PROVIDENCE
Health & Services
Southern California

# TAVR: What We've Learned Over the Years

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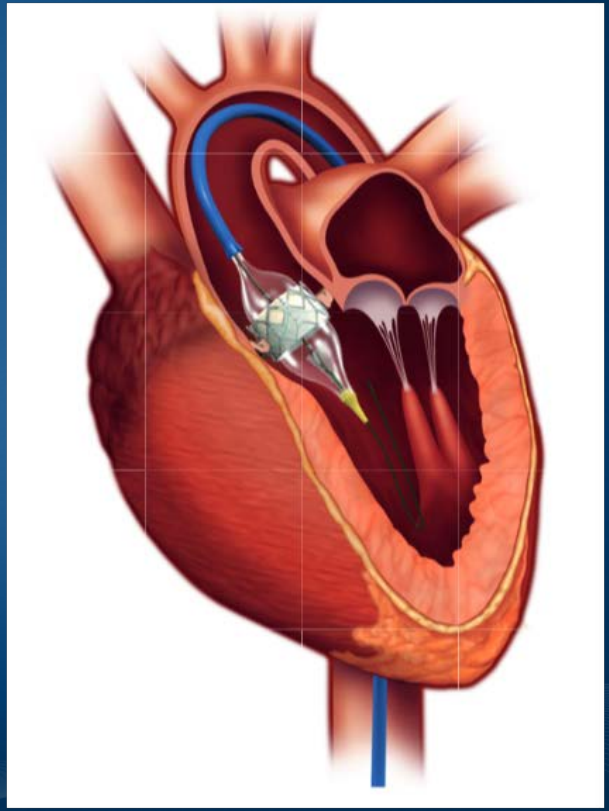
*Division of Cardiology*
*Providence Little Company of Mary*
*South Bay Heart and Vascular Center*

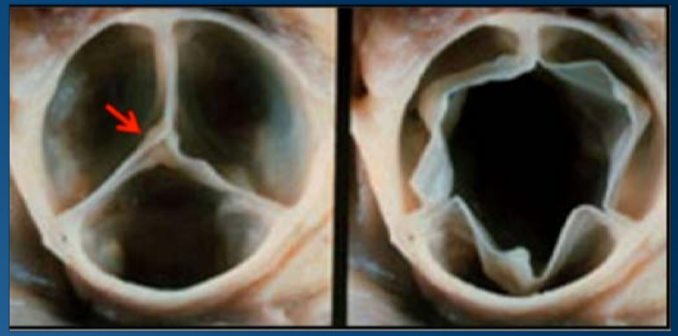



© Curtis D. Tucker 2002
CURTIS DEAN
"Yes! That was very loud Sir, but I said I wanted to hear your *HEART!*"

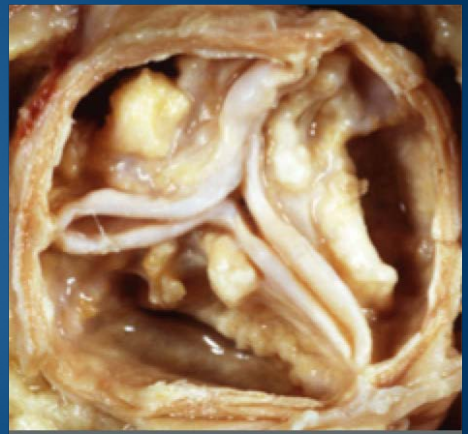
# Overview

- What is Aortic Stenosis and how does it present?
- Treatment options
- History of TAVR
- Brief overview of TAVR landmark studies
- Types of commercially available valves
- TAVR workup, procedure, and post-procedural care
- Cases

# Aortic Stenosis



- 3.4% of population ≥75yo affected with severe aortic stenosis (>570K people in US)[1]
- Prevalence increases with age
- The elderly population will more than double between now and 2050, to 80 million[2]
- Chronic, progressive disease process that is fatal if untreated
  - AVA decreases on average by 0.1cm$^2$/year



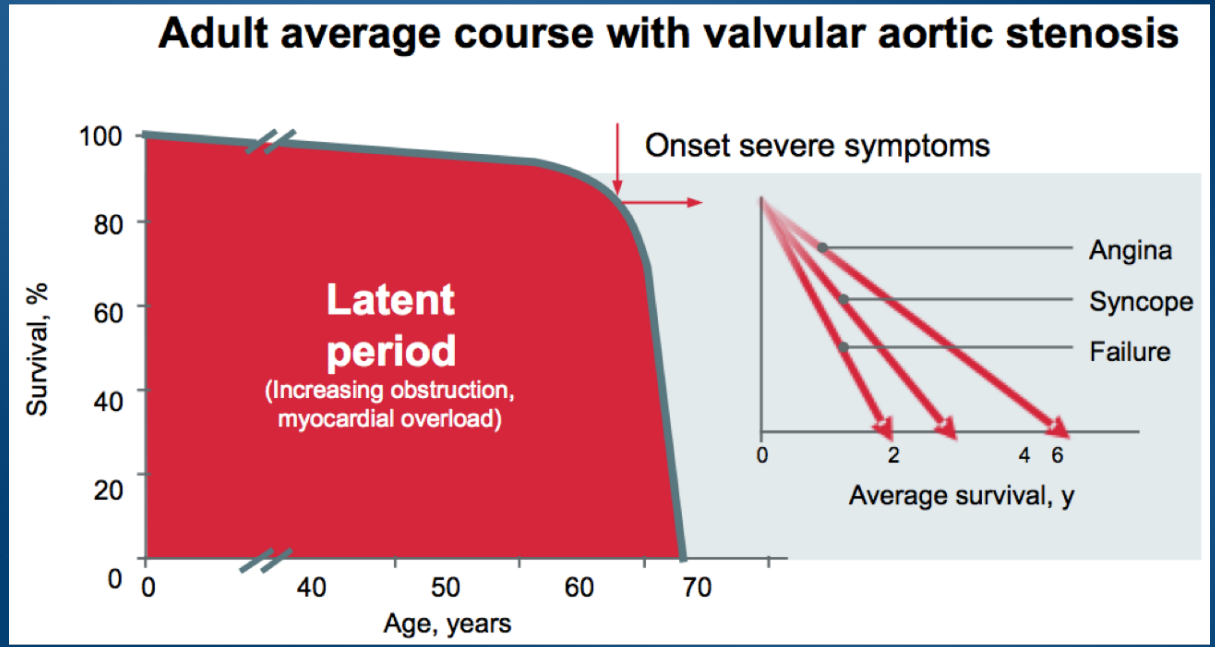
Age-related calcific aortic stenosis

[1]Osnabrugge, et al. Aortic Stenosis in the Elderly. JACC, 2013
[2]US Census Bureau Statistical Brief. May 1995.

# Symptoms

- Angina
- CHF (dyspnea, SOB, peripheral edema, orthopnea, reduced exercise tolerance)
- Presyncope or syncope
- Symptoms commonly misunderstood by patients to be “normal” signs of aging
- Up to 37% of “Asymptomatic” patients can demonstrate symptoms on closer examination
- Up to 29% of patients previously considered asymptomatic can demonstrate symptoms on a supervised exercise treadmill stress test

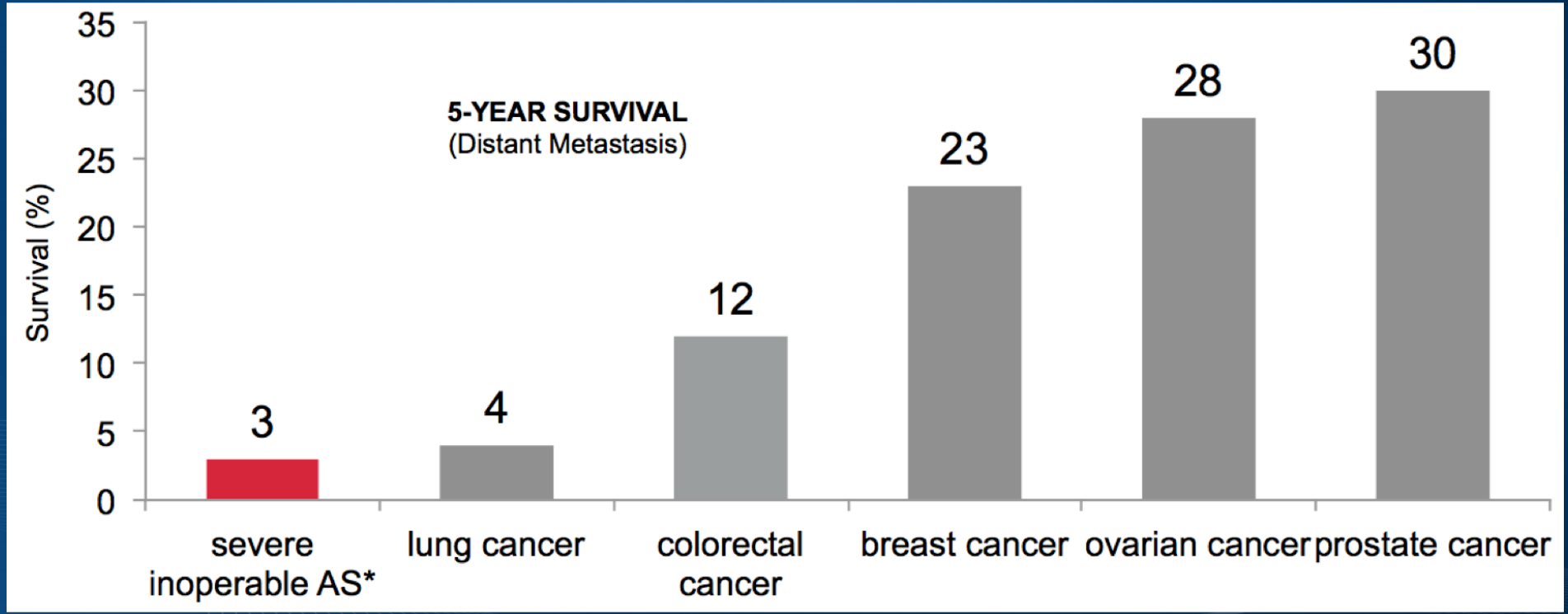
# Treatment for Severe AS is Critical




After the onset of symptoms, 50% survival at 2 years and 20% survival at 5 years without AVR

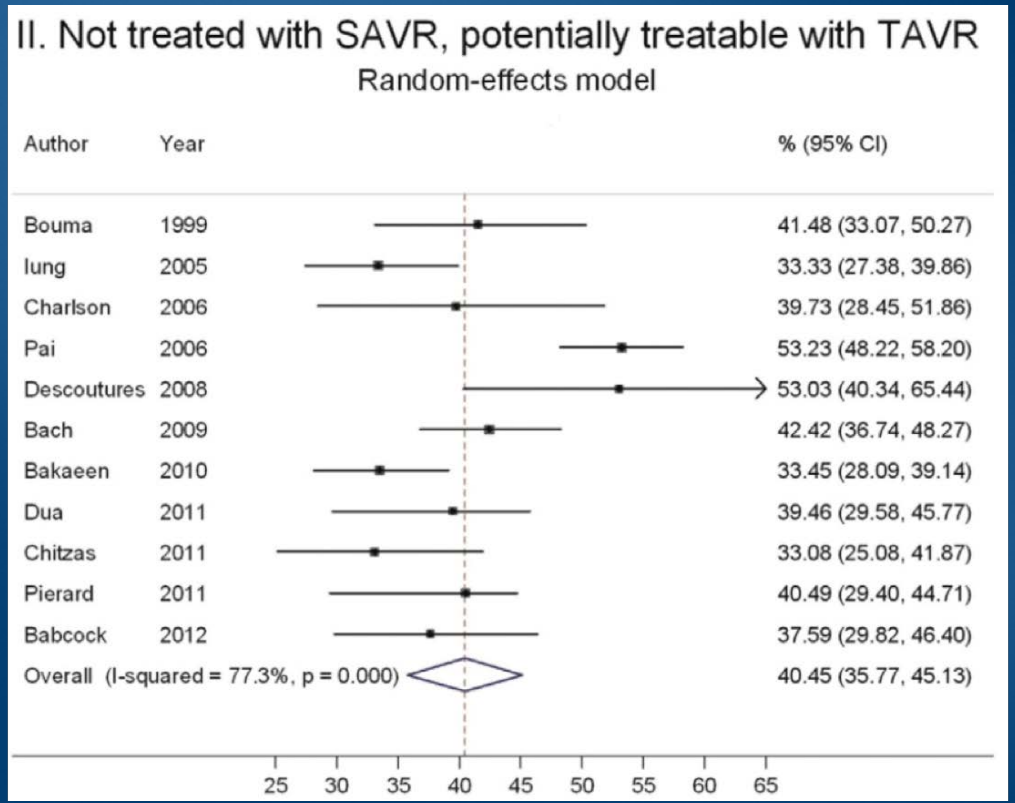
Otto, et al. Timing of aortic valve surgery. Heart, 2000.

# Severe AS Has a Worse Prognosis Than Many Metastatic Cancers




*Using constant hazard ratio. Data on file, Edwards Lifesciences LLC. Analysis courtesy of Murat Tuczu, MD, Cleveland Clinic.

# Prohibitive Risk for Surgical AVR




40.5% of patients with severe symptomatic AS did not undergo SAVR

- Operative risk
- Advanced age
- Comorbidities
- Patient preference

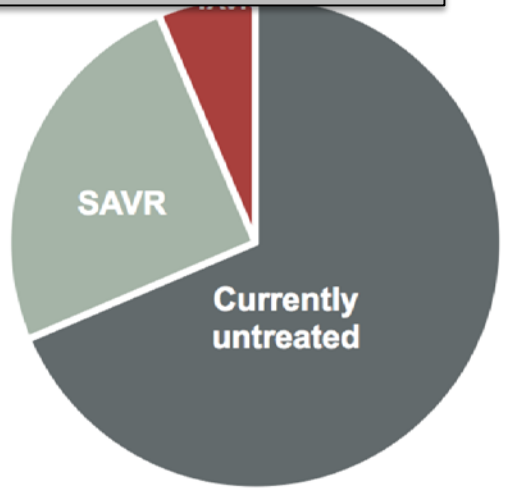
[1]Osnabrugge, et al. Aortic Stenosis in the Elderly. JACC, 2013

# Large Number of US Patients with Severe AS Remain Undertreated

Underdiagnosed due to lack of symptoms/exam findings

Non-referrals

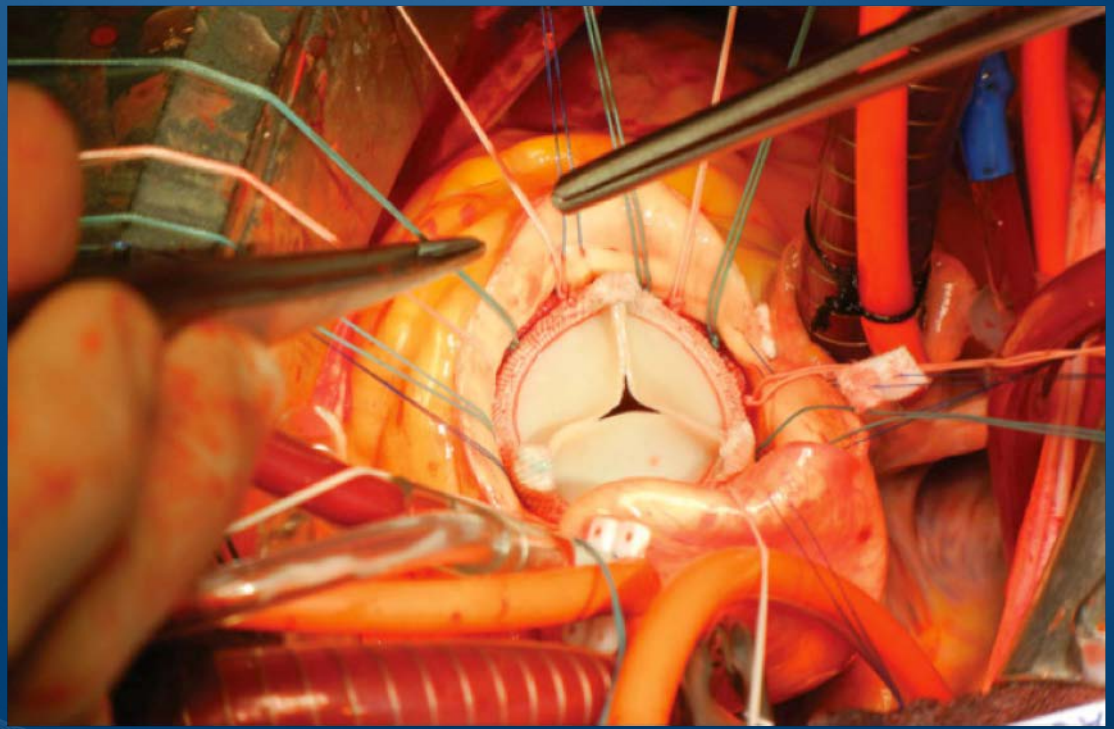
Prohibitive or High Risk for SAVR



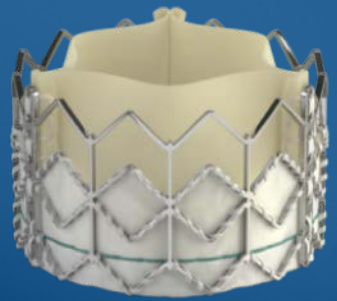

**U.S. severe, symptomatic AS[2]**
(~280,000 patients)

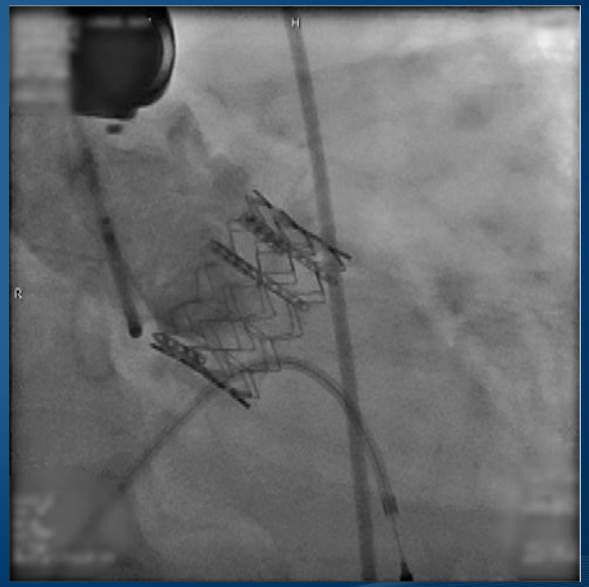
1. Nkomo 2006, Iivanainen 1996, Aronow 1991, Bach 2007, 2014 internal estimates
2. Freed 2010, Iung 2007, Pellikka 2005; 2014 internal estimates

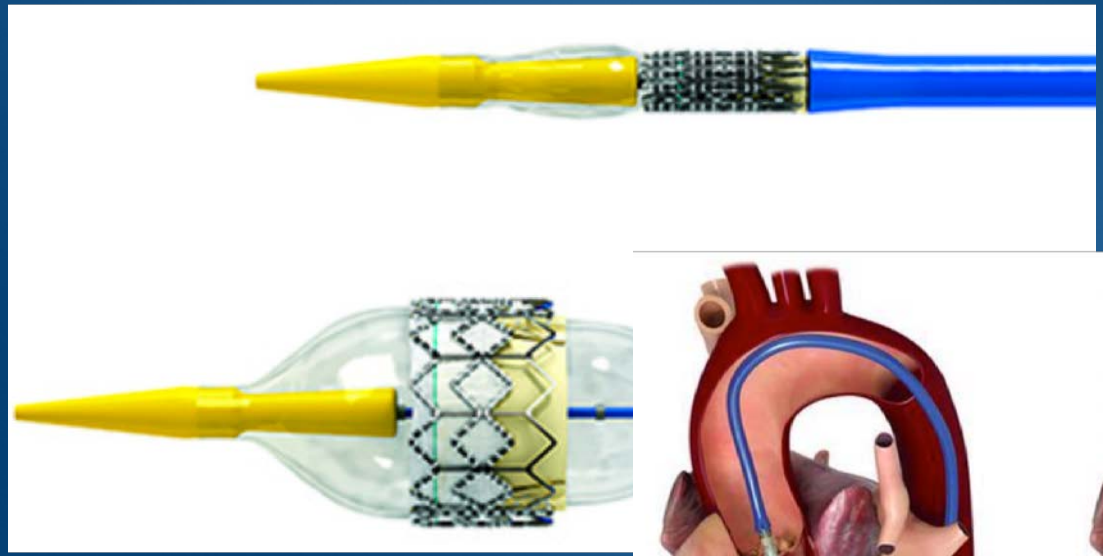
# Surgical Aortic Valve Replacement

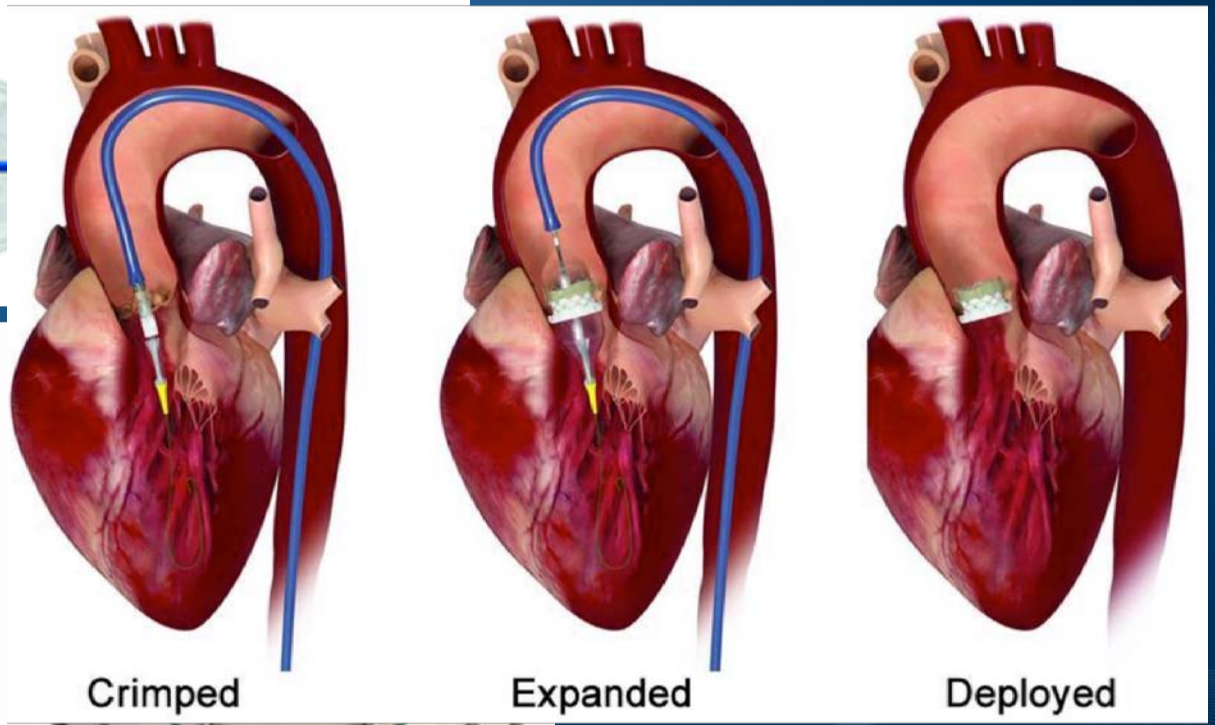


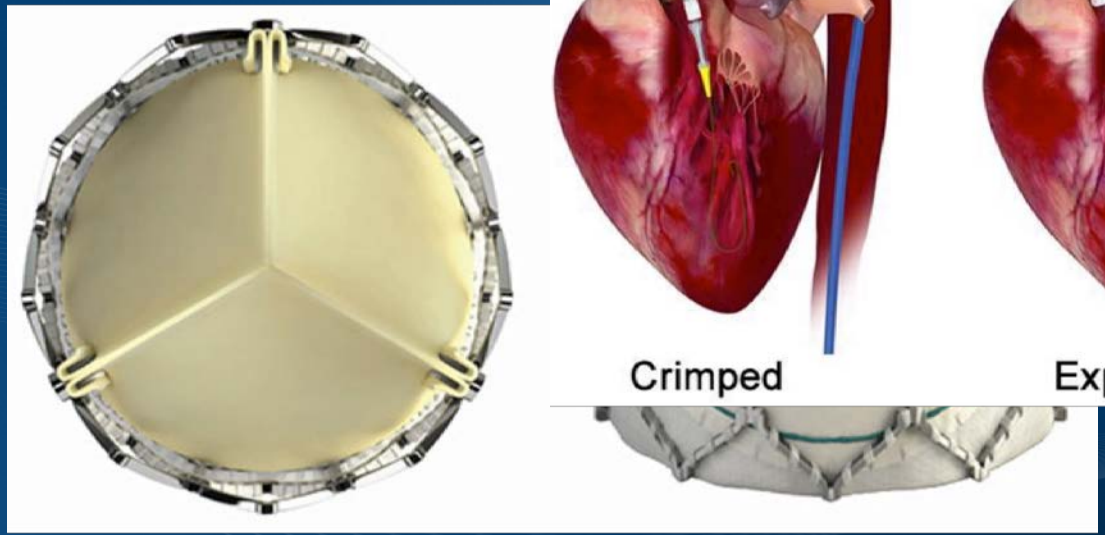
# "[TAVR] IS A REVOLUTIONARY TECHNOLOGY THAT MEETS AN UNFULFILLED CLINICAL NEED FOR A COMMON DISEASE…" DR. ALAIN CRIBIER





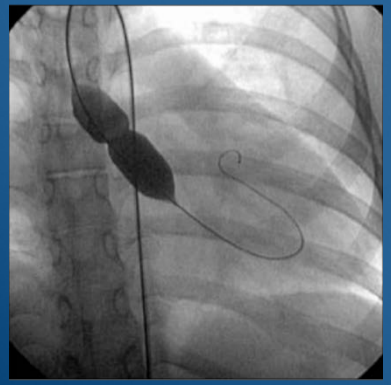



Crimped
Expanded
Deployed



# The Evolution of TAVR

- Treatment for large population of inoperable aortic stenosis patients
- 1985: PABV



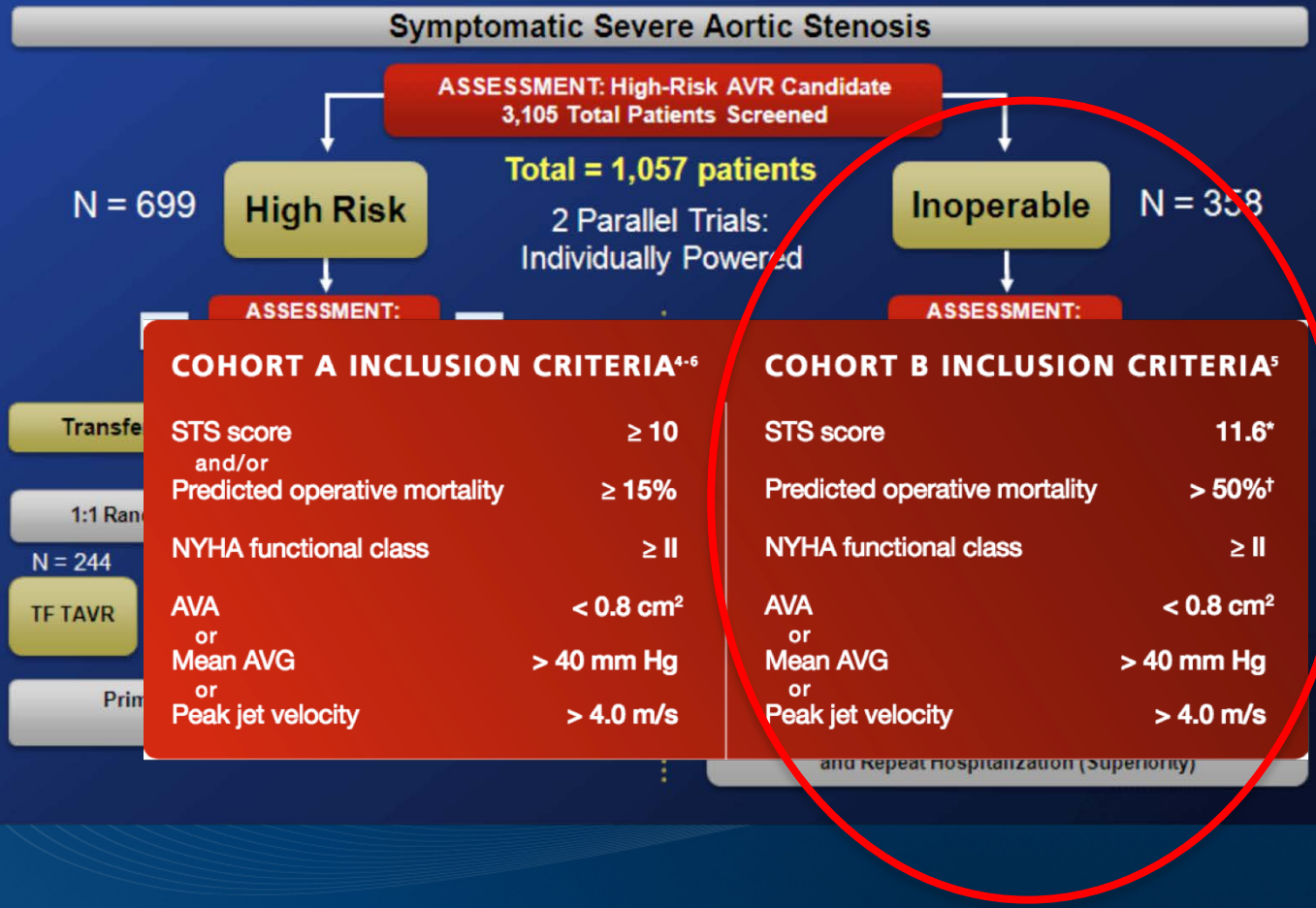
Fell out of favor in late 1980s due to high restenosis rate

- Concept of TAVR emerged in 1990s from observation that high-pressure balloon inflation (4-5atm) could open all calcified valves in a circular fashion
  - Balloon-expandable stent (Palmaz) with valvular structure within stent
  - 1995-1999: Search for biomedical company… “the most stupid idea we’ve ever heard”
- 1999: Created own startup, engineers designed first transcatheter heart valve
- 2000: First implant in beating native heart (sheep)

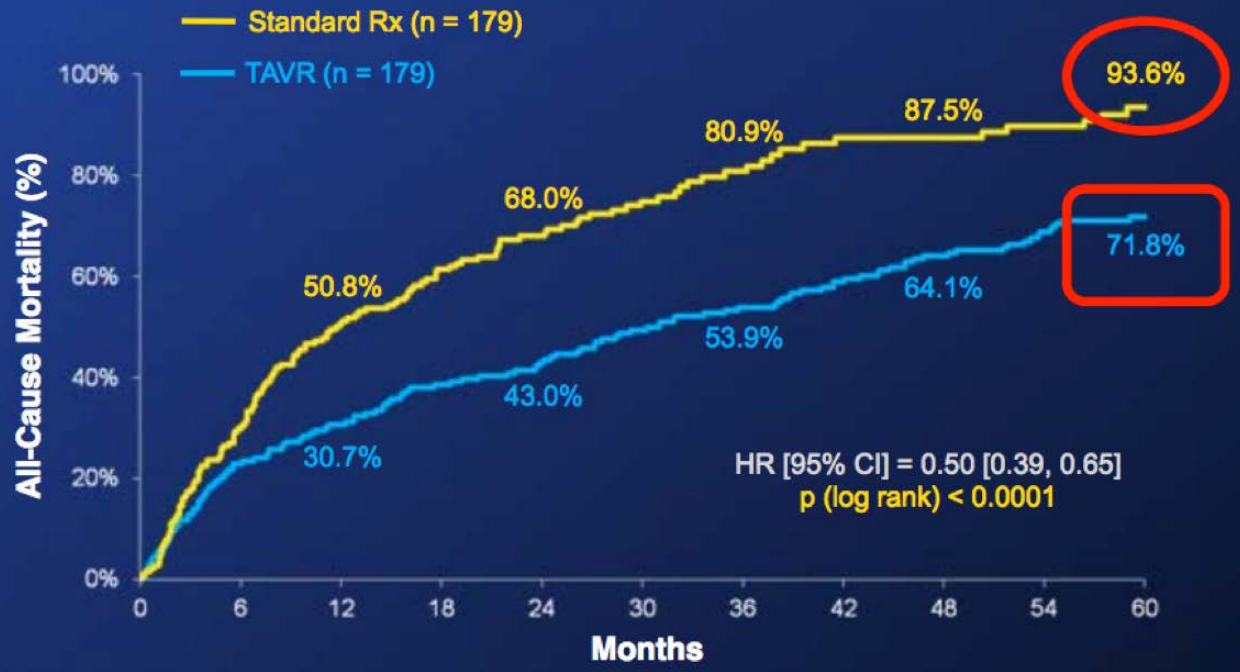
# The Evolution of TAVR

- April 2002: First implant in human
- 2004-2006: Feasibility studies
  - Antegrade delivery via transseptal approach
- 2004: Edwards acquisition
  - Further refinement of THV, delivery techniques, available sizes
- 2007: CE mark approval
- 2010: Landmark PARTNER clinical trial begins in US

# PARTNER Study Design



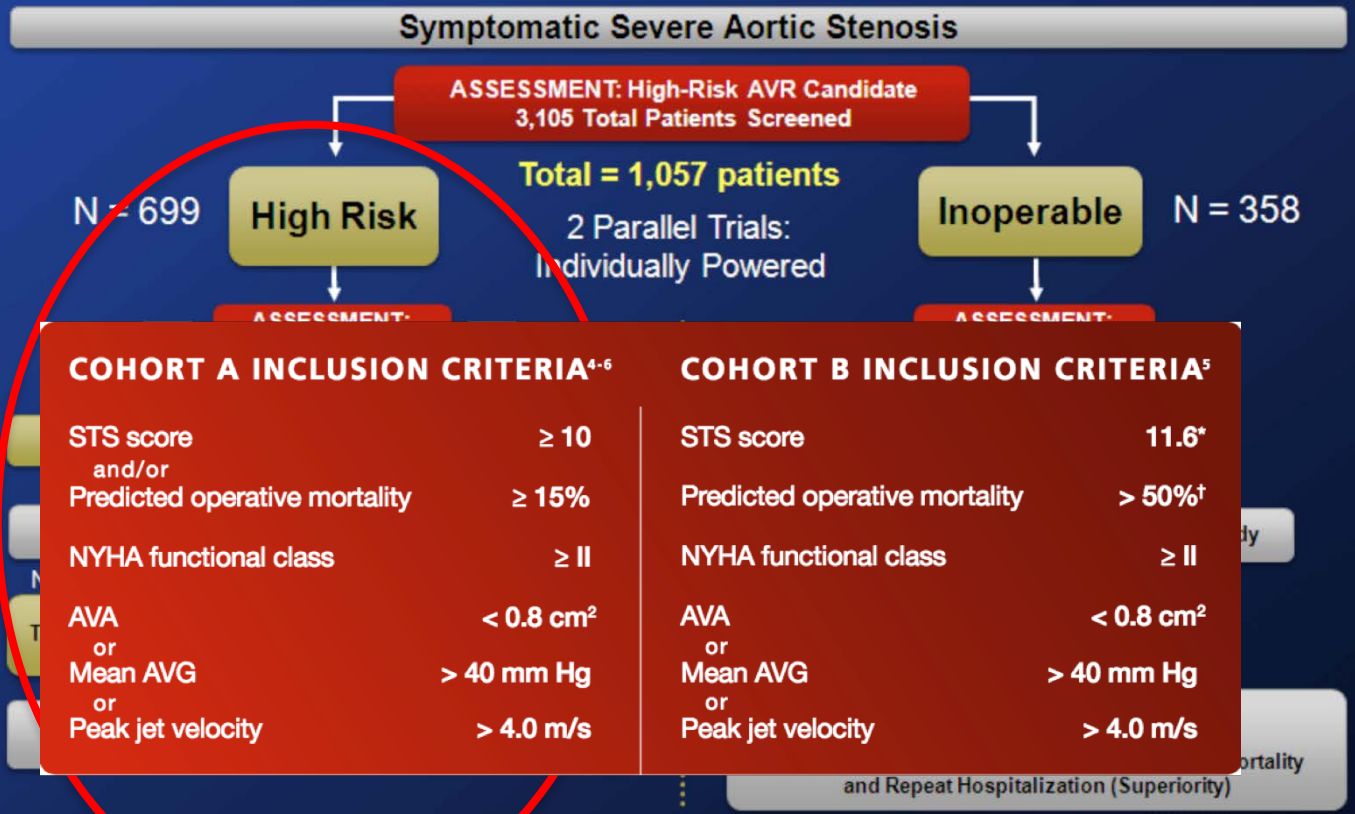
# PARTNER 1B – Inoperable All-Cause Mortality (ITT)




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

***Led to FDA approval of TAVR in 2011 for inoperable patients***

# PARTNER Study Design

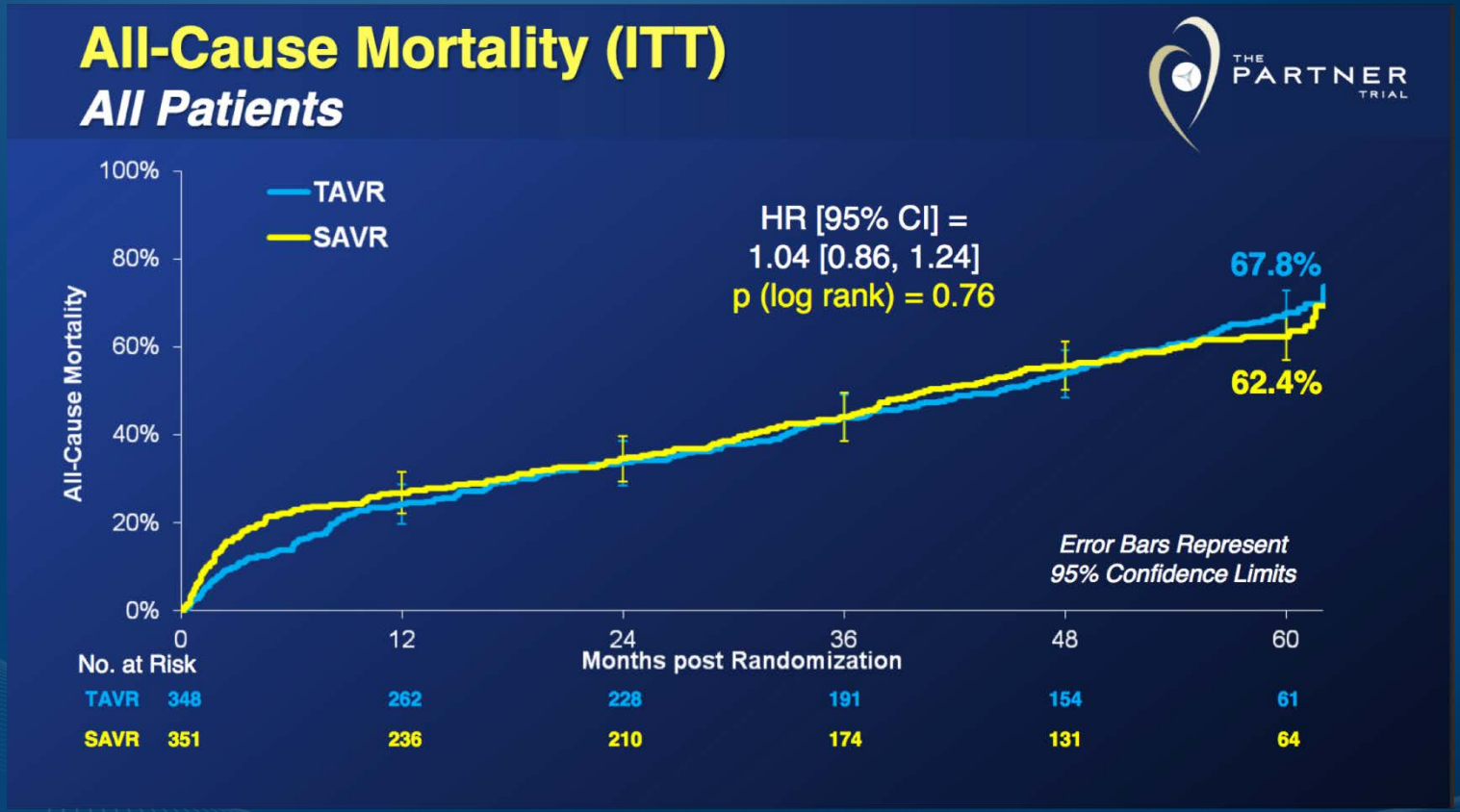


| Outcome | 30 Days[4] Edwards SAPIEN THV (n = 348) | 30 Days[4] AVR (n = 351) | 30 Days[4] *P* Value | 1 Year[4] Edwards SAPIEN THV (n = 348) | 1 Year[4] AVR (n = 358) | 1 Year[4] *P* Value |
|---|---|---|---|---|---|---|
| All-Cause Mortality | 3.4% | 6.5% | .07 | 24.2% | 26.8% | .44 |
| All Stroke 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 |

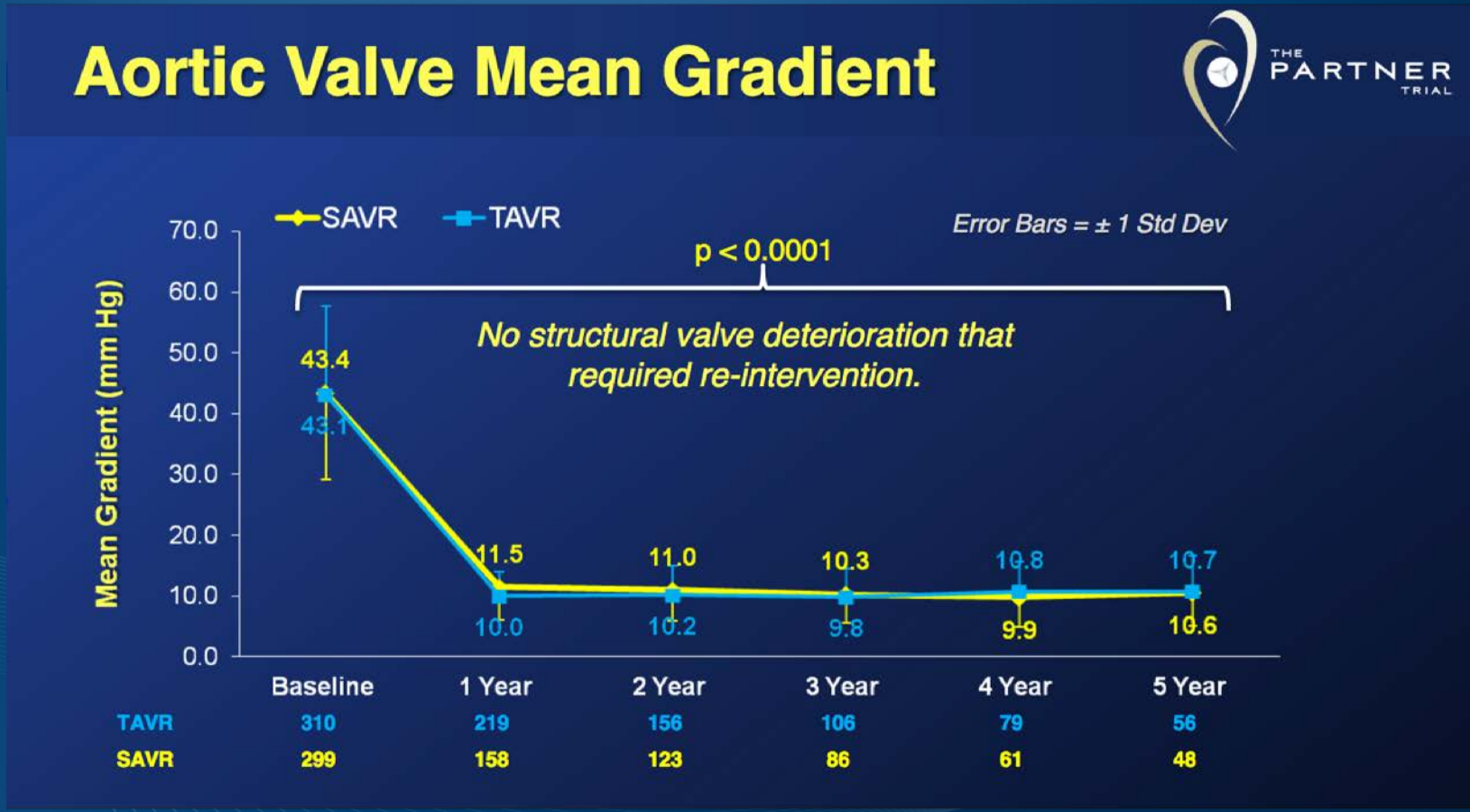
- TAVR noninferior to SAVR at 1 and 5-years for all-cause mortality

***Led to FDA approval of TAVR for high-risk patients in 2014***

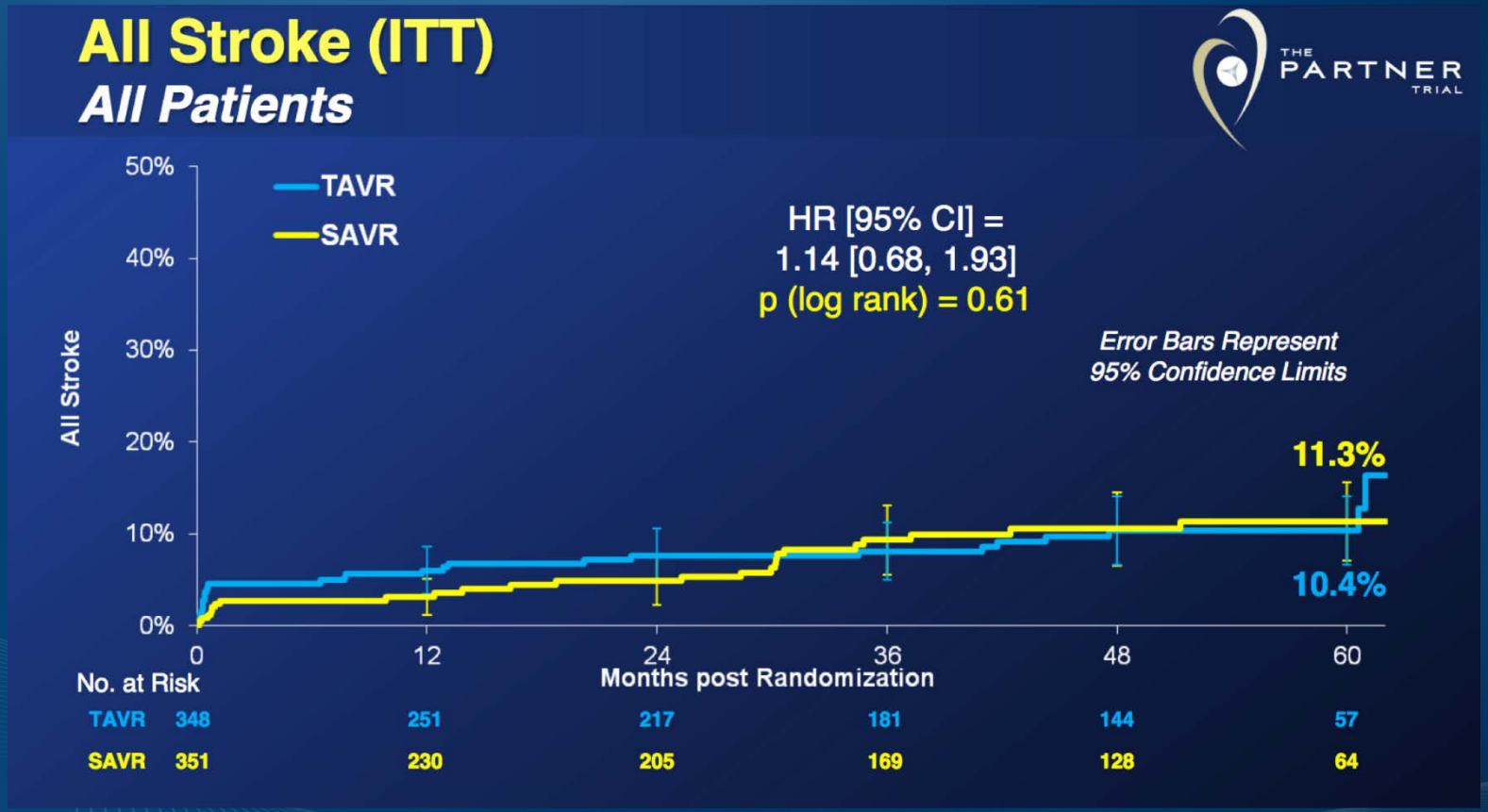
# PARTNER 1A


All-Cause Mortality (ITT)
All Patients
THE PARTNER TRIAL
TAVR
SAVR
HR [95% CI] =
1.04 [0.86, 1.24]
p (log rank) = 0.76
67.8%
62.4%
All-Cause Mortality
100%
80%
60%
40%
20%
0%
Error Bars Represent
95% Confidence Limits
0
12
24
36
48
60
Months post Randomization
No. at Risk
TAVR 348 262 228 191 154 61
SAVR 351 236 210 174 131 64

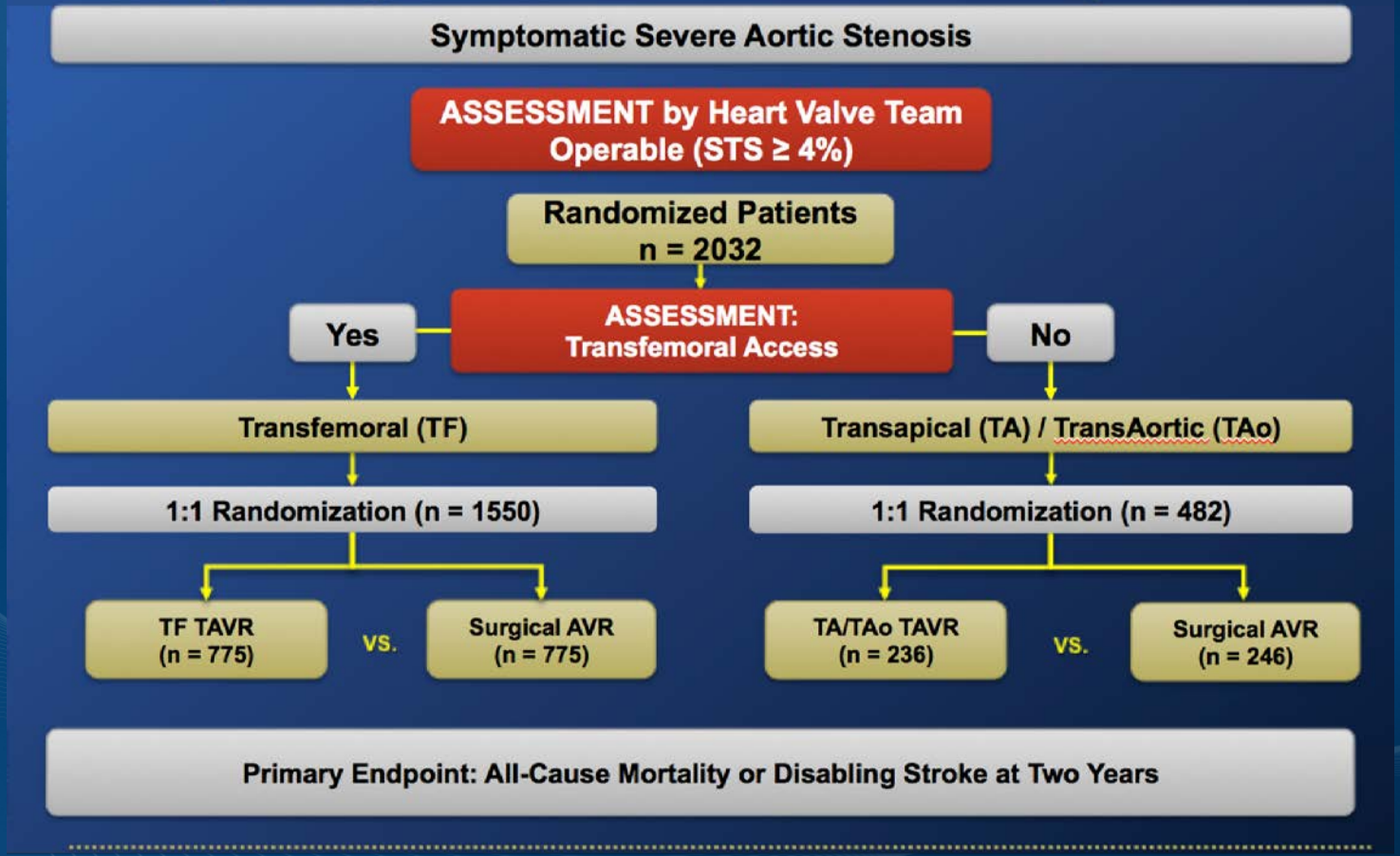
# PARTNER 1A


Aortic Valve Mean Gradient
THE PARTNER TRIAL
SAVR
TAVR
Error Bars = ± 1 Std Dev
p < 0.0001
No structural valve deterioration that required re-intervention.
Mean Gradient (mm Hg)
70.0
60.0
50.0
40.0
30.0
20.0
10.0
0.0
43.4
43.1
11.5
10.0
11.0
10.2
10.3
9.8
10.8
9.9
10.7
10.6
Baseline
1 Year
2 Year
3 Year
4 Year
5 Year
TAVR 310 219 156 106 79 56
SAVR 299 158 123 86 61 48

# PARTNER 1A

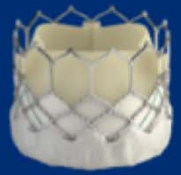

All Stroke (ITT)
All Patients
THE PARTNER TRIAL
TAVR
SAVR
HR [95% CI] =
1.14 [0.68, 1.93]
p (log rank) = 0.61
Error Bars Represent
95% Confidence Limits
All Stroke
50%
40%
30%
20%
10%
0%
11.3%
10.4%
0
12
24
36
48
60
Months post Randomization
No. at Risk
TAVR 348 251 217 181 144 57
SAVR 351 230 205 169 128 64

# The PARTNER 2A Trial
## Study Design



# PARTNER SAPIEN Platforms
## Device Evolution

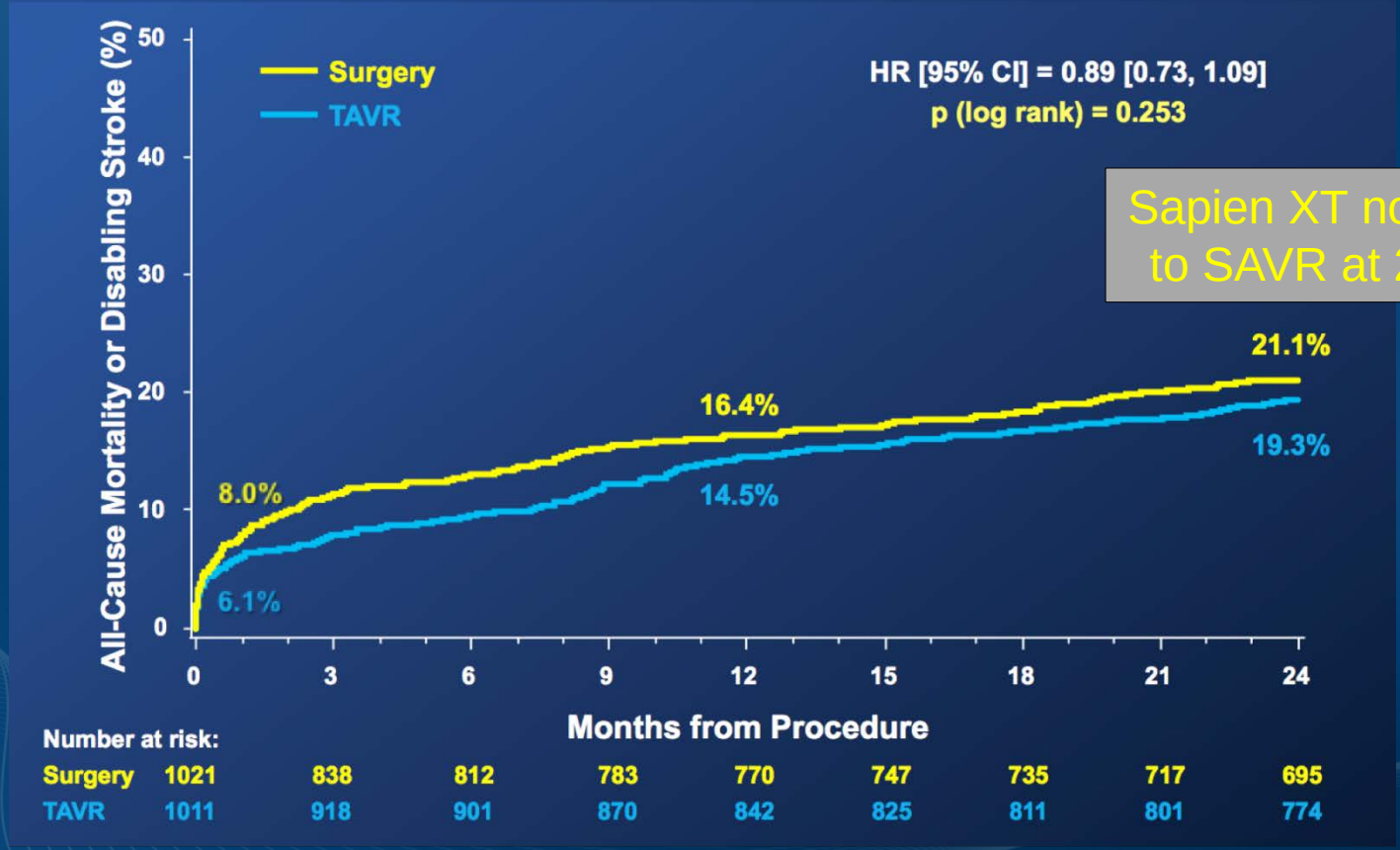
THE PARTNER II TRIAL

| | SAPIEN | SAPIEN XT | SAPIEN 3 |
|---|---|---|---|
| Valve Technology |  |  |  |
| Sheath Compatibility |  22-24F |  16-20F |  14-16F |
| Available Valve Sizes |  23 mm, 26 mm |  23mm, 26mm, 29mm* |  20 mm, 23 mm, 26 mm, 29 mm |

*First Implant Oct 30, 2012

# Primary Endpoint (ITT)
## All-Cause Mortality or Disabling Stroke

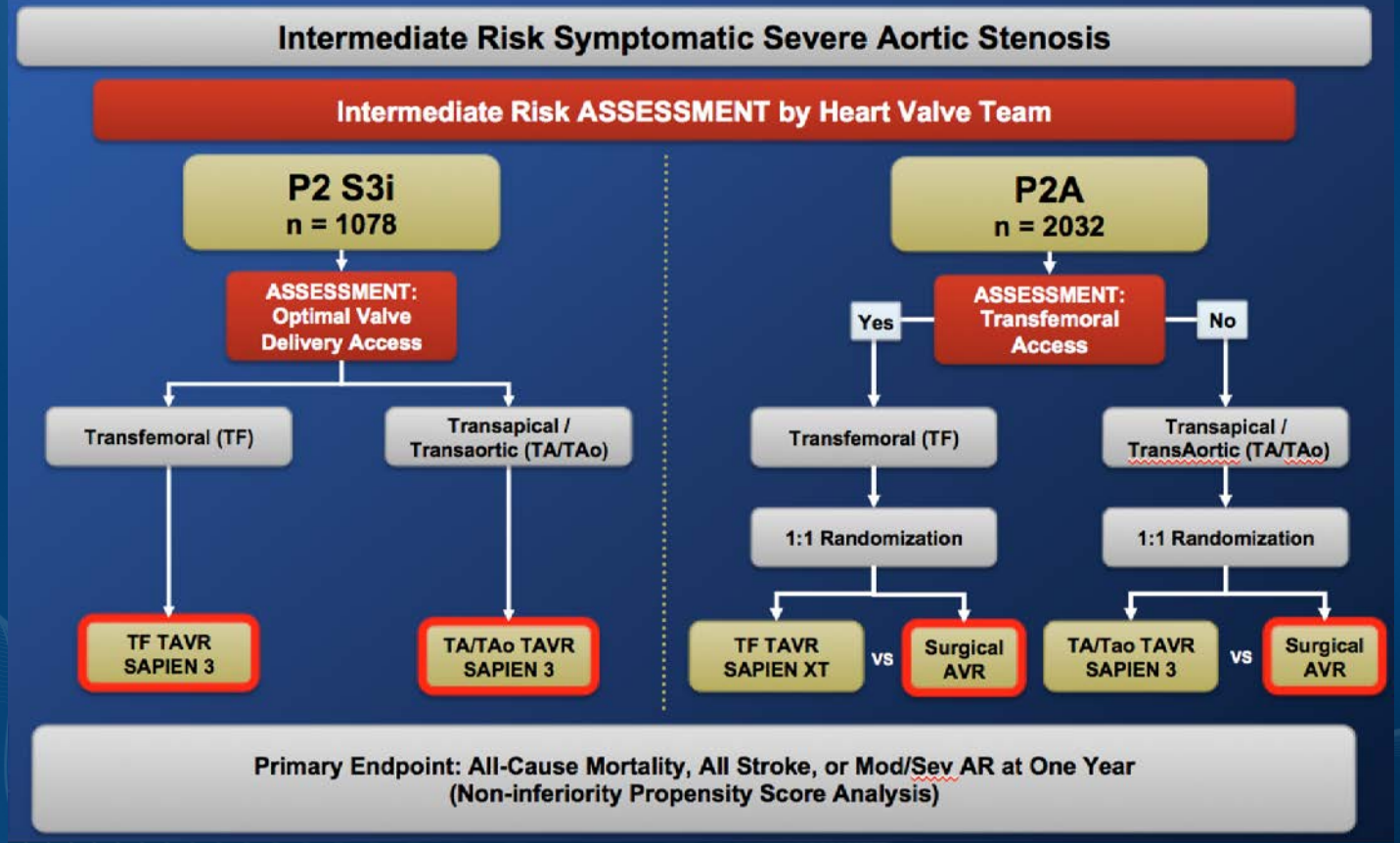
THE PARTNER II TRIAL




Sapien XT noninferior to SAVR at 2 years

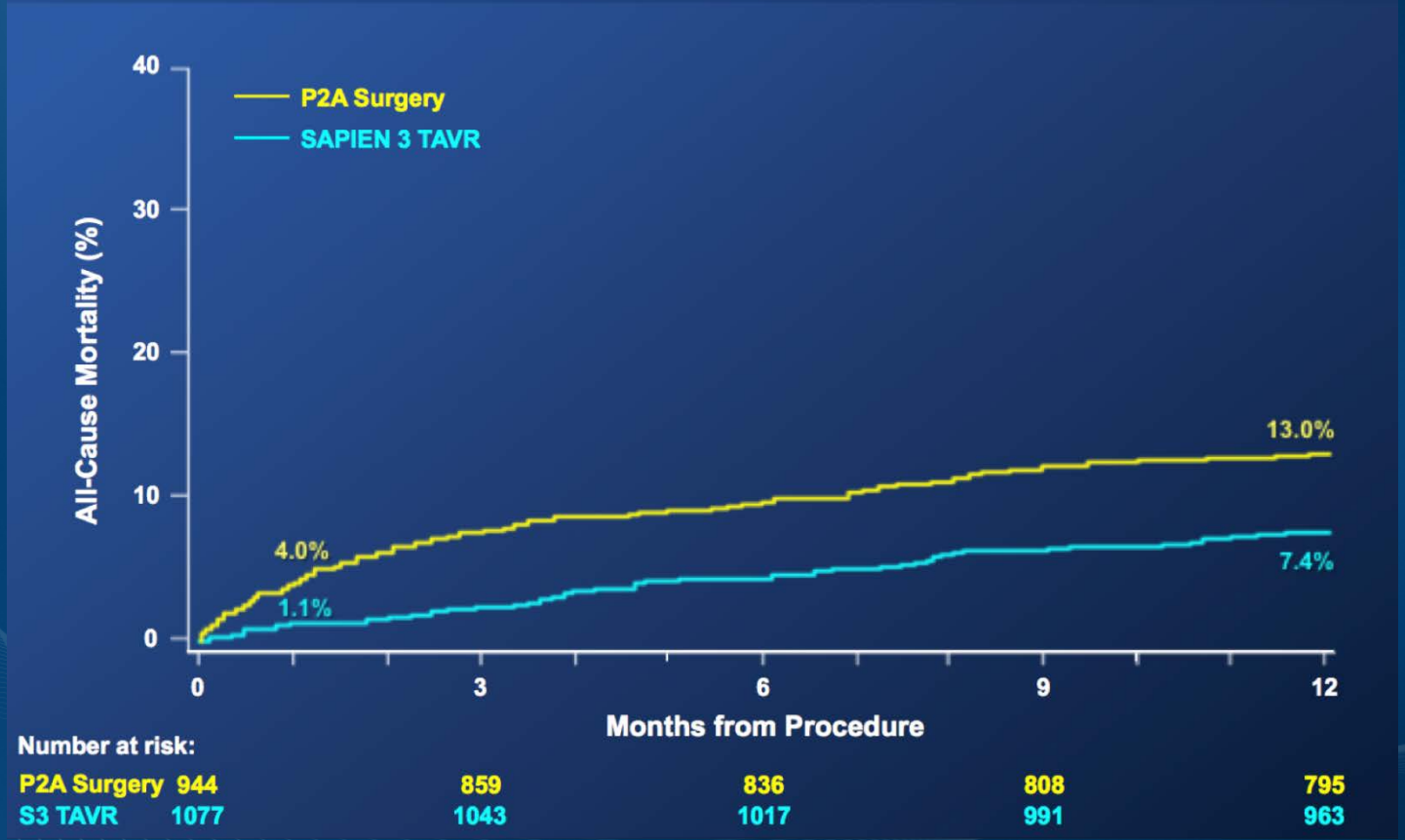
***Led to FDA approval of TAVR in 2016 for intermediate-risk patients***

# The PARTNER 2A and S3i Trials
## Study Design



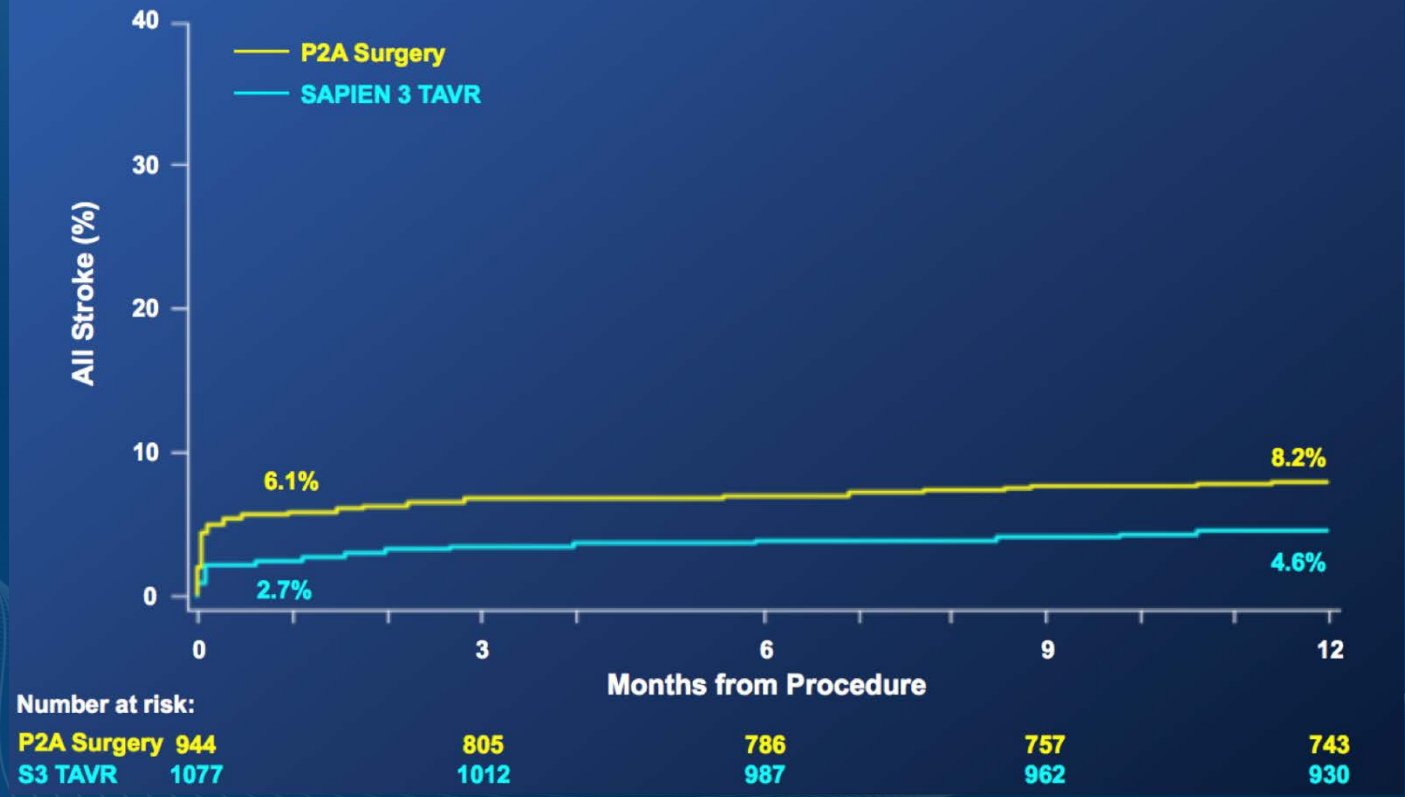
# Unadjusted Time-to-Event Analysis
## All-Cause Mortality (AT)

THE PARTNER II TRIAL



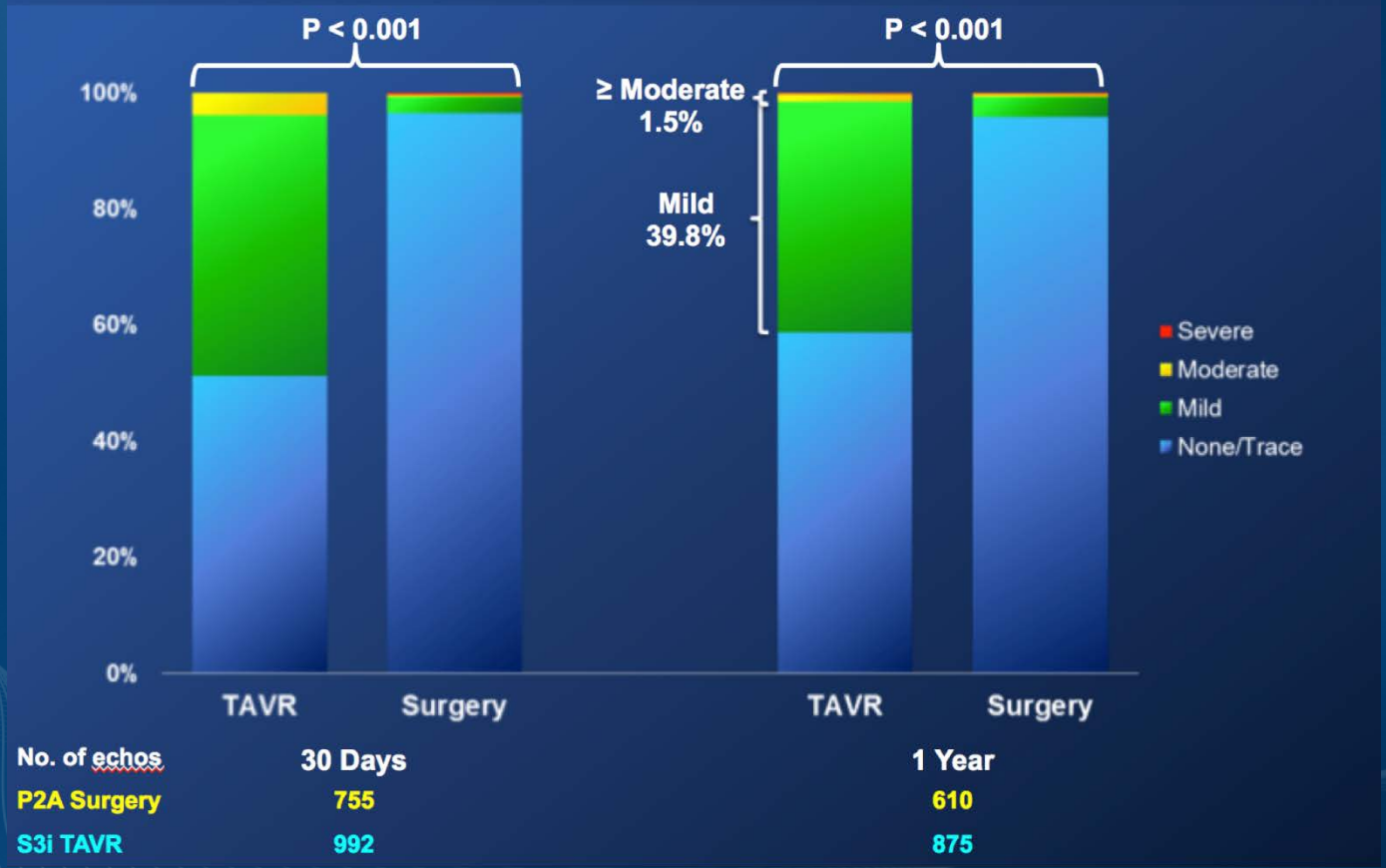
# Unadjusted Time-to-Event Analysis
## All Stroke (AT)

THE PARTNER II TRIAL



# Paravalvular Regurgitation
## 3-Class Grading Scheme (VI)

THE PARTNER II TRIAL




| No. of echos | 30 Days | 1 Year |
|---|---|---|
| P2A Surgery | 755 | 610 |
| S3i TAVR | 992 | 875 |

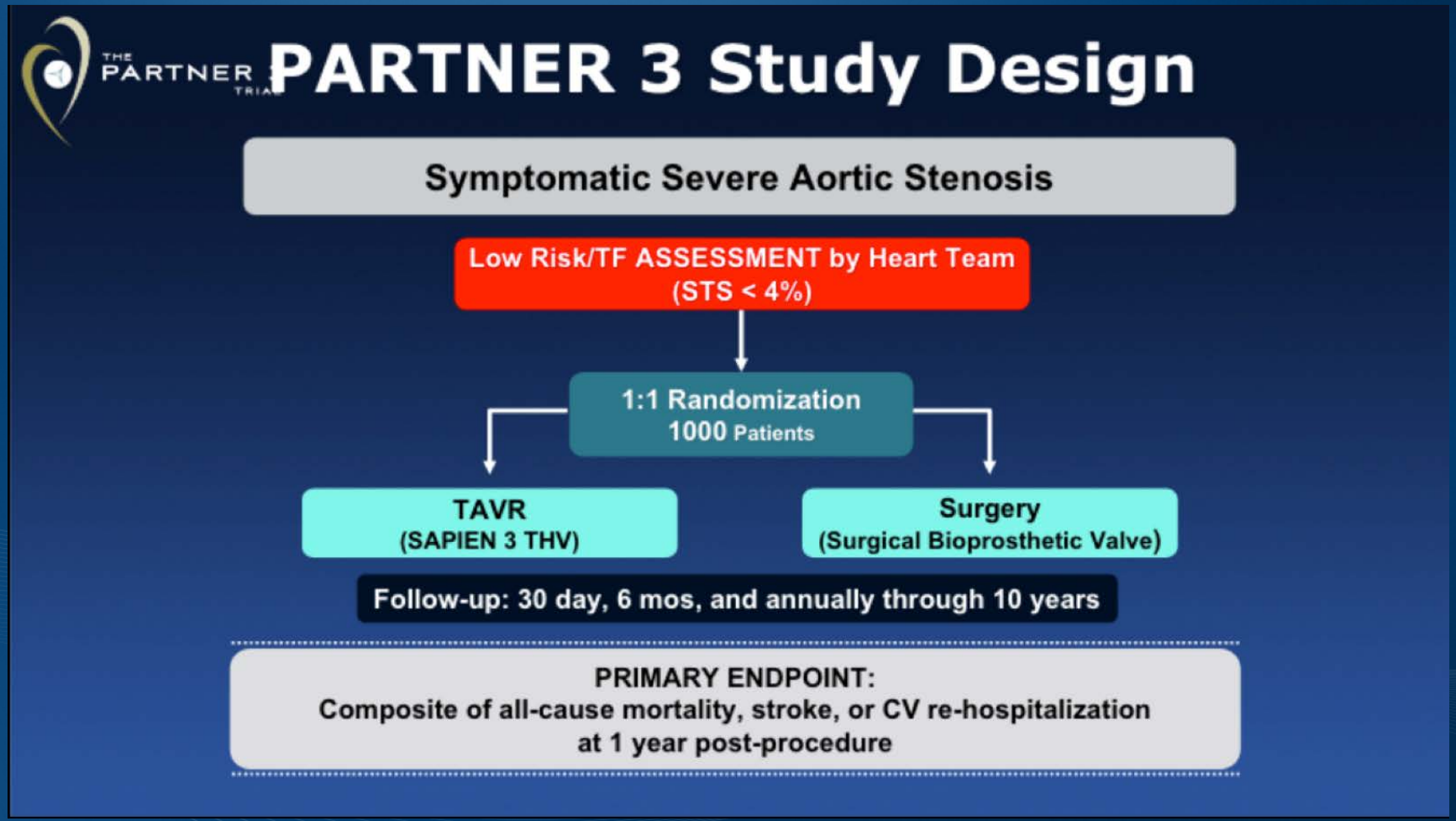
# Other Unadjusted Clinical Outcomes
## At 30 Days and 1 Year (AT)

THE PARTNER II TRIAL

| Events (%) | 30 Days | | 1 Year | |
|---|---|---|---|---|
| | TAVR (n = 1077) | Surgery (n = 944) | TAVR (n = 1077) | Surgery (n = 944) |
| Re-hospitalization | 4.6 | 6.8 | 11.4 | 15.1 |
| MI | 0.3 | 1.9 | 1.8 | 3.1 |
| Major Vascular Complication | 6.1 | 5.4 | --- | --- |
| AKI (Stage III) | 0.5 | 3.3 | --- | --- |
| Life-Threatening/Disabling Bleeding | 4.6 | 46.7 | --- | --- |
| New Atrial Fibrillation | 5.0 | 28.3 | 5.9 | 29.2 |
| New Permanent Pacemaker | 10.2 | 7.3 | 12.4 | 9.4 |
| Re-intervention | 0.1 | 0.0 | 0.6 | 0.5 |
| Endocarditis | 0.2 | 0.0 | 0.8 | 0.7 |


BREAKING NEWS

# PARTNER 3 TRIAL – LOW RISK TAVR VS SAVR



THE PARTNER 3 TRIAL

# Key Inclusion Criteria

## Severe Calcific Aortic Stenosis

- AVA ≤ 1.0 $cm^2$ or AVA index ≤ 0.6 $cm^2/m^2$
- Jet velocity ≥ 4.0 m/s or mean gradient ≥ 40 mmHg, AND
  - NYHA Functional Class ≥ 2, OR
  - Abnormal exercise test with severe SOB, abnormal BP response, or arrhythmia, OR
  - Asymptomatic with LVEF < 50%

## Low Surgical Risk

- Determined by multi-disciplinary heart team
- STS < 4%
- Adjudicated by case review board

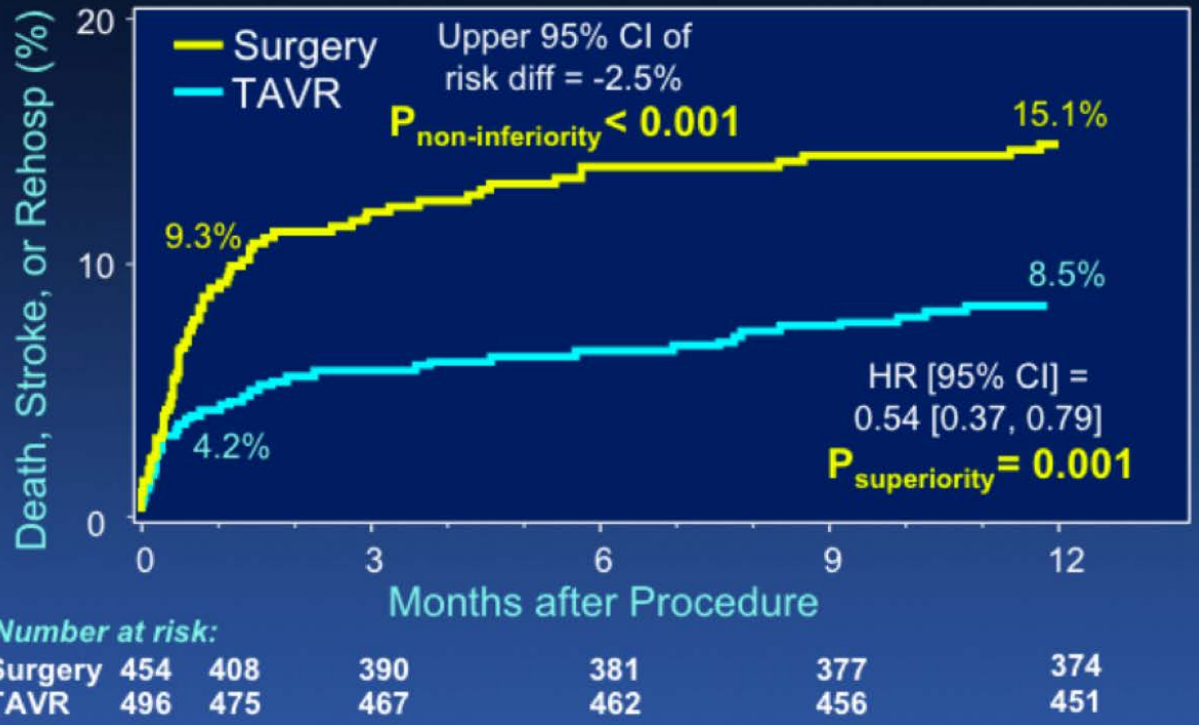
# Baseline Patient Characteristics

% or mean ± SD

| Demographics & Vascular Disease | TAVR (N=496) | Surgery (N=454) | Other Co-Morbidities | TAVR (N=496) | Surgery (N=454) |
|---|---|---|---|---|---|
| Age (years) | 73.3 ± 5.8 | 73.6 ± 6.1 | Diabetes | 31.3% | 30.2% |
| Male | 67.5% | 71.1% | COPD (any) | 5.1% | 6.2% |
| BMI – $kg/m^2$ | 30.7 ± 5.5 | 30.3 ± 5.1 | Pulmonary Hypertension | 4.6% | 5.3% |
| STS Score | 1.9 ± 0.7 | 1.9 ± 0.6 | Creatinine > 2mg/dL | 0.2% | 0.2% |
| NYHA Class III or IV* | 31.3% | 23.8% | Frailty (overall; > 2/4+) | 0 | 0 |
| Coronary Disease | 27.7% | 28.0% | Atrial Fibrillation (h/o) | 15.7% | 18.8% |
| Prior CABG | 3.0% | 1.8% | Permanent Pacemaker | 2.4% | 2.9% |
| Prior CVA | 3.4% | 5.1% | Left Bundle Branch Block | 3.0% | 3.3% |
| Peripheral Vascular Disease | 6.9% | 7.3% | Right Bundle Branch Block | 10.3% | 13.7% |

*p = 0.01

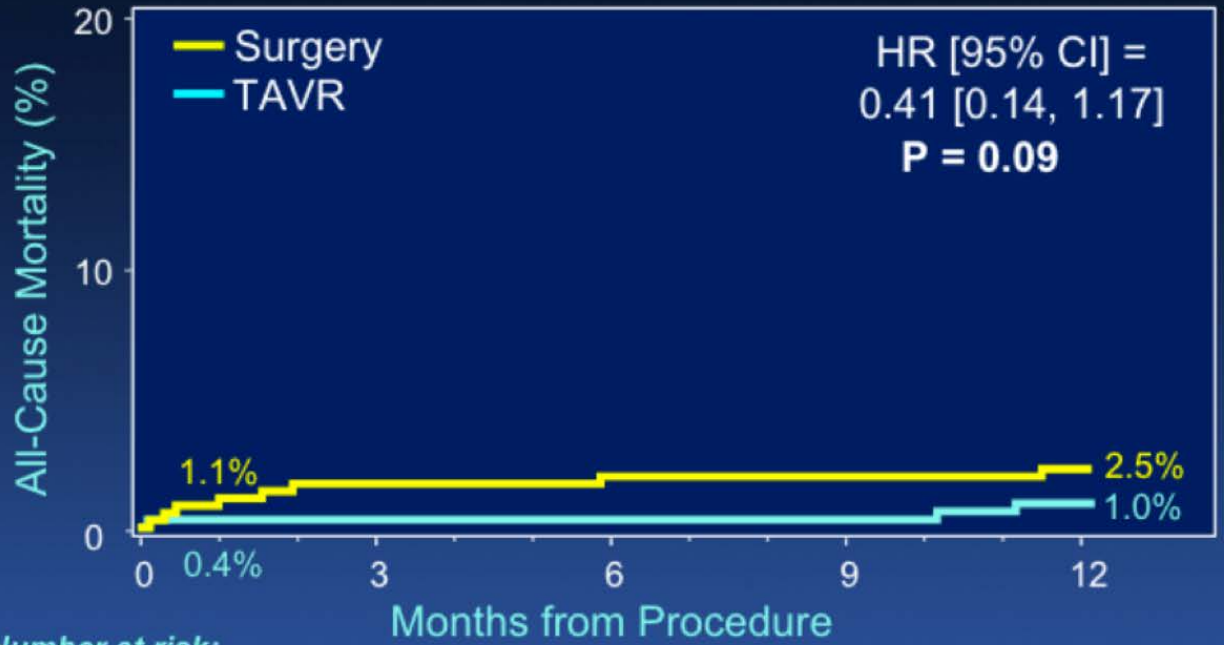
# Primary Endpoint




***Led to FDA approval of TAVR in 2019 for low-risk patients***

THE PARTNER 3 TRIAL

# All-Cause Mortality

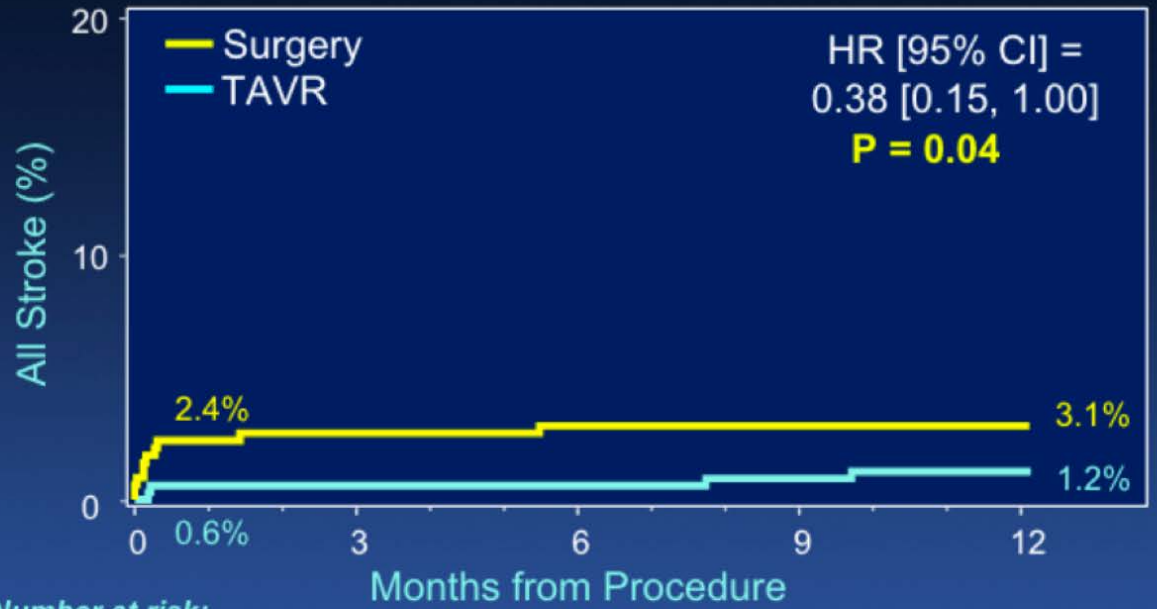



*Number at risk:*

| | | | | | | |
|---|---|---|---|---|---|---|
| Surgery | 454 | 445 | 438 | 433 | 431 | 427 |
| TAVR | 496 | 494 | 494 | 493 | 492 | 488 |

THE PARTNER 3 TRIAL

# All Stroke

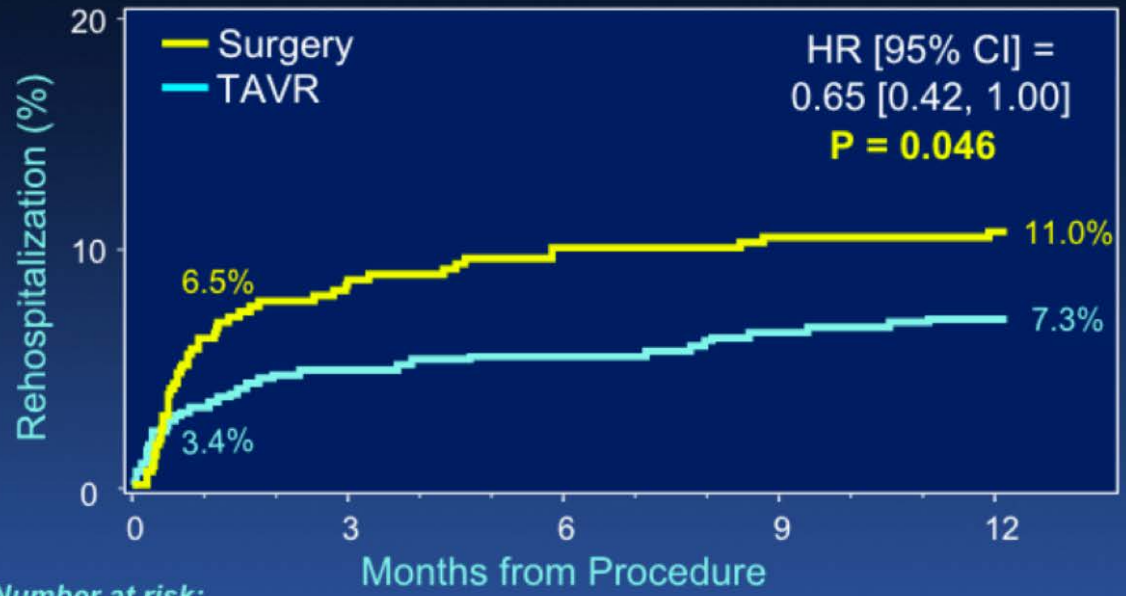



*Number at risk:*

| | | | | | | |
|---|---|---|---|---|---|---|
| Surgery | 454 | 435 | 427 | 423 | 421 | 417 |
| TAVR | 496 | 491 | 491 | 489 | 487 | 484 |

THE PARTNER 3 TRIAL

# Rehospitalization




*Number at risk:*

| | | | | | | |
|---|---|---|---|---|---|---|
| Surgery | 454 | 416 | 399 | 389 | 385 | 382 |
| TAVR | 496 | 477 | 469 | 465 | 459 | 453 |

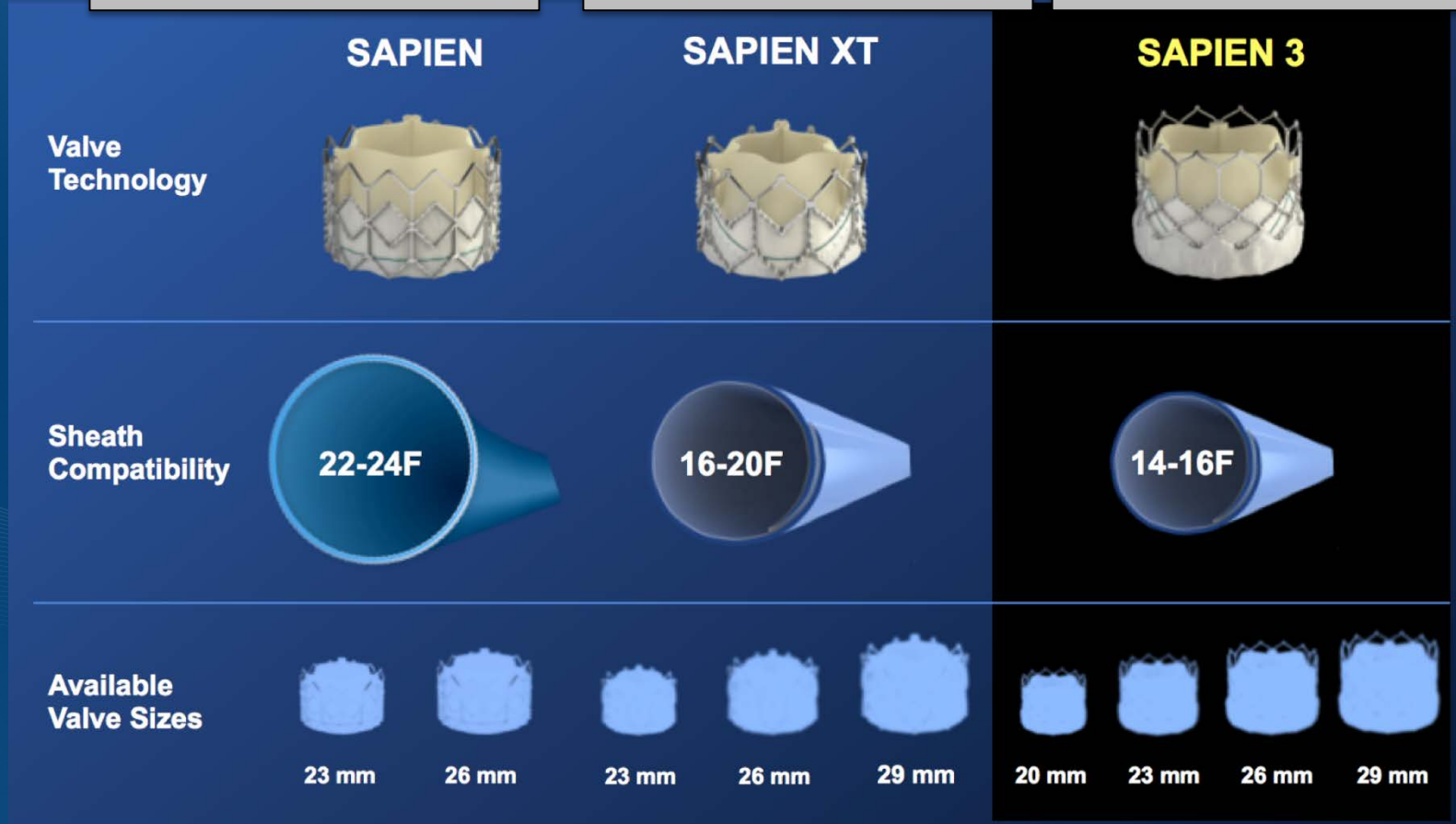
# PARTNER 3 SECONDARY OUTCOMES

- New-onset atrial fibrillation at 30 days: TAVR 5.0% vs SAVR 39.5% ($p<0.001$)
- Death or disabling stroke at 1 year: TAVR 1.0% vs SAVR 2.9% ($p<0.05$)
- Moderate or severe PVL at 1 year: TAVR 0.6% vs SAVR 0.5%
- LOS: TAVR 3 days vs SAVR 7 days ($p<0.001$)
- PPM within 30 days: TAVR 6.5% vs SAVR 4.0% (p = NS)
- Larger improvement in QoL at 30 days, 6 months, and 1 year for TAVR based on KCCQ-OS

Partner 1
Major Vasc Comp 11%
PPM 4%
Disabling stroke 3.8%

Partner 2A
Major Vasc Comp 8%
PPM 8%
Disabling stroke 3.2%

Partner 3
Major Vasc Comp 2.2%
PPM 6.6%
Disabling stroke 1.2%

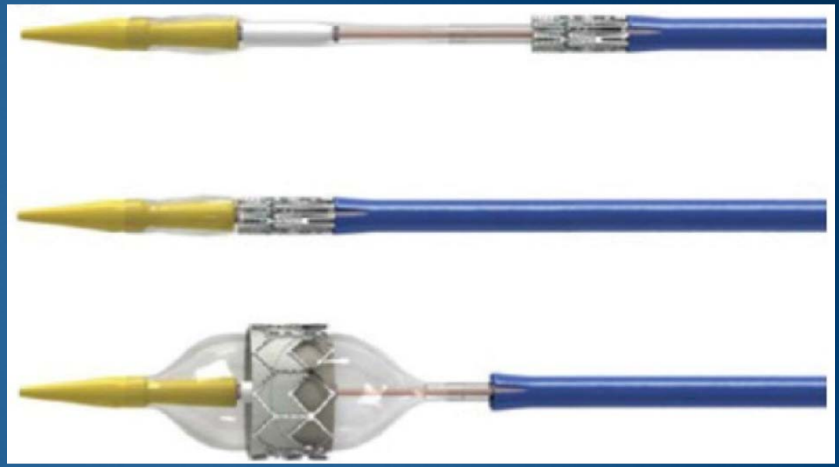


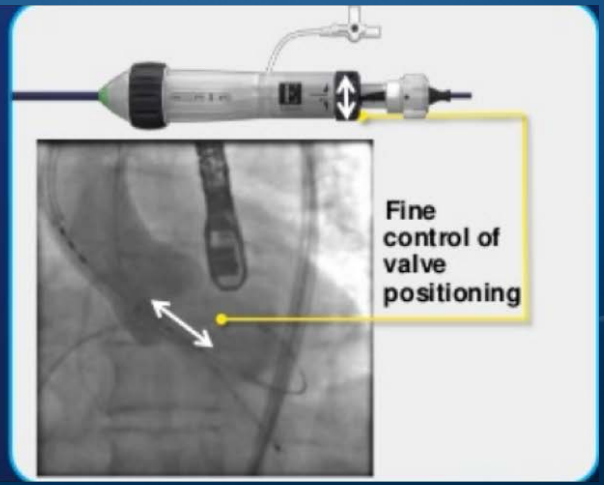
| Low Risk | Intermediate Risk | High Risk | Prohibitive Risk/Nonop |
|---|---|---|---|
| | | PARTNER 1A (2011)-TAVR noninferior to SAVR at 5yrs | PARTNER 1B (2010)- TAVR superior to med Rx at 5 years |
| | | US Pivotal CoreValve Trial (2014)- Survival benefit of TAVR over SAVR at 1 yr | CoreValve Extreme Risk Pivotal Trial (2014)- TAVR superior to med Rx at 1 yr |
| | PARTNER 2A (2016)- TAVR noninferior to SAVR at 2 years | | |
| | PARTNER 2 S3i (2016)- TAVR superior to SAVR at 1 year | | |
| EVOLUT Trial SE TAVR low risk | SURTAVI (2017) CoreValve noninferior to SAVR at 2yrs | | |
| PARTNER 3 S3 TAVR vs SAVR in low risk | | | |

Trends compared to surgery: Significantly less post-op AF, less bleeding, less AKI, better QoL, less stroke

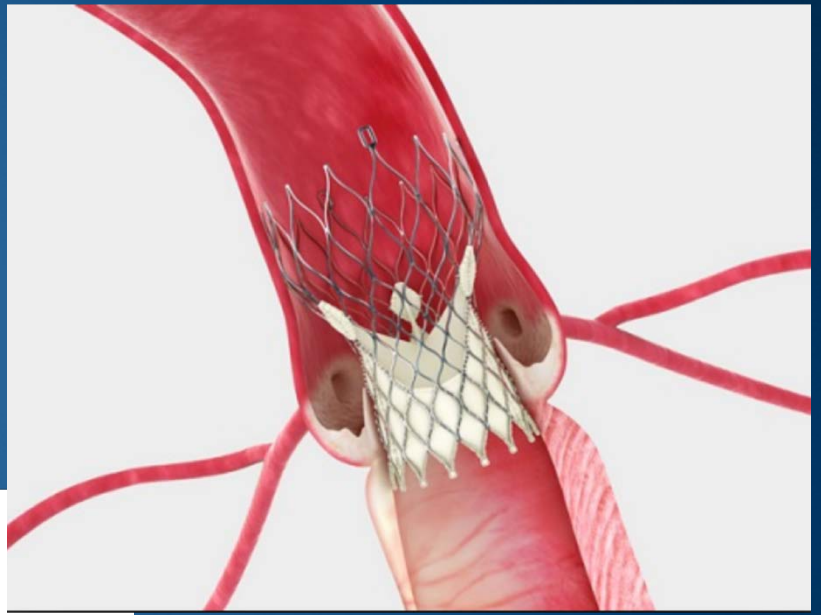
*Valve durability demonstrated out to 8-10 years. No different than surgical valves in terms of change in gradient, AR, need for re-intervention

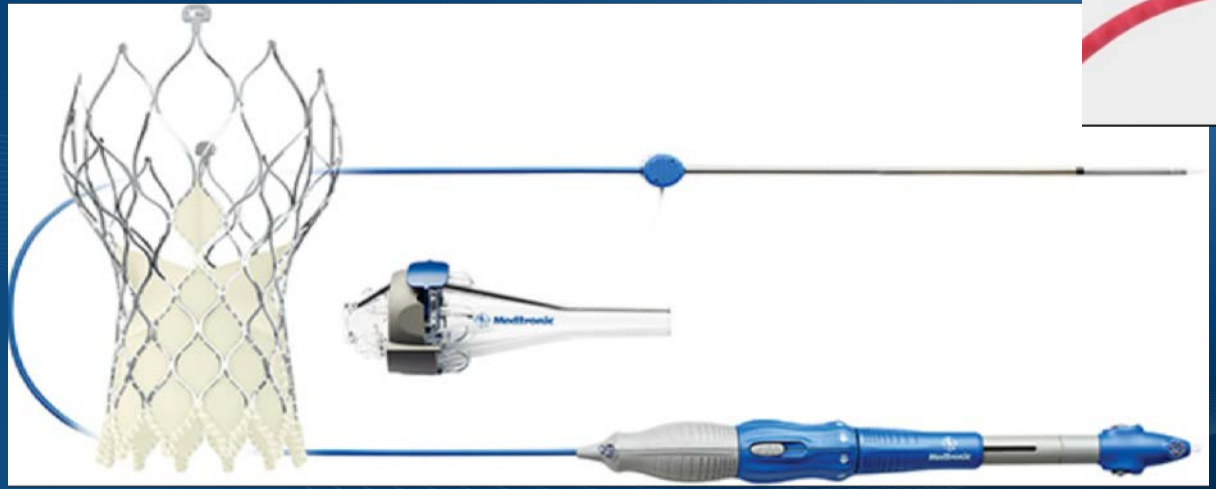
# EDWARDS SAPIEN 3 TRANSCATHETER HEART VALVE®



# MEDTRONIC COREVALVE®





# Sapien versus Evolut Advantages

| Sapien 3 | Evolut R/Pro |
|---|---|
| PPM 6.2% | PPM 10-17% |
| Major stroke 1.1% | Major stroke 1.7-3.3% |
| Annular rupture risk higher | Risk of annular rupture low |
| Rapid pacing deployment | No need for rapid pacing |
| Coronary access | Slightly more challenging |
| | Repositionable |
| Min arterial diameter 7.6-8.6mm | Min arterial diamter: 6-6.7mm |
| | Larger EOA for ViV (supra-annular) |

# FDA Approval

- 2011: TAVR approved for inoperable patients
- 2012: High-risk patients
- 2016: Intermediate or greater risk patients
- 2017: Valve in valve for failed Bioprosthetic MITRAL or AORTIC prostheses (AR or AS)
- 2019: Low risk

# Lotus Valve


Repositionable After
100% Deployed
Braided Nitinol Frame
Adaptive Seal
Bovine Pericardium

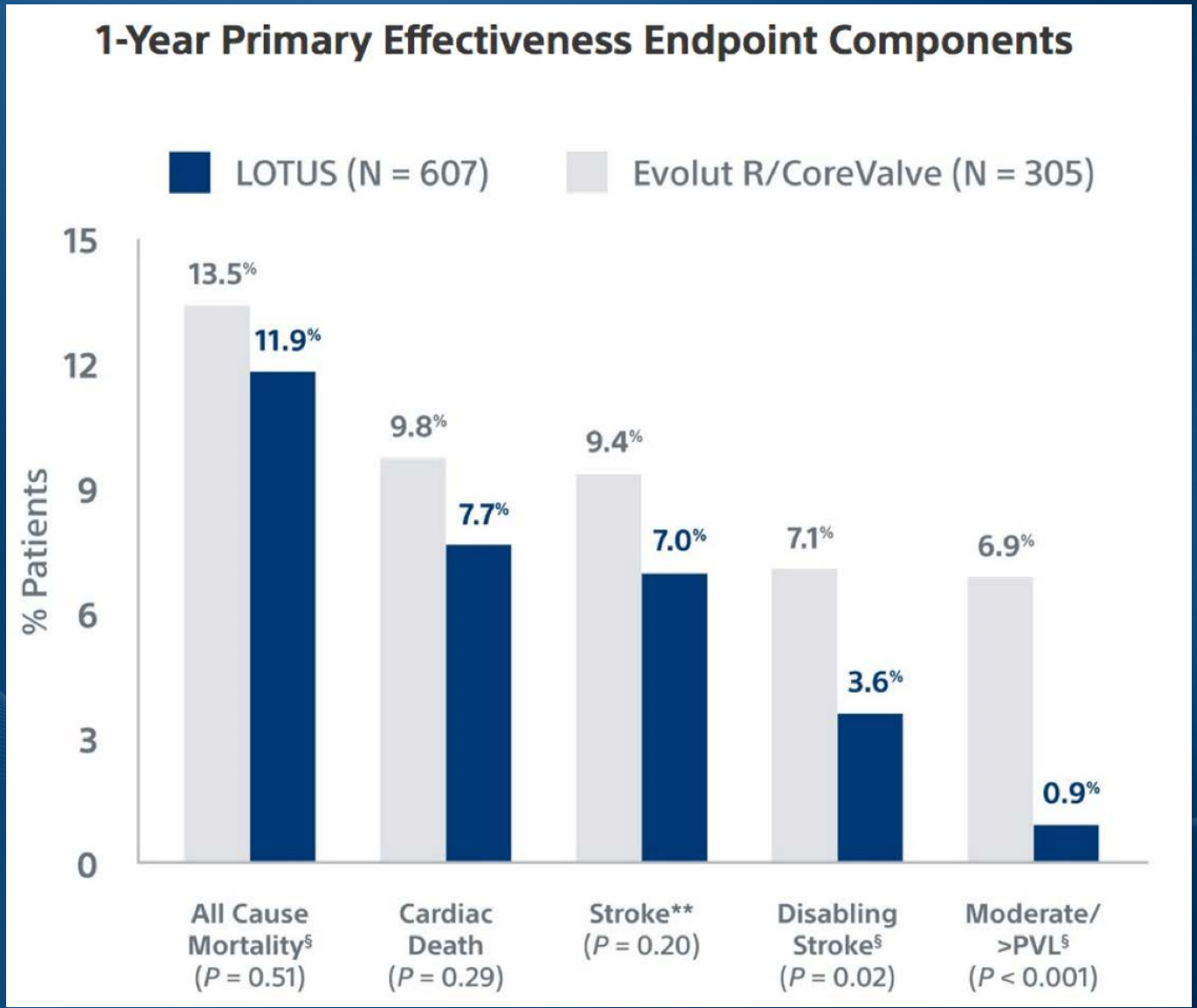
# Lotus Valve

- REPRISE III Study
- High or Extreme-risk severe aortic stenosis
- Lotus valve vs. CoreValve/Evolut
- Results
  - Primary safety outcome at 30 days (mortality, stroke, bleeding, AKI, major vasc complications): 20.3% Lotus, 17.1% CoreValve
  - Primary efficacy outcome at 1 year (mortality, stroke, PVL): 15.4% Lotus, 25.5% CoreValve
  - Moderate to severe PVL: 0.9% Lotus, 6.9% CoreValve
  - Permanent pacemaker: 34.2% Lotus, 18.5% CoreValve

***Led to FDA approval of Lotus Valve in 2019 for high-risk patients***

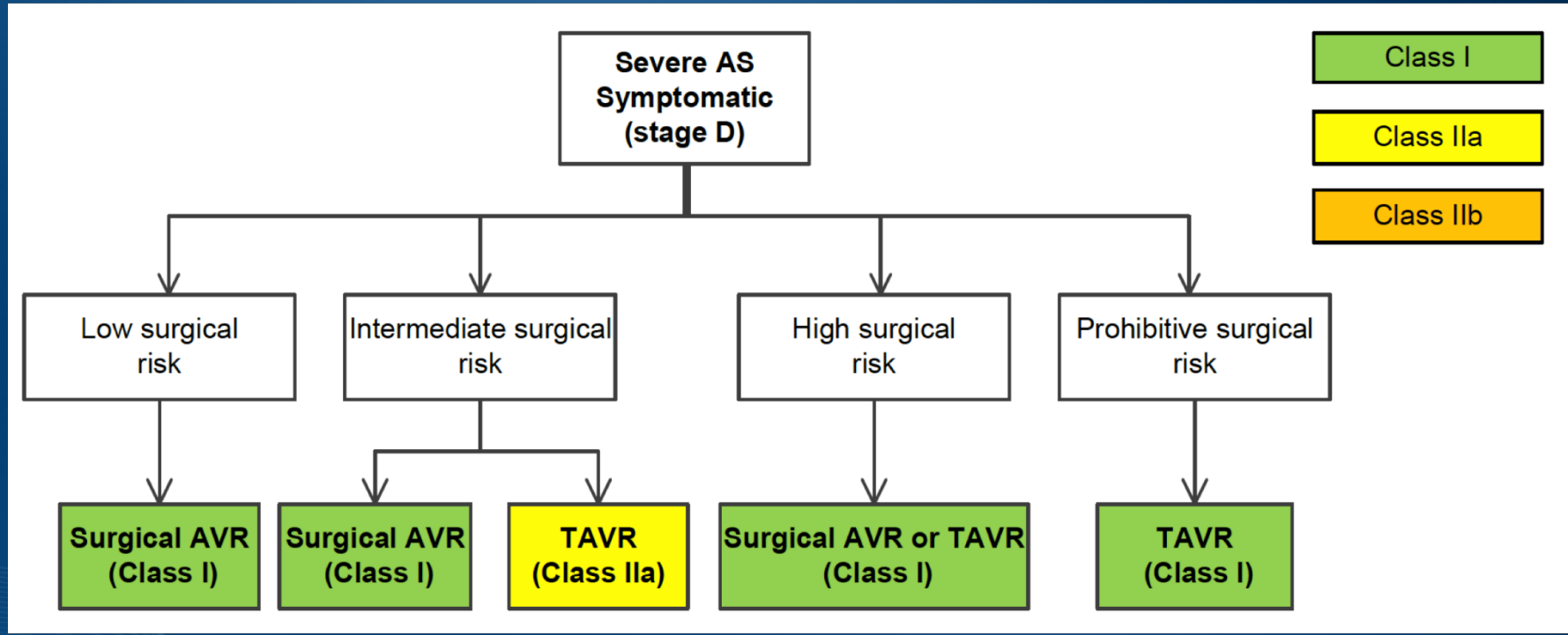
Feldman, et al. JAMA 2018. Reprise III.

# 1-Year Primary Effectiveness Endpoint Components



# A Transformative Technology…

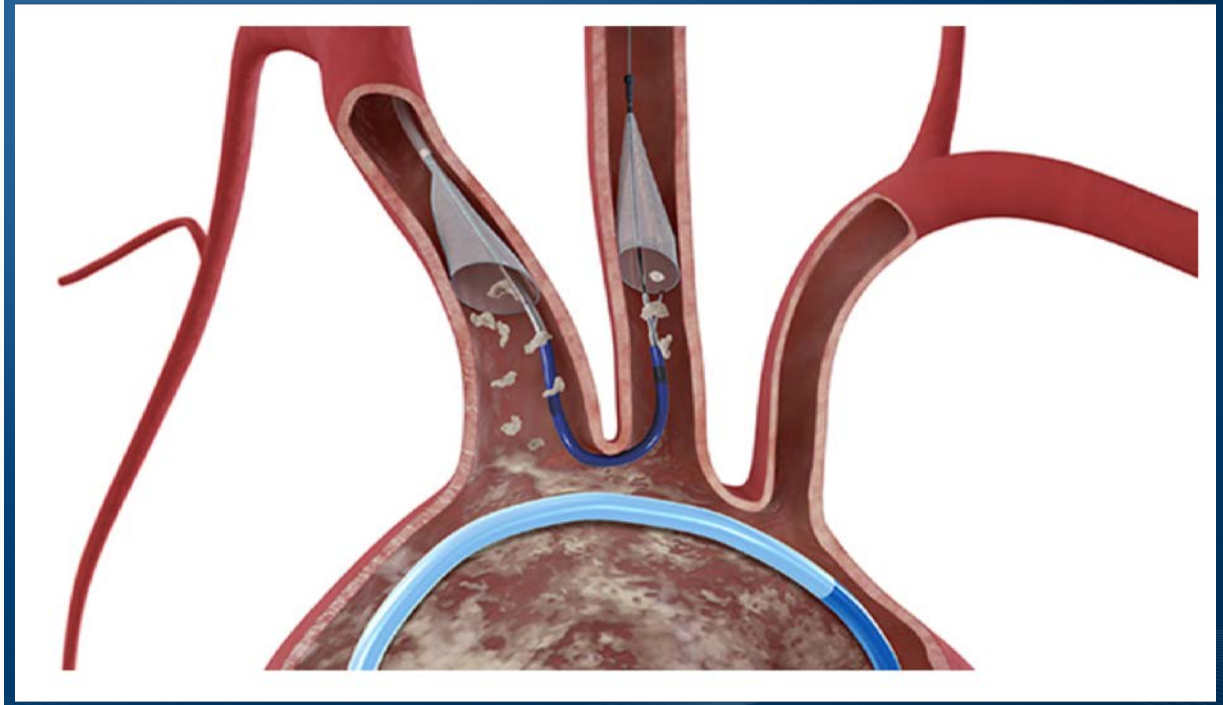
# TAVR versus SAVR in the Patient with Severe AS



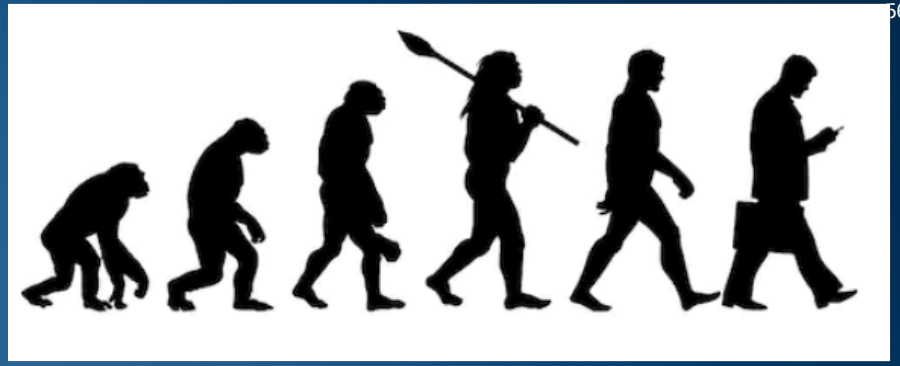

- Severe symptomatic bioprosthetic AS or AR at high or prohibitive risk for reoperation, valve-in-valve TAVR is reasonable

Nishimura, et al. 2017 ACC/AHA Focused Update on VHD

# Cerebral Protection



# The Evolution of TAVR



- Improved valve technology with minimized leak and less pacemaker requirements
- Smaller sheaths to allow for femoral artery access without cutdown
- More flexible catheters to negotiate tortuous and calcified anatomy
- Improved operator and staff experience
- Improved workflow and system processes

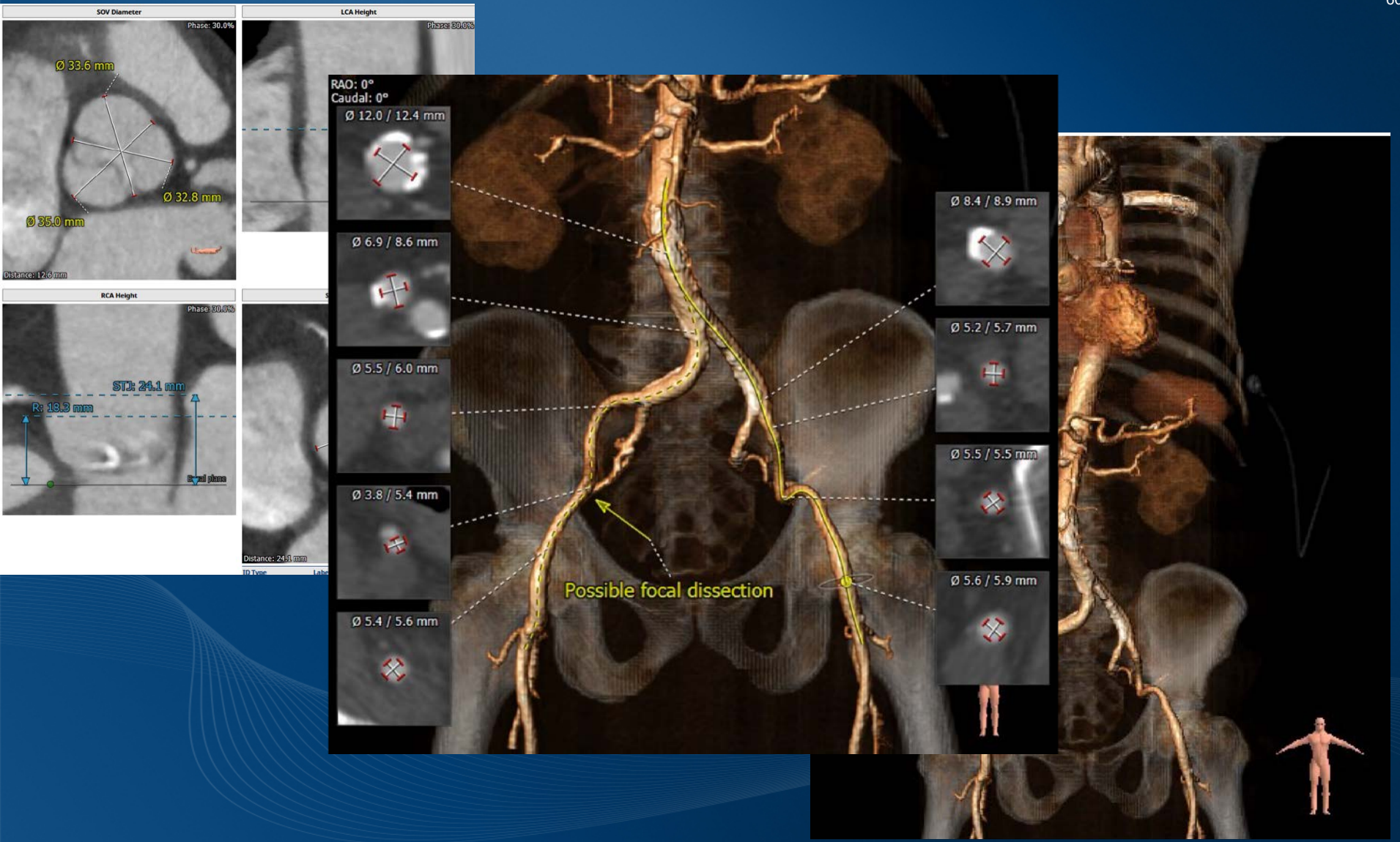
# The Minimalist approach

- Conscious sedation
  - Shorter LOS, in-hospital and 30-day mortality*
- No central IJ lines
- No Foley catheter
- No TEE
- Fast-track ICU protocol (6-hours)
- PCU for lower risk patients

(Hyman et al, Circ. June 19, 2018, Volume 137, Issue 25)

# Workup

- Echocardiogram
- Coronary angiogram
- CT Angiogram Chest, Abdomen, Pelvis with 3D Reconstructions of Heart
- Carotid Ultrasound
- PFTs
- Frailty Test
- Evaluation by CT Surgery
- Evaluation by Palliative Care Team if necessary
- *Discussion with Heart Team*
  - *Anatomic considerations such as calcified annulus or aortic root, is femoral access feasible, presence of CAD*


SOV Diameter
Phase: 30.0%
Ø 33.6 mm
Ø 32.8 mm
Ø 35.0 mm
Distance: 12.0 mm
LCA Height
Phase: 30.0%
RCA Height
Phase: 30.0%
ST: 24.1 mm
R: 18.3 mm
Distance: 24.1 mm
RAO: 0°
Caudal: 0°
Ø 12.0 / 12.4 mm
Ø 6.9 / 8.6 mm
Ø 5.5 / 6.0 mm
Ø 3.8 / 5.4 mm
Ø 5.4 / 5.6 mm
Ø 8.4 / 8.9 mm
Ø 5.2 / 5.7 mm
Ø 5.5 / 5.5 mm
Ø 5.6 / 5.9 mm
Possible focal dissection

# Post-Procedure

- Most patients admitted to PCU
  - ICU if…
    - New conduction disorder requiring pacemaker
    - Intra-procedural hypotension
    - Intra-procedural complication
- Arterial lines discontinued within 4-6 hours if stable
- Ambulation expected 6 hours post-procedure
- Initiation of antiplatelets, ASA + Plavix
- Echo same afternoon or next AM
- Discharge home anticipated next AM (POD1)
- Follow-up with cardiologist in 1 week

# Post-Procedural Complications

- Complete Heart Block
  - Higher suspicion if pre-existing RBBB
- Hypotension
  - Consider pericardial effusion from annular rupture, LV perforation, RV perforation, access site bleeding (retroperitoneal or visible/palpable hematoma)
- Access site bleeding/hematoma
- Stroke
- Acute limb ischemia

# Case

87yo M multiple unprovoked syncopal episodes for the past month, 6 month decline in exercise tolerance preceding. Elevated trop and BNP. Transferred for higher-level of care/cardiac cath.

Cares for wife with severe dementia.

Echo: LV mod dilated with EF 20% (severe global HK), severe LAE, severe low-flow/low-gradient AS (mean gradient 36 mmHg, AVA 0.6 cm2), mild-mod MR, mild TR, PASP 40 mmHg.

Dobutamine Echo: AV gradient 40 mmHg, AVA 0.8 cm2.

Carotid duplex:

No significant stenosis bilaterally.

FEV1:

48% predicted.

Cardiac cath:

Distal LM stenosis extending to LAD/LCx (70% ostial LAD eccentric calcified, 99% ostial LCx). RCA ok.

- Heart Team decision: TAVR
  - STS PROM 10%
  - PABV/Impella support
  - High-risk PCI left main/LAD/Left Circ
  - TAVR with 26mm S3 device

- Echo post-op day 1: LVEF 35%, mean gradient 9mmHg, trivial PVL
- LOS 9 days
- Discharged home and doing well on follow-up

# Case

- 84yo with bioprosthetic aortic valve stenosis (Edwards Perimount 21mm valve placed 2003), acute on chronic diastolic HF, CKD, chronic afib on DOAC, severe MR, severe PAH with multiple recent admissions for HF
- Heart Team decision: TAVR ViV
  - STS PROM 16%
  - Frail
  - Low coronary artery heights with small Sinus of Valsalva (increased risk of coronary obstruction)

# Summary

- TAVR has revolutionized the treatment of aortic stenosis in inoperable patients and those at intermediate to high-risk
- TAVR recently FDA-approved for low-risk patients due to demonstrated superiority with regard to stroke and re-hospitalization
  - Anatomic and patient-specific considerations will help dictate TAVR vs SAVR
- Complications including stroke and need for permanent pacemakers continues to decline as operator experience improves and with improved device technology
- TAVR procedure and post-op care has become increasingly more efficient with reduced ICU time and LOS
- Expect newer devices to be introduced in the next several years
- Cerebral protection device may help to reduce stroke risk

# Future Directions

- Longer-term data needed to demonstrate valve durability, especially in younger patients
- Newer-generation devices with smaller profiles
- Treating Aortic regurgitation
- Defining timing of intervention
- Cost reduction of TAVR
- Just the beginning of the percutaneous valve space…