Three-Year Outcomes of Transcatheter Aortic Valve Replacement (TAVR) in "Inoperable" Patients With Severe Aortic Stenosis: The PARTNER Trial

Samir R. Kapadia, MD
On behalf of The PARTNER Trial Investigators

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THE PARTNER TRIAL

- Samir Kapadia
  - No financial disclosures
  - Member of PARTNER Trial steering committee

- Murat Tuzcu
  - No financial disclosures
  - Member of PARTNER Trial executive committee

Background (1)

- Transcatheter aortic valve replacement (TAVR) is the recommended treatment for “inoperable” patients with severe aortic stenosis (AS), based upon 1-year results of The PARTNER Trial which demonstrated reduced mortality and improved quality of life.
- However, whether clinical benefit and valve performance are sustained beyond two years is unknown and longer term outcomes will importantly alter clinical practice decisions.

Background (2)

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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*

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

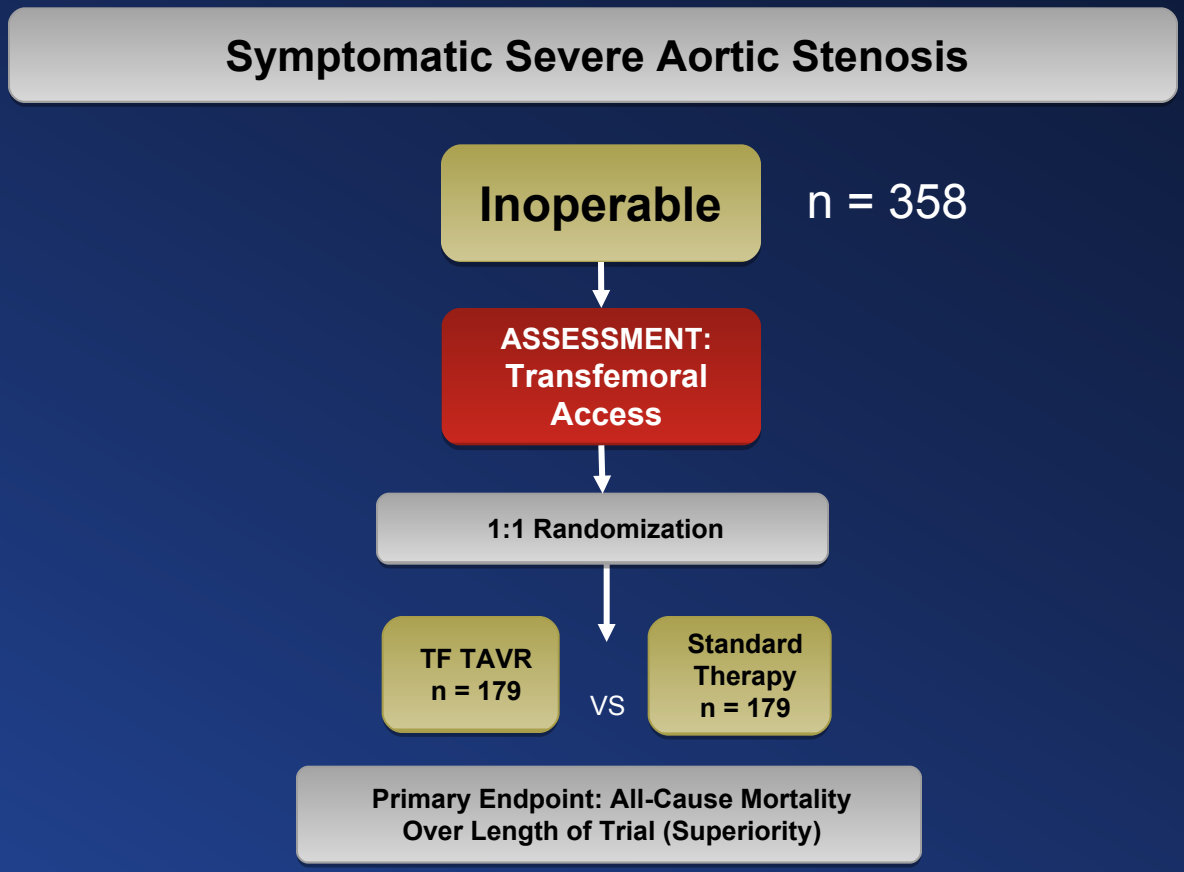
Transcatheter Aortic-Valve Replacement for Inoperable Severe Aortic Stenosis

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*

Objectives

- To evaluate the clinical outcomes of TAVR compared to standard therapy at 3 years in “inoperable” aortic stenosis patients.
- To assess valve hemodynamics and durability using echocardiography.
- To perform subgroup analyses to better define the impact of co-morbidities on outcomes.

PARTNER Study Design



- *Primary endpoint evaluated when all patients reached one year follow-up.*
- *After primary endpoint analysis reached, patients were allowed to cross-over to TAVR.*

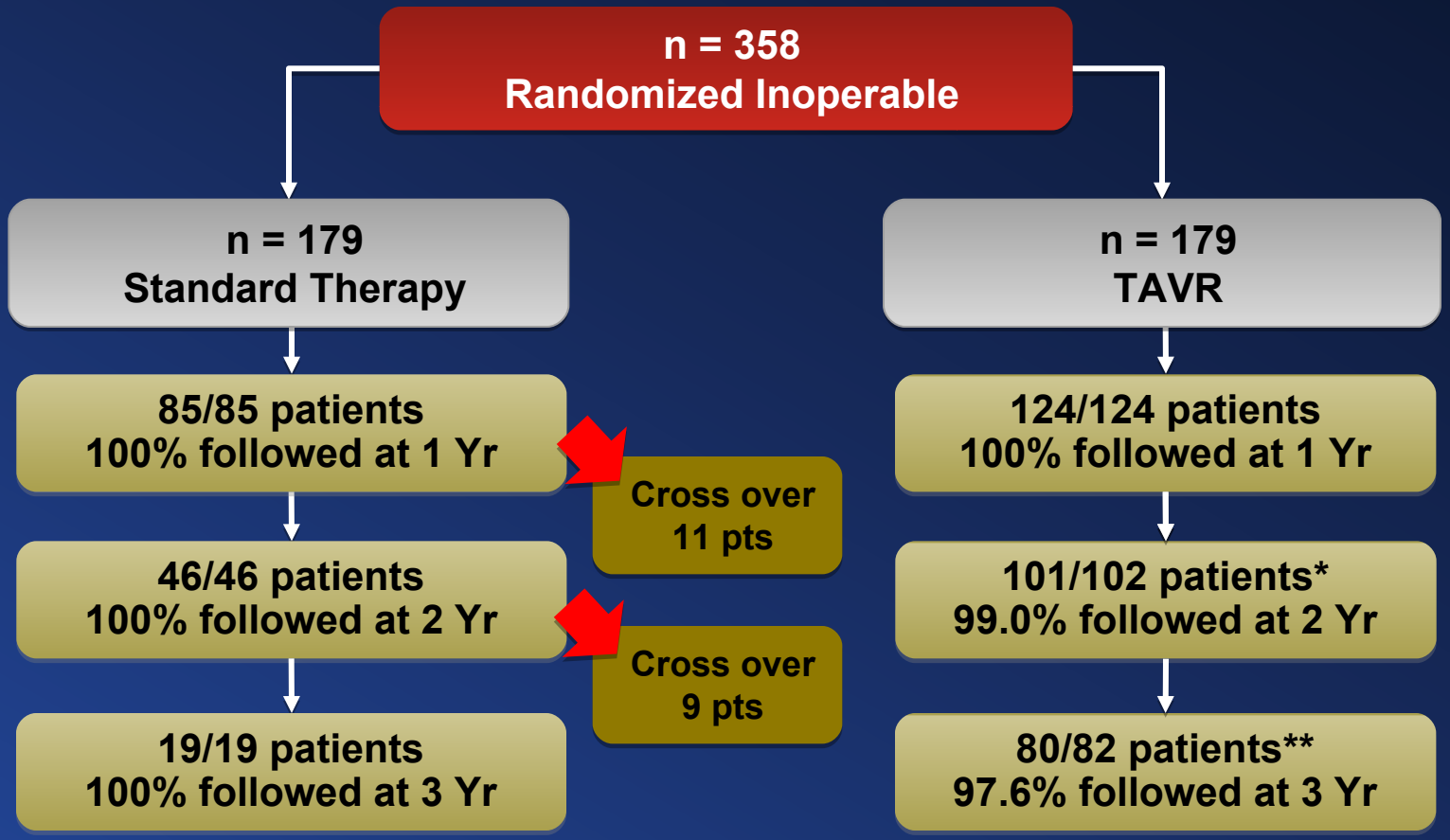
Inclusion Criteria

- Severe calcific aortic stenosis defined as echo derived valve area of < 0.8 cm^2 (EOA index < 0.5 cm^2/m^2), and mean gradient > 40 mmHg or jet velocity > 4.0 m/s.
- NYHA functional class ≥ II
- Inoperable defined as risk of death or serious irreversible morbidity of AVR as assessed by cardiologist and two surgeons exceeding 50%.

Key End-Points for 3 Year Analysis

- All cause mortality
- Cardiac mortality
- Rehospitalization
- Adverse outcomes including stroke, bleeding, renal failure, and MI
- NYHA functional class
- Days alive and out of hospital
- Echo-derived valve areas, transvalvular gradients, and paravalvular aortic regurgitation
- Mortality outcomes stratified by STS score

Study Flow
Inoperable Cohort



- **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*

Statistical Method

- Primary analysis was by “intention-to-treat” (ITT).
- Clinical outcomes were analyzed by ITT with censoring of Standard Rx cross-over patients.
- Additional analysis of death was performed by following cross-over patients with their randomized trial arms.
- Event rates are given as Kaplan-Meier estimates.
- Core lab echo results are presented from the valve implant population (valve retained in position).

Patient Characteristics (1)

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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.

Patient Characteristics (2)

THE PARTNER TRIAL

Characteristic	*TAVR* *n = 179*	*Standard Rx* *n = 179*	*p value*
PVD (%)	30.3	25.1	0.29
COPD			
Any (%)	41.3	52.5	0.04
O_2 dependent (%)	21.2	25.7	0.38
Creatinine > 2 mg/dL (%)	5.6	9.6	0.23
Atrial fibrillation (%)	32.9	48.8	0.04
Perm. pacemaker (%)	22.9	19.5	0.49
Pulmonary HTN (%)	42.4	43.8	0.90
Frailty (%)	18.1	28.0	0.09
Porcelain aorta (%)	19.0	11.2	0.05
Chest wall radiation (%)	8.9	8.4	1.00
Chest wall deformity (%)	8.4	5.0	0.29
Liver disease (%)	3.4	3.4	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

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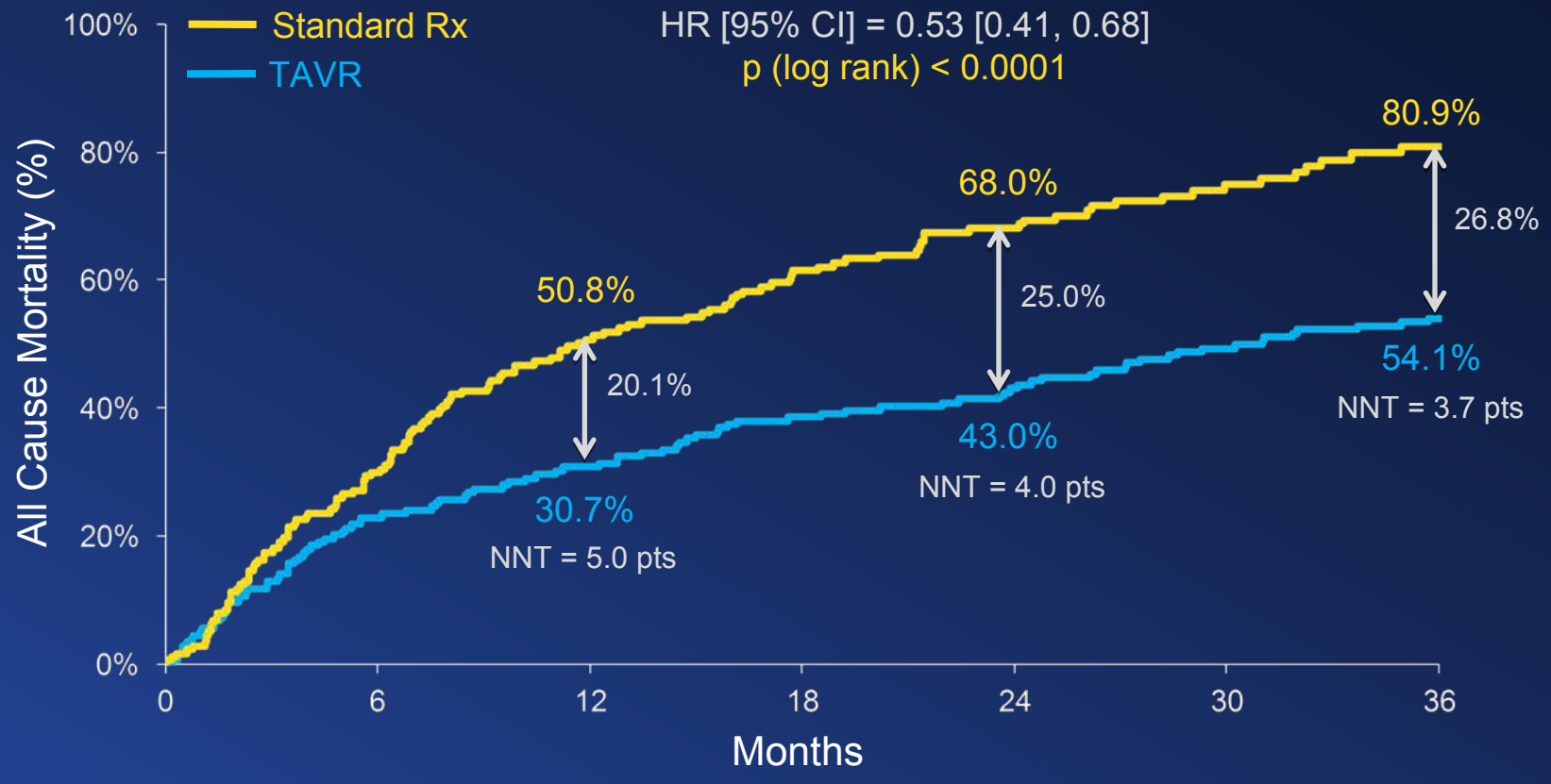
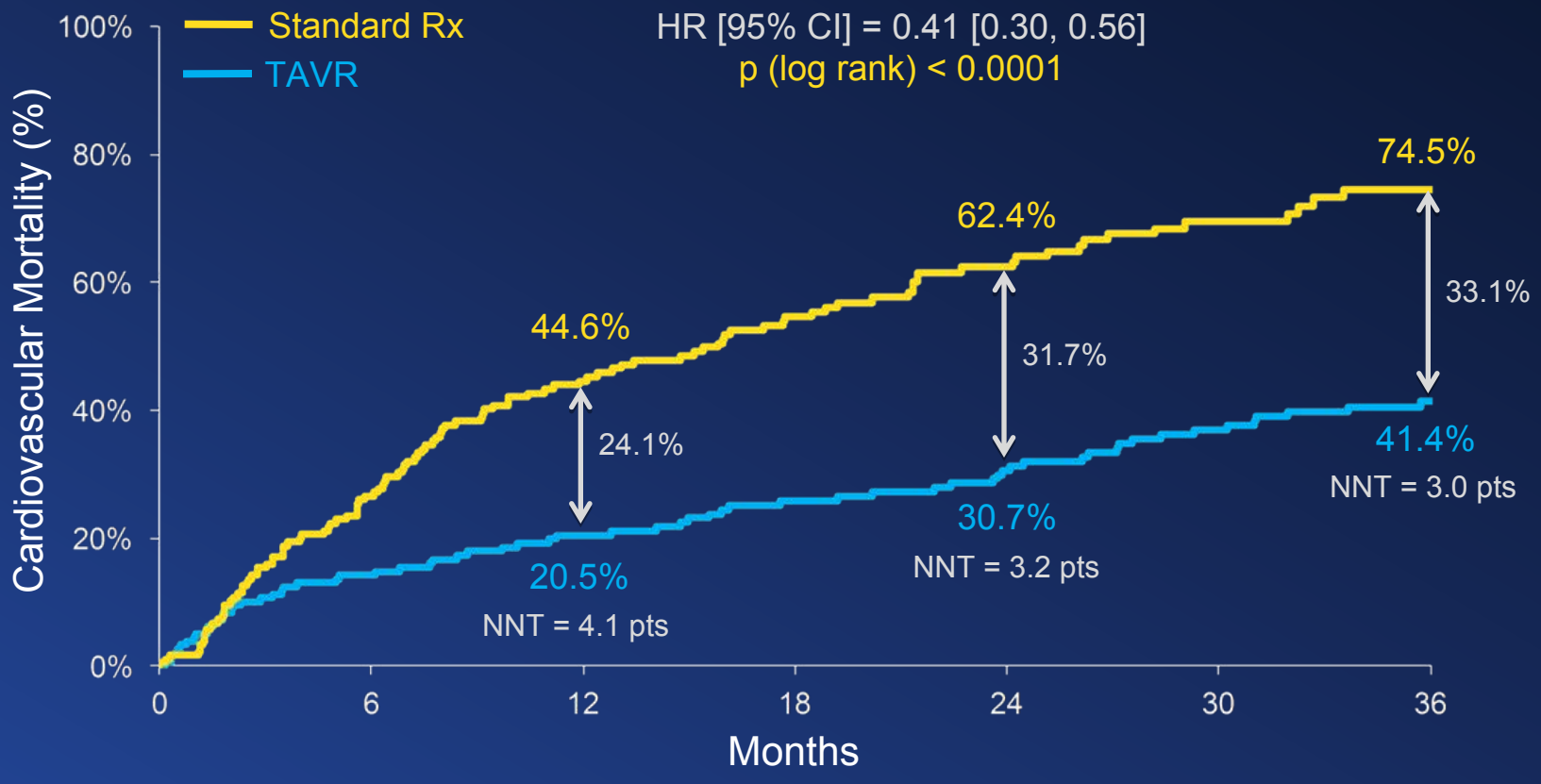


Numbers at Risk

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



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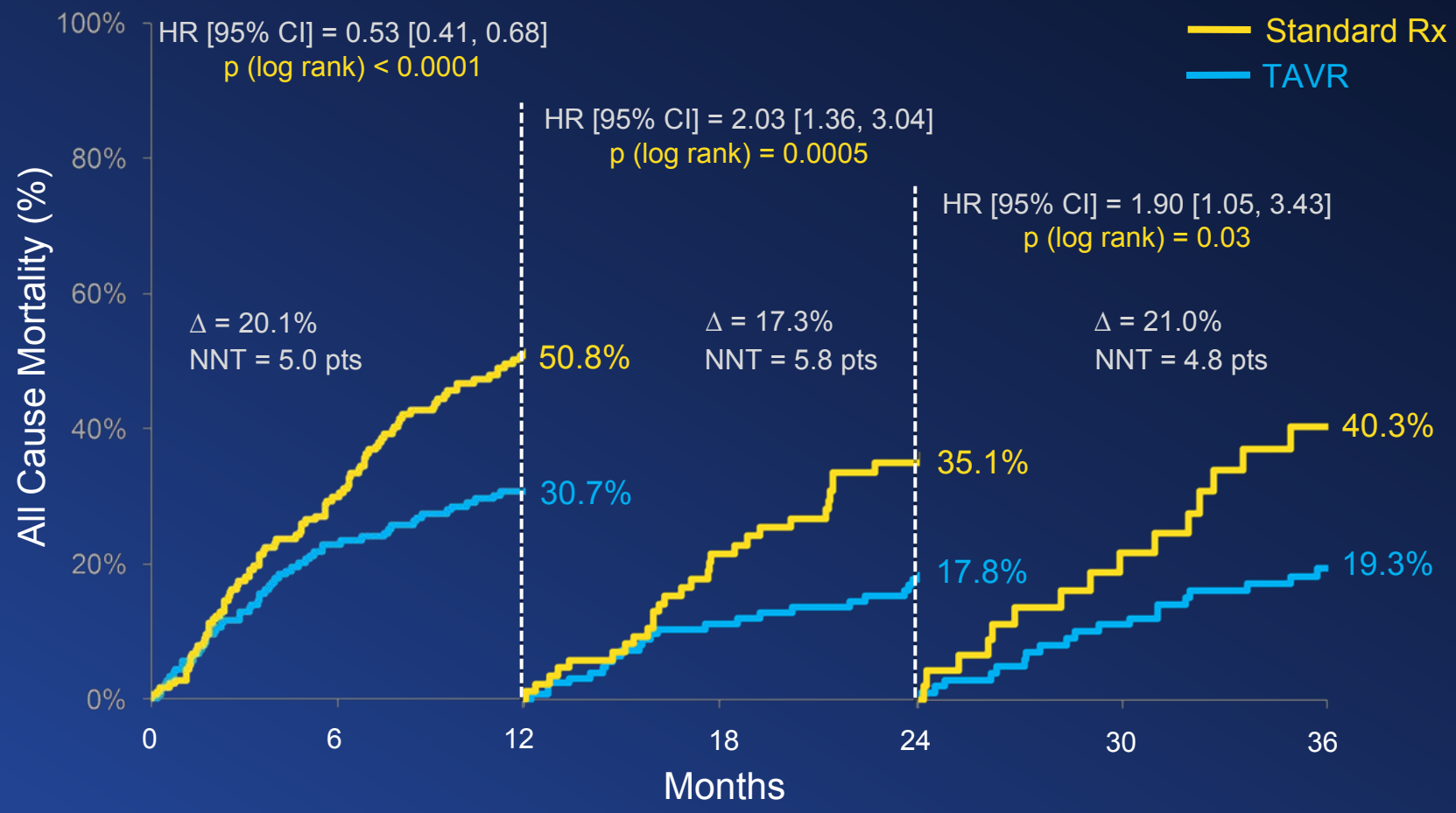
All Cause Mortality (ITT)
Landmark Analysis



Numbers at Risk

Standard Rx	**179**	**121**	**85**	**62**	**46**	**27**	**17**
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Repeat Hospitalization (ITT)

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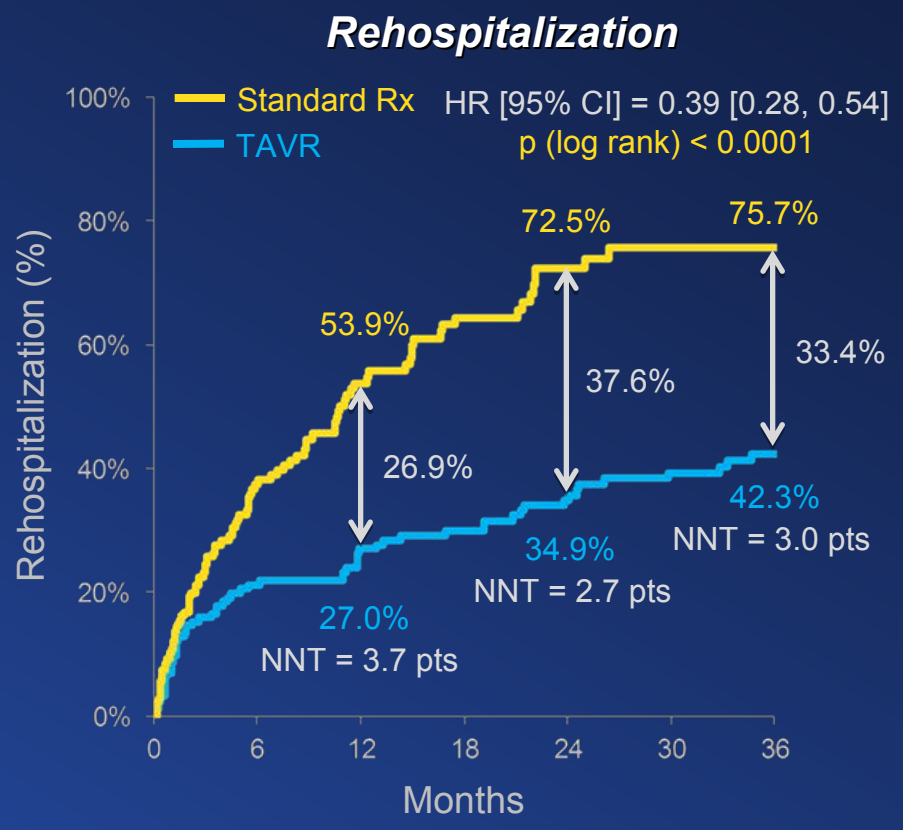
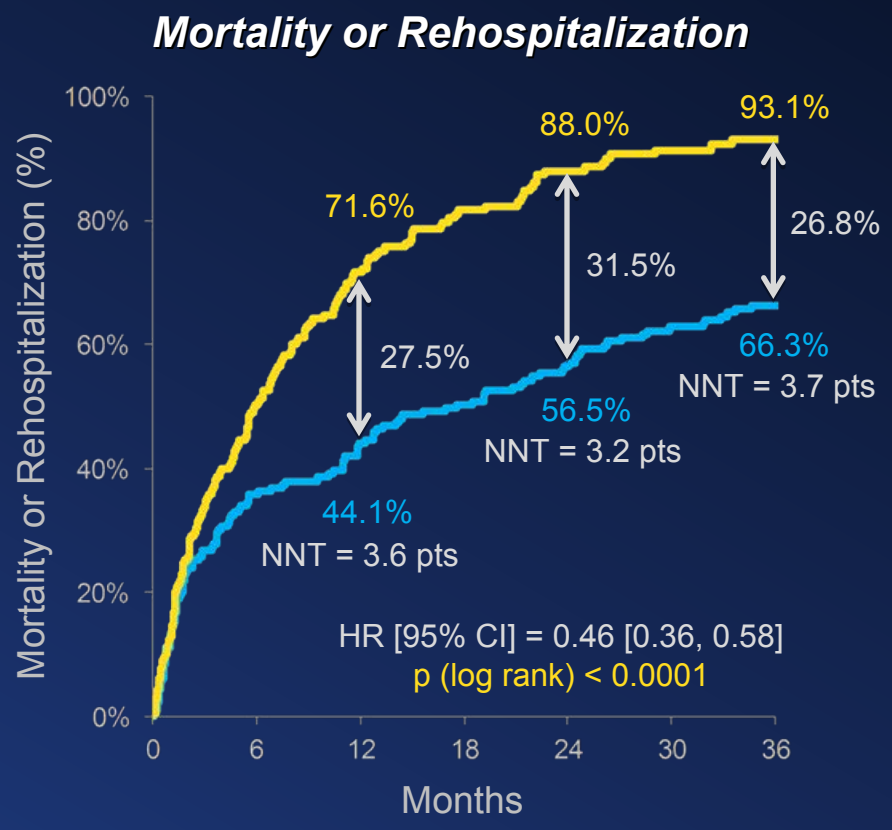




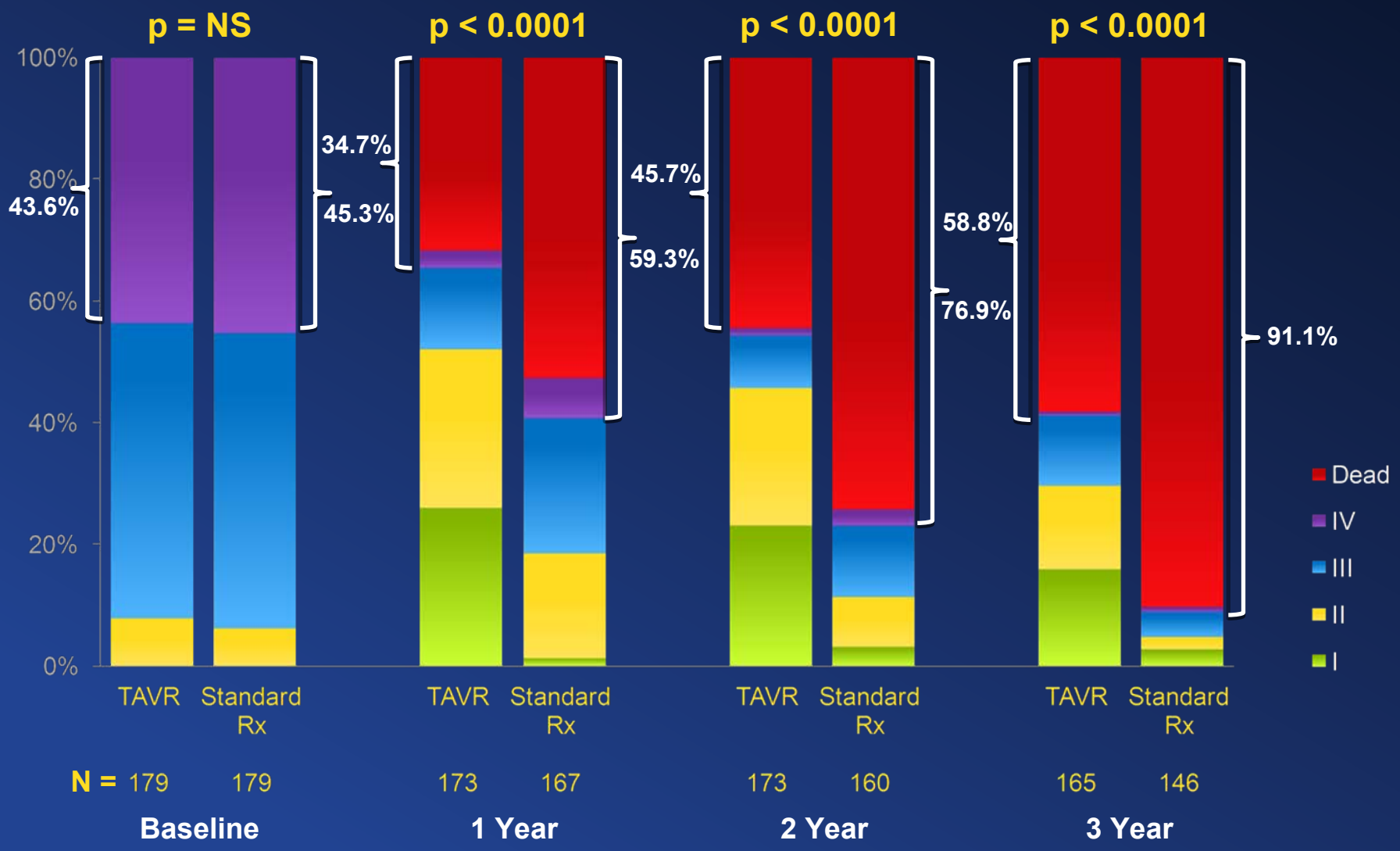
Days Alive Out of Hospital Median [IQR] TAVR 944 [233-1096] Standard Rx 368 [147-1096] **p <.0001**

Numbers at Risk

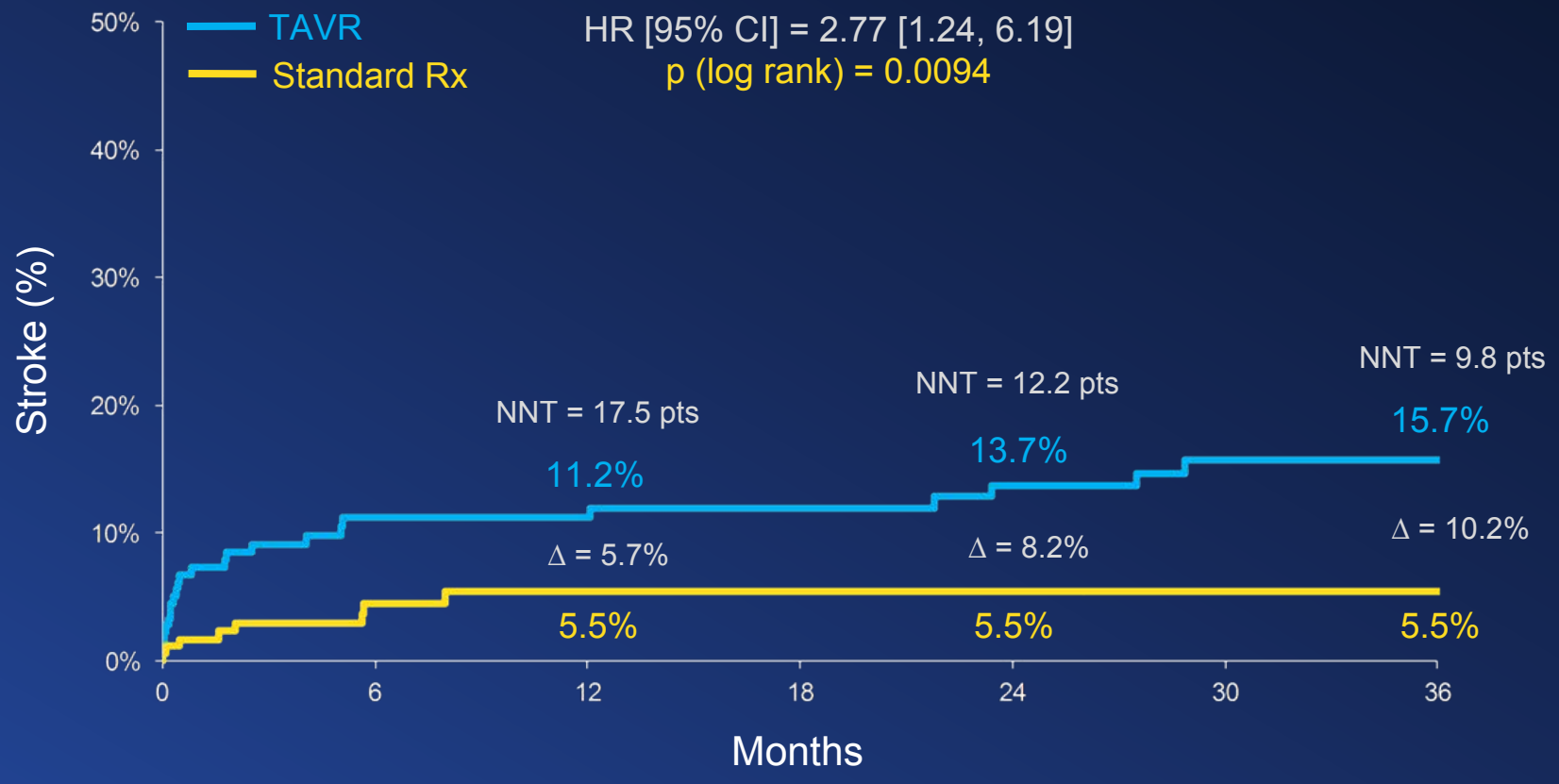
Standard Rx	179	86	49	30	19	11	7
TAVR	179	115	100	89	77	64	49

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

NYHA Class Over Time (ITT)



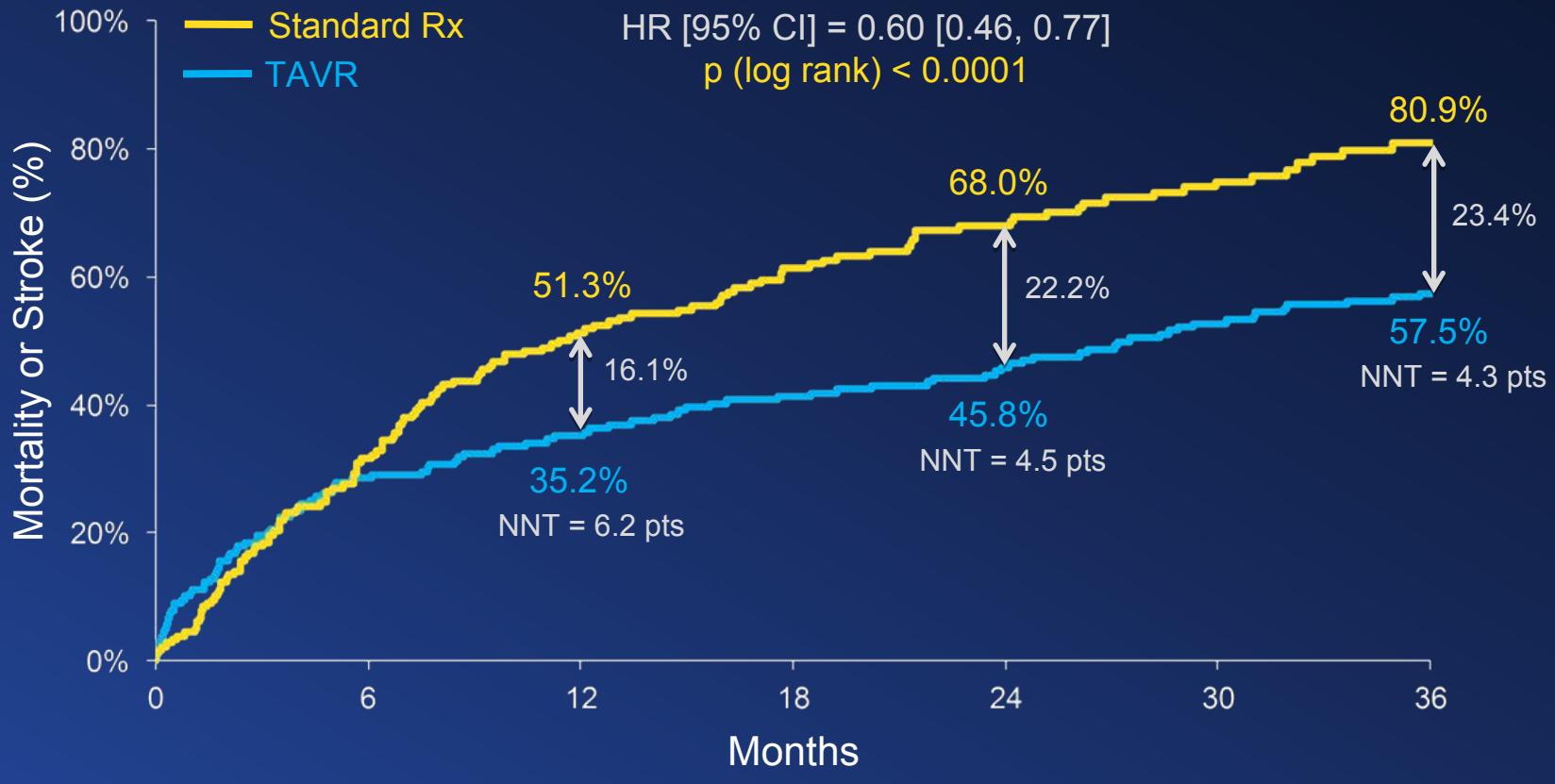
All Stroke (ITT)



Numbers at Risk

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

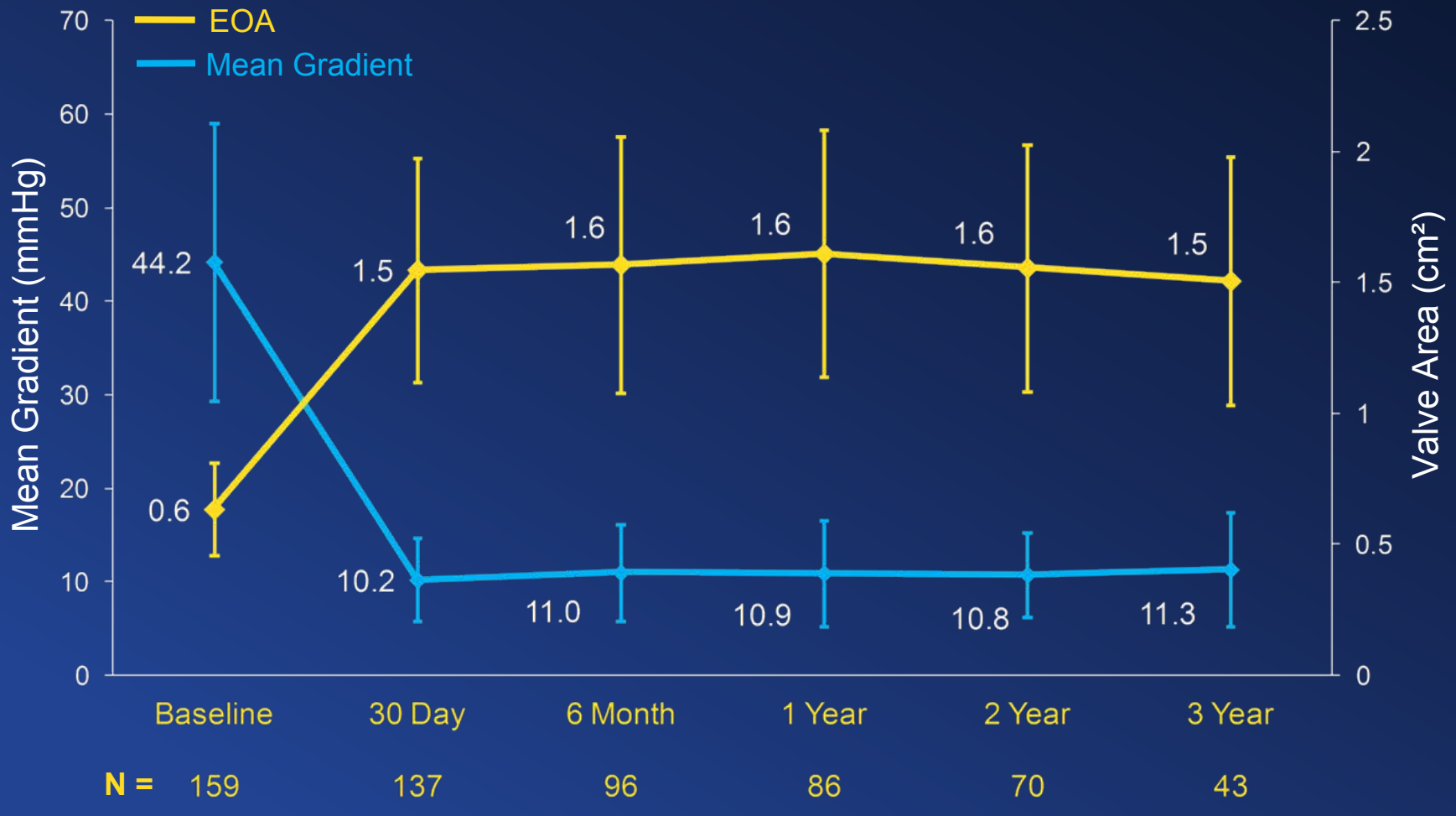
Mortality or Stroke (ITT)



Numbers at Risk

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

Mean Gradient & Valve Area



Error bars = ± 1 Std Dev

Paravalvular Leak

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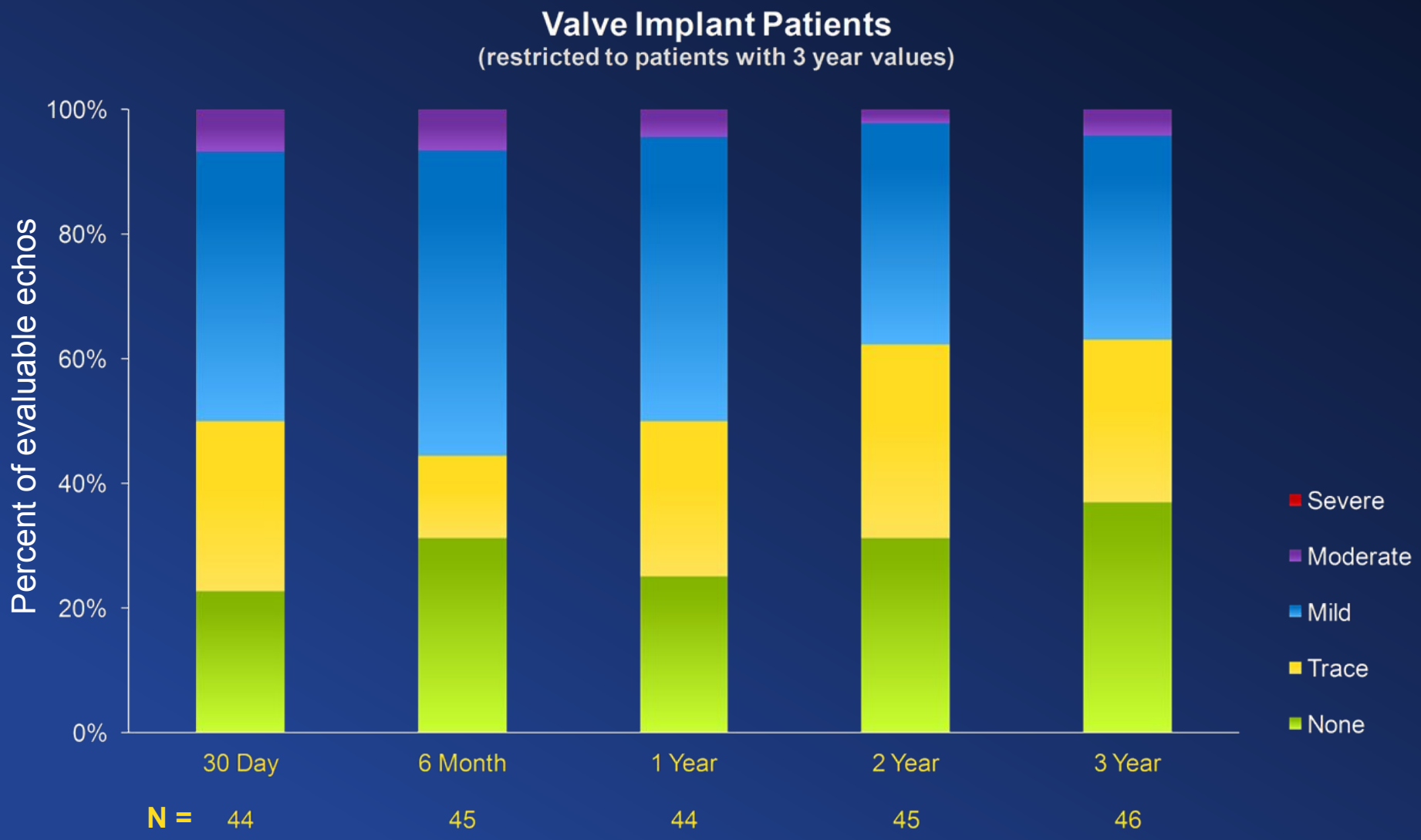
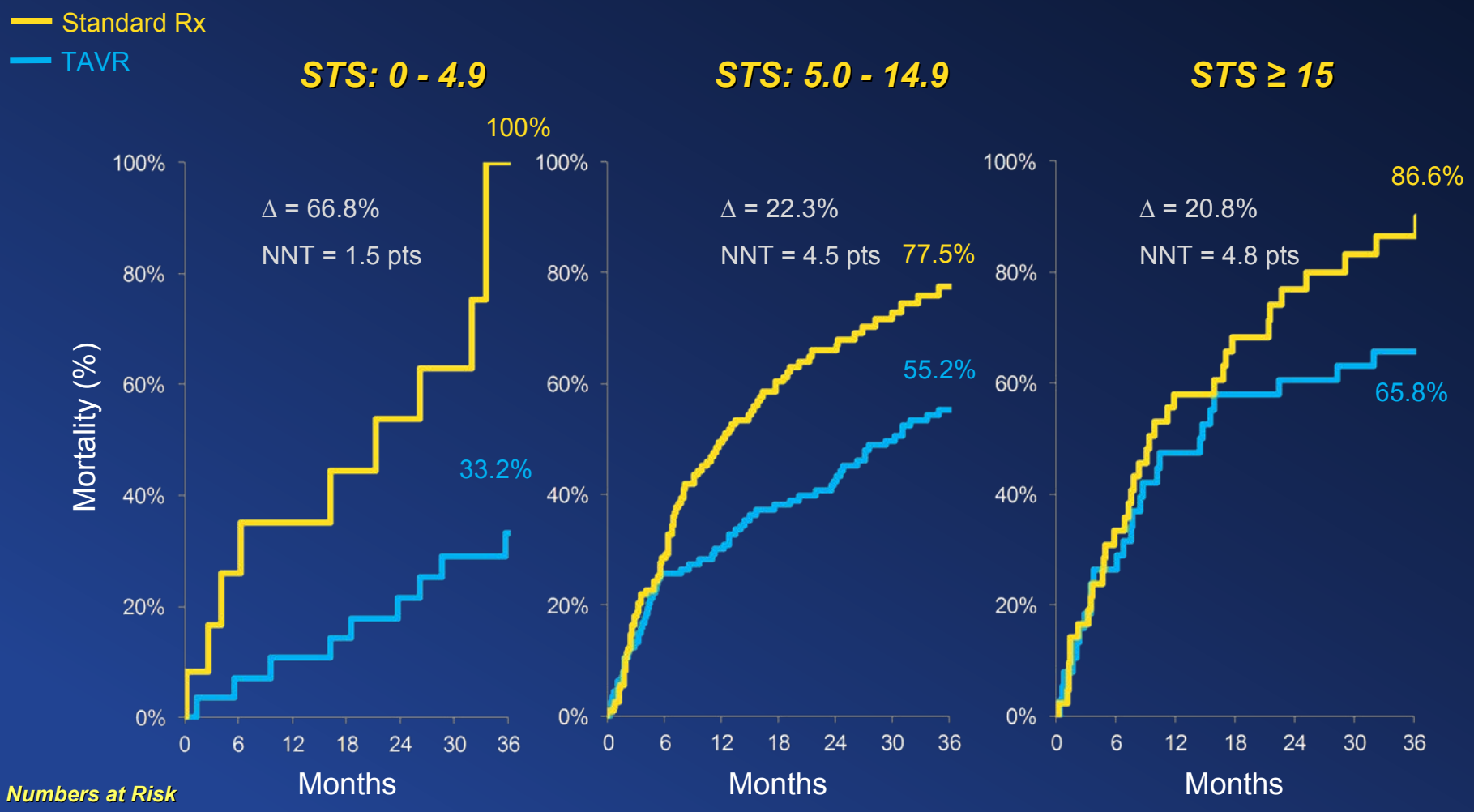


Mortality Stratified by
STS Score (ITT)



Numbers at Risk

Standard Rx	12	8	7	6	5	3	0	123	86	61	44	33	19	13	43	27	17	12	8	5	4
TAVR	28	26	25	24	21	19	16	113	84	79	70	65	55	44	38	28	20	16	15	14	10

PARTNER Secondary Analysis
Pooled Cohort (ITT)

2007 2008 2009

Randomized PARTNER
Cohort B: 358 Patients

May 2007 – March 2009

Randomized PARTNER
Cohort B
Randomized Continued Access: 91 Patients

March 2009 – September 2009

Non-Randomized Continued Access
Cohort B:
235 Patients

September 2009 – July 2011

Randomized PARTNER
Cohort A: 699 Patients

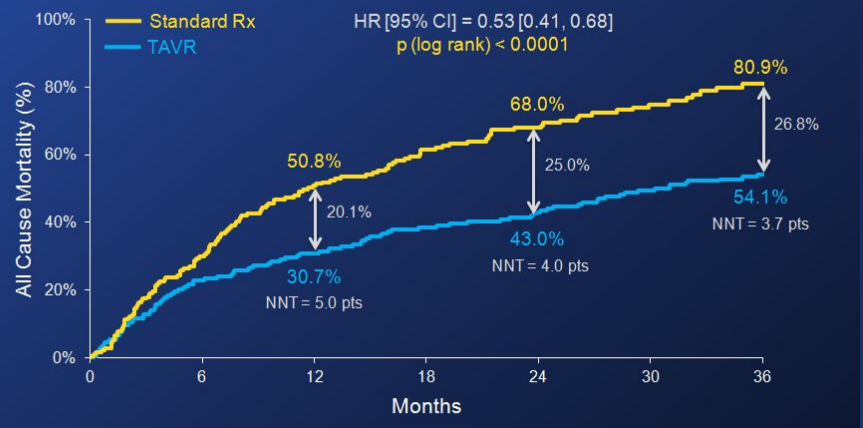
May 2007 – September 2009

Non-Randomized Continued Access
Cohort A:
1,833 Patients

September 2009 – January 2012

Primary Outcome (Composite)
All Cause Mortality

All Cause Mortality (ITT)
Crossover Patients Censored at Crossover



Numbers at Risk

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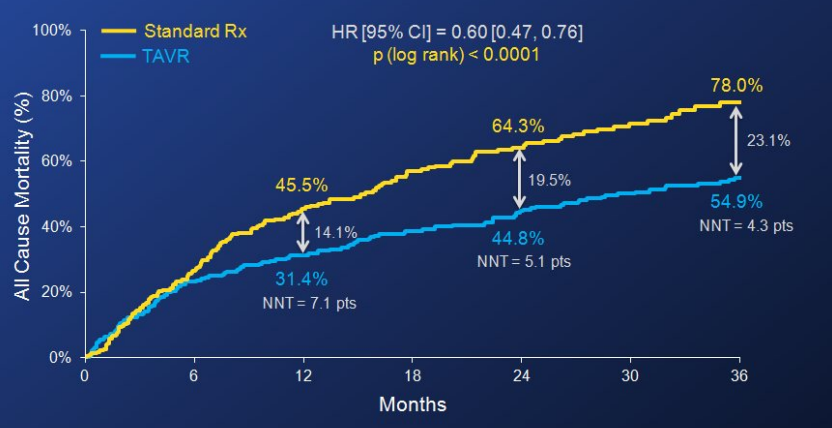
TAVR	179	138	124	110	101	88	70

All Cause Mortality (ITT)
Pooled Randomized
Crossover Patients Censored at Crossover



Numbers at Risk

Standard Rx	229	163	118	77	56	33	17
TAVR	220	169	151	133	117	103	70

Conclusions (1)

- At 3 years follow-up benefits of TAVR were sustained as measured by:
  - All cause mortality
  - Cardiovascular mortality
  - Repeat hospitalization
  - Functional status
- Valve durability was demonstrated with no increase in transvalvular gradient or attrition of valve area.
- Detailed analysis of all randomized inoperable patients showed consistent results for all outcomes.

Conclusions (2)

- Survival benefit of TAVR is dependent on the presence of comorbid illness.
- Without TAVR, mortality is similar irrespective of comorbid illness.

Clinical Implications

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- 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.

Thank You to the Dedicated Study Teams at All PARTNER Investigational Sites


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Backup Slides

Study Flow

Inoperable Cohort – Crossover Patients Followed in Standard Therapy Arm

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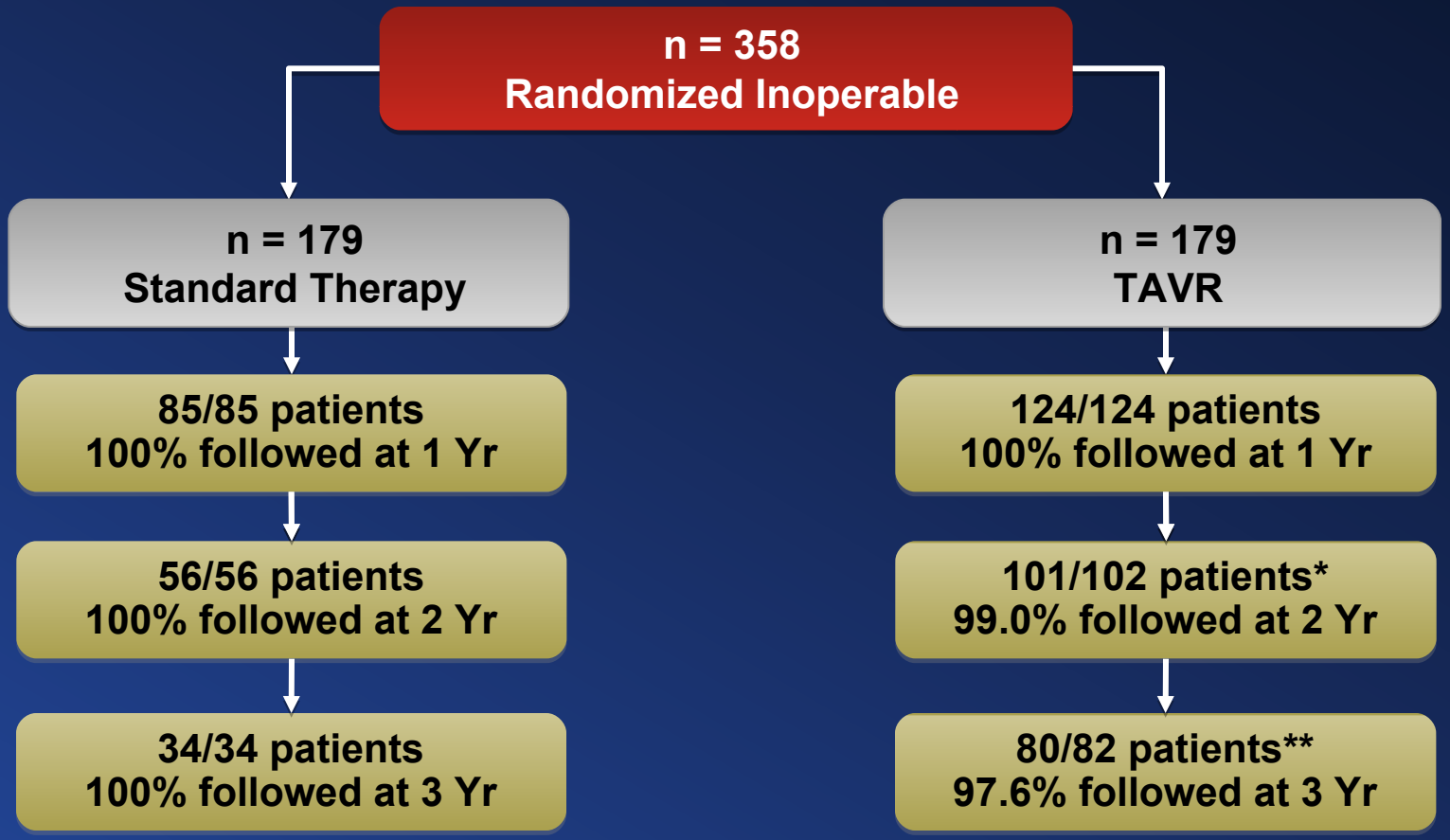


- **One TAVR patient was alive and censored prior to the window*
- ***Two TAVR patients were alive and censored prior to the window (including the one in the same status at 2 years); one TAVR patient withdrew between 2 and 3 years*
- *No patients were lost to follow-up*

Survival of Crossover Patients

1-2 year n = 11		2-3 year n = 9	
Alive, n (%)	**Dead, n (%)**	**Alive, n (%)**	**Dead, n (%)**
8 (72%)	3 (28%)	7 (77%)	2 (22%)
Crossover Follow-up (days)		**Crossover Follow-up (days)**	
522 ± 129	323 ± 248	469 ± 178	110 ± 11

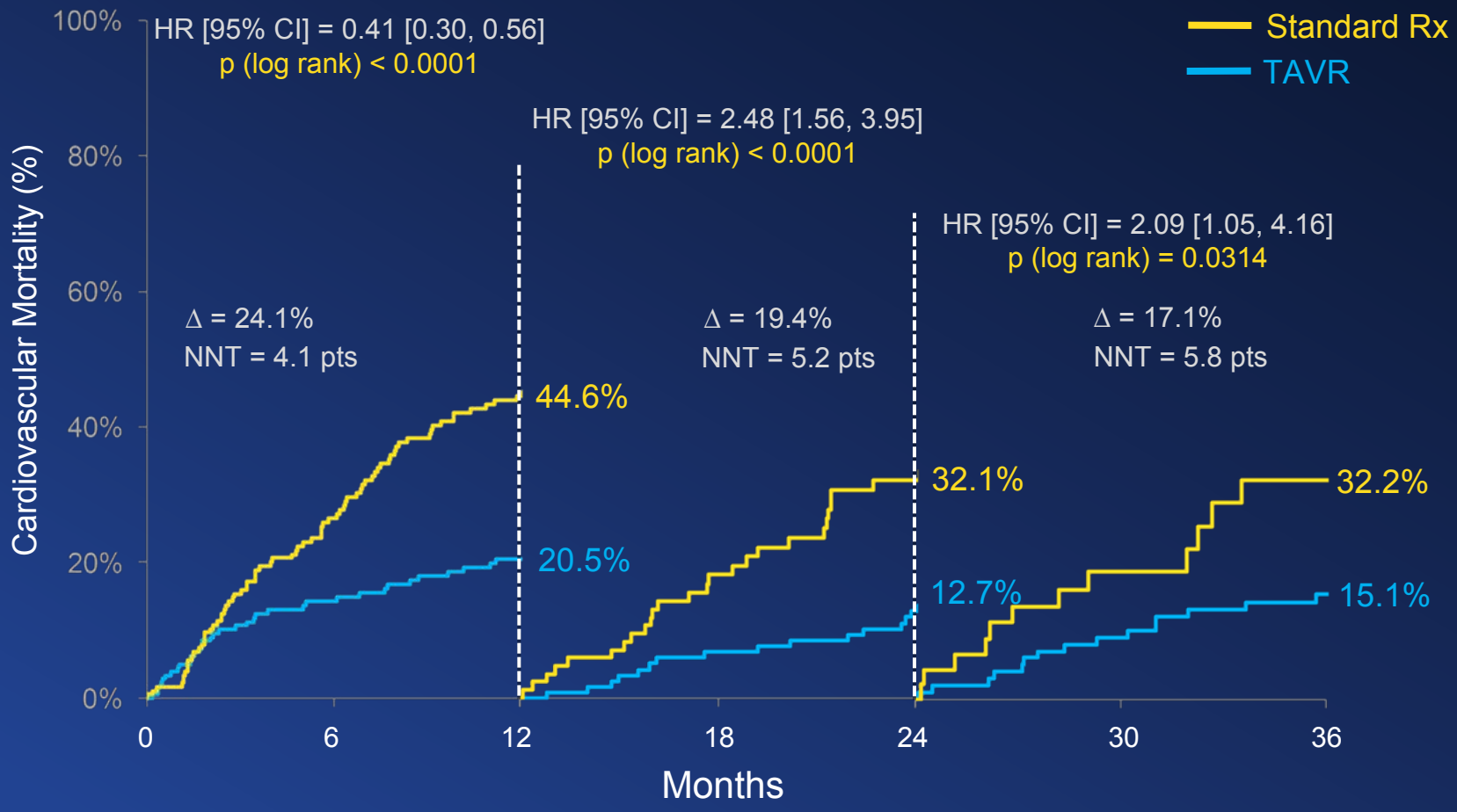
- *No patients crossed over after three years*

Survival of Crossover Patients

Crossover Patients	n	30 Day Mortality Events (%)	1 Year Mortality Events (%)	Last Follow-Up Mortality Events (%)
1-2 year	11	0 (0)	1 (9)	3 (27)
2-3 year	9	0 (0)	2 (22)	2 (22)
All	20	0 (0)	3 (15)	5 (20)

Follow-up of surviving patients = 497 ± 150 days

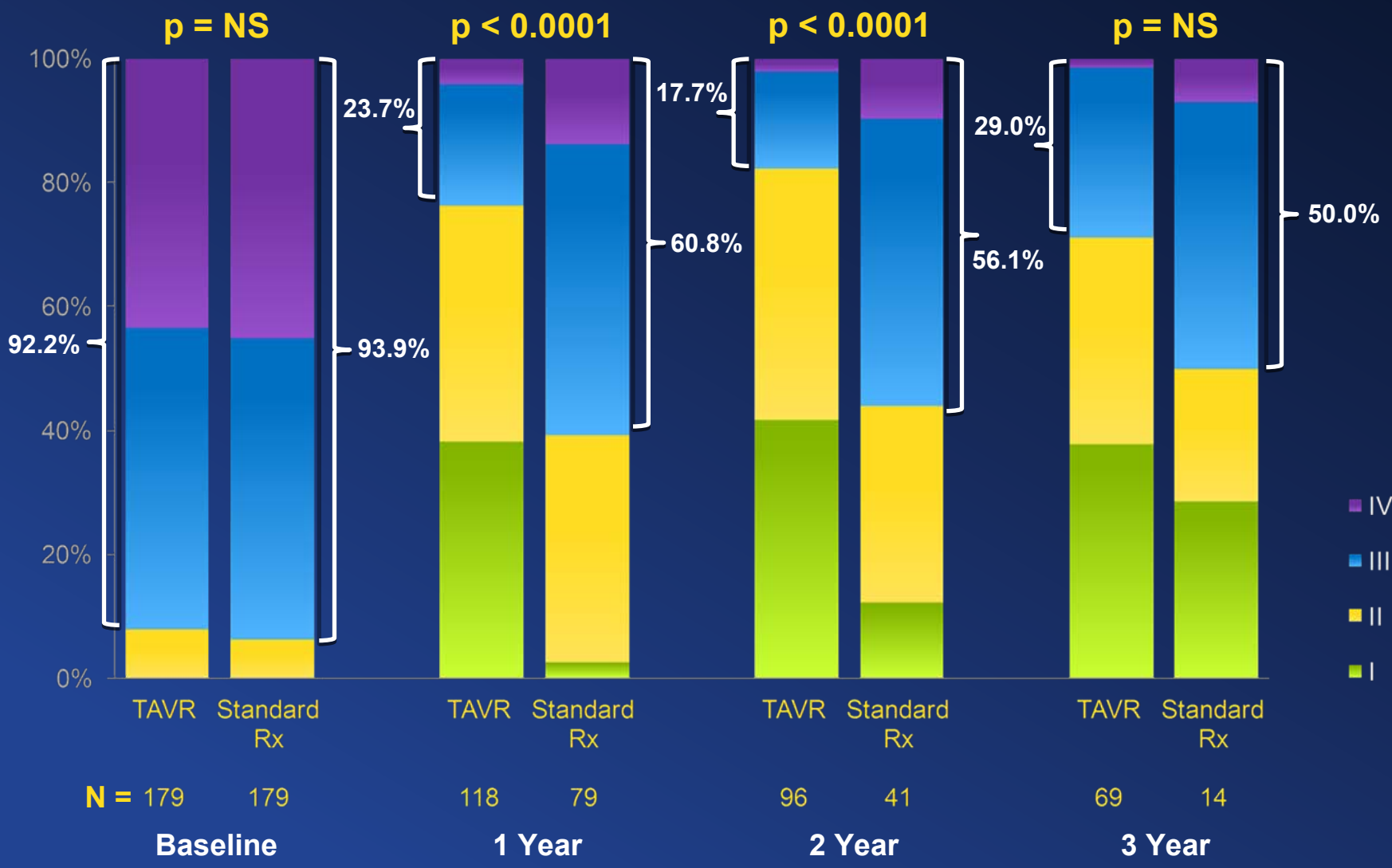
Cardiovascular Mortality (ITT)
Landmark Analysis



Numbers at Risk

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

NYHA Class Over Time (ITT)
Survivors



Adverse Events
Between 2 and 3 years (ITT)

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	3 Year n = 179		2-3 Year n = 179	
Outcome	*TAVR*	*Standard Rx*	*TAVR*	*Standard Rx*
Myocardial infarction				
All, % (n)	4.0 (4)	2.5 (2)	2.4 (2)	0 (0)
Acute kidney injury				
Renal failure (CEC), % (n)	3.2 (5)	11.1 (10)	0 (0)	3.7 (1)
Bleeding – major, % (n)	32.0 (51)	32.9 (28)	3.4 (3)	13.0 (3)
Cardiac re-intervention				
BAV, % (n)	3.8 (5)	85.3 (140)	1.0 (1)	4.7 (2)
TAVR, % (n)	1.7 (3)	4.5 (4)	0 (0)	0 (0)
AVR, % (n)	0.9 (1)	8.9 (11)	0 (0)	0 (0)
Endocarditis, % (n)	2.3 (3)	0.8 (0)	0 (0)	0 (0)
New pacemaker, % (n)	7.6 (11)	8.6 (14)	1.2 (1)	0 (0)

Mortality Stratified by Paravalvular Leak
Valve Implant Patients

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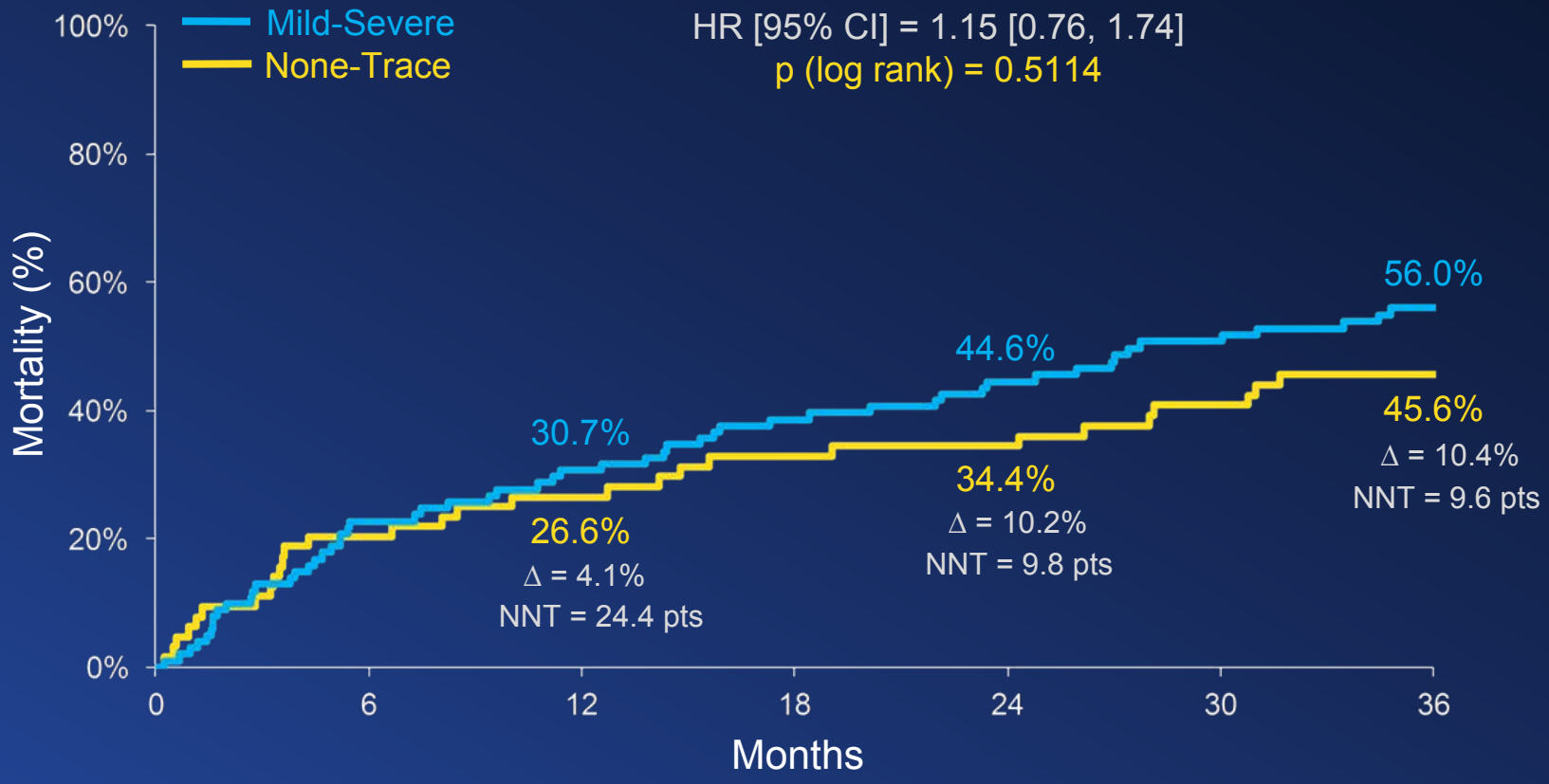

Numbers at Risk

Mild-Severe	101	78	70	62	56	48	35
None-Trace	64	51	47	43	41	37	29

Echo Analysis PV Leak Changes
30 Days Compared to 3 Years

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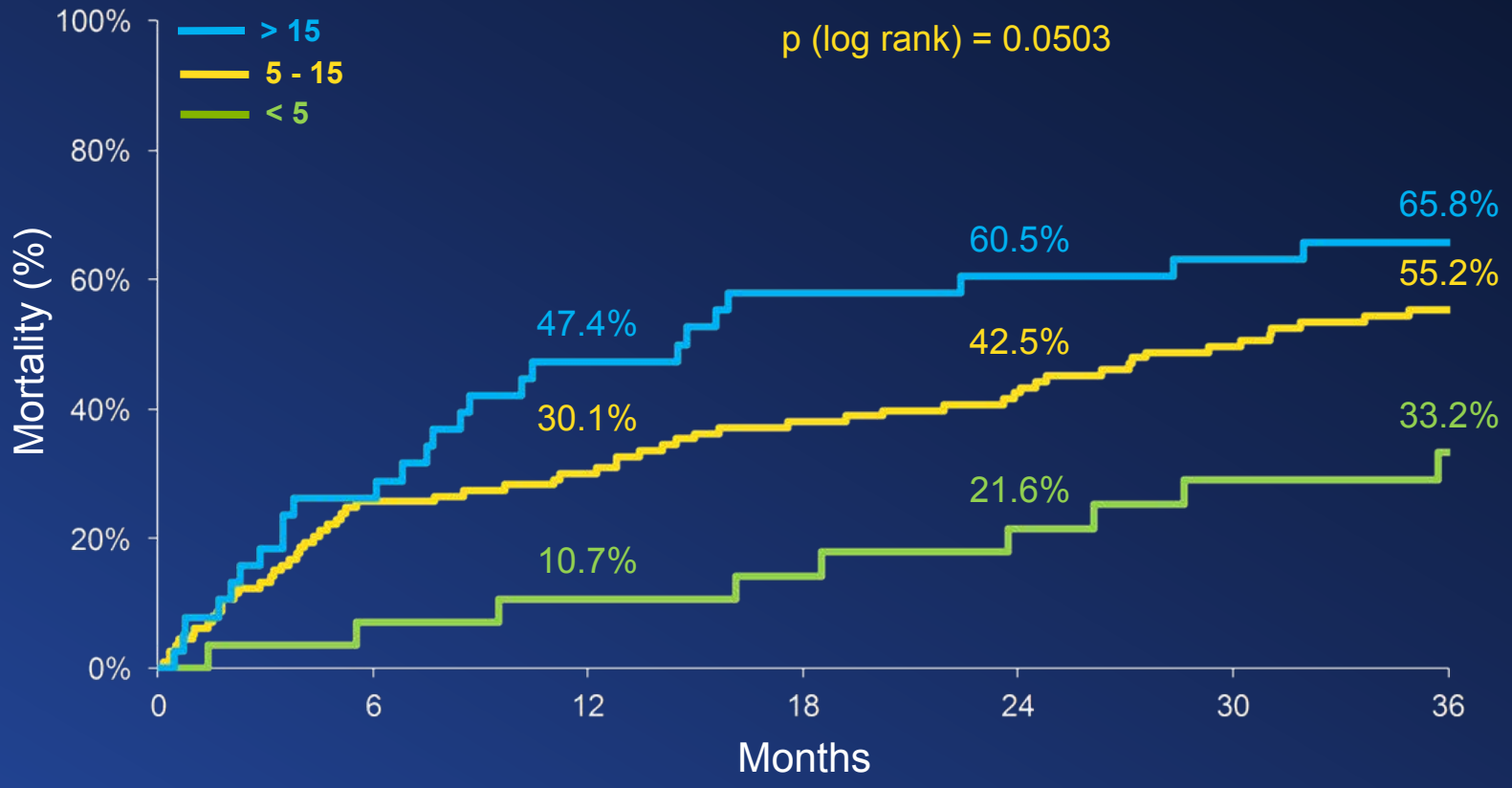
Patients With Data at Both Time Points

		3 Year		
30 Day	*None*	*Trace*	*Mild*	*Moderate*
None	7	3	0	0
Trace	5	5	2	0
Mild	5	1	11	2
Moderate	0	1	2	0

Of the 44 patients alive with data at both 30 days and 3 years:

31.8% Improved *52.3% Unchanged* *16.0% Progressed*

TAVR Mortality Stratified by STS Score (ITT)



Numbers at Risk

> 15	38	28	20	16	15	14	10
5 - 15	113	84	79	70	65	55	44
< 5	28	26	25	24	21	19	16

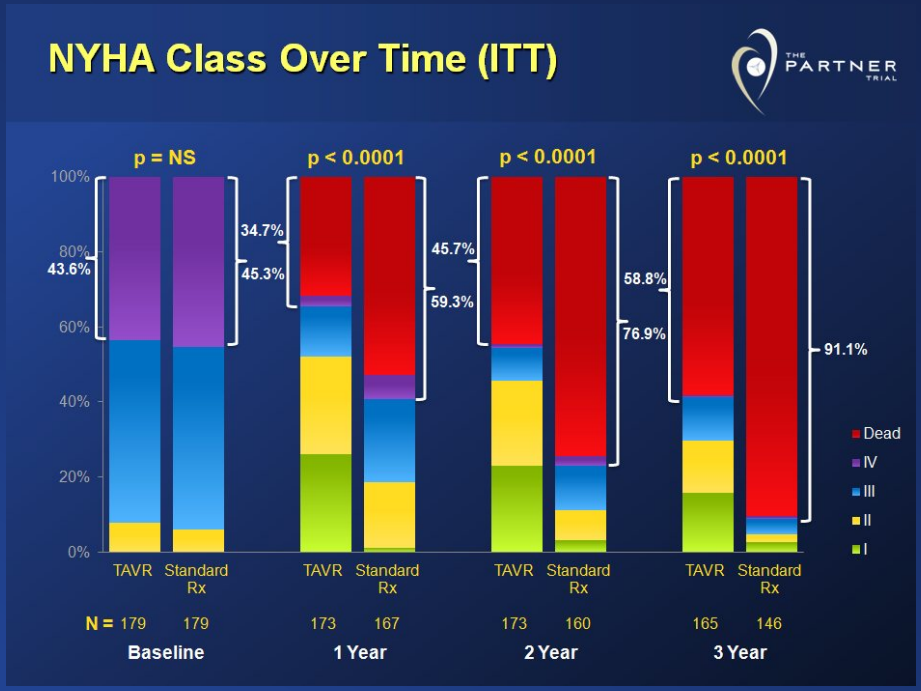
Patient Characteristics (1)
Pooled

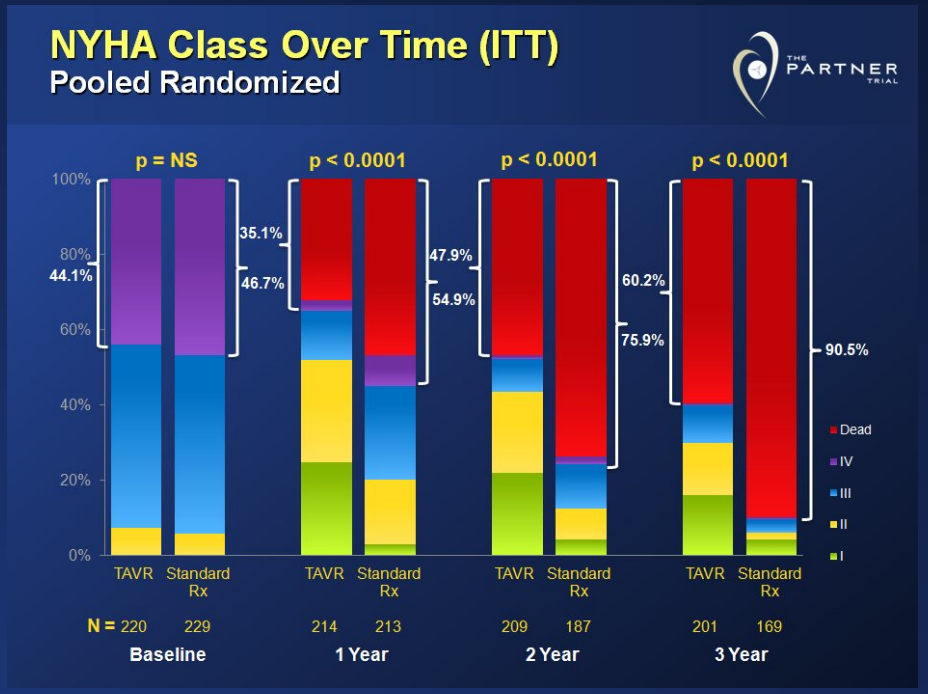
Characteristic	*TAVR* *n = 229*	*Standard Rx* *n = 220*	*p value*
Age – yr (SD)	83.2 (8.5)	83.0 (8.5)	0.8
Male sex (%)	48.5	47.7	0.9
STS Score (SD)	12.2 (5.4)	11.4 (6.0)	0.1
NYHA III or IV (%)	94.3	92.7	0.6
CAD (%)	73.8	65.9	0.08
Prior MI (%)	28.4	22.3	0.1
Prior CABG (%)	42.4	31.8	0.02
Prior PCI (%)	22.7	25.9	0.4
Prior BAV (%)	21.4	13.6	0.04
CVD (%)	25.8	26.8	0.6

Patient Characteristics (2)
Pooled

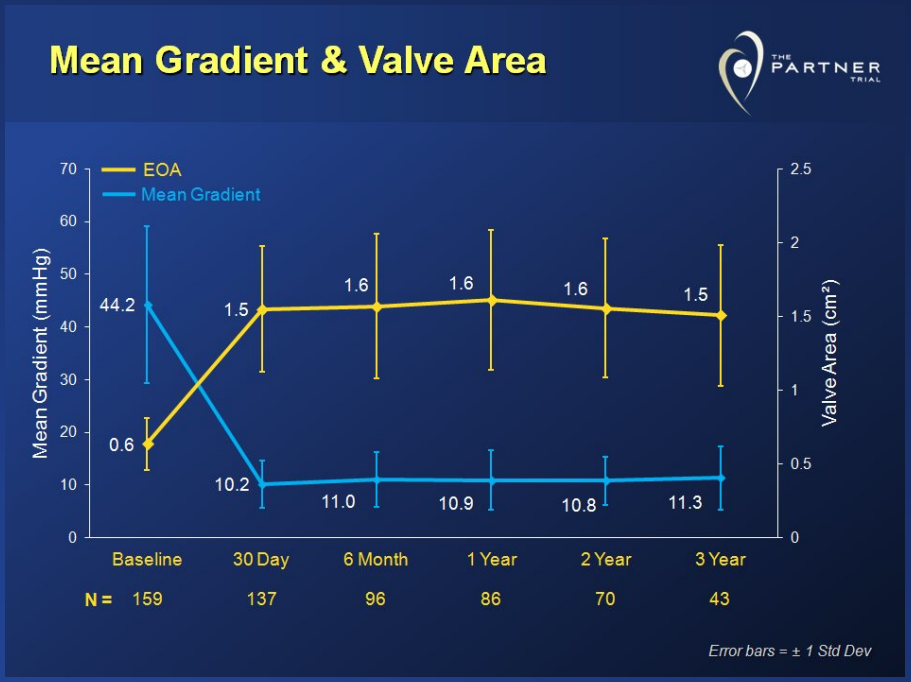
Characteristic	*TAVR* *n = 229*	*Standard Rx* *n = 220*	*p value*
PVD (%)	24.9	30.0	0.2
COPD			
Any (%)	72.9	64.3	0.1
O_2 dependent (%)	24.7	22.0	0.8
Creatinine > 2 mg/dL (%)	8.8	5.5	0.2
Atrial fibrillation (%)	26.6	20.8	0.2
Perm. pacemaker (%)	19.7	20.5	0.9
Pulmonary HTN (%)	50.7	47.7	0.6
Frailty (%)	25.6	17.8	0.1
Porcelain aorta (%)	11.8	18.6	0.049
Chest wall radiation (%)	7.9	7.7	1.0
Chest wall deformity (%)	6.1	7.7	0.6
Liver disease (%)	3.5	5.0	0.4

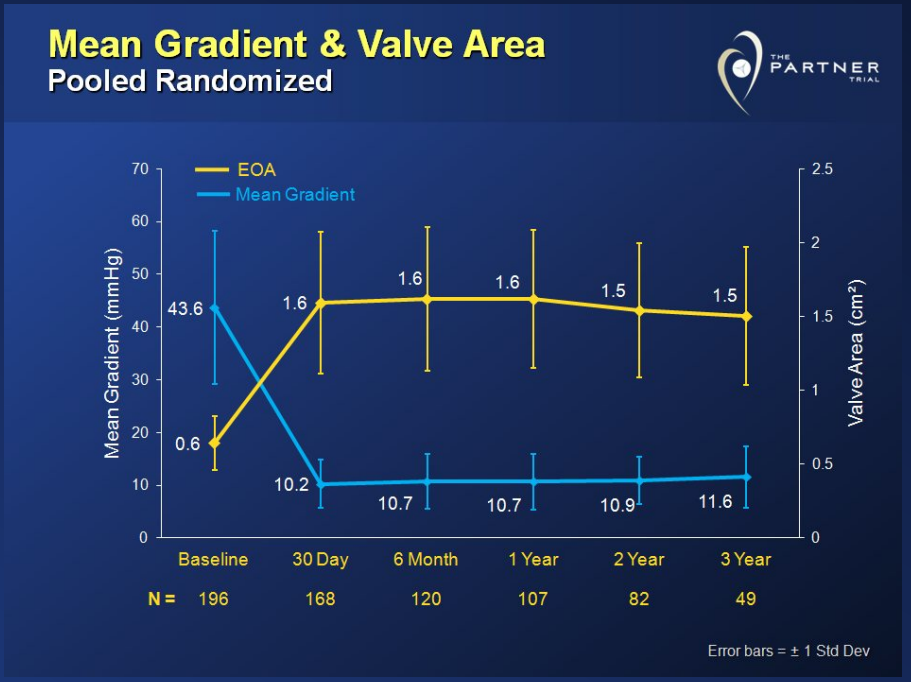
Primary Outcome (Composite)
Functional Status





Primary Outcome (Composite)
Mean Gradient & AVA





Univariate and Multivariate Predictors of Mortality after TAVR

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Univariate Predictors

	Hazard Ratio	*p value*
BMI > 26	0.58 (0.39 – 0.86)	0.007
Peripheral Vascular Disease	1.67 (1.13 – 2.47)	0.01
Oxygen dependent COPD	1.62 (1.05 -2.49)	0.03
History of Stroke or TIA	3.19 (1.28 – 7.92)	0.01
History of CABG	0.64 (0.42 – 0.98)	0.04

Multivariate Predictors

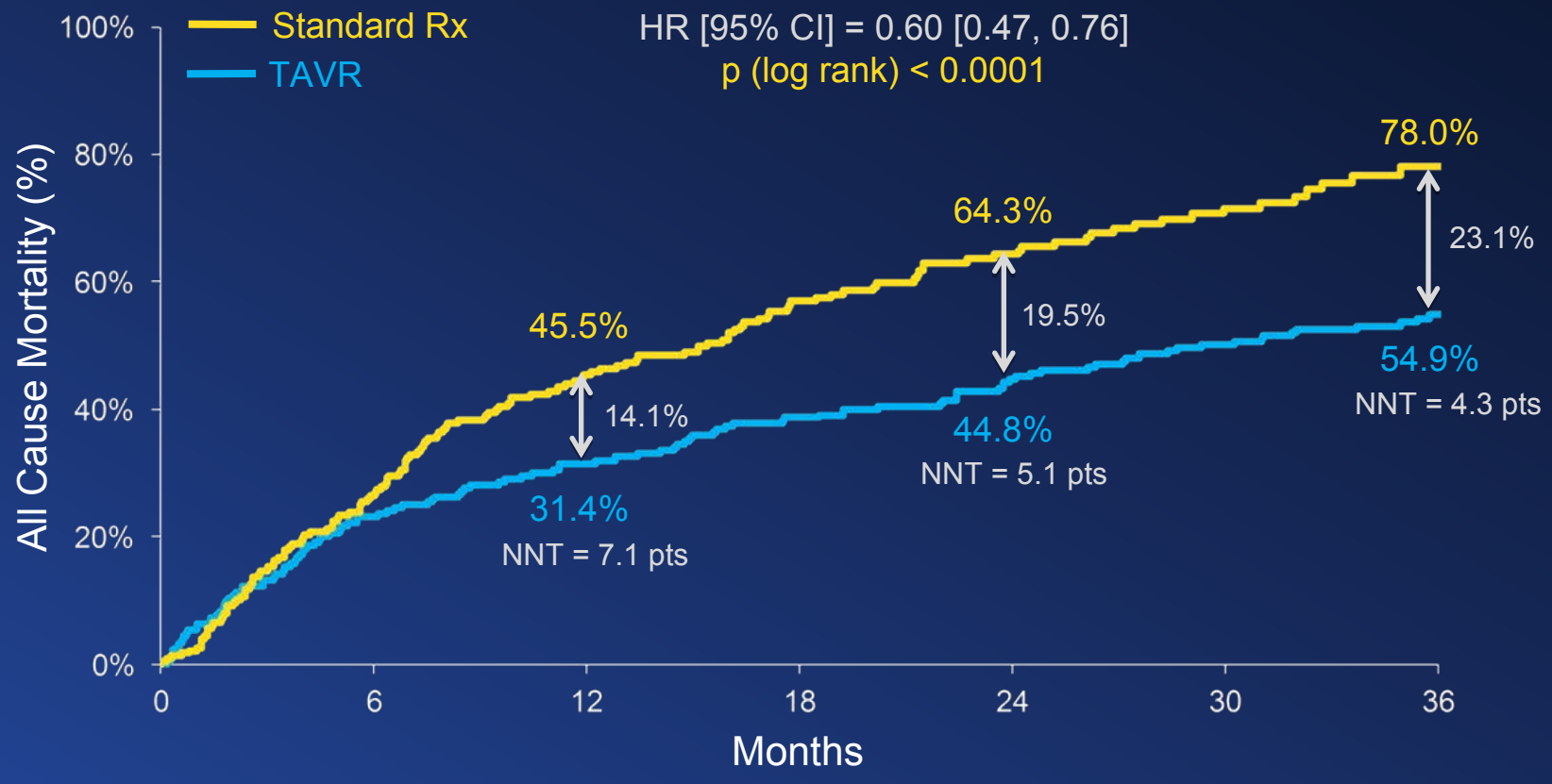
	Hazard Ratio	*p value*
BMI > 26	0.47 (0.31 – 0.70)	0.02
Peripheral Vascular Disease	1.59 (1.07 – 2.38)	0.02
Oxygen dependent COPD	1.83 (1.17 – 2.85)	0.008
Moderate or Severe MR	0.56 (0.33 – 0.94)	0.03

Pooled Randomized

All Cause Mortality (ITT)

Pooled Randomized
Crossover Patients Censored at Crossover

THE PARTNER TRIAL



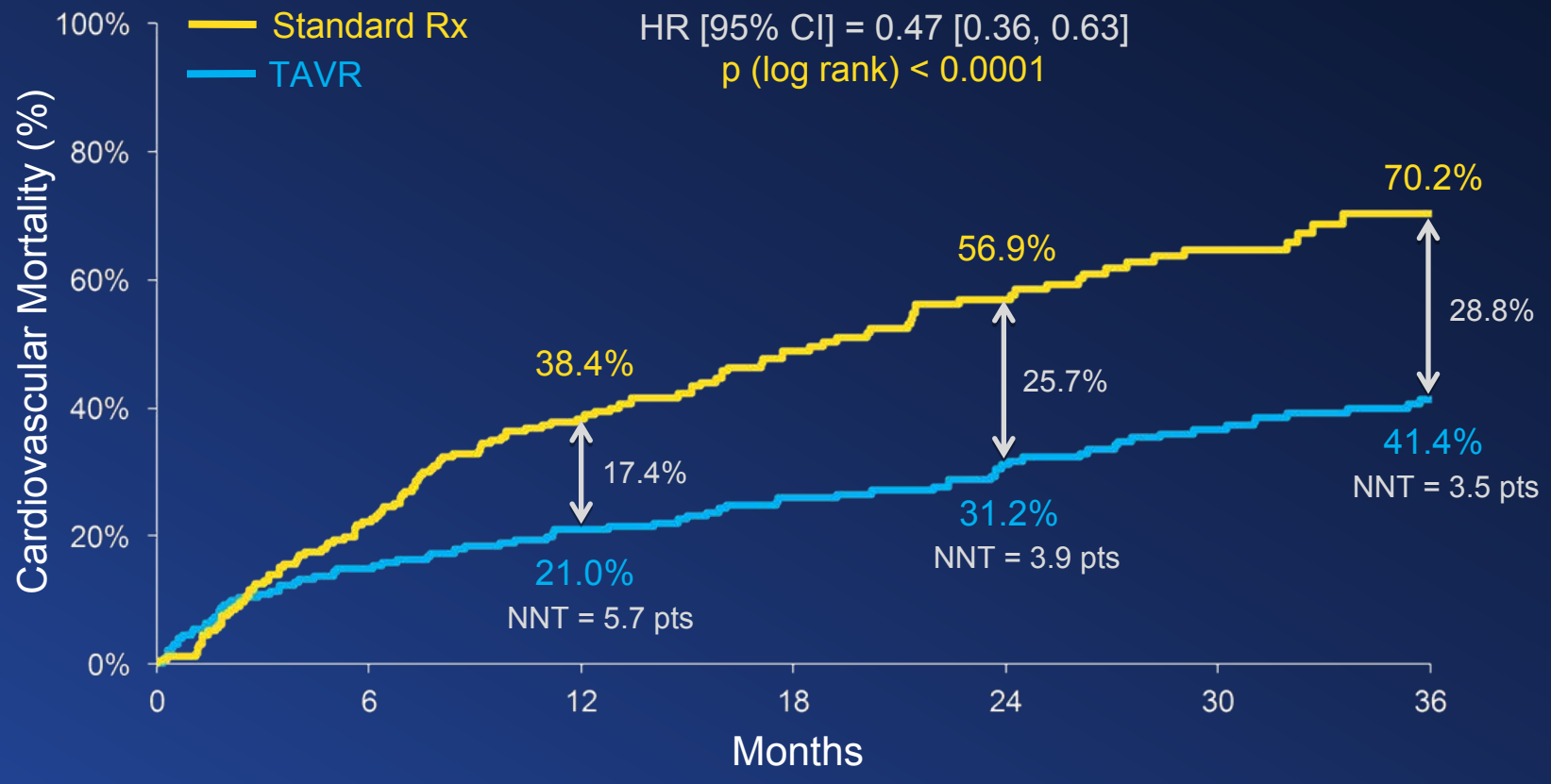
Numbers at Risk

Standard Rx	**229**	**163**	**118**	**77**	**56**	**33**	**17**
TAVR	**220**	**169**	**151**	**133**	**117**	**103**	**70**

Cardiovascular Mortality (ITT)

Pooled Randomized
Crossover Patients Censored at Crossover

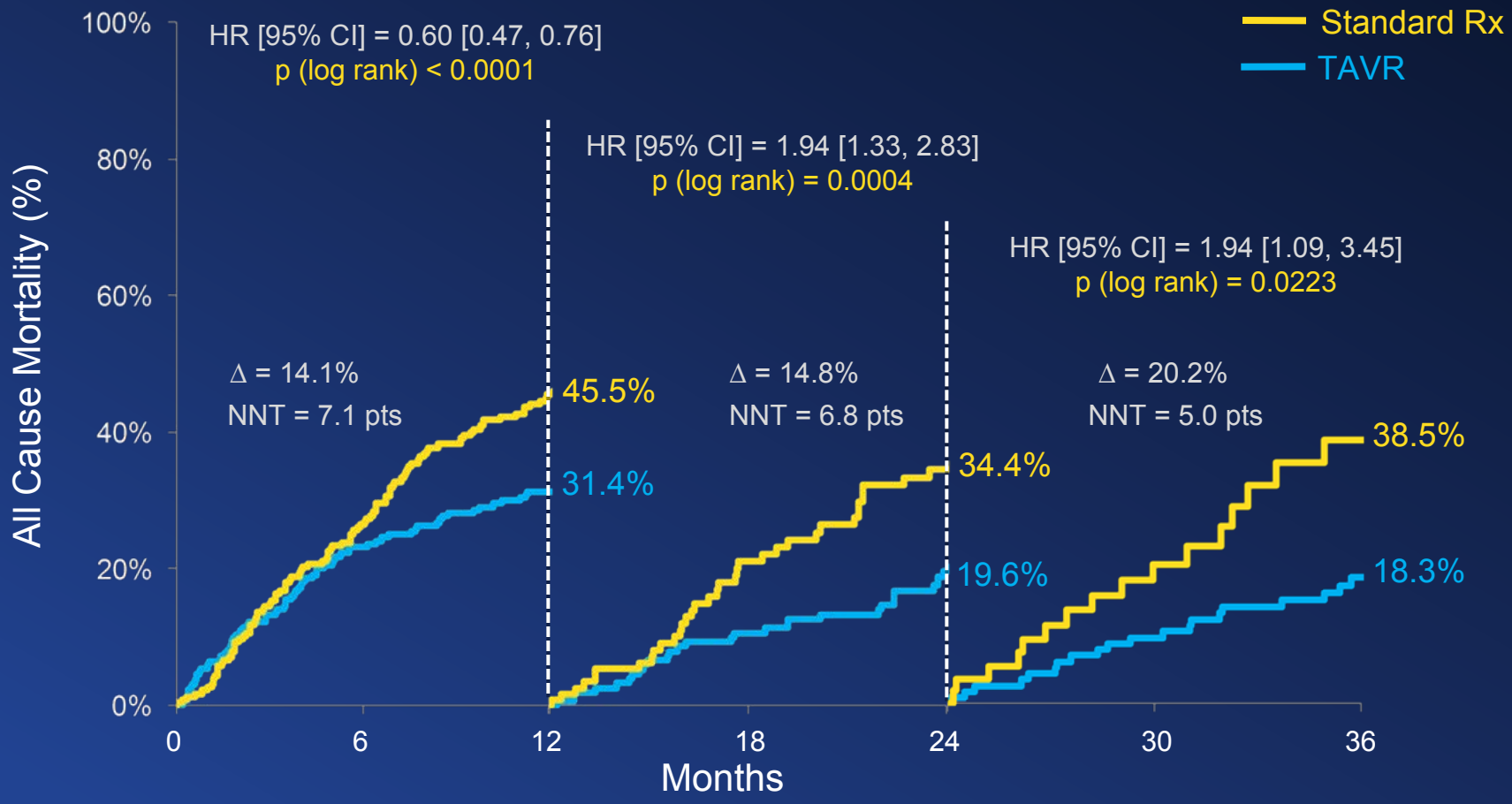
THE PARTNER TRIAL



Numbers at Risk

Standard Rx	**229**	**163**	**118**	**77**	**56**	**33**	**17**
TAVR	**220**	**169**	**151**	**133**	**117**	**103**	**70**

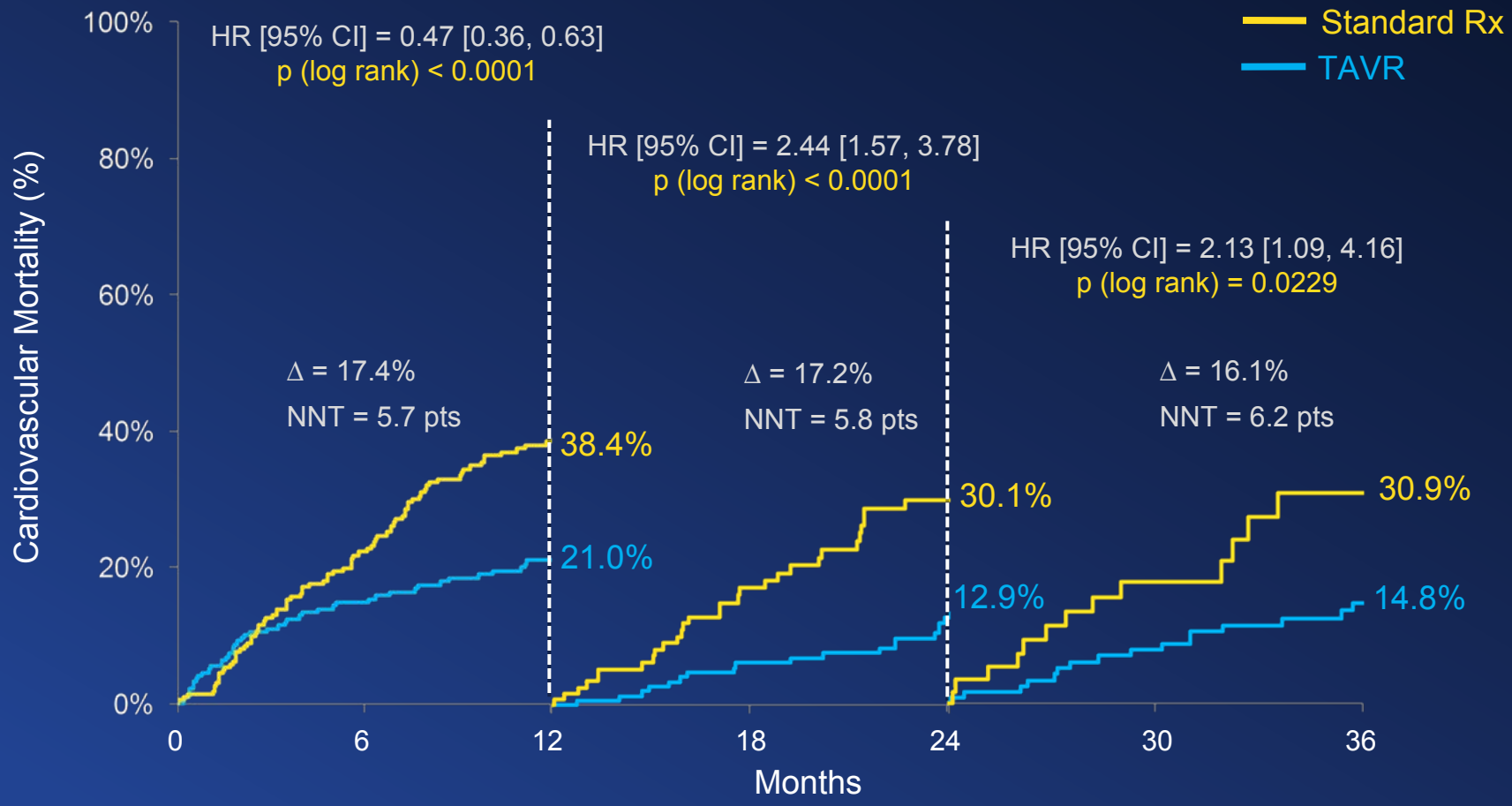
All Cause Mortality (ITT)
Pooled Randomized – Landmark Analysis



Numbers at Risk

Standard Rx	**229**	**163**	**118**	**77**	**56**	**33**	**17**
TAVR	**220**	**169**	**151**	**133**	**117**	**103**	**70**

Cardiovascular Mortality (ITT)
Pooled Randomized – Landmark Analysis



Numbers at Risk

Standard Rx	**229**	**163**	**118**	**77**	**56**	**33**	**17**
TAVR	**220**	**169**	**151**	**133**	**117**	**103**	**70**

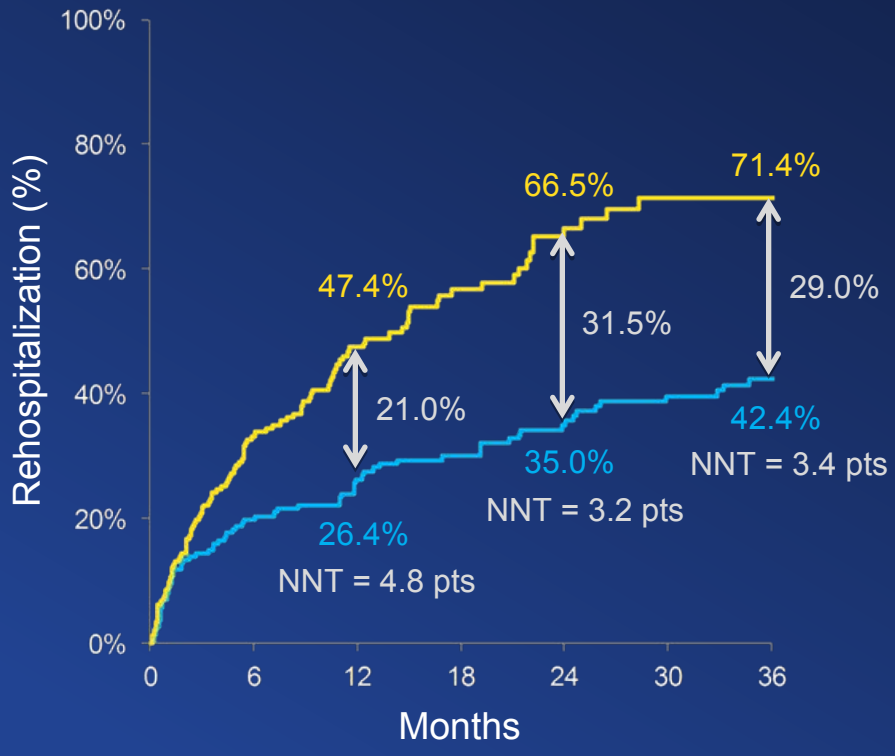
Repeat Hospitalization (ITT)
Pooled Randomized

THE PARTNER TRIAL

Standard Rx
TAVR

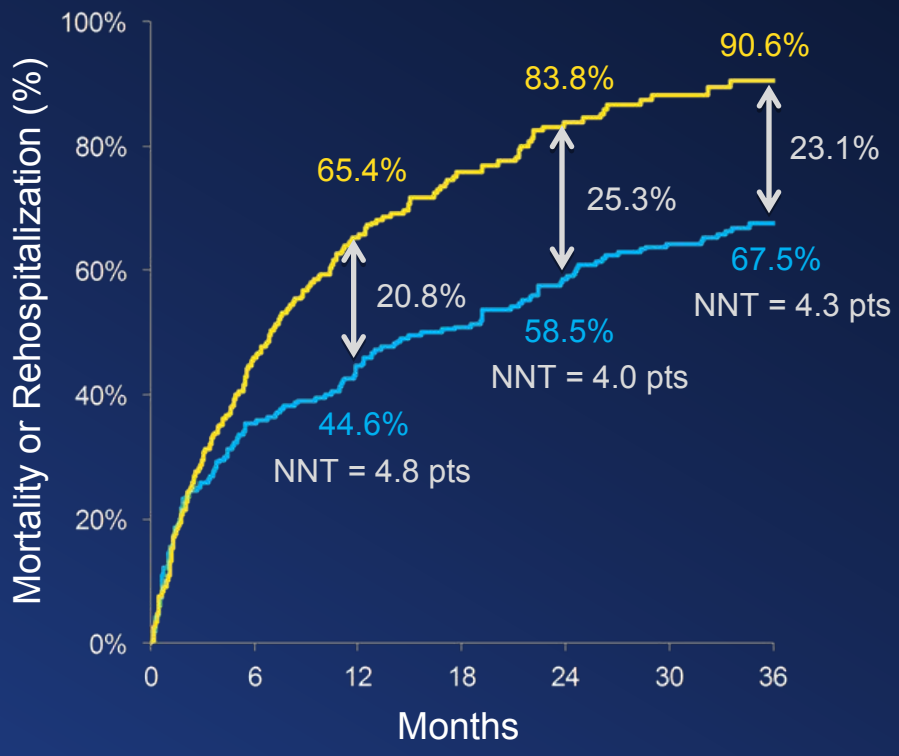
Rehospitalization

HR [95% CI] = 0.45 [0.33, 0.61]
p (log rank) < 0.0001



Mortality or Rehospitalization

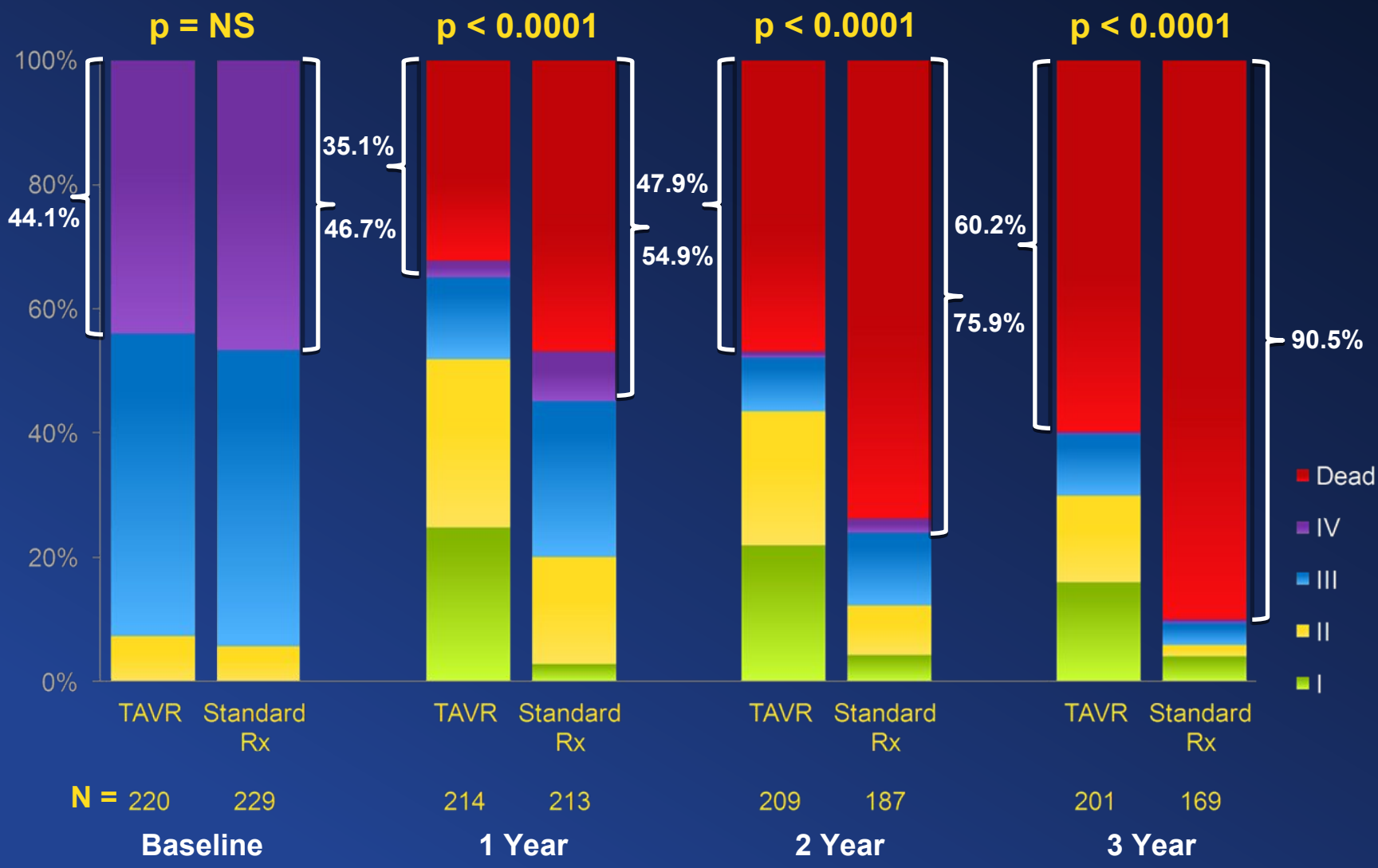
HR [95% CI] = 0.54 [0.44, 0.68]
p (log rank) < 0.0001



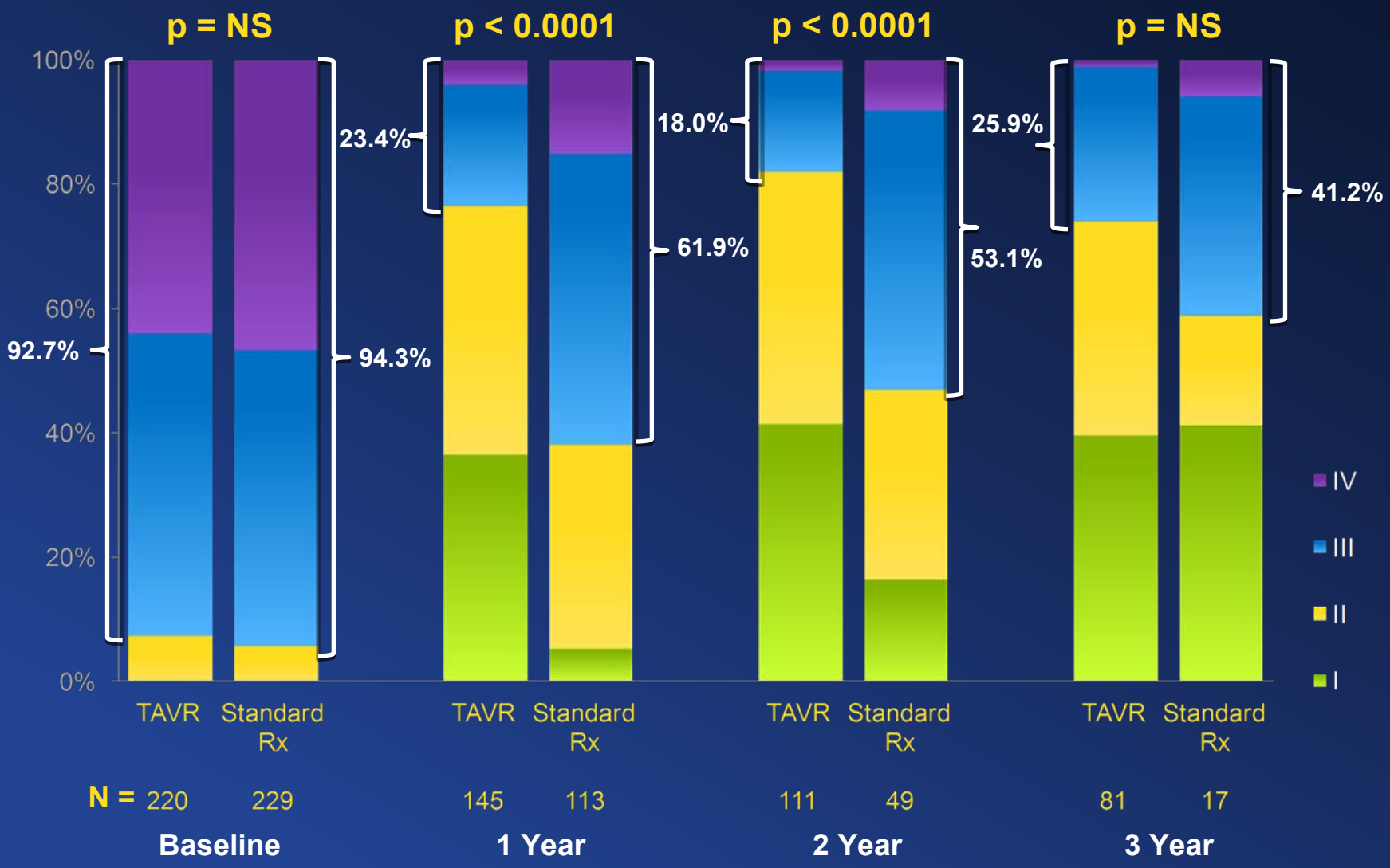
Numbers at Risk

Standard Rx	229	120	74	43	26	14	7		229	120	74	43	26	14	7
TAVR	220	142	122	106	87	73	49		220	142	122	106	87	73	49

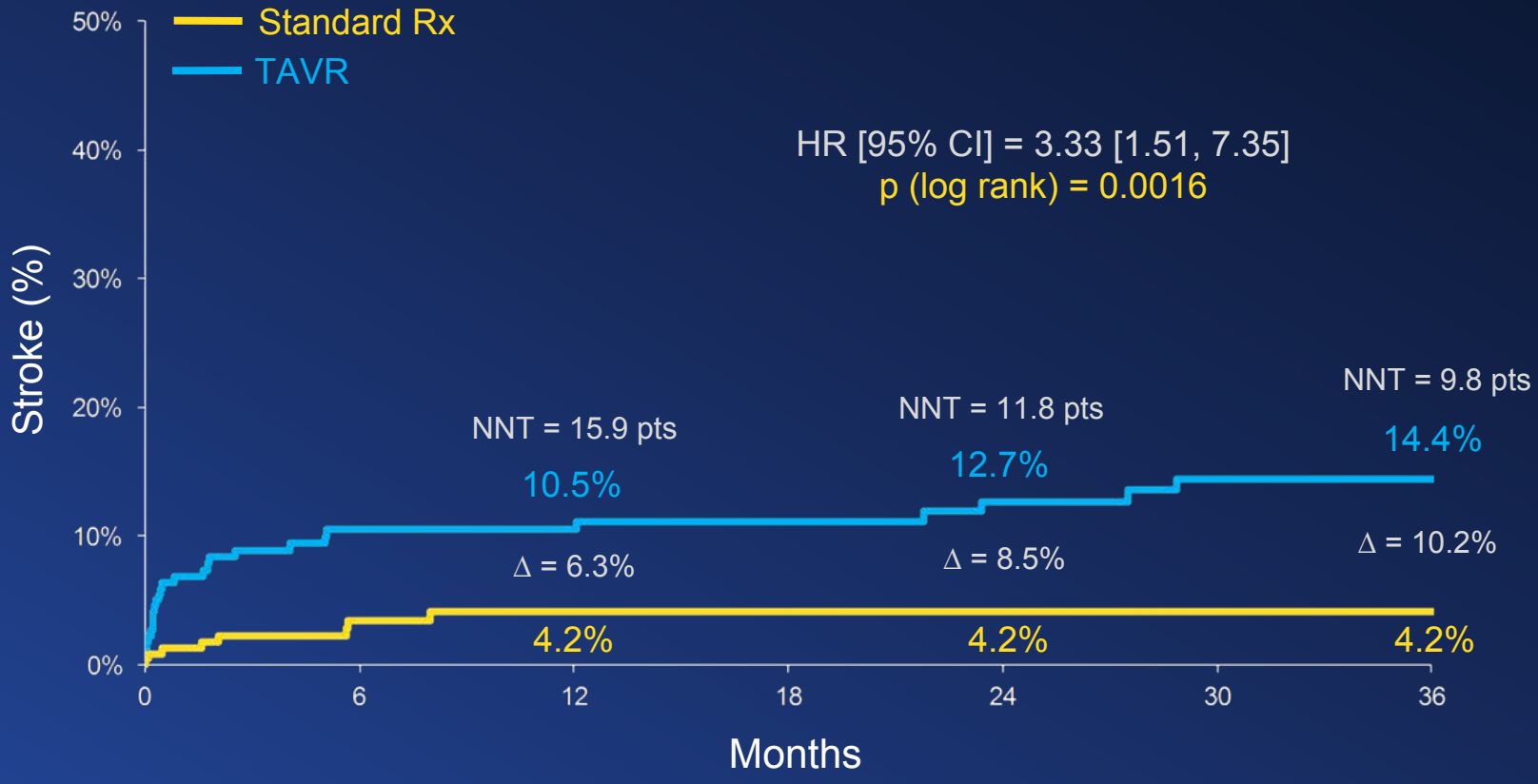
NYHA Class Over Time (ITT)
Pooled Randomized



NYHA Class Over Time (ITT)
Pooled Randomized (Survivors)



All Stroke (ITT)
Pooled Randomized

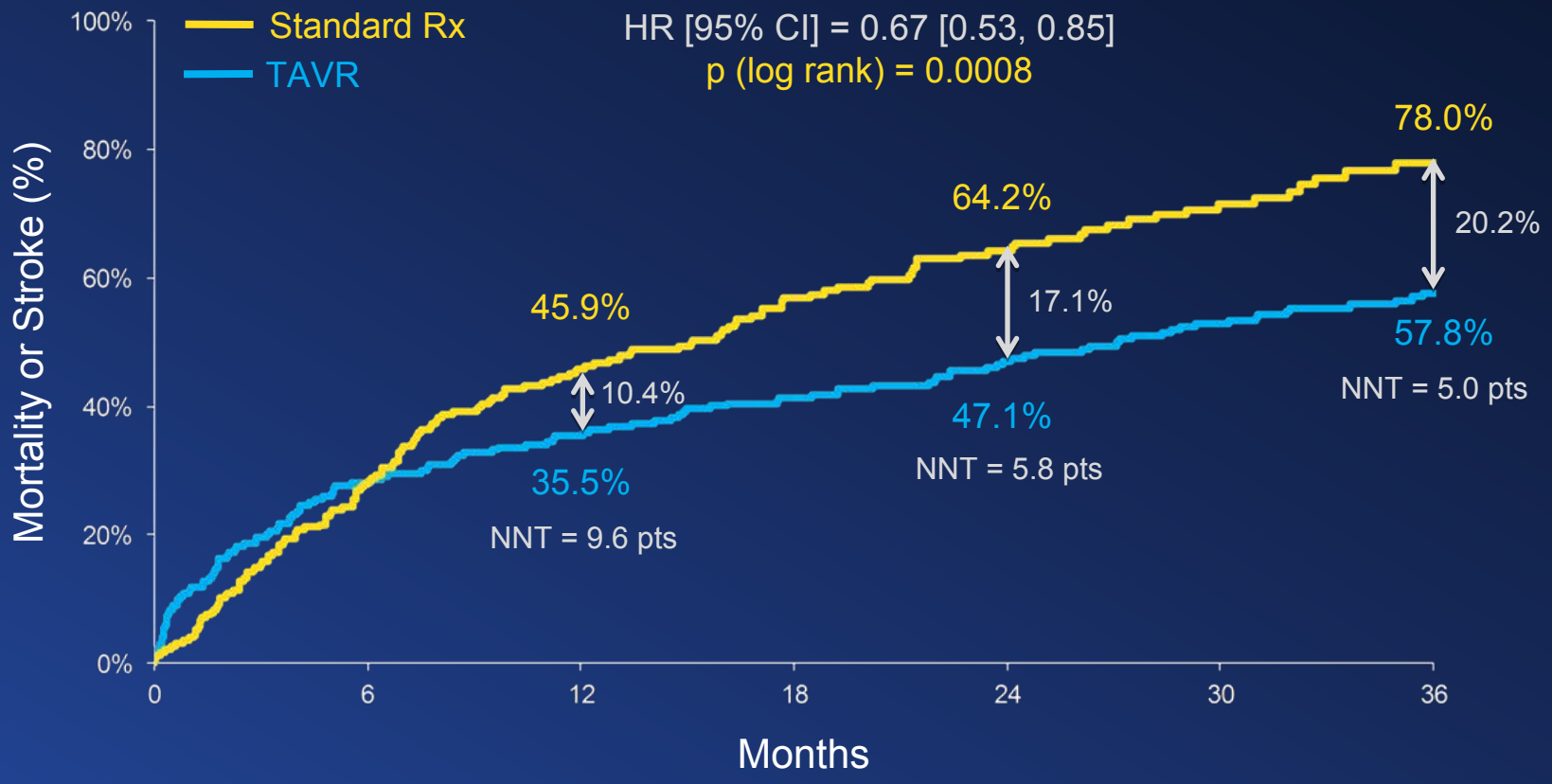


Numbers at Risk

Standard Rx	**229**	**160**	**117**	**77**	**56**	**33**	**17**
TAVR	**220**	**158**	**142**	**127**	**112**	**97**	**65**

Mortality or Stroke (ITT)
Pooled Randomized

THE PARTNER TRIAL



Numbers at Risk

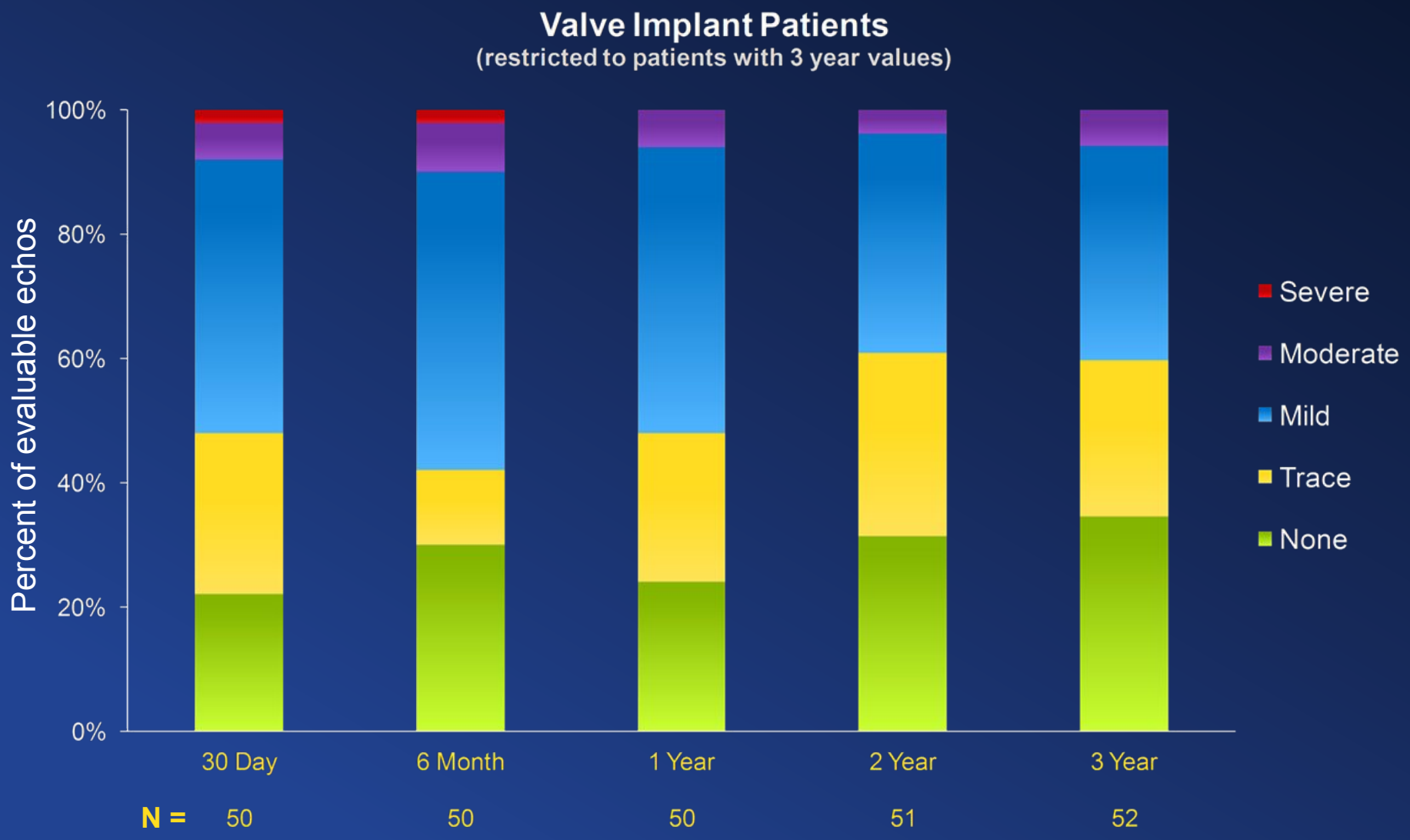
Standard Rx	**229**	**160**	**117**	**77**	**56**	**33**	**17**
TAVR	**220**	**158**	**142**	**127**	**112**	**97**	**65**

Mean Gradient & Valve Area
Pooled Randomized

Error bars = ± 1 Std Dev

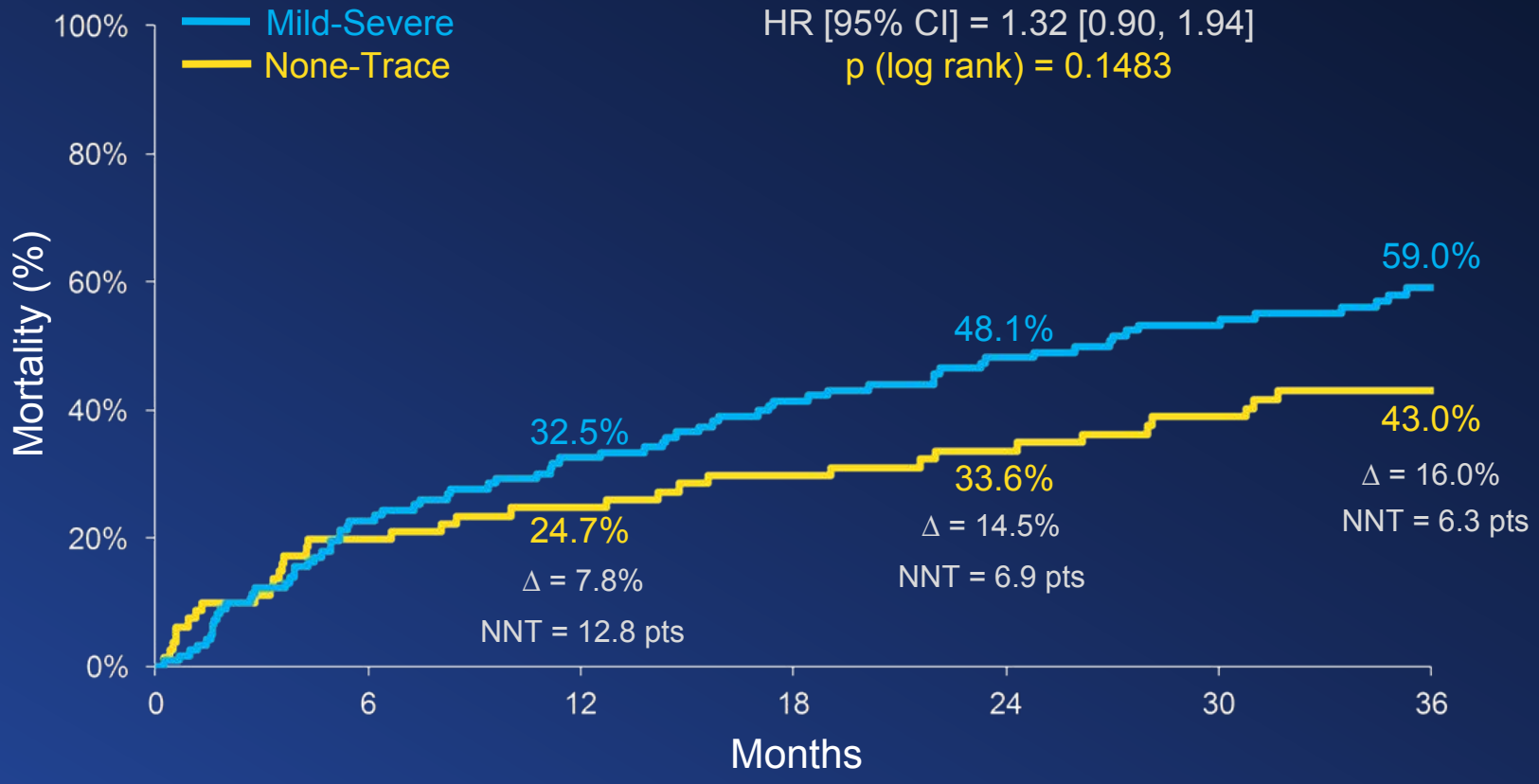
Paravalvular Leak
Pooled Randomized

THE PARTNER TRIAL



Mortality Stratified by Paravalvular Leak (ITT)

Pooled Randomized – Valve Implant Patients

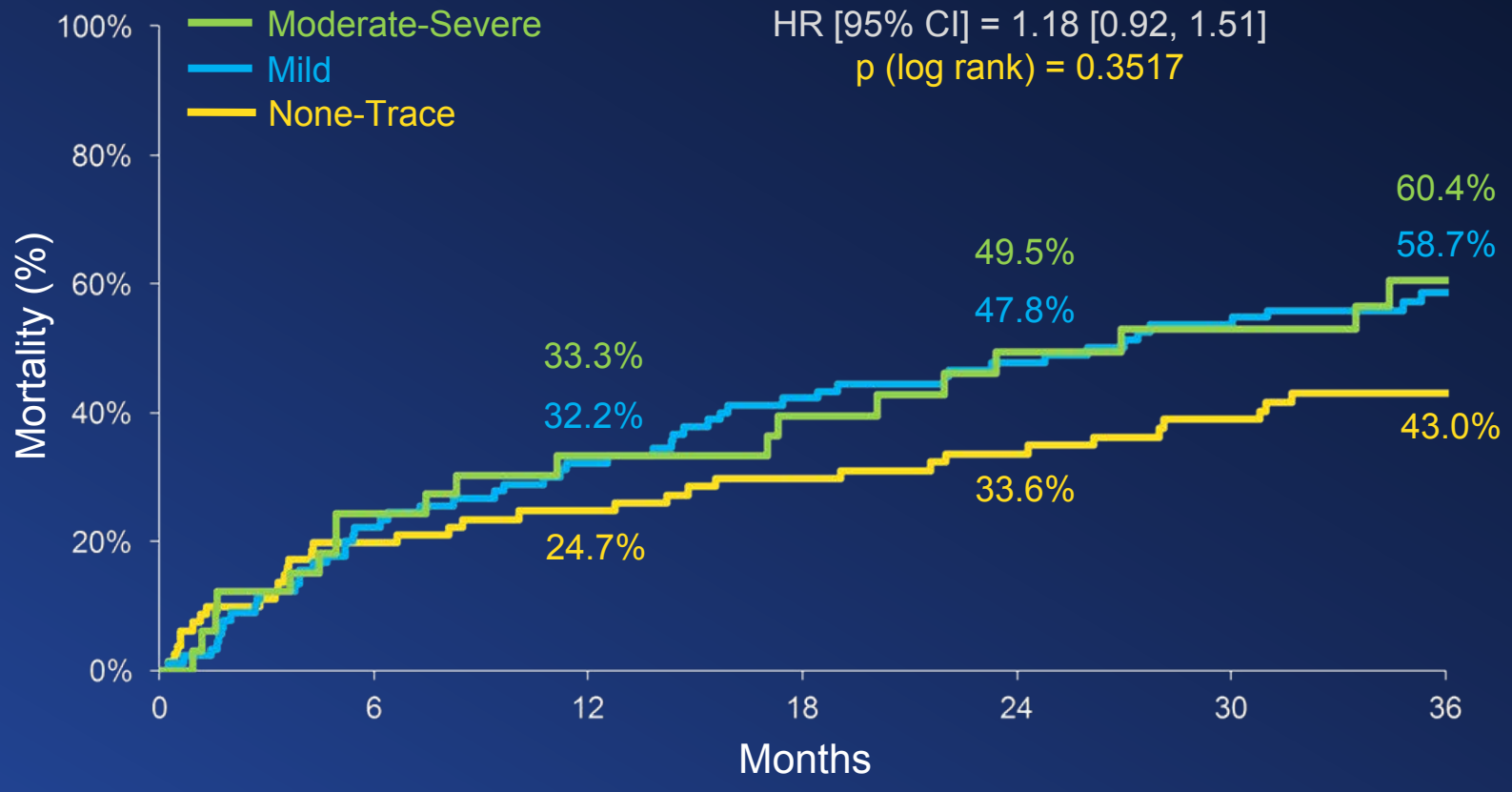


Numbers at Risk

Mild-Severe	123	95	83	72	62	54	35
None-Trace	81	65	61	55	51	46	29

Mortality Stratified by Paravalvular Leak (ITT)

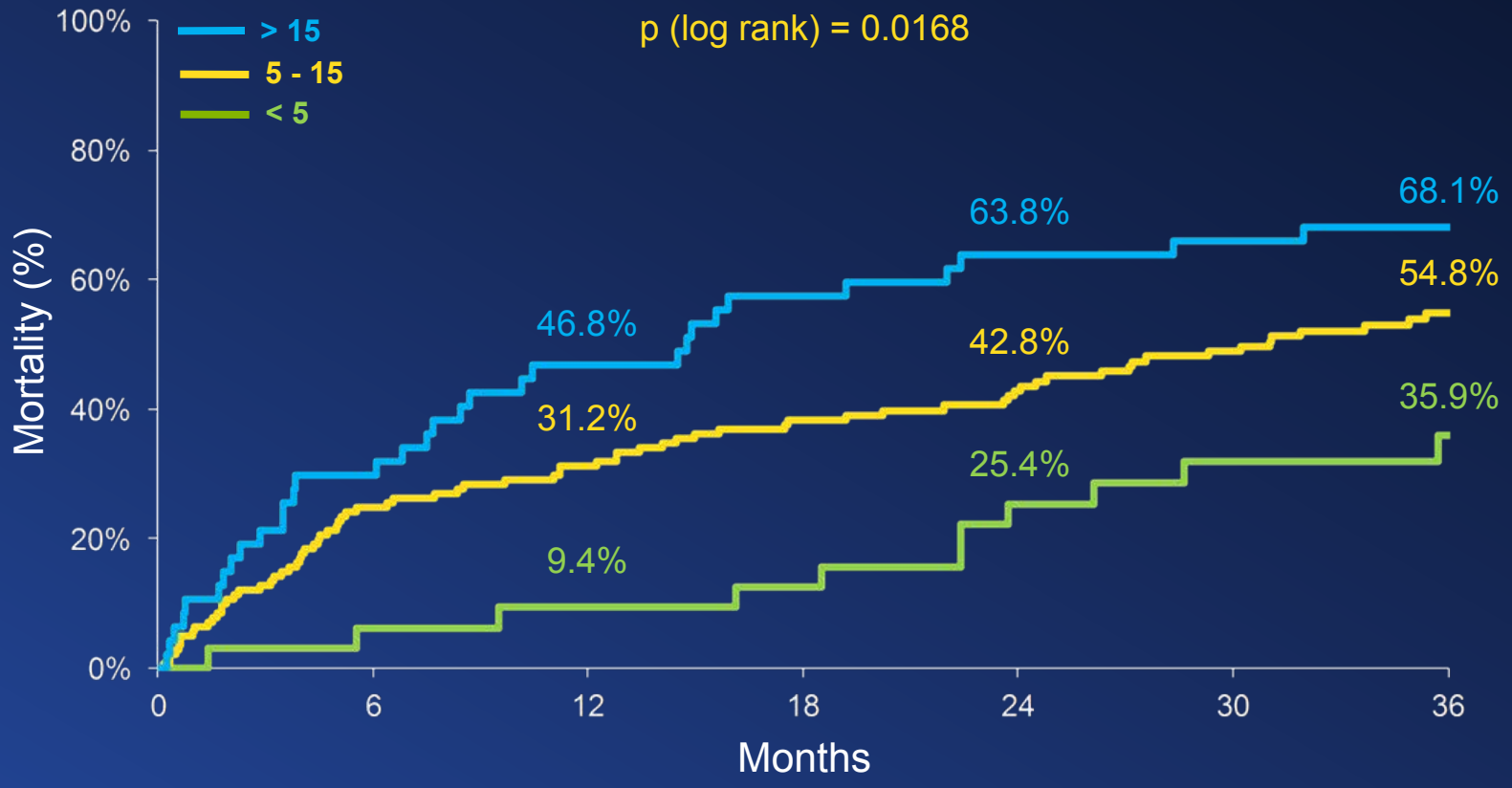
Pooled Randomized – Valve Implant Patients



Numbers at Risk

Mod.-Severe	33	25	22	20	15	14	9
Mild	90	70	61	52	47	40	26
None-Trace	81	65	61	55	51	46	29

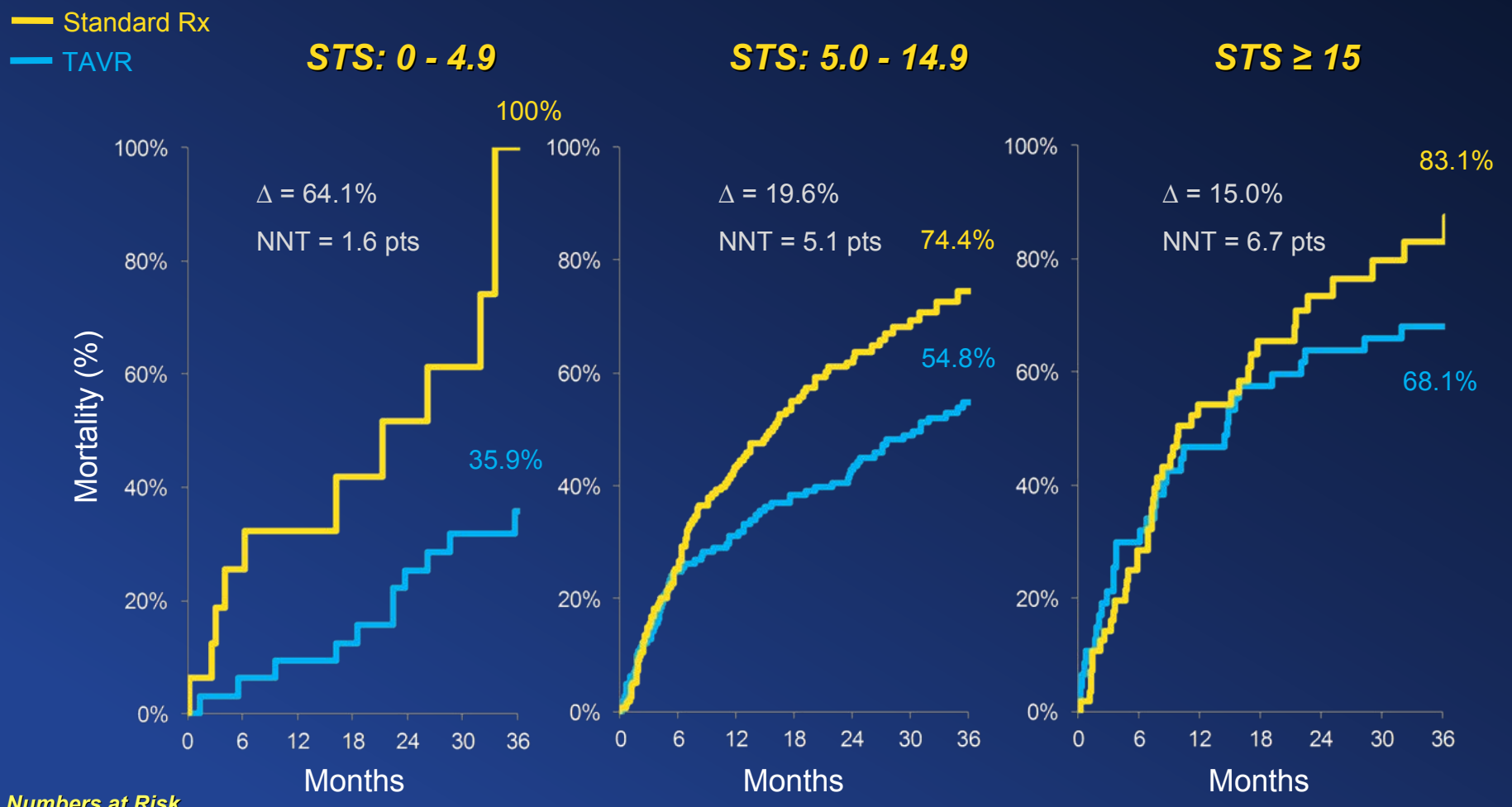
Mortality Stratified by STS Score (ITT)
Pooled Randomized



Numbers at Risk

> 15	47	33	25	20	17	16	10
5 - 15	141	106	97	85	77	66	44
< 5	32	30	29	28	23	21	16

Mortality Stratified by STS Score (ITT)
Pooled Randomized



Numbers at Risk

Standard Rx	16	11	9	6	5	3	0	154	113	84	56	41	24	13	58	39	25	15	10	6	4
TAVR	32	30	29	28	23	21	16	141	106	97	85	77	66	44	47	33	25	20	17	16	10

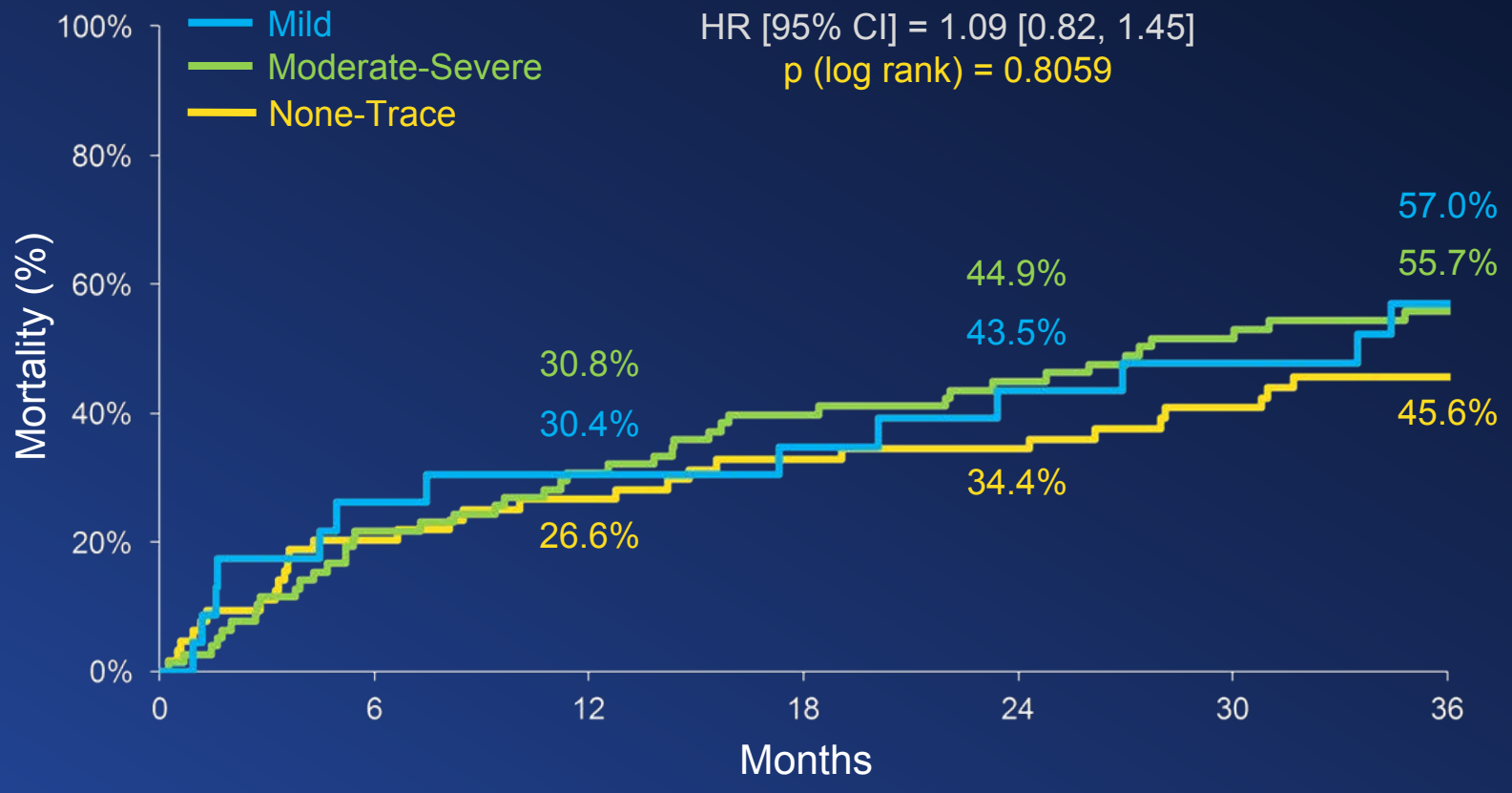
Stroke – Between year 2-3

ITT arm	Age	Days post randomization	Description	Comorbidity	Procedure related*	Device related*	Comments
TAVR	97	879	Ischemic	Blood stream infection, Right carotid stenosis (80%)	No	No	Cerebellar infarct; Linear echodensity on mitral valve, Ao valve: **Mild AI**
TAVR	87	837	Acute infarct with surrounding intraparenchymal bleed	Atrial Fibrillation not on warfarin	No	No	Cerebellar infarct/ hemorrhage; Ao valve: **Ok**

**CEC adjudicated*

Mortality Stratified by Paravalvular Leak
Valve Implant Patients

THE PARTNER TRIAL



Numbers at Risk

Mild	78	61	54	47	43	36	26
Mod.-Severe	23	17	16	15	13	12	9
None-Trace	64	51	47	43	41	37	29