TAVR: FROM HIGH RISK TO EVERYONE?

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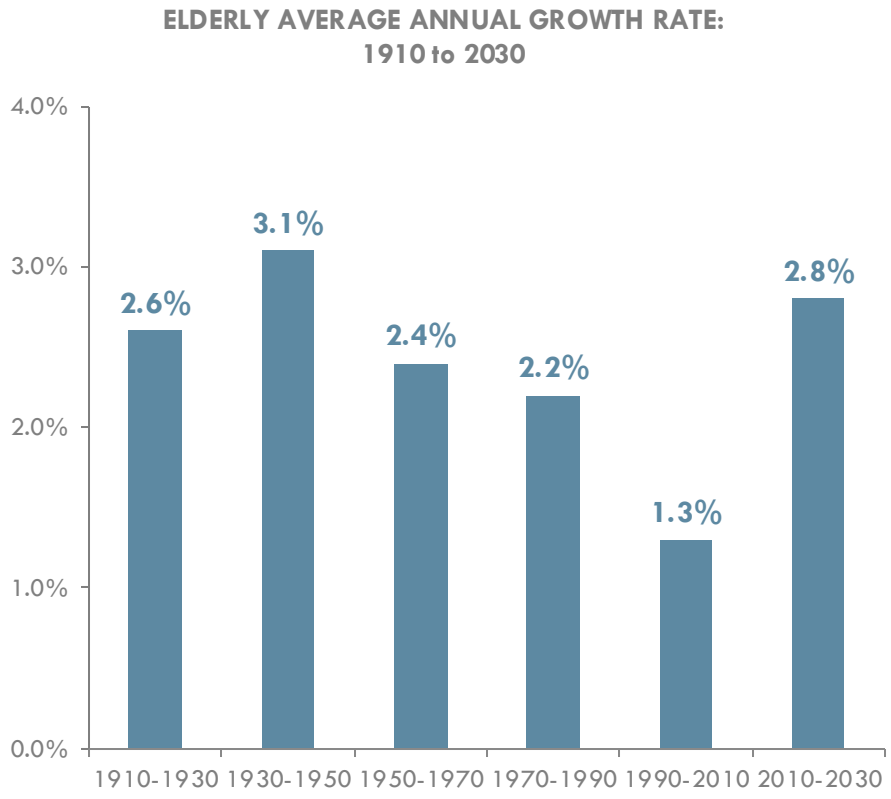
Gates Vascular Institute

POPULATION AT RISK FOR AORTIC STENOSIS IS INCREASING

Approx. 2.5 Million People in the U.S. Over the Age of 75 suffer from this disease.[1]

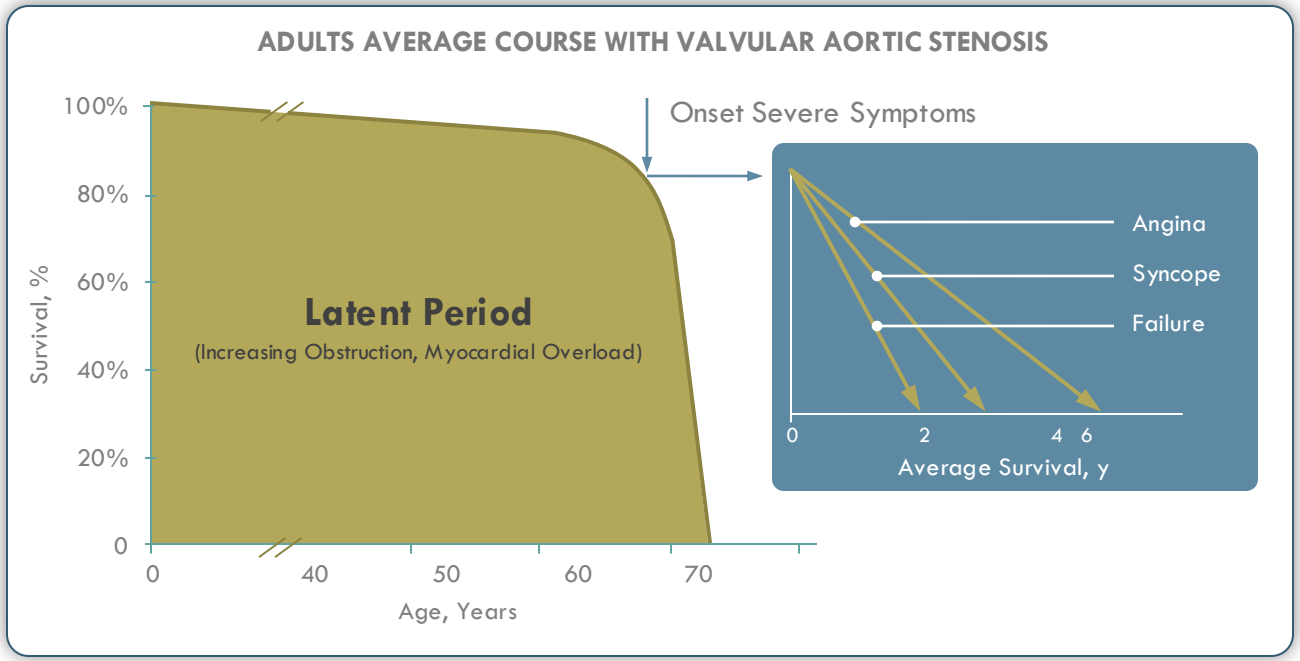
- Aortic Stenosis is estimated to be prevalent with **12.4% of the population over the age of 75.[2]**
- The elderly population will more than double between now and the year 2050, to 80 million.[3]
- 80% of adults with symptomatic aortic stenosis are male[4]



1. U.S. Census Bureau, Population Division. June 2015; **2.** Ruben L.J.et al. Heart. 2000;84:211-21; **3.** U.S. Census Bureau Statistical Brief. May 1995;
4. Ramaraj R, Sorrell VL. Br Med J 2008;336: 550–5.

SEVERE AORTIC STENOSIS IS LIFE THREATENING AND TREATMENT IS CRITICAL[6]

After the onset of symptoms, patients with **severe aortic stenosis** have a **survival rate as low as 50% at 2 years and 20% at 5 years** without aortic valve replacement[7]

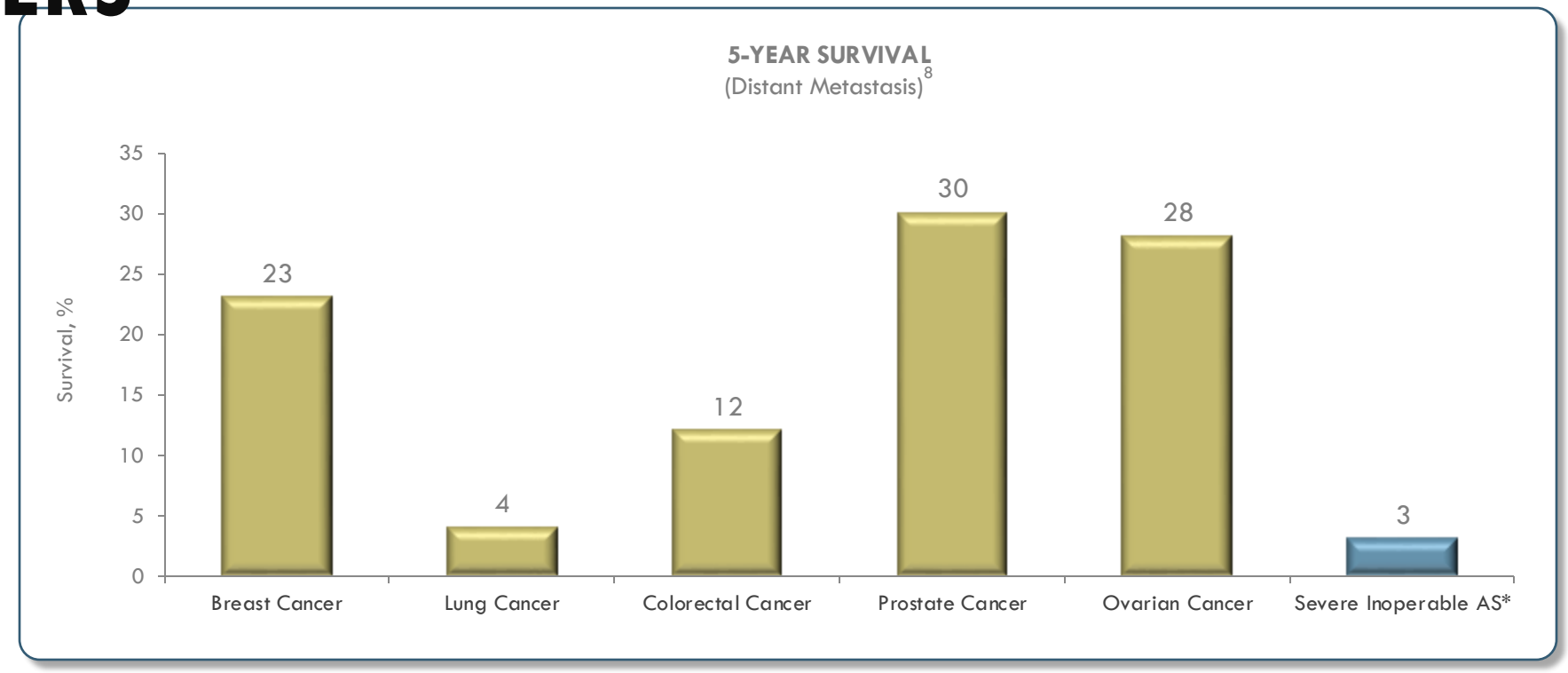


50% of patients died within 1 year without valve replacement

Per the Inoperable Cohort of the PARTNER Trial

6. Lester SJ et al. CHEST 1998;113(4):1109-1114; **7.** Otto CM. Heart. 2000:84:211-218.

WORSE PROGNOSIS THAN MANY METASTATIC CANCERS



5 year survival of breast cancer, lung cancer, prostate cancer, ovarian cancer and severe inoperable aortic stenosis

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

8. National Institutes of Health. http://seer.cancer.gov/statfacts/. Accessed Nov. 2010.

TIMELY INTERVENTION IS CRITICAL FOR PATIENTS WITH SYMPTOMS[9]

In the absence of serious comorbid conditions, aortic valve replacement (AVR) is **indicated in the majority of symptomatic patients** with severe aortic stenosis

Consultation with or referral to a **Heart Valve Center of Excellence** is reasonable when discussing treatment options for:

- Asymptomatic patients with severe valvular heart disease
- Patients with multiple comorbidities for whom valve intervention is considered

Because of the risk of sudden death, **replacing the aortic valve should be performed promptly after the onset of symptoms**

Age is not a contraindication to surgery

9. Nishimura RA et al. JACC. 2014. doi: 10.1016/j.jacc.2014.02.537.

DEFINITION OF SEVERE AORTIC STENOSIS[9]

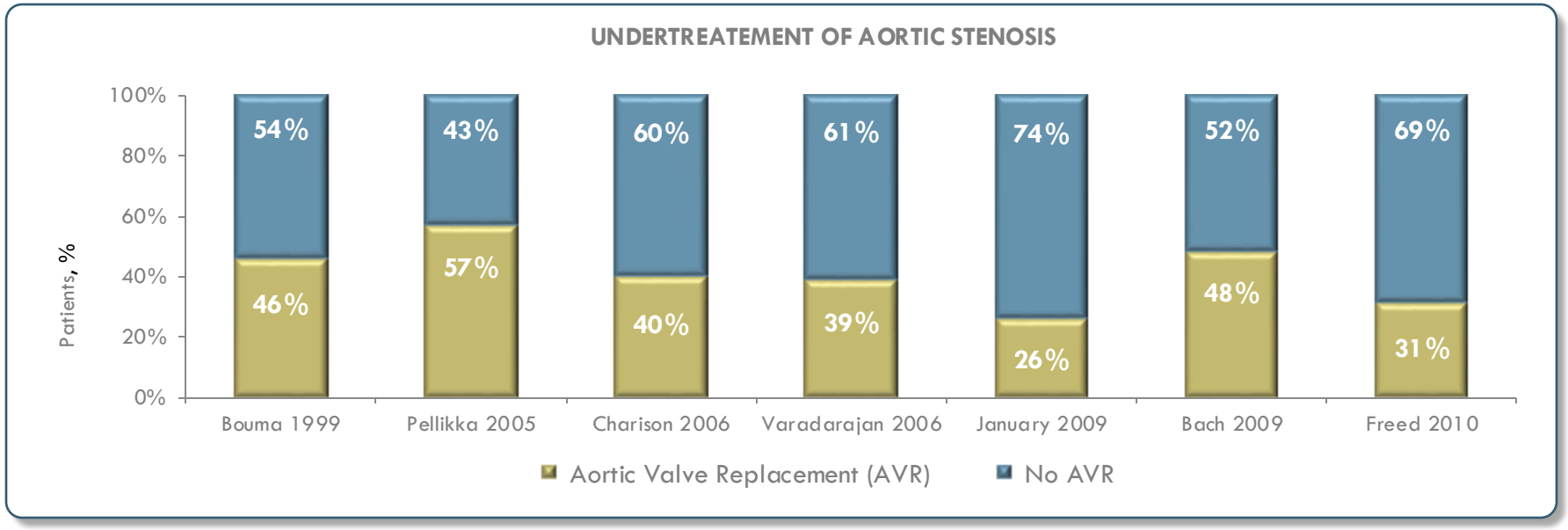
Patients with severe aortic stenosis typically have an aortic valve area ≤ 1.0 cm^2

Definition	Valve Hemodynamics
High-gradient severe aortic stenosis	▪ Aortic **jet velocity ≥ 4 m/s or mean gradient ≥ 40 mmHg** ▪ Or aortic **valve area index ≤ 0.6 cm^2/m^2**
Low-flow/low-gradient with reduced left ventricular ejection fraction	▪ Resting aortic **jet velocity < 4m/s or mean gradient < 40 mmHg** ▪ **Dobutamine stress** echocardiography shows aortic **valve area ≤ 1.0 cm^2 with** aortic **jet velocity ≥ 4m/s** at any flow rate ▪ Left ventricular **ejection fraction < 50%**
Low-gradient with normal left ventricular ejection fraction or paradoxical low-flow	▪ Aortic **jet velocity < 4m/s or mean gradient < 40 mmHg** ▪ Indexed aortic **valve area ≤ 0.6 cm^2/m^2** ▪ **Stroke volume index < 35 mL/m^2 measured when patient is normotensive** (systolic blood pressure < 140 mmHg) ▪ Left ventricular **ejection fraction ≥ 50%**

Symptoms:
Dyspnea or decreased exercise tolerance, heart failure, angina, syncope and presyncope

9. Nishimura RA et al. JACC. 2014. doi: 10.1016/j.jacc.2014.02.537.

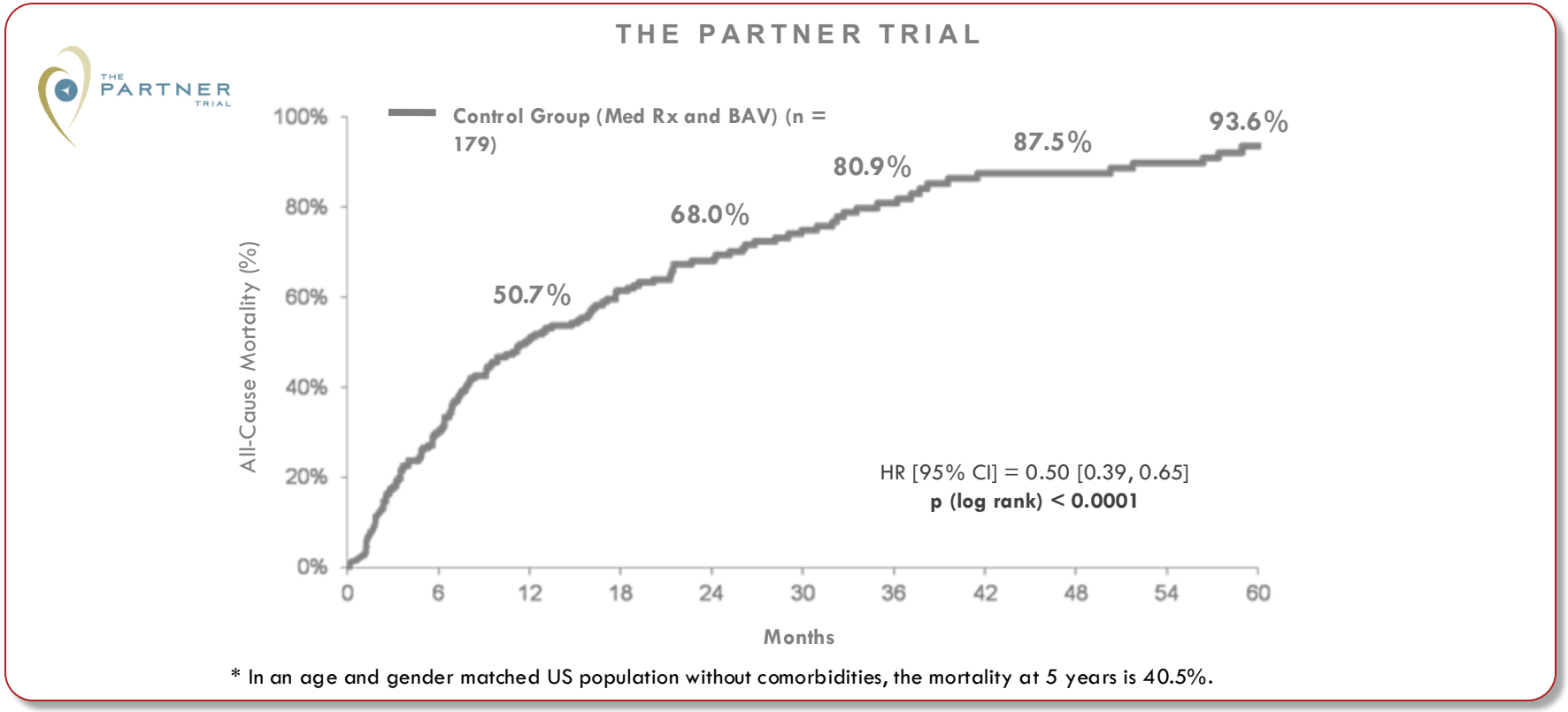
AT LEAST **40%** OF PATIENTS WHO NEED VALVE REPLACEMENT **DO NOT GET TREATMENT**[11-17]



Studies show that patients with severe aortic stenosis are under-diagnosed and under-treated

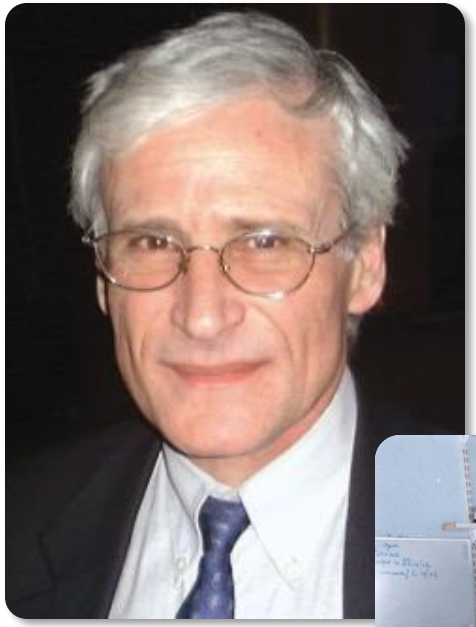
11. Bouma BJ et al. Heart. 1999;82:143-148; **12.** Pellikka PA et al. Circulation. 2005;111:3290-3295; **13.** Charlson E et al. J Heart Valve Dis. 2006;15:312-321; **14.** Varadarajan P et al. Ann Thorac Surg. 2006;82:2111-2115; **15.** Jan F et al. Circulation. 2009;120;S753; **16.** Bach DS et al. Circ Cardiovasc Qual Outcomes. 2009;2:533-539; **17.** Freed BH et al. Am J Cardiol. 2010;105:1339-1342.

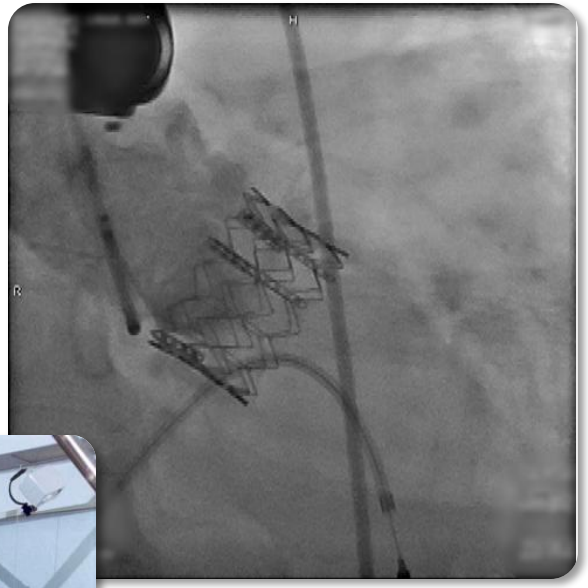
MEDICAL MANAGEMENT AND BAV ARE INADEQUATE THERAPIES FOR INOPERABLE PATIENTS



- Despite frequent BAV, **standard therapy did not alter the dismal course of disease for inoperable patients** in the PARTNER Trial
  - 51% died within 1 year
  - 94% died within 5 years

ALAIN CRIBIER: FIRST HUMAN TRANSCATHETER VALVE REPLACEMENT (2002)



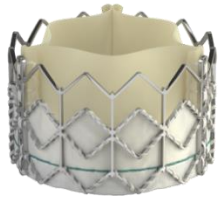


HISTORY OF EDWARDS' TRANSCATHETER HEART VALVE TECHNOLOGY

2005 — First successful TAVR procedure in U.S.

2007 — Landmark PARTNER clinical trials begin in U.S.

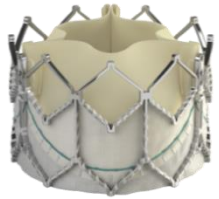
2011 — Edwards **SAPIEN** valve approved in the U.S. for inoperable patients



Edwards SAPIEN Valve

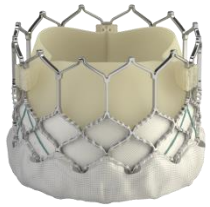
2012 — Edwards **SAPIEN** valve approved in U.S. for high-risk patients

2014 — Edwards **SAPIEN XT** valve approved in U.S. for high or greater risk patients



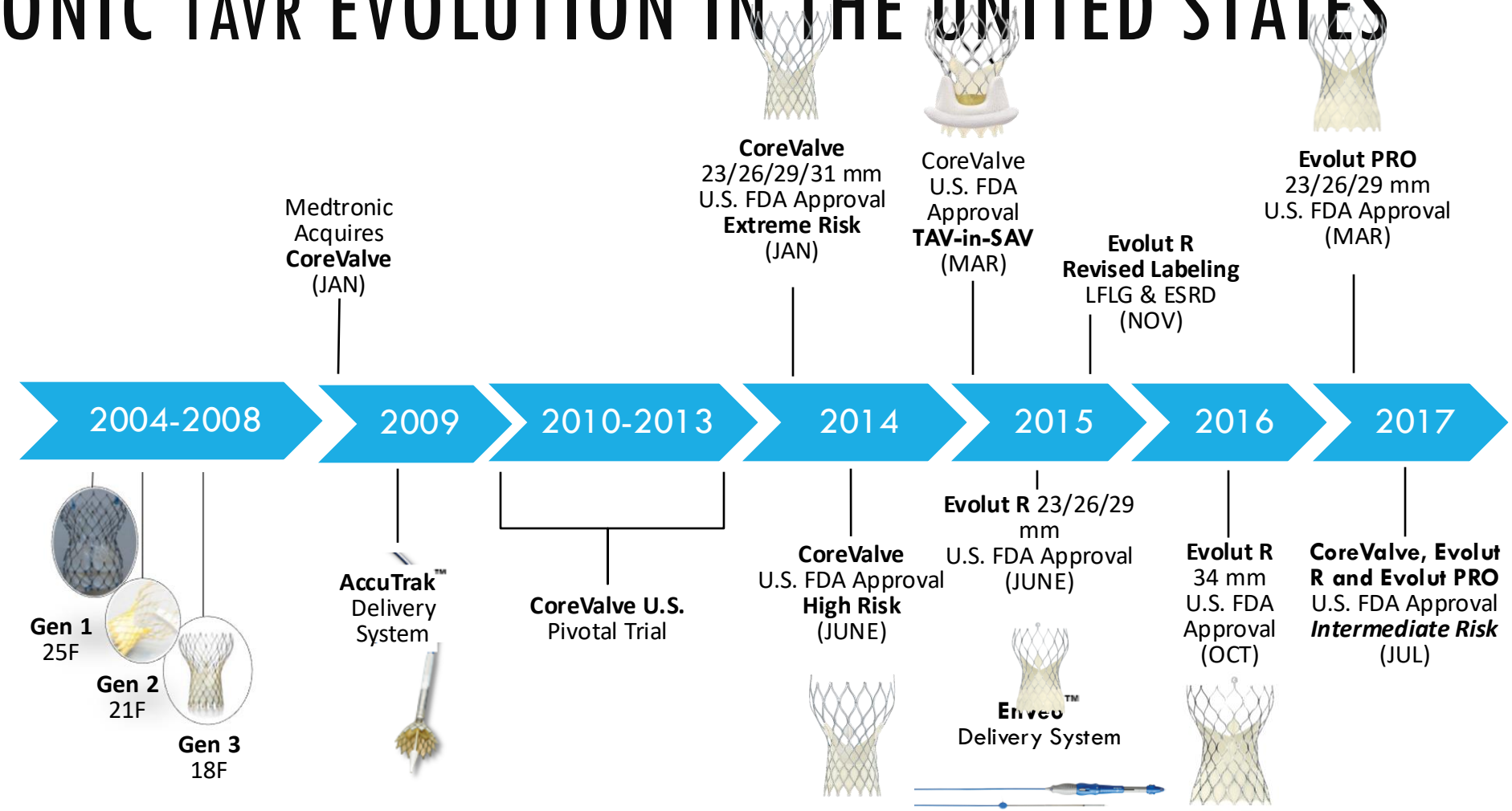
Edwards SAPIEN XT Valve

2015 — Edwards **SAPIEN 3** valve approved in U.S. for **high or greater risk** patients



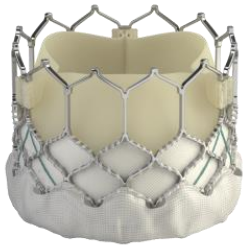
Edwards SAPIEN 3 Valve

MEDTRONIC TAVR EVOLUTION IN THE UNITED STATES



OPTIONS FOR AORTIC VALVE REPLACEMENT PER GUIDELINES[9]

Severe Aortic Stenosis is Defined as: Valve Area < 1.0 cm^2
Mean Gradient > 40 mmHg **OR** Jet Velocity > 4.0 m/s



Transcatheter Heart Valve

Surgical Heart Valve

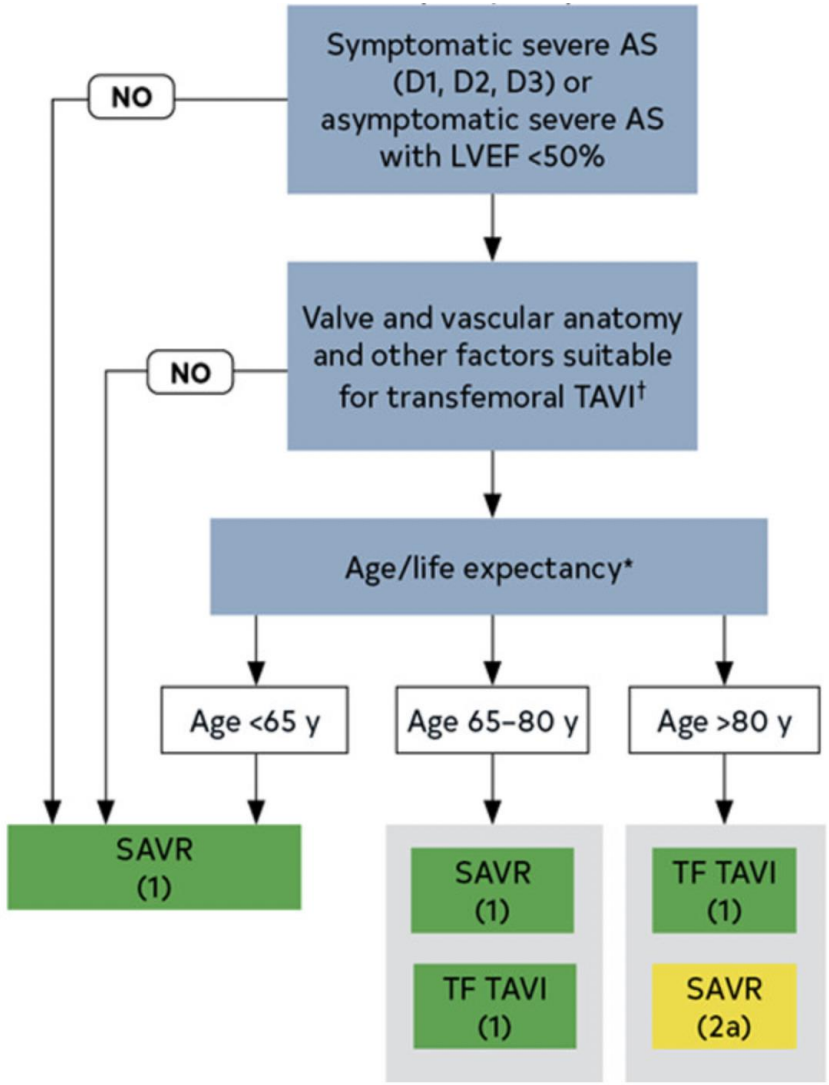
Therapy	Low- to Moderate-Risk	High Risk	Greater Risk
Transcatheter Aortic Valve Replacement (TAVR)	✓	✓	✓
Open-Heart Surgery (AVR)	✓	✓	

High Risk Patients Defined by STS Risk Score > 8%

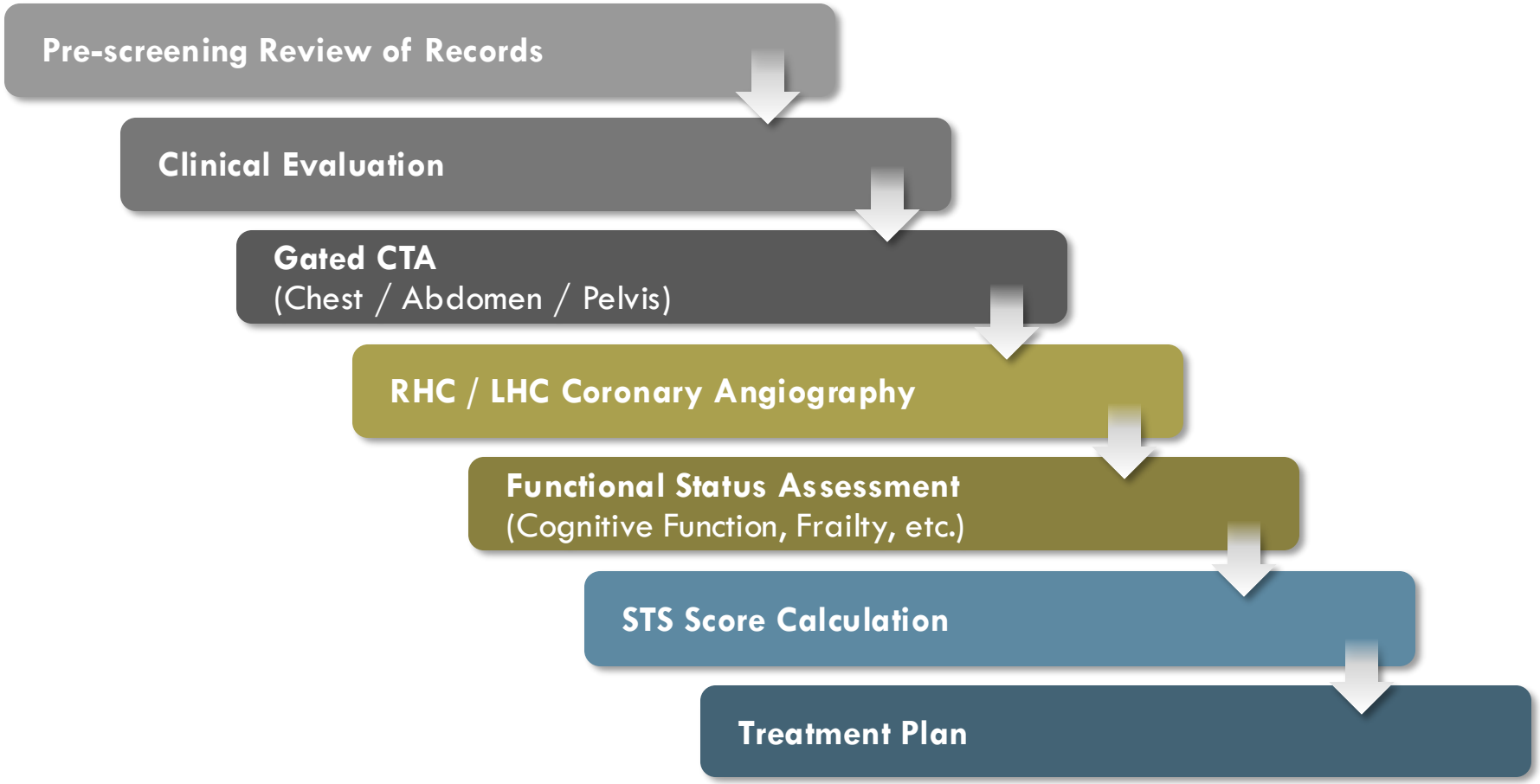
9. Nishimura RA et al. JACC. 2014. doi: 10.1016/j.jacc.2014.02.537.

CHOICE OF TAVR VERSUS SURGICAL AVR IN THE PATIENT WITH SEVERE SYMPTOMATIC AS

AHA/ACC VHD Guidelines

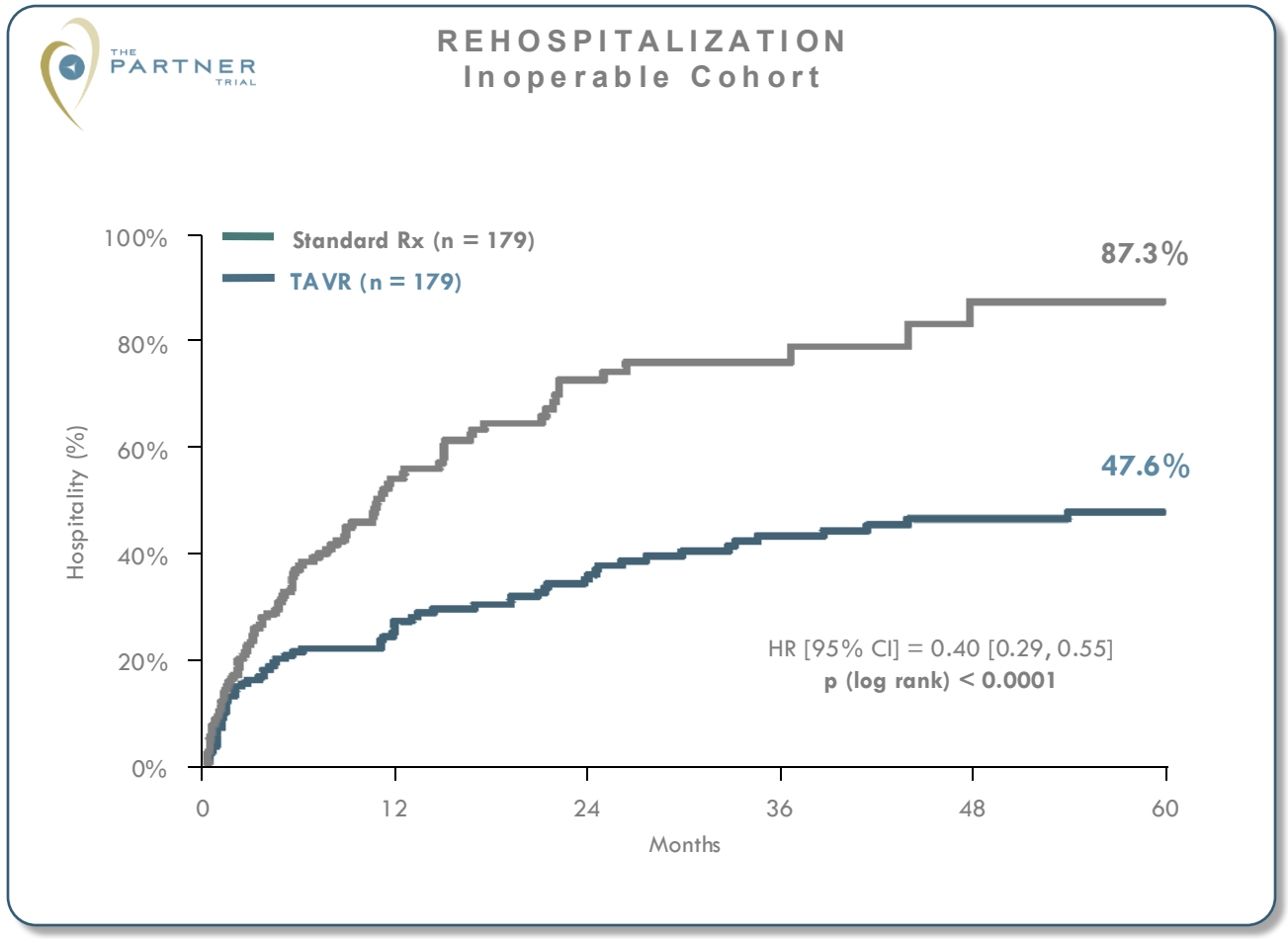


TAVR EVALUATION PATHWAY



Note: The above is a suggested flow for the patient screening process, however, the order in which screening tests are conducted varies depending on the patient's profile and should be at the discretion of the Heart Team.

STANDARD THERAPY PATIENTS WERE REHOSPITALIZED TWICE AS OFTEN AS TAVR PATIENTS

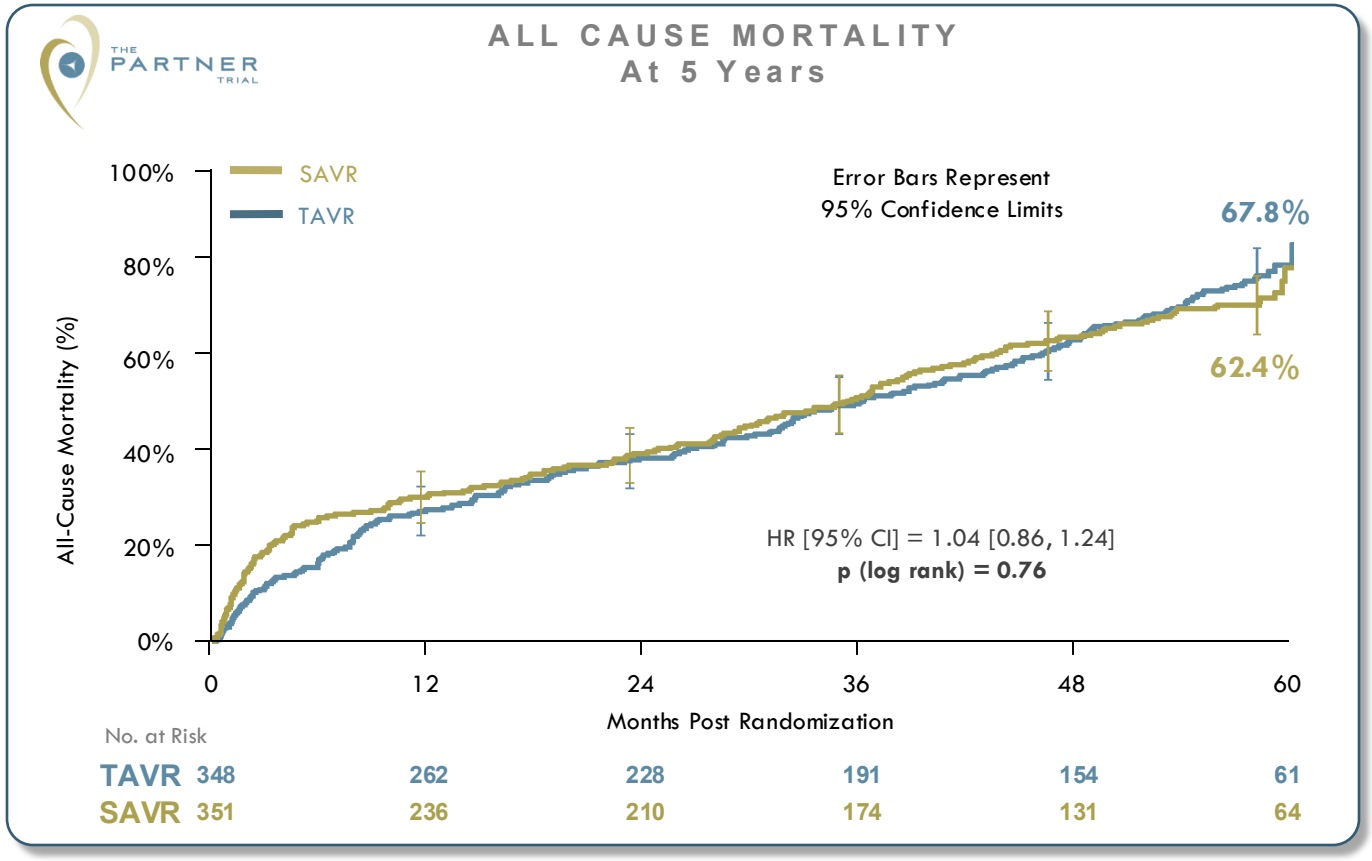


87.3% of patients with standard therapy were rehospitalized for cardiac issues

39.7% absolute reduction of rehospitilization at 5 years

Standard therapy includes medical management and BAV

TAVR IS EQUIVALENT TO SURGERY IN HIGH-RISK PATIENTS



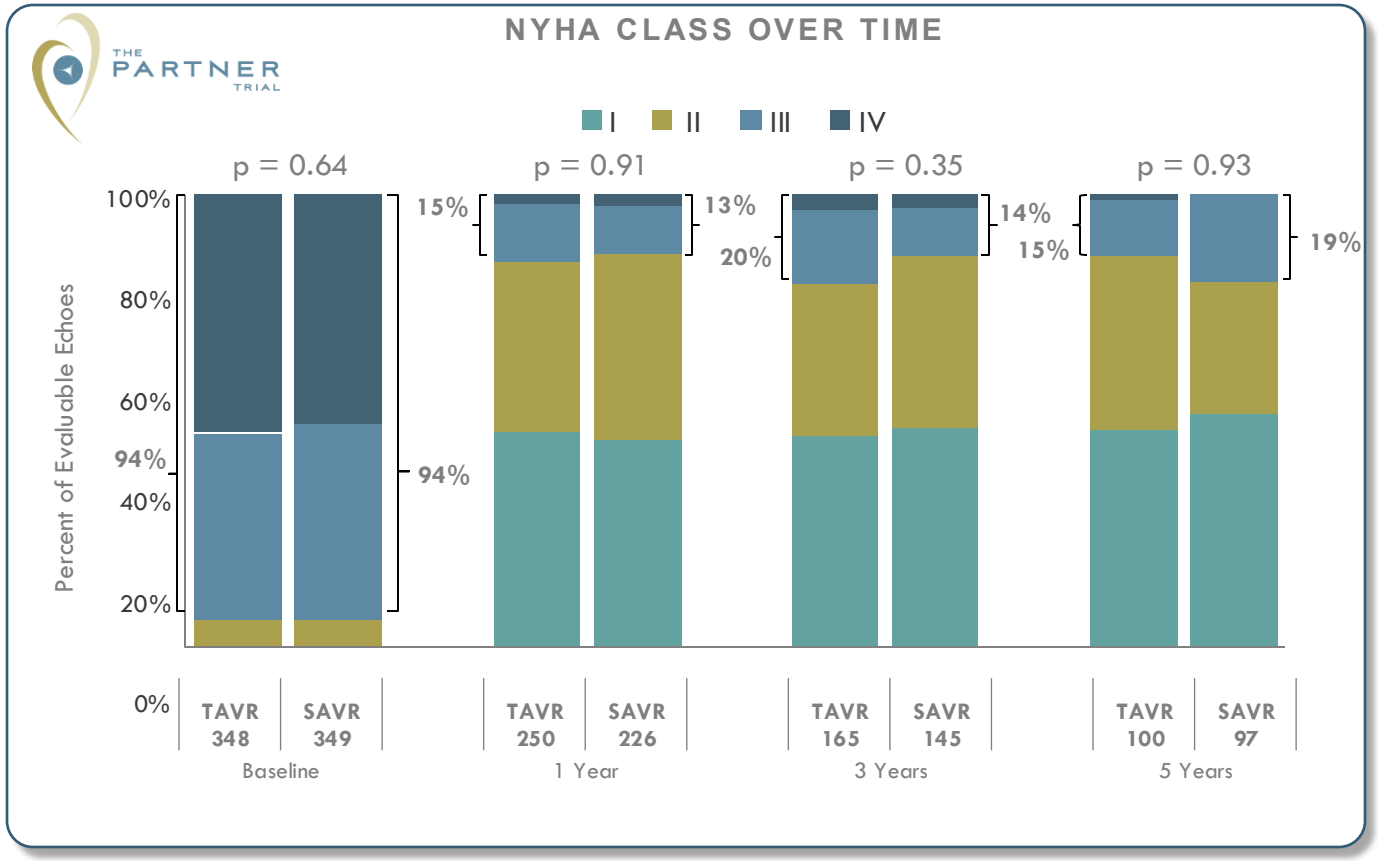
At 5 Years Patients that had TAVR with the Edwards SAPIEN valve showed survival equivalent to SAVR

Per ACC / AHA Guidelines, **TAVR is a reasonable alternative to surgery** in patients who meet an indication for AVR and who have high surgical risk for surgical AVR[9]

9. Nishimura RA et al. JACC. 2014. doi: 10.1016/j.jacc.2014.02.537.

PATIENTS CONTINUED TO SHOW IMPROVED SYMPTOM RELIEF 5 YEARS AFTER TAVR

At both 1 year and 5 year follow up, **85% of Patients** treated with the Edwards SAPIEN valve were in **NYHA Class I or II** compared to only **6% at baseline.**



LONGEST FOLLOW-UP IN ANY TAVR RANDOMIZED STUDY

TAVR vs. Standard Therapy in Inoperable Patients

- Significant mortality benefit
- Statistically significant reduction in hospitalization
- NNT is 5 patients to save a life

TAVR vs. Surgical AVR in High-Risk Patients

- Equivalent mortality benefit
- Persistent symptom relief

5 YEARS of PROVEN VALVE DURABILITY

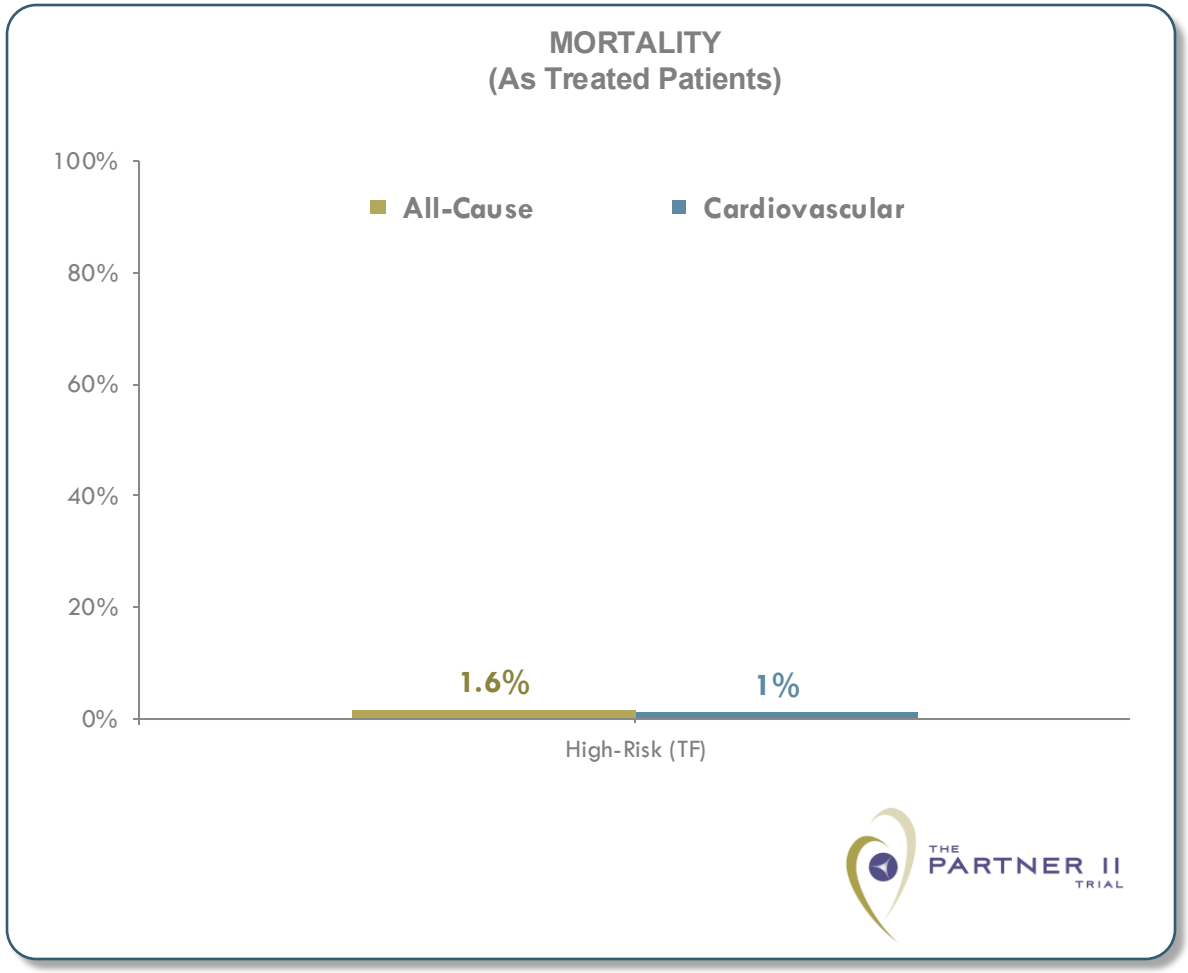
- Sustained hemodynamic performance
- No incidence of structural valve deterioration requiring surgical valve replacement[20]
- Significant and sustained improvement in functional heart class

20. Lancet. 2015 Jun 20;385(9986):2477-84. doi: 10.1016/S0140-6736(15)60308-7. Epub 2015 Mar 15.

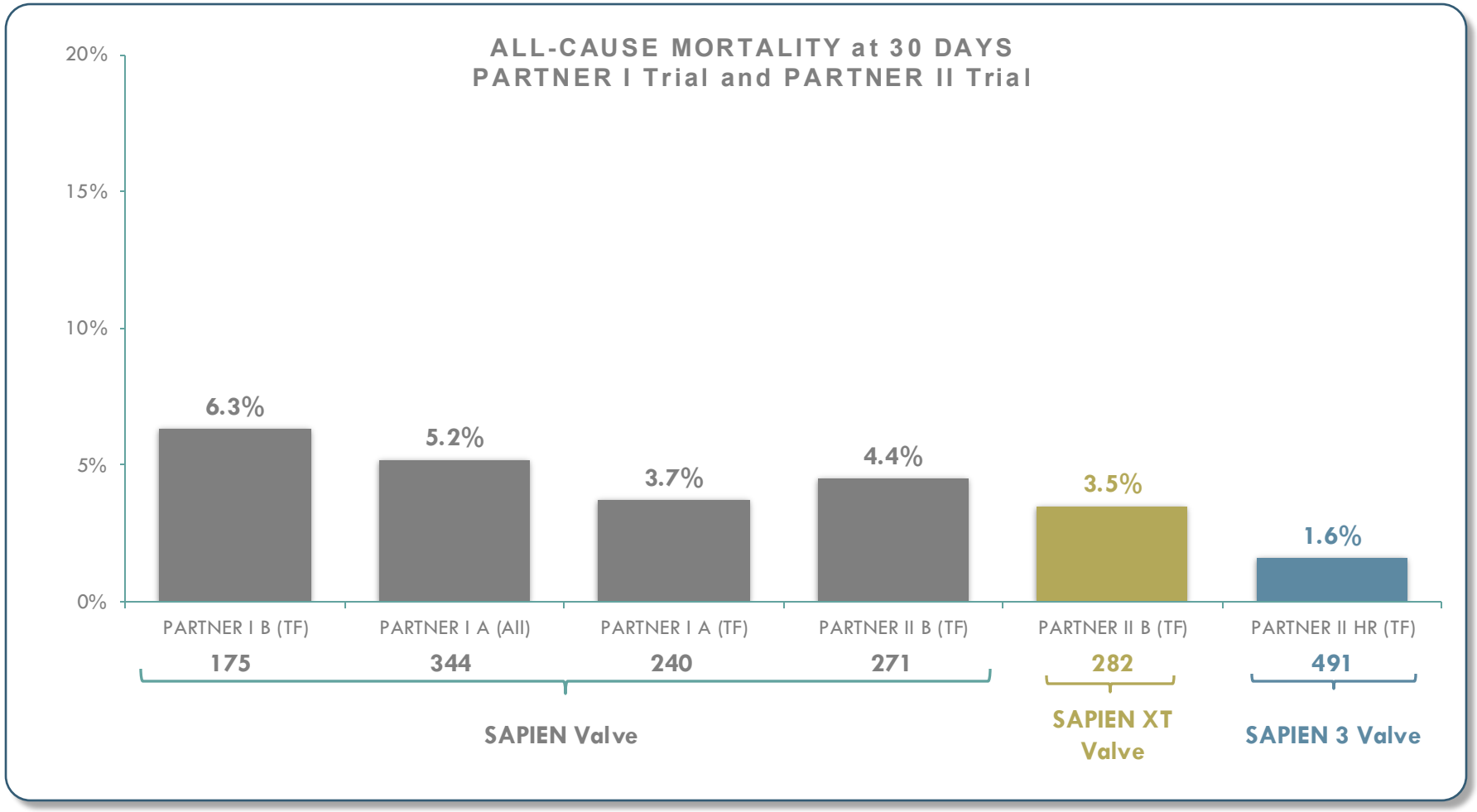
LOW MORTALITY AT 30 DAYS
THE PARTNER II TRIAL: SAPIEN 3 VALVE HIGH-RISK

All-Cause Mortality of the **491 patients** in the PARTNER II Trial was **1.6% at 30 days**

Cardiovascular Mortality was **1.0%**



ALL-CAUSE MORTALITY HAS DECREASED OVERALL



CLINICAL OUTCOMES IMPROVE AS THERAPY EVOLVES

Low Mortality and Stroke Rates
Patient selection, procedural techniques, device evolution

RetroFlex 3
Delivery System

NovaFlex+
Delivery System

Edwards Commander
Delivery System

Improved Vascular Access
Lower profile devices expands treatment possibilities

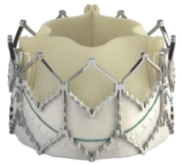
RetroFlex 3
Introducer Sheath

Edwards eSheath
Introducer Set

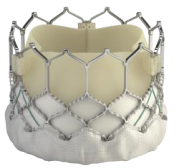
Edwards eSheath
Introducer Set*

Increased Treatment Range
Larger and smaller valves

SAPIEN Valve
23 and 26 mm



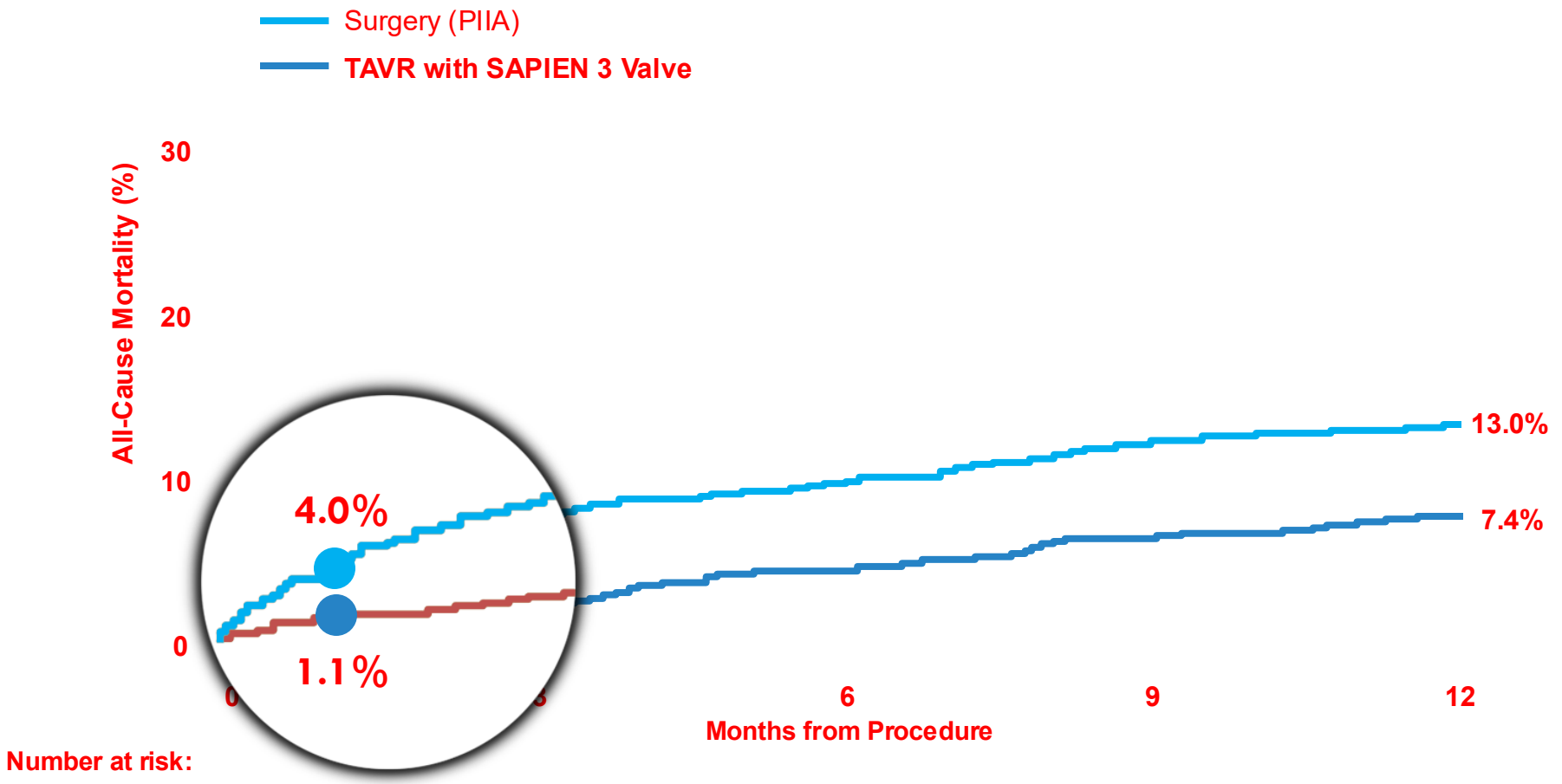
SAPIEN XT Valve
23, 26, 29 mm



SAPIEN 3 Valve
20, 23, 26, 29 mm

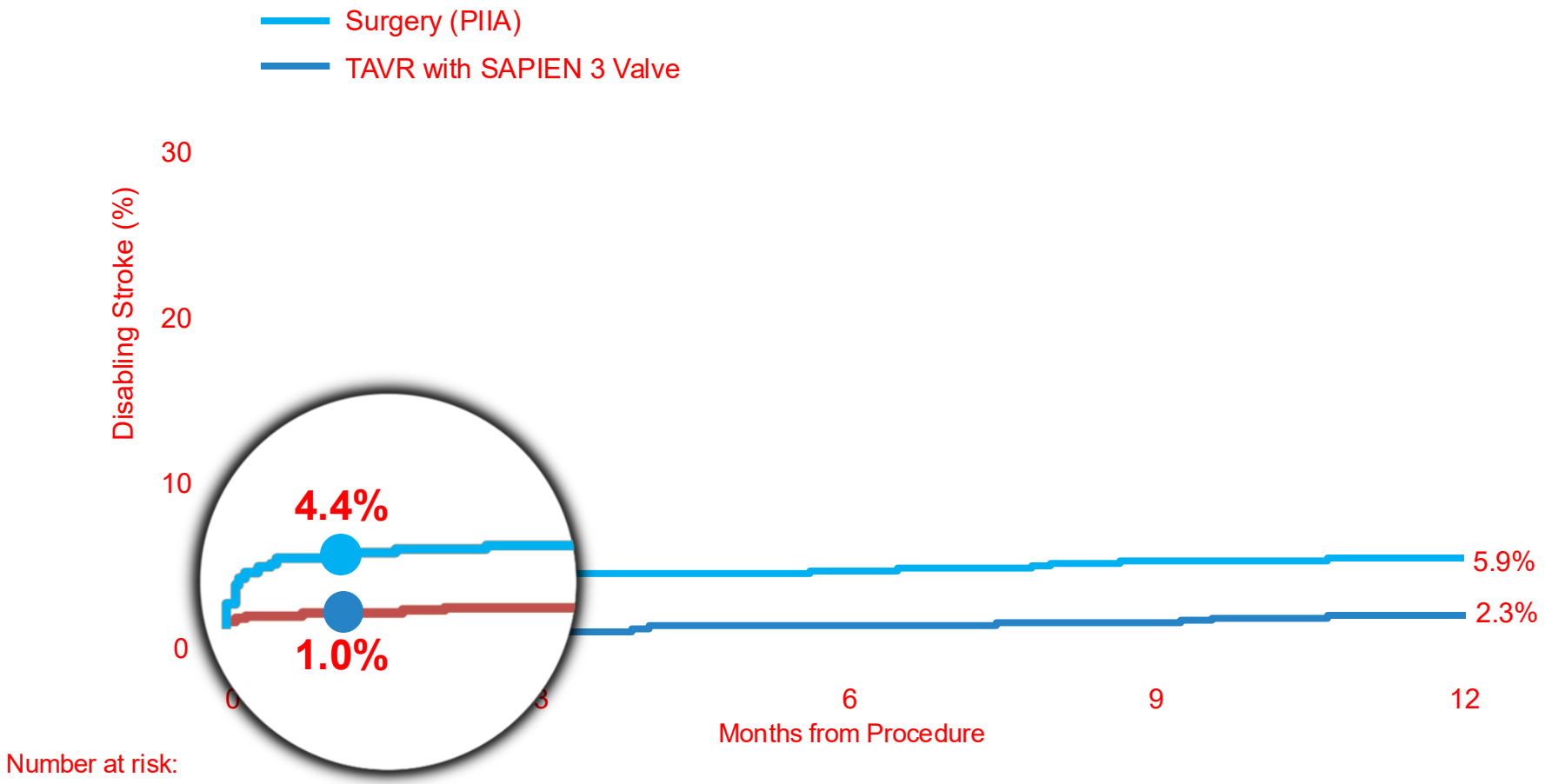
*only used with 20,23,26 valve sizes

ALL-CAUSE MORTALITY*



*The PARTNER II trial intermediate-risk cohort unadjusted clinical event rates.

DISABLING STROKE*



Number at risk:

Surgery	**944**	**825**	**806**	**778**	**764**
SAPIEN 3 TAVR	**1077**	**1033**	**1008**	**884**	**953**

*The PARTNER II trial intermediate-risk cohort unadjusted clinical event rates.

Gates Vascular Institute Symposium

UPDATES IN CARDIAC, VASCULAR & NEUROENDOVASCULAR MEDICINE

Original Article

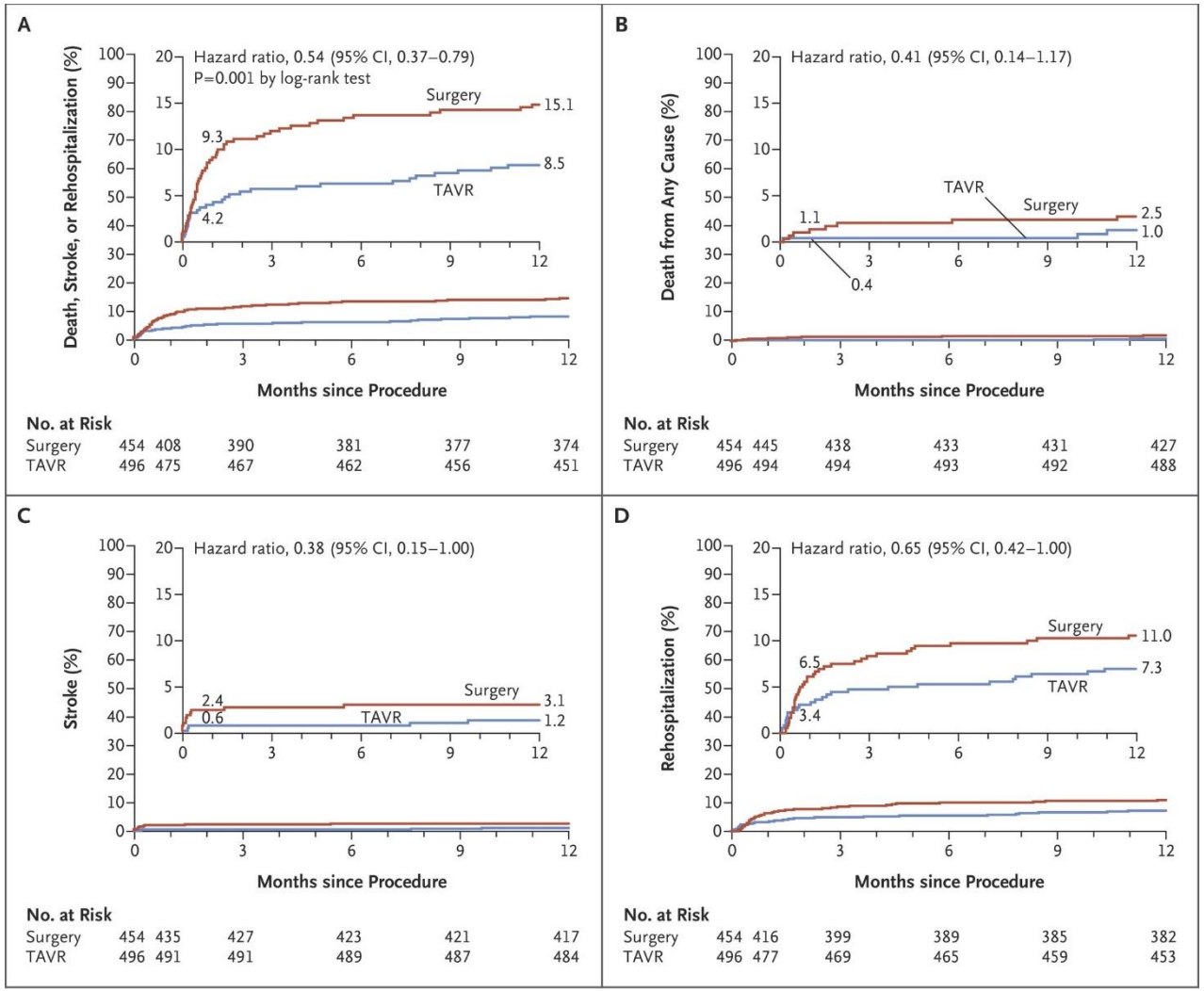
Transcatheter Aortic-Valve Replacement with a Balloon-Expandable Valve in Low-Risk Patients

Michael J. Mack, M.D., Martin B. Leon, M.D., Vinod H. Thourani, M.D., Raj Makkar, M.D., Susheel K. Kodali, M.D., Mark Russo, M.D., Samir R. Kapadia, M.D., S. Chris Malaisrie, M.D., David J. Cohen, M.D., Philippe Pibarot, D.V.M., Ph.D., Jonathon Leipsic, M.D., Rebecca T. Hahn, M.D., Philipp Blanke, M.D., Mathew R. Williams, M.D., James M. McCabe, M.D., David L. Brown, M.D., Vasilis Babaliaros, M.D., Scott Goldman, M.D., Wilson Y. Szeto, M.D., Philippe Genereux, M.D., Ashish Pershad, M.D., Stuart J. Pocock, Ph.D., Maria C. Alu, M.S., John G. Webb, M.D., Craig R. Smith, M.D., for the PARTNER 3 Investigators

The NEW ENGLAND JOURNAL of MEDICINE

Kaleida Health

Time-to-Event Curves for the Primary Composite End Point and the Individual Components of the Primary End Point.



EMBARGOED until the start of the late-breaking clinical trial session on March 17, 2019 at 8:00am CT

Evolut™ Low Risk Trial

Primary Results From the Evolut Low Risk Trial

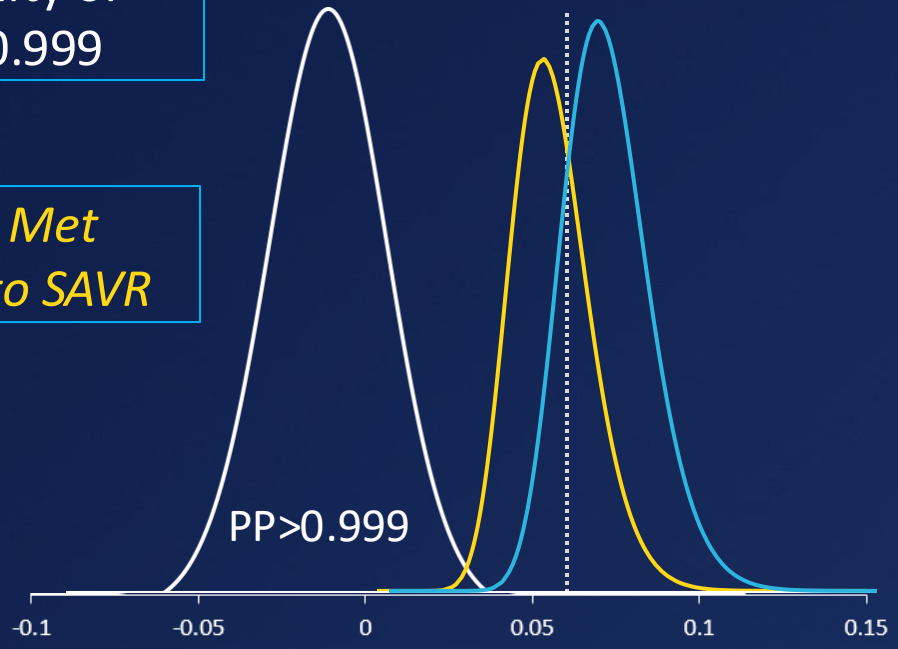
Michael J. Reardon, MD, FACC
Houston Methodist DeBakey Heart & Vascular Institute, Houston, TX
For the Evolut Low Risk Trial Investigators

Primary Endpoint

Evolut™ Low Risk Trial

Posterior probability of noninferiority > 0.999

Primary Endpoint Met
TAVR is noninferior to SAVR



SAVR 6.7%

TAVR 5.3%

TAVR –SAVR difference = -1.4% (95% BCI; -4.9, 2.1)

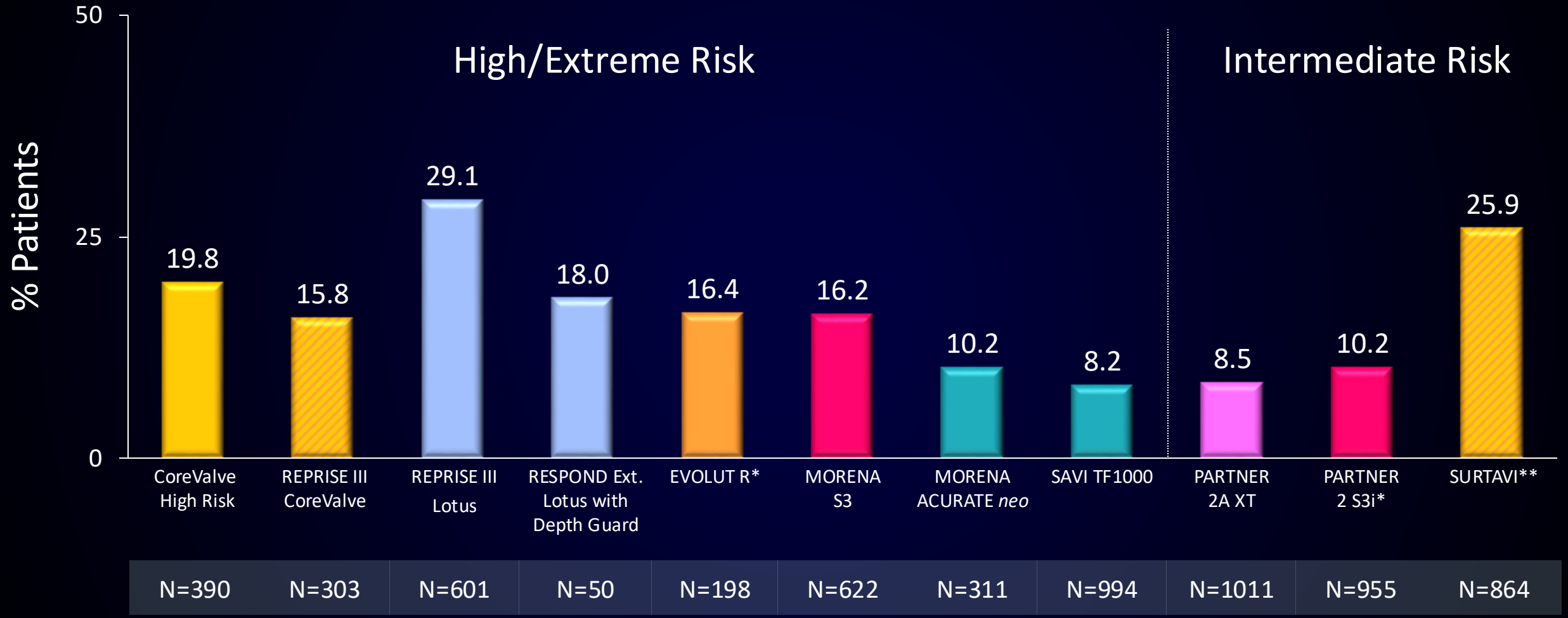
Evolut Low Risk Trial–ACC.19

Access

- Transfemoral Percutaneous (>90%)
- Transfemoral (cutdown)
- Transapical
- Transaortic
- Transaxillary percutaneous
- Transaxillary Cutdown
- Transcaval
- Transcarotid

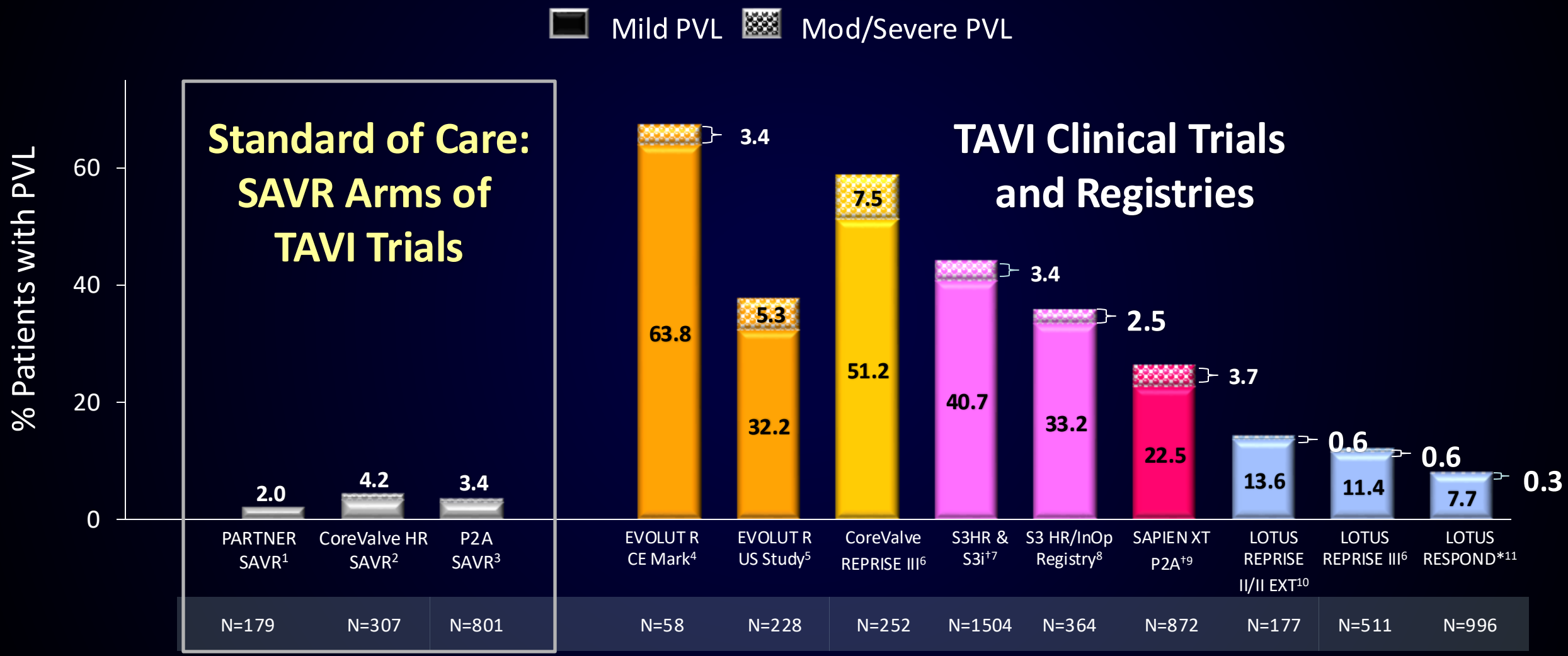
New Permanent Pacemaker to 30 Days

TAVI Clinical Studies



*KM estimate. **Bayesian rate. CoreValve High Risk: Adams, NEJM 2014. REPRISE III: Feldman, JAMA 2018. RESPOND Ext.: Blackman, PCR 2017. EVOLUT R: Popma, TCT 2016. MORENA: Husser, DGK 2017. SAVI TF1000: Möllmann, EuroPCR 2017. PARTNER 2A XT: Leon, NEJM 2016. PARTNER 2 S3i: Thourani, Lancet 2016. SURTAVI: Reardon, NEJM 2017. The Lotus™ Valve System / LOTUS Edge™ Valve System may only be used in countries where it is approved for use. The Lotus™ Valve System / LOTUS Edge™ Valve System is not available for sale in the European Economic Area. Results from different studies are not directly comparable. Information provided for educational purpose only.

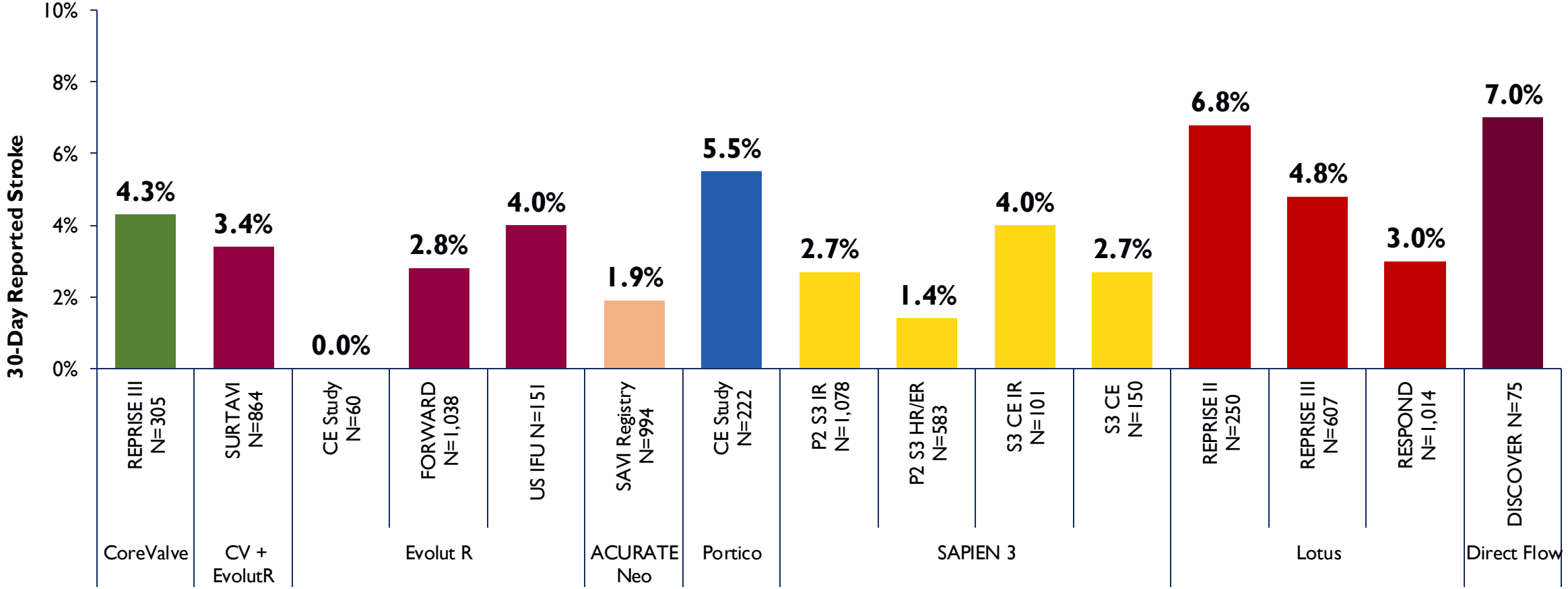
PVL post-TAVI and PVL post-SAVR at 30 days



*7d/Discharge; 30d angiography not mandated per protocol. †Intermediate risk patient population. Results from different studies are not directly comparable. Information provided for educational purpose only. [1]Leon, NEJM 2012 Supp. Appendix. [2]Adams, NEJM 2014 Suppl. Appendix. [3]Thourani, Lancet 2016 Suppl. Appendix. [4]Manoharan, JACC 2015. [5]Popma JACC 2017. [6]Feldman, JAMA 2018 (only echocardiograms with gradable PVL were included). [7]Kodali , EHJ 2016. [8]Hermann, Circulation 2016.[9]Leon NEJM 2016. [10]Meredith, PCR LV 2014. [11]Falk V, PCR 2016.

Results from different studies are not directly comparable. Information provided for educational purpose only.

- Stroke remains an issue (~3.5% average rate) in contemporary TAVR studies
- TAVR device trials tend to emphasize only the major/disabling stroke rates



[1] Feldman, et al., EuroPCR 2017; [2]Manoharan, et al., *J Am Coll Cardiol Intv* 2015; 8: 1359-67; [3]Moellman, et al., PCR London Valves 2015; [4]Grube, et al., EuroPCR 2017; [5]Kodali, et al., *Eur Heart J* 2016; [6]Vahanian, et al., EuroPCR 2015; [7]Webb, et. al. *J Am Coll Cardiol Intv* 2015; 8: 1797-806; [8]DeMarco, et al, TCT 2015; [9]Meredith, et al., PCR London Valves 2015; [10]Falk, et al., EuroPCR 2016; [11]Kodali, TCT 2016; Reardon, M *NEJM* 2017

TAVR: ONLY AT THE GVI

- Highest volume of cases in the State of New York outside of NYC (>4700 cases performed)
- Excellent outcomes with low mortality rates and LOS of 1 day
- Team based approach for every patient
- Access to latest technology
- Clinical trials

- Single Call access, Access to implant date <30 days.

TRANSCATHETER AORTIC VALVE INTERVENTION

COMPETITIVE DEVICE PORTFOLIO

Commercially Available

ABBOTT
Portico **Navitor**

BOSTON SCIENTIFIC
Acurate Neo2

JENAVALVE
Trilogy

MERIL
MyVal

MEDTRONIC
Evolut R/PRO

EDWARDS
Sapien 3
ULTRA

Global TAVR Devices

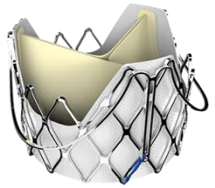
Allegra

Venibri

Hydra

Venus

Vitaflow



J-Valve

NATIVE AORTIC REGURGITATION: THE NEXT FRONTIER

No transcatheter device has received U.S. regulatory approval for the treatment of AR

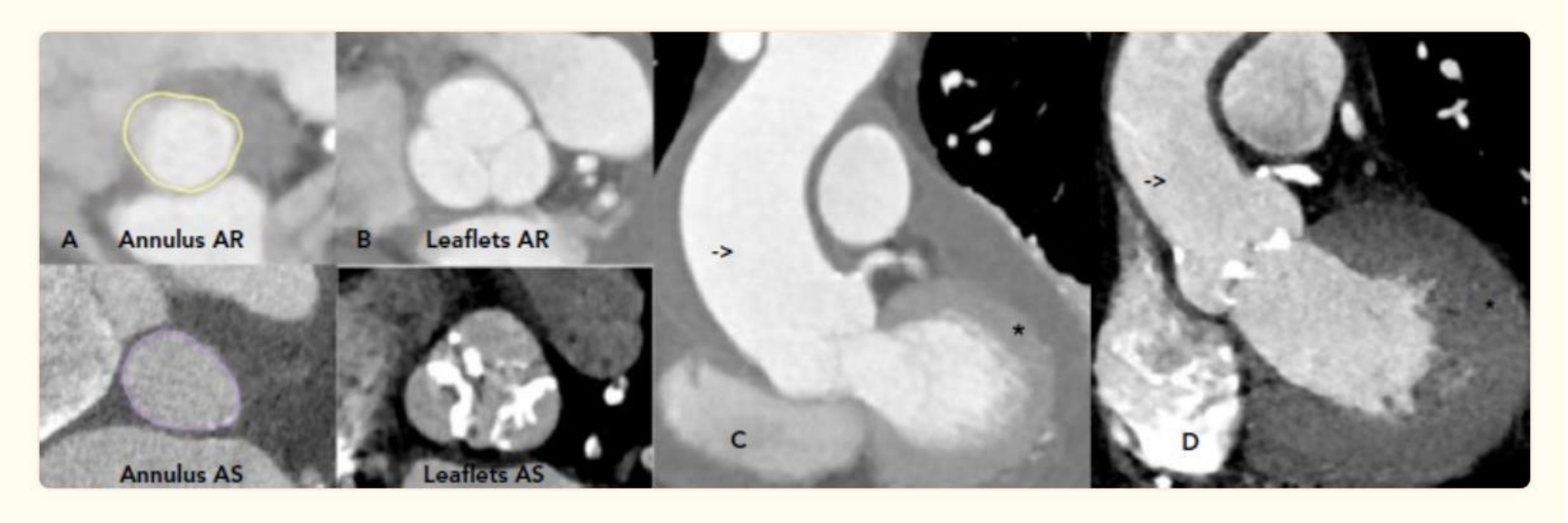
TAVR not recommended in US guidelines

7. TAVI for isolated chronic AR is challenging because of dilation of the aortic annulus and aortic root and, in many patients, lack of sufficient leaflet calcification. Risks of TAVI for treatment of AR include transcatheter valve migration and significant paravalvular leak (29-32). TAVI is rarely feasible, and then only in carefully selected patients with severe AR and HF who have a prohibitive surgical risk and in whom valvular calcification and annular size are appropriate for a transcatheter approach.

3: Harm	B-NR

7. In patients with isolated severe AR who have indications for SAVR and are candidates for surgery, TAVI should not be performed (29-32).

Challenges of TAVR in AR



Lack of Calcium

LV/Root Dilatation

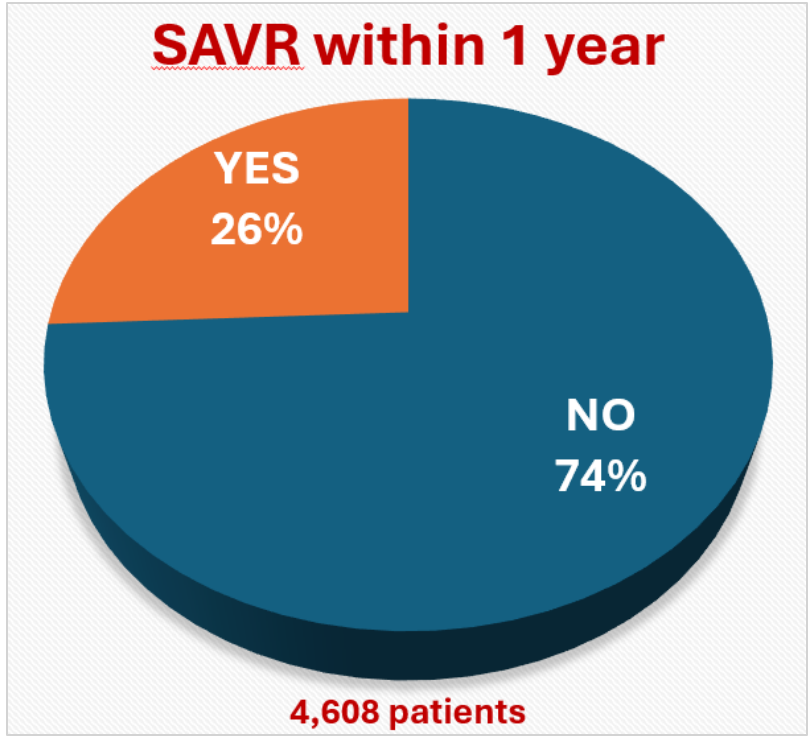
Large Annular Size

Lack of Contrast/Poor visualization

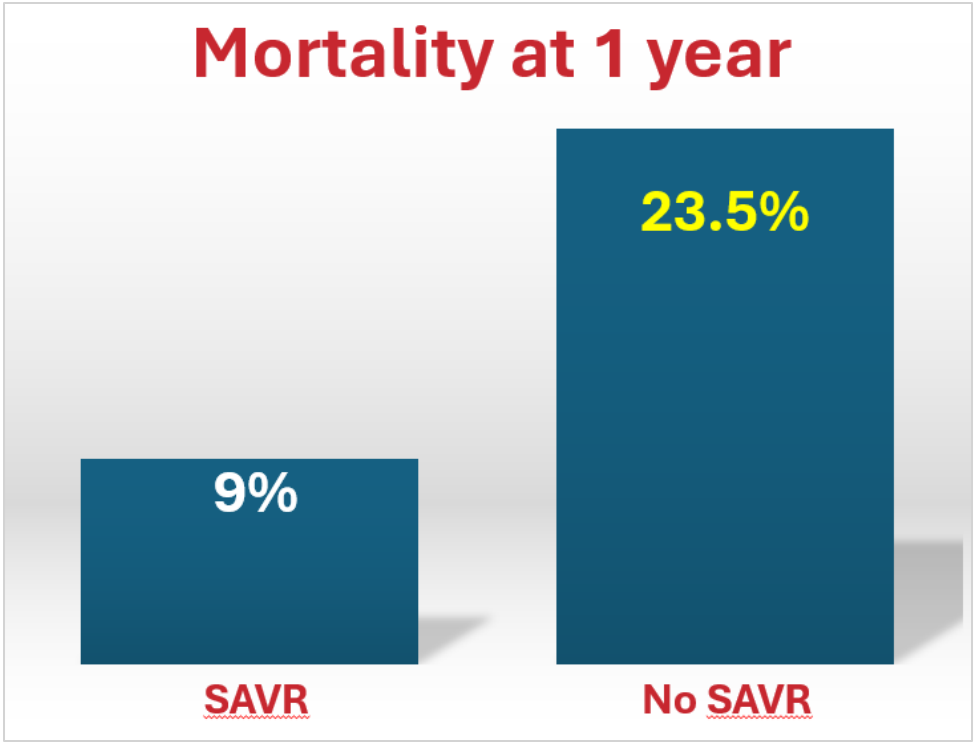
Arias et al. Interv Cardiol. 2019

Aortic Regurgitation:
Undertreated & Associated with Increased Mortality

DRAMATIC UNDERTREATMENT OF SYMPTOMATIC SEVERE AR

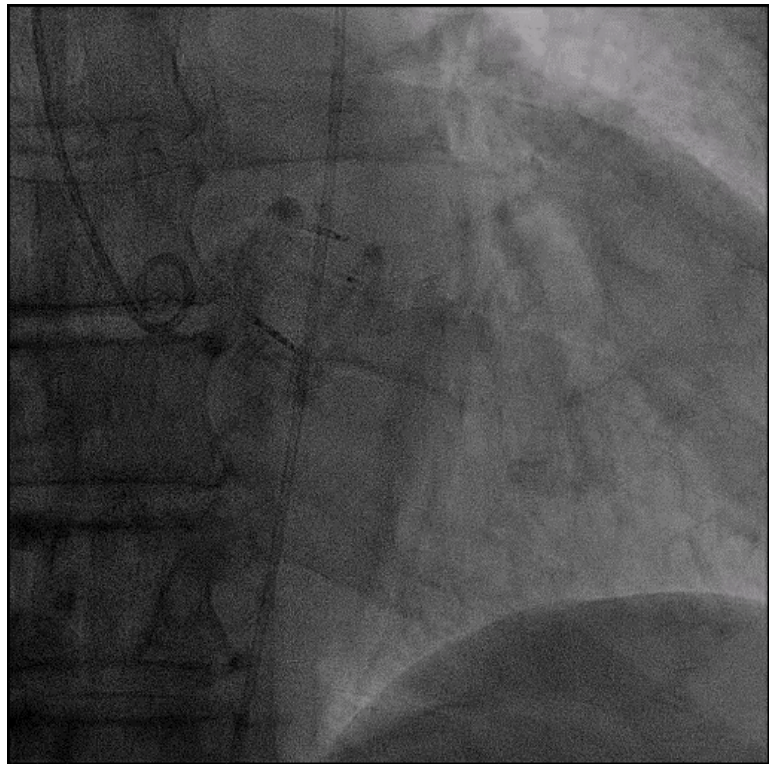


Untreated AR results in a 1-year mortality of 23.5%



Thourani V, et al. Structural Heart. 2021 Nov 2;5(6):608-6018.

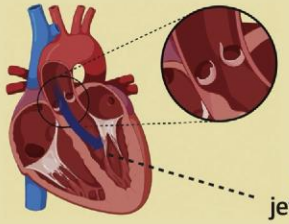
TAVR WITH COMMERCIAL DEVICES



CENTRAL ILLUSTRATION: Meta-Analysis Overview and Findings

Meta-analysis of Dedicated Versus Off-Label TAVR for Native Aortic Valve Regurgitation

Challenges of TAVR in native AR



Aortic annulus dilation → Larger valve sizes, Over-sizing THVs

Absence of calcium for anchoring and stability → Clipping/grasping of leaflets, Sealing ring

Severe aortic regurgitant jet causing "suction effect" → Rapid pacing >120 beats/min

TAVR and THV design specific solutions

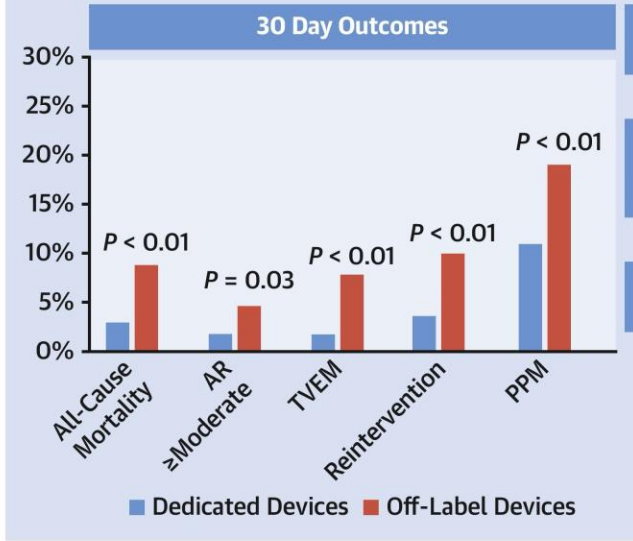
34 Studies

2,162 Patients

1,193 Dedicated Devices

969 Off-label Devices

Mean age = 75.4 ± 0.2 years
STS score = 5.6 ± 0.1 %
Log EuroSCORE = 24.2 ± 0.3%



Device Success
93% vs 82%

Similar risk of:
Stroke
Vascular complications

Mortality at 1 year
6% vs 24%

Samimi S, et al. JACC Cardiovasc Interv. 2024;10.1016/j.jcin.2024.08.042

GUIDELINES

JenaValve Announced ESC Guidelines Recognize TAVI as Class IIb Recommendation for Aortic Regurgitation

Thank you!

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