

# The Edwards Lifesciences SAPIEN™ THV Transcatheter Heart Valve System

Circulatory Systems Device Panel  
July 20, 2011  
Food and Drug Administration



# The Edwards Lifesciences SAPIEN™ THV Transcatheter Heart Valve System

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**Jodi J. Akin, MSN**

Vice President Global Clinical Affairs  
Edwards Lifesciences, LLC

## Requested Indication

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*The Edwards SAPIEN™ Transcatheter Heart Valve, model 9000TFX, sizes 23mm and 26mm, and RetroFlex 3 Delivery System are indicated for transfemoral delivery in patients with severe aortic stenosis who have been determined by a cardiac surgeon to be inoperable for open aortic valve replacement in whom existing co-morbidities would not preclude the expected benefit from correction of the aortic stenosis.*

# ACC/AHA Guidelines for Treatment of Aortic Stenosis

Aortic Valve Replacement (AVR) is a Class I indication in symptomatic patients with severe aortic stenosis

# Circulation

JOURNAL OF THE AMERICAN HEART ASSOCIATION

American Heart  
Association®   
*Learn and Live™*

**2008 Focused Update Incorporated Into the ACC/AHA 2006 Guidelines for the Management of Patients With Valvular Heart Disease: A Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Revise the 1998 Guidelines for the Management of Patients With Valvular Heart Disease)**

Robert O. Bonow, Blase A. Carabello, Kanu Chatterjee, Antonio C. de Leon, Jr, David P. Faxon, Michael D. Freed, William H. Gaasch, Bruce W. Lytle, Rick A. Nishimura, Patrick T. O'Gara, Robert A. O'Rourke, Catherine M. Otto, Pravin M. Shah and Jack S. Shanewise

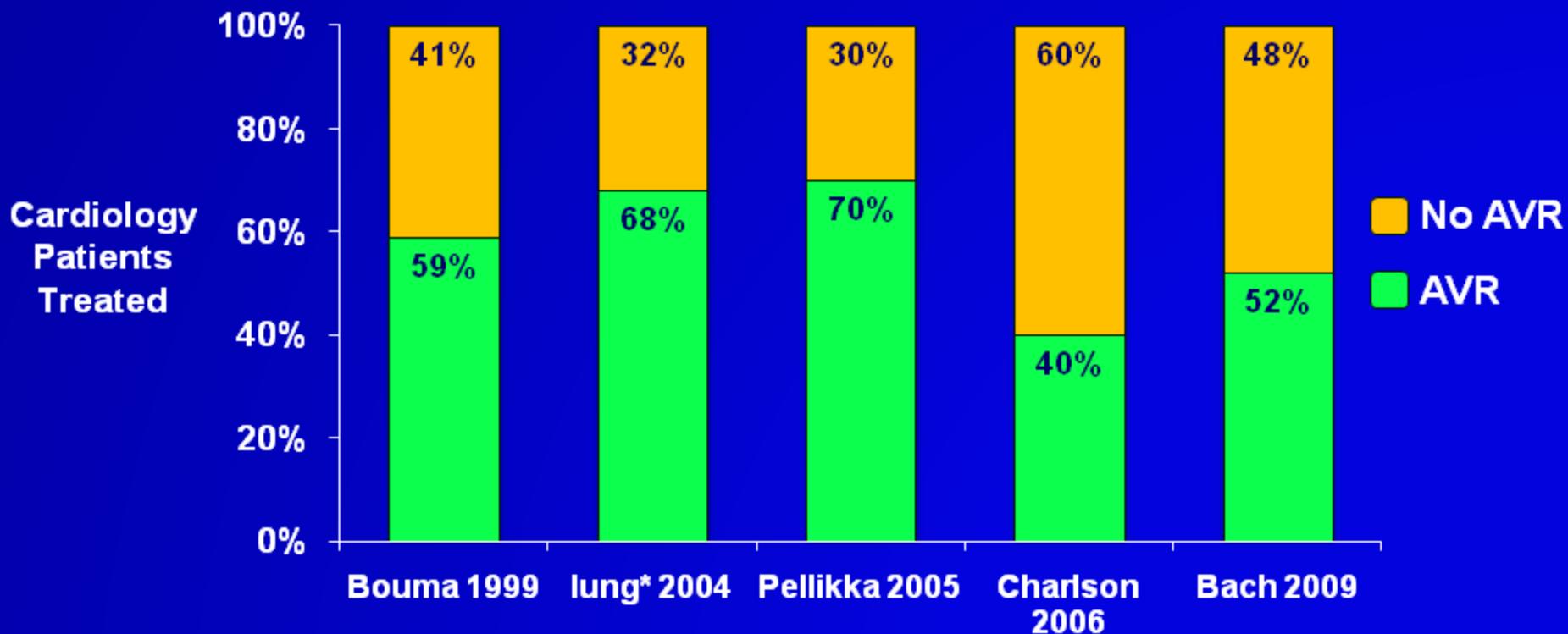
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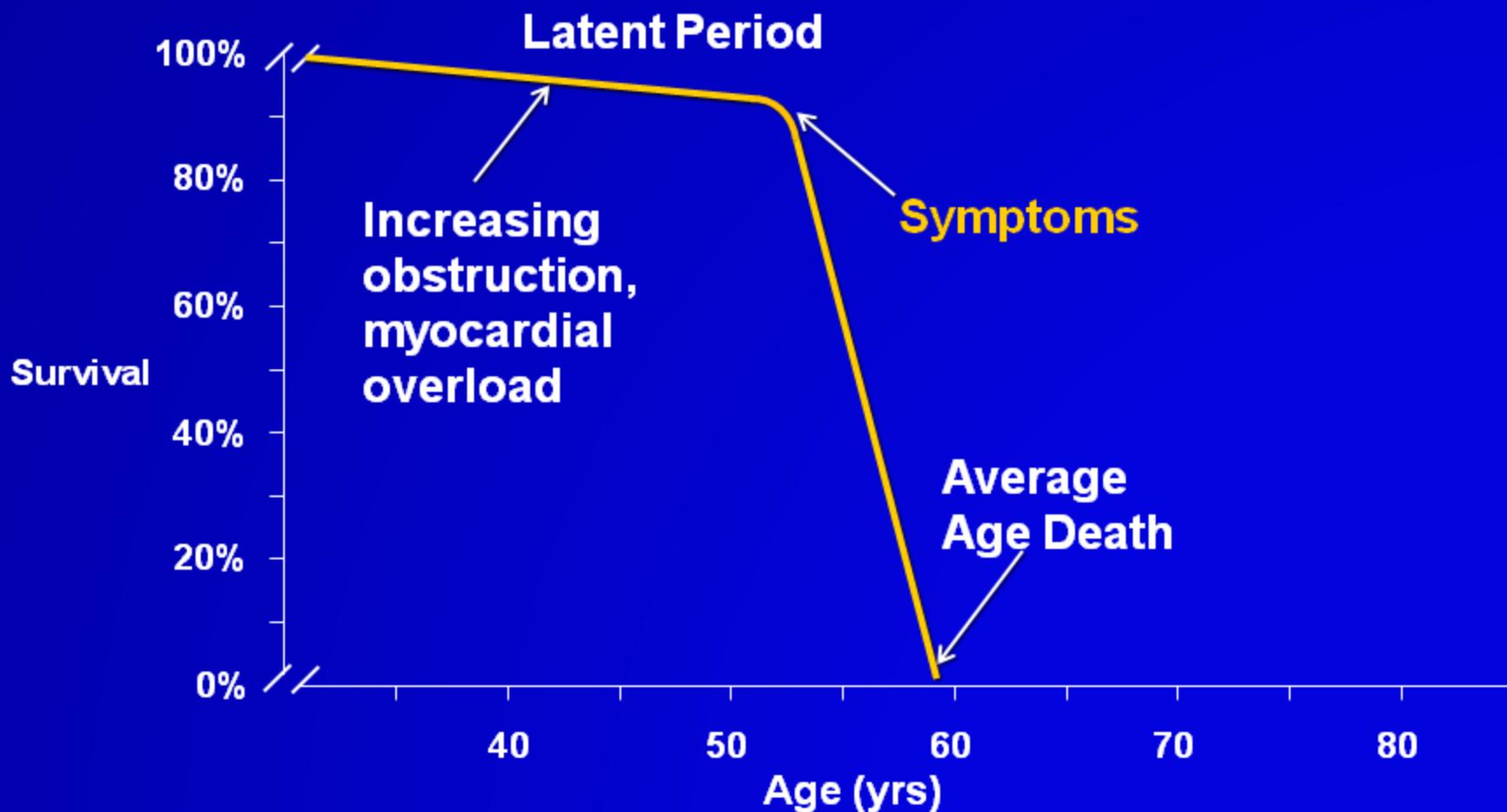
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# 30%-50% of Patients with Severe Aortic Stenosis Are “Untreated”

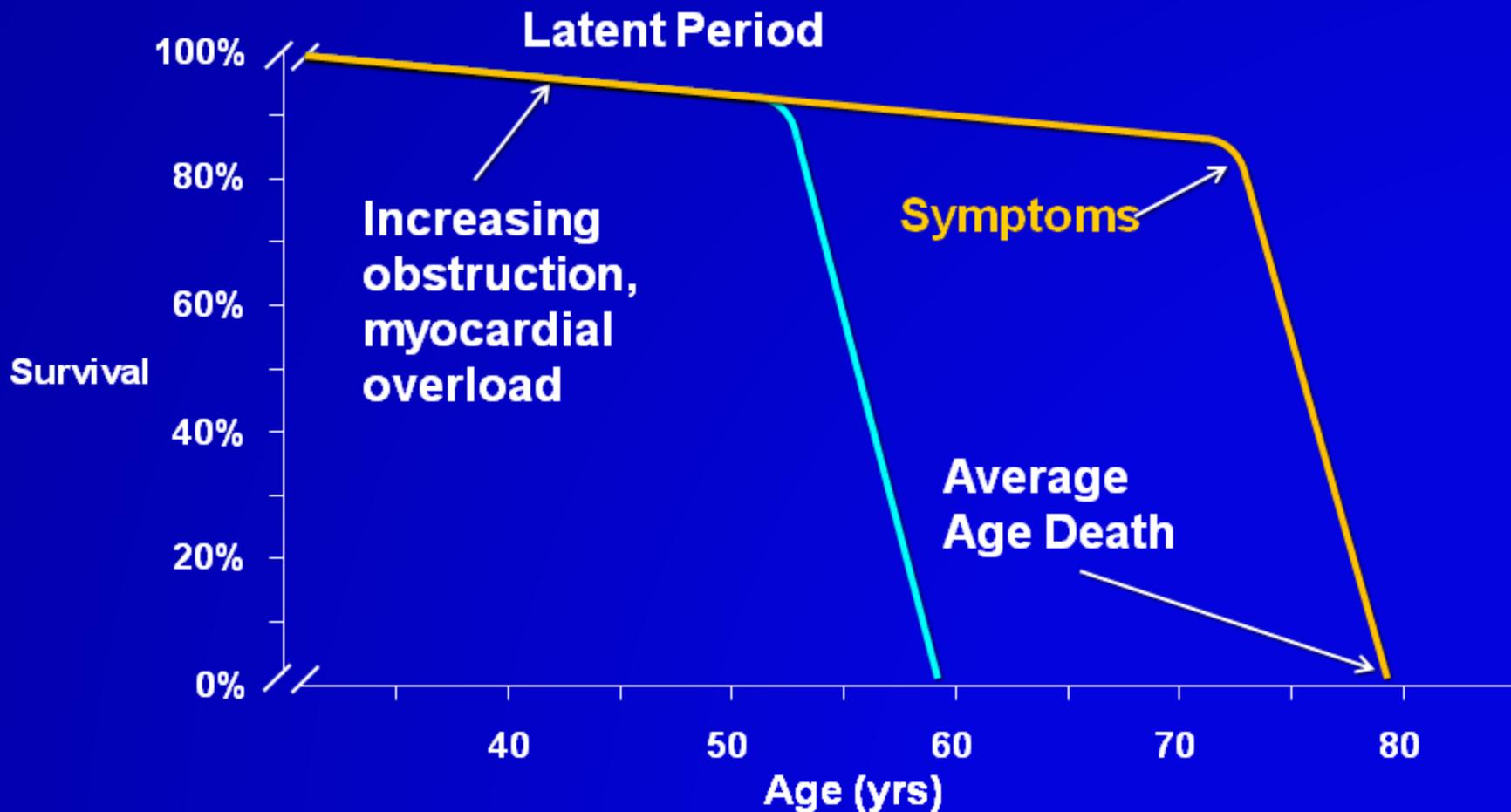


1. Bouma BJ, et al. *Heart*. 1999;82:143-148.
2. lung B, et al. *Eur Heart J*. 2003;24:1231-1243. (\*includes both aortic stenosis and mitral regurgitation patients)
3. Pellikka PA, et al. *Circulation*. 2005;111:3290-3295.
4. Charlson E, et al. *J Heart Valve Dis*. 2006;15:312-321.
5. Bach DS, et al. *Circ Cardiovasc Qual Outcomes*. 2009;2:533-539.

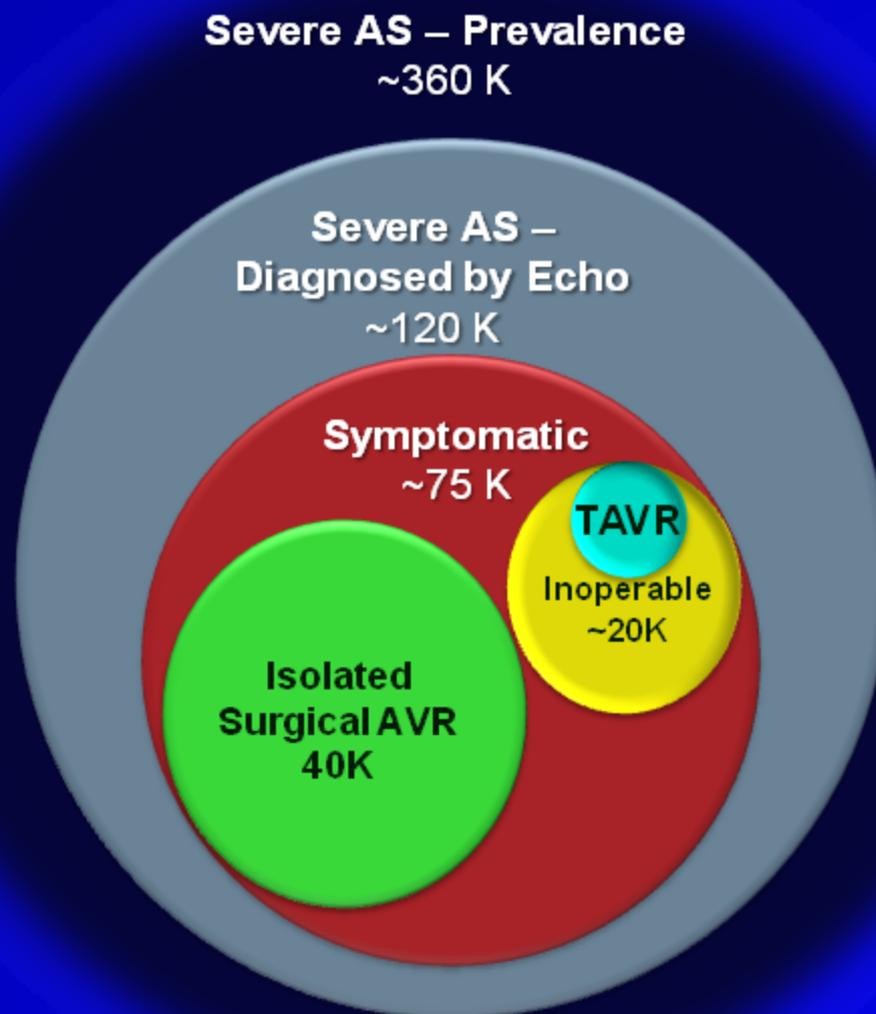
# Natural History of Aortic Stenosis



# Natural History of Aortic Stenosis



# Breakdown of Aortic Stenosis in the United States



# Edwards SAPIEN™ Development and Commercialization Path

1999

2002

2003

2004

2005

2006

2007

2008

2009

2010

2011

Cribier-Edwards n=36

*FIM*

iREVIVE Study

RECAST  
Study

Since 2007, approved  
in 40 countries within  
Europe, Asia, Middle  
East, South America  
and Canada

+15,000 patients implanted worldwide  
+6,000 patients in clinical trials

Edwards SAPIEN n &gt; 5,500

REVIVE  
REVIVAL

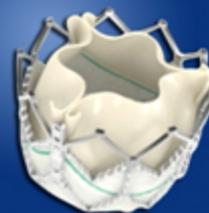
PARTNER EU

The PARTNER Trial

**CE Mark**

SOURCE Registry

Edwards SAPIEN XT n &gt; 1,600

*FIM***CE Mark**

SOURCE XT

PREVAIL

PARTNER  
II Trial

# Edwards SAPIEN™ THV System



**Edwards-SAPIEN™ THV**  
**23mm and 26mm**  
**valve sizes**



**RF 3 Delivery Device**  
**22F and 24F**  
**sheath sizes**

# The PARTNER Trial Results Demonstrate Benefits Outweigh the Risks

- Significant Difference in favor of TAVR
  - All cause mortality
  - Repeat hospitalizations
  - Valve performance
  - Quality of life indices
- Risks of TAVR
  - Stroke
  - Vascular complications
  - Bleeding
  - Paravalvular regurgitation

# Agenda

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The PARTNER Trial  
Study Design and Conduct

**Craig R. Smith, M.D**

Chairman, Department of Surgery  
Columbia University Medical Center

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The PARTNER Trial  
Inoperable Arm  
Study Results

**Martin B. Leon, M.D**

Director, Center for Interventional  
Vascular Therapy  
Columbia University Medical Center

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Global Clinical Experience  
Post Approval Study

**Jodi J. Akin, MSN**

Vice President, Clinical Affairs  
Edwards Lifesciences

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Disciplined Roll-out / Site  
Selection and Training

**Larry Wood**

Corporate Vice President  
Transcatheter Valve Replacement  
Edwards Lifesciences

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## Conflict of Interest

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The Co-Principal Investigators, Drs. Smith and Leon do not own stock in Edwards and have not received financial remuneration for any aspect of their participation in this trial or their participation in this meeting today, excluding travel expenses for trial-related meetings

# The PARTNER Trial

## Study Design and Conduct

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**Craig R. Smith, M.D**

Chairman, Department of Surgery  
Columbia University Medical Center

# Background and Basis of Trial Design: Critical Aortic Stenosis

	<b>Published 1-Year Survival</b>
<b>High Risk Aortic Valve Replacement<sup>1</sup></b>	<b>79% - 93%</b>
<b>TAVR<sup>2</sup></b>	<b>76%</b>
<b>Standard Therapy</b>	
<b>Medical Management<sup>3</sup></b>	<b>49% - 67%</b>
<b>Balloon Aortic Valvuloplasty<sup>4</sup></b>	<b>44% - 58%</b>

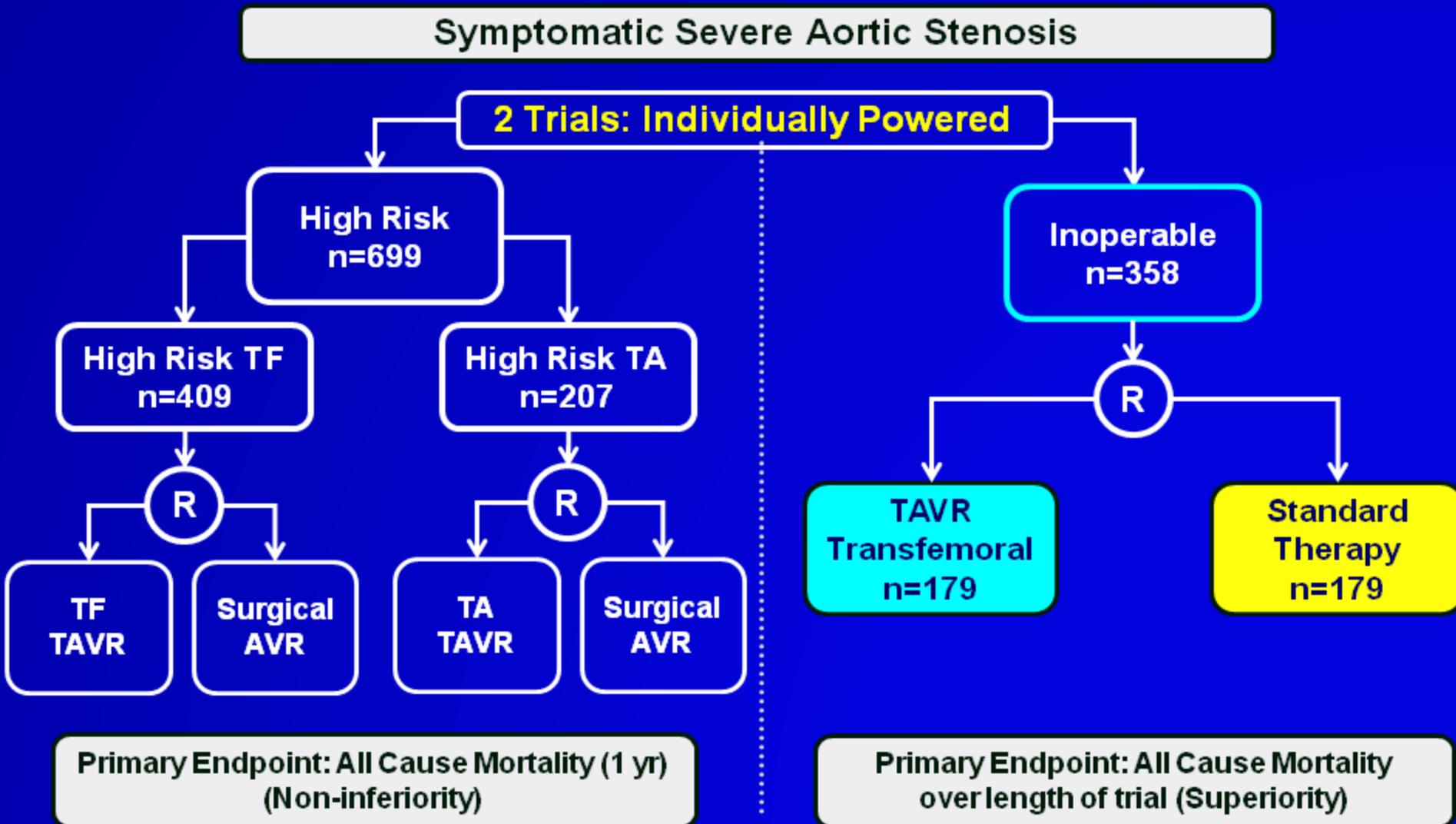
1 Chiappini B et al. Ann Thorac Surg 2004; 78:85-9. Straumann E et al. Br Heart J 1994; 71:449-53. Elayada MA et al. Circulation 1993 Nov; 88(5 Pt 2) II 11-16. Galloway AC et al. Ann Thorac Surg 1990; 49; 84-93.

2 Kodali S et al. Am J Cardiol 2011; 107: 1058-1064

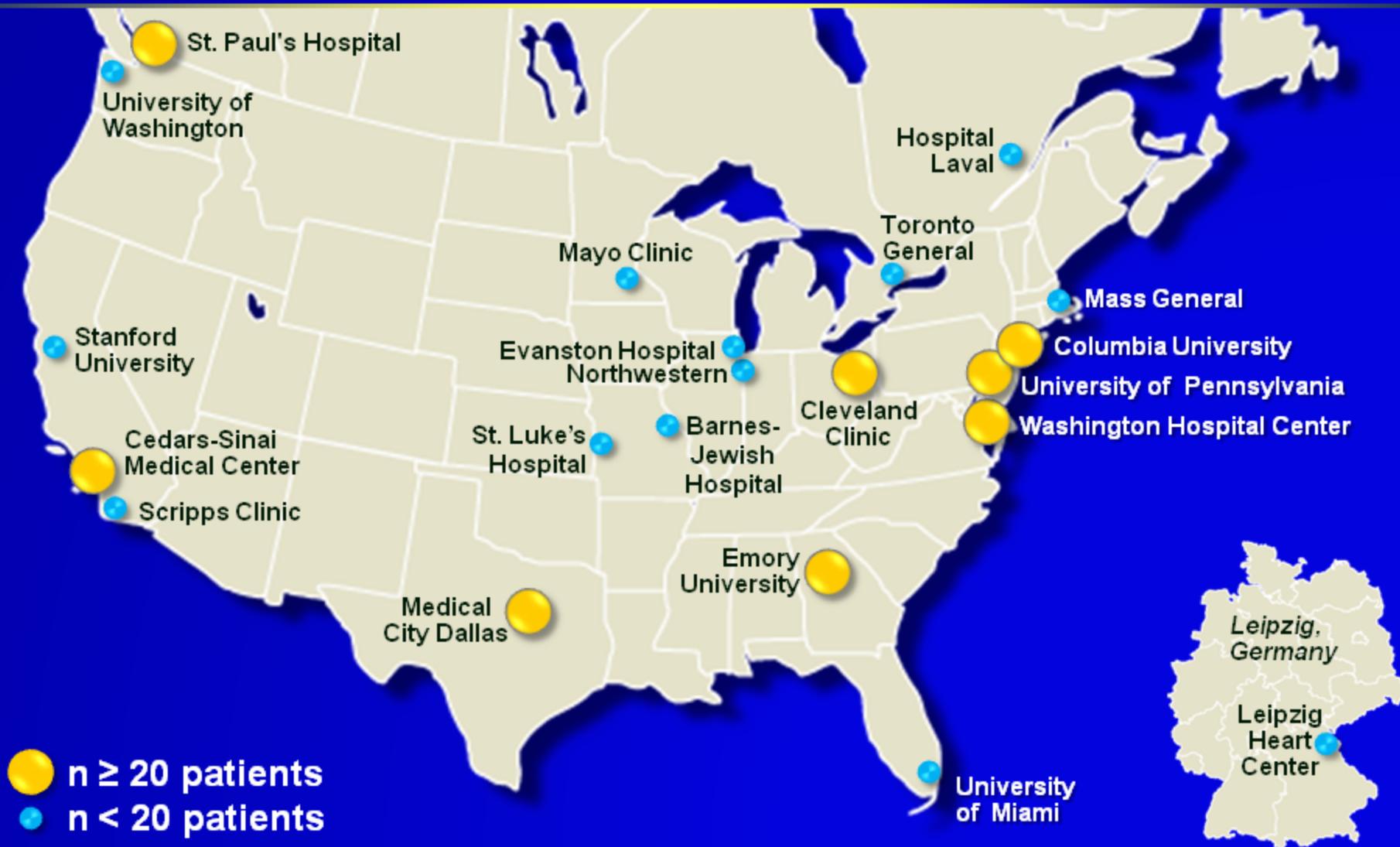
3 Bakaeen FG et al. Ann Thorac Surg 2010 Feb; 89(2) 453-8. Bach DS et al. Circ Cardiovasc Qual Outcomes 2009; 2: 533-539. Varadarajan P et al. Eur J Cardiovasc Surg 2006 Nov; 30(5) 722-7. Bourma BJ et al. Heart 1999; 82:143-148.

4 Shareghi S et al. J Invasive Cardiol 2007; 19(1): 1-5. Agarwal, A et al. Am J Cardiol 2005; 95:43-47. Otto, CM et al. Circulation 1994; 89:642-650. Lieberman, EB et al. Circulation 1994; 90 (part2):II-205-II-208.

# PARTNER Trial Design



# Multicenter Trial, Largely United States



# Study Sites Without Prior TAVR Experience



# Site Selection

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- Presence of Heart Team
  - Cardiac Surgery
  - Clinical Cardiology
  - Interventional Cardiology
  - Echocardiography
  - Anesthesiology
- Surgeon with substantial experience performing high risk aortic valve surgery
- Infrastructure suitable for the procedure
- Clinical research team

# Training and Proctoring

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- Foundational Didactic Course
- Device Preparation and Use Training
- Simulation Training
- Case proctoring – Minimum 2 cases
- Roll-ins – 2 allowed; not included in analysis

## Case Screening

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- Screening work-up: clinical evaluation, echo, cath, vascular access assessment
- Case review webcast presentations: cohort assignment and treatment strategy
- Inoperability determined by 2 surgeons, confirmed by case review
- Treatment within 2 weeks of randomization

# The TAVR Procedure

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- Environment
  - Sterile catheterization / hybrid operating suite
  - Anesthesia
  - Imaging systems
    - Fixed cineflourosopic imaging,
    - Transesophageal echo
- Pre-procedure
  - Sizing of valve and delivery system selected per pre-specified criteria
  - Team roles and procedure choreographed for consistency and efficiency

# TAVR Animation

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# Defining The Inoperable Patient

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## No Validated Instrument for “Inoperable”

- Surgical risk scores (e.g. Society of Thoracic Surgeons' STS, EuroSCORE) provide a “biomarker” of expected procedural morbidity and mortality in the inoperable patient
- Anticipate that STS scores will be bi-modal
  - High STS: one or multiple STS risk elements that exceed thresholds considered safe for operation. (eg. Severe COPD)
  - Low STS: low-prevalence, multiple technical and clinical factors that are not part of the STS risk model. (eg. Severely calcified aorta)

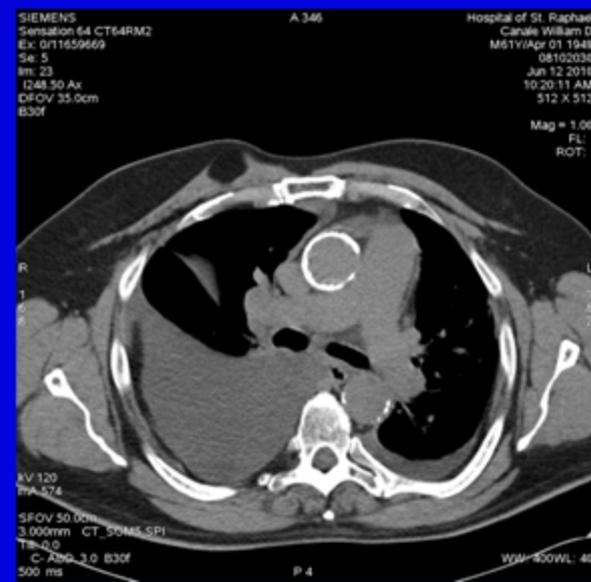
# The Society of Thoracic Surgery Predicted Risk Outcomes Model for Aortic Valve Replacement Surgery

- Risk model derived from data set of 67,292 patients with isolated AVR from 2002 to 2006 (updated in 2007)
- 29 variables (*demographics, risk factors, previous interventions, cardiac status, hemodynamics*) used to calculate operative risk
- Estimates 30 day mortality risk

Valve (AVRepl, MV Repl, MVRrepl)	
<b>B. Demographics</b>	
Patient Age (140)	
Gender (150)	
RaceBlack (192)	
RaceAsian (193)	
Ethnicity (199)	
<b>D. Risk Factors</b>	
Weight (350)	
Height (360)	
Diabetes (400)	
Diabetes Control (410)	
Last Preop Creatinine Level (430)	
Renal Failure-Dialysis (450)	
Hypertension (460)	
Infectious Endocarditis Type (500)	
Chronic Lung Disease (510)	
Immunosuppressive Treatment (520)	
Peripheral Arterial Disease (530)	
Cerebrovascular Disease (540)	
Cerebrovascular Accident (552)	
<b>E. Previous Interventions</b>	
Previous CAB (600)	
Previous Valve (610)	
Previous PCI Interval (670)	
<b>F. Preoperative Cardiac Status</b>	
Previous Myocardial Infarction Timing (760)	
Heart Failure (770)	
Classification-NYHA (775)	
Cardiac Presentation on Admission (791)	
Cardiogenic Shock (810)	
Resuscitation (830)	
Arrhythmia Afib / Aflutter (853)	
<b>G. Preoperative Medications</b>	
Inotropes (970)	
<b>H. Hemodynamics and Cath</b>	
Number of Diseased Vessels (1050)	
Left Main Disease (1060)	
Ejection Fraction (1080)	
Aortic Stenosis (1120)	
Mitral Stenosis (1140)	
Aortic Insufficiency (1170)	
Mitral Insufficiency (1180)	
Tricuspid Insufficiency (1190)	
<b>I. Operative</b>	
Incidence (1230)	
Status (1240)	
IABP-Timing (1440)	
<b>K. Valve Surgery</b>	
Mitral Procedure (1640)	

# Inoperable Example 1: Low STS Score Technically Inoperable

- 61 yo Male, 165 cm ,90 kg
- HTN, Dyslipidemia
- Creatinine 1.5 mg/dL
- Sleep apnea (CPAP)
- **Hodgkin's lymphoma (19 yrs ago, s/p radiation tx)**
- DM type 2 (oral treatment)
- NYHA III for 1 year; NYHA IV recently admitted
- CAD - PCI in 2010
- **Severely Calcified Aorta (porcelain)**
- STS 1.5 %



## Inoperable Example 2: High STS Score Multiple Co-morbidities

- 91 year old male
- HTN, CAD (prior CABG and PCI)
- Atrial fibrillation
- Chronic renal insufficiency (Cr = 2.5 mg/dL)
- Myelodysplastic syndrome (Hgb 9 g/dL)
- COPD (home O<sub>2</sub>), FEV<sub>1</sub> < 50% predicted
- DM (insulin-dependent)
- LV dysfunction (EF = 25%)
- NYHA IV, urgent treatment
- STS 29.3%

## Governing Definition of Inoperable

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- Inoperability based on guideline-driven judgment by experienced cardiac surgeons
  - *Risk of death or serious irreversible morbidity exceeded the probability of meaningful improvement*
- "Before TAVR, would I operate on this patient?" The answer must be "no."

# Ascertainment Safety and Endpoint Adjudication

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# Clinical Assessments

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- Patients assessed at 7 days or discharge, 30 days, 6 and 12 months and then annually for 5 years
- Sweep analysis by phone follow-up after last patient enrolled reached one year

# Clinical Endpoint Adjudication

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- CEC composed of physicians with relevant expertise
  - Cardiac surgery (n=2)
  - Vascular surgery (n=1)
  - Cardiology (n=2)
  - Interventional cardiology (n=1)
  - Neurology (n=1)
- Used FDA and Valve Academic Research Consortium (VARC) consensus definitions

# Eligibility Criteria

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## Key Selection Criteria

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- Meets definition of inoperable
- Severe calcific aortic stenosis
  - Echo derived valve area of  $< 0.8 \text{ cm}^2$   
(EOA index  $< 0.5 \text{ cm}^2/\text{m}^2$ ), mean gradient  $> 40 \text{ mmHg}$  or jet velocity  $> 4.0 \text{ m/s}$
- New York Heart Association (NYHA) functional Class II or greater

## Selected Anatomical Exclusion Criteria

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- Bicuspid or non-calcified aortic valve
- Aortic annulus diameter  $< 18$  or  $> 25$  mm
- Iliac-femoral dimensions or disease which preclude safe sheath insertion
- Severe LV dysfunction (LVEF  $< 20\%$ )
- Untreated CAD requiring revascularization

## Selected Clinical Exclusion Criteria

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- Acute MI within 1 month
- CVA or TIA within 6 months
- Certain cardiac procedures
  - BAV / BMS within 1 month
  - DES within 6 months
- Creatinine > 3.0 mg/dL or dialysis dependent
- Upper GI Bleed within 3 months

## Study Design & Conduct

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- Prospective, consecutively enrolled
- No compassionate/emergency use
- Blinded randomization scheme
  - Centrally administered
  - Random, undisclosed variable block sizes by site
  - No mechanism to reassign
- Data 100% monitored

# Study Endpoints

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# Primary Endpoint

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- Freedom from death (Survival) over the course of the trial
- Superiority test (two-sided)
- 85% power to detect a difference,  $\alpha = 0.05$

## Co-Primary Composite Endpoint

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- Added early in trial
- Hierarchical composite all cause mortality and repeat hospitalization
- Non-parametric method described by Finkelstein and Schoenfeld (multiple pair-wise comparisons)
- > 95% power to detect a difference,  $\alpha = 0.05$
- Multiple comparison adjustment by Hochberg method

## Four Pre-specified Secondary Endpoints

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1. Composite endpoint: Time from randomization to the first occurrence of a major event within one year
  - Death
  - All stroke
  - Myocardial Infarction
  - Renal failure
2. Total hospital days through one year
3. NYHA functional classification at one year
4. 6-minute walk test at one year

# Key Protocol Definitions

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- Rehospitalization
- Stroke
- Bleeding
- Vascular Complications

# Rehospitalization

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- Rehospitalization for Symptoms of Aortic Stenosis
  - Heart failure
  - Angina
  - Syncope
- Rehospitalization for procedure-related complications

# Stroke Definition

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- Focal neurologic deficit
  - Lasting 24 hours or
  - < 24 hours with imaging findings of acute infarction or hemorrhage
- Further classified as
  - Ischemic
  - Hemorrhagic

# Stroke Ascertainment

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- NIH Stroke Scale exam performed by certified examiner at
  - Baseline
  - 7 days / discharge
  - 30 days
  - 6 months
  - 12 months
  - Annually to 5 years
- Imaging in event of positive findings
- CEC adjudication and classification per source documents

# Major Vascular Complications

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- Any thoracic aortic dissection
- Access-related vascular injury leading to either death, need for significant blood transfusions (> 3 U), unplanned percutaneous or surgical intervention, or irreversible end-organ damage
- Distal embolization (non-cerebral) from a vascular source requiring surgery or resulting in amputation or irreversible end-organ damage

# Major Bleeding Events

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- Bleeding causing
  - Death
  - Prolonged hospitalization > 24 hours
  - Requiring pericardiocentesis or open and/or endovascular procedure for repair of hemostasis
  - Permanent disability (eg. blindness)
  - Need for transfusion > 3 u PRC within 24 hours

# Summary Trial Design and Conduct

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- Disciplined, surgeon-driven definition of “inoperable”
- Unique collaboration between specialties in the treatment of valve disease
- Addition of key secondary endpoints and definitions
- Mortality trial

# The PARTNER Trial Inoperable Patient Study Results

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**Martin B. Leon, M.D**

Director, Center for Interventional  
Vascular Therapy

Columbia University Medical Center

# Baseline Characteristics

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# Patient Characteristics: Demographic

Characteristic	TAVR (n=179)		Standard Tx (n=179)	
	n		n	
Age – years (Mean ± SD)	179	83.1 ± 8.6	179	83.2 ± 8.3
Female	97	54.2%	95	53.1%
STS Score (Mean ± SD)	179	11.2 ± 5.8	179	11.9 ± 4.8
NYHA Class III or IV	165	92.2%	168	93.9%

# Patient Characteristics: Vasculopathy

Characteristic	TAVR (n=179)		Standard Tx (n=179)	
	n	%	n	%
CAD	121	67.6	133	74.3
Previous MI	33	18.6	47	26.4
Previous CABG	58	32.4	73	40.8
Previous PCI	47	26.3	39	21.8
Previous BAV	25	16.2	39	24.4
Cerebrovascular disease	48	27.4	46	26.9
Peripheral vascular disease	55	30.9	45	25.1

# Patient Characteristics: Co-morbidities

Characteristic	TAVR (n=179)		Standard Tx (n=179)	
	n	%	n	%
<b>COPD – Any*</b>	<b>74</b>	<b>41.3</b>	<b>94</b>	<b>52.5</b>
Creatinine >2mg/dL	8	4.5	16	9.0
<b>Atrial fibrillation*</b>	<b>28</b>	<b>32.9</b>	<b>39</b>	<b>48.8</b>
Permanent pacemaker	35	19.6	31	17.3
Pulmonary hypertension	50	42.4	53	43.8

\* Difference was statistically significant;  $p < 0.05$

# Patient Characteristics: Inoperable Features

Characteristic	TAVR (n=179)		Standard Tx (n=179)	
	n	%	n	%
COPD - Oxygen dependent	38	21.2	46	25.7
Frailty	21	18.1	33	28.0
<b>Severely calcified aorta*</b>	<b>34</b>	<b>19.0</b>	<b>20</b>	<b>11.2</b>
Chest wall radiation	16	8.9	15	8.4
Chest wall deformity	15	8.4	9	5.0
Liver disease	6	3.4	6	3.4

\* Difference was statistically significant;  $p < 0.05$

# Patient Characteristics: Echocardiography

Characteristic	TAVR (n=179)		Standard Tx (n=179)	
	Mean	SD	Mean	SD
Aortic valve area (cm <sup>2</sup> )	0.6	± 0.2	0.6	± 0.2
Mean AV gradient (mm Hg)	44.5	± 15.7	43.0	± 15.3
Mean LVEF (%)	53.9	± 13.1	51.1	± 14.3
		%		%
Mod-Severe MR (%) (≥ 3+)		22.2		23.0

# Treatments Received

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# Treatments Received: Standard Therapy Patients

	Standard Tx (n=179)			Standard Tx (n=179)	
	n	%		n	%
<b>First 30 Days</b>			<b>After 30 Days (≤ 1 yr)</b>		
Medical Management	56	31.3%	First time BAV	21	11.7%
BAV only	117	65.4%	Repeat BAV	37	20.7%
BAV followed by AVR	3	1.7%	TAVR OUS*	4	2.2%
AVR (1), LV Ao Conduit (2)	3	1.7%	AVR (9) /LV Ao Conduit (3)**	12	6.7%

- Sole Medical management: 17.9%
- Total BAV treatment: 78.8%
- Total Surgical or TAVR OUS intervention: 12.3%

\* All had prior BAV

\*\*9 had prior BAV

# Treatments Received: TAVR Patients

Patient Disposition	TAVR (n=179)	
	n	%
Patients with Valve Implanted*	170	95.0%
No Valve Implanted	9	5.0%
Died prior to TAVR	2	1.1%
TEE annulus too large	2	1.1%
Access failure**	5	2.8%

- Of the 7 alive without implant:
  - 6 received BAV
  - 1 medical management only

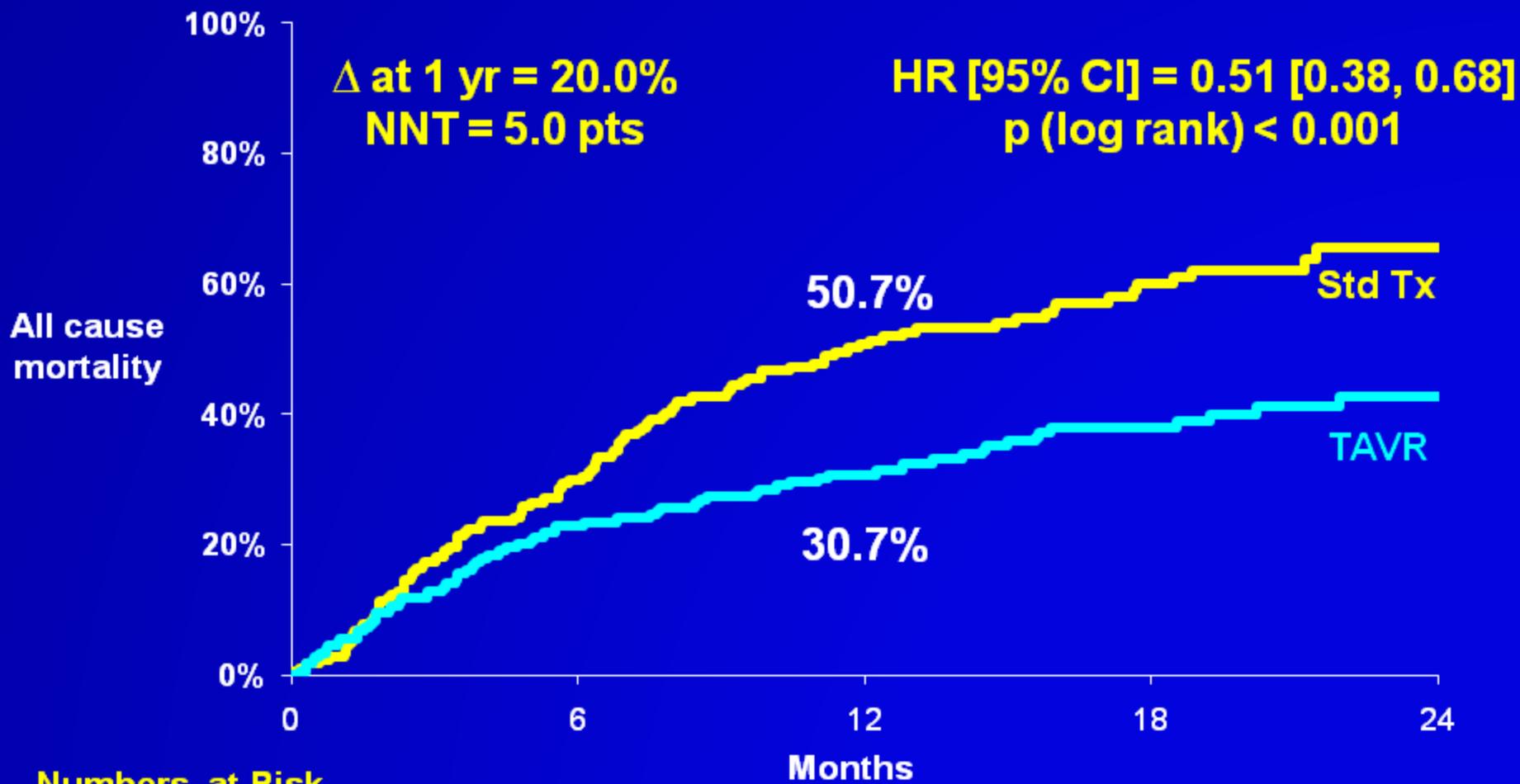
\*Median time to TAVR 6 days

\*\* Failure to advance sheath/delivery system (4) or to cross aortic valve (1)

# Primary Endpoints

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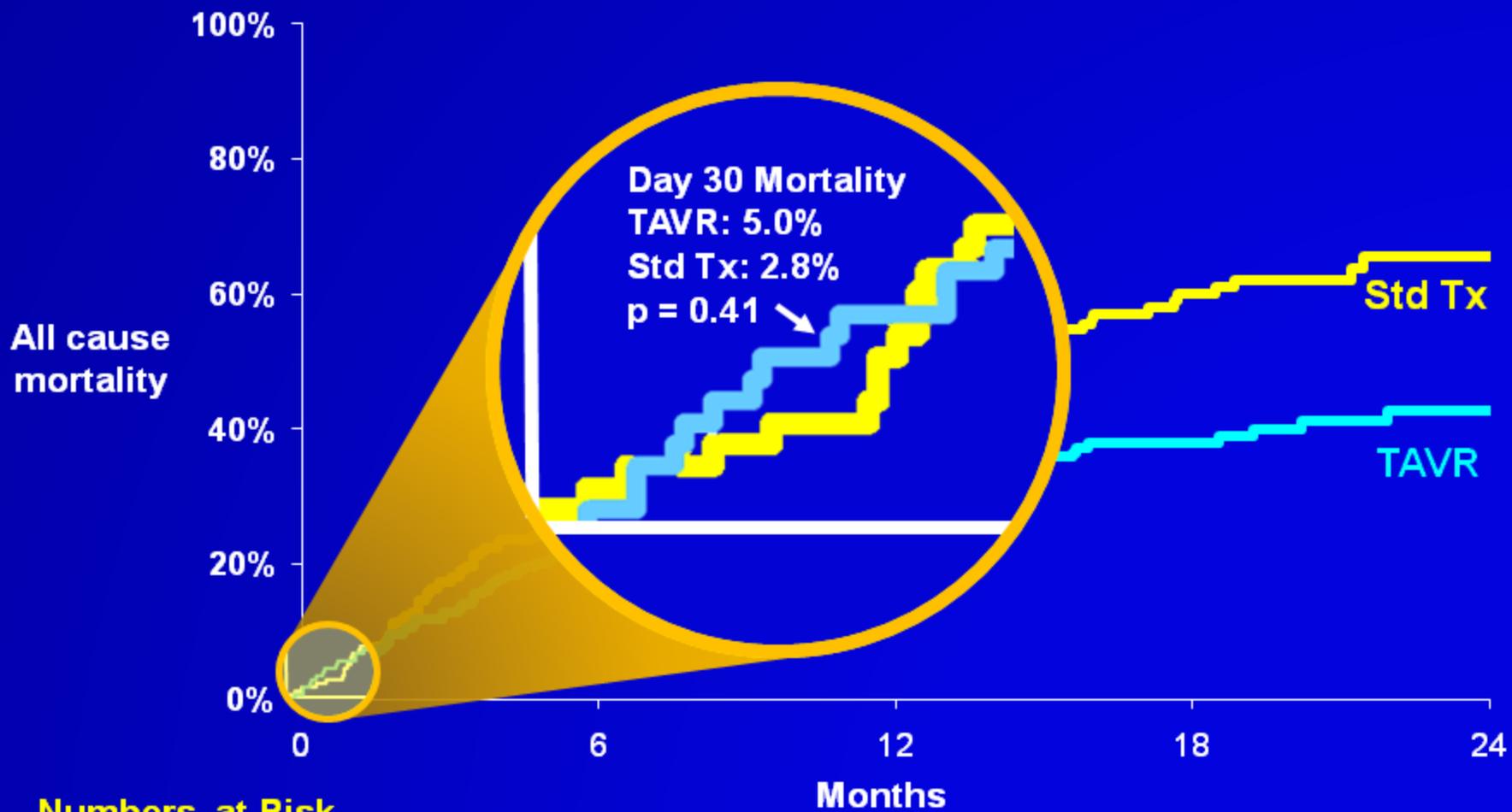
# Primary Endpoint: All Cause Mortality



## Numbers at Risk

	0	6	12	18	24
Std Tx	179	121	85	56	24
TAVR	179	138	124	103	60

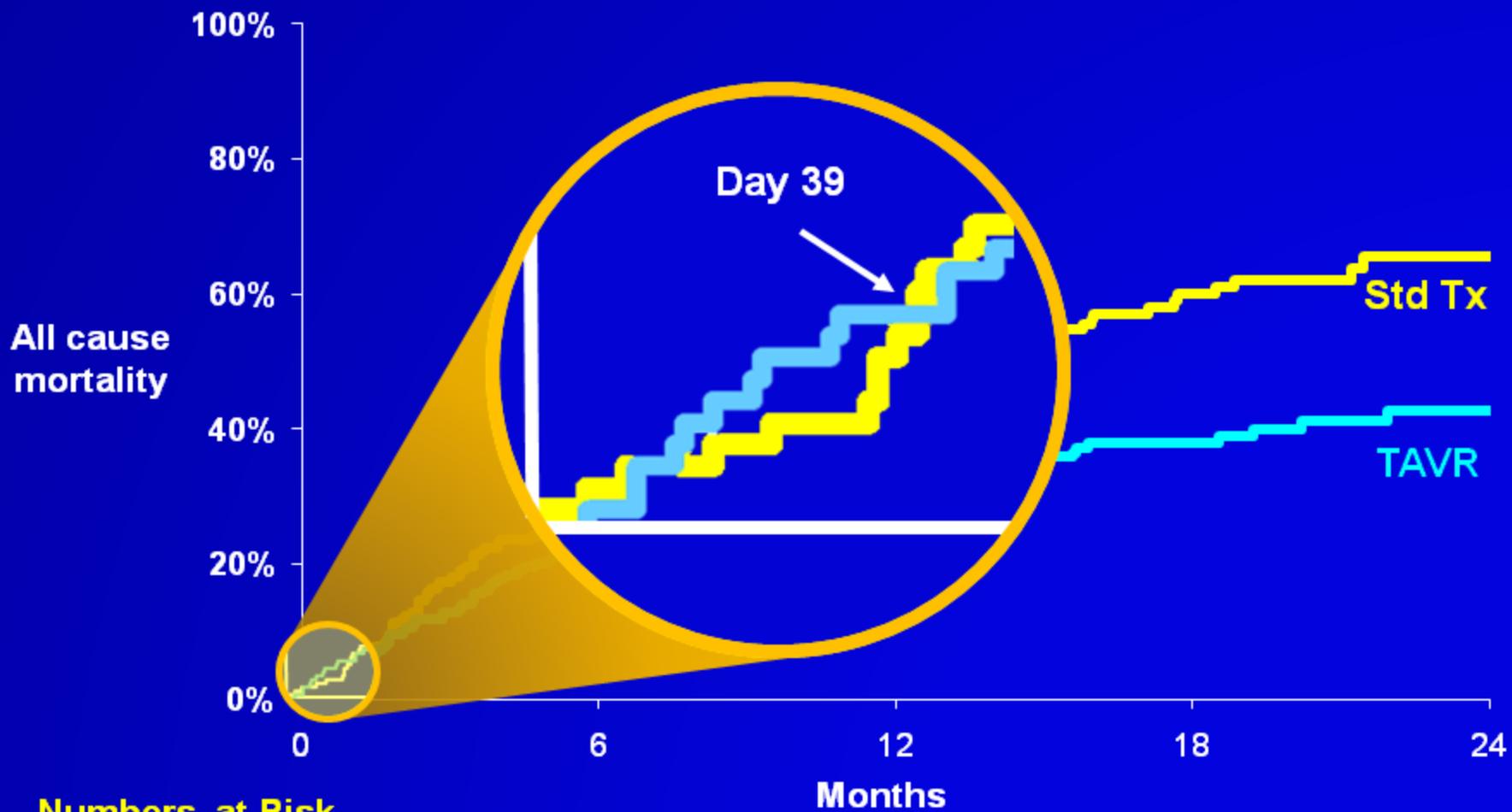
# Primary Endpoint: All Cause Mortality



## Numbers at Risk

<b>Std Tx</b>	<b>179</b>	<b>121</b>	<b>85</b>	<b>56</b>	<b>24</b>
<b>TAVR</b>	<b>179</b>	<b>138</b>	<b>124</b>	<b>103</b>	<b>60</b>

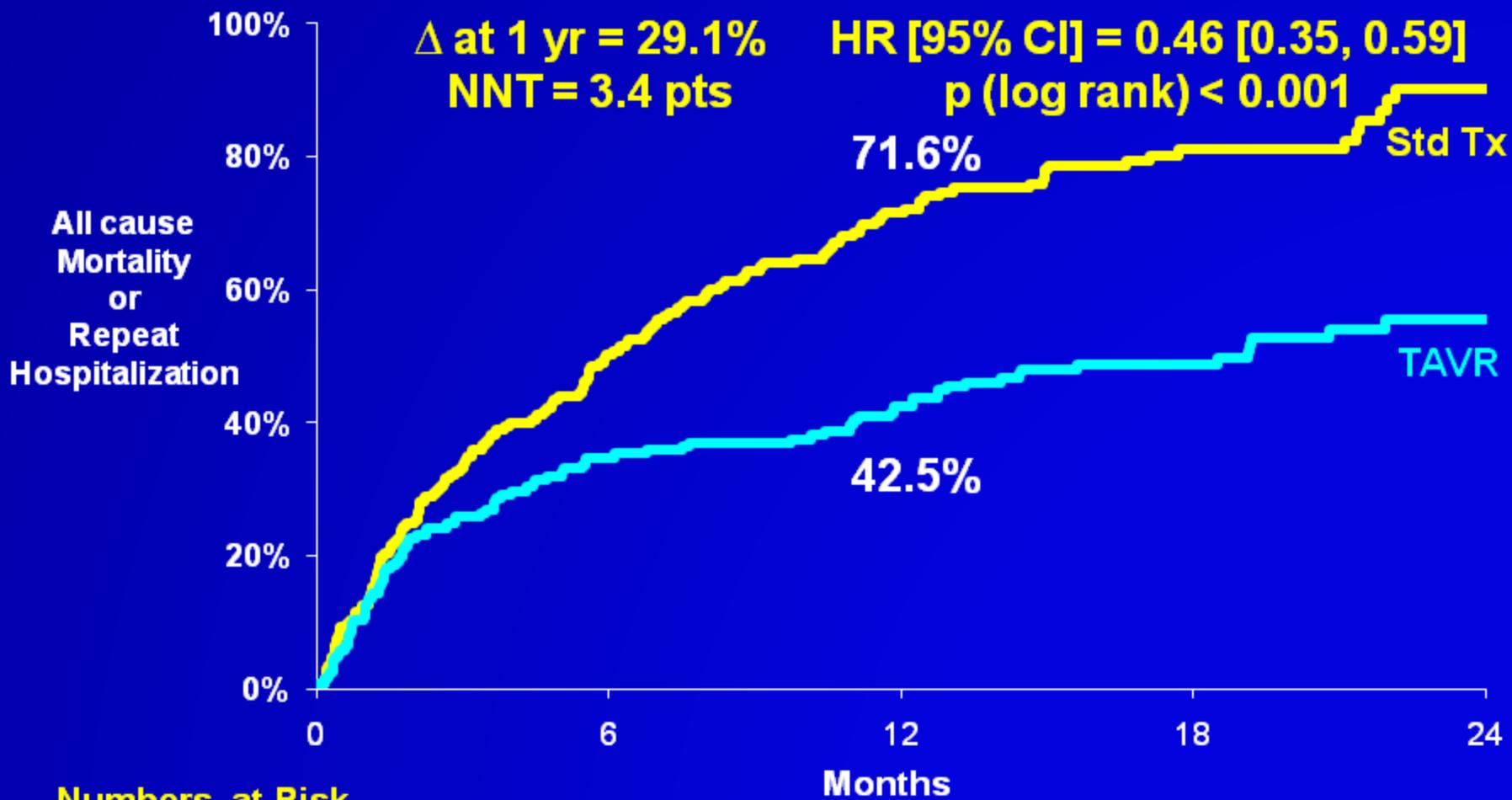
# Primary Endpoint: All Cause Mortality



## Numbers at Risk

	0	6	12	18	24
Std Tx	179	121	85	56	24
TAVR	179	138	124	103	60

# Co-primary Endpoint Non-hierarchical Analysis: Mortality or Repeat Hospitalization



## Numbers at Risk

	0	6	12	18	24
Std Tx	179	86	49	29	10
TAVR	179	116	101	85	49

# Post Hoc Effect Analyses for Baseline Imbalances: All Cause Mortality

Subgroup	TAVR (%) (n=179)	Std Tx (%) (n=179)	RR (95% CI)	RR (95% CI)	p-int
<b>Atrial Fib</b>					
No	26.1	43.8		0.53 (0.34, 0.81)	0.97
Yes	35.2	57.8		0.52 (0.36, 0.76)	
<b>COPD</b>					
No	26.7	49.1		0.51 (0.34, 0.75)	0.59
Yes	36.5	52.8		0.59 (0.40, 0.89)	
<b>Calcified Aorta</b>					
No	31.0	52.2		0.53 (0.39, 0.72)	0.83
Yes	29.4	41.6		0.58 (0.28, 1.22)	
<b>CAD</b>					
No	32.8	51.8		0.62 (0.37, 1.04)	0.49
Yes	29.8	50.8		0.50 (0.36, 0.70)	

TAVR Better      Std Tx Better

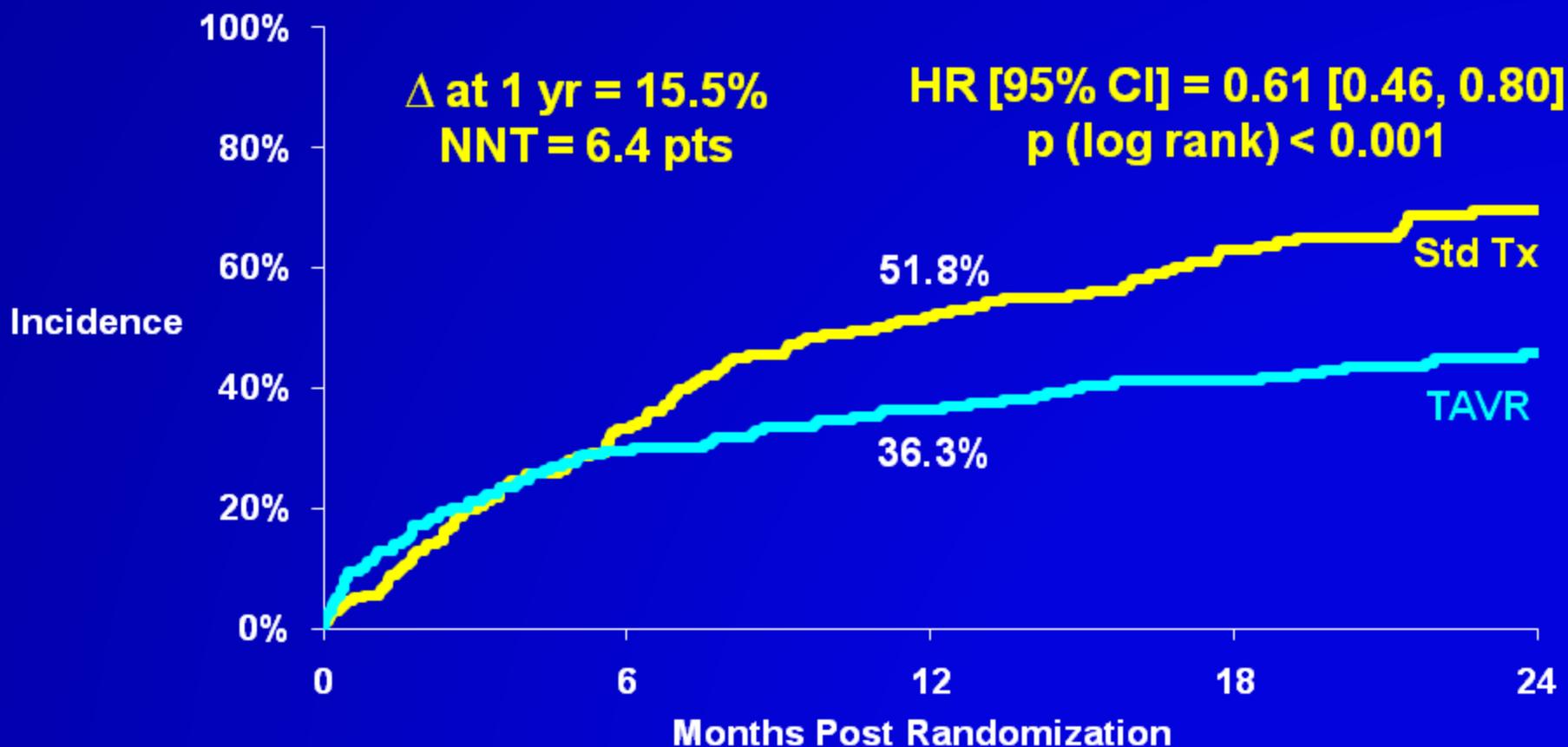


## Pre-specified Secondary Endpoints

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1. Time from randomization to first occurrence of death, stroke, MI or renal failure
2. Total hospital days through 1 year
3. New York Heart Association functional class at 1 year
4. 6-minute walk test

# Time to First Occurrence of Death, Stroke, MI or Renal Failure



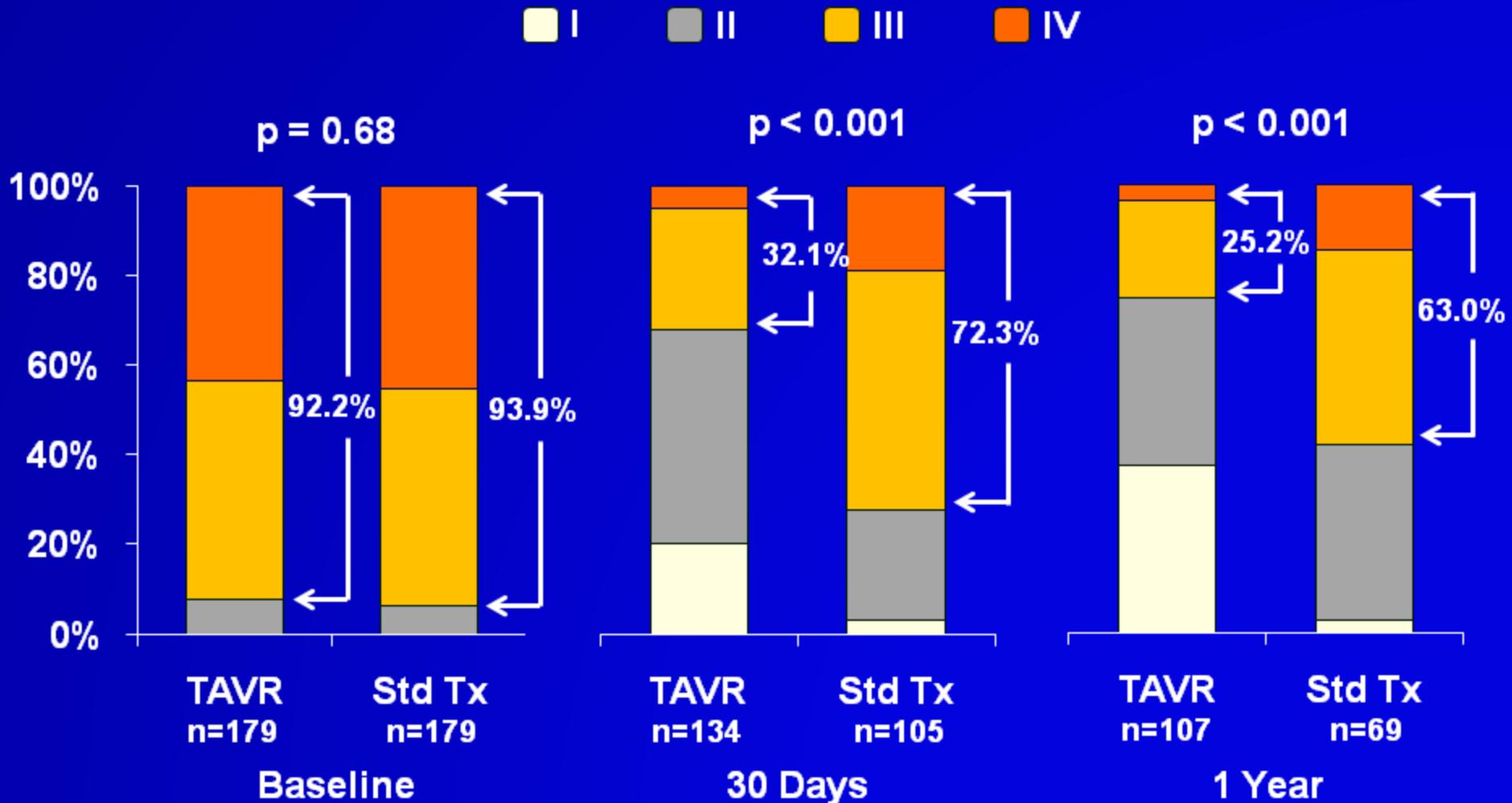
## Numbers at Risk

<b>Std Tx</b>	<b>179</b>	<b>115</b>	<b>83</b>	<b>55</b>	<b>24</b>
<b>TAVR</b>	<b>179</b>	<b>126</b>	<b>114</b>	<b>97</b>	<b>56</b>

# Hospitalization Through 1 Year

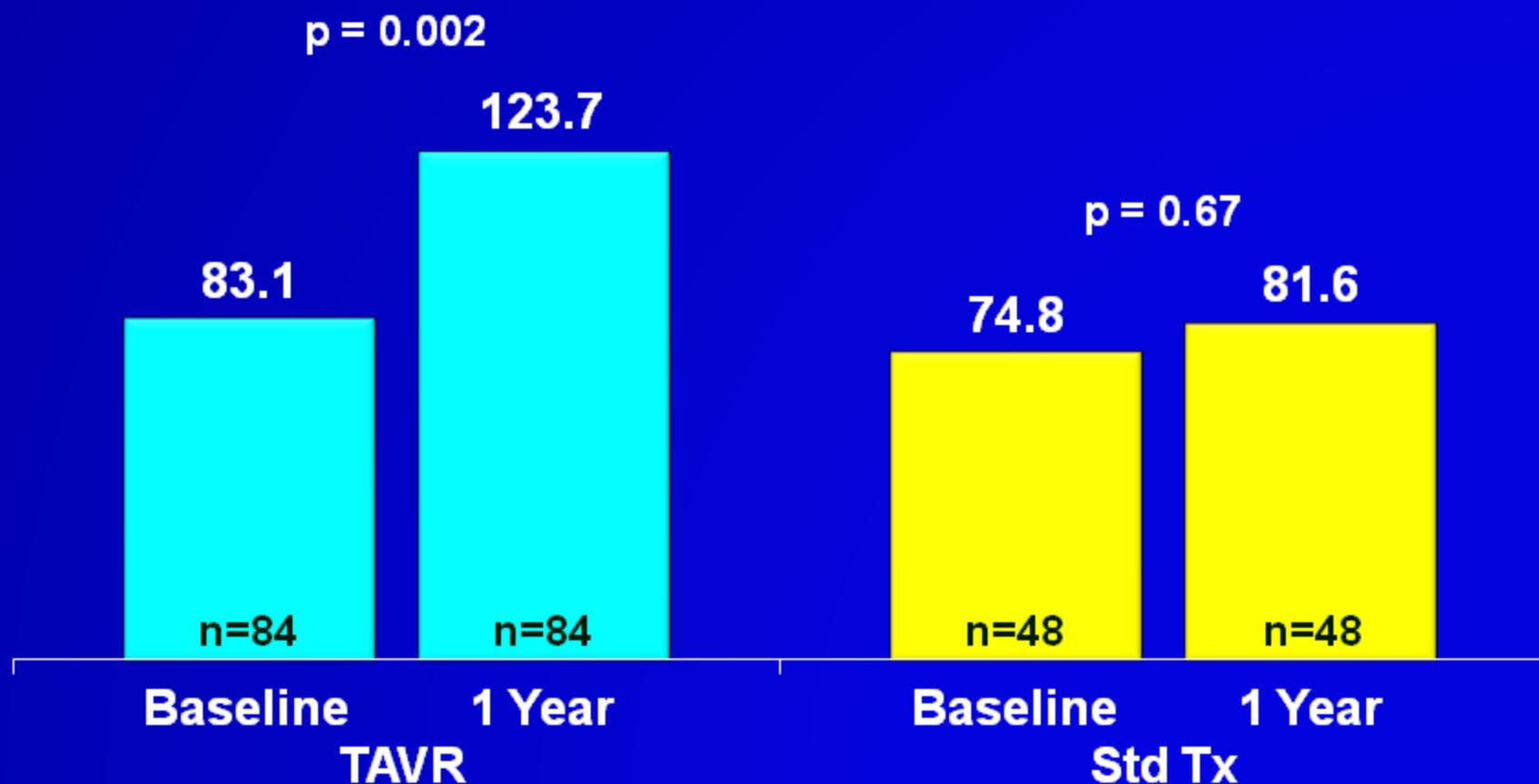
	<b>TAVR</b>	<b>Standard Tx</b>	<b>p</b>
<b>Total Hospital Days</b>	<b>18.4 ± 20.3</b>	<b>13.8 ± 17.9</b>	<b>&lt;0.001</b>
<b>Days Alive Out of Hospital</b>	<b>273.8 ± 128.5</b>	<b>210.2 ± 146.9</b>	<b>&lt;0.001</b>
<b>Repeat Hospitalization (%)</b>	<b>22.3%</b>	<b>44.1%</b>	<b>&lt;0.001</b>

# NYHA Class Over Time: Survivors



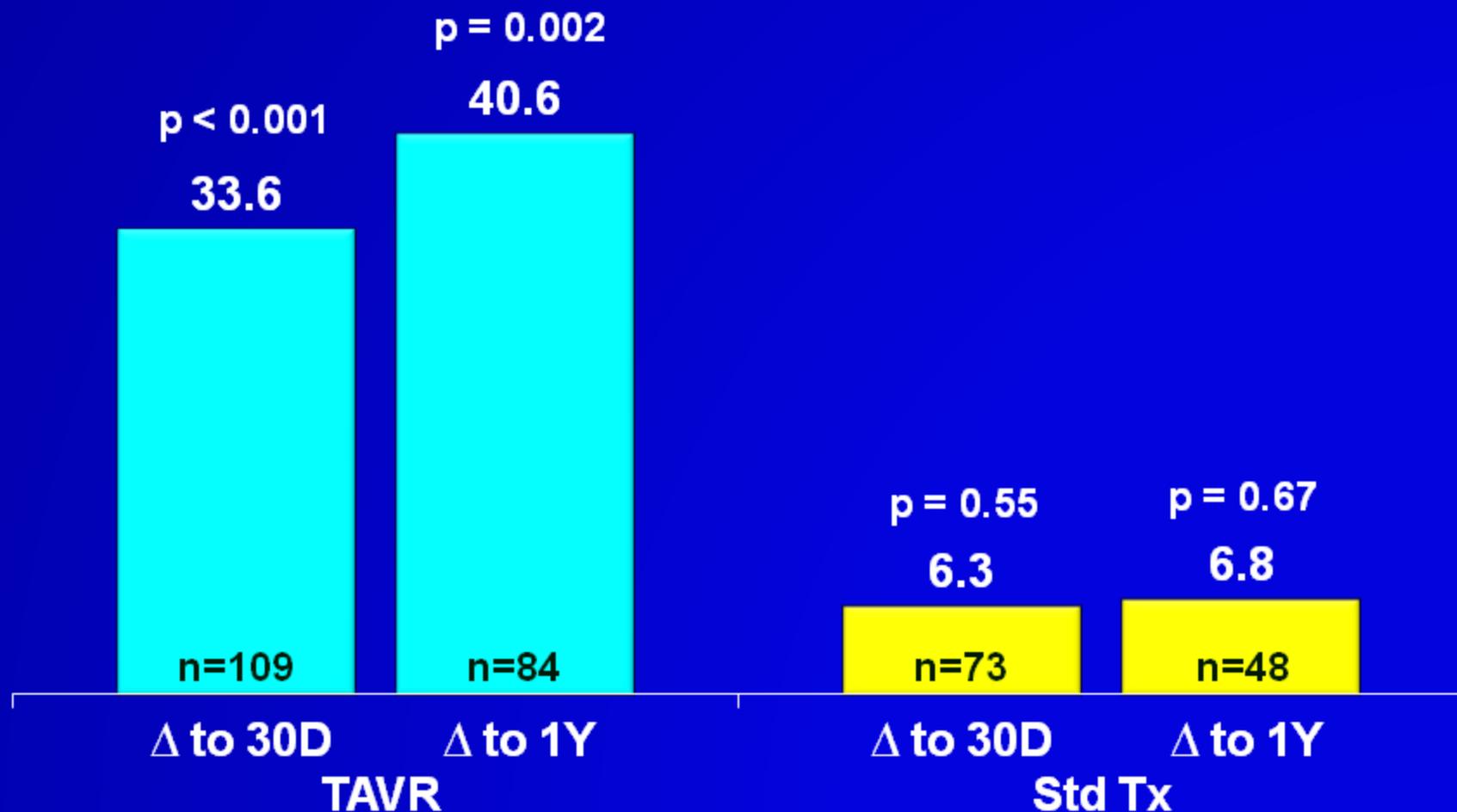
# Six-Minute Walk Tests

Total Walking Distance (meters) – Paired Data



# Six-Minute Walk Tests

Increased Walking Distance (meters) Compared With Baseline – Paired Data



# Quality of Life Evaluation

---

## QOL Endpoints Measured: General and Heart Failure Specific

---

**Instrument**

**Description/Role**

---

**KCCQ**

**Heart failure specific QOL**

---

**SF-12**

**Physical  
Mental health**

---

**EQ-5D**

**Generic instrument for assessment  
of utilities and QALYs**

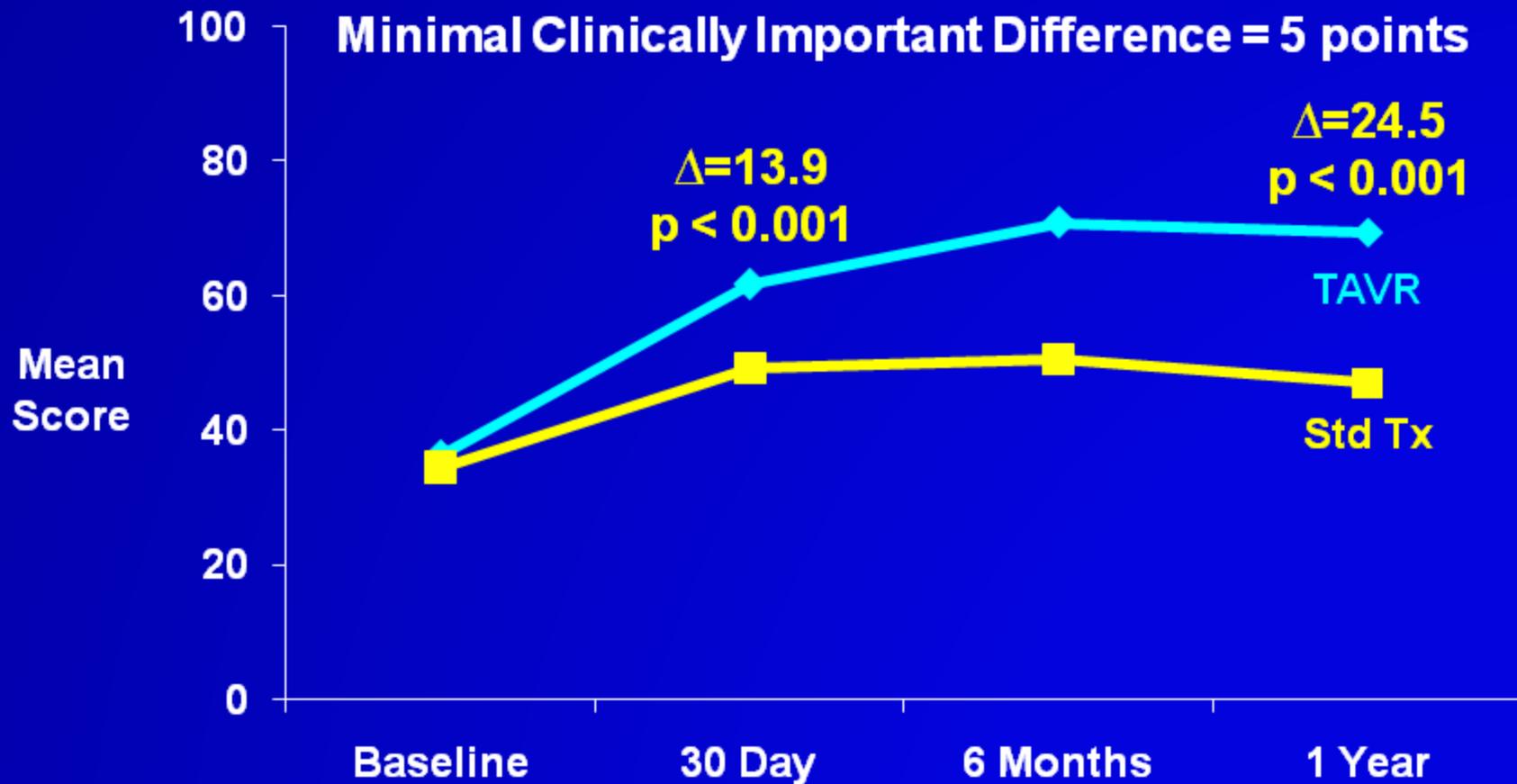
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# KCCQ Development and Validation

- 23 items that measure 4 clinically relevant domains of health status from the patient's perspective\*
  - Symptoms
  - Quality of life
  - Physical limitation
  - Social limitation
- Individual scales combined into a global summary scale (KCCQ Overall Summary)
- Scores: 0-100 (higher = better)
- Minimal Clinically Important Difference = 5 points

\*Data obtained and analyzed by an independent core laboratory

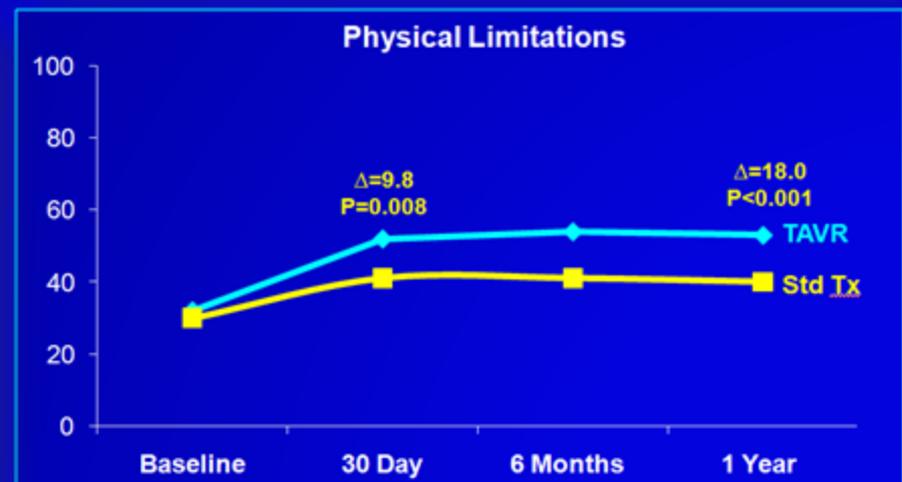
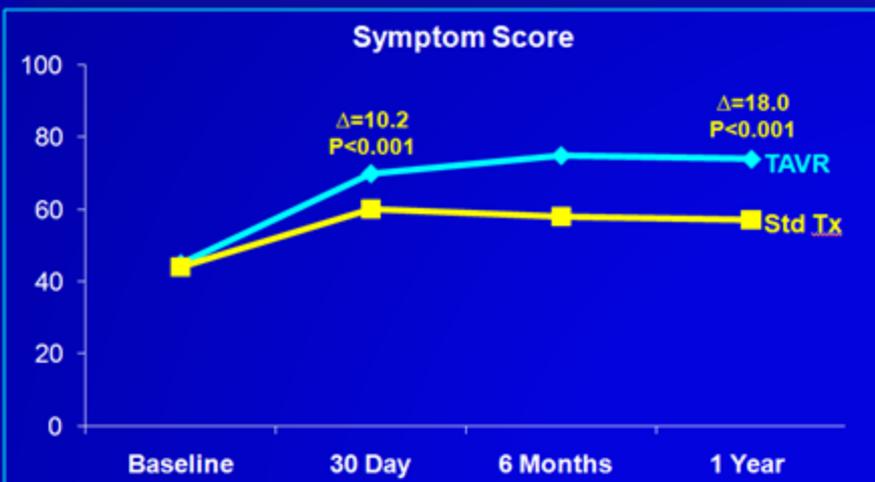
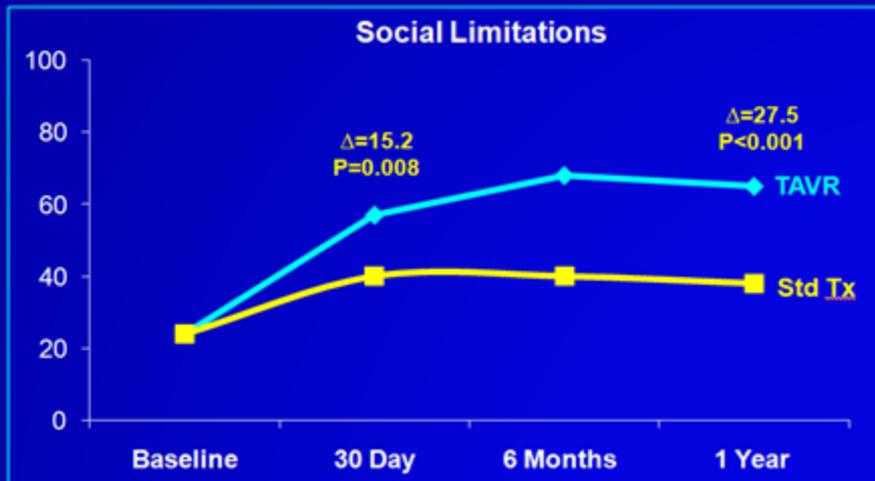
# KCCQ Overall Score at 30 Days and 1 Year



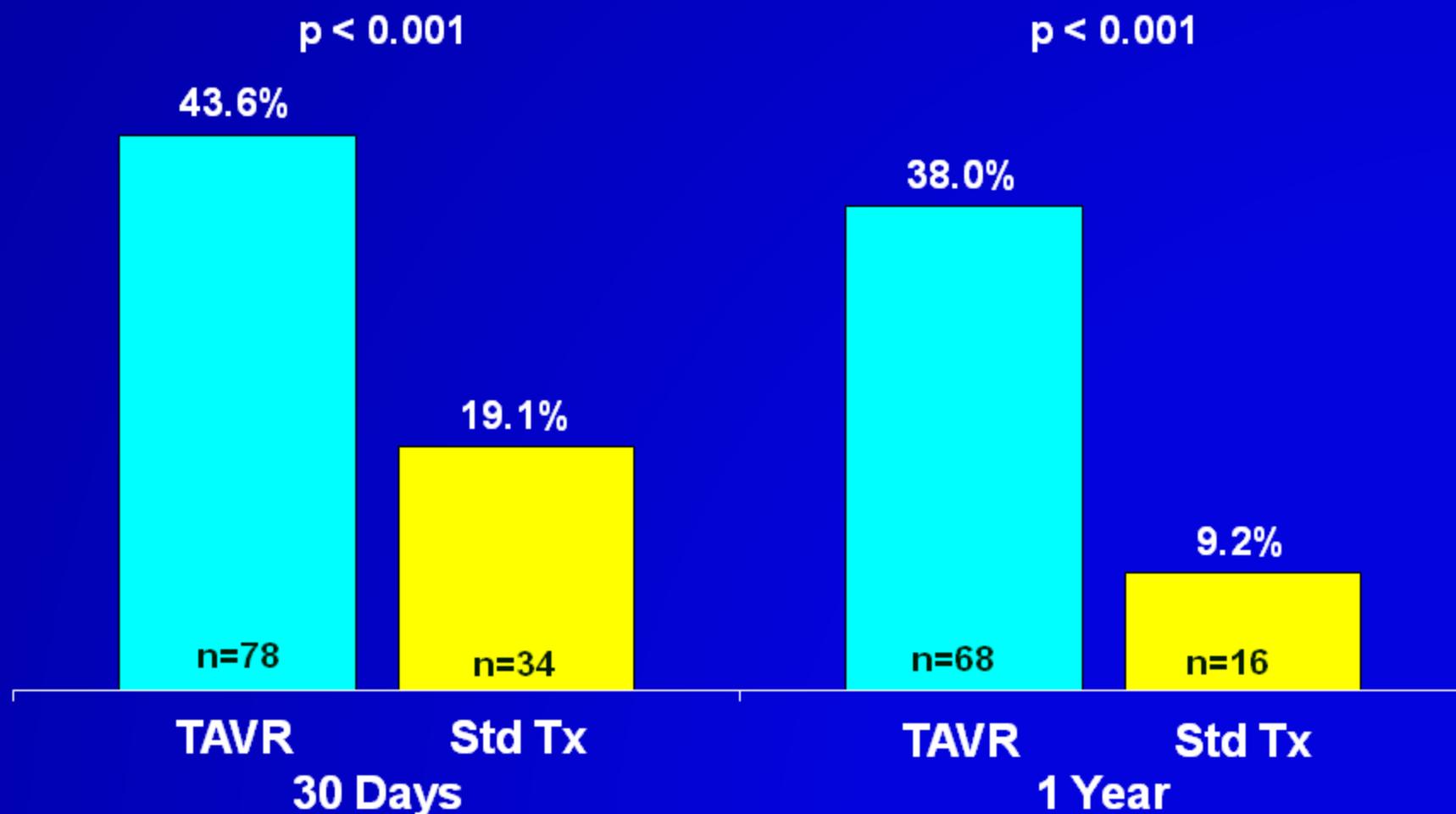
## Numbers Observed

TAVR (n)	170	147	121	110
Std Tx (n)	157	134	92	70

# KCCQ Subscales at 30 Days and 1 Year



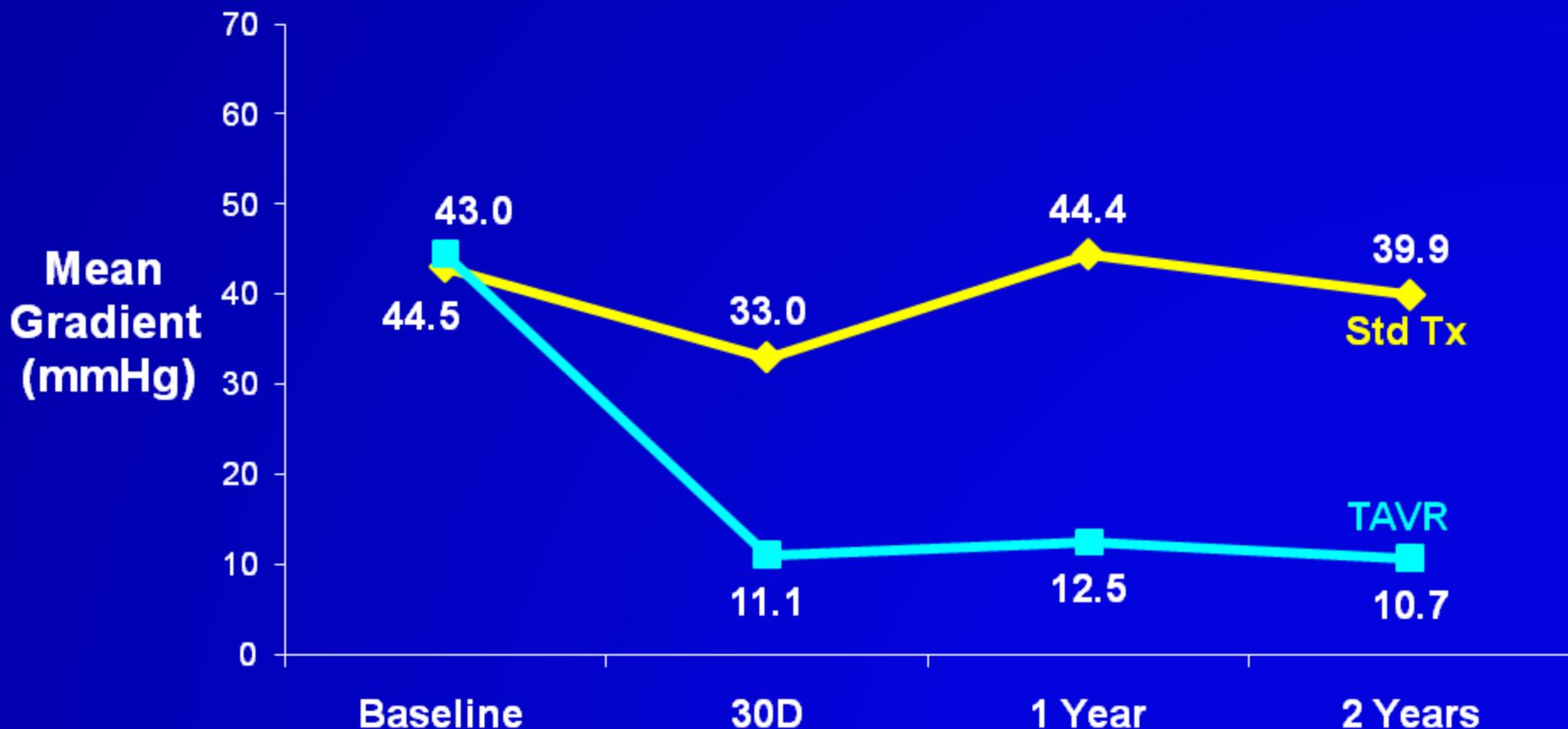
# QOL Survival Analysis: Alive and KCCQ Score Improved $\geq 20$ points vs. Baseline



# Echocardiography Assessments of Valve Function

---

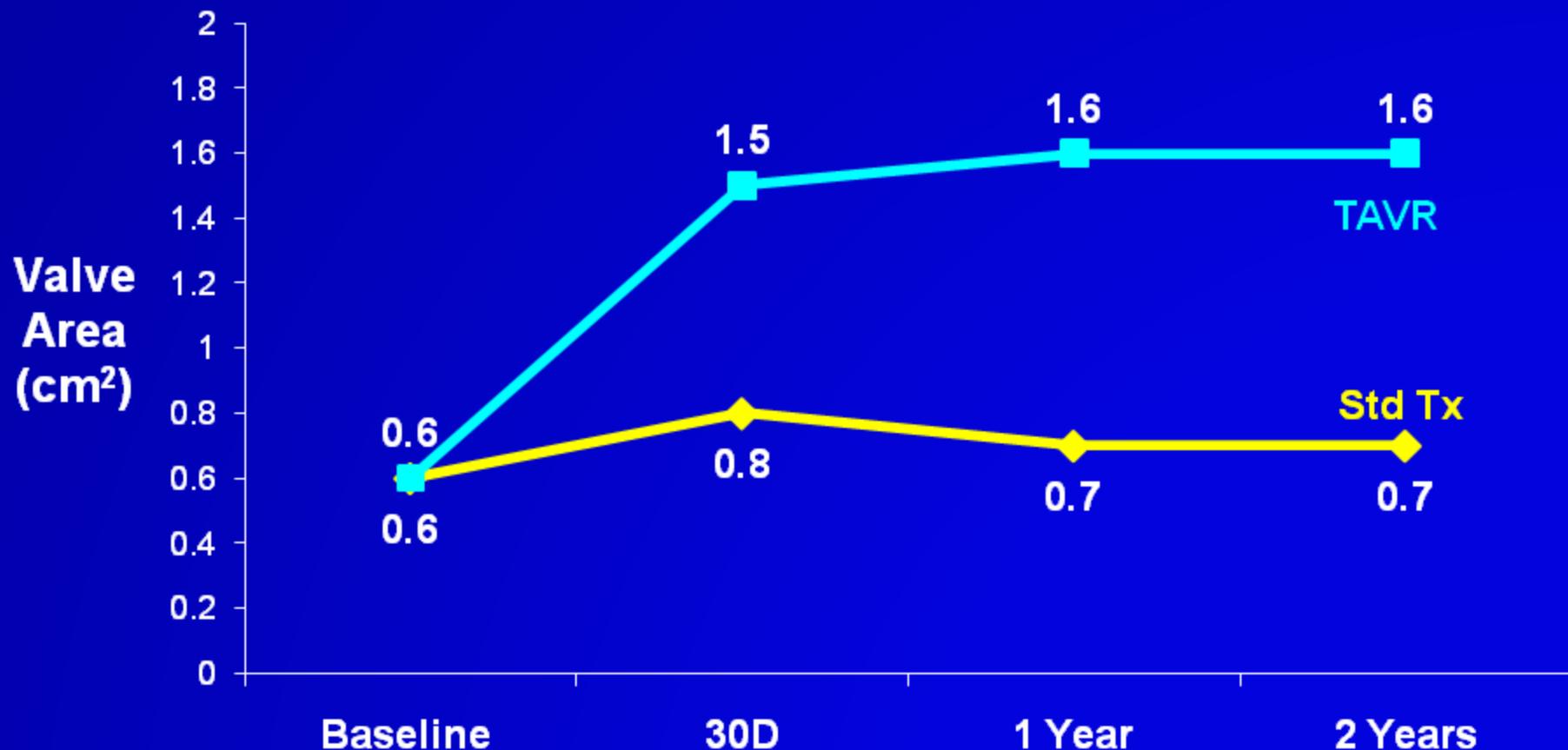
# Echocardiography Assessments: Mean Gradients at 30 Days, 1 and 2 Years



## Number Observed

Std Tx (n)	172	124	54	12
TAVR (n)	166	148	92	38

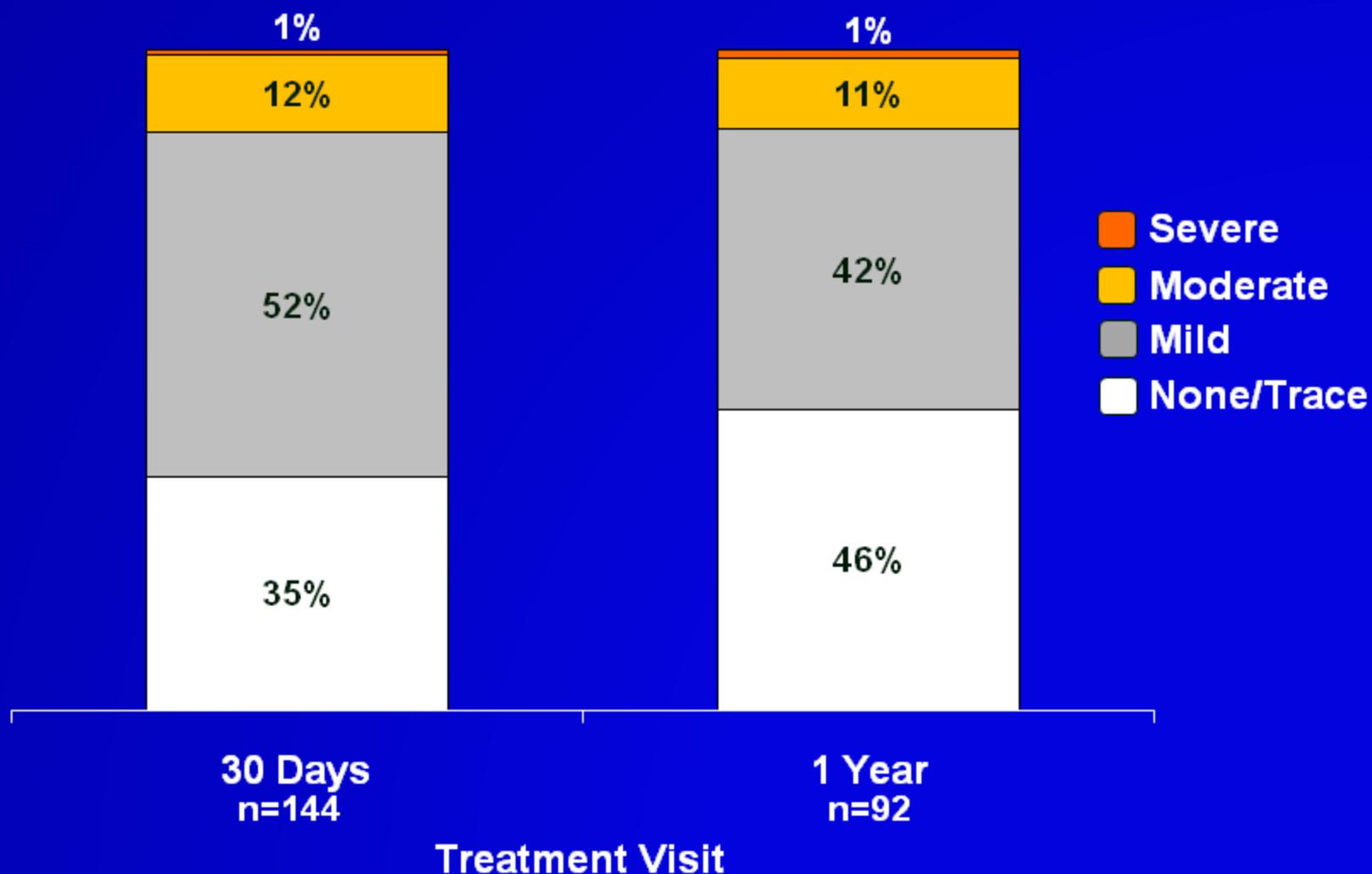
# Echocardiography Assessments: AV Areas at 30 Days, 1 and 2 Years



## Number Observed

Std Tx (n)	166	122	53	12
TAVR (n)	162	142	86	38

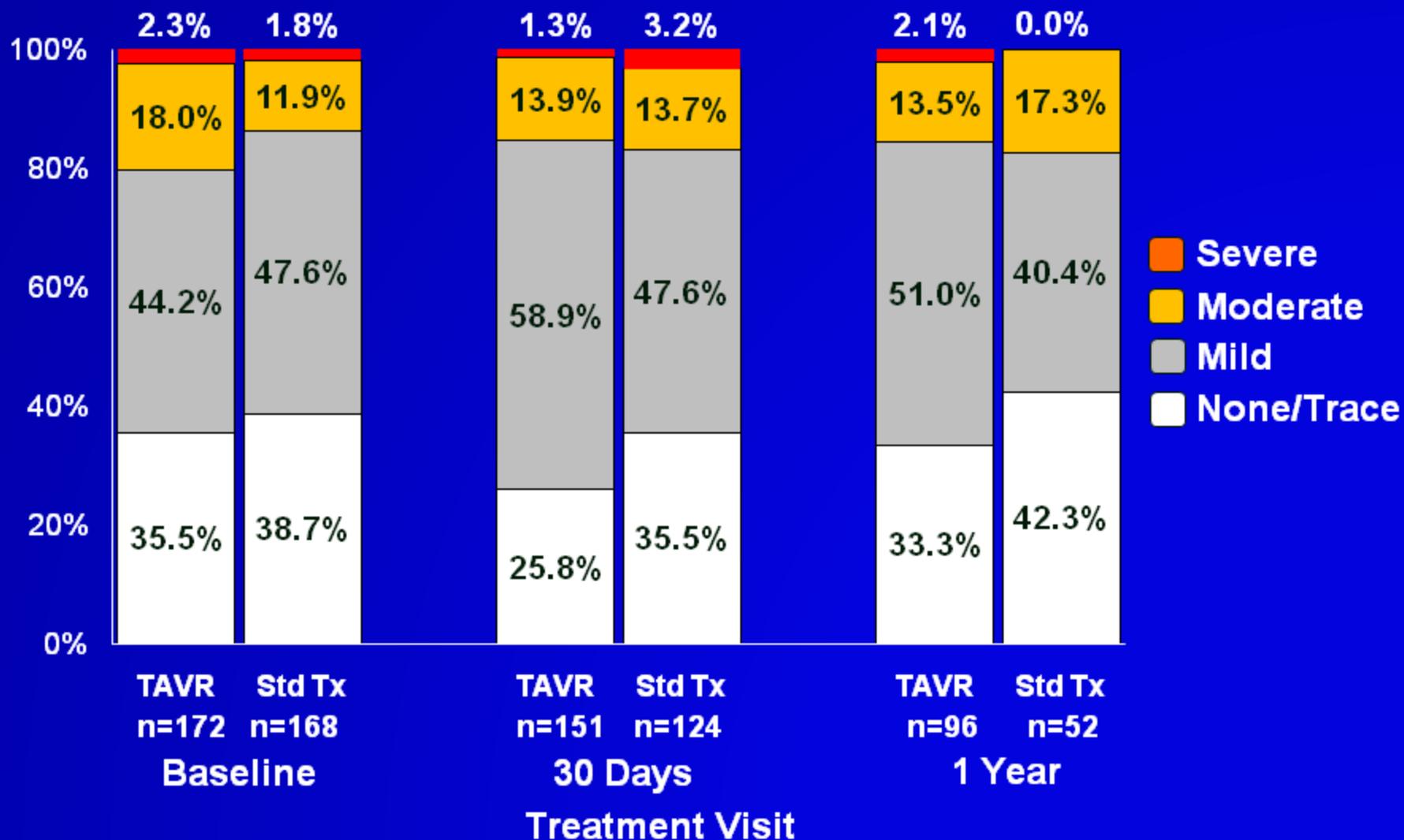
# Paravalvular Regurgitation after TAVR at 30 Days and 1 Year



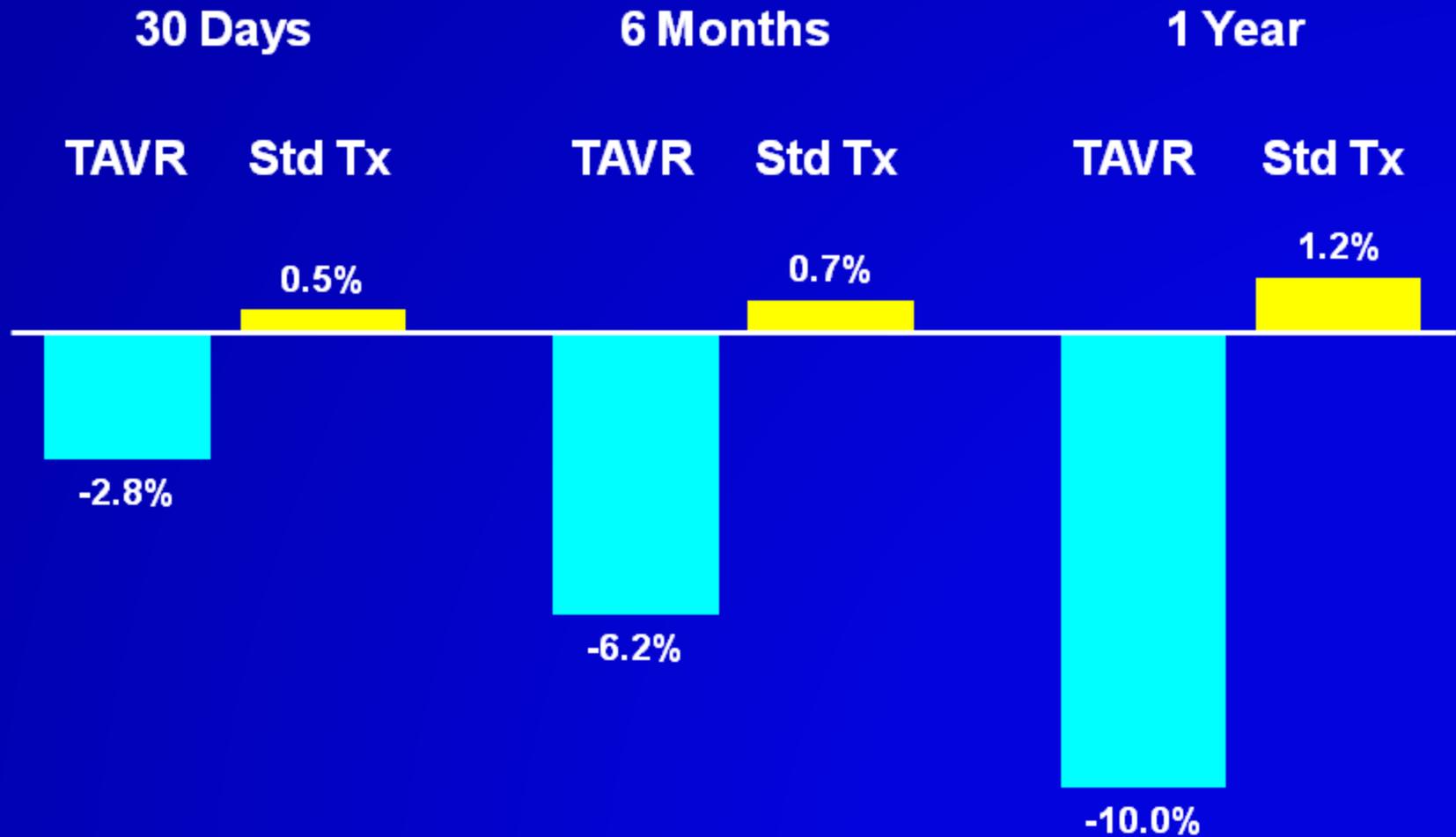
# Echo Analysis PV Leak Changes at 30 Days Compared to 1 Year

30 Day	1 Year			
	None / Trace	Mild	Moderate	Severe
None / Trace	28	8	1	0
Mild	12	24	2	1
Moderate	0	4	5	0
Severe	0	0	1	0
20% Improved		66% Unchanged		14% Progressed

# Total Aortic Regurgitation Central and Paravalvular



# Left Ventricular Mass Index Percent Change From Baseline



## Outcomes of Special Interest

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1. Neurological
2. Vascular
3. Bleeding
4. Arrhythmias

# Intent-to-Treat (ITT) vs. As-Treated (AT) Analysis

---

- ITT defined from randomization
- AT defined differently for each group
  - TAVR: from procedure start
  - Standard Tx: from randomization
- Given this phenomenon the following analyses are shown as ITT

# Stroke Classifications

---

- Diagnosis of stroke and etiology
- CEC Classifications
  - TIA or stroke
  - Causes assessed as either ischemic, hemorrhagic, or unknown (conforms to new VARC and FDA consensus definitions)

# Stroke Classifications

---

- Diagnosis of stroke and etiology
- CEC Classifications
  - TIA or stroke
  - Causes assessed as either ischemic, hemorrhagic, or unknown (conforms to new VARC and FDA consensus definitions)
- Post-hoc severity ranking (minor and major, based upon modified Rankin score  $\geq 2$ )

# The Modified Rankin Scale

## Minor

- |   |  |
|---|--|
| 0 | No symptoms  |
| 1 | No significant disability<br>Able to carry out all usual activities, despite some symptoms |

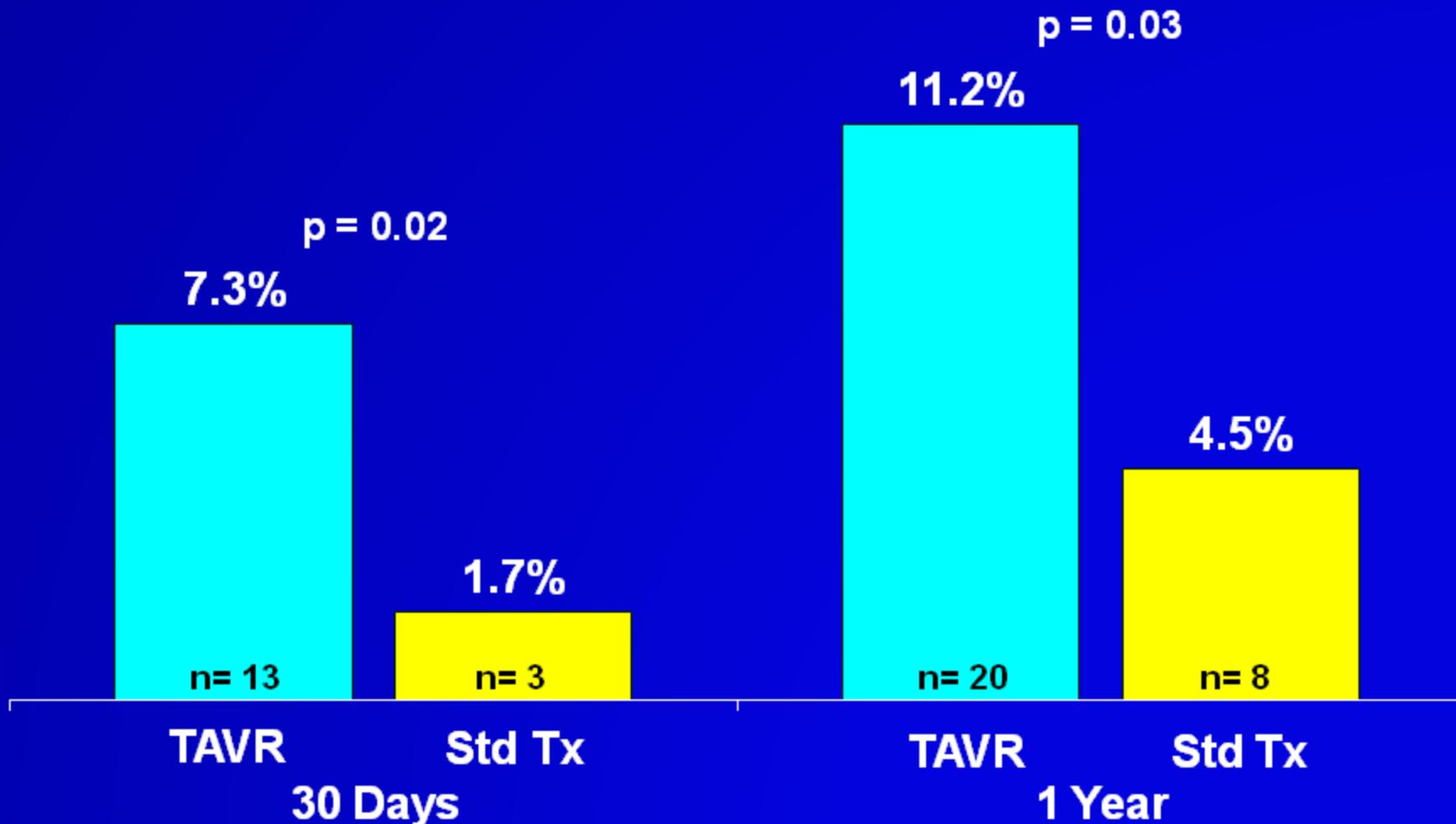
## Major

- |   |   |
|---|---|
| 2 | Slight disability. Able to look after own affairs without assistance, but unable to carry out all previous activities |
| 3 | Moderate disability. Requires some help, but able to walk unassisted  |
| 4 | Moderately severe disability. Unable to attend to own bodily needs without assistance, and unable to walk unassisted  |
| 5 | Severe disability. Requires constant nursing care and attention, bedridden, incontinent                               |
| 6 | Death   |

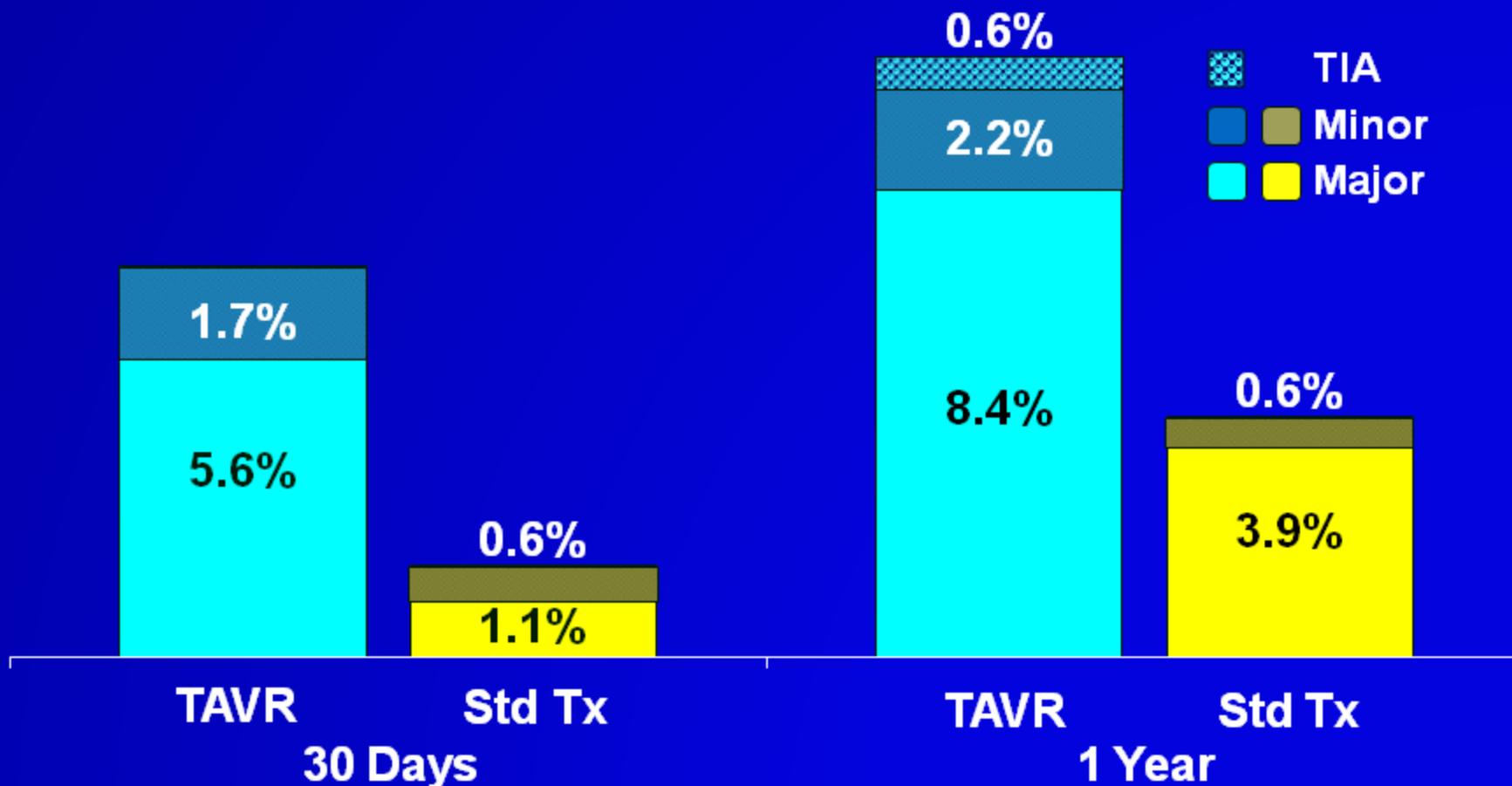
# Neurological Outcomes at 30 Days and 1 Year

Event	30 Days				1 Year			
	TAVR (n=179)		Std Tx (n=179)		TAVR (n=179)		Std Tx (n=179)	
	n	%	n	%	n	%	n	%
<b>Stroke or TIA</b>	<b>13</b>	<b>7.3%</b>	<b>3</b>	<b>1.7%</b>	<b>20</b>	<b>11.2%</b>	<b>8</b>	<b>4.5%</b>
<b>TIA</b>	<b>0</b>	<b>-</b>	<b>0</b>	<b>-</b>	<b>1</b>	<b>0.6%</b>	<b>0</b>	<b>-</b>
<b>Stroke</b>								
<b>Minor</b>	<b>3</b>	<b>1.7%</b>	<b>1</b>	<b>0.6%</b>	<b>4</b>	<b>2.2%</b>	<b>1</b>	<b>0.6%</b>
<b>Major</b>	<b>10</b>	<b>5.6%</b>	<b>2</b>	<b>1.1%</b>	<b>15</b>	<b>8.4%</b>	<b>7</b>	<b>3.9%</b>

# All Neurological Events (Stroke and TIA) at 30 Days & 1 Year

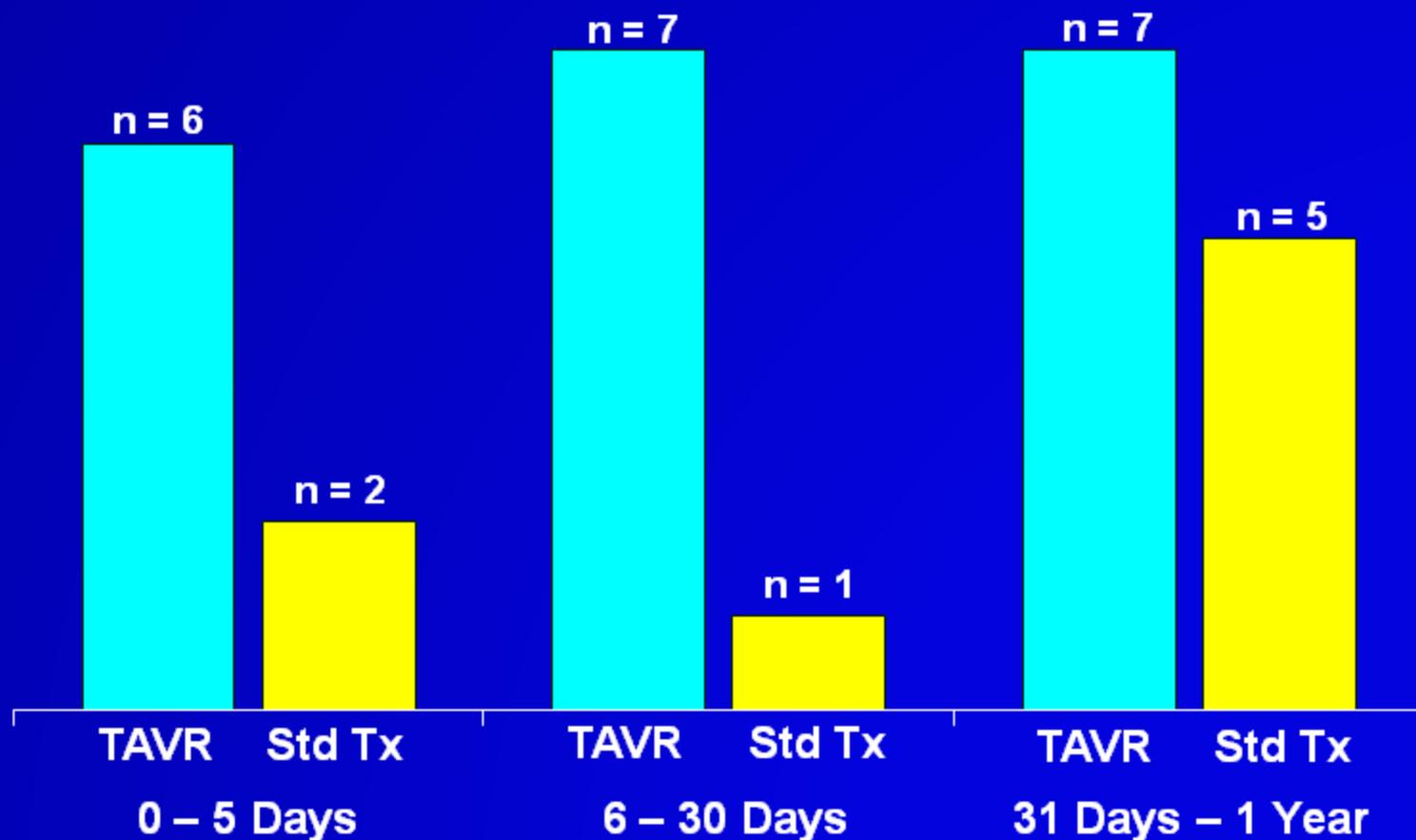


# Classification of All Neurological Events at 30 Days & 1 Year



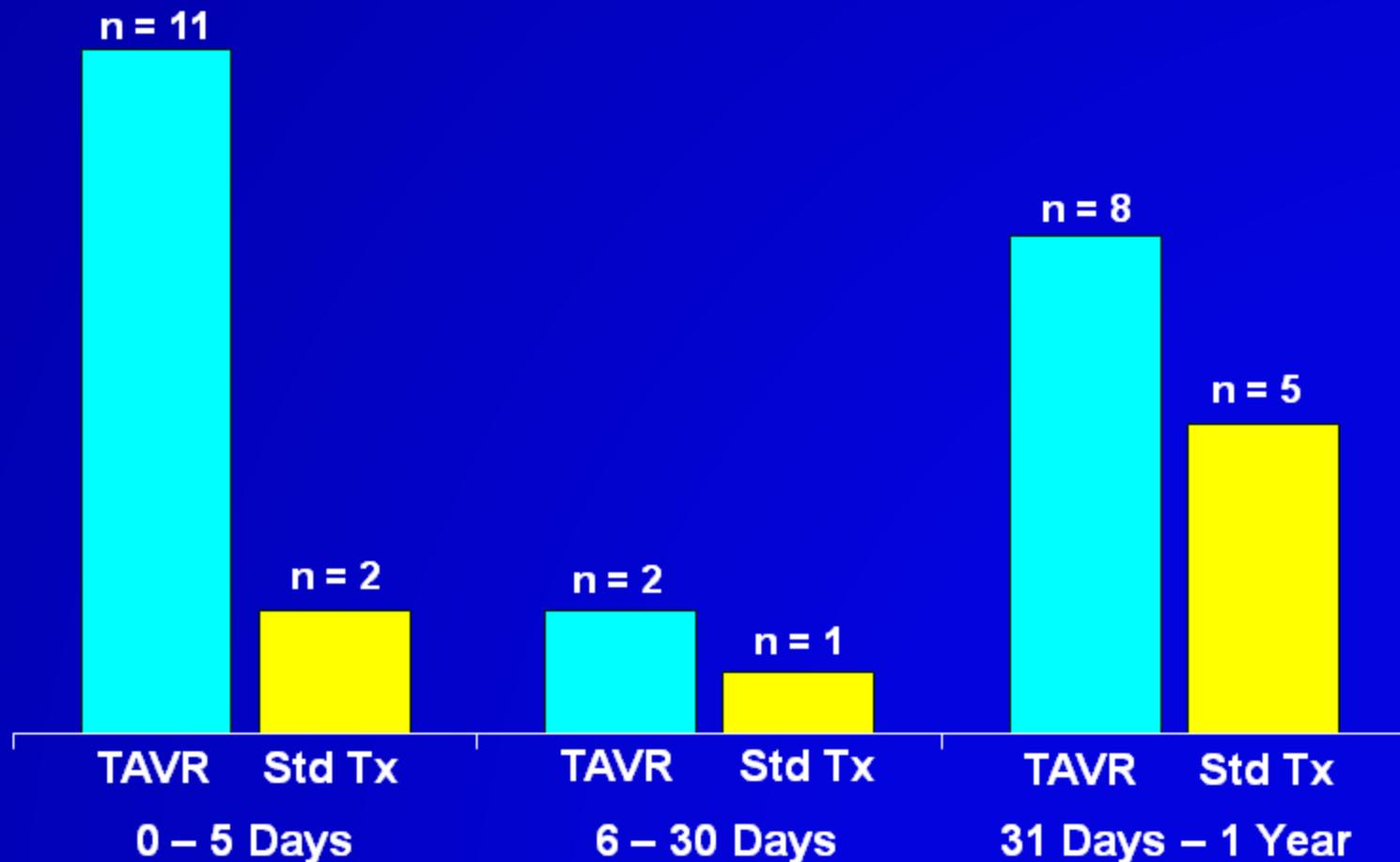
# Timing of Neurological Events

## Number of Patients (ITT Population)

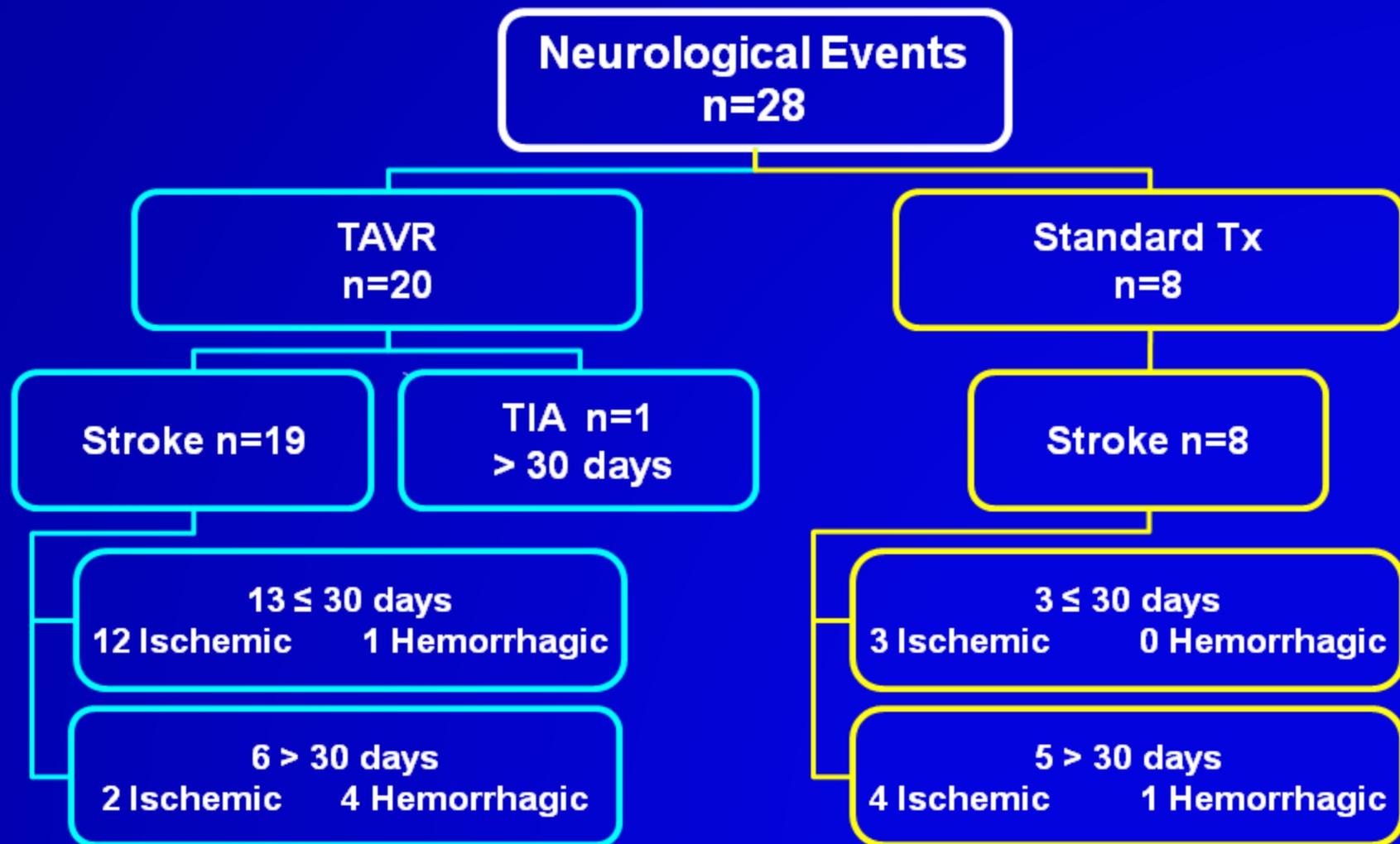


# Timing of Neurological Events

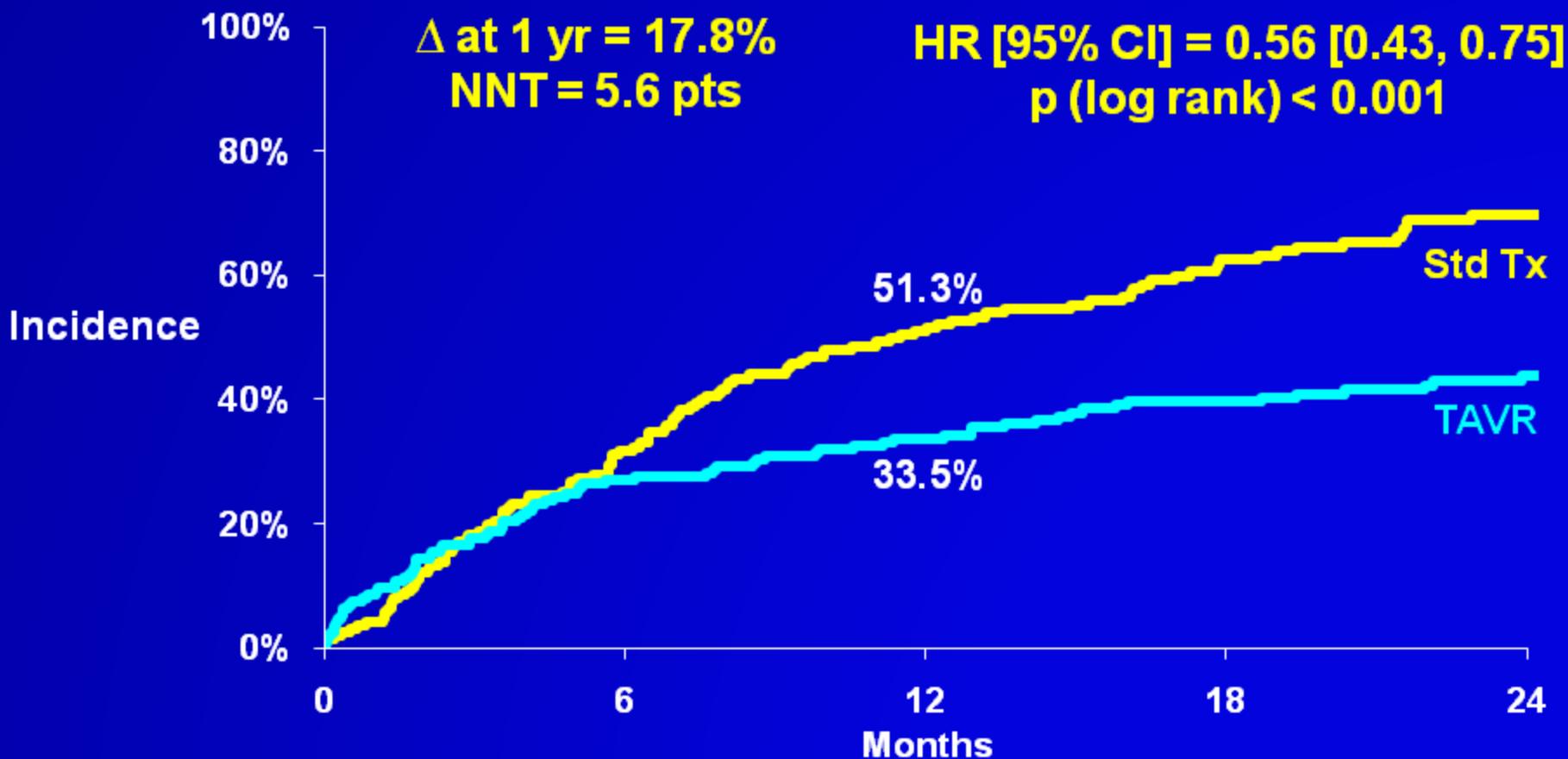
## Number of Patients (AT Population)



# Etiology of Neurological Events Within 1 Year from Randomization



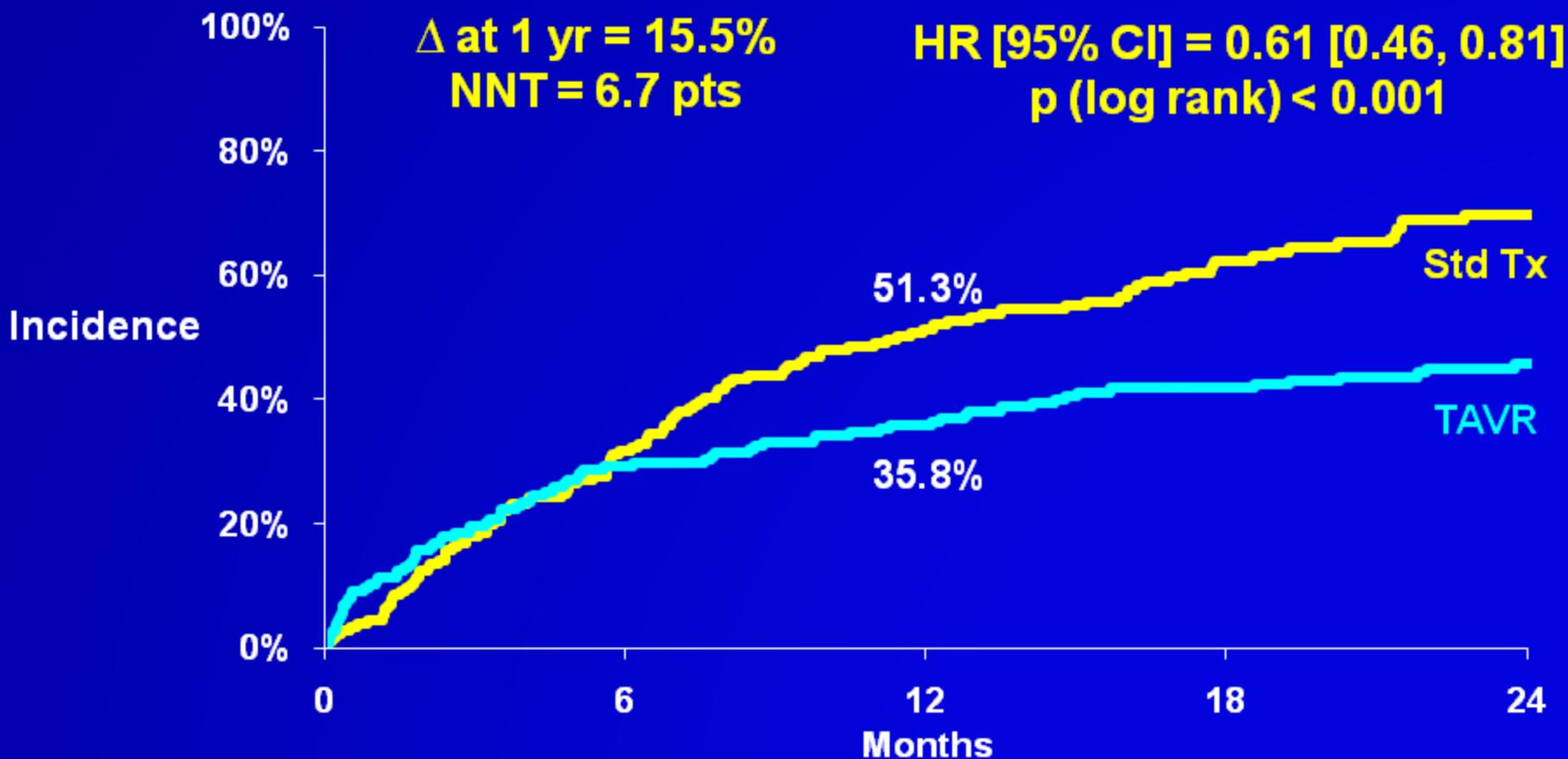
# Mortality or Major Stroke



## Numbers at Risk

Std Tx	179	118	84	56	24
TAVR	179	131	119	100	58

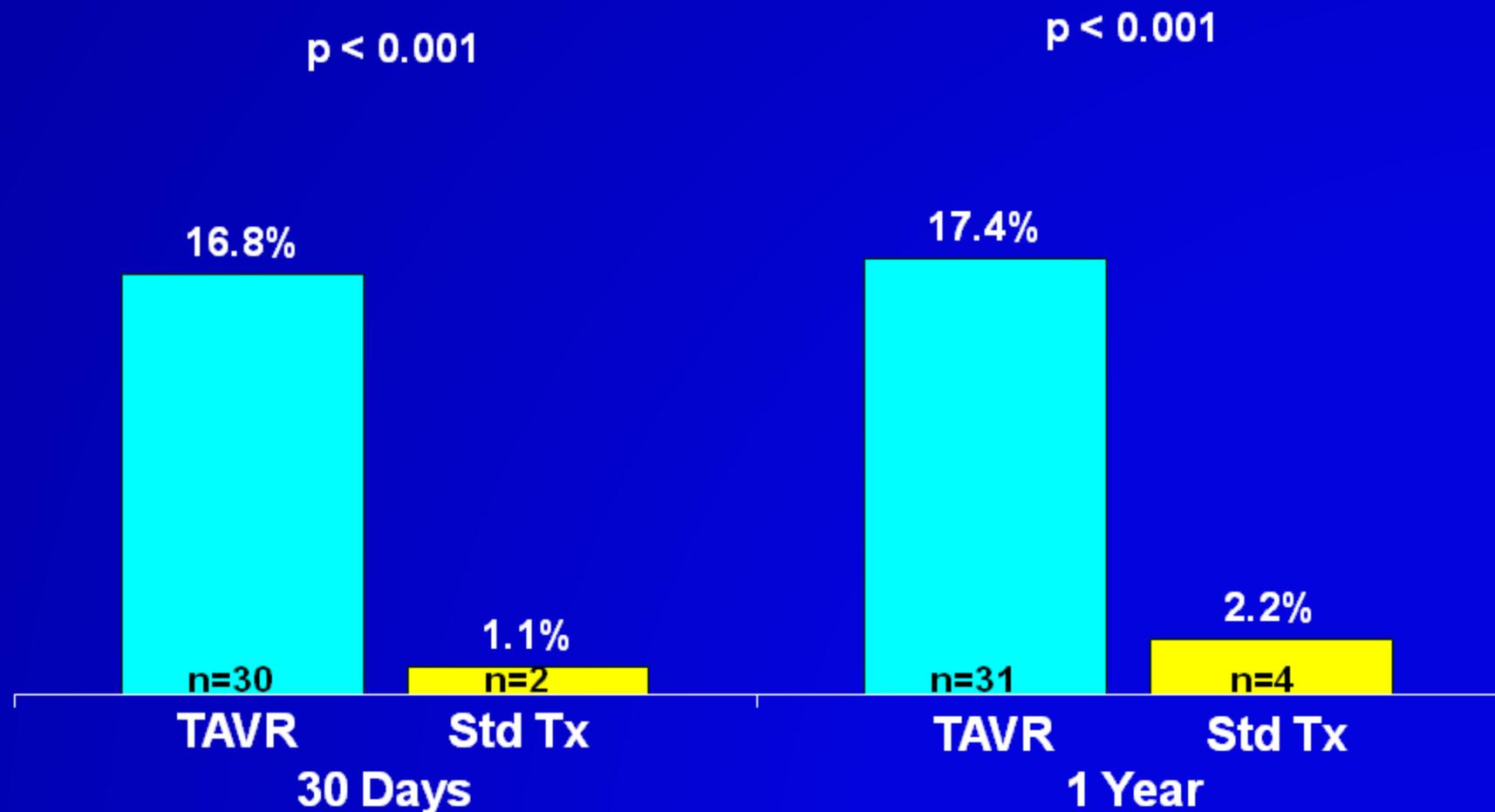
# Mortality or All Neurological Events



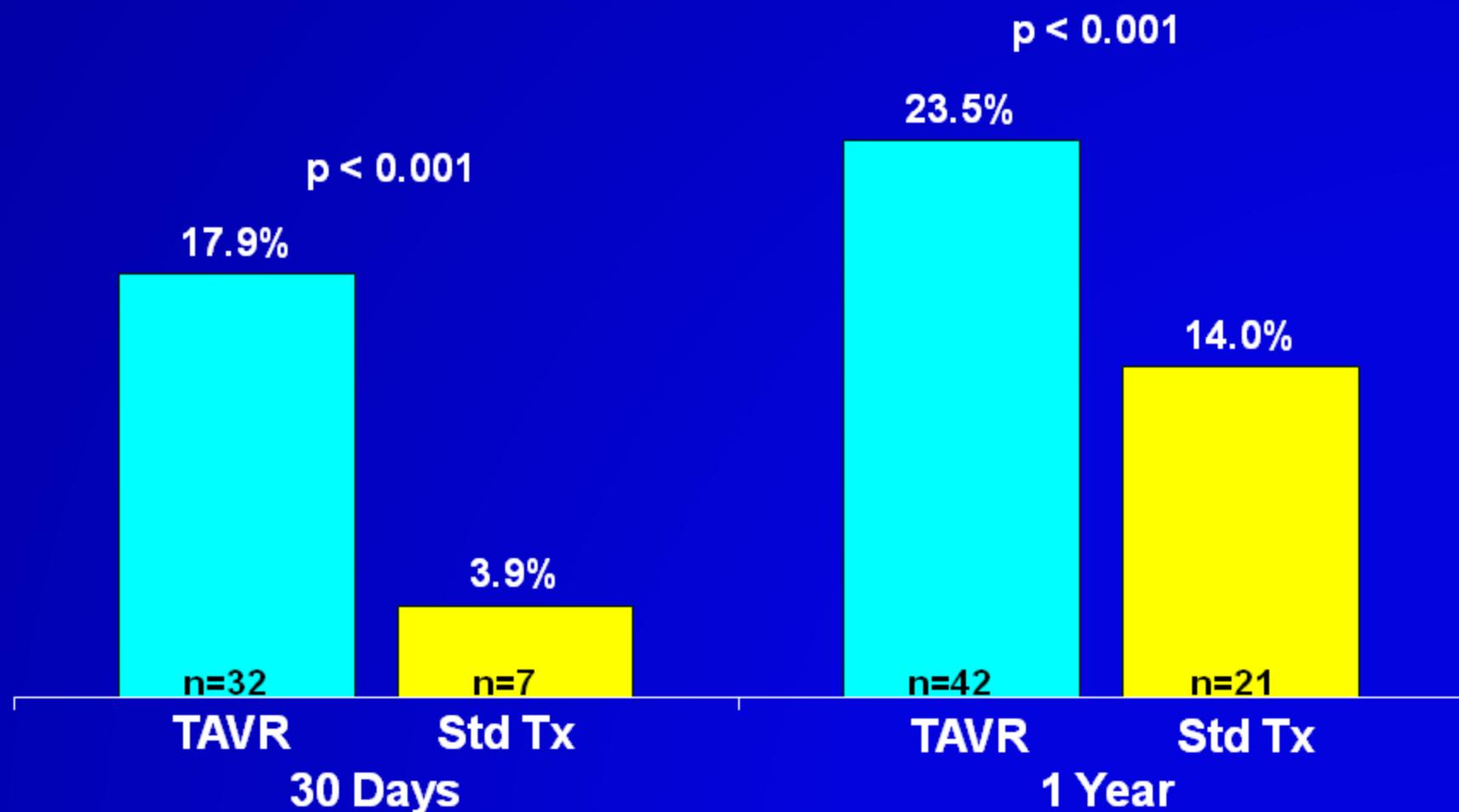
## Numbers at Risk

Std Tx	179	118	84	56	24
TAVR	179	127	115	96	55

# Major Vascular Complications at 30 Days & 1 Year



# Major Bleeding Events at 30 Days & 1 Year (ITT)



## Mortality in TAVR Patients With Major Stroke, Major Vascular or Major Bleeding Events

	30 Days (n=179)		1 Year (n=179)	
	n	%	n	%
<b>Major Stroke (n=15)</b>	<b>3</b>	<b>20.0%</b>	<b>7</b>	<b>46.7%</b>
<b>Major Vascular (n=31)</b>	<b>3</b>	<b>9.7%</b>	<b>11</b>	<b>35.5%</b>
<b>Major Bleeding (n=42)</b>	<b>4</b>	<b>9.5%</b>	<b>16</b>	<b>38.1%</b>

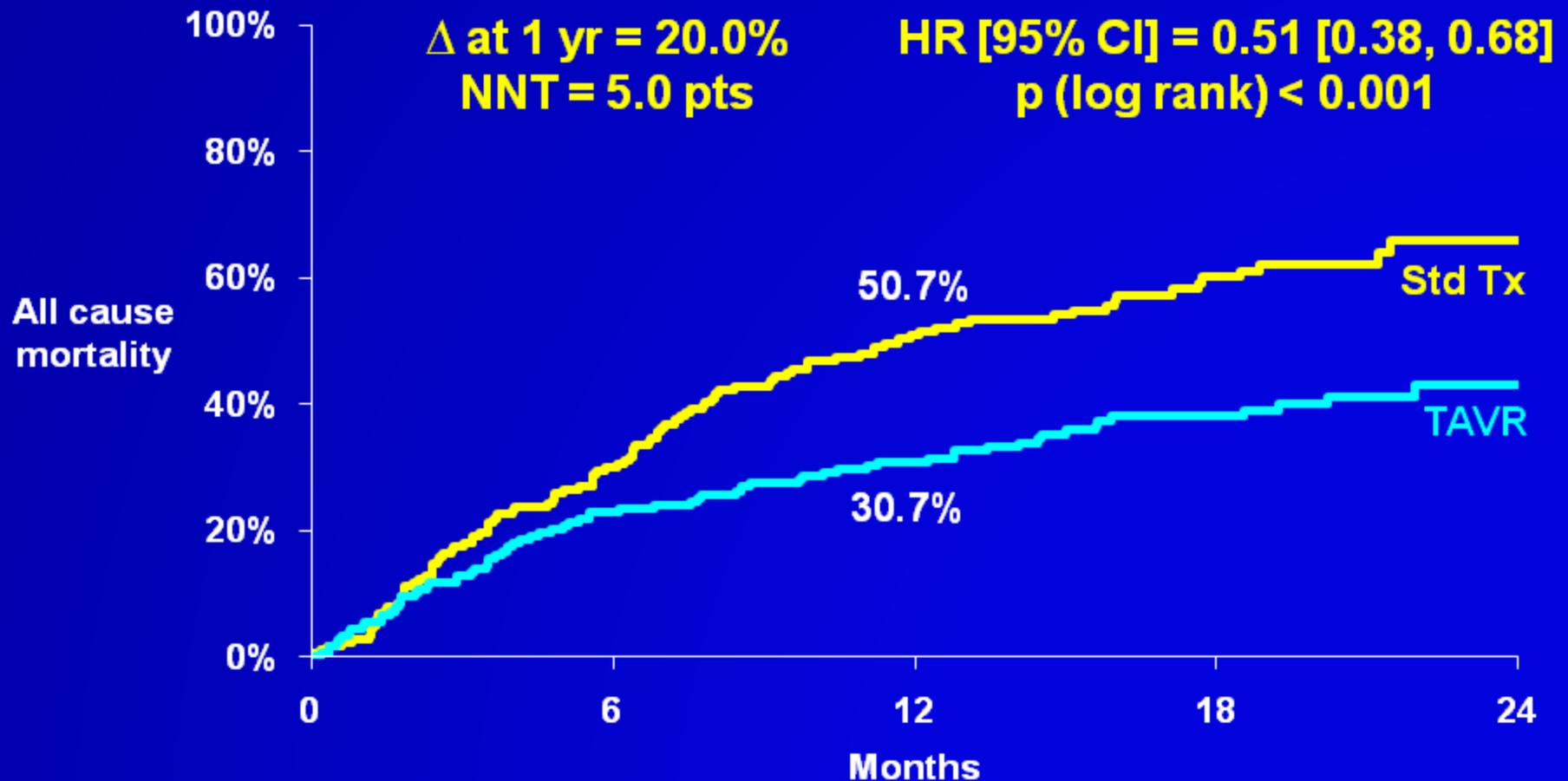
# Arrhythmias at 30 Days & 1 Year

Outcome	30 Days (n=179)			1 Year (n=179)		
	TAVR	Std Tx	p	TAVR	Std Tx	p
<b>Arrhythmias</b>						
New atrial fibrillation (%)	0.6	1.1	1.00	0.6	1.7	0.62
New pacemaker (%)	3.4	5.0	0.60	4.5	7.8	0.27
Endocarditis (%)	0	0	-	1.1	0.6	0.31

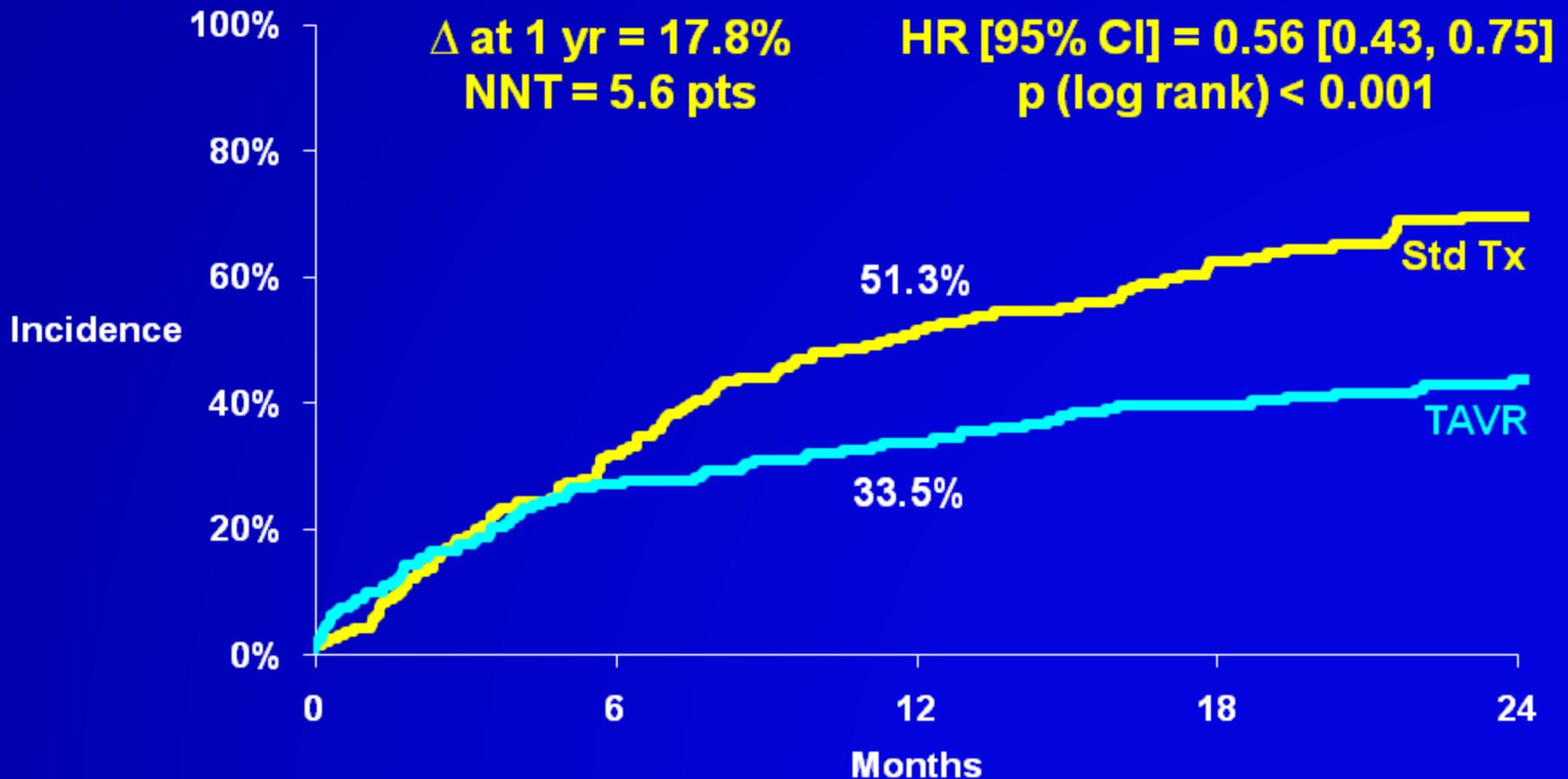
# Summary

---

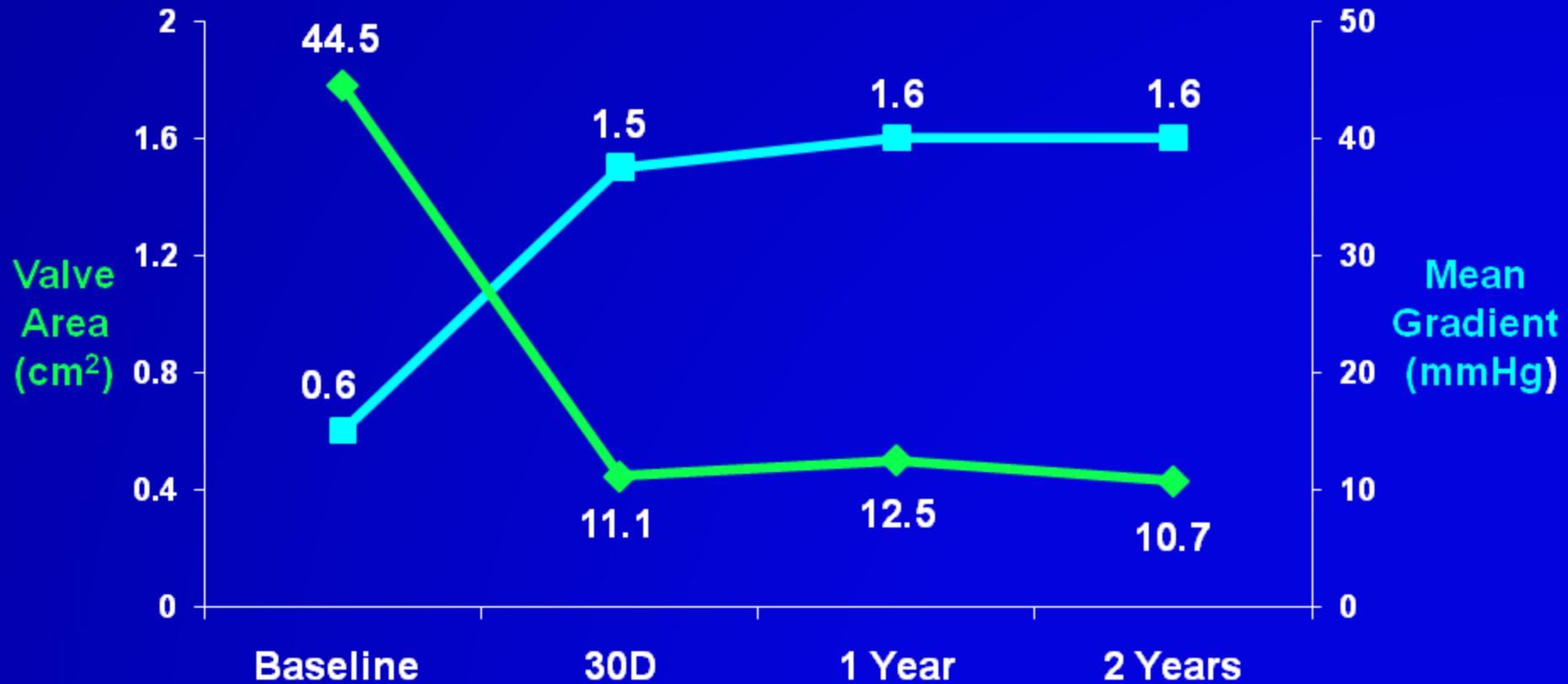
# Primary Endpoint: All Cause Mortality



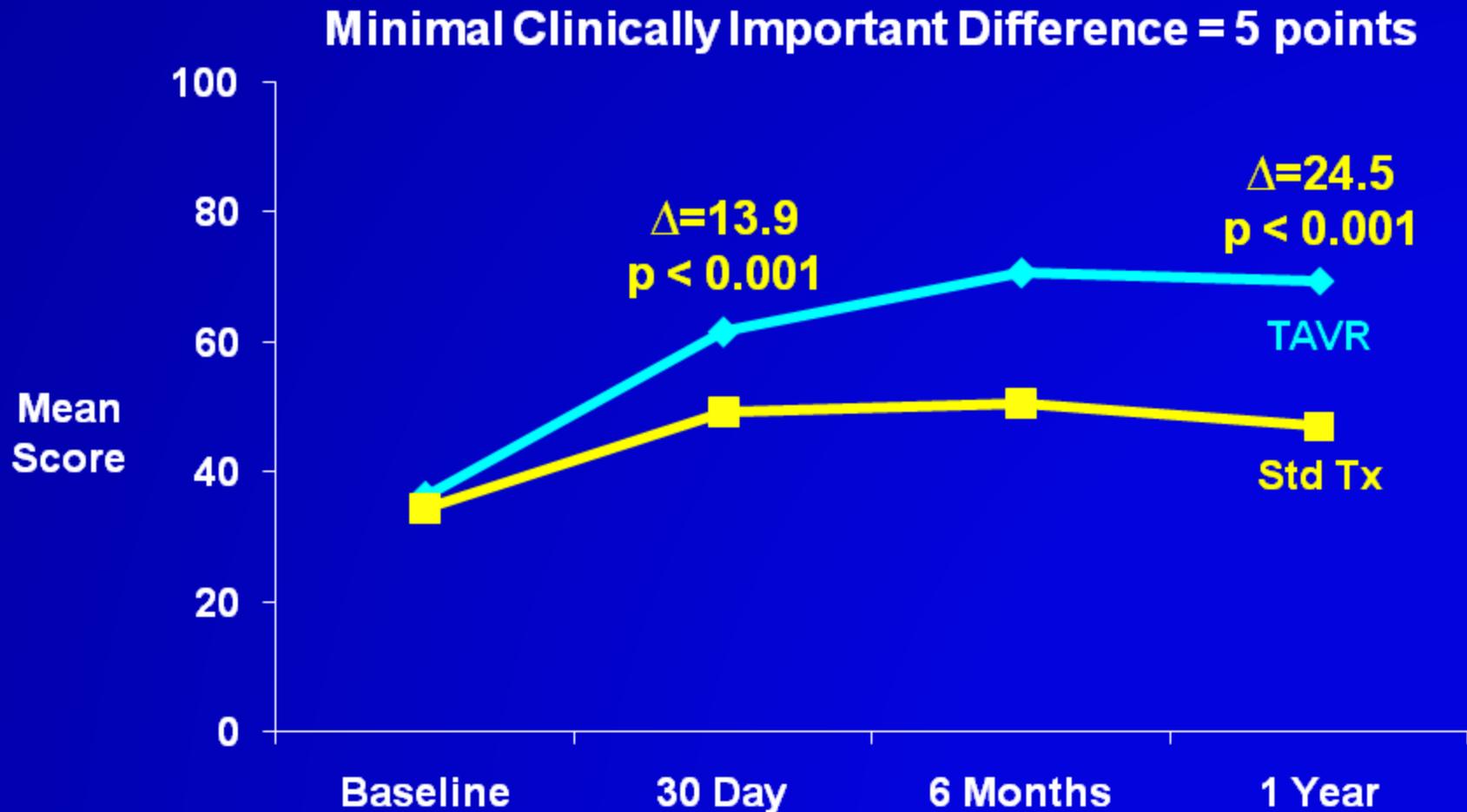
# Mortality or Major Stroke



# Echocardiography Assessments



# KCCQ Overall Score at 30 Days and 1 Year



# Global Clinical Experience Post Approval Study

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**Jodi J. Akin, MSN**

Vice President, Clinical Affairs

Edwards Lifesciences

# Edwards SAPIEN Clinical Data Sources

## Edwards SAPIEN Studies > 5,500 Patients

## Transfemoral n = 2,848

First in Man

RECAST  
I-REVIVE  
n = 36

RECAST  
I-REVIVE  
n = 36

Feasibility CE Approval

REVIVE n = 106  
TRAVERCE n = 172  
REVIVAL n = 95

REVIVE n = 106  
REVIVAL n = 55

Post CE Approval

PARTNER EU n = 130  
SOURCE n = 2,307

PARTNER EU n = 62  
SOURCE n = 920

Pivotal Randomized  
Control Trial

PARTNER US  
n = 358 (inoperable)  
n = 699 (high risk)

PARTNER US  
n = 358 (inoperable)  
n = 409 (high risk)

Continued Access

PARTNER US  
n = 1,609

PARTNER US  
n = 902

# Independent Studies

## 1,779 Patients in Independent Registries

---

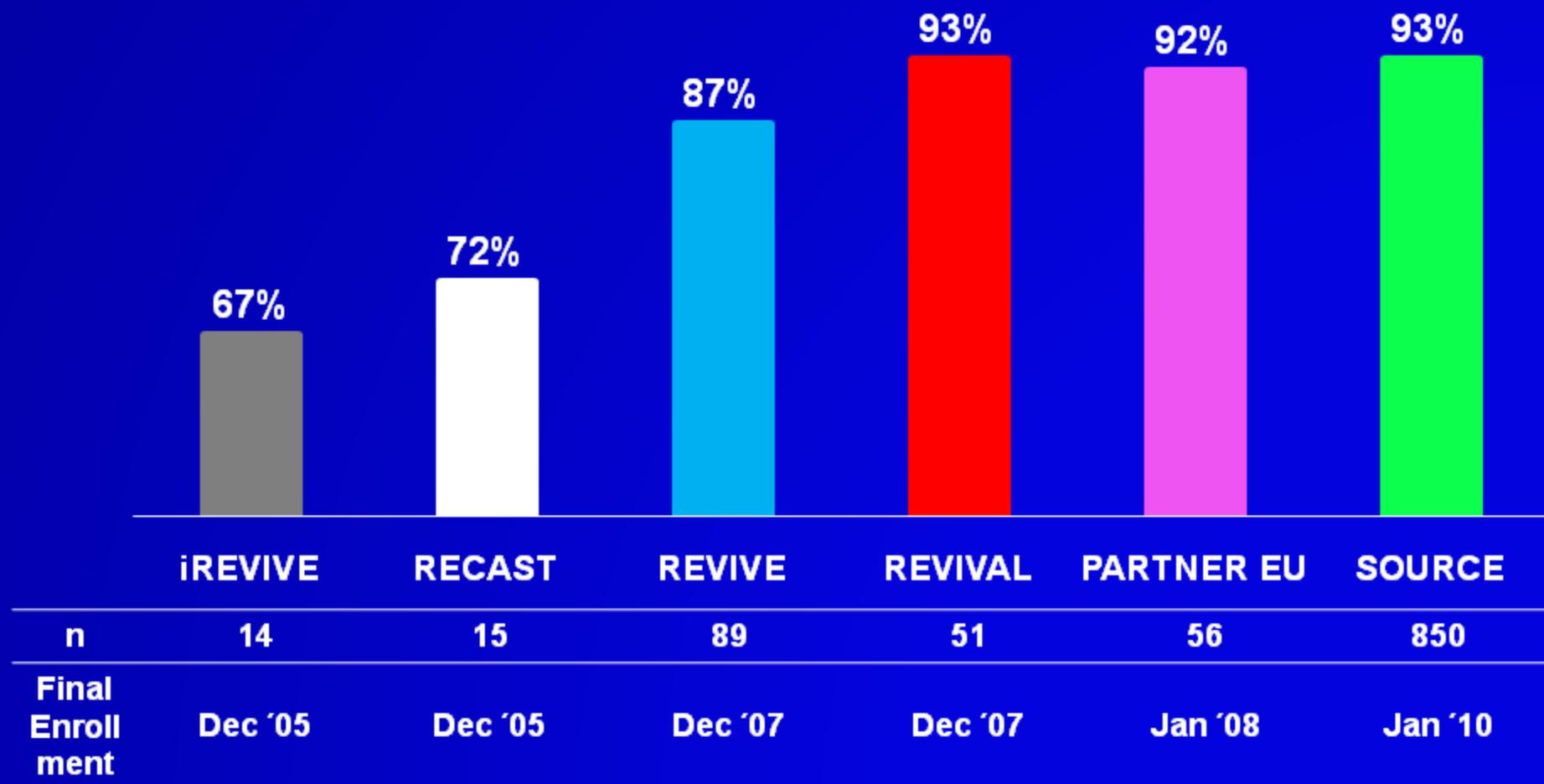
**French Registry**  
n = 1,137

**Belgian Registry**  
n = 303

**Canadian Registry**  
n = 339

# Edwards SAPIEN™ Outcomes Over Time

## 30 Day Survival



# All Edwards SAPIEN™ THV Studies Demographics

	<b>REVIVE, REVIVAL, PARTNER EU n=222</b>	<b>SOURCE Registry TF** n=920</b>	<b>France Registry n=1,137</b>	<b>Belgium Registry n=303</b>	<b>Canada Registry TF n=162</b>	<b>PARTNER Inoperable Cohort n=179</b>
<b>Age (yrs)</b>	<b>83</b>	<b>82</b>	<b>83</b>	<b>83</b>	<b>83</b>	<b>83</b>
<b>Female (%)</b>	<b>55</b>	<b>56</b>	<b>49</b>	<b>46</b>	<b>44</b>	<b>54</b>
<b>EuroSCORE (mean, %)</b>	<b>26</b>	<b>24</b>	<b>23</b>	<b>29</b>	<b>26</b>	<b>26</b>
<b>NYHA Class III/IV (%)</b>	<b>89</b>	<b>76</b>	<b>75</b>	<b>80</b>	<b>93</b>	<b>92</b>
<b>Aortic valve area (cm<sup>2</sup>)</b>	<b>0.59</b>	<b>0.70</b>	<b>0.67</b>	<b>0.60</b>	<b>0.63</b>	<b>0.60</b>
<b>Mean gradient (%)</b>	<b>45</b>	<b>49</b>	<b>48</b>	<b>47</b>	<b>48</b>	<b>45</b>
<b>Prior CABG (%)</b>	<b>26</b>	<b>15</b>	<b>19</b>	<b>20</b>	<b>30</b>	<b>37</b>
<b>Ejection Fraction (%)</b>	<b>51</b>	<b>52</b>	<b>53</b>	<b>50</b>	<b>55</b>	<b>54</b>

\* Rodes-Cabau et al., Transcatheter Aortic Valve Implantation for the Treatment of Severe Symptomatic Aortic Stenosis in Patients at Very High or Prohibitive Surgical Risk: Acute and Late Outcomes of the Multicenter Canadian Experience. JACC. 2010 Mar 16; 55 (11)

^ Wendler et al., Trans-apical aortic valve implantation: univariate and multivariate analyses of the early results from the SOURCE registry. EJCTS. 2010 March (published ahead of print)

\*\* Data Extract: 28 April 2011 POOLED MONITORED STUDIES: REVIVE, REVIVAL, PARTNER EU

# All Edwards SAPIEN™ THV Studies Clinical Outcomes

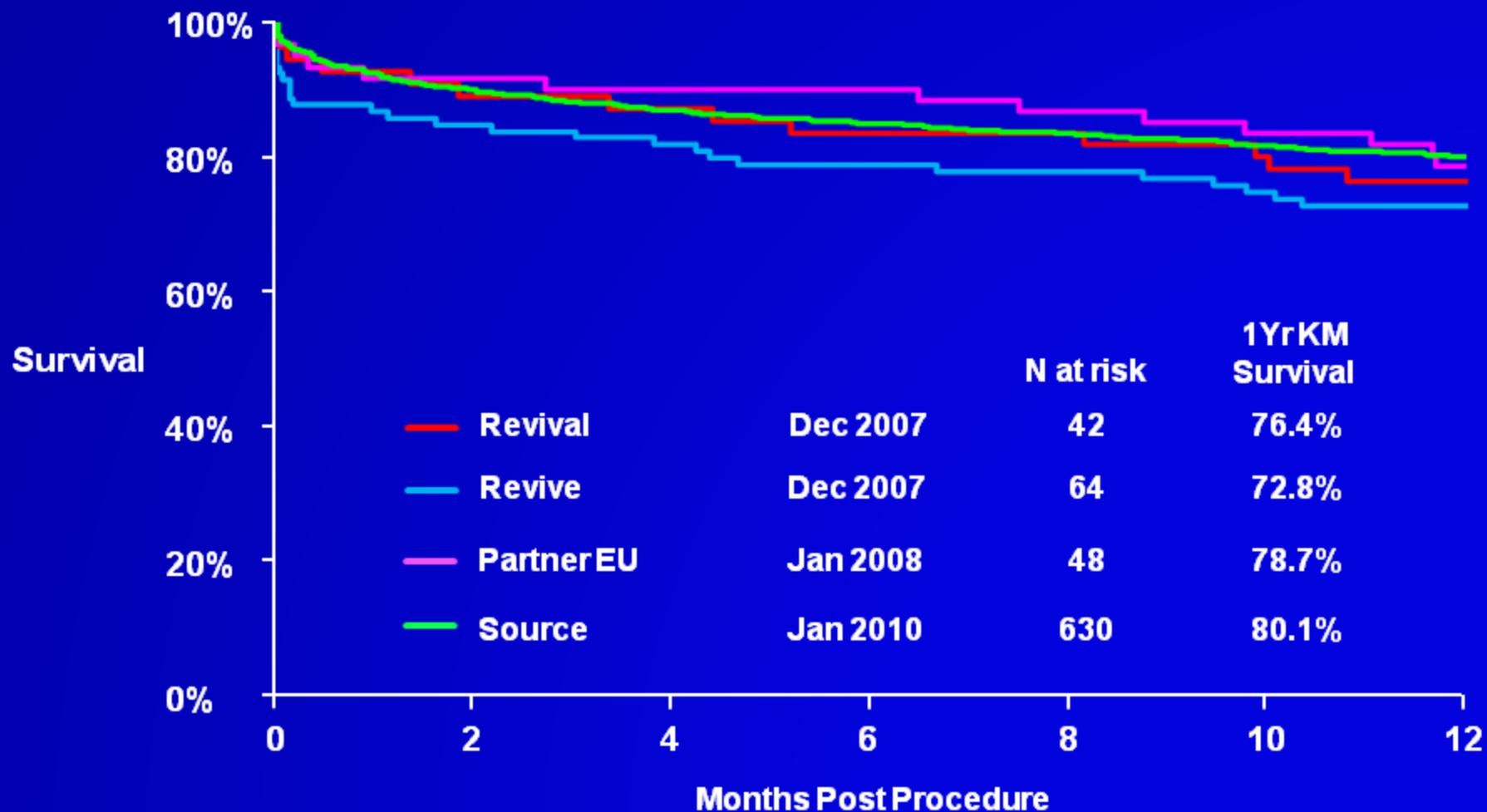
	<b>REVIVE, REVIVAL, PARTNER EU n=222</b>	<b>SOURCE Registry TF** n=920</b>	<b>France Registry n=1,137</b>	<b>Belgium Registry n=303</b>	<b>Canada Registry TF n=162</b>	<b>PARTNER Inoperable Cohort n=179</b>
<b>Freedom from Death (%)</b>	<b>89.6</b>	<b>92.5</b>	<b>92.2</b>	<b>92.0</b>	<b>90.5</b>	<b>95.0</b>
<b>Stroke (%)</b>	<b>3.3</b>	<b>3.5</b>	<b>3.5</b>	<b>5.0</b>	<b>3.0</b>	<b>7.3</b>
<b>Major Vascular Complications (%)</b>	<b>27.9</b>	<b>11.3</b>	<b>11.3</b>	<b>-</b>	<b>13.1</b>	<b>16.2</b>
<b>Permanent Pacemaker (%)</b>	<b>1.8</b>	<b>6.7</b>	<b>8.5</b>	<b>4.0</b>	<b>3.6</b>	<b>3.4</b>

\* Rodes-Cabau et al., Transcatheter Aortic Valve Implantation for the Treatment of Severe Symptomatic Aortic Stenosis in Patients at Very High or Prohibitive Surgical Risk: Acute and Late Outcomes of the Multicenter Canadian Experience. JACC. 2010 Mar 16; 55 (11)

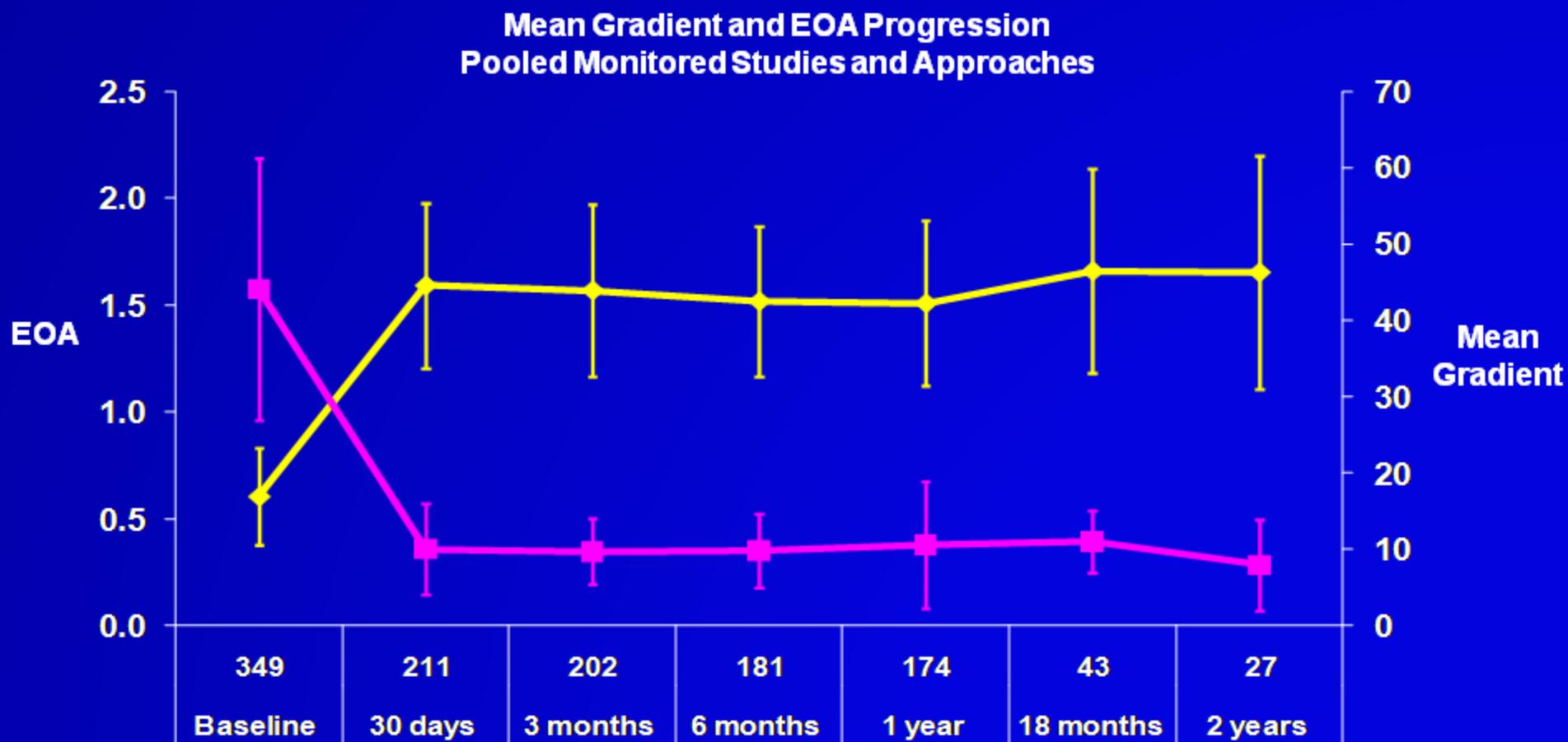
^ Wendler et al., Trans-apical aortic valve implantation: univariate and multivariate analyses of the early results from the SOURCE registry. EJCTS. 2010 March (published ahead of print)

\*\* Data Extract: 28 April 2011 POOLED MONITORED STUDIES: REVIVE, REVIVAL, PARTNER EU

# SAPIEN THV™ Transfemoral 1 Year Survival

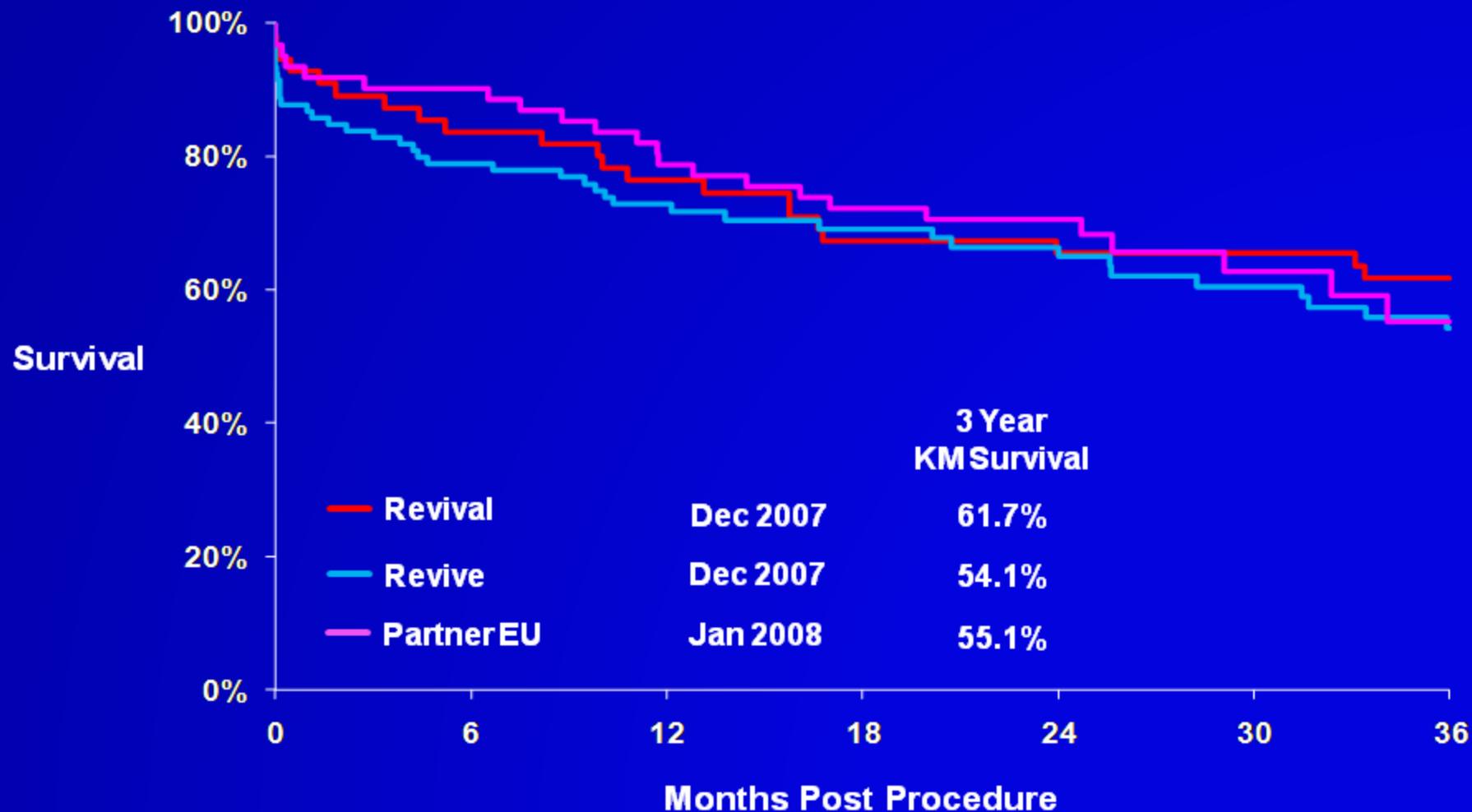


# REVIVE, REVIVAL, PARTNER EU: Available Echo Outcomes to 2 years



Error bars at  $\pm 1$  Standard Deviation

# SAPIEN THV™ Transfemoral 3-Year Survival



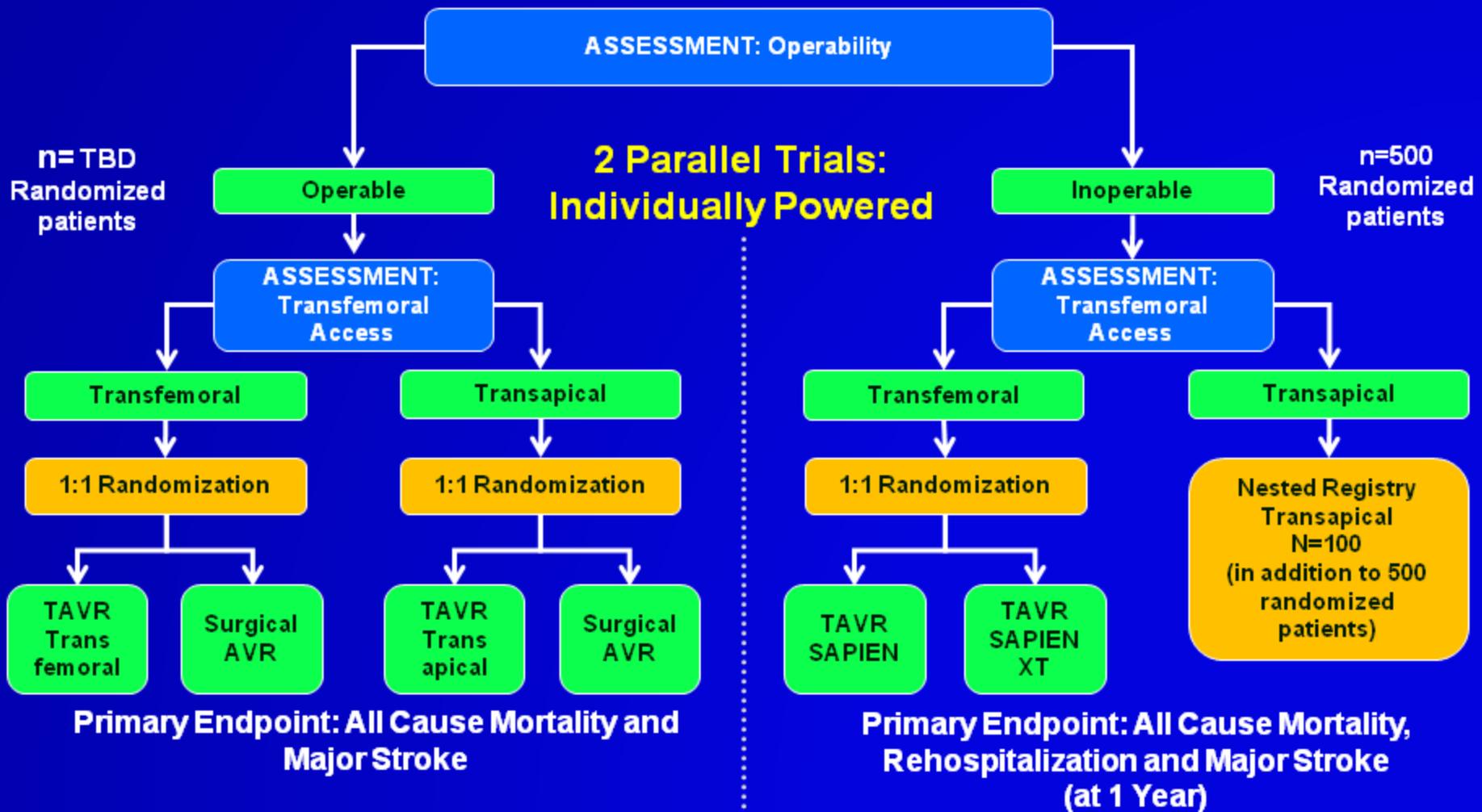
# Next Generation Clinical Studies with Edwards SAPIEN XT™ Platform

- Studies for next generation SAPIEN XT
  - PREVAIL TF, n = 212
  - PREVAIL TA, n = 213
  - SOURCE XT, n = 1300\*
  - The PARTNER II Trial\*

\* Studies are currently enrolling

# SAPIEN XT™: The PARTNER II Trial

## Symptomatic Severe Aortic Stenosis



## Summary

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- > 5,500 SAPIEN™ patients in clinical studies
- > 1,700 patients in independent registries
- 3-year effectiveness, safety and performance data support The PARTNER Trial results
- Outcomes continue to improve with experience
- US commercialization will incorporate lessons from these large data series

# Post Approval Study (PAS)

---

# Background

---

- Longer term results (2 to 5 years) from US and global clinical studies are emerging
- Post Approval Study should take into consideration the
  - Vast clinical experience with SAPIEN™
  - Age and risk profile of the patient population
  - Existing commitment to long term follow-up
  - Indication requested

# Objectives of the PAS

---

## ■ Aims

- Long term safety and effectiveness
- Long term valve durability
- Adherence to indication
- Learning curve/training effectiveness

## ■ Opportunities

- Partnership with professional societies in a longitudinal National Registry to evaluate aortic valve therapies

# Two Post Approval Studies Requested by FDA

---

- Post Approval Study 1
  - Extend scope of the Partner Trial to include long term Quality of Life measures
- Post Approval Study 2
  - Prospective, consecutive enrollment in a random, representative sample of commercial sites who did not participate in The PARTNER Trial
  - Hypothesis driven endpoints
  - Short and long term outcomes

# Post Approval Study 1: Extend Scope of The PARTNER Trial

---

- Post approval study will include all inoperable randomized and continued access patients (n=425)
- Annual clinical and echo follow up for 5 years
- DSMB / CEC
- Source record monitored (100%)
- Echo core lab
- *Addition of 5 year QOL measures (requested by FDA)*

# Post Approval Study 2: Requested by FDA

- n > 1000 inoperable patients
  - 1.2 x OPC non-inferiority margin
- Hypothesis driven, non-inferiority design, pre-specified individually powered endpoints
  - All neurological events
  - Major vascular events
  - Major bleeding events
  - Learning curve assessment
  - Valve durability to 5 years
  - Quality of Life to 5 years
- This trial design would necessitate an infrastructure similar to The PARTNER Trial

# Edwards Post Approval Study Proposal

- Post Approval Study 1 – The PARTNER Trial (without addition of QOL)
- Post Approval Study 2 – an Observational Study
  - Controlled, prospective, consecutively enrolled study in randomly selected sites representative of commercial cases in first year
  - Up to 750 patients
  - Procedure, 30 day and annual outcomes to 5 years
- Transition Post Approval Study 2 to the National Aortic Stenosis Outcomes Registry independently operated by the ACC / STS

# Edwards Plans for Site Selection and Participation in the PAS

- Rigorous process for site selection including:
  - Capability and commitment to collect and report clinical data
  - Participation in both National Cardiovascular Data Registry (NCDR), Society of Thoracic Surgery Predicted Risk Assessment Model (STS PROM), or a national registry
- Random selection of sites to participate in the post approval study from the first 150 sites vetted prior to launch

# Conclusions

---

- Edwards has demonstrated leadership and partnership with the professional societies to conduct clinical trials that drive evidence-based training, product and procedure development and responsible commercialization in TAVR globally
- We are committed to maintaining this standard as we launch TAVR for the inoperable patient in the United States

# Disciplined Roll-out Site Selection and Training

---

**Larry Wood**

Corporate Vice President

Transcatheter Valve Replacement

Edwards Lifesciences

# Edwards SAPIEN Transcatheter Heart Valve Program

---

- The Edwards SAPIEN valve commercially launched in Europe in Q4 2007
- Globally ~400 centers have implanted more than 15,000 Edwards transcatheter heart valves
- All centers completed Edwards training program
- Cornerstone of our transcatheter heart valve program: An unrelenting focus on excellent patient outcomes

# THV Training Program – A Commitment to the Heart Team Approach

---

- Every center in Europe trained included both cardiothoracic surgeons and interventional cardiologists
- Edwards declined to commercialize in centers where cardiac surgery support was not available

# Multi-disciplinary Training Program

---

- Foundational Didactic Course
- Simulation Training
- Device Preparation and Use Training
- Case Observation
- Peer Proctoring
- Clinical Specialist Support
- Continuing Education

# Edwards Lifesciences' THV Physician Training Process – Pre-training

## SITE ACTIVATION

Heart  
Team  
Training  
Initiation

Device &  
Procedure  
Training  
Manual

Radiology-  
Specific  
Screening  
Video

Echo-  
Specific  
Screening  
Video

Patient  
Screening  
eLearning  
& Test

# Physician Training Process

## Pre-Training

Patient  
Screening

Patient Case  
Submission  
for Pre-  
approval

Procedural  
Training  
Manual

## Fundamentals

Didactic

Taped Cases

Device Demo

Simulation

Patient Case  
Reviews

# Edwards Lifesciences' THV Physician Training Process

## DAY 1

Multidisciplinary Team Setup  
& Patient Screening –  
Non-Operative  
Echo  
Vascular /CT  
Comorbidities

Each site presents  
2 cases

Procedure Room Setup –  
Equipment, Staff  
Case Observation –  
Taped Standard Case, step  
by step decision making,  
rationale and potential  
complications

## DAY 2

Complications  
Management – How to  
avoid, detect, manage

Device Demo &  
Simulations

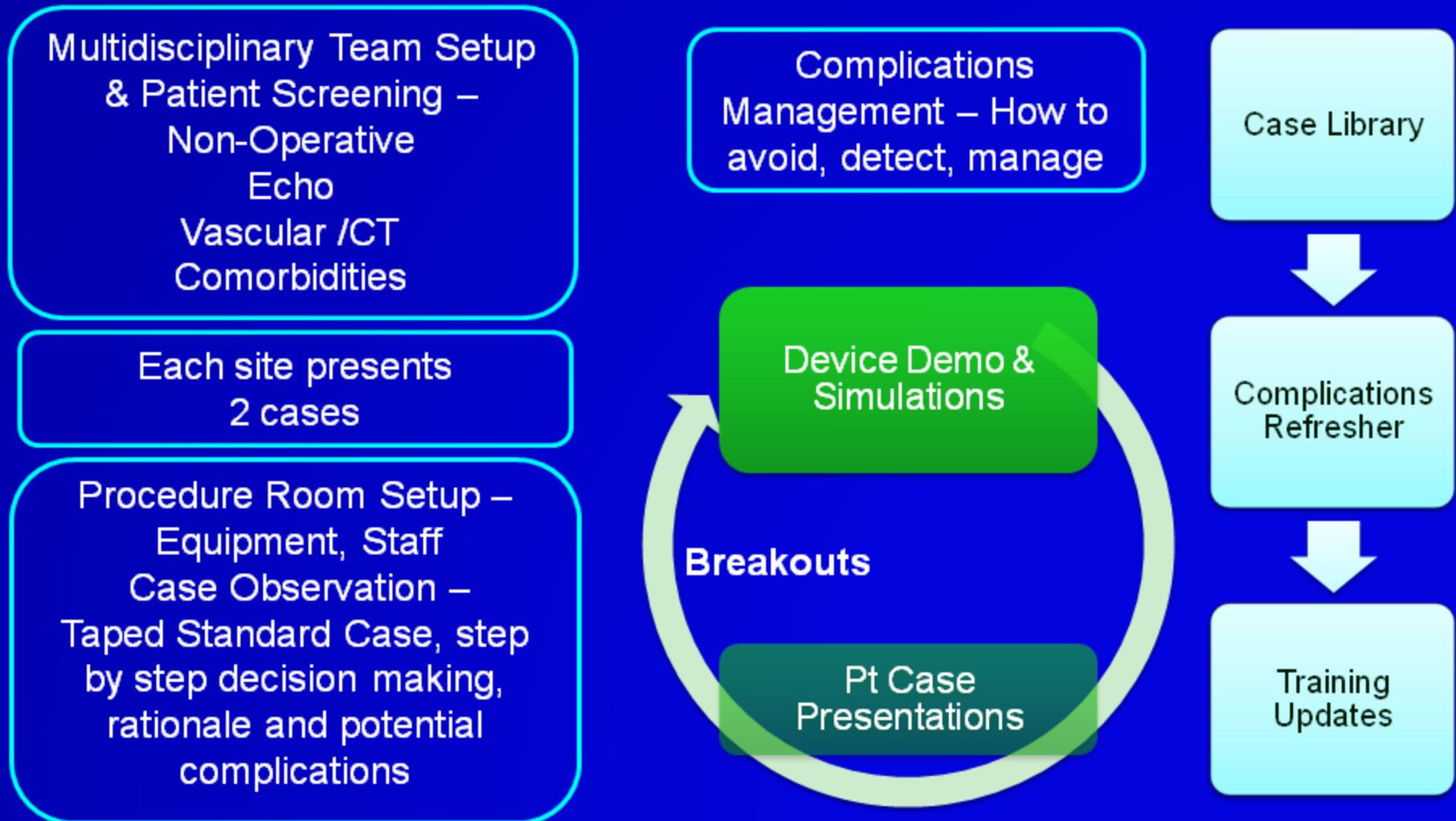
**Breakouts**

Pt Case  
Presentations

Case Library

Complications  
Refresher

Training  
Updates



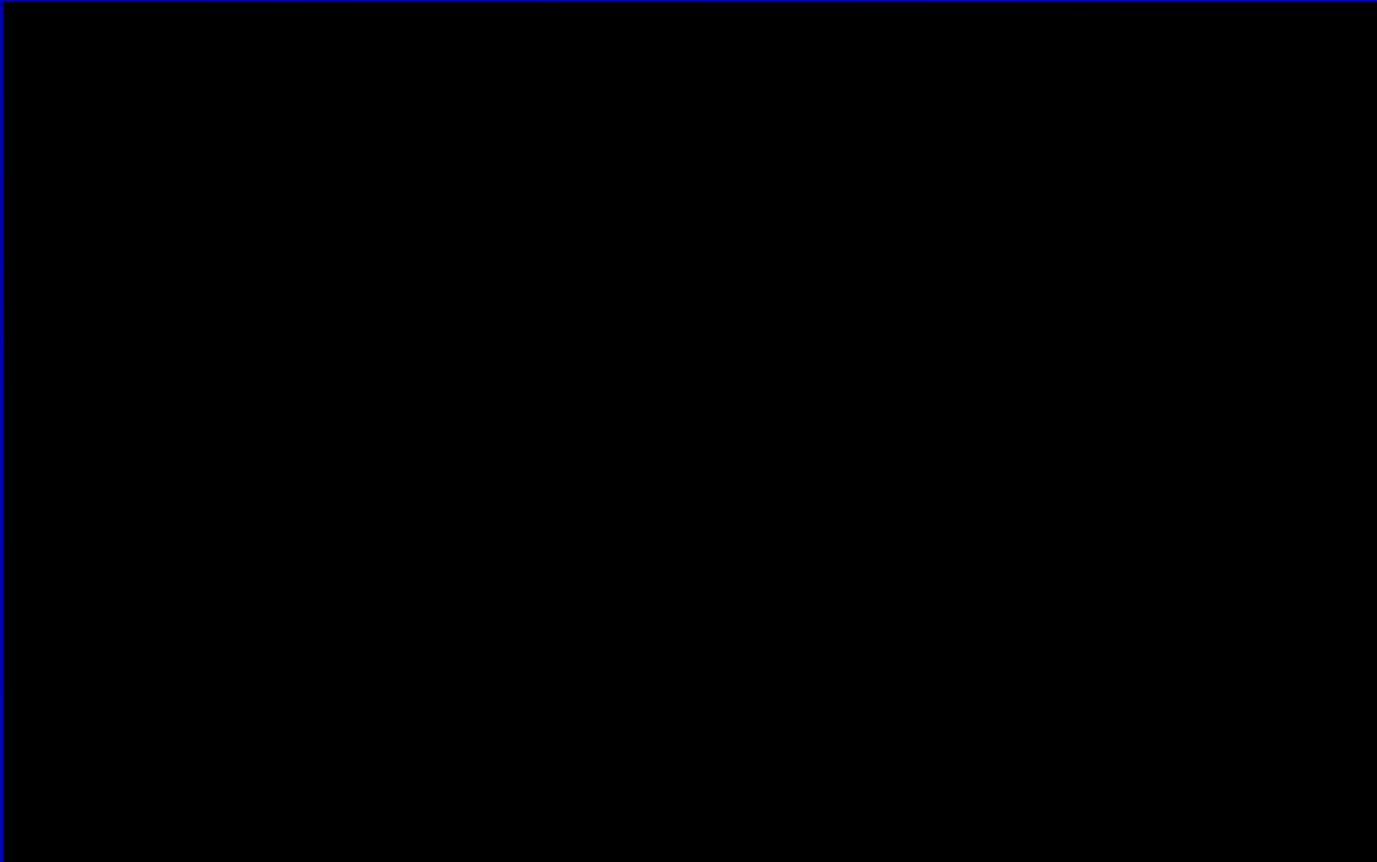
# Advanced Simulation

- Utilizes actual delivery systems
- Provides visual and tactile feedback
- Captures metrics
- Mimics pace
- Allows for complication management training



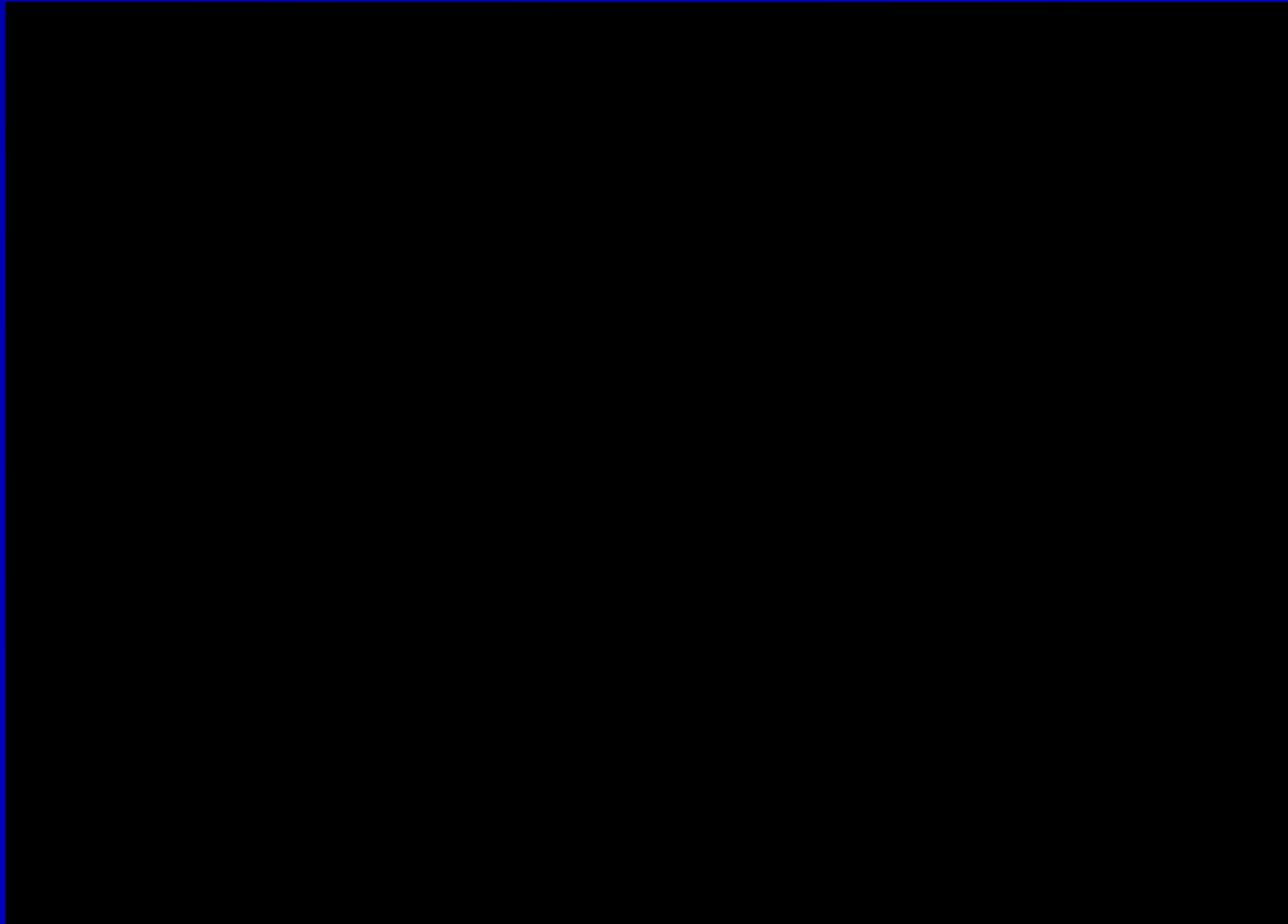
# Deployment Simulation

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# Actual Deployment

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# Physician Training Process

## Pre-Training

Patient  
Screening

Patient Case  
Submission  
for Pre-  
approval

Procedural  
Training  
Manual

## Fundamentals

Didactic

Taped Cases

Device Demo

Simulation

Patient Case  
Reviews

## Proctoring

Until Proctor,  
Site and FCS  
are satisfied

No fewer  
than 2 cases  
(avg = 5)

## Clinical Specialist Case

Proctor  
available

Proctoring  
until Clinical  
Specialist  
deems ready  
for  
independence

# Experienced Field Clinical Specialist Support Cases

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- Primarily former Cath Lab techs or trained Physician Assistants
- Device preparation
- Review any updates to training materials
- Provide proctor or screening support for challenging cases
- Ultimately train sites to independence, determined by outcomes

# Physician Training Process

## Pre-Training

Patient  
Screening

Patient Case  
Submission  
for Pre-  
approval

Procedural  
Training  
Manual

## Fundamentals

Didactic

Taped Cases

Device Demo

Simulation

Patient Case  
Reviews

## Proctoring

Until Proctor,  
Site and  
Field Clinical  
Specialist  
(FCS) are  
satisfied

No fewer  
than 2 cases  
(avg = 5)

## Clinical Specialist Case

Proctor  
available

Proctoring  
until FCS  
deems ready  
for  
independence

## Independence

Proctor or  
FCS available  
if needed

24/7 Tech  
Support

Continued  
Education &  
Training

## **Robust Physician Training Program Produces a High Procedural Success Rate**

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- Operational in Europe for 3 ½ years
- Trained > 1,600 physicians on patient selection and device use
- Hosted > 1,500 proctored cases
- Supported > 8,000 clinical cases
- Procedure outcomes have been maintained as tracked in the SOURCE Registry

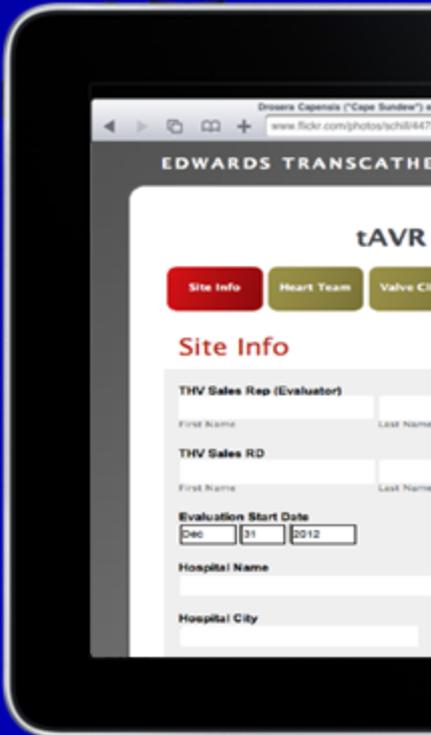
# Site Selection Process Includes Quantitative and Qualitative Methods

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- Presence of Heart Team (Cardiac Surgery, Cardiology, Echocardiographer, Anesthesiologist)
- Infrastructure for imaging and sterile environment
- Ability to track and report clinical outcomes
- Multi-disciplinary valve clinic environment
- Support of Administration
- Procedure Volume

# Comprehensive Valving Process

TAVR Site



Question	Volume		Heart Team						Valve Clinic					
	1		2						3					
PCI Volume														
sAVR Volume														
Dedicated IC														
Dedicated CTS														
Dedicated Anesthesiologist														
Dedicated Echocardiographer														
Dedicated Head Nurse / Tech														
Dedicated Room (Same room each time)														
Was CTS with IC @ mtg?														
Strength of IC/CTS Relationship														
Multi-disciplinary Valve Clinic														
Strength of Valve Clinic														
Direct Outreach & Education														
Strength of Outreach														
Institution #1	3	1	5	6	9	10	1	2	3	4	2	1	8	10
Institution #2	5	6	9	10	1	2	3	4	10	1	2	3	4	3
Institution #3	8	10	1	2	3	4	4	2	1	8	5	9	10	8
Institution #4	4	2	1	8	5	6	9	10	1	2	3	4	8	5
Institution #5	9	10	10	1	2	3	4	6	4	2	1	8	4	4
Institution #6	8	3	4	5	6	9	10	1	2	3	4	6	6	9
Institution #7	5	6	9	10	1	2	3	4	4	10	1	2	3	4
Institution #8	2	4	2	1	8	10	1	2	3	4	4	2	1	8
Institution #9	9	10	5	6	9	5	6	9	10	1	2	3	4	8

Question	Heart Team						Valve Clinic						
	2						3						
Dedicated CTS													
Dedicated Anesthesiologist													
Dedicated Echocardiographer													
Dedicated Head Nurse / Tech													
Dedicated Room (Same room each time)													
Was CTS with IC @ mtg?													
Strength of IC/CTS Relationship													
Multi-disciplinary Valve Clinic													
Strength of Valve Clinic													
Direct Outreach & Education													
Strength of Outreach													
Institution #1	5	9	10	1	2	3	4	10	1	2	3	4	3
Institution #2	2	3	4	4	2	1	8	5	9	10	8		
Institution #3	8	5	6	9	10	1	2	3	4	8	5		
Institution #4	1	2	3	4	6	4	2	1	8	4	4		
Institution #5	5	6	9	10	1	2	3	4	6	6	9		
Institution #6	0	1	2	3	4	4	10	1	2	3	4		
Institution #7	1	8	10	1	2	3	4	4	2	1	8		
Institution #8	5	9	5	6	9	10	1	2	3	4	8		

Final Prioritization

## Disciplined Roll-out

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- Of the 2000 Interventional Cardiology and 1200 Cardiac Surgery programs in the United States, we expect to train between 150-250 sites in the first year of commercialization paced by procedure and 30 day outcomes
- Heart Teams (cardiac surgeon and cardiologists) will be trained to document patient selection in the patient medical record

## Benefits of TAVR Outweigh the Risks

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- Significant reduction in mortality compared to best standard therapy ( $p < 0.001$ )
- Significant improvements in Quality of Life
- Even when considering major complications the benefits of TAVR clearly outweigh the risks

# The Edwards Lifesciences SAPIEN™ THV Transcatheter Heart Valve System

Circulatory Systems Device Panel

July 20, 2011

Food and Drug Administration

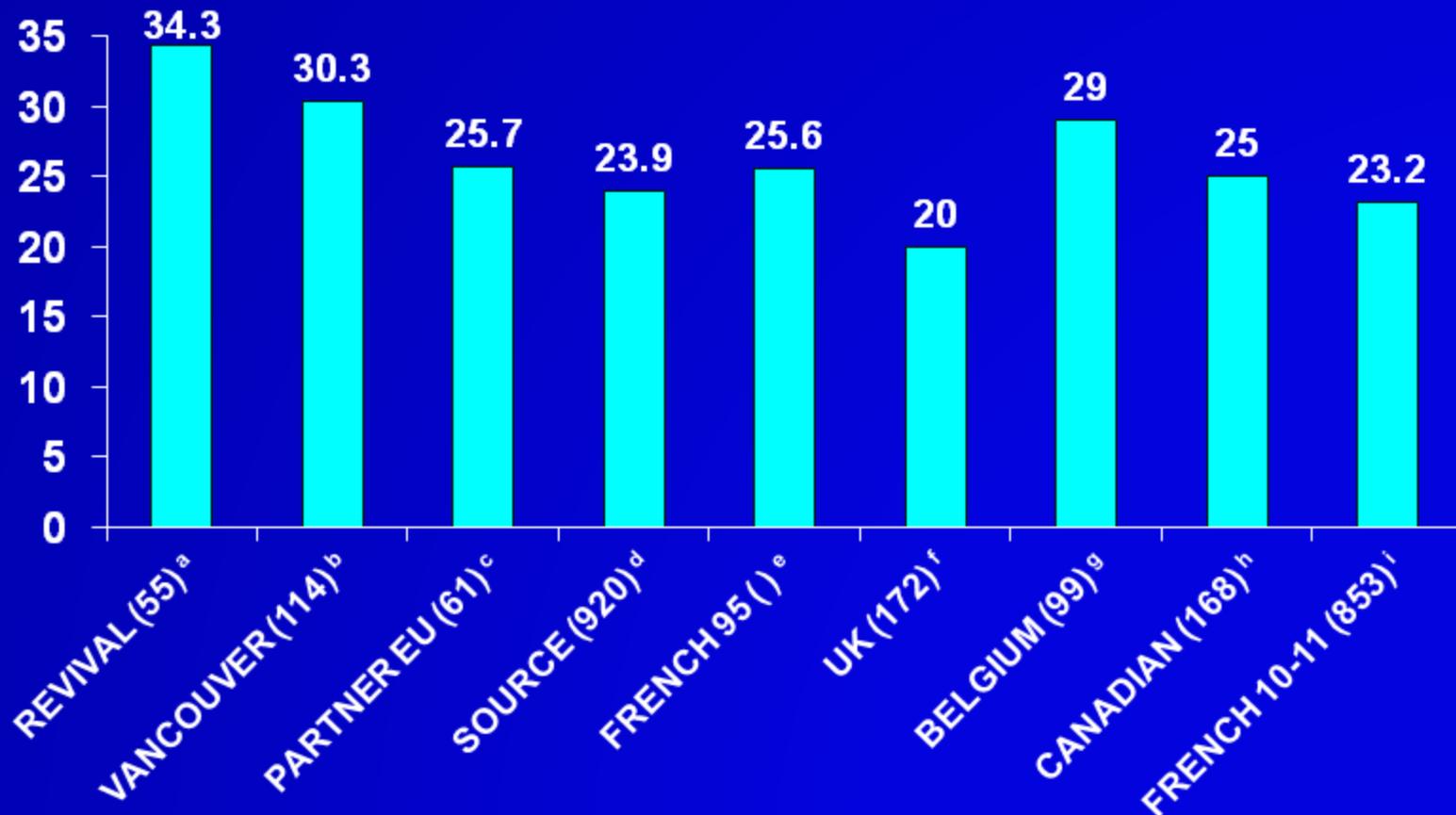


# Backup Slides

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# TAVR Registries – Logistic Euro Scores

Edward SAPIEN (TF)



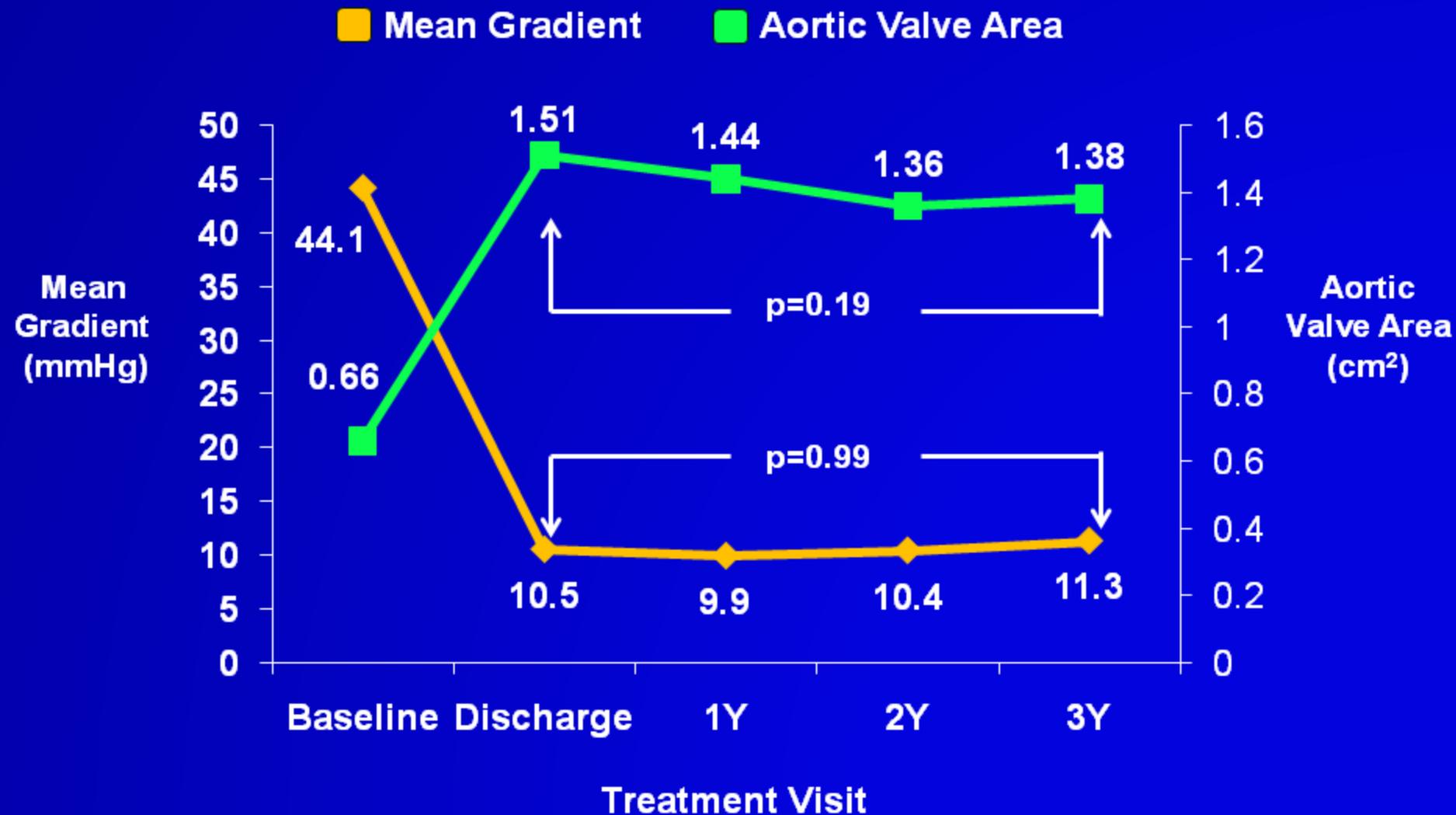
<sup>a</sup>Kodali et al AJC 2011;107:1058-1064; <sup>b</sup>Webb TCT 2008; <sup>c</sup>Lefevre et al EurHeartJ 2011;32:148-57; <sup>d</sup>Thomas et al Euro PCR 2011; <sup>e</sup>Eltchaninoff Eur Heart J 2010; Sept 15, 2010 epub; <sup>f</sup>Ludman EuroPCR 2010; <sup>g</sup>Belgium; <sup>h</sup>Rodes-Cabau et al. JACC 2010;55:In Press; <sup>i</sup>Gilard M EuroPCR 2011

## Baseline Characteristics – General

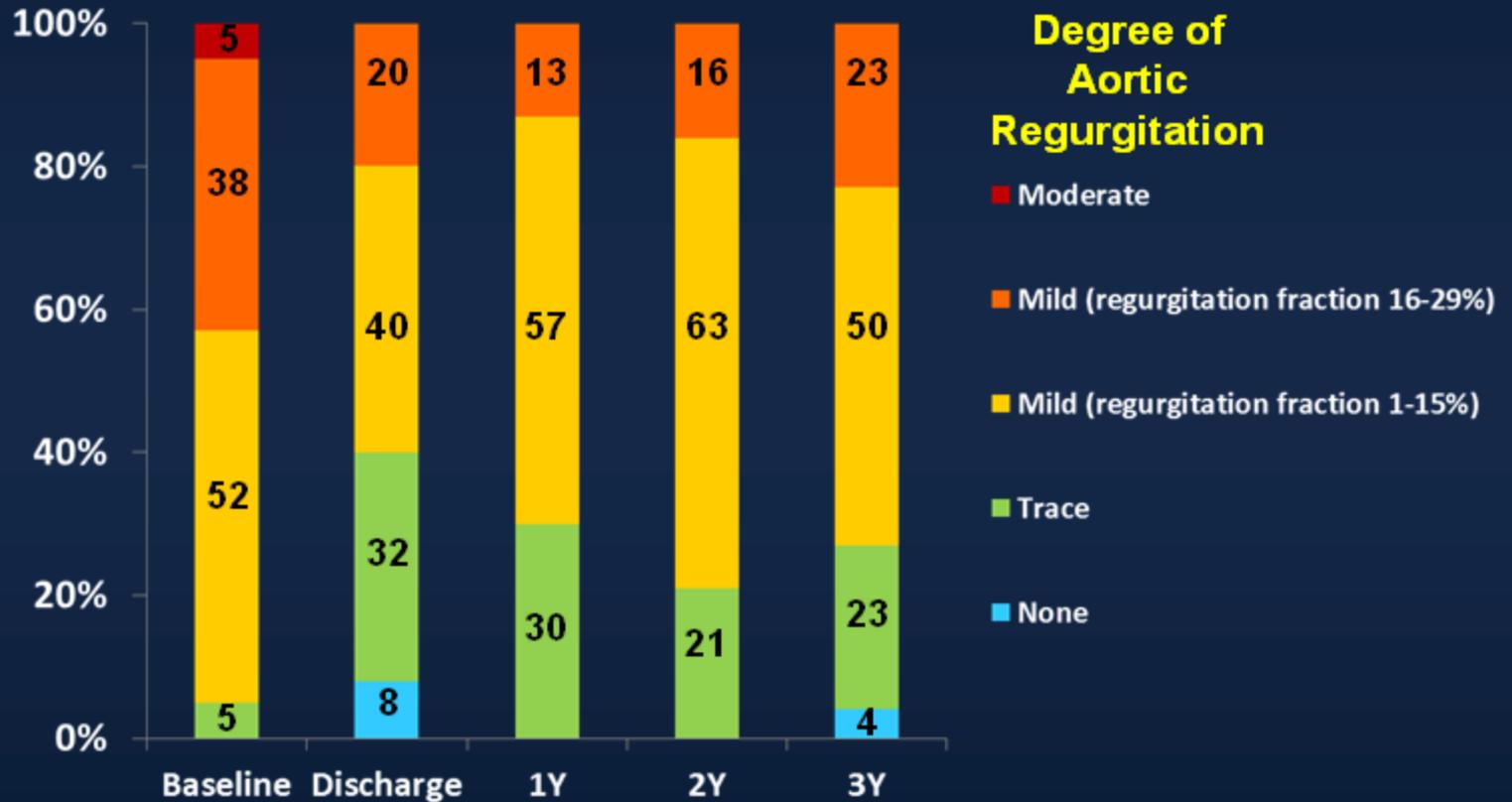
	Cohort I (n=1038)	Cohort II (n=1269)	p
Age (yrs)	81.2 ± 6.9	81.1 ± 6.9	0.77
Female (n/%)	576 (55.5%)	745 (58.7%)	0.06
BMI (kg/m <sup>2</sup> )	26.1 ± 4.5	26.6 ± 5.0	0.1
Diabetes (n/%)	281 (27.1%)	347 (27.3%)	0.89
Respiratory disease (n/%)	212 (20.4%)	233 (18.4%)	0.23
Renal insufficiency (n/%)	305 (29.4%)	356 (28.1%)	0.49
Peripheral vascular disease (n/%)	210 (20.2%)	250 (19.7%)	0.76
Porcelain aorta (n/%)	86 (8.3%)	92 (7.2%)	0.39
Cerebral vascular accident (n/%)	57 (5.5%)	78 (6.1%)	0.53
Carotid artery stenosis >50% (n/%)	132 (12.7%)	140 (11.0%)	0.22
<b>Logistic EuroSCORE</b>	<b>27.6 ± 15.5</b>	<b>25.0 ± 15.3</b>	<b>&lt;0.001</b>

# Canadian Long-term Echo

## Mean Gradient and Aortic Valve Area



# Aortic Regurgitation

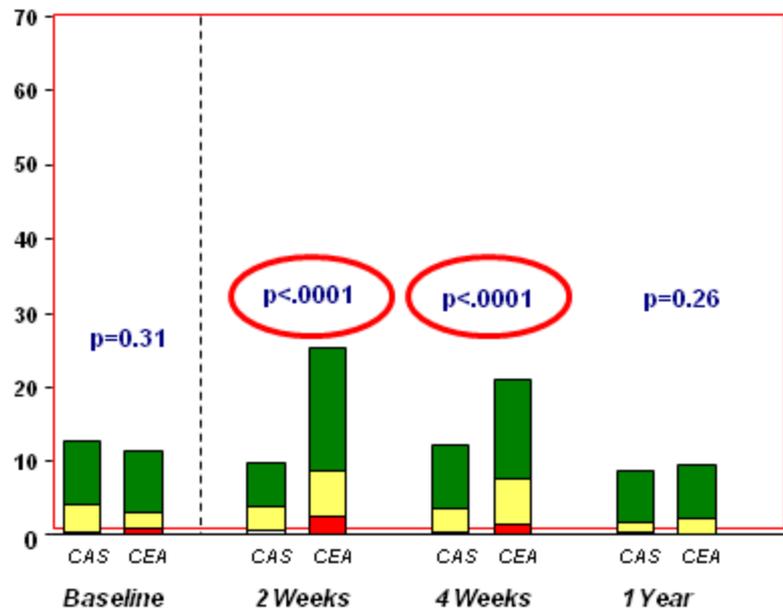


# CREST

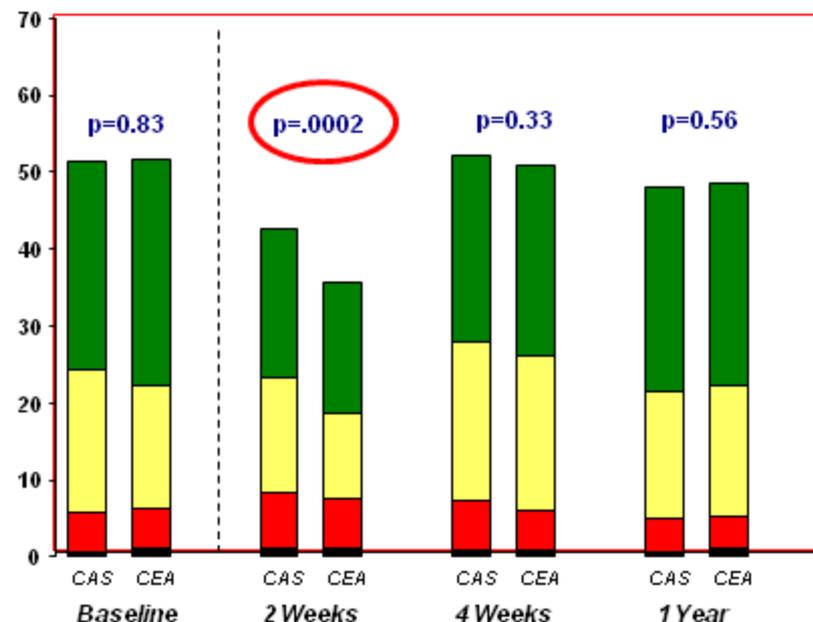
## *selected secondary endpoints*

- Age
- Sex
- Stroke
- MI
- QOL
- Cost Effectiveness

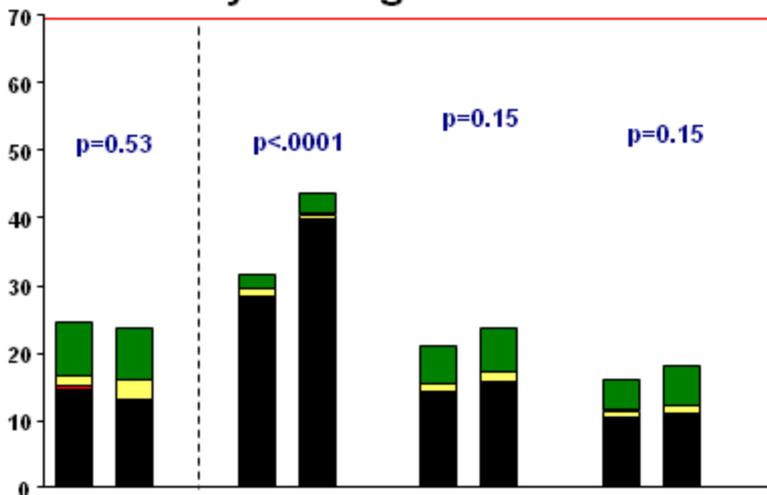
### Difficulty Eating or Swallowing



### Difficulty Walking

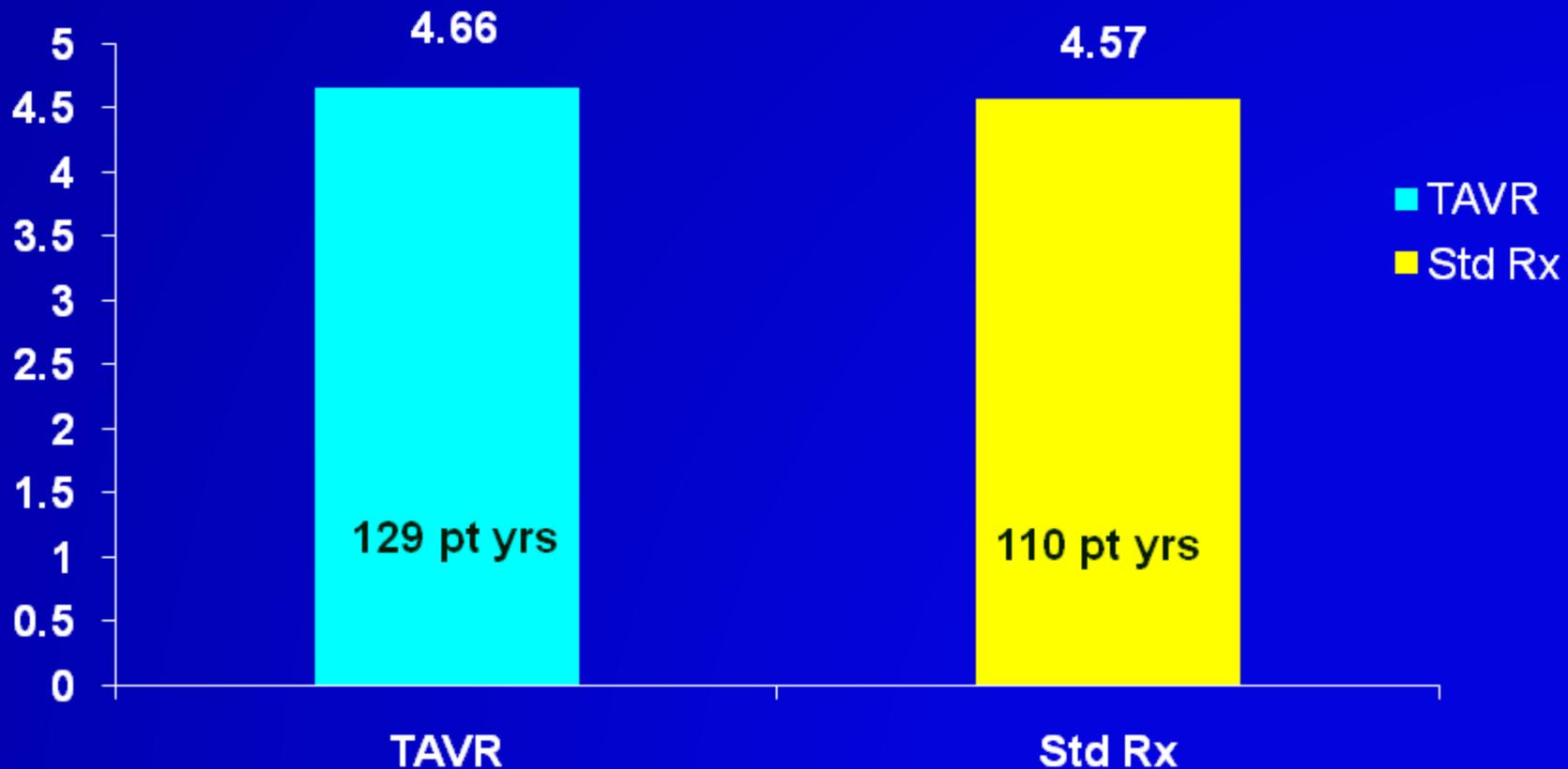


### Difficulty Driving



- Mild Difficulty
- Moderate Difficulty
- Severe Difficulty
- Unable

# Linearized Rate for all Stroke – Time Period 31 – 365 Days

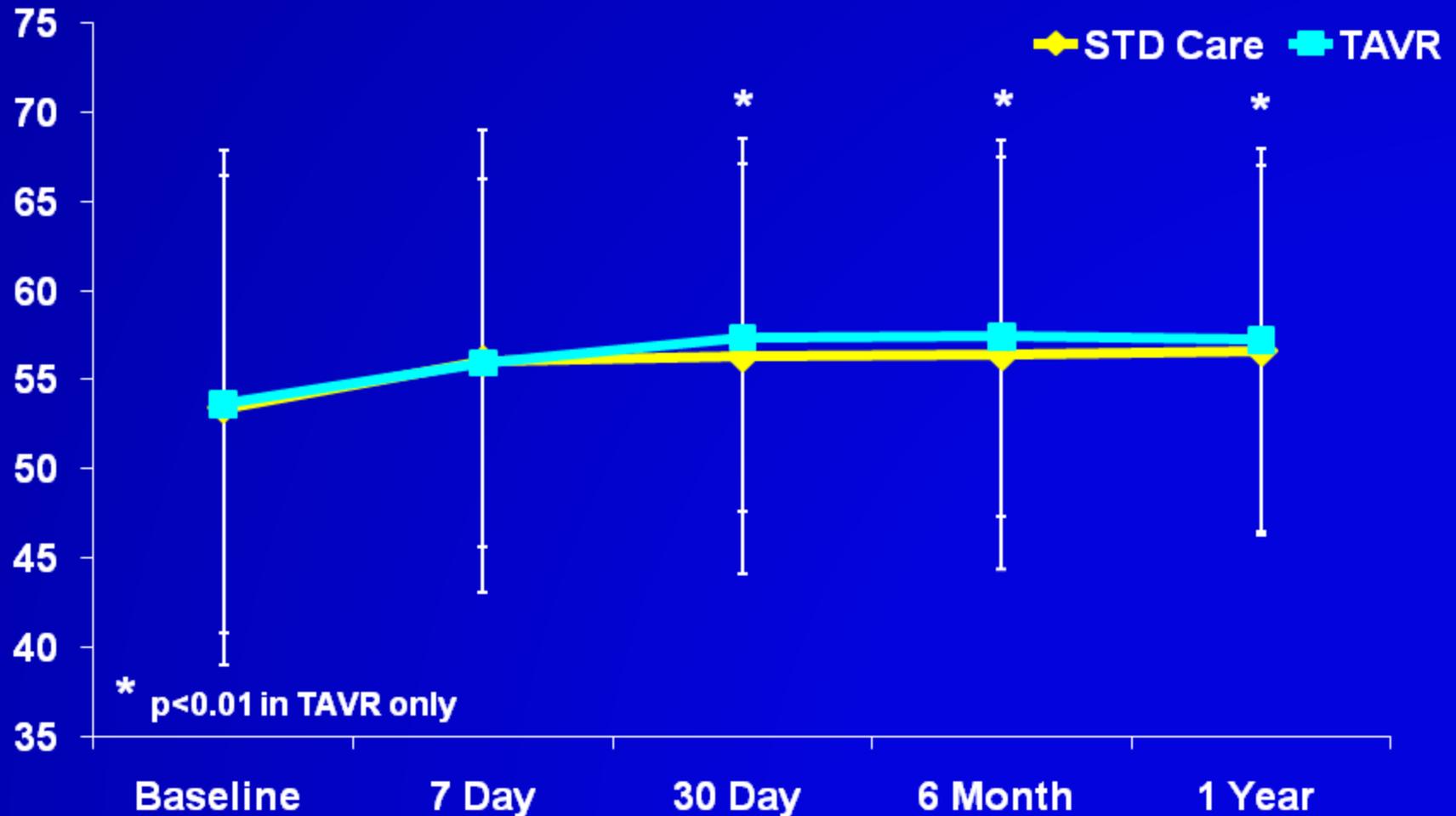


# Echocardiography Outcomes

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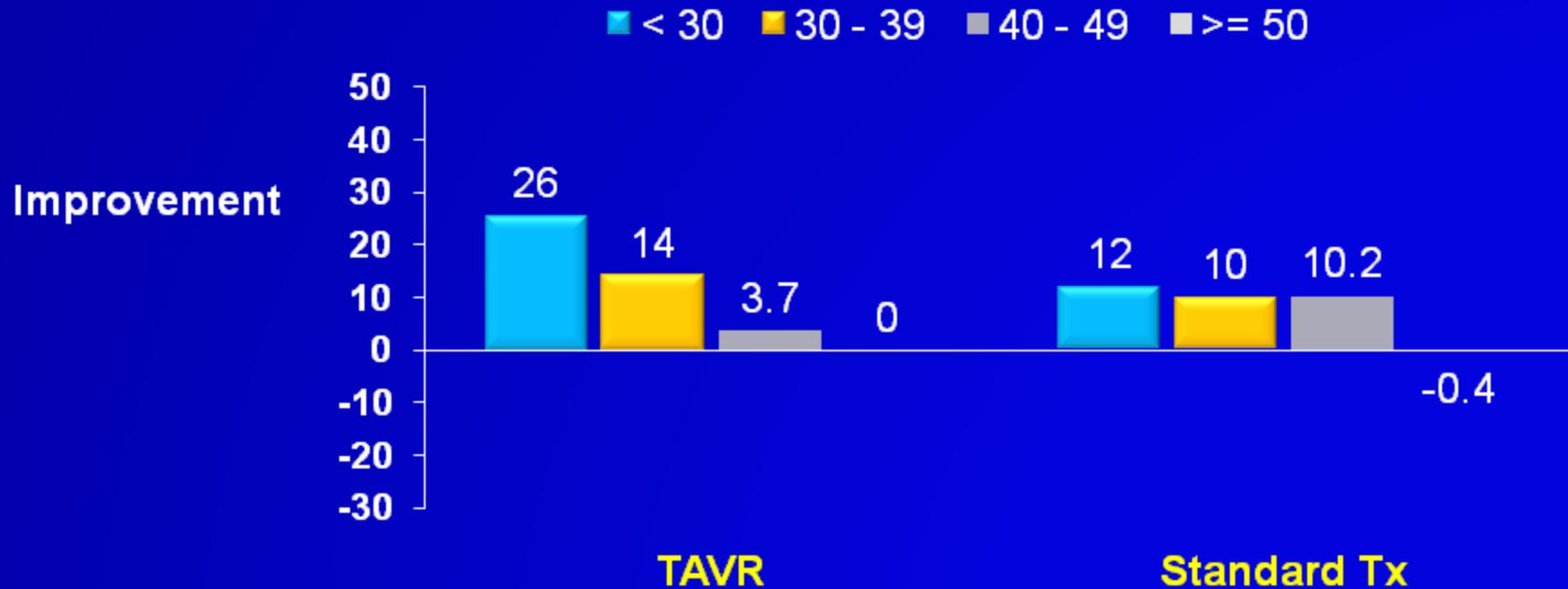
LVEF Improvement

# LV Ejection Fraction (%)

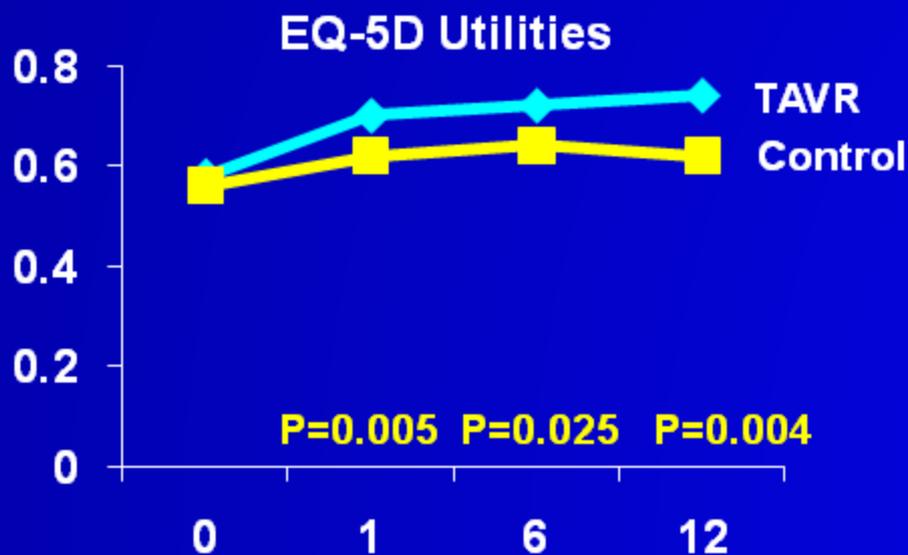
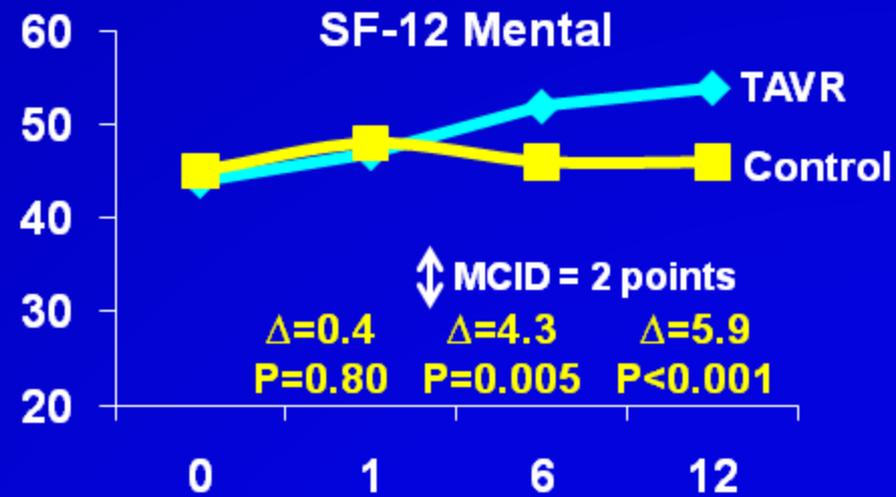
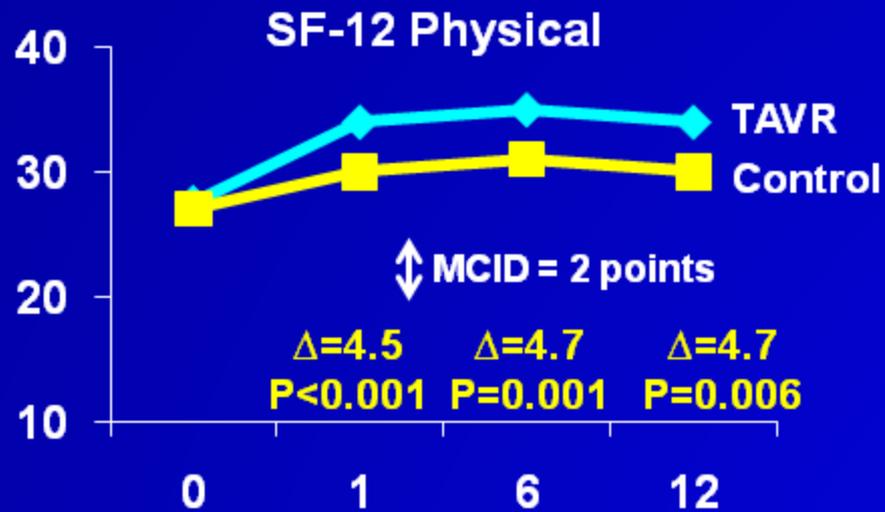


# Ejection Fraction

## Improvement from baseline Stratified by Baseline EF



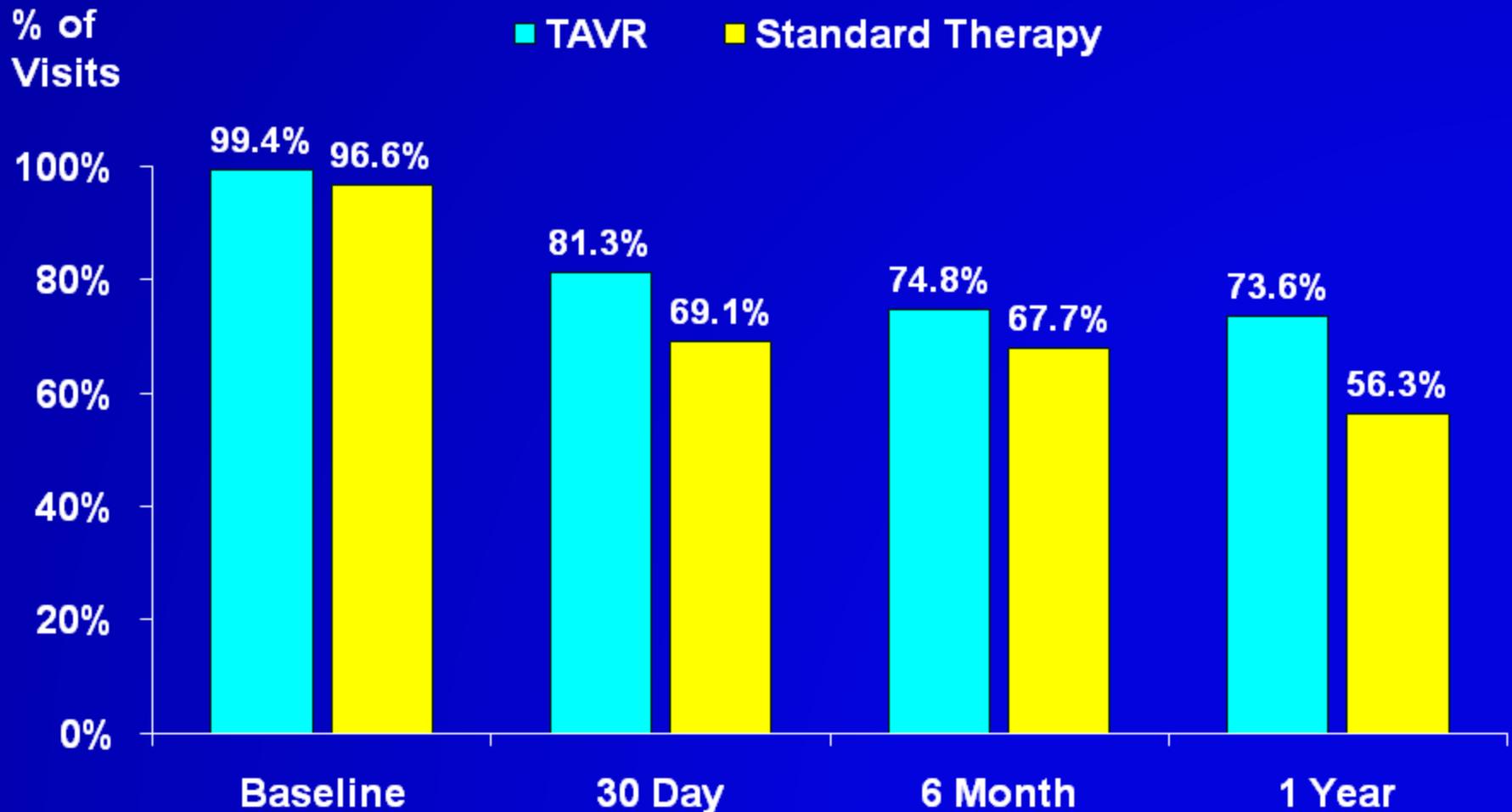
# SF 12- Generic QOL and Utilities



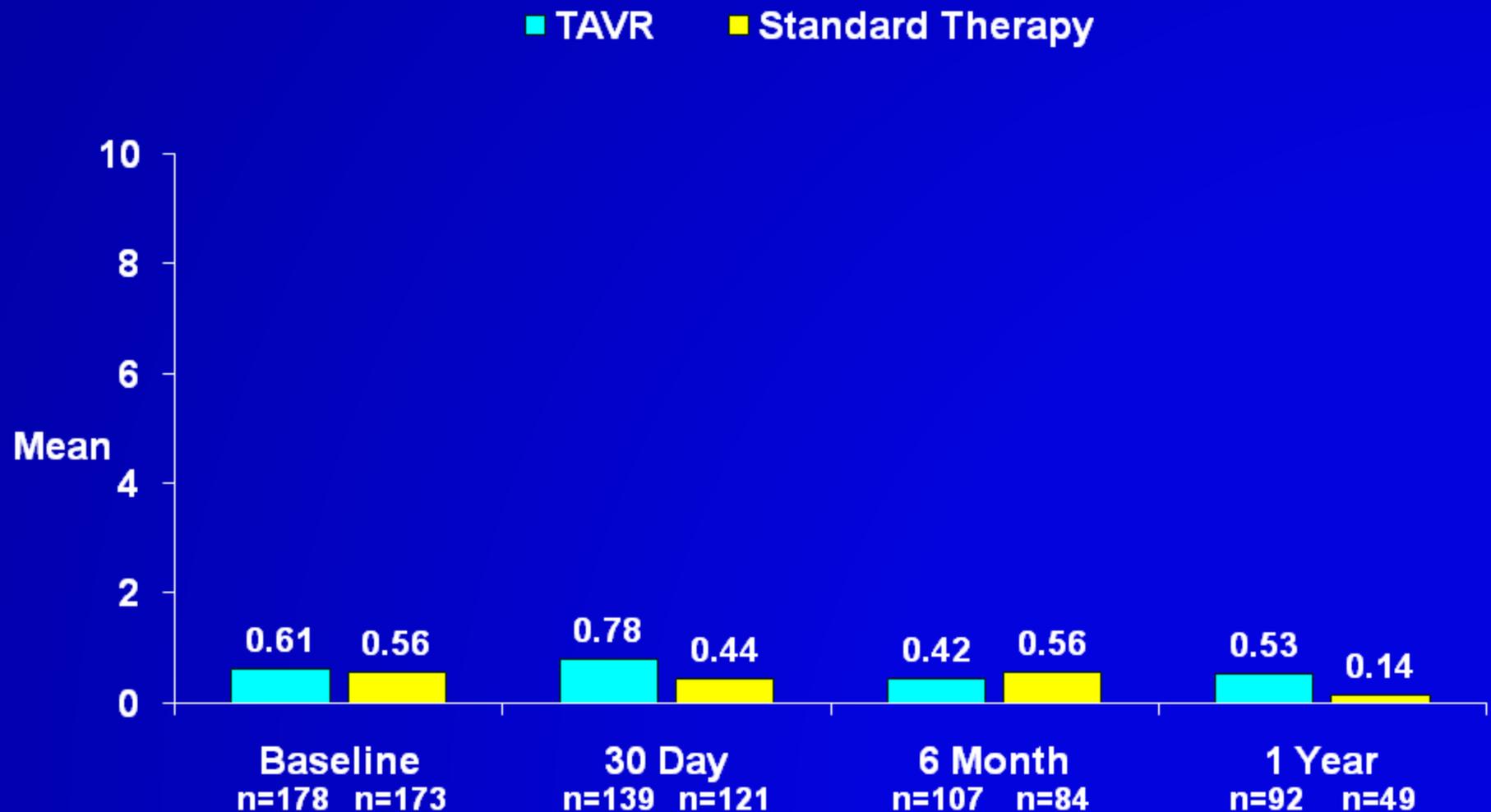
MCID = minimum clinically important difference

# Variable NIH Stroke Score

## Percent of visits with NIHSS Evaluated



# Variable NIH Stroke Score



# Changes in KCCQ Scores in Patients with Neurological Events at 30 Days and 1 Year (TAVR)

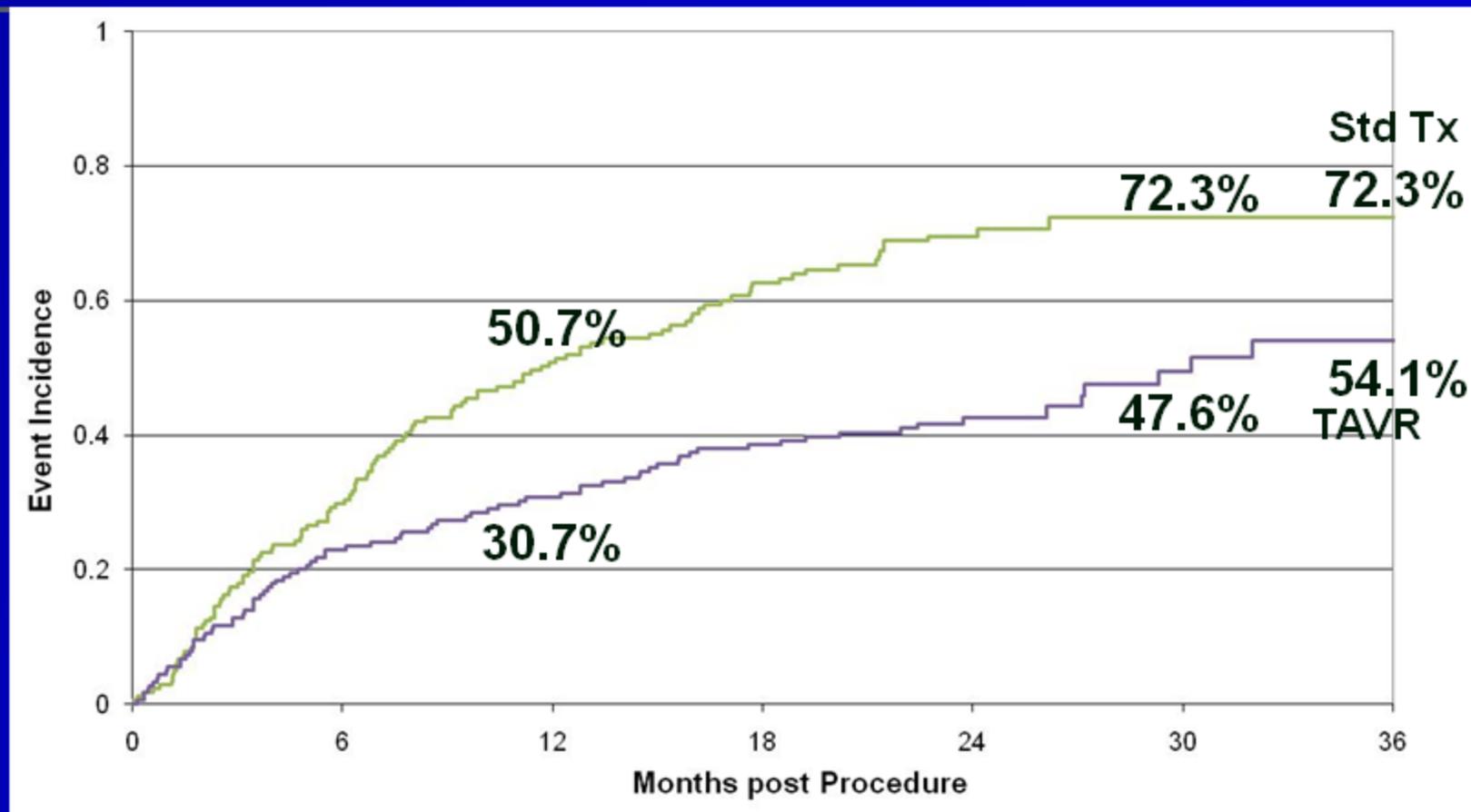
## Event $\leq$ 30 days

	Dead	Worse	Better	Missing
30 Day	3	3	6	1
1 Year	6	0	3	4

## Event $>$ 30 days

	Dead	Worse	Better	Missing
30 Day	0	0	9	2
1 Year	5	0	4	2

# Primary Endpoint: 3-Year All Cause Mortality (ITT)

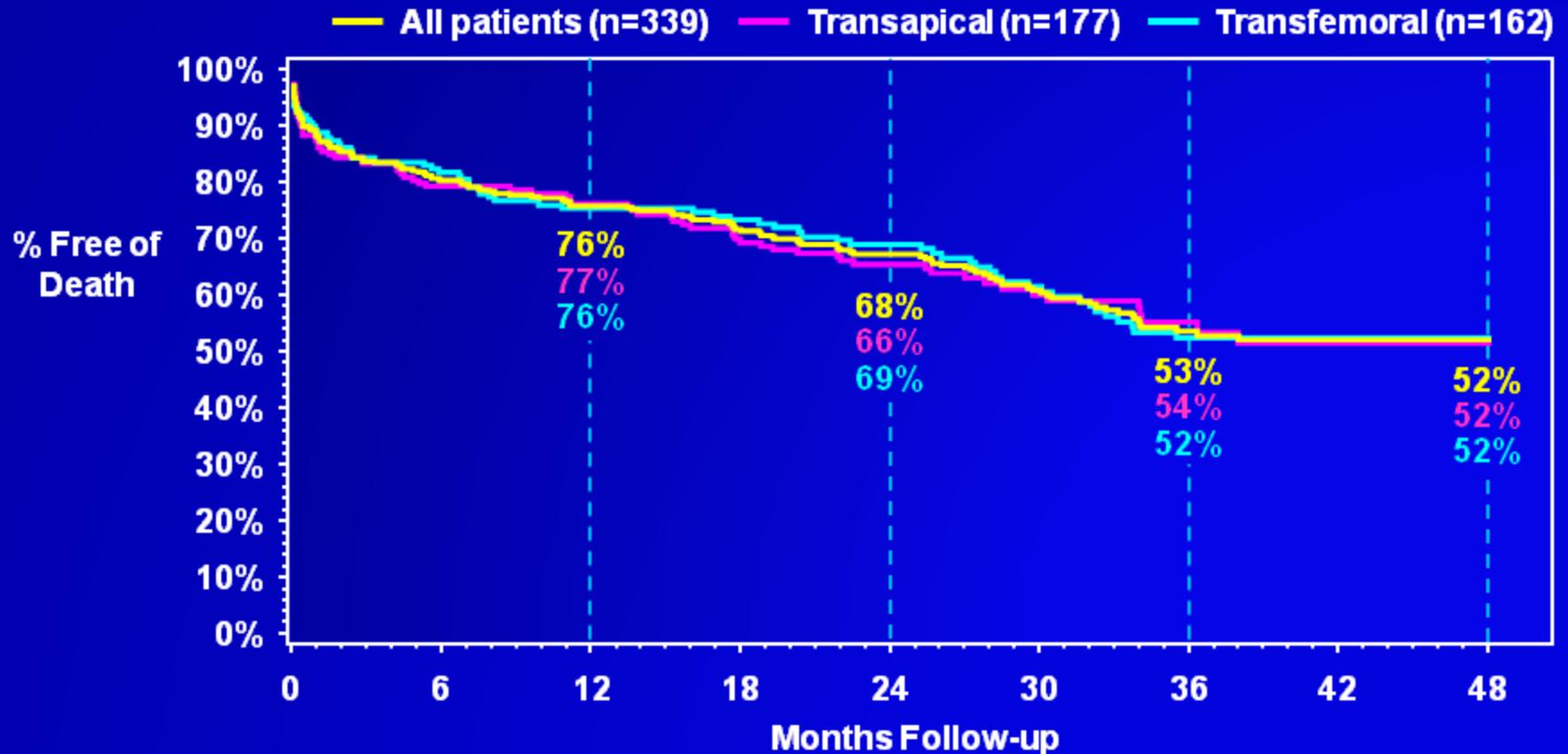


## Numbers at Risk

Std Tx	179	85	29	9	2
TAVR	179	124	61	25	4

# 48 Month Follow-Up Survival Curves

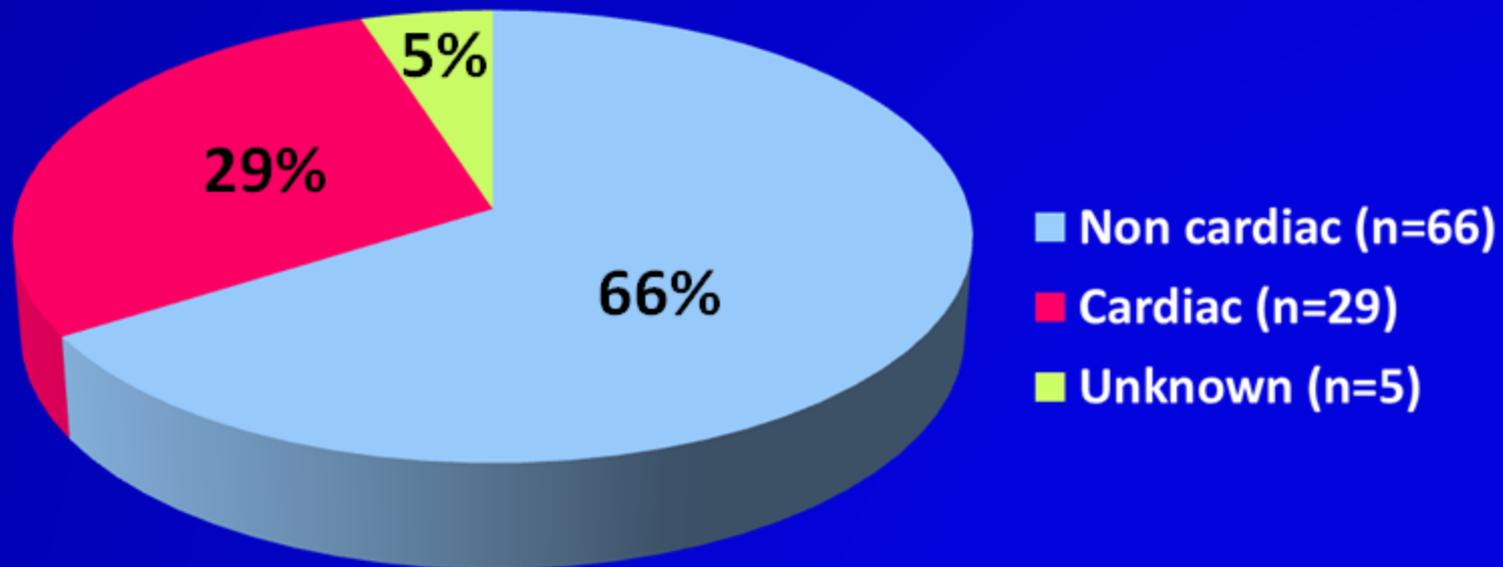
## Canadian Multicenter Experience



<b>All Patients</b>	339	266	243	215	179	124	75	40	14
<b>Transapical</b>	177	137	128	111	88	58	32	14	3
<b>Transfemoral</b>	162	129	115	104	91	66	43	26	11

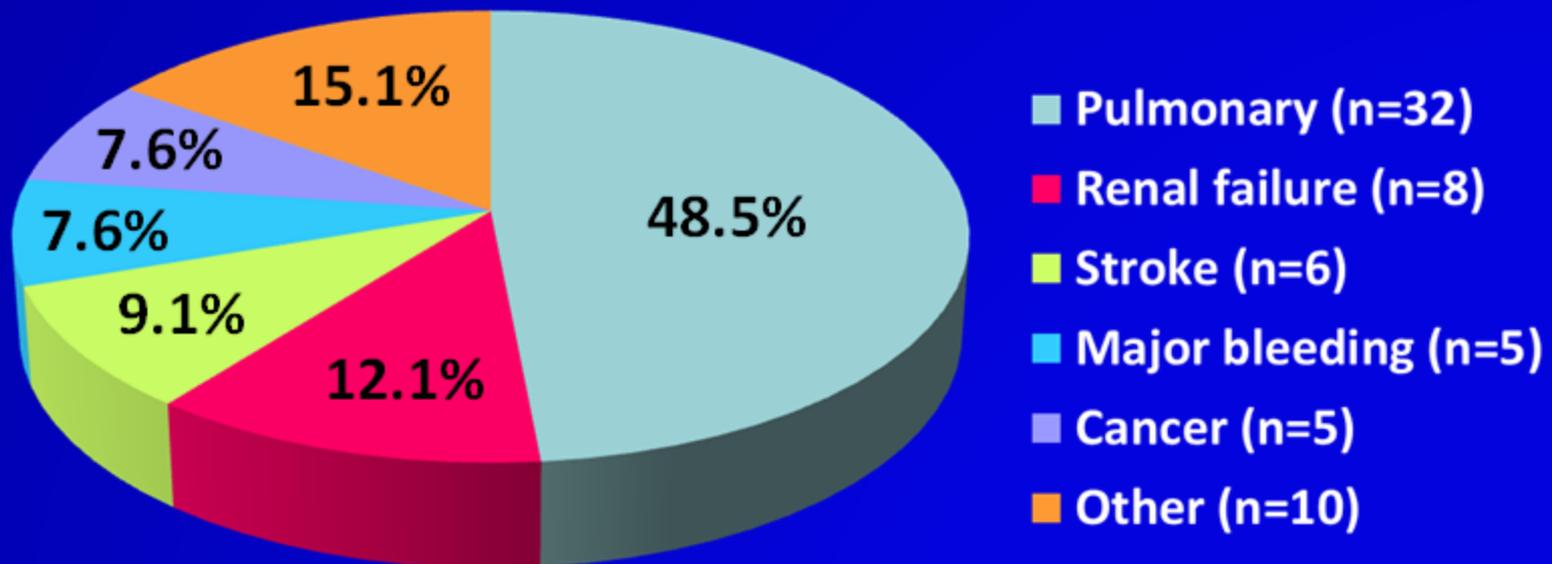
# CAUSES OF DEATH AT FOLLOW-UP

## Multicenter Canadian Experience (n=100)



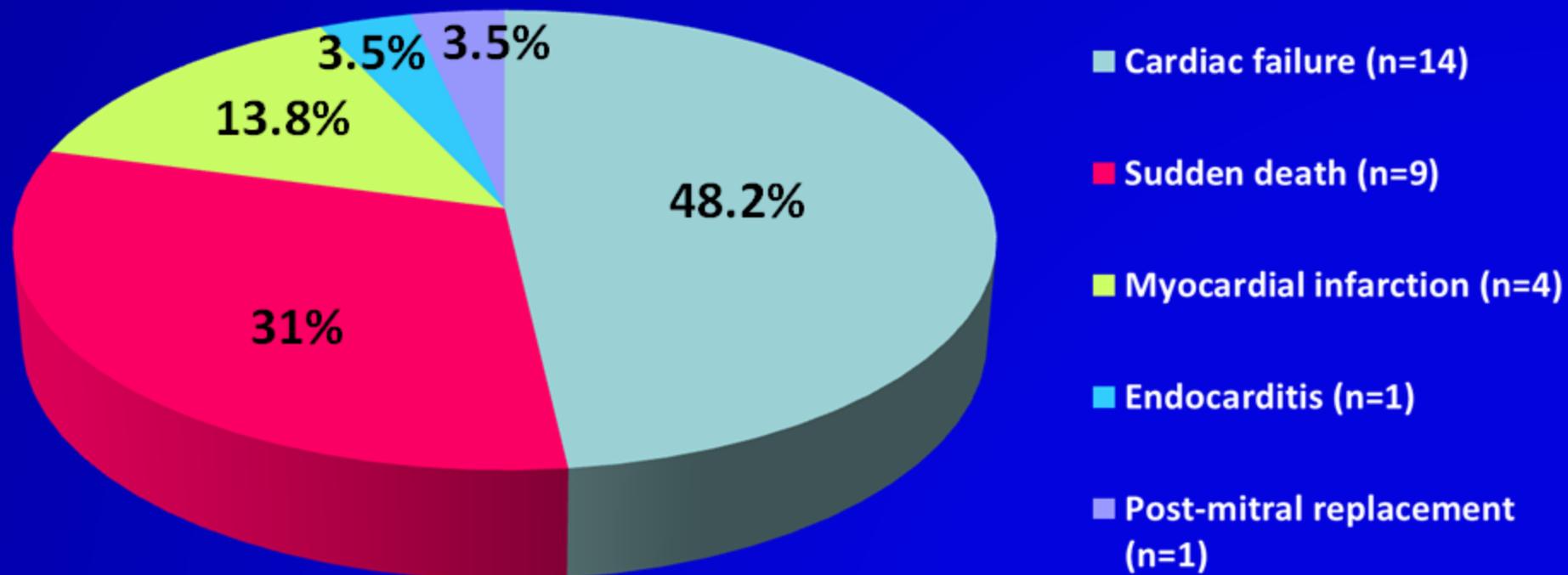
# CAUSES OF NON-CARDIAC DEATH AT FOLLOW-UP

## Multicenter Canadian Experience (n=66)



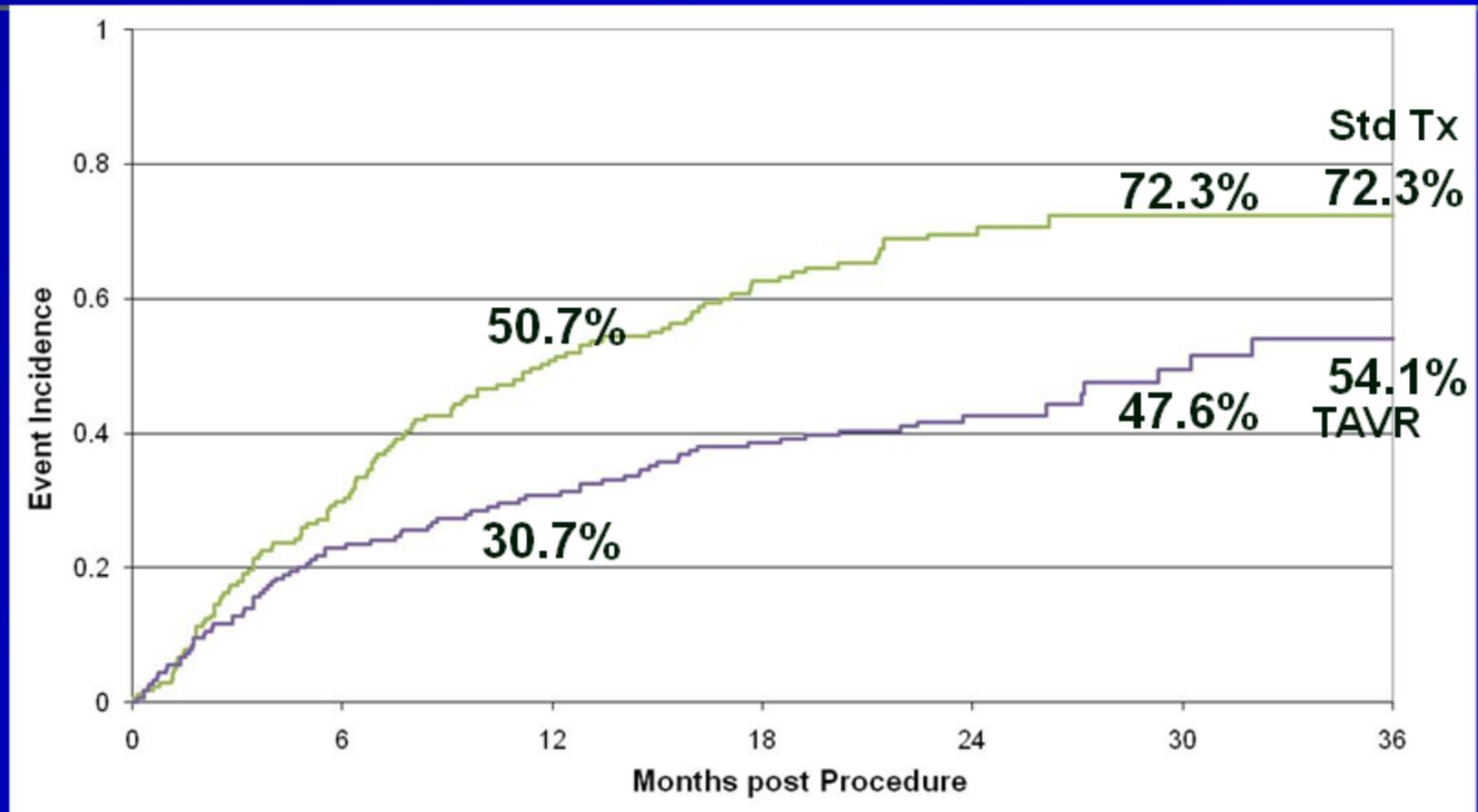
# CAUSES OF CARDIAC DEATH AT FOLLOW-UP

## Canadian Experience (n=29)



**No cases of structural valve failure during the follow-up period**

# Primary Endpoint: 3-Year All Cause Mortality (ITT)



## Numbers at Risk

<b>Std Tx</b>	<b>179</b>	<b>85</b>	<b>29</b>	<b>9</b>	<b>2</b>
<b>TAVR</b>	<b>179</b>	<b>124</b>	<b>61</b>	<b>25</b>	<b>4</b>

# All-Cause Mortality (AT Population)

Population	Statistics	Event	Roll-in Cohort	Non-randomized Continued Access
			TAVR	TAVR
AT	No. of patients		20	52
	No. of person-years		32.6	11.2
	No. of patients died (%)	Early death(days<=30)	0(0%)	9(17.3%)
		Death at 1 year	2(10.0%)	16(30.8%)
		Late death(days>30)	2(10.0%)	7(13.5%)
		Death	2(10.0%)	16(30.8%)
	Death rate per 100 pys	Early death(days<=30)	0.00	264.67
		Death at 1 year	10.78	143.34
		Late death(days>30)	6.45	90.19
	KM Survival Rate at 30 Days (95%CI)(%)	Death	100.0 (100.0,100.0)	81.9 (71.2,92.6)

# All-Cause Mortality (ITT Population)

Population	Statistics	Event	Randomized Continued Access	
			TAVR	Standard Rx
ITT	No. of patients		41	49
	No. of person-years		23.8	31.4
	No. of patients died(%)	Early death(days<=30)	4(9.8%)	1(2.0%)
		Death at 1 year	13(31.7%)	10(20.4%)
		Late death(days>30)	9(22.0%)	9(18.4%)
		Death	13(31.7%)	10(20.4%)
	Death rate per 100 pys	Early death(days<=30)	125.41	25.17
		Death at 1 year	54.72	31.81
		Late death(days>30)	43.75	32.77
	KM Survival Rate at 30 Days (95%CI)(%)	Death	90.2 (81.2,99.3)	97.9 (93.9,100.0)

# Major Stroke (ITT Population)

Population	Statistics	Event	Randomized Continued Access	
			TAVR	Standard Rx
ITT	No. of patients		41	49
	No. of person-years		22.9	31.4
	No. of patients with event(%)	Early event(days<=30)	1(2.4%)	0(0%)
		Event at 1 year	1(2.4%)	0(0%)
		Late event(days>30)	0(0%)	0(0%)
		Event	1(2.4%)	0(0%)
	Event rate per 100 pys	Early event(days<=30)	31.96	0.00
		Event at 1 year	4.37	0.00
		Late event(days>30)	0.00	0.00
		Event	4.37	0.00
	KM event free rate at 30 days(95%CI)(%)	Event	97.5 (92.7,100.0)	100.0 (100.0,100.0)

# A Tremendous Collaboration – Thank You

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- The PARTNER Site Heart Teams
- The PARTNER Trial Executive Committee
- Dedicated monitors, clinical specialists and trial staff
- DSMB, CEC, CoreLabs, Biostatisticians
- The FDA
- The patients and families