Cerebral Embolic Protection During TAVR: Where We Are After TCT?

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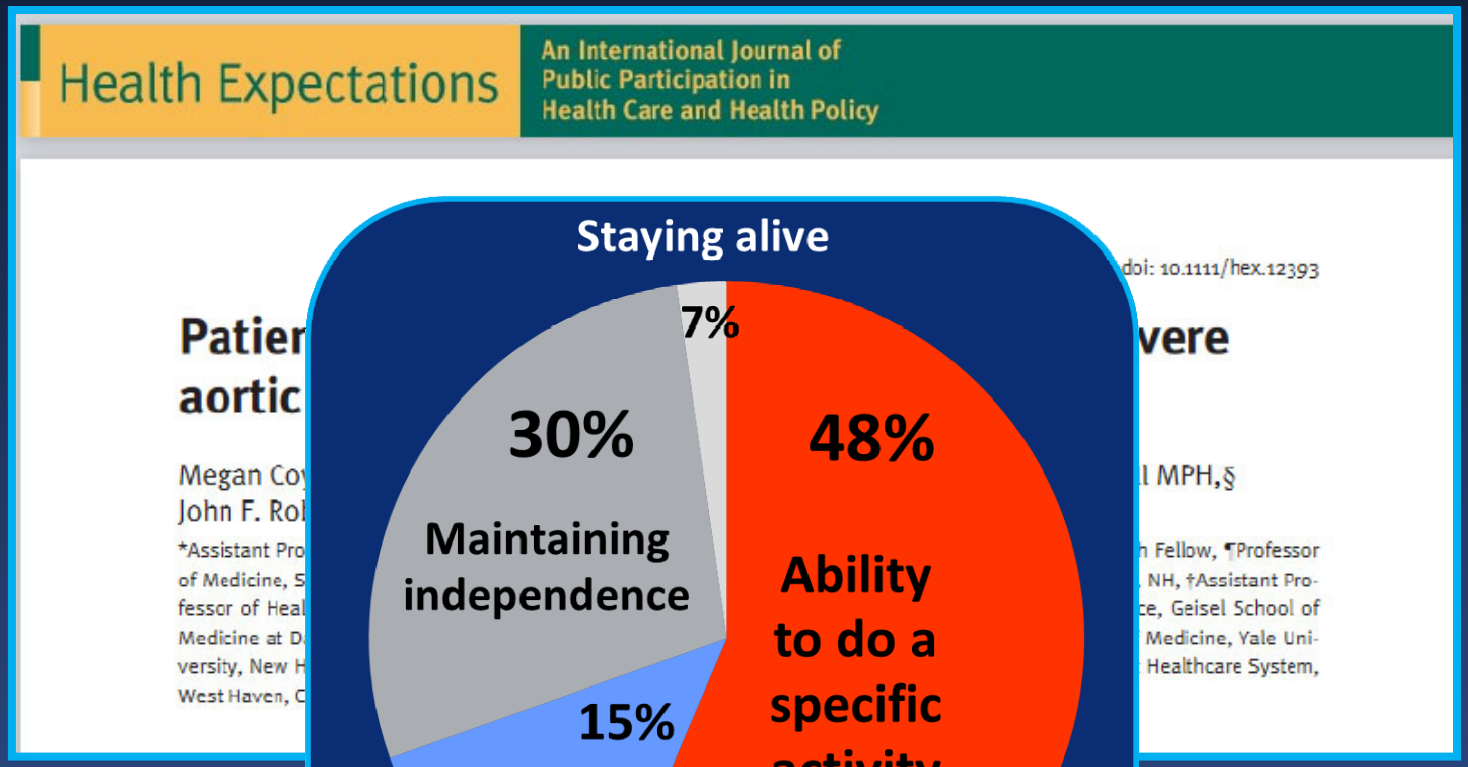
Disclosure Statement of Financial Interest

I, Jeffrey W. Moses, DO NOT have a financial interest/arrangement or affiliation with one or more organizations that could be perceived as a real or apparent conflict of interest in the context of the subject of this presentation.

Patient Perceptions and Expectations



Strokes Can Be Unpredictable

Procedural Experience for Transcatheter Aortic Valve Replacement and Relation to Outcomes

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John D.
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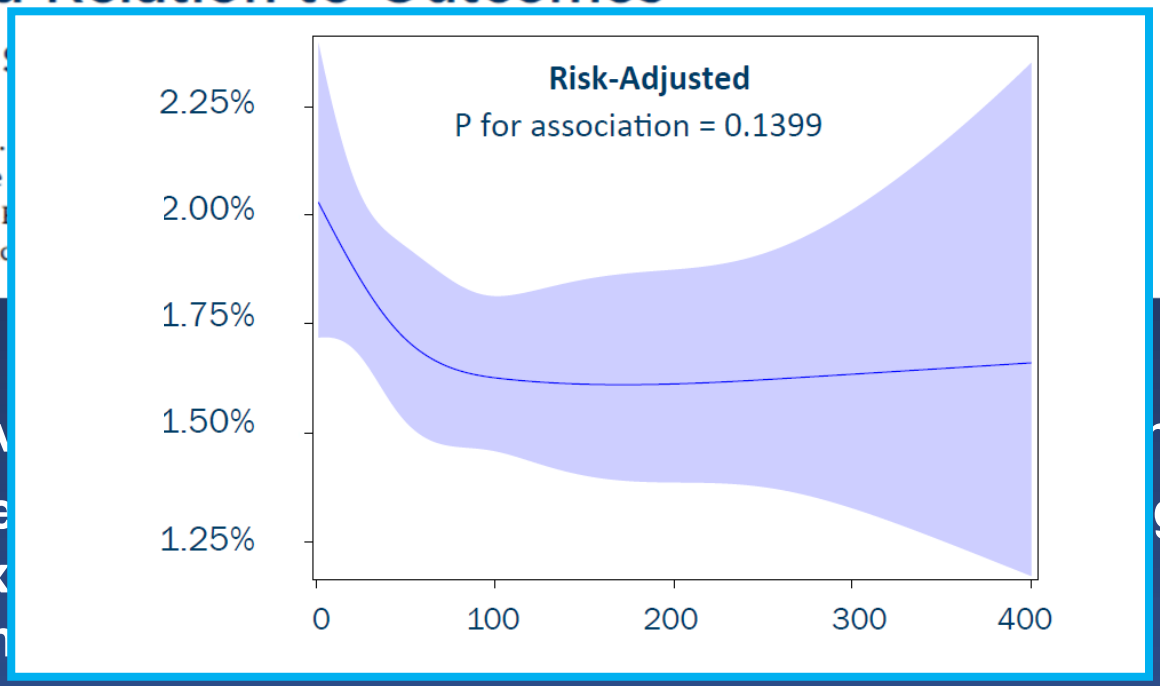
Eric D. I
Frederic



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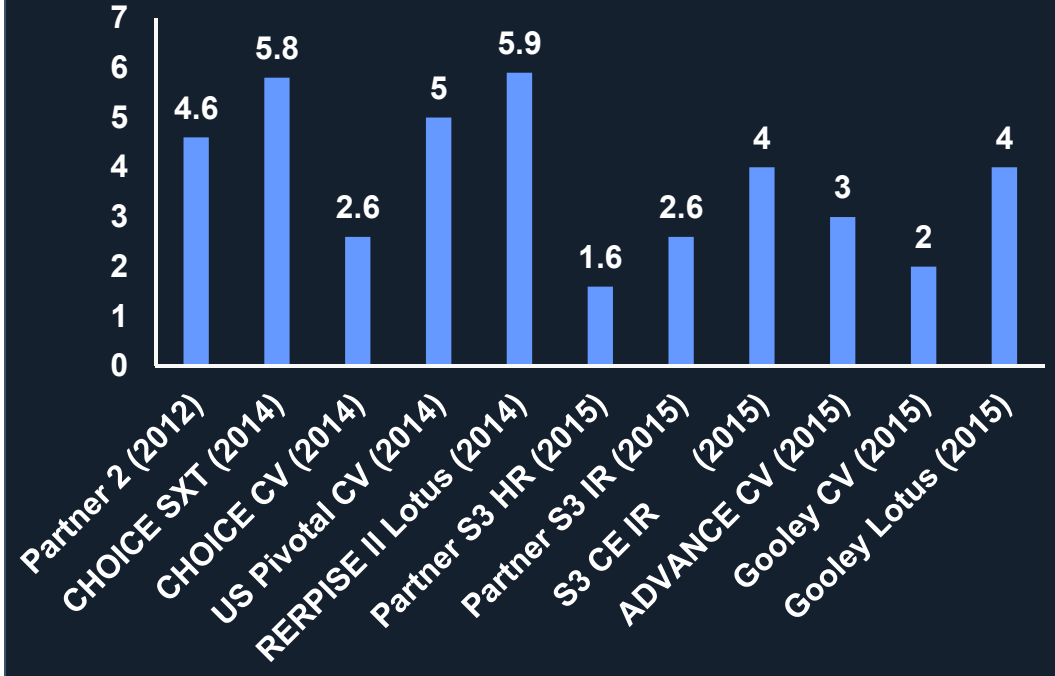
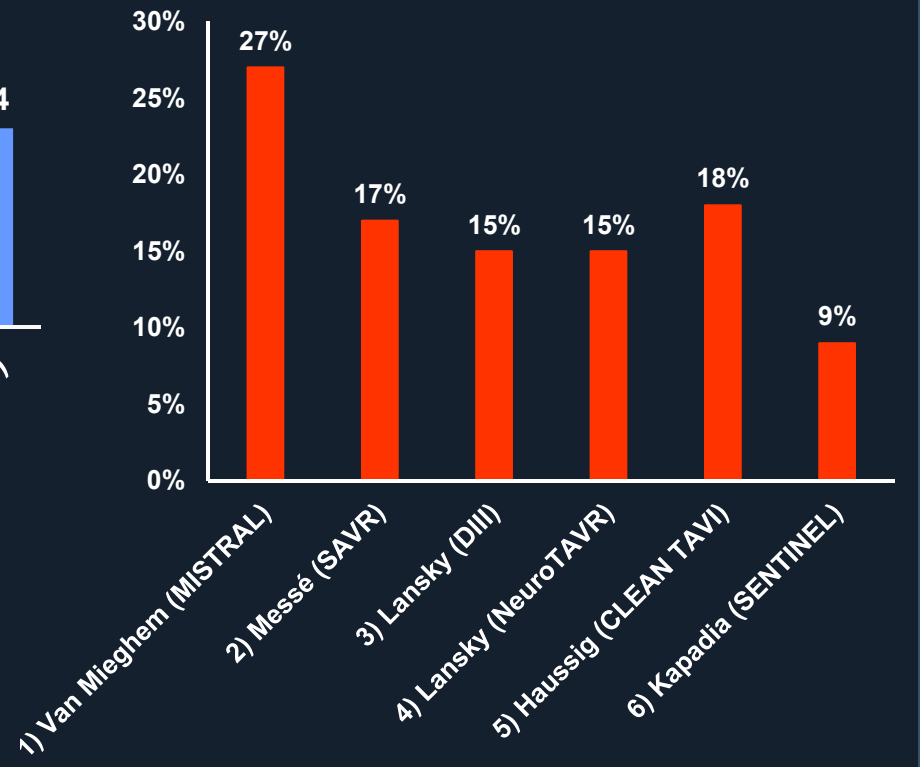
Stroke Underreported in TAVR Studies

In reported clinical trials stroke rates with TAVR range from 1.6%-5.9%



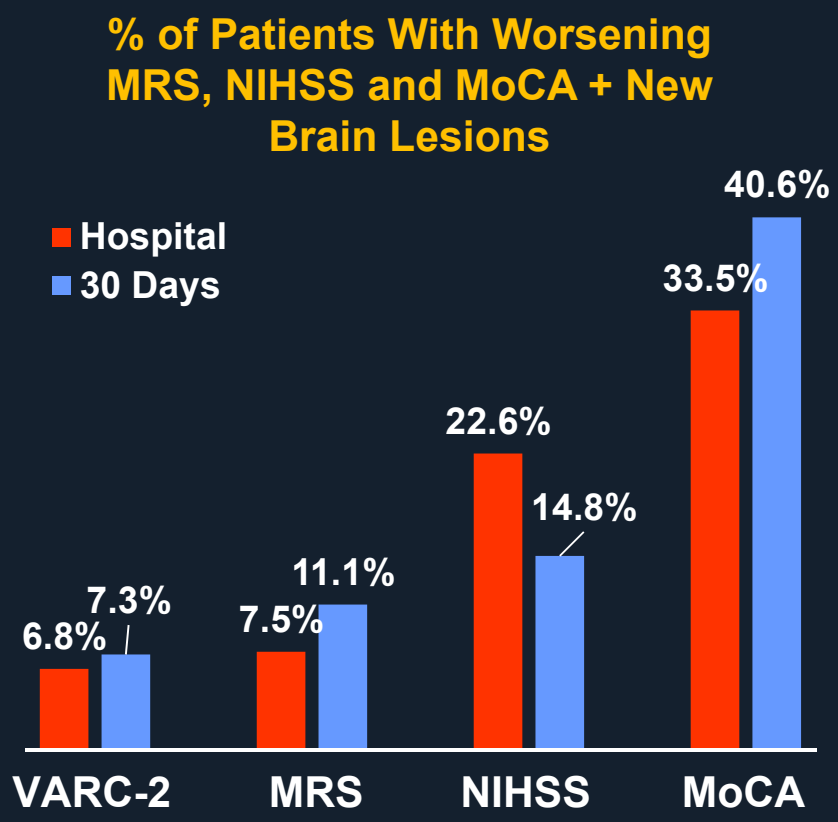
- Neurologist identified deficits and worsening neurocognition with new Brain MRI lesions and/or higher lesion volume
- Stroke range is 9-27% by AHA/ASA guidelines



[1] Van Mieghem NM, *EuroIntervention*. 2016;12:499.
[2] Messe S, *Circulation*. 2014;129:2253.
[3] Lansky AJ, *Eur Heart J*. 2015;36:2070.
[4] Lansky AJ, *AJC* 2016;118:1519.
[5] Haussig S, *JAMA*. 2016;316:592.
[6] Kapadia SR, *JACC*. 2017;69:367.

US NeuroTAVR Trial: Outcome

Neurologic And Cognitive Impairment After Unprotected TAVR In USA (5 High Volume TAVR Centers)



- Contemporary US Registry of 44 patients undergoing unprotected TAVR
- Stroke defined by AHA/ASA stroke definitions are common:
  - Discharge: 22.6%
  - 30-Days: 14.8%
- MoCA scores (surrogate of Cognition) get worse in 40% of patients after TAVR

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Lansky et al *AJC* (2016),
http://dx.doi.org/10.1016/j.amjcard.2016.08.013

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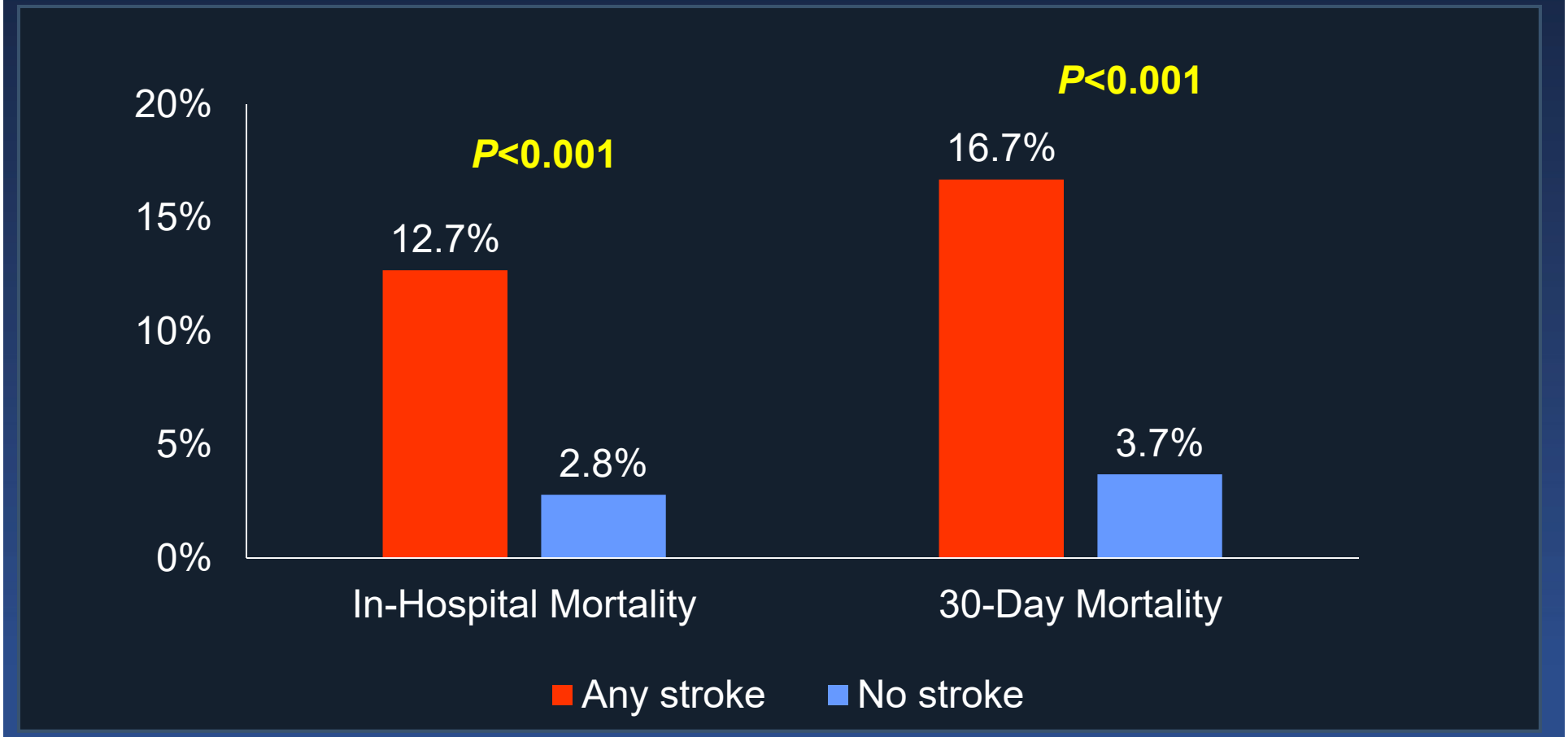
TVT: Association of Post TAVR Stroke with Mortality



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Huded et al, *JAMA* 2019

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Consequences of Stroke

Mortality:

TAVR patients suffering disabling stroke : 1-year mortality of 67% vs. 12% and 2-year mortality of 83% vs. 20%.[1]

PHYSICAL FUNCTIONING:

40% : moderate to severe permanent disability

55%-75% of "fully recovered" withresidual dysfunction in at least one limb.[2-3]

EFFECT OF STROKE AND WHITE MATTER LESIONS IN WORKING POPULATION

44% return to work,

33% significant financial strains,

79% report social isolation[4].

even without a stroke note impaired social cognition, leading predictor of occupational disability, and ability to maintain relationships with family and friends[5]

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[1] Adams DH, *N Engl J Med.* 2014;370:1790. [2] Connolly SJ, *N Engl J Med.* 2009;361:1139. [3] Daniel K, Stroke. 2009;40:e431. [4] Lai SM, *Stroke.* 2002;33:1840, [5] Cotter *J Neurology* 2017;87:1727

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The Economic Burden of Strokes Post-TAVR

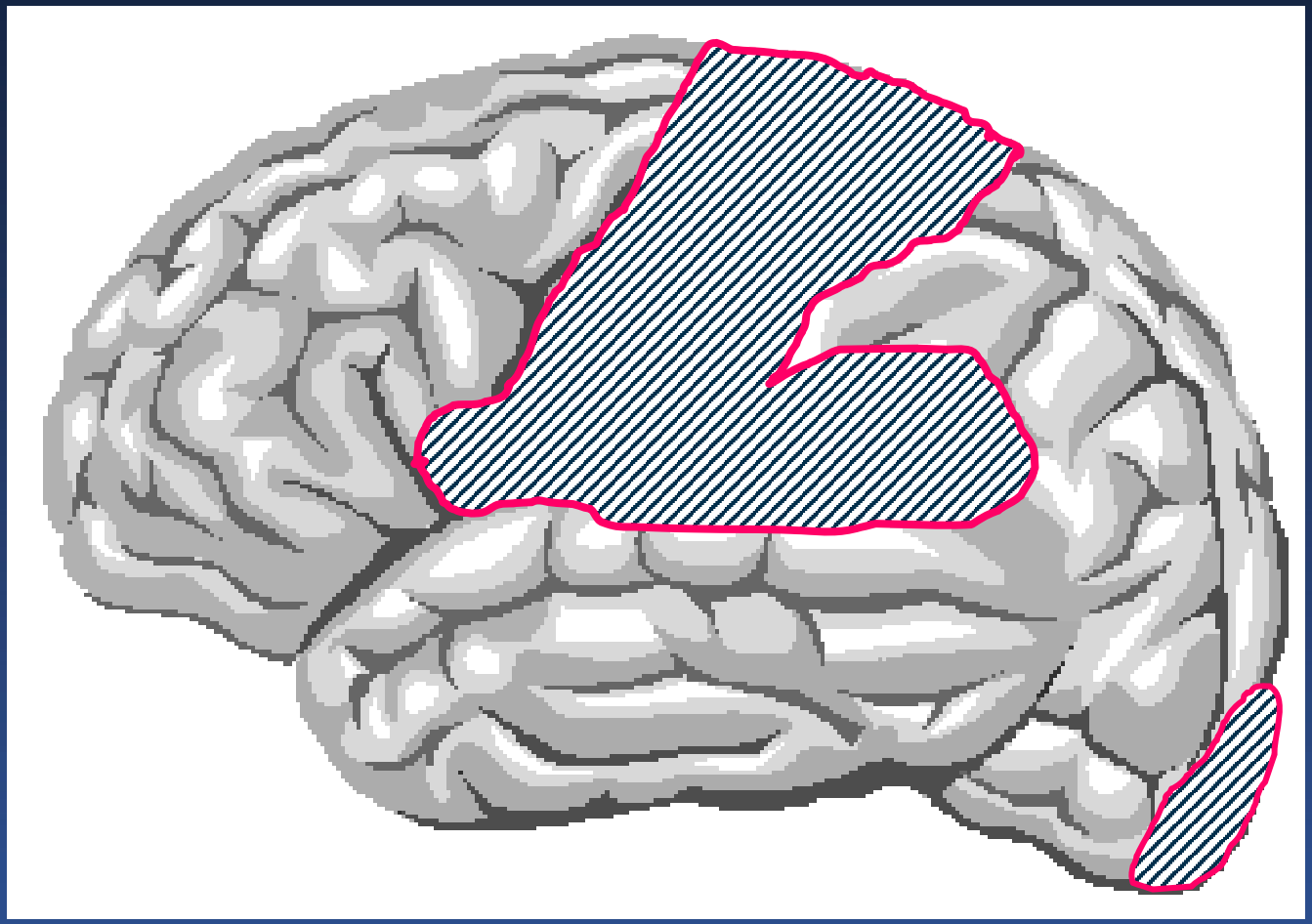
- Among 30,830 TAVR patients from the National Readmission Database, 776 (2.5%) were reported to have suffered acute ischemic stroke

- After propensity matching, TAVR patients who suffered acute ischemic stroke had higher rates of:
  - in-hospital death (11.3% vs 4.1%)
  - Prolonged hospitalizations (15d vs 9d)
  - Non-home discharges (66.1% vs 29.8%)
  - Hospital charges (~$60-80,000 higher)
  - 30-day readmissions (20.5% vs. 15.6%)
- Their repeat hospitalizations were also longer, more costly and associated with higher mortality ($p < 0.001$)

Alkhouli M, Alqahtani F, et al. Outcomes of Acute Ischemic Stroke After TAVR: Potential Impact of Embolic Protection ACC 2018

Cognition and TAVR

Brain Regions Assessed by NIH Stroke Scale



* Courtesy Ronald Lazar

"Silent" Cerebral Emboli & TAVR

- Every step of TAVR puts a patient at risk of stroke (crossing the aortic valve, valvuloplasty, valve placement, etc.)[1]
- Cerebral embolization demonstrated by DWI MRI is common with TAVR occurring in 68-98% of cases.[2-4]
- Cerebral emboli detected on DWI MRI increase the risk of clinically overt stroke by 2-4 times and lead to cognitive dysfunction, depression, impaired mobility, dementia, and increased mortality.[5-6]
- The greater the volume of DWI lesions seen on MRI the greater the long-term risk of cognitive dysfunction and long-term dementia.[5-6]

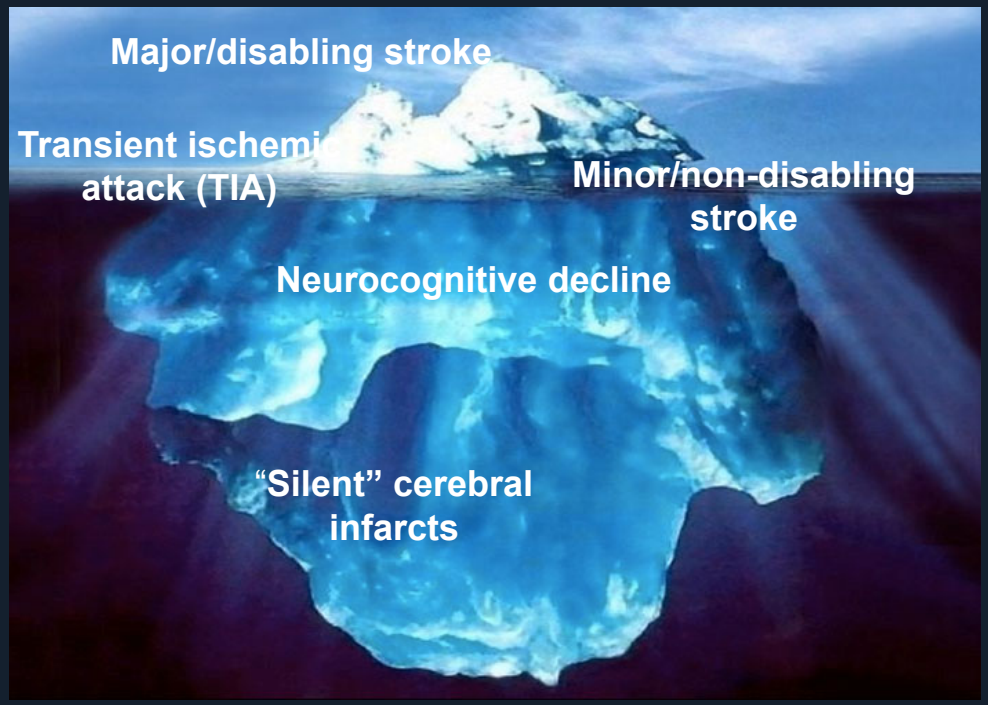
[1]Kahlert, *Circulation*. 2012;216:1245-1255
[2]Arnold S, *J Am Coll Cardiol Intv.* 2010;3:1126
[3]Haussig S, *JAMA* 2016;316:592
[4]Lansky AJ, *Eur Heart J.* 2015;36:2070. | [5]Sacco RL, *Stroke*. 2013;44:00
[6]Vermeer SE, *Lancet* Neurol 2007;6:611

Most Cerebral Damage in TAVR is Unseen

Clinically apparent

Subtle and often undetected

Clinically unrecognized



Clinical exam, NIHSS, mRS

MMSE, MoCA

Neurocognitive test batteries

Neuroimaging

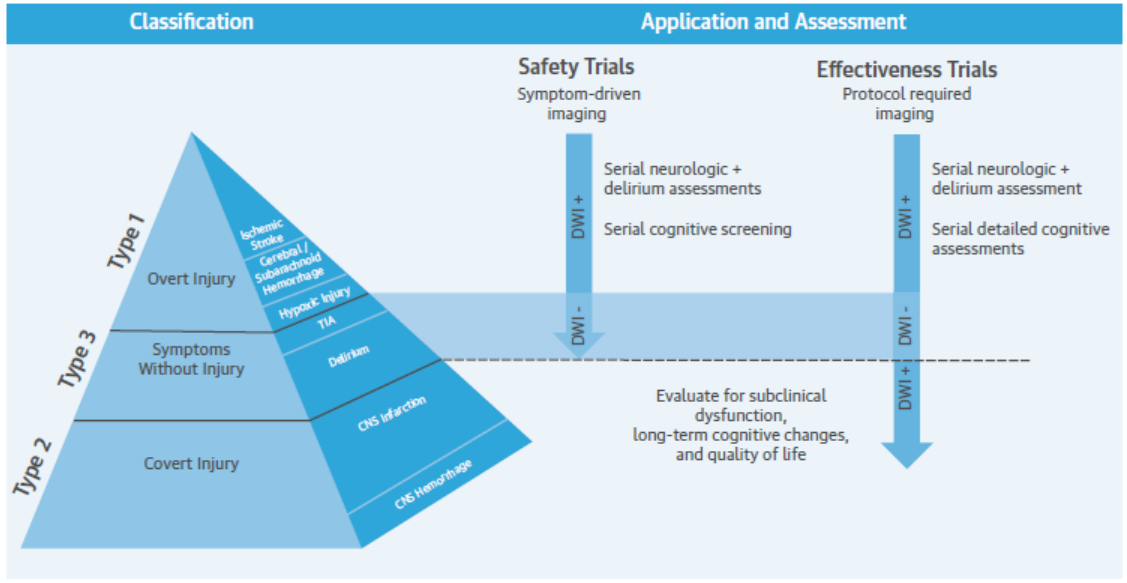
….but can have far-reaching effects

Proposed Standardized Neurological Endpoints for Cardiovascular Clinical Trials

An Academic Research Consortium Initiative

Alexandra J. Lansky, MD,[a,b,c] Steven R. Messé, MD,[d] Adam M. Brickman, PhD,[e] Michael Dwyer, PhD,[f] H. Bart van der Worp, MD, PhD,[g] Ronald M. Lazar, PhD,[e] Cody G. Pietras, MS,[a,b] Kevin J. Abrams, MD,[h] Eugene McFadden, MD,[i] Nils H. Petersen, MD,[j] Jeffrey Browndyke, PhD,[k] Bernard Prendergast, MD,[l]

CENTRAL ILLUSTRATION Neurologic Academic Research Consortium Consensus: Classification, Application, and Assessment of Neurological Events in Clinical Trials



Lansky, A.J. et al. J Am Coll Cardiol. 2017;69(6):679-91.

Timing of Strokes after TAVR

Insights Into Timing, Risk Factors, and Outcomes of Stroke and Transient Ischemic Attack After Transcatheter Aortic Valve Replacement in the PARTNER Trial (Placement of

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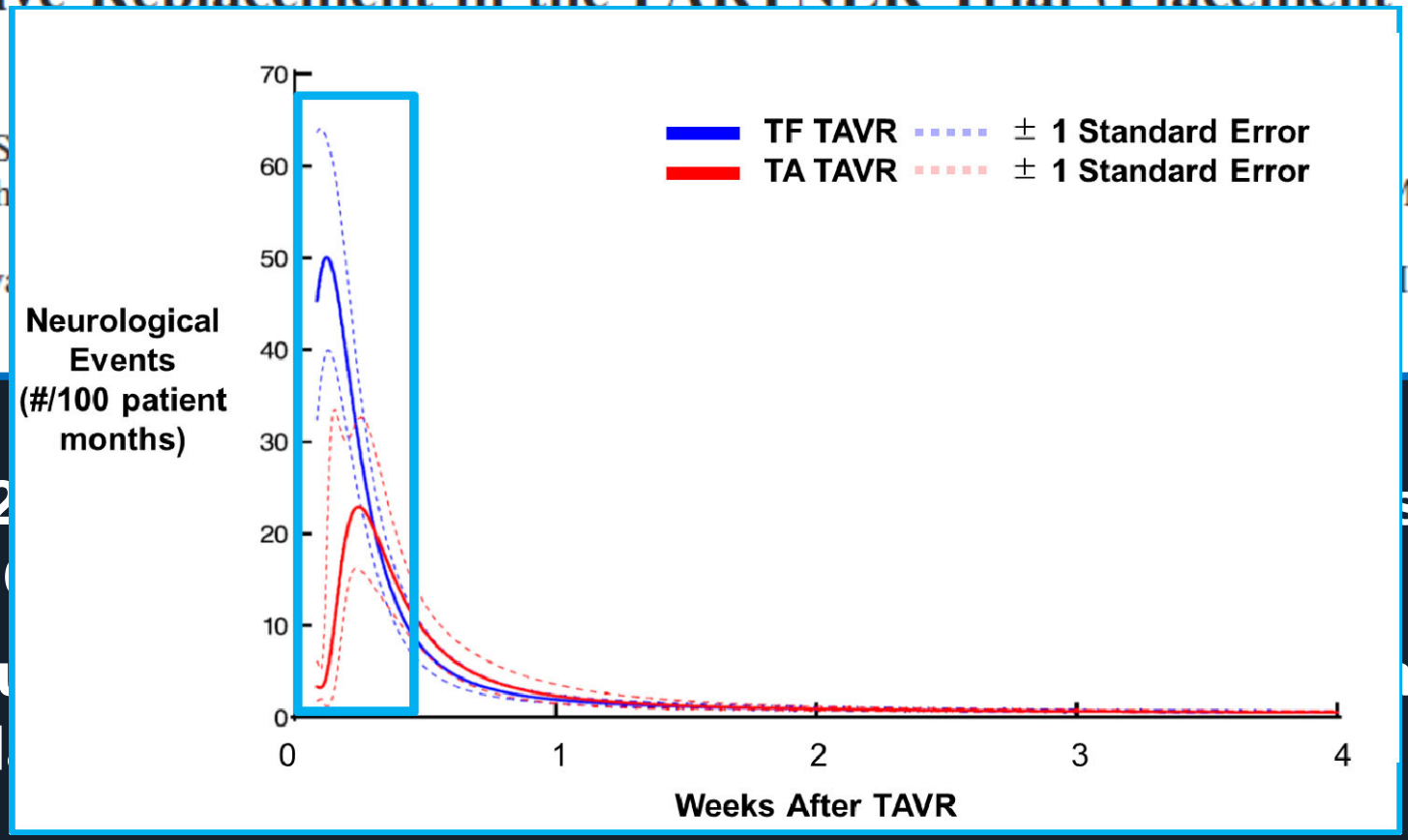

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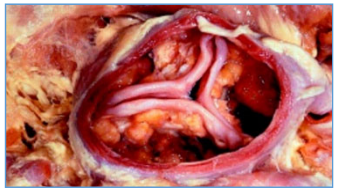
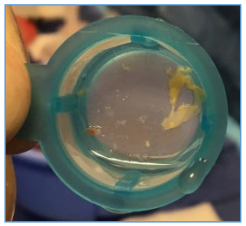
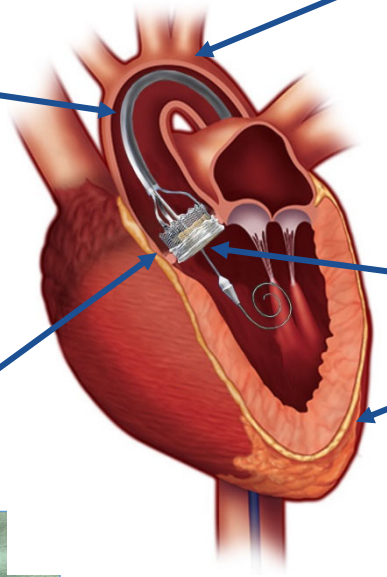
Sources of Debris During TAVR

ASCENDING ARCH
Arterial wall, calcific and atherosclerotic material

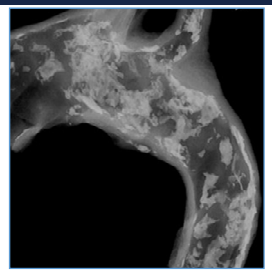




STENOTIC VALVE
Leaflet tissue and calcific deposits

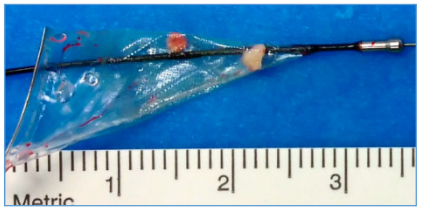


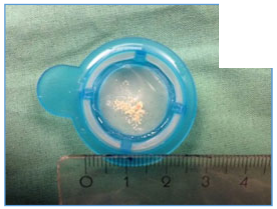
TRANSVERSE ARCH
Arterial wall, calcific and atherosclerotic material

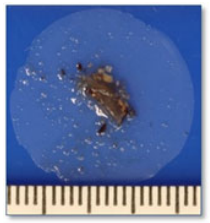


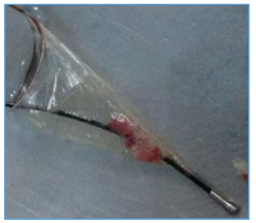
TAVR DEVICES
Foreign material

NATIVE HEART
Myocardium



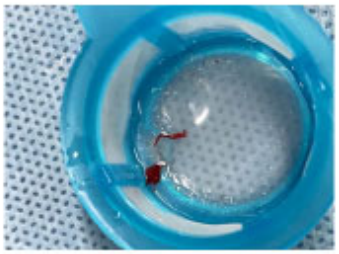




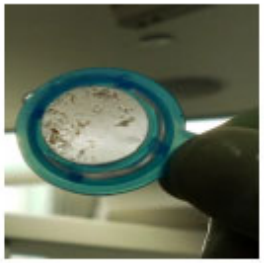


SENTINEL CEP – After FDA Approval
Embolic Debris Captured

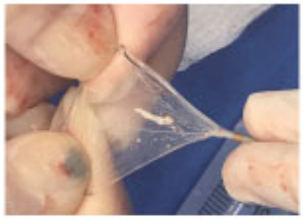
Recent Images of Debris Captured During TAVR with Sentinel®



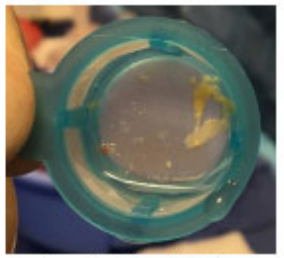
Cedar Sinai, Los Angeles, CA USA
Evolut-R
July 2017



Pinnacle Health, Harrisburg, PA USA
S3
August 2017



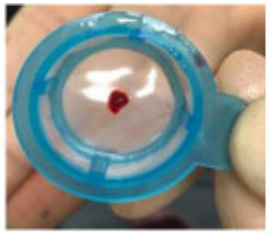
WVU-Ruby Memorial Hospital
Morganton, WV USA
S3
September 2017



New York-Presbyterian
Weill Cornell, NY, NY USA
Evolut Pro
November 2017

Kaleida Health, Buffalo, NY USA
S3
September 2017

Billings Clinic, Billings MT USA
S3
October 2017



St Thomas Hospital, London
Symetis Acurate neo TF
September 2017

Princeton Baptist Hospital,
Birmingham, AL USA
November 2017

Predictors of Stroke, Neuro Events or MRI Findings

Author	N	Event rate	Approach	Clinical predictors	Anatomical predictors
Tay et al 2011	253	9%	TA/TF	H/O stroke/TIA	Carotid stenosis*
Nuis et al 2012	214	9%	TF	New onset AF	Baseline AR >3+
Amat Santos et al 2012	138	6.5%	TA/TF	New onset AF	None
Franco et al 2012	211	4.7%	TA/TF	None	Post-dilation
Miller et al 2012	344	9%	TA/TF	History of stroke Non TF-TAVR candidate	Smaller AVA
Cabau et al 2011	60	68% (MRI)	TA/TF	Male, History of CAD	Higher AVG
Fairbairn et al 2012	31	77% (MRI)	TF	Age	Aortic atheroma
Nombela-Franco et al 2012	1061	5.1%	TA/TF	Balloon postdilatation, valve dislodgement, New onset AF, PVD, Prior CVA	

Predictors for Particles ≥1000 um

	Particles >1000 um	
	OR (95% CI)	*P* value
Baseline characteristics		
Male gender	0.66 (0.38-1.15)	0.14
History of AVR/TAVR	2.74 (0.94-7.94)	0.06
Hypertension	0.86 (0.45-1.62)	0.64
Femoral access	0.10 (0.008-1.276)	0.08
Pre-dilatation	1.70 (0.75-3.86)	0.21
Post-dilatation	1.34 (0.67-2.69)	0.41
(Functional) bicuspid	2.81 (1.26-6.28)	0.01
THV-type used		
Sapien*3*	1.00 (reference)	-
Evolut R/PRO	1.35 (0.66-2.77)	0.42
Lotus	2.58 (1.25-5.32)	0.01

More than Average Amount of Material

	More than average material	
	OR (95% CI)	*P* value
Baseline characteristics		
Male gender	1.07 (0.57-1.99)	0.84
History of AVR/TAVR	0.65 (0.18-2.39)	0.52
Hypertension	1.85 (0.85-3.99)	0.12
History of stroke	0.25 (0.07-0.91)	0.04
Pre-dilatation	1.15 (0.58-2.28)	0.21
Use of repositioning	3.00 (1.44-6.23)	0.41
THV-type used		
Sapien*3*	1.00 (reference)	-
Evolut R/PRO	1.35 (0.66-2.77)	0.42
Lotus	1.21 (0.49-3.02)	0.01

Results are displayed as OR (95% CI)
Abbreviations: AVR = Aortic Valve Replacement; TAVR = Transcatheter Aortic Valve Replacement

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Erasmus MC University Medical Center Rotterdam

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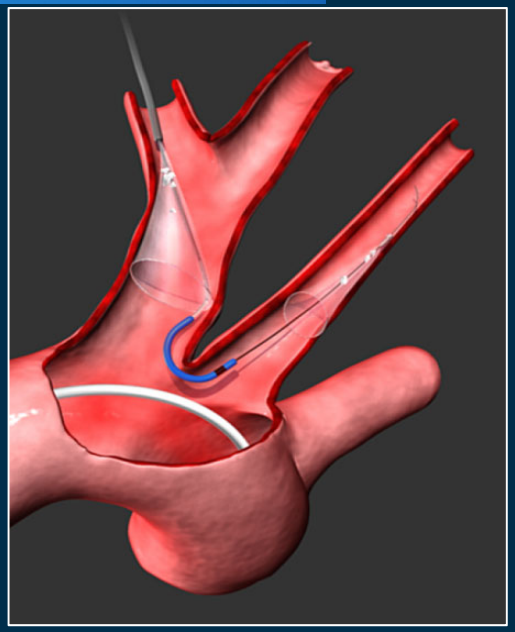
Clinical Trials

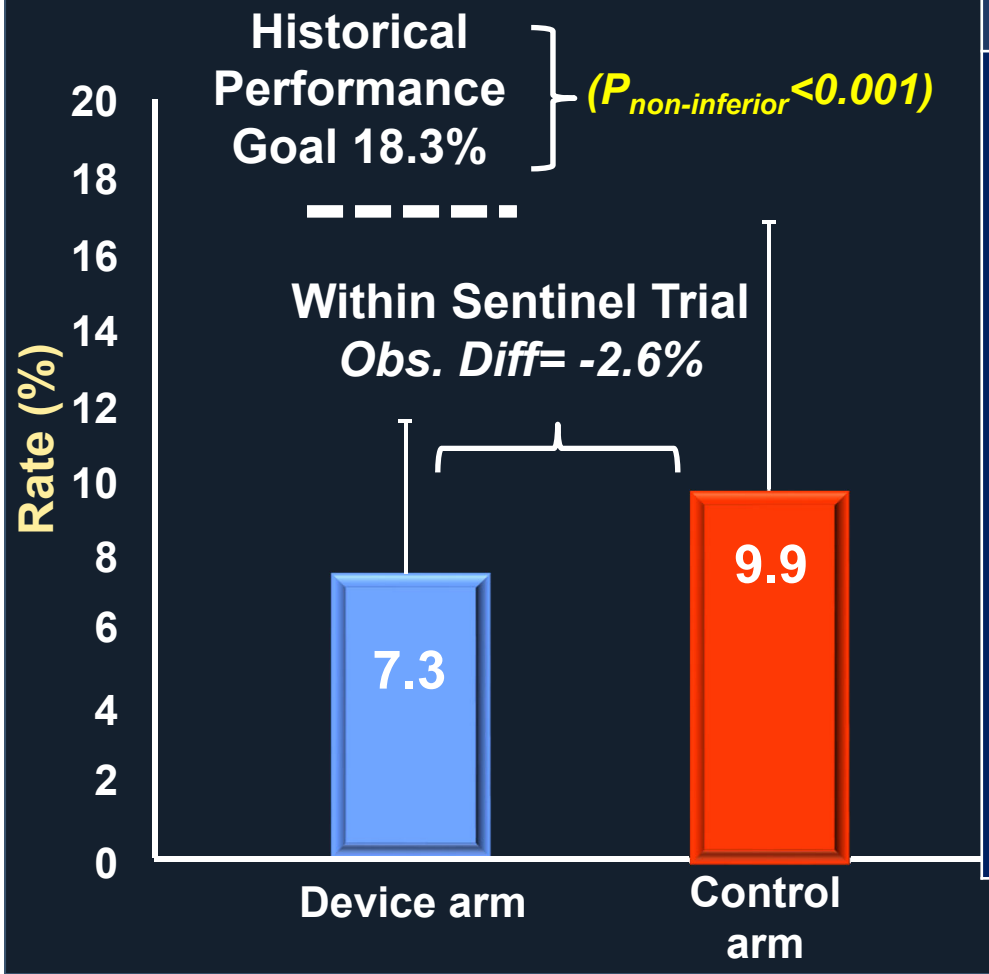
Sentinel Cerebral Protection Systems



- Dual independent filters designed for embolic debris capture and removal
  in two of the three cerebral branches
  - Innominate artery and left common carotid artery
- Right transradial 6F sheath access

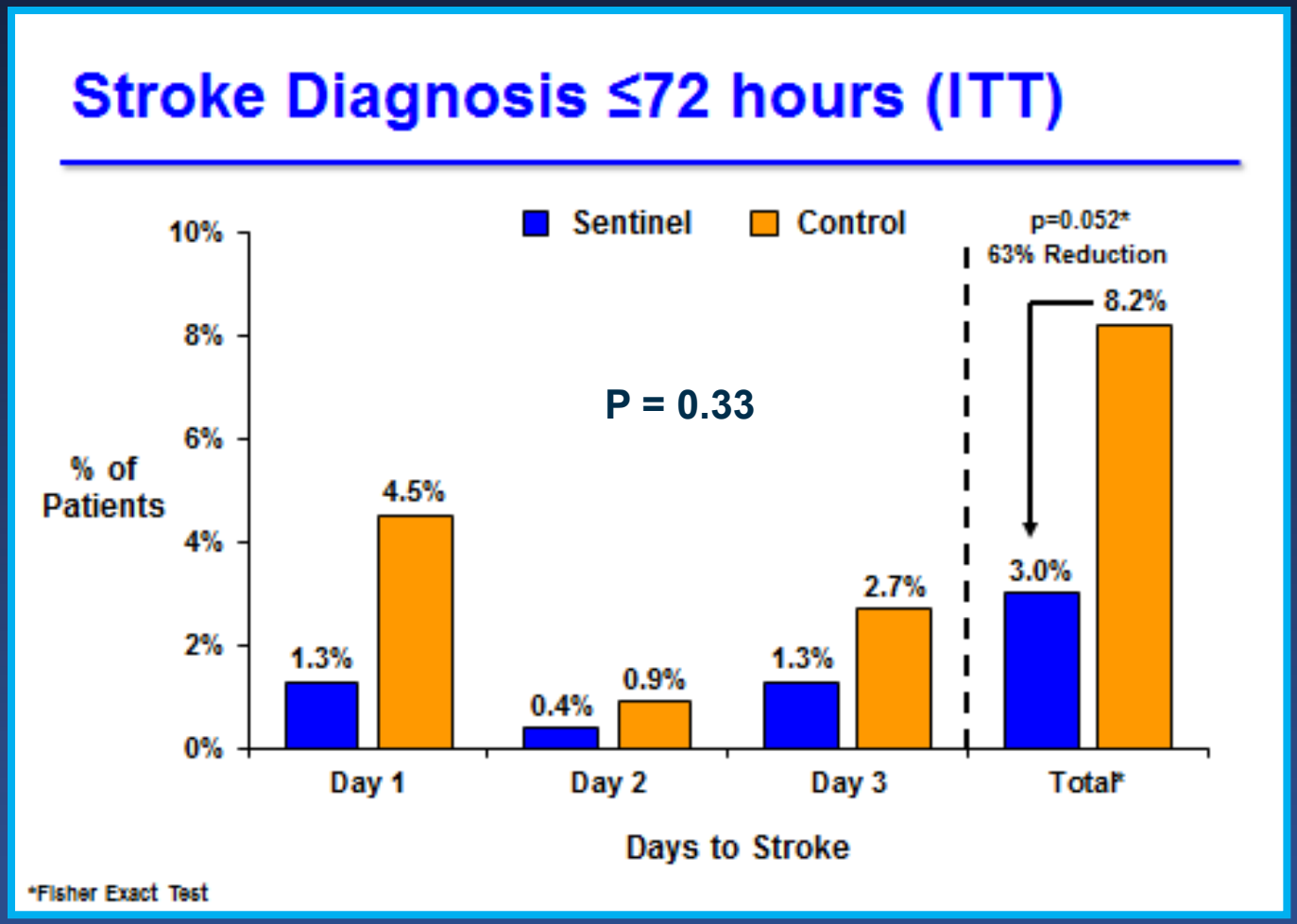
Primary Safety Endpoint (NI):
All Cause Death, Stroke, AKI Stage 3

30-Day MACCE



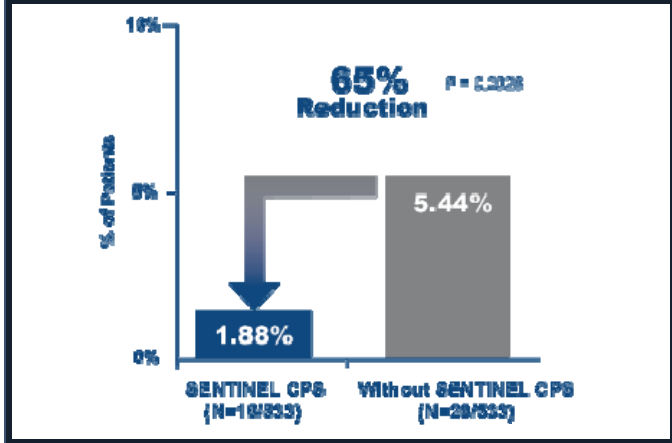
	Device Arm (n=234)	Control Arm (n=111)	*P* value
30-Day Clinical Outcomes			
Any MACCE†	7.3%	9.9%	0.40
Death (all-cause)	1.3%	1.8%	0.65
Stroke	5.6%	9.1%	0.25
Disabling	0.9%	0.9%	1.00
Non-disabling	4.8%	8.2%	0.22
AKI (Stage 3)	0.4%	0%	1.00
TIA	0.4%	0%	1.00
Sentinel Site Complications	0.4%	N/A	0.53

SENTINEL CEP Randomized Trial
Clinical Outcomes

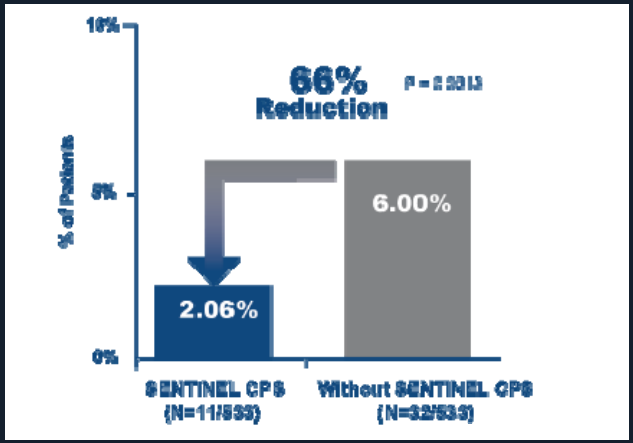


Largest Patient-level Pooled Propensity-Matched Analysis to Date Demonstrates Reductions in Peri- procedural (≤ 72 h) Stroke, Mortality or Stroke and Disabling Stroke with Routine SENTINEL CPS Use

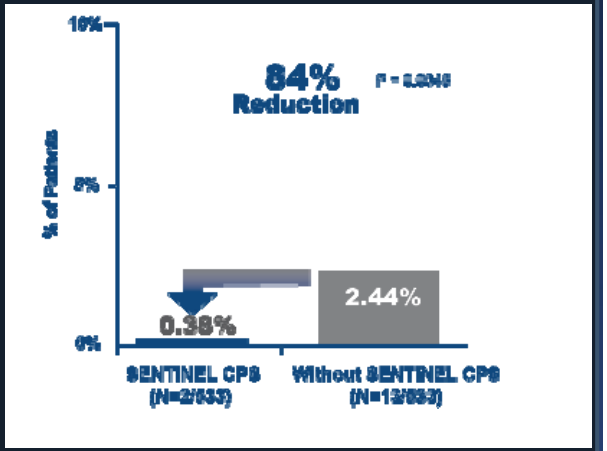
All-procedural Stroke



Mortality or Stroke



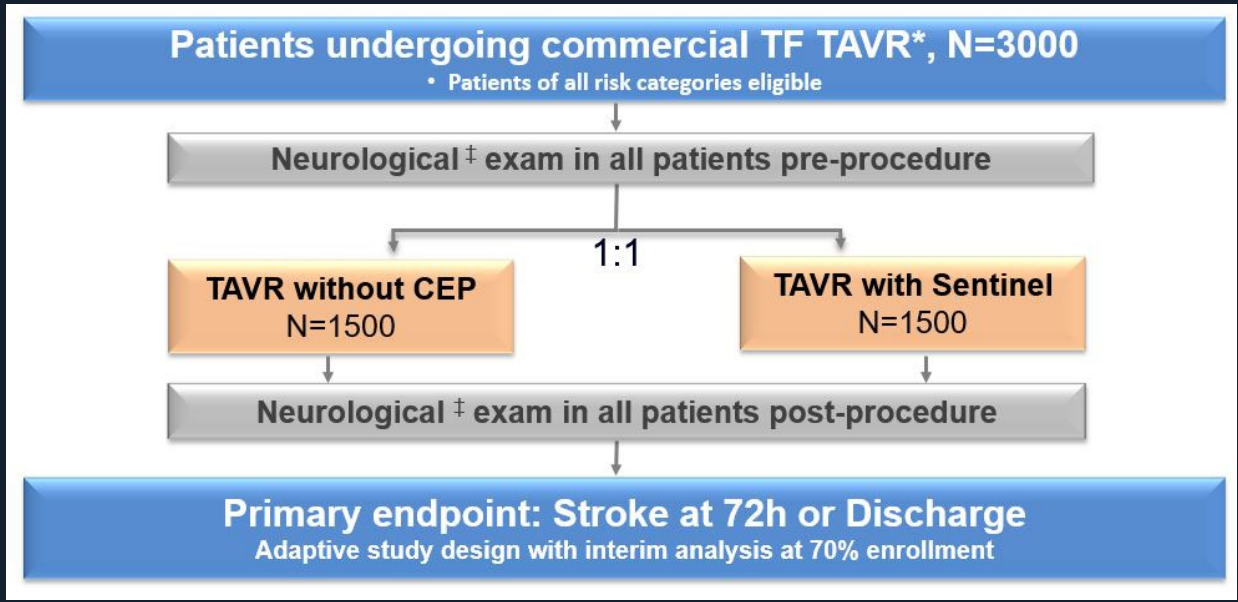
Disabling Stroke



- Patient level meta-analysis demonstrates a reduction in -related (≤ 72 h) stroke with SENTINEL CPS, using VARC-2 criteria
- Analysis was based on n=1306 patients with severe aortic stenosis from the SENTINEL IDE RCT Trial (n=363), CLEAN-TAVI RCT (n=100) and SENTINEL all-comers study (n=843)
- Data were propensity score-matched for valve type, STS score, A-fib, gender, diabetes mellitus, CAD and PVD

SENTINEL Randomized Controlled Trial Underway

PROTECTED TAVR

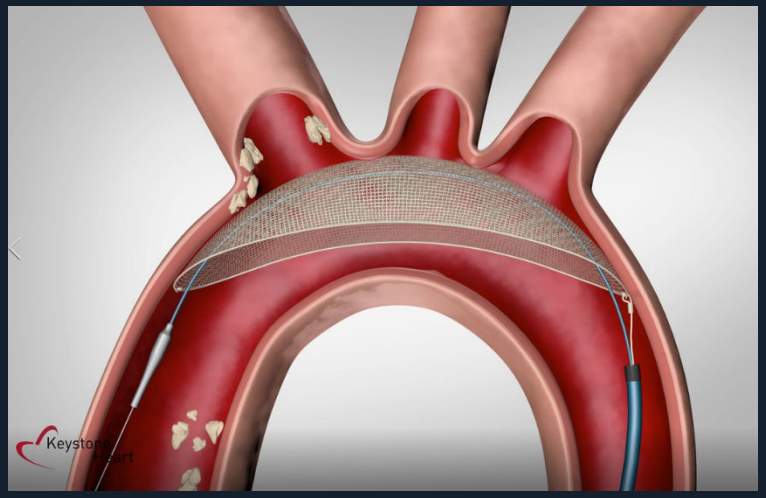


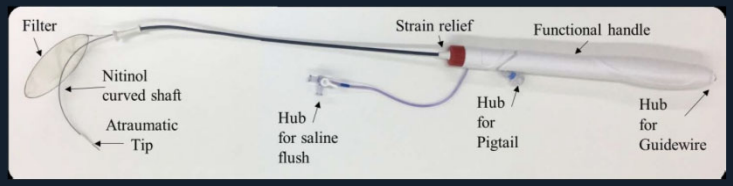
Primary Endpoint: To assess the rate of stroke through 72 h post-TAVR or discharge, whichever comes first.
Stroke defined as all stroke (hemorrhagic, ischemic, or undetermined status; disabling or nondisabling)

Inclusion Criteria:
- **Documented aortic valve stenosis and is treated with an approved TAVR device via TF access**
- **Recommended artery diameter: 9-15 mm for the brachiocephalic artery and 6.5-10 mm in LCC**

clinicaltrials.gov/ct2/show/NCT04149535?term=protected+TAVR&draw=2&rank=1

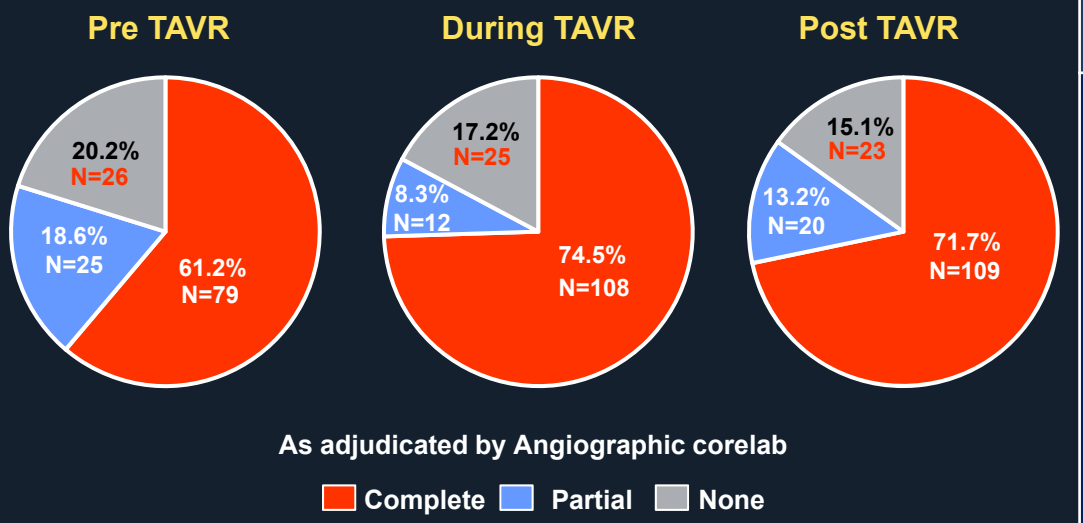
Keystone Heart TriGUARD *3*





- Self-positioning, nitinol frame without stabilizers
- PEEK mesh (pore size 115 x 145 µm)
- Filter area = 68.3 cm^2
- 8 Fr OTW delivery
- Accommodates a diagnostic pigtail

TriGUARD *3* Performance and Cerebral Coverage



Performance Measures	Combined TriGUARD *3* (N=157)
Successful deployment	100%
Successful on 1st attempt	98.1%
Technical Success	71%
Procedure Success	69.7%
Device Interaction	9.6%
Deployment Time Mean ± SD	2.81 ± 5.69

Full Coverage Throughout: 59.3%
All devices successfully deployed and retrieved

Technical Success: Full coverage in the absence of device interaction
Procedure success: Technical success without TG3-related in-hospital MACCE

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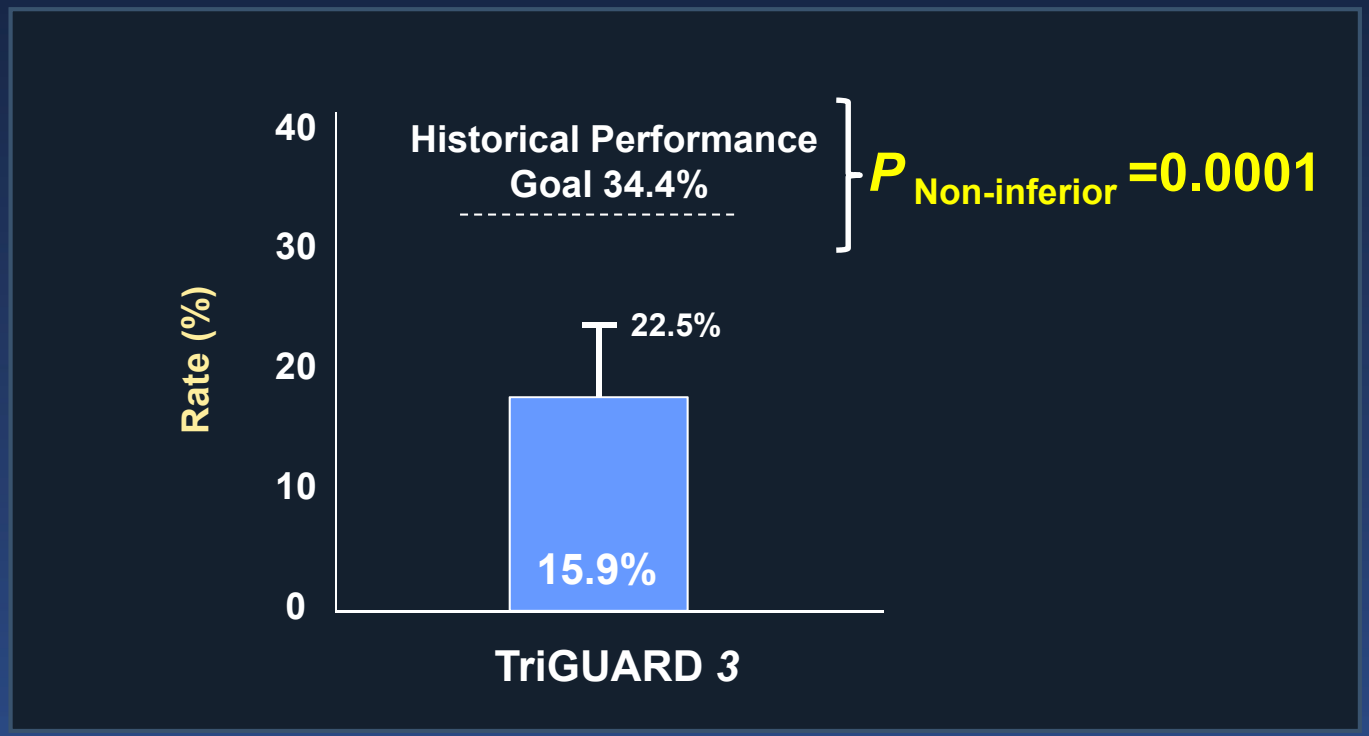
Primary Safety Endpoint: 30 Day MACE



Efficacy Endpoints: TG vs Control

	TriGUARD *3*	Pooled Controls	*P* value
Primary Outcomes	112	119	
Primary Efficacy Score	-8.58 ± 120.76	8.08 ± 116.51	0.857
Win percentage, %	45.7	54.3	–
Component event rates			
All-cause mortality or any stroke at 30 days, %	9.8	6.7	0.475
NIHSS worsening predischarge, %	14.1	7.6	0.176
Cerebral ischemic lesions, %	85.0	84.9	1.000
Total cerebral lesion volume, mm^3, Median (IQR)	215.39 (68.13, 619.71)	188.09 (52.08, 453.12)	0.405

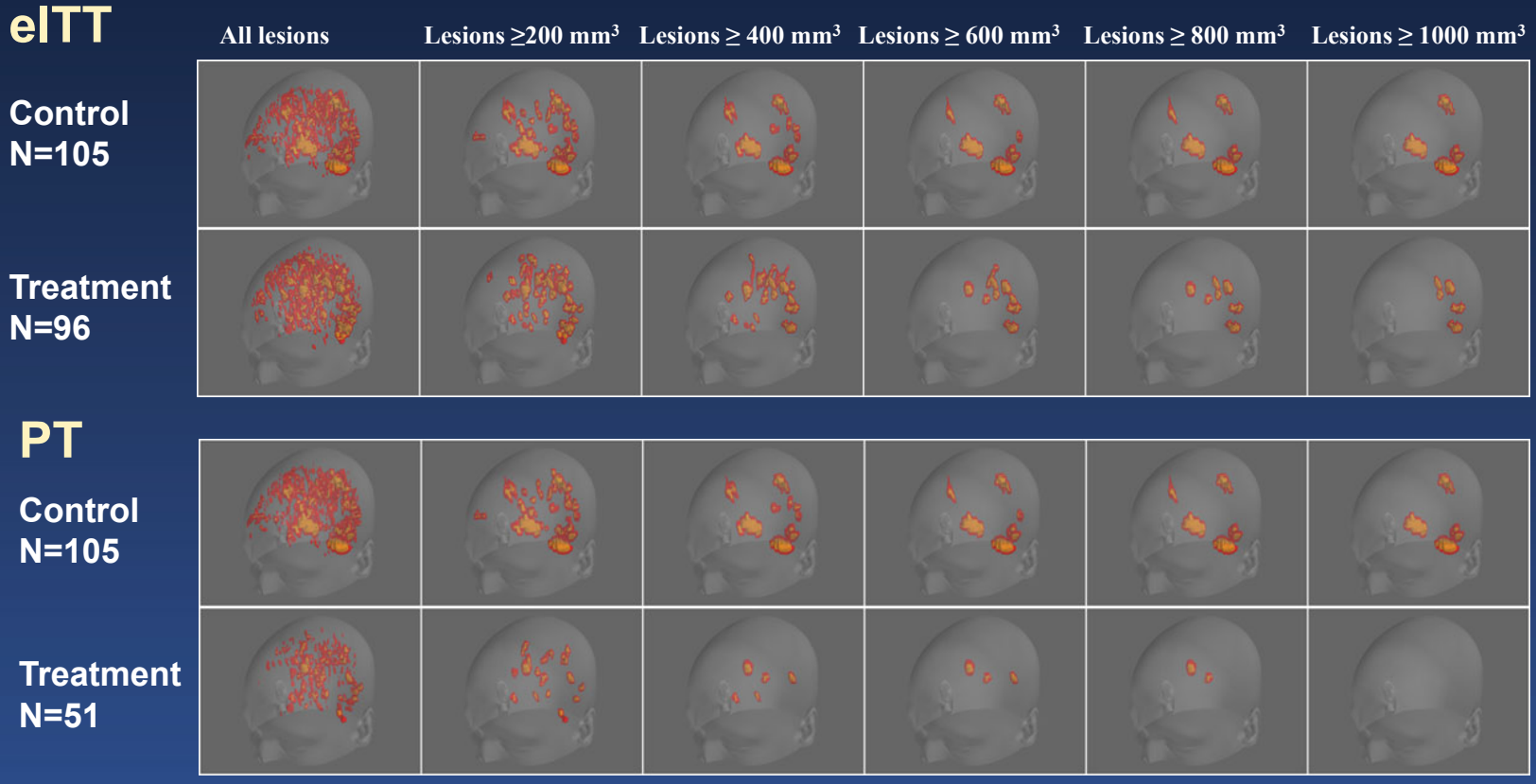
Prespecified primary efficacy population was randomized TG3 vs pooled controls
Win percentage= wins/wins+losses (removes ties)

Rationale for Post Hoc Analysis

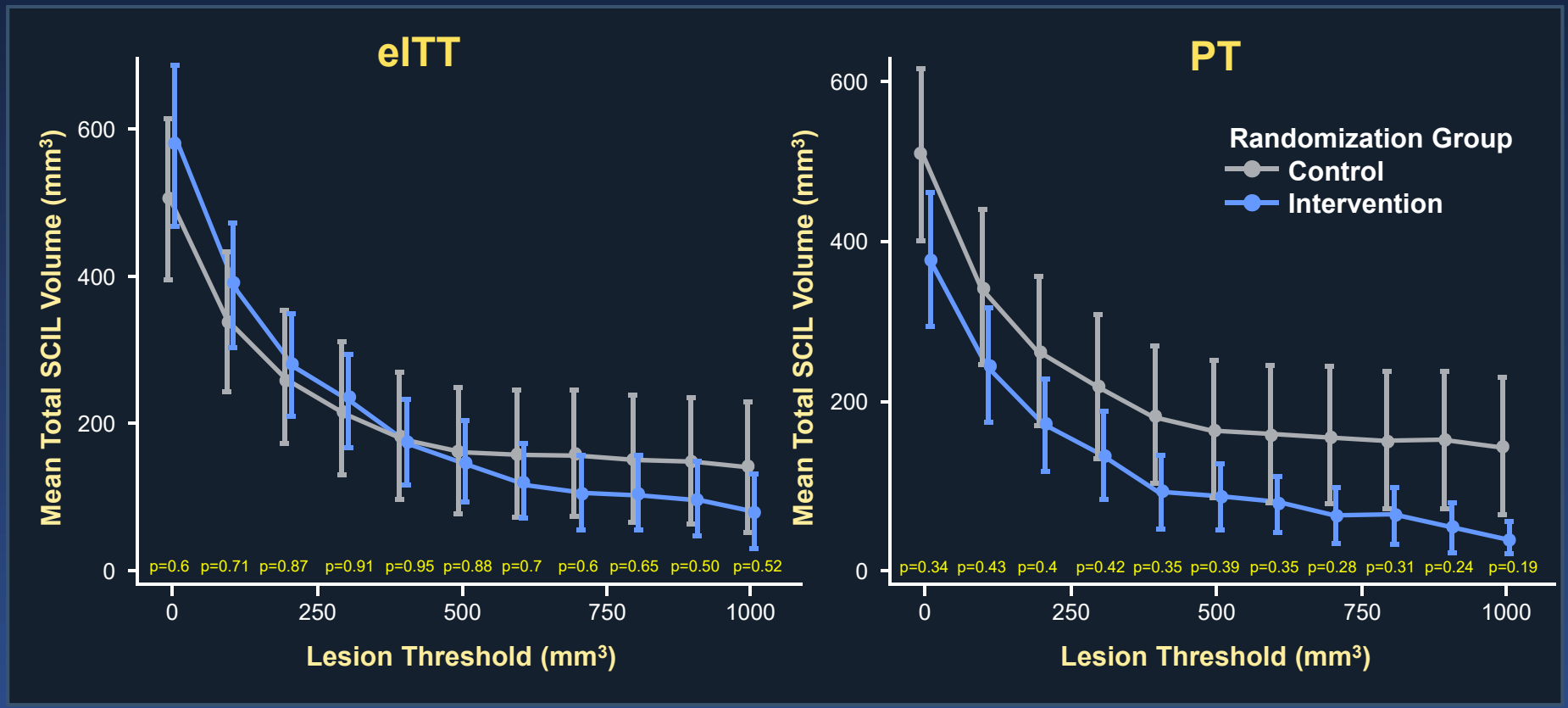
- Numerous studies have demonstrated that lesion size on DW MRI after a procedure is associated with clinical symptoms including stroke and post-operative cognitive decline[18,28-30]
- To evaluate whether TG*3* had a differential impact in preventing different lesion sizes, a multi-threshold, lesion-wise analysis was performed to investigate per-patient supra-threshold cerebral ischemic lesion (SCIL) volume above incremental thresholds from >100mm^3 to >1000mm^3

18. Kapadia SR. *J Am Coll Cardiol.* 2017;69(4):367-377.
28. Messé SR, *Circulation*. 2014;129(22):2253-2261.
29. Giovannetti T,. *Ann Thorac Surg*. 2019;107(3):787-794.
30. Bonati LH, *Lancet Neurol*. 2010;9(4):353-36

Suprathreshold Lesion Volume Analysis in eITT and PT



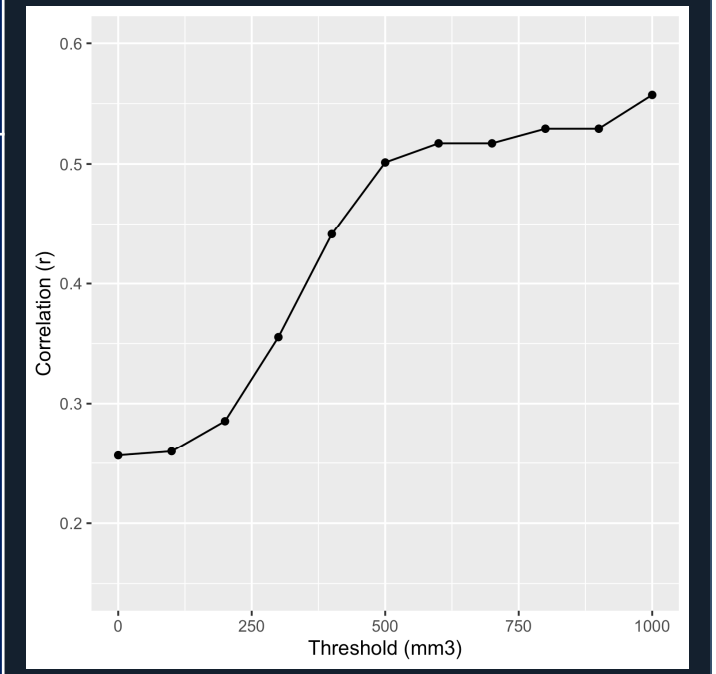
Average New Super-threshold Lesion Volumes: eITT & PT



MRI and NIHSS Association

- Correlation between subjects' total lesion volume (SCIL) and NIHSS changes was actually higher when eliminating very small lesions < 500 mm^3
- This suggests that small lesions are not only less consequential, but may be actively confounding

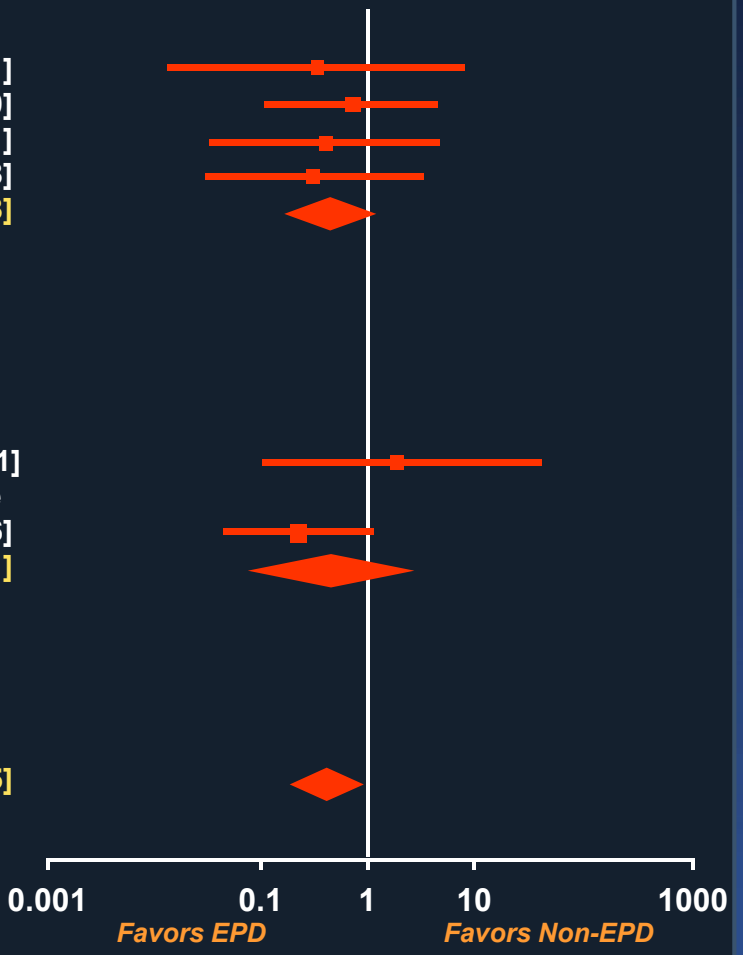
Correlation between SCIL volume and NIHSS score change		
Threshold (mm^3)	r	*p*
0.000	0.256	0.01
100.000	0.260	0.009
200.000	0.285	0.004
300.000	0.355	<0.001
400.000	0.441	<0.001
500.000	0.501	<0.001
600.000	0.517	<0.001
700.000	0.517	<0.001
800.000	0.529	<0.001
900.000	0.529	<0.001
1000.000	0.557	<0.001



CEP Meta-analysis 8 Studies 731 Patients

Mortality

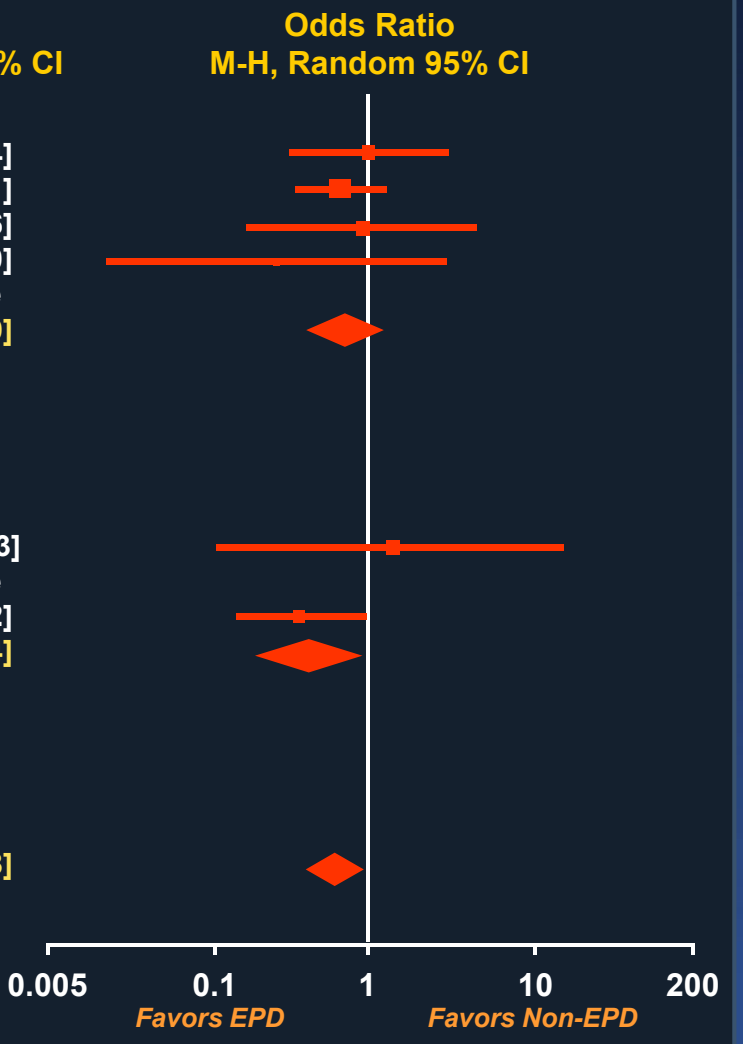
Study or Subgroup	EPD Events	EPD Total	No-EPD Events	No-EPD Total	Weight	Odds Ratio M-H, Random 95% CI
1.1.2 RCTs						
Haussig S	0	50	1	50	7.5%	0.33 [0.01, 8.21]
Kapadia SR	3	234	2	111	24.1%	0.71 [0.12, 4.30]
Lansky JA	1	46	2	39	13.1%	0.41 [0.04, 4.71]
Van Mieghem NM	1	32	3	33	14.6%	0.32 [0.03, 3.28]
Subtotal (95% CI)		362		233	59.3%	0.47 [0.15, 1.48]
Total events	5		8			
Heterogeneity: Tau^2=0.00; Chi^2=0.36, df=3 (P=0.95); I^2=0%						
Test for overall effect: Z=1.29 (P=0.20)						
1.1.2 non RCTs						
Rodes-Cahau J	3	41	0	11	8.5%	2.09 [0.10, 43.51]
Samim M	0	15	0	37		Not estimable
Seeger et al	2	280	8	280	32.2%	0.24 [0.05, 1.16]
Subtotal (95% CI)		336		328	40.7%	0.47 [0.07, 3.31]
Total events	5		8			
Heterogeneity: Tau^2=0.79; Chi^2=1.52, df=1 (P=0.22); I^2=34%						
Test for overall effect: Z=0.75 (P=0.45)						
Total (95% CI)		698		561	100.0%	0.43 [0.18, 1.05]
Total events	10		15			
Heterogeneity: Tau^2=0.00; Chi^2=1.93, df=5 (P=0.86); I^2=0%						
Test for overall effect: Z=1.86 (P=0.06)						
Test for subgroup differences: Chi^2=0.00 df=1 (P=0.99), I^2=0%						



CEP Meta-analysis 8 Studies 731 Patients

Stroke

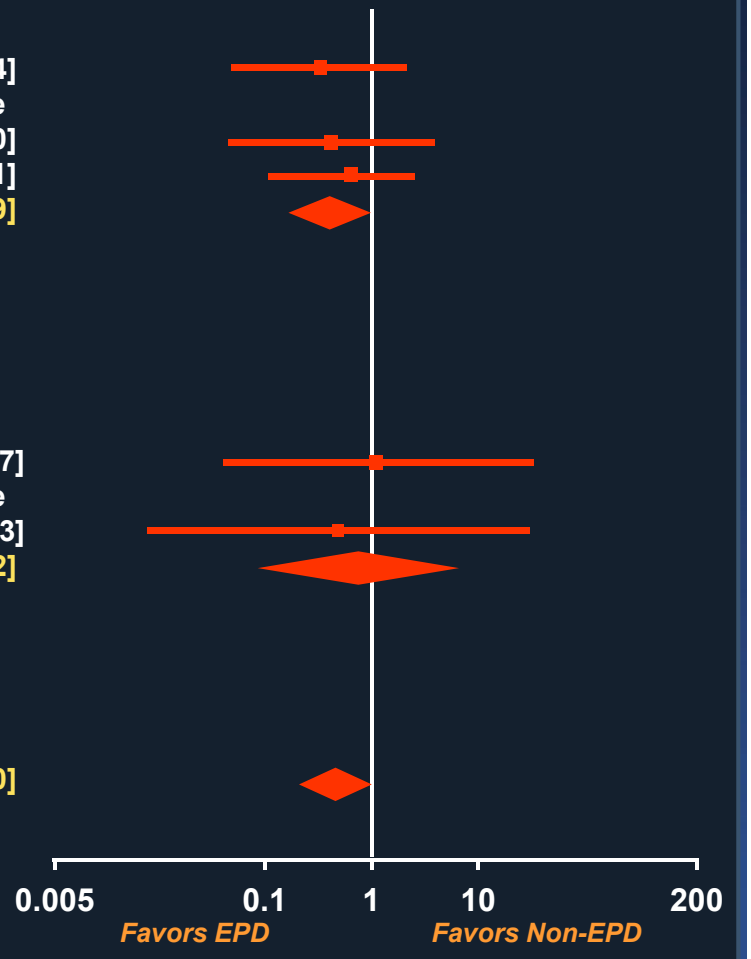
Study or Subgroup	EPD Events	EPD Total	No-EPD Events	No-EPD Total	Weight	Odds Ratio M-H, Random 95% CI
2.1.1 RCTs						
Haussig S	4	50	4	50	15.6%	1.00 [0.24, 4.24]
Kapadia SR	13	231	10	110	44.2%	0.60 [0.25, 1.41]
Lansky JA	2	45	2	39	8.1%	0.84 [0.11, 6.26]
Van Mieghem NM	0	32	2	33	3.4%	0.19 [0.01, 4.20]
Wendt D	0	14	0	16		Not estimable
Subtotal (95% CI)		373		248	71.3%	0.66 [0.33, 1.29]
Total events	19		18			
Heterogeneity: Tau^2=0.00; Chi^2=1.04, df=3 (P=0.79); I^2=0%						
Test for overall effect: Z=1.22 (P=0.22)						
1.1.2 non RCTs						
Rodes-Cahau J	2	41	0	11	3.4%	1.46 [0.07, 32.53]
Samim M	0	15	0	37		Not estimable
Seeger et al	4	280	13	280	25.3%	0.30 [0.10, 0.92]
Subtotal (95% CI)		336		328	28.7%	0.36 [0.12, 1.04]
Total events	5		8			
Heterogeneity: Tau^2=0.00; Chi^2=0.89, df=1 (P=0.35); I^2=0%						
Test for overall effect: Z=1.89 (P=0.06)						
Total (95% CI)		709		576	100.0%	0.55 [0.31, 0.98]
Total events	25		31			
Heterogeneity: Tau^2=0.00; Chi^2=2.82, df=5 (P=0.73); I^2=0%						
Test for overall effect: Z=2.04 (P=0.04)						
Test for subgroup differences: Chi^2=0.89 df=1 (P=0.35), I^2=0%						



CEP Meta-analysis 8 Studies 731 Patients

Patients with New Lesions

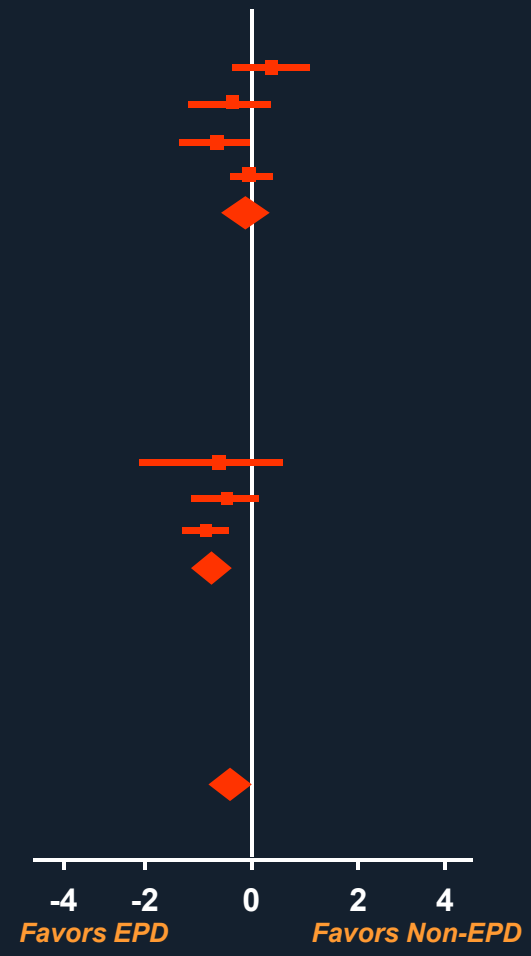
Study or Subgroup	EPD Events	EPD Total	No-EPD Events	No-EPD Total	Odds Ratio M-H, Random 95% CI
6.1.1 Balloon Expandable					
Lansky JA	12	18	14	17	0.37 [0.08, 1.74]
Rodés-Cahau J	34	34	6	6	Not estimable
Van Mieghem NM	11	16	10	12	0.44 [0.07, 2.80]
Wendt D	8	14	11	16	0.61 [0.14, 2.71]
Subtotal (95% CI)		83		51	0.47 [0.18, 1.19]
Total events	85		41		
Heterogeneity: Tau^2=0.00; Chi^2=0.21, df=2 (P=0.90); I^2=0%					
Test for overall effect: Z=1.60 (P=0.11)					
6.1.2 Self Expandable					
Haussig S	48	49	44	45	1.09 [0.07, 17.97]
Lansky JA	7	7	9	9	Not estimable
Van Mieghem NM	5	6	3	3	0.52 [0.02, 16.83]
Subtotal (95% CI)		62		57	0.82 [0.09, 7.22]
Total events	60		56		
Heterogeneity: Tau^2=0.00; Chi^2=0.10, df=1 (P=0.75); I^2=0%					
Test for overall effect: Z=0.18 (P=0.86)					
Total (95% CI)		145		108	0.51 [0.22, 1.20]
Total events	125		97		
Heterogeneity: Tau^2=0.00; Chi^2=0.53 df=4 (P=0.97); I^2=0%					
Test for overall effect: Z=1.54 (P=0.12)					
Test for subgroup differences: Chi^2=0.21 df=1 (P=0.64), I^2=0%					



CEP Meta-analysis 8 Studies 731 Patients

Number of Lesions per Patient

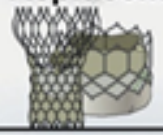
Study or Subgroup	EPD Mean	EPD SD	EPD Total	Non-EPD Mean	Non-EPD SD	Non-EPD Total	Std. Mean Difference IV, Random 95% CI
Balloon Expandable							
Rodés-Cahau et al 2014	7.83	7.407	34	4.67	4.444	6	0.44 [-0.44, 1.31]
Van Mieghem et al 2015	1.9	2.44	16	3	3.7	12	-0.35 [-1.11, 0.40]
Wendt D et al 2015	2.3	1.2	14	3.1	1	16	-0.71 [-1.45, 0.03]
Kapadia et al 2016	4.48	5.61	67	4.4	5.02	70	0.01 [-0.32, 0.35]
Subtotal (95% CI)			131			104	-0.14 [-0.54, 0.27]
Heterogeneity: Tau^2=0.07; Chi^2=4.91, df=3 (P=0.18); I^2=39%							
Test for overall effect: Z=0.66 (P=0.51)							
Self Expandable							
Van Mieghem et al 2015	4.33	3.704	6	7.33	2.96	3	-0.76 [-2.22, 0.70]
Kapadia et al 2016	5.33	8.75	21	9.83	7.88	24	-0.53 [-1.13, 0.06]
Haussig et al 2016	8.33	5.19	49	16.67	10.74	45	-0.99 [-1.42, -0.56]
Subtotal (95% CI)			76			72	-0.83 [-1.17, -0.49]
Heterogeneity: Tau^2=0.00; Chi^2=1.52 df=2 (P=0.47); I^2=0%							
Test for overall effect: Z=4.81 (P<0.00001)							
Total (95% CI)			207			176	-041 [-0.82, 0.00]
Heterogeneity: Tau^2=0.18; Chi^2=17.81 df=6 (P=0.007); I^2=66%							
Test for overall effect: Z=1.95 (P=0.05)							
Test for subgroup differences: Chi^2=6.71 df=1 (P=0.010), I^2=85.1%							



What's New?

Ischemic Stroke With Cerebral Protection System During Transcatheter Aortic Value Replacement

Nationwide inpatient sample database 2017 (after approval of Sentinel CPS device)
(36,220 TAVR discharges) Sentinel CPS used in 525 patients, not used in 35,695 patients

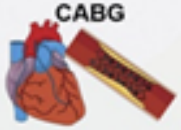


Before propensity-score matching
Sentinel CPS patients

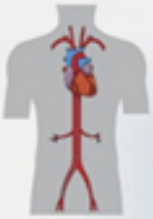
Less peripheral artery disease

No carotid artery disease

Less prior PCI or CABG



Procedure performed mainly in large teaching hospitals



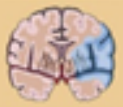
All underwent percutaneous TAVR

CPS (n = 525)

Outcomes in propensity-matched cohorts

No CPS (n = 1,050)

Lower risk of ischemic stroke
1% vs. 3.8%, OR 0.24 (0.09-0.62), p = 0.003



Lower risk of in-hospital mortality
0% vs. 1 %, p = 0.036

Similar in-hospital complications

A similar risk of vascular complications, blood transfusion, renal complications, length of stay and discharge to nursing facility

higher index hospitalization cost
$47,783 vs. $44,578, p = 0.002

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Megaly et al. *J Am Coll Cardiol Intv.* 2020;13:2149-55

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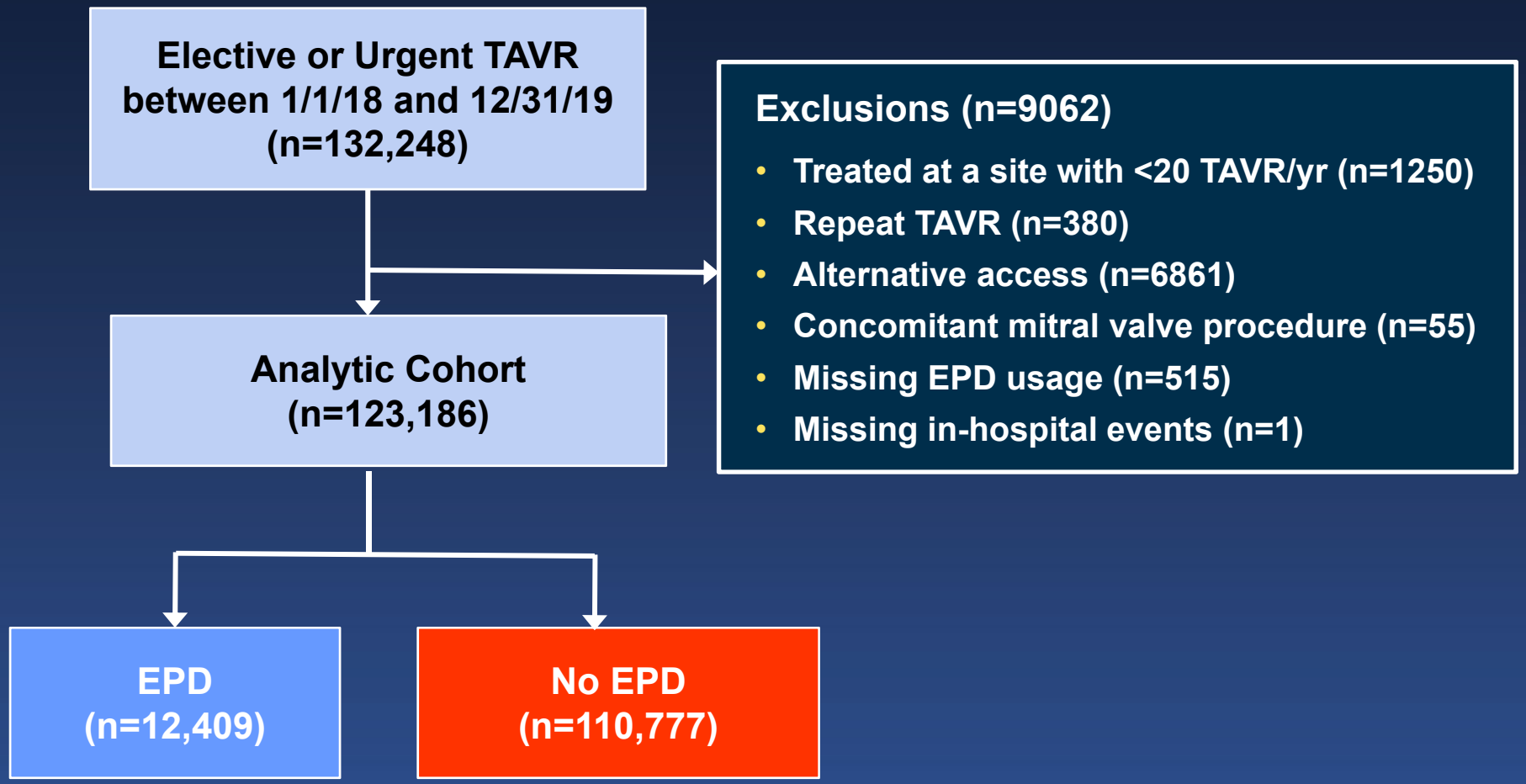
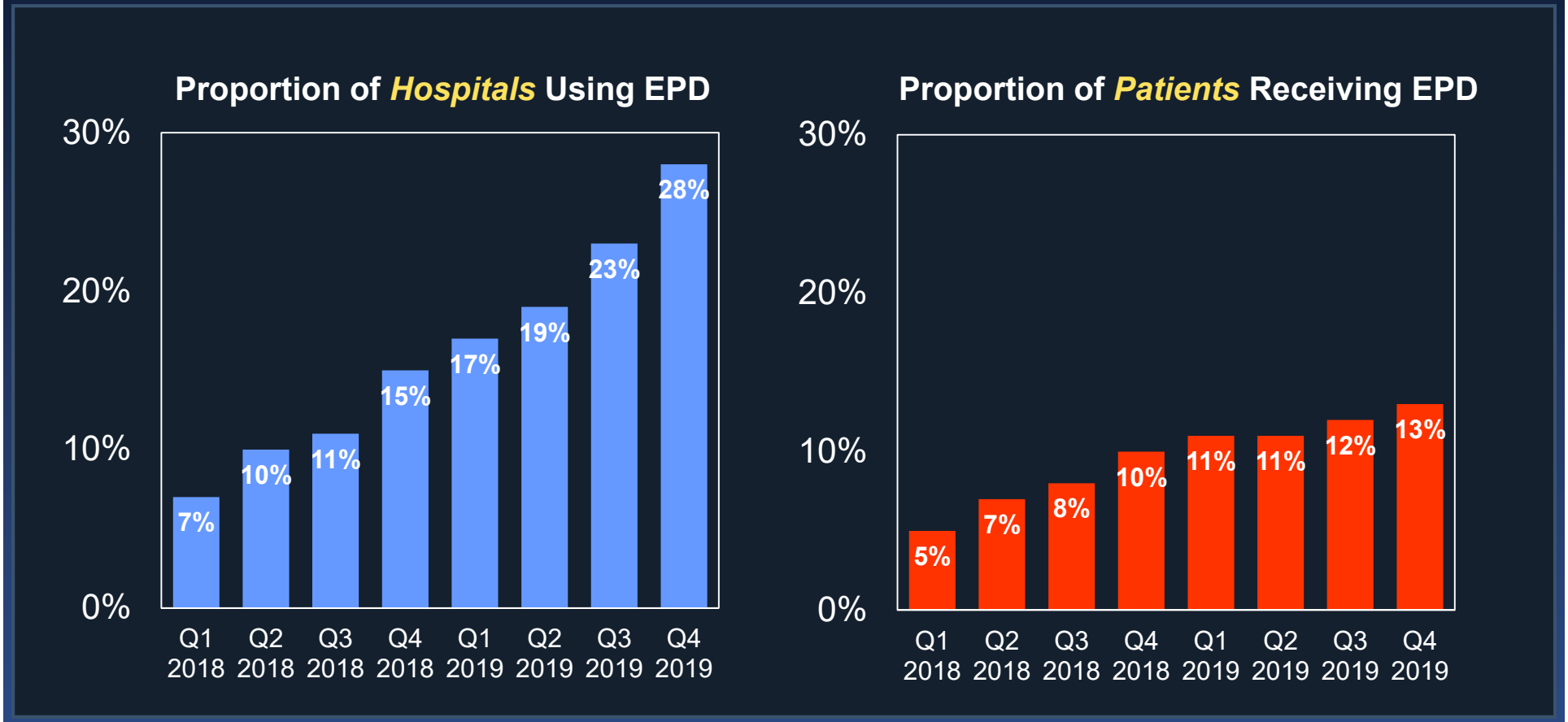
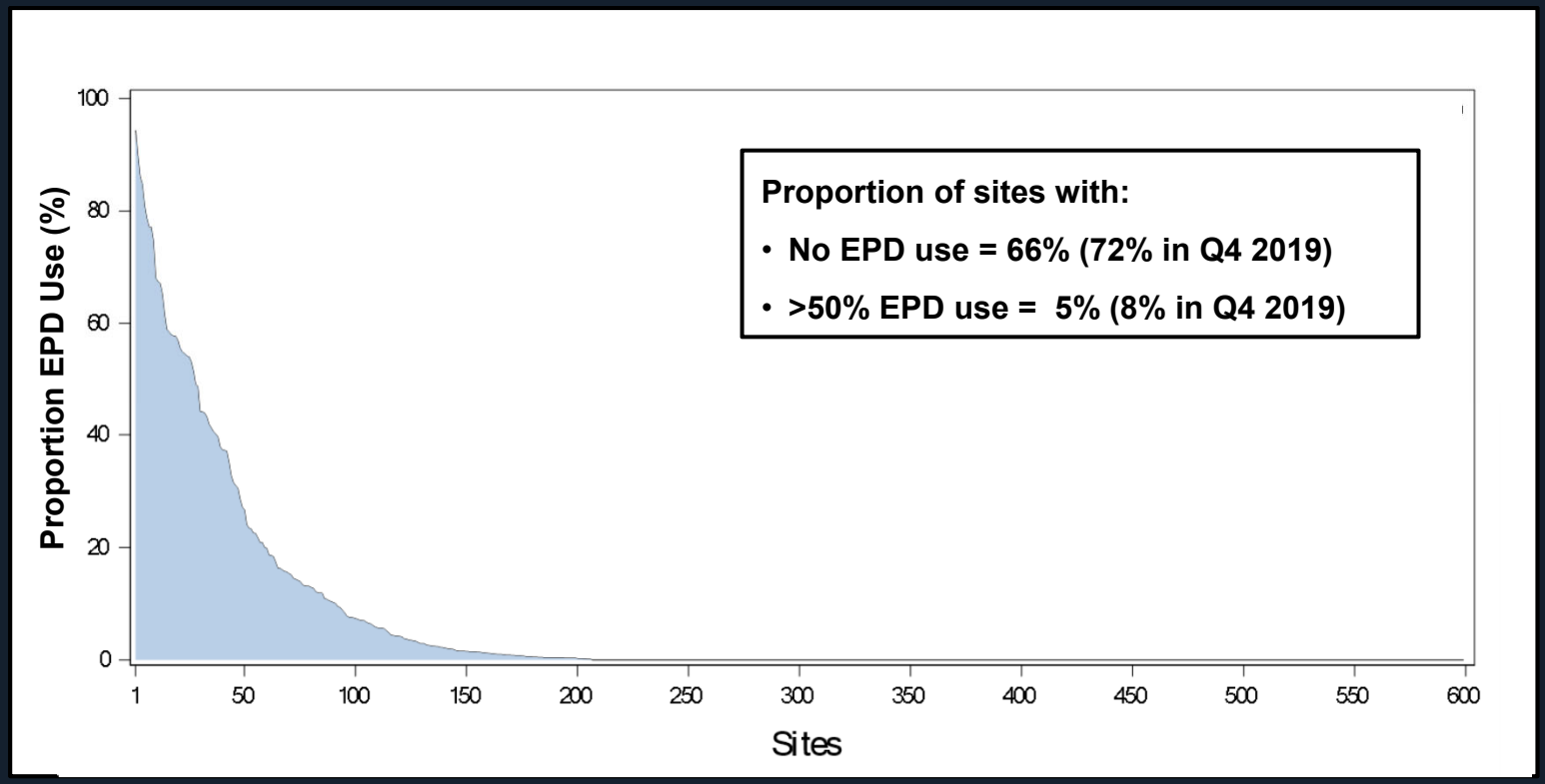

Elective or Urgent TAVR between 1/1/18 and 12/31/19 (n=132,248)
Exclusions (n=9062)
Treated at a site with <20 TAVR/yr (n=1250)
Repeat TAVR (n=380)
Alternative access (n=6861)
Concomitant mitral valve procedure (n=55)
Missing EPD usage (n=515)
Missing in-hospital events (n=1)
Analytic Cohort (n=123,186)
EPD (n=12,409)
No EPD (n=110,777)

EPD Utilization by Calendar Quarter

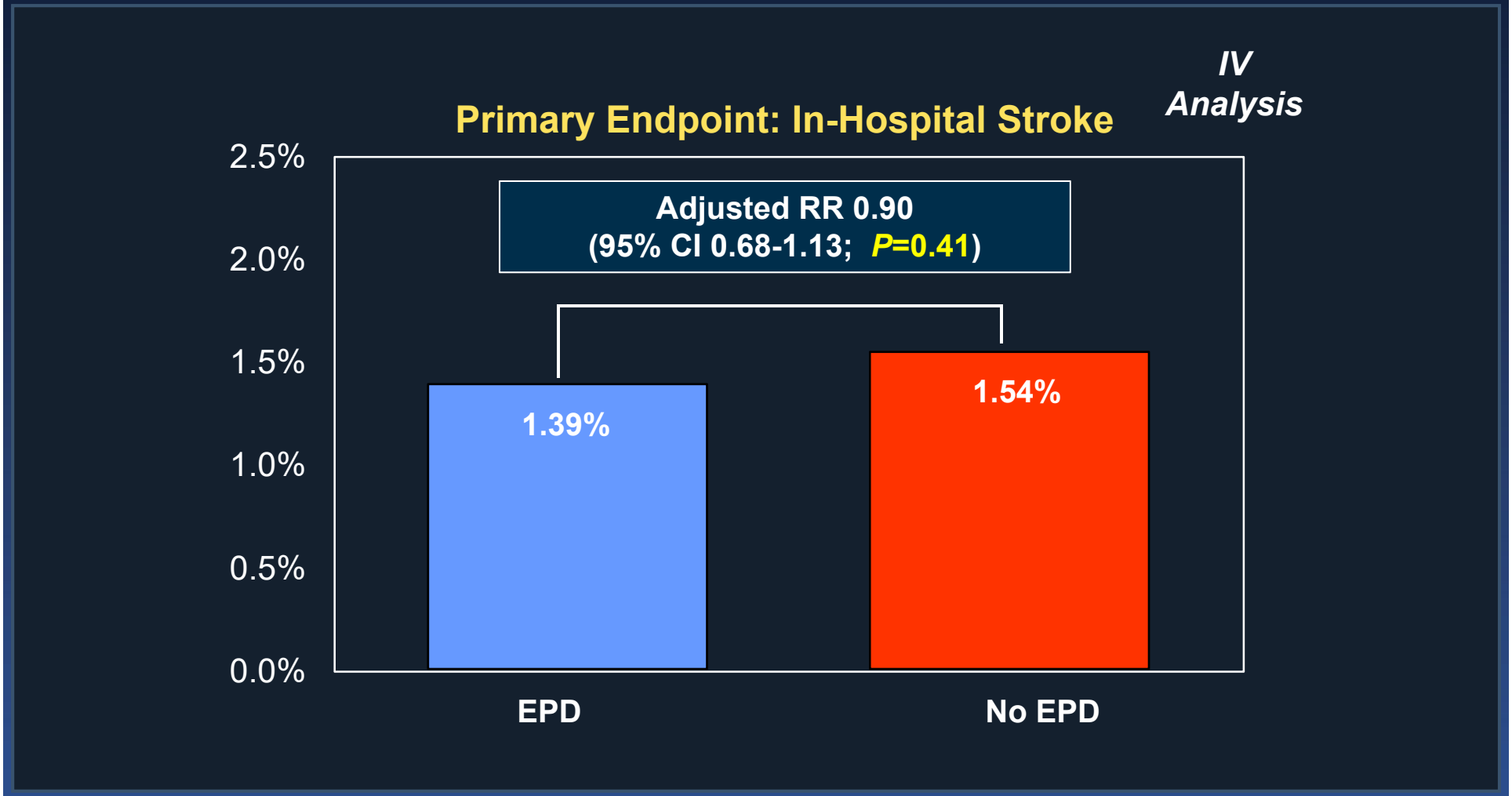


Variation in EPD Use by Hospital (2018-2019)

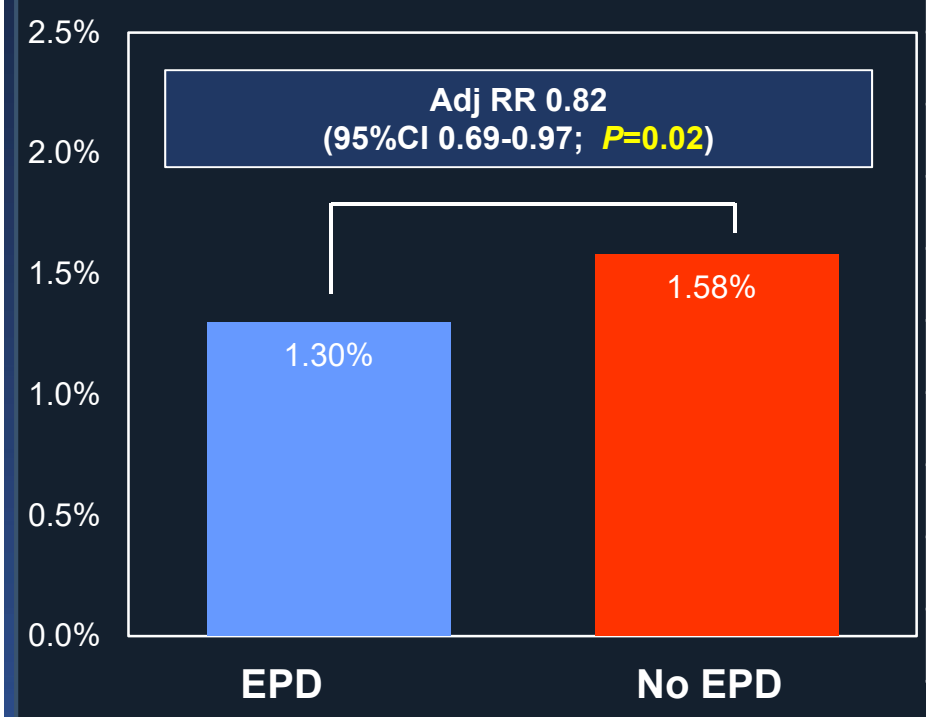


Q1 2019-Q4 2019 (n=599 sites)

Results: Instrumental Variable Analysis



Results: Propensity-Weighted Analysis



Propensity-Weighted Analysis

	EPD	No EPD	Adjusted RR (95% CI)	Adj *P*-Value
In-Hosp. Outcomes				
Death or Stroke	2.1%	2.5%	0.84 (0.73-0.98)	0.03
Death	0.9%	1.1%	0.86 (0.66-1.10)	0.23
Device Success	97.3%	97.3%	1.01 (0.76-1.35)	0.93
Major Bleeding	4.7%	4.3%	1.09 (0.95-1.24)	0.22
GI or GU Bleed	0.6%	0.5%	1.29 (0.92-1.81)	0.14
30-day Outcomes				
Stroke	1.9%	2.2%	0.85 (0.73-0.99)	0.04
Death	1.7%	2.2%	0.78 (0.64-0.95)	0.01

* All results risk-adjusted based on overlap propensity weights

Where Do We Go From Here

The Evolution of Embolic Protection

First Generation

Deflector: Embrella (Edwards)

Capture: Sentinel (Claret, Boston Scientific)

Second generation

Deflectors:

TriGuard (Keystone), ProtEmbo (Protembis), PointGuard

Deflection and capture:

Emblok, Emboliner (Emboline), Captis (Filterlex)

Future Sentinel?

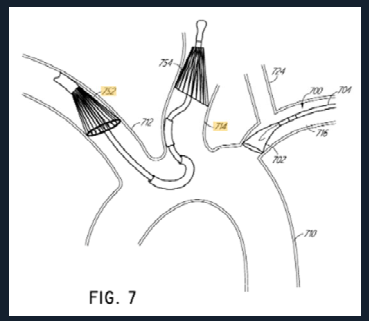
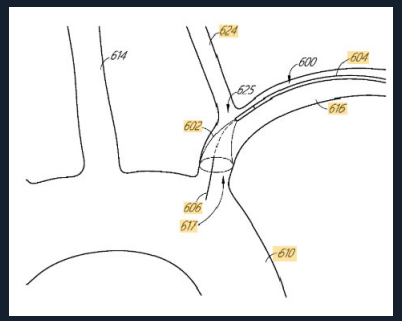


FIG. 7



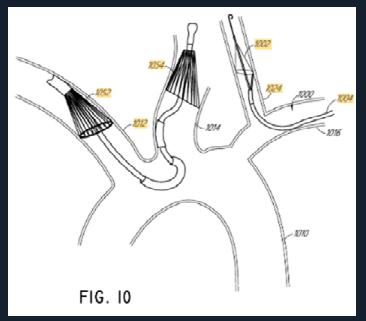


FIG. 10

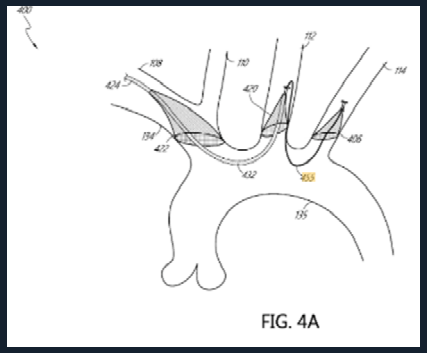


FIG. 4A

FIG. 2E

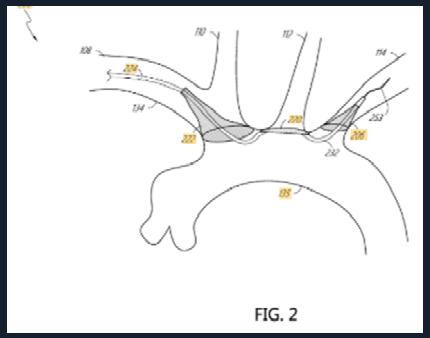


FIG. 2

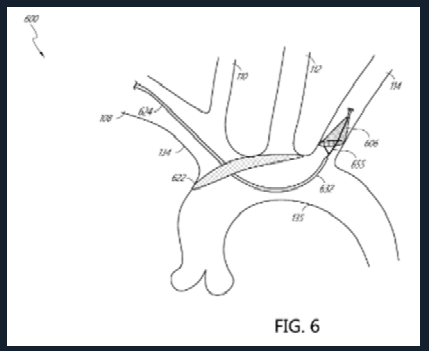


FIG. 6

Cardiovascular Research Foundation®

US Patents: US9566144B2, US20180235742A1

Columbia University Medical Center
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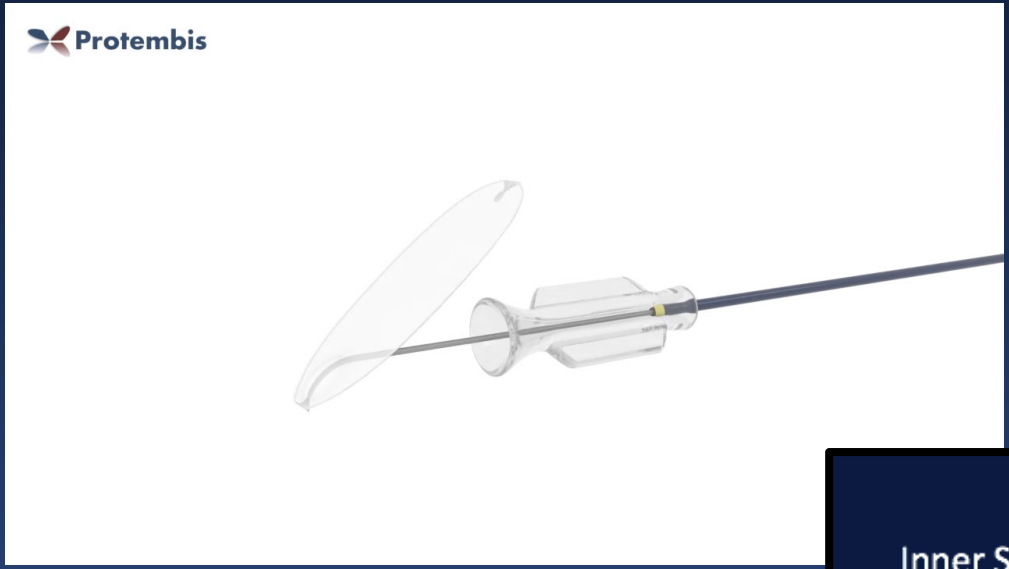
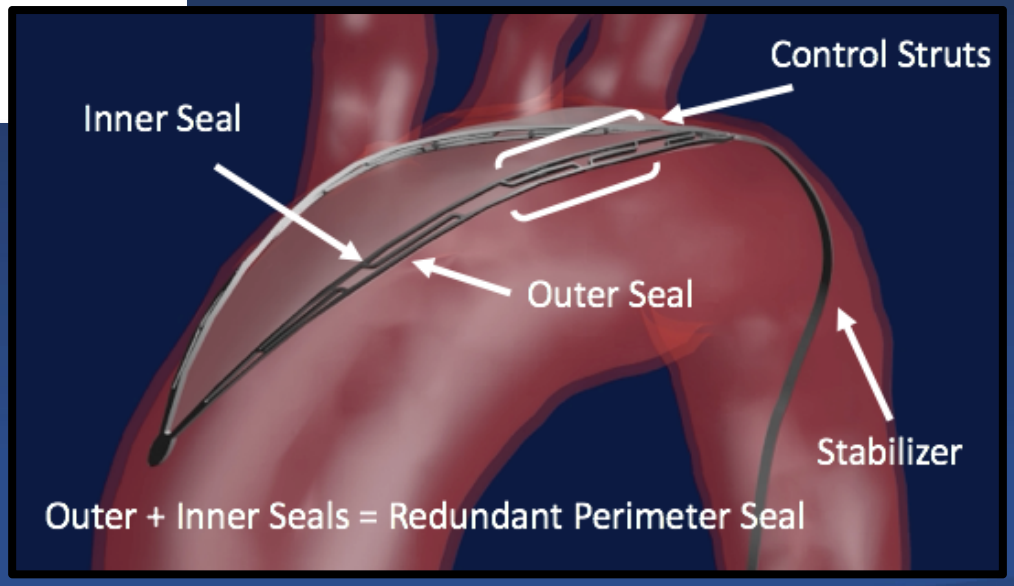
Deflectors:

ProtEmbo



Point-Guard



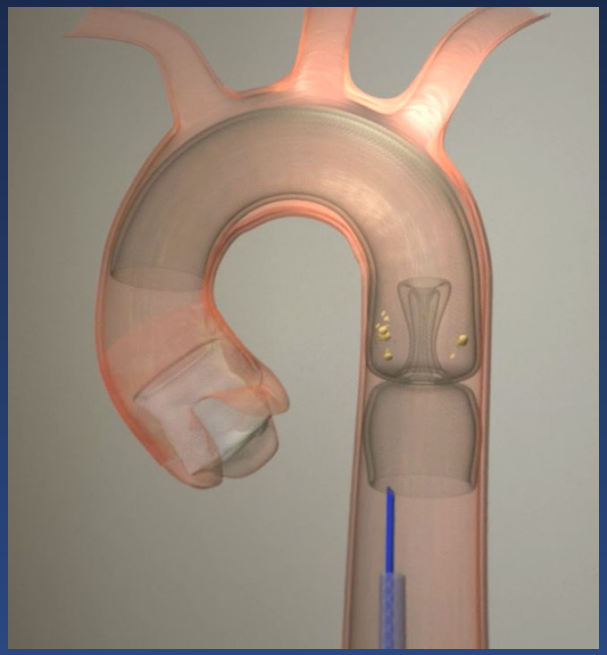
- Left radial (6Fr)
- Simple and quick deployment
- Complete cerebral protection
- 60µm pore size

Deflection and Capture

Full-Body Embolic Protection

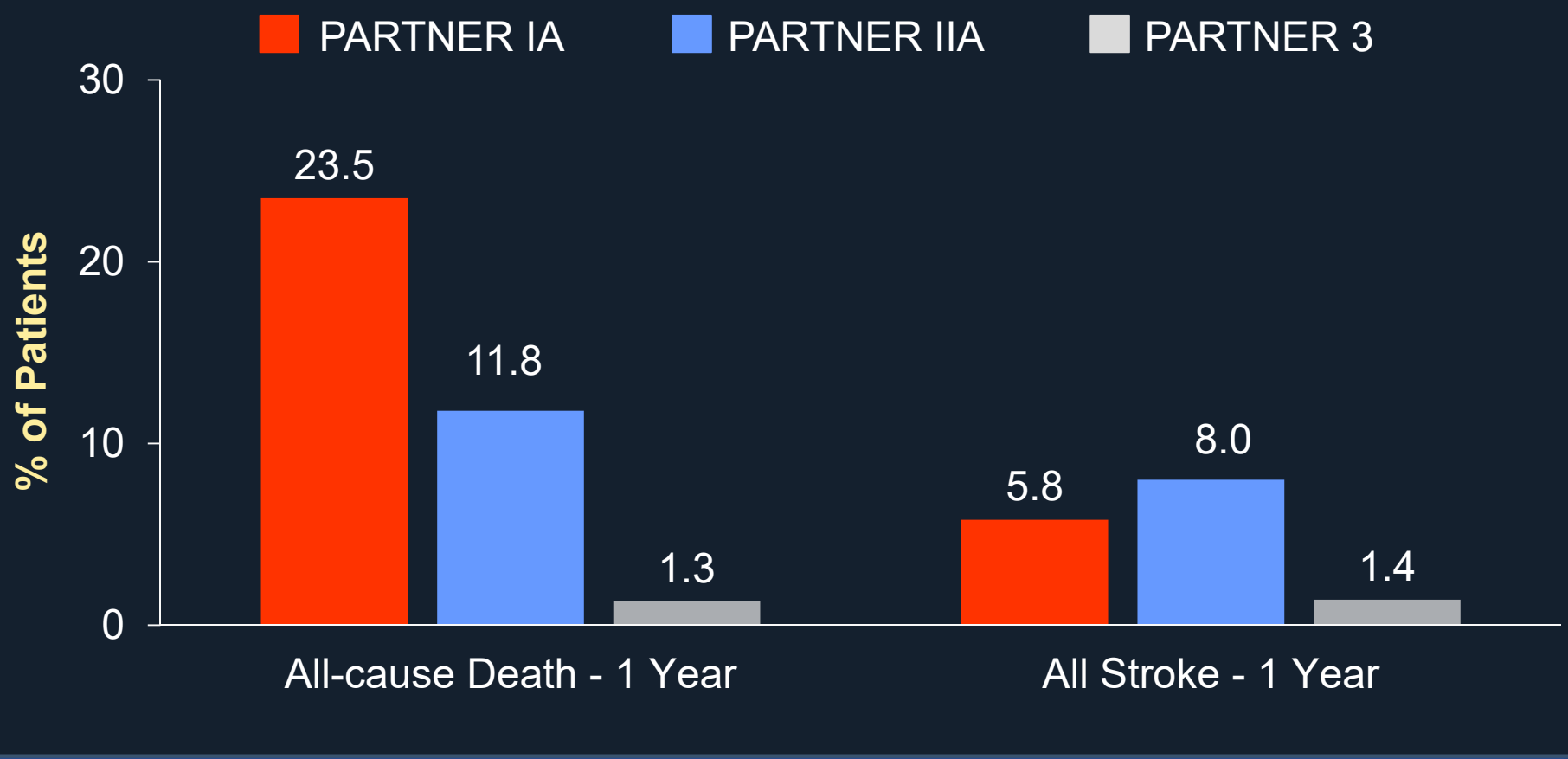
Emblok

Emboliner



CAPTIS

The PARTNER Trials:
From High to Low Risk (AT)



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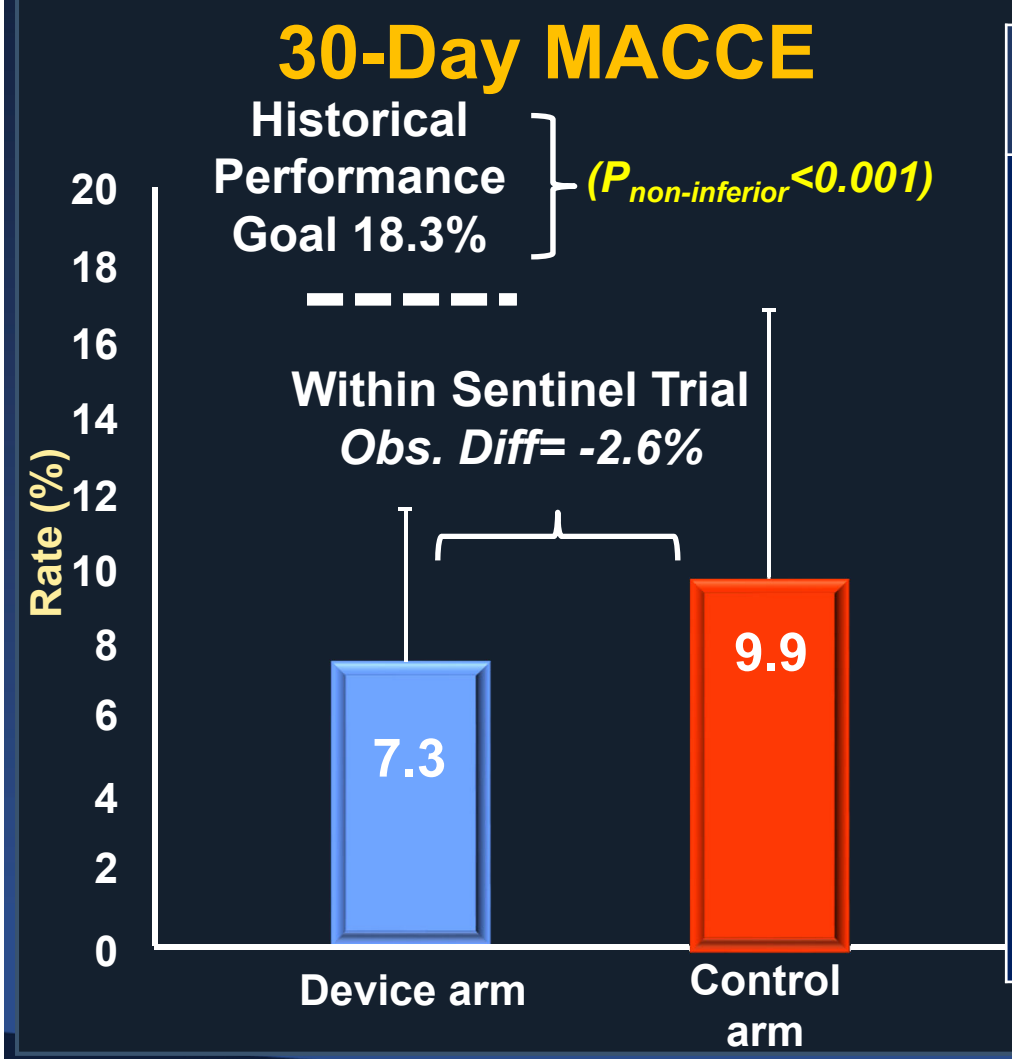
NewYork-Presbyterian

What is the Calculation?: Stroke in Sentinal



	Device Arm (n=234)	Control Arm (n=111)	*P* value
30-Day Clinical Outcomes			
Any MACCE†	7.3%	9.9%	0.40
Death (all-cause)	1.3%	1.8%	0.65
Stroke	5.6%	9.1%	0.25
Disabling	0.9%	0.9%	1.00
Non-disabling	4.8%	8.2%	0.22
AKI (Stage 3)	0.4%	0%	1.00
TIA	0.4%	0%	1.00
Sentinel Site Complications	0.4%	N/A	0.53

What is the Path Forward?

Lessons Learned:

Neuroarc proposed detailed cognitive and imaging endpoints , but…

- **No differences seen in MoCa in Sentinel or REFLECT I**
- **Difficulty in administration led to abandonment in REFLECT II**
- **Who will follow patients for 5 to 10 years for dementia or cognitive decline?**

What is the Path Forward?

- **VARC-2 30 Day Endpoints**

Inject more noise in the system

Endpoints need to be more tailored to an ancillary device

Where Do We Go From Here?

- Do We Compare to Predicate or SOC? (i.e., Sentinel)
  - If so how do we do 2-3000pt trials?
- Combination of safety and MRI endpoints (ie lesion size analysis)?
- 72-hour stroke
  - Disabling vs. non-disabiing ?
- Target an event rich population?

We Need Better Tools: TASK Study

TASK study

Inclusion Criteria

- All comers study
- All valve types
- Trans-femoral approach

8,779 Patients

Primary End Point

Stroke or TIA within 24 hours of TAVI

127 Acute stroke events

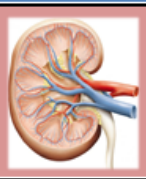
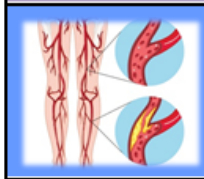
1.4% of all cases

TASK Score Design

- Pre-procedural candidate parameters
- Parameters derived from multivariate analysis
- Equivalent power to each TASK score parameter

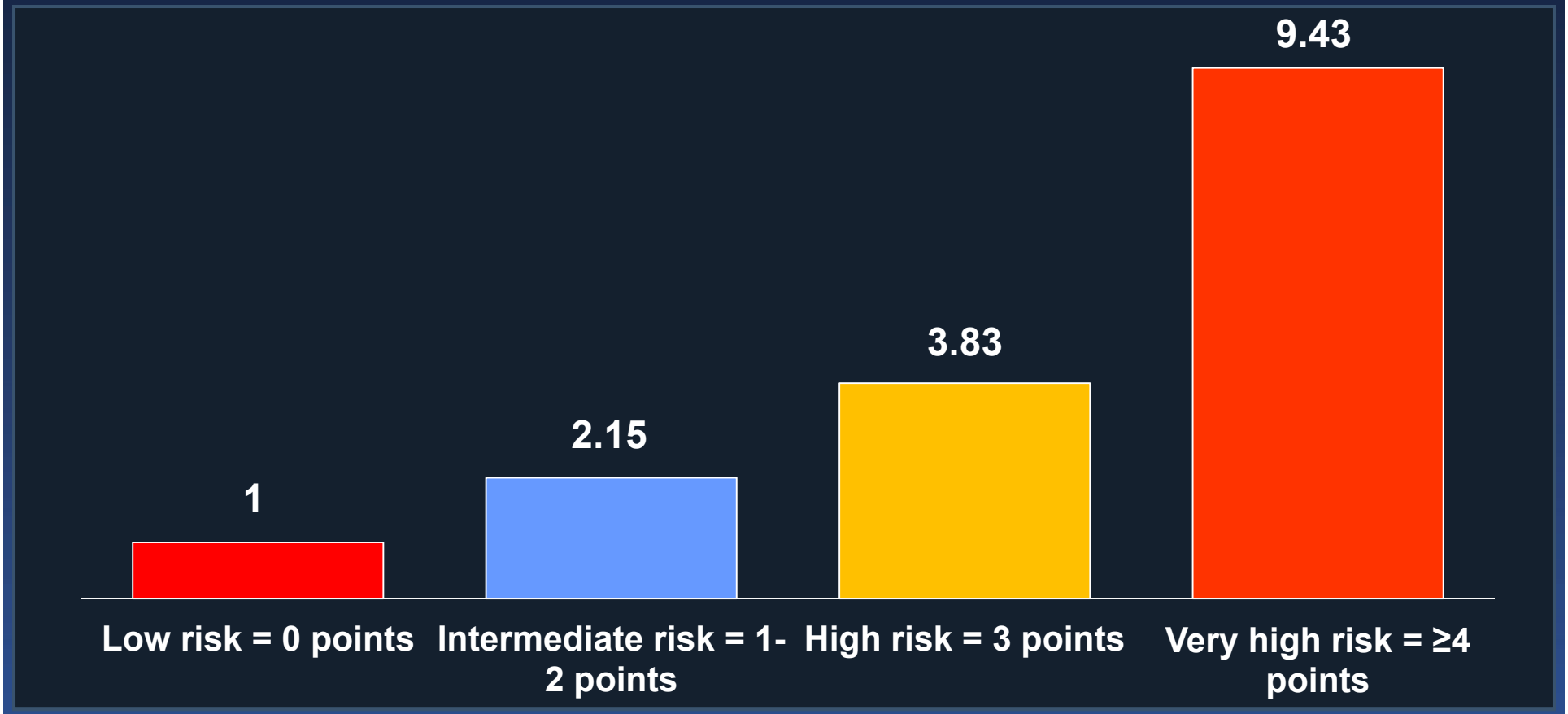
Better Tools ? TASK Score

TASK study

	No history of previous stroke		0 Points
	History of previous stroke		1 Point
	Normal Renal function	GFR≥60	0 Points
	Chronic Kidney disease	GFR<60	1 Point
	Balloon Expandable Valve		0 Point
	Non-Balloon Expandable Valve		1 Point
	Normal Body Weight	BMI≥25	0 Points
	Low Body Weight	BMI<25	1 Point
	No Peripheral vascular disease		0 points
	Peripheral vascular disease		1 Points

TASK points	Acute stroke rate
0	0.6%
1	0.8%
2	1.6%
3	2.3%
4	4.5%
5	16%

Relative Risk of Acute Stroke According to TASK Score



Conclusions

- Overt and covert stroke are significant complications of TAVR which may be of greater consequence as we move in to lower risk, younger populations
- The weight of evidence indicates that CEP reduces lesions but current evidence on stroke reduction is tentative
- Fortunately several large are underway /planned in the near future
- The pathway for further device approval is in flux and needs creative strategies to provide persuasive evidence of effectiveness and utility