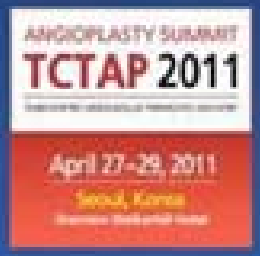
Perspectives from the PARTNER Trial

Martin B. Leon, MD

Columbia University Medical Center
Cardiovascular Research Foundation
New York City



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 — 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.

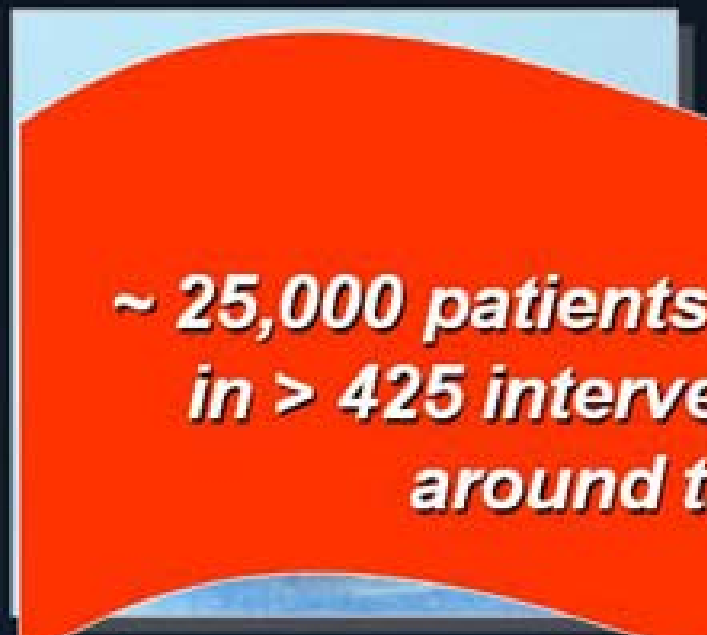
April 16, 2002

Cardiovascular Research Foundation

Columbia University Medical Center
NewYork-Presbyterian

TAVR Technologies

Current Generation Devices



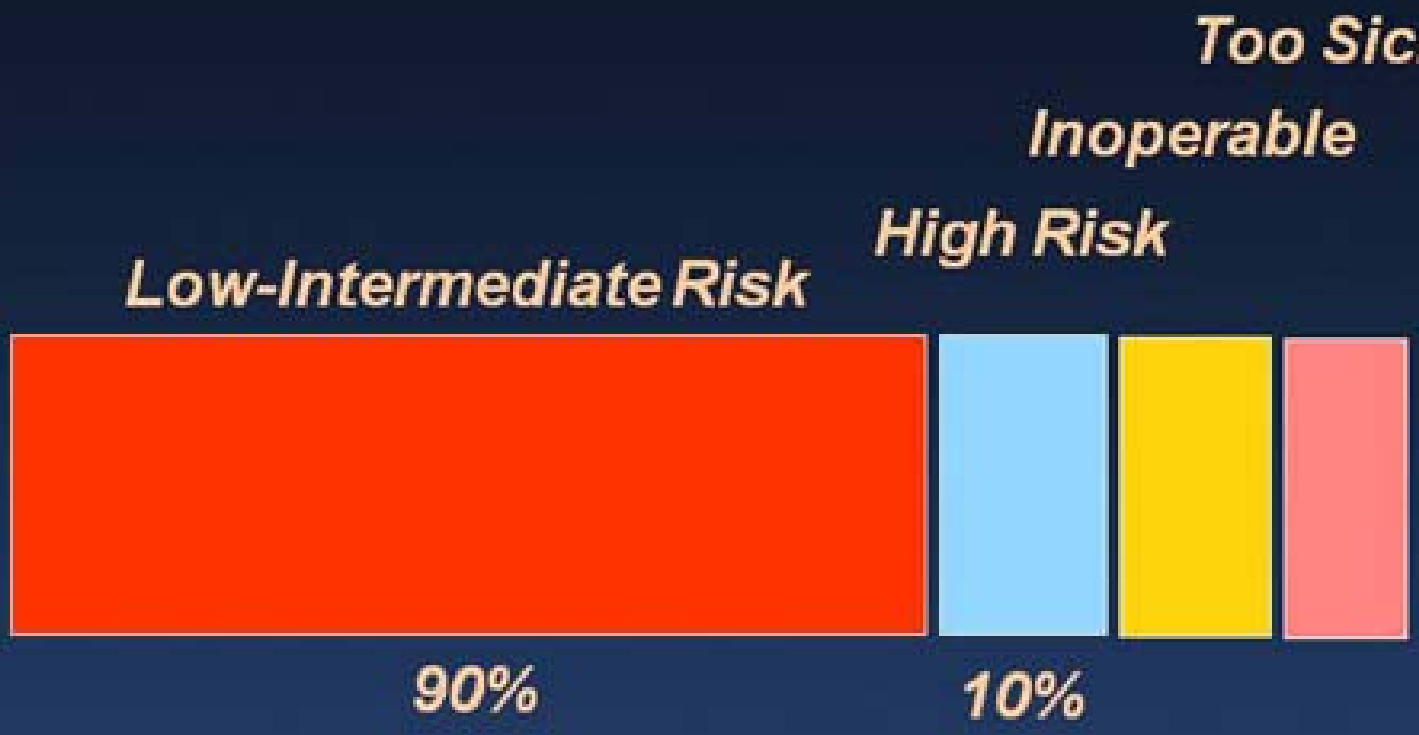
~ 25,000 patients treated thru 2010 in > 425 interventional centers around the world!

Edwards Lifesciences

ive

TAVR Categories
(risk is a continuum)

Operable AS patients



TAVR 2011

CARDIOVASCULAR RESEARCH FOUNDATION

COLUMBIA UNIVERSITY MEDICAL CENTER
NewYork-Presbyterian

TAVR - Background

- Many patients with severe aortic stenosis, esp. those who may be at "high risk" for open surgery, do not receive surgical AVR.
- There has been explosive growth in transcatheter aortic valve implantation (TAVR) since the first procedure in 2002.
- Although patient selection, operator skills, and technology have improved, all previous TAVR studies have been observational registries, without standardization of endpoint definitions, without formal CECs, and without an independent echo core lab.

VARC MANUSCRIPT

CLINICAL RESEARCH — Valvular Medicine

Standardized Endpoint Definitions for Transcatheter Aortic Valve Implantation Clinical Trials

A Consensus Report From the Valve Academic Research Consortium

Martin B. Leon, Nicolo Piazza, Eugenia Nikolsky, Eugene H. Blackstone, Donald E. Cutlip, Arie Pieter Kappetein, Mitchell W. Krucoff, Michael Mack, Roxana Mehran, Craig Miller, Marie-angèle Morel, John Petersen, Jeffrey J. Popma, Johanna J. M. Takkenberg, Alec Vahanian, Gerrit-Anne van Es, Pascal Vranckx, John G. Webb, Stephan Windecker, Patrick W. Serruys

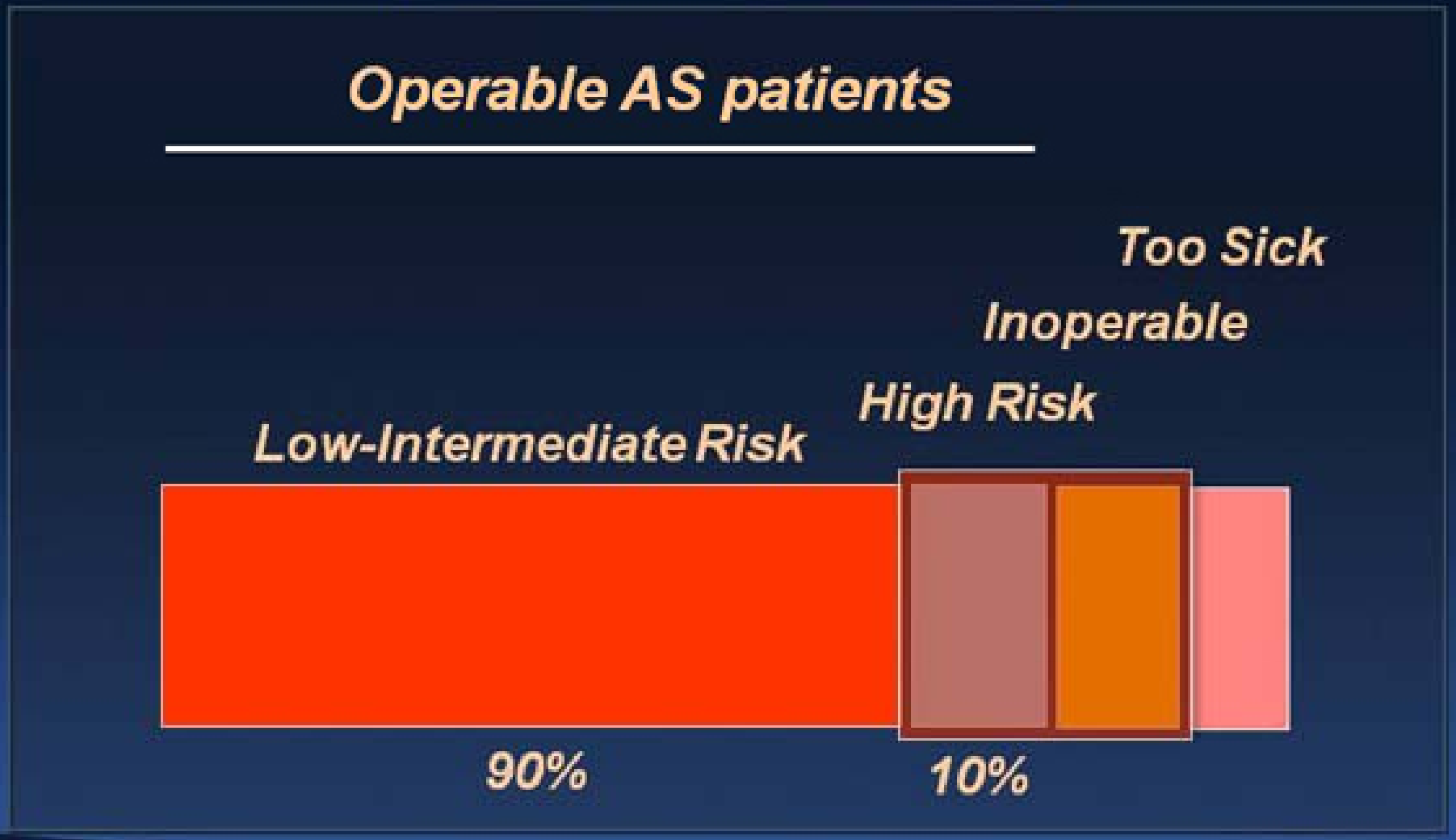
New York, New York

TAVR - Background

- There is a paucity of evidence-based clinical data to substantiate incremental benefits of TAVR compared with current standard therapies.

NO RANDOMIZED CLINICAL TRIALS

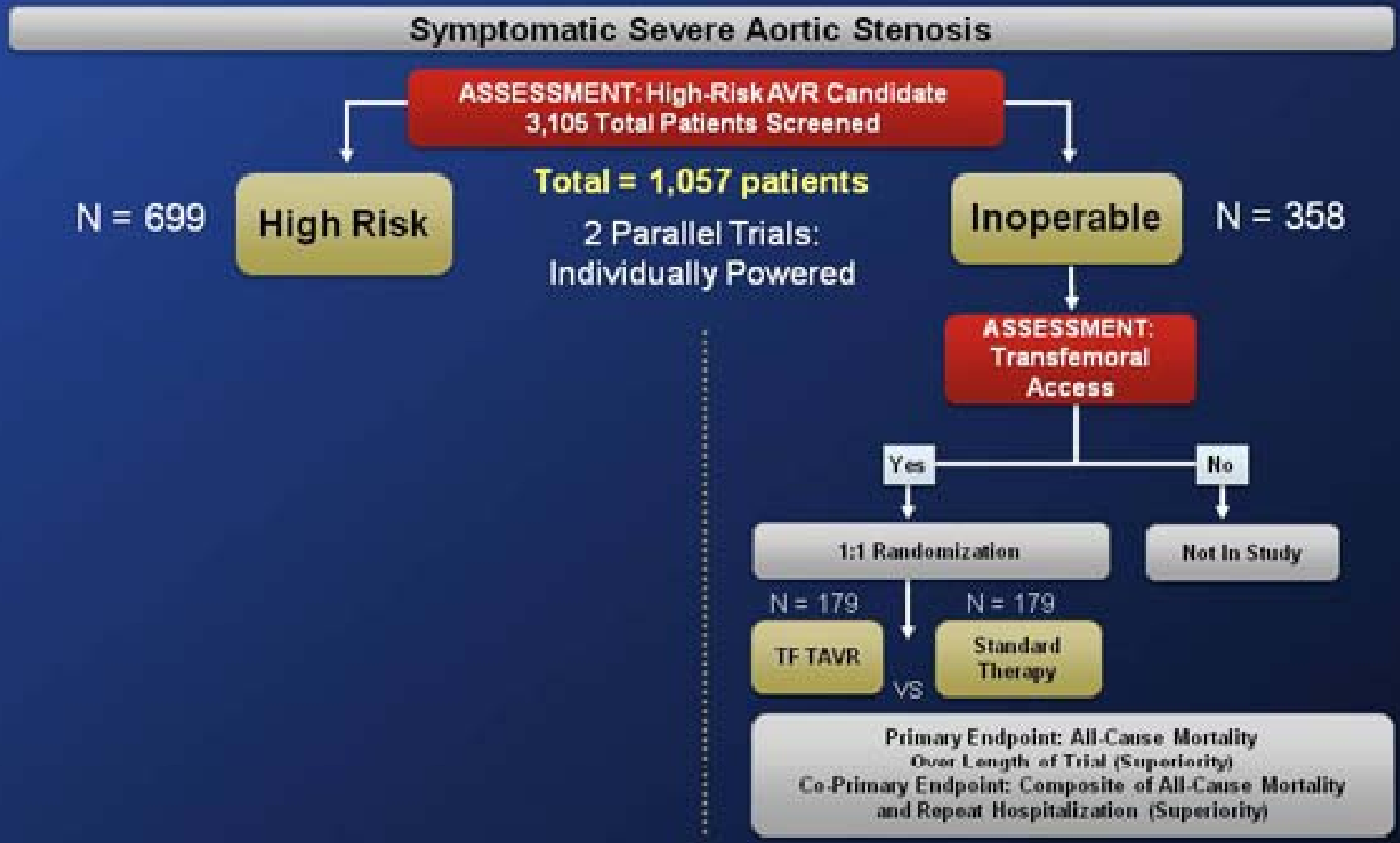
TAVR Categories
(risk is a continuum)



TAVR 2011

Study Design

PARTNER Study Design



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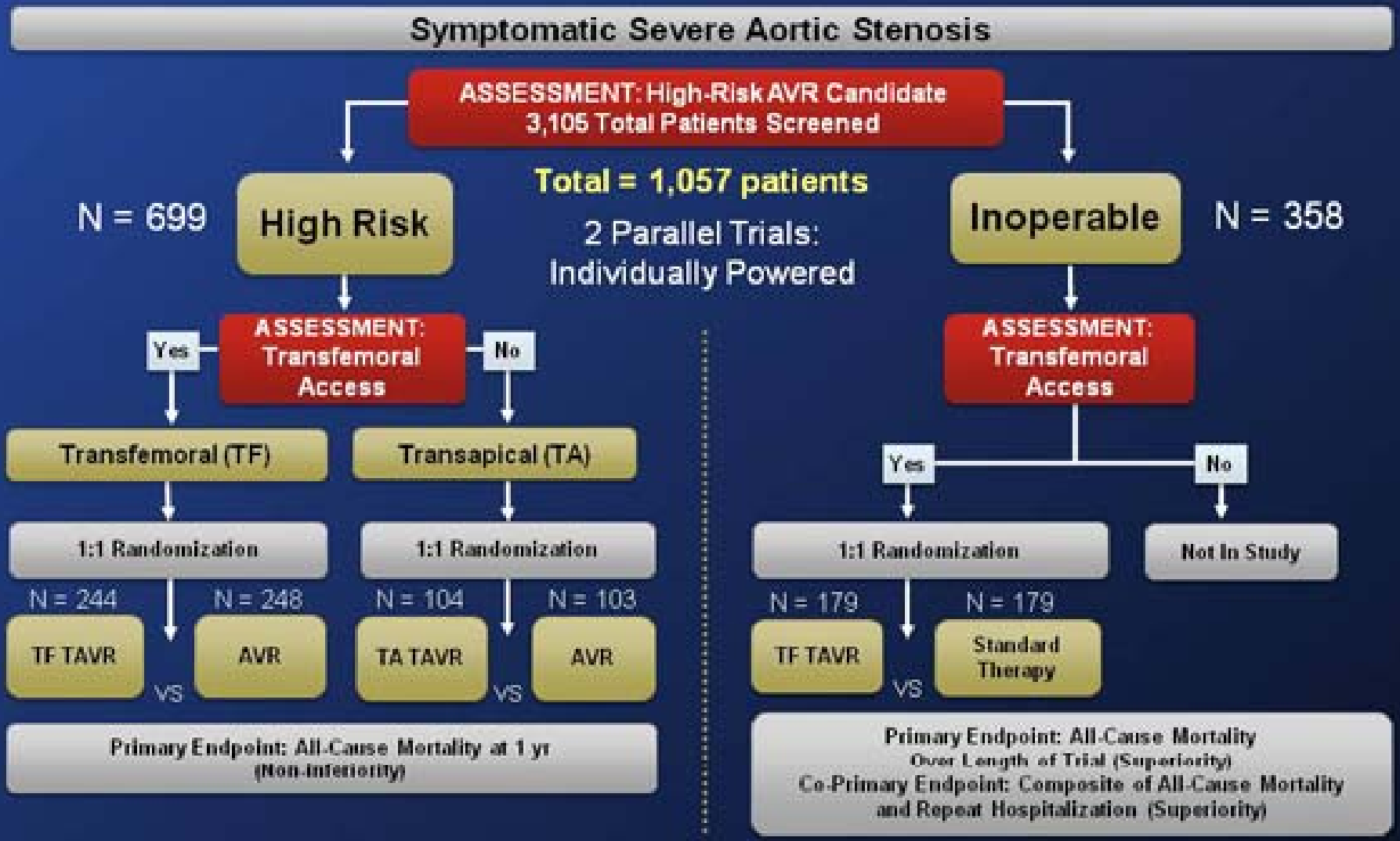
The NEW ENGLAND JOURNAL of MEDICINE

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

THE PARTNER TRIAL

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

Other Important Endpoints (1)

Safety:

- Neurologic events
  - Prospective: Stroke and stroke plus TIA (all neuro events)
  - Retrospective: Major stroke (modified Rankin Score ≥ 2 @ ≥ 30 days)
- Major vascular complications (VARC definition)
- Major bleeding (modified VARC definition)
- Repeat hospitalization
- New pacemakers and new-onset atrial fibrillation (ECG core lab)
- Procedural events (assigned therapy aborted or converted to AVR, multiple valves, etc.)
- Surgical complications (re-op for bleeding, sternal infection, etc.)

Other Important Endpoints (2)

THE PARTNER TRIAL

Clinical Effectiveness and Valve Performance:

- NYHA symptoms
- Six-minute walk tests
- Quality-of-life measures and cost-effectiveness (core lab)
- Echocardiography assessment of valve performance (core lab)
  - Peak and mean gradients
  - Effective orifice area
  - Bioprosthetic valve regurgitation (esp. para-valvular)
  - Other: LV ejection fraction, MR, LV mass, evidence of structural valve deterioration

Inclusion Criteria

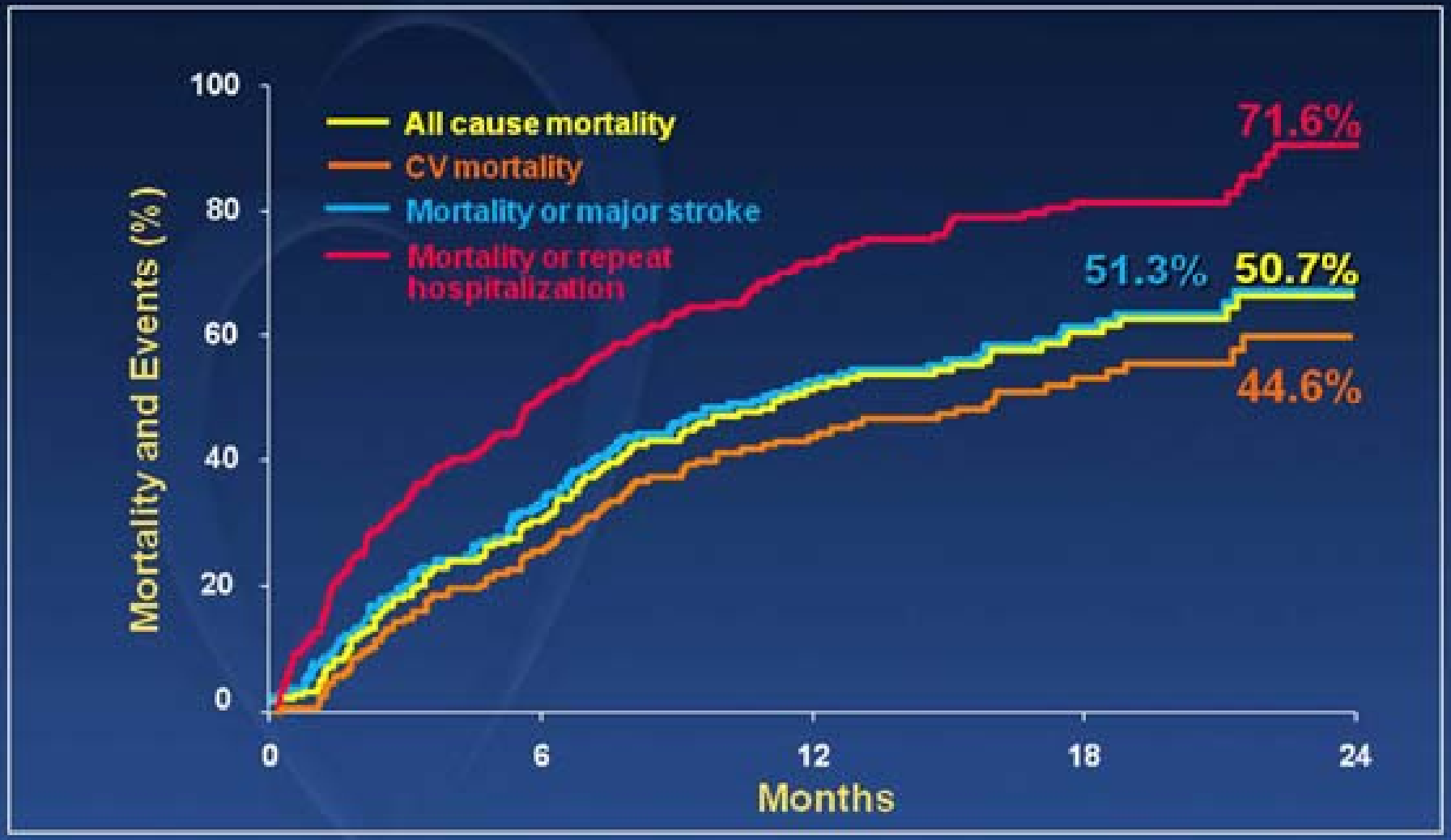
- *Severe AS:* Echo-derived AVA < 0.8 cm^2 (*or* AVA index < 0.5 cm^2/m^2) and mean AVG > 40 mm Hg *or* peak jet velocity > 4.0 m/s
- *Cardiac Symptoms:* NYHA Functional Class ≥ II

- *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

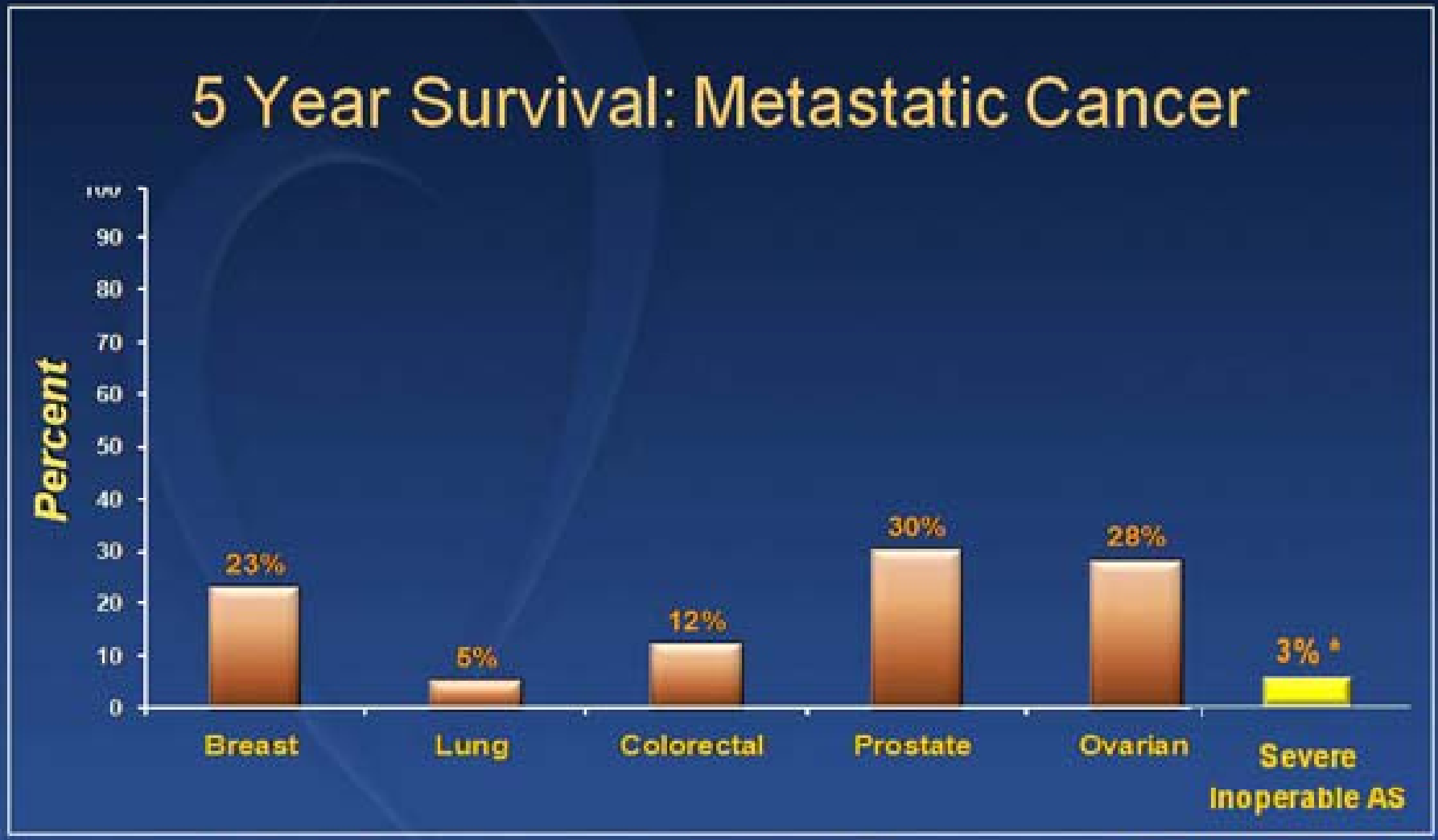
Main Outcomes: Inoperable

Standard Therapy Outcomes



Mortality in Standard Rx

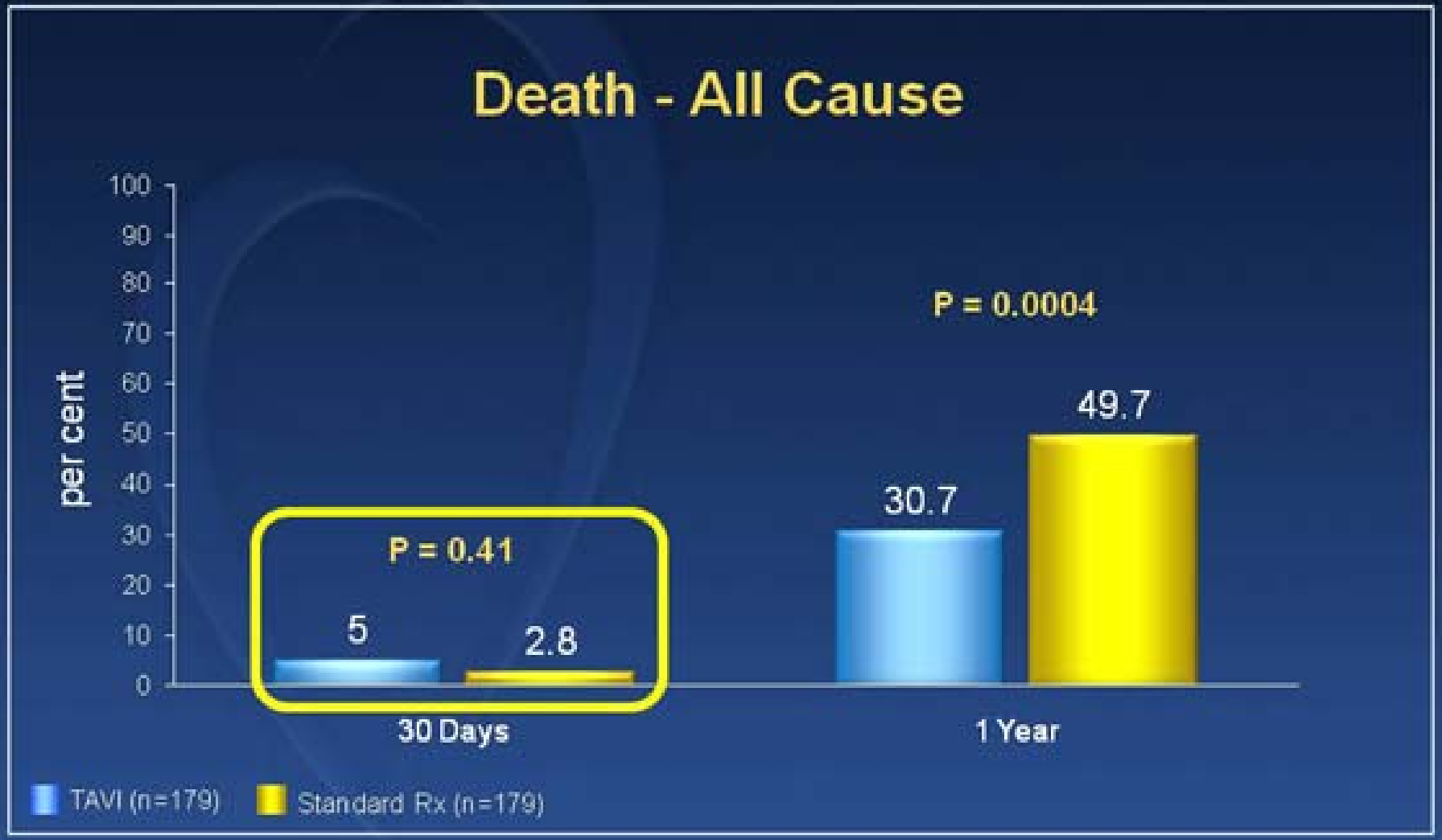
Perspectives



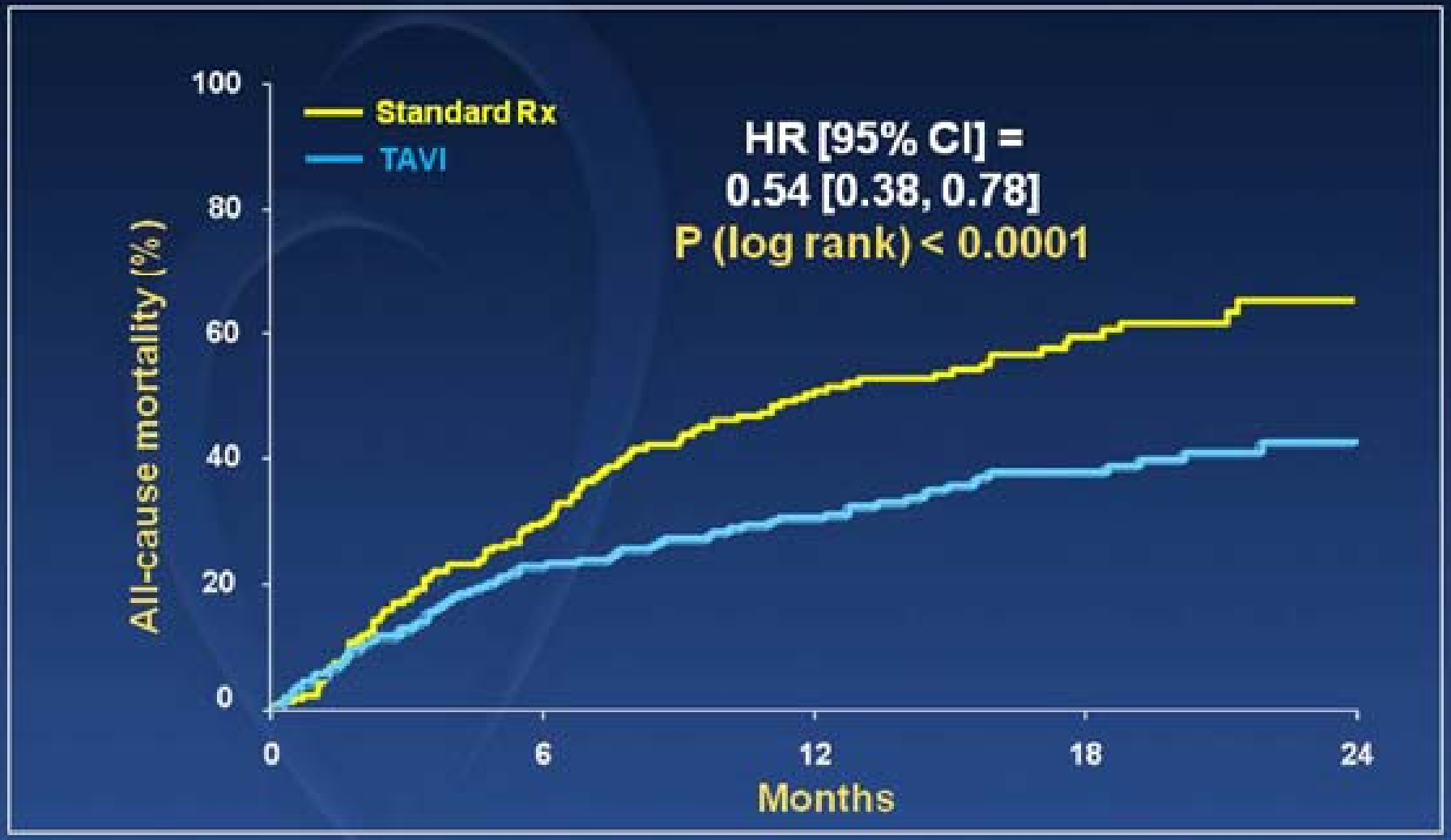
Courtesy of Murat Tuzcu, Interventional PI, CCF

** Constant Hazard Model*

Clinical Outcomes at 30 Days and 1 Year

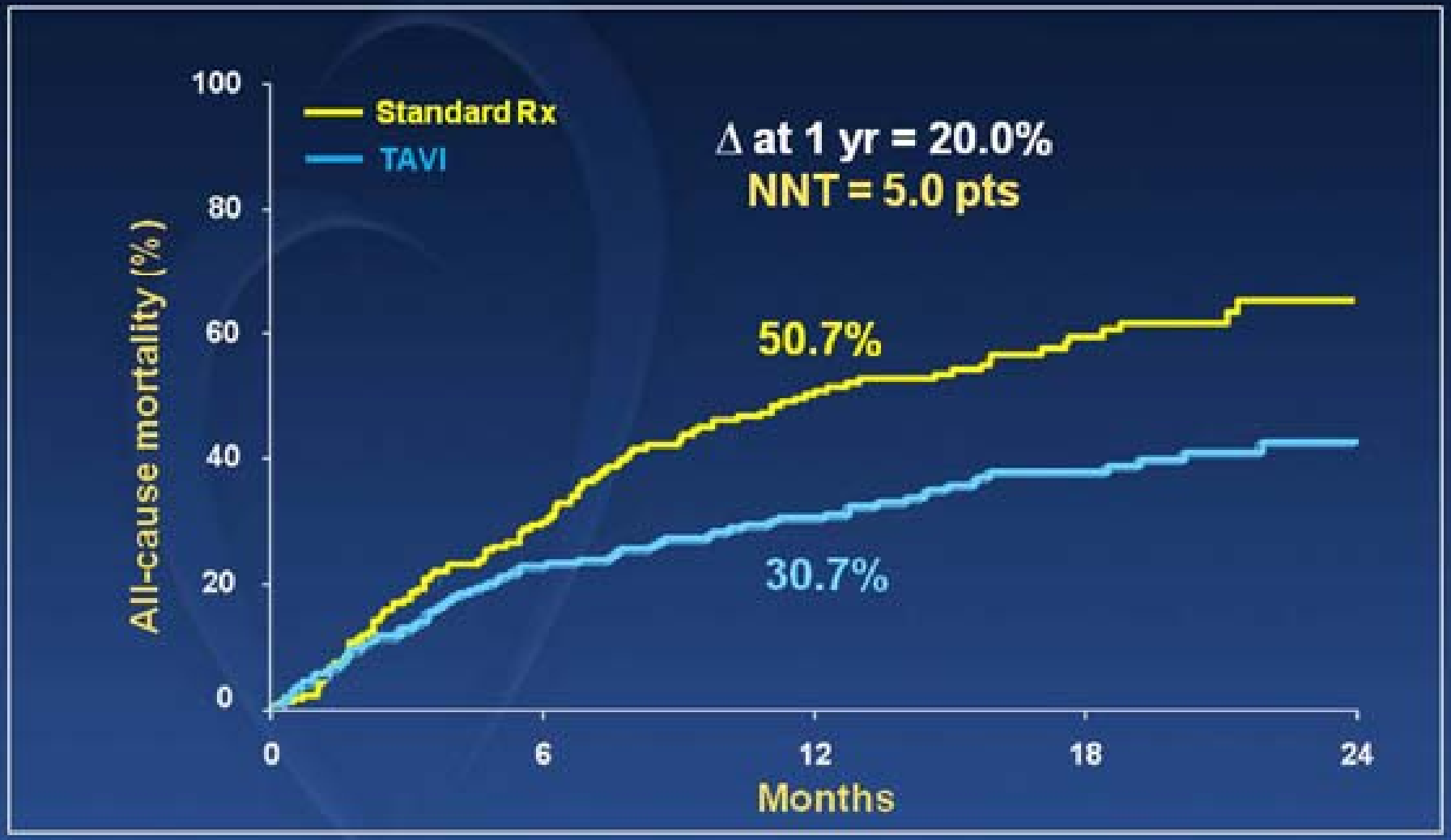


1ry Endpt - All Cause Mortality



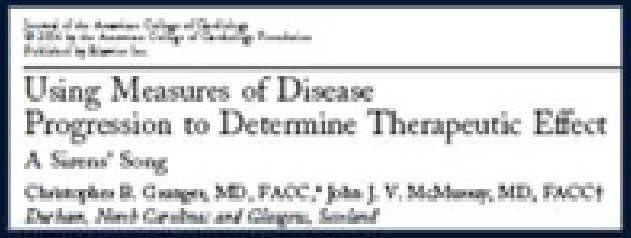
Numbers at Risk					
TAVI	179	138	122	67	26
Standard Rx	**179**	**121**	**83**	**41**	**12**

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



Using Measures of Disease Progression to Determine Therapeutic Effect

A Sirens' Song

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

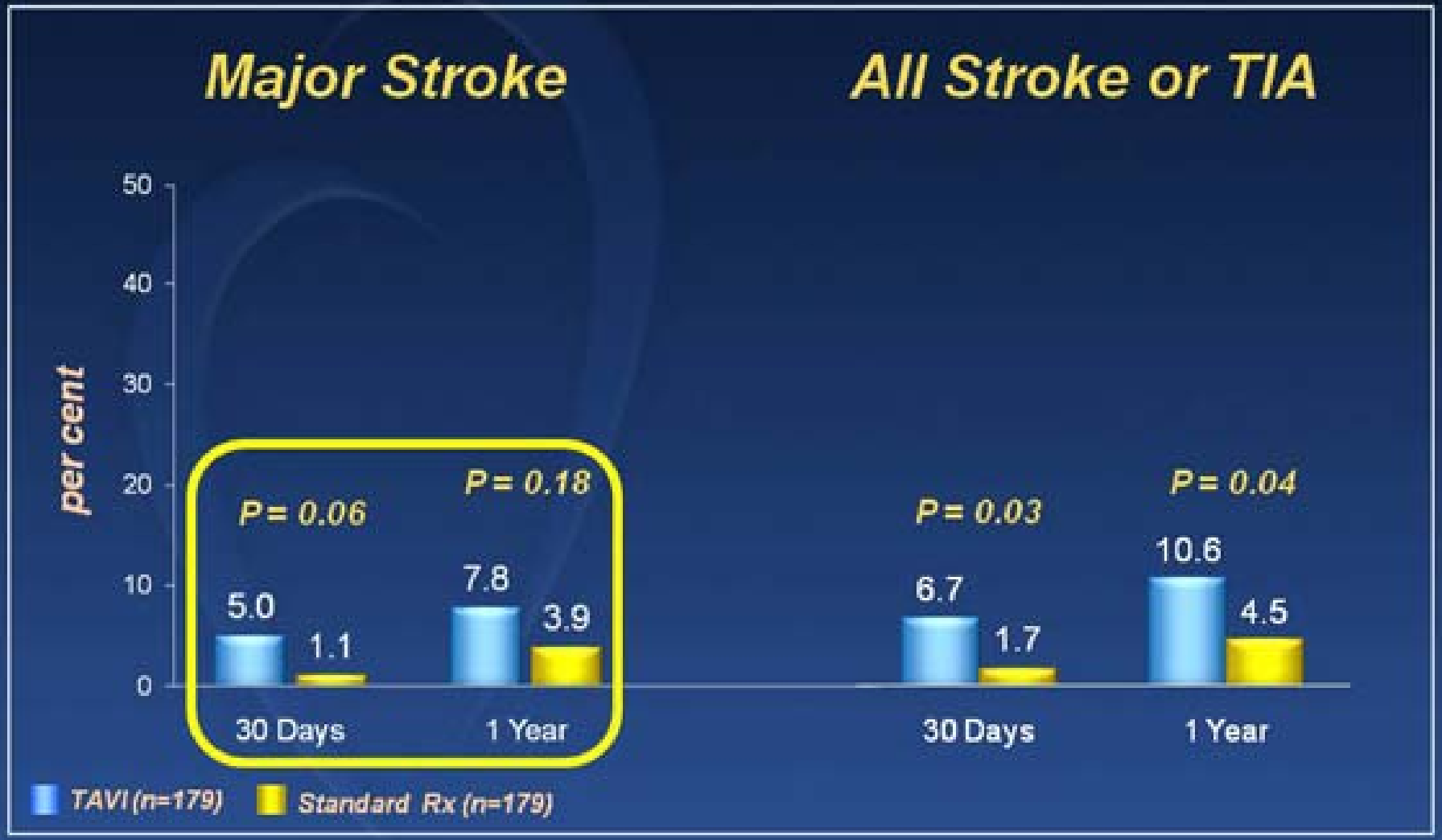
Durham, North Carolina; and Glasgow, Scotland

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%

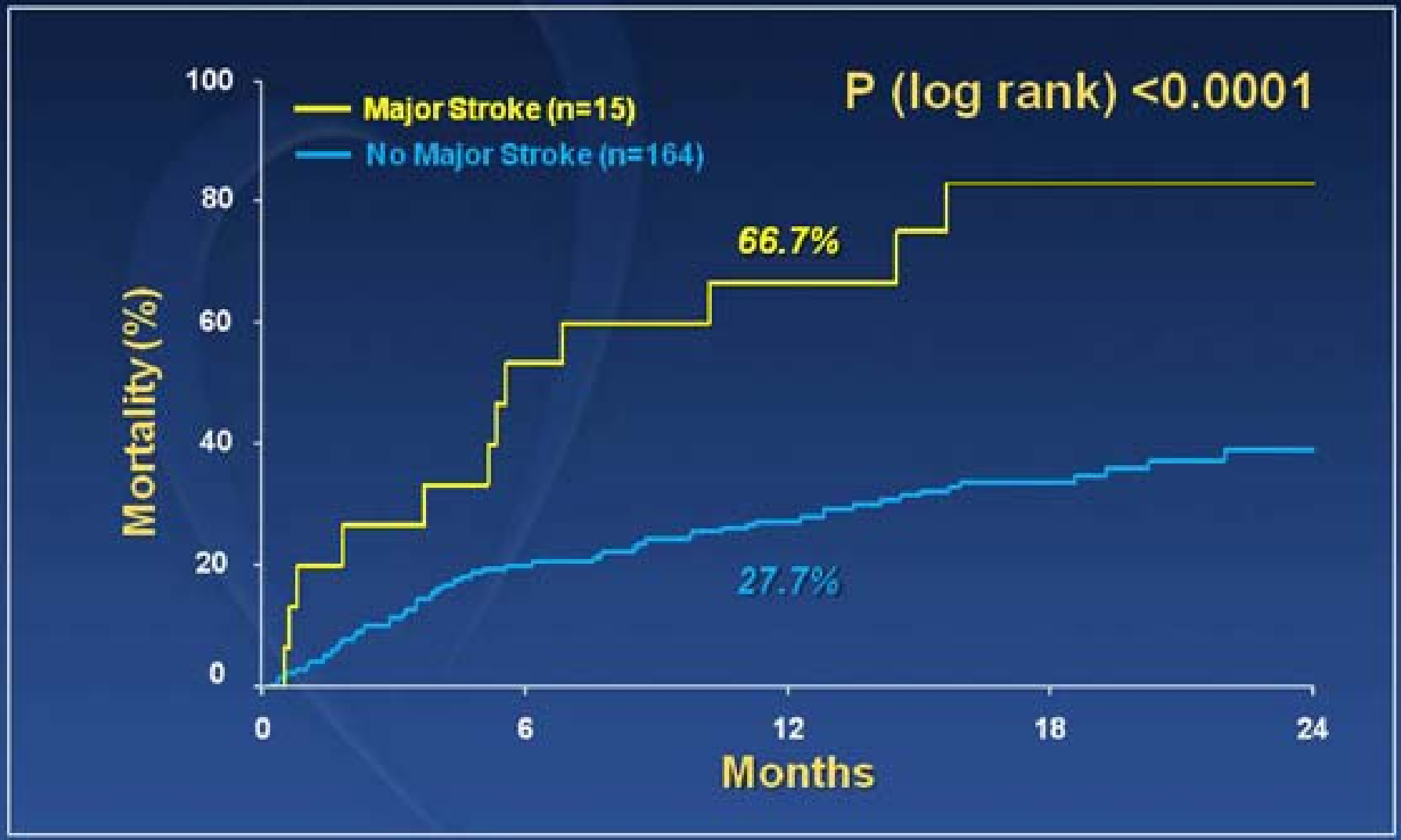
Adapted from Granger CB and McMurray JJV
JACC 2006; 48:434

Clinical Outcomes at 30 Days and 1 Year

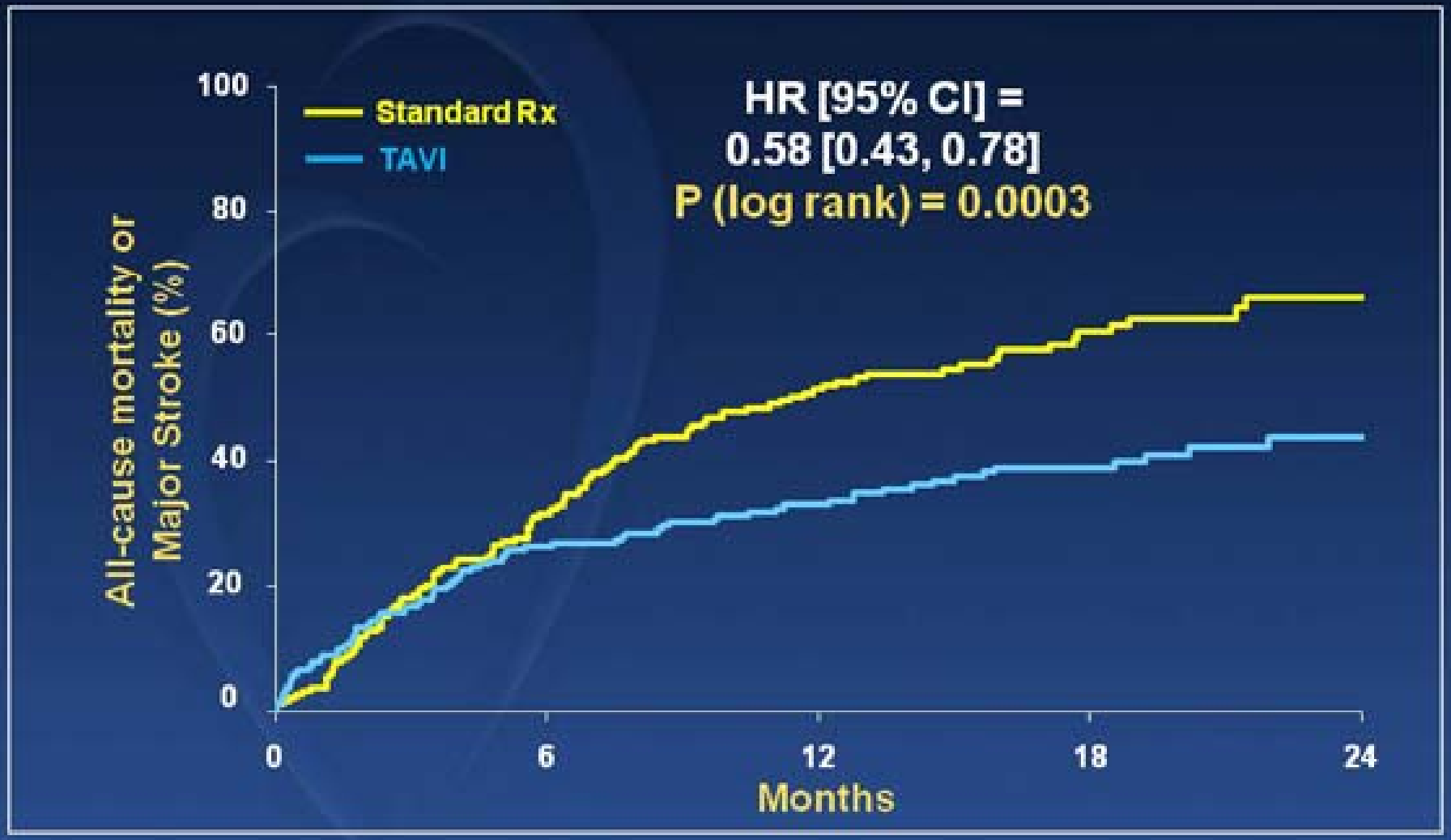


Mortality vs. Major Stroke

TAVI patients

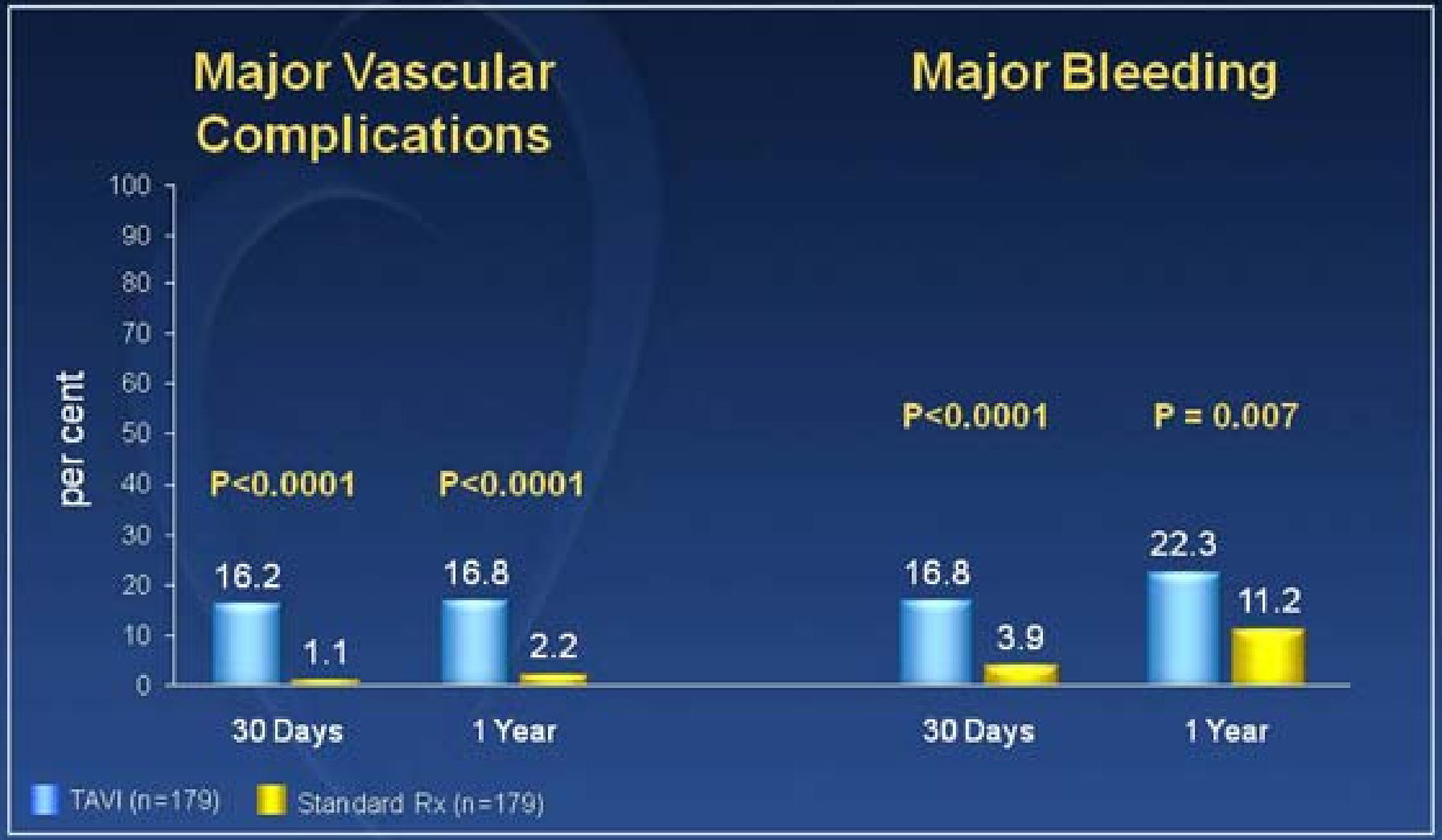


Mortality or Major Stroke



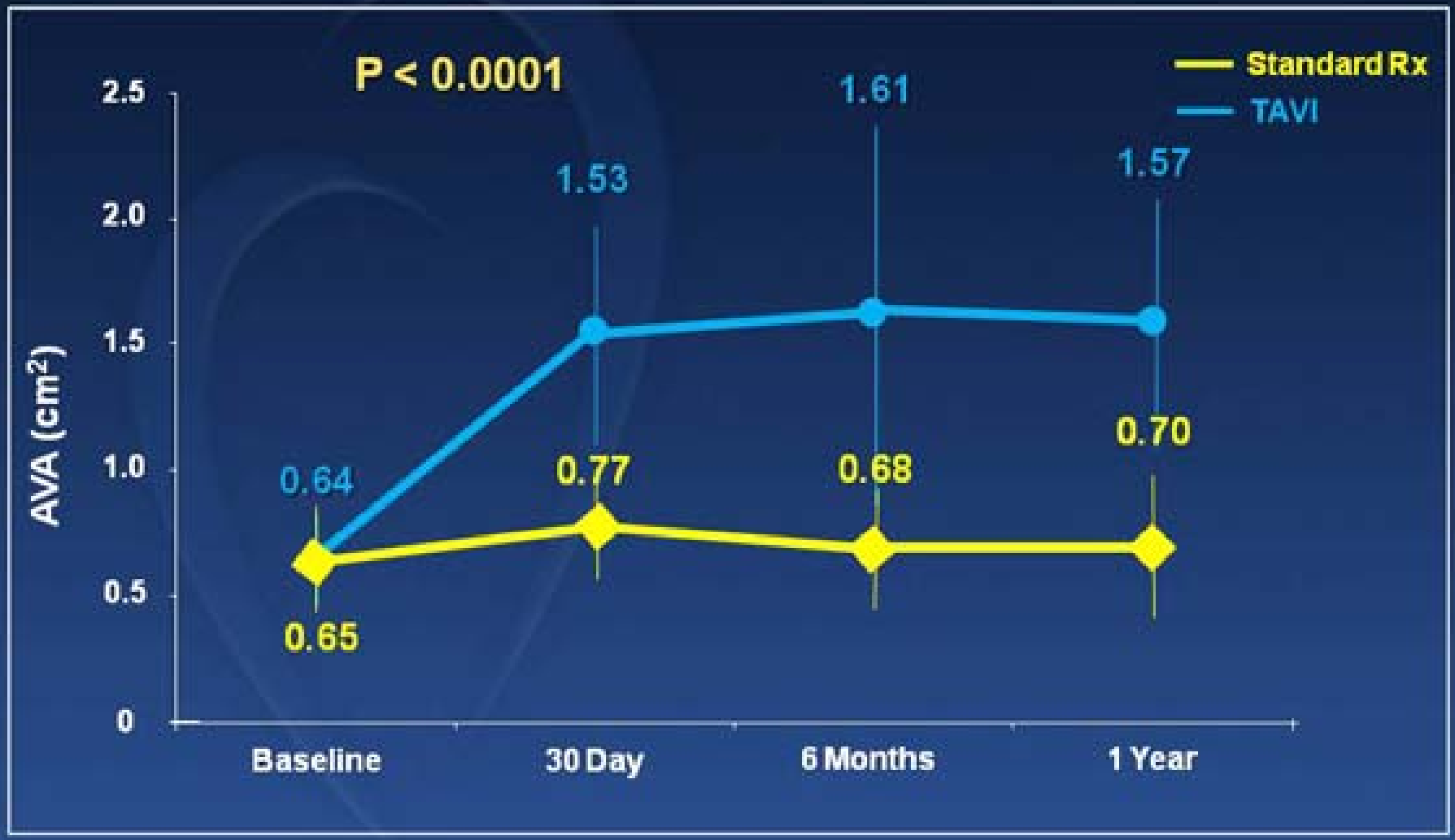
Numbers at Risk					
TAVI	179	132	118	56	25
Standard Rx	**179**	**118**	**83**	**41**	**12**

Clinical Outcomes at 30 Days and 1 Year



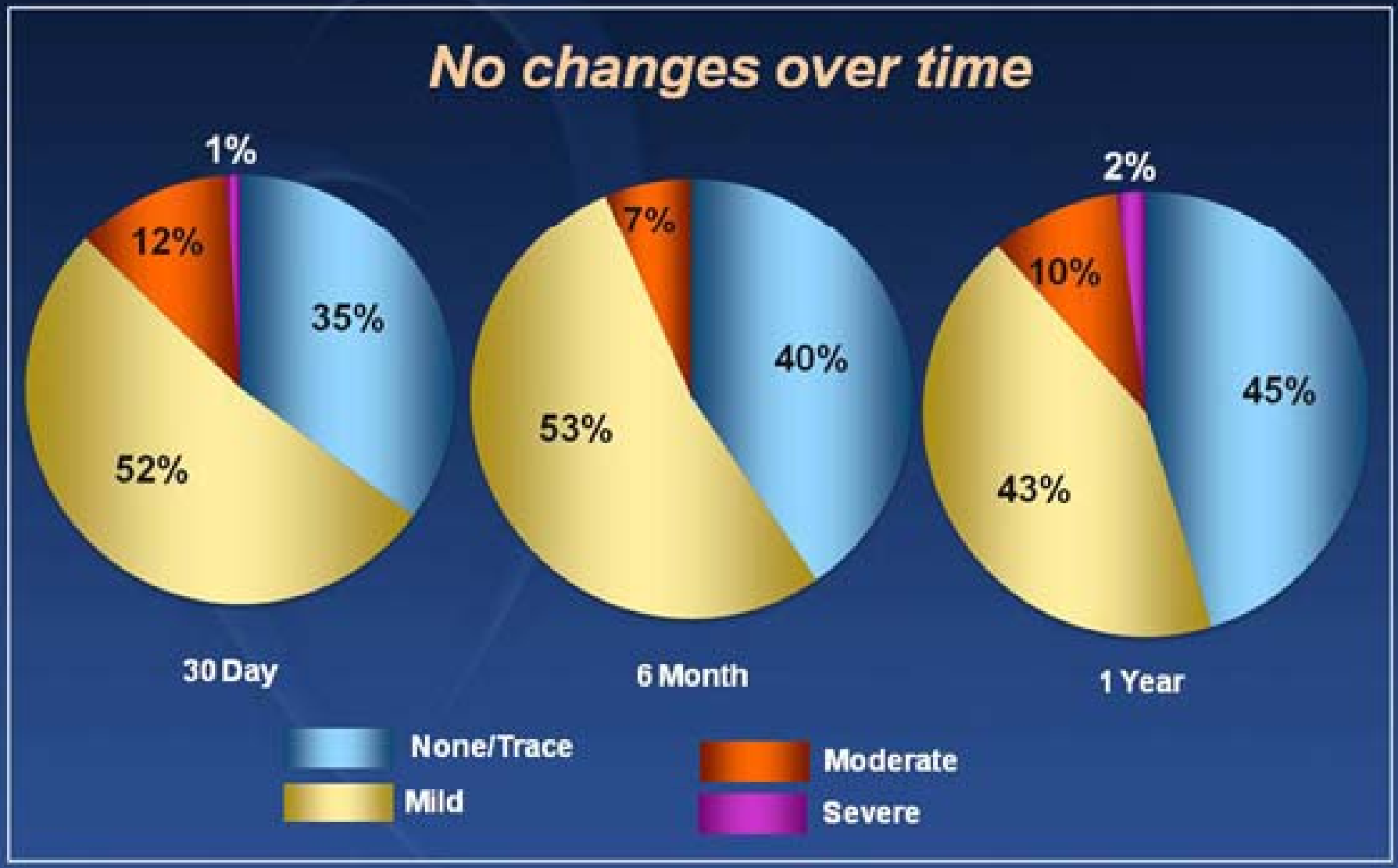
Clinical Outcomes at 30 Days and 1 Year

Aortic Valve Areas Over Time

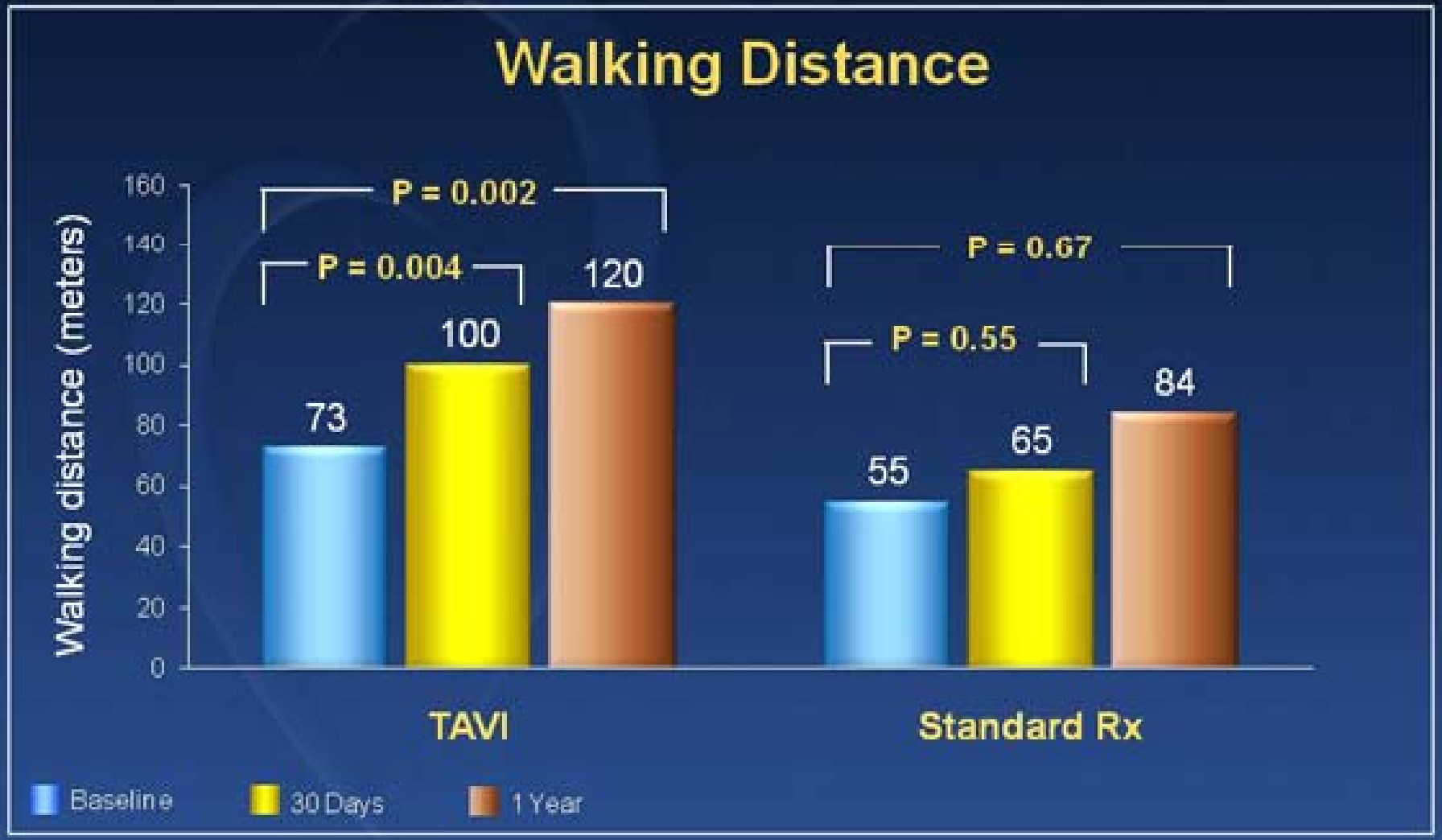


Error bars = ± 1 Std Dev

Paravalvular Regurgitation: TAVI

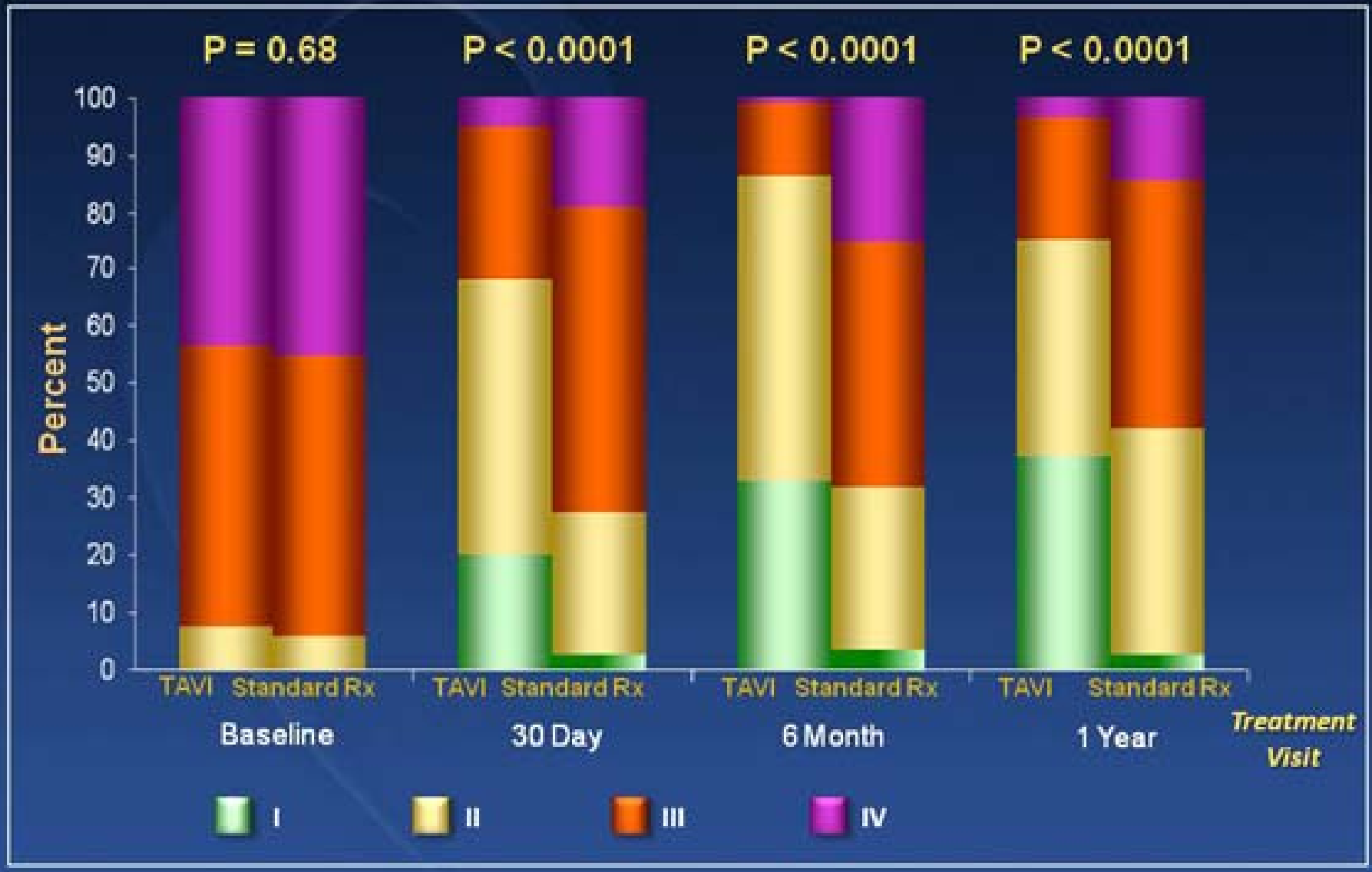


Six-Minute Walk Tests

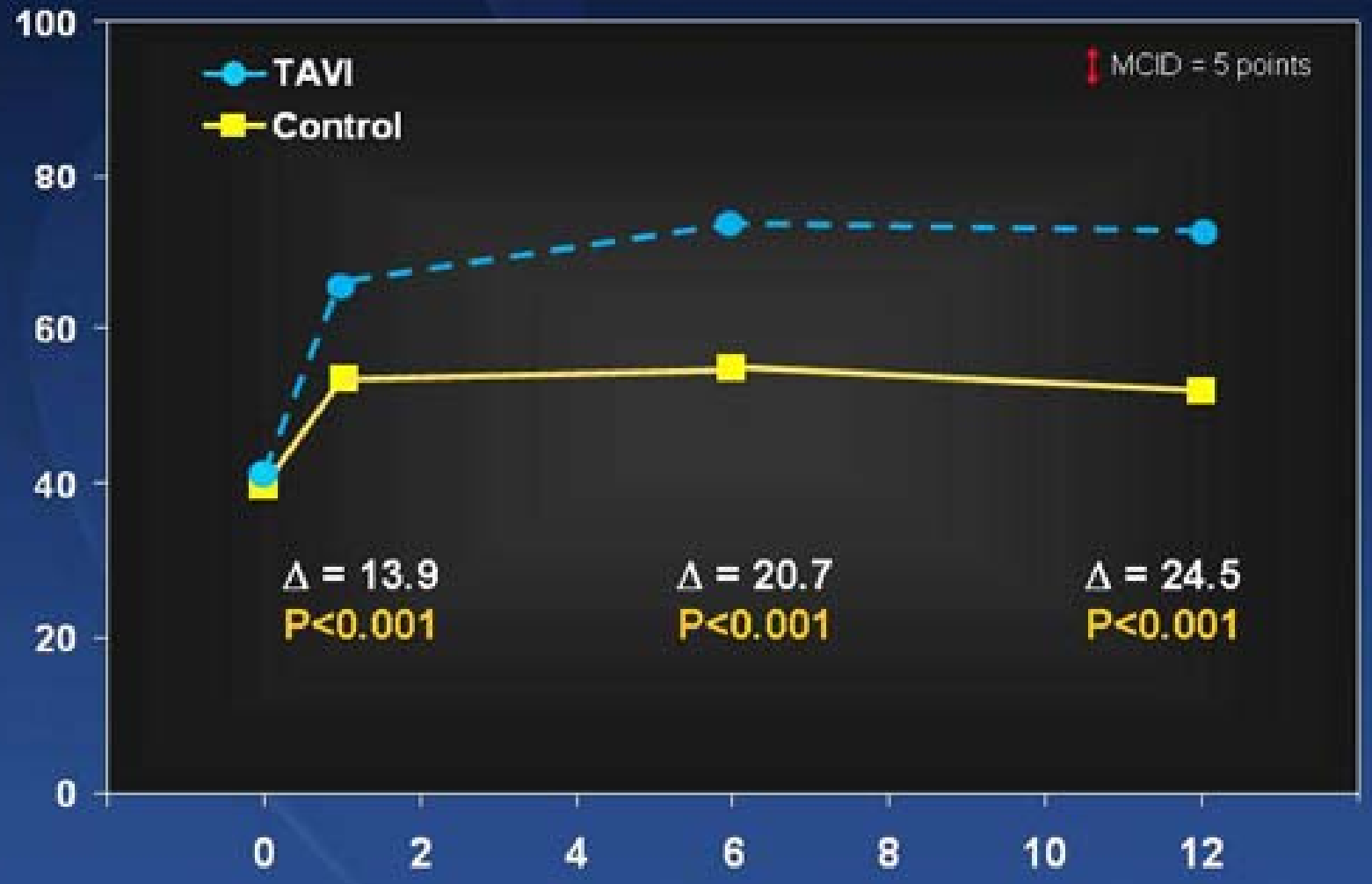


NYHA Class Over Time

Survivors



Primary Endpoint: KCCQ Overall Summary



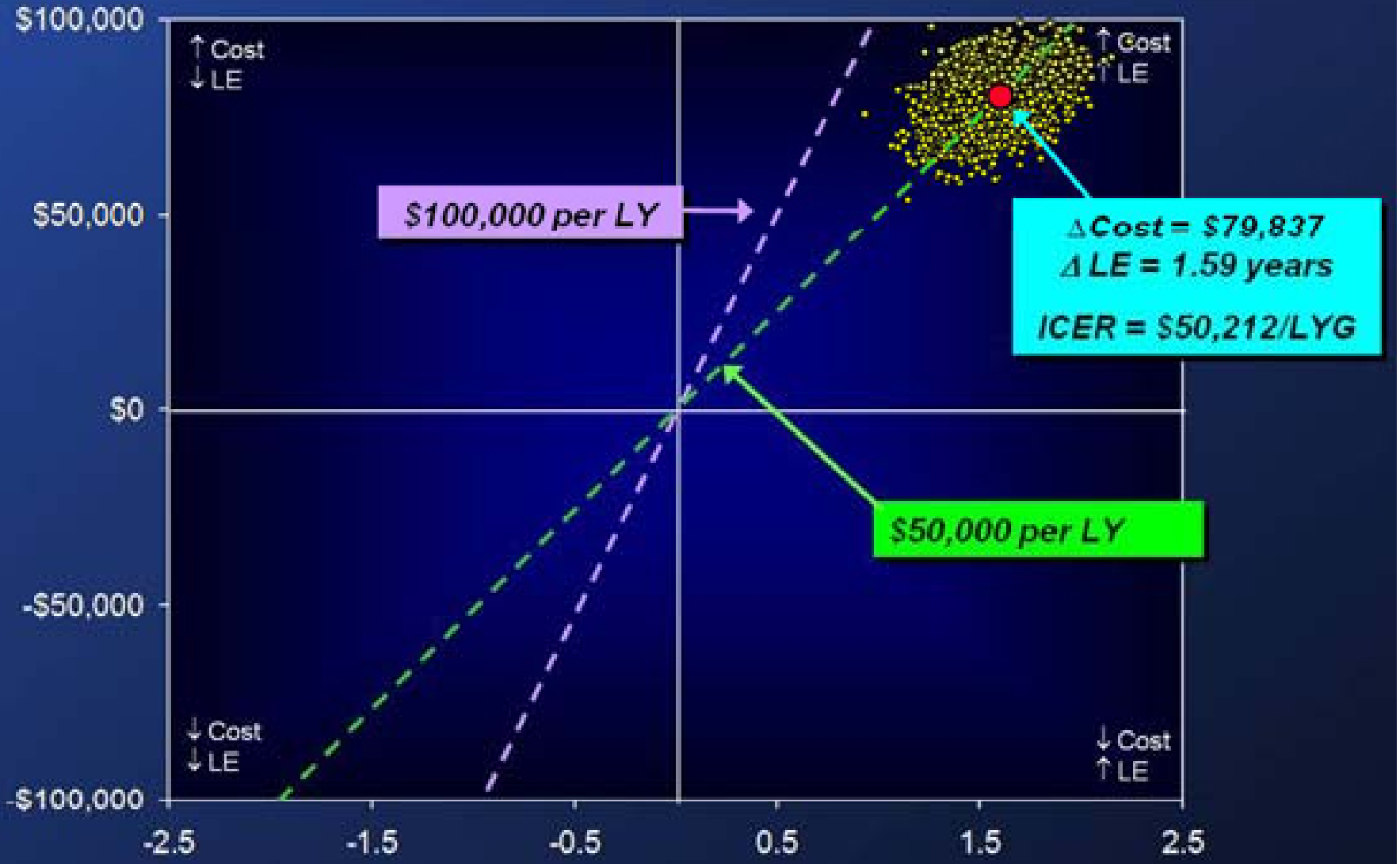
MCID = minimum clinically important difference

PARTNER QOL Analyses

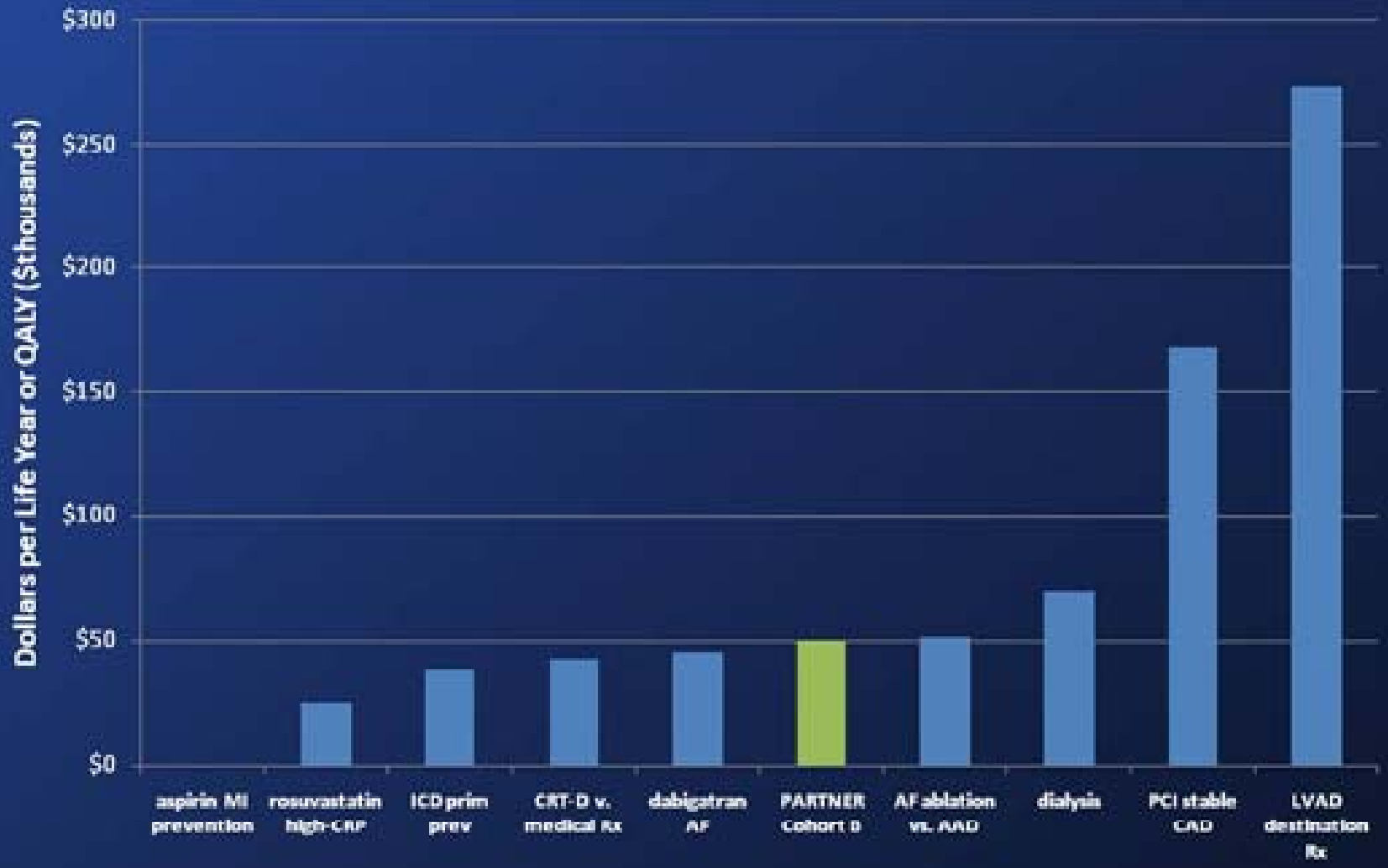
TAVR not only adds years to life, but also, adds life to years!

Cost-Effectiveness of TAVR vs. Control

Lifetime Results



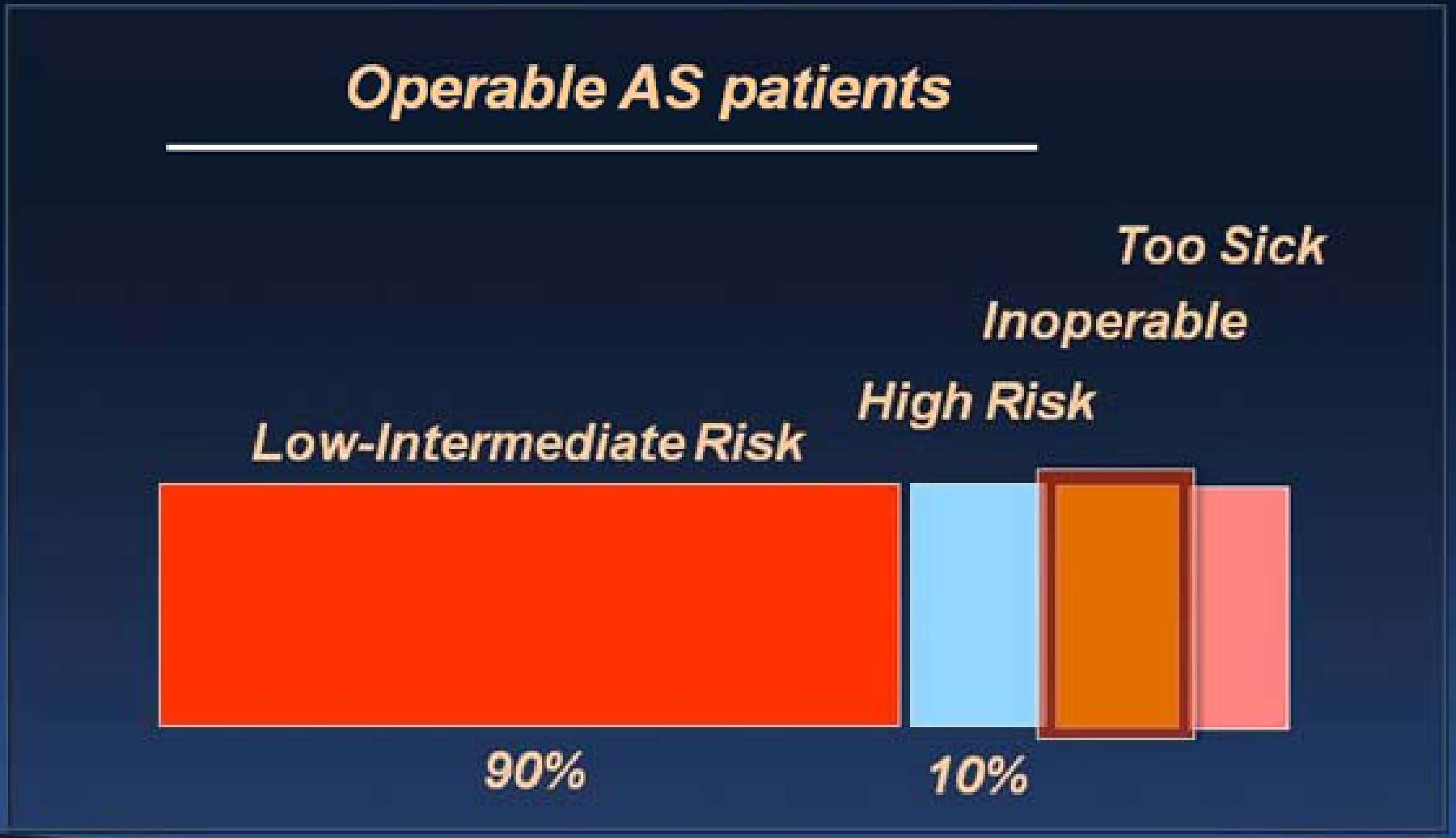
Published Cost Effectiveness Estimates



PARTNER Perspectives - "Inoperable"

- The HEART VALVE TEAM approach is now the preferred model for optimal TAVR success.
- Standard therapy is associated with a prohibitive 1-year mortality.
- TAVR resulted in…
  - Low (~5%) 30-day mortality
  - Historic reduction in 1-year mortality
  - Improved symptoms in survivors
  - New complications (e.g. strokes, vascular, PVL)
- ***Balloon-expandable TAVR is the new standard-of-care for inoperable patients with severe AS!***

TAVR Categories
(risk is a continuum)



TAVR 2011

Main Outcomes: High Risk

High Risk: Patient Characteristics -1

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

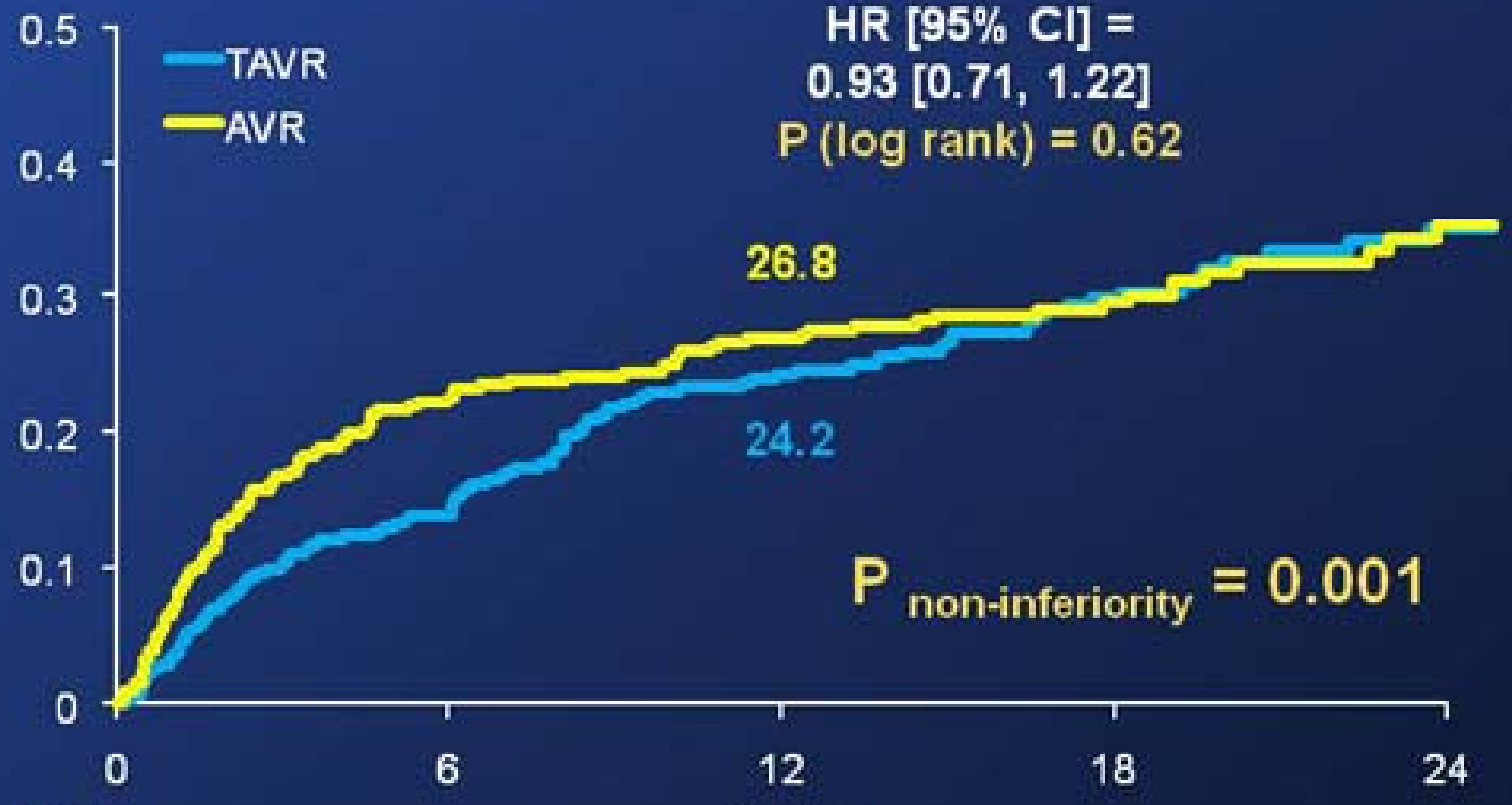
High Risk: Patient Characteristics -2

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

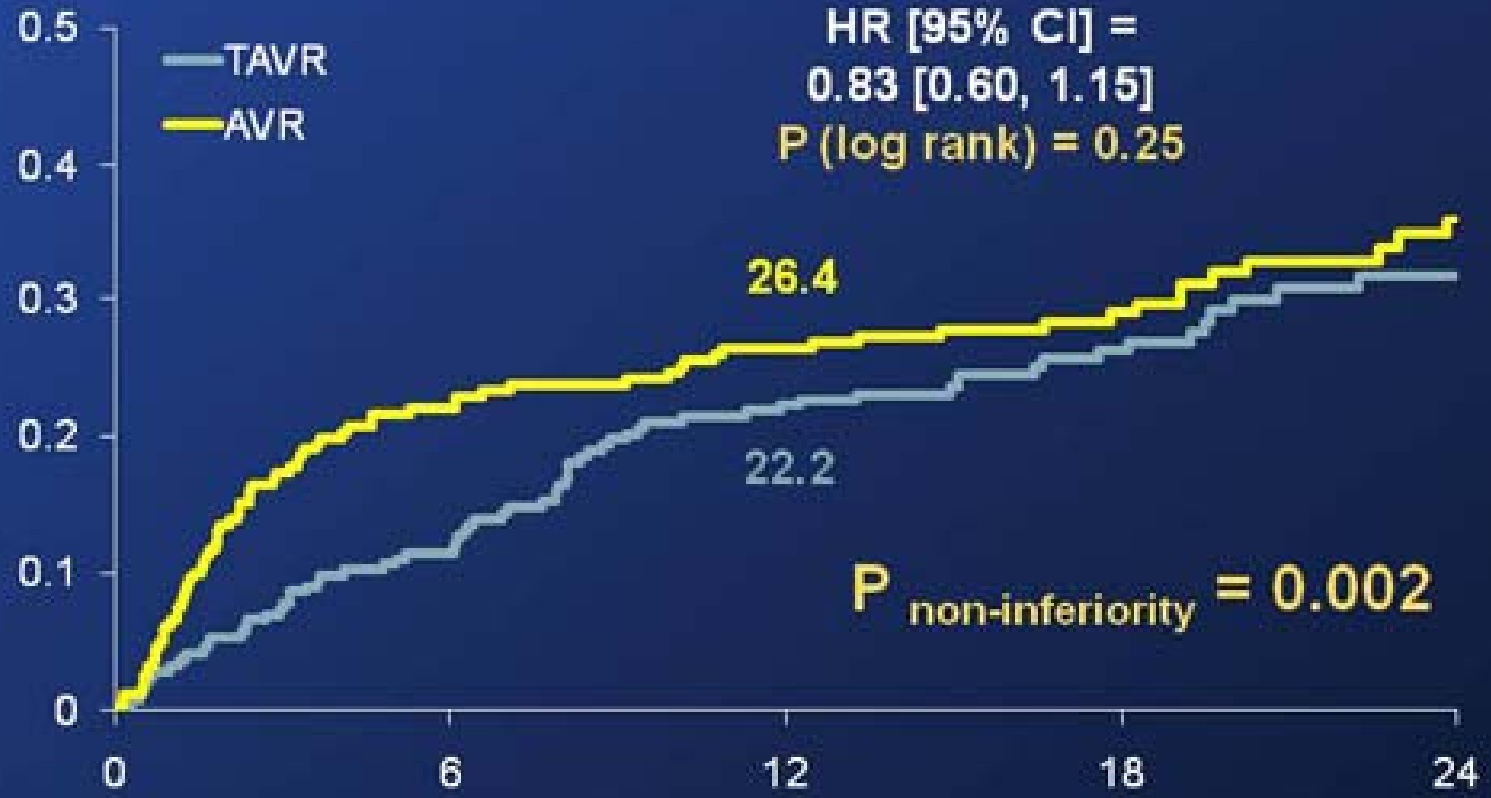
Primary Endpoint:
All-Cause Mortality at 1 Year

THE PARTNER TRIAL



No. at Risk					
TAVR	348	298	260	147	67
AVR	351	252	236	139	65

All-Cause Mortality
Transfemoral (N=492)



No. at Risk					
TAVR	244	215	188	119	59
AVR	248	180	168	109	56

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

THE PARTNER TRIAL

All-Cause Mortality at 30 Days

	All Patients no. of patients (%)			TF Patients no. of patients (%)			TA Patients no. of patients (%)		
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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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Clinical Outcomes at 30 Days and 1 Year
All Patients (N=699)

THE PARTNER TRIAL

Outcome	30 Days			1 Year		
	TAVR (N = 348)	AVR (N = 351)	p-value	TAVR (N = 348)	AVR (N = 351)	p-value
All mortality – no. (%)	12 (3.4)	22 (6.5)	0.07	84 (24.2)	89 (26.8)	0.44
Cardiac mortality – no. (%)	11 (3.2)	10 (3.0)	0.90	47 (14.3)	40 (13.0)	0.63
Rehospitalization – no. (%)	15 (4.4)	12 (3.7)	0.64	58 (18.2)	45 (15.5)	0.38
Death or rehosp – no. (%)	25 (7.2)	33 (9.7)	0.24	120 (34.6)	119 (35.9)	0.73
MI – no. (%)	0	2 (0.6)	0.16	1 (0.4)	2 (0.6)	0.69
Acute kidney inj* – no. (%)	10 (2.9)	10 (3.0)	0.95	18 (5.4)	20 (6.5)	0.56

** Renal replacement therapy*

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)

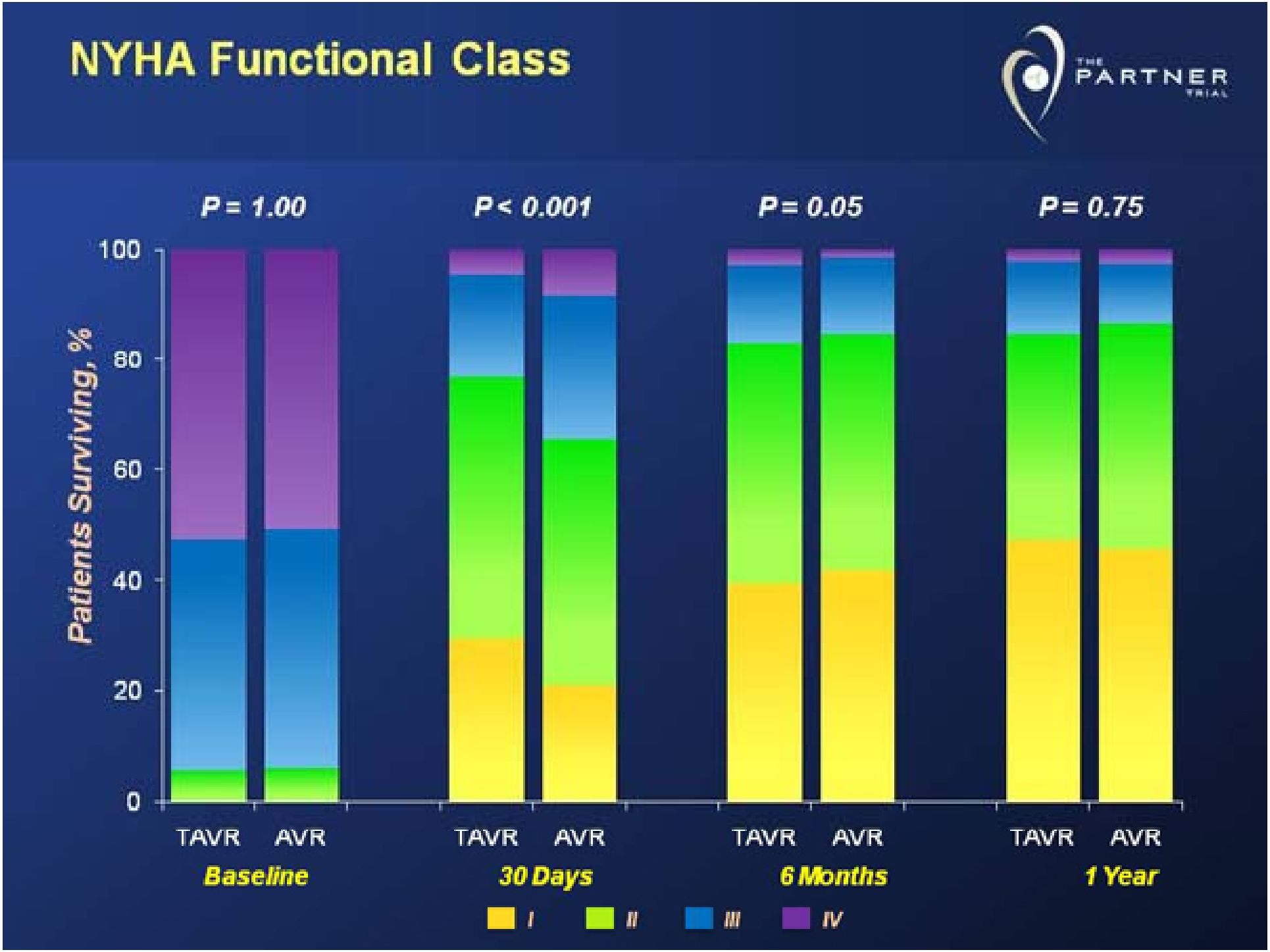
THE PARTNER TRIAL

	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

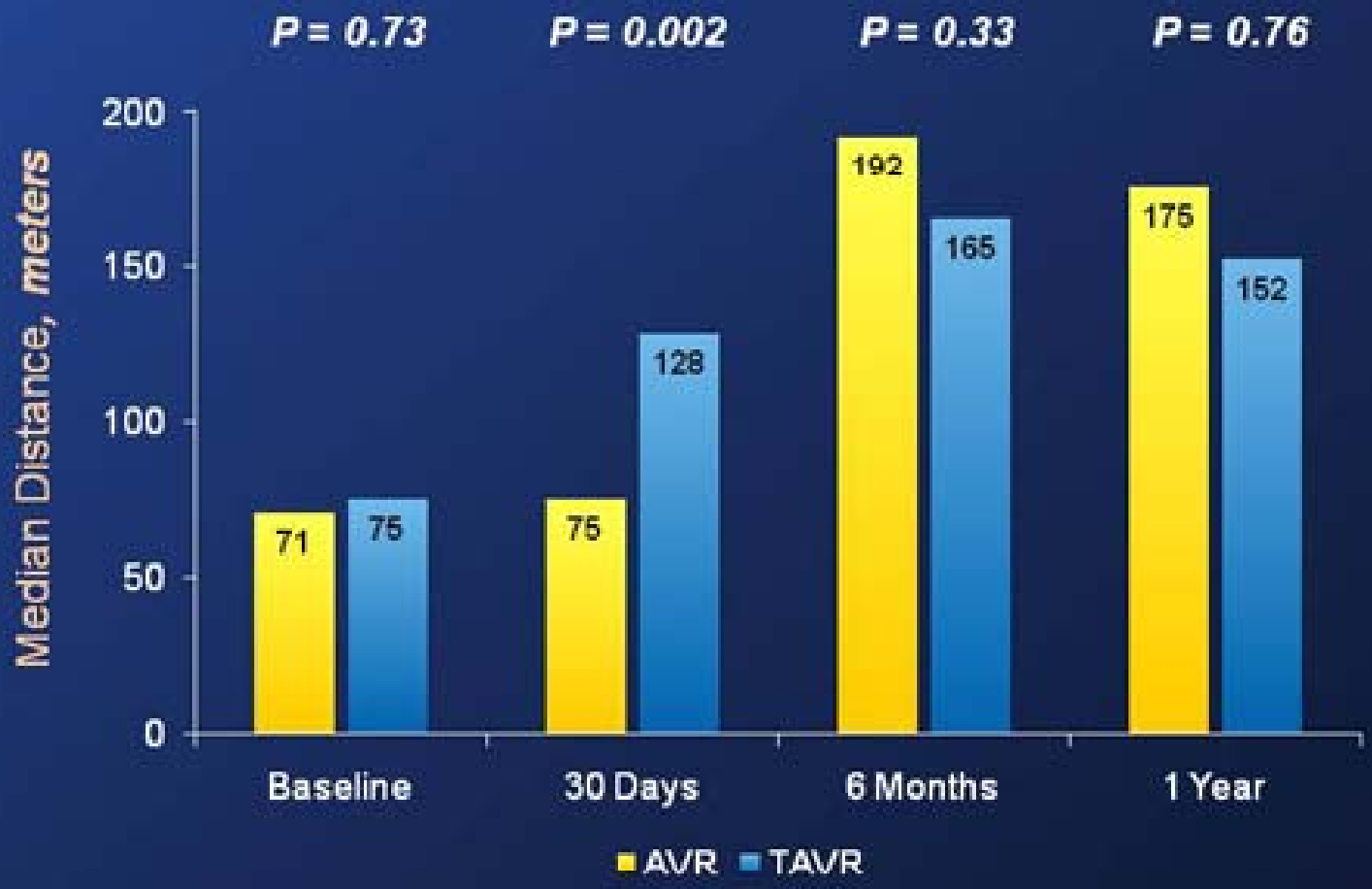
All-Cause Mortality or Stroke
All Patients (N=699)

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

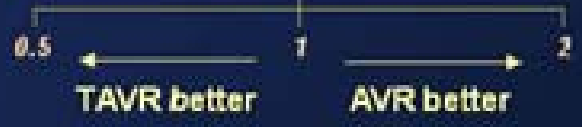
THE PARTNER TRIAL

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)	

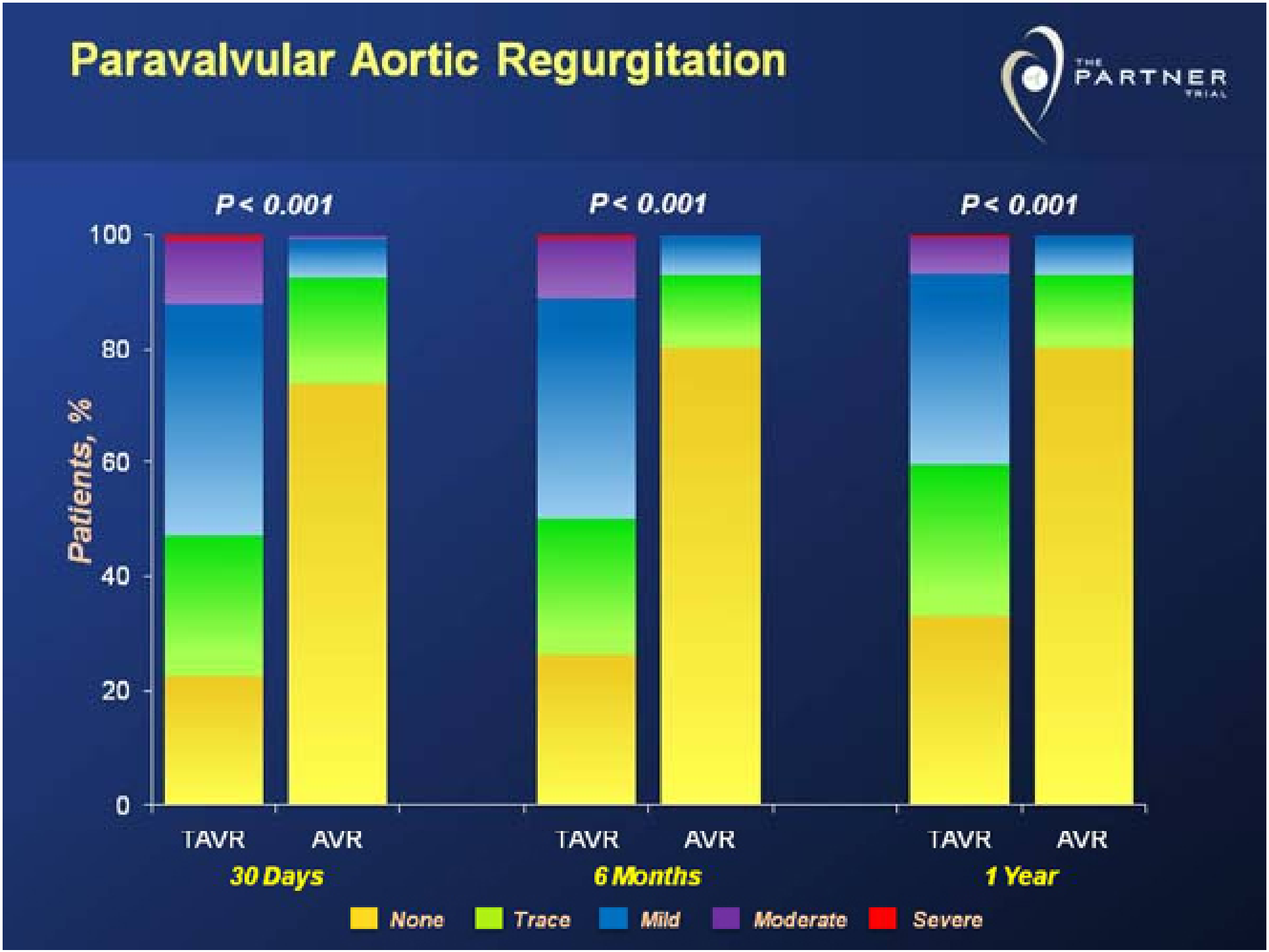


Echo Findings
Hemodynamic Assessments

THE PARTNER TRIAL

	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



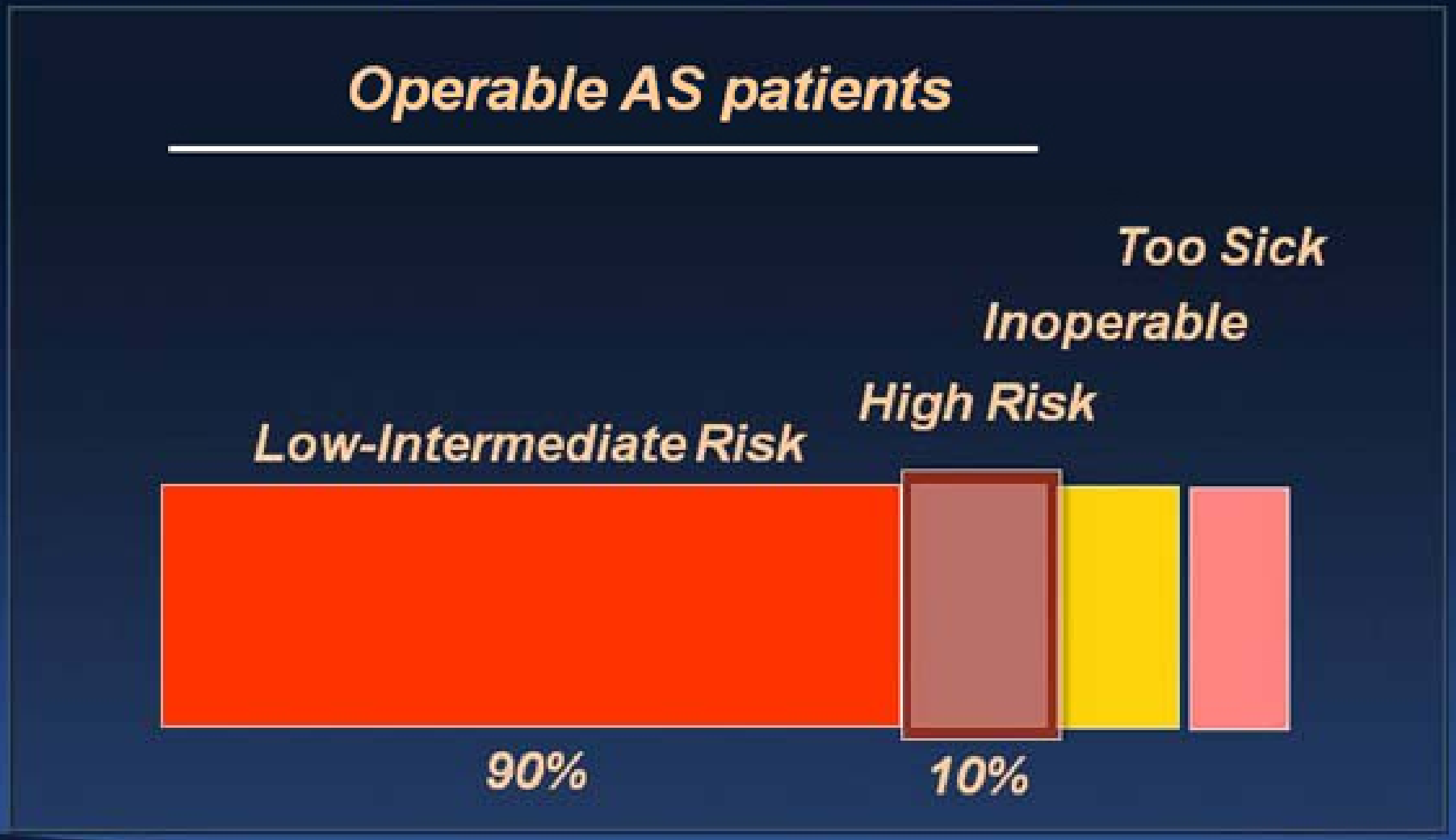
PARTNER Perspectives - "High Risk"

- TAVR and AVR procedural mortality were similar and better than anticipated (30 days: TAVR 3.4%, AVR 6.5%, P=0.07) .
- Mortality at 1-year was also similar for TAVR and AVR (1^{ry} endpoint); $P_{non\text{-}inferiority}$ = 0.001.
- TAVR resulted in…
  - Earlier improvement in symptoms (= at 1-year)
  - Improved echo AV gradients-areas (small;;
  - Different peri-procedural hazards – TAVR increased strokes, vascular complics, PVL and AVR increased bleeding and new onset AF

PARTNER - "High Risk"

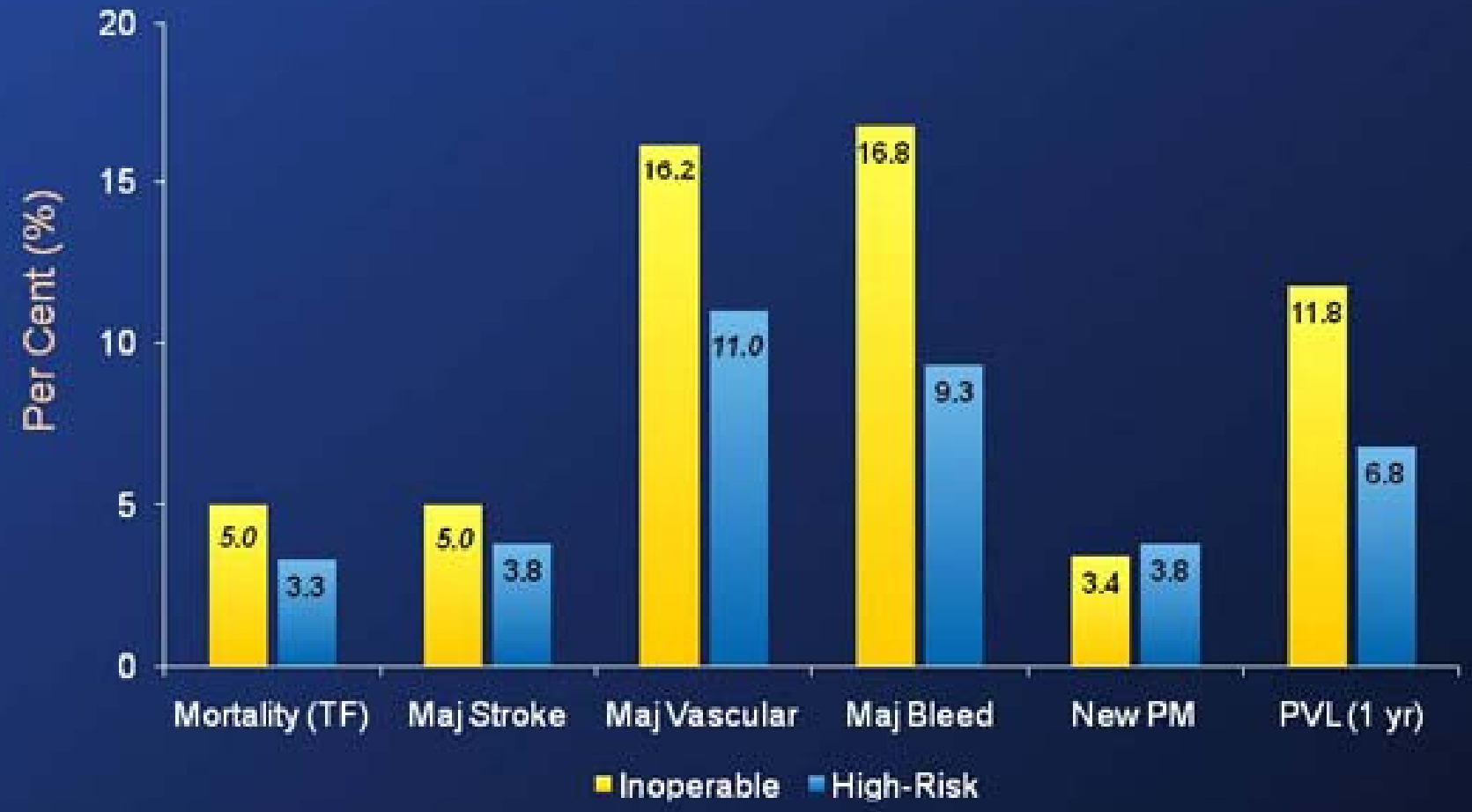
- *Balloon-expandable TAVR is an exciting new alternative therapy to surgical AVR in selected high-risk patients with severe AS!*
- *The positive momentum from the PARTNER RCT will stimulate an explosion of new TAVR trials designed to improve outcomes and expand clinical indications!!!*

TAVR Categories
(risk is a continuum)



TAVR 2011

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



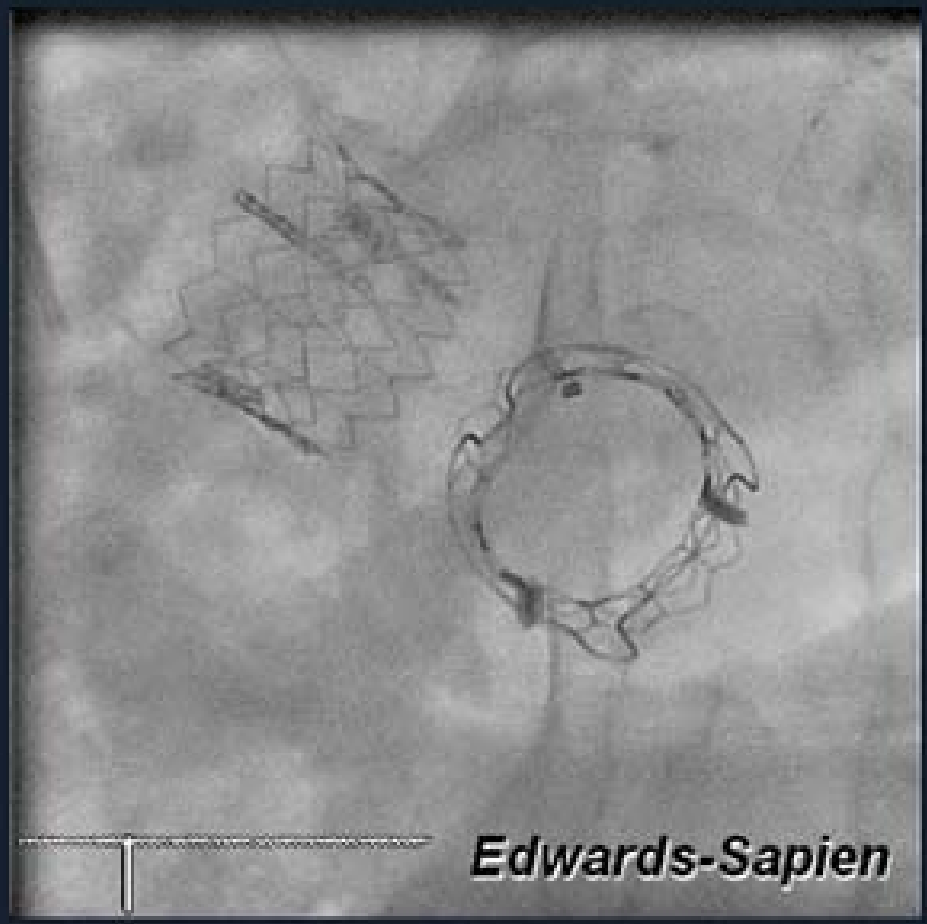
TAVR 2011
Next Clinical Targets

- Valve-in-valve for bio-prosthetic aortic and mitral valve failure
- Lower risk AS patients (? intermediate risk)
- Mixed AS and CAD patients
- Asymptomatic severe AS
- Low flow - low gradient AS (impedance mismatch)
- Aortic regurgitation

TAVR 2011
Endless Possibilities!

Trans-apical AVR

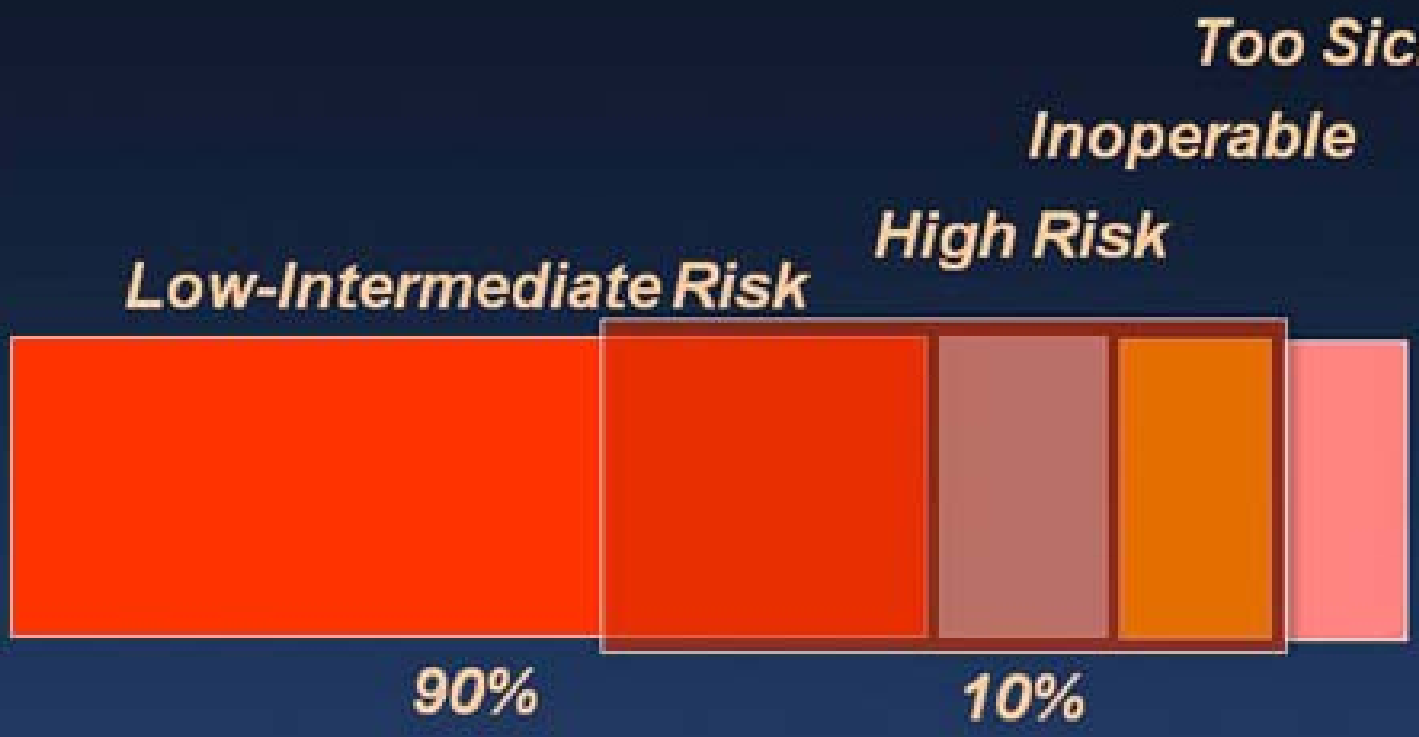
Trans-apical MVR (valve-in-valve)



Courtesy of Dr. John Webb

TAVR Categories
(risk is a continuum)

Operable AS patients



TAVR 2011
Accessory Devices

- Cerebral embolic protection
- New balloon and "other" valvuloplasty catheter systems
- Access site management (esp. closure and including trans-apical)
- Adjunctive imaging, positioning and telemanipulation systems (e.g. 3D echo, CT, 3D angio, electro-mechanical)

TAVR 2011

Cerebral Embolic Protection

SMT ***Embrella*** ***Claret***

Deflectors and Filters

TAVR 2011

- So, what could go wrong? ***…a lot***
  - valve durability
  - perspectives on complications (esp. stroke)
  - long-term effects of mild para-valvular leaks
  - cost-effectiveness
  - results cw surgical AVR
  - surgical counter-offensive (may depend on viability of TA in the future)
  - sponsor impatience (training, site penetration)
  - imponderables…

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