Five-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

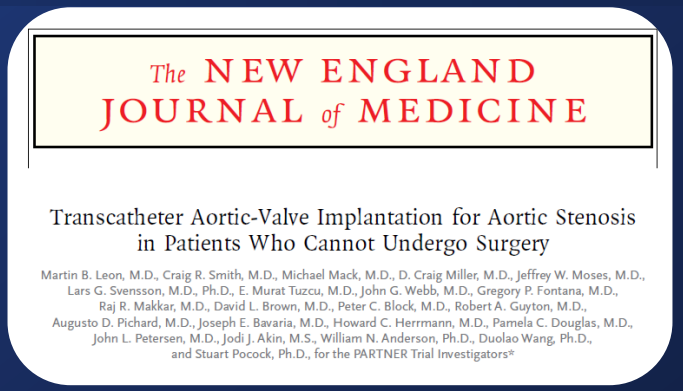
TCT 2014 | September 13, 2014

THE PARTNER TRIAL

All faculty disclosures are available on the CRF Events App and online at www.crf.org/tct

Background

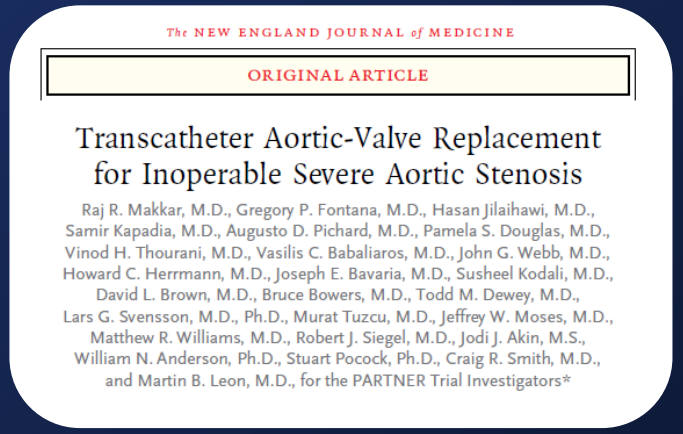
- Transcatheter aortic valve replacement (TAVR) is the recommended treatment for “inoperable” patients with severe aortic stenosis (AS).
- Long term clinical benefit and valve performance in this population remain unknown.



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*



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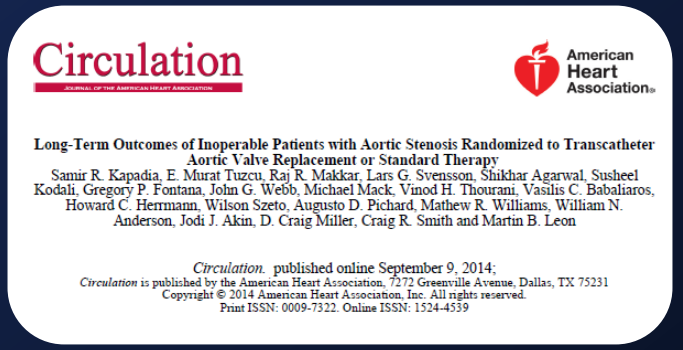
ORIGINAL ARTICLE

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*



Circulation

JOURNAL OF THE AMERICAN HEART ASSOCIATION

American Heart Association

Long-Term Outcomes of Inoperable Patients with Aortic Stenosis Randomized to Transcatheter Aortic Valve Replacement or Standard Therapy

Samir R. Kapadia, E. Murat Tuzcu, Raj R. Makkar, Lars G. Svensson, Shikhar Agarwal, Susheel Kodali, Gregory P. Fontana, John G. Webb, Michael Mack, Vinod H. Thourani, Vasilis C. Babaliaros, Howard C. Herrmann, Wilson Szeto, Augusto D. Pichard, Mathew R. Williams, William N. Anderson, Jodi J. Akin, D. Craig Miller, Craig R. Smith and Martin B. Leon

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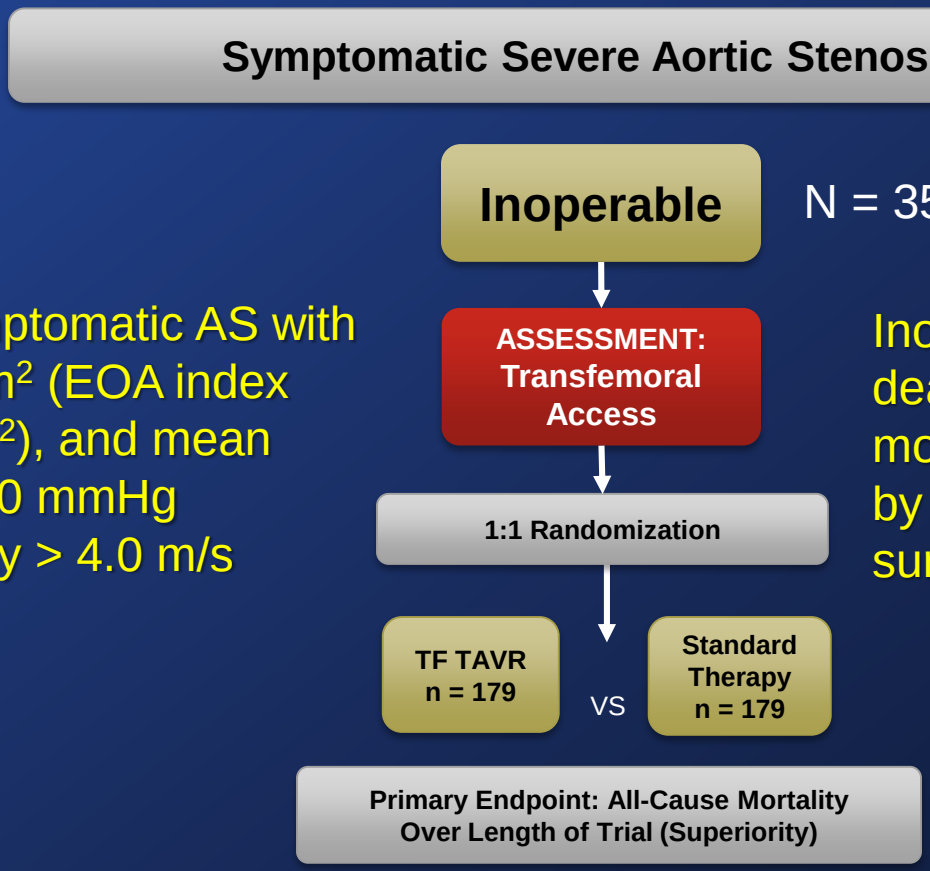
PARTNER Study Design



Severe Symptomatic AS with AVA< 0.8 cm^2 (EOA index < 0.5 cm^2/m^2), and mean gradient > 40 mmHg or jet velocity > 4.0 m/s

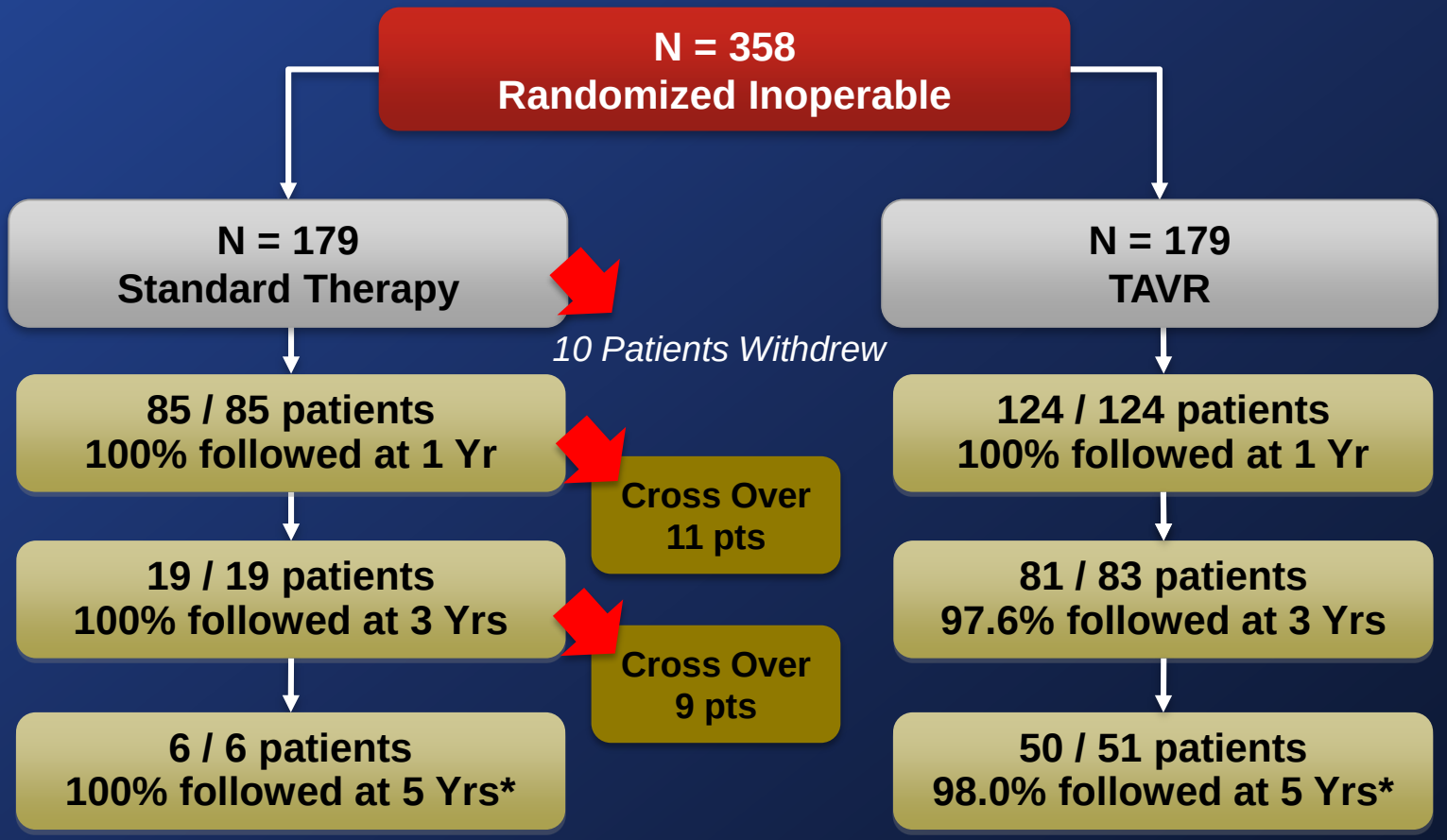
Inoperable defined as risk of death or serious irreversible morbidity of AVR as assessed by cardiologist and two surgeons exceeding 50%.

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

Key End-Points for 5 Year Analysis

- All-Cause Mortality
- Cardiac Mortality
- Re-hospitalization
- Stroke
- NYHA functional class
- Echo-derived valve areas, transvalvular gradients, and paravalvular leak.
- Mortality outcomes stratified by STS score, paravalvular leak and age.

Study Flow
Inoperable Cohort

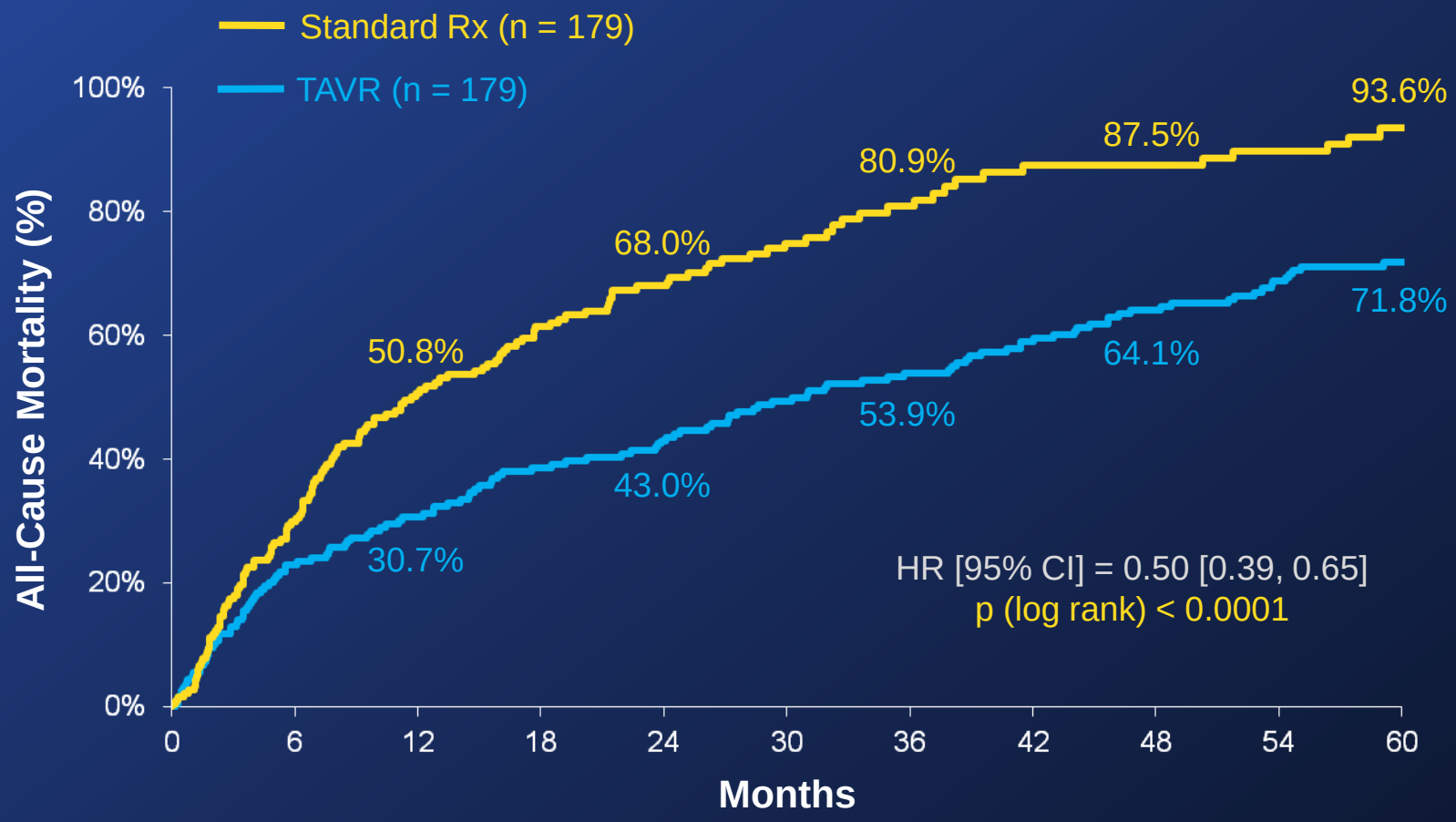


** ± 2 months follow-up window*

Patient Characteristics

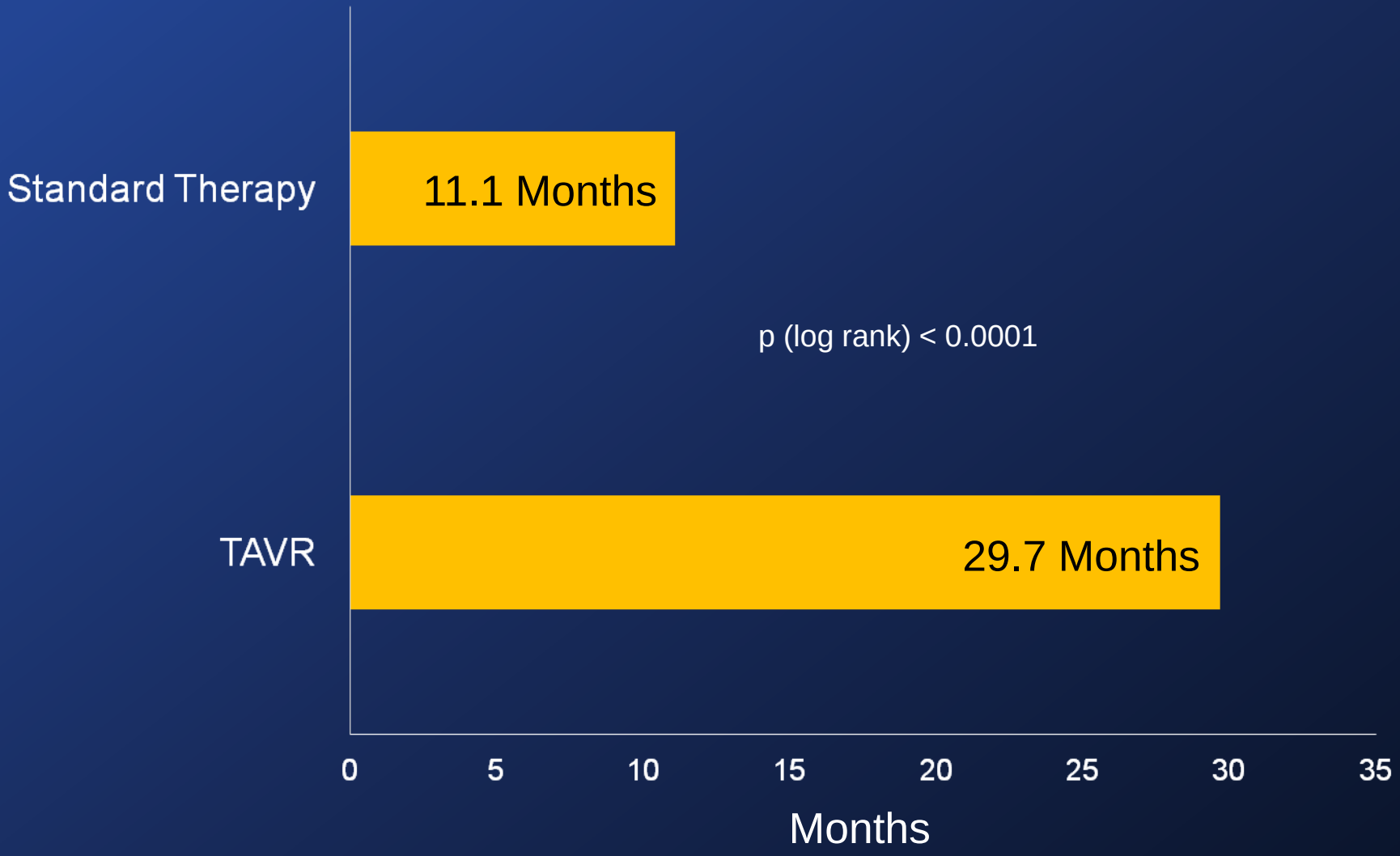
Characteristic	TAVR N = 179	Standard Rx N = 179	p-value
Age – yr	83.1 ± 8.6	83.2 ± 8.3	0.95
Male sex (%)	45.8	46.9	0.92
STS Score	11.2 ± 5.8	12.1 ± 6.1	0.14
NYHA			
I or II (%)	7.8	6.1	0.68
III or IV (%)	92.2	93.9	0.68
CAD (%)	67.6	74.3	0.20
COPD			
Any (%)	41.3	52.5	0.04
O_2 dependent (%)	21.2	25.7	0.38
Creatinine > 2 mg/dL (%)	5.6	9.6	0.23
Frailty (%)	18.1	28.0	0.09
Porcelain aorta (%)	19.0	11.2	0.05
Chest wall radiation (%)	8.9	8.4	1.00

All-Cause Mortality (ITT)
Crossover Patients Censored at Crossover

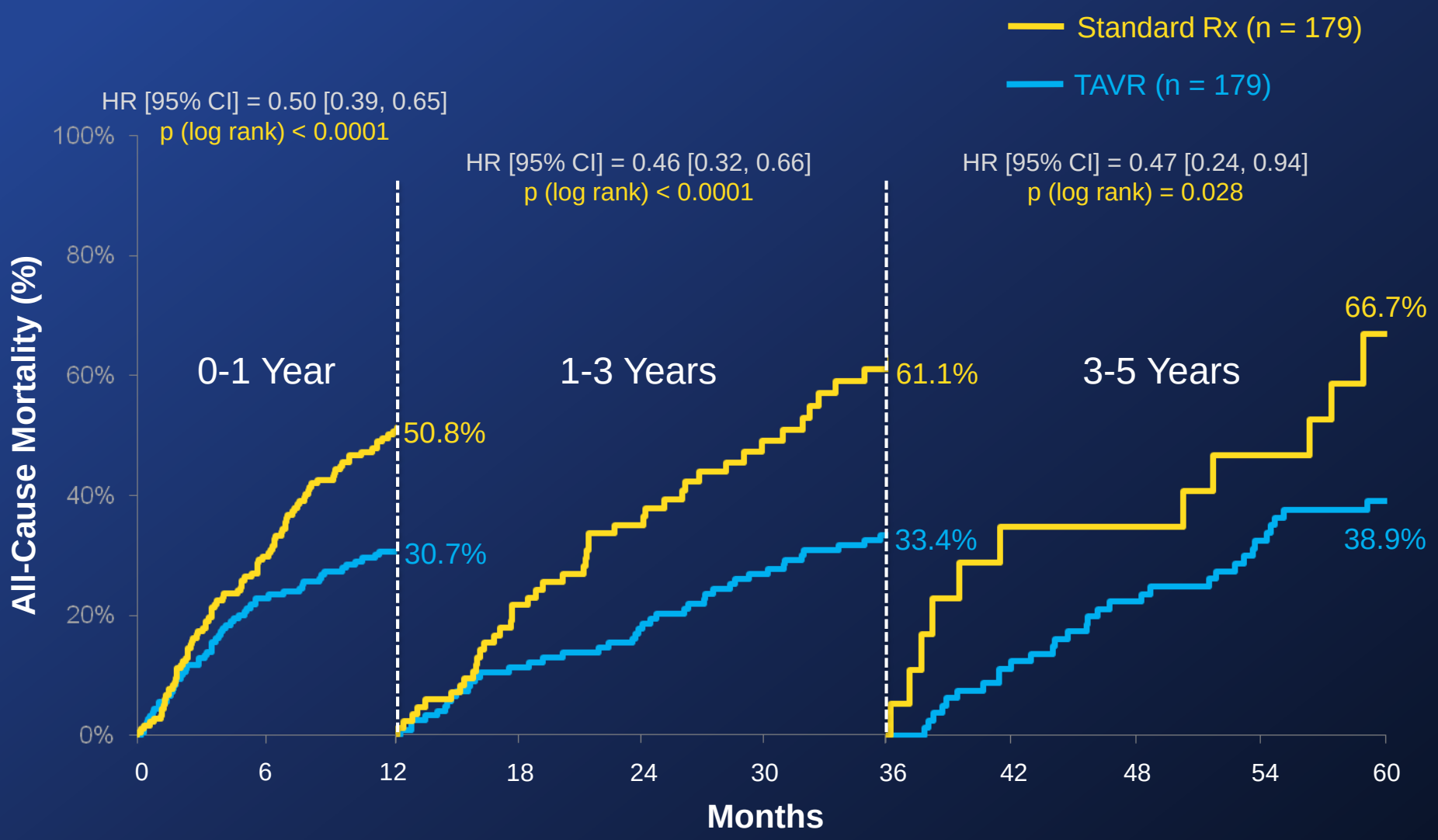


** In an age and gender matched US population without comorbidities, the mortality at 5 years is 40.5%.*

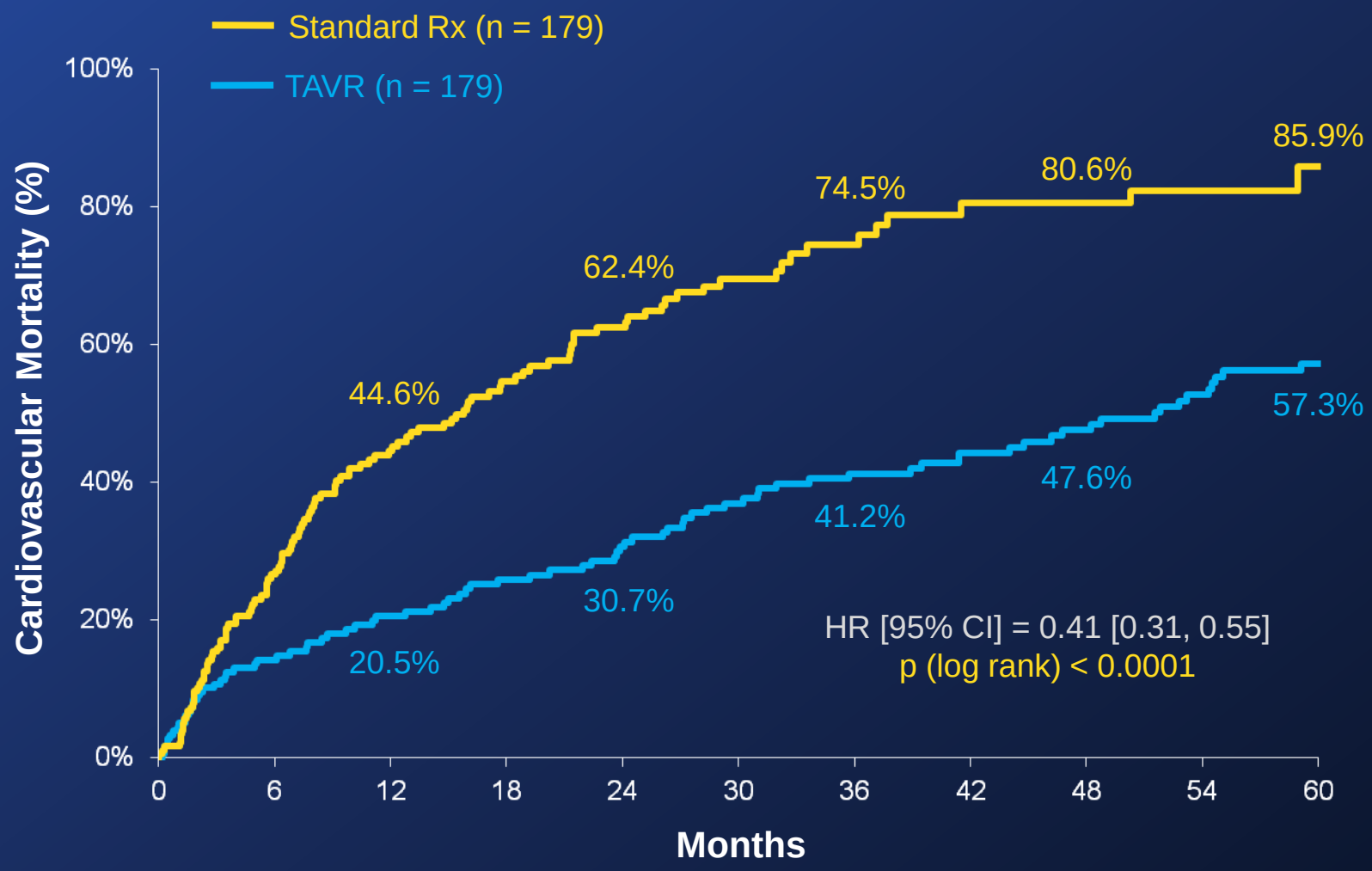
Median Survival



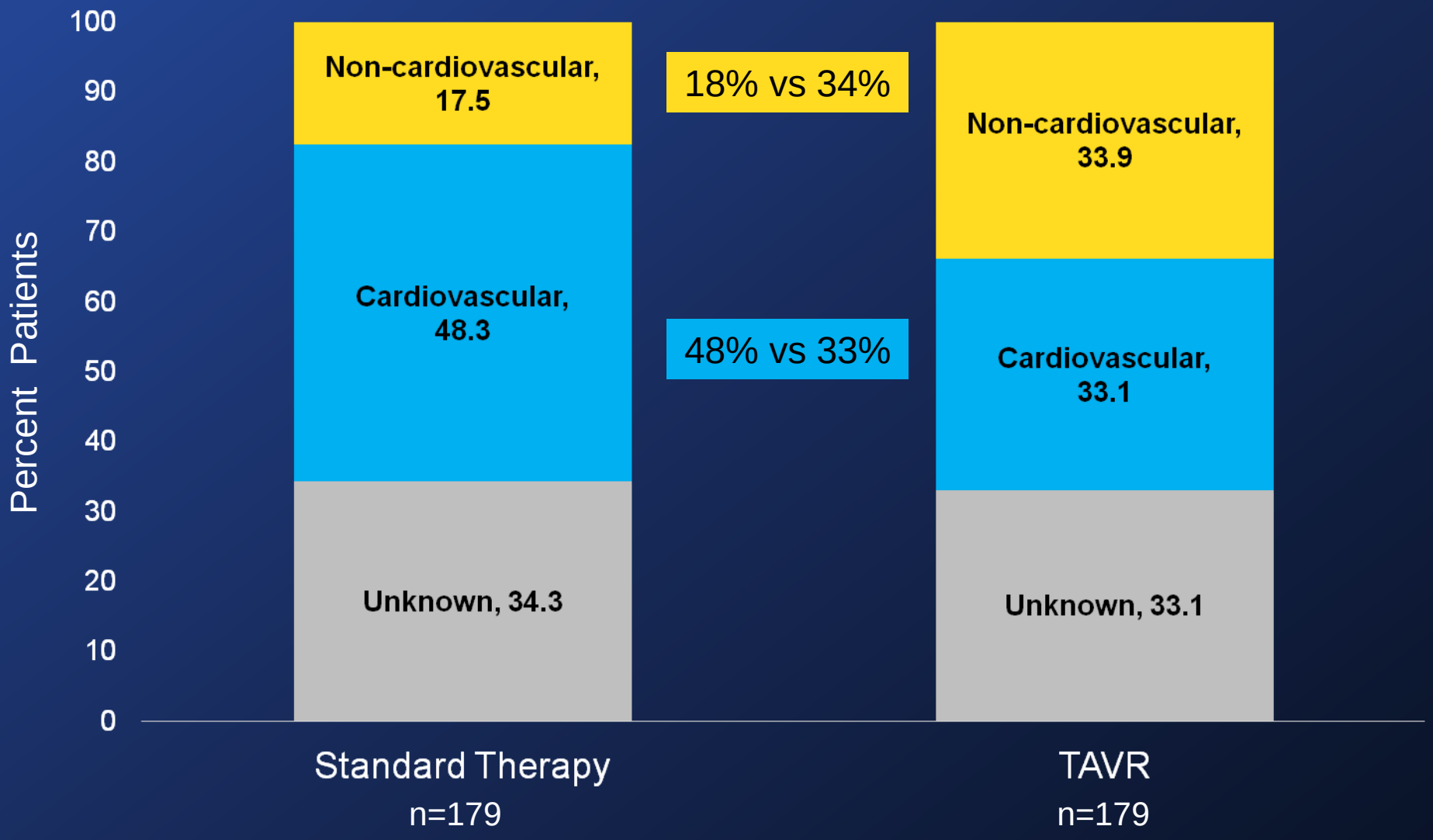
All-Cause Mortality (ITT)
Landmark Analysis



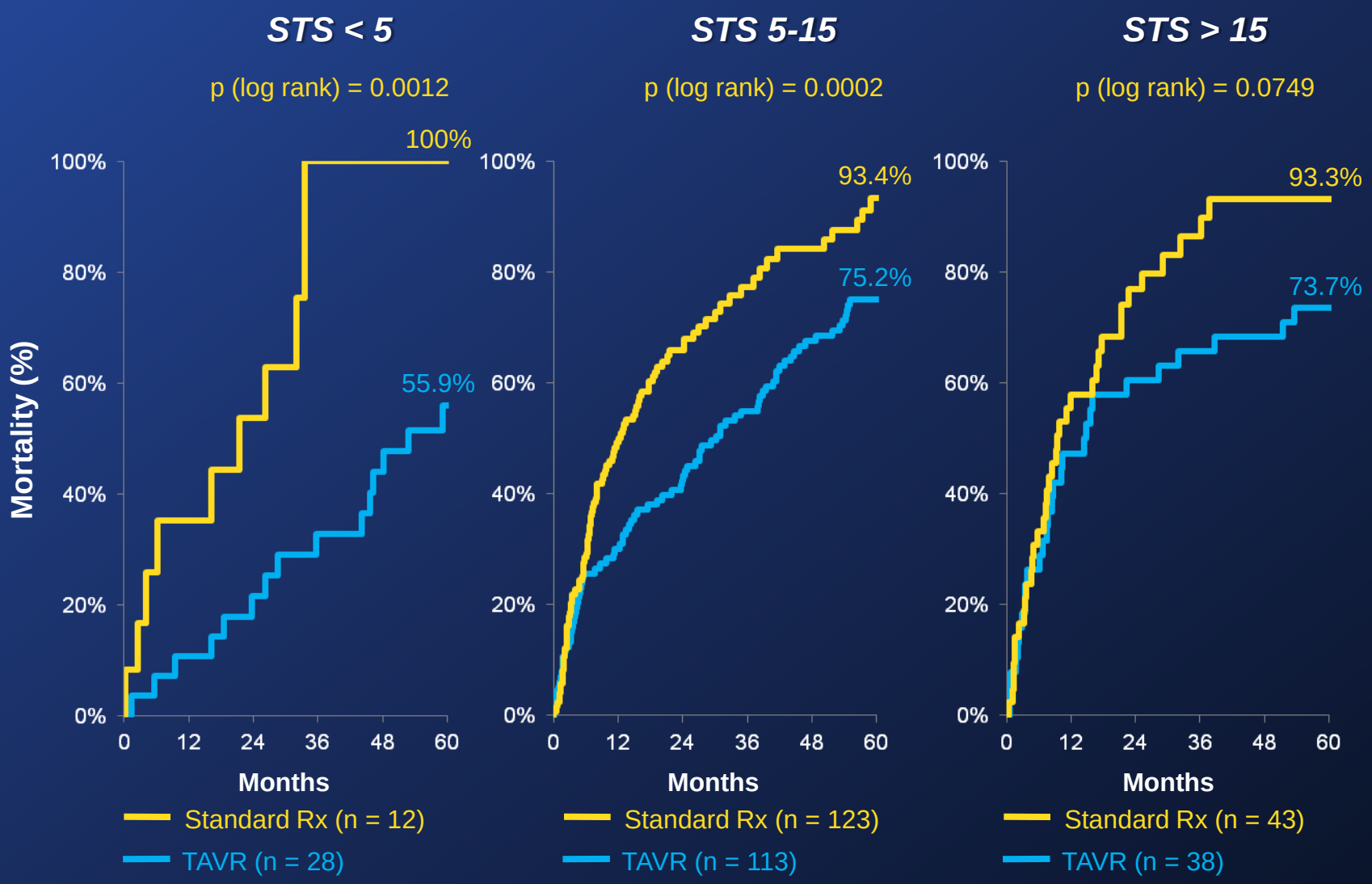
Cardiovascular Mortality (ITT)
Crossover Patients Censored at Crossover



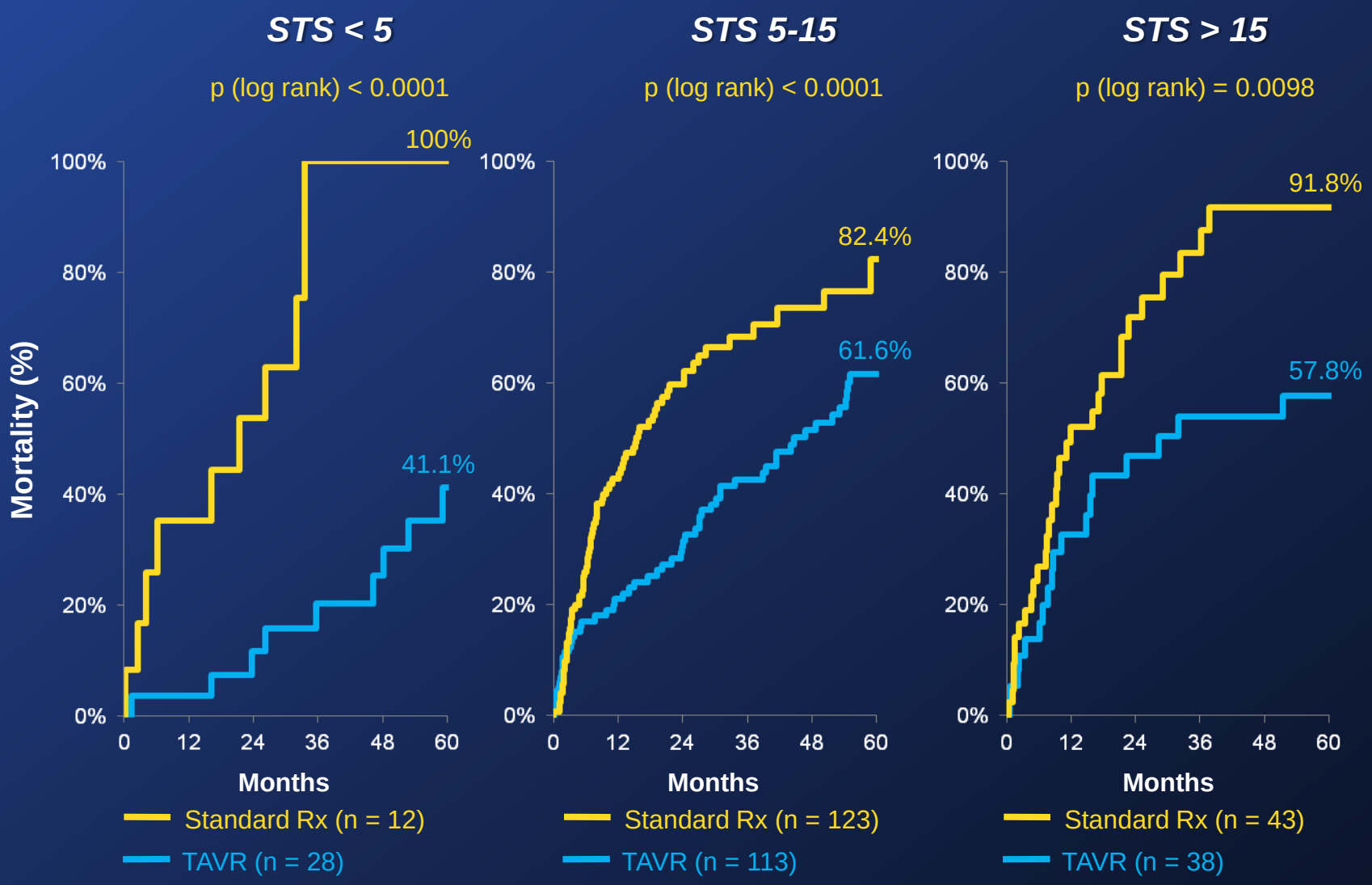
Causes of Death



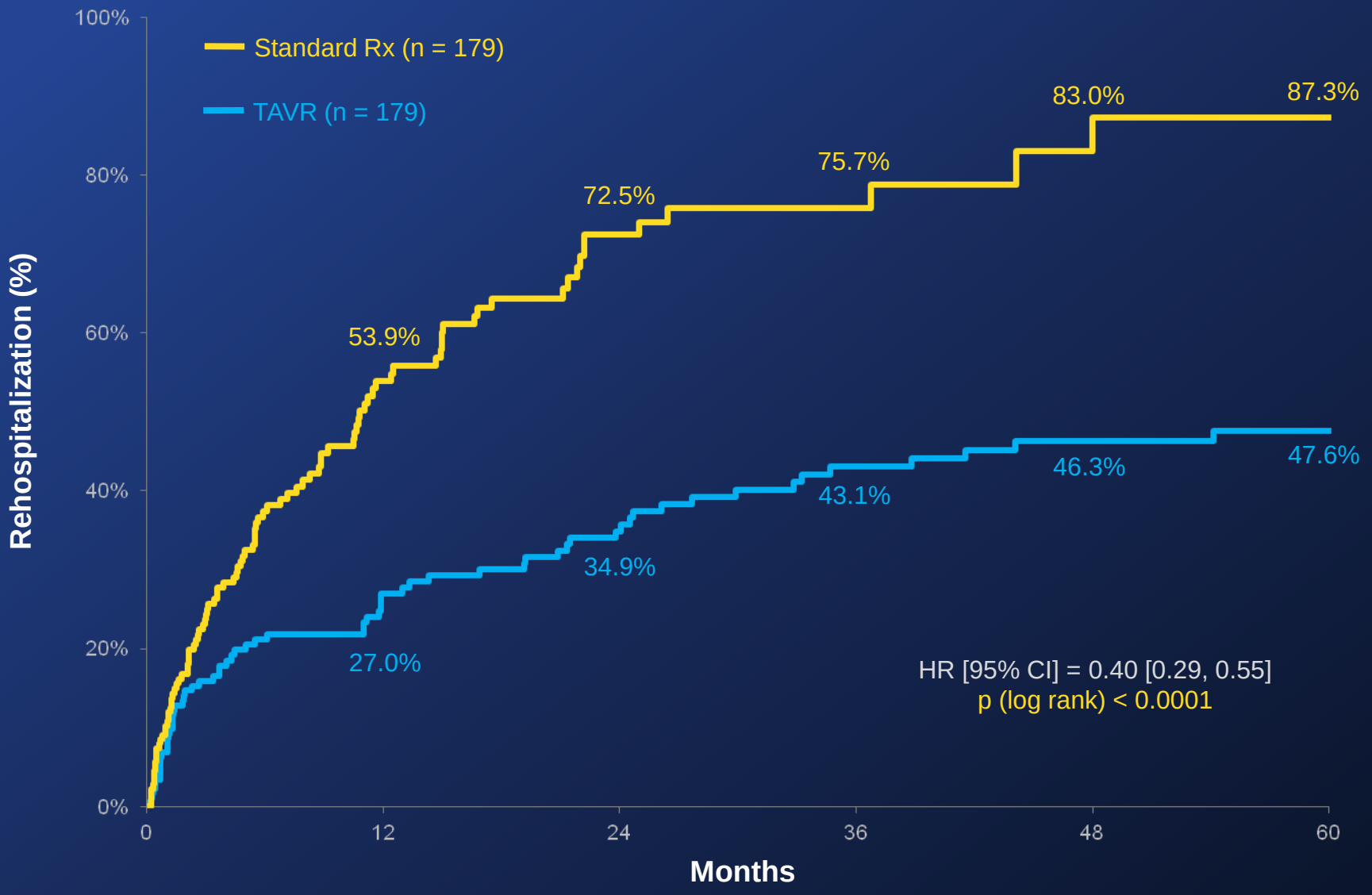
All-Cause Mortality Stratified by STS Score (ITT)



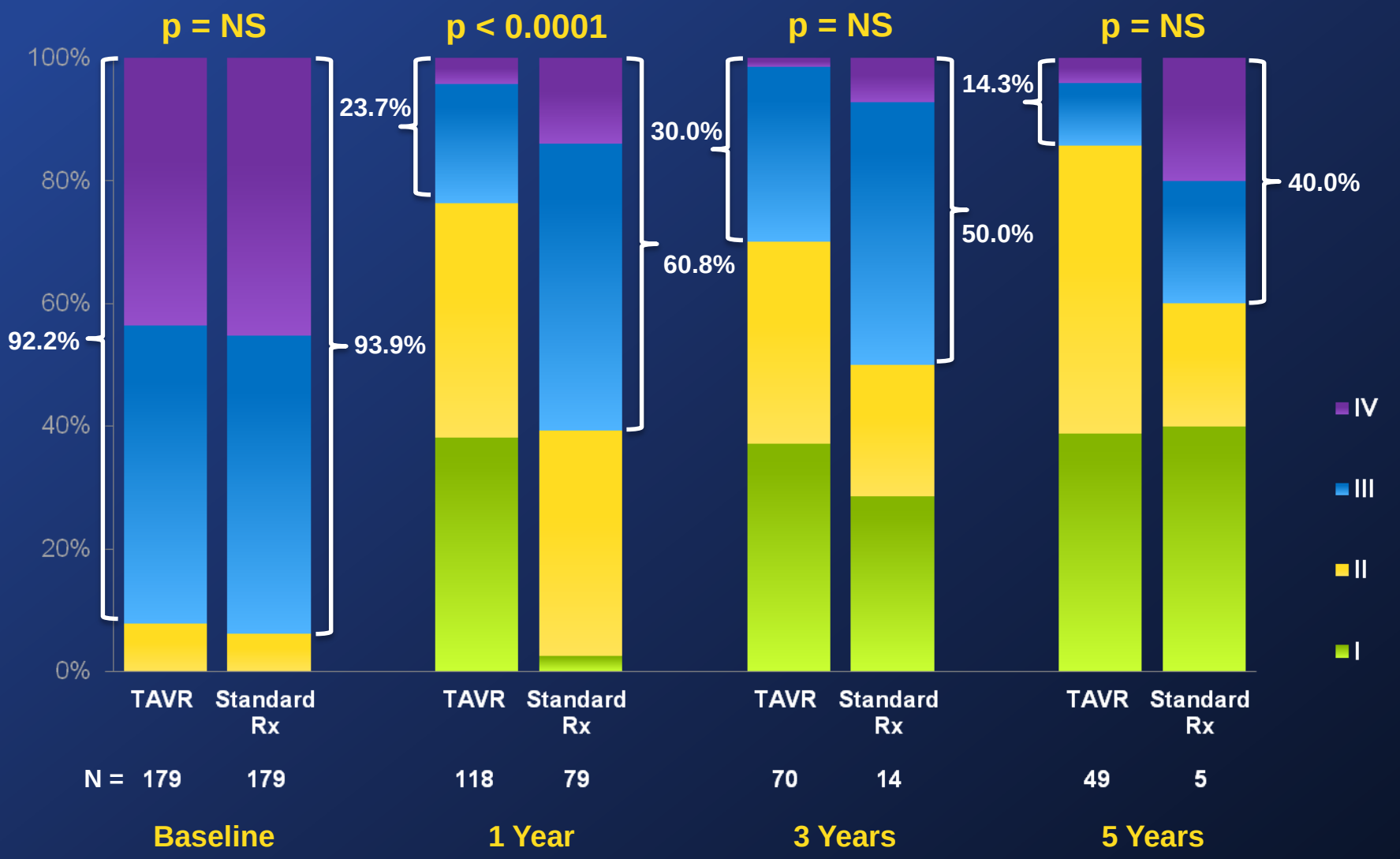
Cardiovascular Mortality Stratified by STS Score (ITT)



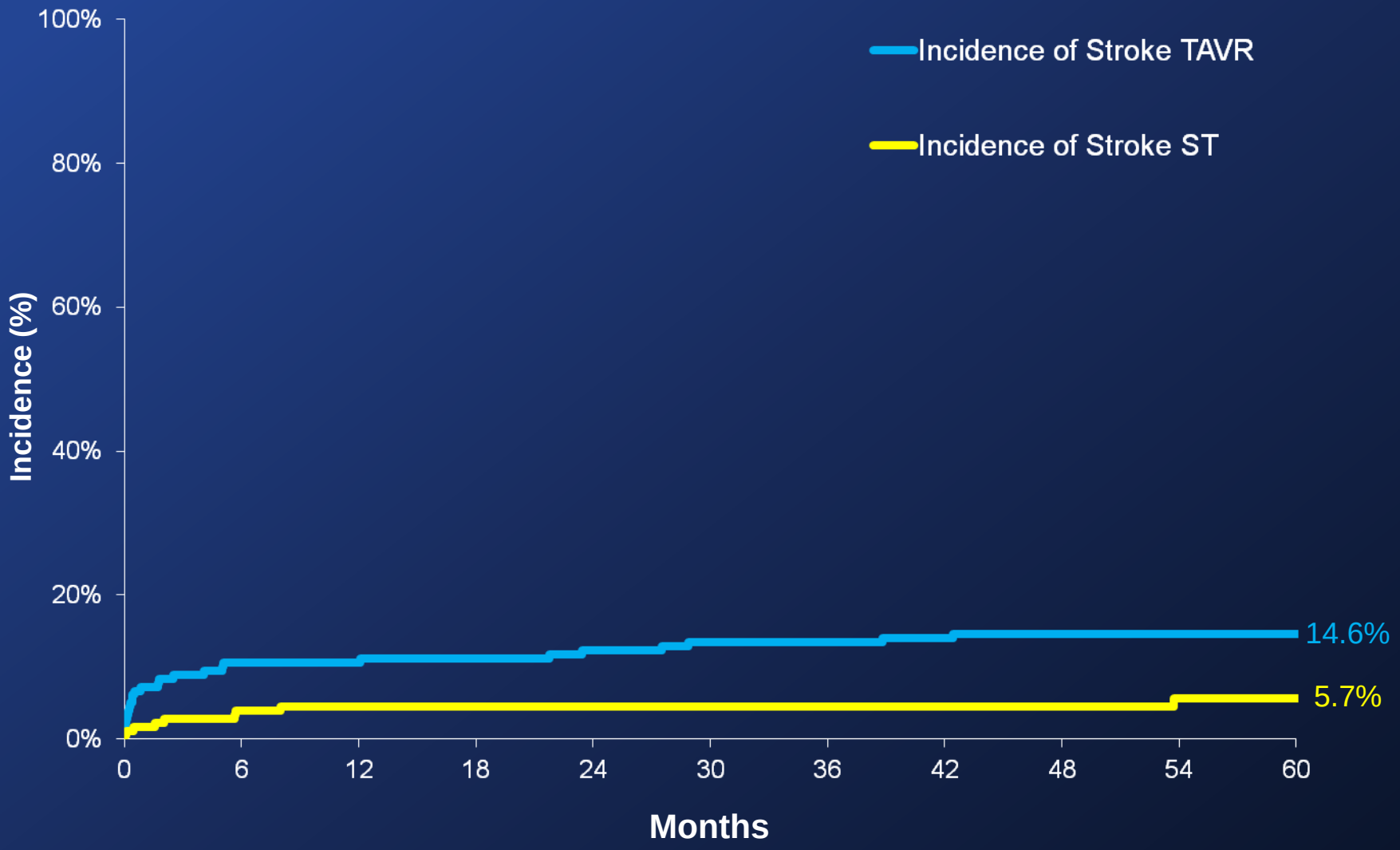
Repeat Hospitalization (ITT)



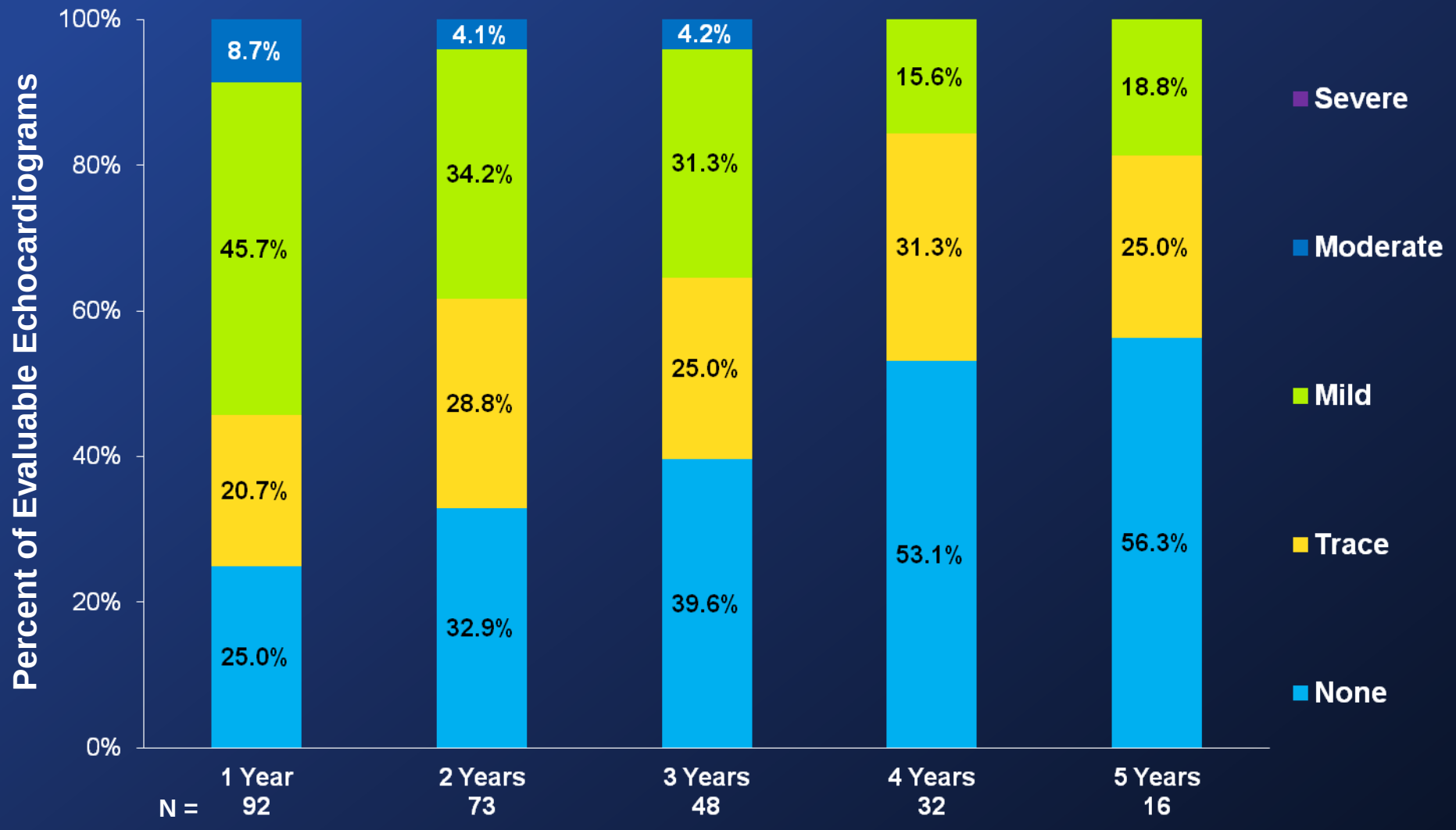
NYHA Class Over Time (ITT)
Survivors



Competing Risks Analysis (ITT)
Death and Stroke



Paravalvular Leak (AT)



Mortality by Paravalvular Leak

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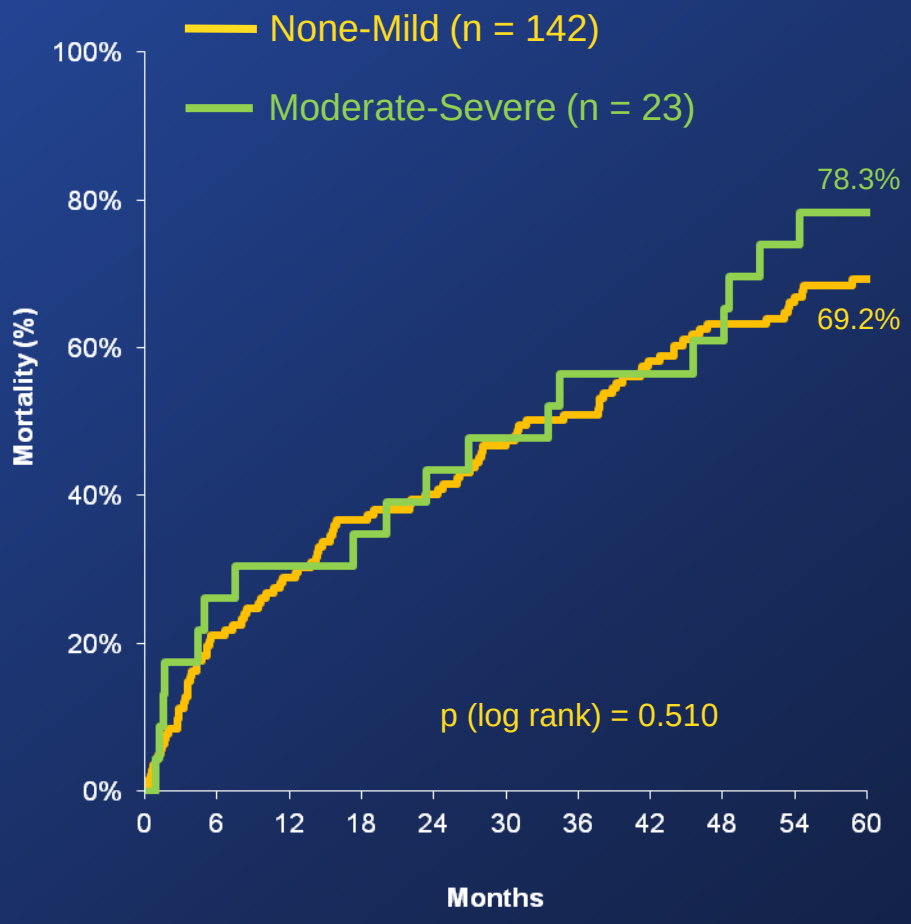
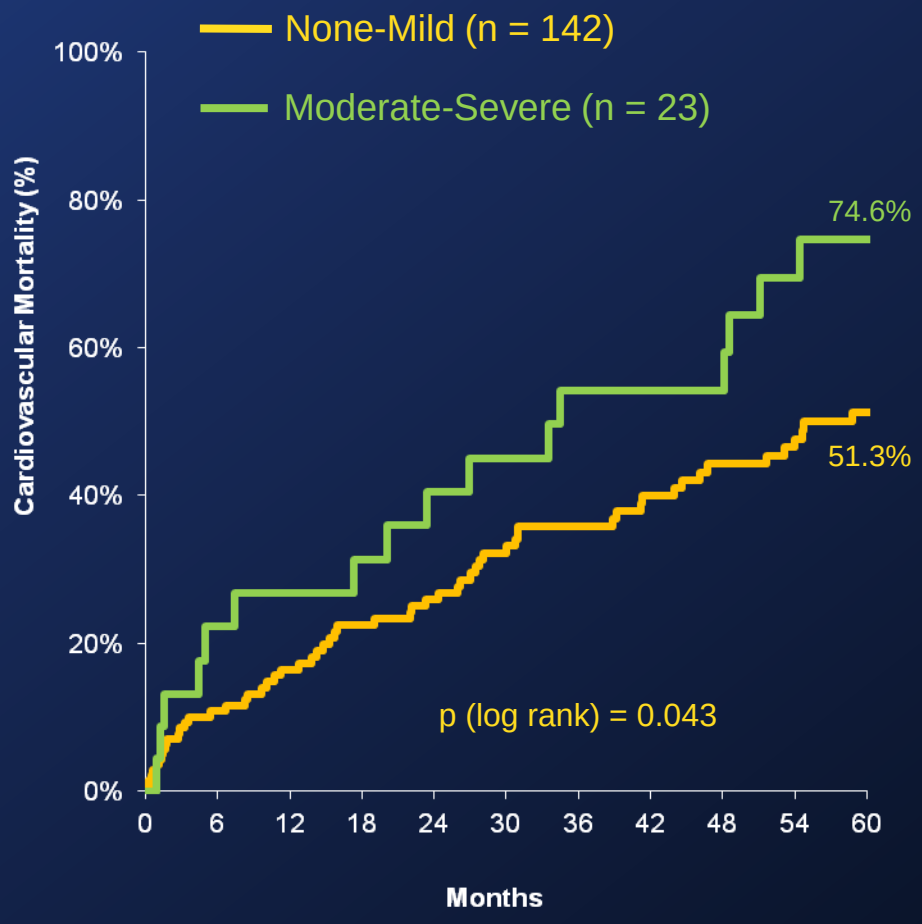
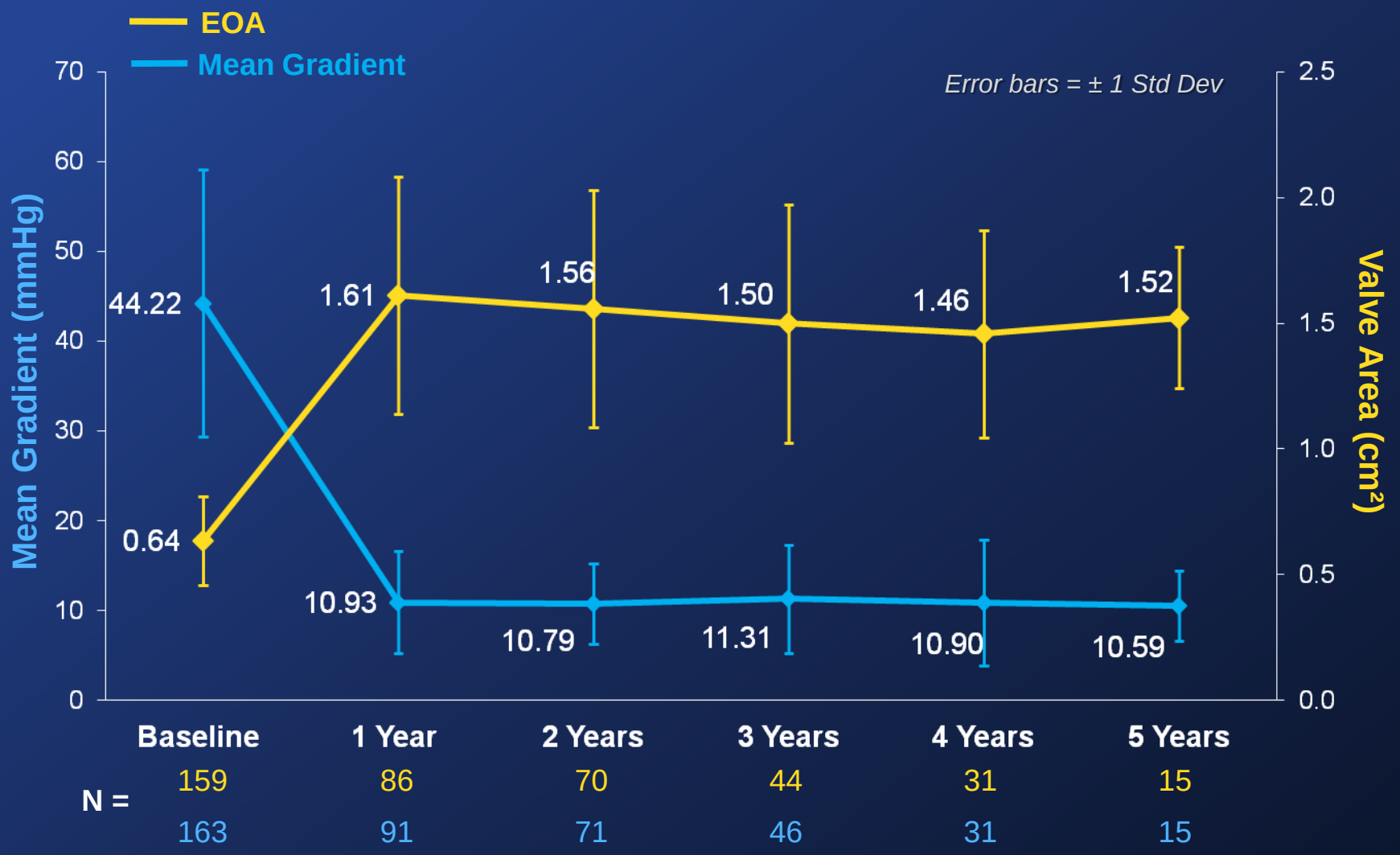
All-Cause Mortality



Cardiovascular Mortality



Mean Gradient & Valve Area (AT)



Mean Gradient & Valve Area (AT)

Restricted to Patients with 5 Year Data

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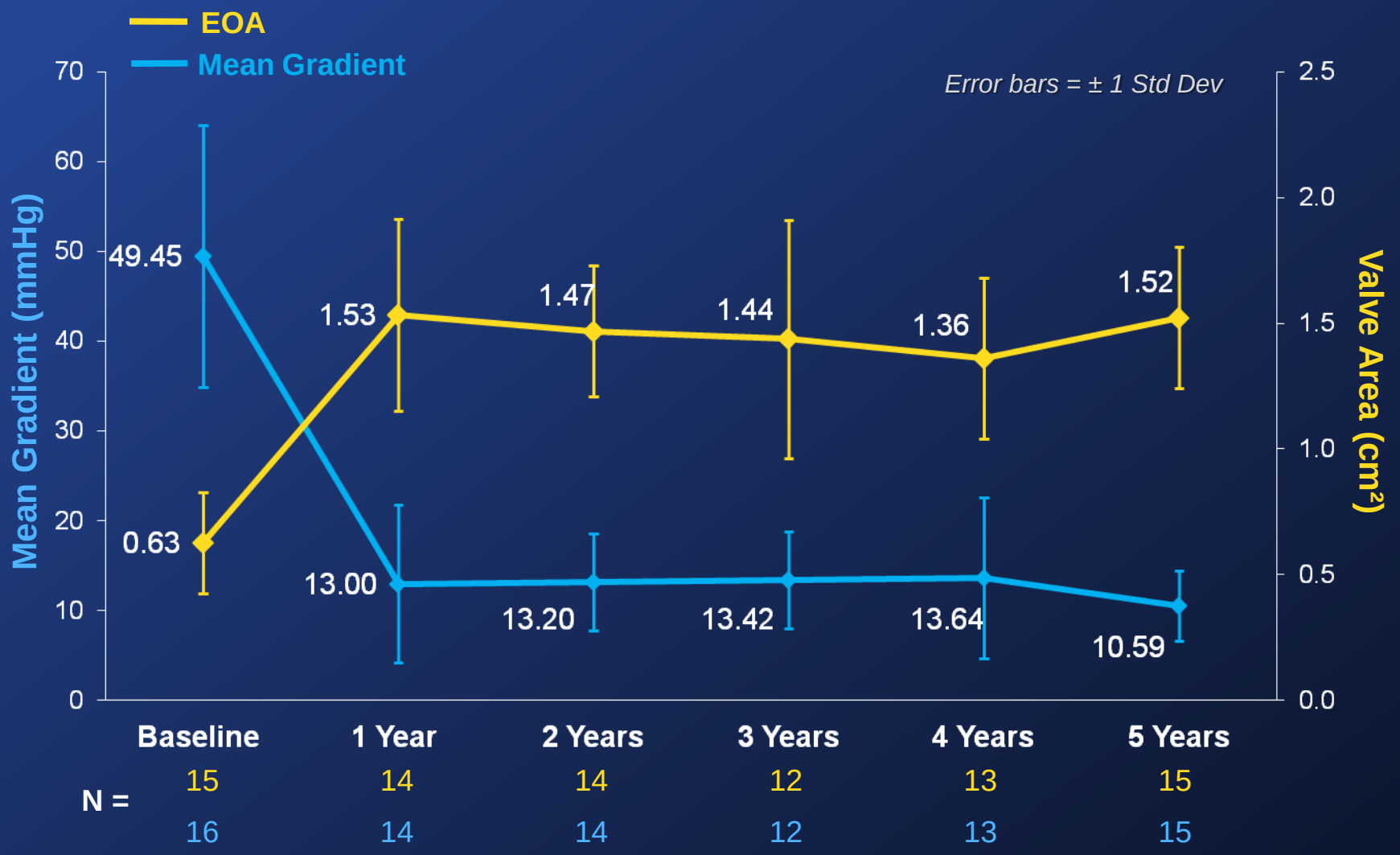
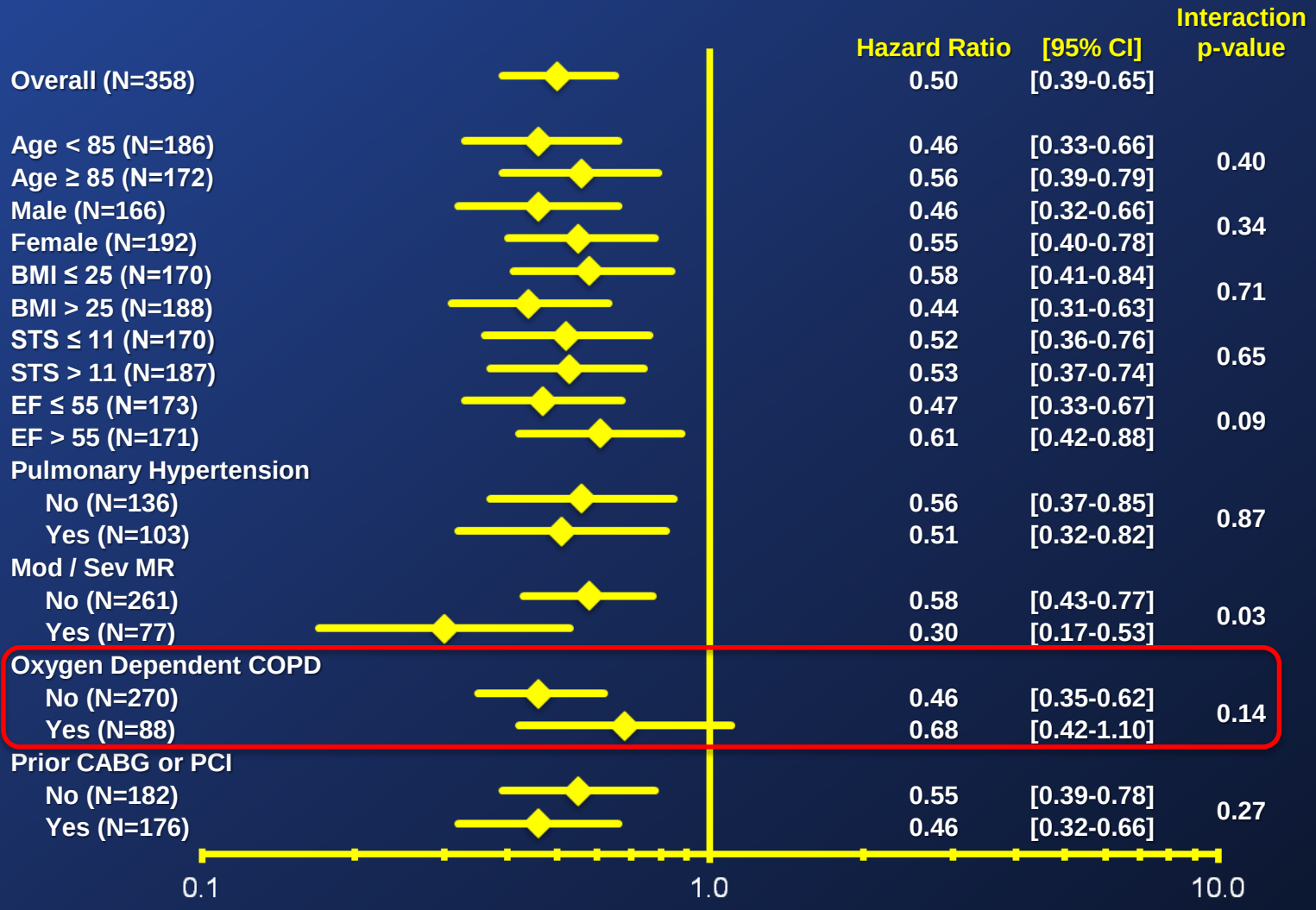
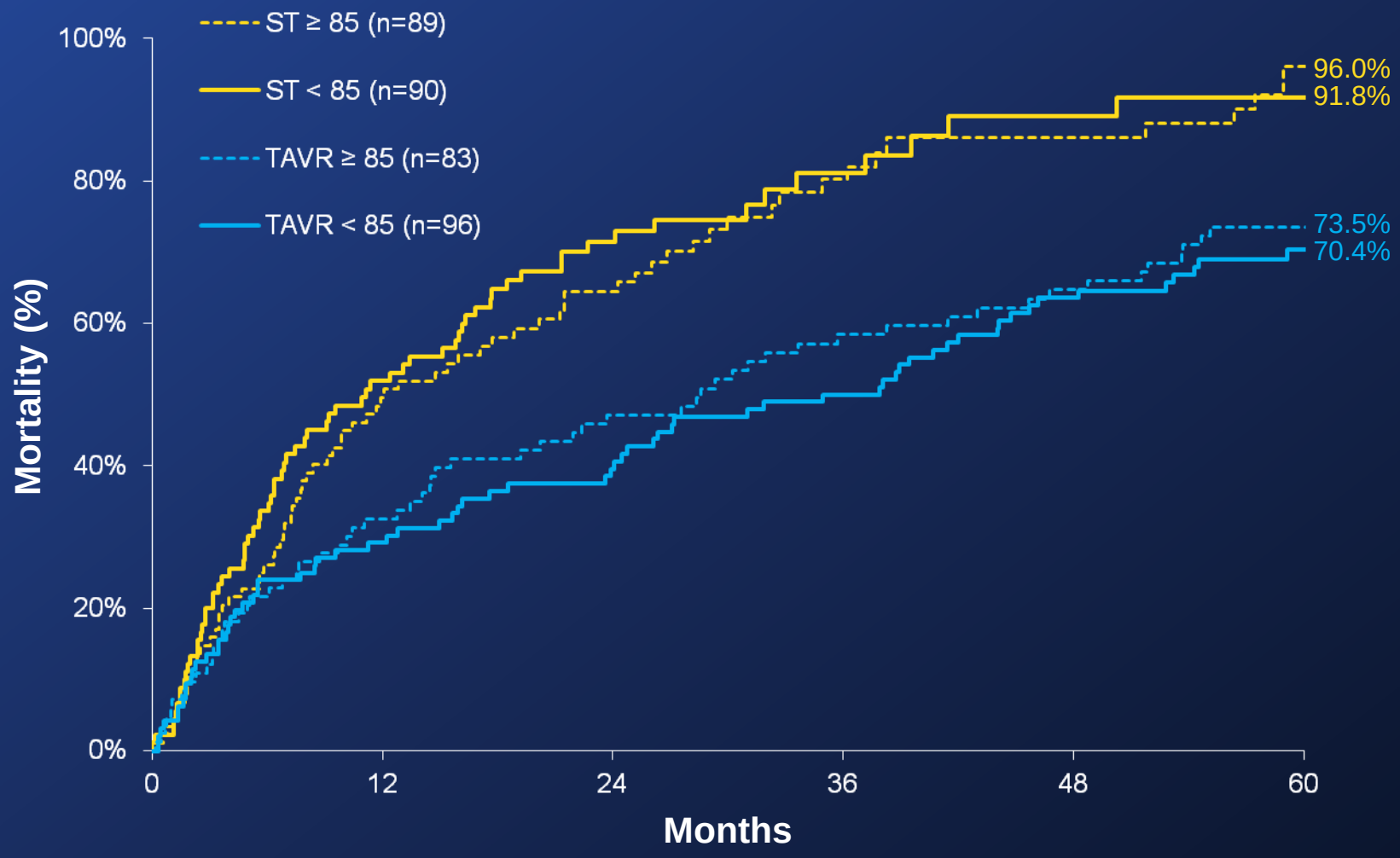


Subgroup Analysis
All-Cause Mortality



TAVR Mortality Stratified by Age (ITT)



Clinical Observations

- Mortality benefit was similar in elderly (>85 yr) patients compared to those ≤85 years.
- Cardiovascular mortality and all-cause mortality benefit was seen even in patients with high STS score.
- Patients with O2 dependent COPD may have less mortality benefit.
- Beyond early procedural risk of stroke there was no persistent risk over 5-year follow up.
- Moderate and severe paravalvular leak is associated with higher cardiovascular mortality particularly in patients with less comorbidities.

Main Conclusions

- At 5 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.

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

Back-Up Slides

Aortic Stenosis

By JOHN ROSS, JR., M.D. AND EUGENE BRAUNWALD, M.D.

THE ADVENT of corrective operations for various forms of heart disease has placed increasing emphasis upon the need for

sons. Ten of 12 patients with severe aortic stenosis (transvalvar pressure gradients ≥ 50 mm Hg, or effective aortic valve orifices ≤ 0.70 cm^2/m^2 BSA) who were followed for at least five years after catheterization are now dead.[14]

The advanced age at death of patients with severe acquired stenosis has been a remarkably consistent feature of this disease; this age has averaged 63 years in males. In several studies that were based on analysis of data obtained at postmortem examination,[2–5, 15–17] the average durations of various symptoms were as follows: angina pectoris three years, syncope three years, dyspnea two years, and congestive heart failure 1½ to 2 years. Moreover, in more than 80% of these patients who

patients with isolated valvular aortic stenosis of rheumatic etiology and patients without a history of rheumatic fever who have isolated

usually begin during the sixth decade of life,

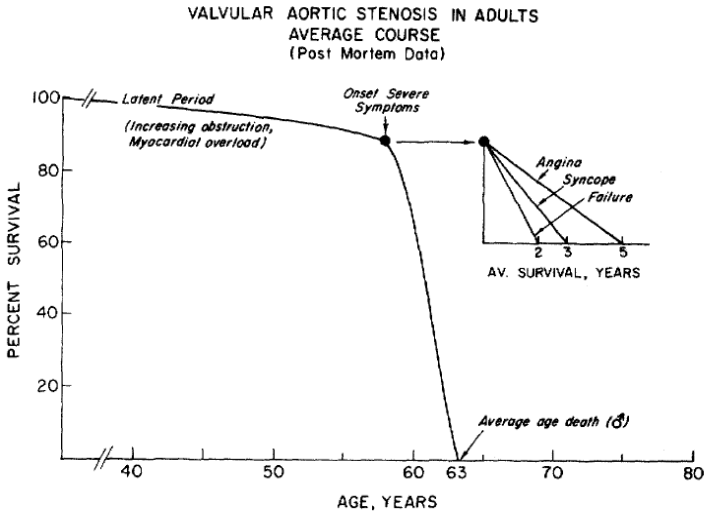


Figure 1

Average course of valvular aortic stenosis in adults. Data assembled from postmortem studies.

Supplement V to Circulation, Vols. XXXVII and XXXVIII, July 1968

14. FRANK, S., AND ROSS, J., JR.: Natural history of severe, acquired valvular aortic stenosis. (abstr.) Amer J Cardiol 19: 128, 1967.

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All-Cause Mortality (ITT)
Patients Followed Post-Crossover

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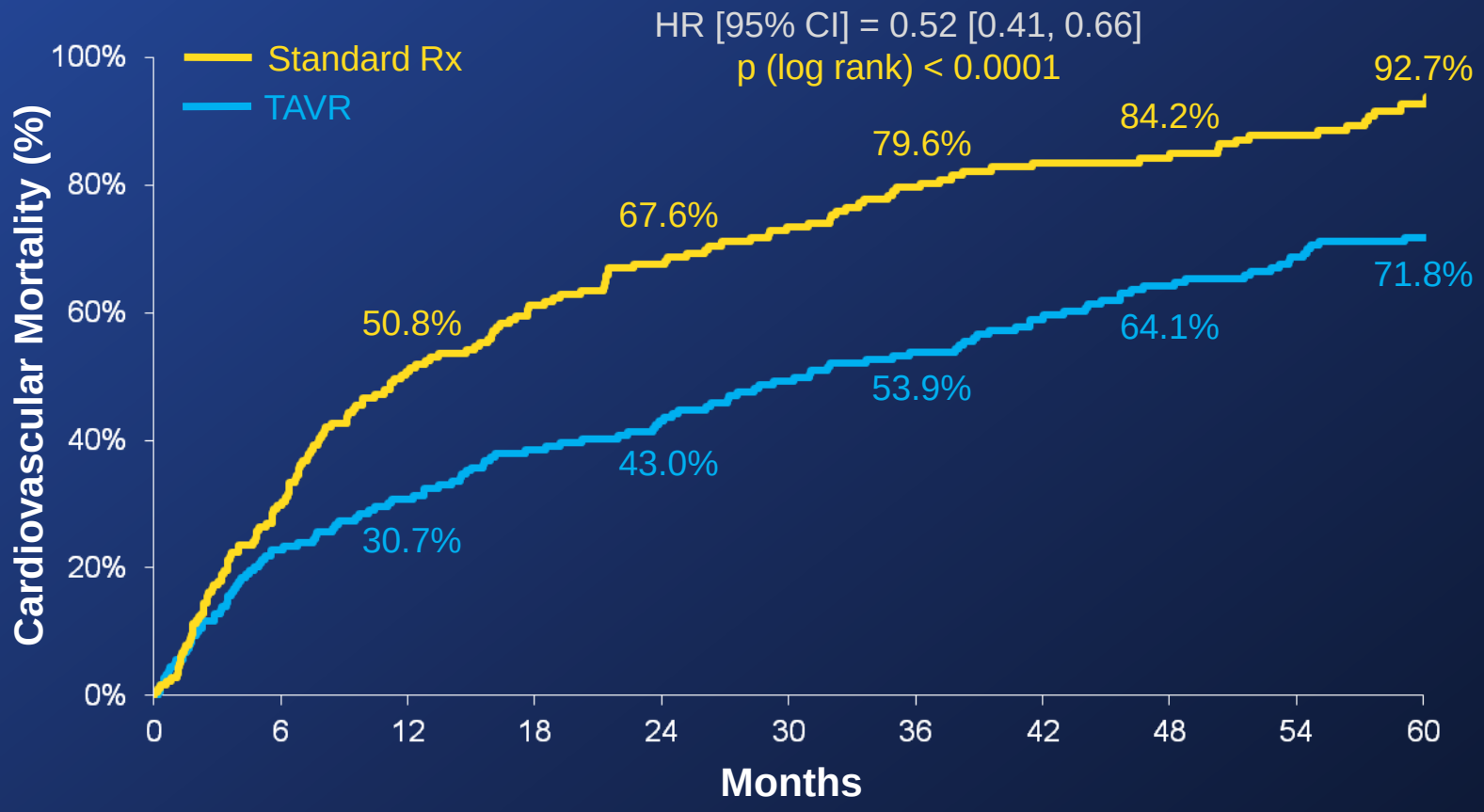
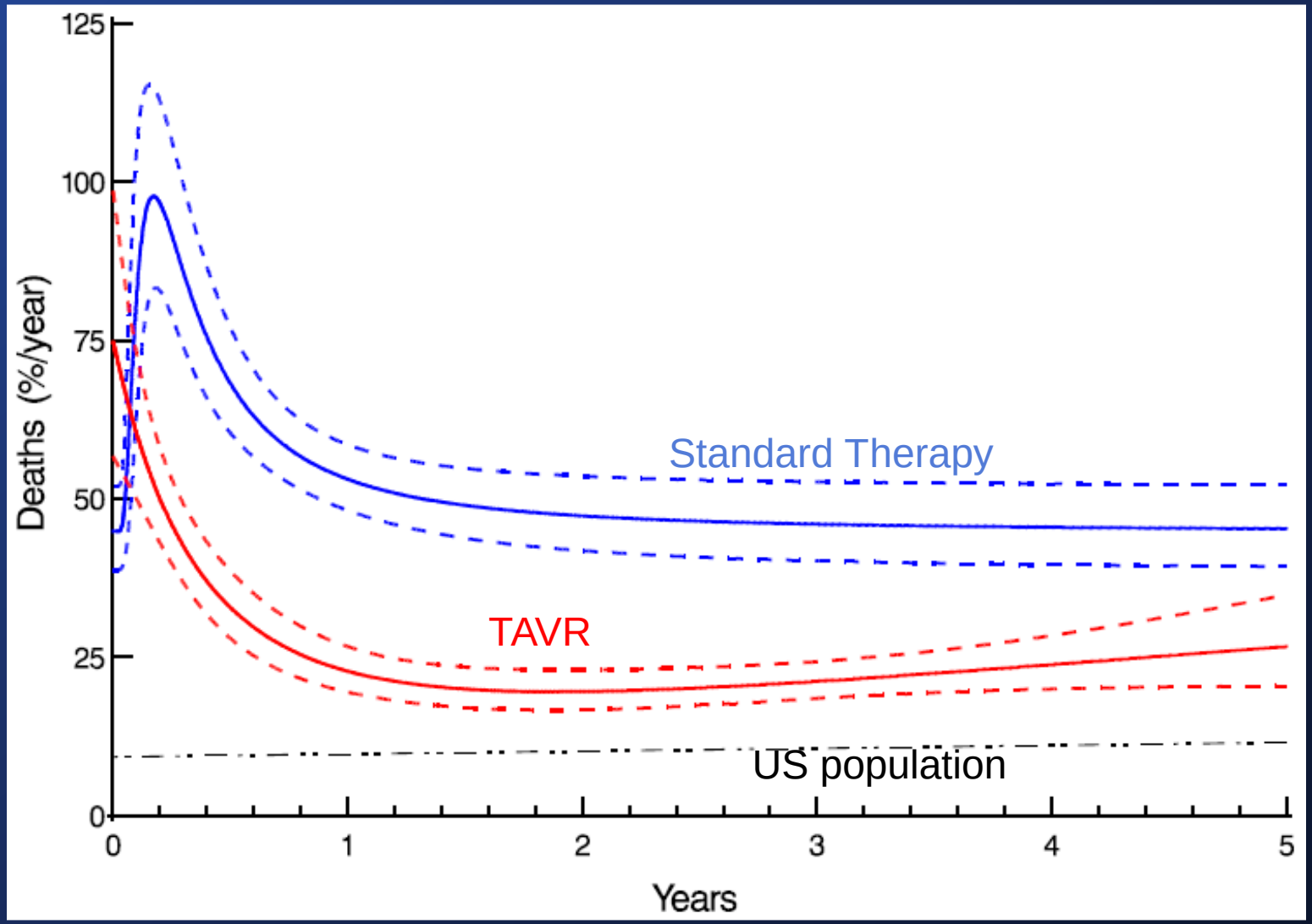


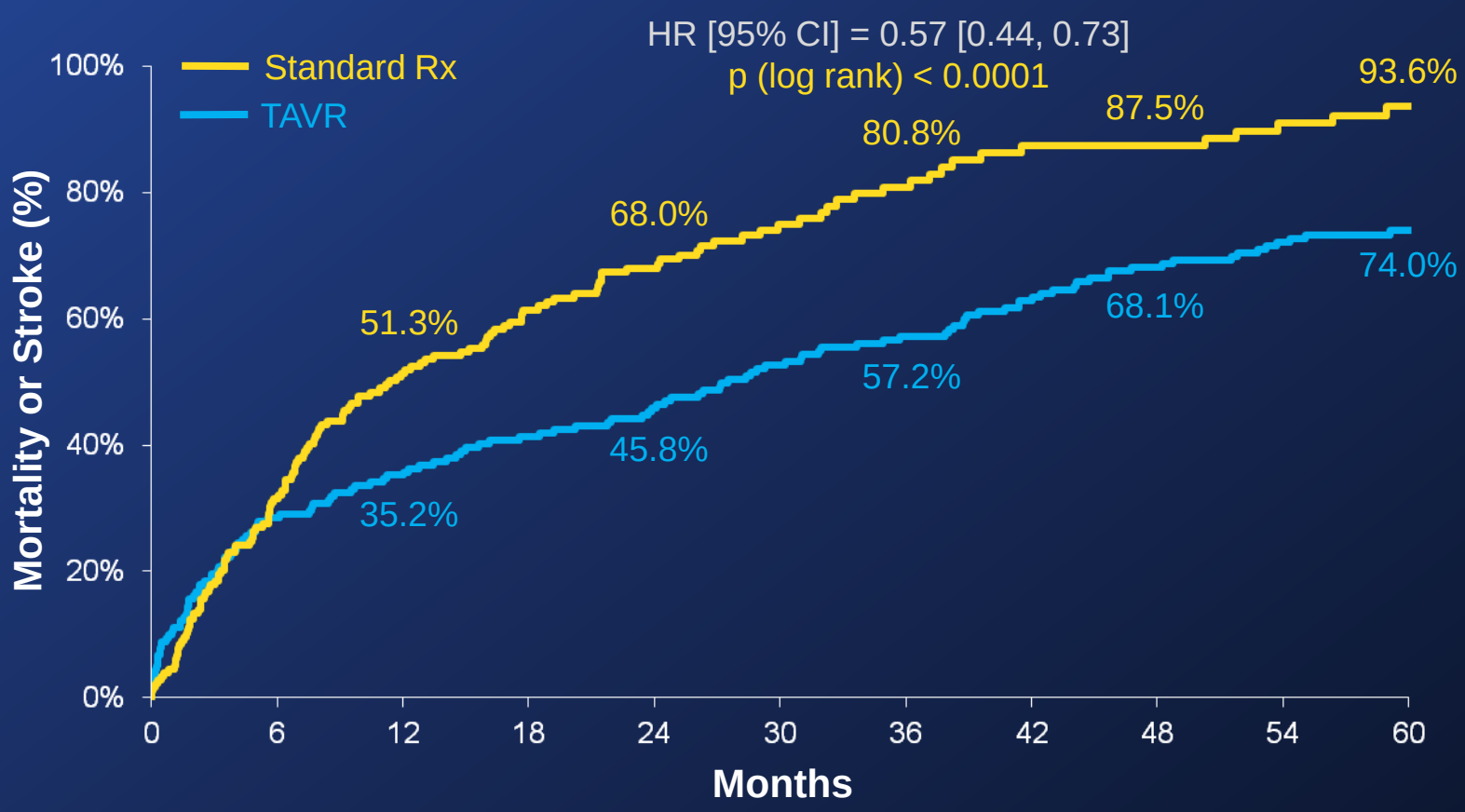
Numbers at Risk

Standard Rx	**179**	**121**	**85**	**67**	**56**	**43**	**33**	**25**	**22**	**17**	**6**
TAVR	**179**	**138**	**124**	**110**	**101**	**89**	**81**	**72**	**63**	**53**	**35**

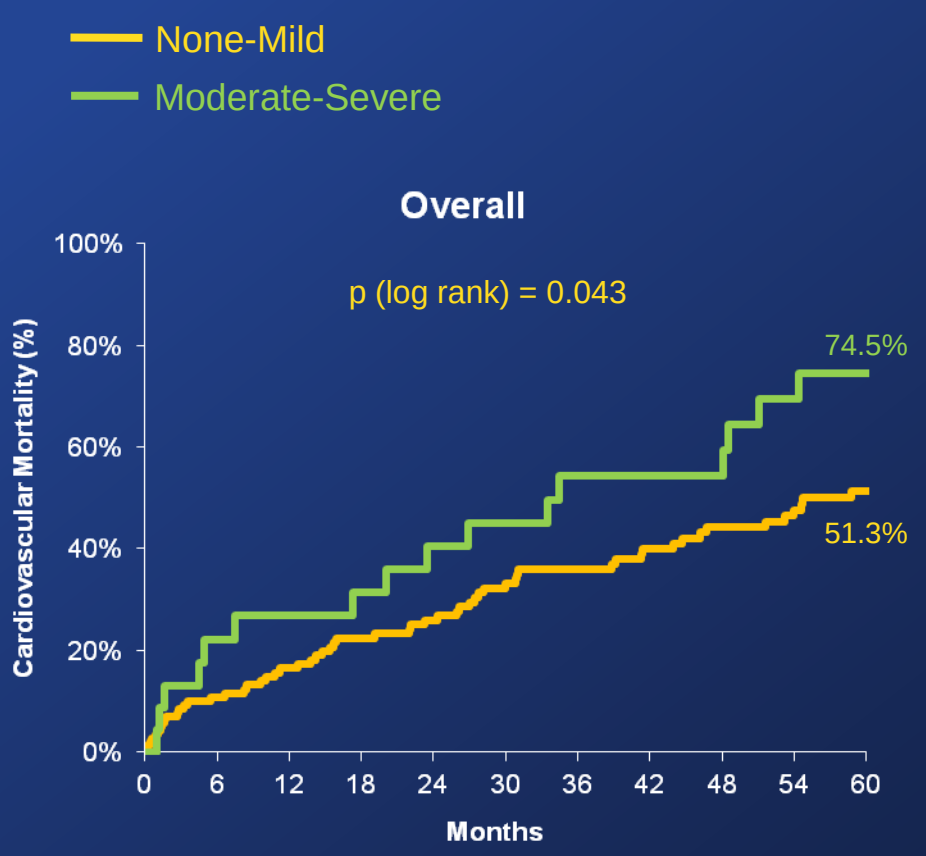
Instantaneous Risk of Death
Hazard Function

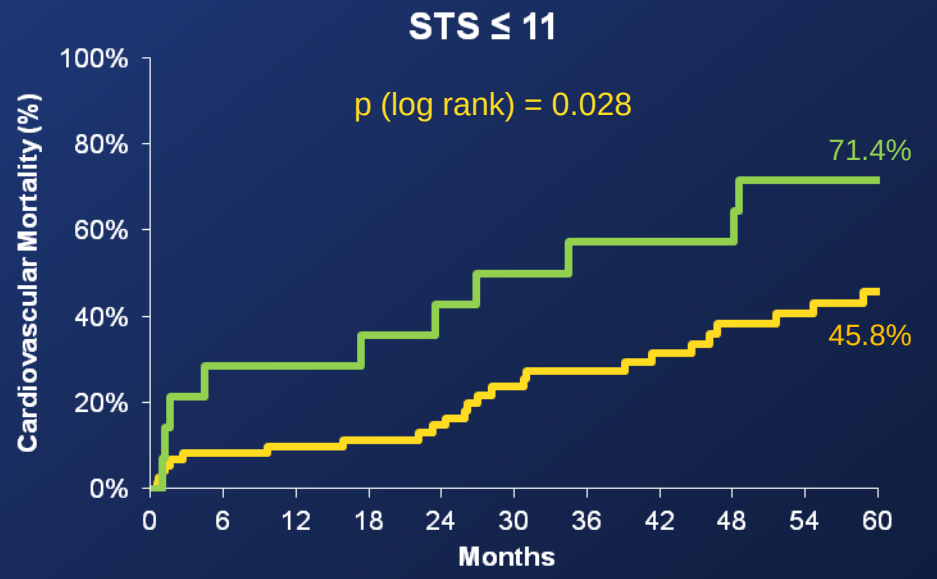


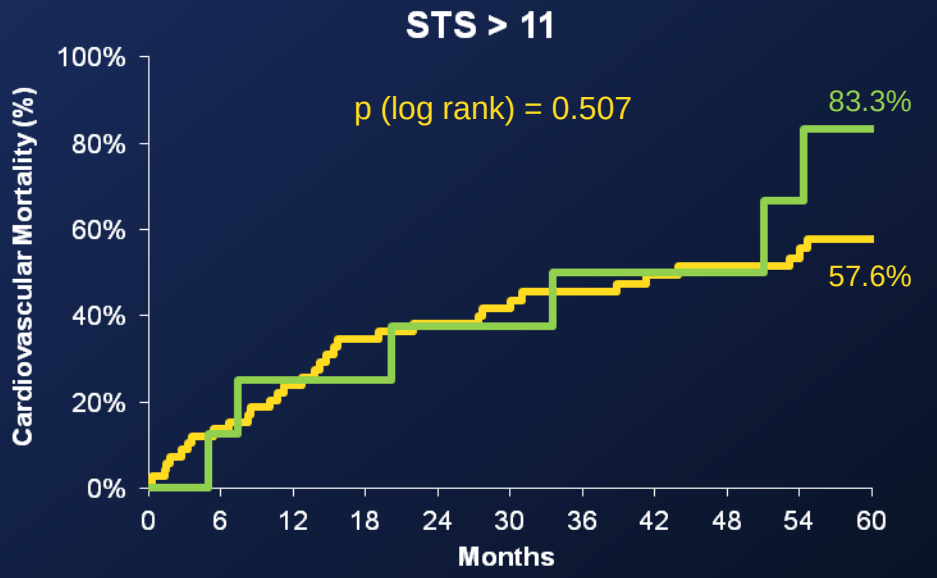
Mortality or Stroke (ITT)



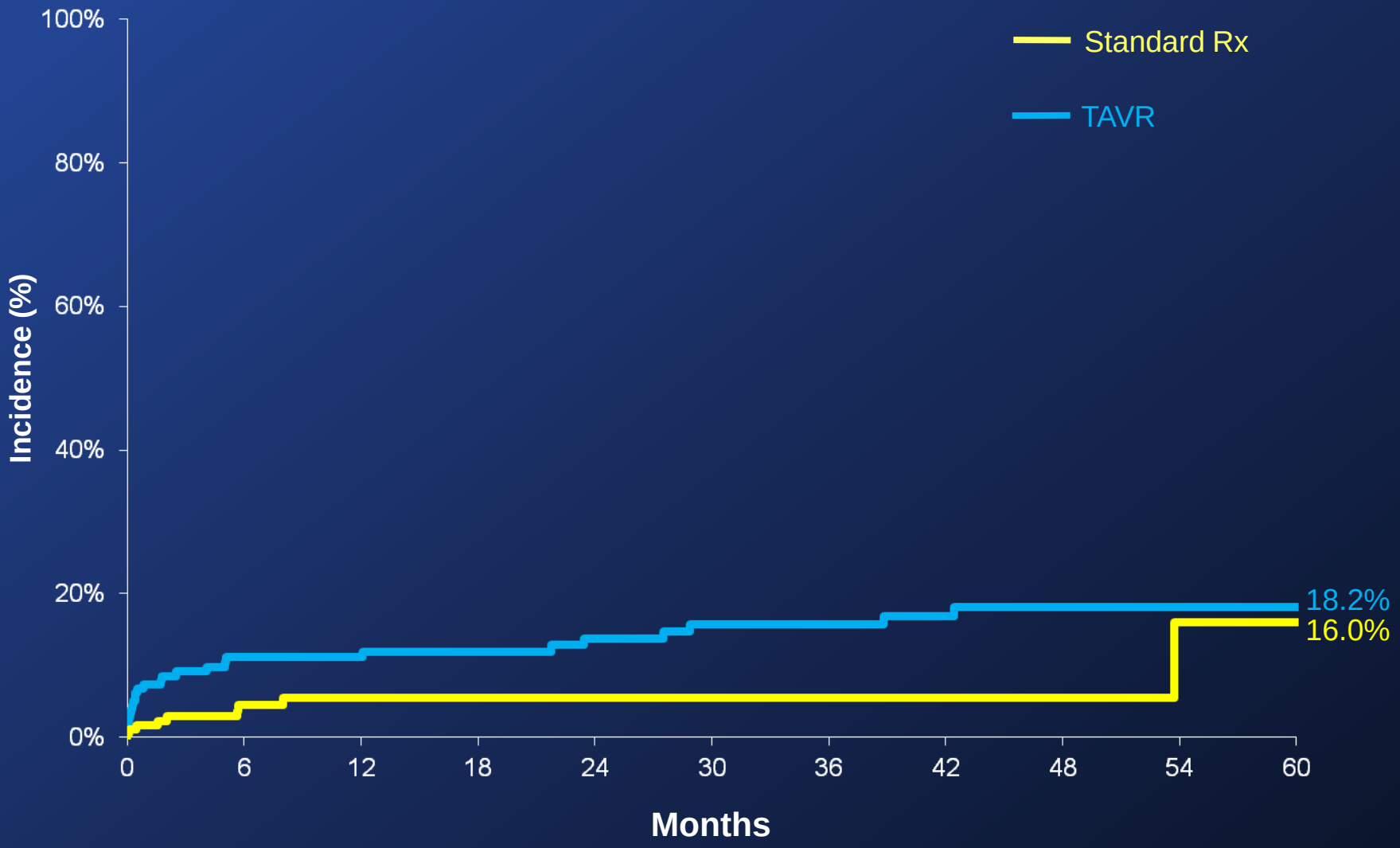
Cardiovascular Mortality by Paravalvular Leak Stratified by STS (AT)



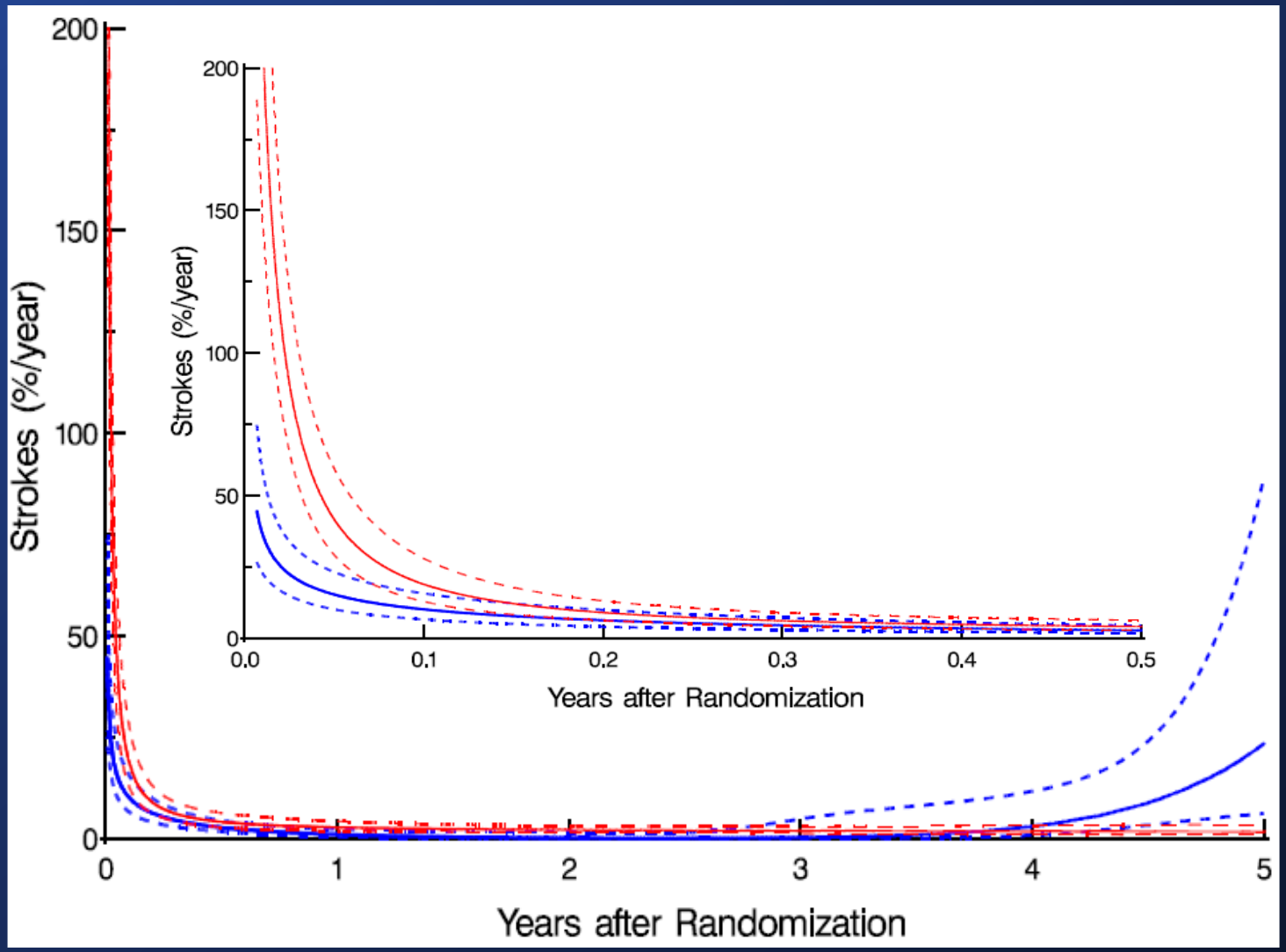




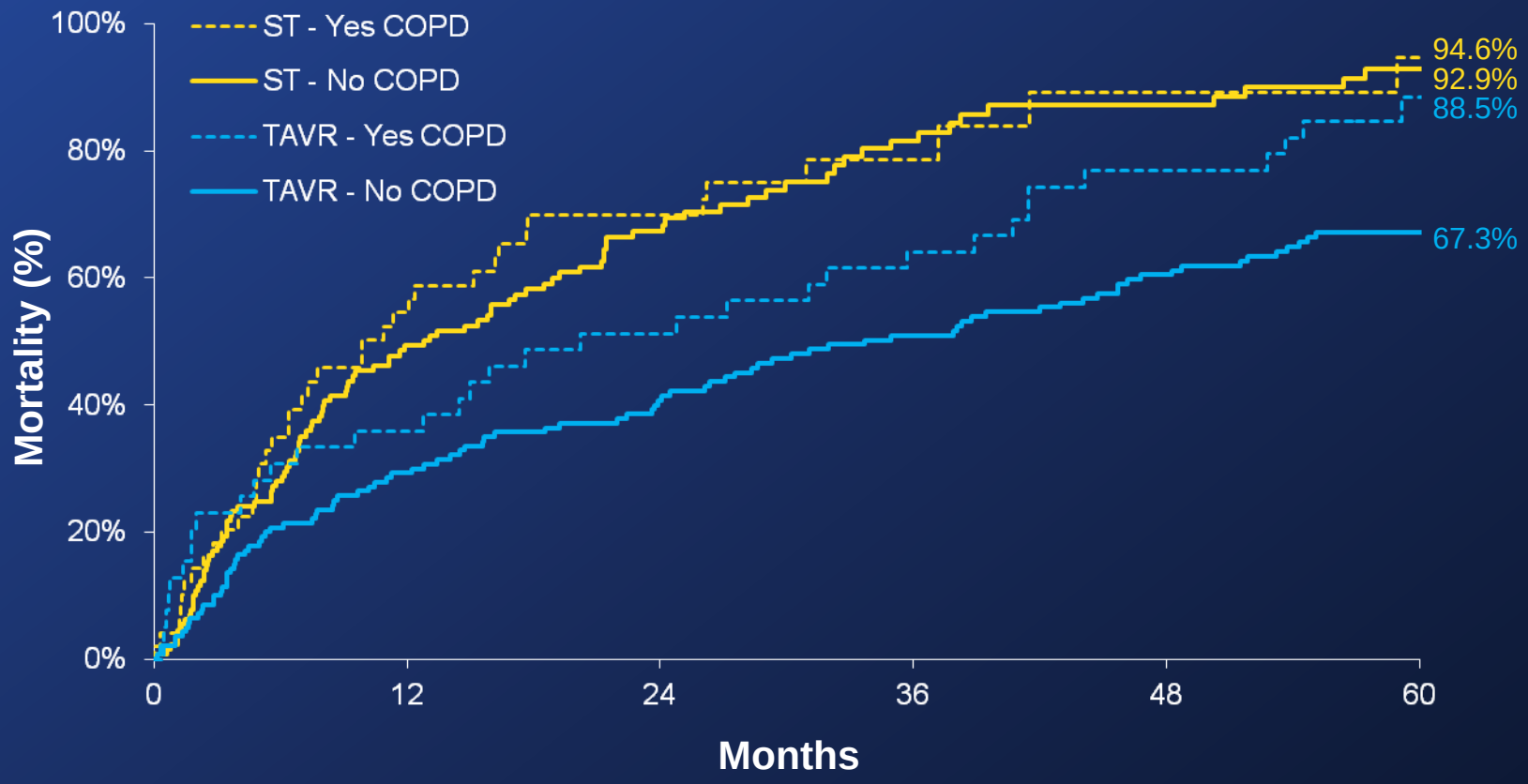
Stroke (ITT)


100%
80%
60%
40%
20%
0%
Incidence (%)
0
6
12
18
24
30
36
42
48
54
60
Months
Standard Rx
TAVR
18.2%
16.0%

Stroke Analysis
Instantaneous Risk of Stroke



TAVR Mortality Stratified by Oxygen Dependent COPD (ITT)



Numbers at Risk

ST - Yes COPD	49	21	12	5	2	1
ST - No COPD	130	64	34	14	9	2
TAVR - Yes COPD	39	25	19	14	9	1
TAVR - No COPD	140	99	82	67	54	34

Univariate and Multivariate Predictors of Mortality after TAVR

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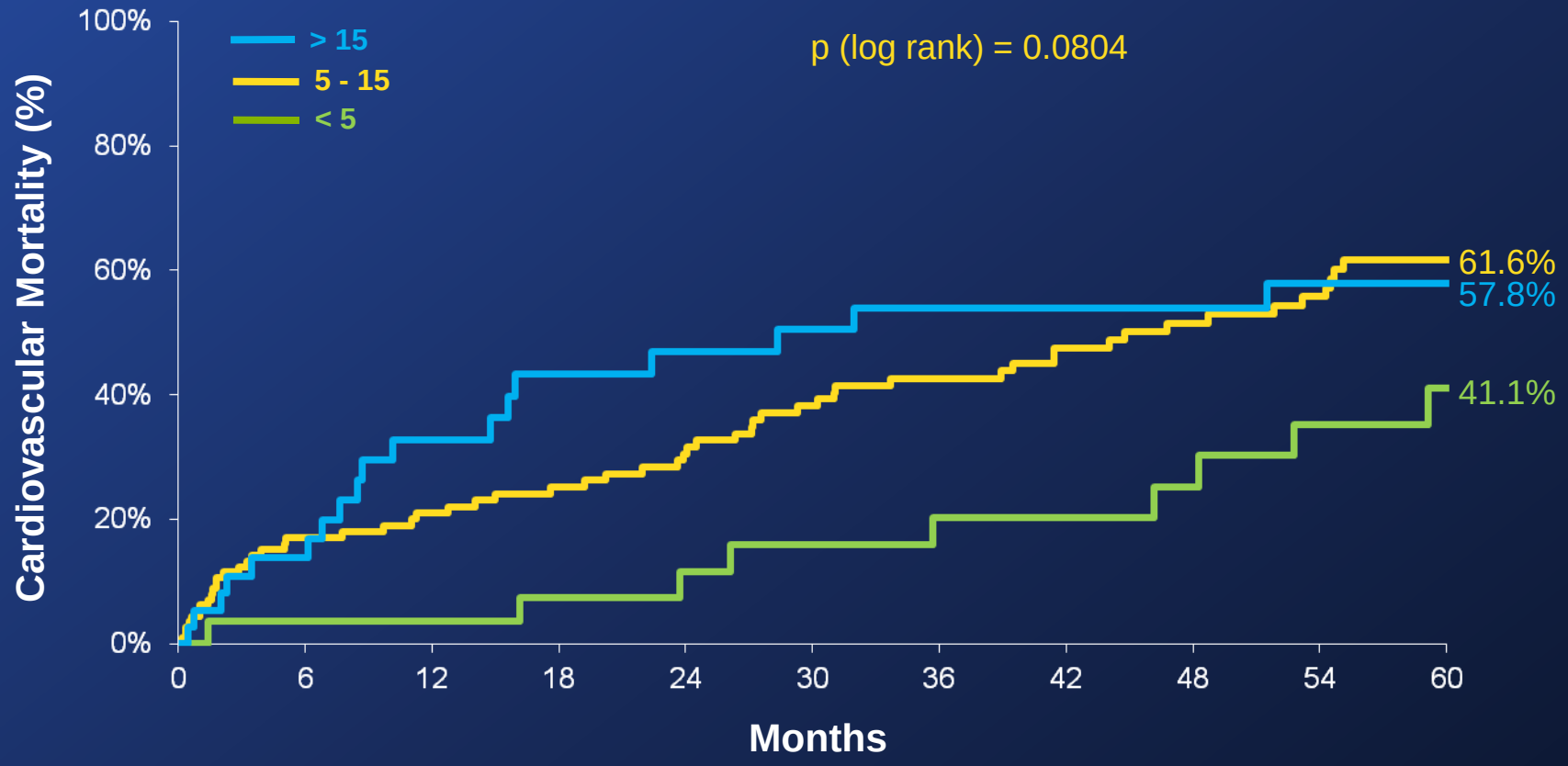
Univariate Predictors

	Hazard Ratio	*p-value*
BMI > 26	0.64 (0.45 – 0.91)	0.01
History of Stroke or TIA	3.18 (1.28 – 7.92)	0.01
Peripheral Vascular Disease	1.58 (1.10 -2.27)	0.01
Oxygen Dependent COPD	1.63 (1.10 – 2.42)	0.01

Multivariate Predictors

	Hazard Ratio	*p-value*
BMI > 26	0.50 (0.34 – 0.73)	< 0.01
Oxygen dependent COPD	1.83 (1.22 – 2.75)	< 0.01
Peripheral Vascular Disease	1.53 (1.04 – 2.24)	0.03
Moderate or Severe MR	0.60 (0.37 – 0.97)	0.04

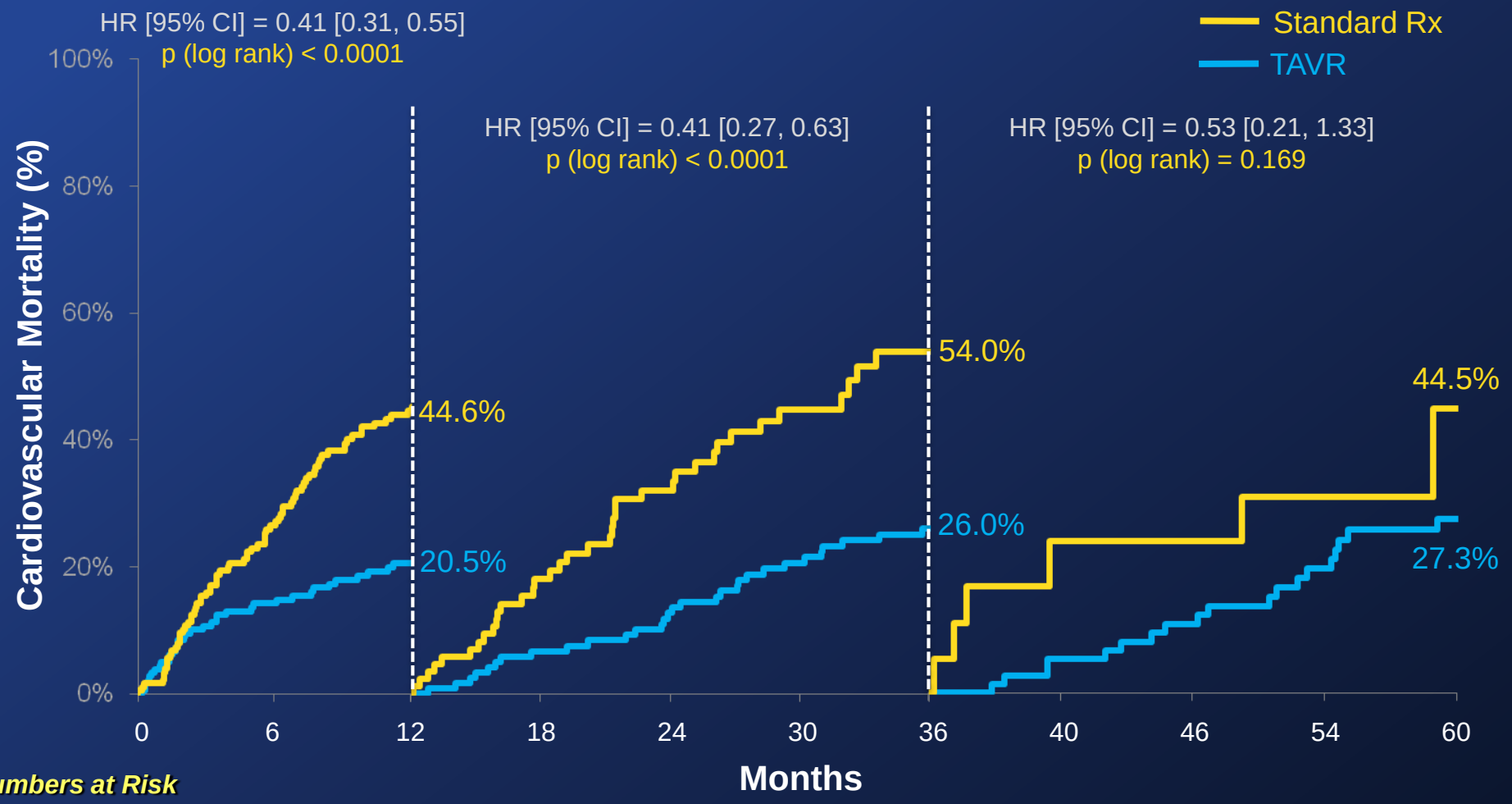
TAVR Cardiovascular Mortality Stratified by STS Score (ITT)



Numbers at Risk

> 15	38	28	20	16	15	14	13	12	12	10	6
5 - 15	113	84	79	70	65	56	50	42	36	30	19
< 5	28	26	25	24	21	19	18	18	15	13	10

Cardiovascular Mortality (ITT)
Landmark Analysis

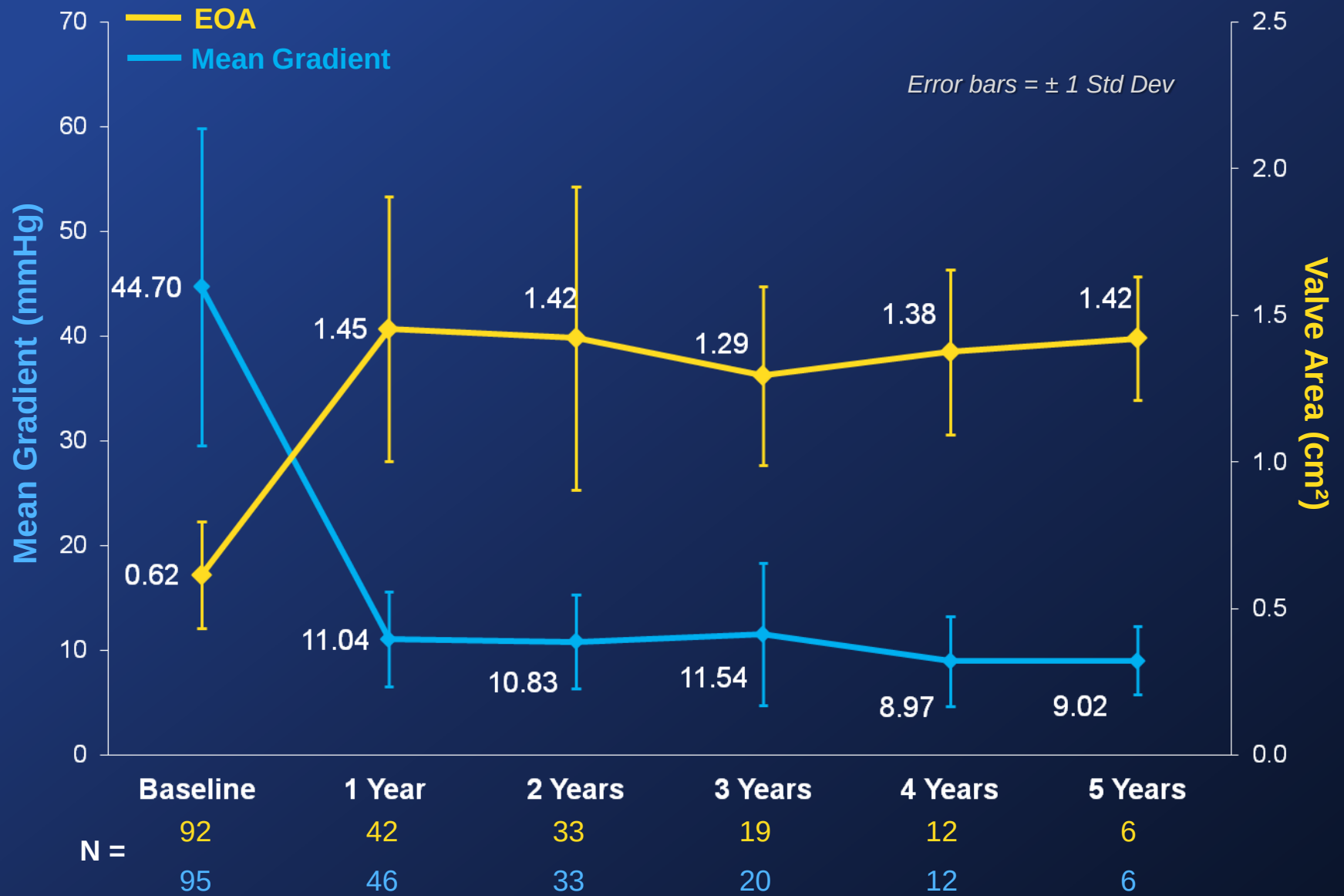


Numbers at Risk

Std. Rx	**179**	**121**	**85**	**62**	**46**	**27**	**19**	**11**	**11**	**9**	**3**
TAVR	**179**	**138**	**124**	**110**	**101**	**89**	**81**	**72**	**63**	**53**	**35**

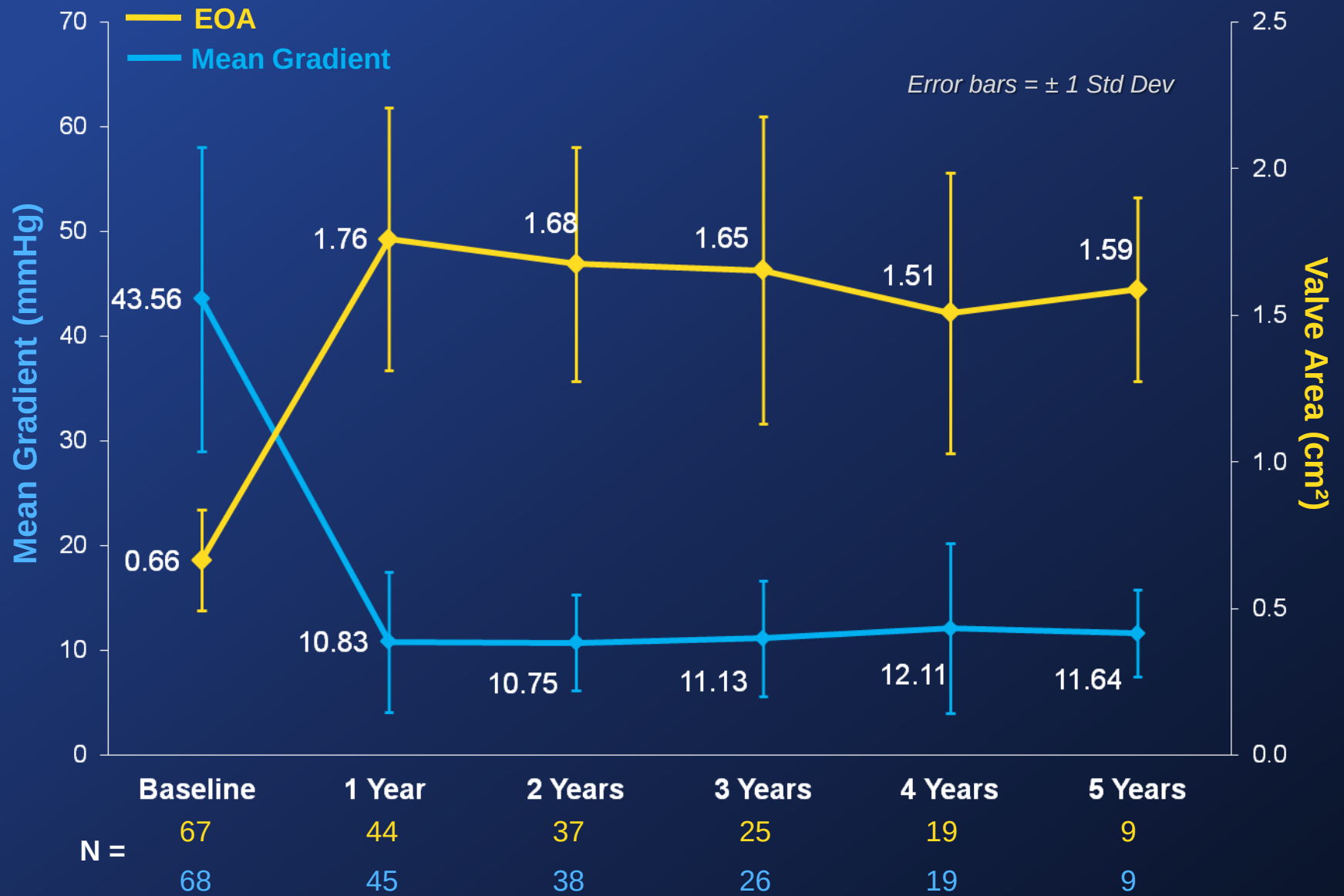
Mean Gradient & Valve Area (AT)

Valve Durability (23mm)



Mean Gradient & Valve Area (AT)

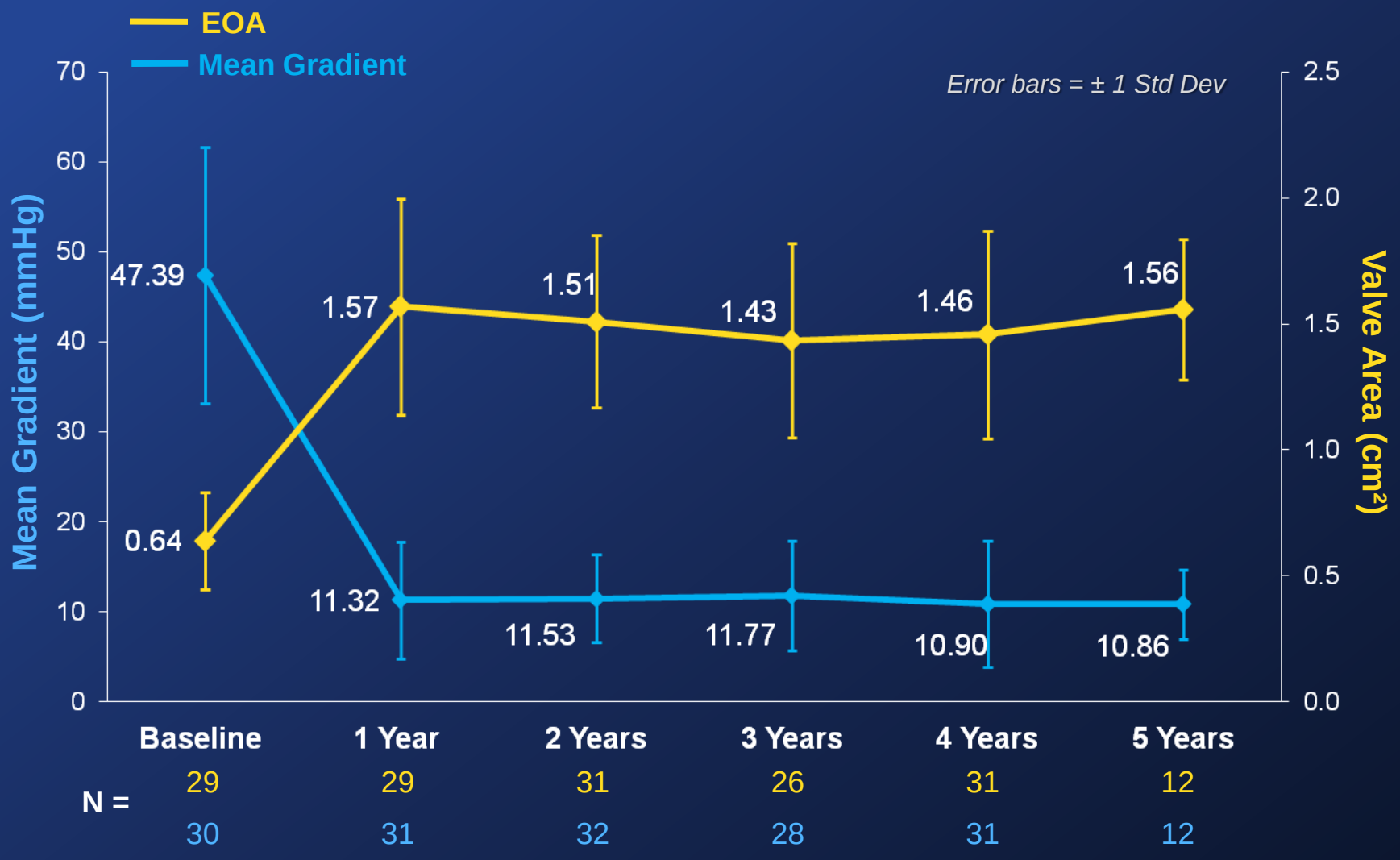
Valve Durability (26mm)



Mean Gradient & Valve Area (AT)

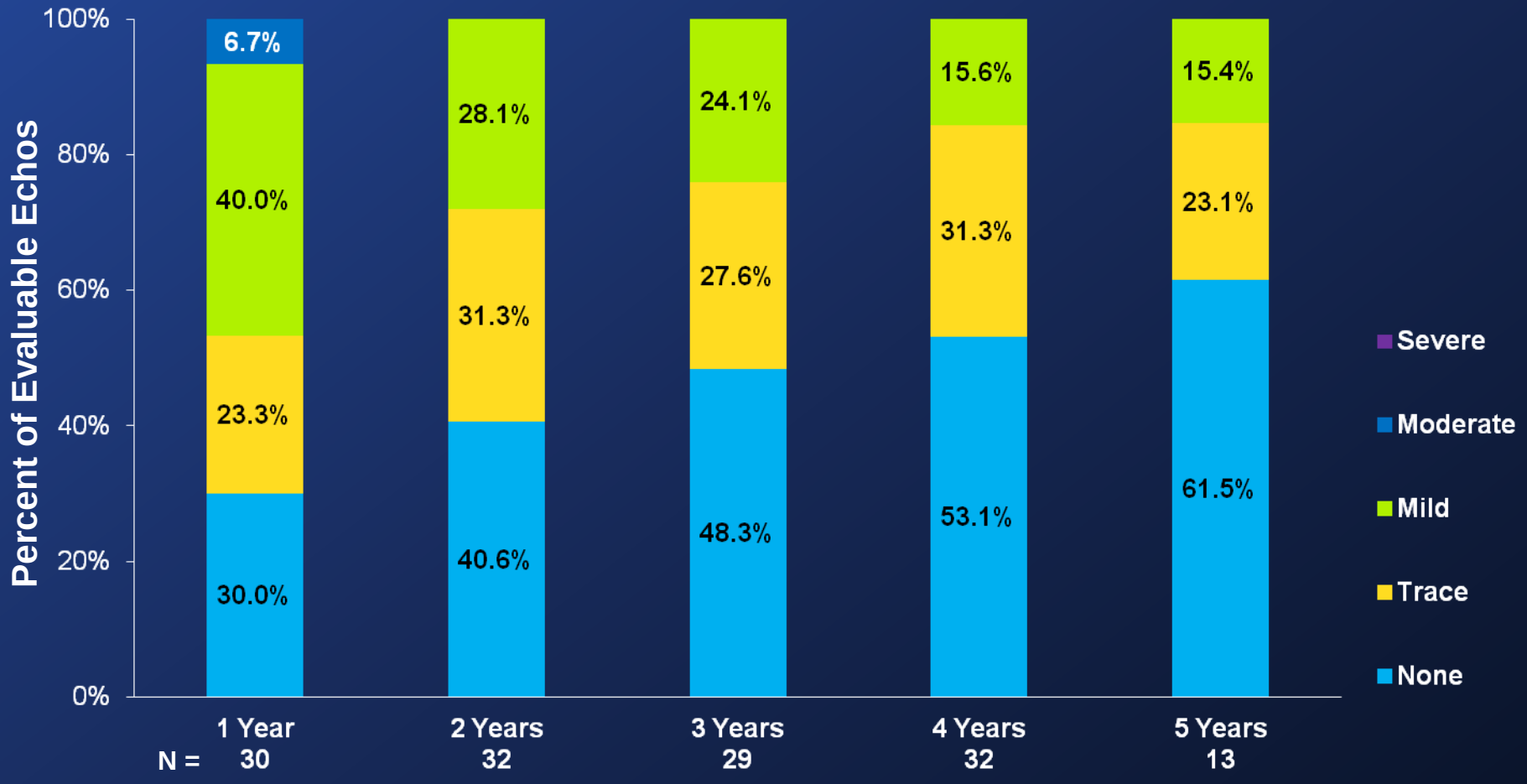
Restricted to Patients with 4 Year Data

THE PARTNER TRIAL



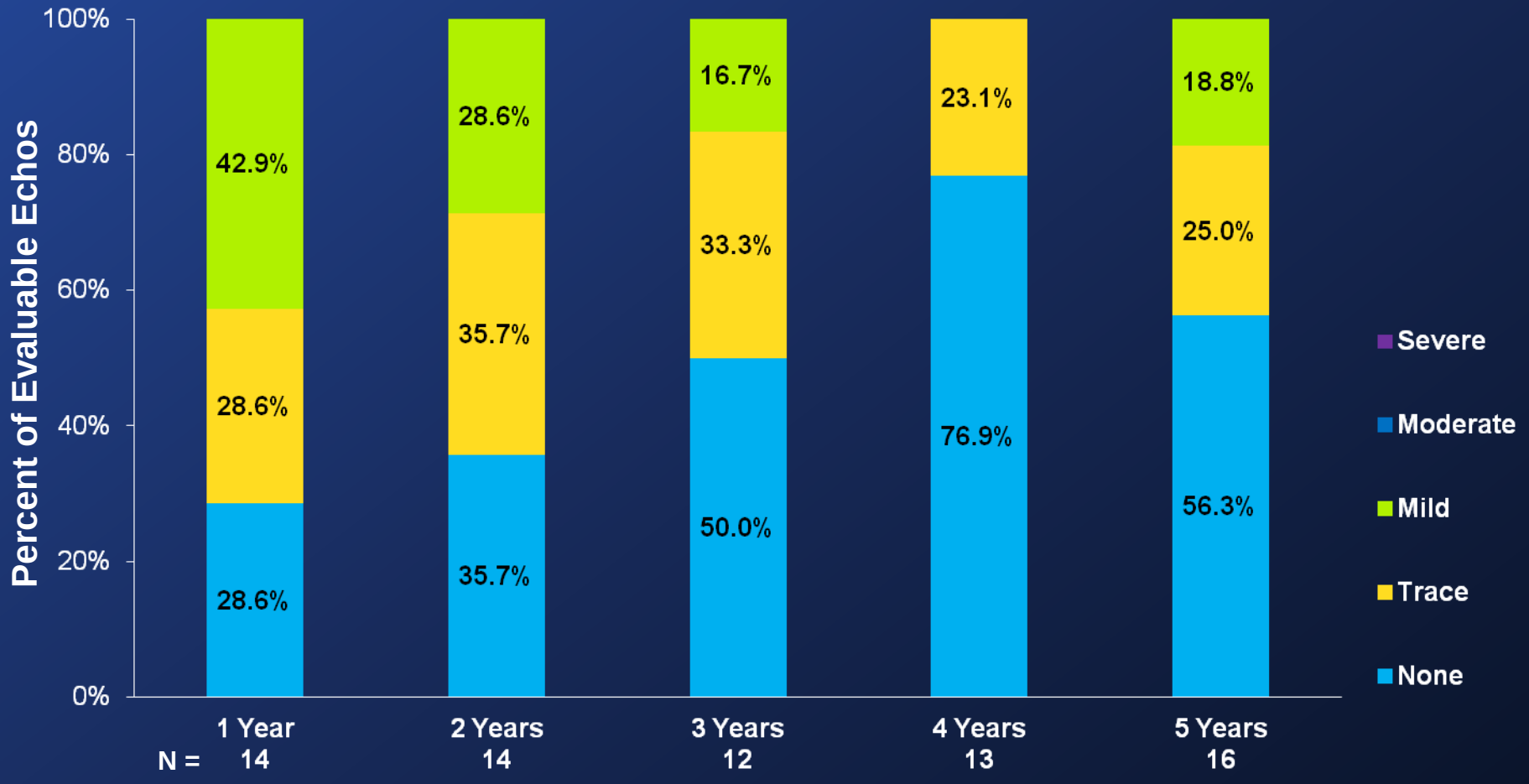
Paravalvular Leak (AT)

Restricted to Patients with 4 Year Values

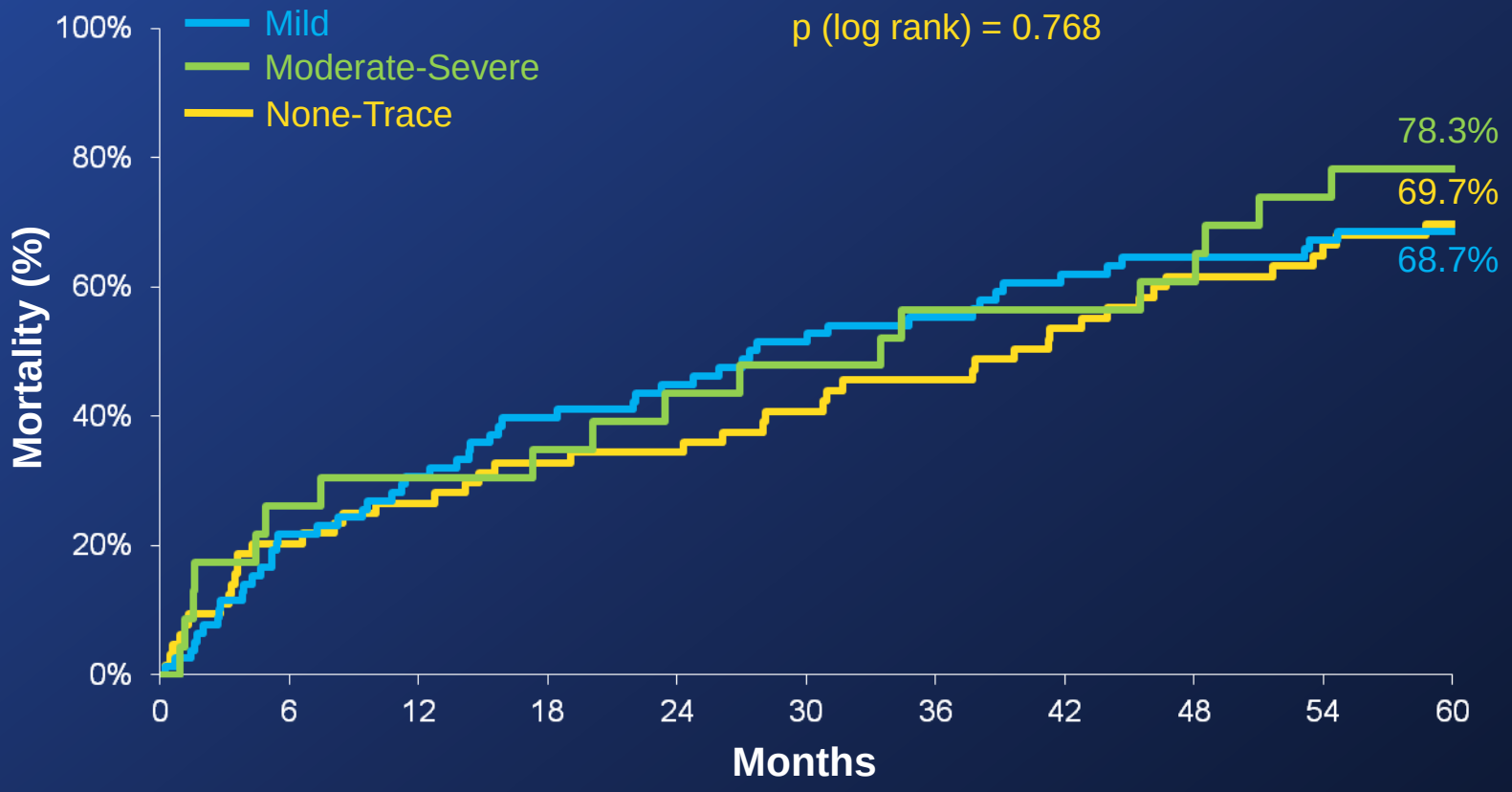


Paravalvular Leak (AT)

Restricted to Patients with 5 Year Values



Mortality Stratified by Paravalvular Leak (AT)
Valve Implant Patients

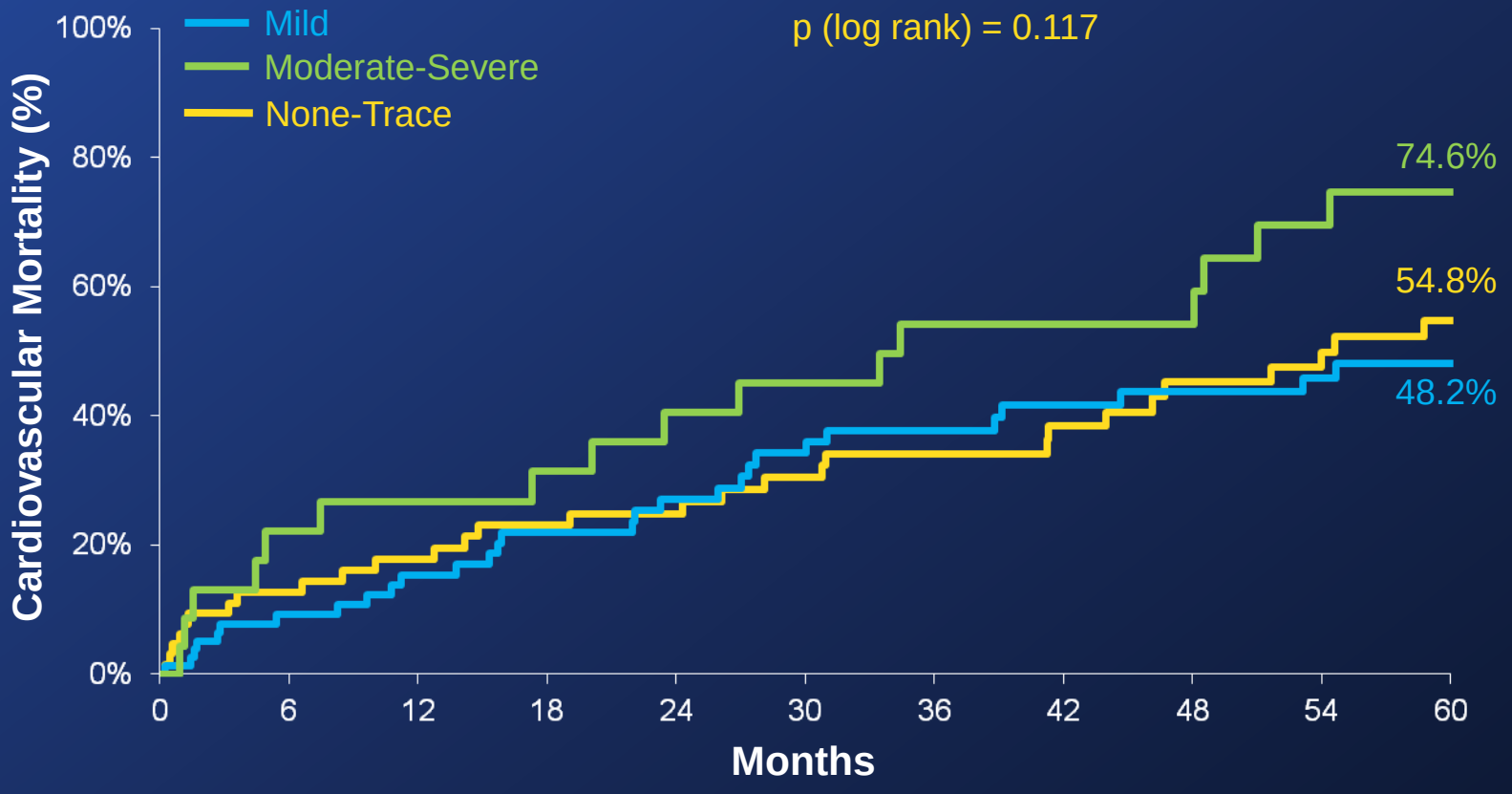


Numbers at Risk

Mild	78	61	54	47	43	37	34	29	27	24	12
Mod.-Severe	23	17	16	15	13	12	10	10	9	6	4
None-Trace	64	51	47	43	41	37	34	29	24	21	12

Cardiovascular Mortality Stratified by Paravalvular Leak (AT)

Valve Implant Patients



Numbers at Risk

Mild	78	61	54	47	43	37	34	29	27	24	12
Mod.-Severe	23	17	16	15	13	12	10	10	9	6	4
None-Trace	64	51	47	43	41	37	34	29	24	21	12

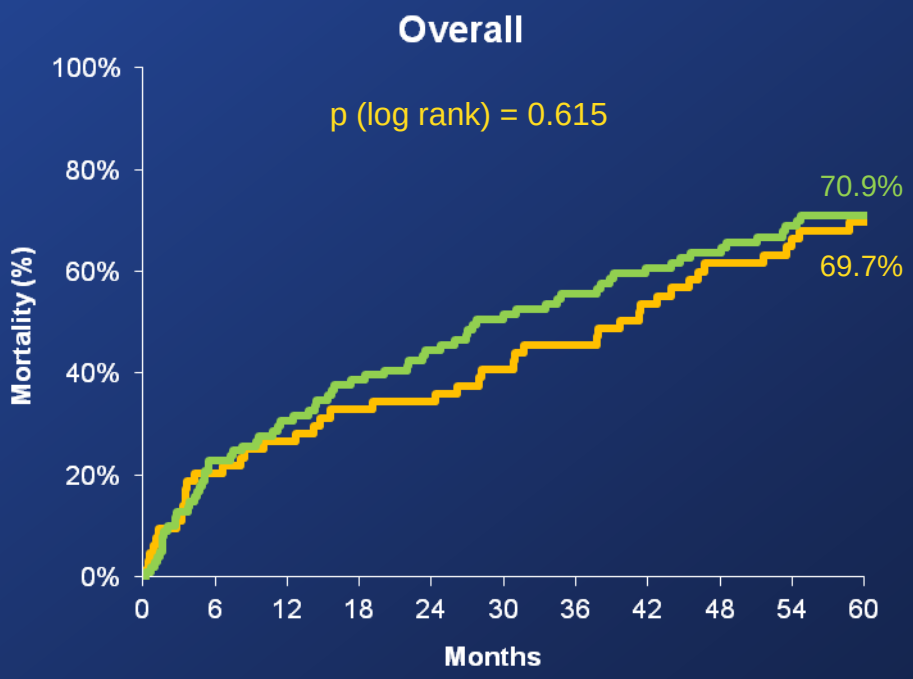
Mortality by Paravalvular Leak Stratified by STS (AT)

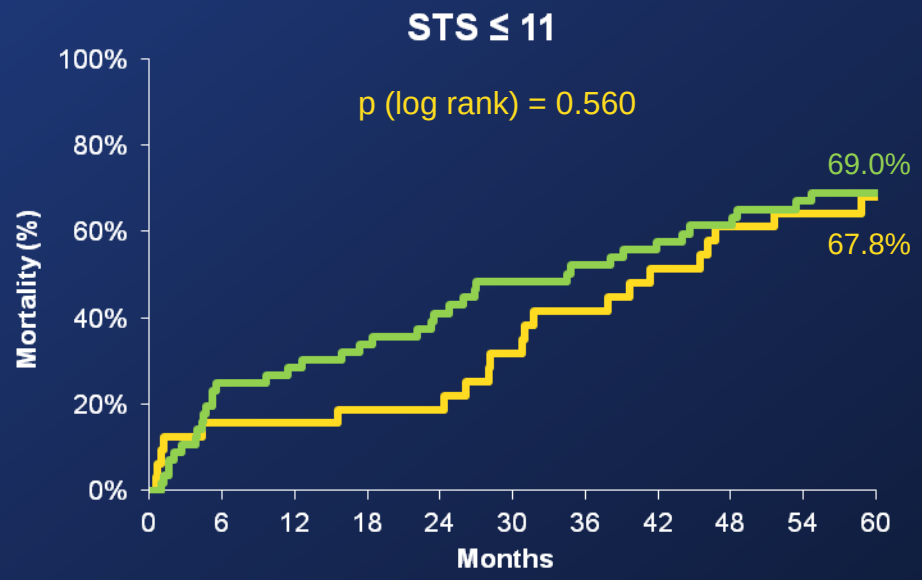
Valve Implant Patients

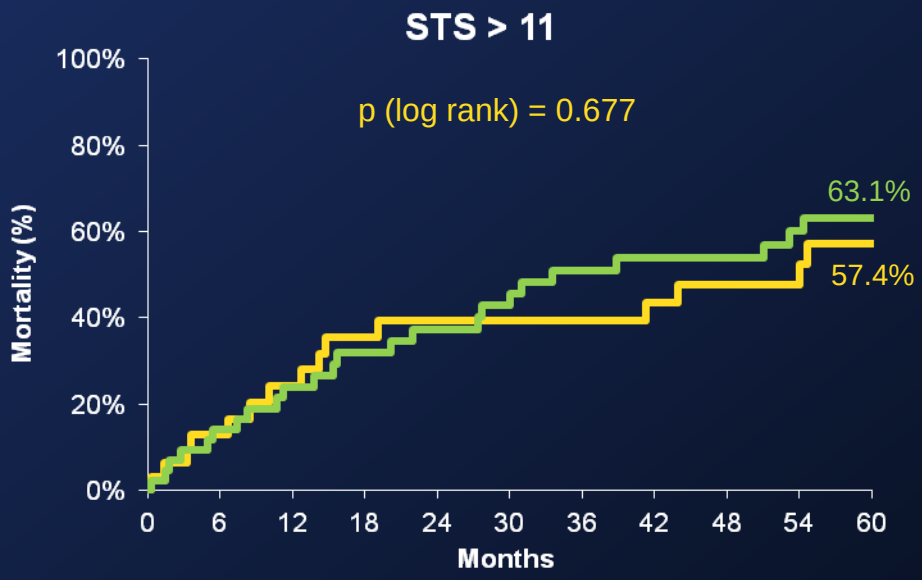
THE PARTNER TRIAL

None-Trace

Mild-Severe







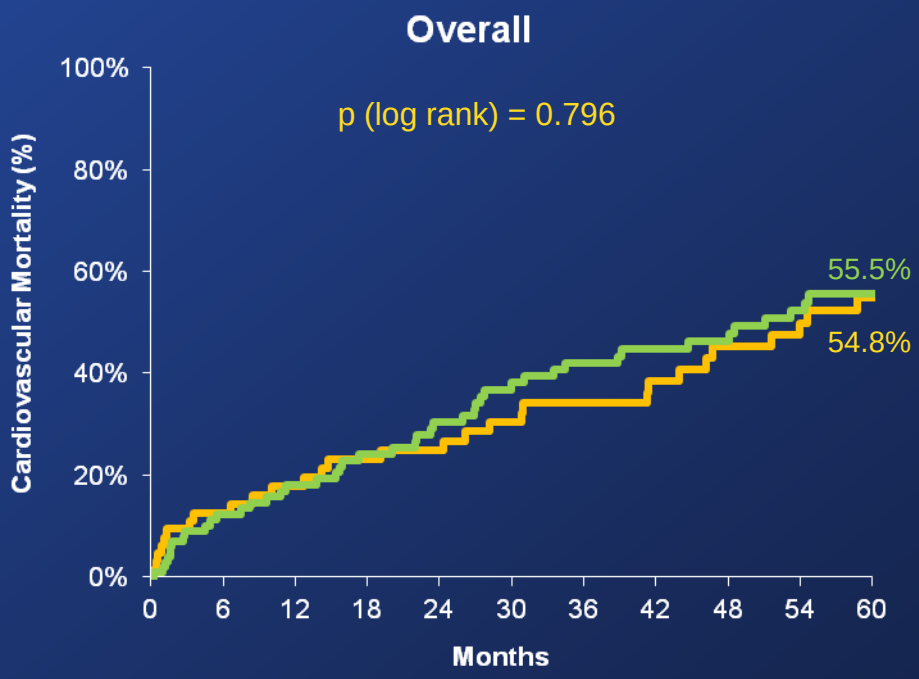
Cardiovascular Mortality by Paravalvular Leak Stratified by STS (AT)

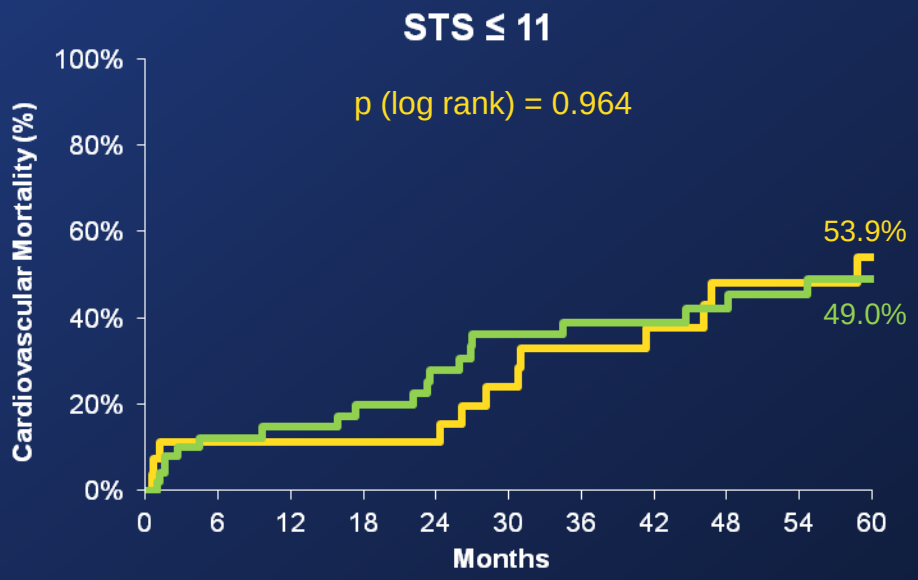
Valve Implant Patients

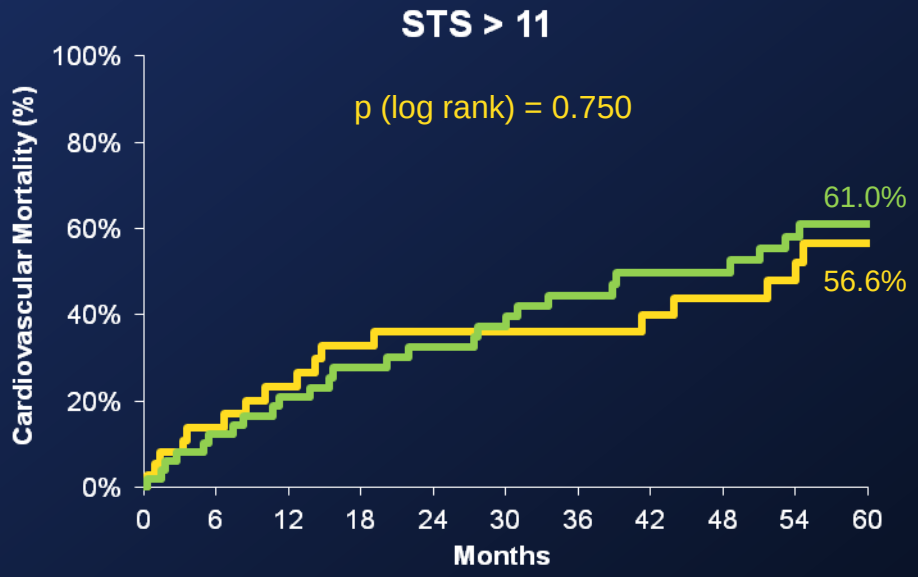
THE PARTNER TRIAL

None-Trace

Mild-Severe





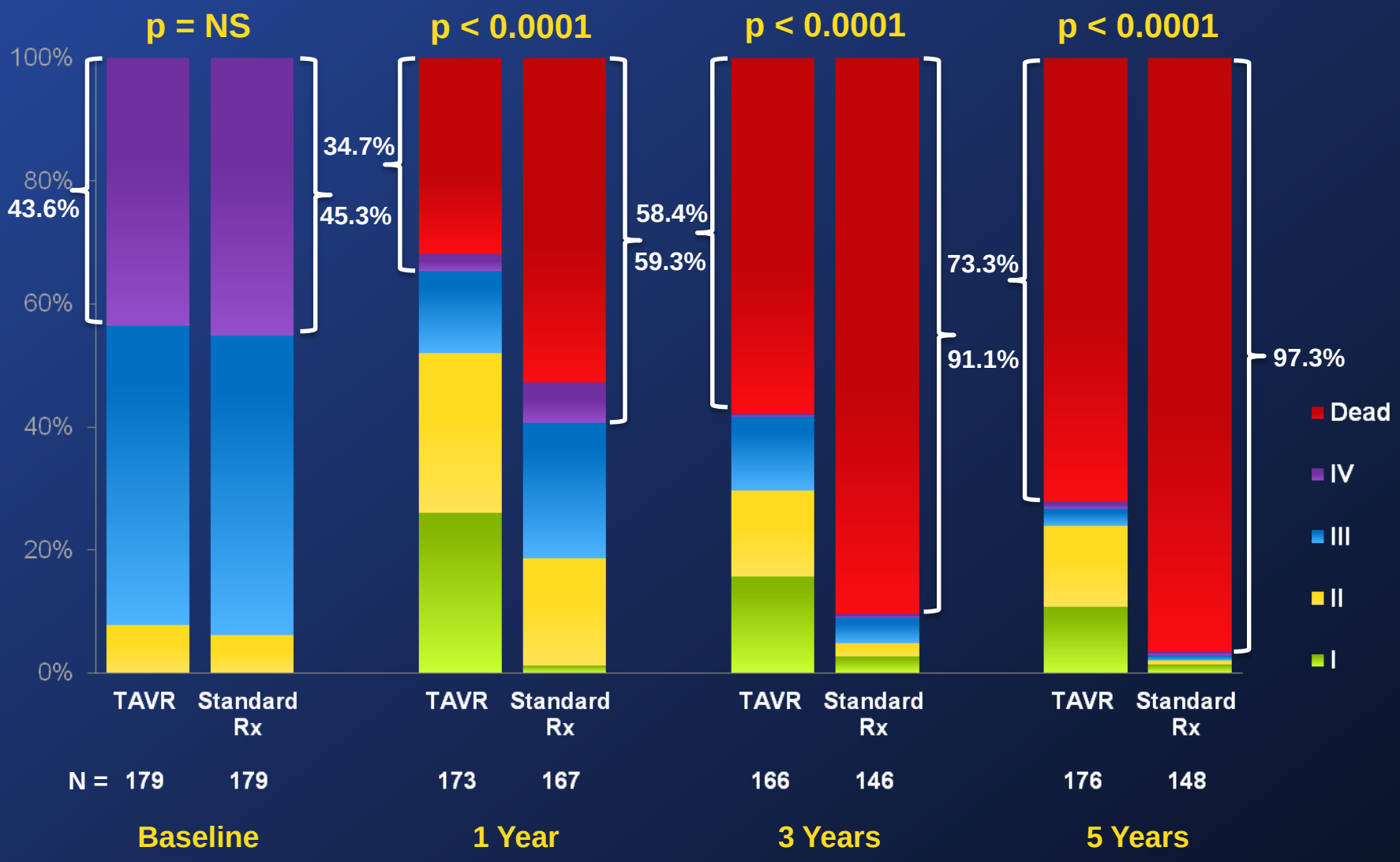


Mean Survival and Months Alive and Out of Hospital

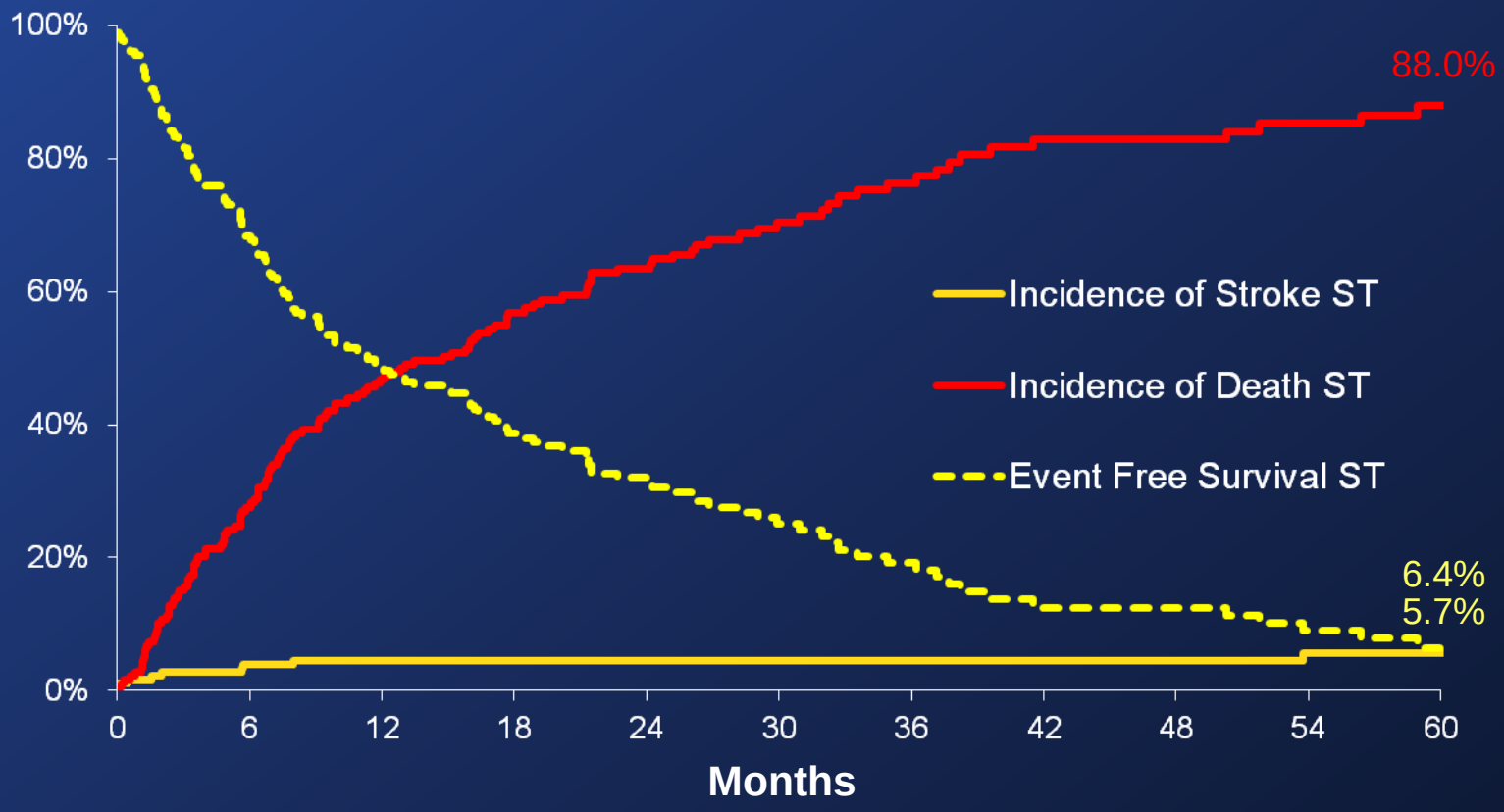
		Survival	Out of Hospital
Standard Therapy	Mean†	19.1	18.5
	Q1	4.8	4.5
	Median	11.7	11.1
	Q3	30.9	29.9
TAVR	Mean†	31.7	30.6
	Q1	7.7	6.6
	Median	31.0	29.7
	Q3	NA	NA

† Means are biased downwards because of censoring

NYHA Class Over Time (ITT)



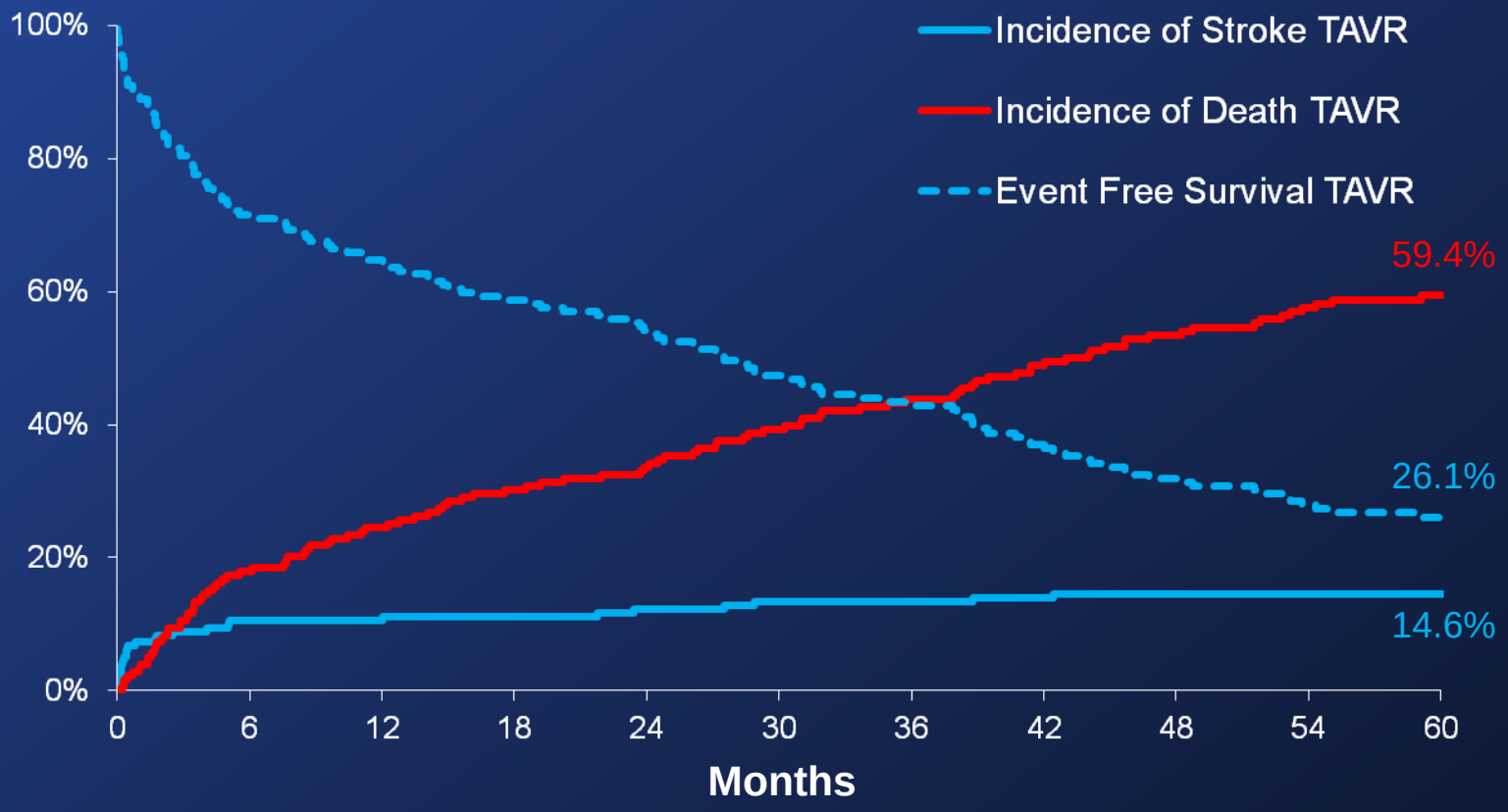
Death and Stroke Competing Risks (ITT)
Standard Therapy



Numbers at Risk

Standard Rx	179	118	84	62	46	27	19	11	11	8	3

Death and Stroke Competing Risks (ITT)
TAVR



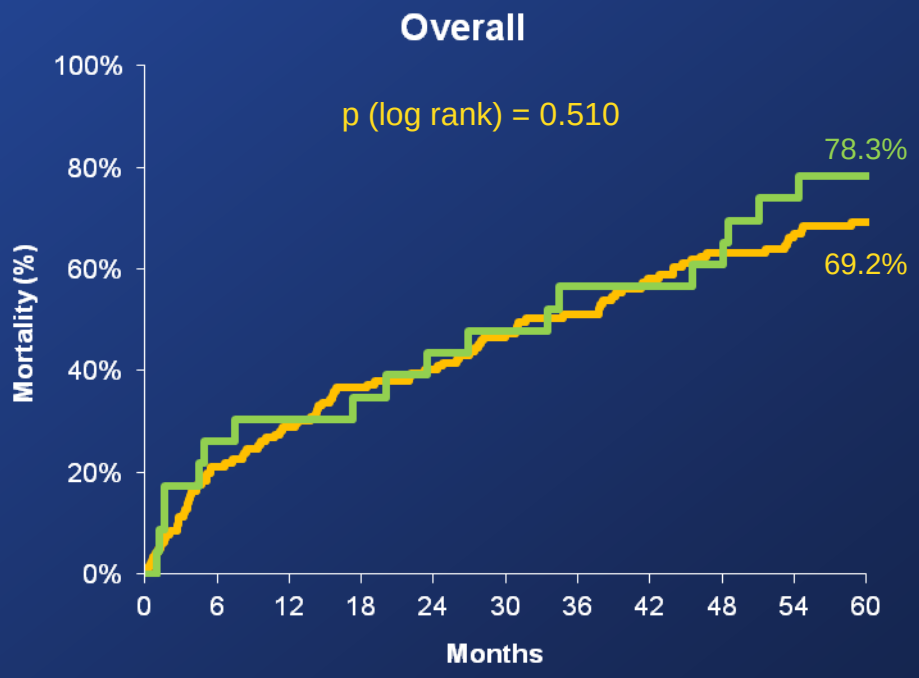
Numbers at Risk

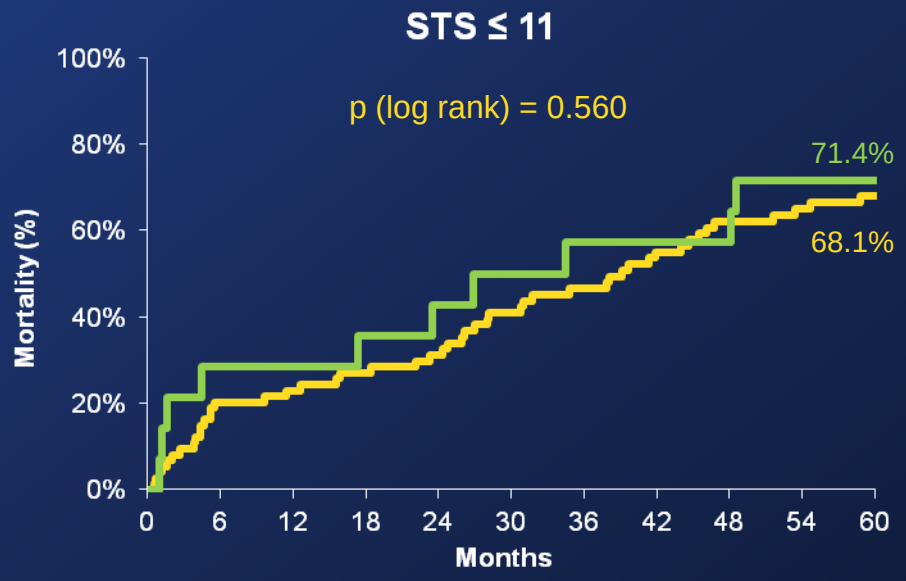
TAVR	179	128	116	105	96	83	75	65	56	48	34

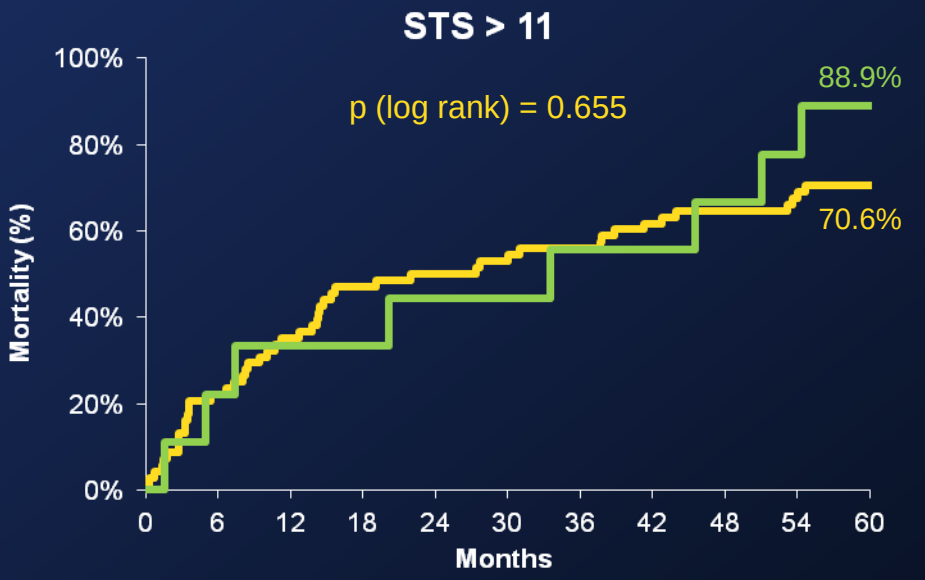
Mortality by Paravalvular Leak Stratified by STS (AT)

THE PARTNER TRIAL

None-Mild
Moderate-Severe





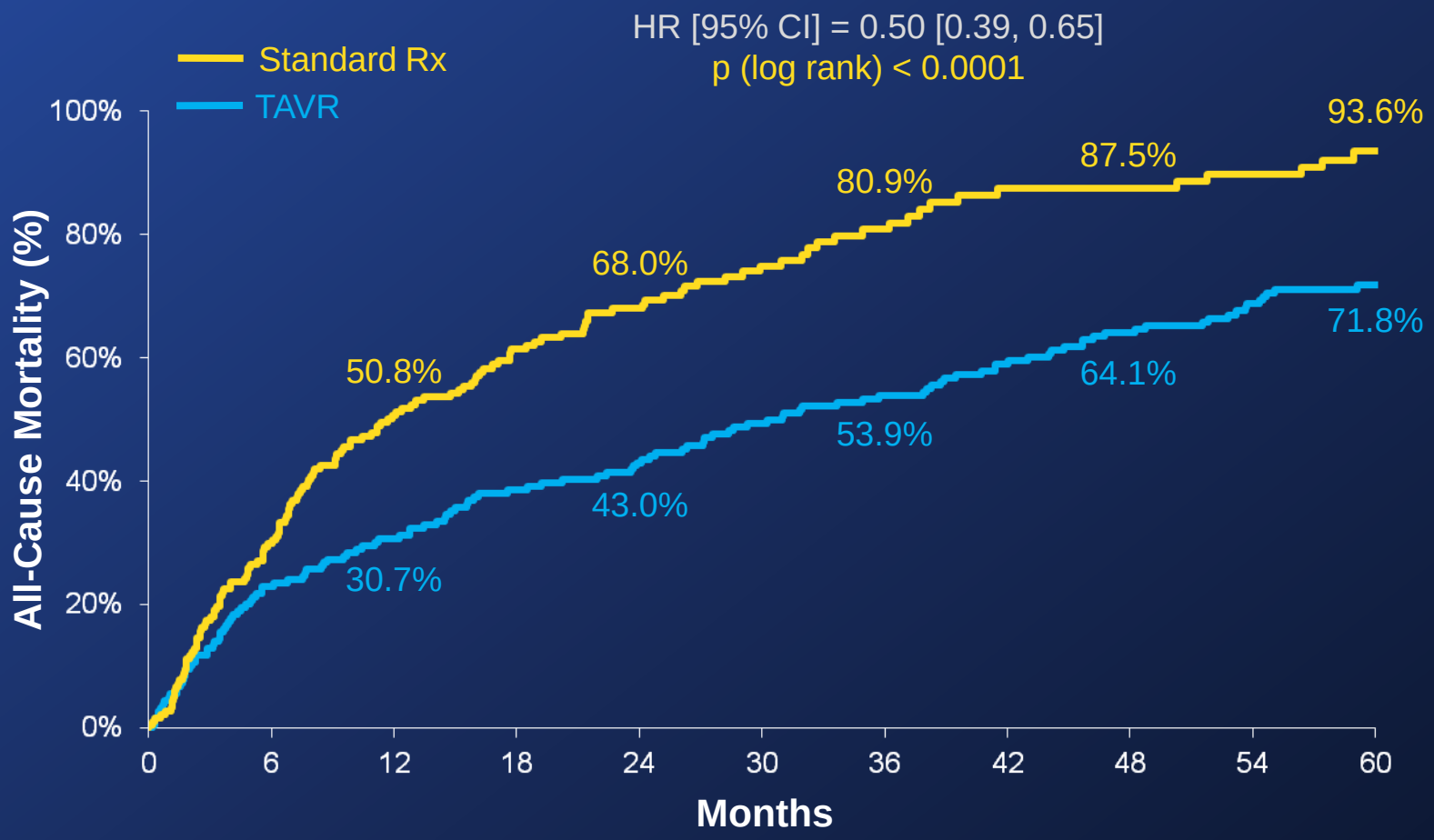


Presented Slides That Include Number of Patients at Risk

All-Cause Mortality (ITT)

Crossover Patients Censored at Crossover

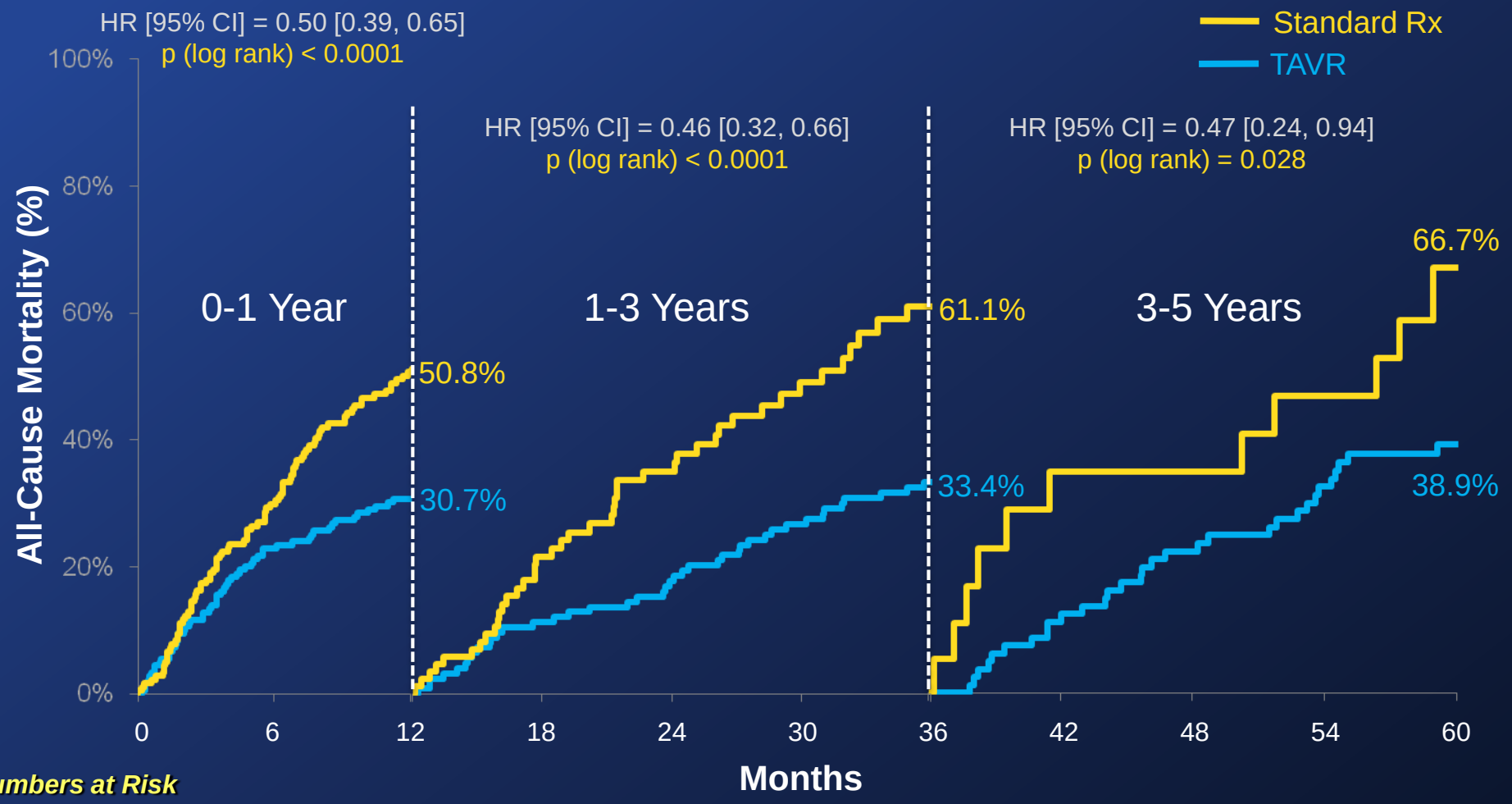
THE PARTNER TRIAL



Numbers at Risk

Standard Rx	**179**	**121**	**85**	**62**	**46**	**27**	**19**	**11**	**11**	**9**	**3**
TAVR	**179**	**138**	**124**	**110**	**101**	**89**	**81**	**72**	**63**	**53**	**35**

All-Cause Mortality (ITT)
Landmark Analysis

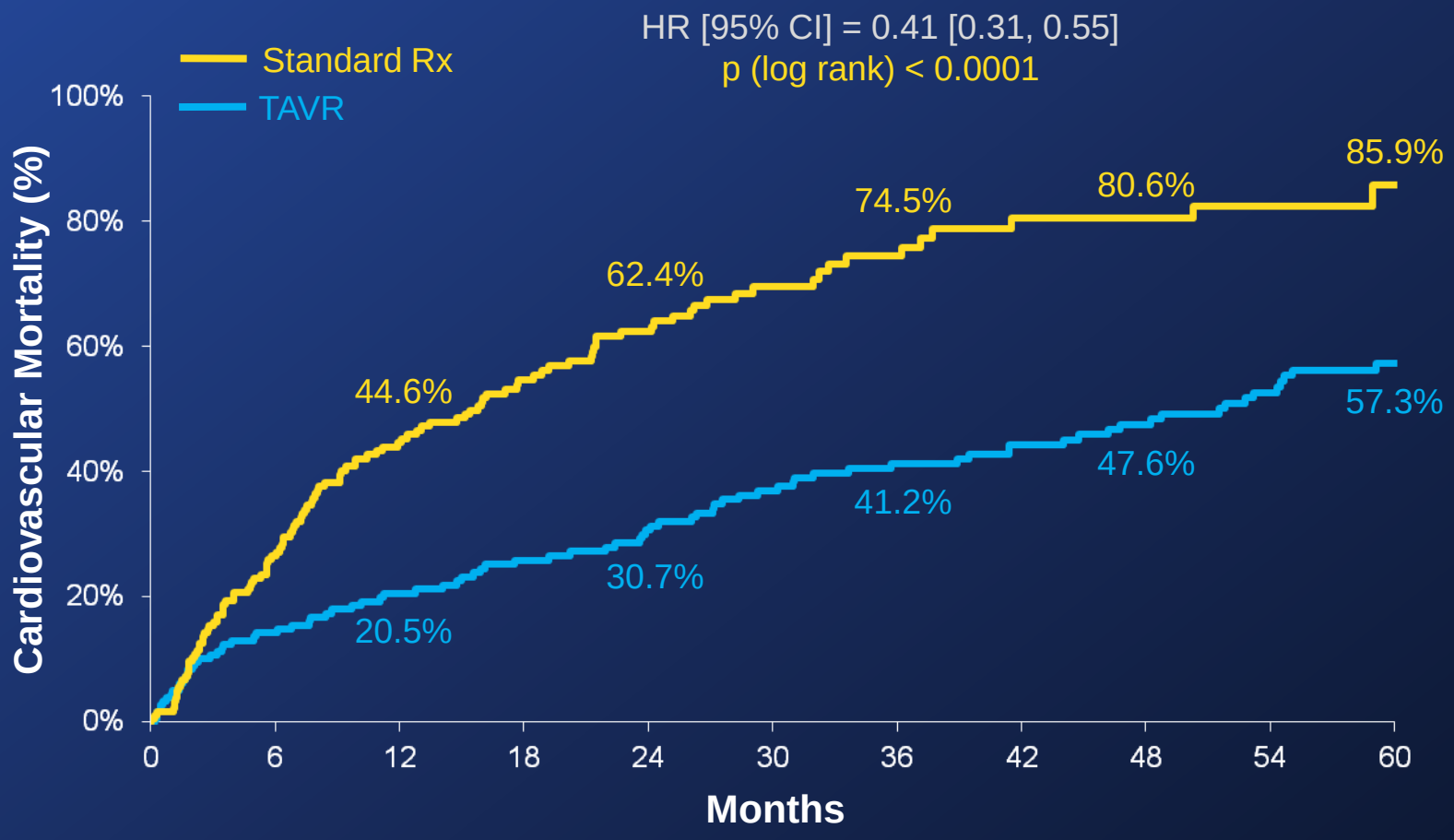


Numbers at Risk

Std. Rx	**179**	**121**	**85**	**62**	**46**	**27**	**19**	**11**	**11**	**9**	**3**
TAVR	**179**	**138**	**124**	**110**	**101**	**89**	**81**	**72**	**63**	**53**	**35**

Cardiovascular Mortality (ITT)
Crossover Patients Censored at Crossover

THE PARTNER TRIAL

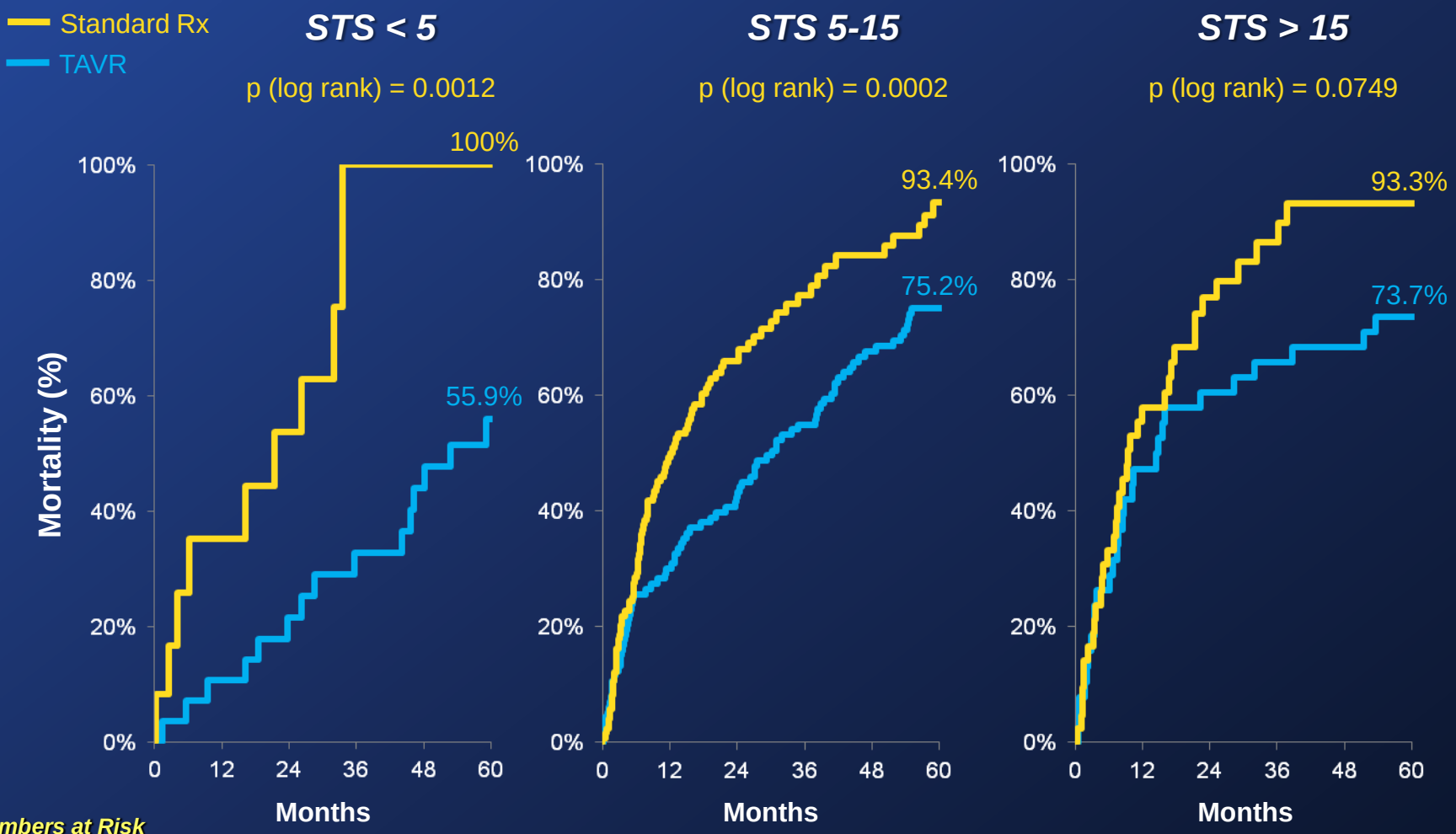


Numbers at Risk

Standard Rx	179	121	85	62	46	27	19	11	11	9	3
TAVR	179	138	124	110	101	89	81	72	63	53	35

All-Cause Mortality Stratified by STS Score (ITT)

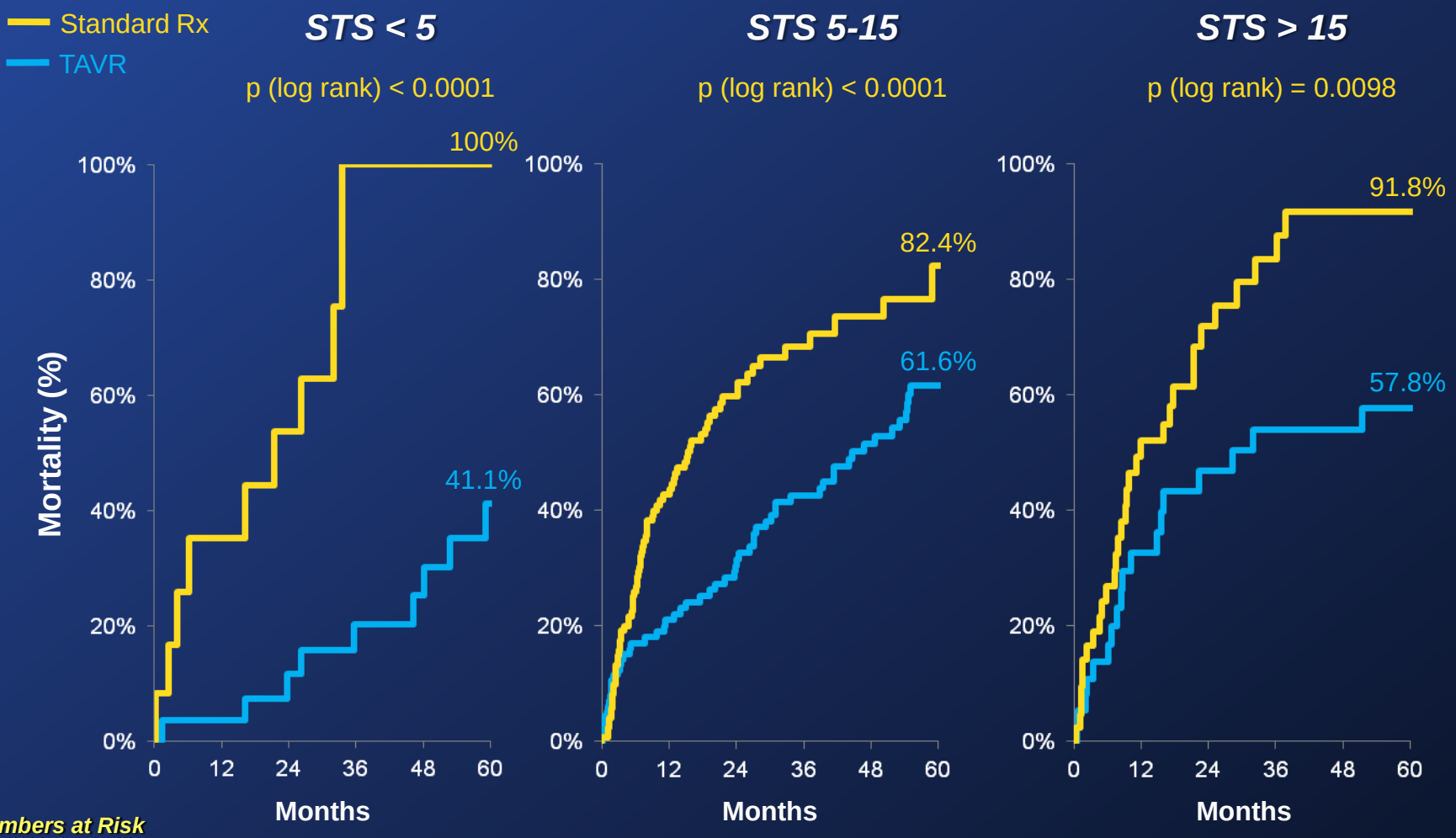
THE PARTNER TRIAL



Numbers at Risk

Standard Rx	12	7	5	0	0	0	123	61	33	15	9	2	43	17	8	4	2	1
TAVR	28	25	21	18	15	10	113	79	65	50	36	19	38	20	15	16	12	6

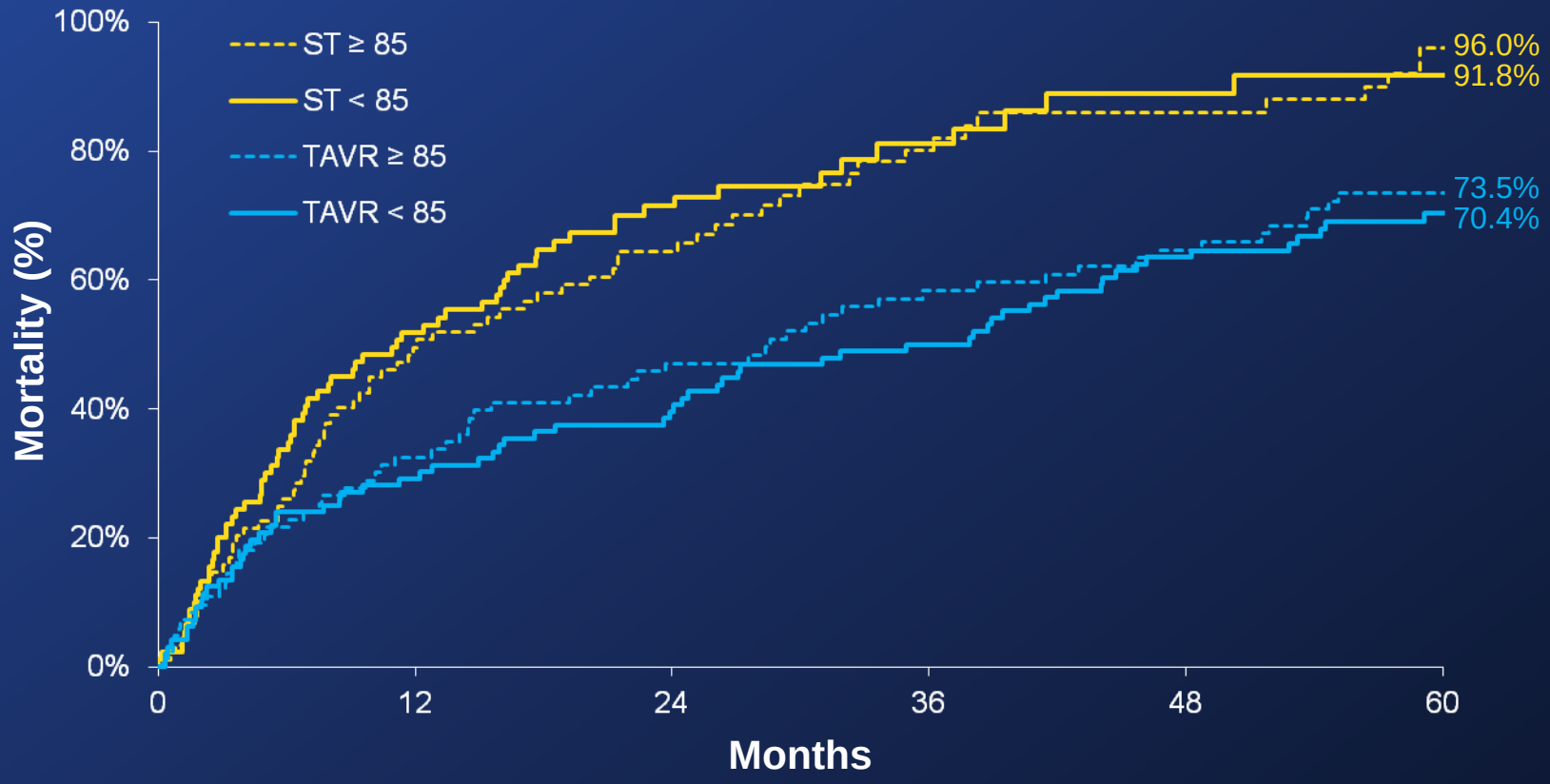
Cardiovascular Mortality Stratified by STS Score (ITT)



Numbers at Risk

Standard Rx	12	7	5	0	0	0	123	61	33	15	9	2	43	17	8	4	2	1
TAVR	28	25	21	18	15	10	113	79	65	50	36	19	38	20	15	16	12	6

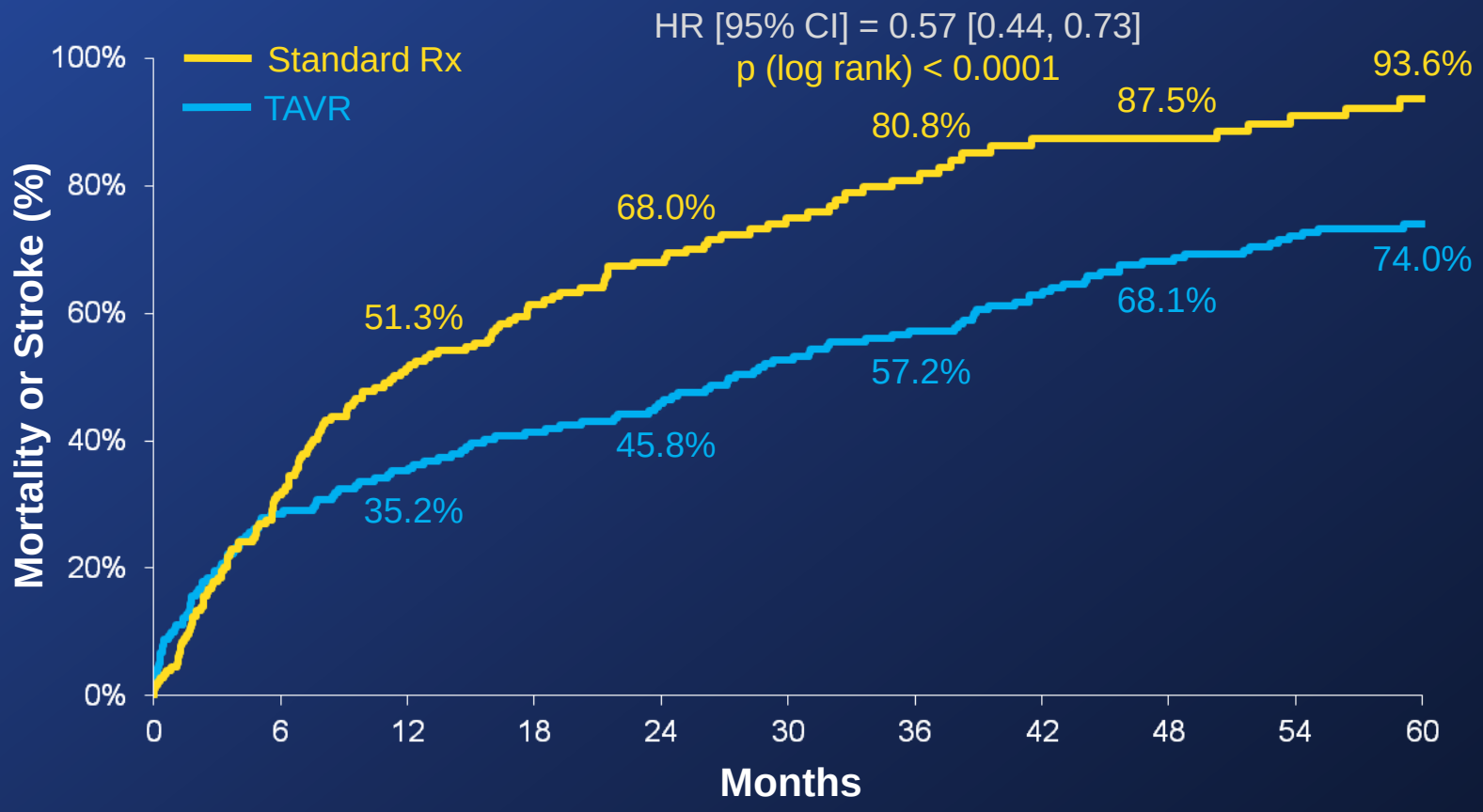
TAVR Mortality Stratified by Age (ITT)



Numbers at Risk

ST ≥ 85	89	43	27	11	7	1
ST < 85	90	42	19	8	4	2
TAVR ≥ 85	83	56	43	33	28	16
TAVR < 85	96	68	58	48	35	19

Mortality or Stroke (ITT)



Numbers at Risk

Standard Rx	**179**	**118**	**84**	**62**	**46**	**27**	**19**	**11**	**11**	**8**	**3**
TAVR	**179**	**128**	**116**	**105**	**96**	**83**	**75**	**65**	**56**	**48**	**34**