Valvular Heart Disease & New Treatment Options

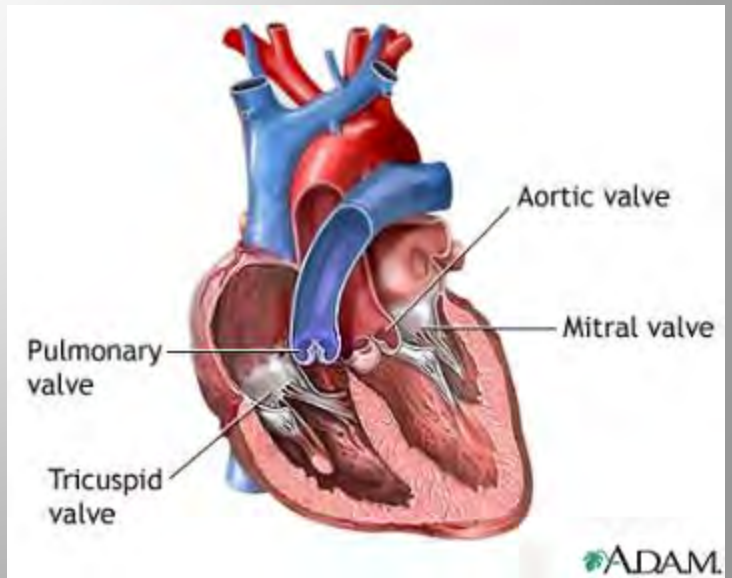
Andrea Ennis, RN, MSN

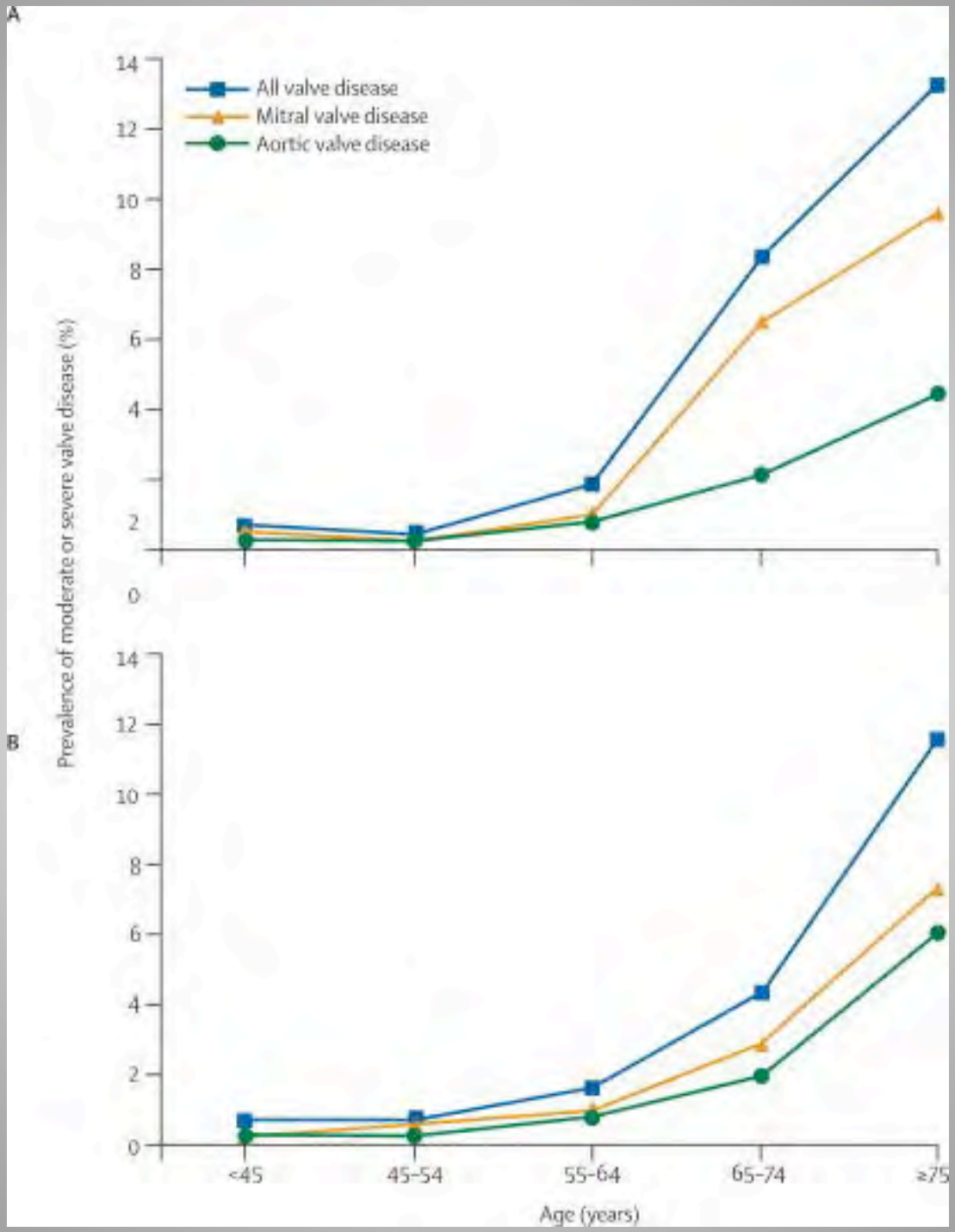
Objectives

- Describe the etiology and pathophysiology of the various valve disorders
- Explain the various symptoms associated with valve disease
- Discuss the physical exam findings and diagnostic testing
- Explain current treatment options, with emphasis on the aortic and mitral valves
- Discuss the new treatment options

Etiology

- Valvular heart disease (VHD) accounts for 10-20% of all cardiac surgical procedures in the US
- Most common form of VHD
  - degenerative valve disease in US
  - rheumatic heart disease in developing nations
- Disease of the elderly
  - >65 – 2%
  - >75 – 3%
  - >85 – 4%

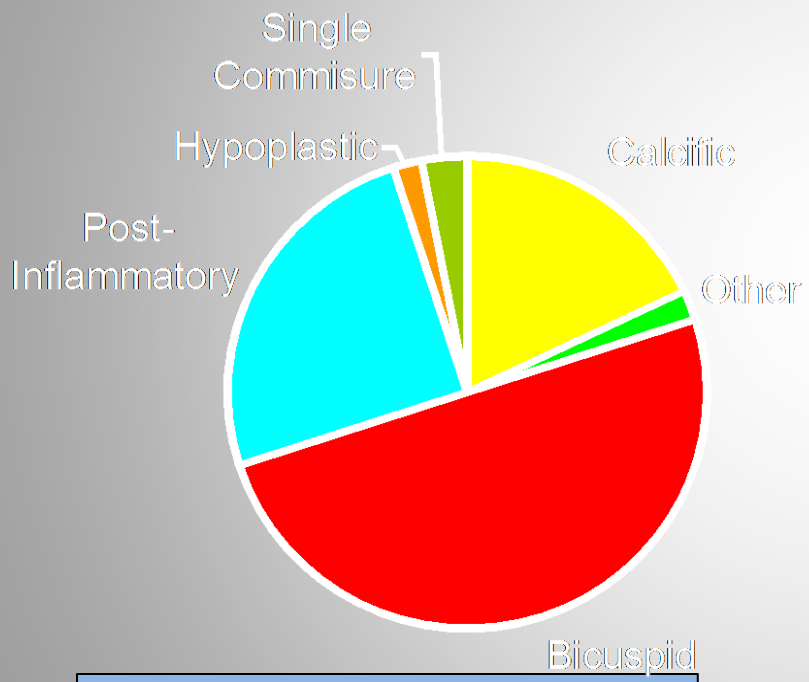



A
B
All valve disease
Mitral valve disease
Aortic valve disease
Prevalence of moderate or severe valve disease (%)
14
12
10
8
6
4
2
0
<45
45–54
55–64
65–74
≥75
Age (years)

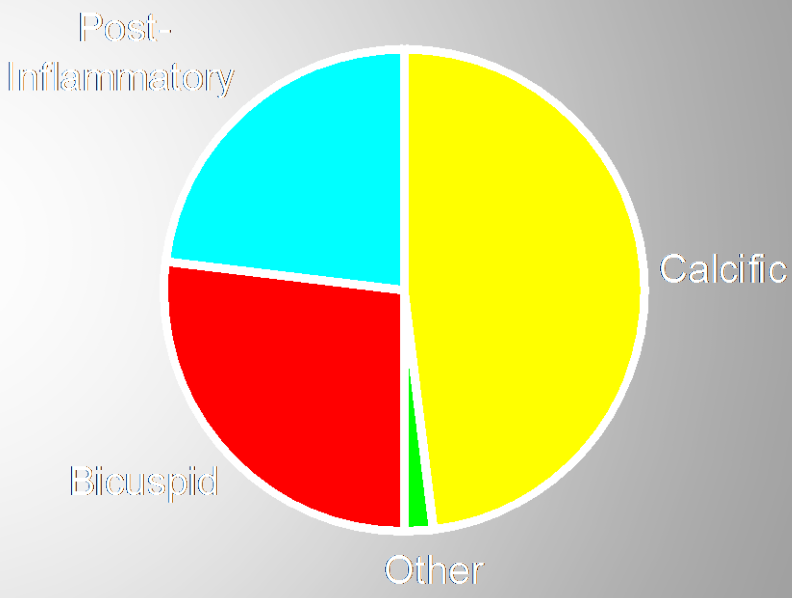
Aortic Stenosis

- Third most common form of CV disease
- Caused by degenerative calcification of trileaflet valve or progressive stenosis of congenital bicupsid valve
- Risk factors for calcification are similar as those for atherosclerosis

Aortic Stenosis: Etiology
Most Common Cause: 'Degenerative' or 'Calcific'

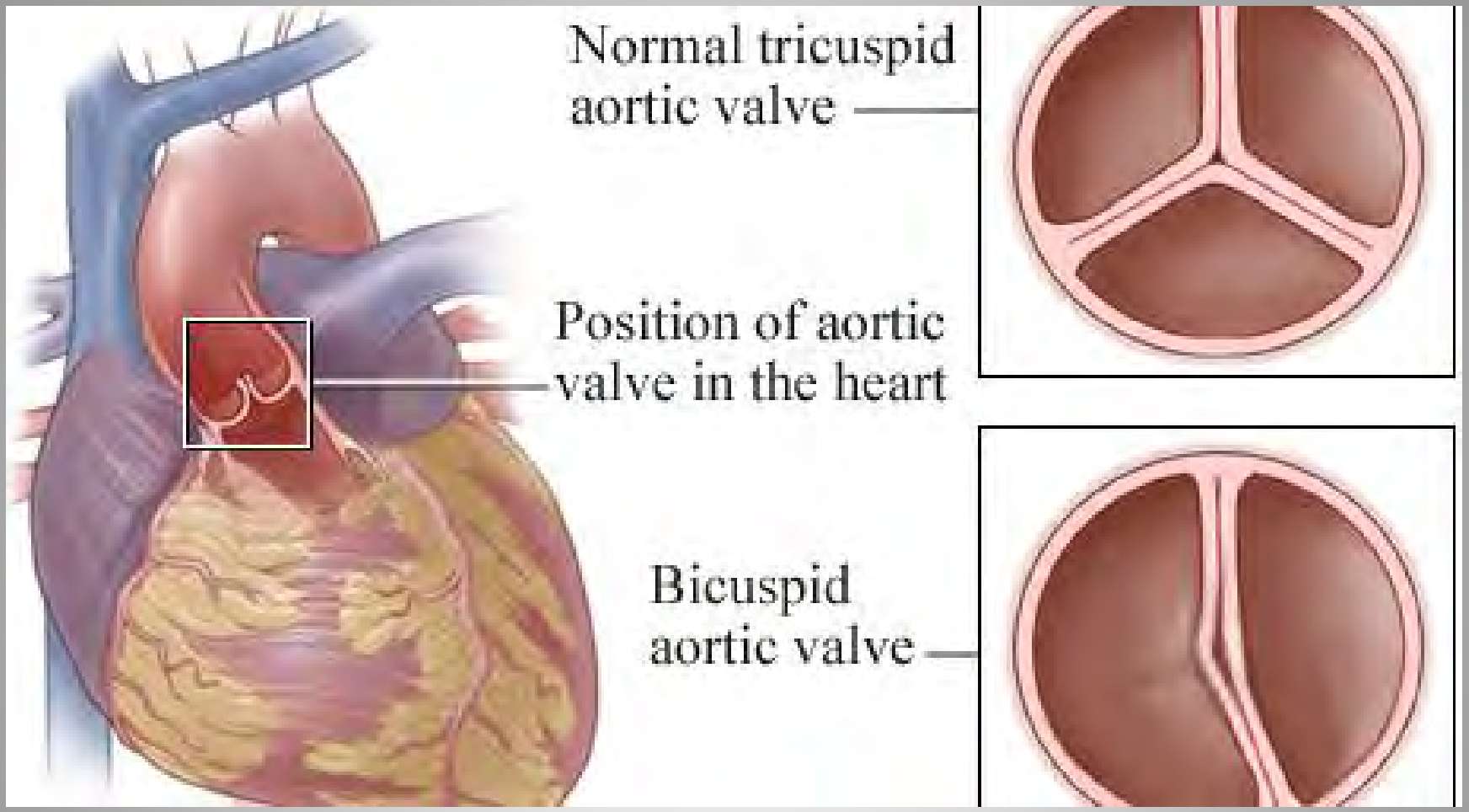


Age < 70 years

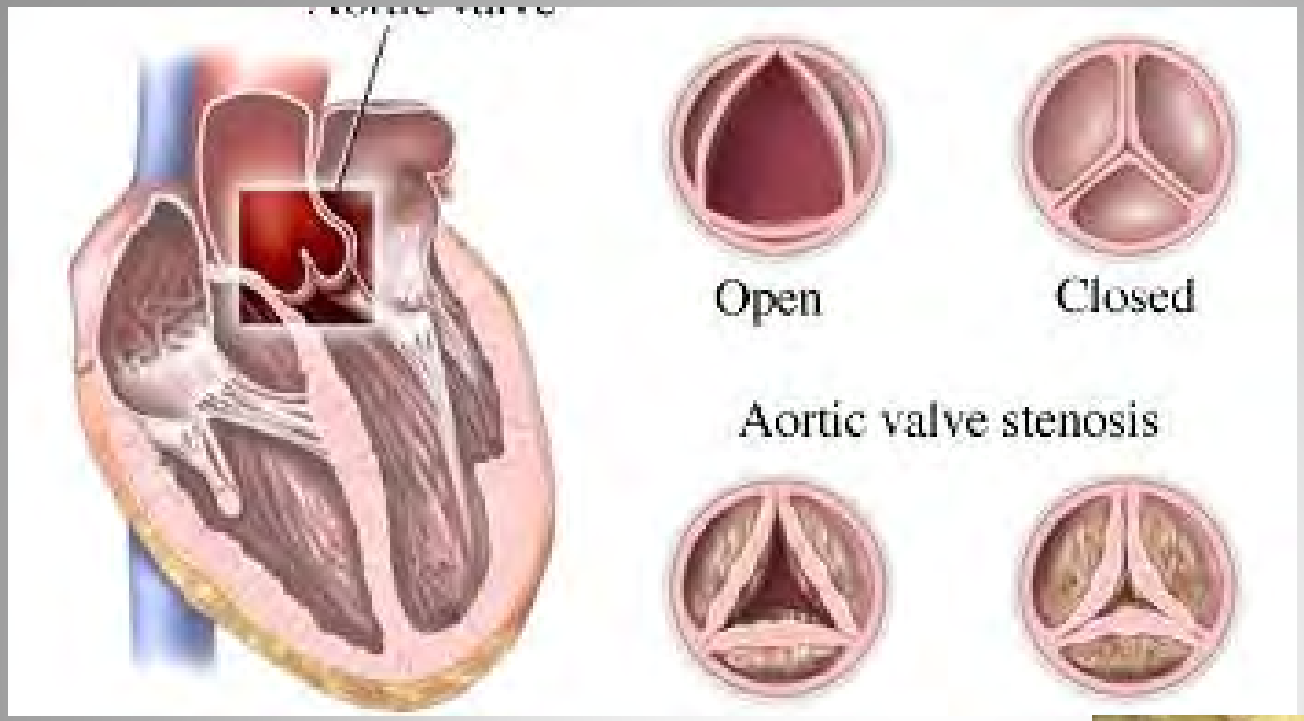


Age > 70 years

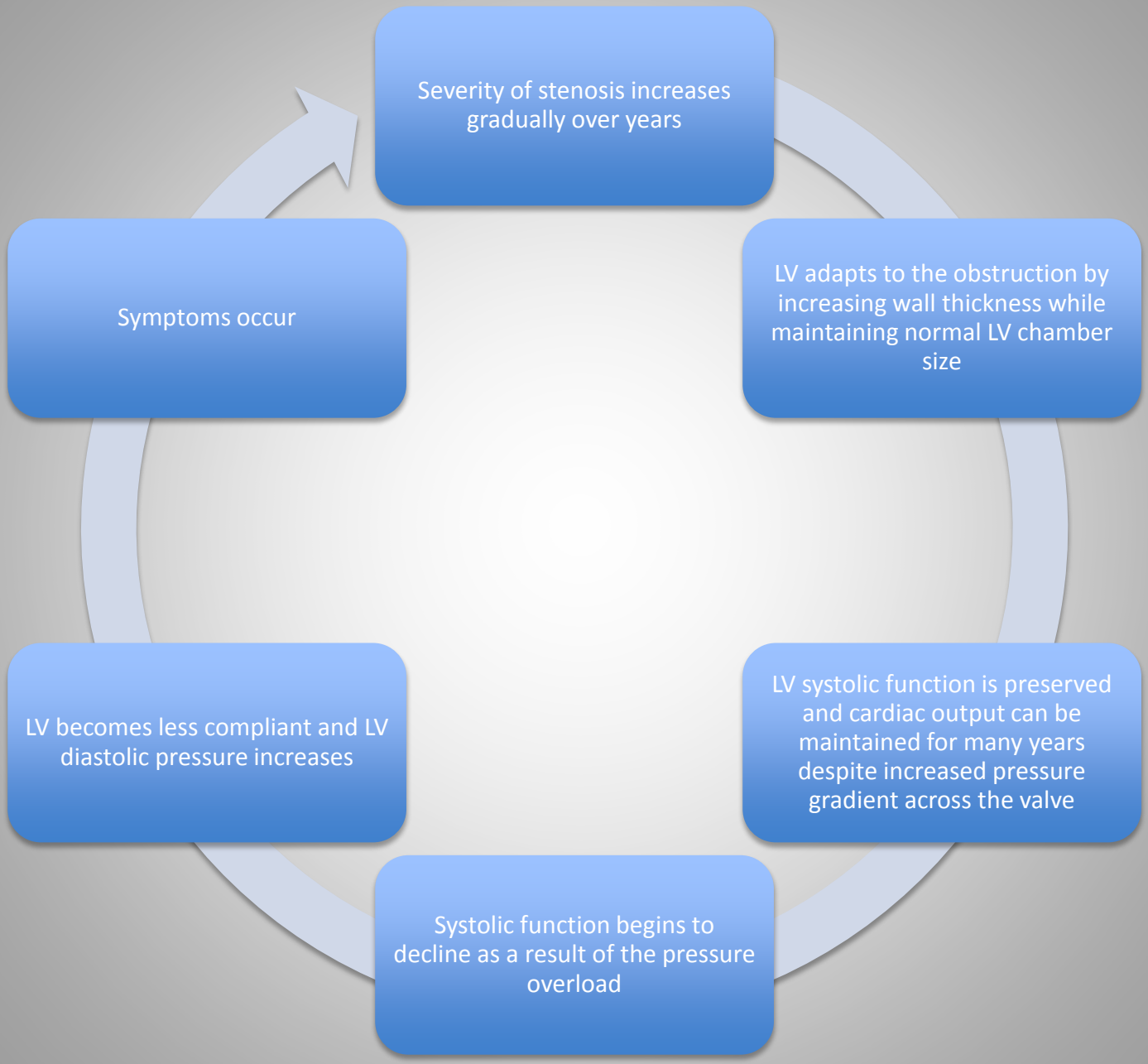
Passik CS et al. *Mayo Clinic Proc* 1987;62:119.



Bicuspid aortic valve

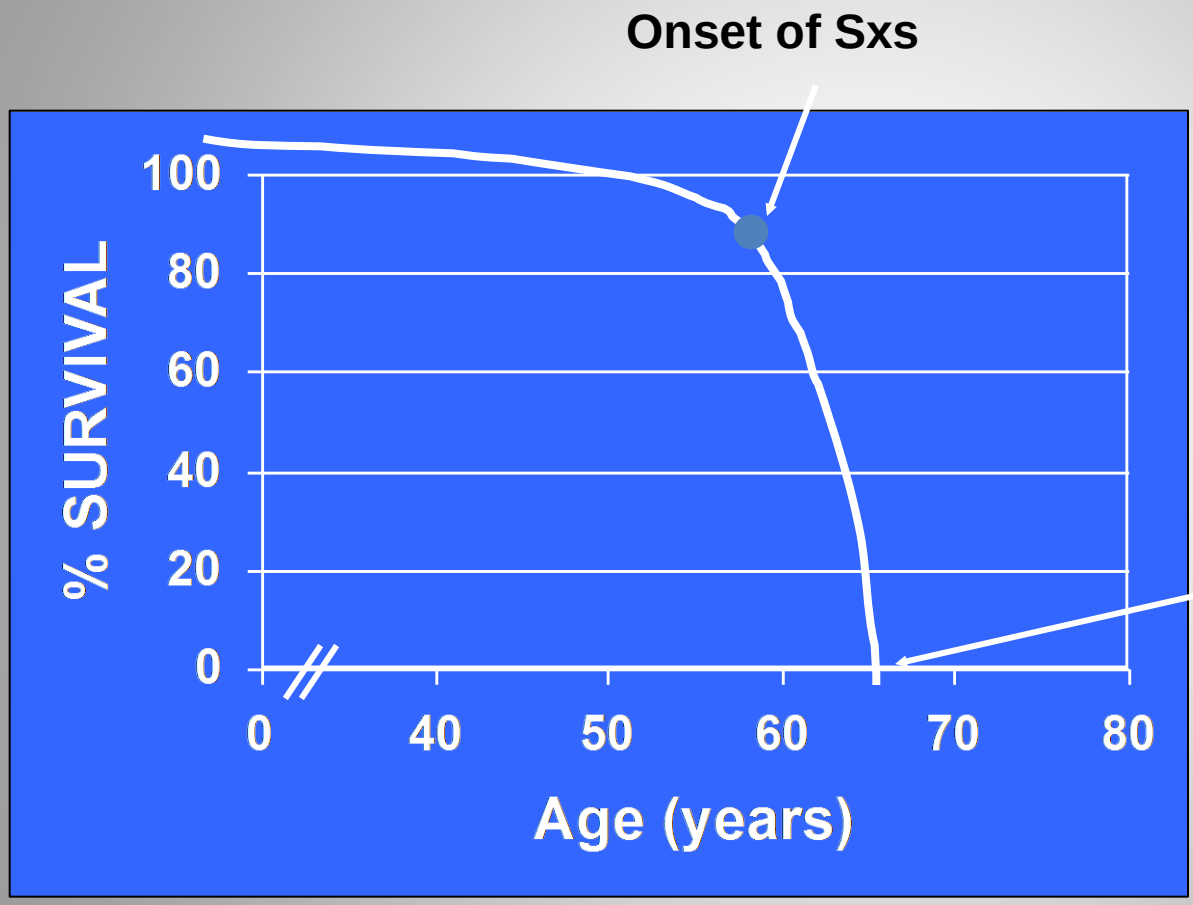


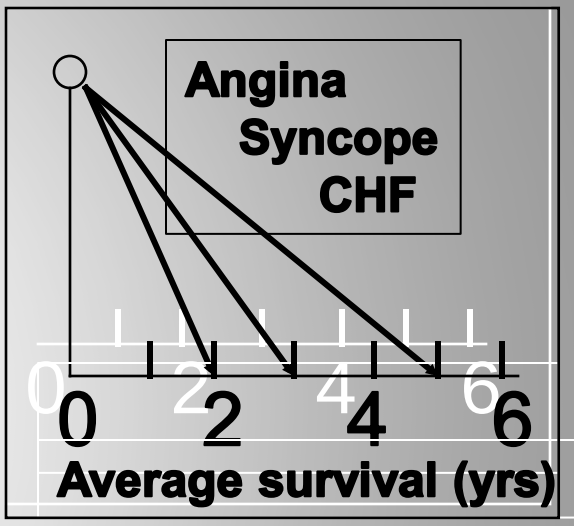
Calcific Aortic Valve


Severity of stenosis increases gradually over years
LV adapts to the obstruction by increasing wall thickness while maintaining normal LV chamber size
LV systolic function is preserved and cardiac output can be maintained for many years despite increased pressure gradient across the valve
Systolic function begins to decline as a result of the pressure overload
LV becomes less compliant and LV diastolic pressure increases
Symptoms occur

- Natural history
  - Process develops gradually – over decades
  - Prolonged latent period – no symptoms
    - GOOD OUTCOME: No Treatment
  - Eventually symptoms occur
    - POOR OUTCOME: Treatment Needed
- Symptoms
  - Angina
  - Syncope
  - Dyspnea and/or heart failure
- Average survival 2-3 years after symptom onset

Aortic Stenosis: Symptoms Indicate Poor Outcome





Average age of death

Ross J, Braunwald E. *Circulation* 1968.

ACC/AHA Classification of the Severity of Valve Disease - Aortic Stenosis

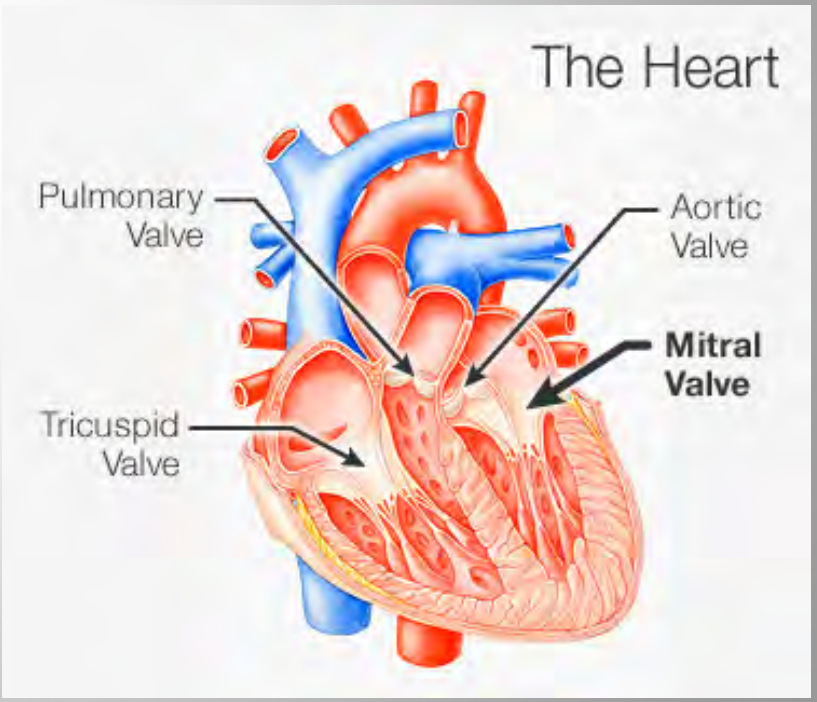
Indicator	Mild	Moderate	Severe
Jet velocity (m/second)	Less than 3.0	3.0-4.0	Greater than 4.0
Mean gradient (mm Hg)	Less than 25	25-40	Greater than 40
Valve area (cm2)	Greater than 1.5	1.0-1.5	Less than 1.0

Aortic Stenosis Physical Examination

- Systolic murmur of a harsh crescendo-decrescendo along left sternal border; radiates to upper right sternal border and carotid arteries
- Pulsus parvus et tardus – diminished and delayed carotid
- Fourth heart sound
- Precordial thrill

Mitral Regurgitation

- Affects 2% of population; male = female
- Acute
  - Endocarditis
  - Papillary muscle rupture
- Chronic
  - Rheumatic fever
  - Marfan's syndrome



ACC/AHA Classification of the Severity of Valve Disease – Mitral Regurgitation

	Mild	Moderate	Severe
Angiographic grade	1+	2+	3+
Color Doppler jet area	Small, central jet	Signs of MR greater than mild present but no criteria for severe MR	Vena contracta width greater than 0.7 cm with large central MR jet or a wall-impinging jet of any size, swirling in left atrium

Mitral Regurgitation

- Physical Examination
  - Holosystolic murmur; at the apex
  - Apical pulse brisk and hyperdynamic
- Symptoms
  - Heart failure symptoms
  - Palpitations
  - Pulmonary Edema

Mitral Valve Prolapse

- One or both mitral leaflets extend or protrude abnormally above the mitral annulus into LA
- Previous high prevalence
- Symptoms
  - Chest pain, dyspnea, anxiety and palpitations
- Treatment
  - Beta blockers for patients with symptoms
  - Alcohol, tobacco and caffeine cessation
  - Antibiotic prophylaxis controversial
    - Not recommended for use with MVP in the absence of MR

Aortic Regurgitation

- Acute
  - Infective endocarditis
  - Trauma
- Chronic
  - Rheumatic fever
  - Bicuspid AV
  - Marfan's Syndrome
  - Ehlers-Danlos Syndrome
  - SLE

ACC/AHA Classification of the Severity of Valve Disease – Aortic Reguritation

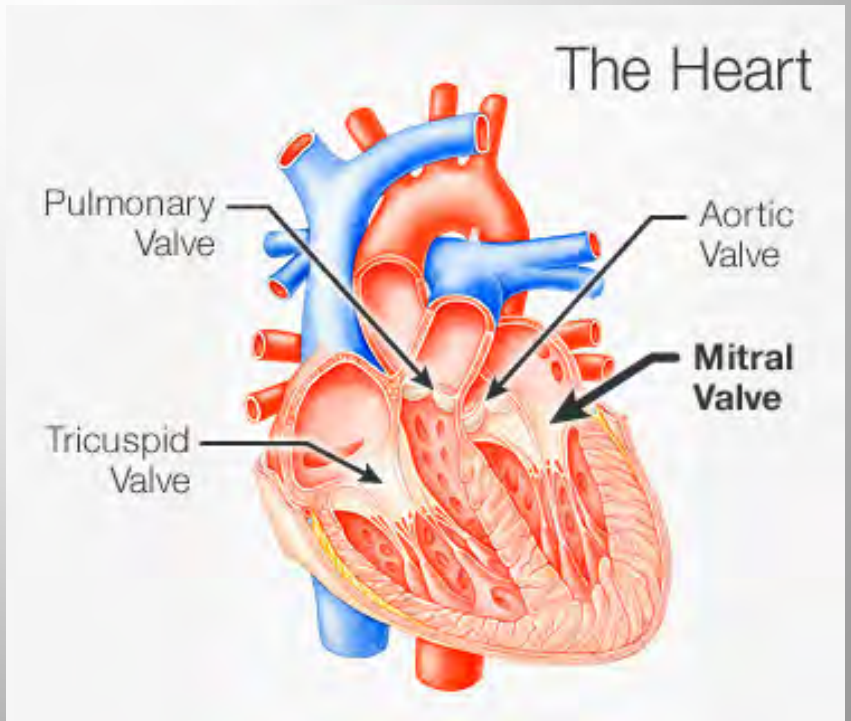
	Mild	Moderate	Severe
Angiographic grade	1+	2+	3+
Color Doppler jet width	Central jet, width less than 25% of LVOT	Greater than mild but no signs of severe AR	Central jet, width greater than 65% LVOT

Aortic Regurgitation

- Physical Examination
  - Diastolic blowing murmur along left sternal border
  - Diastolic rumble over apex
  - Signs of severe disease
    - Hyperdynamic circulation
    - Quincke's pulse – alternating blanching and erythema of the nailbed with gentle pressure
    - Musset's sign – head bobbing

Mitral Stenosis

- Most common valvular heart disease during pregnancy
- Almost always caused by rheumatic heart disease



Mitral Stenosis

- Physical Examination
  - Opening snap followed by a low pitched diastolic rumble
  - Murmur best heard with the bell of the stethoscope; lying on the left side

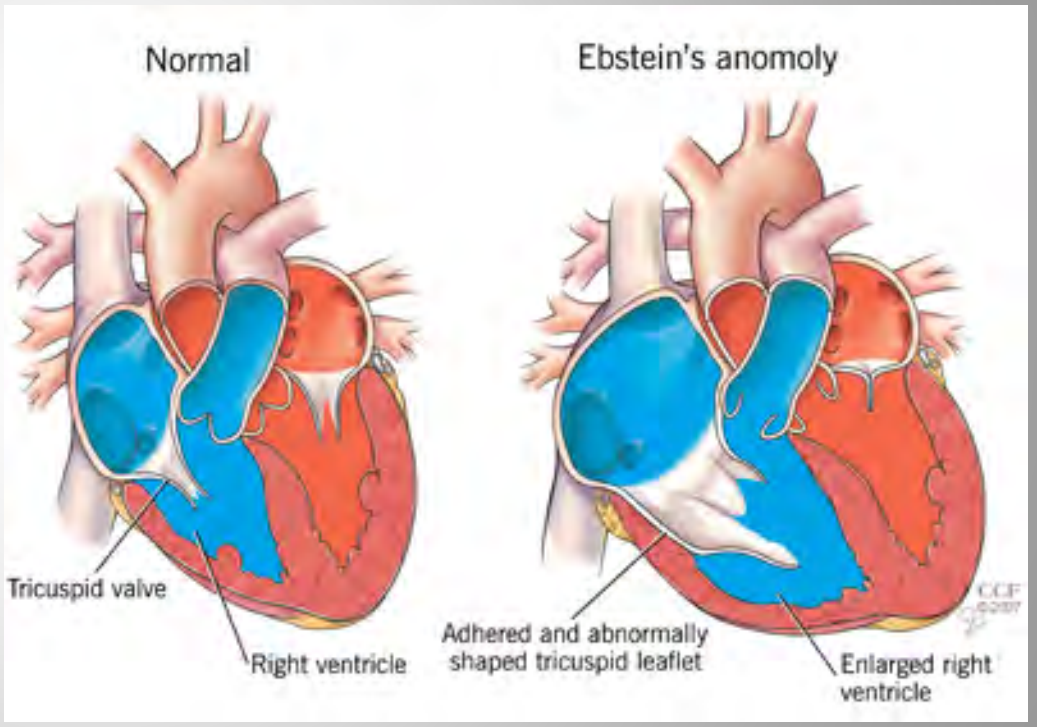
Symptoms include: heart failure symptoms, palpitations, chest pain, thromboembolism, ascites and edema

ACC/AHA Classification of the Severity of Valve Disease – Mitral Stenosis

	Mild	Moderate	Severe
Mean gradient (mm Hg)	Less than 5	5-10	Greater than 10
Pulmonary artery systolic pressure (mm Hg)	Less than 30	30-50	Greater than 50
Valve area (cm2)	Greater than 1.5	1.0-1.5	Less than 1.0

Tricuspid Valve Disease

- Very uncommon in young adults
  - Trauma, bacterial endocarditis in IV drug use, VSD
- Congential
  - Ebstein's anomaly



- Treatment indication
  - Severe TR with deteriorating exercise capacity
  - Severe TR with progressive cyanosis and O2sat <80% at rest or exercise

Heart Sounds

Findings	Murmur	S1	S2	Maneuvers
Aortic Stenosis	**Mid to late systolic**	**Normal**	**Single or split**	**Murmur softer with Valsalva maneuver**
Mitral Stenosis	Diastolic rumble	Loud	Normal	Murmur increased with brief exercise
Aortic Regurgitation	Blowing diastolic	Soft	Normal	Murmur increased with handgrip or squatting
Mitral Regurgitation	Holosystolic	Soft	Normal or split	Murmur louder with Valsalva maneuver

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Diagnostic Testing

- Chest Radiography
- EKG
- Echocardiography
- CT scan
- Cardiac MRI
- Cardiac catheterization
- Exercise testing

Diagnostic Testing

	Aortic Stenosis	Mitral Stenosis	Aortic Regurgitation	Mitral Regurgitation
Chest X-Ray	Calcific AV Enlarged LA/LV	LA enlargement	LV hypertrophy Dilated aorta	Dilated LV
Echo	LV hypertrophy Thick, immobile AV Dilated aortic root	LA enlargement Thick, calcified mitral valve	Dilated aortic root Reversal of blood flow in aorta	Mitral reverse flow Dilated LA/LV Decreased LV function
EKG	LV hypertrophy LA abnormality			LA enlargement

Indications for valve replacement

- Severe valve disease with symptoms
- Asymptomatic patients with severe valve disease and LV dysfunction
- Patients with severe valve disease undergoing CABG or surgery on the aorta or other valves

Therapy for Aortic Stenosis
Aortic Valve Replacement

- AVR: standard of care
- Excellent surgical outcomes
- *<u>High risk predictors</u>*
  - Age>80
  - NYHA Class III or IV
  - EF<30%
  - Emergency operation
  - Concomitant CABG

CLOSE TO HOME

"His heartbeat has been like that ever since he had the pig valve installed."

Aortic Valve Replacement: Denied Surgery

Euro Heart Survey on Valvular Heart Disease

n = 5,001 Patients

33% DID NOT HAVE SURGERY

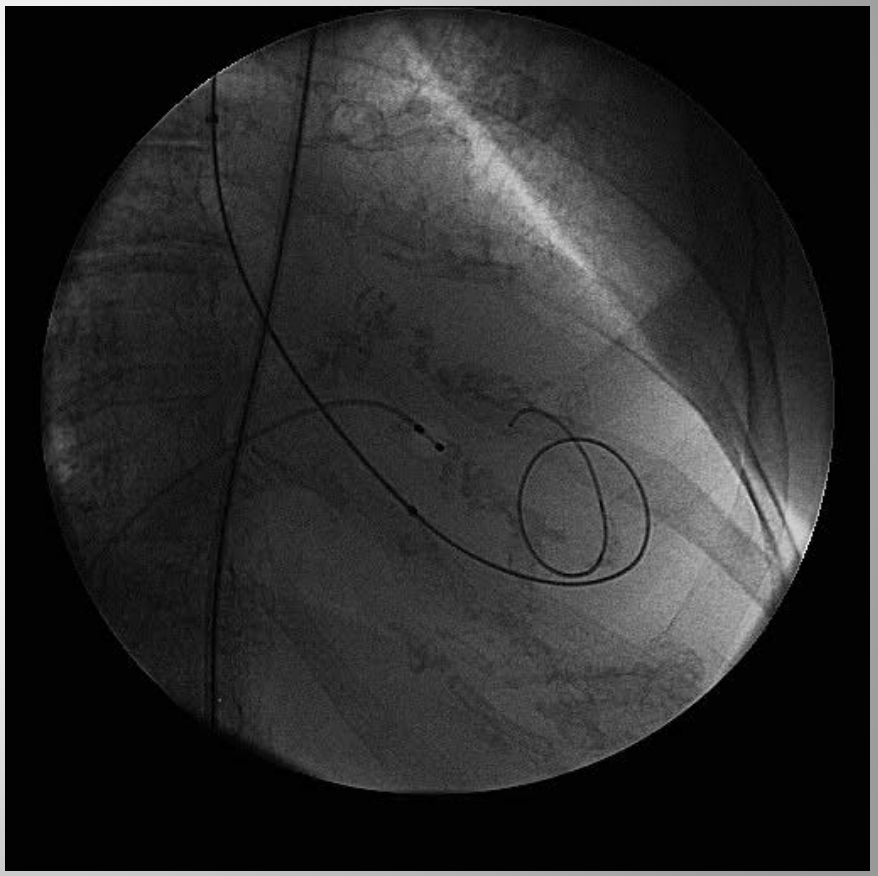
=> Annual Mortality 15 to 25%

Iung B. et al. *Eur. Heart Journal* 2003;24:1231-1243

Ross et al. *Circulation* 1968; 38 Suppl V : V-61-7

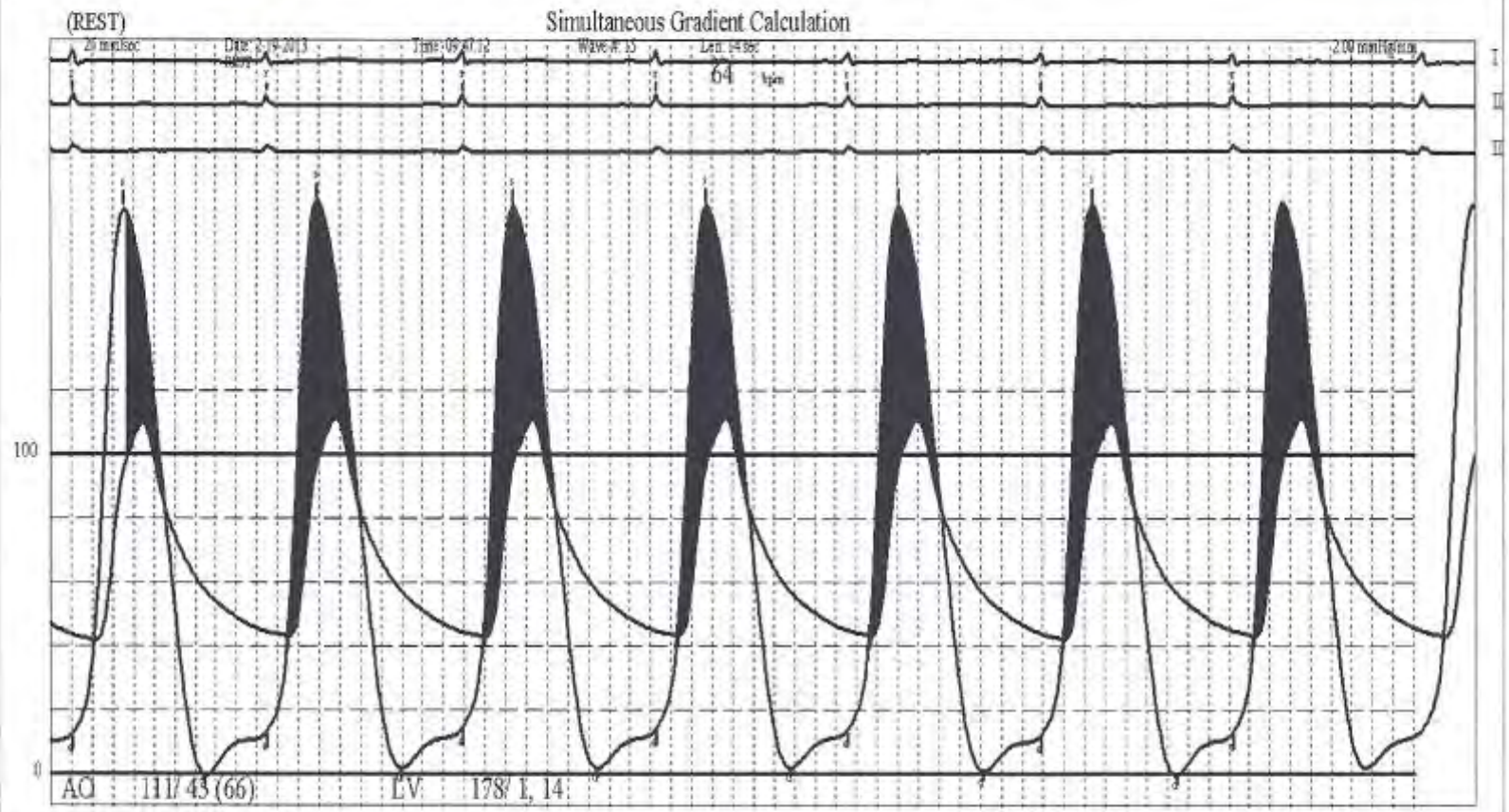
Catheter Based Therapy for Aortic Stenosis
Balloon Aortic Valvuloplasty

- Described by Cribier 1985
- 20 to 25 mm balloon
- Results assessed during procedure
- Final AVA: 0.7 to 1.0 cm2
- Short term improvement in *most* patients



STENOTIC VALVE

Name [redacted]	Date [redacted]
MRN: [redacted]	Proc: CATH- AORTIC VALVUOPLASTY

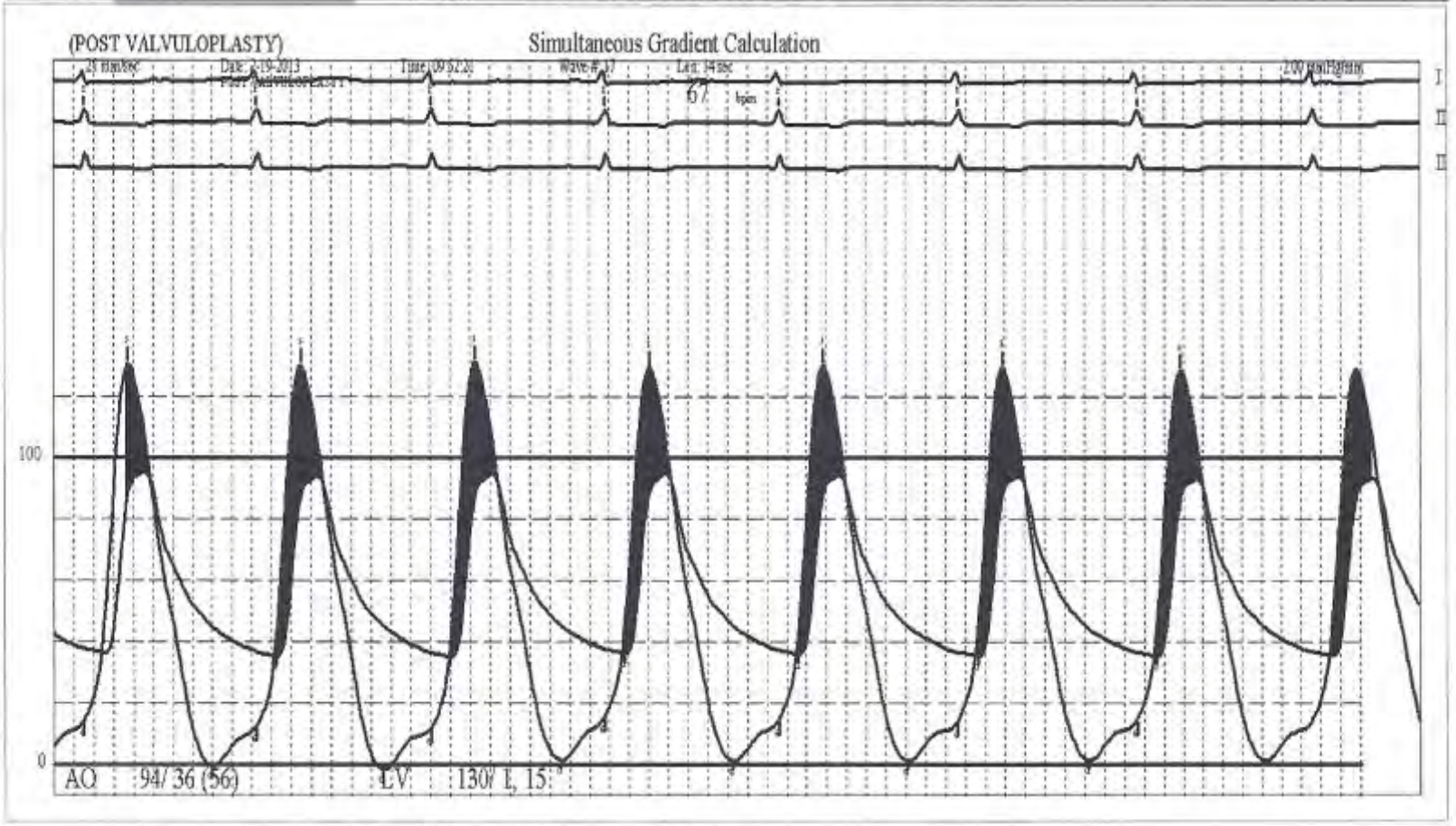


Calculations

	CO	HR	Mean	P-P	INS-PK	Perd	Area	Index	K
Thermal	2.84	64	48.27	67.0	86.65	344	0.42	0.36	44.3

STENOTIC VALVE

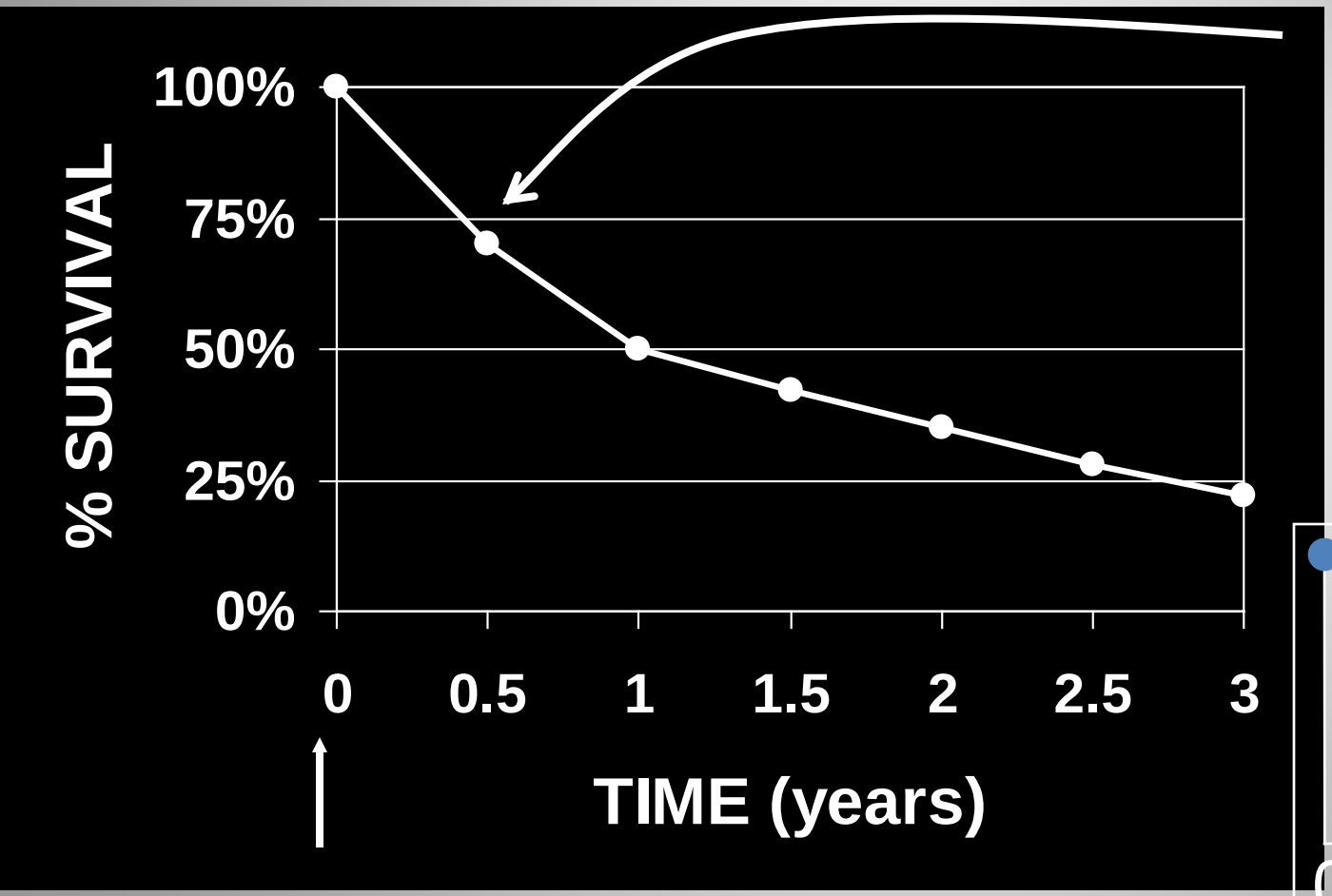
Name: [redacted]	Date: [redacted]
MRN: [redacted]	Proc: CATH- AORTIC VALVUOPLASTY



Calculations

	CO	HR	Mean	P-P	INS-PK	Perd	Area	Index	K
Other	2.80	67	30.24	36.0	53.08	249	0.69	0.59	44.3

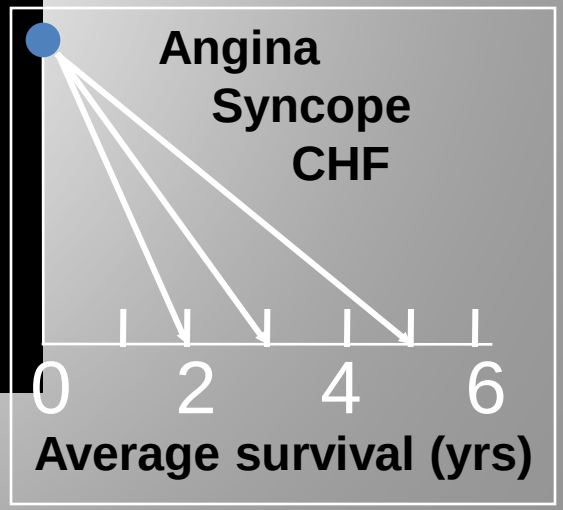
Balloon Aortic Valvuloplasty: Poor Long Term Results



PABV

@6 mos ~75% survival rate

@ 3 years ~25% survival



Lieberman et al. *JACC* 1995;26:1522-8.

Balloon Aortic Valvuloplasty: ACC/AHA Guidelines

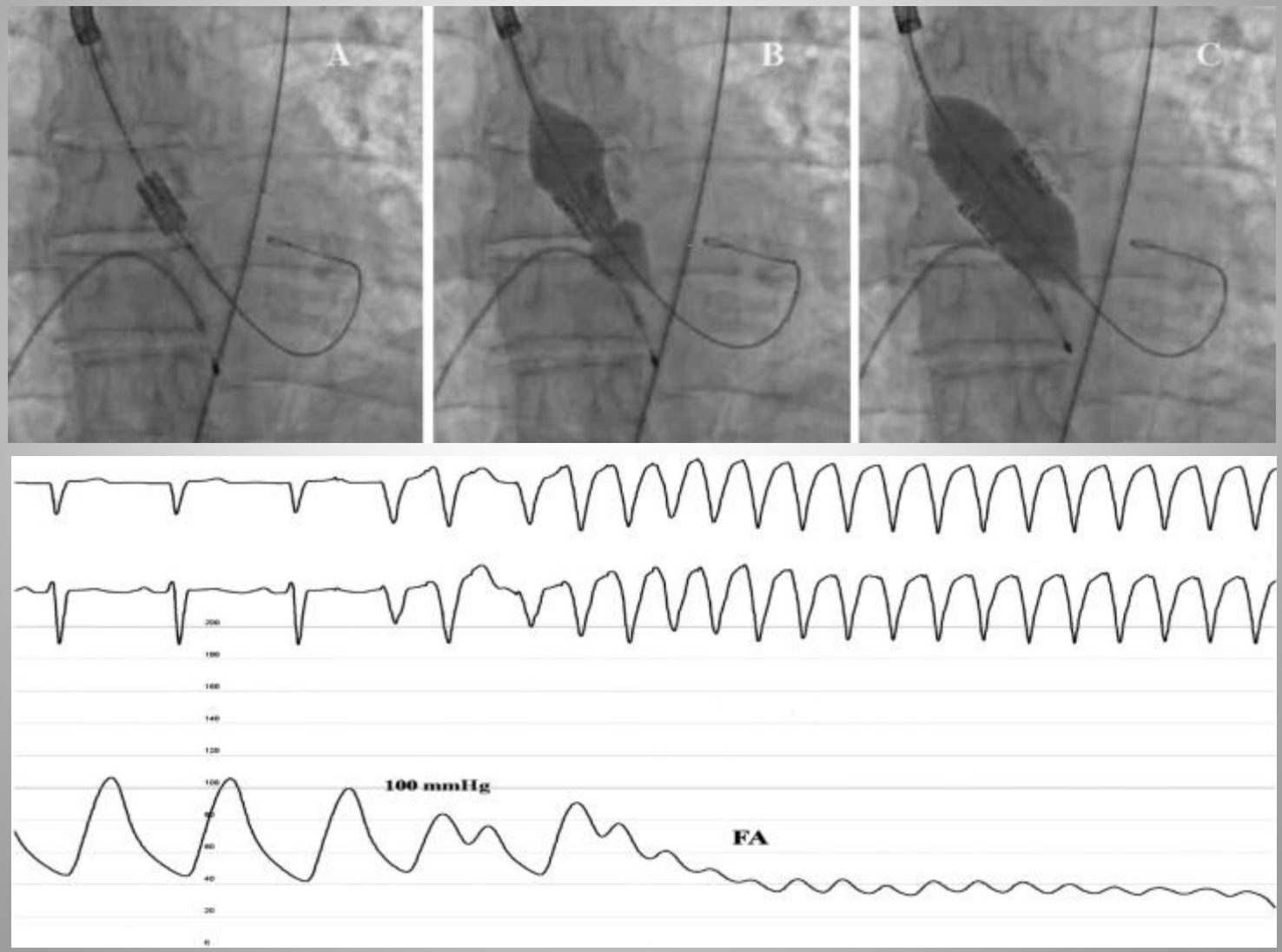
INDICATION	*CLASS*
1. ‘Bridge’ to surgery in unstable patients who are at a high risk for AVR	IIa
2. Palliation in patients with serious co-morbid conditions	IIb
3. Patients who require urgent non-cardiac surgery	IIb
4. An alternative to AVR	III

Could the Results be Better? : First Case: Percutaneous Aortic Valve

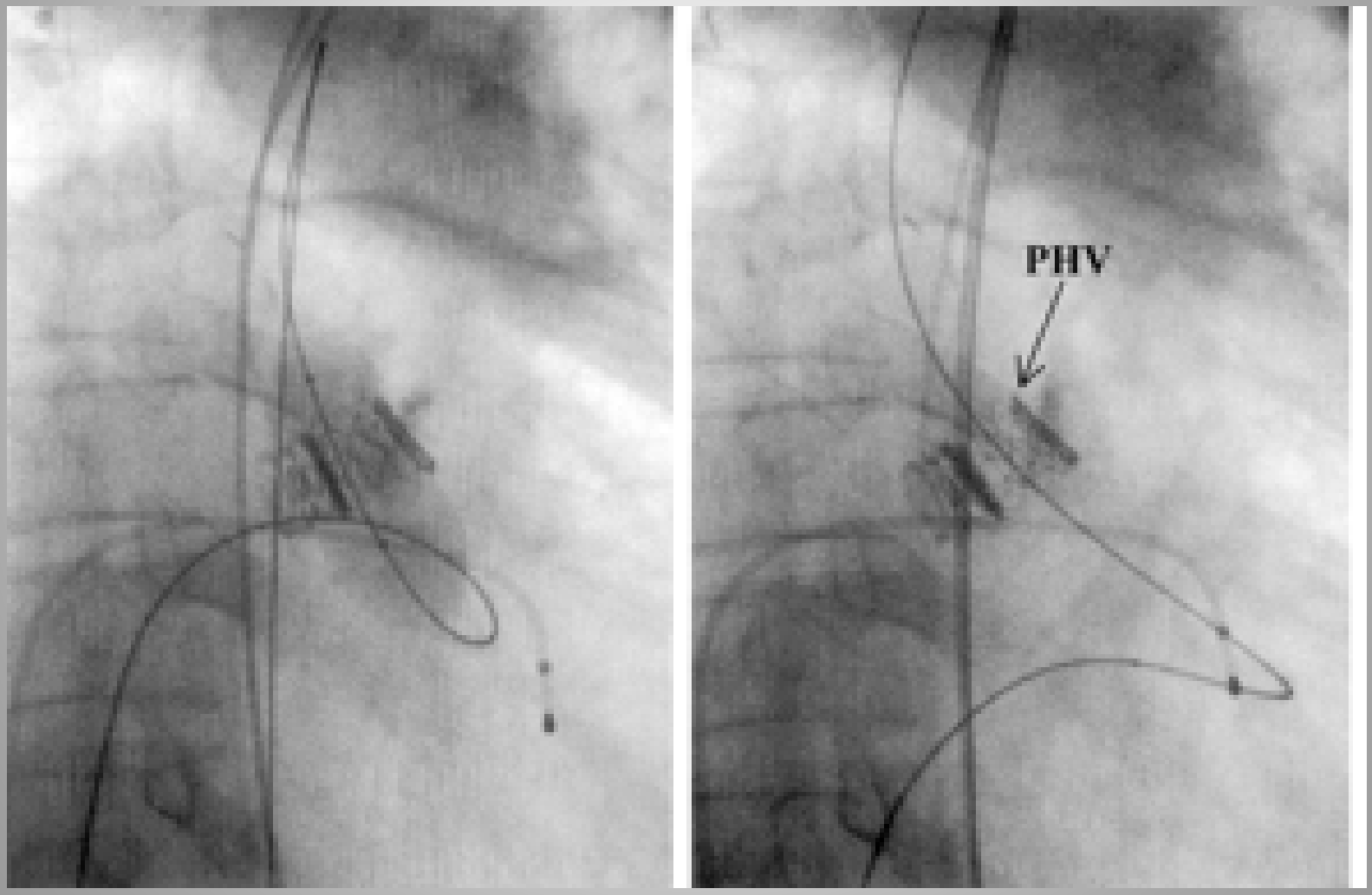
- 57 year old male severe AS (AVA 0.6 cm^2; meanΔ 30)
- Severe LV dysfunction EF 14%
- PVD, Aorto-Bifemoral bypass graft
- Silicosis, Lung CA, Chronic Pancreatitis
- Cardiogenic shock with sub-acute ischemia of right leg (occlusion of right limb of bypass graft)
- PABV: AVA 1.06 cm^2; meanΔ 13
- Recurrent cardiogenic shock, SBP 70 mm Hg on pressors $\Rightarrow$ ***Percutaneous Aortic Valve***

Cribier A et al *Circulation* 2002;106:3006-08.

Catheter Based Therapy for Aortic Stenosis
Percutaneous Aortic Valve



Catheter Based Therapy for Aortic Stenosis
Percutaneous Aortic Valve



First Case: Percutaneous Aortic Valve Clinical Follow-Up

- Following procedure: mean Δ 6; AVA 1.9 cm^2
- 48 hrs pressors weaned to off
- Follow-UP TEE performed at 1, 4, 7, 9 wks with stable valve function. EF remained poor 13 to 20%
- Multiple other issues: PE, sepsis and worsening right leg ischemia $\rightarrow$ mid-thigh amputation D70
- Following amputation, progressive decline and lack of healing at surgical site and Death D119
- **No recurrent CHF**

Cribier A et al *Circulation* 2002;106:3006-08.

History

- 1985 – Cribier described aortic valvuloplasty
- 1992 - Henning Andersen described the first transcatheter aortic stent valve
  - Constructed of a handmade wire frame within which was sewn a porcine aortic valve, crimped onto a balloon catheter and implanted transarterially into a pig
- 2002 – 1st percutaneous valve implantation in pulmonary position in a human
- 2002 – Cribier performed first clinical antegrade transcatheter placement of AV prosethesis

Catheter Based Therapy for Aortic Stenosis
Alain Cribier: Percutaneous Aortic Valve

20 no-option patients treated in FRANCE

50% male, mean age 78±10 yrs (57 to 91)

All with NYHA class IV; four cardiogenic shock

All patients refused surgery by four cardiac surgeons secondary to cardiac and non-cardiac factors

Expected surgical mortality ~ 50%

Percutaneous Aortic Valve: Procedural Results

Success 17/20 (85%)

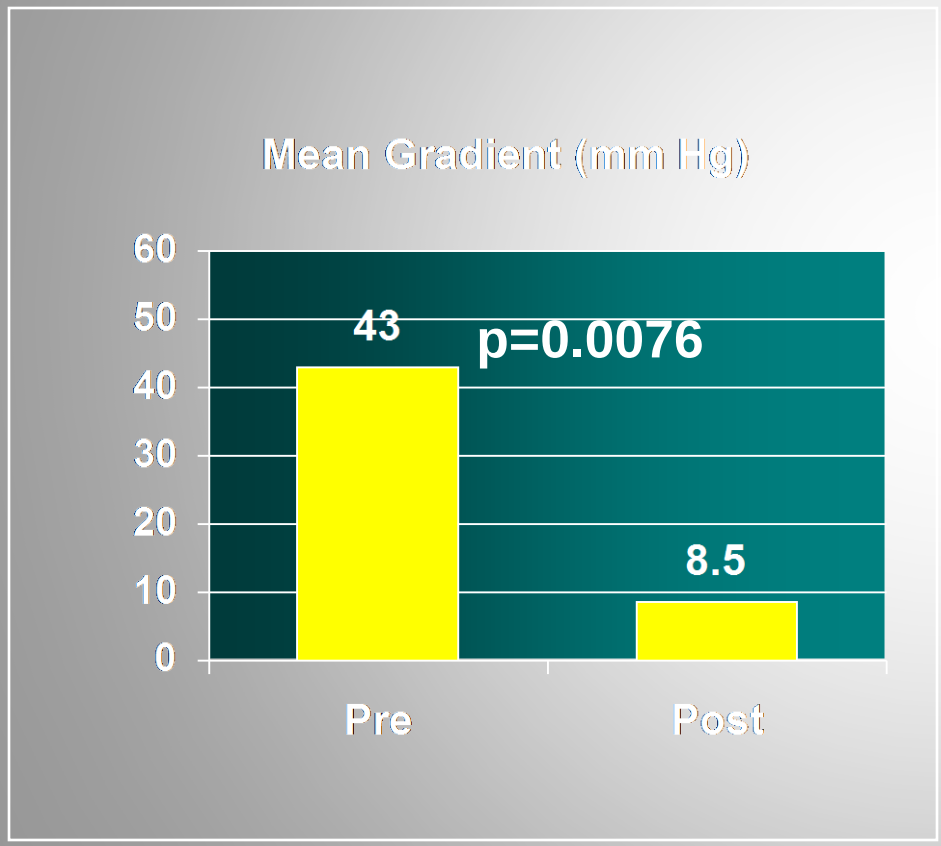
Technical Failures 4 (3 pts)

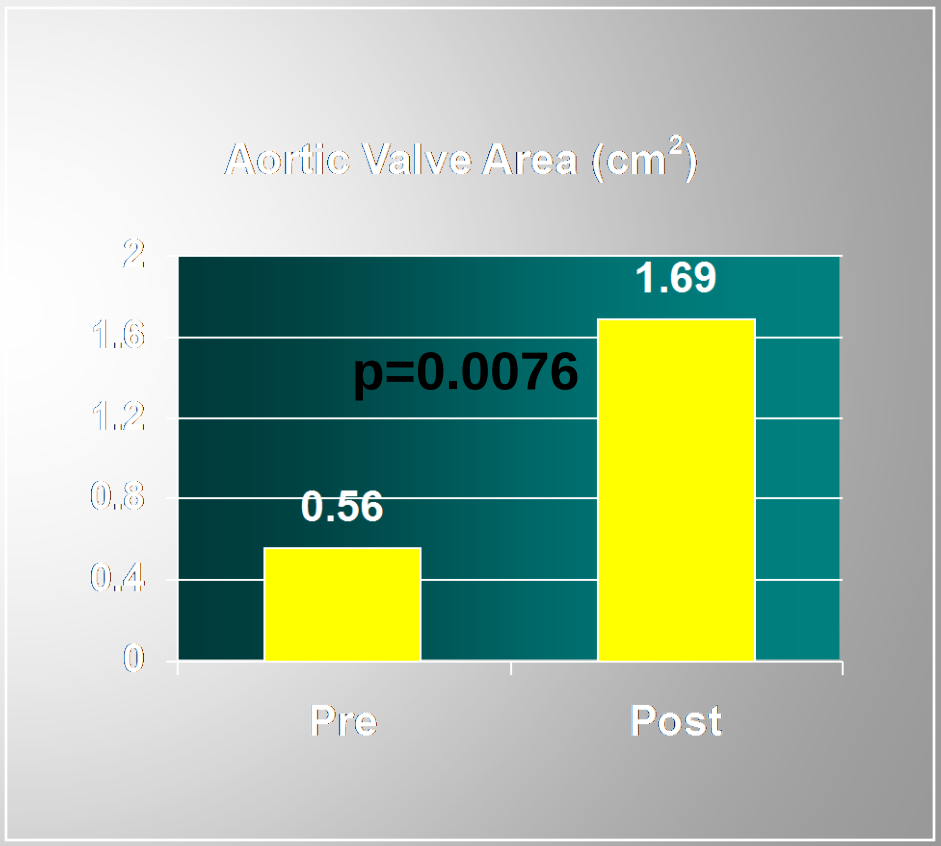
- 1 valve migrated → severe AR → death
- 3 failures to cross aortic valve with valve

Complications

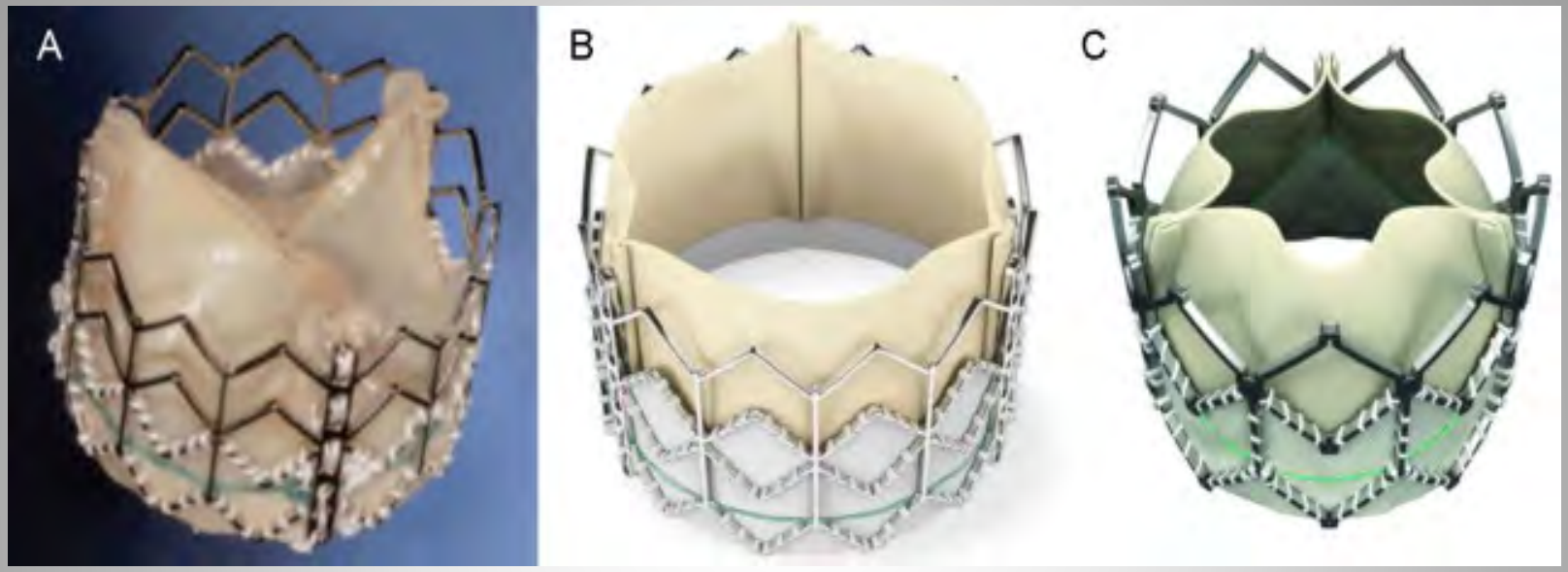
- 1 stroke secondary to crossing valve
- 1 RV perforation from pacer
- 2 procedural deaths

Percutaneous Aortic Valve: Procedural Results





Balloon expandable valve evolution Edwards Lifesciences Inc.



A – Original Cribier-Edwards valve

Constructed from a laser-cut stainless steel tubular frame with equine pericardium valve leaflets

B – Edwards SAPIEN transcatheter heart valve

More durable bovine pericardium and a higher sealing cuff to reduce paravalvular leaks low-profile

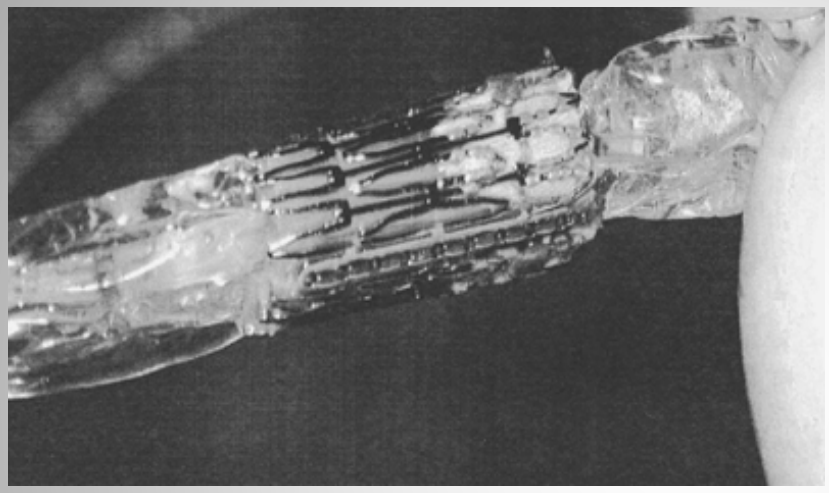
C - Edwards SAPIEN-XT valve

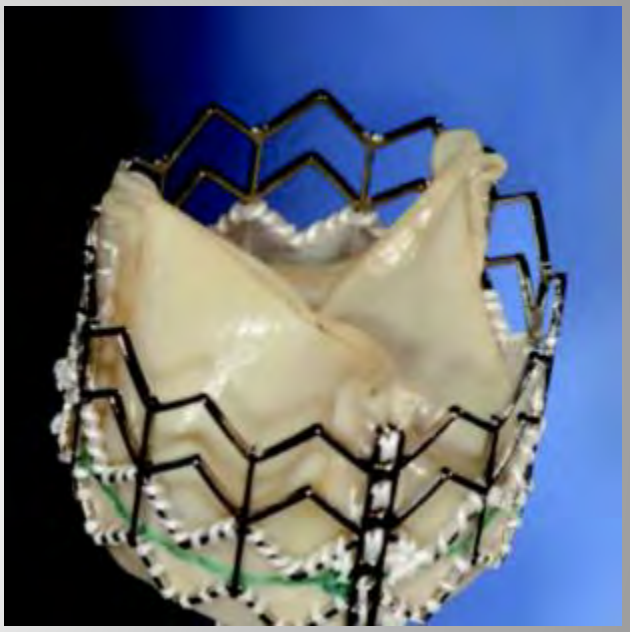
Stainless steel was replaced with a cobalt chromium alloy frame

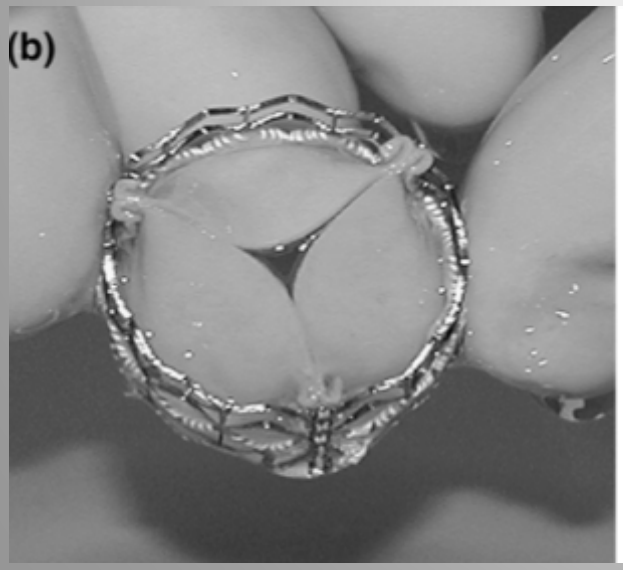
Reengineered leaflets

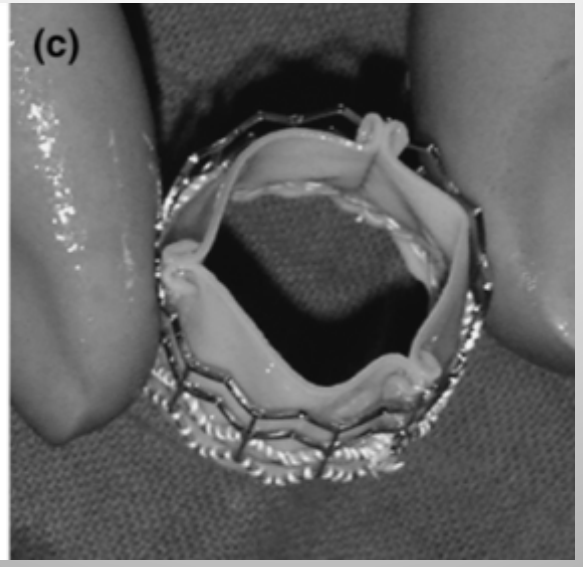
Small diameter system

Catheter Based Therapy for Aortic Stenosis
Percutaneous Aortic Valve



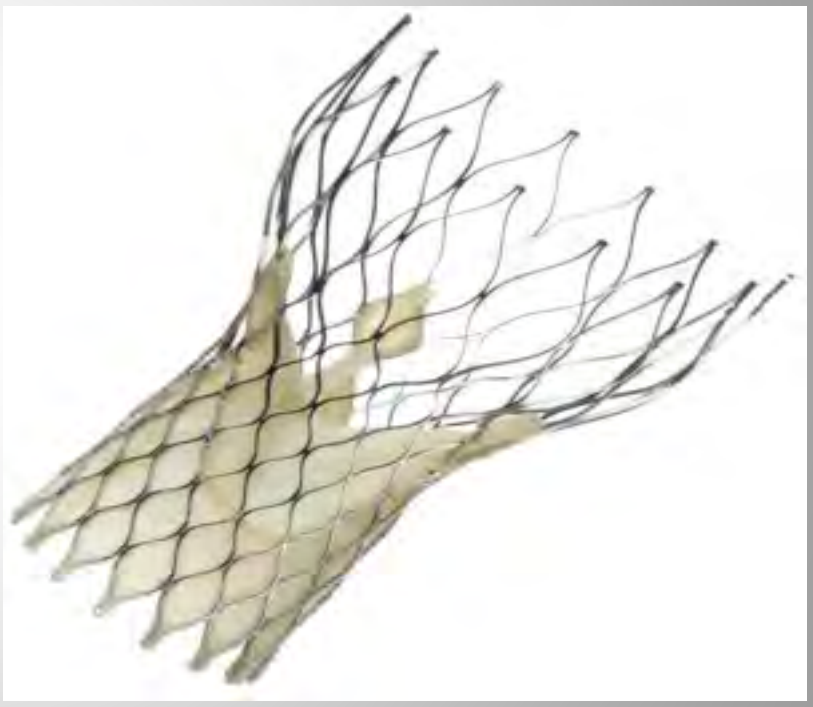






CoreValve
Medtronic Inc.

- In 2005 CoreValve developed
- Self expanding
- Valve frame constructed of nitinol
- Leaflets constructed of porcine pericardium
- Only limited non-randomized comparisons are available
- Deployment of the CoreValve device may be more intuitive, and does not require rapid pacing
- Can (up to a point) be repositioned or retrieved, although this process is not without complications
- Atrioventricular block requiring pacemaker implantation is much more common



CoreValve delivery system

Work up

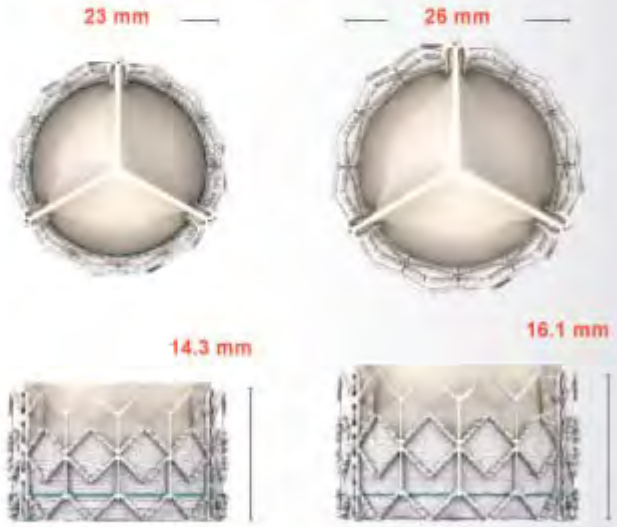
- Echocardiogram
- CT scan
  - Best at assessing for calcification
- Coronary angiogram
- Aortic root angiogram
- Lower extremity angiogram

Percutaneous Aortic Valve Implantation

- Right heart catheterization
- TEE – 3D
- Fluoroscopy
- Temporary Pacemaker

EDWARDS SAPIEN TRANSCATHETER HEART VALVE

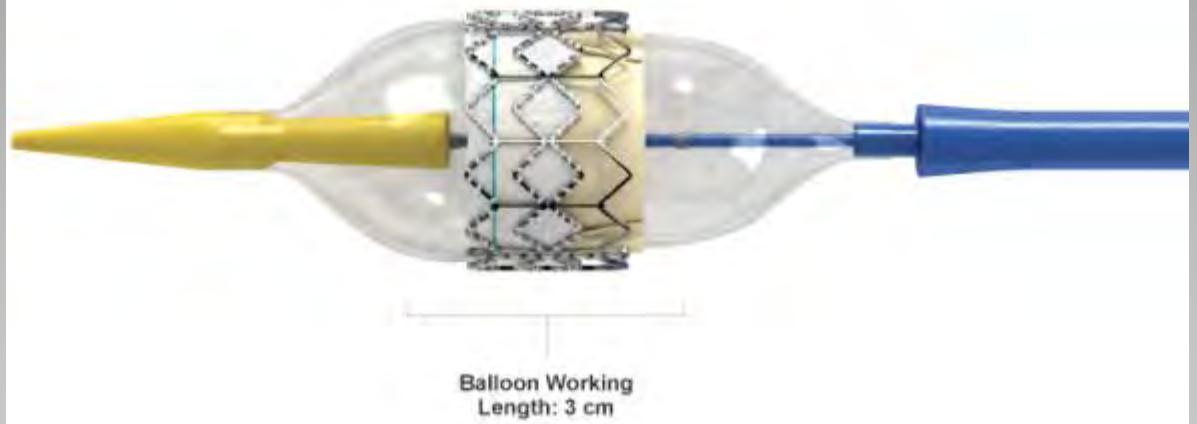
Available in Two Sizes

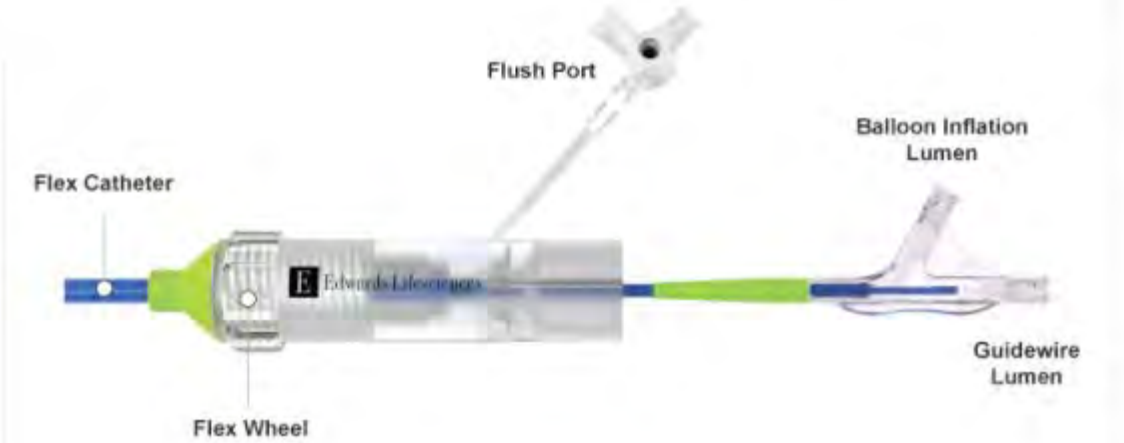


Annulus Range

18-22 mm	21-25 mm

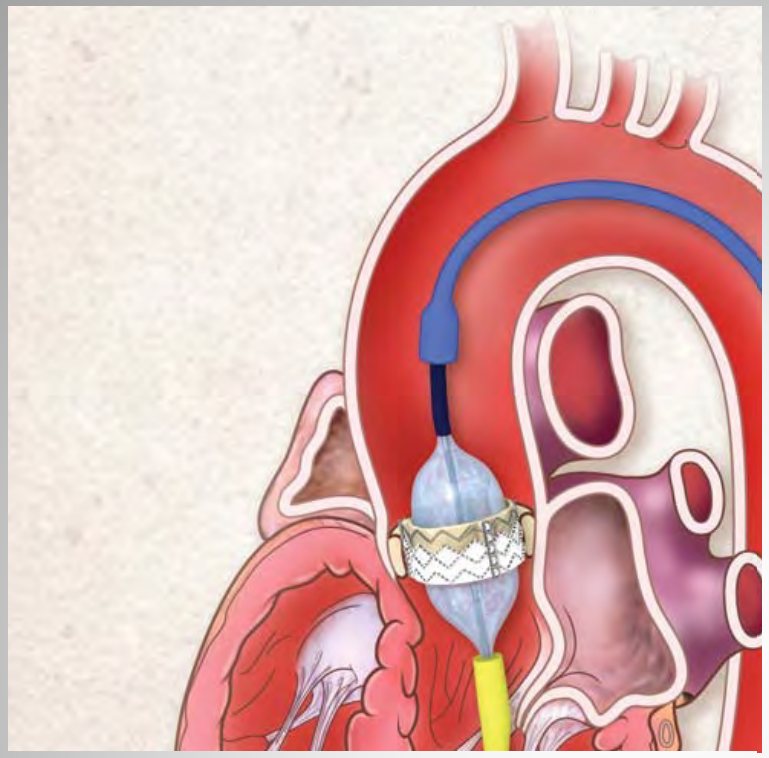
RETROFLEX 3 DELIVERY SYSTEM



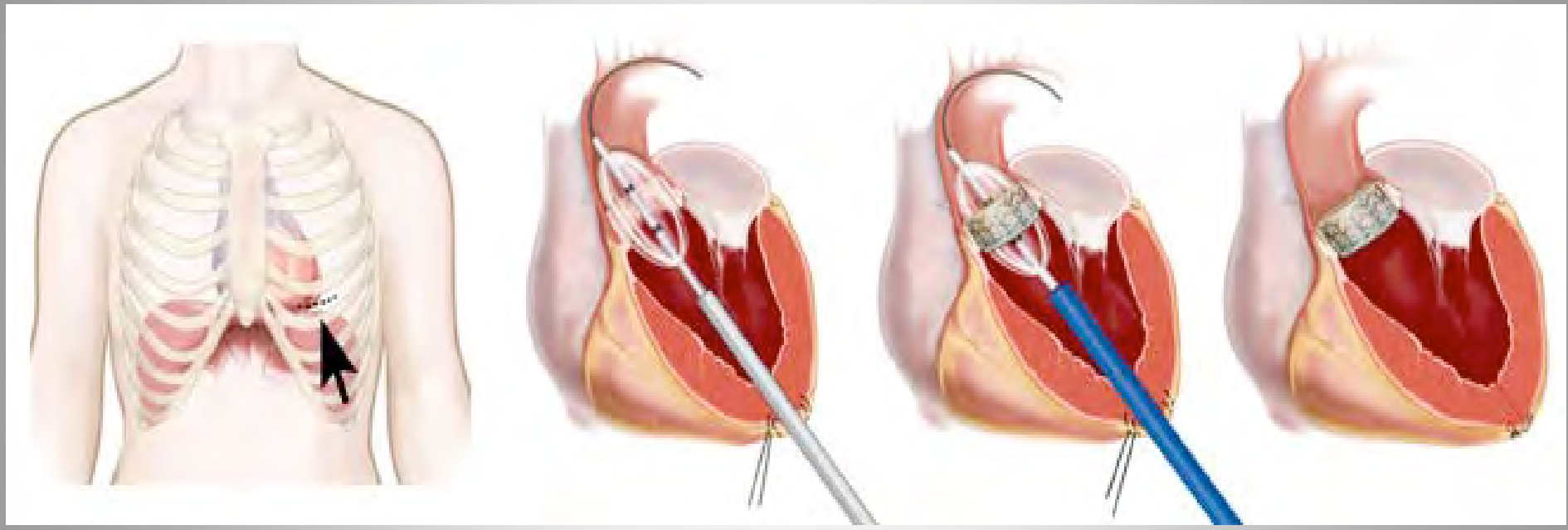


ADDITIONAL SPECIFICATIONS

Guidewire Compatibility: 0.035"



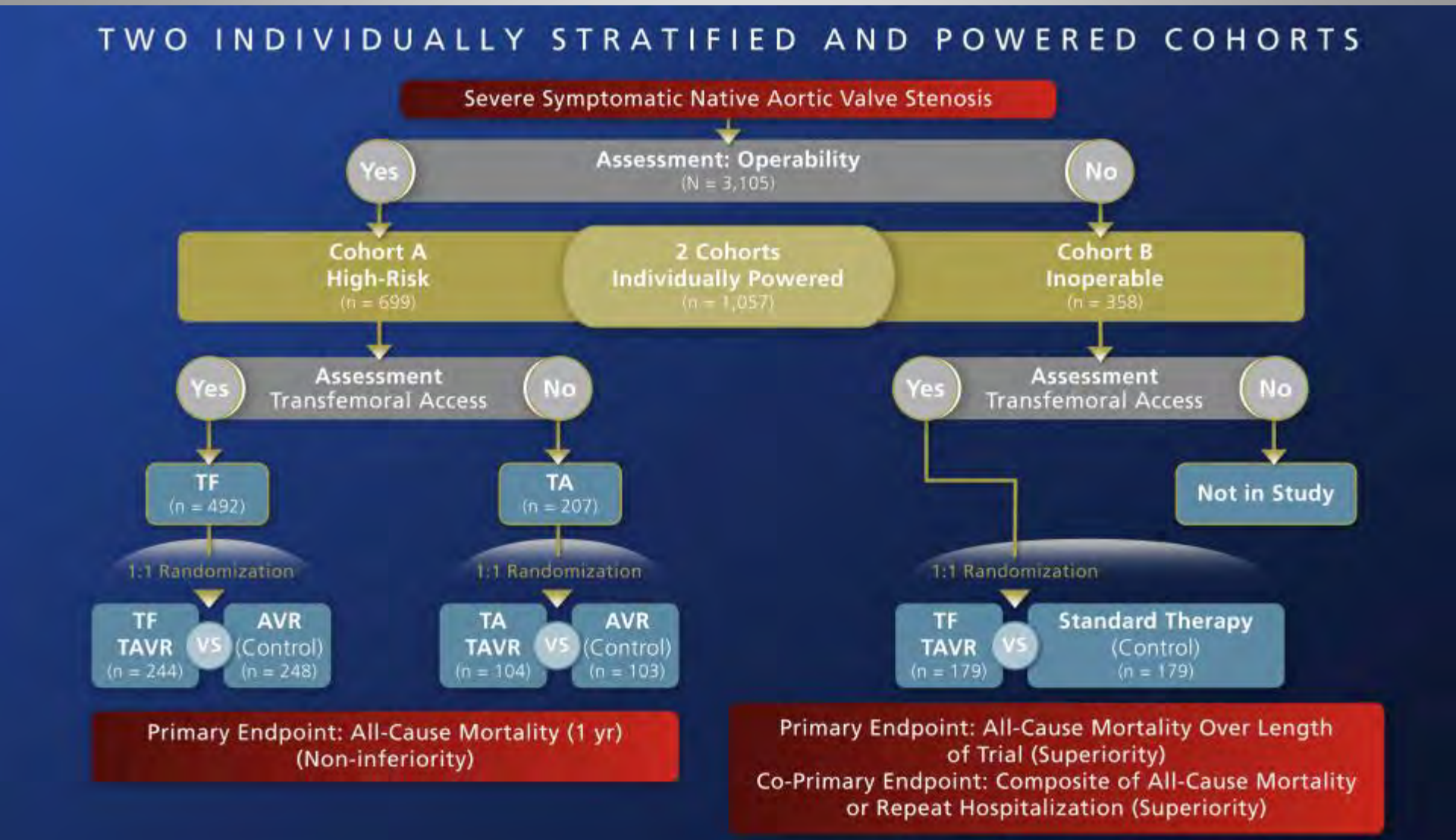
Transapical Approach



PARTNER Trial

- Placement of AoRtic TranNscathetER Valves
- Multicenter randomized clinical trial
- 2 parallel trials
- High risk 700 patients –TAVI (TF/TA) vs AVR ***Cohort A***
- Inoperable 358 patients TAVI (TF) vs Standard Rx (BAV 86%) ***Cohort B***
- Use of Edwards Sapien – bovine pericardial valve

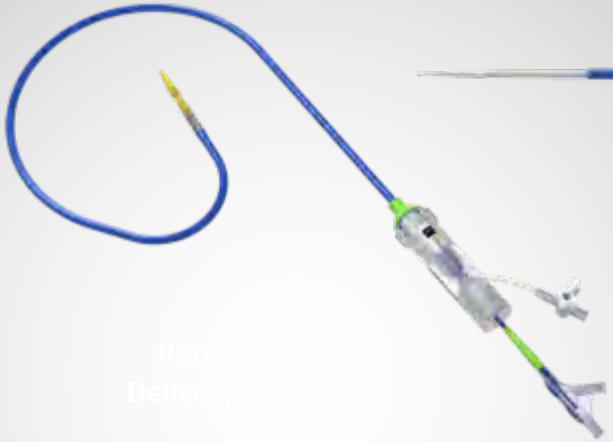
Rigorous Study Design



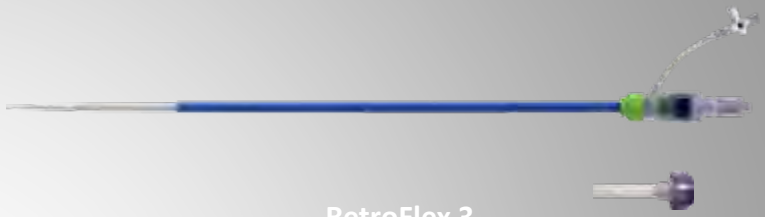
TA, transapical; TF, transfemoral.

The PARTNER Trial Study Devices

Edwards SAPIEN Transcatheter Heart Valve



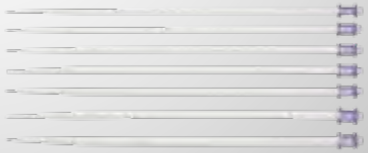
RetroFlex Delivery System



RetroFlex 3 Introducer Sheath Set

Crimper

RetroFlex Balloon Catheter



RetroFlex Dilator Kit

Atrion Inflation Devices

Cohort A

Edwards SAPIEN Transcatheter Heart Valve (THV) compared to AVR in high risk patients with severe symptomatic aortic stenosis

Results announced in 2011 at ACC

Original Article

Transcatheter versus Surgical Aortic-Valve Replacement in High-Risk Patients

Craig R. Smith, M.D., Martin B. Leon, M.D., Michael J. 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., Mathew Williams, M.D., Todd Dewey, M.D., Samir Kapadia, M.D., Vasilis Babaliaros, M.D., Vinod H. Thourani, M.D., Paul Corso, M.D., Augusto D. Pichard, M.D., Joseph E. Bavaria, M.D., Howard C. Herrmann, M.D., Jodi J. Akin, M.S., William N. Anderson, Ph.D., Duolao Wang, Ph.D., Stuart J. Pocock, Ph.D., for the PARTNER Trial Investigators

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Baseline Characteristics of the Patients.

Table 1. **Baseline Characteristics of the Patients.***

Characteristic	Transcatheter Replacement (N=348)	Surgical Replacement (N=351)	P Value
Age — yr	83.6±6.8	84.5±6.4	0.07
Male sex — no./total no. (%)	201/348 (57.8)	198/349 (56.7)	0.82
Society of Thoracic Surgeons score†	11.8±3.3	11.7±3.5	0.61
Logistic EuroSCORE†	29.3±16.5	29.2±15.6	0.93
New York Heart Association class — no./total no. (%)			0.79
II	20/348 (5.7)	21/349 (6.0)	
III or IV	328/348 (94.3)	328/349 (94.0)	
Coronary artery disease — no./total no. (%)	260/347 (74.9)	266/346 (76.9)	0.59
Previous myocardial infarction — no./total no. (%)	92/343 (26.8)	103/343 (30.0)	0.40
Previous CABG — no./total no. (%)	147/345 (42.6)	152/344 (44.2)	0.70
Previous PCI — no./total no. (%)	116/341 (34.0)	110/338 (32.5)	0.68
Previous balloon aortic valvuloplasty — no./total no. (%)	46/344 (13.4)	35/344 (10.2)	0.24
Cerebral vascular disease — no./total no. (%)	95/324 (29.3)	87/317 (27.4)	0.60
Peripheral vascular disease — no./total no. (%)	148/344 (43.0)	142/341 (41.6)	0.76
COPD — no./total no. (%)			
Any	151/348 (43.4)	151/351 (43.0)	0.94
Oxygen-dependent	32/348 (9.2)	25/351 (7.1)	0.34
Creatinine level >2 mg/dl (177 μmol/liter) — no./total no. (%)	38/343 (11.1)	24/344 (7.0)	0.06
Atrial fibrillation — no./total no. (%)	80/196 (40.8)	73/171 (42.7)	0.75
Permanent pacemaker — no./total no. (%)	69/345 (20.0)	76/347 (21.9)	0.58
Pulmonary hypertension — no./total no. (%)	125/295 (42.4)	110/302 (36.4)	0.15
Frail condition — no./total no. (%)	46/295 (15.6)	53/301 (17.6)	0.58
Extensively calcified aorta — no./total no. (%)	2/348 (0.6)	4/351 (1.1)	0.69
Deleterious effects of chest-wall irradiation — no./total no. (%)	3/348 (0.9)	3/351 (0.9)	1.00
Chest-wall deformity — no./total no. (%)	0	1/351 (0.3)	1.00
Liver disease — no./total no. (%)	7/344 (2.0)	9/346 (2.6)	0.80
Aortic-valve area — cm^2	0.7±0.2	0.6±0.2	0.13
Aortic-valve gradient — mm Hg	42.7±14.6	43.5±14.3	0.45
Left ventricular ejection fraction — %	52.5±13.5	53.3±12.8	0.45
Moderate or severe mitral regurgitation — no./total no. (%)	66/334 (19.8)	71/333 (21.3)	0.63

* Plus–minus values are means ±SD. CABG denotes coronary-artery bypass grafting, COPD chronic obstructive pulmonary disease, and PCI percutaneous coronary intervention.

† Scores on the risk model of the Society of Thoracic Surgeons (STS) and scores on the logistic EuroSCORE scale are algorithms that are based on the presence of coexisting illnesses in order to predict the 30-day operative mortality. The STS score equals the predicted mortality expressed as a percentage. Less than 5% of patients in the population on which the STS algorithm is based had a predicted operative mortality (risk score) of more than 10%. The EuroSCORE algorithm generates a score that is typically two to three times the STS score for the same patient.

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Clinical Outcomes at 30 Days and 1 Year in the Intention-to-Treat Population.

Table 2. Clinical Outcomes at 30 Days and 1 Year in the Intention-to-Treat Population.*

Outcome	30 Days			1 Year		
	Transcatheter Replacement (N=348)	Surgical Replacement (N=351)	P Value	Transcatheter Replacement (N=348)	Surgical Replacement (N=351)	P Value
	no. of patients (%)			*no. of patients (%)*		
Death						
From any cause	12 (3.4)	22 (6.5)	0.07	84 (24.2)	89 (26.8)	0.44
From cardiac causes	11 (3.2)	10 (3.0)	0.90	47 (14.3)	40 (13.0)	0.63
Repeat hospitalization	15 (4.4)	12 (3.7)	0.64	58 (18.2)	45 (15.5)	0.38
Death or repeat hospitalization	25 (7.2)	33 (9.7)	0.24	120 (34.6)	119 (35.9)	0.73
Stroke or transient ischemic attack						
Either	19 (5.5)	8 (2.4)	0.04	27 (8.3)	13 (4.3)	0.04
Transient ischemic attack	3 (0.9)	1 (0.3)	0.33	7 (2.3)	4 (1.5)	0.47
Stroke						
Minor	3 (0.9)	1 (0.3)	0.34	3 (0.9)	2 (0.7)	0.84
Major	13 (3.8)	7 (2.1)	0.20	17 (5.1)	8 (2.4)	0.07
Death from any cause or major stroke	24 (6.9)	28 (8.2)	0.52	92 (26.5)	93 (28.0)	0.68
Myocardial infarction	0	2 (0.6)	0.16	1 (0.4)	2 (0.6)	0.69
Vascular complication						
Any	59 (17.0)	13 (3.8)	<0.001	62 (18.0)	16 (4.8)	<0.001
Major	38 (11.0)	11 (3.2)	<0.001	39 (11.3)	12 (3.5)	<0.001
Acute kidney injury						
Creatinine >3 mg/dl (265 μmol/liter)	4 (1.2)	4 (1.2)	0.95	12 (3.9)	8 (2.7)	0.41
Renal-replacement therapy	10 (2.9)	10 (3.0)	0.95	18 (5.4)	20 (6.5)	0.56
Major bleeding	32 (9.3)	67 (19.5)	<0.001	49 (14.7)	85 (25.7)	<0.001
Endocarditis	0	1 (0.3)	0.32	2 (0.6)	3 (1.0)	0.63
New-onset atrial fibrillation†	30 (8.6)	56 (16.0)	0.006	42 (12.1)	60 (17.1)	0.07
New pacemaker	13 (3.8)	12 (3.6)	0.89	19 (5.7)	16 (5.0)	0.68

* All percentages are Kaplan–Meier estimates at the specific time point and thus do not equal the number of patients divided by the total number in the study group.
† The presence of new-onset atrial fibrillation was determined in an electrocardiography core laboratory.

Smith CR et al. N Engl J Med 2011;364:2187-2198

Primary end point was rate of death from any cause at 1 year

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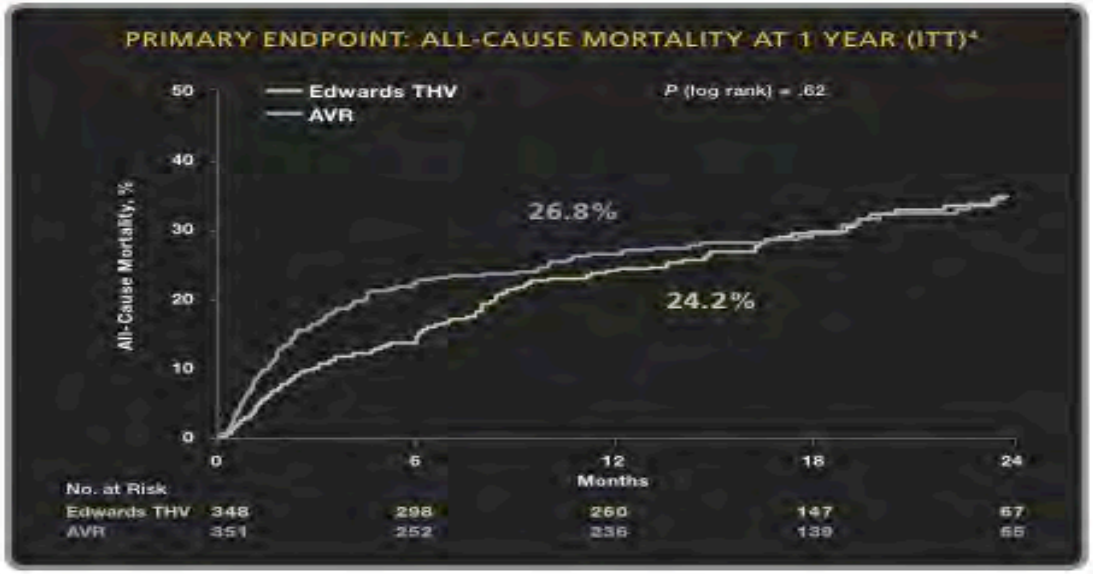
Survival With Edwards SAPIEN THV Was Equivalent to AVR in High-Risk Patients



Mortality at 1 year

Edwards SAPIEN THV **24.2%**

AVR **26.8%**

(P = .001 for non-inferiority)[4]

RESULTS FOR BOTH PROCEDURES EXCEEDED EXPECTATIONS*[4,6]

AVR

Expected 30-day mortality rate: **11.8%**

Observed 30-day mortality rate: **8.0%**

O:E ratio = 0.68

Edwards SAPIEN THV

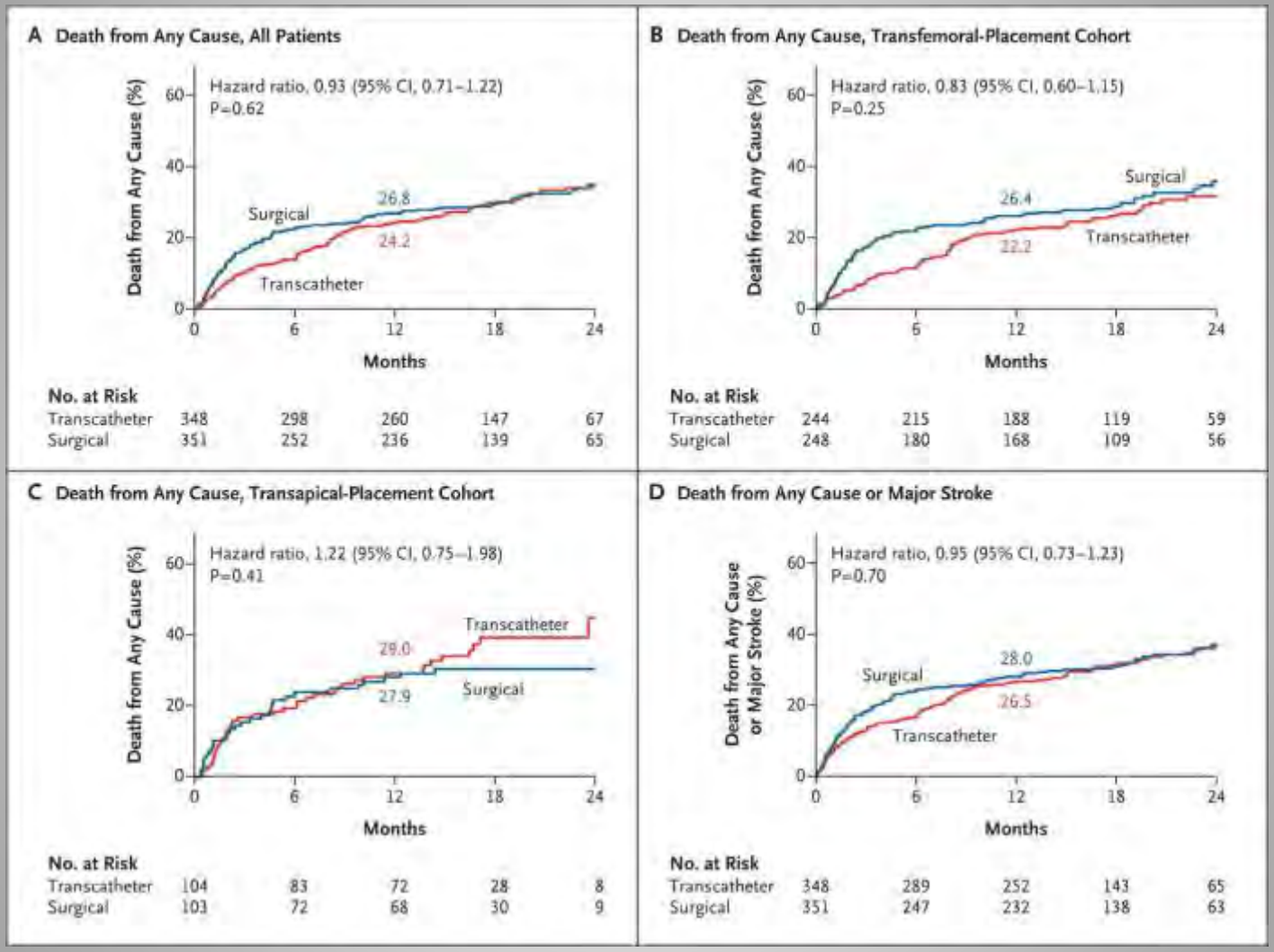
Expected 30-day mortality rate: **11.7%**

Observed 30-day mortality rate: **5.2%**

O:E ratio = 0.44

*As-treated (AT) analysis.
ITT, intent to treat.

Time-to-Event Curves for the Primary End Point and Other Selected End Points.



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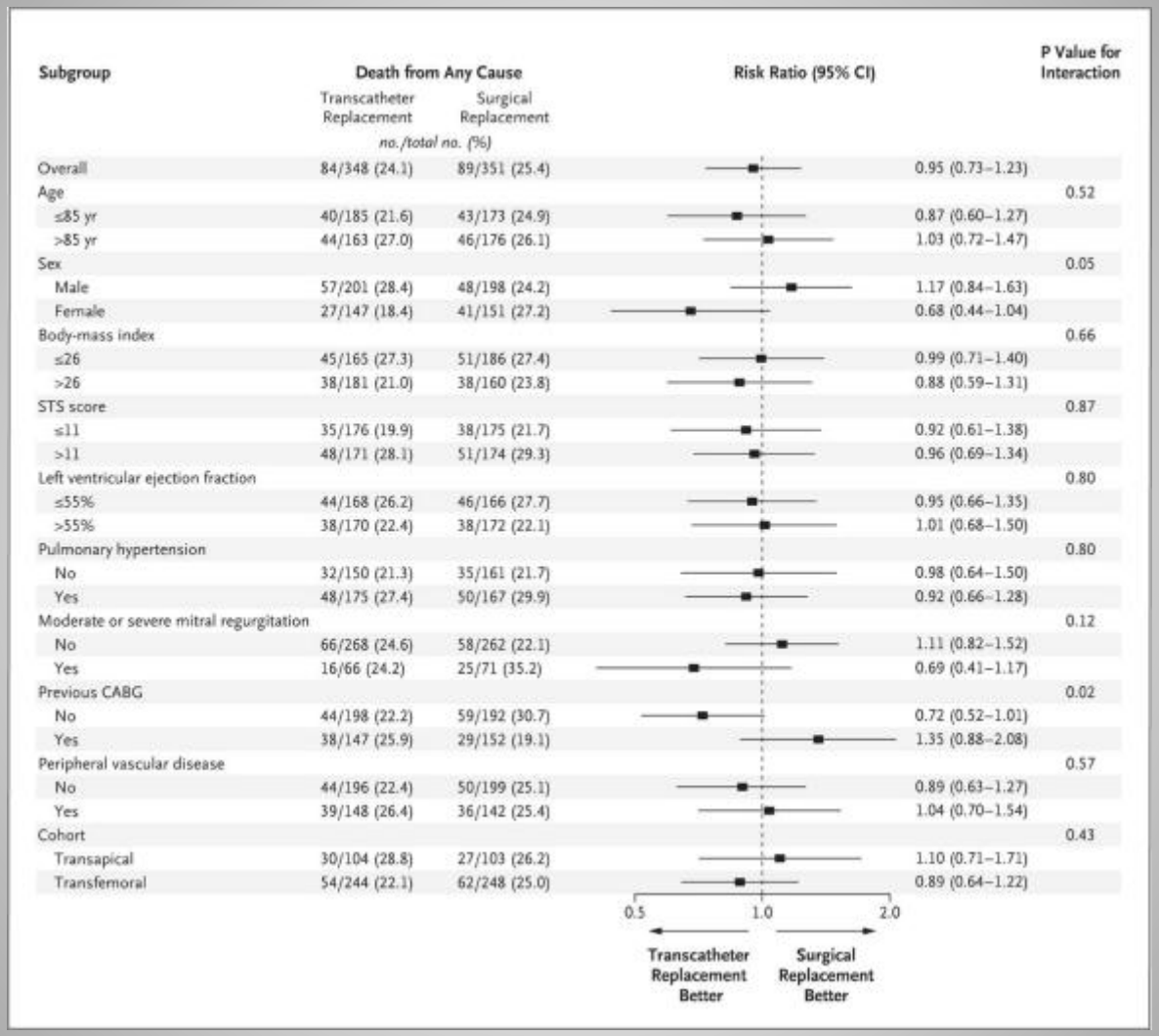
Subgroup Analyses for Death from Any Cause at 1 Year.



Subgroup	Death from Any Cause: Transcatheter Replacement	Death from Any Cause: Surgical Replacement	Risk Ratio (95% CI)	P Value for Interaction
	no./total no. (%)			
Overall	84/348 (24.1)	89/351 (25.4)	0.95 (0.73–1.23)	
Age				0.52
≤85 yr	40/185 (21.6)	43/173 (24.9)	0.87 (0.60–1.27)	
>85 yr	44/163 (27.0)	46/176 (26.1)	1.03 (0.72–1.47)	
Sex				0.05
Male	57/201 (28.4)	48/198 (24.2)	1.17 (0.84–1.63)	
Female	27/147 (18.4)	41/151 (27.2)	0.68 (0.44–1.04)	
Body-mass index				0.66
≤26	45/165 (27.3)	51/186 (27.4)	0.99 (0.71–1.40)	
>26	38/181 (21.0)	38/160 (23.8)	0.88 (0.59–1.31)	
STS score				0.87
≤11	35/176 (19.9)	38/175 (21.7)	0.92 (0.61–1.38)	
>11	48/171 (28.1)	51/174 (29.3)	0.96 (0.69–1.34)	
Left ventricular ejection fraction				0.80
≤55%	44/168 (26.2)	46/166 (27.7)	0.95 (0.66–1.35)	
>55%	38/170 (22.4)	38/172 (22.1)	1.01 (0.68–1.50)	
Pulmonary hypertension				0.80
No	32/150 (21.3)	35/161 (21.7)	0.98 (0.64–1.50)	
Yes	48/175 (27.4)	50/167 (29.9)	0.92 (0.66–1.28)	
Moderate or severe mitral regurgitation				0.12
No	66/268 (24.6)	58/262 (22.1)	1.11 (0.82–1.52)	
Yes	16/66 (24.2)	25/71 (35.2)	0.69 (0.41–1.17)	
Previous CABG				0.02
No	44/198 (22.2)	59/192 (30.7)	0.72 (0.52–1.01)	
Yes	38/147 (25.9)	29/152 (19.1)	1.35 (0.88–2.08)	
Peripheral vascular disease				0.57
No	44/196 (22.4)	50/199 (25.1)	0.89 (0.63–1.27)	
Yes	39/148 (26.4)	36/142 (25.4)	1.04 (0.70–1.54)	
Cohort				0.43
Transapical	30/104 (28.8)	27/103 (26.2)	1.10 (0.71–1.71)	
Transfemoral	54/244 (22.1)	62/248 (25.0)	0.89 (0.64–1.22)	

Smith CR et al. N Engl J Med 2011;364:2187-2198

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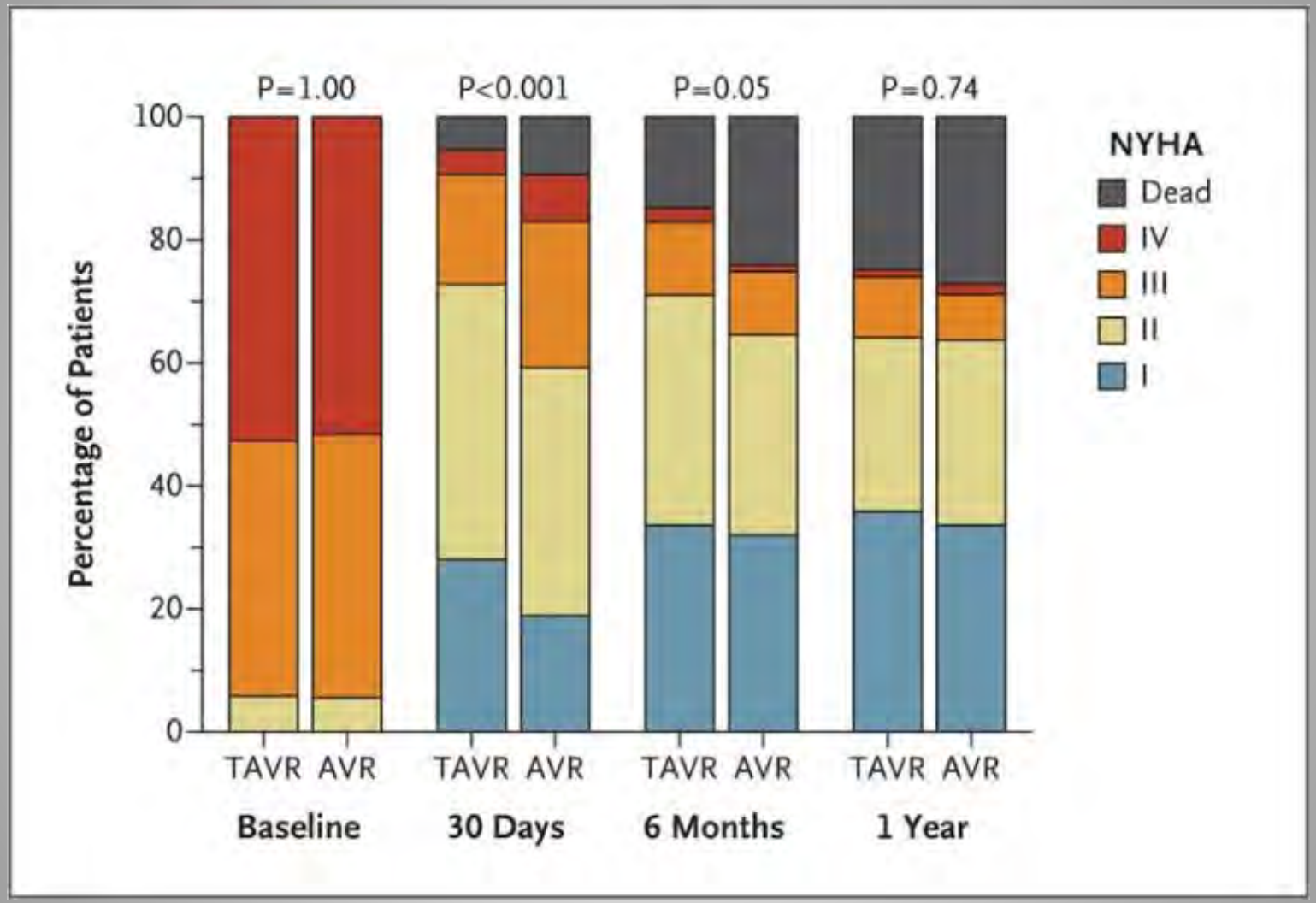
Symptom Status.



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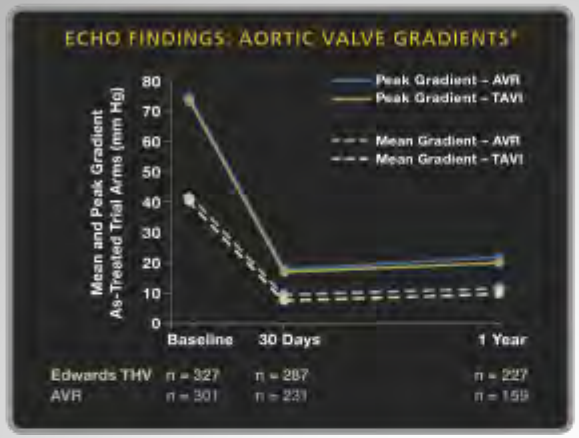
AVR and Edwards SAPIEN THV Improved Hemodynamics and Sustained Valve Performance



Carpentier–Edwards PERIMOUNT Magna Ease Heart Valve

Edwards SAPIEN Transcatheter Heart Valve

Consistent hemodynamics and valve performance between Edwards SAPIEN THV and Edwards Magna Ease**[4]

Edwards SAPIEN THV Rapidly Improved Symptoms, With Results Equivalent to AVR at 1 Year

85% of patients in NYHA class I or II at 1 year[4]

- Symptom improvement favored Edwards SAPIEN THV at 30 days and was similar to that with AVR at 1 year[4]

*A range of surgical valve sizes were used in the AVR arm and both the 23 mm and the 26 mm SAPIEN valves were used in the TAVI arm. Edwards surgical valves were used in 90% of patients in the AVR arm.[4]

Clinical Outcomes: High-Risk Patients

Both TAVI and AVR were associated with important but different periprocedural hazards.

	30 Days[4]			1 Year[4]		
Outcome	Edwards SAPIEN THV (n = 348)	AVR (n = 351)	***P* Value**	Edwards SAPIEN THV (n = 348)	AVR (n = 358)	***P* Value**
All-Cause Mortality	3.4%	6.5%	.07	24.2%	26.8%	.44
All Stroke or TIA	5.5%	2.4%	.04	8.3%	4.3%	.04
Major Stroke	3.8%	2.1%	.20	5.1%	2.4%	.07
Major Vascular Complications	11.0%	3.2%	< .01	11.3%	3.5%	< .01
Major Bleeding	9.3%	19.5%	< .01	14.7%	25.7%	< .01
New Atrial Fibrillation	8.6%	16.0%	< .01	12.1%	17.1%	< .07
New Pacemaker	3.8%	3.6%	.89	5.7%	5.0%	.68

Edwards SAPIEN THV:
Statistically higher incidence of all stroke or TIA and major vascular complications

AVR:
Statistically higher incidence of major bleeding and new atrial fibrillation

Conclusions

- In high-risk patients with severe aortic stenosis, transcatheter and surgical procedures for aortic-valve replacement were associated with similar rates of survival at 1 year, although there were important differences in periprocedural risks.
- Transcatheter replacement is an alternative to surgery replacement in a well chosen, high risk subgroups of patients with aortic stenosis.

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Cohort B

Edwards SAPIEN Transcatheter Heart Valve (THV) compared to standard therapy (best medical management) in operable patients with severe symptomatic aortic stenosis

Results announced in 2010 in NEJM

Background

September 22, 2010 on NEJM.org

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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*

An Elderly and Highly Symptomatic Population

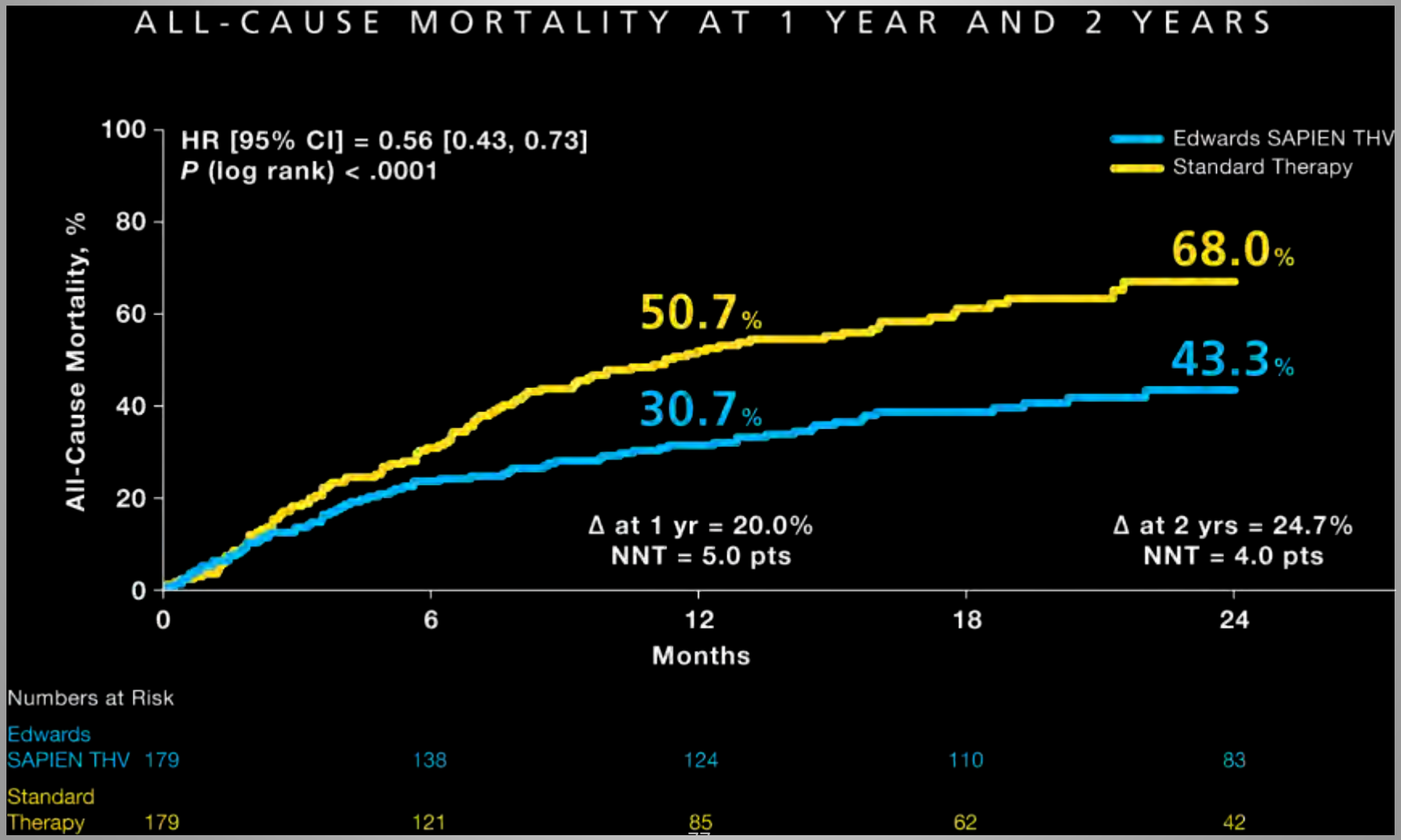
Characteristic	Edwards SAPIEN THV n = 179	Standard Therapy n = 179	*P* Value
Age (yr)	83.1 ± 8.6	83.2 ± 8.3	.95
Male sex (%)	45.8	46.9	.92
STS Score	11.2 ± 5.8	11.9 ± 4.8	.21
Logistic EuroSCORE	26.4 ± 17.2	30.4 ± 19.1	.04
NYHA			
I or II (%)	7.8	6.1	.68
III or IV (%)	92.2	93.9	.68
CAD (%)	67.6	74.3	.20
Prior MI (%)	18.6	26.4	.10
Prior CABG (%)	32.4	40.8	.12
Prior PCI (%)	26.3	21.8	.39
Prior BAV (%)	16.2	24.4	.09
CVD (%)	27.4	26.9	1.00

BAV, balloon aortic valvuloplasty; CABG, coronary artery bypass graft; CAD, coronary artery disease; CVD, cardiovascular disease; MI, myocardial infarction; NYHA, New York Heart Association; PCI, percutaneous coronary intervention; STS, Society of Thoracic Surgeons.

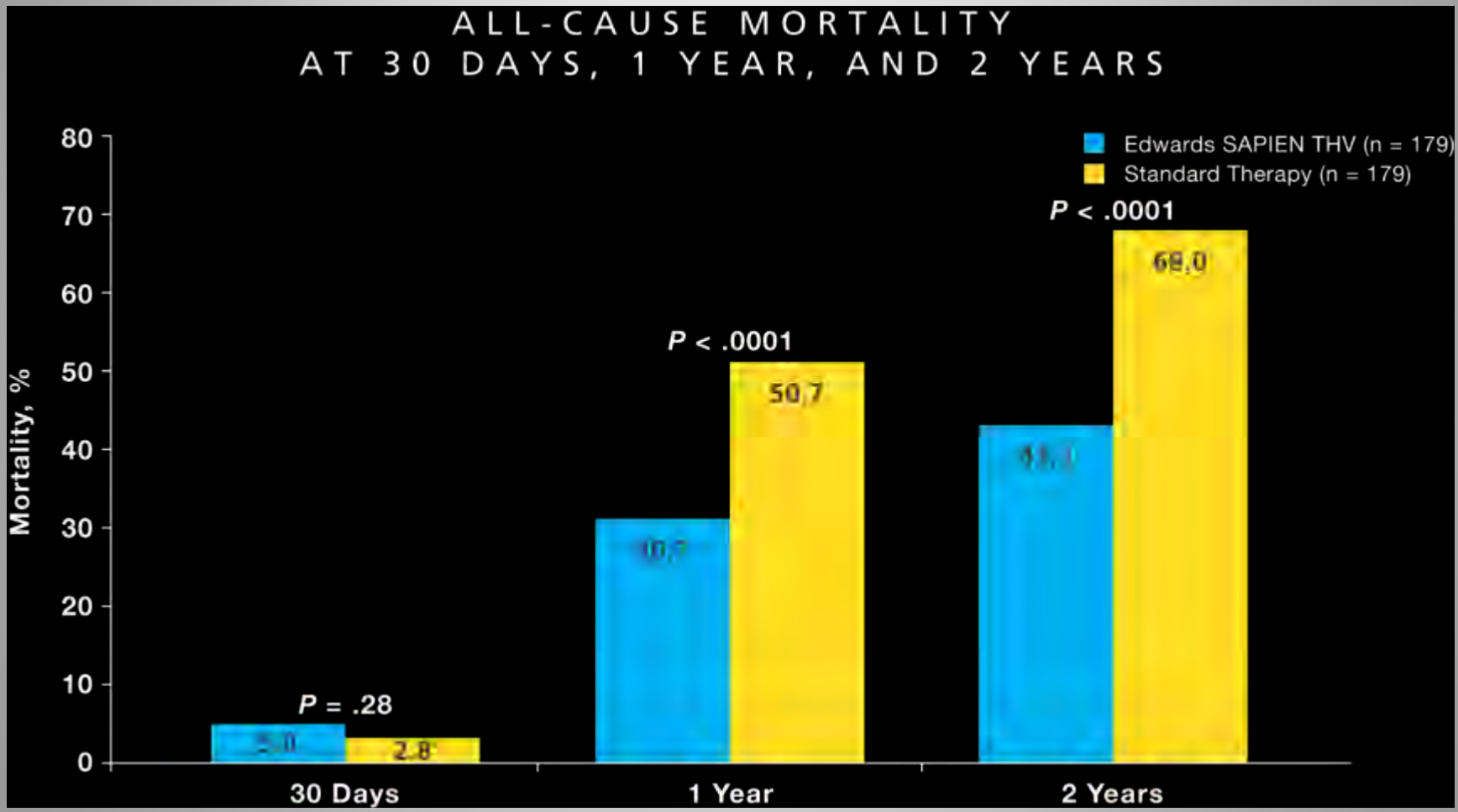
Patients Had Multiple Severe Comorbidities

Characteristic	Edwards SAPIEN THV n = 179	Standard Therapy n = 179	*P* Value
Peripheral valve disease (%)	30.9	25.1	.24
Chronic obstructive pulmonary disease			
Any (%)	41.3	52.5	.04
O_2-dependent (%)	21.2	25.7	.38
Creatinine > 2 mg/dL (%)	4.5	9.0	.10
Atrial fibrillation (%)	32.9	48.8	.04
Permanent pacemaker (%)	19.6	17.3	.68
Pulmonary hypertension (%)	42.4	43.8	.90
Frailty (%)	18.1	28.0	.09
Porcelain aorta (%)	19.0	11.2	.05
Chest wall irradiation (%)	8.9	8.4	1.00
Chest wall deformity (%)	8.4	5.0	.29
Liver disease (%)	3.4	3.4	1.00

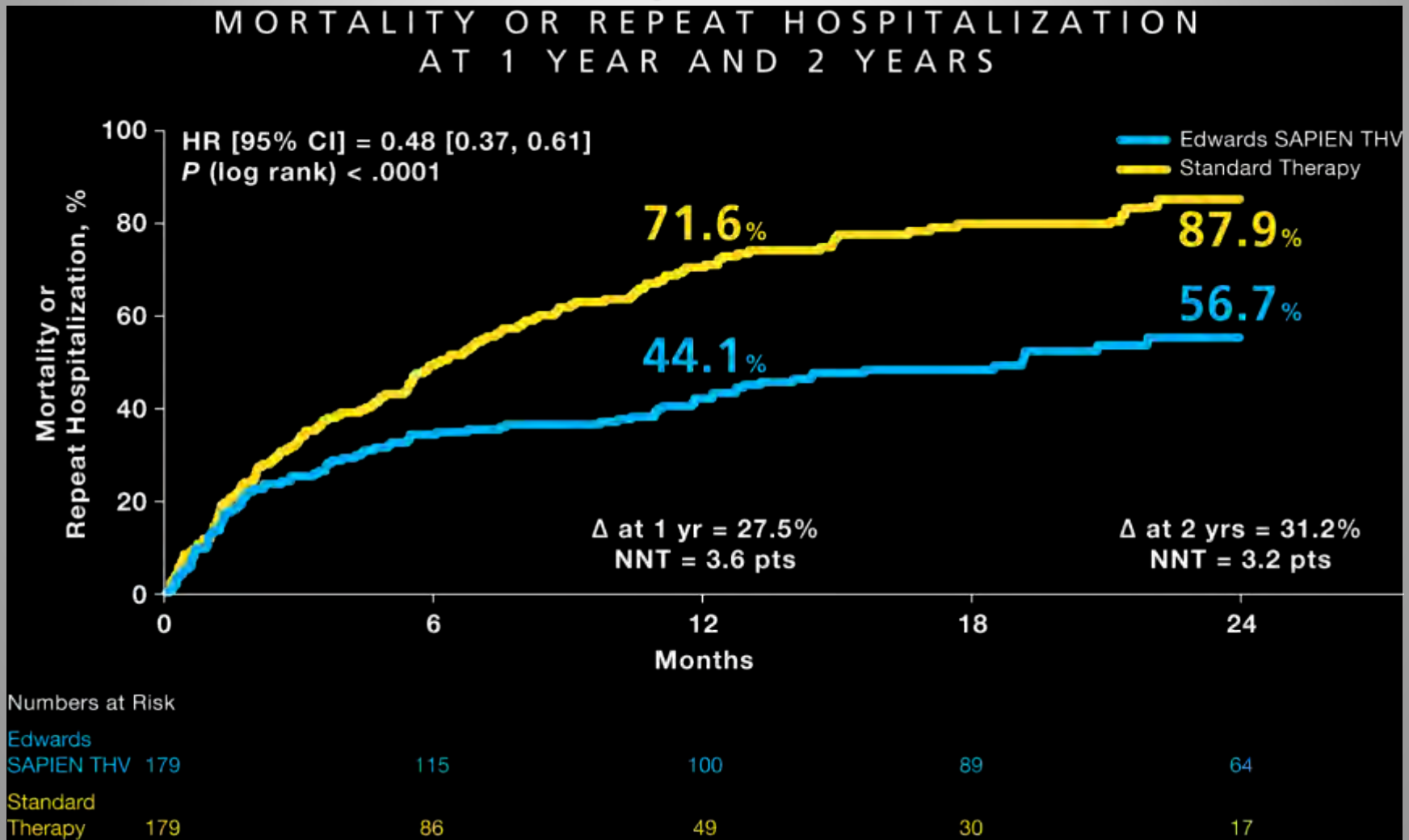
Absolute Reduction in Mortality



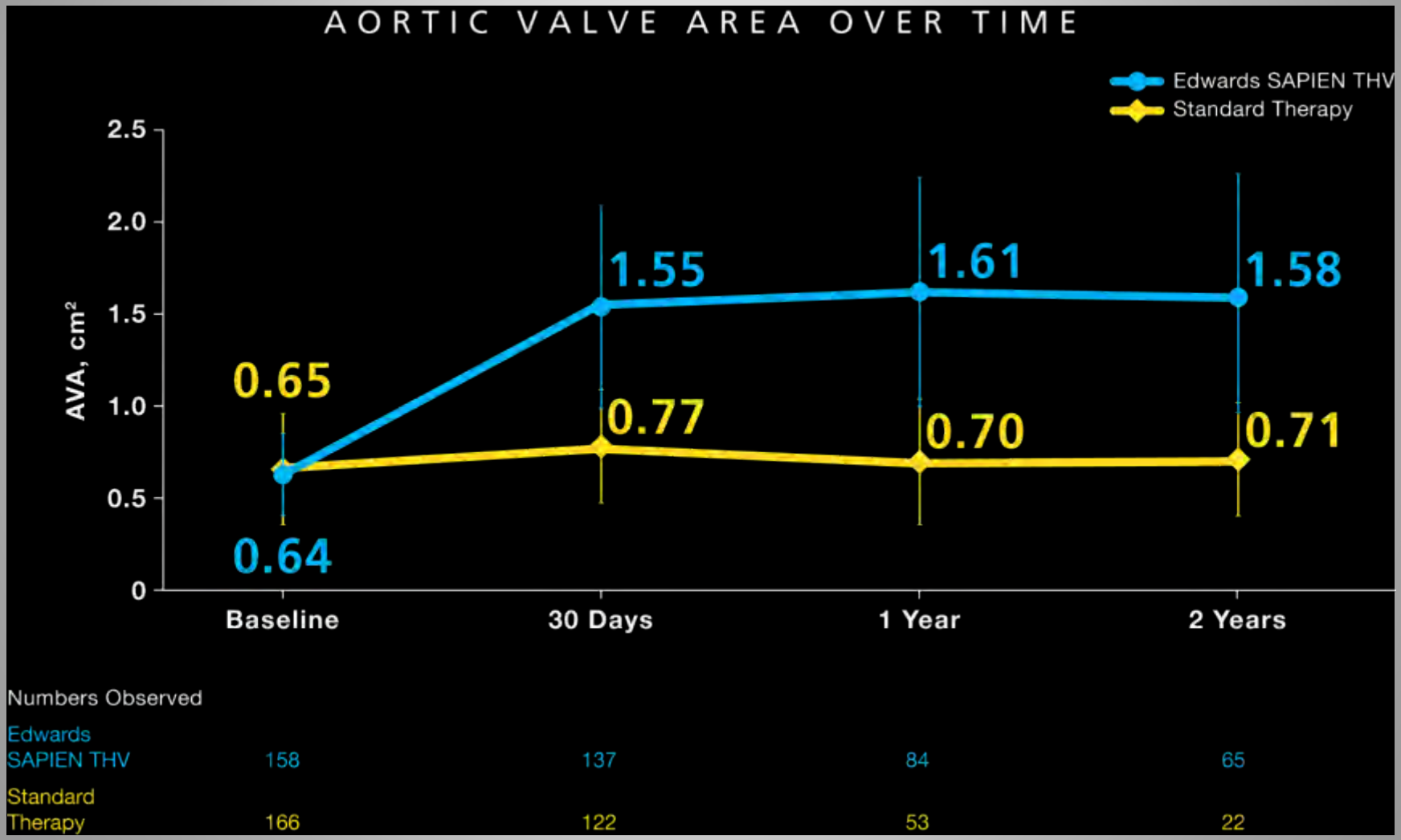
25% Absolute Reduction in Mortality



> 30% Absolute Reduction in Mortality or Repeat Hospitalization



Increased Valve Area



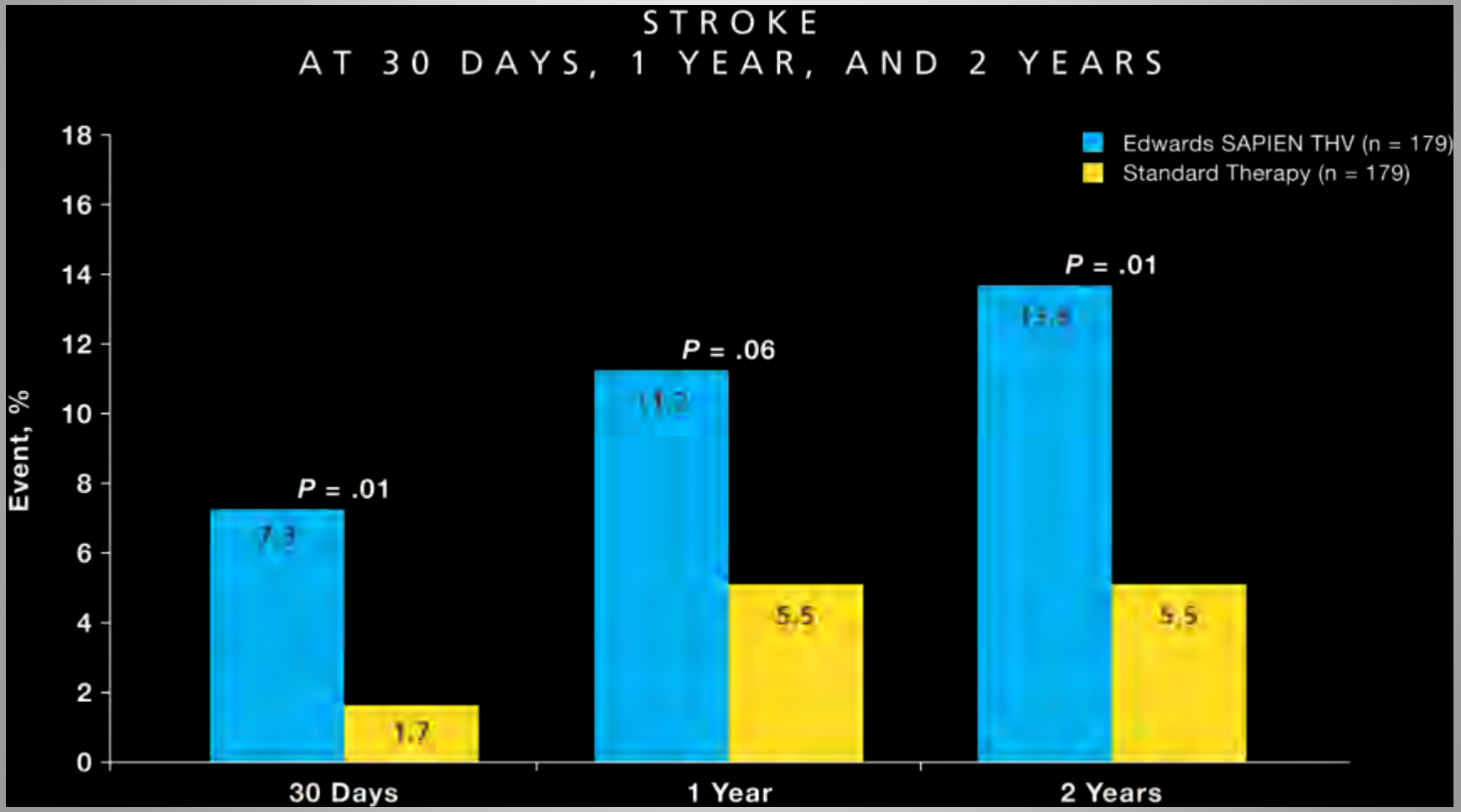
Error bars = ± 1 Std Dev

Reduction in Symptoms and Restoration of Quality of Life

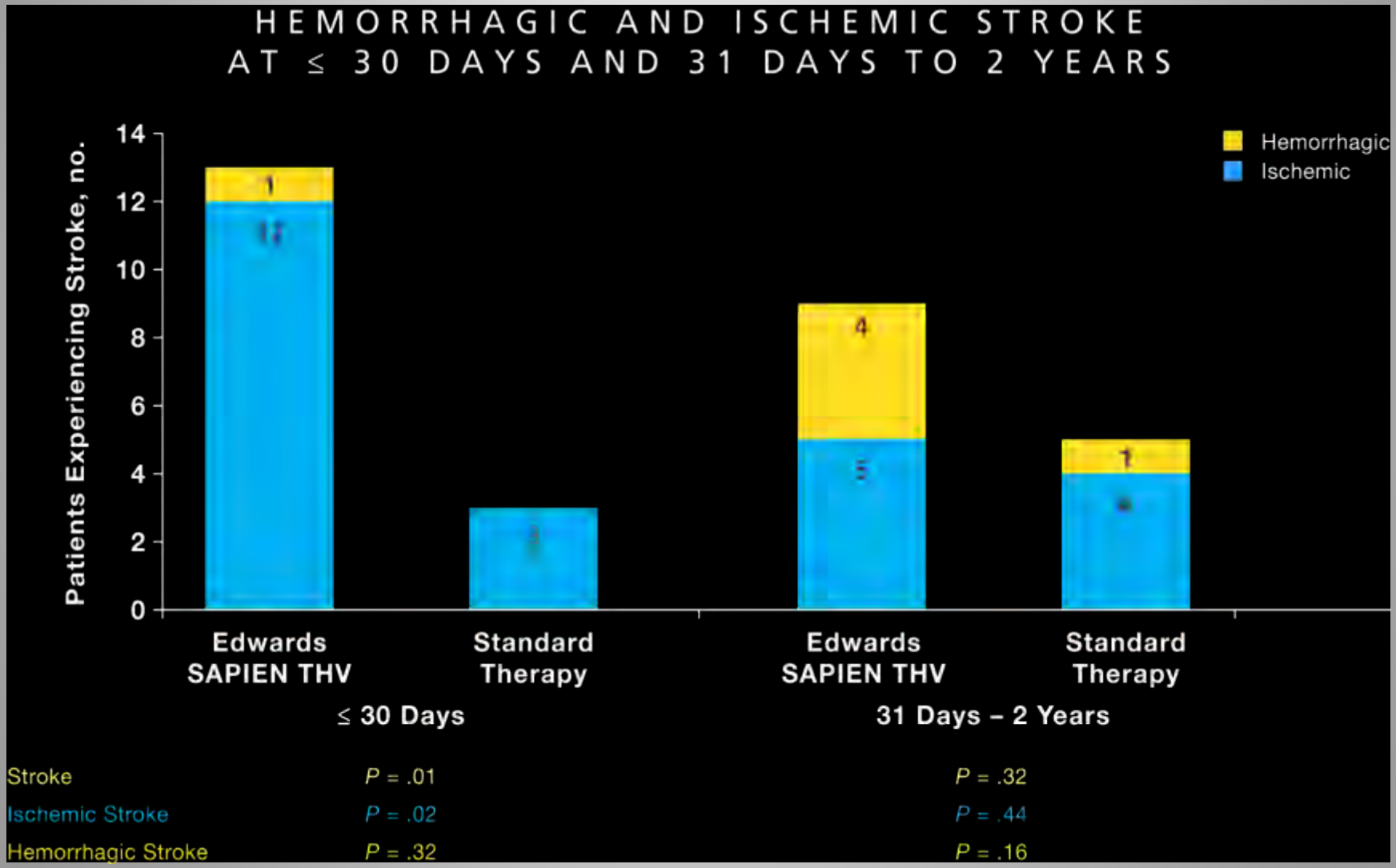
- *At 1 year, patients that underwent TAVR with the Edwards SAPIEN THV showed significant improvements in:*
- ***NYHA functional class***
- ***Kansas City Cardiomyopathy Questionnaire (KCCQ)***
- ***SF-12***
- ***6-minute walk test***

Complications

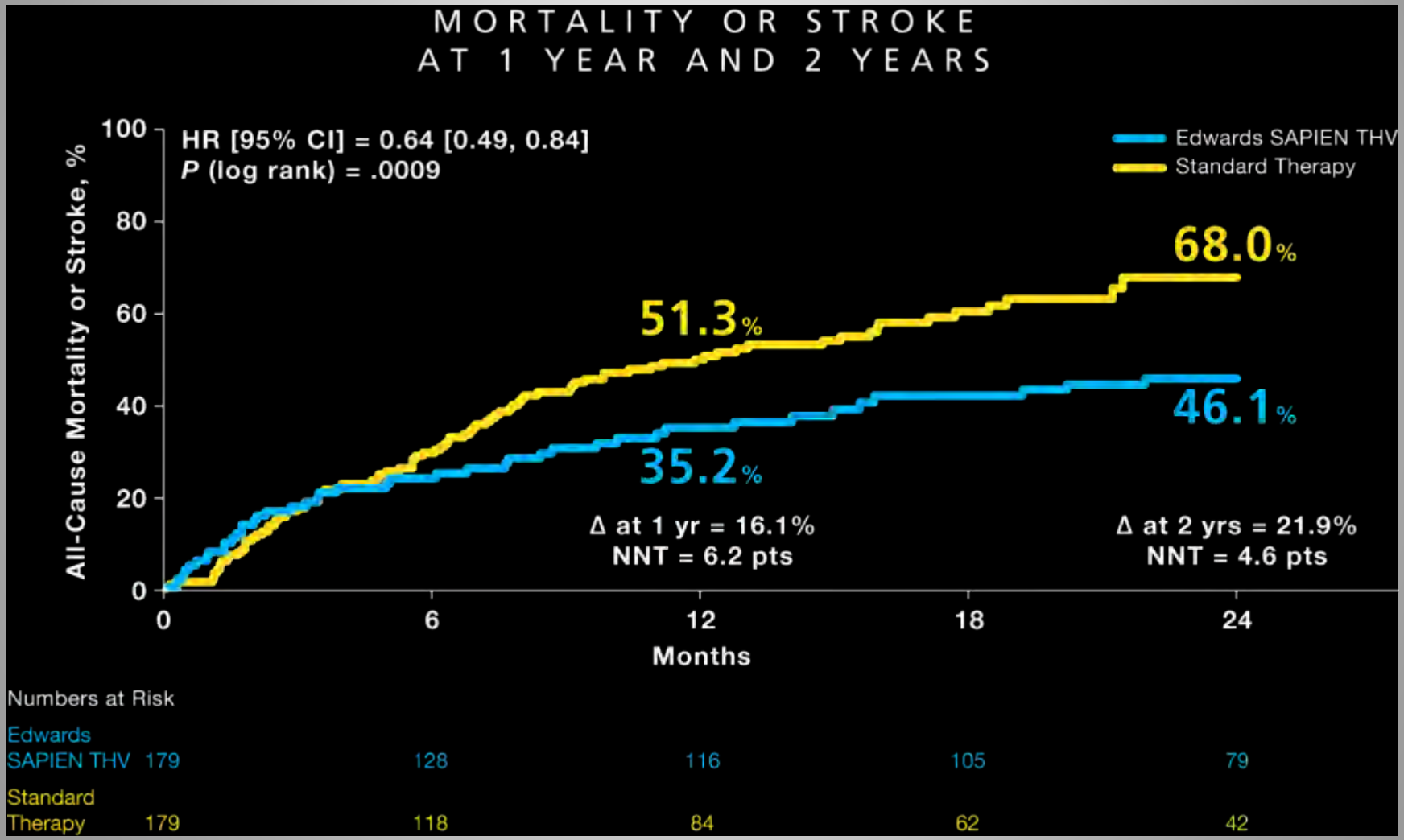
Higher Incidence of Stroke



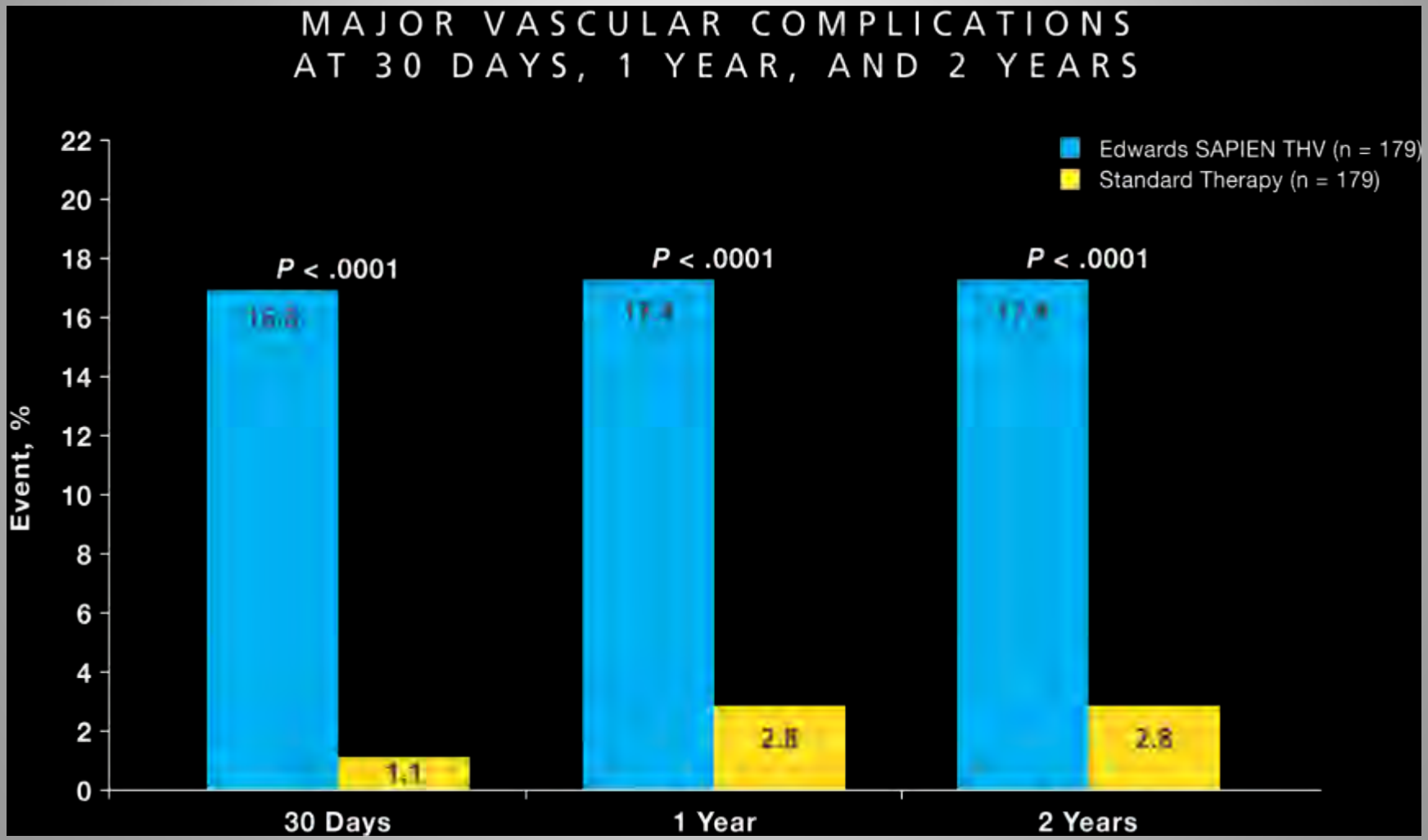
Stroke by Type



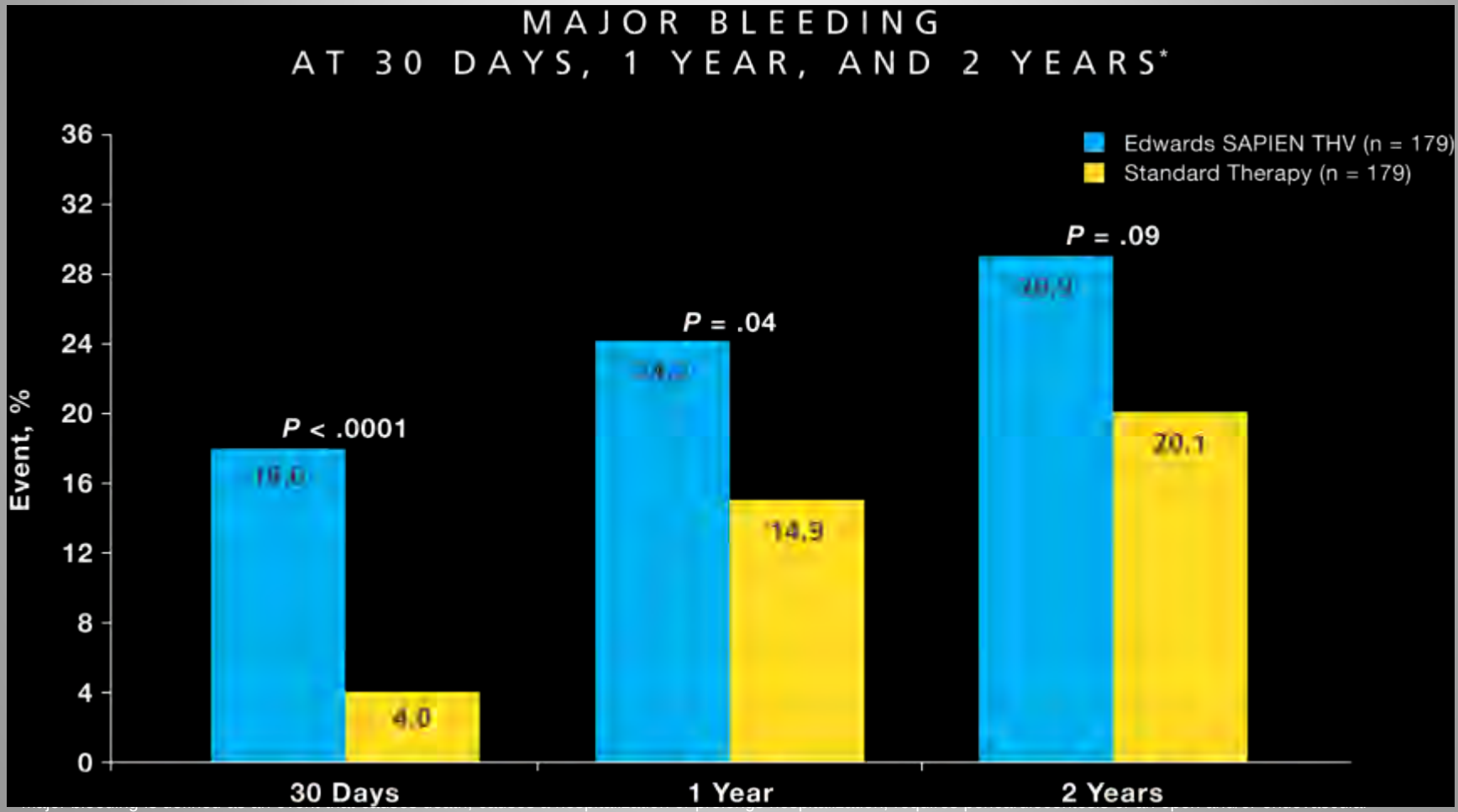
Mortality or Stroke



Higher Incidence of Major Vascular Complications

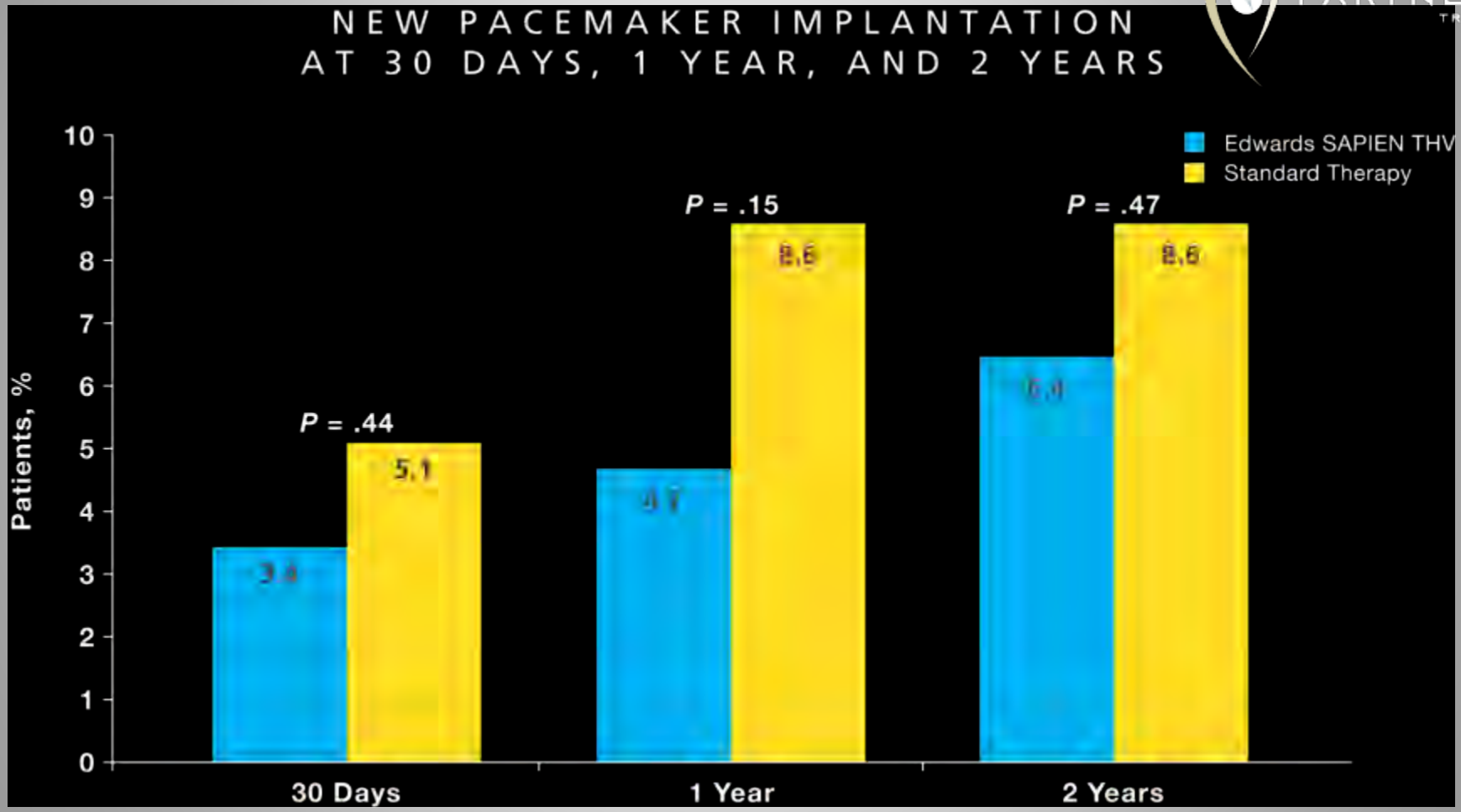


Higher Incidence of Major Bleeding



procedure for repair or hemostasis; causes permanent disability (eg, blindness, paralysis, hearing loss); or requires transfusion of > 3 units of blood within a 24-hour period.

New Pacemaker Implantation



Conclusions

- *At 2 years, in patients with severe symptomatic aortic valve stenosis who were not suitable candidates for surgery*
  - *20% absolute reduction in mortality*
  - *29% absolute reduction in all-cause mortality or repeat hospitalization at 1 year*
  - *75% of SAPIEN patients were NYHA Class I or II*
  - *Need to treat 5 patients to save a life!*

Clinical Implications

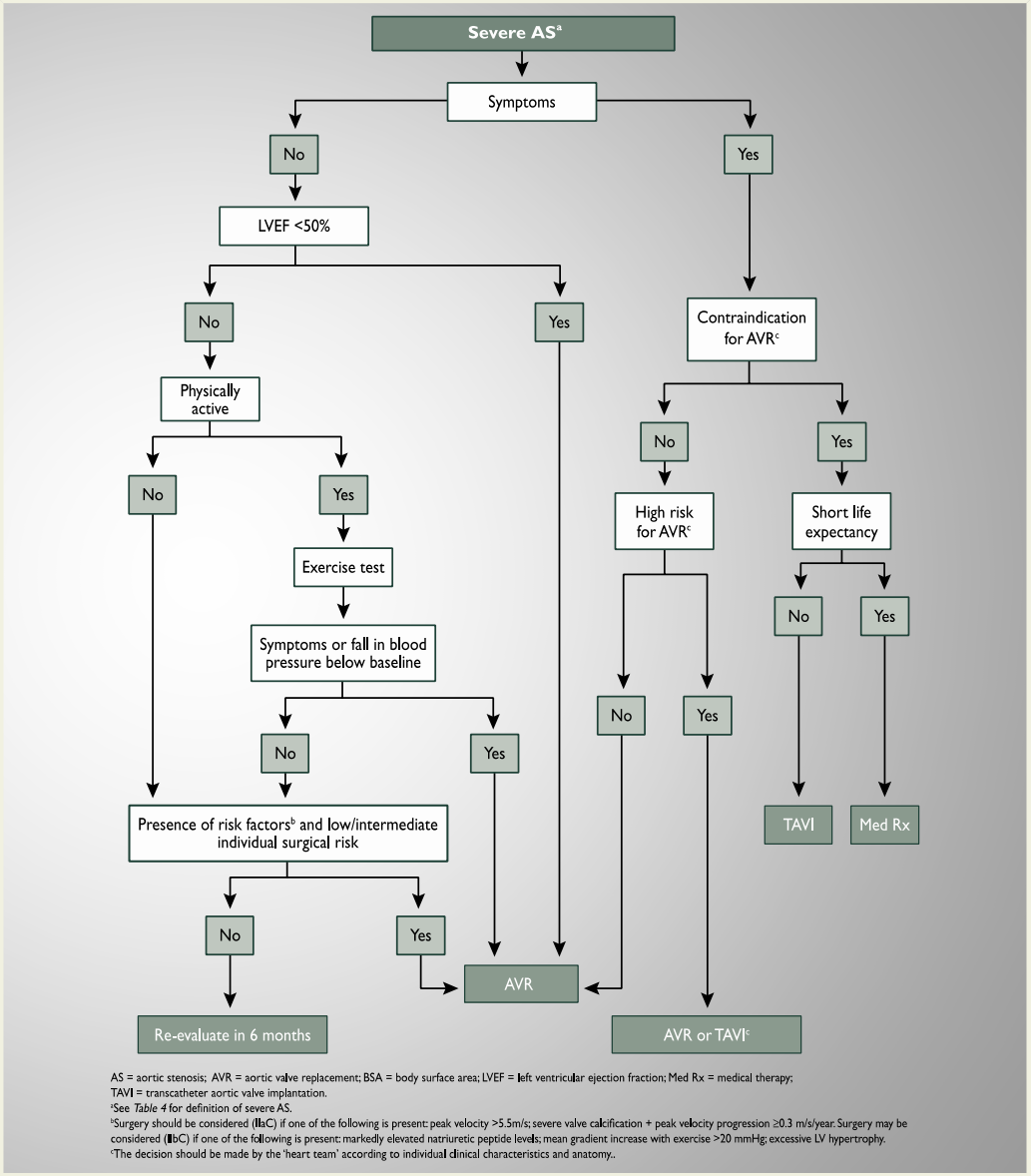
- *Two-year data continued to support the role of treatment with the Edwards SAPIEN THV as the standard of care for patients with severe symptomatic native aortic valve stenosis who are not surgical candidates*
- ***The ultimate value will depend on careful selection of patients, and yet do not have extreme comorbidities that overwhelm the benefits and render the intervention futile***

Where are we today?

Low Risk	Intermediate Risk	High Risk Cohort A	Inoperable Cohort B	Extreme Risk Inoperable with co-morbities
AVR	?AVR vs. TAVR?	AVR or TAVR	TAVR	Medical Treatment And/or Valvuloplasty

Guidelines for the management of valvular heart disease(version 2012)

The Joint Task Force of Valvular Heart Disease of the European Society of Cardiology (ESC) and the European Association for Cardio-Thoracic Surgery (EACTS)



ts with low gradient and low ejection fraction is detailed in the text.

Table 10 Contraindications for transcatheter aortic valve implantation

Absolute contraindications
Absence of a 'heart team' and no cardiac surgery on the site
Appropriateness of TAVI, as an alternative to AVR, not confirmed by a 'heart team'
Clinical
Estimated life expectancy <1 year Improvement of quality of life by TAVI unlikely because of comorbidities Severe primary associated disease of other valves with major contribution to the patient's symptoms, that can be treated only by surgery
Anatomical
Inadequate annulus size (<18 mm, >29 mm[a])
Thrombus in the left ventricle
Active endocarditis
Elevated risk of coronary ostium obstruction (asymmetric valve calcification, short distance between annulus and coronary ostium, small aortic sinuses)
Plaques with mobile thrombi in the ascending aorta, or arch
For transfemoral/subclavian approach: inadequate vascular access (vessel size, calcification, tortuosity)
Relative contraindications
Bicuspid or non-calcified valves
Untreated coronary artery disease requiring revascularization
Haemodynamic instability
LVEF <20%
For transapical approach: severe pulmonary disease, LV apex not accessible

tation.

[a]Contraindication when using the current devices.

well as the technical suitability of TAVI and access issues, should be best able to make decisions in this patient population.[113]

Contraindications, both clinical and anatomical, should be identified (*Table 10*). Eligible patients should have a life expectancy of more than 1 year and should also be likely to gain improvement

5.5 Medical therapy

The progression of degenerative AS is an active process, sharing a number of similarities with atherosclerosis. Although several retrospective reports have shown beneficial effects of statins and ACE

Table 11 Recommendations for the use of transcatheter aortic valve implantation

Recommendations	Class [a]	Level [b]	Ref [c]
TAVI should only be undertaken with a multidisciplinary 'heart team' including cardiologists and cardiac surgeons and other specialists if necessary.	I	C	
TAVI should only be performed in hospitals with cardiac surgery on-site.	I	C	
TAVI is indicated in patients with severe symptomatic AS who are not suitable for AVR as assessed by a 'heart team' and who are likely to gain improvement in their quality of life and to have a life expectancy of more than 1 year after consideration of their comorbidities.	I	B	99
TAVI should be considered in high-risk patients with severe symptomatic AS who may still be suitable for surgery, but in whom TAVI is favoured by a 'heart team' based on the individual risk profile and anatomic suitability.	IIa	B	97

tions.

echocardiography with a focus on haemodynamic progression, LV function and hypertrophy, and the ascending aorta. Type and interval of follow-up should be determined on the basis of the initial examination.

Asymptomatic severe AS should be re-evaluated at least every 6 months for the occurrence of symptoms, change in exercise tolerance (ideally using exercise testing if symptoms are doubtful), and change in echo parameters. Measurement of natriuretic peptides

valve area 1.0–1.5 cm^2)—will, in general, benefit from concomitant AVR. It has also been suggested that if age is <70 years and, more importantly, an average rate of AS progression of 5 mmHg per year is documented, patients may benefit from valve replacement at the time of coronary surgery once the baseline peak gradient exceeds 30 mmHg.[117] Individual judgement is recommended, taking into consideration BSA, haemodynamic data, leaflet calcification, progression rate of AS, patient life expectancy and associated comorbidities, as well as the individual risk of either concomitant valve replacement or late reoperation.

Patients with severe symptomatic AS and diffuse CAD that cannot be revascularized should not be denied AVR, even though this is a high-risk group.

A few studies have recommended the potential use of percutaneous coronary intervention in place of CABG in patients with AS. However, currently the available data are not sufficient to recommend this approach, apart from selected high-risk patients with acute coronary syndromes or in patients with non-severe AS.

Combined percutaneous coronary intervention and TAVI have been shown to be feasible, but require more data before a firm recommendation can be made. The question of whether to proceed, as well as the chronology of interventions, should be the subject of individualized discussion, based on the patient's clinical condition, coronary anatomy, and myocardium at risk.

When MR is associated with severe AS, its severity may be overestimated in the presence of the high ventricular pressures and careful quantification is required (see *General comments*, Section 3). As long as there are no morphological leaflet abnormalities (flail or prolapse, post-rheumatic changes, or signs of infective endocarditis), mitral annulus dilatation or marked abnormalities of LV geometry, surgical intervention on the mitral valve is in general not necessary and non-severe secondary MR usually improves after the aortic valve is treated.

Concomitant aneurysm/dilatation of the ascending aorta requires the same treatment as in AR (see Section 4).

For congenital AS, see the ESC Guidelines on grown-up congenital heart disease.[11]

6. Mitral regurgitation

In Europe, MR is the second most frequent valve disease requiring surgery.[1] Treatment has been redefined as a result of the good

Patient Selection is KEY!

- High risk surgical patients?
- Inoperable patients
- Minimize independent risk factors

	Hazard Ratio	P value
Hemodynamic support during TAVR	3.77	0.001
Creatinine >2mg/dl	1.06	0.039
Diabetes Mellitus	0.54	0.006
Prior Liver Disease	4.11	0.001
Total Mini Mental State Exam Score	0.94	0.022
Prior Renal Disease	1.60	0.041
STS Risk Score	1.08	0.001

Predictors of futility with transcutaneous aortic valve replacement therapy (TAVR): An analysis from the PARTNER randomized trial. *J Am Coll Cardiol.* 2012; 60(17_S).

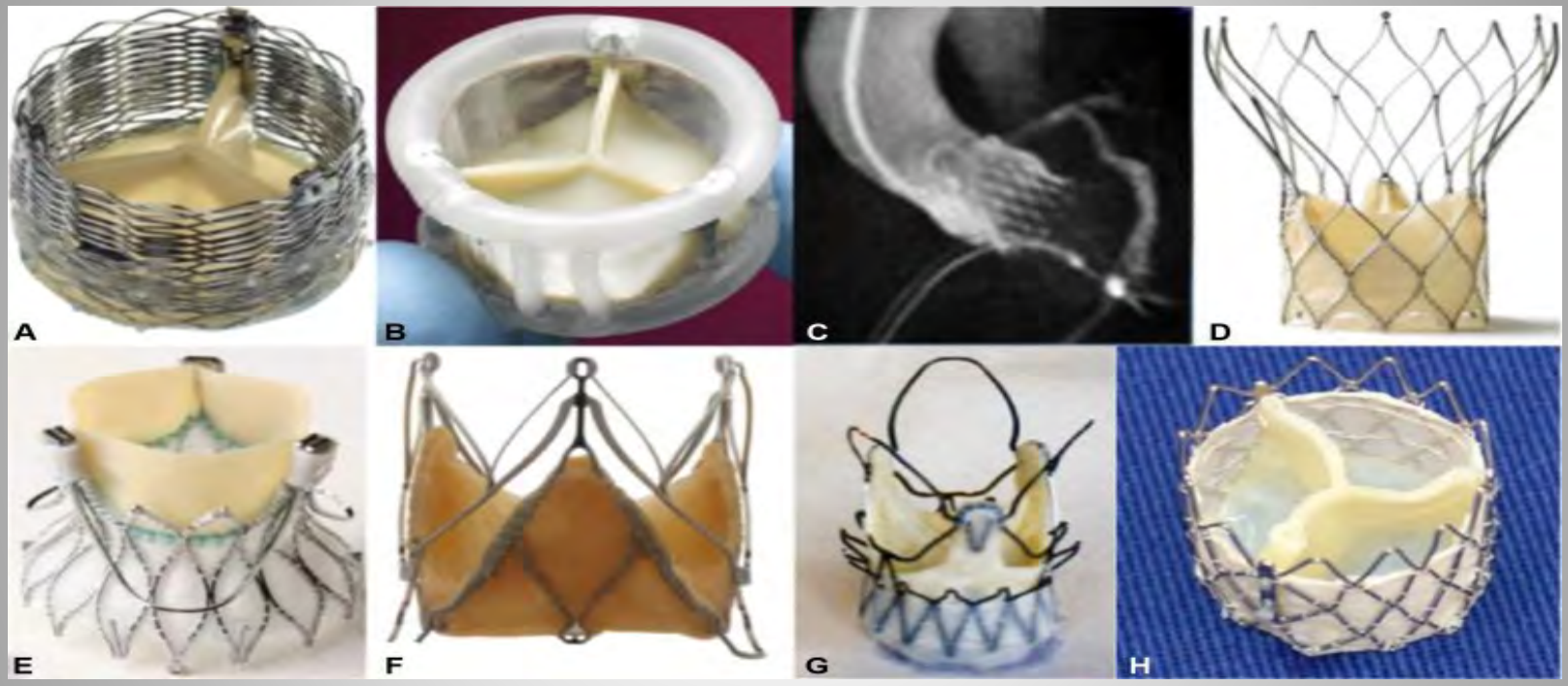
Where are we today?

- Commercial use for high risk or inoperable aortic valve disease
  - Sapien valve 23 mm, 26 mm
- Continuing PARTNER 2 and SURTAVI enrollment
  - PARTNER 2 – Edwards Sapien XT in intermediate surgical risk patients
  - SURTAVI – Medtronic CoreValve in intermediate surgical risk patients

For the future…

- Alternative access sites
- Smaller sheath sizes
- New valves
  - Sapien XT - 23 mm, 26 mm, 29 mm through 18F
  - Sapien 3 – 20 mm, 23 mm, 26 mm through 14F TF and 16F TA; 29 mm; external sealing

Valves of the future



Mitral Valve Disease

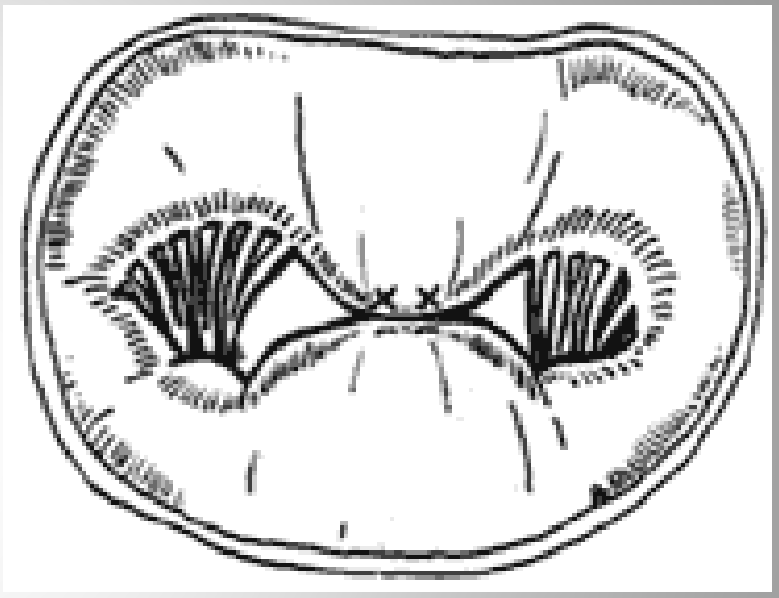
- Approximately 4 million people have significant mitral valve insufficiency
- Approximately 50,000 of these patients undergo surgery each year in the United States (20% of affected patients)
  - Repair is preferred over replacement
  - Surgery risk
- Another 200,000 remain affected by MR

MitraClip Mitral Valve Repair System

- Developed and manufacted by Evalve, Inc.
- Catheter-based therapy intended to reduce mitral regurgitation (MR)
- 3,000 commercial performed; 1,500 study patients in U.S.
- Less-invasive mitral valve repair/percutaneous
- Venous access
- Removable

- The system consists of three major subsystems:
  - A Steerable Guide Catheter
  - A Clip Delivery System
  - The MitraClip device (implant)

Double-Orifice Technique



- Alfieri stich
  - pioneered in Italy by
    Dr. Ottavio Alfieri
  - 1990's – increasing used
    in MR treatment and repair
- Involves suturing together the two leaflets of the mitral valve. The valve continues to open on both sides of the suture, allowing blood flow through the valve from the left atrium to left ventricle, while assuring proper valve closure
- Mitral Clip based upon this technique

EVEREST II (Endovascular Valve Edge-to-Edge Repair Study)

EVEREST II (Endovascular Valve Edge-to-Edge Repair Study)

T Feldman (Evanston Hospital, Evanston, IL)
American College of Cardiology 2010 Scientific Sessions/i2 Summit

- The first randomized trial to compare outcomes with MitraClip vs surgery
- Population and treatment:

  279 patients with significant mitral regurgitation (3+ to 4+); patients had to be symptomatic or have documented LV dysfunction

  Randomized 2:1 to the MitraClip procedure or to surgical repair or replacement at the surgeon's discretion
- Outcomes:

  Primary efficacy end point: major adverse events at 30 days (to show superiority) and clinical success rate[a]

  Primary safety end point: wide-ranging combination of adverse events including death, major stroke, reoperation, urgent/emergent surgery, MI, renal failure, and blood transfusions, among others

a. Freedom from a combination of death, mitral-valve surgery or reoperation for mitral-valve dysfunction, and an improvement of at least two grades of mitral regurgitation at 12 months (designed to demonstrate noninferiority of the clip device)

EVEREST II: Primary endpoints

Per protocol cohort

dysfunction,
MR≥2+ at 12 months

NorthShore University HealthSystem
Evanston Hospital

EVEREST II: Primary safety endpoint

Per protocol cohort

30 Day MAE, non-hierarchical	# Patients experiencing event Device Group (n=136)	 Control Group (n=79)
Death	0	2 (2.5%)
Major Stroke	0	2 (2.5%)
Re-operation of Mitral Valve	0	1 (1.3%)
Urgent / Emergent CV Surgery	0	4 (5.1%)
Myocardial Infarction	0	0
Renal Failure	0	0
Deep Wound Infection	0	0
Ventilation >48 hrs	0	4 (5.1%)
New Onset Permanent Atrial Fib	0	0
Septicemia	0	0
GI Complication Requiring Surgery	1 (0.7%)	0
All Transfusions ≥2 units*	12 (8.8%)	42 (53.2%)
TOTAL % of Patients with MAE	**9.6%**	**57.0%**
	p<0.0001*	
	(95% CI 34.4%, 60.4%)	

*p<0.0001 if include Major Bleeding only

EVEREST II: Results

- The primary safety end point (per-protocol analysis) significantly favored the percutaneous procedure at 30 days—need for blood transfusions was the main driver (8.8% vs 53.2%)
- The overall clinical success rate was numerically higher in the surgery group for the primary efficacy end point (per-protocol analysis)—87.8% vs 72.4%—but this difference met the prespecified noninferiority hypothesis of 31%

Safety and efficacy end points at 30 days

End point	Clip (%)	Surgery (%)
Safety, per protocol	9.6	57.0
Efficacy, per protocol	72.4	87.8
Safety, intention to treat	15	47.9
Efficacy, intention to treat	66.9	74.2

All between-group differences statistically significant

EVEREST II: summary

- Safety & effectiveness endpoints met
  - Safety: MAE rate at 30 days
    - MitraClip device patients: 9.6%
    - MV surgery patients: 57%
  - Effectiveness: Clinical Success Rate at 12 months
    - MitraClip device patients: 72%
    - MV Surgery patients: 88%
- Clinical benefit demonstrated for MitraClip System and MV surgery patients through 12 months
  - Improved LV function
  - Improved NYHA Functional Class
  - Improved Quality of Life
- Surgery remains an option after the MitraClip procedure

Patient Selection

- Important!
- High risk surgical patients
- Functional MR patients
- Selected low risk degenerative MR patients
- No rheumatic valve disease patients