TAVR in Intermediate Risk Populations /Optimizing Systems for TAVR

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Disclosure Statement of Financial Interest

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Within the past 12 months, I or my spouse/partner have had a financial interest/arrangement or affiliation with the organization(s) listed below.

Affiliation/Financial Relationship	Company
• Grant/Research Support	• Abbott Vascular,Boston Scientific, St Jude Medical, Circulite, Coherex, Gore, Biotronics
• Consulting Fees/Honoraria	• Abbott Vascular, Boston Scientific, St Jude Medical, Gore
• Other Financial Benefit	• Coherex, Biosensors International

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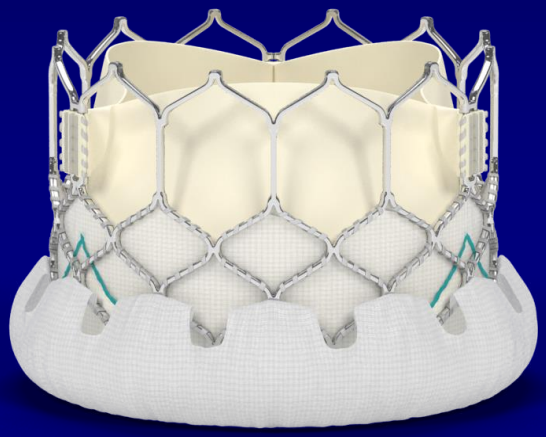
TAVR: The new standard of care

- TAVR once considered a destructive technology is standard of care for high and intermediate risk patients with aortic stenosis
- TAVR is most well studied procedure in Cardiac sciences, and low risk trials have completely enrollment
- Improvements of technology/procedure have made this treatment option suitable for all patients with Aortic stenosis irrespective of age

Two most common Implants used worldwide (>200,000 cases)

Balloon Expandable TAVR



Sapien 3 THV(Edwards Lifesceinces)

Self Expanding TAVR

The Medtronic Evolut™ PRO TAVR system

Clinical Evidence for TAVR

- Partner I, 2A, 2B trial
- S3 single arm study
- Pivotal trial using the Core valve
  - Single arm high risk study
  - Pivotal study vs surgery
  - SURTAVI Trial

Evidence of TAVR in intermediate risk patients

- Partner 2A and S3i trials
- SURTAVI trial
- Ongoing post market registries

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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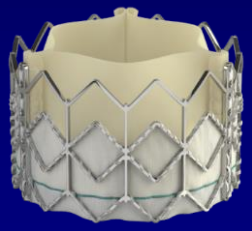
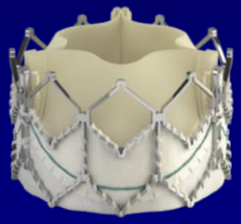
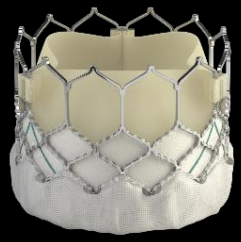
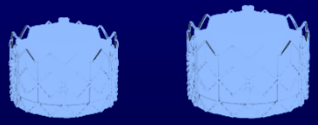
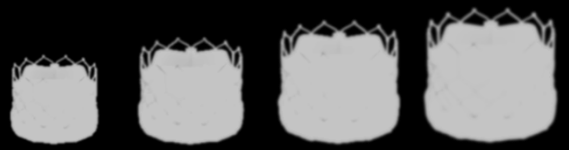
SAPIEN Platforms in PARTNER
Device Evolution

	SAPIEN	SAPIEN XT	SAPIEN 3
Valve Technology			
Sheath Compatibility	 22-24F	16-20F 	14-16F 
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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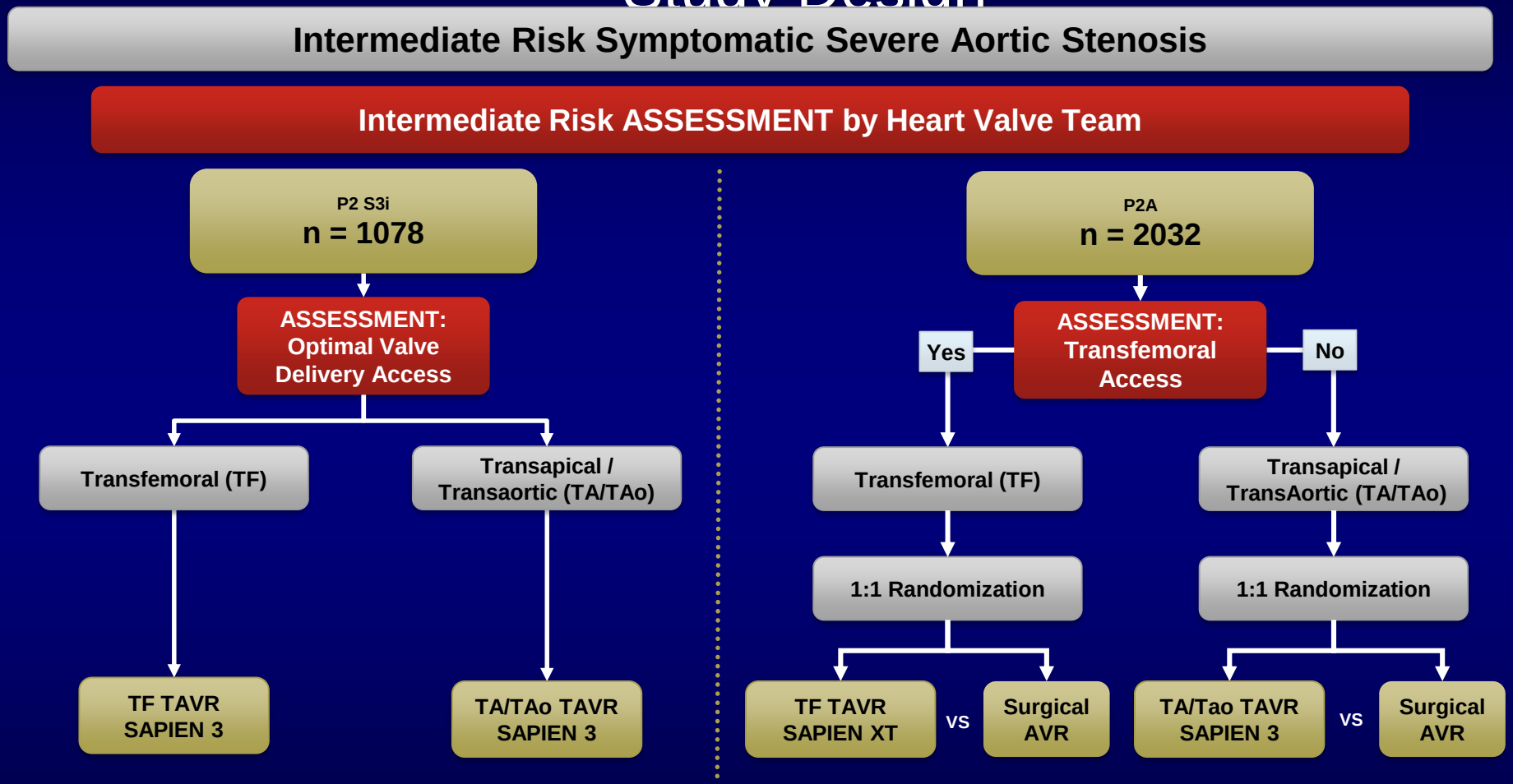
The PARTNER 2A and S3i Trials

Study Design



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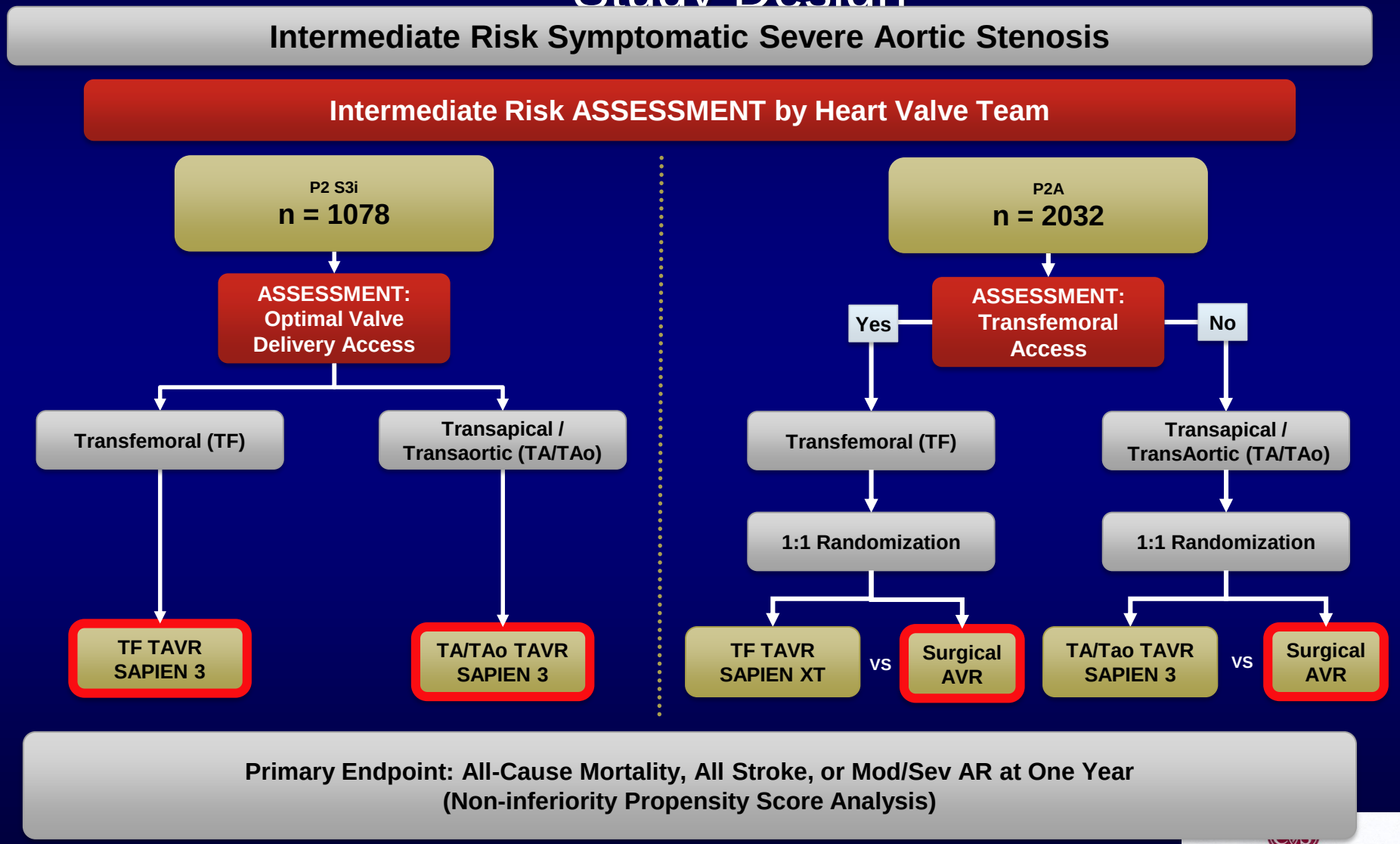
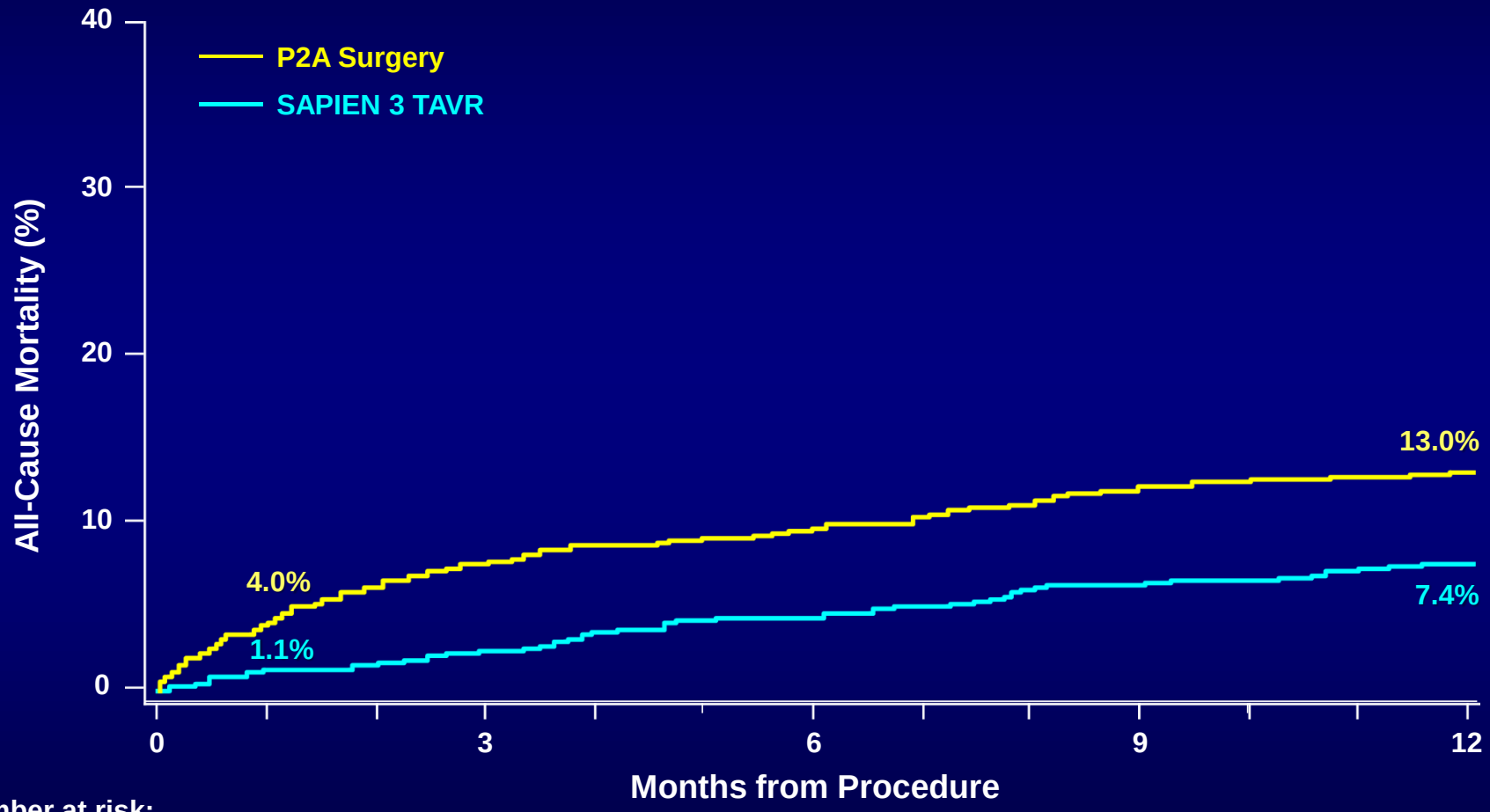
Study Design



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



Number at risk:

P2A Surgery	944	859	836	808	795
S3 TAVR	1077	1043	1017	991	963

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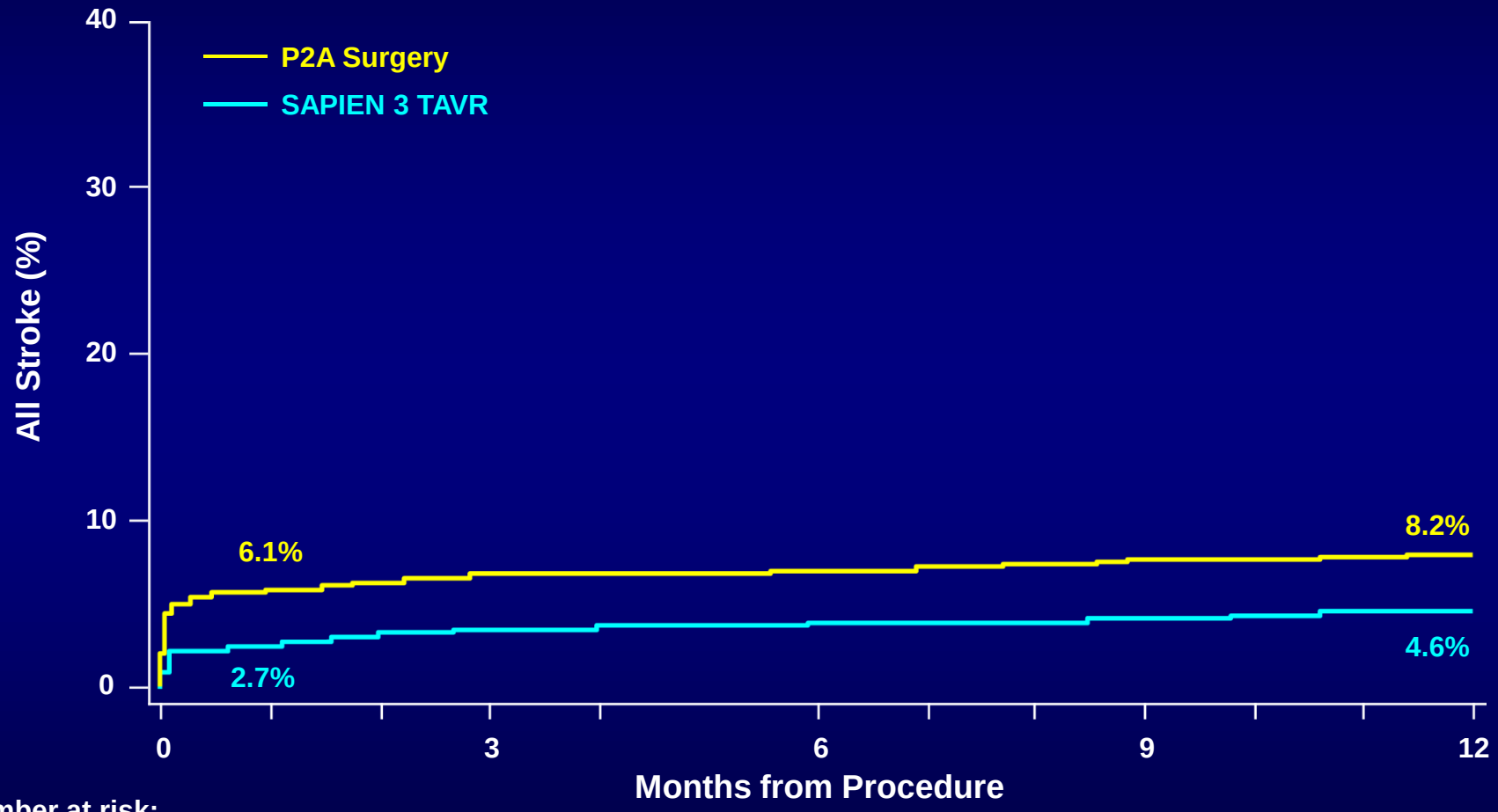
Unadjusted Time-to-Event Analysis

All Stroke (AT)



Number at risk:

P2A Surgery	944	805	786	757	743
S3 TAVR	1077	1012	987	962	930

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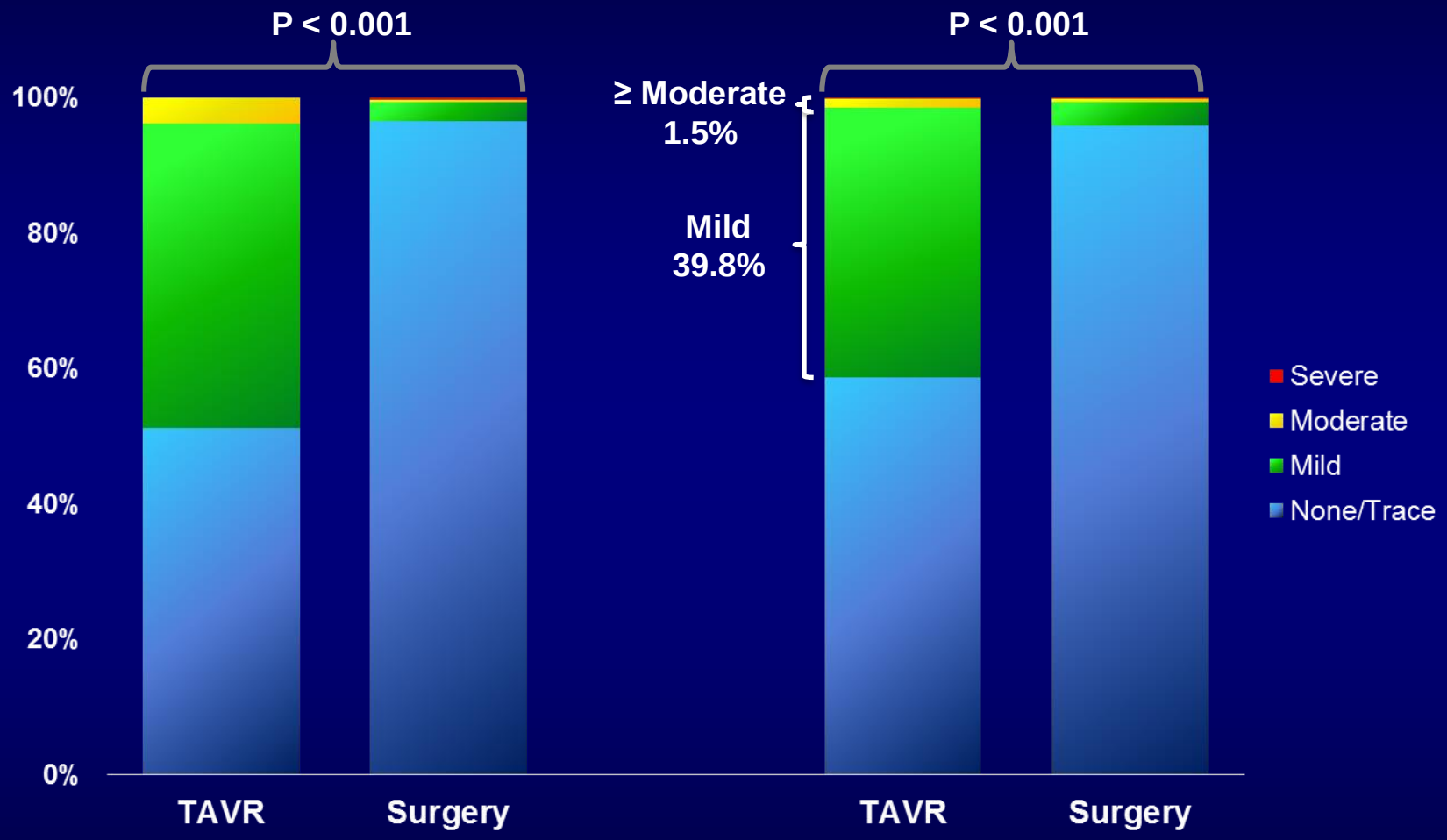
Other Unadjusted Clinical Outcomes
At 30 Days and 1 Year (AT)

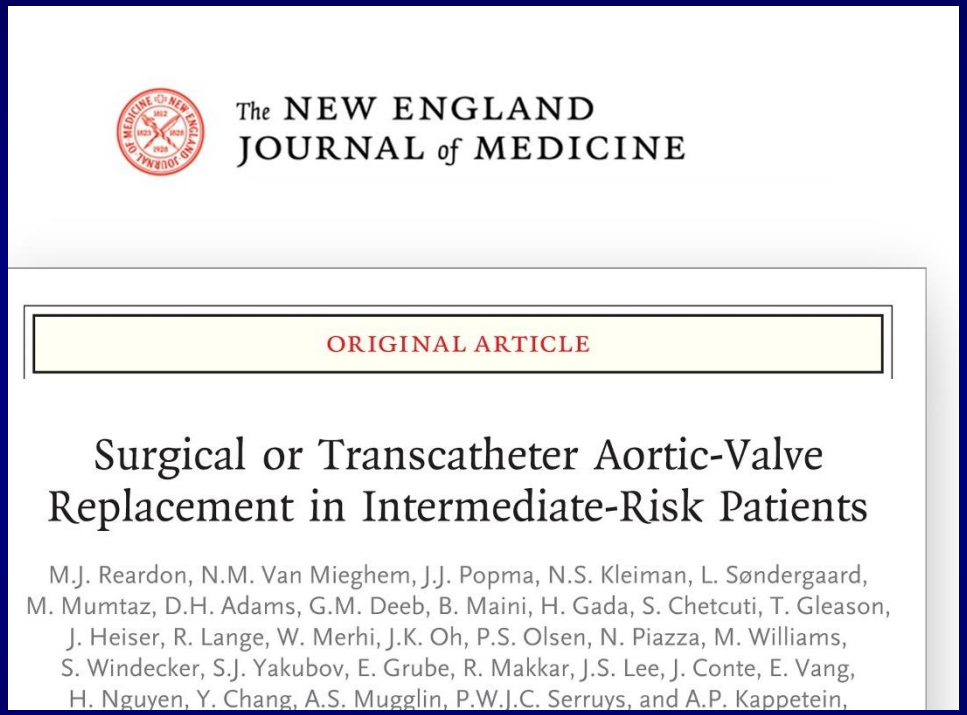
Events (%)	30 Days		1 Year	
	TAVR (n = 1077)	Surgery (n = 944)	TAVR (n = 1077)	Surgery (n = 944)
Re-hospitalization	4.6	6.8	11.4	15.1
MI	0.3	1.9	1.8	3.1
Major Vascular Complication	6.1	5.4	---	---
AKI (Stage III)	0.5	3.3	---	---
Life-Threatening/Disabling Bleeding	4.6	46.7	---	---
New Atrial Fibrillation	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

Paravalvular Regurgitation
3-Class Grading Scheme (VI)



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

SURTAVI Trial



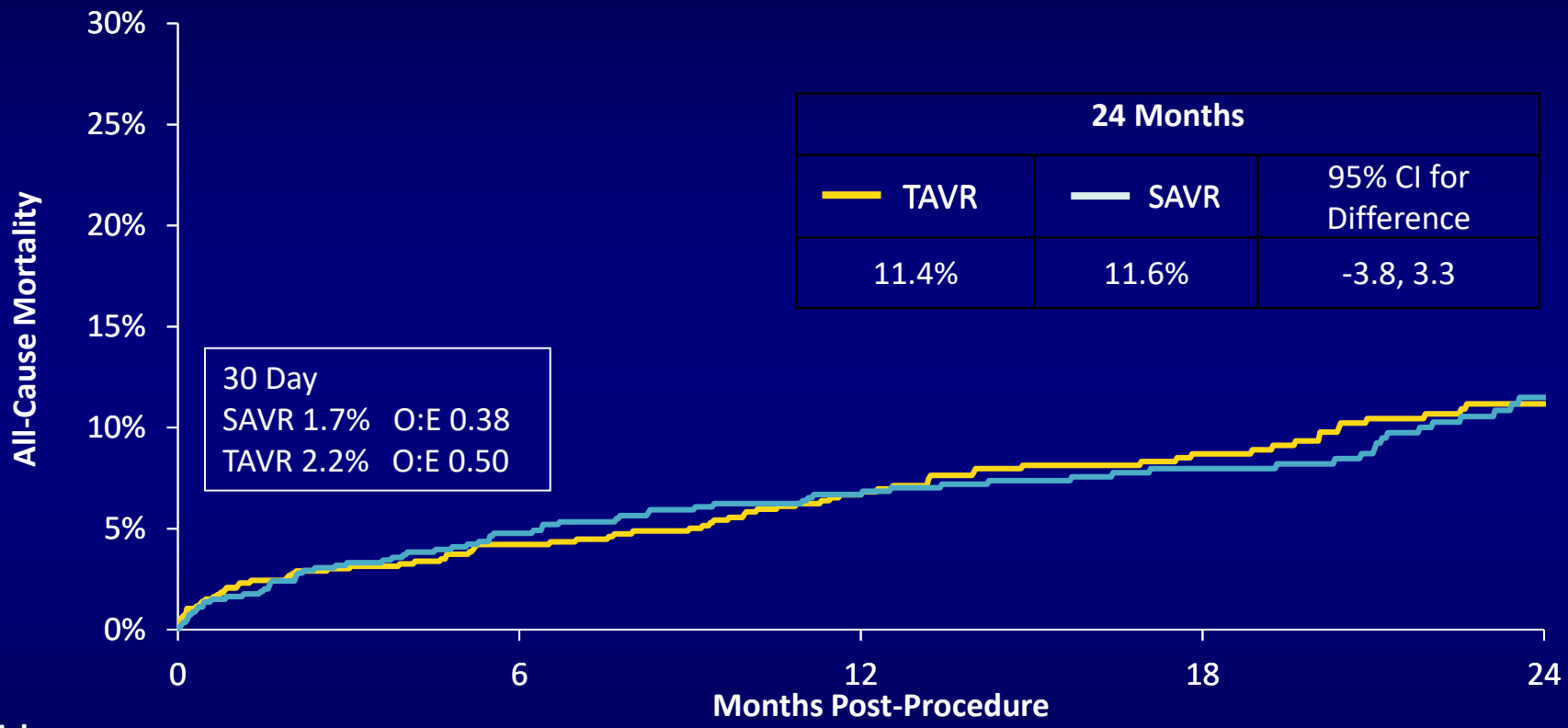
The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

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

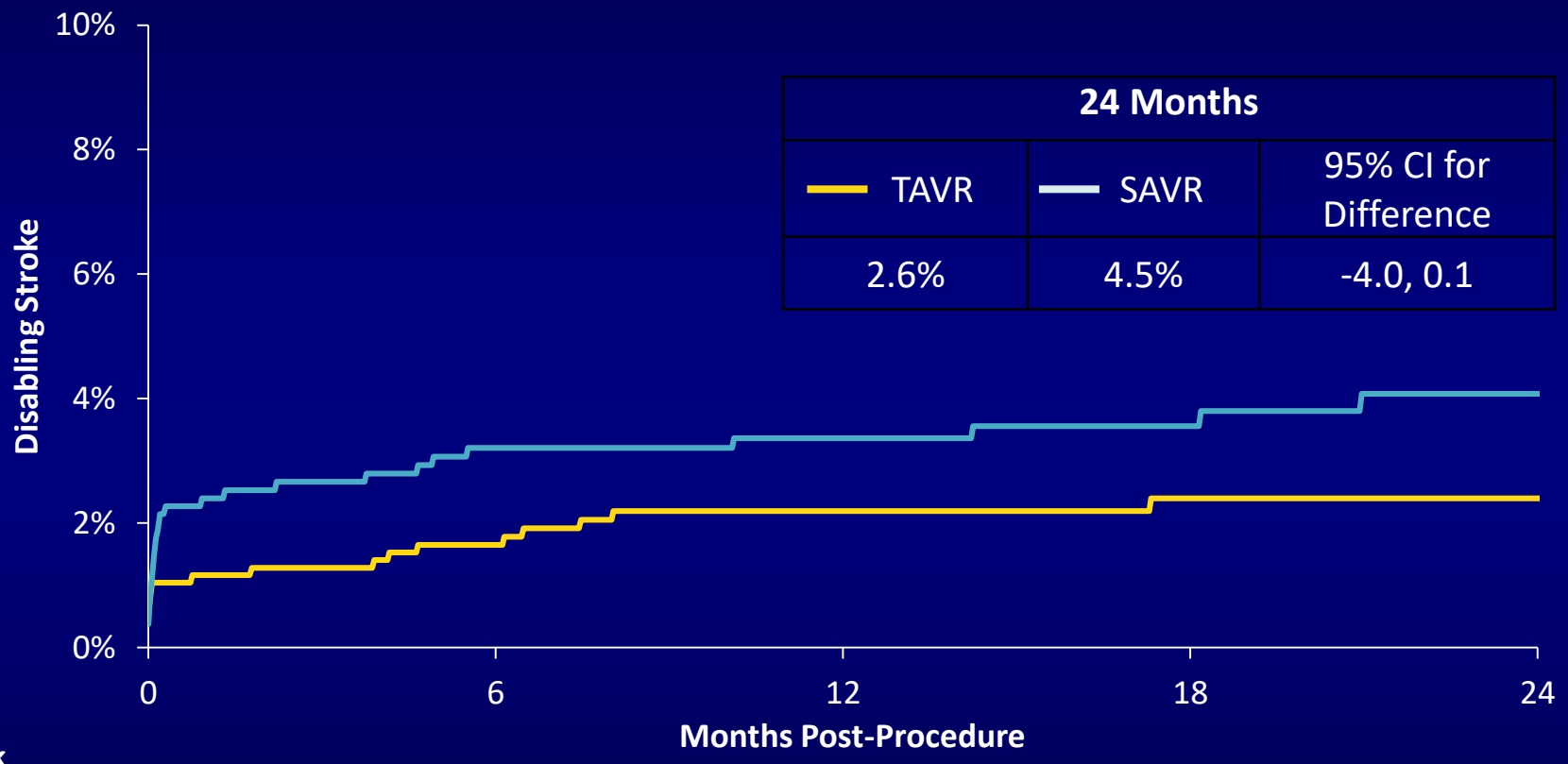
M.J. Reardon, N.M. Van Mieghem, J.J. Popma, N.S. Kleiman, L. Søndergaard, M. Mumtaz, D.H. Adams, G.M. Deeb, B. Maini, H. Gada, S. Chetcuti, T. Gleason, J. Heiser, R. Lange, W. Merhi, J.K. Oh, P.S. Olsen, N. Piazza, M. Williams, S. Windecker, S.J. Yakubov, E. Grube, R. Makkar, J.S. Lee, J. Conte, E. Vang, H. Nguyen, Y. Chang, A.S. Mugglin, P.W.J.C. Serruys, and A.P. Kappetein,

SURTAVI: All-Cause Mortality



No. at Risk					
SAVR	796	690	569	414	249
TAVR	864	762	621	465	280

SURTAVI: Disabling Stroke



No. at Risk					
SAVR	796	674	555	407	241
TAVR	864	755	612	456	272

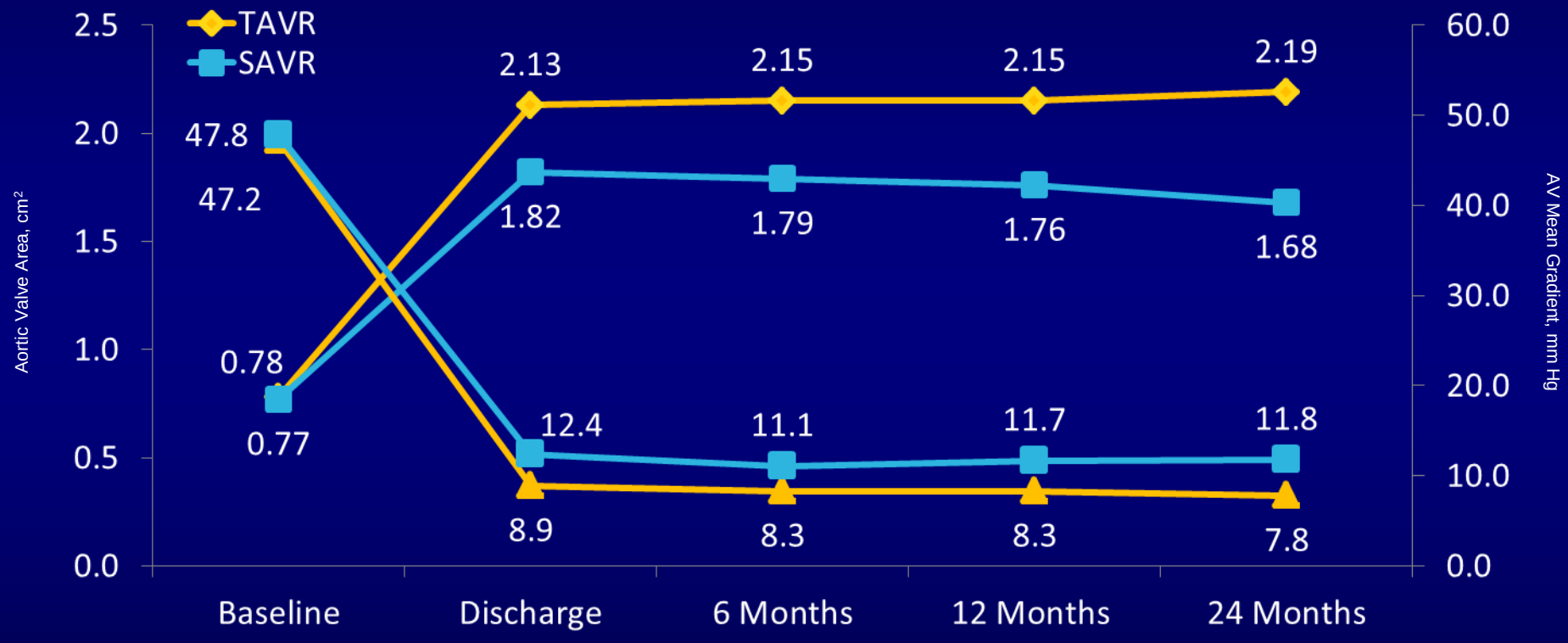
30-Day Safety and Procedure-related Complications

	TAVR (N=864)	SAVR (N=796)	95% CI for Difference
All-cause mortality or disabling stroke	2.8	3.9	-2.8, 0.7
All-cause mortality	2.2	1.7	-0.9, 1.8
Disabling stroke	1.2	2.5	-2.6, 0.1
All stroke	3.4	5.6	-4.2, -0.2
Overt life-threatening or major bleeding	12.2	9.3	-0.1, 5.9
Transfusion of PRBCs* - n (%)			
0 units	756 (87.5)	469 (58.9)	24.4, 32.5
2 – 4 units	48 (5.6)	136 (17.1)	-14.5, -8.5
≥ 4 units	31 (3.6)	101 (12.7)	-11.7, -6.5
Acute kidney injury, stage 2-3	1.7	4.4	-4.4, -1.0
Major vascular complication	6.0	1.1	3.2, 6.7
Cardiac perforation	1.7	0.9	-0.2, 2.0
Cardiogenic shock	1.1	3.8	-4.2, -1.1
Permanent pacemaker implant	25.9	6.6	15.9, 22.7
Atrial fibrillation	12.9	43.4	-34.7, -26.4

*Percentage rates, all others are Bayesian rates

Hemodynamics*

TAVR had significantly better valve performance over SAVR at all follow-up visits



*Core lab adjudicated

TAVR vs Surgery in Intermediate risk patients

Summary: Contemporary data

- TAVR is superior in mortality and disabling stroke at 30 days to 1 year follow up
- TAVR achieves a better Orifice area
- Lower morbidity
- TAVR is associated with higher incidence of Aortic regurgitation and pacer compared to SAVR

How did we achieve this outcome

- Improved valve platforms
- Improved case selection
- Operator experience/training

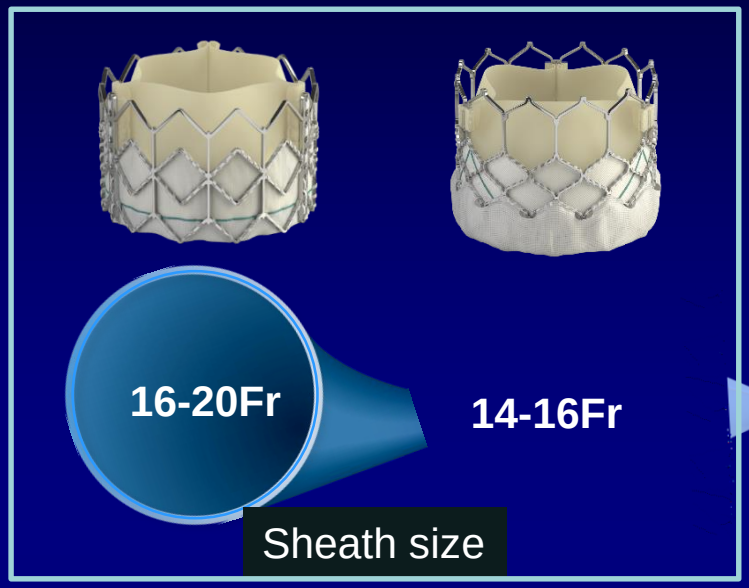
Issues about TAVR

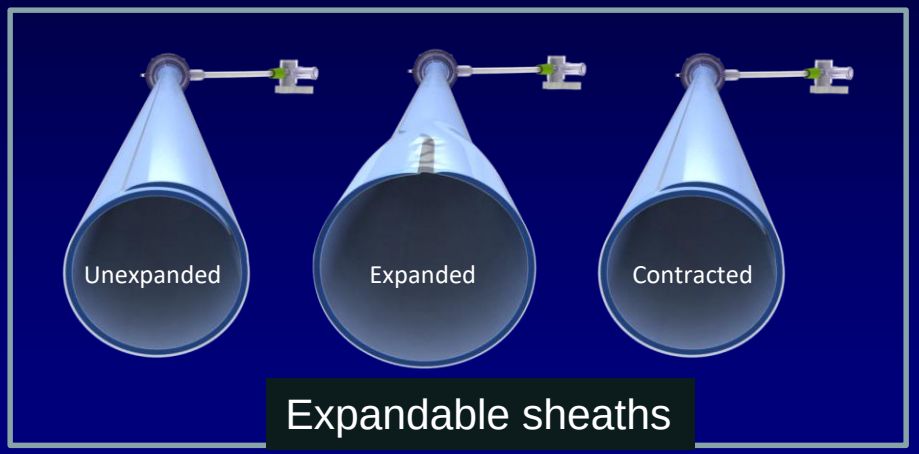
- Vascular complications
- Pacermaker implants
- Perivalvular aortic regurgitation
- Periprocedural stroke
- Leaflet thrombosis/degeneration

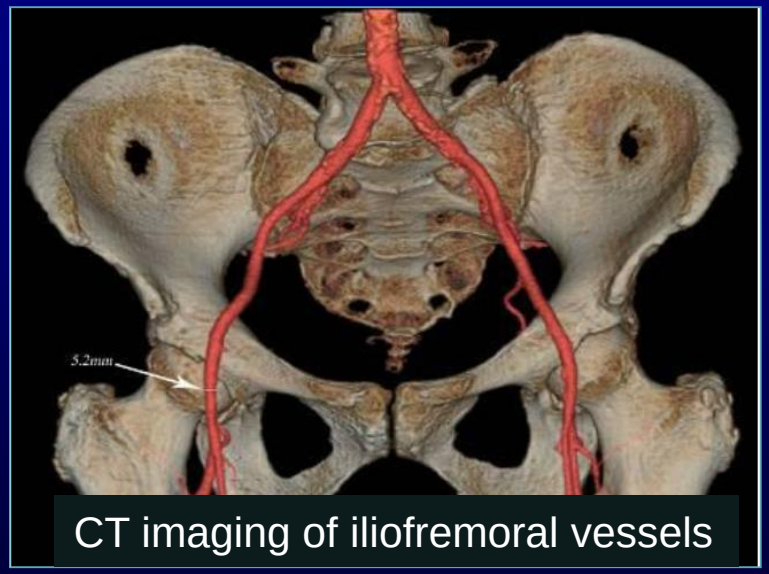
Solutions

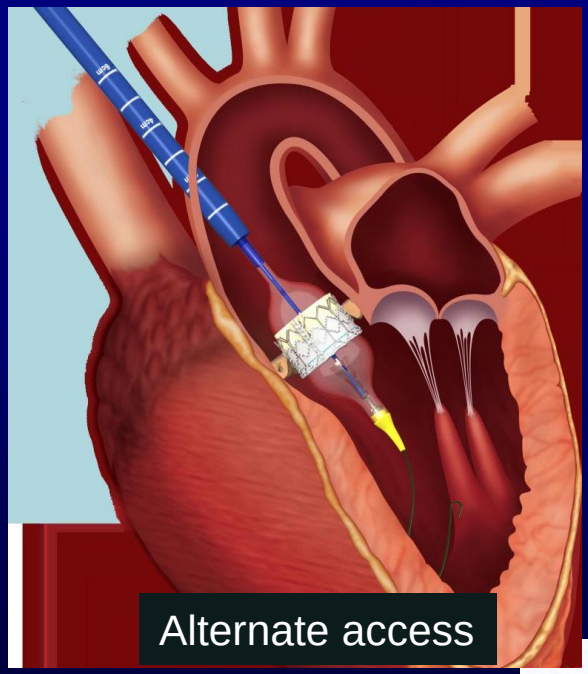
- Vascular complications have dramatically reduced with reduction in size of sheath
- Perivalvular AI, has reduced with design of the culf around the valve, and better sizing
- Pacemaker requirement is still there, but reduced with optimal valve deployment
- Stroke is prevented by cerebral protection devices

Strategies to reduce vascular complications









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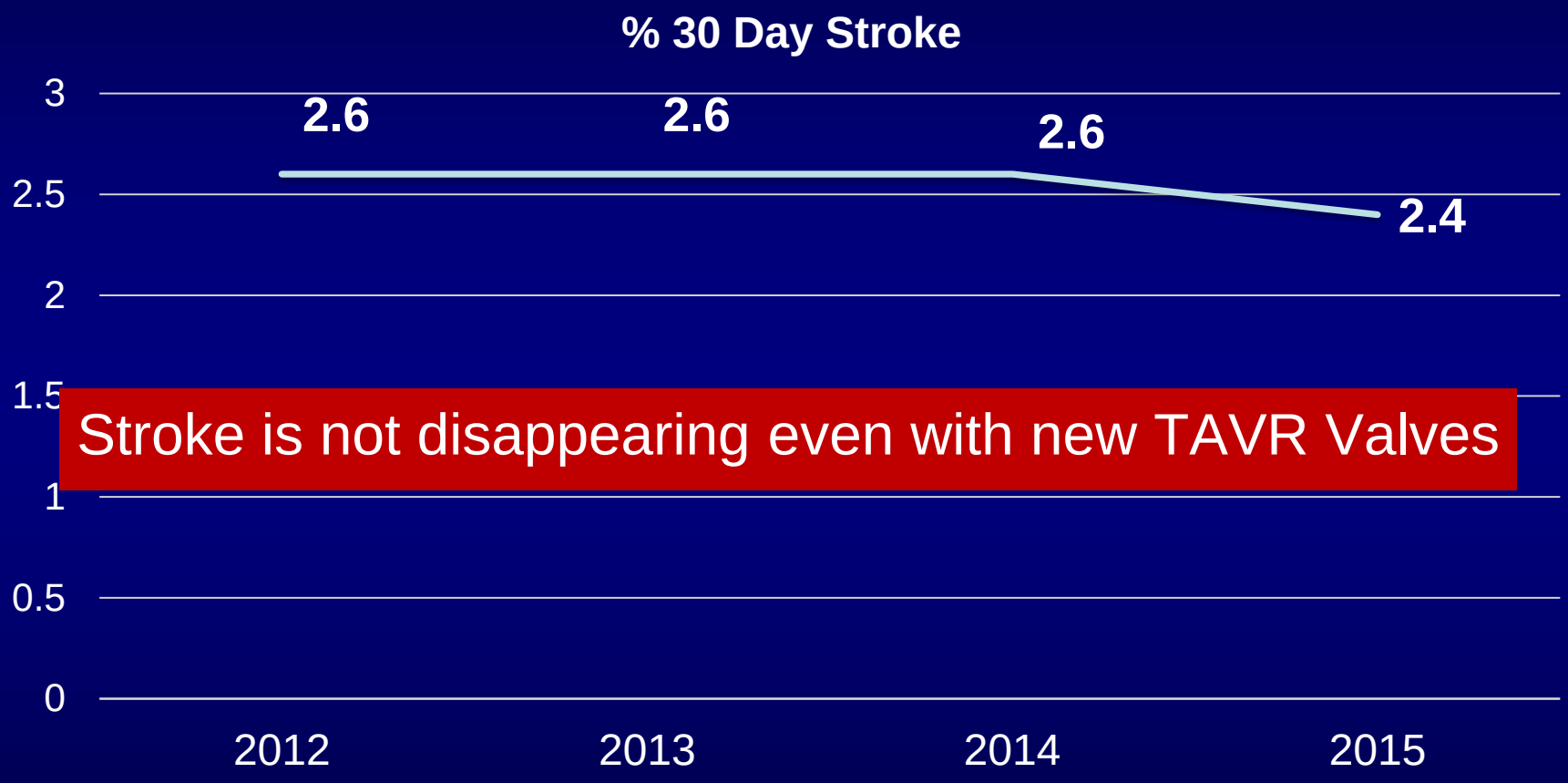
US TVT Registry Stroke Rate



Stroke is not disappearing even with new TAVR Valves

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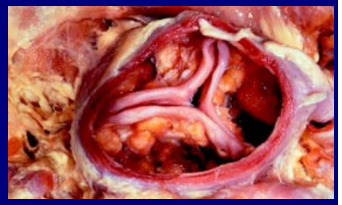
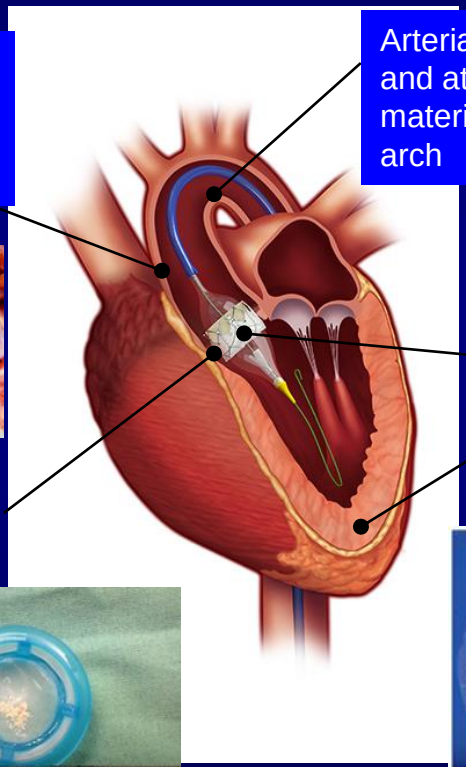
Embolic Debris is Derived from a Variety of Sources During TAVR

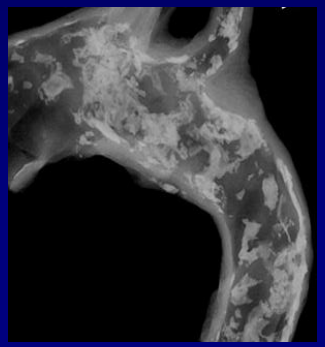
Arterial wall and calcific and atherosclerotic material from ascending arch



Valve leaflet tissue and calcific deposits from stenotic valve

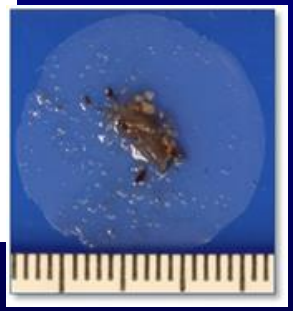


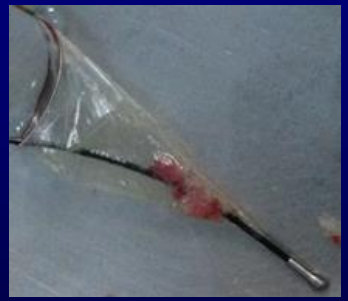
Arterial wall and calcific and atherosclerotic material from transverse arch



Foreign material from TAVR devices

Myocardium

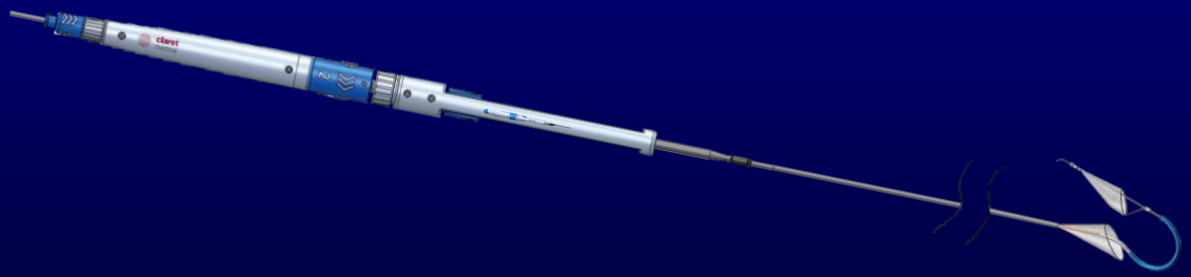




Courtesy: Dr Makkar

Claret Medical® Sentinel® Cerebral Protection System

- Dual independent filters for embolic debris capture and removal
- Right transradial 6F sheath
- access
- Deflectable sheath facilitates cannulation of LCC
- Low profile in aortic arch to minimize interaction with TAVR delivery catheter



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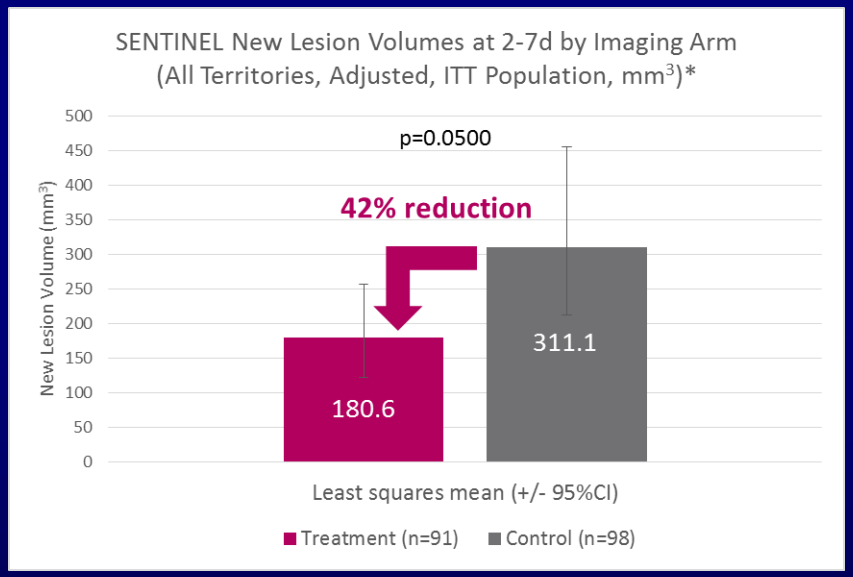
Average STS score was 6.0% for SENTINEL subjects

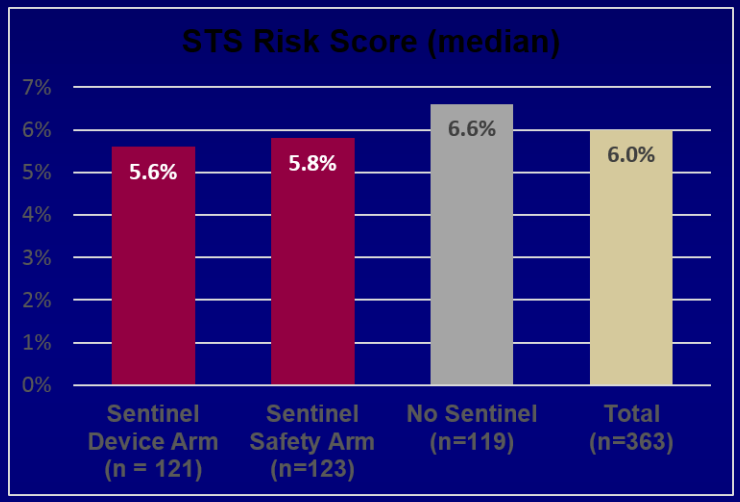
Cerebral protection captured debris in 99% of patients and reduced cerebral damage by >42%

SENTINEL

- Average STS score 6.0% (SD 3.2%)
- Cerebral embolic debris was captured in 99% of SENTINEL patients treated with Claret (n=103)



*Adjusted for baseline FLAIR lesion volume and valve type
ITT= Intention to Treat Population



Kapadia, et al. Cerebral embolic protection during transcatheter aortic valve replacement. *JACC*. doi: 10.1016/j.jacc.2016.10.023.

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SENTINEL study shows neurologist adjudicated stroke rate for the control arm (unprotected TAVR) of 9.1%

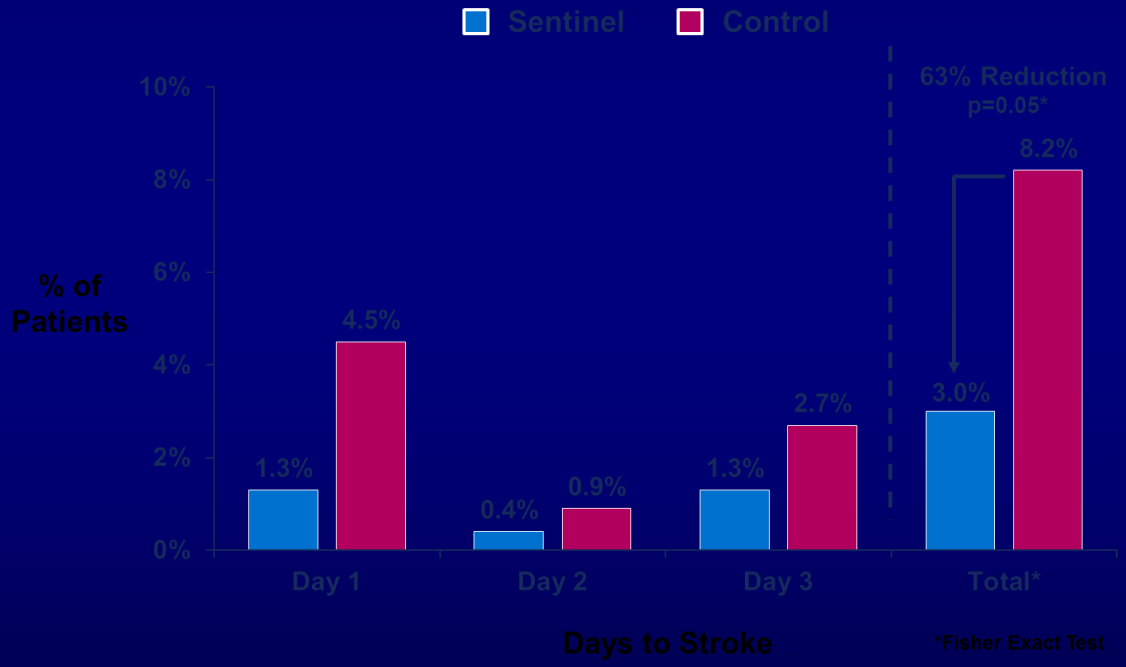
	Device Arm (n=234)	Control Arm (n=111)	p-value
30-day Clinical Outcomes			
Any MACCE†	7.3% (17/234)	9.9% (11/111)	0.40
Death (all-cause)	1.3% (3/234)	1.8% (2/111)	0.65
Stroke	5.6% (13/231)	9.1% (10/110)	0.25
Disabling	0.9% (2/231)	0.9% (1/109)	1.00
Non-disabling	4.8% (11/231)	8.2% (9/110)	0.22
AKI (Stage 3)	0.4% (1/231)	0%	1.00
TIA	0.4% (1/231)	0%	1.00
Sentinel Access Site Complications	0.4% (1/244)	N/A	0.53

†MACCE defined as All Death, All Stroke, Acute Kidney Injury (Stage 3) as 72 hours or discharge, whichever occurs first

Kapadia, et al. Cerebral embolic protection during transcatheter aortic valve replacement. *JACC.* doi: 10.1016/j.jacc.2016.10.023.

SENTINEL study shows significant procedural stroke reduction

Results from SENTINEL multi-national randomized trial of n=363 TAVI patients with vs. without protection using Sentinel™ cerebral embolic protection system shows a significant reduction in procedural stroke (63%)



SENTINEL trial. Data presented at Sentinel FDA Advisory Panel, February 23, 2017

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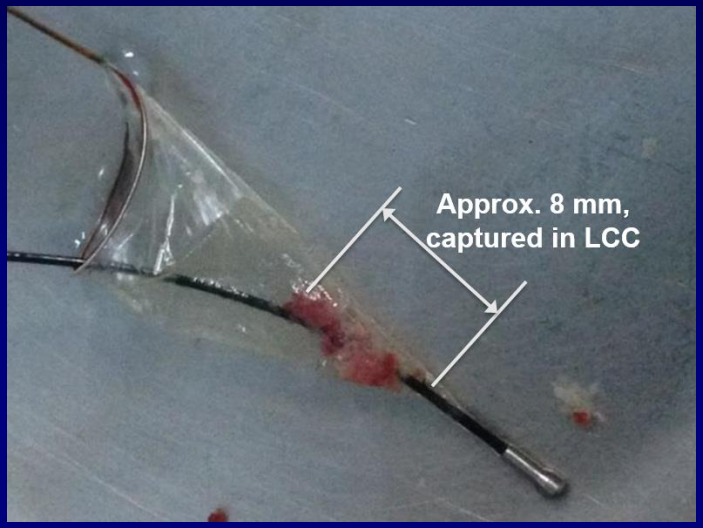
Clinical summary

- Transcatheter cerebral embolic protection(TCEP) is safe
- Embolic debris was captured in 99% of patients
- No significant reduction of new lesion volume by MRI

Kapadia S et al. J Am Coll Cardiol 2017;69:367-77

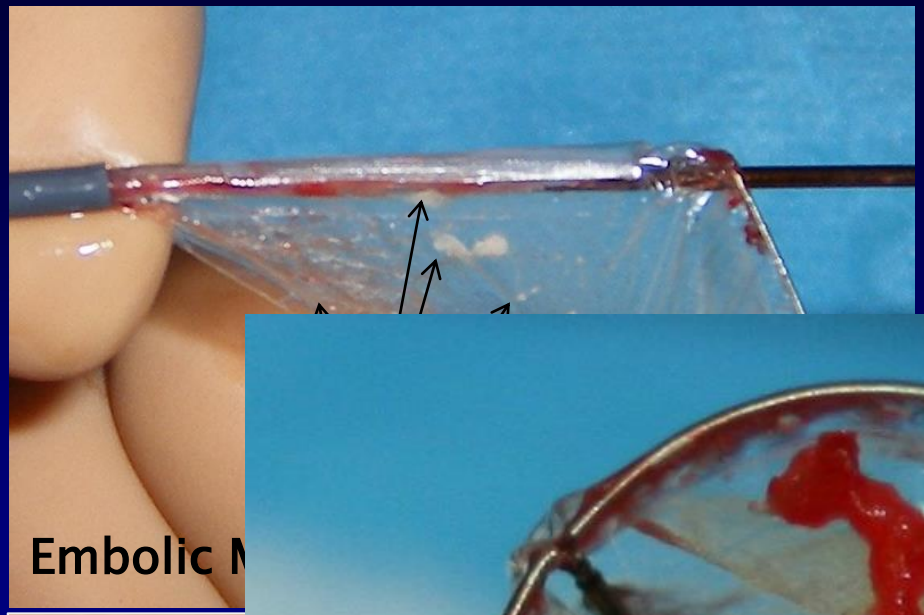
Is Cerebral Protection Necessary?

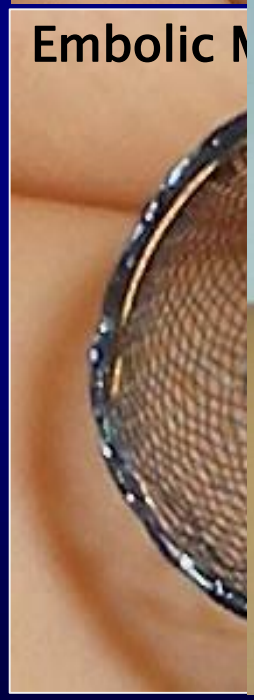


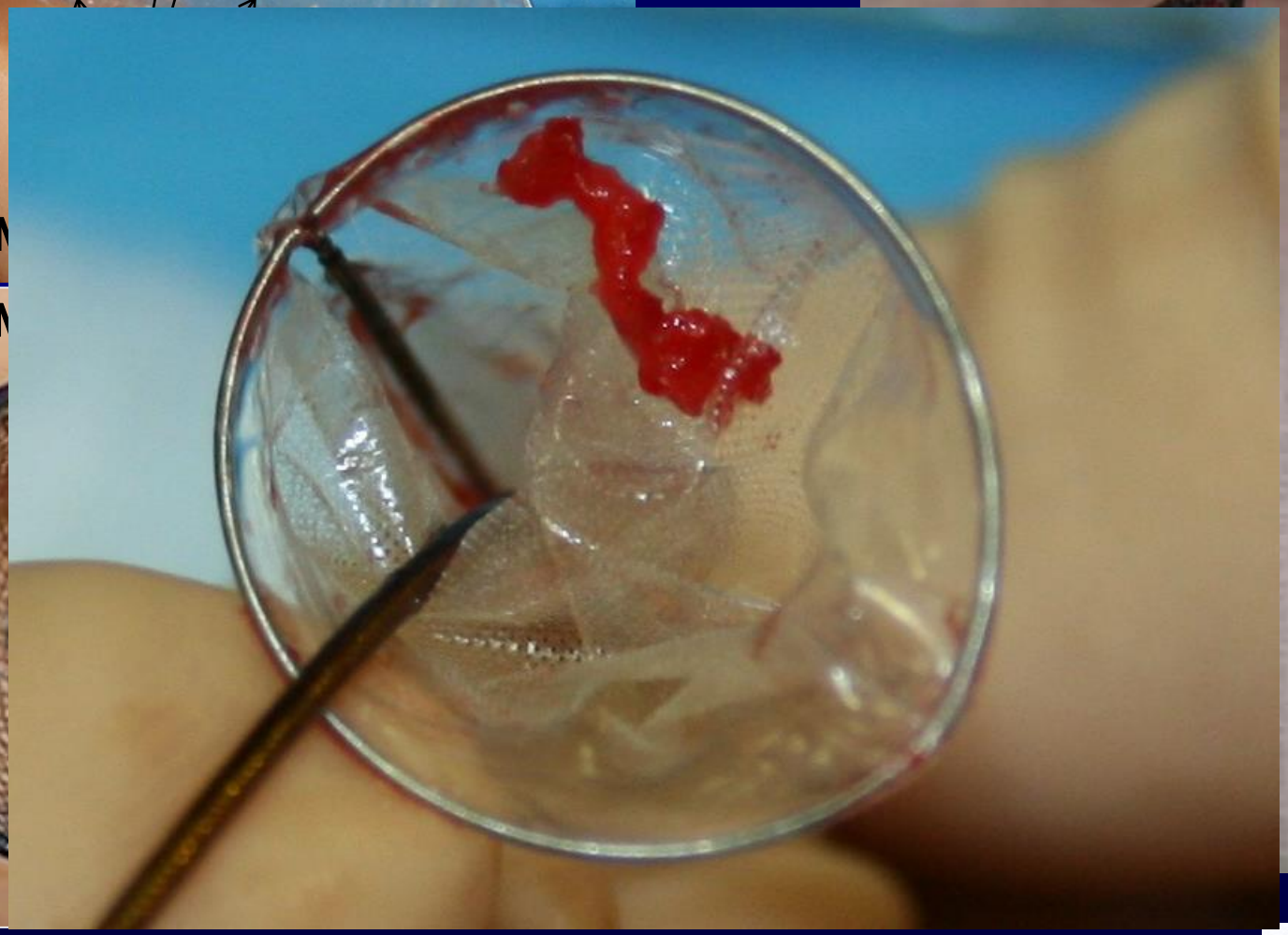
Would you take a chance and drive without a seatbelt?

You never know when you'll need protection

Embolic Material after TAVR







Leaflet thrombosis

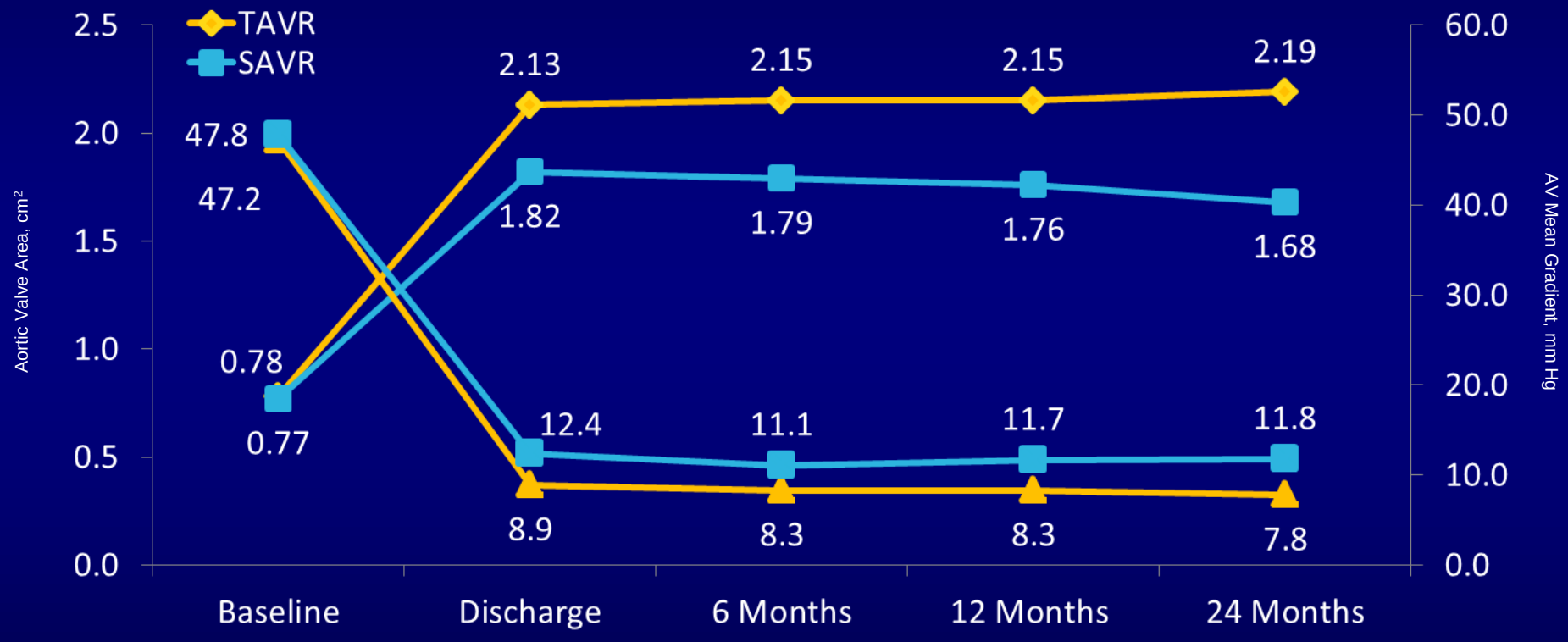
- Still an issue: present on both surgical and TAVR valves
- Might be lower in suprannular valves

Valve orifice

- TAVR has clearly shown in two studies to reveal a better valve area
- Low risk of Patient prosthetic mismatch

Hemodynamics*

TAVR had significantly better valve performance over SAVR at all follow-up visits



*Core lab adjudicated

TAVR and Low risk patients

- Low risk is not equal to low age
- Concerns of TAVR in young patients
  - Durability
  - Leaflet thrombosis/degeneration
  - Increased use of pacer
  - Higher proportion of bicuspid aortic pathology
- Low risk trials will need longer follow up
  - Enroller older patients with few comorbidities
- Very young patients
  - New generation mechanical valves is still the best option

Conclusions

- TAVR should be the default therapy in most cases of aortic valve stenosis, irrespective or risk
- Surgical valve replacement should be reserved for only
  - very young patients
  - aortic valve disease and aortic aneurysm
  - Some cases of bicuspid aortic valve stenosis

Future

- Cardiac surgeons will have to consult interventional cardiologist prior to offering surgery to any patient with valve disease