Cerebral Protection: During TAVR: Why and How?

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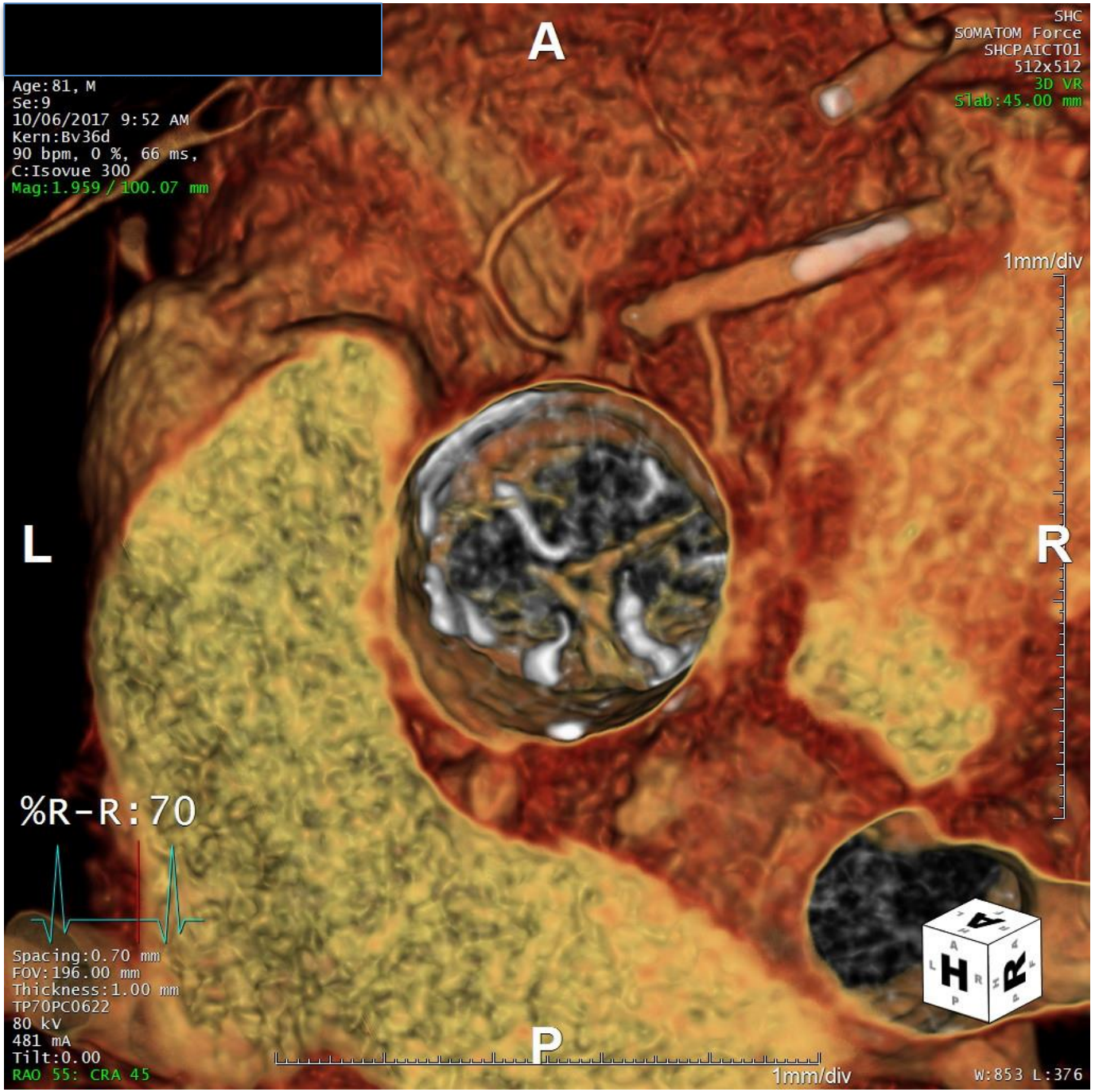
Disclosure Statement of Financial Interest

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	• Edwards Lifesciences, Abbott
• Scientific Advisory Board	• Medtronic, Abbott
• Executive Physician Council	• Boston Scientific Corp

2017 Case Presentation : B.I.

- 81 year old man with HTN, HL,COPD, PAD with severe symptomatic AS with SOB.
- AS: Mean gradient 31mmHg, EF 34%. V1/V2 0.22
  - Dobutamine stress: 4mcg/kg/min stopped due to VT
- CAD: No significant disease
- COPD: FEV1 17%, DLCO 31%
- PAD: aorto-bifemoral with Dacron grafts, aorto-renal and IMA bypass, carotid bruits, renal artery stenosis
- STS: 12.1%, stroke risk 2.5%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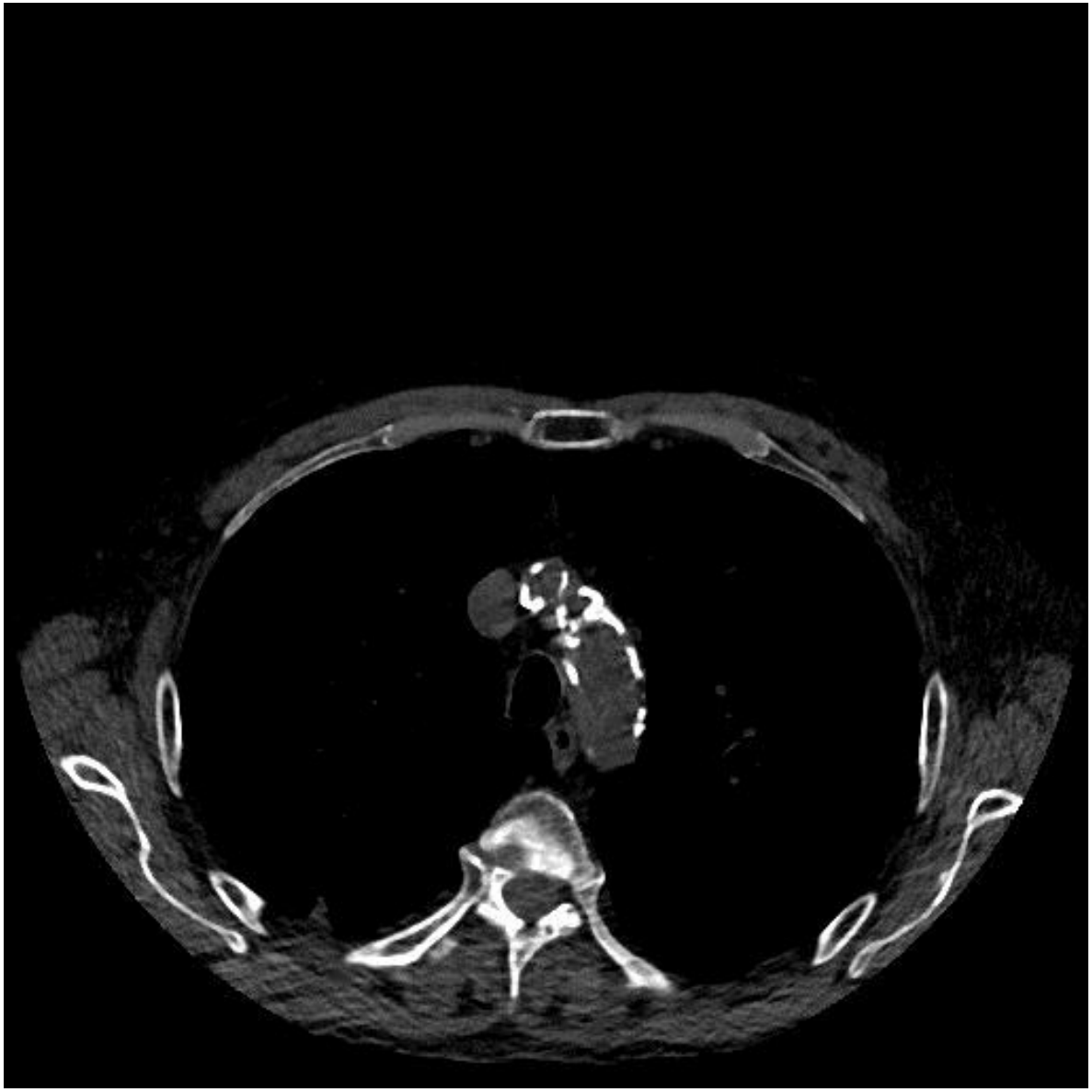
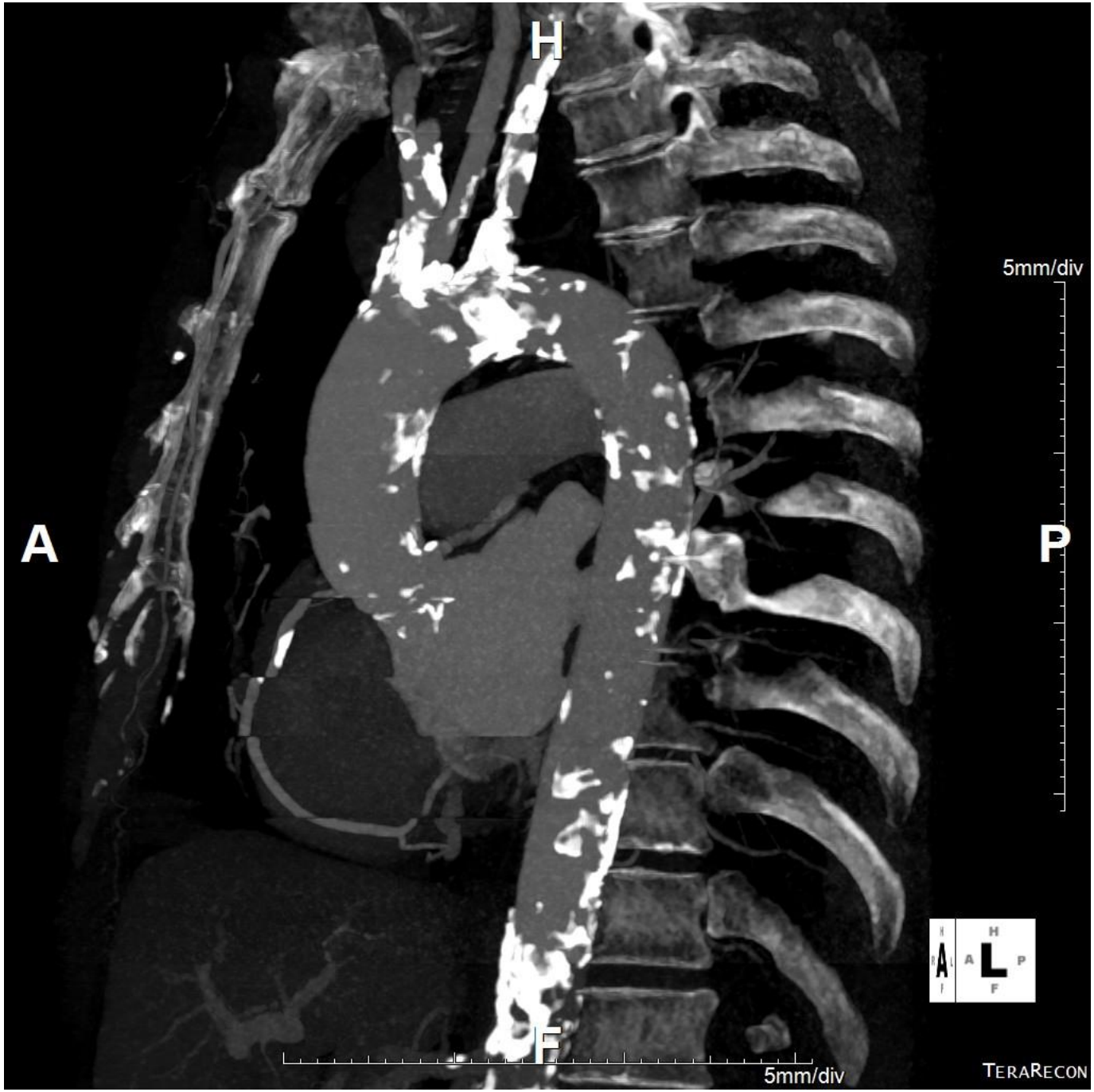
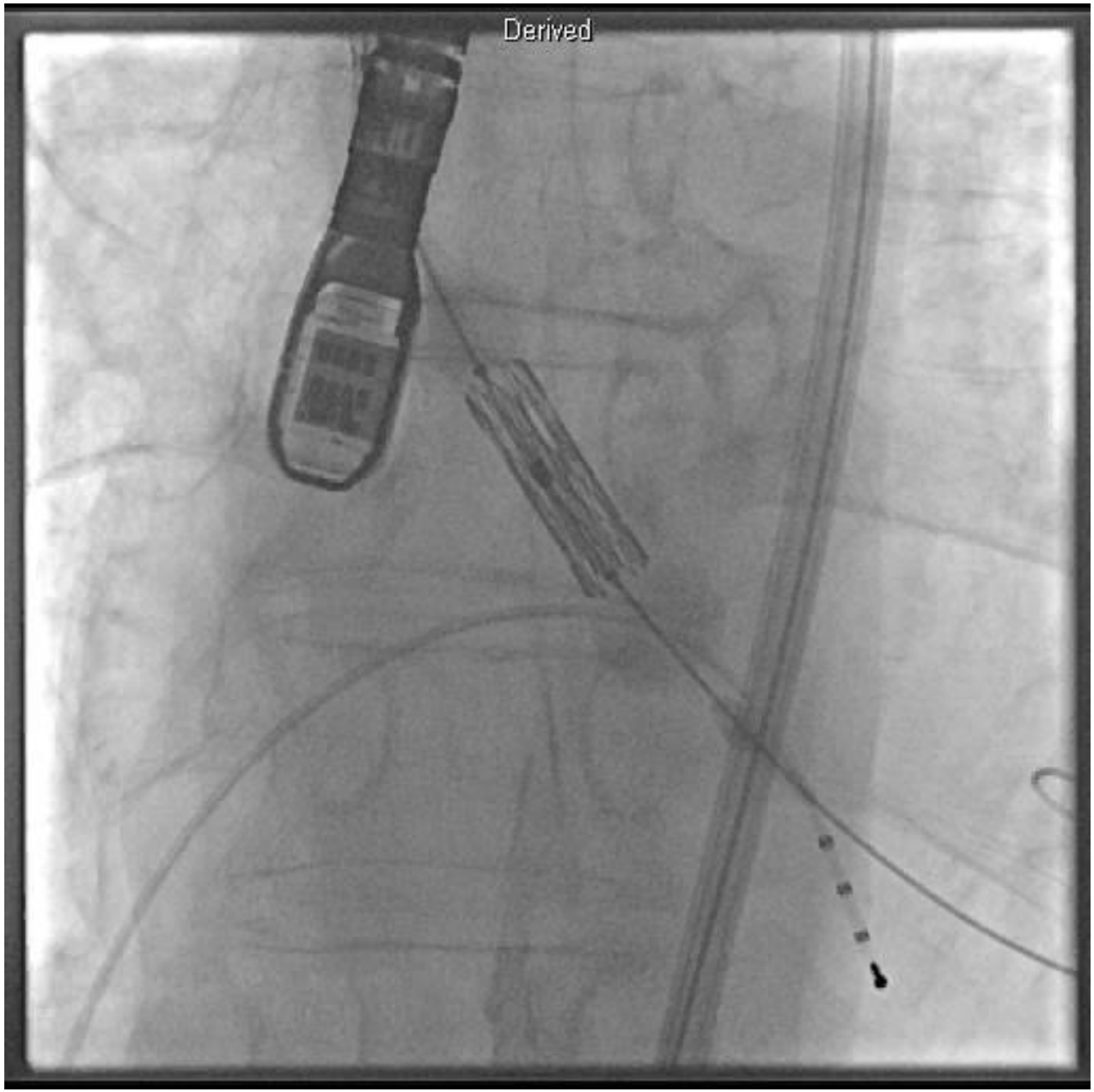
R
P
SHC
SOMATOM Force
SHCPAICT01
512x512
3D VR
Slab:45.00 mm
Age:81, M
Se:9
10/06/2017 9:52 AM
Kern:Bv36d
90 bpm, 0 %, 66 ms,
C:Isovue 300
Mag:1.959 / 100.07 mm
1mm/div
%R-R:70
Spacing:0.70 mm
FOV:196.00 mm
Thickness:1.00 mm
TP70PC0622
80 kV
481 mA
Tilt:0.00
RAO 55: CRA 45
1mm/div
W:853 L:376




H
A
P
F
5mm/div
5mm/div
TERARECON

Case Presentation (2): B.I.

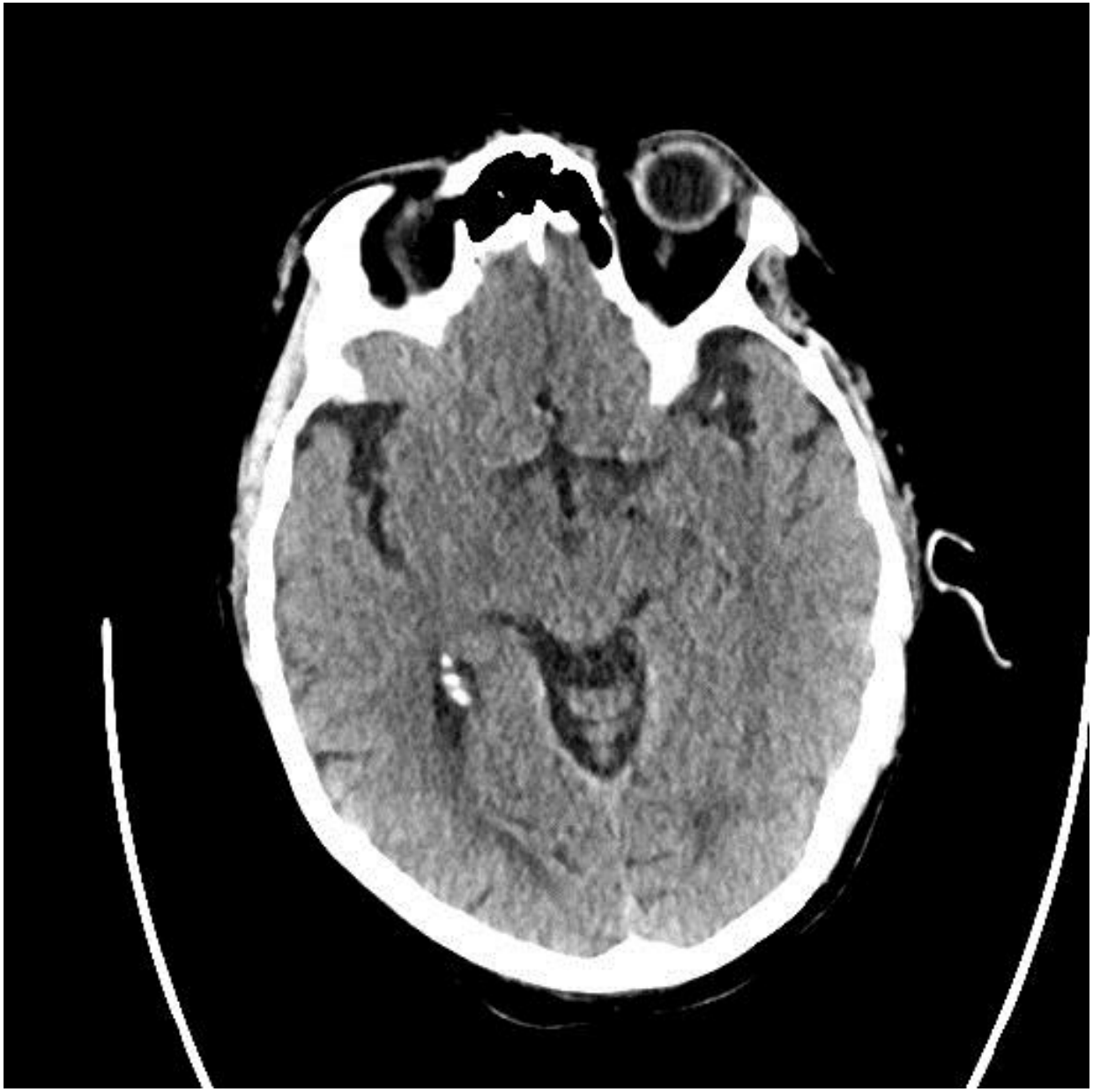
- High Risk TAVR 26mm Sapien 3
- Cut down to Dacron aortabifemoral graft
- Calcified arch and great vessels
- No cerebral protection (not approved yet)

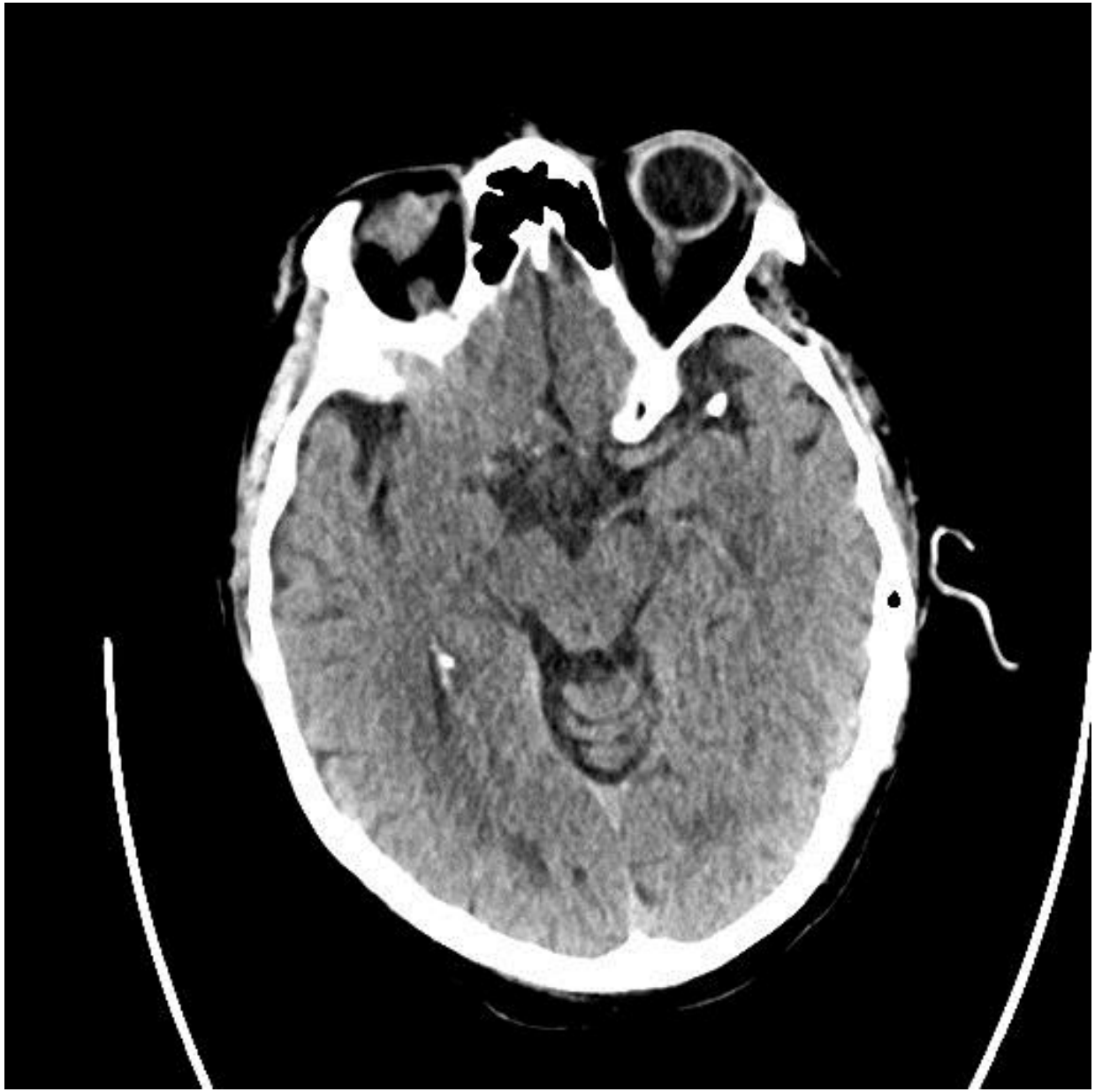

Derived

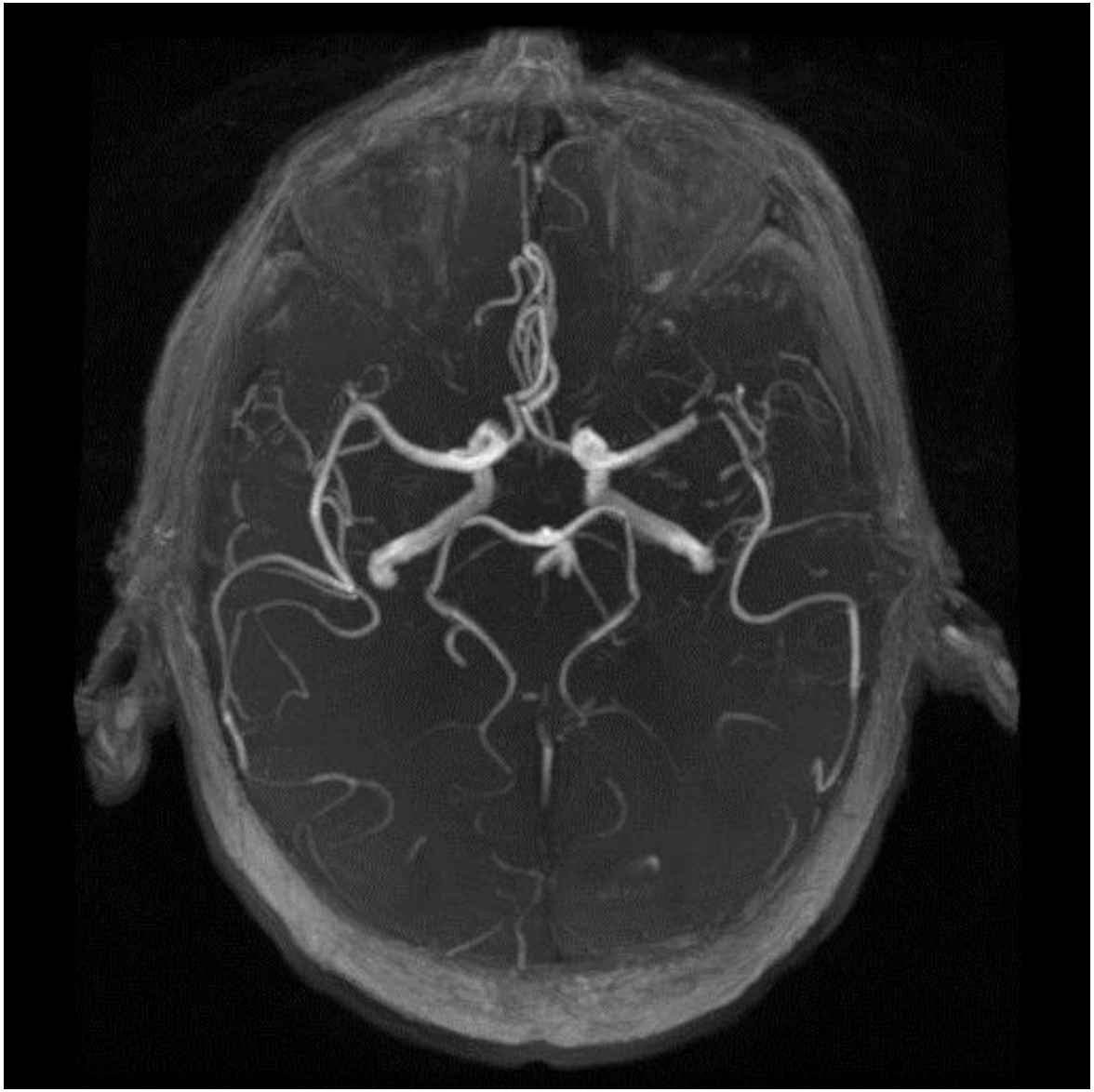
Case Presentation (3): B.I.

- Successful TAVR deployment with trace perivalvular leak
- Repair of Dacron aorto-bifemoral graft
- Extubated, awake, responsive and moves all extremities. Transferred from recovery to cardiac floor
- In usual state at 5AM, at 6:20AM, found to have fluctuating dysarthria, aphasia, R facial droop and R-hemiplegia. Improve with higher BP of greater than 150. Stroke Code was called.

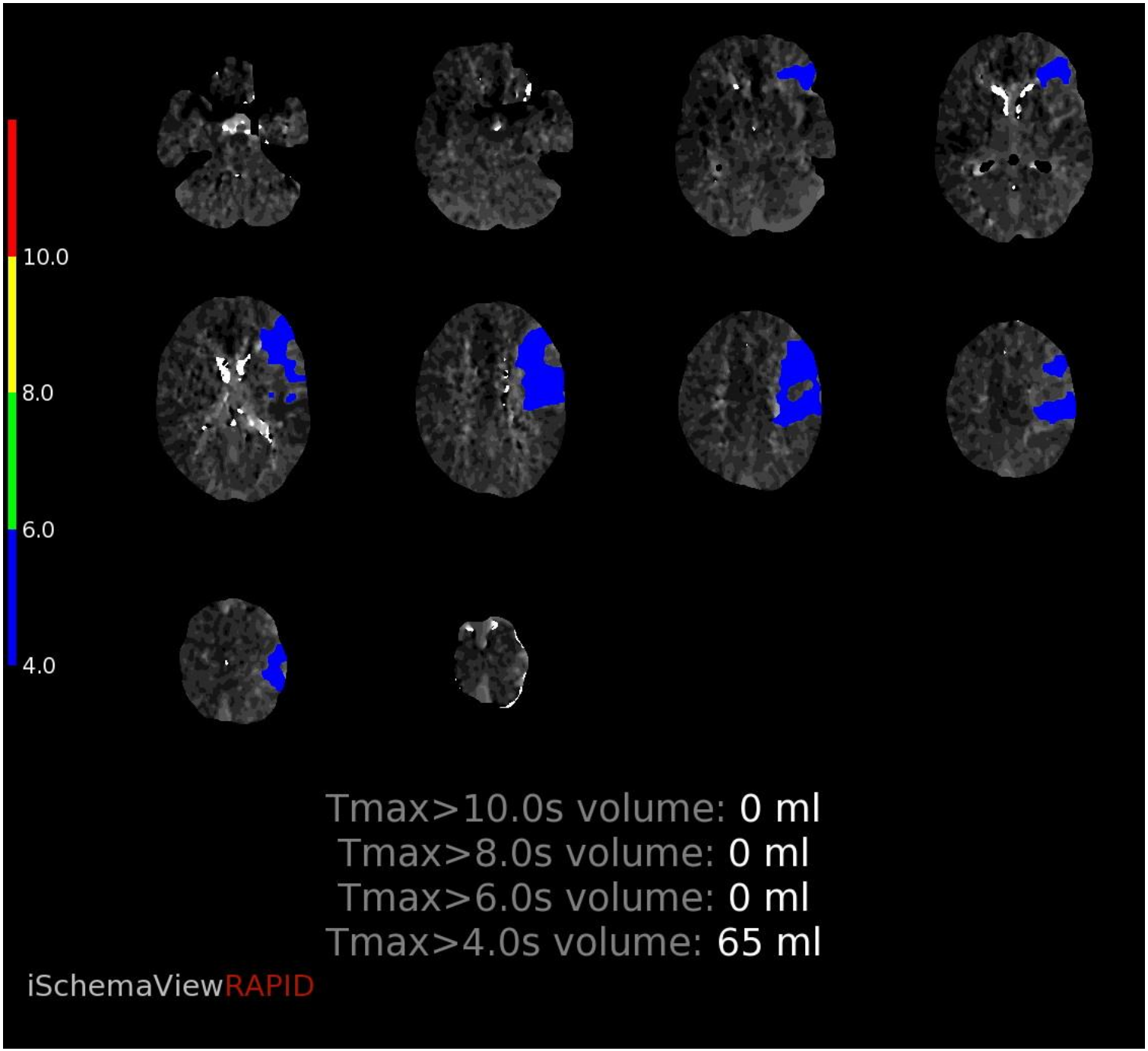
6:45AM







9:06 AM


10.0
8.0
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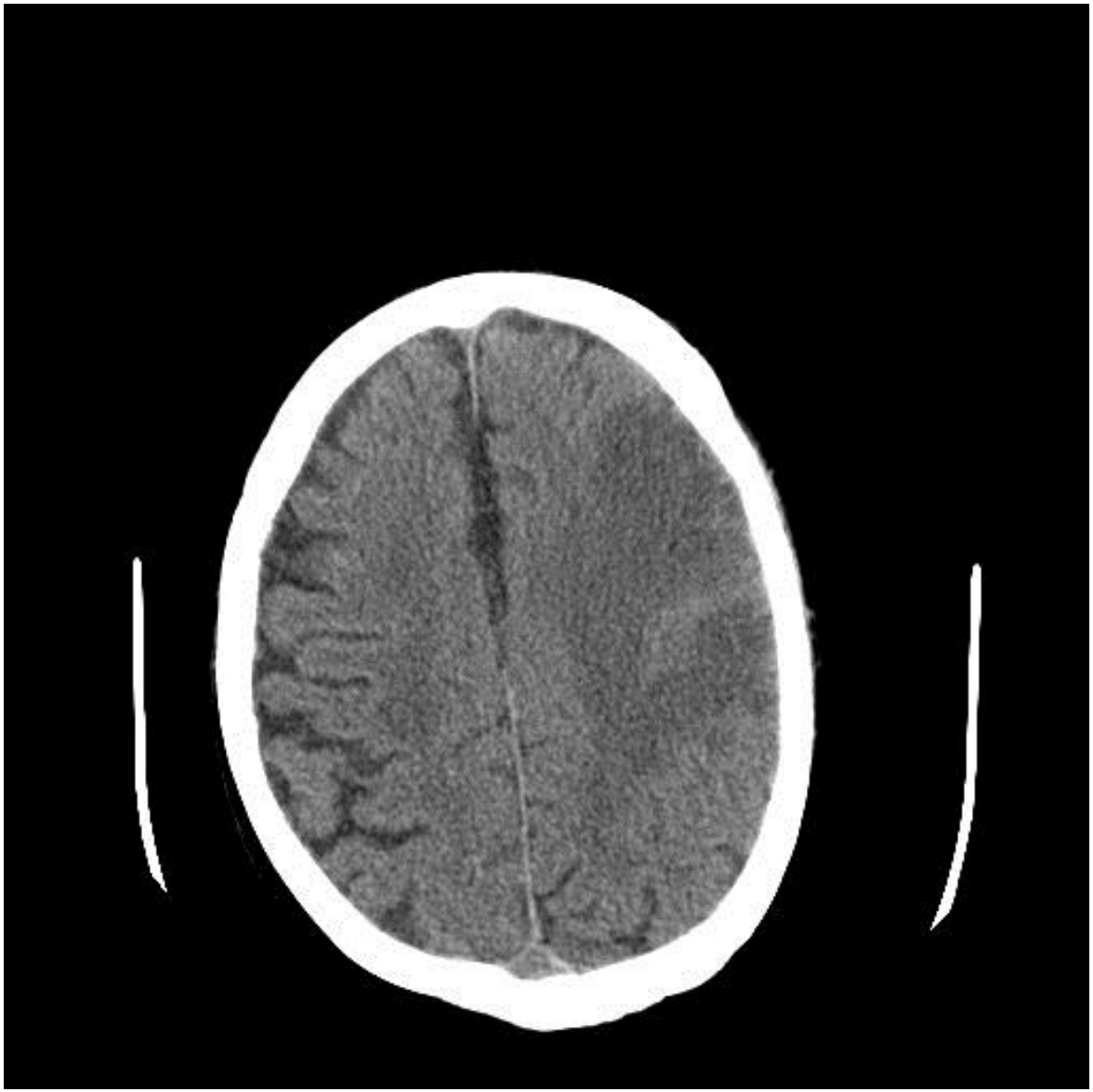
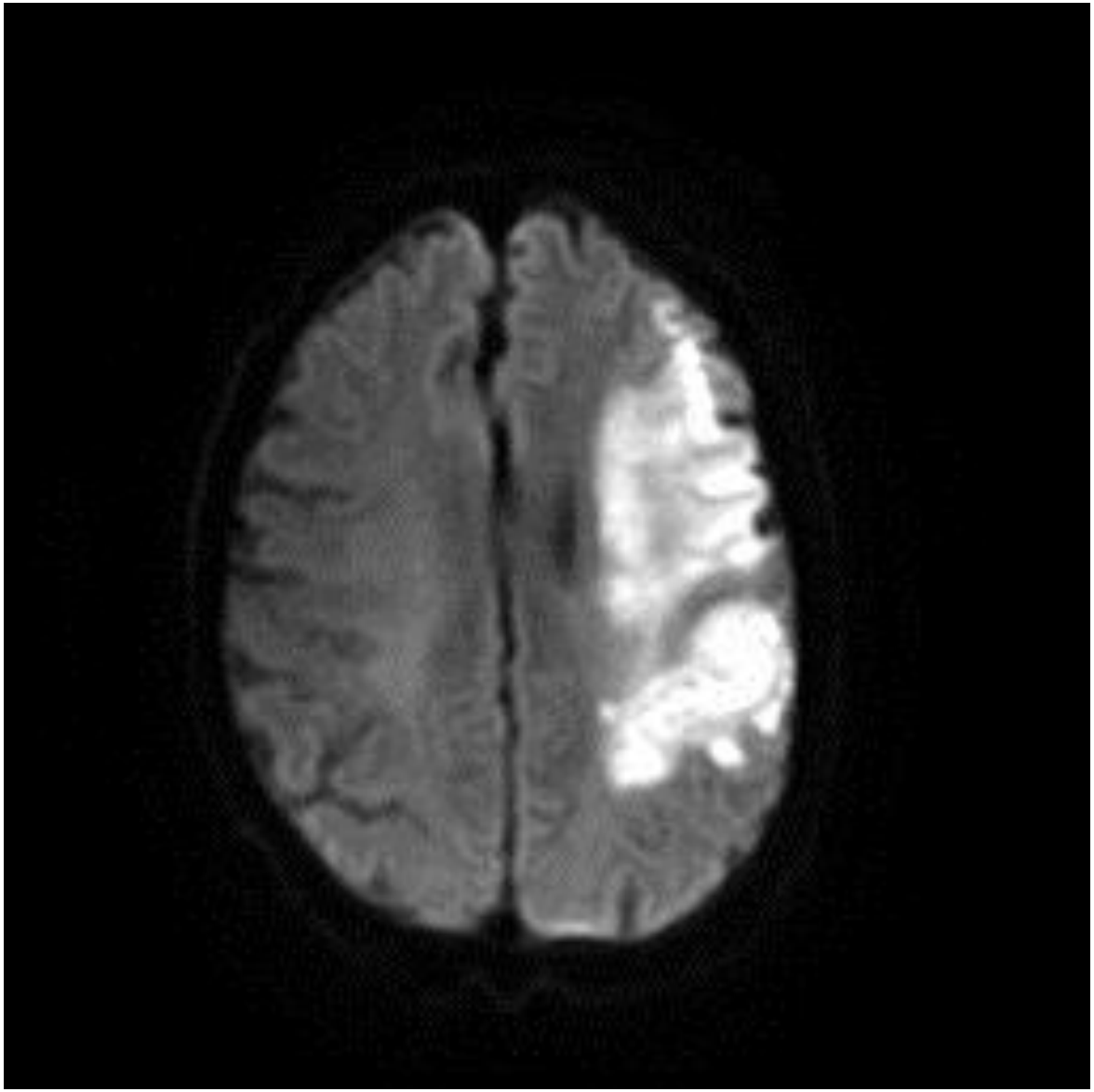
Tmax>10.0s volume: 0 ml
Tmax>8.0s volume: 0 ml
Tmax>6.0s volume: 0 ml
Tmax>4.0s volume: 65 ml
iSchemaViewRAPID

tPA given at 9;30AM

Repeat CT at 12:45 PM



Next Day
MRI

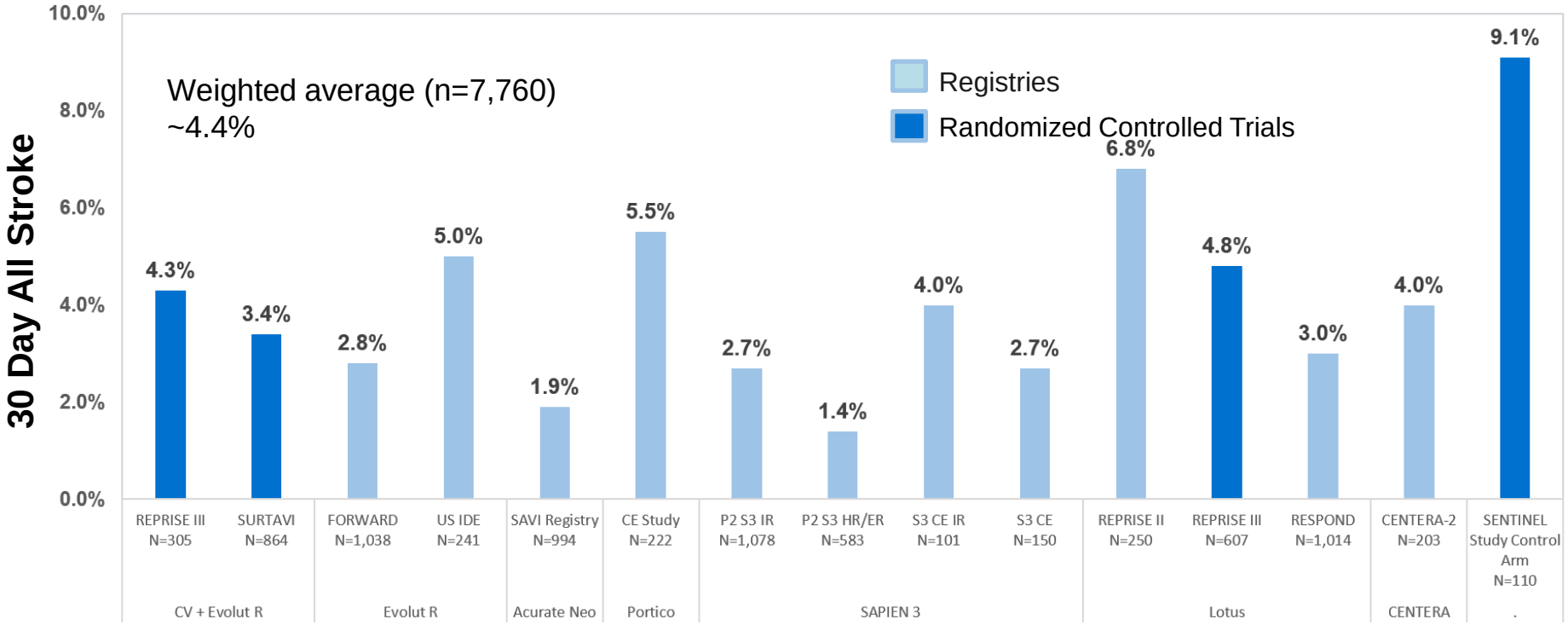


Case Presentation (4): B.I.

- CTA: Embolus vs calcified stenosis in left MCA bifurcation and M2. No complete occlusion on CTA, slight decrease perfusion by CBF.
- Moderate occlusion of left common carotid; severe occlusion of left vertebral; moderate to severe narrowing of right common carotid.
- MRI confirms acute stroke. tPA given within 3 hours.
- Large groin hematoma.
- No hemorrhagic transformation but no improvement
- 3 days post-TAVR, family withdrawn support.

Would Cerebral Protection Prevented the CVA?

TAVR 30-day All-Stroke Rates with Contemporary Devices



[1]Feldman, et al., presented at EuroPCR 2017; [2]Manoharan, et al., *J Am Coll Cardiol Intv* 2015; 8: 1359-67; [3]Moellman, et al., presented at PCR London Valves 2015; [4]Grube, et al., presented at EuroPCR 2017; [5]Kodali, et al., *Eur Heart J* 2016; doi:10.1093/eurheartj/ehw112; [6]Vahanian, et al., presented at EuroPCR 2015; [7]Webb, et. al. *J Am Coll Cardiol Intv* 2015; 8: 1797-806; [8]DeMarco, et al, presented at TCT 2015; [9]Meredith, et al., presented at PCR London Valves 2015; [10]Falk, et al. Eur Heart J. 2017; [11]Kodali, presented at TCT 2016; Reardon, M Published in NEJM March 2017 [12]Reichenspurner et al, JACC 2017

- 95% of SENTINEL patients were evaluated prospectively by neurologists.
- Clinical Events Committee included 2 stroke neurologists.

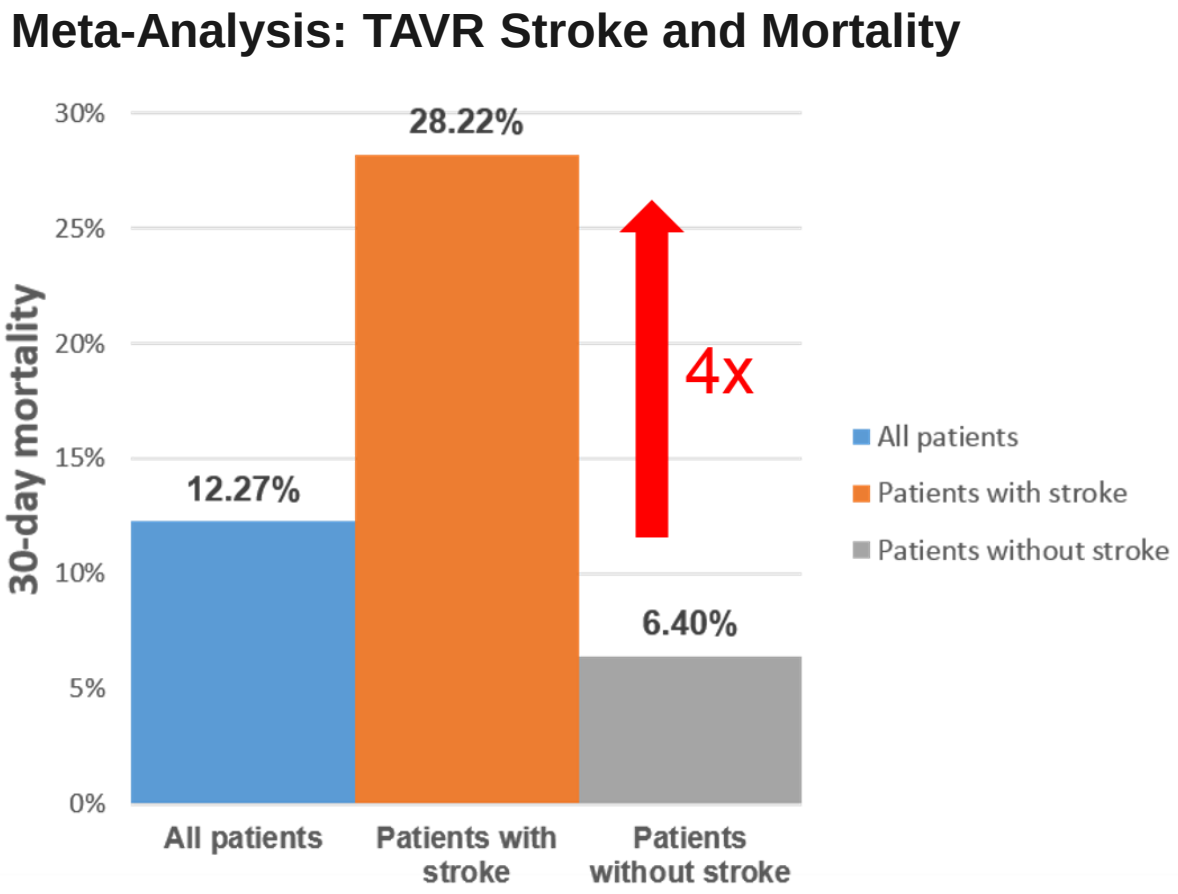
THE PARTNER 3 TRIAL

Pre-specified Secondary Endpoints

Subject to Multiplicity Adjustment

Order of Testing	Endpoint	TAVR (N=496)	Surgery (N=454)	Treatment Effect [95% CI]	P-value
1	New onset atrial fibrillation at 30 days	5.0%	39.5%	0.10 [0.06, 0.16]	<0.001
2	Length of index hospitalization (days)	3.0 (2.0, 3.0)	7.0 (6.0, 8.0)	-4.0 [-4.0, -3.0]	<0.001
3	All-cause death, all stroke, or rehospitalizations at 1 year	8.5%	15.1%	0.54 [0.37, 0.79]	0.001
4	Death, KCCQ < 45 or KCCQ decrease from baseline ≥ 10 points at 30 days	3.9%	30.6%	-26.7% [-31.4%, -22.1%]	<0.001
5	Death or all stroke at 30 days	1.0%	3.3%	0.30 [0.11, 0.83]	0.01
6	All stroke at 30 days	0.6%	2.4%	0.25 [0.07, 0.88]	0.02

Stroke increases mortality



Muralidharan et al. *Am J Cardiol* 2016

What are, or are not, predictors of stroke and cerebral damage in TAVR?

Factor	Is or is not a predictor of/ associated with	Outcome	Patient Segment	Trial Type	Size	Reference
Logistic EuroSCORE	**is not a predictor of**	**Stroke**	TAVR (Log EuroSCORE average 16-33)	Meta-analysis of EU Registries	9,786	Zeinah et al EU TAVR Registry Review and Meta Analysis. ACTA 2015
Post-dilatation and valve dislodgement	is a predictor of	Stroke and TIA	Severe AS TAVR (STS 4-10)	Case series	1,061	Nombela-Franco, et al. Circulation 2012
Transarterial vs Transapical access	is a predictor of	Stroke and TIA	Severe AS TAVR (log EuroSCORE 25 +/-5)	Meta-analysis	10,037	Eggebrecht, et al. Eurointervention 2012
Smaller indexed valve area, Cerebrovascular disease, TAVR vs SAVR	is a predictor of	Stroke or TIA	Severe AS high-risk (STS 10-15)	RCT (PARTNER)	657	Miller, et al. JTCVS 2012
Age, hyperlipidemia, post-dil	is a predictor of	DW-MRI lesion number post TAVR	Severe AS TAVR	Case series	42	Samim, et al. Clin Res Cardiol 2015
Age, severity of atheroma (arch and descending), catheterization time	is a predictor of	DW-MRI lesion number post TAVR	Severe AS TAVR, CoreValve	Case series	31	Fairbairn, et al. Heart 2012
Peak transaortic gradient	is a predictor of	DW-MRI total lesion volume post TAVR	Severe AS TAVR	Case series	42	Samim, et al. Clin Res Cardiol 2015

Stroke is a Procedural Issue

TAVR stroke occurs peri-procedurally (<72 hours)

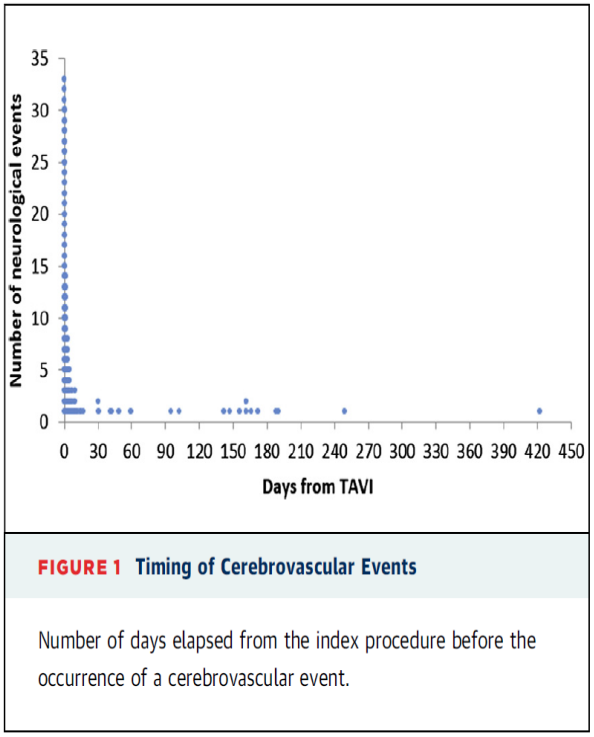


FIGURE 1 Timing of Cerebrovascular Events

Number of days elapsed from the index procedure before the occurrence of a cerebrovascular event.

FRANCE-2 Registry (n=3,191)[1]

- ***CVE most frequently occur day 0-1***
- ***>50% are major strokes***

Stroke

Timing, Predictive Factors, and Prognostic Value of Cerebrovascular Events in a Large Cohort of Patients Undergoing Transcatheter Aortic Valve Implantation

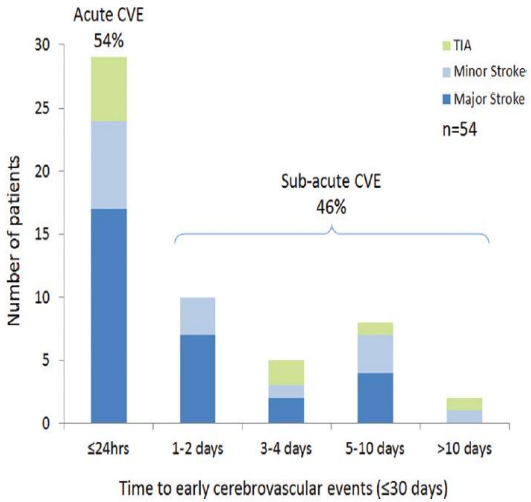
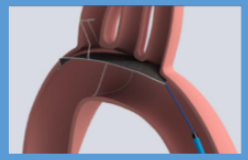


Figure 2. Timing of cerebrovascular events (CVEs) within 30 days after transcatheter aortic valve implantation. TIA indicates transient ischemic attack.

Multi-center cohort (n=1,061)[2]

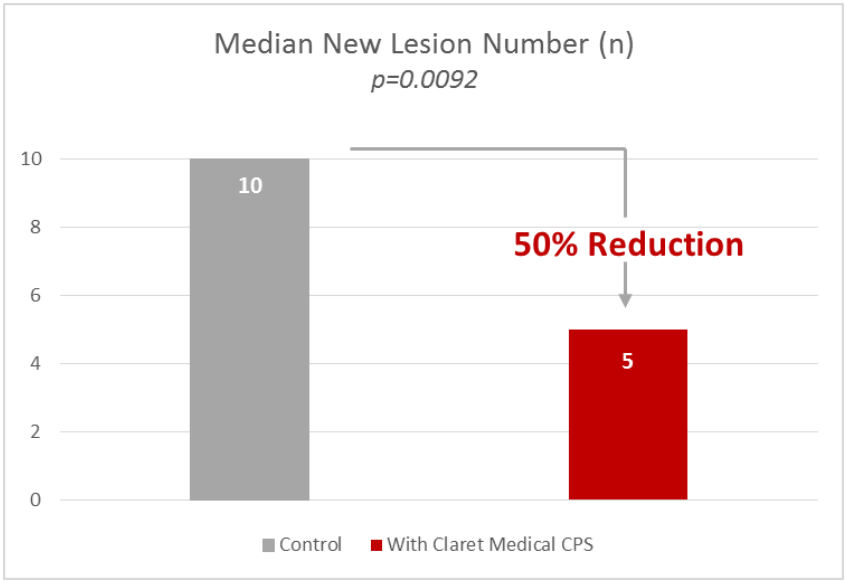
- ***CVE most frequently occur day 0-1***
- ***>50% are major strokes***
- ***>95% of strokes are ischemic***

Cerebral Protection

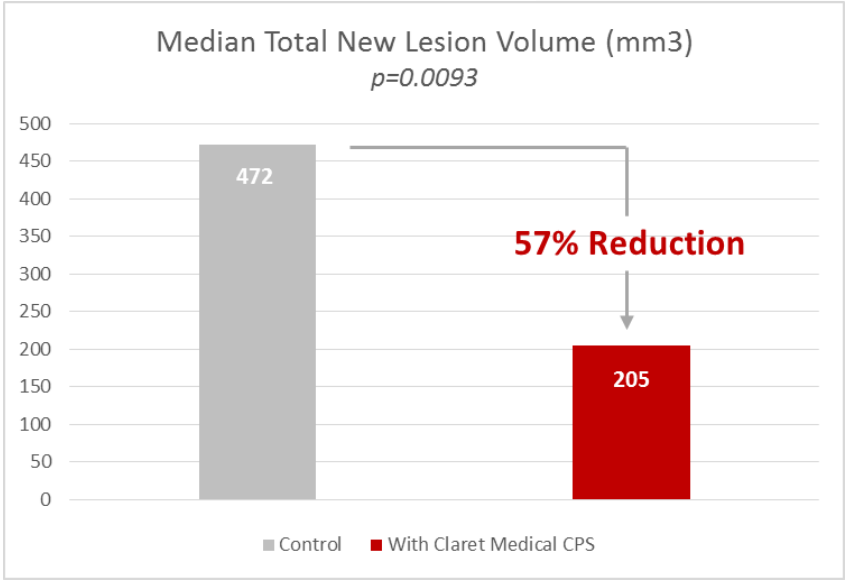
Company and Product	Claret Medical Sentinel 	Keystone TriGuard 	Edwards Embrella 	ICS Emblok 	Transverse Point-Guard 
EU Status	CE Mark 97% market share	CE Mark 3% market share	CE Mark <3% market share	FIM first clinical case March 15, 2017	Pre-clinical/prototype
US Status	IDE study completed Positive FDA Panel Feb 23, 2017	IDE trial underway	No IDE yet	No IDE yet	No IDE yet
Access	6 Fr Right Radial	9Fr TF	Right Radial	12Fr TF sheath	TF
Debris	Captures and removes	Deflects downstream	Deflects downstream	Captures and removes	Deflects downstream
Placement and Interaction with TAVR devices	Not in aortic arch	Sits in aortic arch. Devices must pass over and back across	Sits in aortic arch. Devices must pass over and back across	Sits in ascending aorta Devices must pass over and back across	Sits in aortic arch. Devices must pass over and back across

CLEAN-TAVI shows Claret filters significantly reduce lesion number and volume

Lesion Number per Patient



Total Lesion Volume per Patient



Claret Montage Cerebral Protection System significantly reduces new cerebral lesion number and volume at 7 days, as measured by DW-MRI

CLEAN TAVI, Linke et al

SENTINEL Study Design

Pivotal trial confirming the therapeutic importance of embolic debris capture and removal during TAVR

Objective: Assess the safety and efficacy of the Claret Medical Sentinel Cerebral Protection System in reducing the volume and number of new ischemic lesions in the brain and their potential impact on neurocognitive function

US Co-PIs:
Samir Kapadia, MD, *Cleveland Clinic*
Susheel Kodali, MD, *Columbia U Med*
German Co-PI:
Axel Linke, MD, Leipzig U

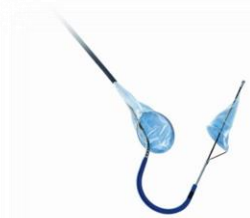
Population: Subjects with severe symptomatic calcified native aortic valve stenosis who meet the commercially-approved indications for TAVR with the Edwards Sapien THV/XT/S3 or Medtronic CoreValve/Evolut-R
N=296 subjects randomized 1:1:1
at sites in the U.S and Germany.

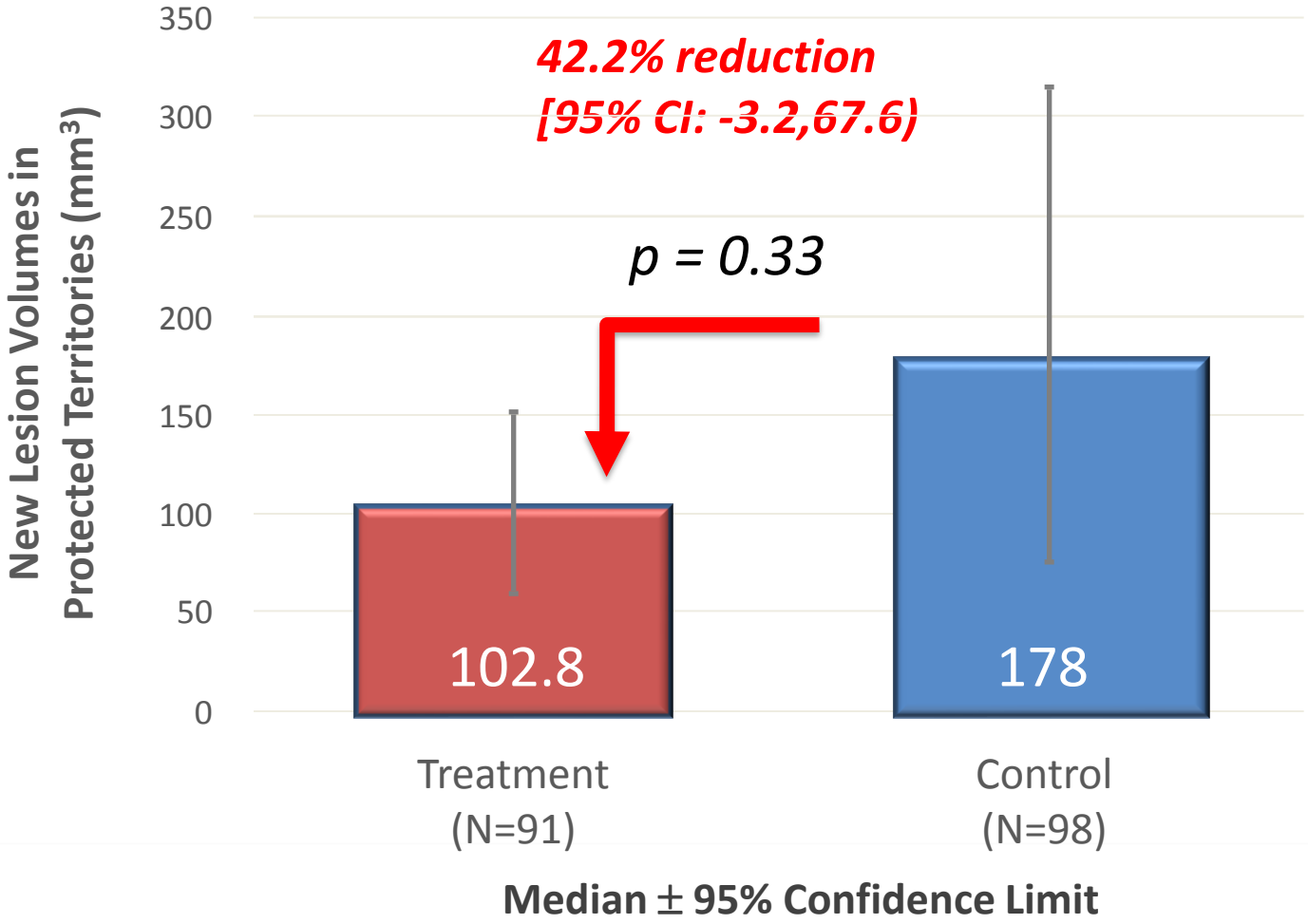
- **SAFETY ARM** — TAVR with Sentinel
  - Safety Follow-up
- **TEST ARM** — TAVR with Sentinel
  - Histopathology
  - Safety Follow-up
  - MRI Assessments
  - Neurological and Neurocognitive Tests
- **CONTROL ARM** — TAVR only
  - Neurological and Neurocognitive Tests

Primary (superiority) Efficacy Endpoint: Reduction in median total new lesion volume assessed by 3T DW-MR by baseline subtraction .
Primary (non-inferiority) Safety Endpoint: Occurrence of all MACCE at 30 days.

Sentinel Trial

Primary Efficacy Endpoint

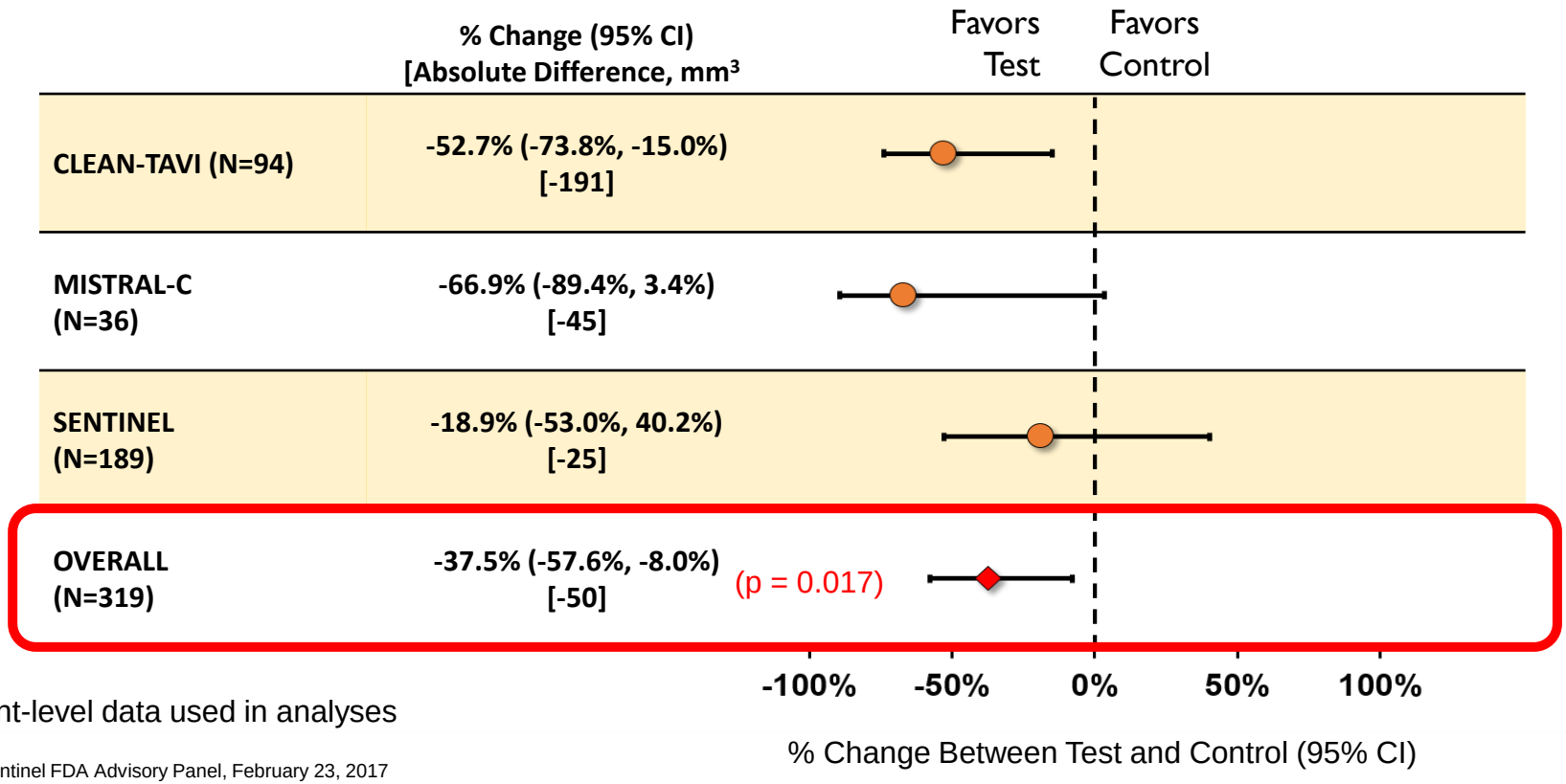




Why did Sentinel Not Meet Primary Endpoint?

- Multicenter vs Single Center
- Greater variability
  - Multiple valve types used
  - More variability in timing of MRI
  - More operators with less experience
- Differences in patient population – Higher baseline burden of disease
- MRI is the wrong endpoint
- There is no difference with embolic protection

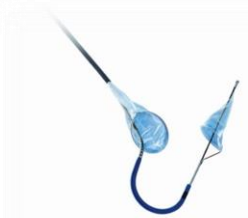
Meta-Analysis of Effectiveness*
Change in Mean New Lesion Volumes (Protected Territories)



*Patient-level data used in analyses

Data presented at Sentinel FDA Advisory Panel, February 23, 2017

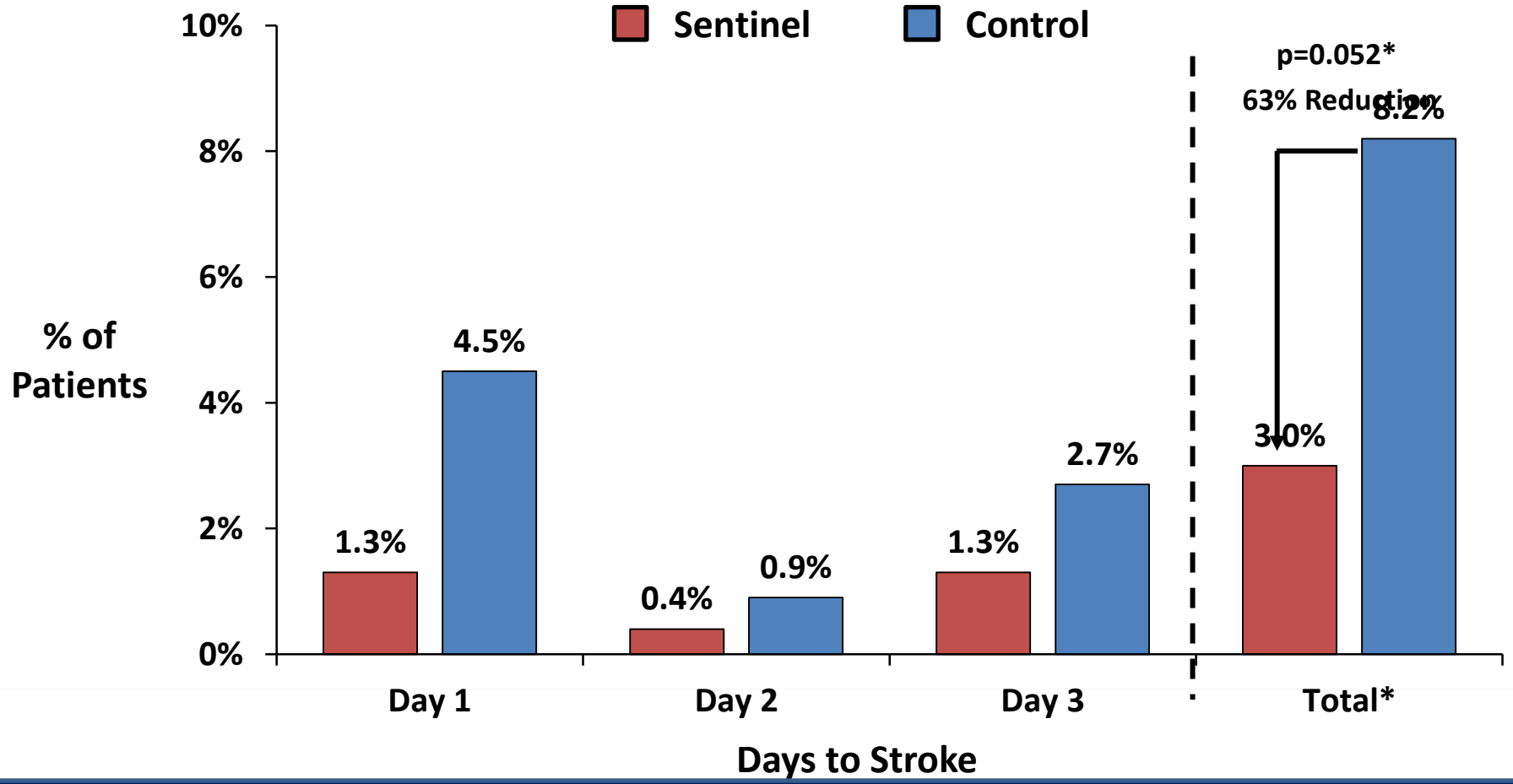
30-Day Clinical Outcomes Sentinel Trial



	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 Access Site Complications	0.4%	N/A	0.53

†MACCE defined as Death (any cause), Stroke (any), Acute Kidney Injury (Stage 3)

Stroke Diagnosis ≤72 hours (Analyzed ITT)



NeuroProtection During TAVR

Clinical Events Meta-Analysis of 5 Randomized Trials

JACC
JOURNAL OF THE AMERICAN COLLEGE OF CARDIOLOGY

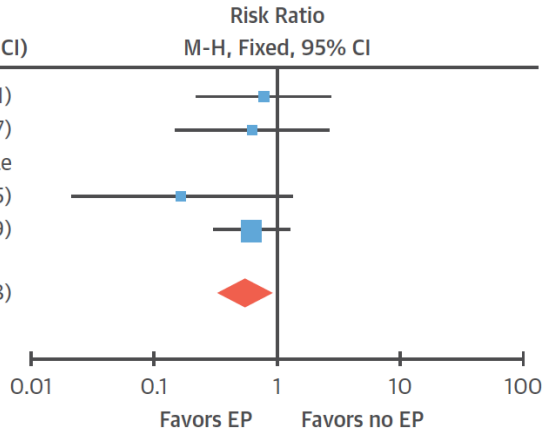
FIGURE 1 Clinical Outcomes in Patients Undergoing TAVR With Versus Without Embolic Protection Devices

Death or stroke

Study or Subgroup	Embolic protection Events	Total	No embolic protection Events	Total	Weight	Risk Ratio M-H, Fixed (95% CI)
CLEAN-TAVI	4	50	5	50	15.9%	0.80 (0.23-2.81)
DEFLECT-III	3	46	4	39	13.7%	0.64 (0.15-2.67)
EMBOL-X	0	14	0	16		Not estimable
MISTRAL-C	1	32	6	33	18.7%	0.17 (0.02-1.35)
SENTINEL	16	234	12	111	51.7%	0.63 (0.31-1.29)
Total (95% CI)		376		249	100.0%	0.57 (0.33-0.98)
Total events	24		27			

Heterogeneity: $Chi^2 = 1.68$, $df = 3$ ($P = 0.64$); $I^2 = 0\%$

Test for overall effect: $Z = 2.01$ ($P = 0.04$)



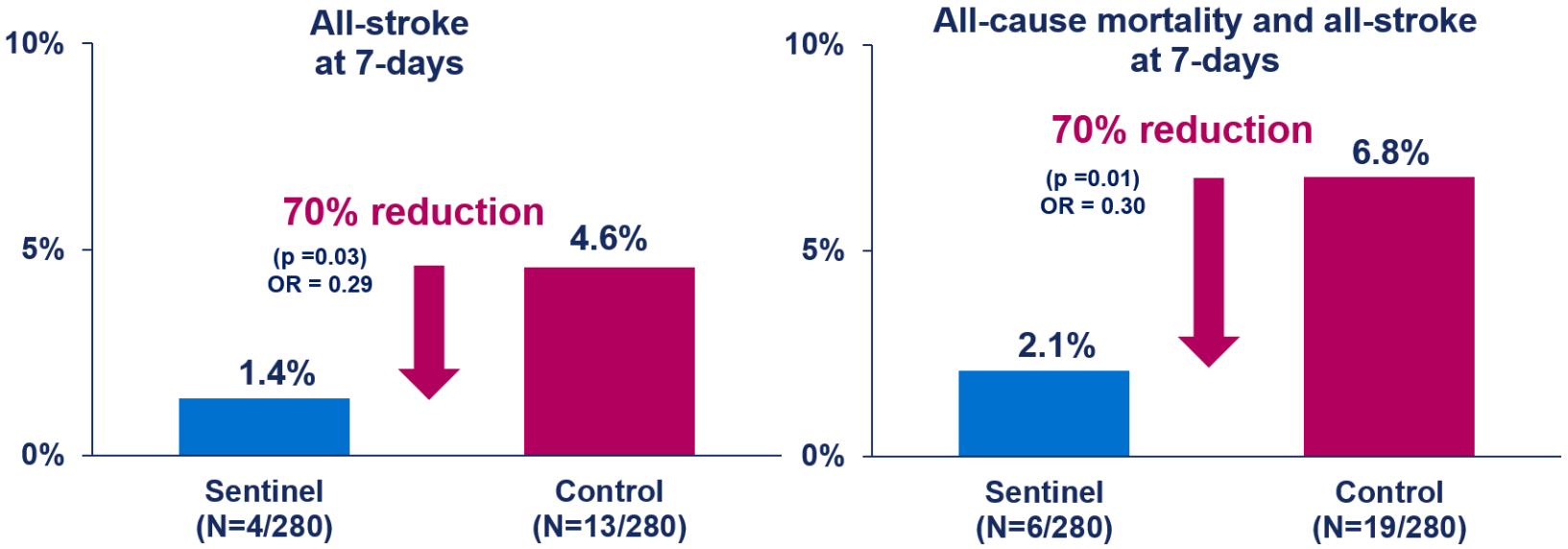
Pooled effect estimates for the risk of death or stroke according to the use of cerebral embolic protection versus not during TAVR. CI = confidence interval; CLEAN-TAVI = Claret Embolic Protection and TAVI; DEFLECT-III = A Prospective, Randomized Evaluation of the TriGuard HDH Embolic Deflection Device During TAVI; EP = embolic protection; M-H = Mantel-Haenszel; MISTRAL-C = MRI Investigation With Claret; SENTINEL = Cerebral Protection in Transcatheter Aortic Valve Replacement; TAVR = transcatheter aortic valve replacement.

Giustino G, Sorrentino S, Mehran R, Faggioni M, Dangas G: JACC 2017 - in press

Real World Experience

Ulm Sentinel study shows significant 70% stroke and death reduction

- 802 **all-comer consecutive** TAVI patients at University of Ulm were prospectively enrolled
- A **propensity-score analysis** was done matching the 280 patients protected with Sentinel to 280 control patients

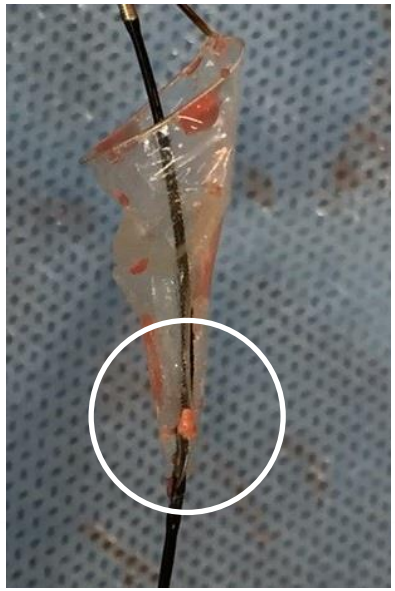


- In multivariable analysis, **TAVI without cerebral emboli protection (p=0.044)** was the only independent predictor for stroke at 7-days
- **TAVI without cerebral emboli protection (p=0.028)** and STS score (<8 vs. ≥8) (p=0.021) were the only independent predictors for mortality and stroke at 7-days

Wörhle J, Seeger J, et al. DGK Mannheim 2017; CSI-Ulm-TAVI Study clinicaltrials.gov NCT02162069

The Case *for* Embolic Protection

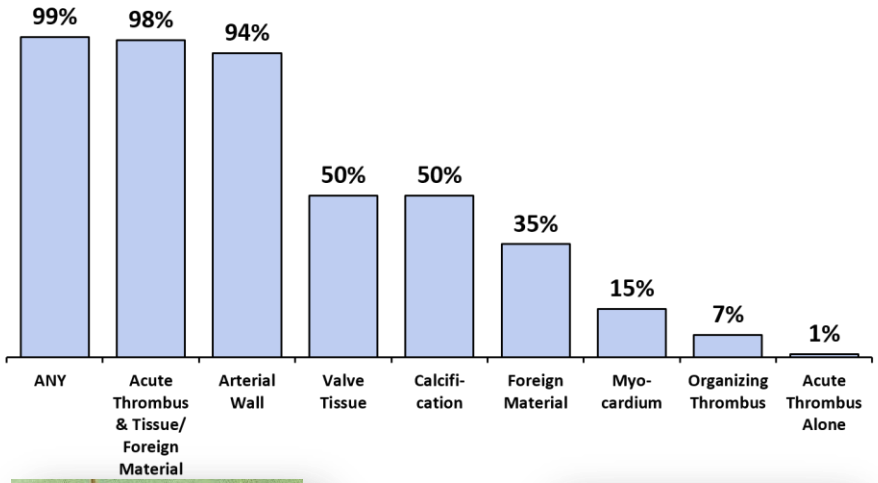
- Carotid stent experience
- MRI abnormalities – "Silent" infarcts are not benign
- Studies have demonstrated that embolic protection devices reduce *MRI abnormalities* after TAVR
  - CLEAN TAVI
  - DEFLECT III
- Potential for clinical benefit beyond stroke – Cognitive improvement
- If we can prevent embolic events, why not do so?

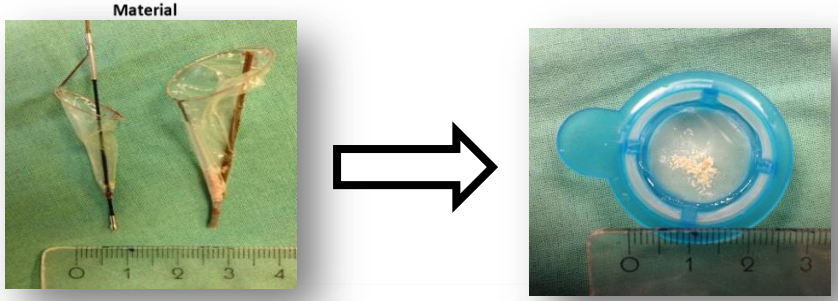


SENTINEL Study - Debris Capture

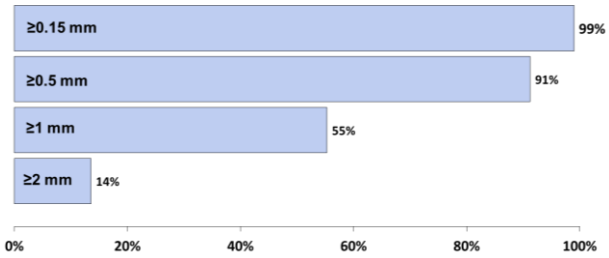
Debris captured in 99% of TAVR patients

Patients with Captured Debris (%)

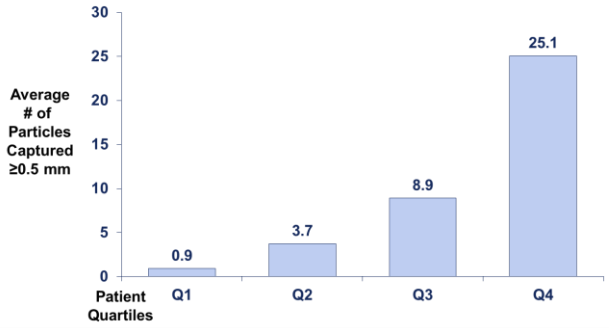




Percent of Patients with at Least One Particle of Given Size



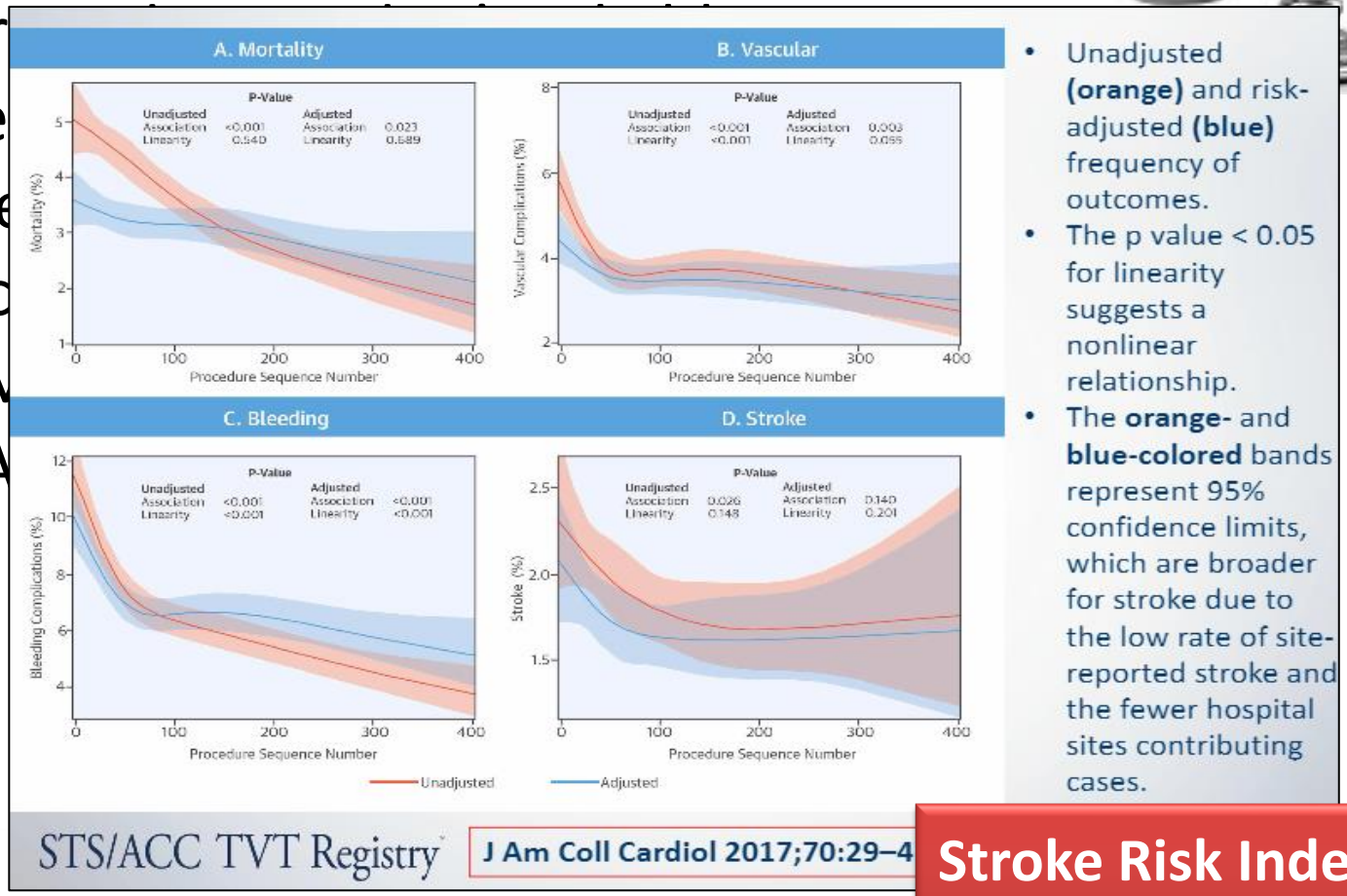
1 in 4 Patients had an average of 25 Particles ≥0.5 mm in Size Captured and Removed



Virmani R, et al. CVPath. SENTINEL trial. Data presented at Sentinel FDA Advisory Panel, February 23, 2017

The Case *against* Embolic Protection

- Stroke rates are decreasing
- Curr
  cere
- Incre
  proc
  - M
  - A



- Unadjusted **(orange)** and risk-adjusted **(blue)** frequency of outcomes.
- The p value < 0.05 for linearity suggests a nonlinear relationship.
- The **orange-** and **blue-colored** bands represent 95% confidence limits, which are broader for stroke due to the low rate of site-reported stroke and the fewer hospital sites contributing cases.

STS/ACC TVT Registry

J Am Coll Cardiol 2017;70:29–4

Stroke Risk Independent of Experience and Operator Volume

The Case *against* Embolic Protection

- Stroke rates are decreasing
- Current devices don't reliably protect all cerebral vessels
- Increases complexity and risk of procedure
  - Manipulation of cerebral vessels
  - Additional vascular access
- COST and TIME!!!

Conclusion

- In the current era of TAVR, stroke is still a devastation outcome and occurs in about 3% in high risk but the rate is falling to less than 1% in low risk cohort.
- Predictability is poor, atheroma load/CVA may be the best additional predicator
- CEP will help to decrease some peri-procedural stroke but not all
- The highest risk patient (e.g. our patient) will need complete vascular protection.