PARTNER Percutaneous TAVR: What Have We Learned?

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NewYork-Presbyterian

Presenter Disclosure Information for TCTAP 2011; April 27-29, 2011

Martin B. Leon, M.D.

NON-PAID Consultant:
Edwards Lifesciences, Medtronic

Consultant:
Symetis

Equity Relationship:
Claret, Sadra

Dr. Alain Cribier

First-in-Man PIONEER

Circulation
JOURNAL OF THE AMERICAN HEART ASSOCIATION
American Heart Association
Learn and Live

Percutaneous Transcatheter Implantation of an Aortic Valve Prosthesis for Calcific Aortic Stenosis

First Human Case Description

Alain Cribier, MD; Helene Eltchaninoff, MD; Assaf Bash, PhD; Nicolas Borenstein, MD; Christophe Tron, MD; Fabrice Bauer, MD; Genevieve Derumeaux, MD; Frederic Anselme, MD; François Laborde, MD; Martin B. Leon, MD

Conclusions— Nonsurgical implantation of a prosthetic heart valve can be successfully achieved with immediate and midterm hemodynamic and clinical improvement.

April 16, 2002

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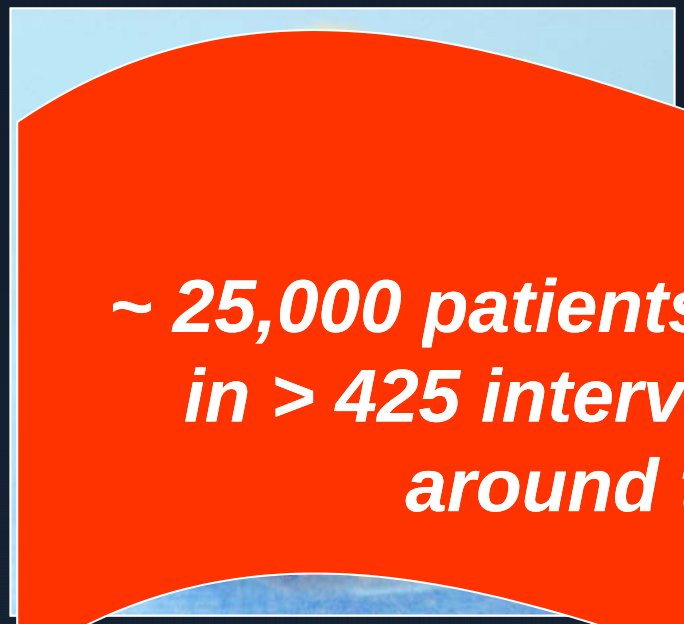
TAVR Technologies

Current Generation Devices



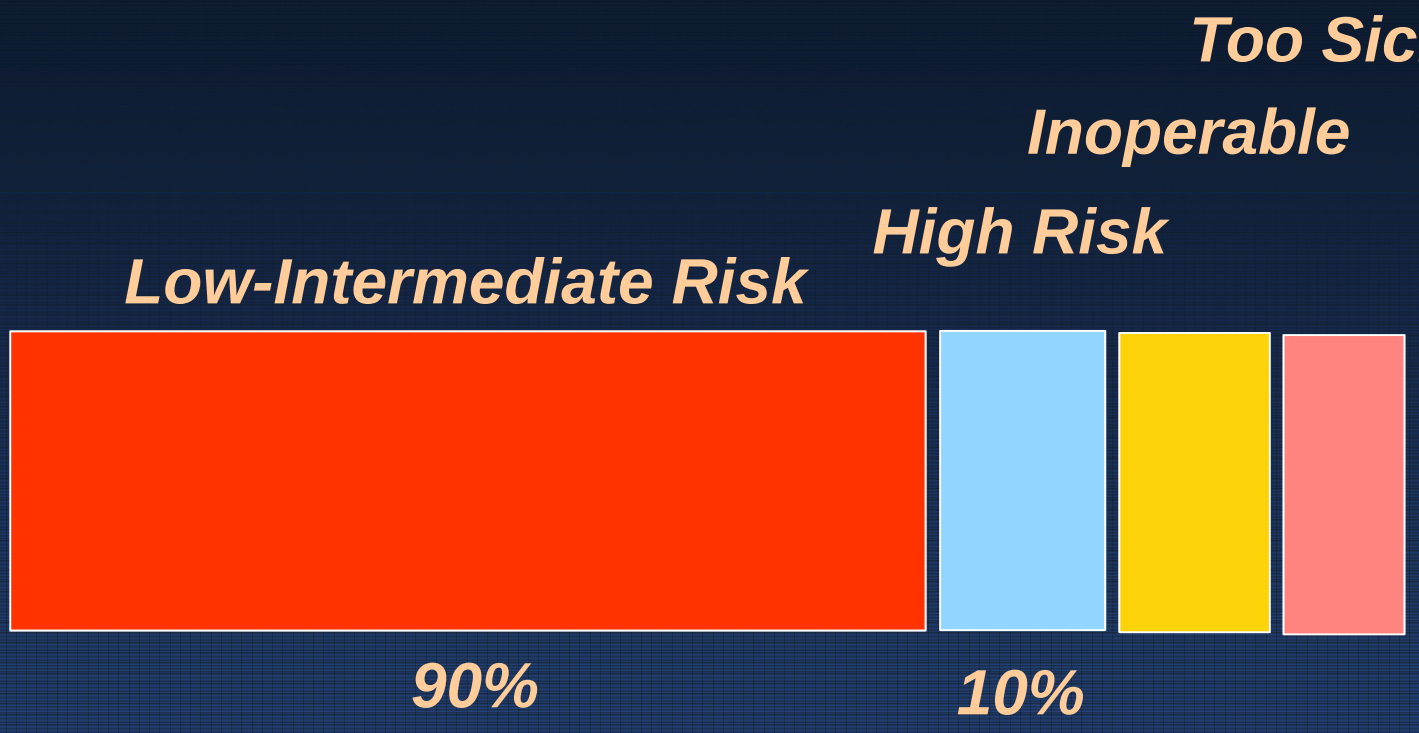
~ 25,000 patients treated thru 2010 in > 425 interventional centers around the world!

Edwards Lifesciences

ative

TAVR Categories
(risk is a continuum)

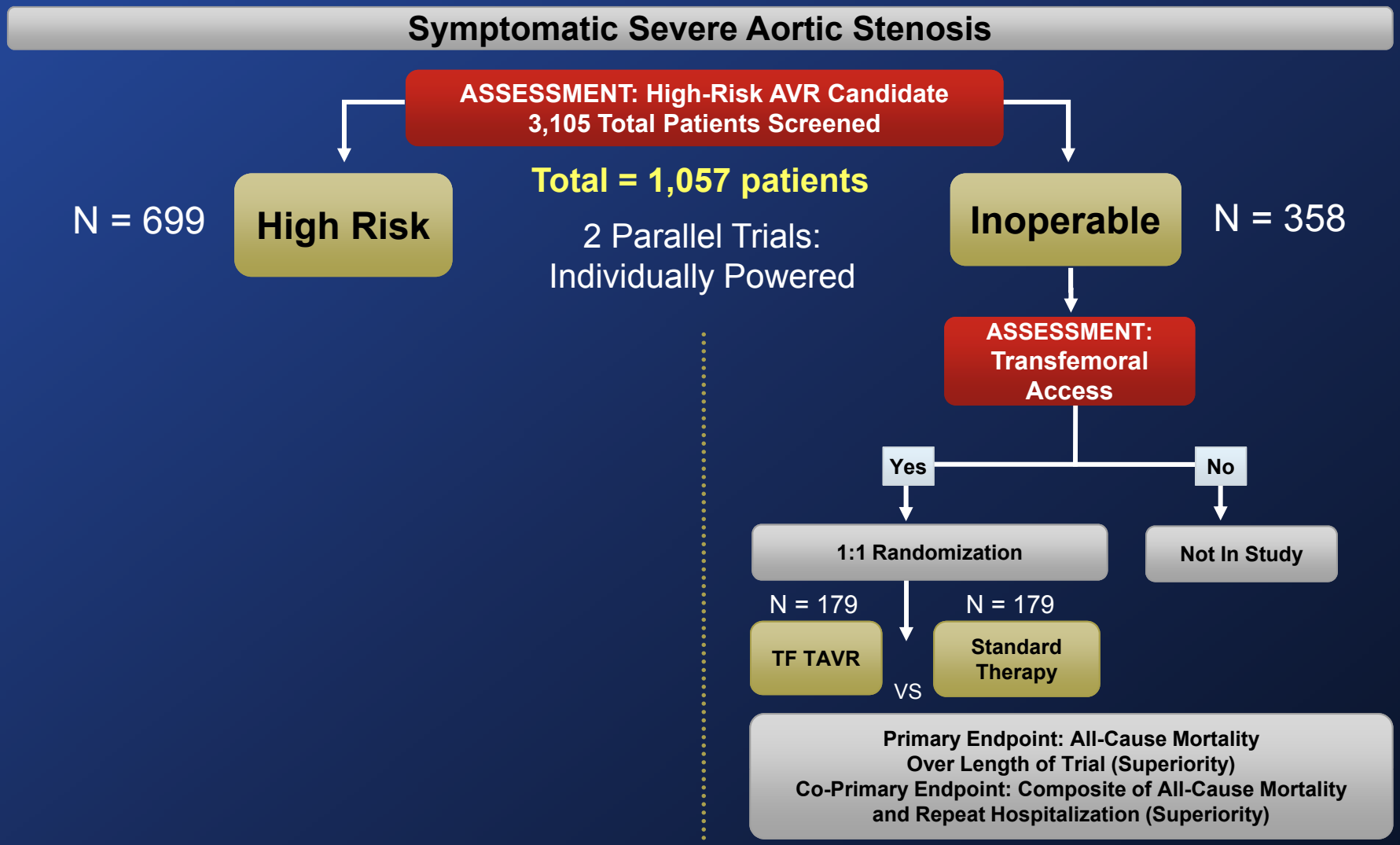
Operable AS patients



TAVR 2011 - PARTNER

Study Design

PARTNER Study Design



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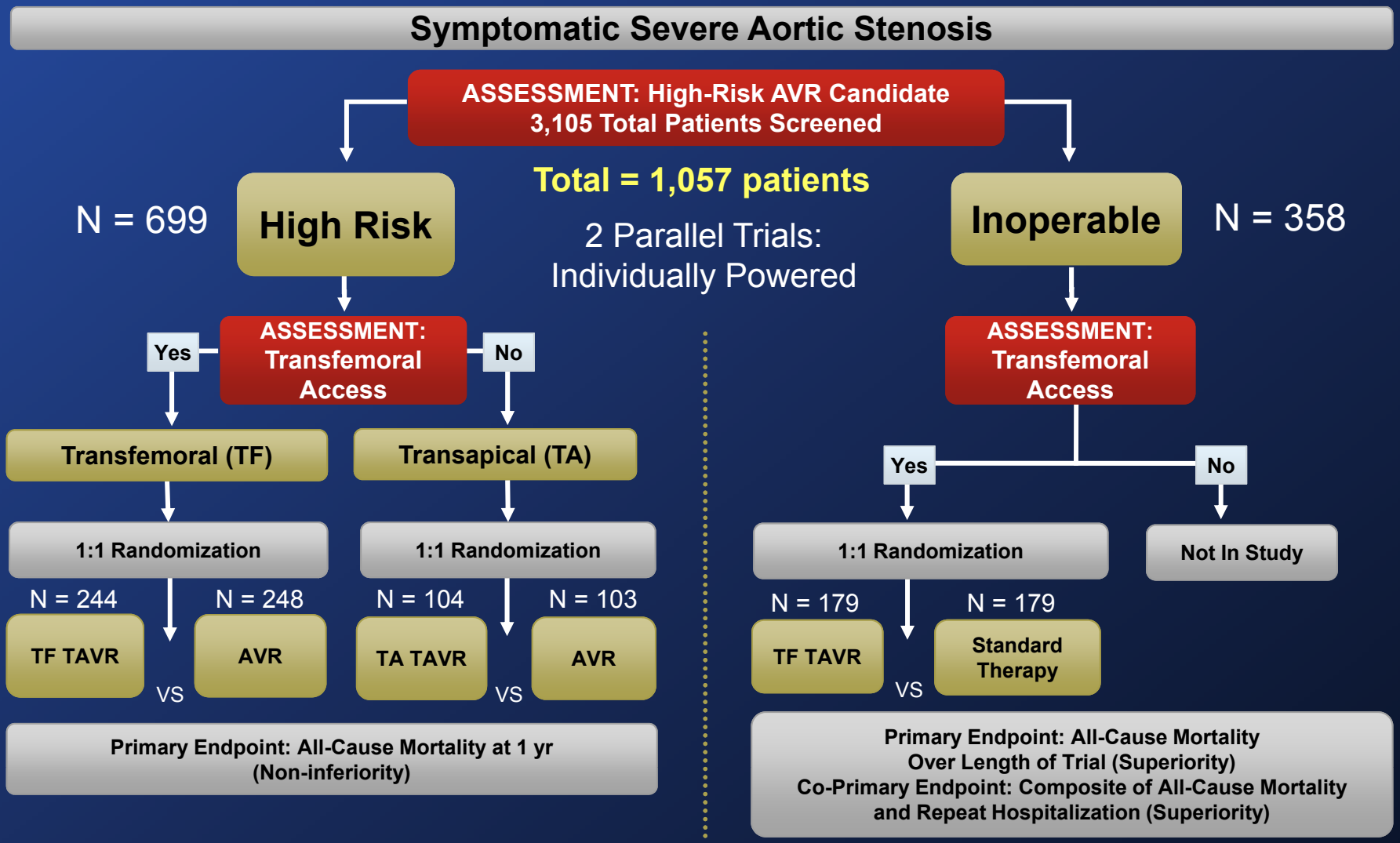
The NEW ENGLAND JOURNAL of MEDICINE

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*

On behalf of the Executive Committee, the Investigator Sites, and the courageous patients who participated in the PARTNER trial!

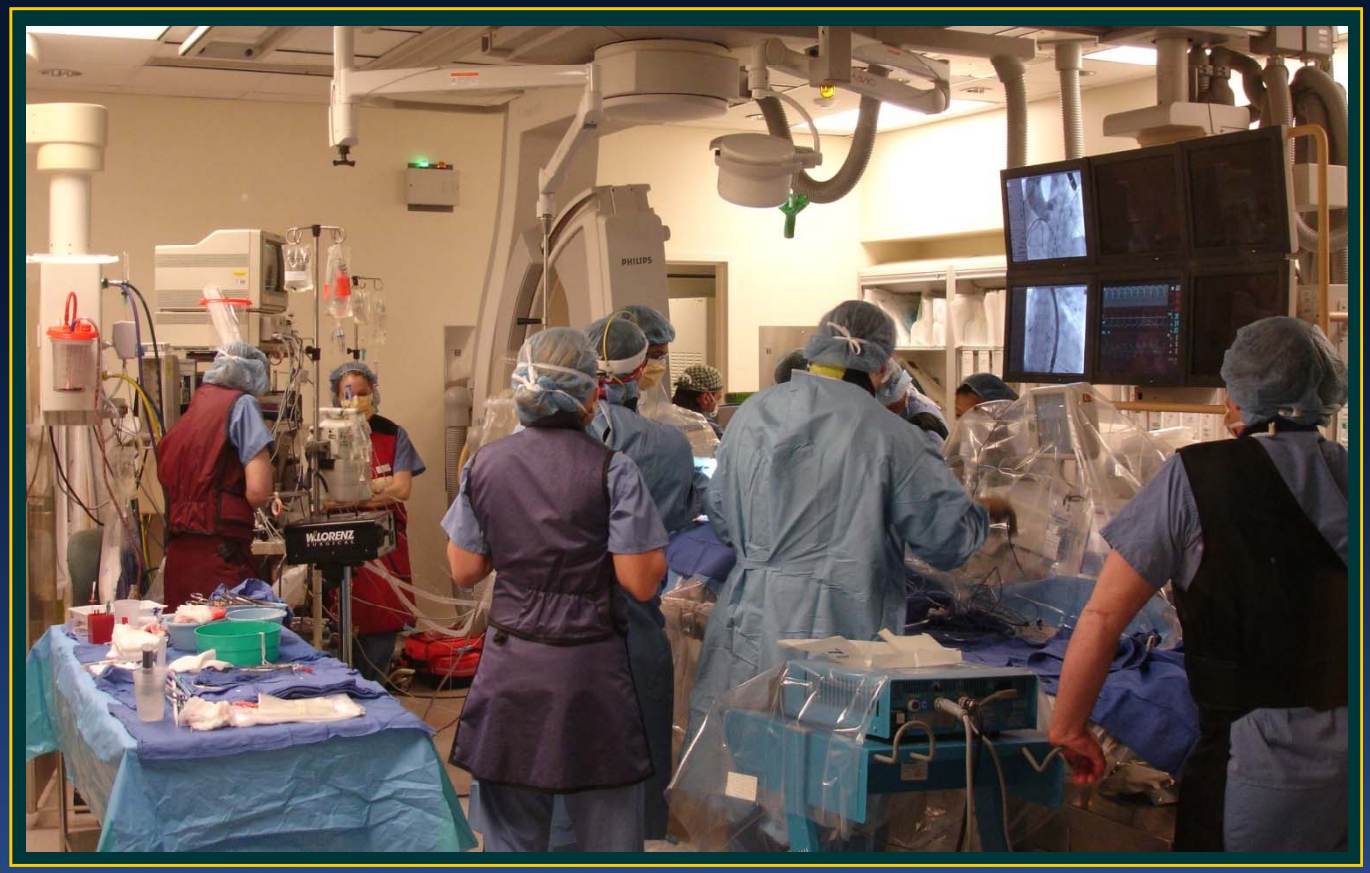
PARTNER Study Design



Executive Committee

Jeff Moses Marty Leon John Webb Michael Mack

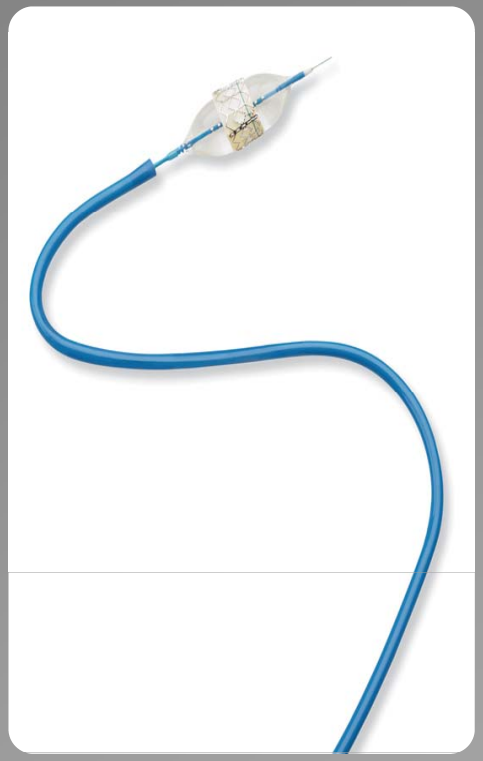
Transcatheter AVR
Hybrid OR-Cath Lab



A unique collaborative experience!

Study Devices

Edwards SAPIEN THV
23 and 26 mm valves



RetroFlex
22 and 24 F sheaths

Ascendra
24 and 26 F sheaths

Primary Endpoint

- *Inoperable cohort: All-cause mortality over the duration of the trial (superiority vs. standard Rx)*
- *High surgical risk cohort: All-cause mortality at one year (non-inferiority vs. AVR)*
  - Analysis by intent-to-treat
  - Crossovers not permitted (except when assigned therapy unsuccessful)
  - All patients followed for ≥ one year

Inclusion Criteria

- *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 Cohort:* Risk of death or serious irreversible morbidity as assessed by cardiologist and two surgeons must exceed 50%
- *High Surgical Risk Cohort:* Predicted risk of operative mortality ≥ 15% (determined by site surgeon and cardiologist); guideline = STS score ≥ 10

TAVR 2011 - PARTNER

Lessons Learned

PARTNER - Lessons Learned

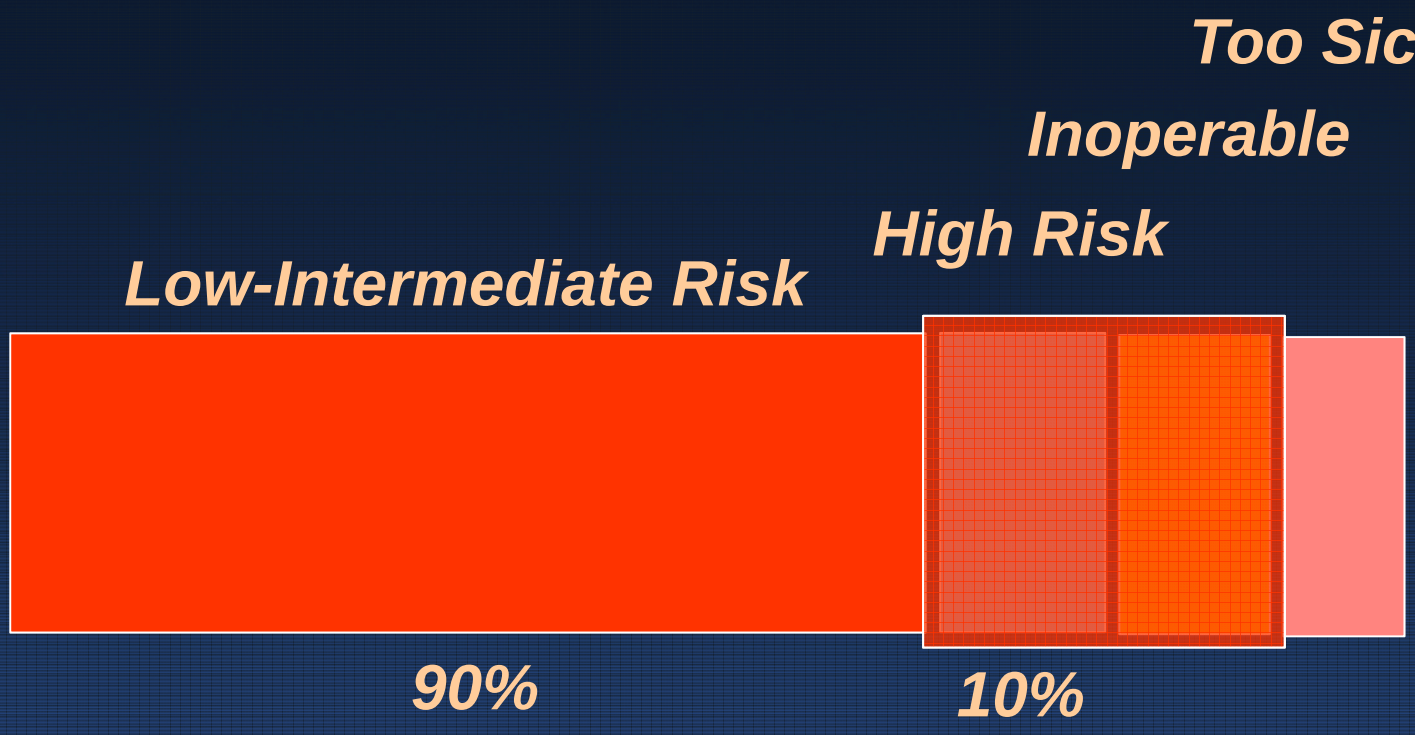
- Standard therapy for patients with severe AS and symptoms results in PROFOUND early mortality – worse than most metastatic cancers!
- The HEART VALVE TEAM approach is our model to achieve optimal TAVR clinical outcomes!
  - Multi-disciplinary physician team (including surgery)
  - Careful case screening
  - Hybrid cath lab – OR
  - Rigorous training and technique
  - Meticulous post-procedure management
- TAVR is the new standard-of-care for inoperable AS patients!

PARTNER - Lessons Learned

- TAVR is a new alternative for “high risk” operable AS patients (similar early and late mortality)
- Peri-procedural hazards are different with TAVR vs. AVR
  - Increased strokes, vascular complications, and para-valvular regurgitation after TAVR
  - Increased bleeding and new onset AF after AVR
- Future expanded clinical indications for TAVR and expected reduction in complications with improved technique and further device evolution!

TAVR Categories
(risk is a continuum)

Operable AS patients



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Main Outcomes: Inoperable

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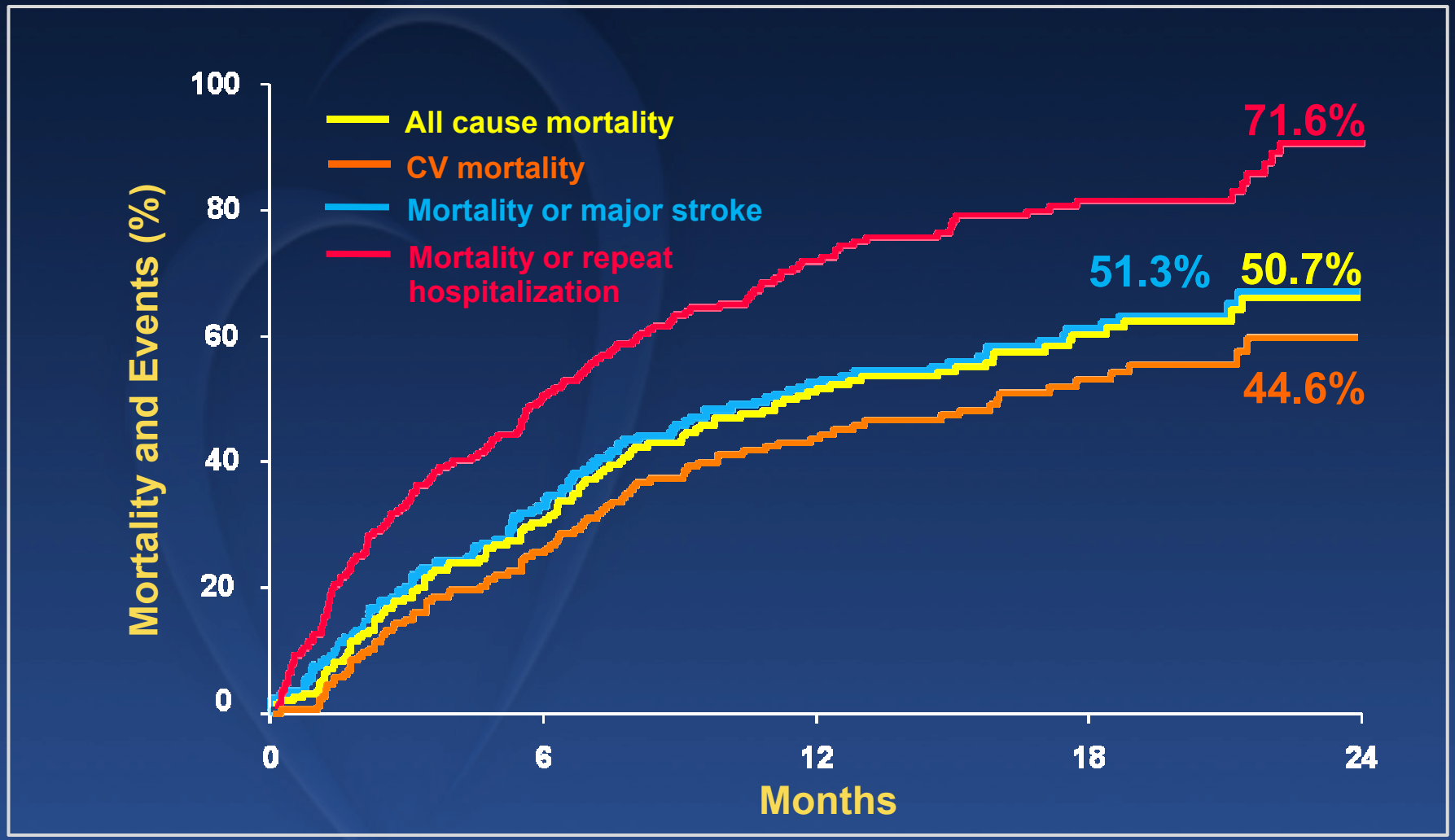
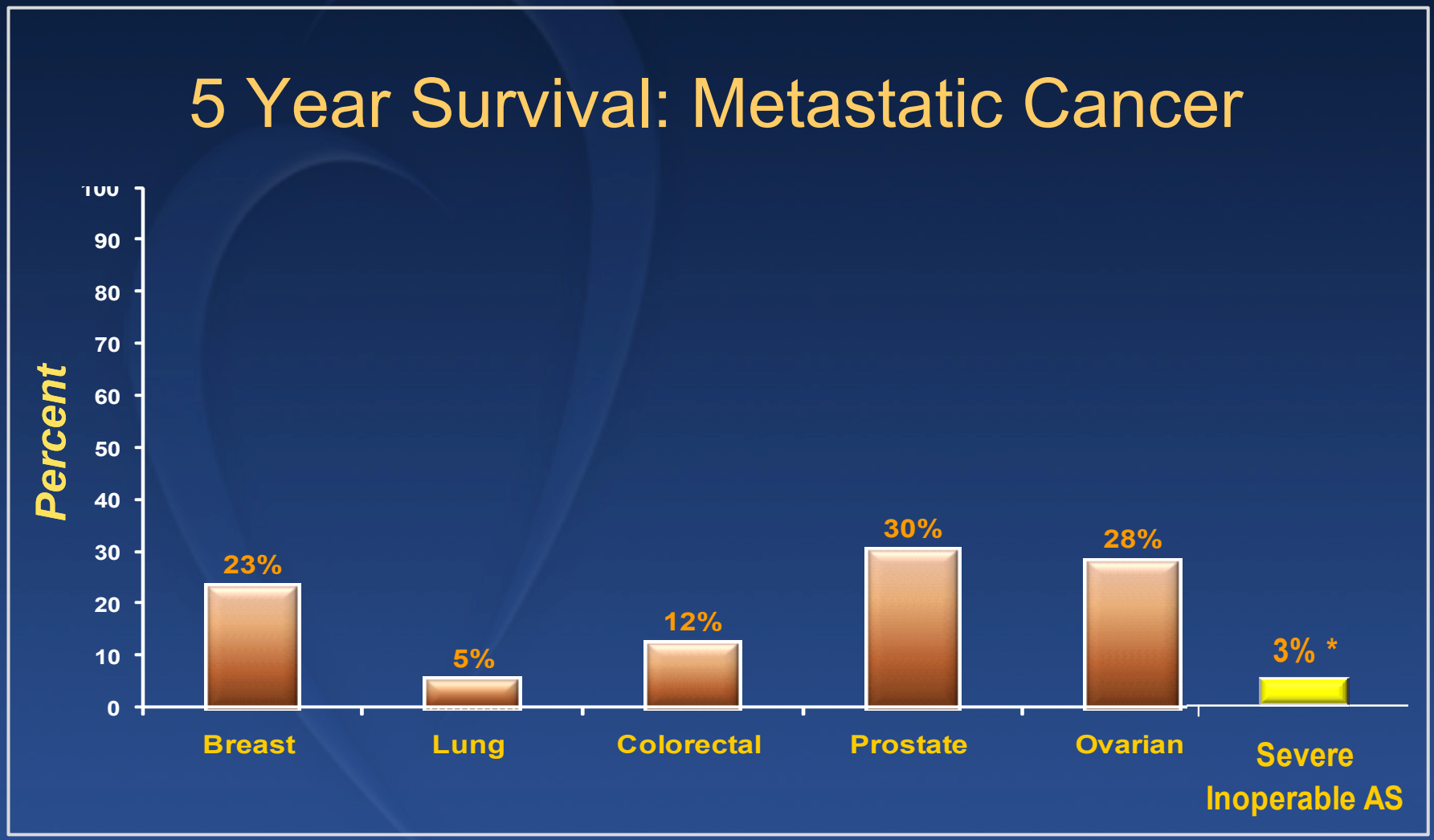
Standard Therapy Outcomes



Mortality in Standard Rx

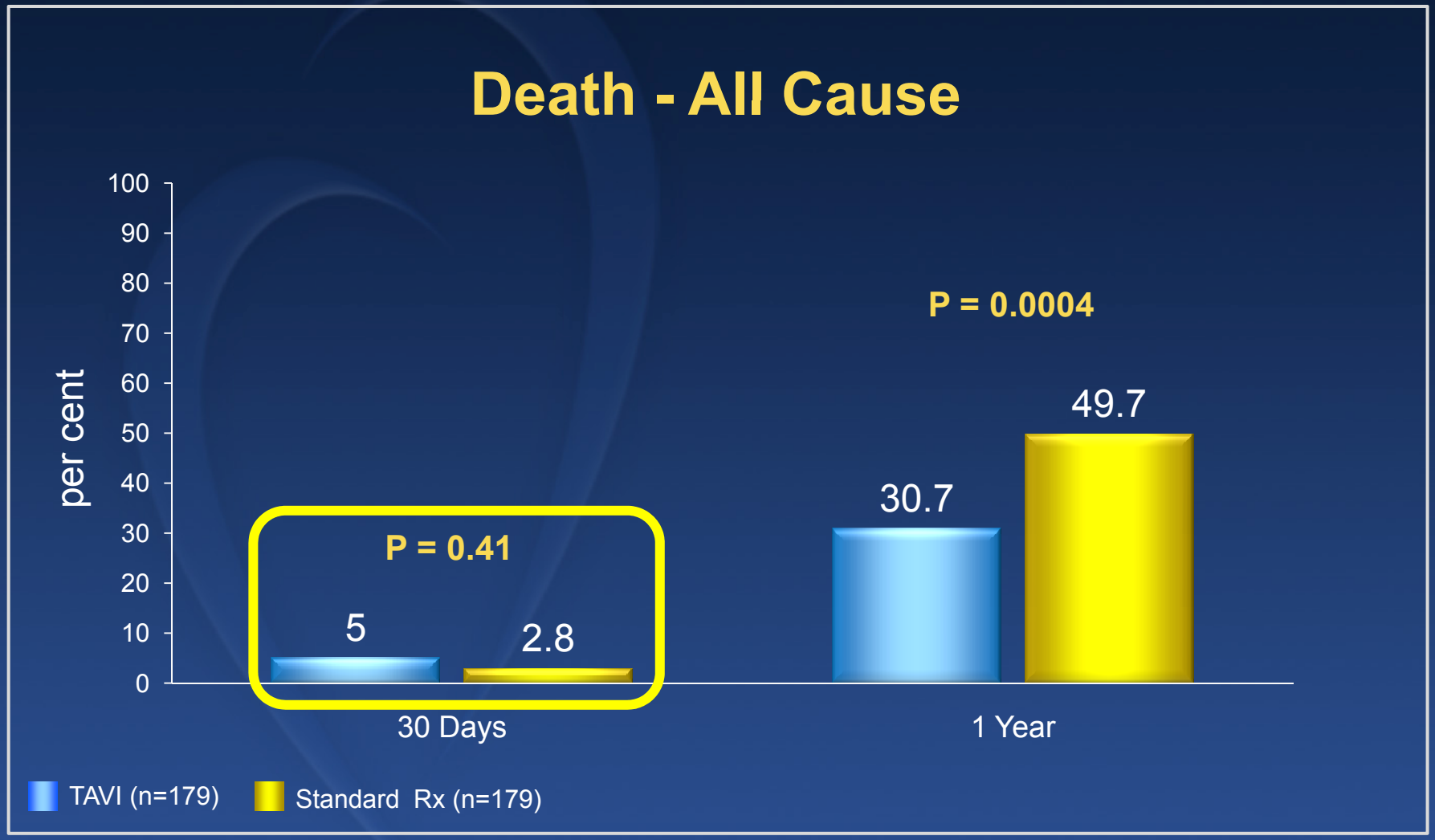
Perspectives



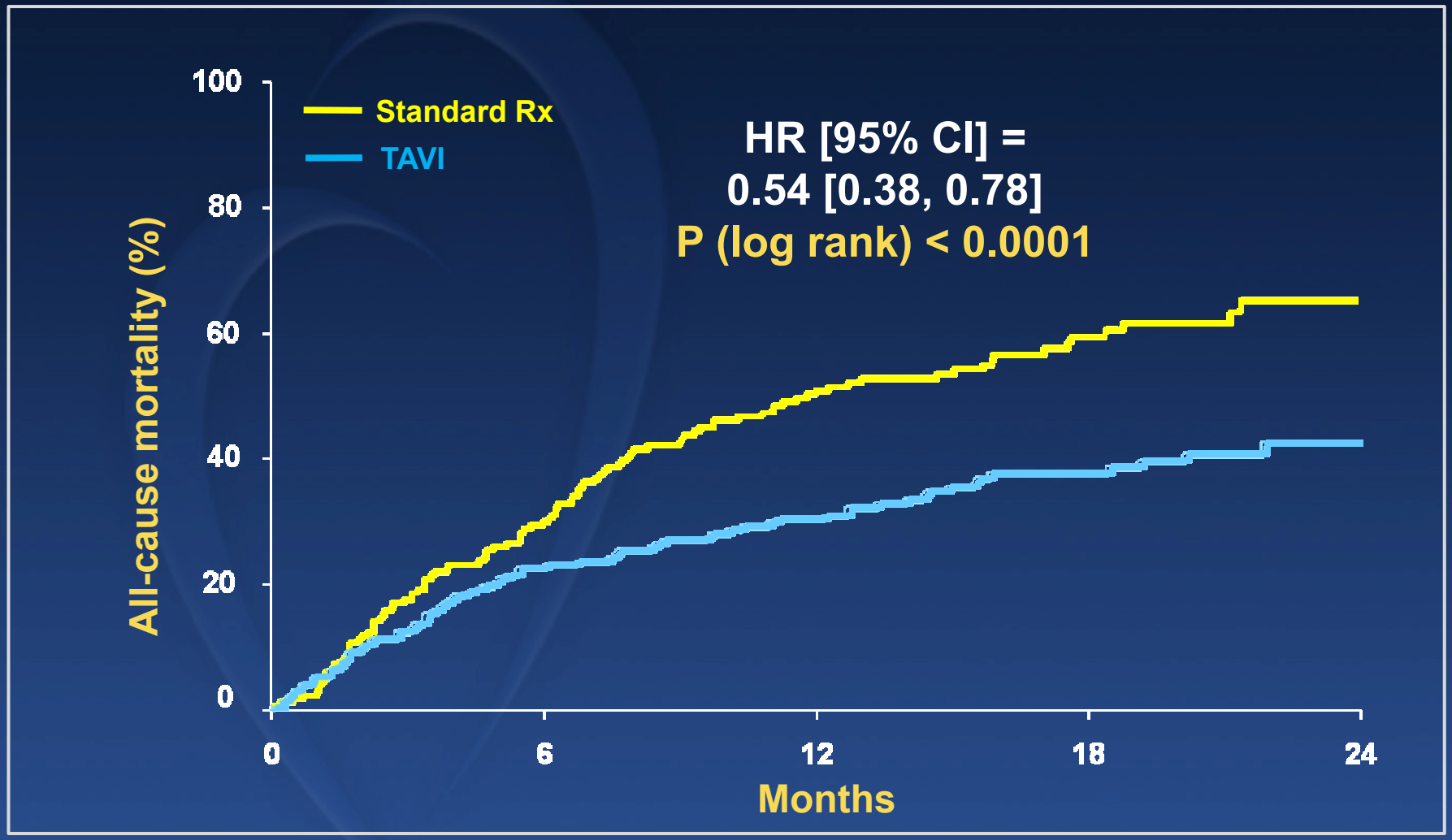
Courtesy of Murat Tuzcu, Interventional PI, CCF

** Constant Hazard Model*

Clinical Outcomes at 30 Days and 1 Year

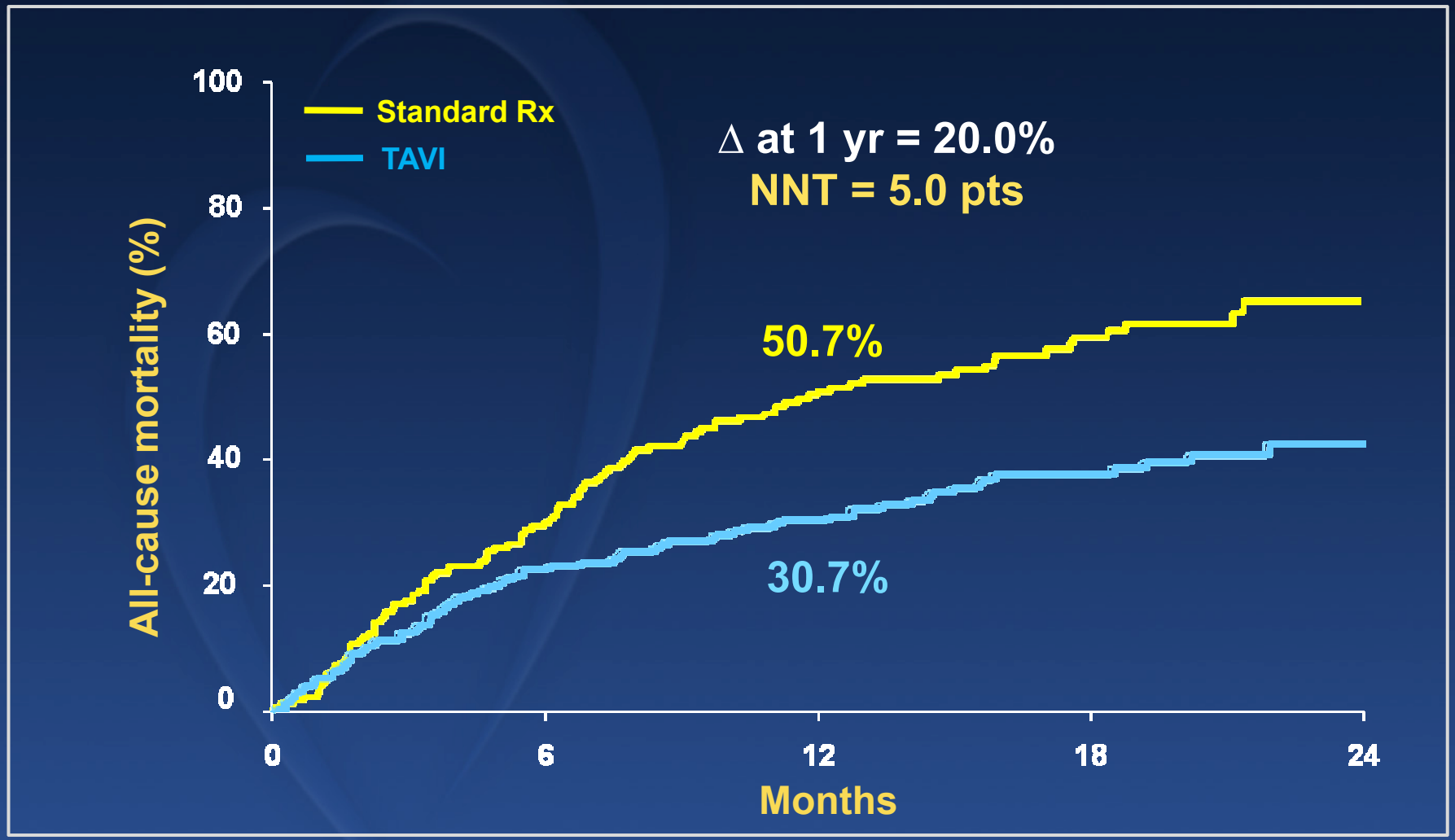


1ry Endpt - All Cause Mortality



Numbers at Risk					
TAVI	179	138	122	67	26
Standard Rx	179	121	83	41	12

1ry Endpt - All Cause Mortality



Numbers at Risk					
TAVI	179	138	122	67	26
Standard Rx	179	121	83	41	12

5 Medical Therapies Proven to Reduce Death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Published by Elsevier Inc.

Using Measures of Disease Progression to Determine Therapeutic Effect

A Sirens' Song

Christopher B. Granger, MD, FACC,* John J. V. McMurray, MD, FACC†

Durham, North Carolina; and Glasgow, Scotland

Conclusion: **"Large clinical outcome trials must remain the basis for informing clinicians on which treatments improve clinical outcomes."**

Therapy	Indication	# pts	Reduction in deaths	
			Relative	Absolute
Aspirin	MI	18,773	23%	2.4%
Fibrinolytics	MI	58,000	18%	1.8%
Beta blocker	MI	28,970	13%	1.3%
ACE inhibitor	MI	101,000	6.5%	0.6%
Aspirin	2nd prev	54,360	15%	1.2%
Beta blocker	2nd prev	20,312	21%	2.1%
Statins	2nd prev	17,617	23%	2.7%
ACE inhibitor	2nd prev	9,297	17%	1.9%

Adapted from Granger CB and McMurray JJV
JACC 2006; 48:434

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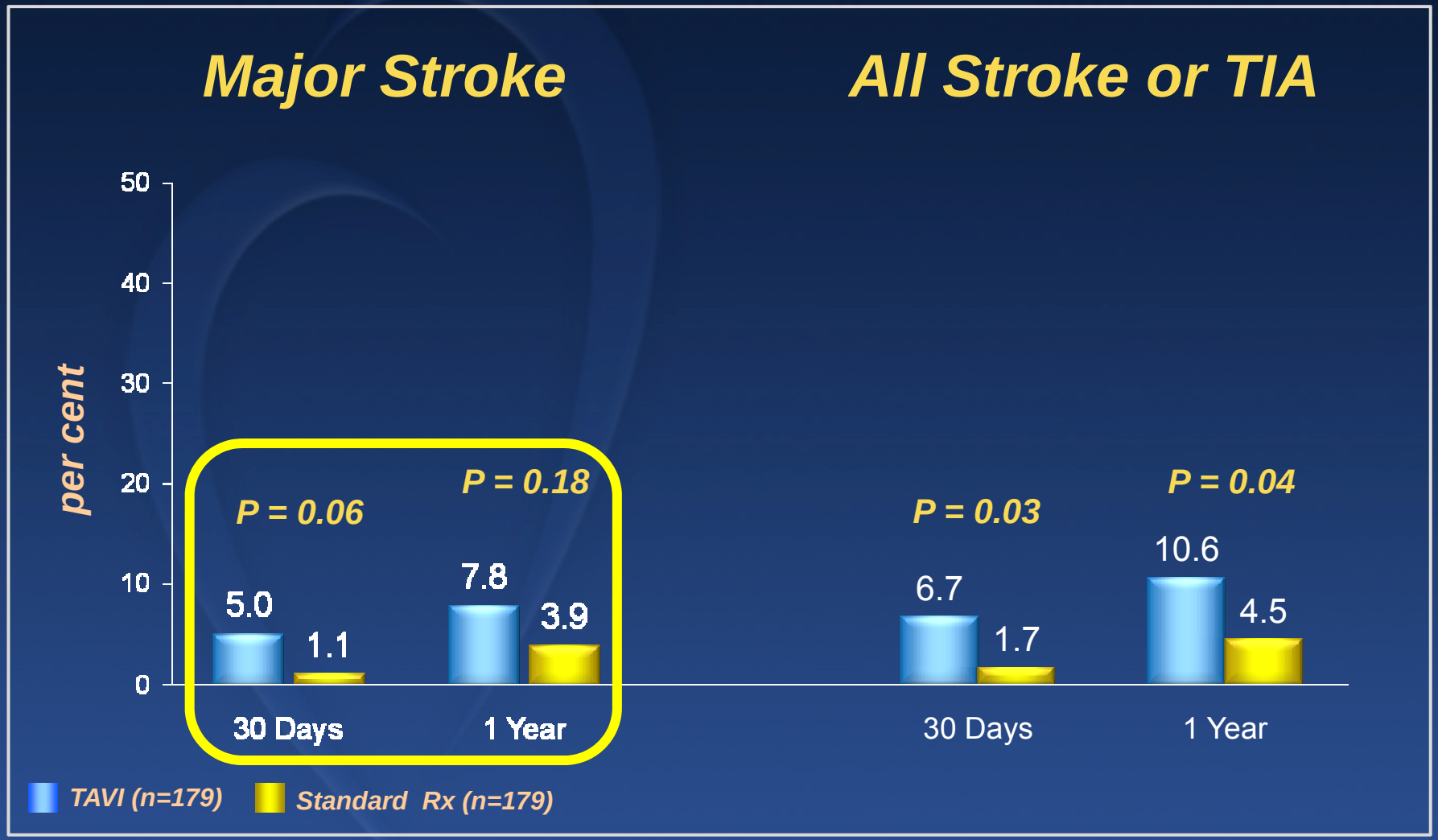
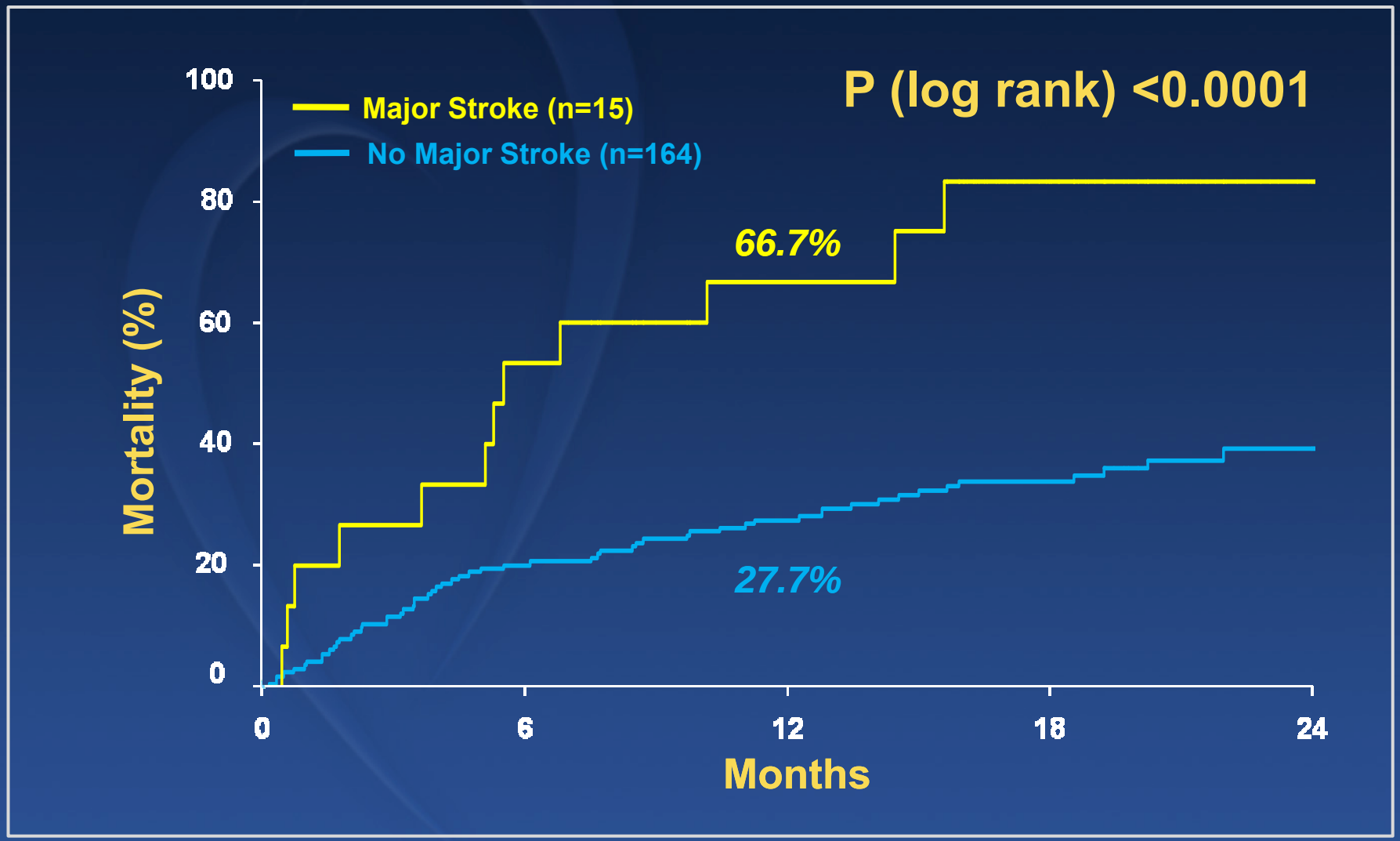
Clinical Outcomes at 30 Days and 1 Year

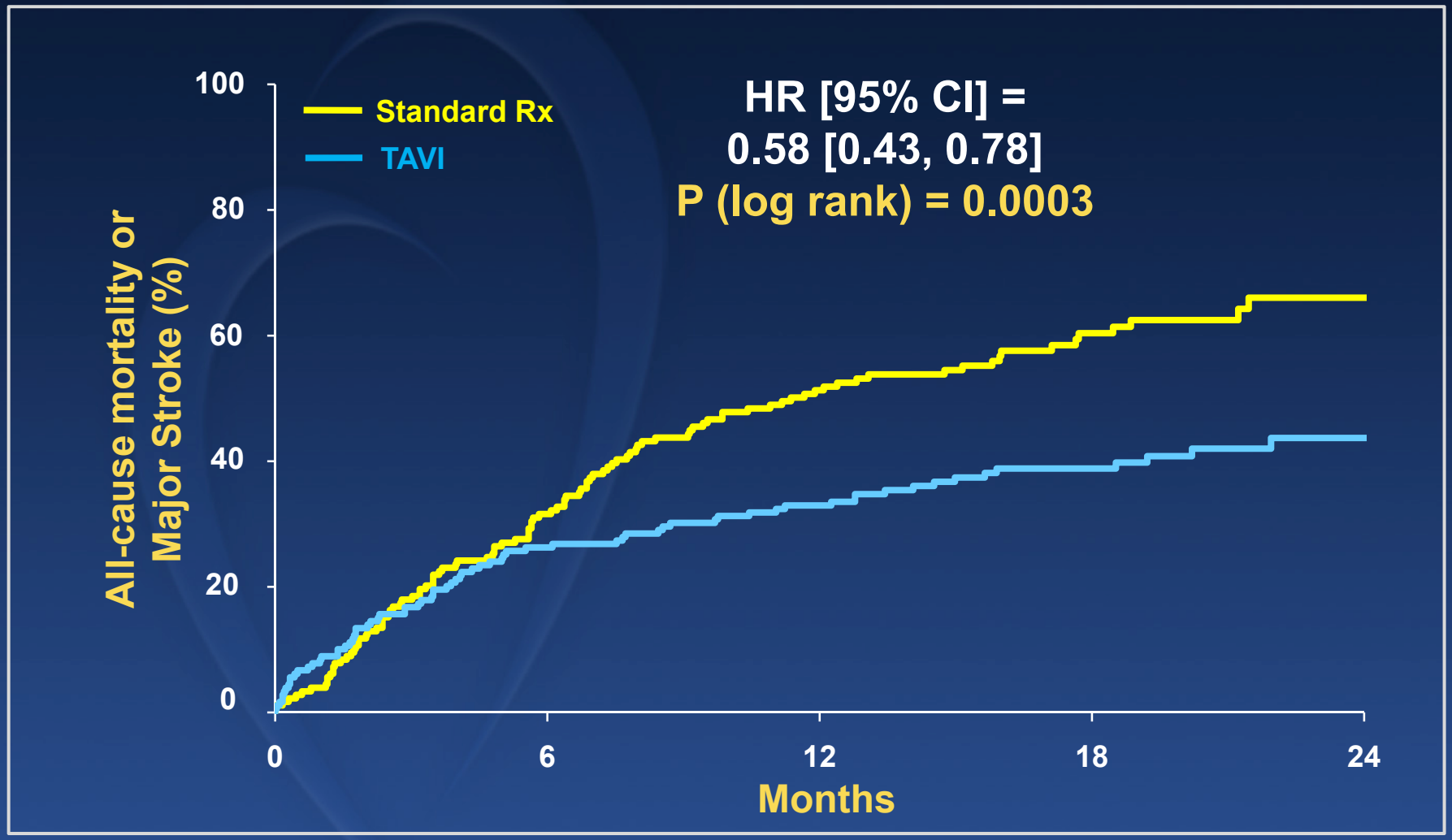


Mortality vs. Major Stroke

TAVI patients

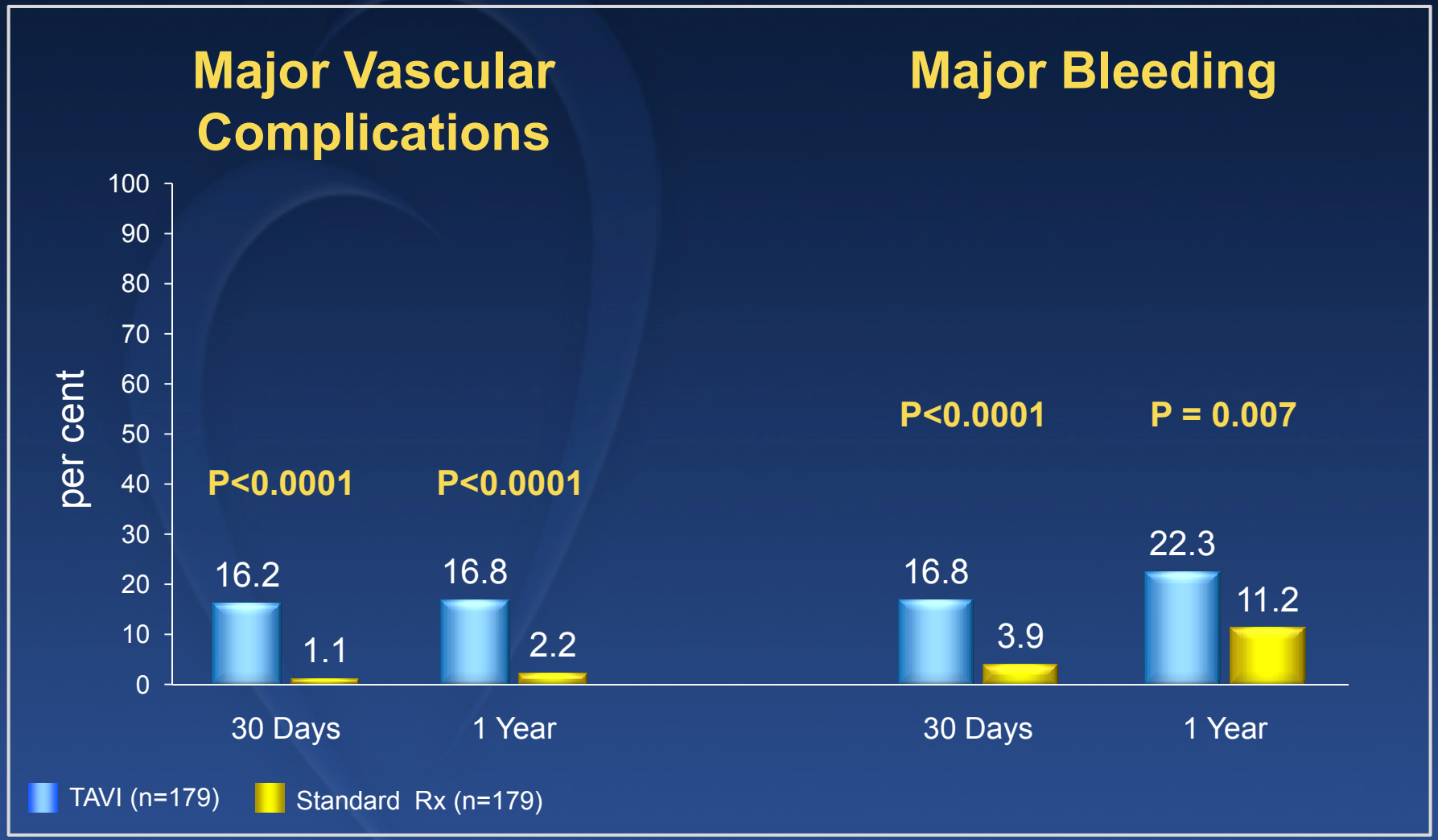


Mortality or Major Stroke

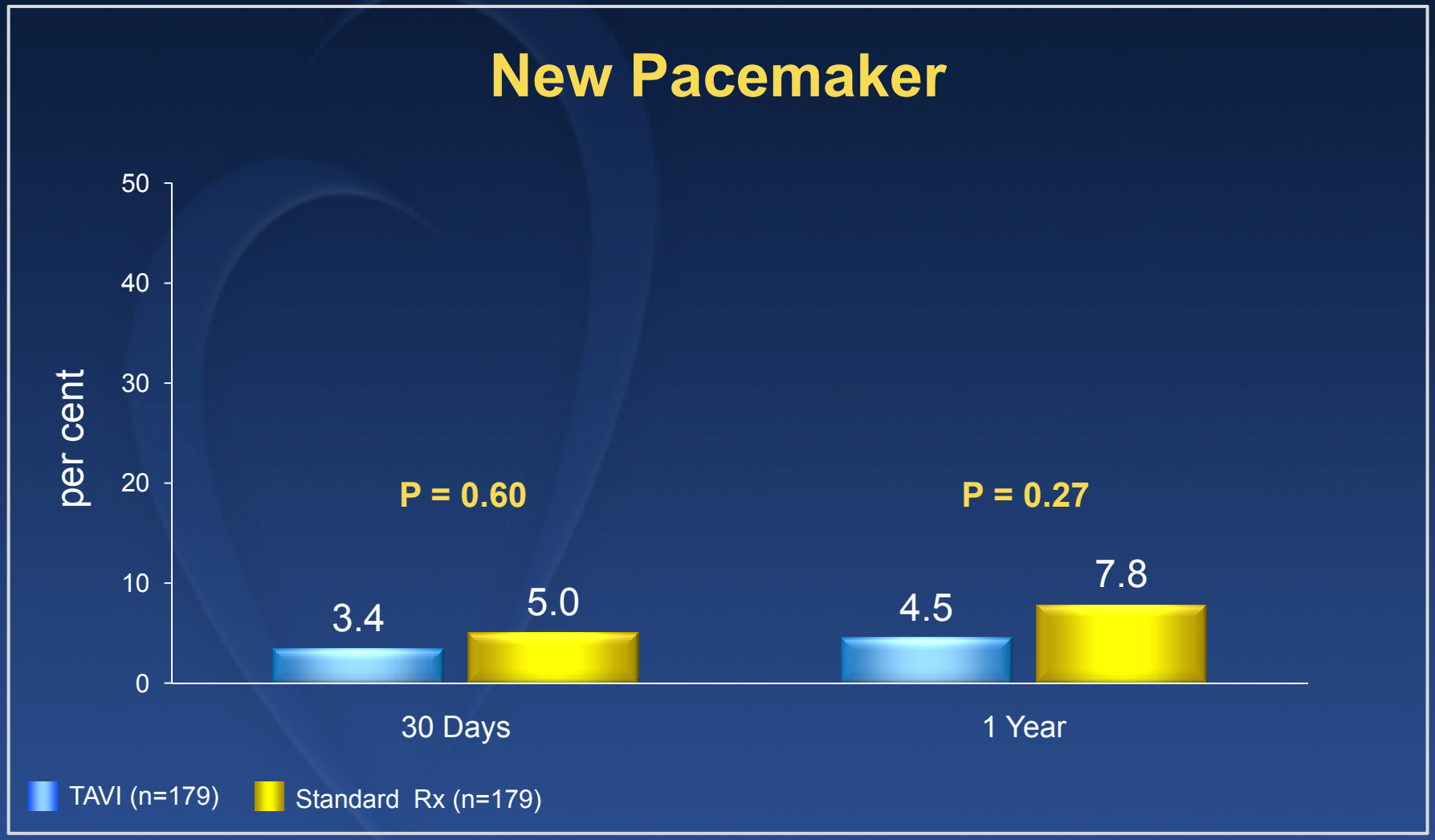


Numbers at Risk					
TAVI	179	132	118	56	25
Standard Rx	179	118	83	41	12

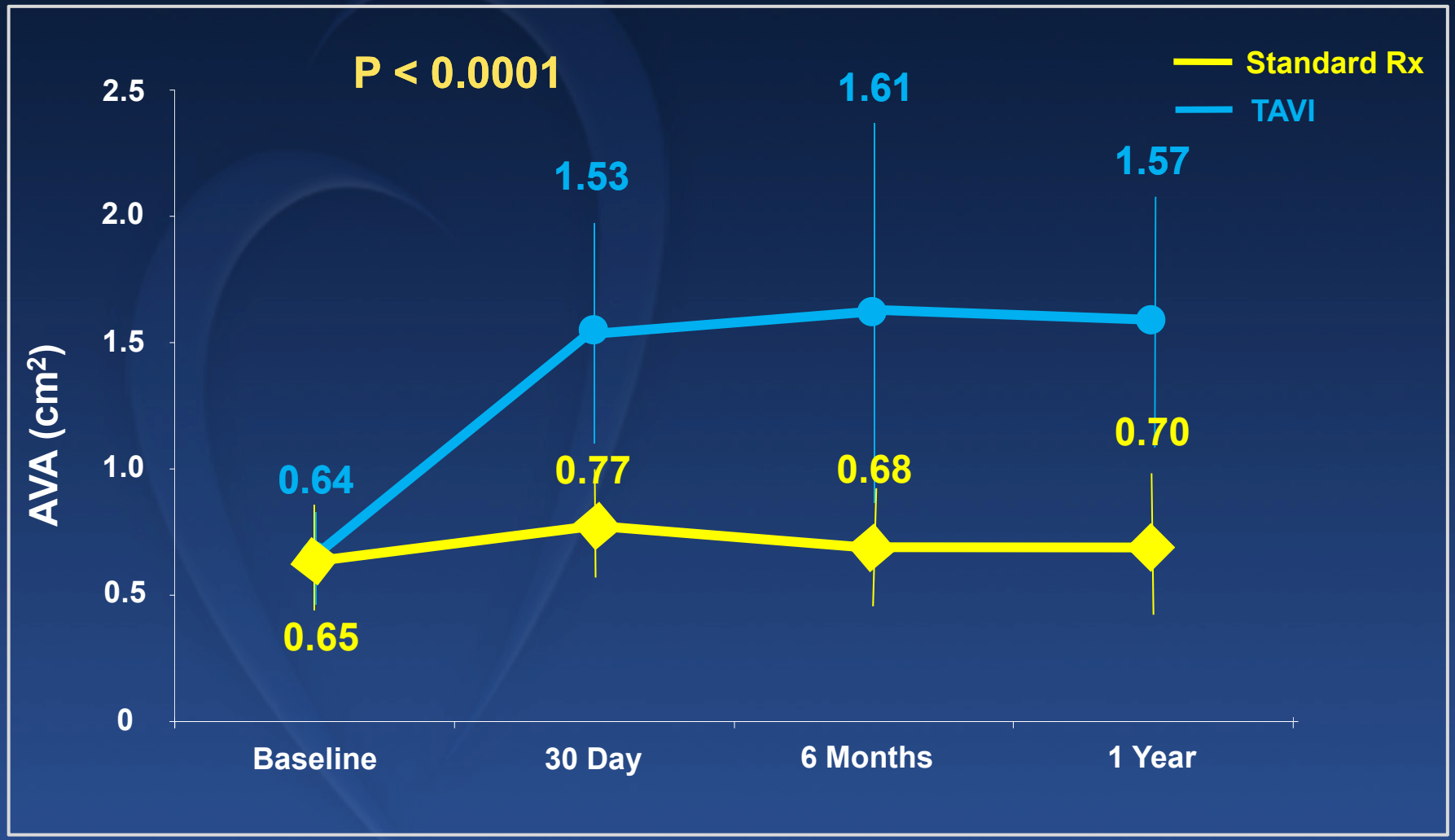
Clinical Outcomes at 30 Days and 1 Year



Clinical Outcomes at 30 Days and 1 Year



Aortic Valve Areas Over Time

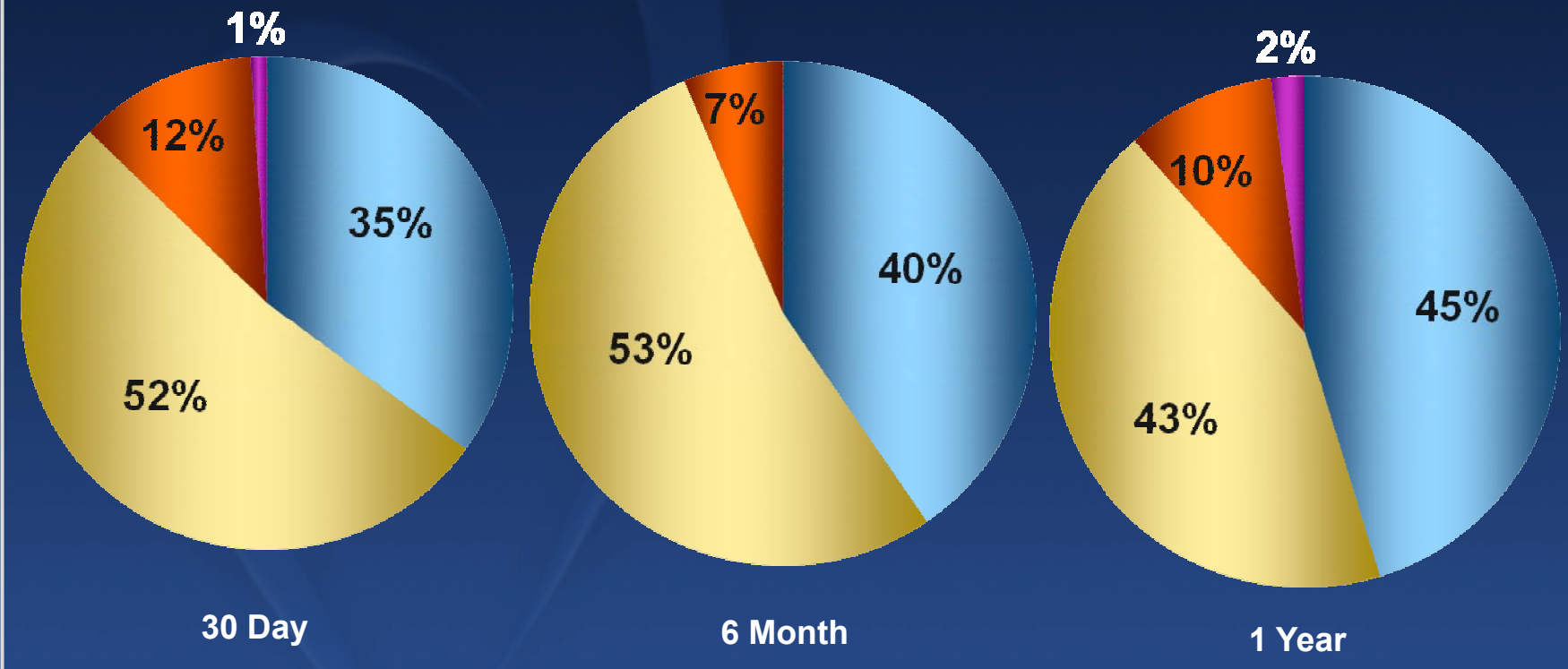


Error bars = ± 1 Std Dev

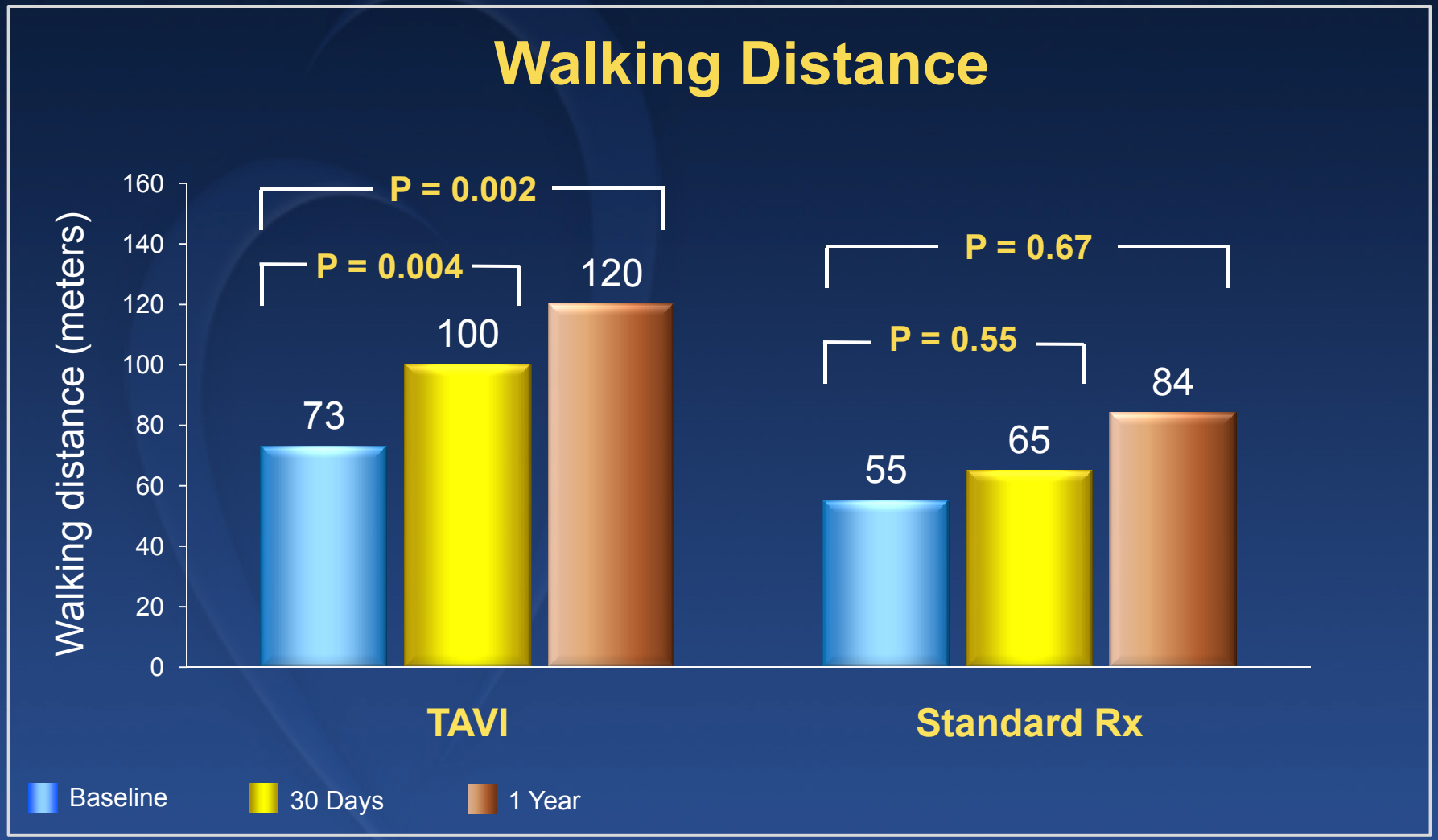
Paravalvular Regurgitation: TAVI

THE PARTNER TRIAL

No changes over time

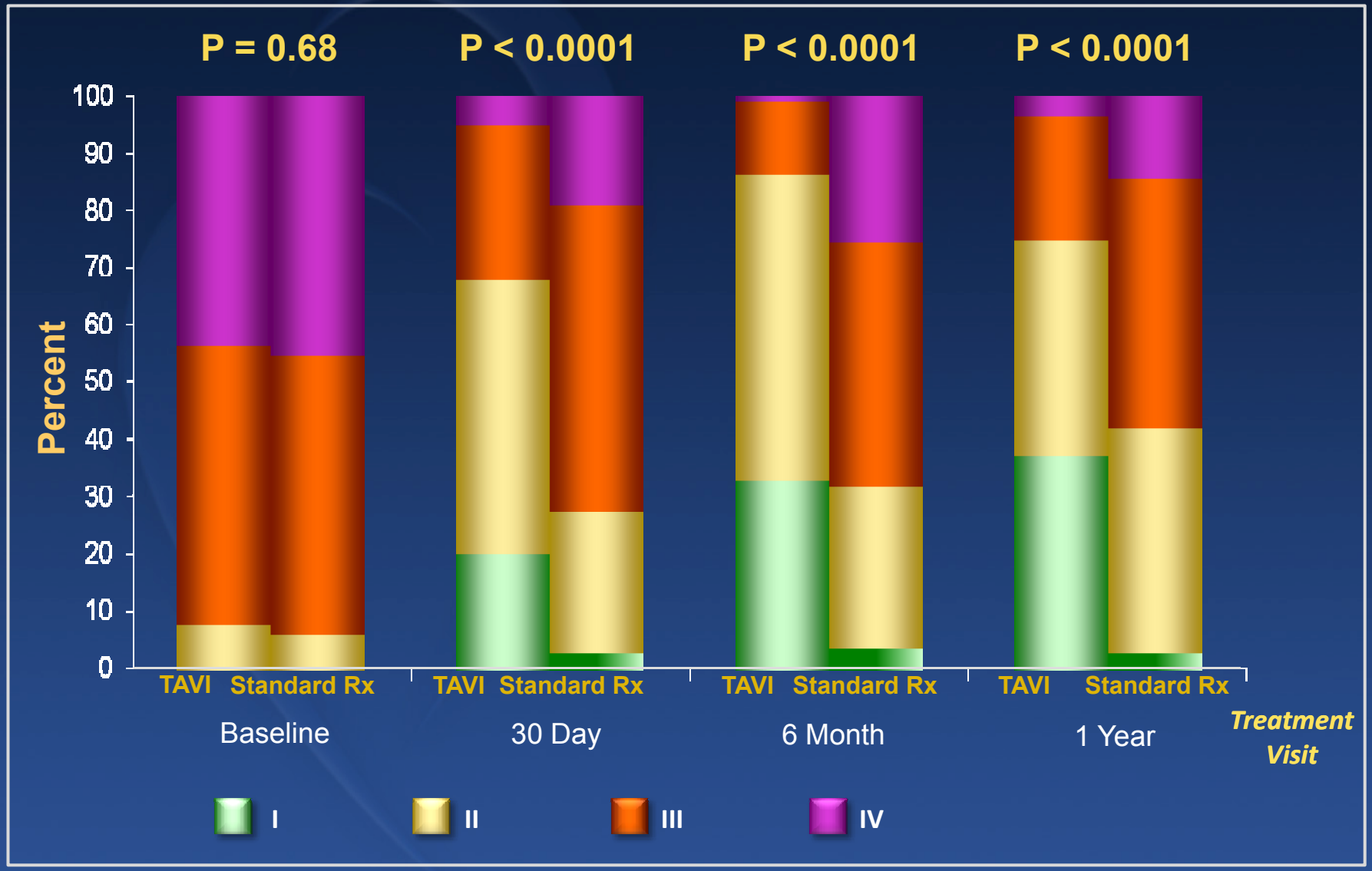


Six-Minute Walk Tests

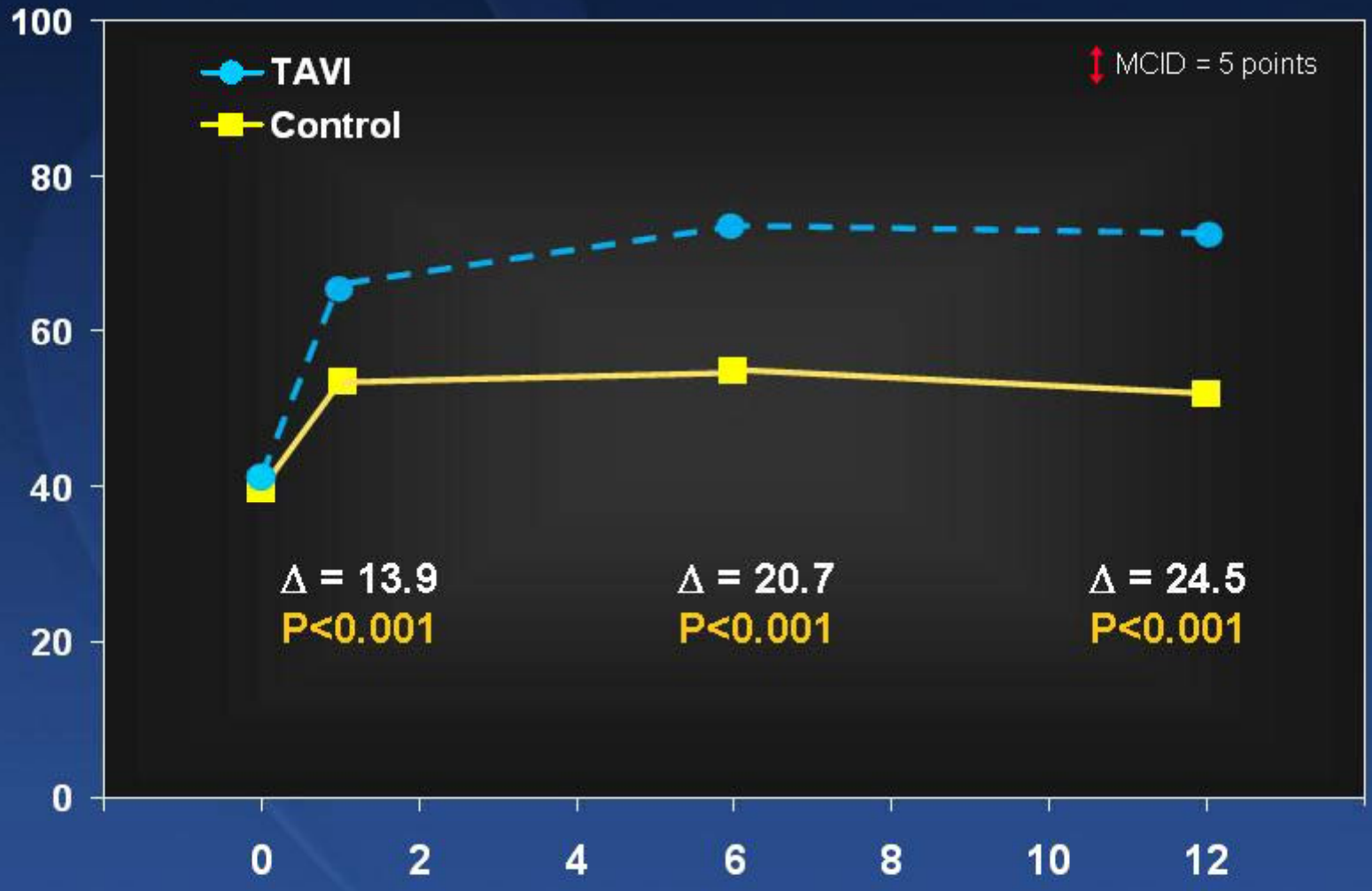


NYHA Class Over Time

Survivors



Primary Endpoint: KCCQ Overall Summary

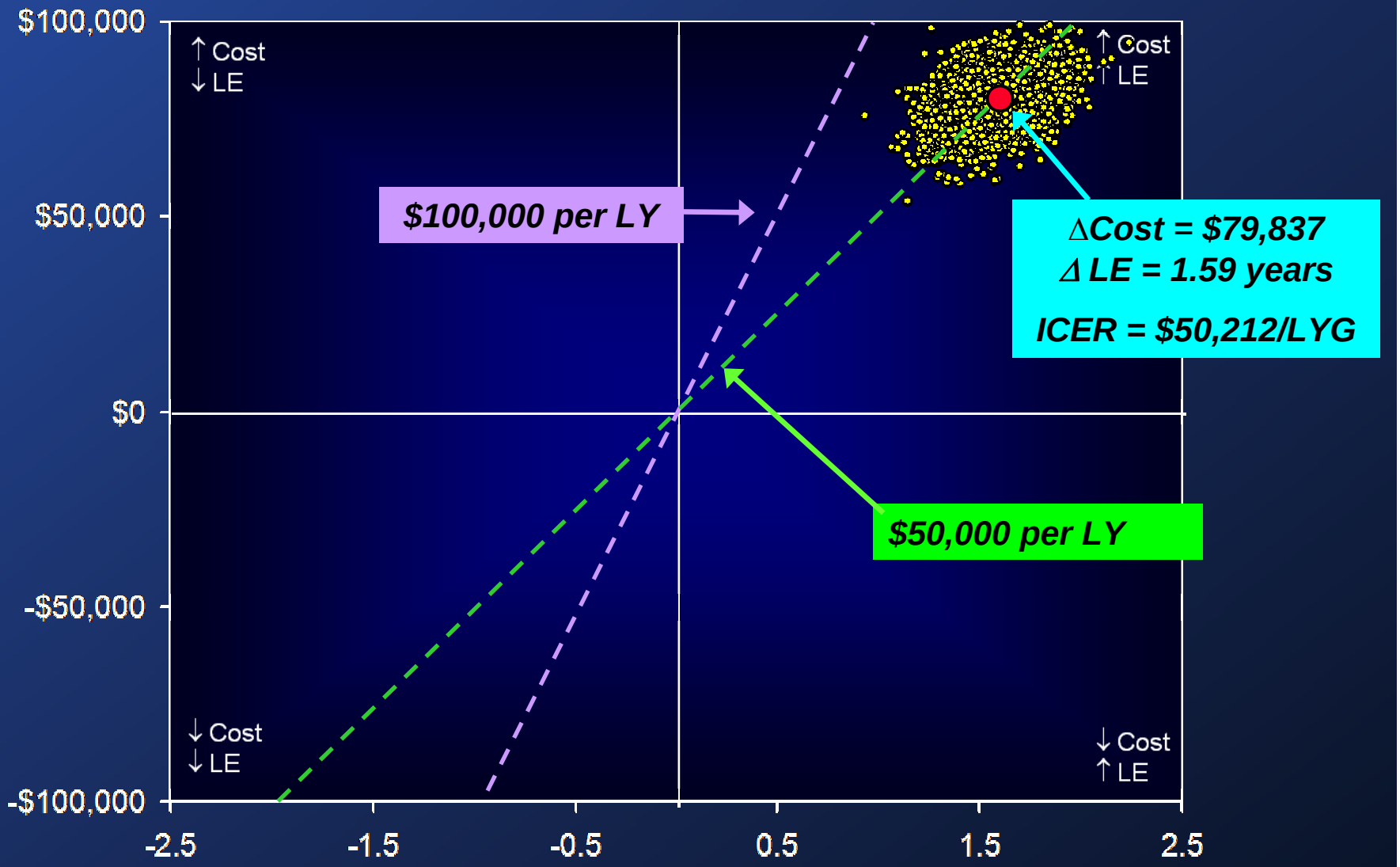


MCID = minimum clinically important difference

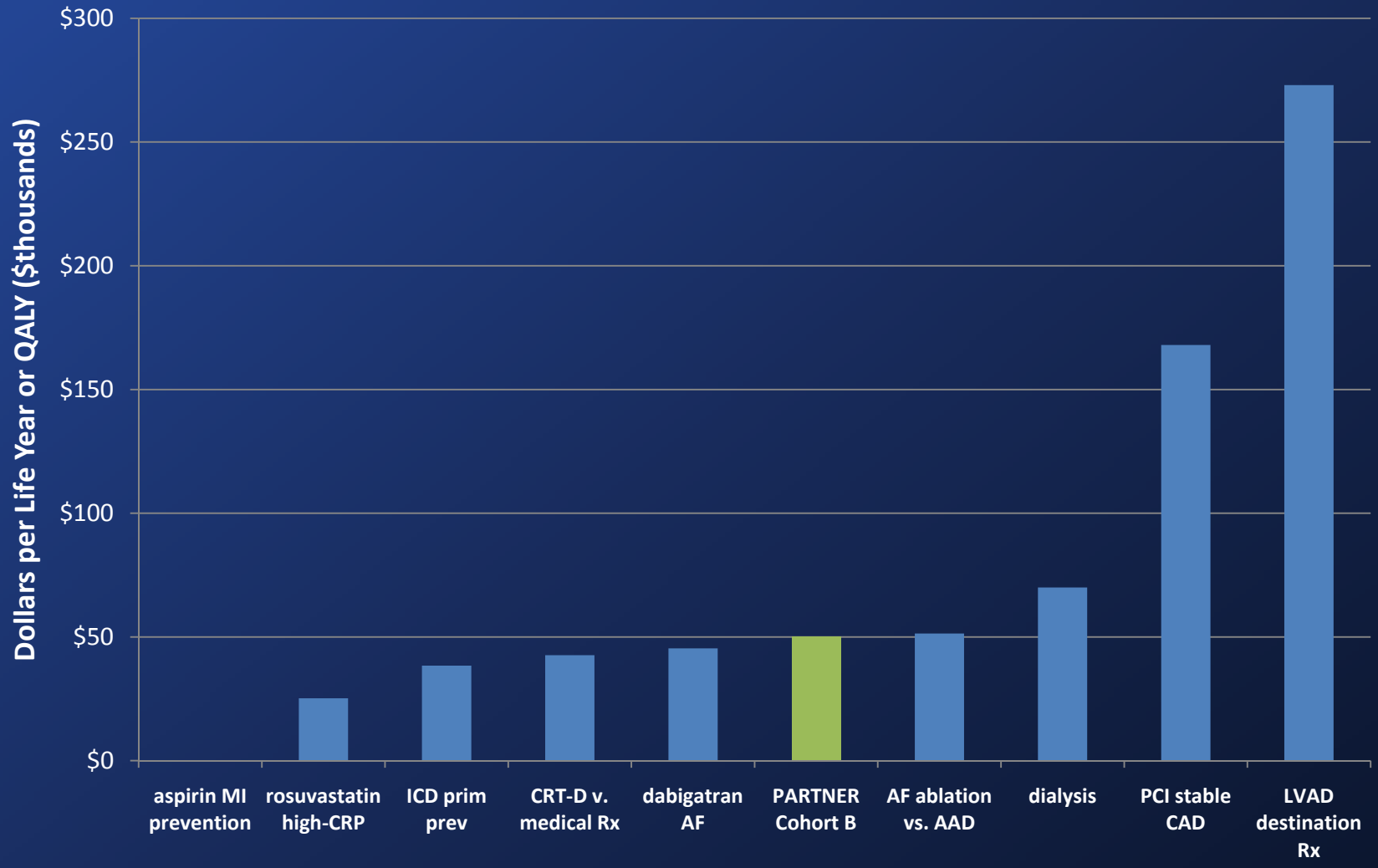
PARTNER QOL Analyses

TAVR not only adds years to life, but also, adds life to years!

Cost-Effectiveness of TAVR vs. Control
Lifetime Results



Published Cost Effectiveness Estimates



TAVR 2011 - PARTNER

Main Outcomes: High Risk

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High Risk: Patient Characteristics -1

THE PARTNER TRIAL

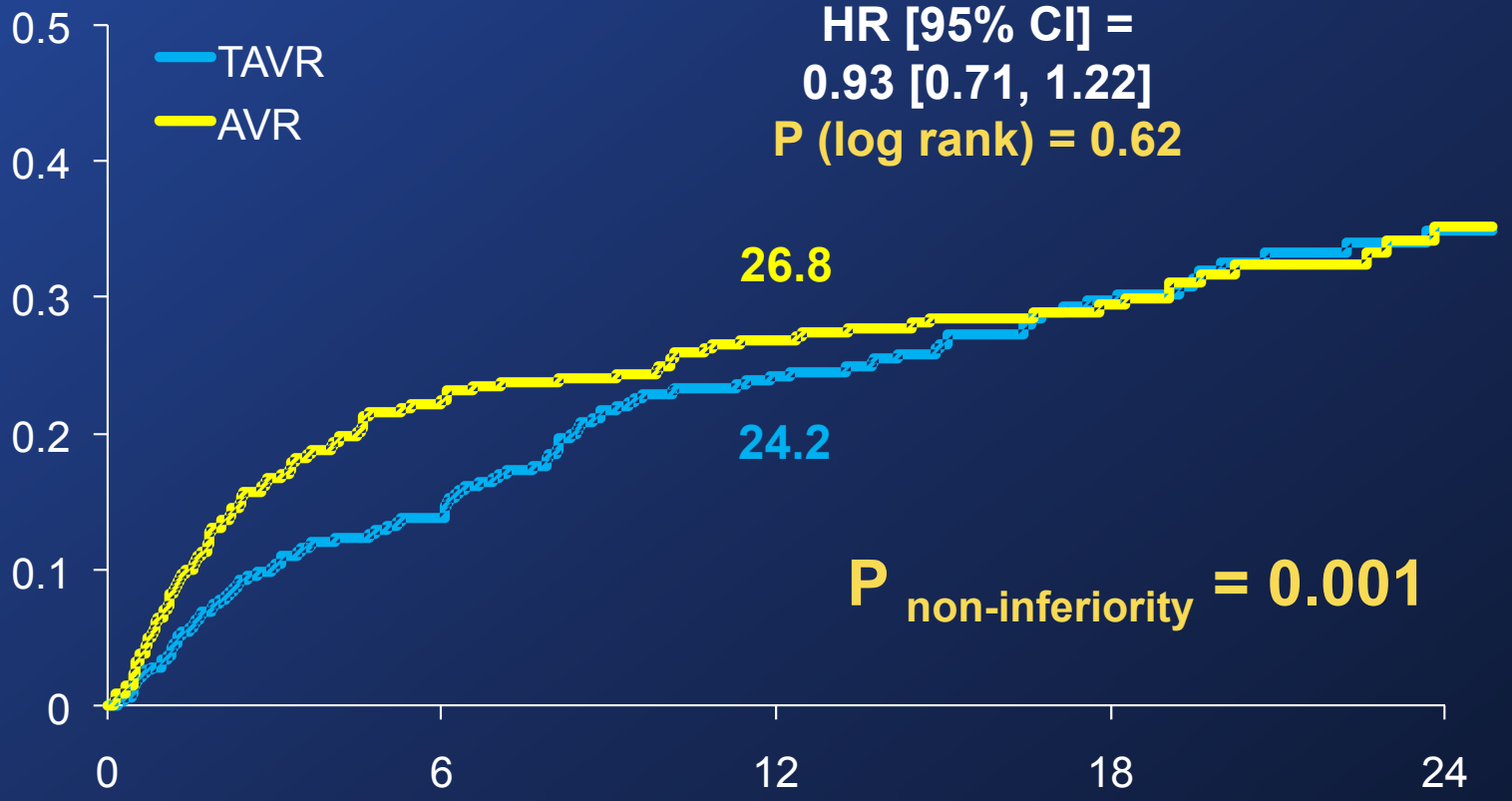
Characteristic	*TAVR (N = 348)*	*AVR (N = 351)*	*p-value*
Age (yr)	83.6 ± 6.8	84.5 ± 6.4	0.07
Male sex - %	57.8	56.7	0.82
STS Score	11.8 ± 3.3	11.7 ± 3.5	0.61
Logistic EuroSCORE	29.3 ± 16.5	29.2 ± 15.6	0.93
NYHA			0.79
II - %	5.7	6.0	
III or IV - %	94.3	94.0	
CAD - %	74.9	76.9	0.59
Previous MI - %	26.8	30.0	0.40
Prior CV Intervention - %	72.1	71.6	0.93
Prior CABG - %	42.6	44.2	0.70
Prior PCI - %	34.0	32.5	0.68
Prior BAV - %	13.4	10.2	0.24
Cerebrovascular disease - %	29.3	27.4	0.60

High Risk: Patient Characteristics -2

THE PARTNER TRIAL

Characteristic	*TAVR (N = 348)*	*AVR (N = 351)*	*p-value*
Peripheral vascular disease - %	43.0	41.6	0.76
COPD			
Any	43.4	43.0	0.94
Oxygen dependent	9.2	7.1	0.34
Creatinine > 2mg/dL - %	11.1	7.0	0.06
Atrial fibrillation - %	40.8	42.7	0.75
Permanent pacemaker - %	20.0	21.9	0.58
Pulmonary hypertension - %	42.4	36.4	0.15
Frailty - %	15.6	17.6	0.58
Porcelain aorta - %	0.6	1.1	0.69
Chest wall radiation - %	0.9	0.9	1.00
Liver disease - %	2.0	2.6	0.80

Primary Endpoint:
All-Cause Mortality at 1 Year



No. at Risk

TAVR	348	298	260	147	67
AVR	351	252	236	139	65

All-Cause Mortality at 30 Days and 1 Year
Patient Subgroups

All-Cause Mortality at 30 Days

	All Patients no. of patients (%)			TF Patients no. of patients (%)			TA Patients no. of patients (%)		
	TAVR	AVR	*p*-value	TAVR	AVR	*p*-value	TAVR	AVR	*p*-value
ITT	12 (3.4)	22 (6.5)	0.07	8 (3.3)	15 (6.2)	0.13	4 (3.8)	7 (7.0)	0.32
AT	18 (5.2)	25 (8.0)	0.15	9 (3.7)	18 (8.2)	0.05	9 (8.7)	7 (7.6)	0.79

All-Cause Mortality at 1 Year

	All Patients no. of patients (%)			TF Patients no. of patients (%)			TA Patients no. of patients (%)		
	TAVR	AVR	*p*-value	TAVR	AVR	*p*-value	TAVR	AVR	*p*-value
ITT	84 (24.2)	89 (26.8)	0.44	54 (22.2)	62 (26.4)	0.29	30 (29.0)	27 (27.9)	0.85
AT	81 (23.7)	78 (25.2)	0.64	51 (21.3)	55 (25.2)	0.33	30 (29.1)	23 (25.3)	0.55

All-Cause Mortality at 30 Days and 1 Year
Patient Subgroups

All-Cause Mortality at 30 Days

	All Patients no. of patients (%)			TF Patients no. of patients (%)			TA Patients no. of patients (%)		
	TAVR	AVR	*p*-value	TAVR	AVR	*p*-value	TAVR	AVR	*p*-value
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All-Cause Mortality at 1 Year

	All Patients no. of patients (%)			TF Patients no. of patients (%)			TA Patients no. of patients (%)		
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AT	81 (23.7)	78 (25.2)	0.64	51 (21.3)	55 (25.2)	0.33	30 (29.1)	23 (25.3)	0.55

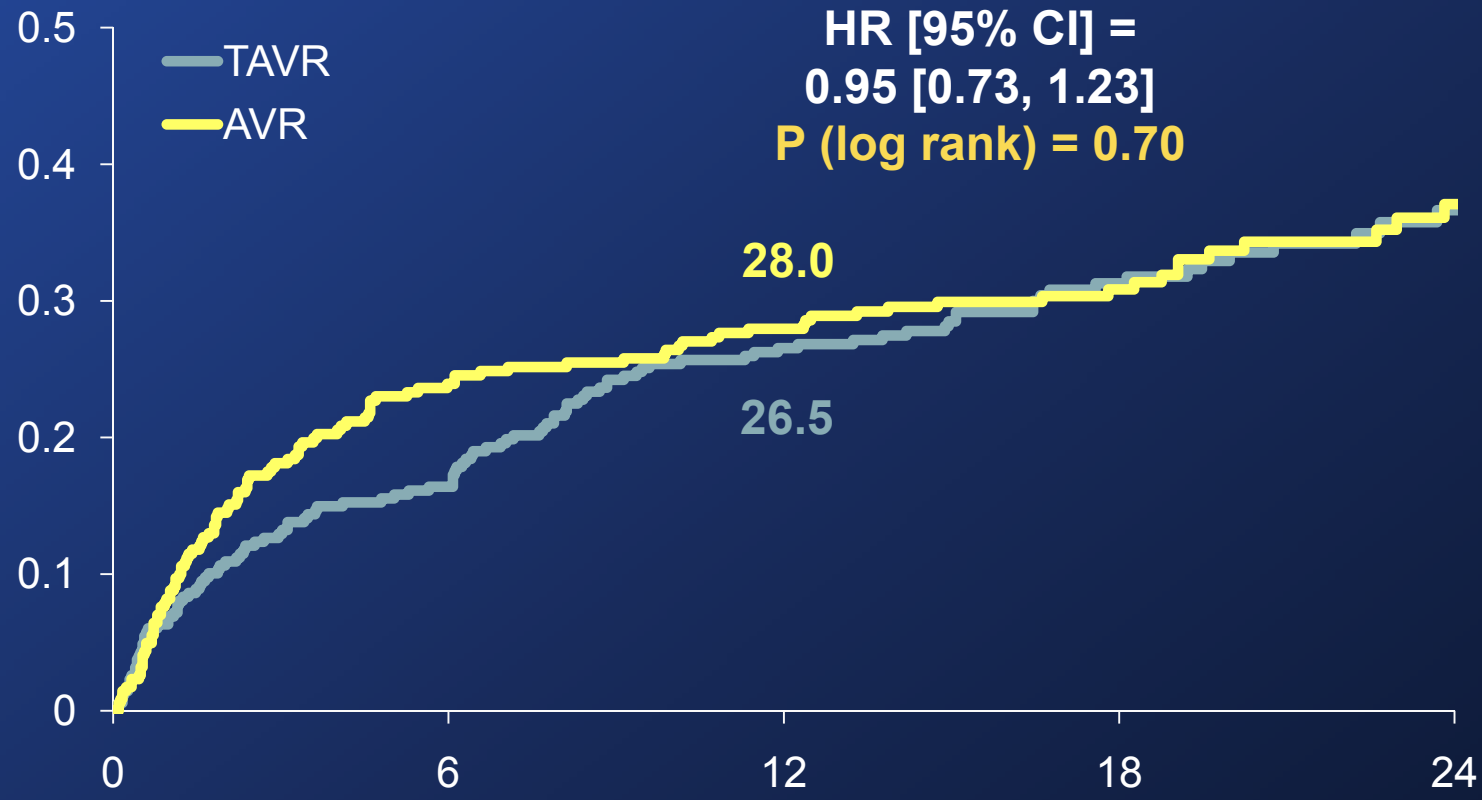
Clinical Outcomes at 30 Days and 1 Year
All Patients (N=699)

	30 Days			1 Year		
Outcome	*TAVR (N = 348)*	*AVR (N = 351)*	*p-value*	*TAVR (N = 348)*	*AVR (N = 351)*	*p-value*
Vascular complications						
All – no. (%)	59 (17.0)	13 (3.8)	<0.01	62 (18.0)	16 (4.8)	<0.01
Major – no. (%)	38 (11.0)	11 (3.2)	<0.01	39 (11.3)	12 (3.5)	<0.01
Major bleeding – no. (%)	32 (9.3)	67 (19.5)	<0.01	49 (14.7)	85 (25.7)	<0.01
Endocarditis – no. (%)	0 (0.0)	1 (0.3)	0.32	2 (0.6)	3 (1.0)	0.63
New AF – no. (%)	30 (8.6)	56 (16.0)	< 0.01	42 (12.1)	60 (17.1)	0.07
New PM – no. (%)	13 (3.8)	12 (3.6)	0.89	19 (5.7)	16 (5.0)	0.68

Neurological Events at 30 Days and 1 Year
All Patients (N=699)

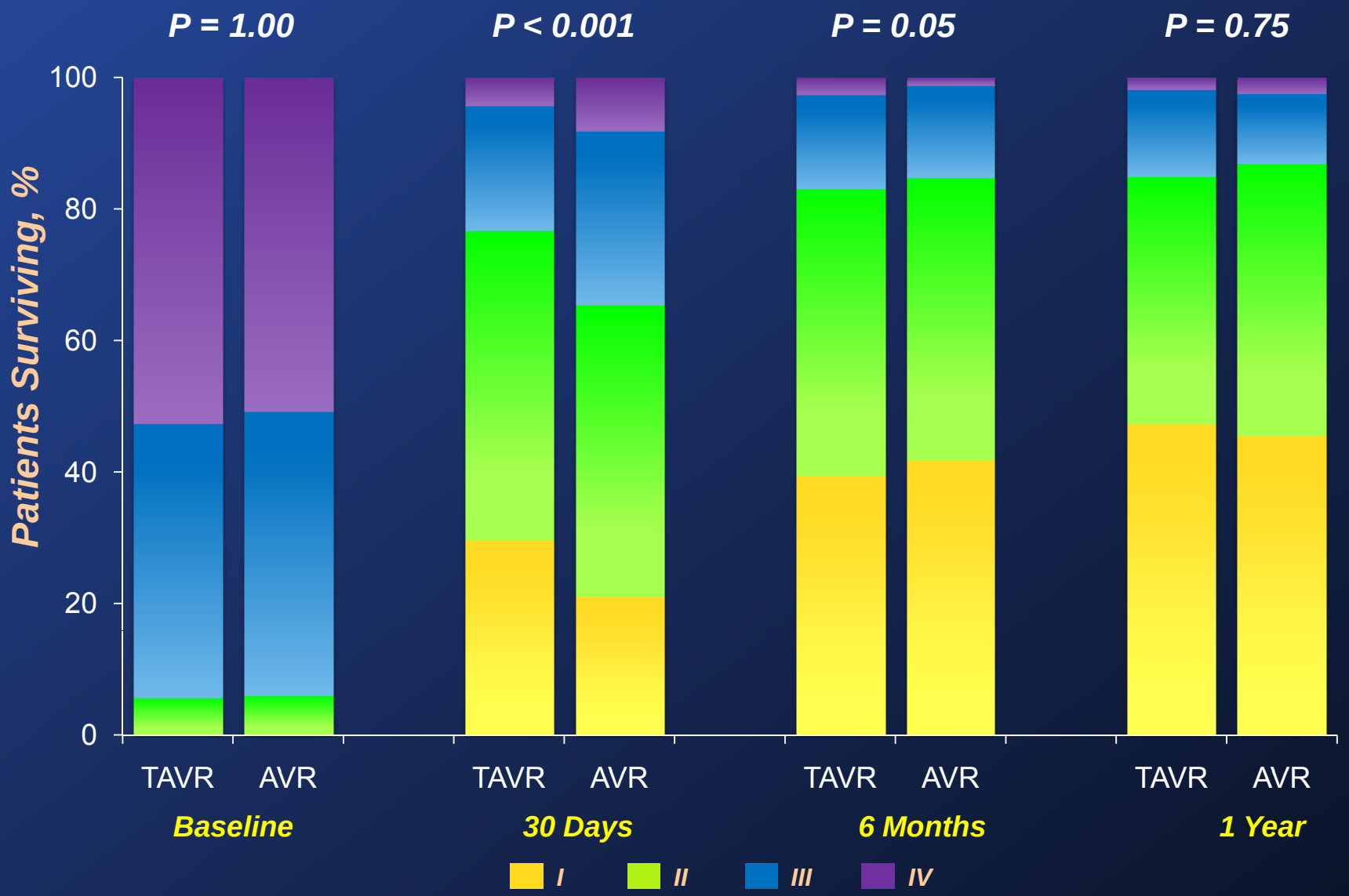
	30 Days			1 Year		
Outcome	*TAVR (N = 348)*	*AVR (N = 351)*	*p-value*	*TAVR (N = 348)*	*AVR (N = 351)*	*p-value*
All Stroke or TIA – no. (%)	19 (5.5)	8 (2.4)	0.04	27 (8.3)	13 (4.3)	0.04
TIA – no. (%)	3 (0.9)	1 (0.3)	0.33	7 (2.3)	4 (1.5)	0.47
All Stroke – no. (%)	16 (4.6)	8 (2.4)	0.12	20 (6.0)	10 (3.2)	0.08
Major Stroke – no. (%)	13 (3.8)	7 (2.1)	0.20	17 (5.1)	8 (2.4)	0.07
Minor Stroke – no. (%)	3 (0.9)	1 (0.3)	0.34	3 (0.9)	2 (0.7)	0.84
Death/maj stroke – no. (%)	24 (6.9)	28 (8.2)	0.52	92 (26.5)	93 (28.0)	0.68

All-Cause Mortality or Stroke
All Patients (N=699)

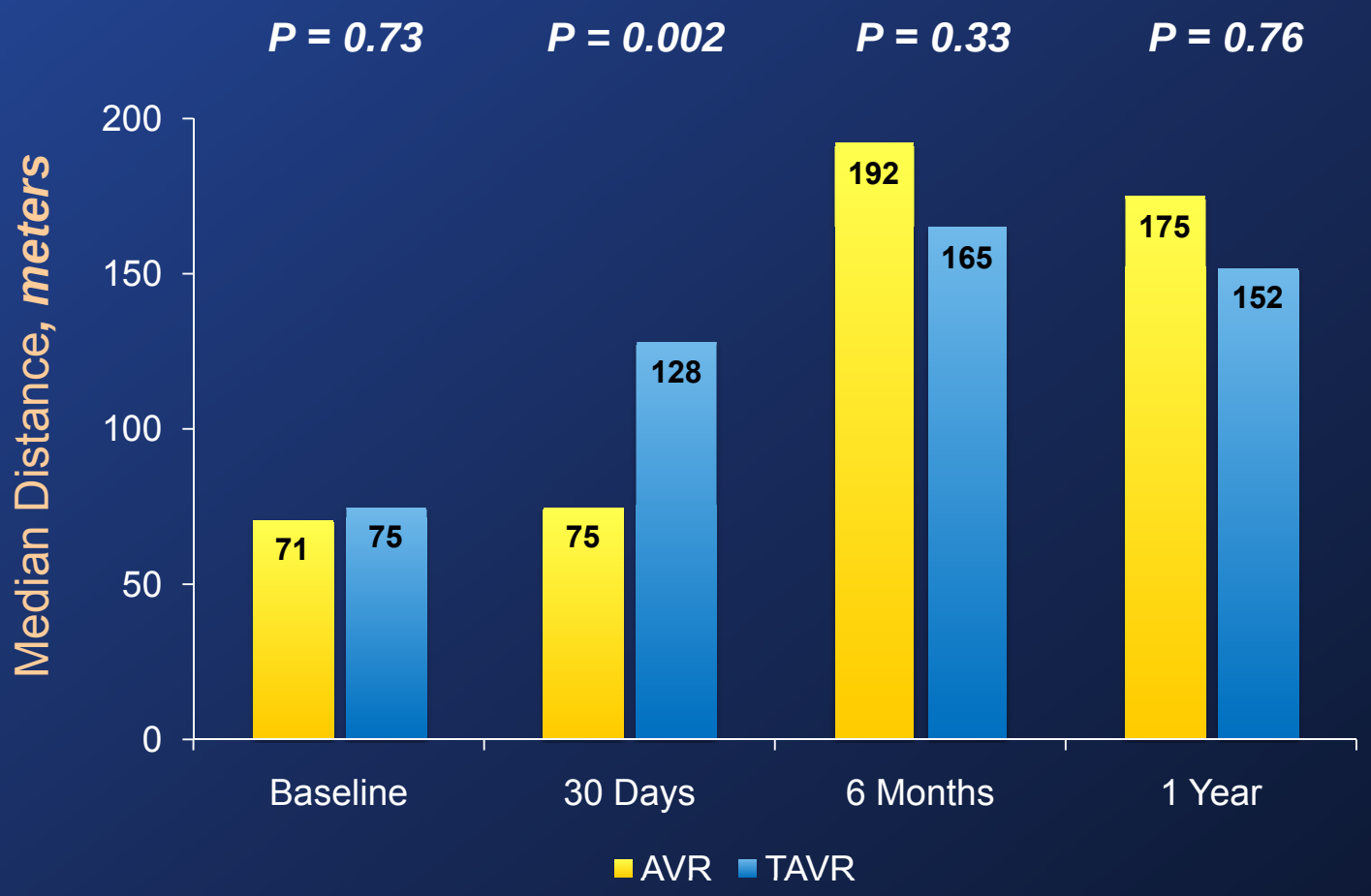


No. at Risk					
TAVR	348	289	252	143	65
AVR	351	247	232	138	63

NYHA Functional Class



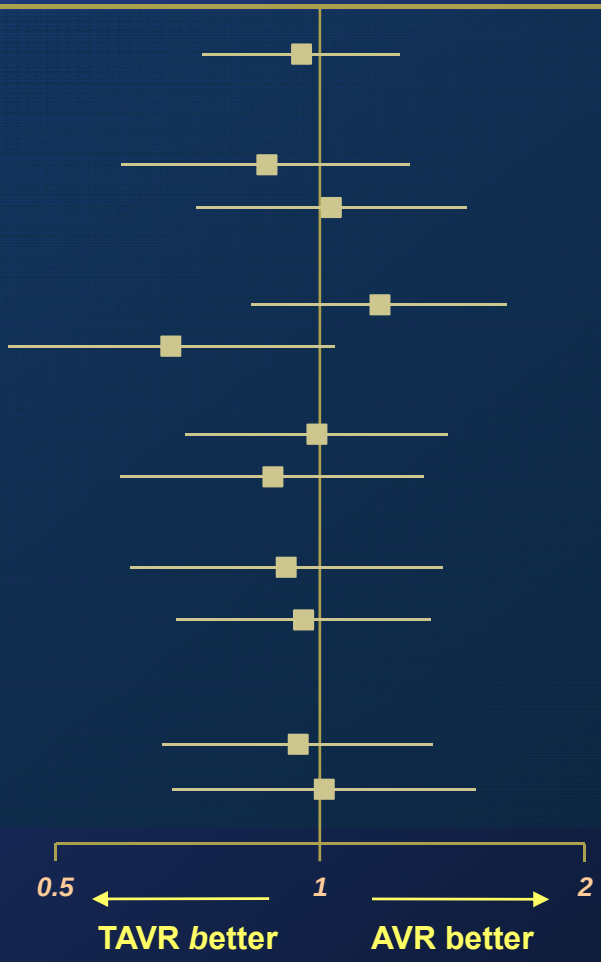
Six-Minute Walk Test
All Patients (N=699)



Subgroup Analyses of Treatment Effect
All-Cause Mortality at 1 Year

THE PARTNER TRIAL

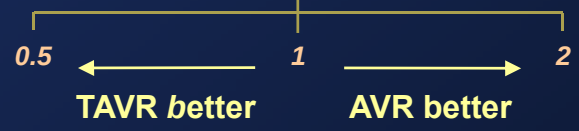
Subgroup	TAVR (%) n=348	AVR (%) n=351	RR (95% CI)	P-value for interaction
Overall	24.1	25.4	0.95(0.73-1.23)	
Age				
<85	21.6	24.9	0.87(0.60-1.27)	0.52
>85	27.0	26.1	1.03(0.72-1.47)	
Sex				
Male	28.4	24.2	1.17(0.84-1.63)	0.045
Female	18.4	27.2	1.17(0.84-1.63)	
BMI				
<26	27.3	27.4	0.68(0.44-1.04)	0.66
>26	21.0	23.8	0.99(0.71-1.40)	
STS score				
<11	19.9	21.7	0.88(0.59-1.31)	0.87
>11	28.1	29.3	0.92(0.61-1.38)	
LV ejection fraction				
<55	26.2	27.7	0.96(0.69-1.34)	0.80
>55	22.4	22.1	1.01(0.68-1.50)	



Subgroup Analyses of Treatment Effect
All-Cause Mortality at 1 Year

THE PARTNER TRIAL

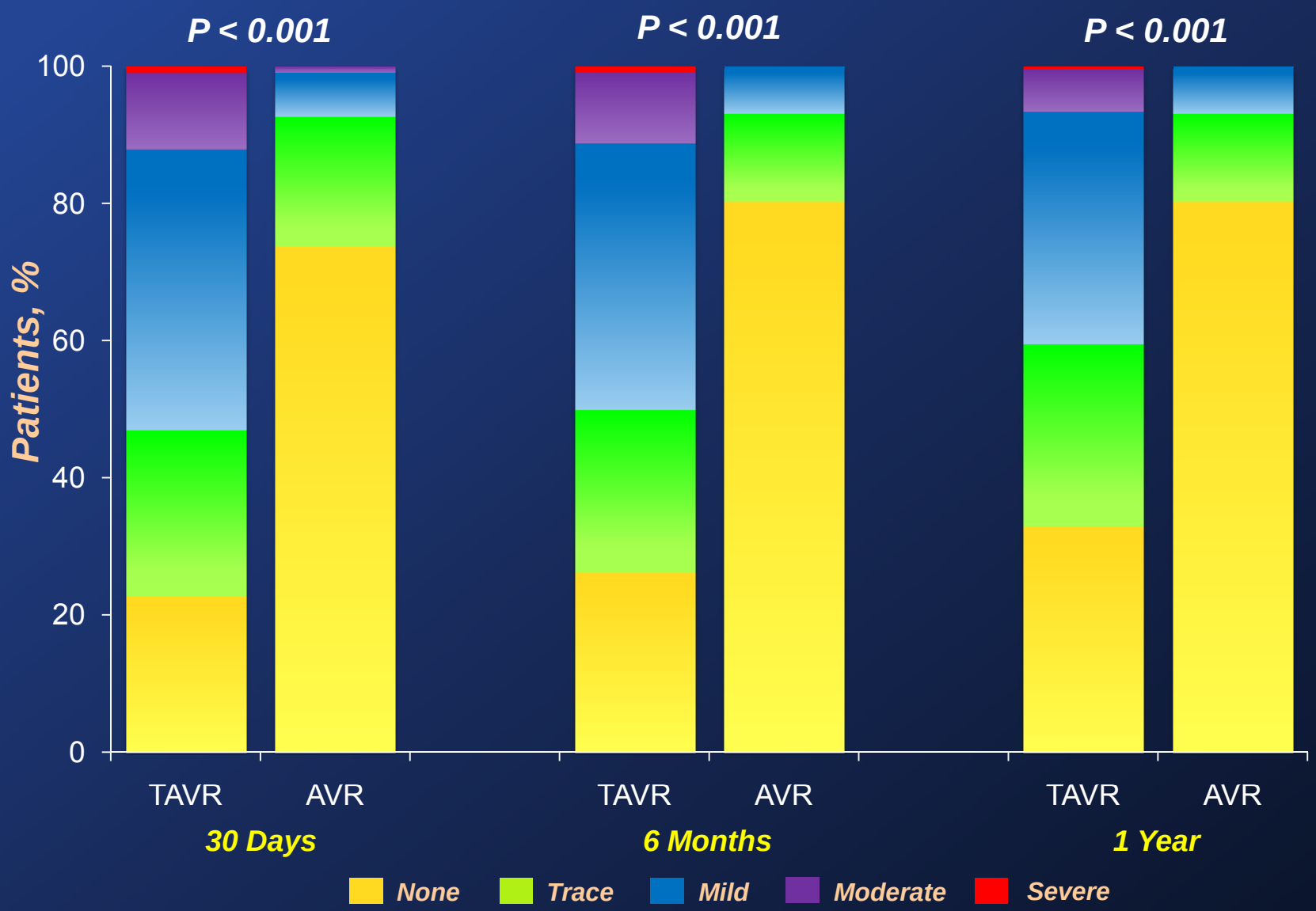
Subgroup	TAVR (%) n=348	AVR (%) n=351	RR (95% CI)	P-value for interaction
Pulmonary hypertension				
No	21.3	21.7	0.98(0.64-1.50)	0.80
Yes	27.4	29.9	0.92(0.66-1.28)	
Mitral regurgitation				
No	24.6	22.1	1.11(0.82-1.52)	0.12
Yes	24.2	35.2	0.69(0.41-1.17)	
Prior CABG				
No	22.2	30.7	0.72(0.52-1.01)	0.02
Yes	25.9	19.1	1.35(0.88-2.08)	
Peripheral vasc disease				
No	22.4	25.1	0.89(0.63-1.27)	0.57
Yes	26.4	25.4	1.04(0.70-1.54)	
Cohort				
TA	28.8	26.2	1.10(0.71-1.71)	0.43
TF	22.1	25.0	0.89(0.64-1.22)	



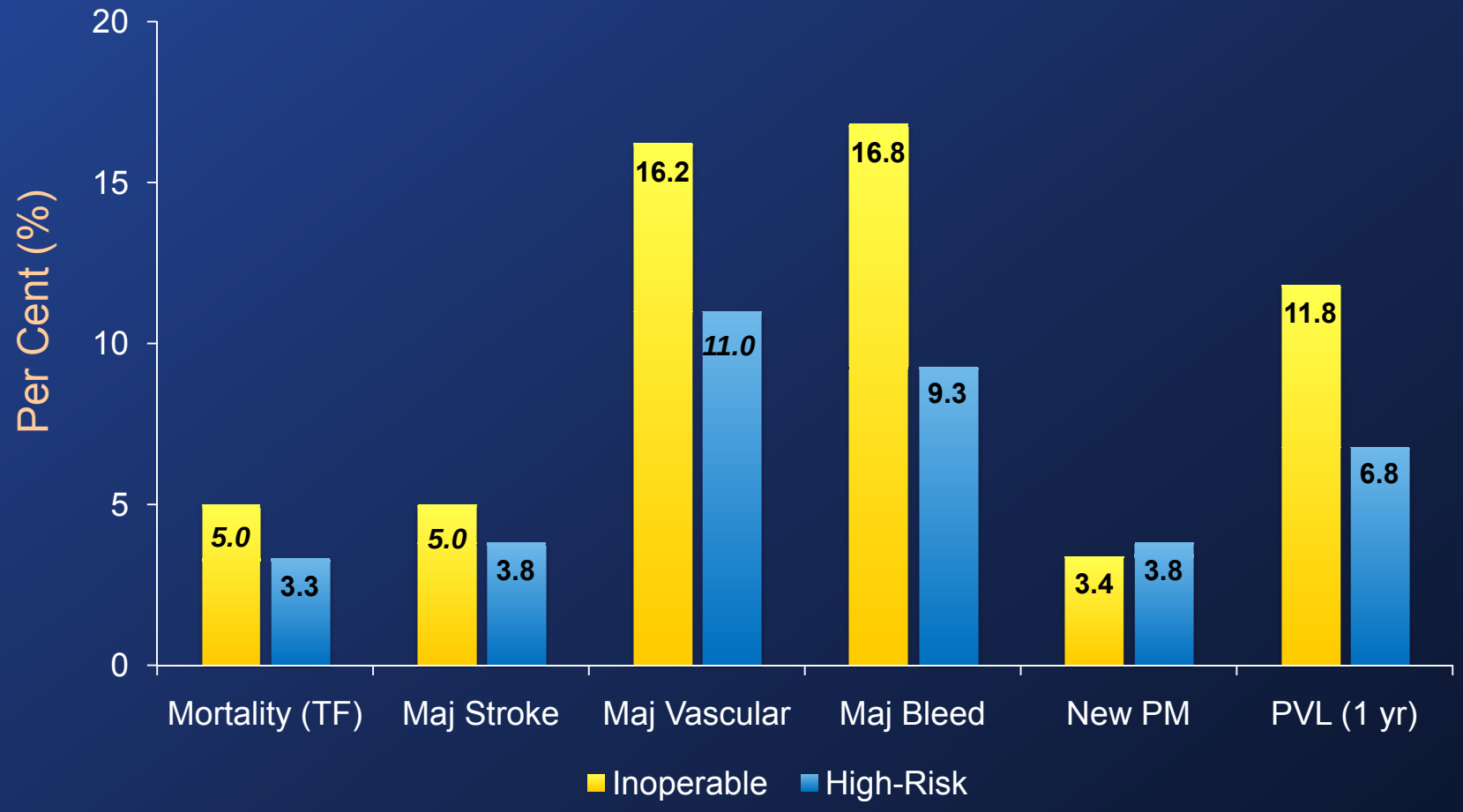
Echo Findings
Hemodynamic Assessments

	30 Days			1 Year		
Finding	*TAVR*	*AVR*	*p-value*	*TAVR*	*AVR*	*p-value*
Mean grad - mmHg	9.9 ± 4.8	10.8 ± 5.0	0.04	10.2 ± 4.3	11.5 ± 5.4	0.008
AVA - cm^2	1.7 ± 0.5	1.5 ± 0.4	0.001	1.6 ± 0.5	1.4 ± 0.5	0.002
LV EF - %	55.5 ± 11.4	56.0 ± 11.4	0.63	56.6 ± 10.5	57.1 ± 10.3	0.64

Paravalvular Aortic Regurgitation



PARTNER Comparison of Outcomes
High-Risk vs. Inoperable Patients - ITT



PARTNER Final Thoughts

Rarely, in Medical Research,

has so dramatic an improvement in Survival,

been achieved in such a Short Time,

with so few Iterations;

And it is only the Beginning of a Flooding Tide,

that Floats All Boats!!!

Courtesy of Lars Svensson; Surgical PI Cleveland Clinic and Member of the Executive Committee, PARTNER trial