Is TAVR Now Indicated in Even Low Risk Aortic Valve Disease Patients

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Potential conflicts of interest

Saibal Kar, MD:

❑ **I do not have any potential conflict of interest**

☑ **I have the following potential conflicts of interest to report:**

Honorarium:	Abbott Vascular, Boston Scientific
Institutional grant/research support:	Abbott Vascular, Boston Scientific, Cardiokinetix, Mitralign
Consultant:	Abbott Vascular, Boston Scientific

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Introduction

- >17,000 Cases are performed per year in US.
- TAVR is FDA approved for high and extreme surgical risk patients with symptomatic Aortic stenosis(AS)
- Studies on intermediate risk patients have been completed
- Ongoing trials on low/moderate risk surgical patients are enrolling subjects

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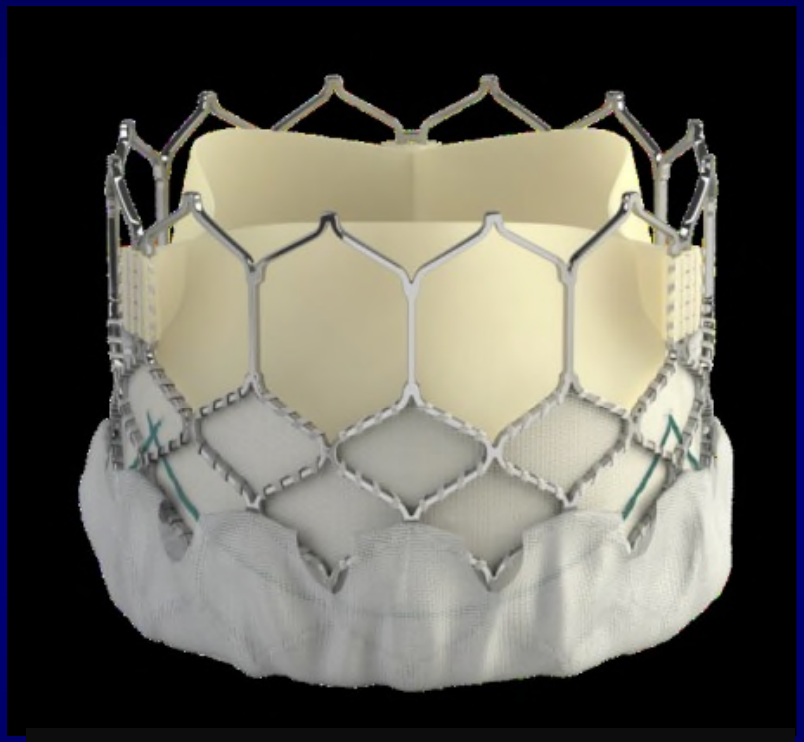
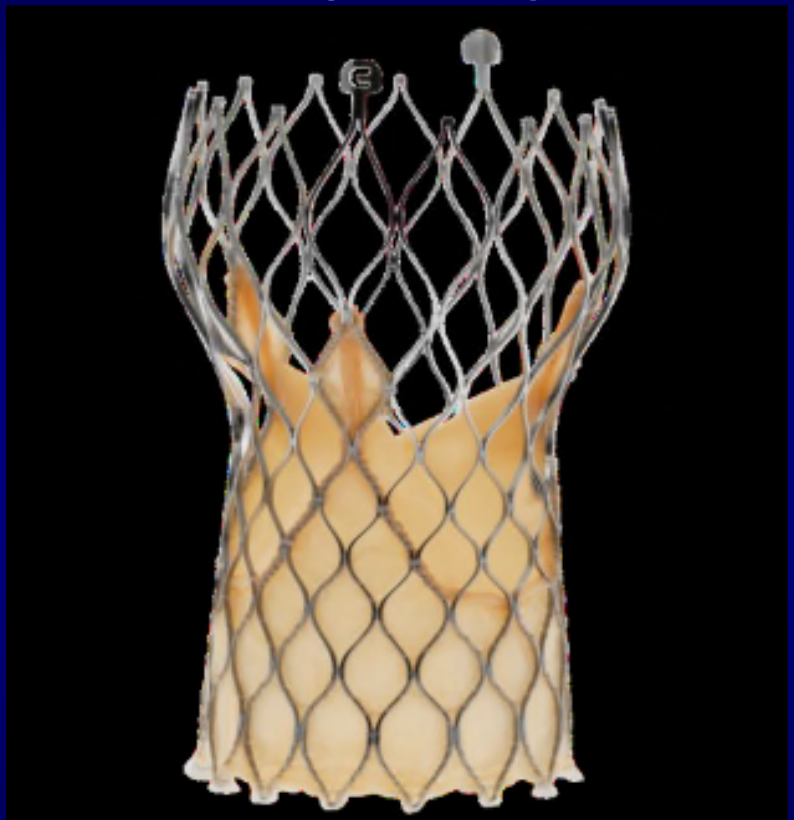
FDA approved TAVR platforms

Balloon Expandable



Edwards SAPIEN 3 Transcatheter Heart Valve

Self – Expanding



Medtronic EvoluteR Transcatheter Heart Valve

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TAVR valve in trials in US

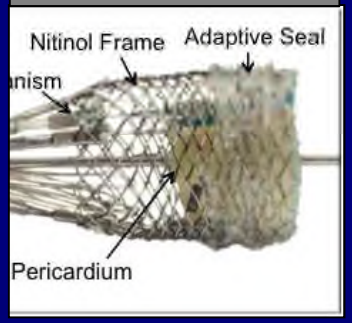
Trials on low/moderate risk patients

Sapien 3

Evolute

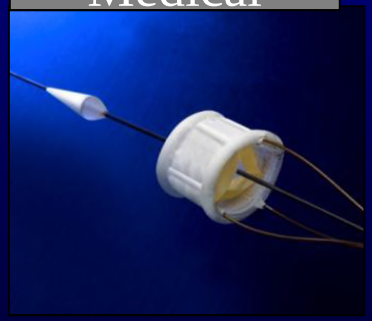
Trials on extreme/high risk patients

Lotus



St. Jude Portico

Direct Flow Medical



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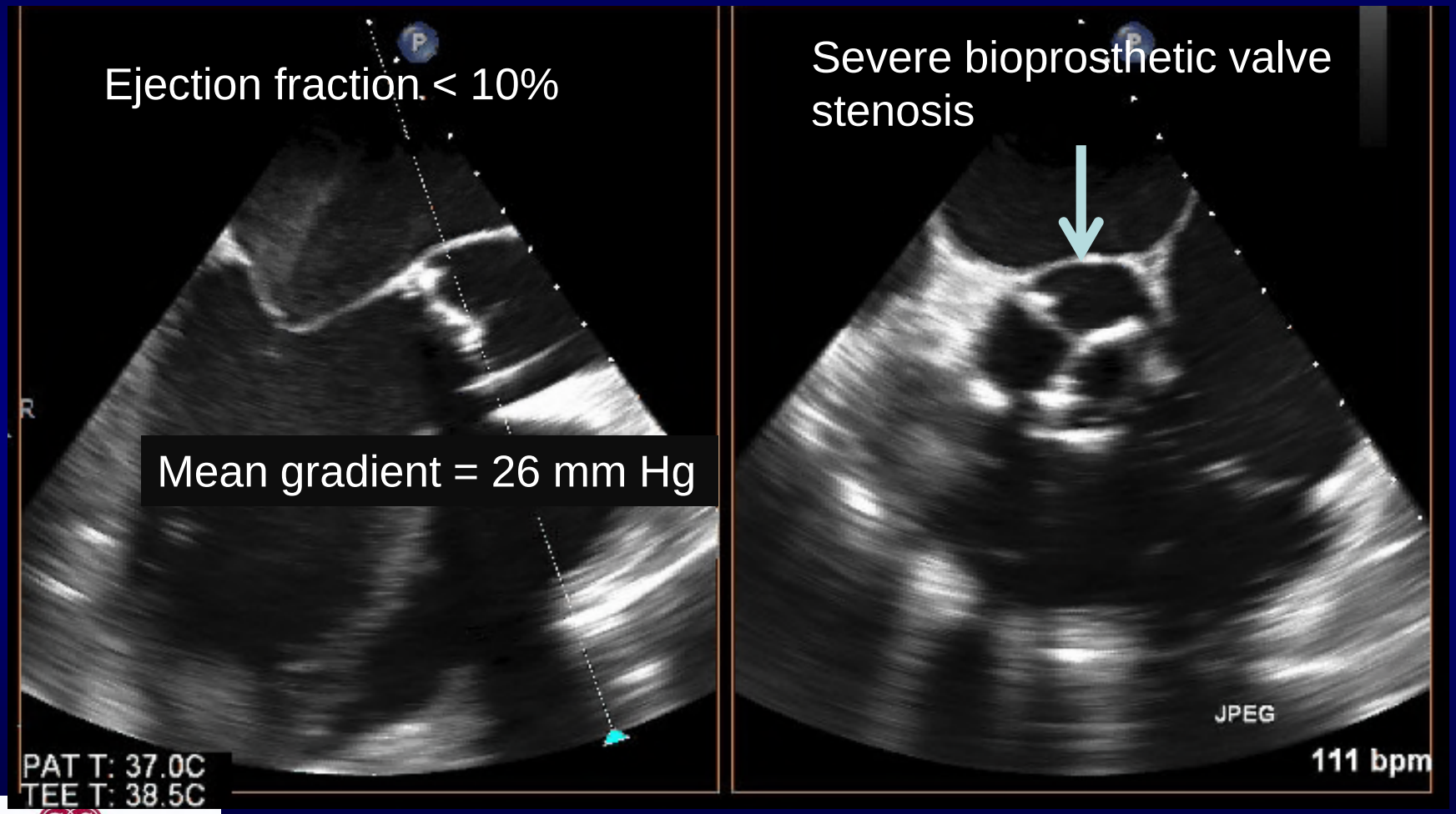
61 yr old male gasping for breath: history of aortic replacement in 2007. in Cardiogenic shock referred to evaluation of transplant/assist device



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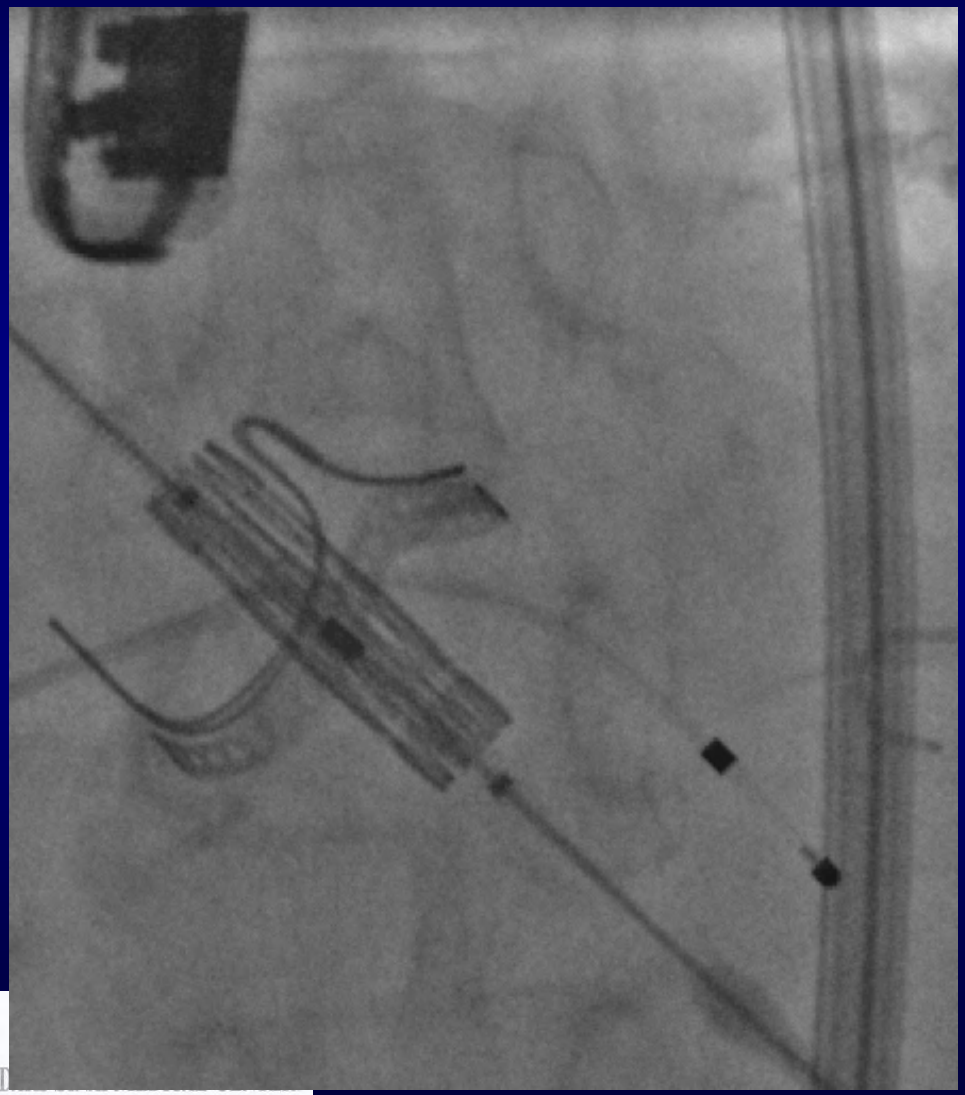
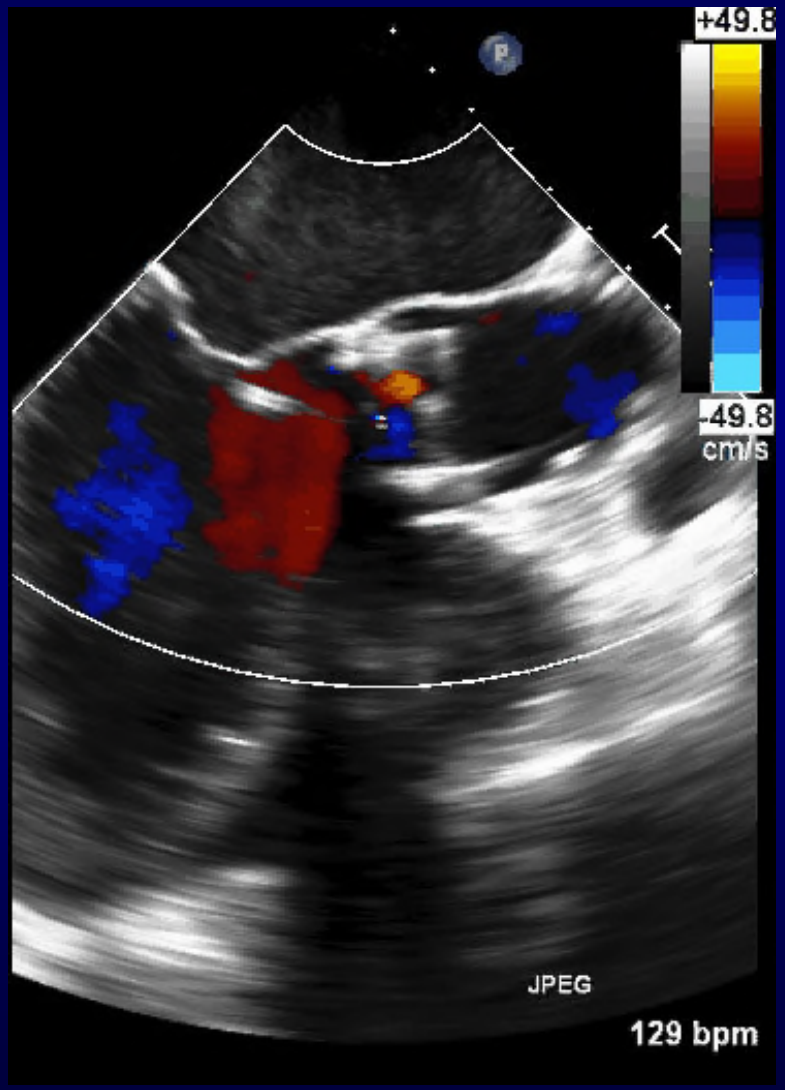
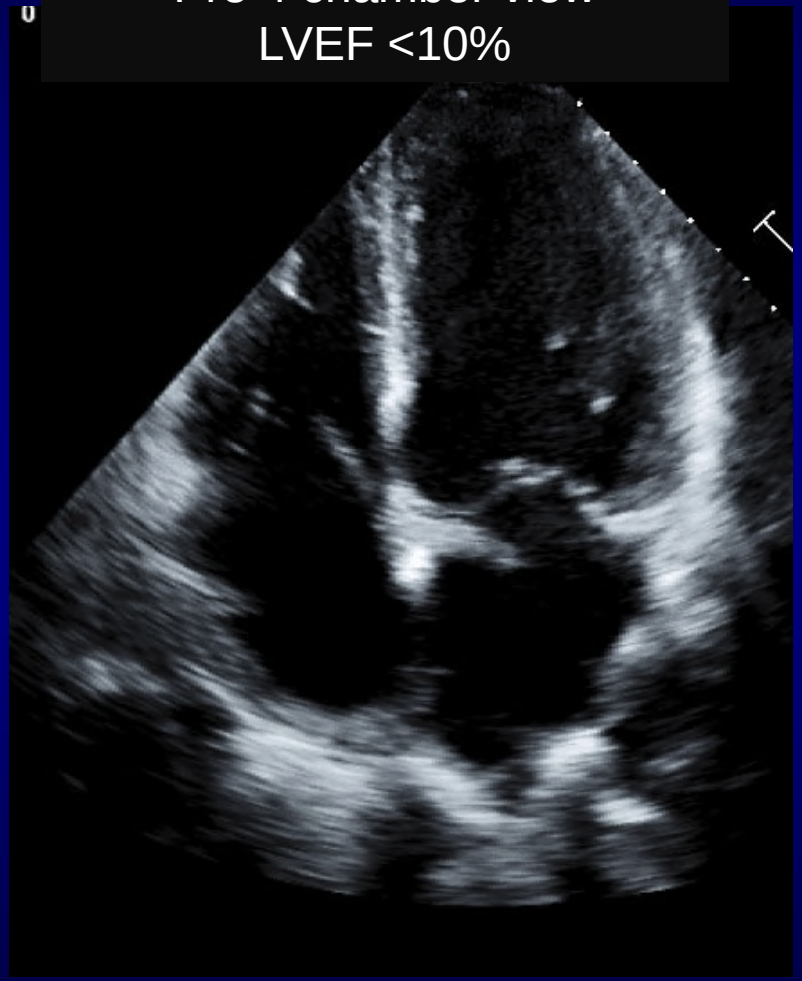
Urgent TAVR using a 26 mm SAPIEN 3 valve (no support)



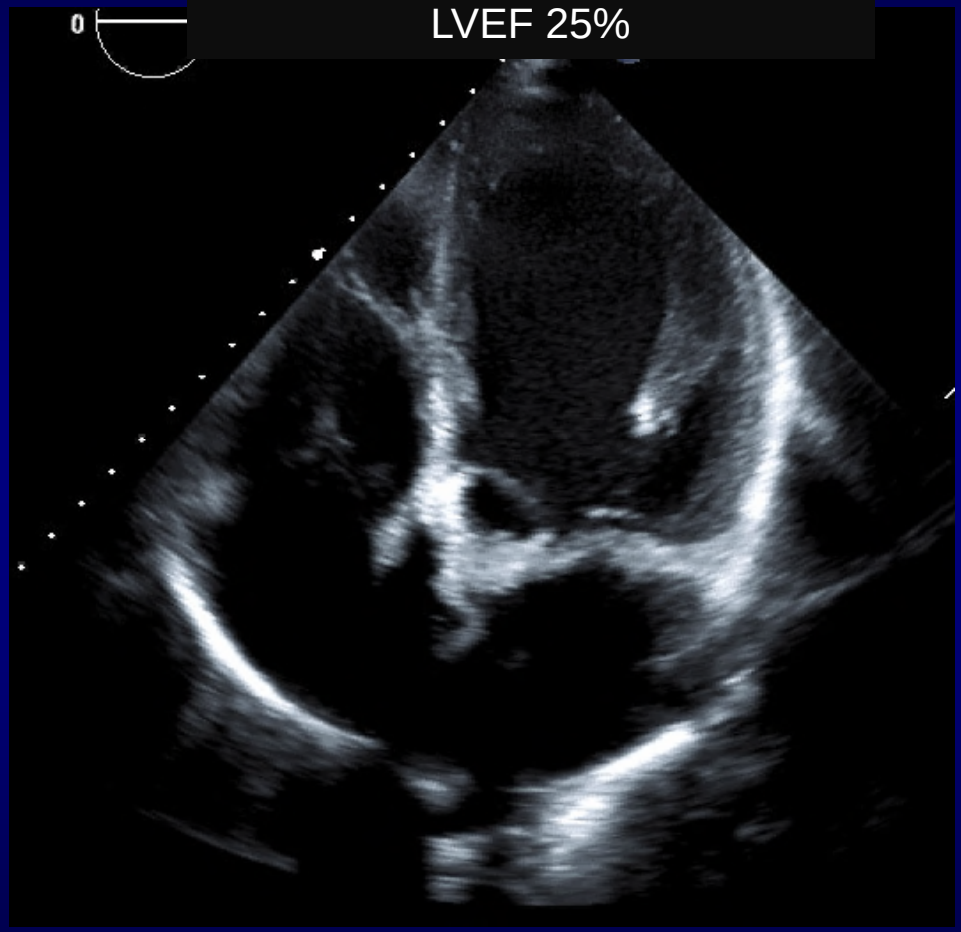


Discharged home in a week

Pre 4 chamber view
LVEF <10%



Day 4 4 chamber view
LVEF 25%



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LV dysfunction improved
Trace AR, Peak PG = 16 mmHg, Mean PG = 10 mmHg

Clinical evidence supporting TAVR in intermediate risk patients

- Final results of the PARTNER II trial
- SAPIEN 3 TAVR Compared with Surgery in Intermediate-Risk Patients: Propensity score analysis
- 3 year data of the Corevalve Pivotal study

The PARTNER 2A Trial

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Transcatheter or Surgical Aortic-Valve Replacement in Intermediate-Risk Patients

Martin B. Leon, M.D., Craig R. Smith, M.D., Michael J. Mack, M.D., Raj R. Makkar, M.D., Lars G. Svensson, M.D., Ph.D., Susheel K. Kodali, M.D., Vinod H. Thourani, M.D., E. Murat Tuzcu, M.D., D. Craig Miller, M.D., Howard C. Herrmann, M.D., Darshan Doshi, M.D., David J. Cohen, M.D., Augusto D. Pichard, M.D., Samir Kapadia, M.D., Todd Dewey, M.D., Vasilis Babaliaros, M.D., Wilson Y. Szeto, M.D., Mathew R. Williams, M.D., Dean Kereiakes, M.D., Alan Zajarias, M.D., Kevin L. Greason, M.D., Brian K. Whisenant, M.D., Robert W. Hodson, M.D., Jeffrey W. Moses, M.D., Alfredo Trento, M.D., David L. Brown, M.D., William F. Fearon, M.D., Philippe Pibarot, D.V.M., Ph.D., Rebecca T. Hahn, M.D., Wael A. Jaber, M.D., William N. Anderson, Ph.D., Maria C. Alu, M.M., and John G. Webb, M.D., for the PARTNER 2 Investigators*

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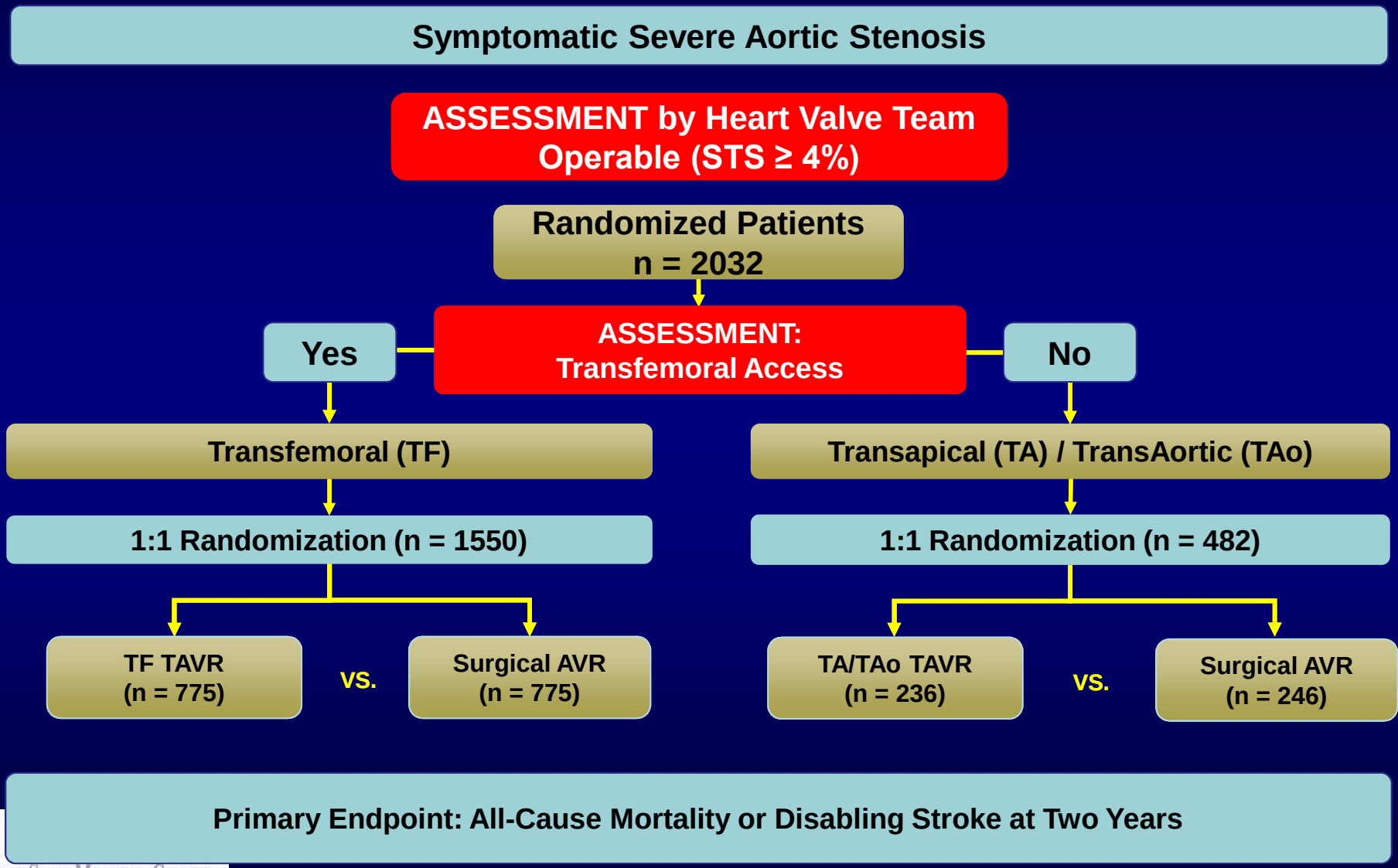
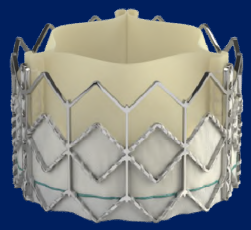
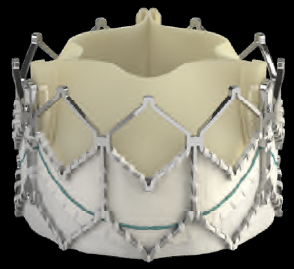
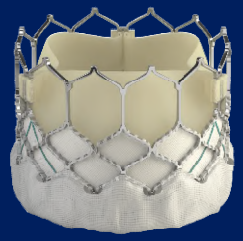
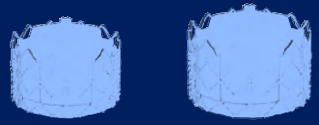
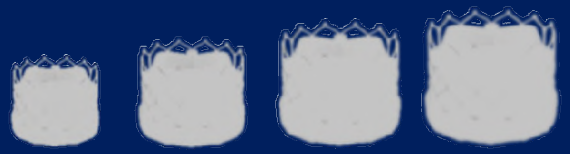
N Engl J Med 2016;374:1609-20

The PARTNER 2A Trial

Study Design



PARTNER SAPIEN Platforms
Device Evolution

	SAPIEN	SAPIEN XT	SAPIEN 3
Valve Technology			
Sheath Compatibility			
Available Valve Sizes	 23 mm 26 mm	 23mm 26mm 29mm*	 20 mm 23 mm 26 mm 29 mm

*First Implant Oct 30, 2012

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Primary Endpoint

- Non-hierarchical composite of *all-cause mortality or disabling stroke* at two years*
- Intention-to-treat population is the primary analysis;
  - As-Treated (AT) population also a pre-specified, powered analysis
  - Transfemoral (TF) subgroup pre-specified
- All patients followed for at least 2 years
- Event rates by Kaplan-Meier estimates

*Disabling stroke = CEC adjudicated stroke by a neurologist with a modified Rankin score of 2 or greater at 30 or 90-day evaluation

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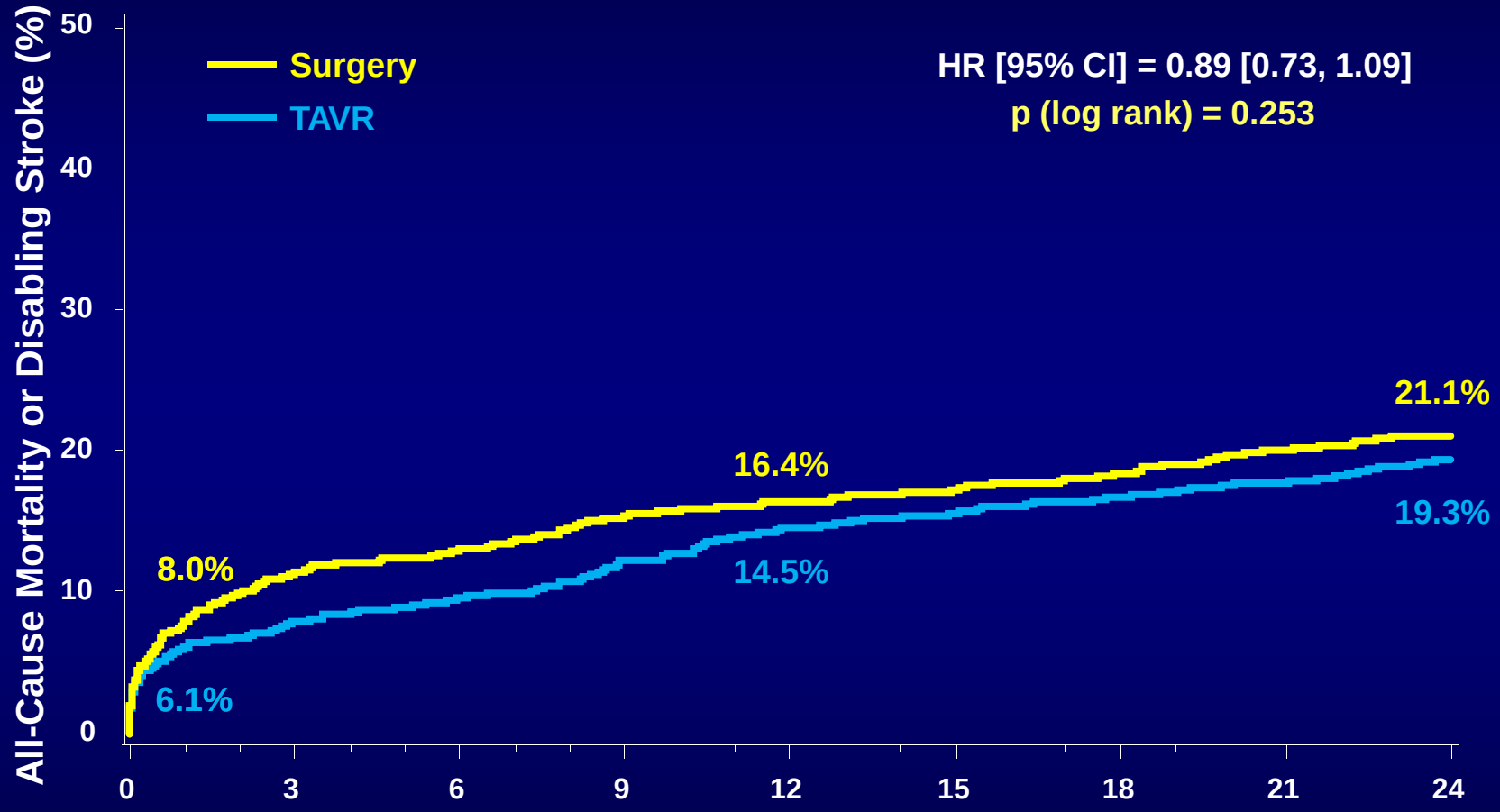
Primary Endpoint (ITT)
All-Cause Mortality or Disabling Stroke



Number at risk:

Surgery	1021	838	812	783	770	747	735	717	695
TAVR	1011	918	901	870	842	825	811	801	774

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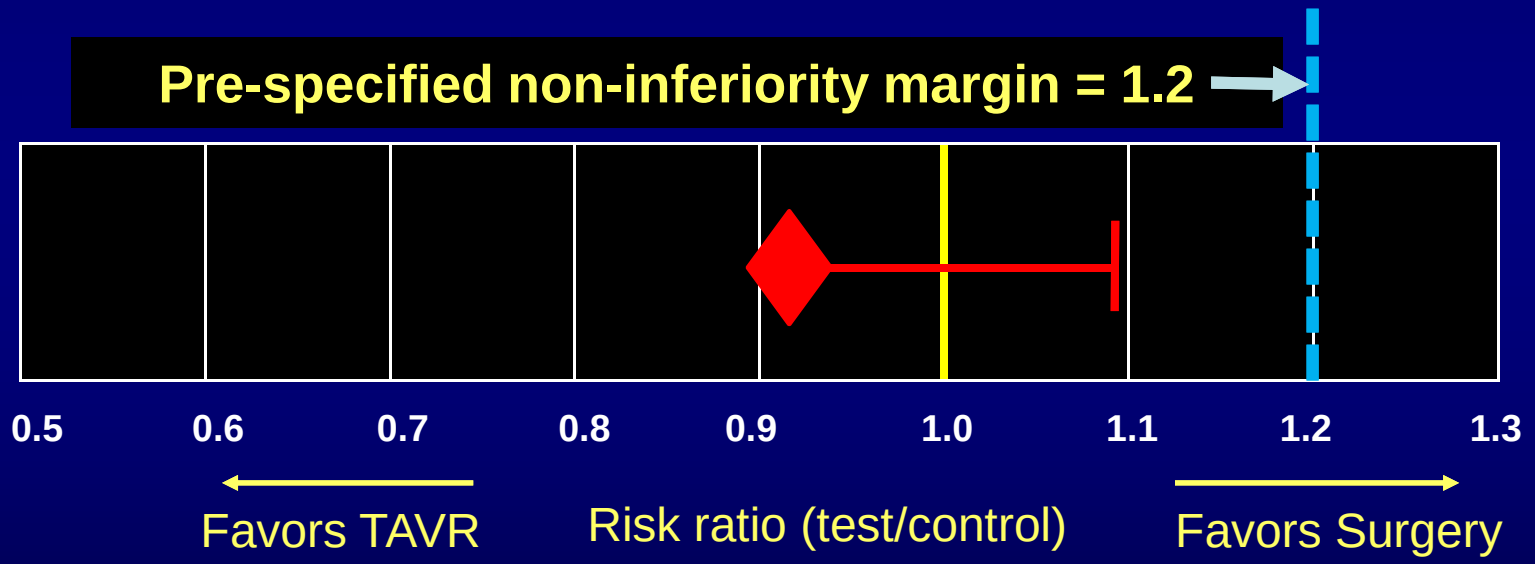
Primary Endpoint (ITT)
All-cause Mortality or Disabling Stroke

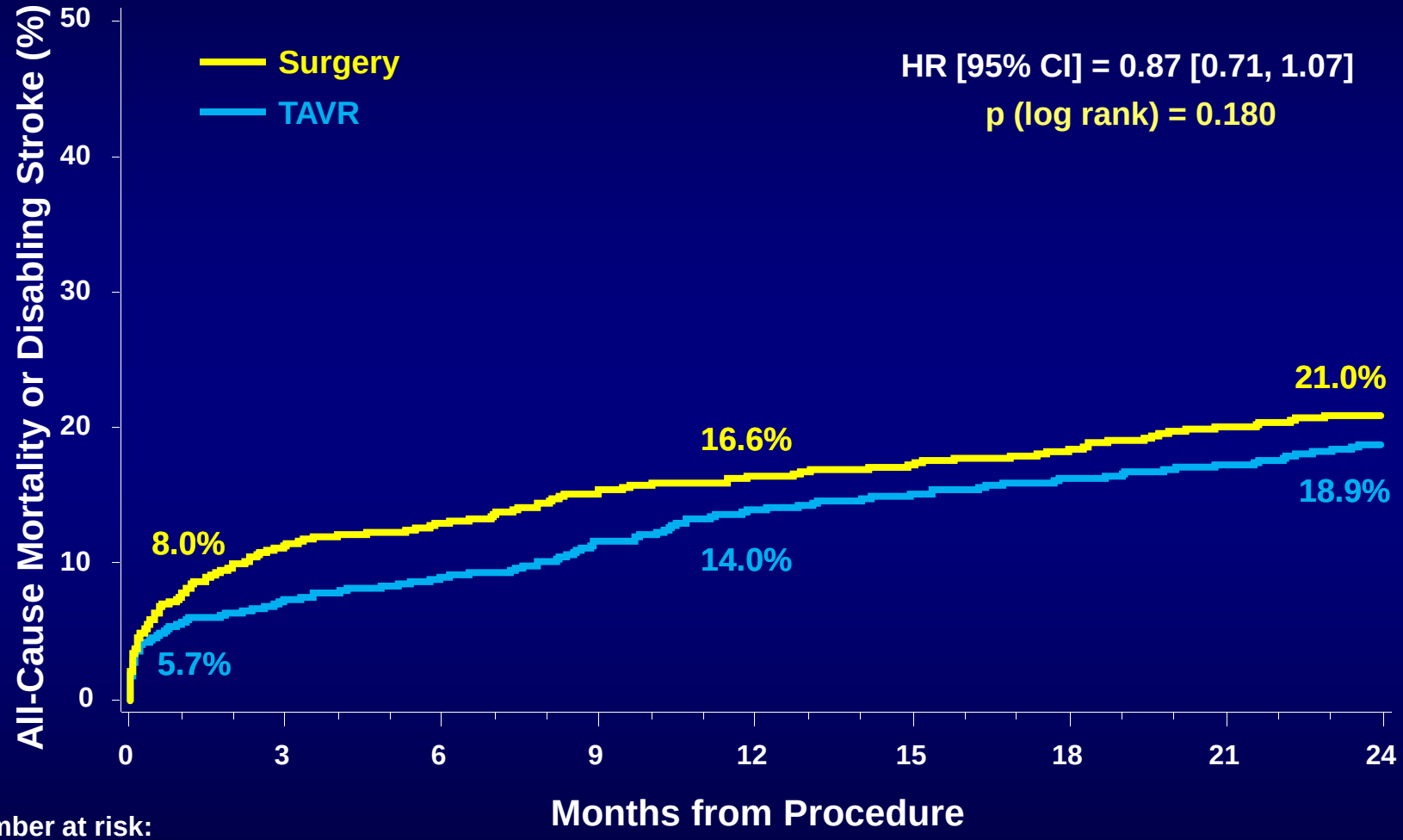
TAVR	SAVR		
n = 1011	n = 1021	Relative Risk Ratio	0.92
19.3%	21.1%	Upper 1-sided 97.5%CI	1.09

Non-Inferiority
p-value = 0.001



Primary Non-Inferiority Endpoint Met

Primary Endpoint (AT)
All-Cause Mortality or Disabling Stroke



Number at risk:

Surgery	944	826	807	779	766	743	731	715	694
TAVR	994	917	900	870	842	825	811	801	774

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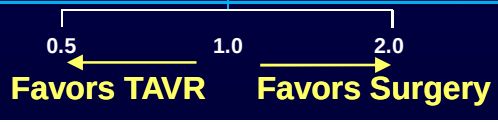
Primary Endpoint
Subgroup Analysis (ITT)

Subgroup	TAVR (%) n = 1011	AVR (%) n = 1021	Hazard Ratio (95% CI)	HR (95% CI)	p-value for interaction
Overall	19.3	21.1		0.89 [0.73-1.09]	
Age					0.96
< 85	18.0	19.5		0.90 [0.69-1.17]	
≥ 85	21.5	23.6		0.89 [0.65-1.20]	
Sex					0.37
Female	16.9	20.3		0.81 [0.59-1.10]	
Male	21.4	21.7		0.96 [0.74-1.25]	
STS Score					0.60
≤ 5	15.8	18.4		0.84 [0.61-1.16]	
> 5	22.4	23.1		0.94 [0.73-1.21]	
LV Ejection Fraction					0.27
≤ 55	19.1	21.5		0.84 [0.56-1.25]	
> 55	20.1	18.0		1.11 [0.81-1.53]	
Mod or Severe Mitral Regurgitation					0.53
No	17.8	20.3		0.85 [0.67-1.08]	
Yes	25.9	24.4		1.00 [0.64-1.57]	
Previous CABG					0.69
No	20.6	22.2		0.91 [0.73-1.13]	
Yes	15.3	18.0		0.82 [0.53-1.27]	
Peripheral Vascular Disease					0.47
No	18.2	20.7		0.85 [0.67-1.09]	
Yes	22.3	22.0		0.99 [0.71-1.40]	
15 Foot Walk Test					0.43
≤ 7 secs	17.7	20.9		0.82 [0.62-1.09]	
> 7 secs	20.7	20.8		0.97 [0.71-1.31]	
Access Route					0.06
Transfemoral	16.8	20.4		0.79 [0.62-1.00]	
Transthoracic	27.7	23.4		1.21 [0.84-1.74]	



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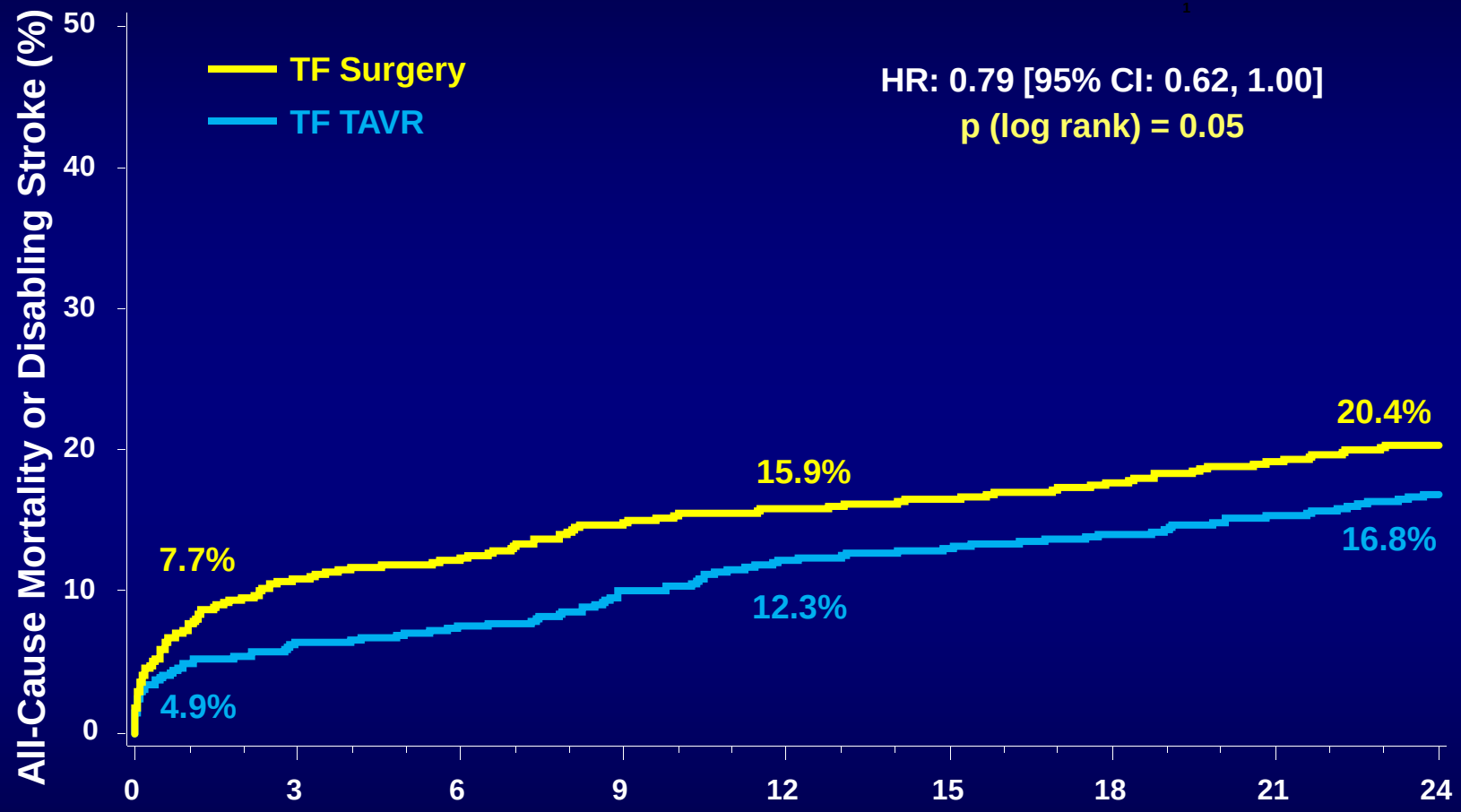
TF Primary Endpoint (ITT)
All-cause Mortality or Disabling Stroke



Number at risk:									
TF Surgery	775	643	628	604	595	577	569	557	538
TF TAVR	775	718	709	685	663	652	644	634	612

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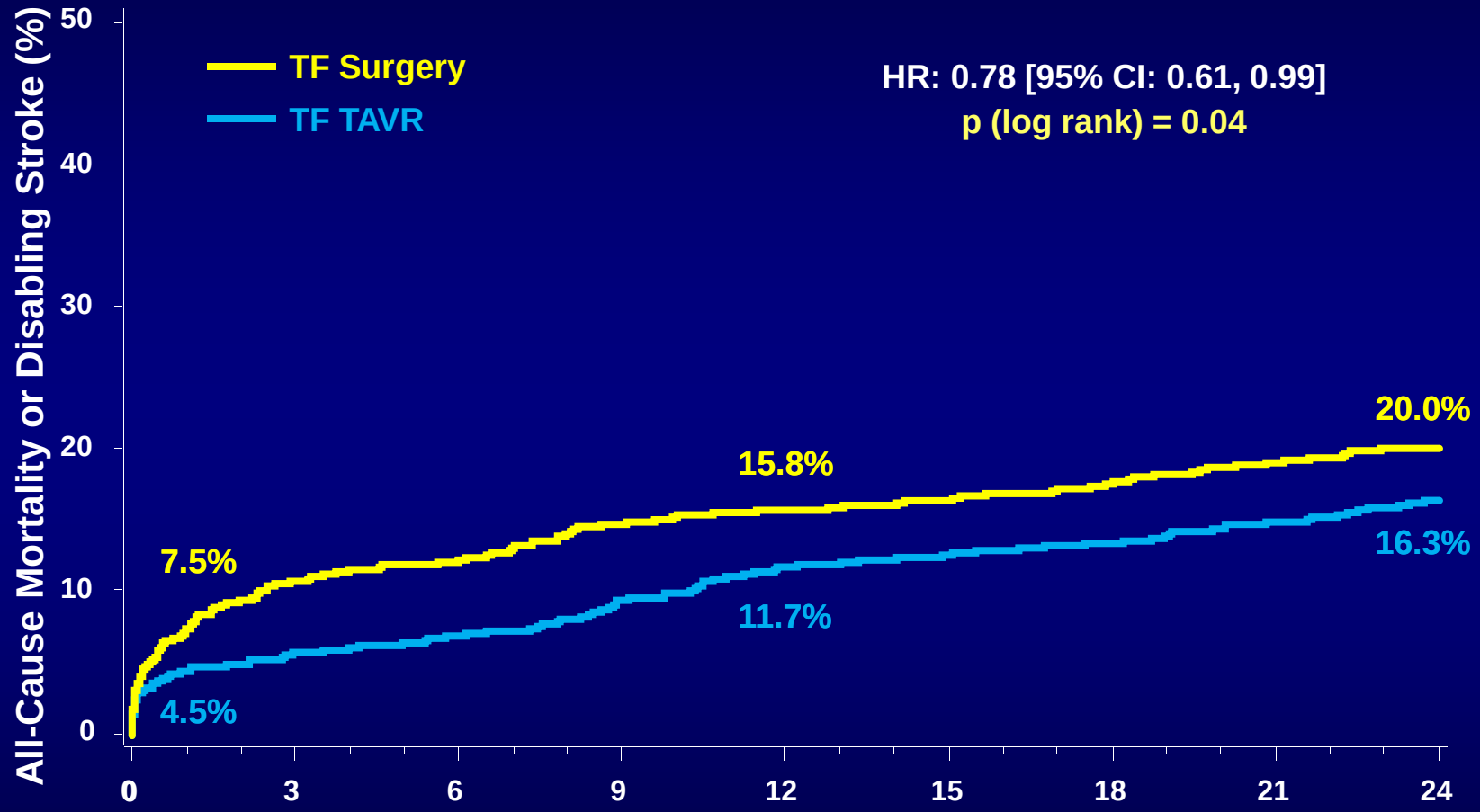
TF Primary Endpoint (AT)

All-Cause Mortality or Disabling Stroke



Number at risk:									
TF Surgery	722	636	624	600	591	573	565	555	537
TF TAVR	762	717	708	685	663	652	644	634	612

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Other Clinical Endpoints (ITT)
At 30 Days and 2 Years

Events (%)	30 Days			2 Years		
	TAVR (n = 1011)	Surgery (n = 1021)	p-value*	TAVR (n = 1011)	Surgery (n = 1021)	p-value*
Rehospitalization	6.5	6.5	0.99	19.6	17.3	0.22
MI	1.2	1.9	0.22	3.6	4.1	0.56
Major Vascular Complications	7.9	5.0	0.008	8.6	5.5	0.006
Life-Threatening / Disabling Bleeding	10.4	43.4	<0.001	17.3	47.0	<0.001
AKI (Stage III)	1.3	3.1	0.006	3.8	6.2	0.02
New Atrial Fibrillation	9.1	26.4	<0.001	11.3	27.3	<0.001
New Permanent Pacemaker	8.5	6.9	0.17	11.8	10.3	0.29
Re-intervention	0.4	0.0	0.05	1.4	0.6	0.09
Endocarditis	0.0	0.0	NA	1.2	0.7	0.22

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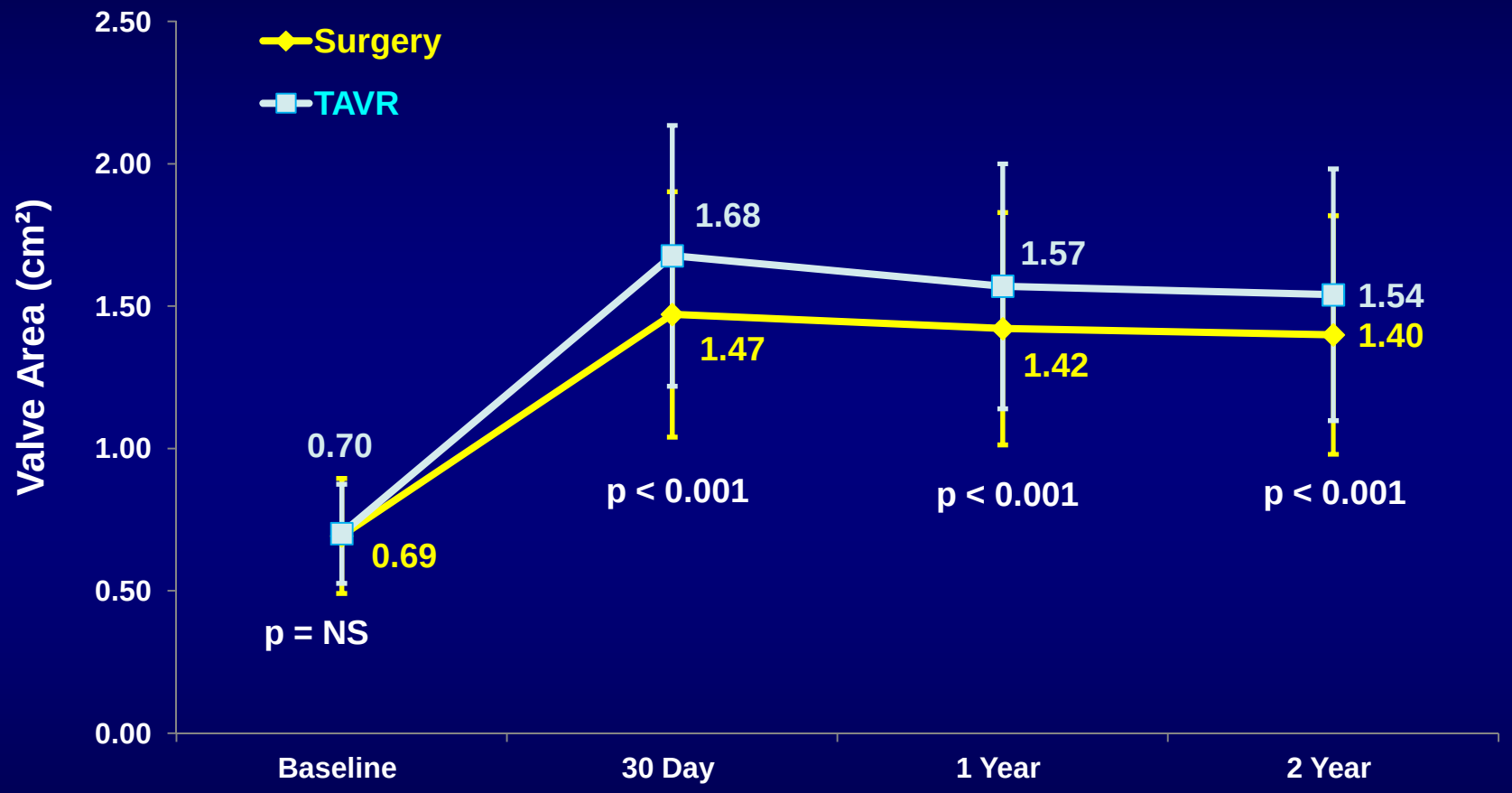
KM estimates, p-values are point in time

Echocardiography Findings (VI)
Aortic Valve Area



No. of Echos				
Surgery	861	727	590	488
TAVR	899	829	695	567

Error bars represent ± Standard Deviation

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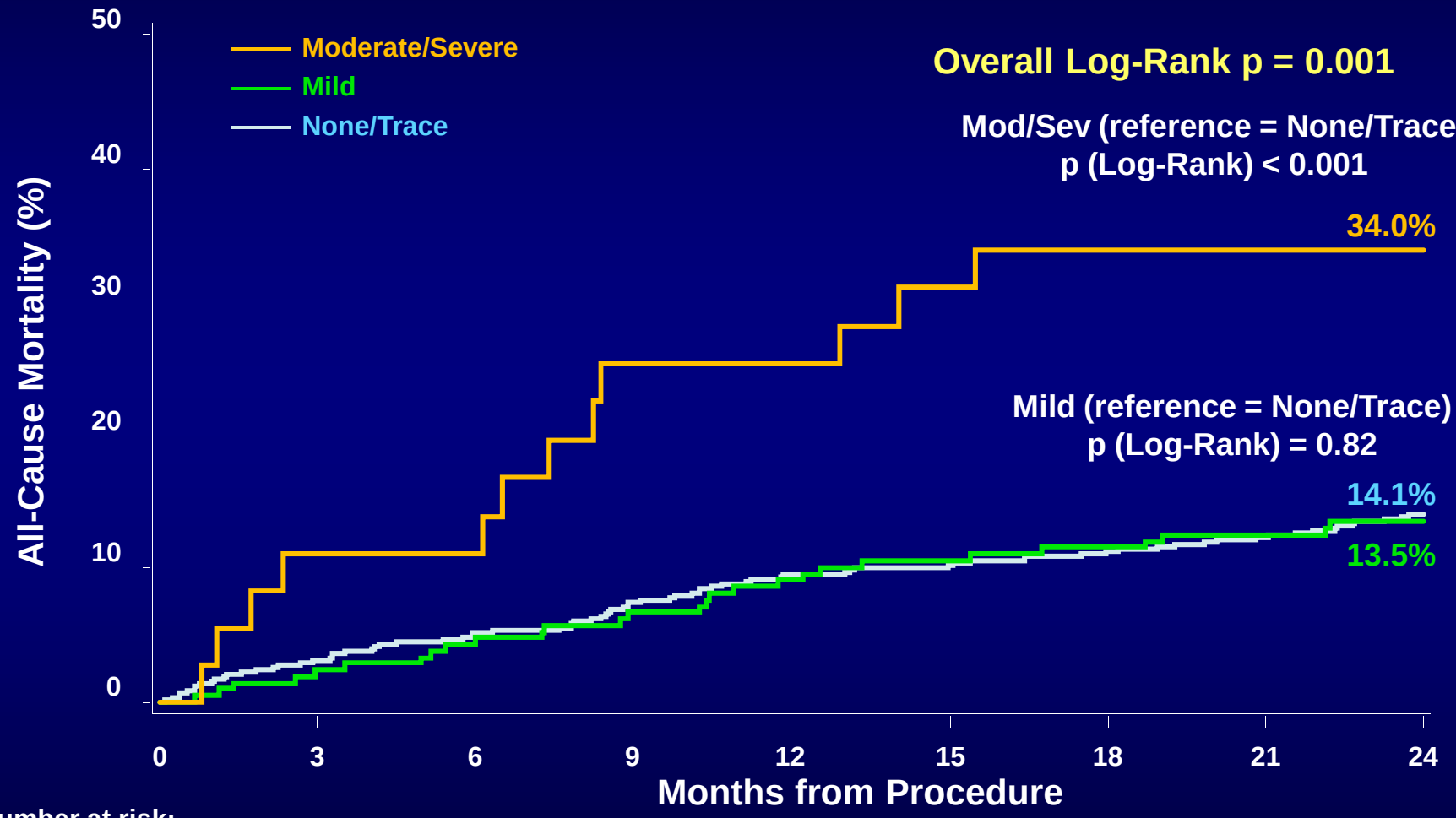
Severity of PVR at 30 Days and All-cause Mortality at 2 Years (VI)



Number at risk:

Moderate/Sev	36	32	32	26	26	24	22	22	21
Mild	210	204	199	194	188	184	182	180	175
None/Trace	701	678	664	647	628	621	612	605	585

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The PARTNER 2A Trial
Conclusions (1)

In intermediate-risk patients with symptomatic severe aortic stenosis, results from the PARTNER 2A trial demonstrated that...

- TAVR using SAPIEN XT and surgery were similar (non-inferior) for the primary endpoint (all-cause mortality or disabling stroke) at 2 years.
- In the transfemoral subgroup (76% of patients), TAVR using SAPIEN XT significantly reduced all-cause mortality or disabling stroke vs. surgery (ITT: p = 0.05, AT: p = 0.04).

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The PARTNER 2A Trial
Conclusions (2)

- Other clinical outcomes:
  - TAVR reduced AKI, severe bleeding, new AF, and LOS
  - Surgery reduced vascular complications and PVR
- The SAPIEN XT valve significantly increased echo AVA compared to surgery.
- In the SAPIEN XT TAVR cohort, moderate or severe PVR, but not mild PVR, was associated with increased mortality at 2 years.

SAPIEN 3 TAVR Compared with Surgery in Intermediate-Risk Patients:

A Propensity Score Analysis

Transcatheter aortic valve replacement versus surgical valve replacement in intermediate-risk patients: a propensity score analysis

Vinod H Thourani, Susheel Kodali, Raj R Makkar, Howard C Herrmann, Mathew Williams, Vasilis Babaliaros, Richard Smalling, Scott Lim, S Chris Malaisrie, Samir Kapadia, Wilson Y Szeto, Kevin L Greason, Dean Kereiakes, Gorav Ailawadi, Brian K Whisenant, Chandan Devireddy, Jonathon Leipsic, Rebecca T Hahn, Philippe Pibarot, Neil J Weissman, Wael A Jaber, David J Cohen, Rakesh Suri, E Murat Tuzcu, Lars G Svensson, John G Webb, Jeffrey W Moses, Michael J Mack, D Craig Miller, Craig R Smith, Maria C Alu, Rupa Parvataneni, Ralph B D'Agostino Jr, Martin B Leon

Lancet 2016; 387:2218-2225

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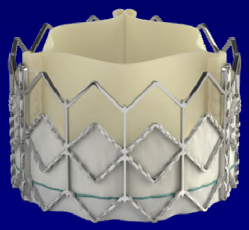
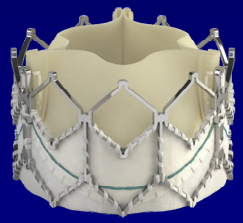
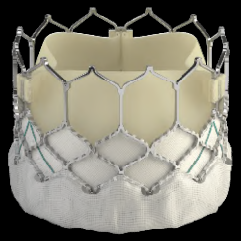
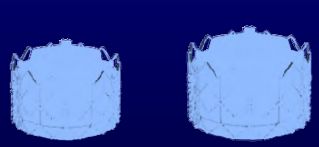
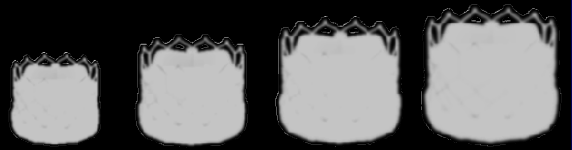
SAPIEN Platforms in PARTNER
Device Evolution

	SAPIEN	SAPIEN XT	SAPIEN 3
Valve Technology			
Sheath Compatibility			
Available Valve Sizes	 23 mm, 26 mm	 23 mm, 26 mm, 29 mm	 20 mm, 23 mm, 26 mm, 29 mm

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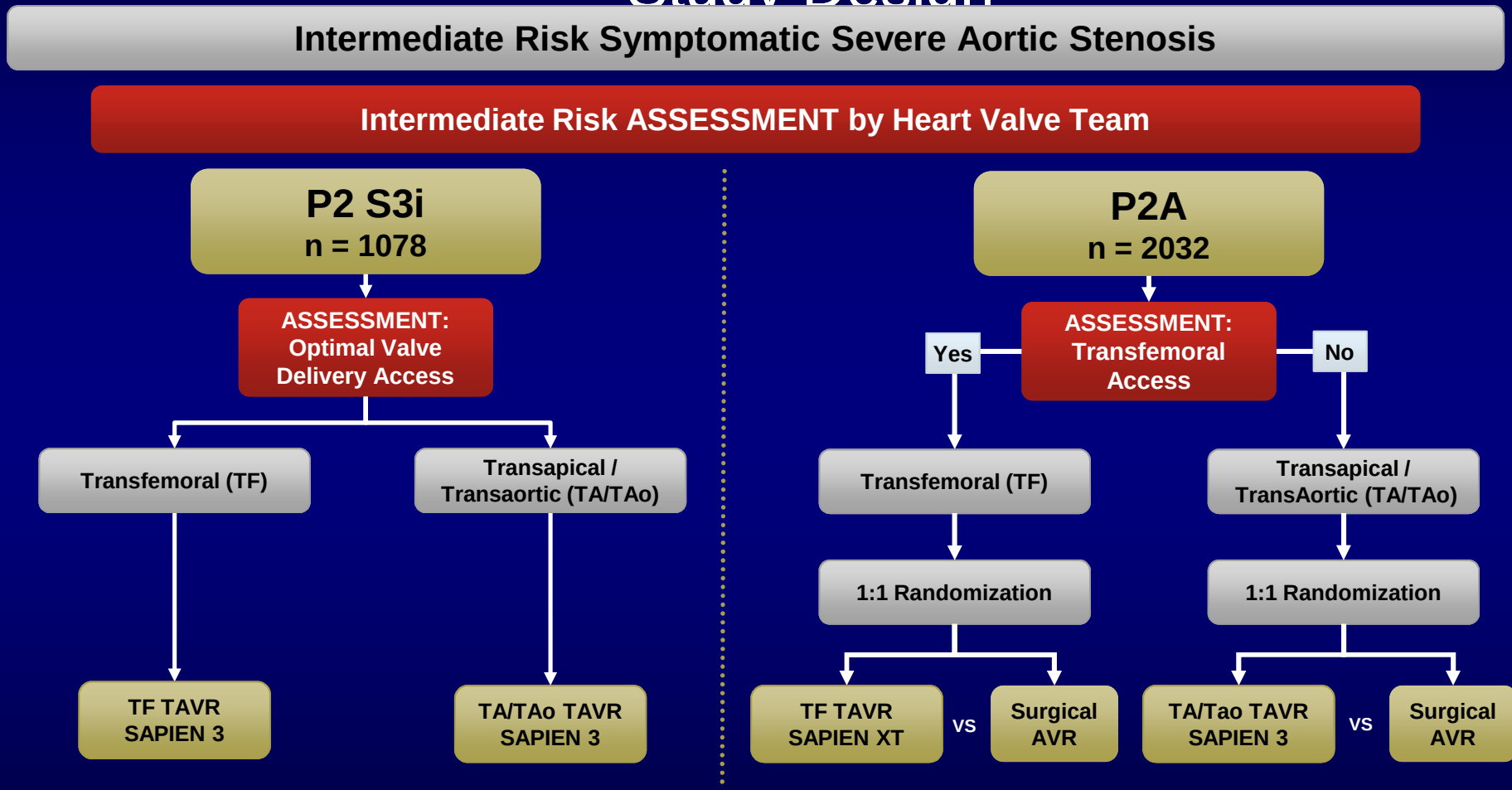
The PARTNER 2A and S3i Trials

Study Design



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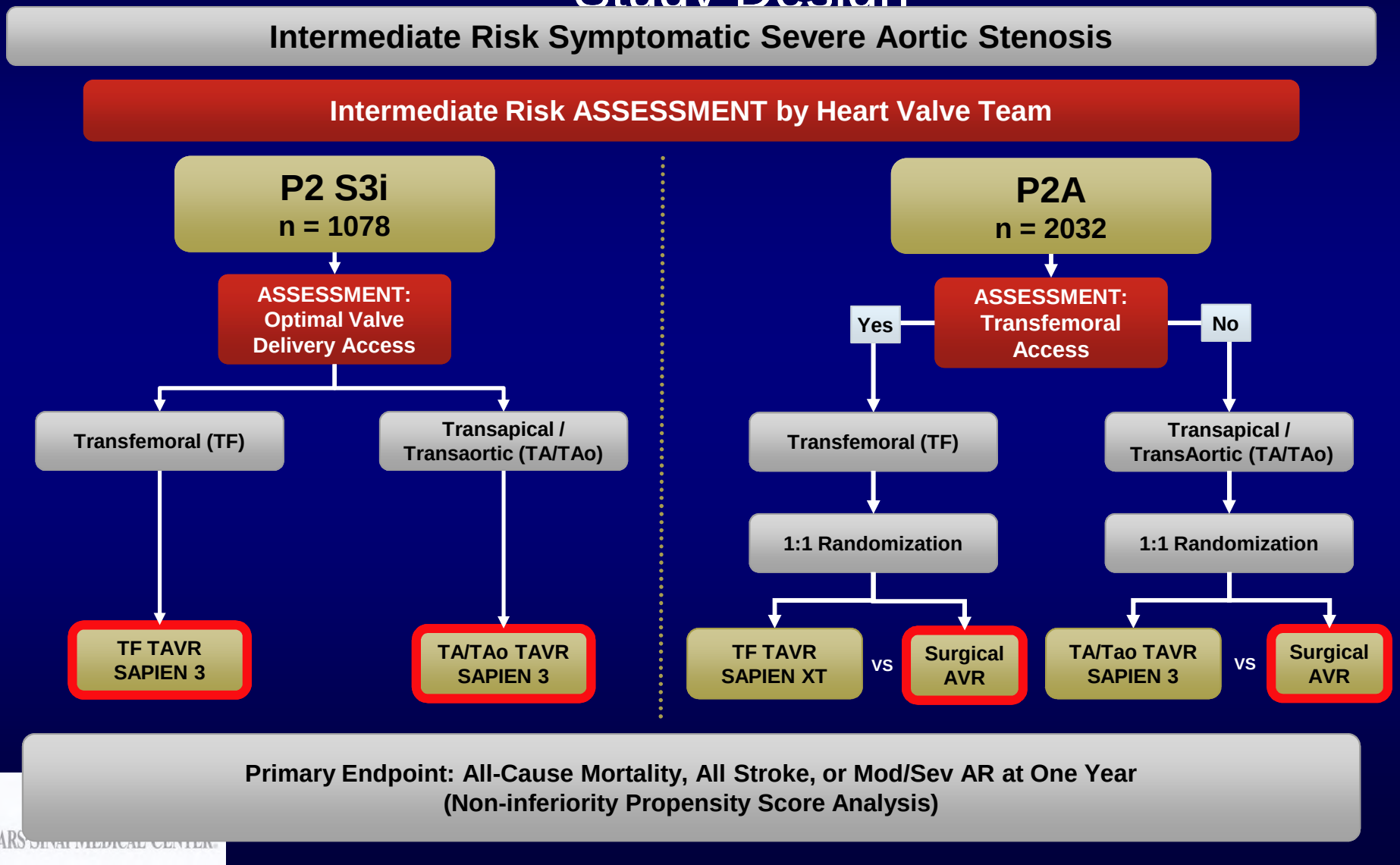
The PARTNER 2A and S3i Trials

Study Design

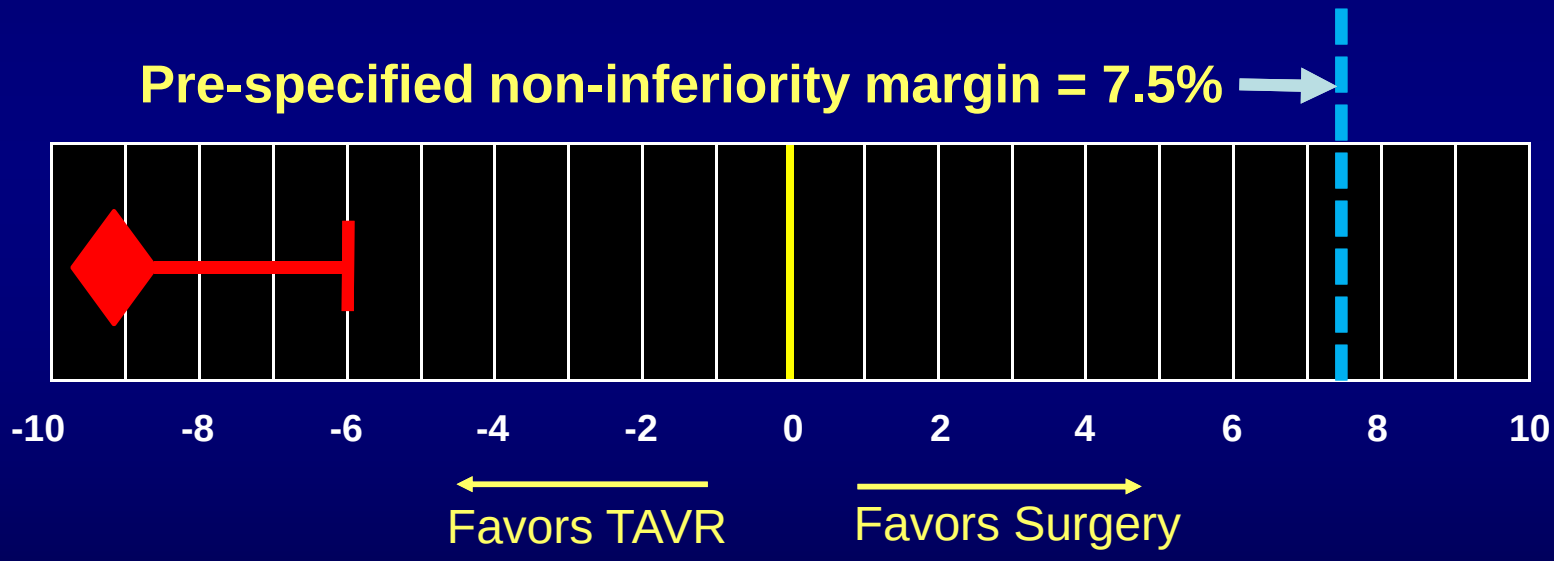


Primary Endpoint - Non-inferiority

Death, Stroke, or AR ≥ Mod at 1 Year (VI)

Weighted Difference	-9.2%
Upper 1-sided 95% CI	-6.0%

Non-Inferiority p-value < 0.001



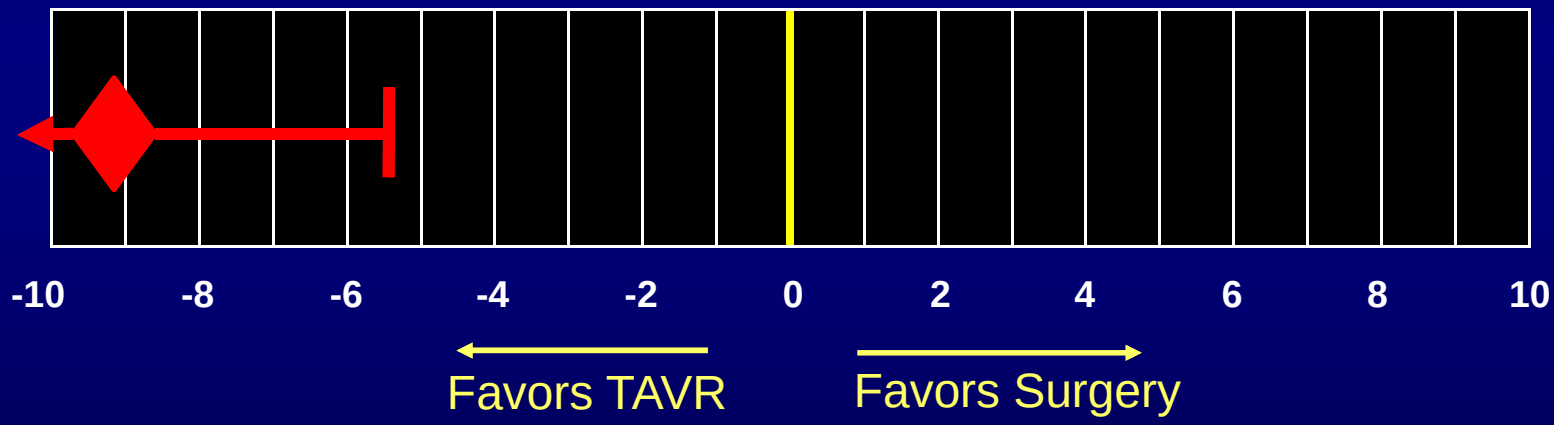
Primary Non-Inferiority Endpoint Met

Primary Endpoint - Superiority

Death, Stroke, or AR ≥ Mod at 1 Year (VI)

Weighted Difference	**-9.2%**
Upper 2-sided 95.0% CI	**-5.4%**

Superiority Testing
p-value < 0.001



Superiority Achieved

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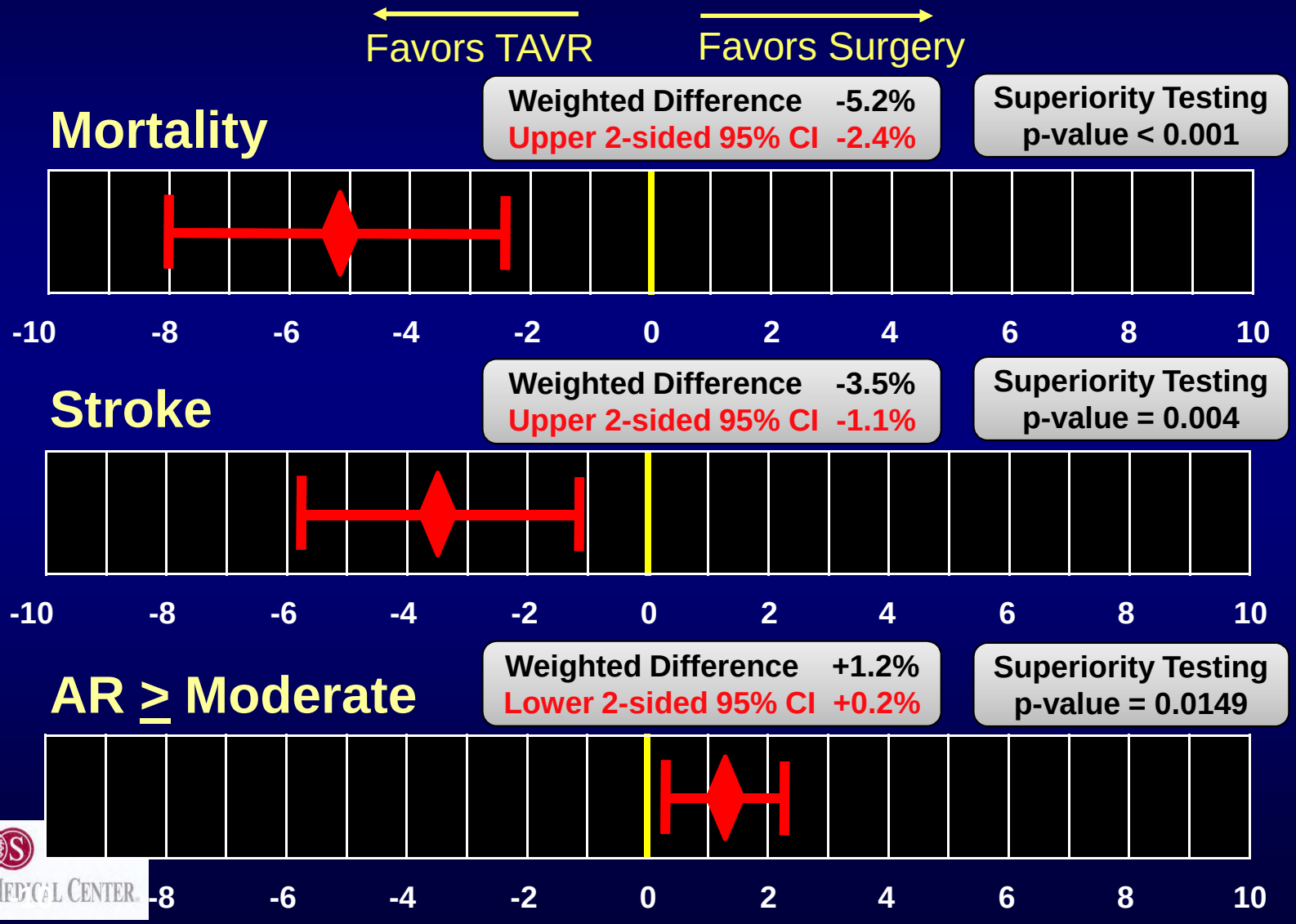
Superiority Analysis
Components of Primary Endpoint (VI)



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The PARTNER 2A and S3i Trials
Conclusions

- A propensity score analysis comparing SAPIEN 3 TAVR with surgery from PARTNER 2A in intermediate-risk patients at 1 year demonstrated:
  - Superiority of SAPIEN 3 TAVR for the primary endpoint, all-cause mortality, and all stroke
  - Superiority of surgery for AR ≥ moderate

Clinical evidence supporting TAVR in intermediate risk patients

- Final results of the PARTNER II trial
- SAPIEN 3 TAVR Compared with Surgery in Intermediate-Risk Patients: Propensity score analysis
- **3 year data of the Corevalve Pivotal study**

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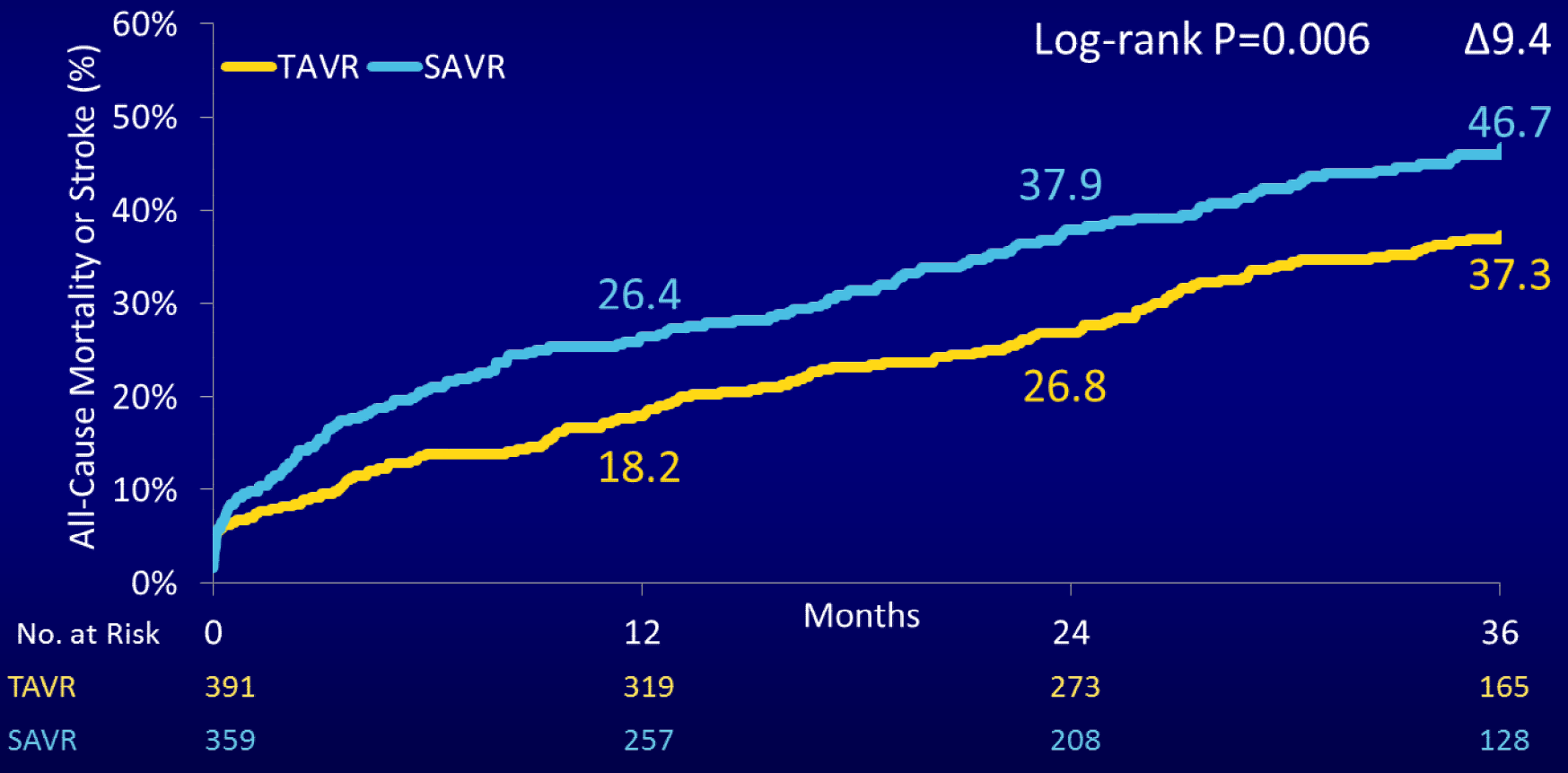
High risk patients: 3 year follow up of Core valve study (TAVR versus SAVR) All-Cause Mortality or Stroke

ACC2016



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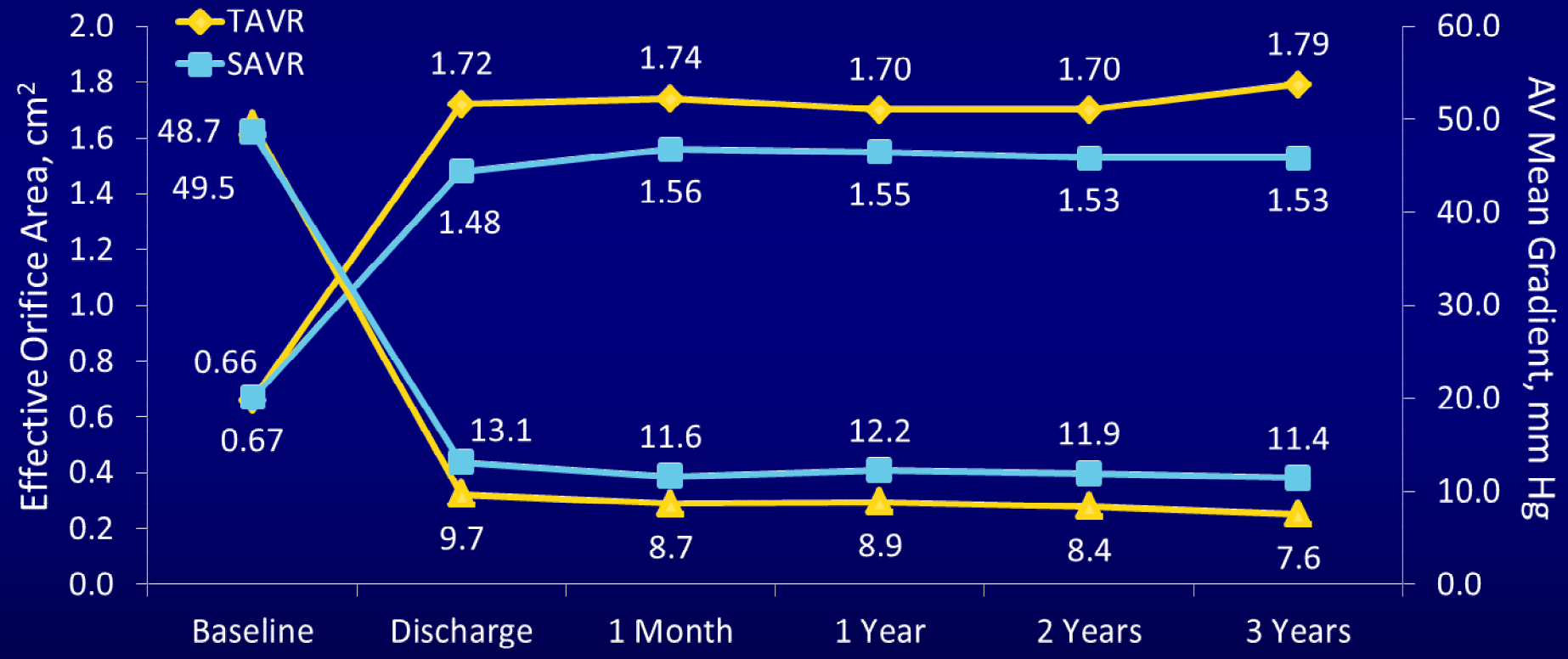
Core Valve Hemodynamics*

ACC2016

TAVR had significantly better valve performance vs SAVR at all follow-ups (P<0.001)



*Site-reported

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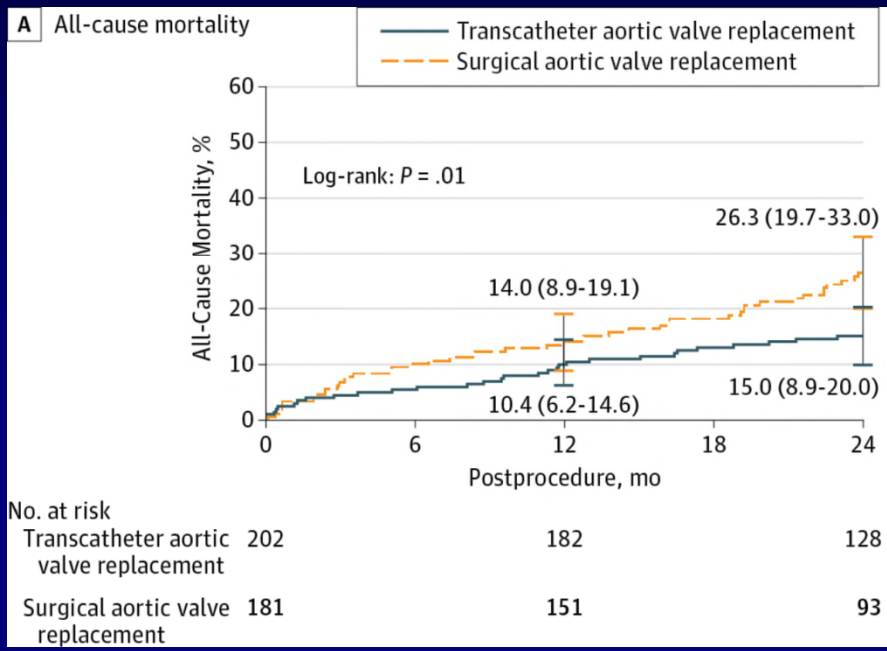
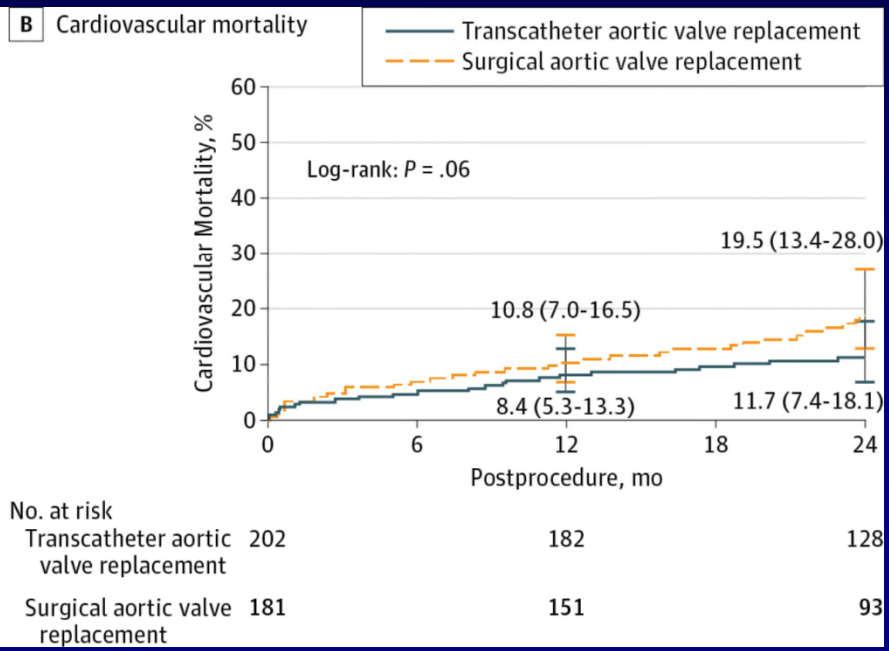
Outcomes in the Randomized CoreValve US Pivotal High-risk Trial in Patients With a Society of Thoracic Surgeons Risk Score of 7% or Less





Reardon M et al. JAMA Cardiol. Published online August 17, 2016. doi:10.1001/jamacardio.2016.2257

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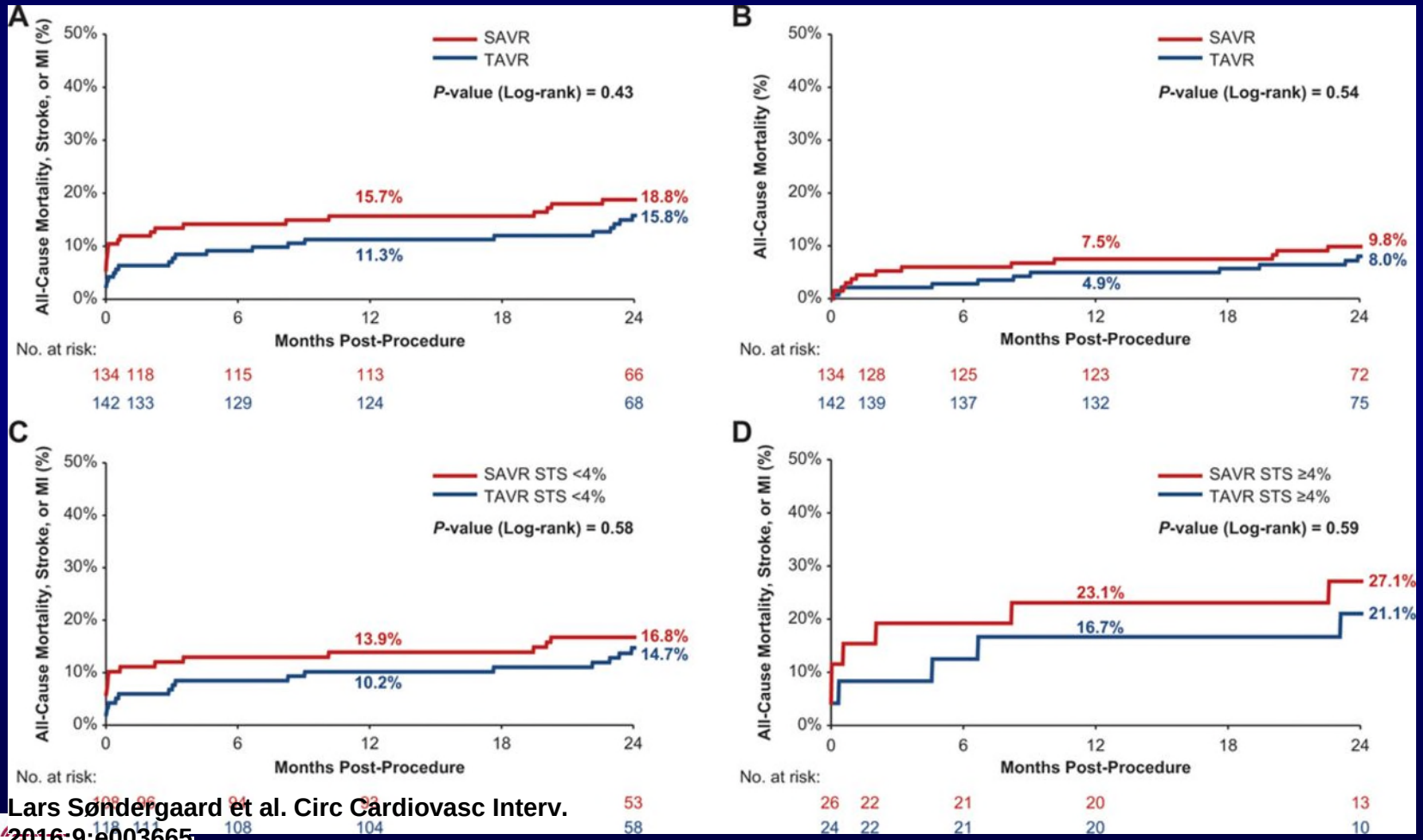
Two-Year Outcomes in Patients With Severe Aortic Valve Stenosis Randomized to Transcatheter Versus Surgical Aortic Valve Replacement

by Lars Søndergaard, Daniel Andreas Steinbrüchel, Nikolaj Ihlemann, Henrik Nissen, Bo Juel Kjeldsen, Petur Petursson, Anh Thuc Ngo, Niels Thue Olsen, Yanping Chang, Olaf Walter Franzen, Thomas Engstrøm, Peter Clemmensen, Peter Skov Olsen, and Hans Gustav Hørsted Thyregod

Circ Cardiovasc Interv
Volume 9(6):e003665
June 13, 2016

Kaplan–Meier curves depicting (A) a composite rate of all-cause mortality, all stroke, and myocardial infarction (MI); (B) all-cause mortality; (C) composite rate of all-cause mortality, all stroke, and MI in transcatheter aortic valve replacement (TAVR) and surgical aortic valve replacement (SAVR) patients with Society of Thoracic Surgeons Predicted Risk of Mortality (STS-PROM) <4%; and (D) composite rate of all-cause mortality, stroke, and MI in TAVR and SAVR patients with STS-PROM ≥4%.



Lars Søndergaard et al. Circ Cardiovasc Interv. 2016;9:e003665

Summary: Transcatheter aortic valve replacement

- TAVR is preferred treatment option of high and intermediate surgical risk patients
- Evidence of durability of the valve
- Continued improvements in technology will minimize the paravalvular AI, heart block, and stroke rates
- Further research of cerebral protection and valve thrombosis are ongoing

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Conclusions: Status in US

- TAVR is FDA approved for extreme/high surgical risk patients
- FDA has expanded the of indication for ***intermediate risk patients*** using the SAPIEN 3 valve
- In the real world intermediate risk patients are being treated with TAVR
  - Ongoing registries
  - Indication creep: physician preference
- Ongoing trials are evaluating the role of TAVR in low/moderate risk patients

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Ongoing low risk TAVR trials

- PARTNER 3: Low risk patients with AS
- Low risk study using the EvoluteR valve

Do We really need these low risk studies

- Other than for reimbursement it is probably not necessary to do these large scale studies
- There is significant indication creep already in US and Europe for intermediate and low risk patients
- The boundary between low risk and intermediate risk is very blurry

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Future

- Cardiac surgeons will have to consult interventional cardiologist prior to offering surgery to any patient with aortic stenosis