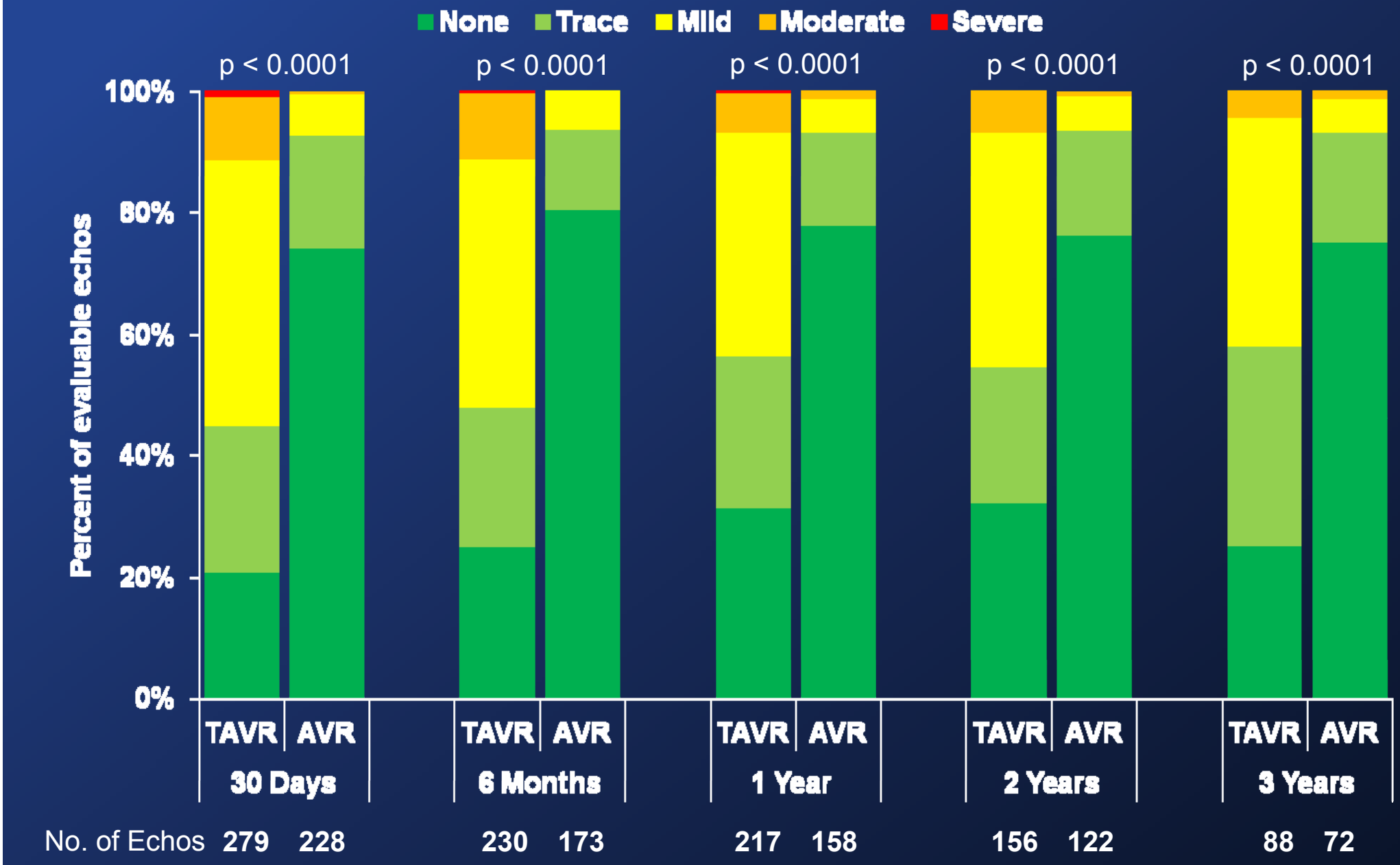
Clinical Outcomes at 1, 2, and 3 Years (ITT)
All Patients (N=699)

	1 Year			2 Years			3 Years		
Outcome	***AVR (N = 351)***	***TAVR (N = 348)***	***p-value***	***AVR (N = 351)***	***TAVR (N = 348)***	***p-value***	***AVR (N = 351)***	***TAVR (N = 348)***	***p-value***
Major Vasc. Comp. – no. (%)	13 (3.8)	42 (12.1)	<0.001	13 (3.8)	43 (12.5)	<0.001	13 (3.8)	43 (12.5)	<0.001
Major Bleeding – no. (%)	88 (26.7)	52 (15.7)	<0.001	95 (29.5)	61 (19.3)	0.003	99 (31.5)	64 (20.8)	0.003
New PM – no. (%)	16 (5.0)	21 (6.4)	0.44	19 (6.3)	24 (7.6)	0.54	20 (6.8)	25 (8.1)	0.56
Endocarditis – no. (%)	3 (1.0)	2 (0.6)	0.63	3 (1.0)	4 (1.5)	0.62	6 (2.6)	4 (1.5)	0.37
SVD§ Requiring AVR	0	0		0	0		0	0	
MI – no. (%)	2 (0.6)	0	0.16	4 (1.5)	0	0.05	6 (2.7)	2 (1.1)	0.23
Acute Kidney Inj.* – no. (%)	20 (6.5)	18 (5.4)	0.57	22 (7.3)	20 (6.2)	0.59	23 (7.9)	22 (7.2)	0.76

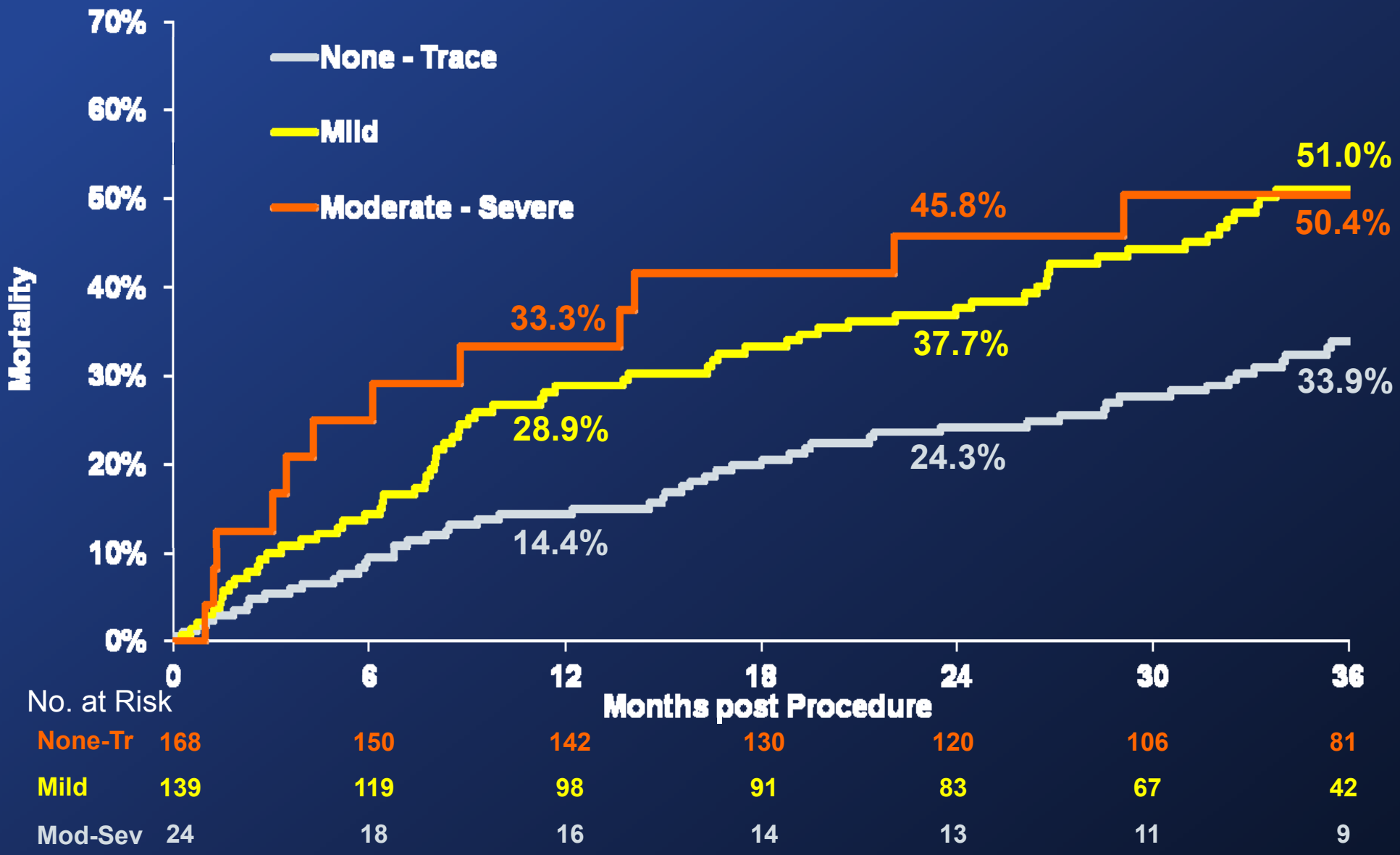
§ SVD = Structural Valve Deterioration

* Renal replacement therapy

Paravalvular Aortic Regurgitation (AT)

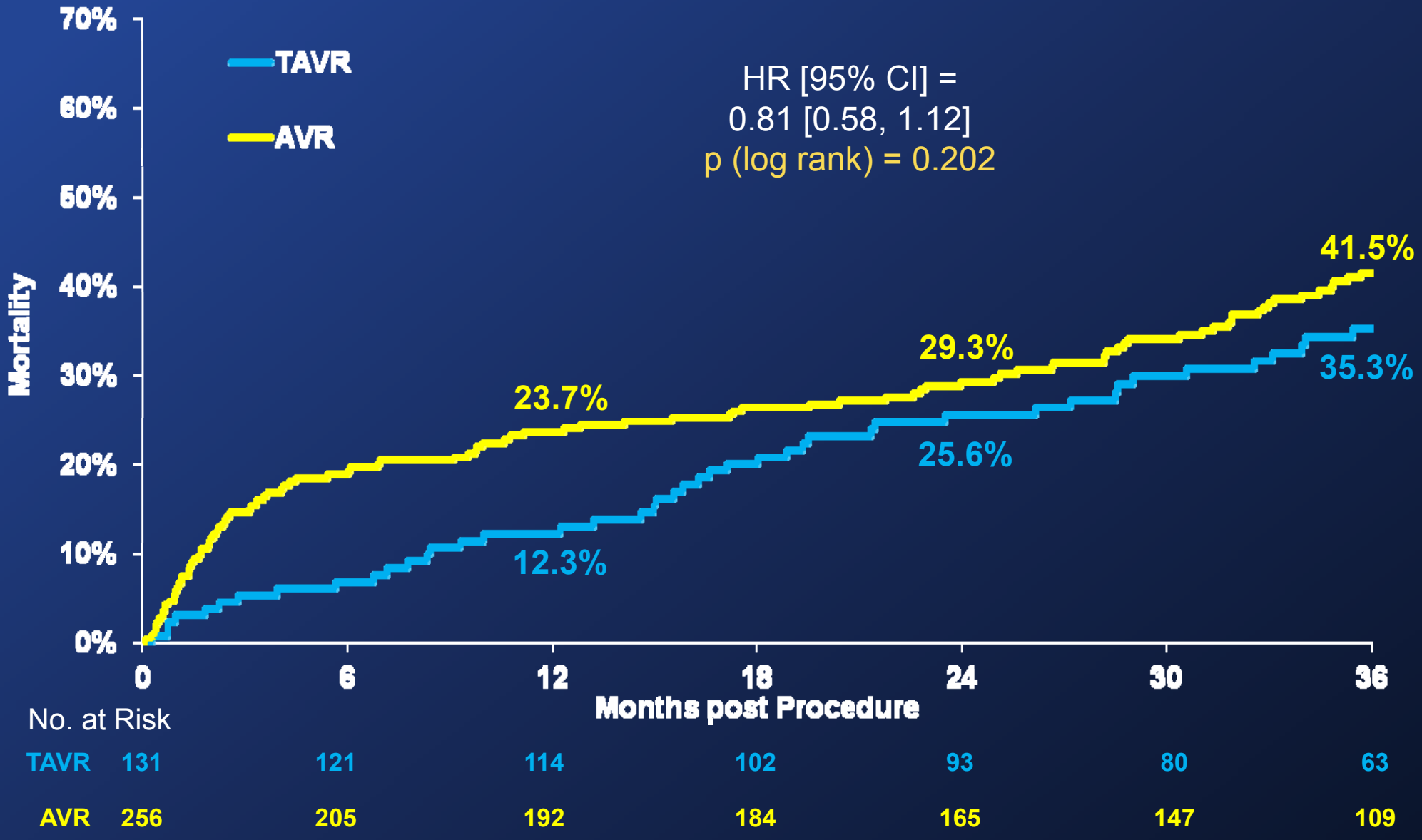


Impact of Mild PVL on Mortality (AT)
TAVR Patients



Mortality in Patients with None-Trace AR (AT)

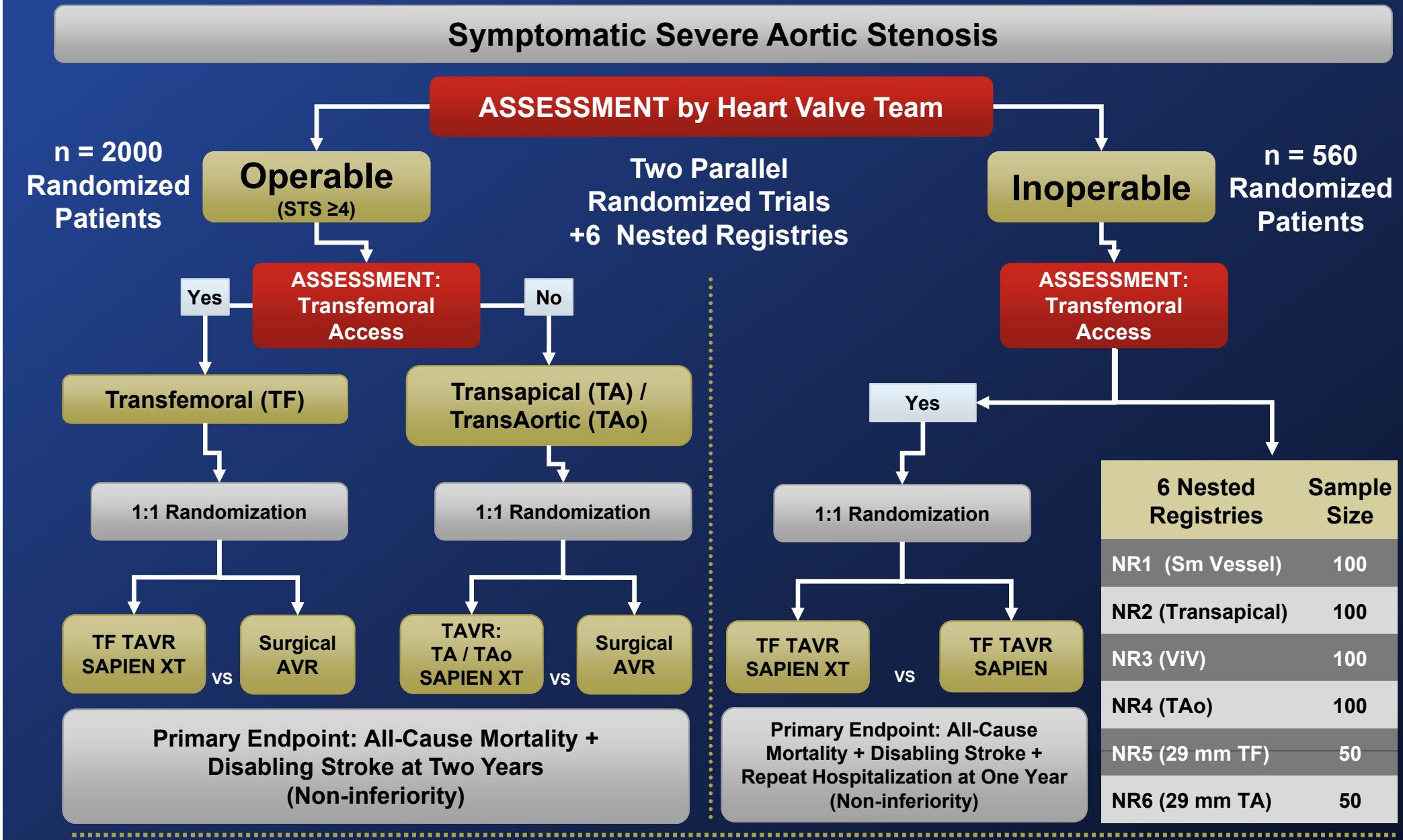
TAVR vs AVR



Implications

- 3-year results from the high-risk operable PARTNER cohort indicate…
  - TAVR should be considered an alternative to surgery with similar mortality and similar other major clinical outcomes
  - Peri-procedural stroke concerns after TAVR have diminished with longer term follow-up
  - TAVR valve hemodynamics have remained stable, although peri-procedural regurgitation (even mild) has emerged as a predictor of late mortality
- Future efforts should be directed towards reducing TAVR procedure-related complications, including strokes, vascular events, and paravalvular regurgitation

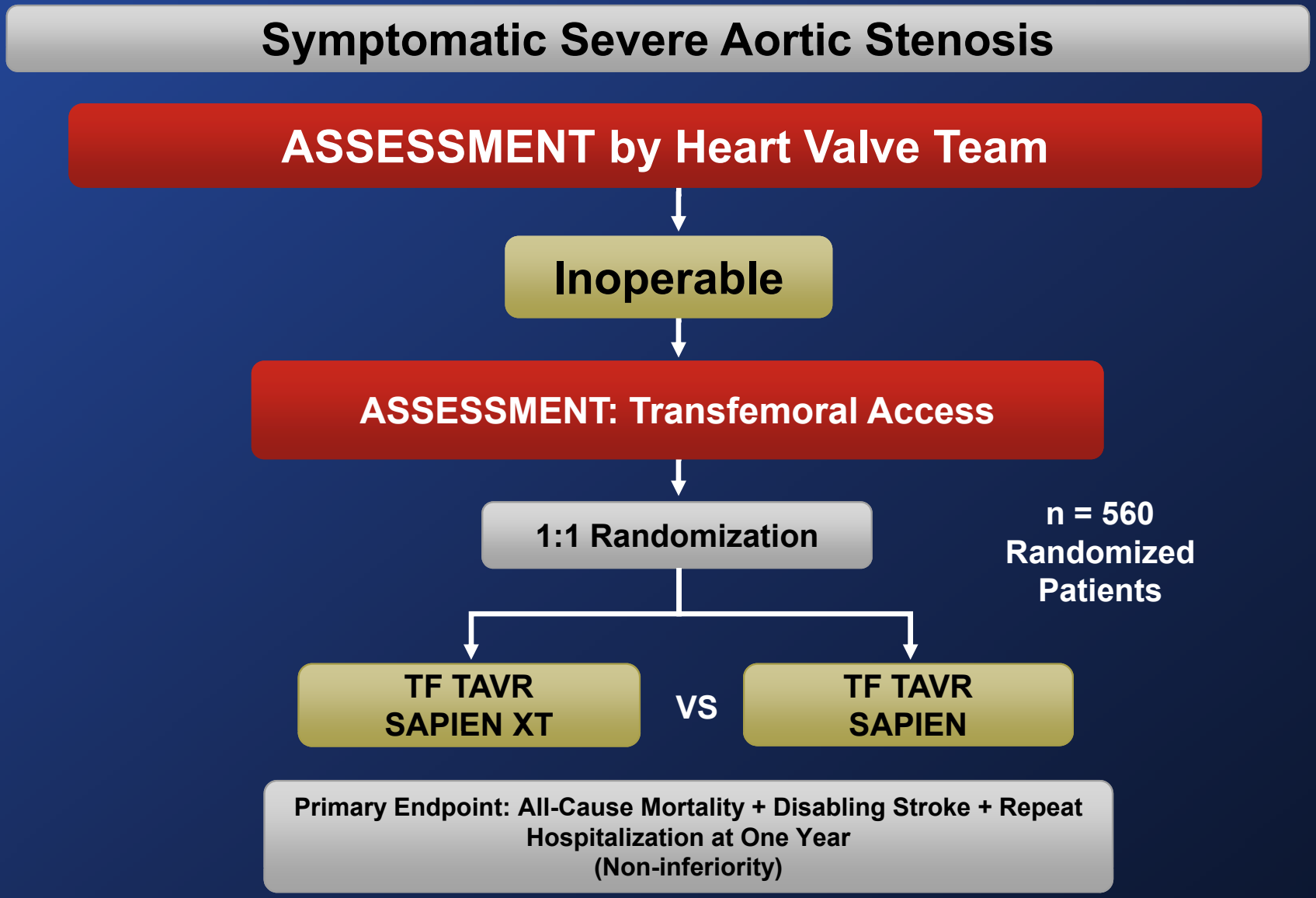
The PARTNER II Trial
Study Design



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

The PARTNER II Inoperable Cohort

Study Design



Martin B. Leon, MD in ACC 2013

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

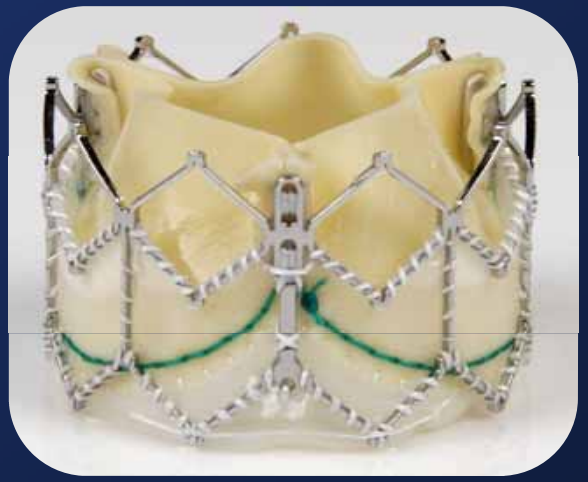
NEW LEAFLET GEOMETRY
- Partially closed

SAPIEN THV

Stainless Steel

SAPIEN XT THV

Cobalt-chromium



RetroFlex 3

NovaFlex

Sheath Size Comparison

THE PARTNER II TRIAL

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

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

Procedural Factors (AT)

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

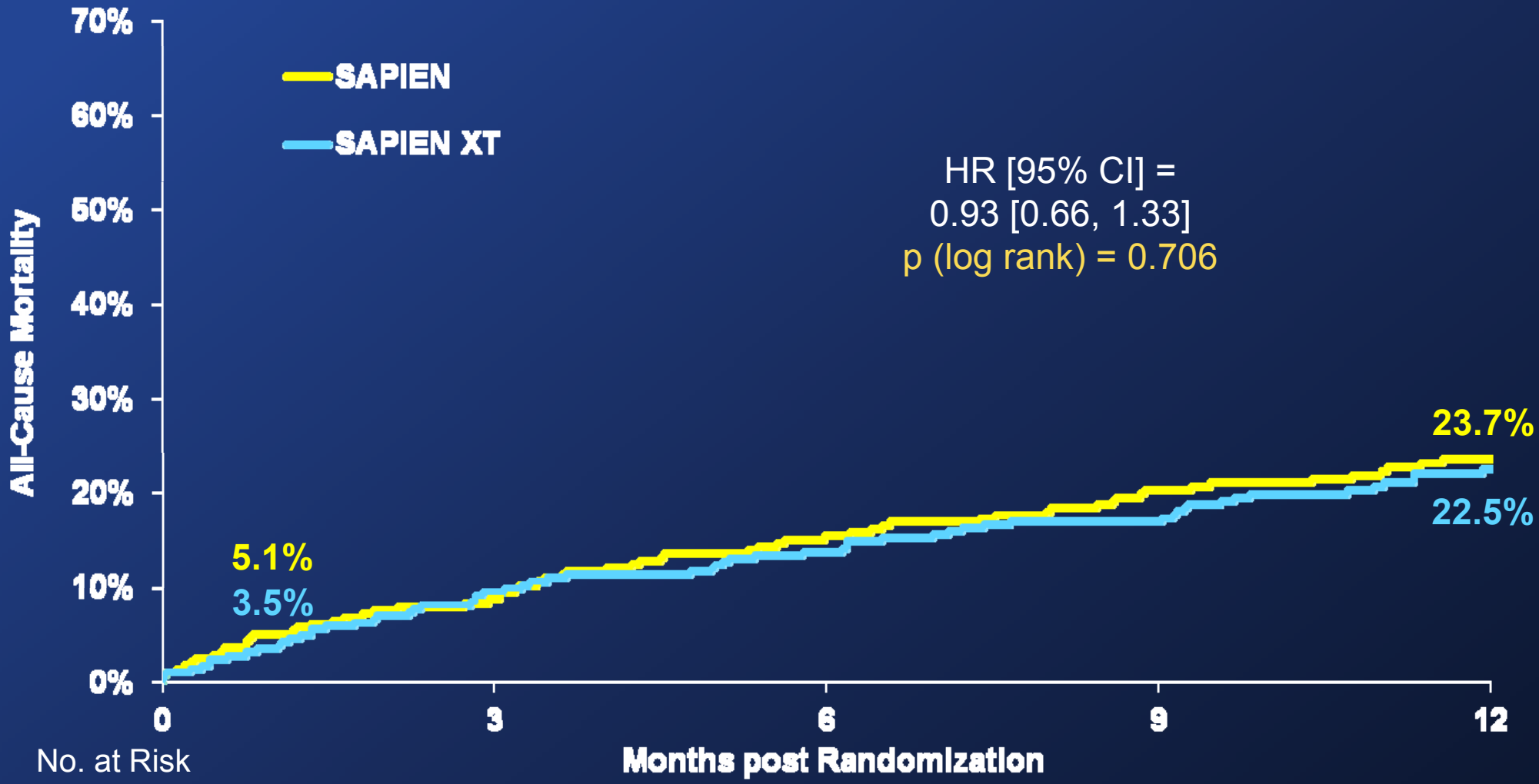
	SAPIEN (n=271)		SAPIEN XT (n=282)		
Events	**n**	**%**	**n**	**%**	**p-value**
Vascular:					
Major	42	15.5	27	9.6	0.04
Minor	20	7.4	14	5.0	0.23
Bleeding:					
Disabling	34	12.6	22	7.8	0.06
Major	44	16.4	44	15.7	0.84
Patients with transfusions	80	29.5	73	25.9	0.40

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

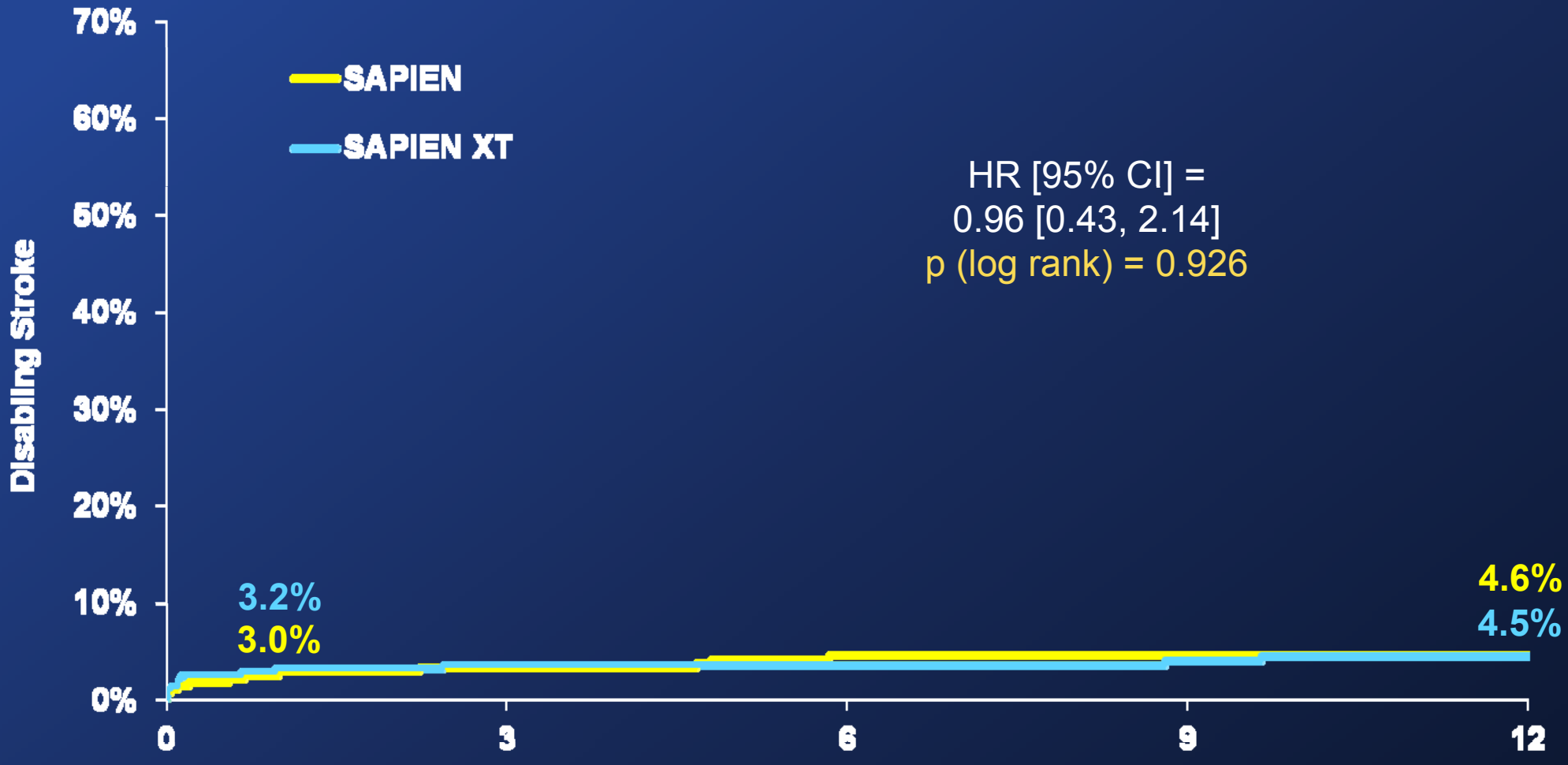
All-Cause Mortality (ITT)



No. at Risk

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

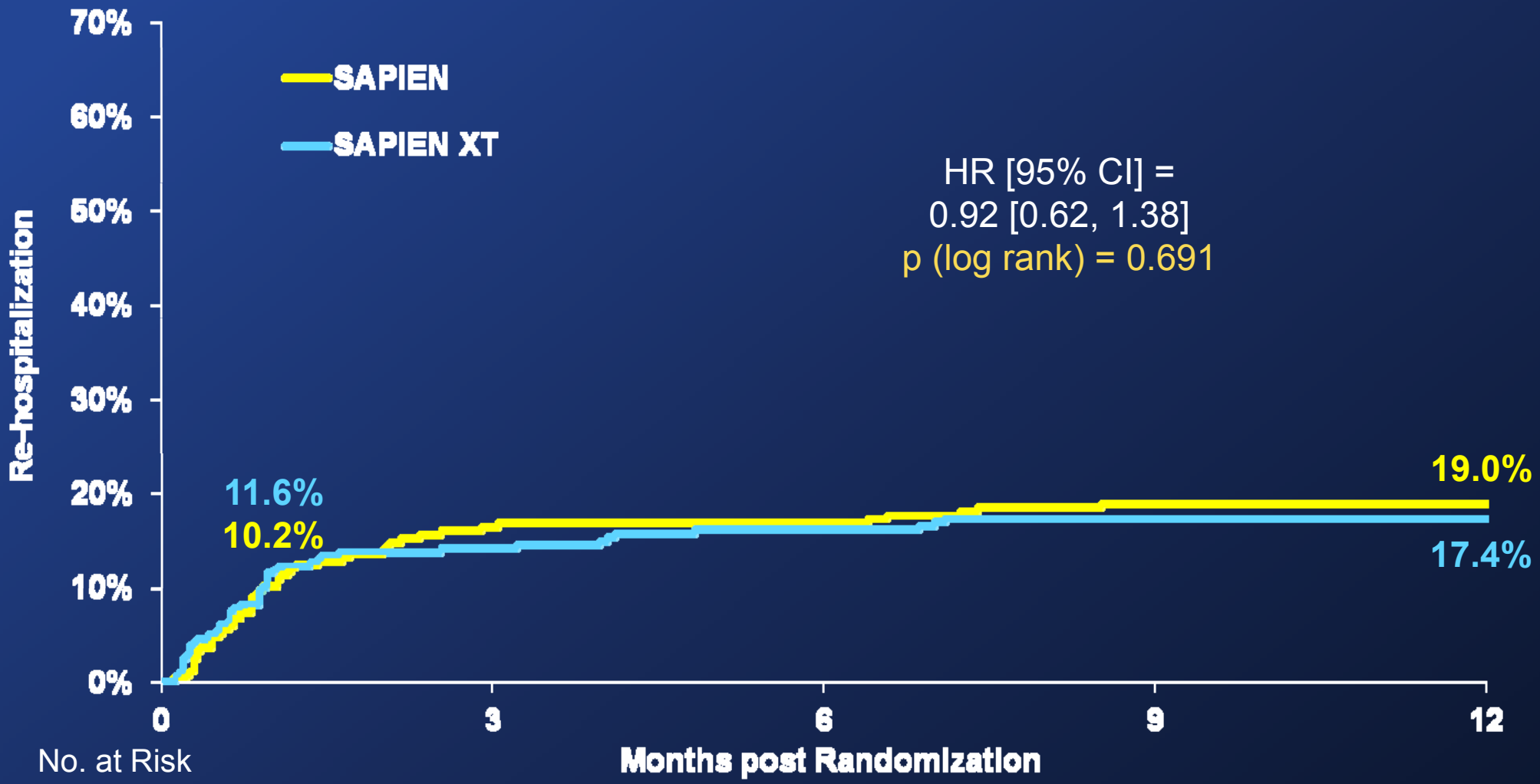
Disabling Stroke (ITT)



No. at Risk

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

Re-hospitalization (ITT)

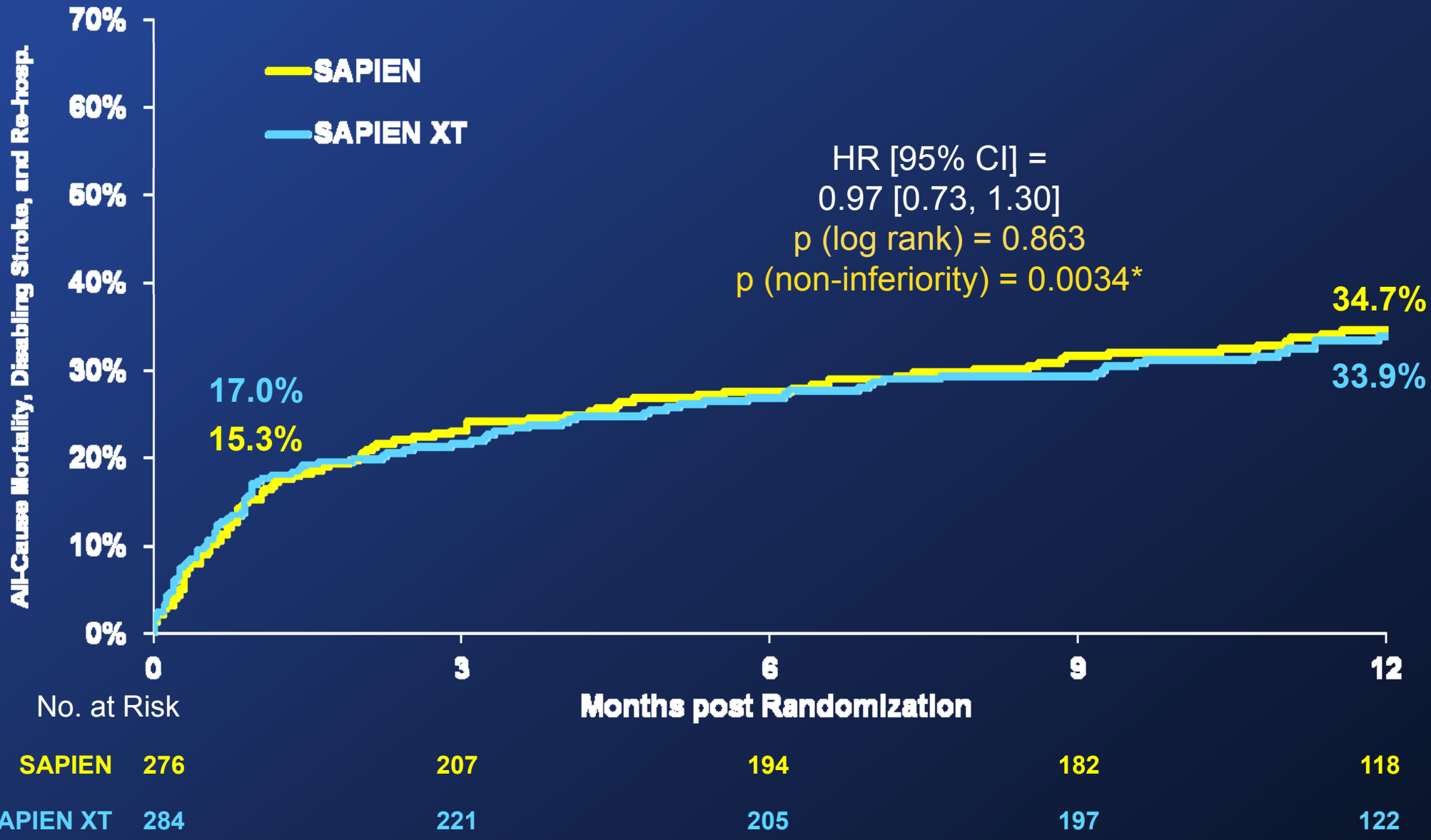


No. at Risk

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

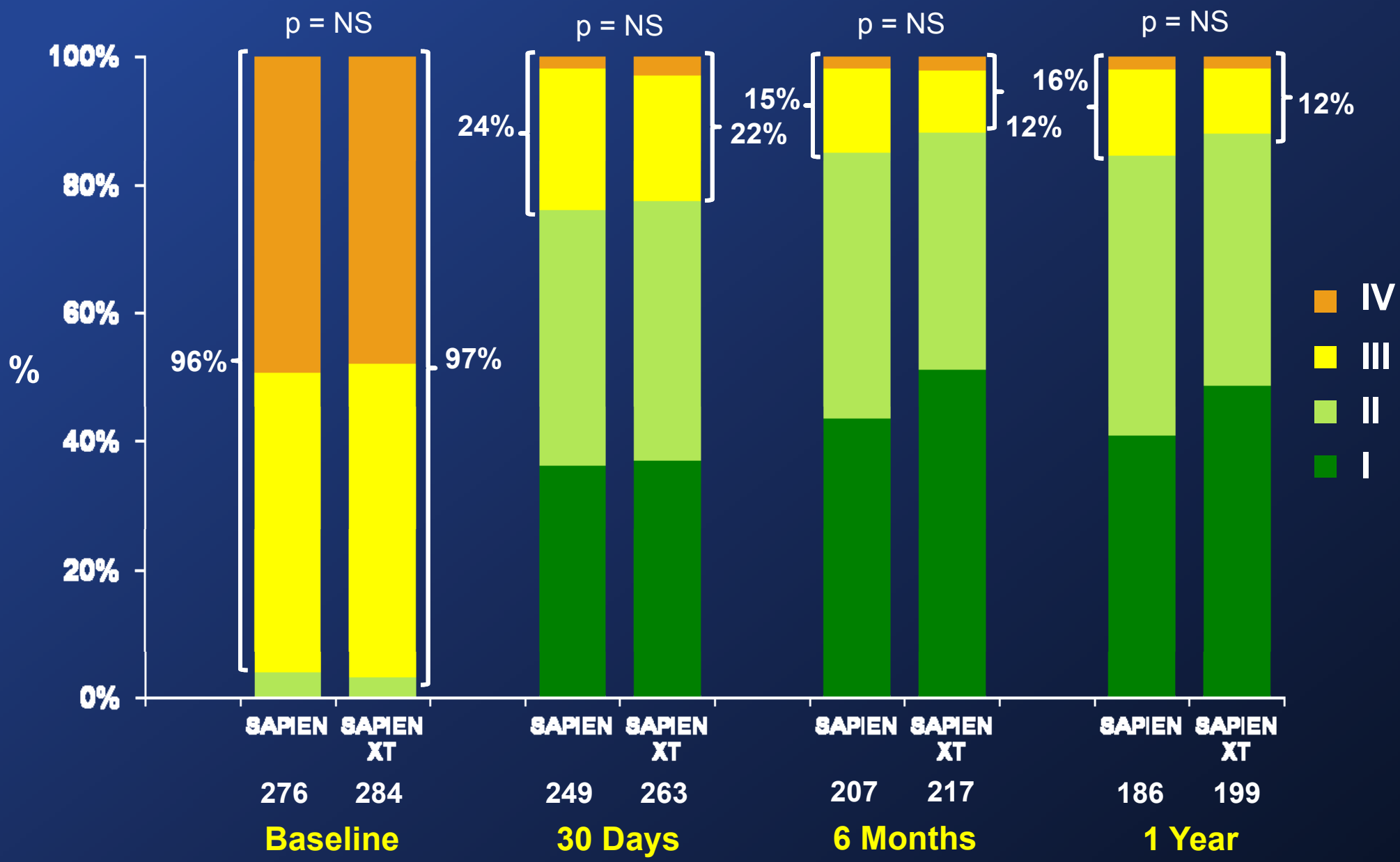


No. at Risk

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

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

NYHA Class Survivors (ITT)



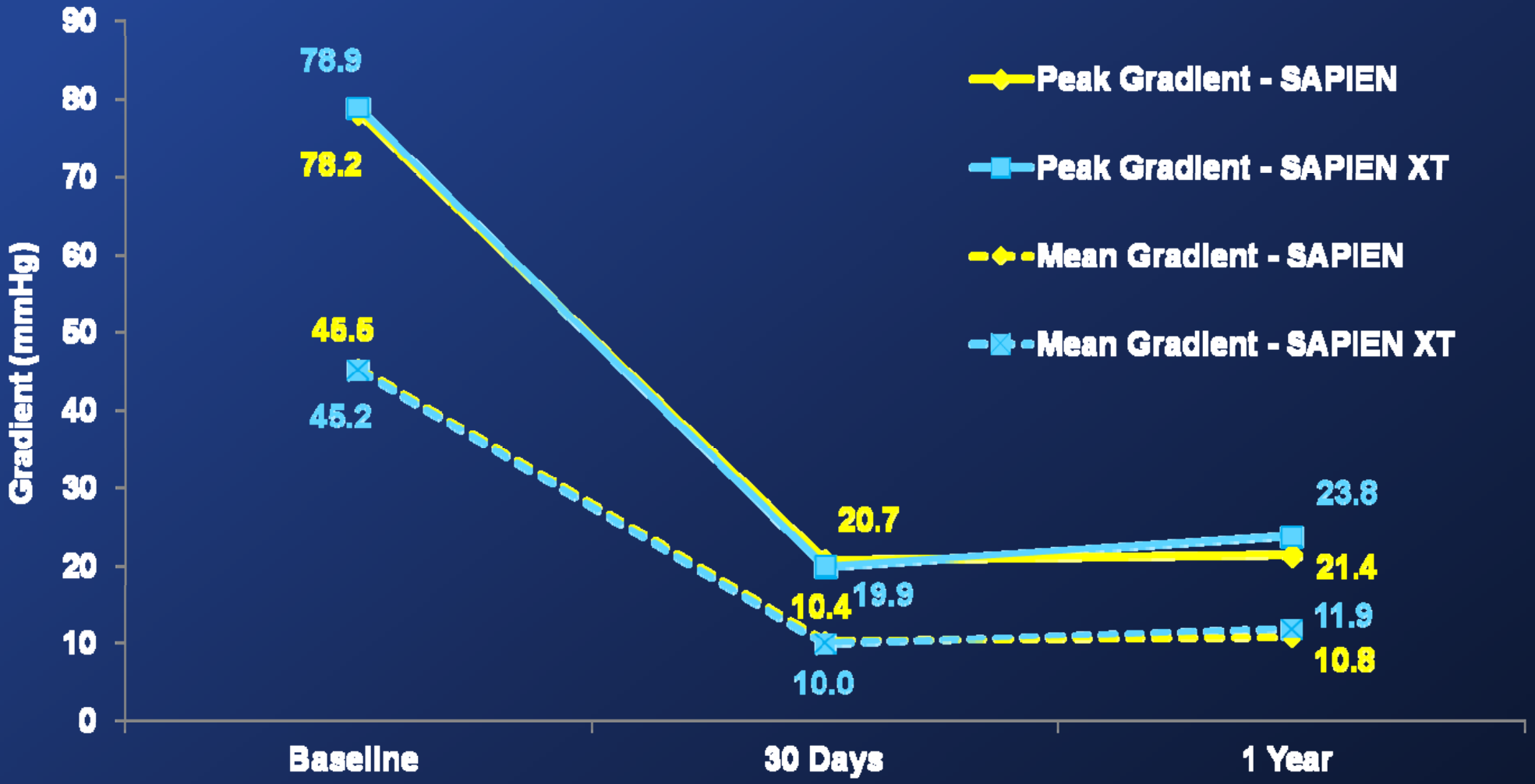
Echocardiographic Findings:
Aortic Valve Area (AT, Valve Implanted)

THE PARTNER II TRIAL

No. of Echos			
SAPIEN	229	215	112
SAPIEN XT	256	233	117

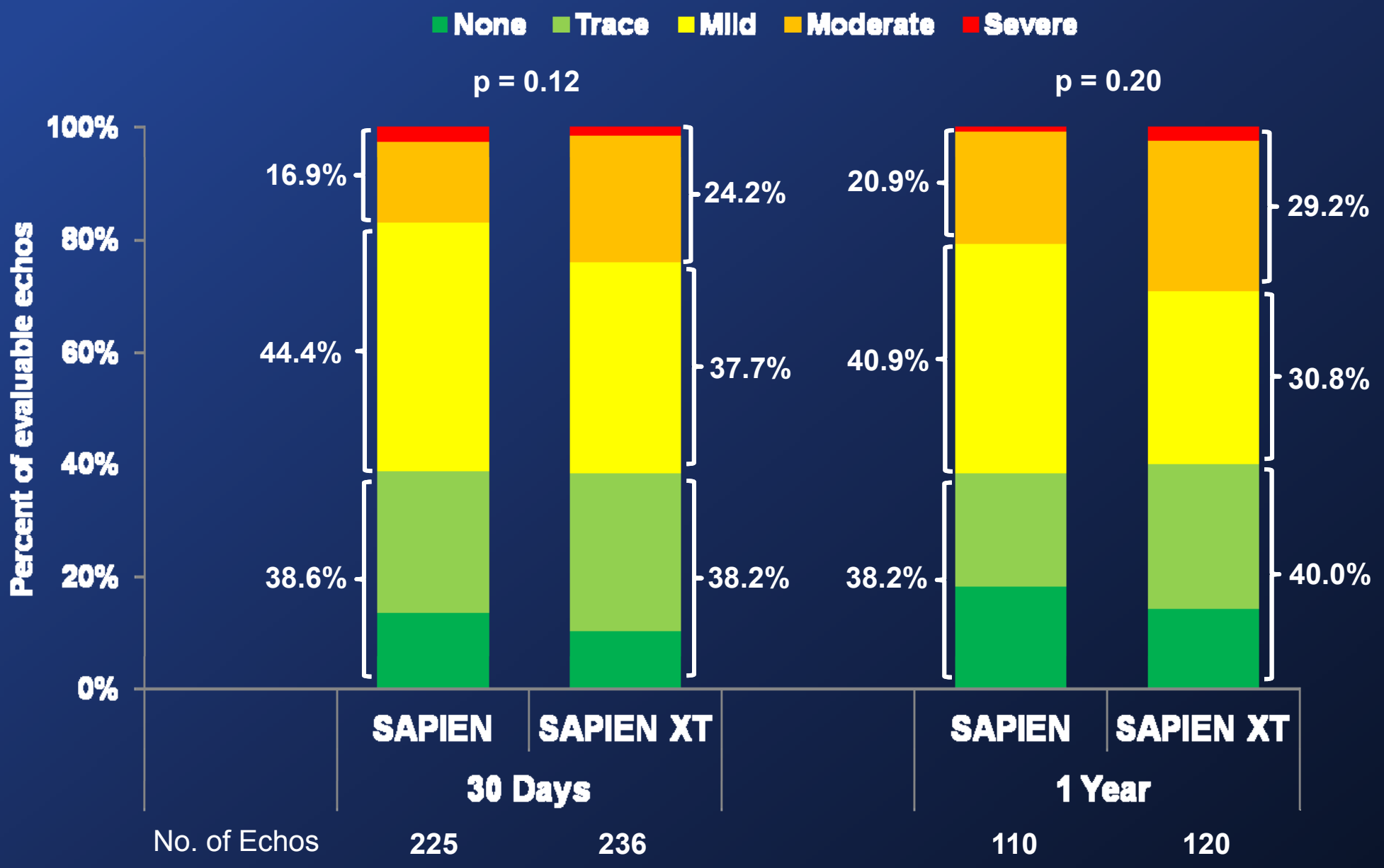
Echocardiographic Findings:
Mean & Peak Gradients (AT, Valve Implant)

THE PARTNER II TRIAL



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

Paravalvular Aortic Regurgitation (Valve Implant)



Implications

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.