Cerebral Protection during TAVR
State-of-the-Art

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Disclosure

Physician Name	Company/Relationship
Speaker Bureau/Advisory Board:	Medtronic: C, SB, AB, OF LivaNova: C, SB, AB Highlife: AB, SB Boston Scientific: C, SB, AB
Equity Interest:	Millipede: E, SB, C, InSeal Medical: E, AB, CardioValve: E, SB, Claret: E, AB Shockwave: E, AB Valve Medical: E, AB Mitra/Trilign E, AB, SB

Key

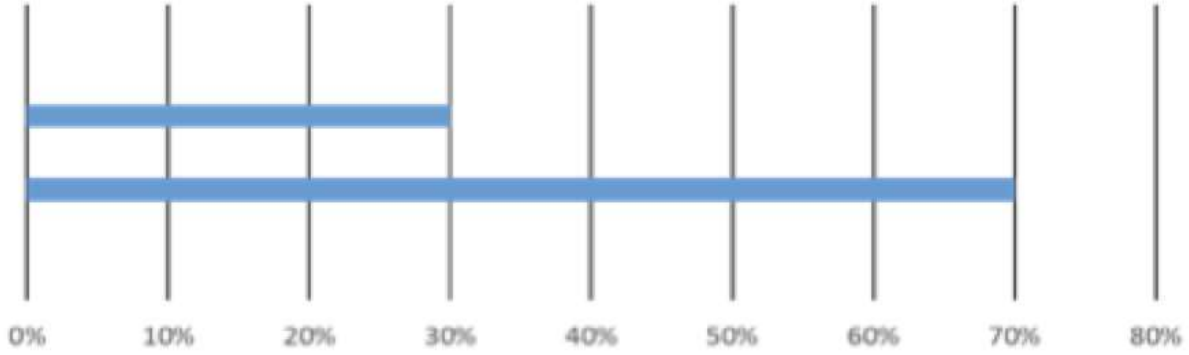
G – Grant and or Research Support E – Equity Interests S – Salary, AB – Advisory Board
C – Consulting fees, Honoraria R – Royalty Income I – Intellectual Property Rights
SB – Speaker's Bureau O – Ownership OF – Other Financial Benefits

Procedural Strokes - Significant Concern For TAVI Patients

Audience Response from Cerebral Protection Session at ACC 2016:

- *What is the biggest concern for your patients undergoing TAVI?*

1. Having general anesthesia: 0%
2. Risk of dying: 30%
3. ***Suffering stroke:*** ***70%***
4. Other: 0%



- *Is cerebral protection necessary during TAVI?*

1. No, never: 0%
2. Maybe (continue reviewing data): 20%
3. ***Yes, in selected patients:*** ***80%***
4. Yes, always: 0%

Hawkey M., ACC 2016

The arguments that you always hear

1. Stroke in TAVR is declining with every generation of TAVR system
2. In high volume centers or experienced operators, stroke has almost disappeared
3. Stroke is more prevalent in high-risk patients as low-risk patients will have less debris
4. Cerebral Protection is complicated to use and adds time to my procedure
5. It adds risk to my procedure
6. There is no evidence that it actually reduces stroke like carotid filter do
7. There is no evidence that strokes are procedural in nature so why not use NOACs post procedure
8. The only available device (Sentinel) doesn’t cover all four arteries supplying blood to the brain
9. Sometimes stroke appears 2 to 3 days post procedure
10. It costs too much

Some Facts…

What is a stroke?

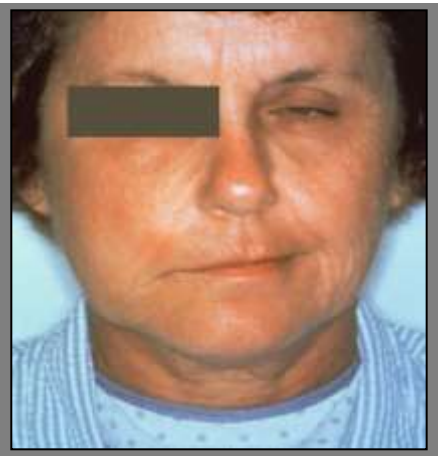
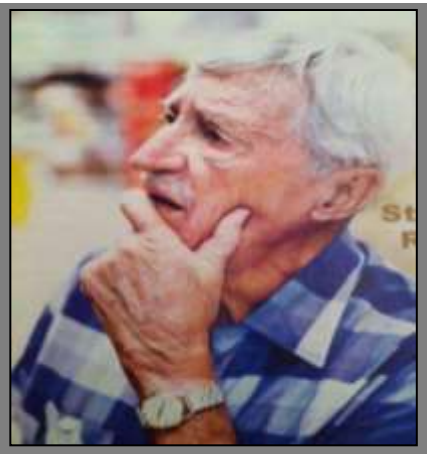
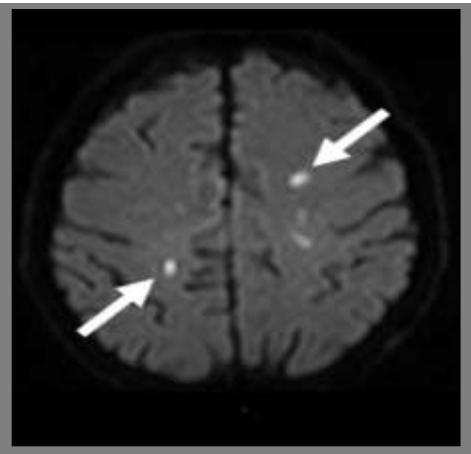
Duration of focal or global neurological deficit* (using specific criteria) 24hrs; OR 24hrs if neuroimaging documents a new hemorrhage or infarct; OR the neurological deficit results in death.

**Neurological deficit* = acute episode of a focal or global neurological deficit with at least one of the following: change in the level of consciousness, hemiplegia, hemiparesis, numbness, or sensory loss affecting one side of the body, dysphasia or aphasia, hemianopia, amaurosis fugax, or other neurological signs or symptoms consistent with stroke

Defining stroke has been a contested and evolving discussion in the clinical arena. Definitions vary by clinician, clinical specialties, and studies

Sacco, R et al: AHA/ASA Expert Consensus Document. An Updated Definition of Stroke for the 21st Century. Stroke. 2013;44:2064-2089.

Cerebral Injury


obvious - apparent - quiet - subtle - silent - subclinical

2-4% ***3-10%*** ***15-20%*** ***68-84%*** ***?%***

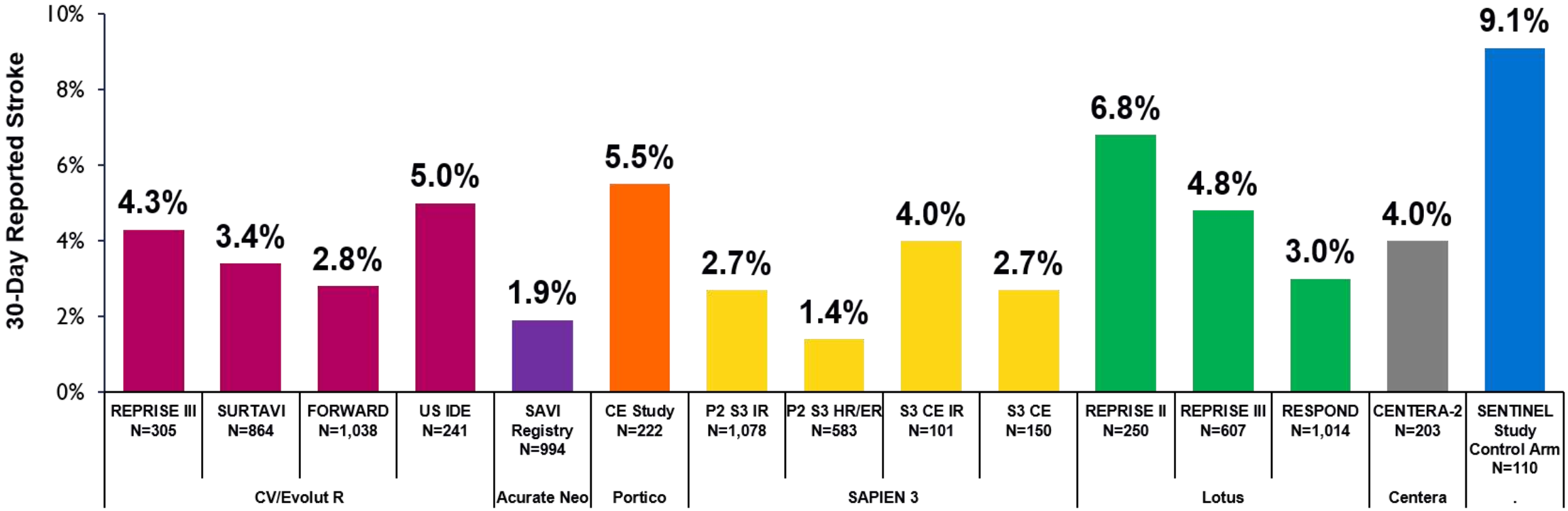
<u>Known consequences of cerebral injury:</u>

Increased risk of:

- *later CVA,*
- *cognitive impairment,*
- *vascular dementia*

TAVI 30-day All-Stroke Rates with Contemporary Devices

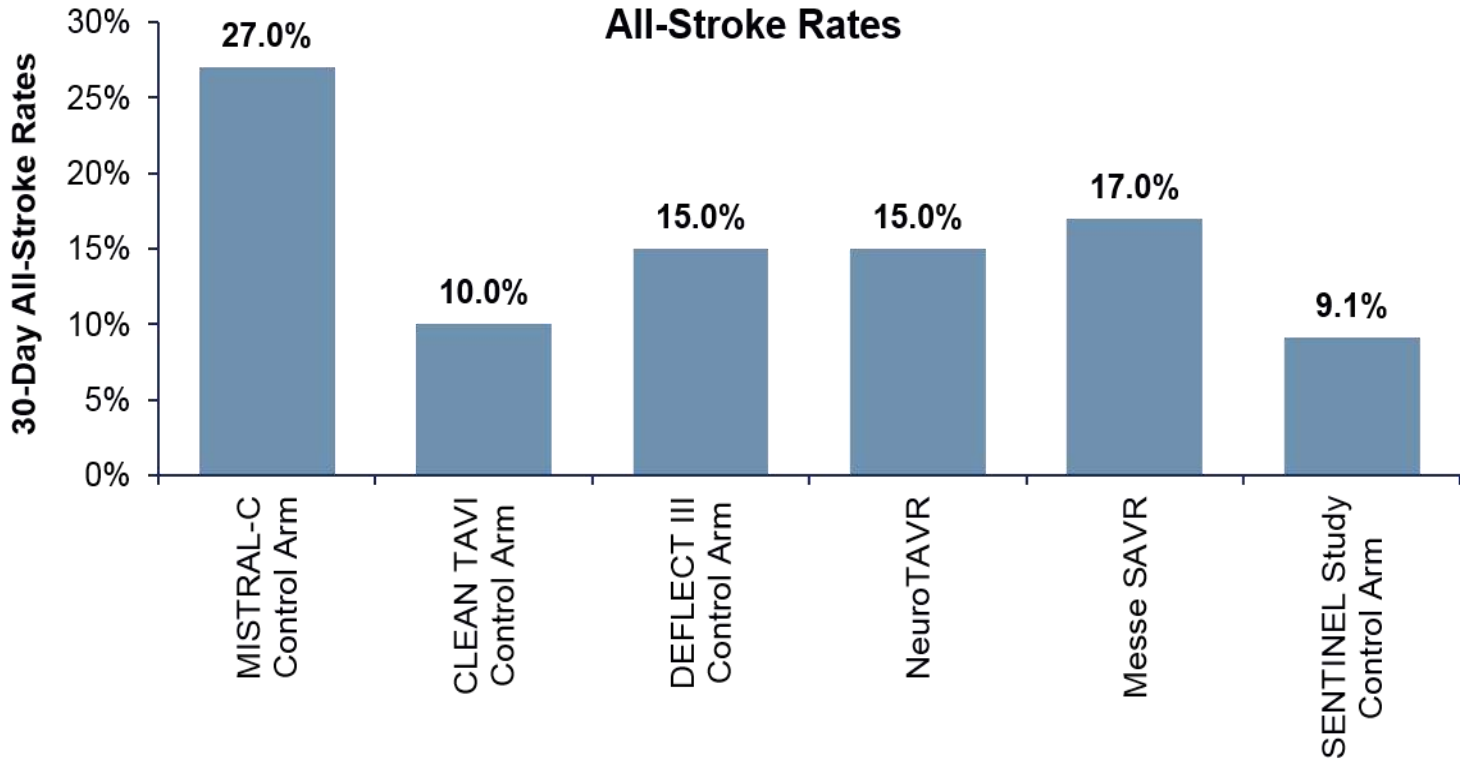
- Stroke remains an issue ***(~4.4% average rate)*** in contemporary TAVI studies.
- TAVI device trials tend to emphasize only the major/disabling stroke rates.



[1] Feldman, et al., EuroPCR 2017; [2]Manoharan, et al., J Am Coll Cardiol Intv 2015; 8: 1359-67; [3]Moellman, et al., PCR London Valves 2015; [4]Grube, et al., EuroPCR 2017; [5]Kodali, et al., Eur Heart J 2016; [6]Vahanian, et al., EuroPCR 2015; [7]Webb, et. al. J Am Coll Cardiol Intv 2015; 8: 1797-806; [8]DeMarco, et al, TCT 2015; [9]Meredith, et al., PCR London Valves 2015; [10]Falk, et al. Eur Heart J 2017; [11]Kodali, TCT 2016; [12]Reardon, M NEJM 2017; [13]Reichenspurner H, et al., JACC 2017; [14]Popma et al, JACC:CVInt 2017;10(3):268-75

Strokes Often Under-Recognized and Under-Reported in TAVI and SAVR

- True clinical stroke rates in TAVI and SAVR are likely higher than usually recognized and reported.
- Stroke definitions and classifications have changed over time with neuroimaging advances.[1-3]
- Most studies do not use routine imaging or proactive discharge exam by neurologists.
- Studies using routine discharge exam by neurologists show higher clinical stroke rates.[4]



[1]Mokin, *Expert Review Of Neurotherapeutics*, 2016, [2]Leon B *et al.* J Am Coll Cardiol, 2011;57:259-69,
[3]Kappetein A *et al.,* European Heart J., 2012;33:2403-18,' [4]Messé S, *et al.*, Circulation.2014;129:2253-61.

Stroke is a Procedural Issue

❖ TAVI stroke occurs peri-procedurally (< 72 hours).

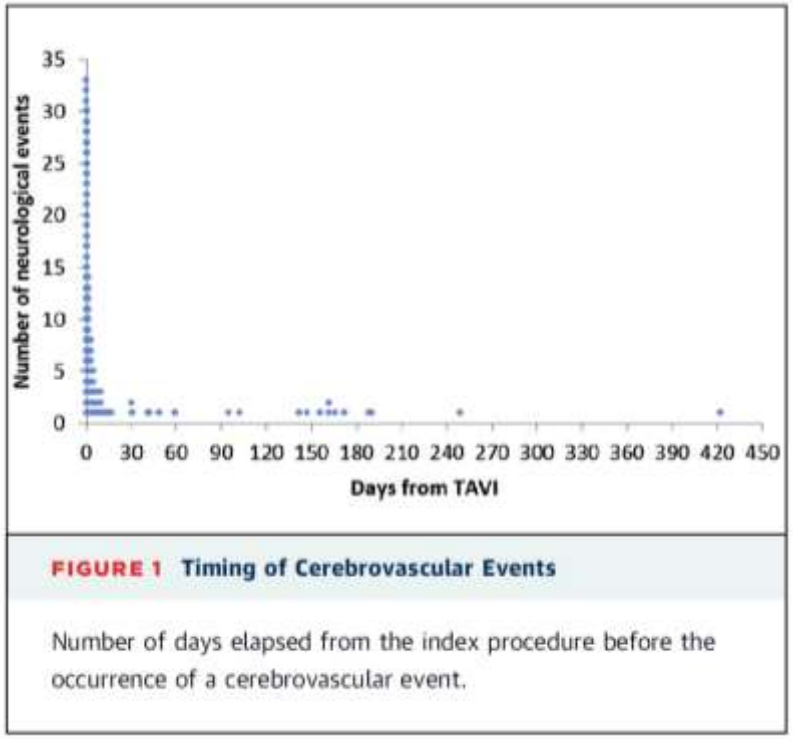


FIGURE 1 Timing of Cerebrovascular Events

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

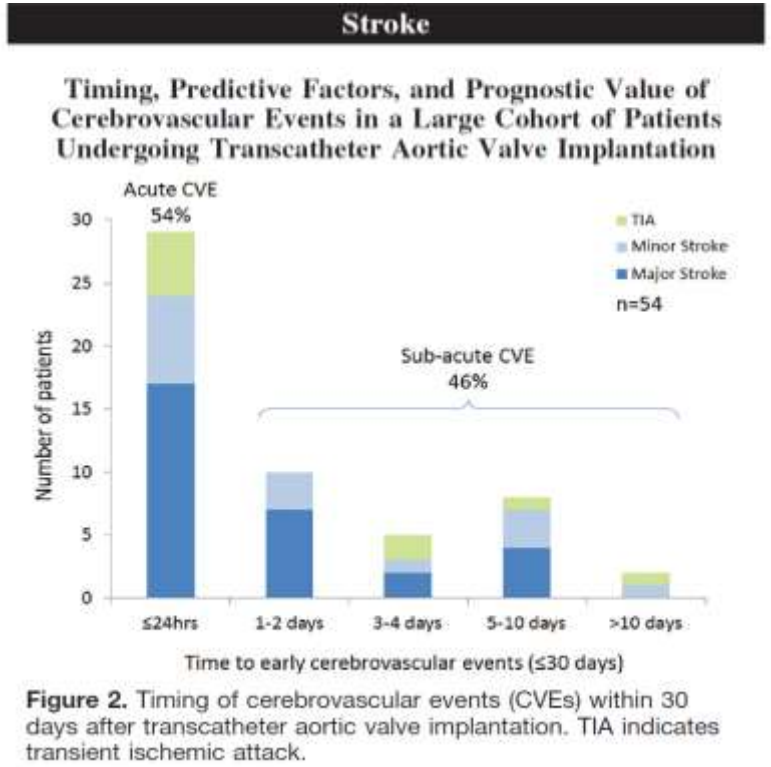


Figure 2. Timing of cerebrovascular events (CVEs) within 30 days after transcatheter aortic valve implantation. TIA indicates transient ischemic attack.

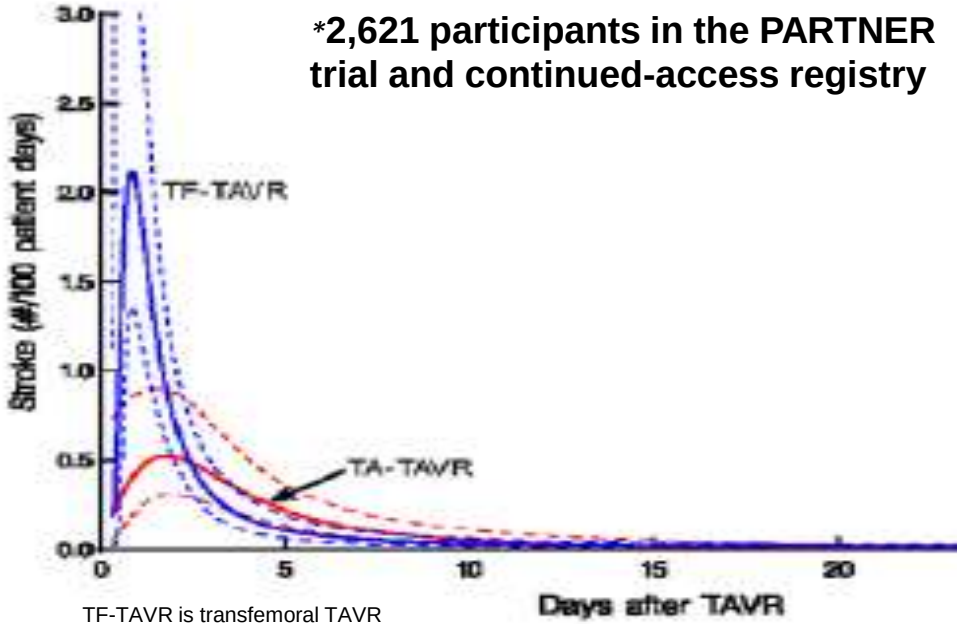
Multi-center cohort (n=1,061)[2]

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

[1]Tchétché et al. *J Am Coll Cardiol Intv* 2014
[2]Nombela-Franco et al., *Circulation* 2012

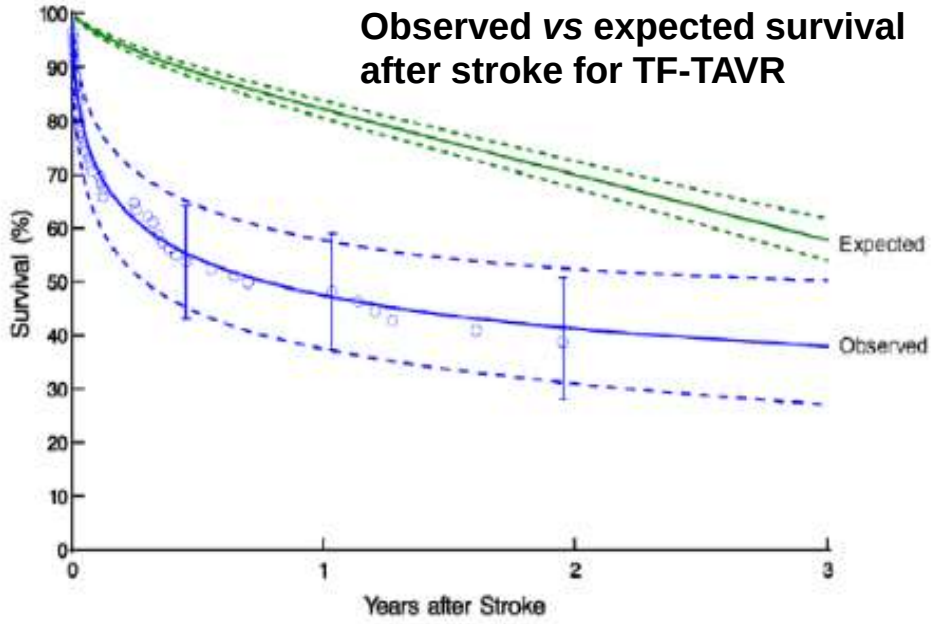
Timing, Risk Factors, Outcomes of Stroke, TIA after TAVI: PARTNER Data*

- Timing and impact of stroke and TIA after TAVI highlight the need for embolic protection devices, anti-platelet therapy and procedural modifications.
- Risk of stroke or TIA is highest early after TAVI (85% occurring within 1 week).
- Stroke and TIA after TAVI are associated with an increased risk of 1-yr mortality.



***2,621 participants in the PARTNER trial and continued-access registry**

TF-TAVR is transfemoral TAVR
TA-TAVR is transapical TAVR



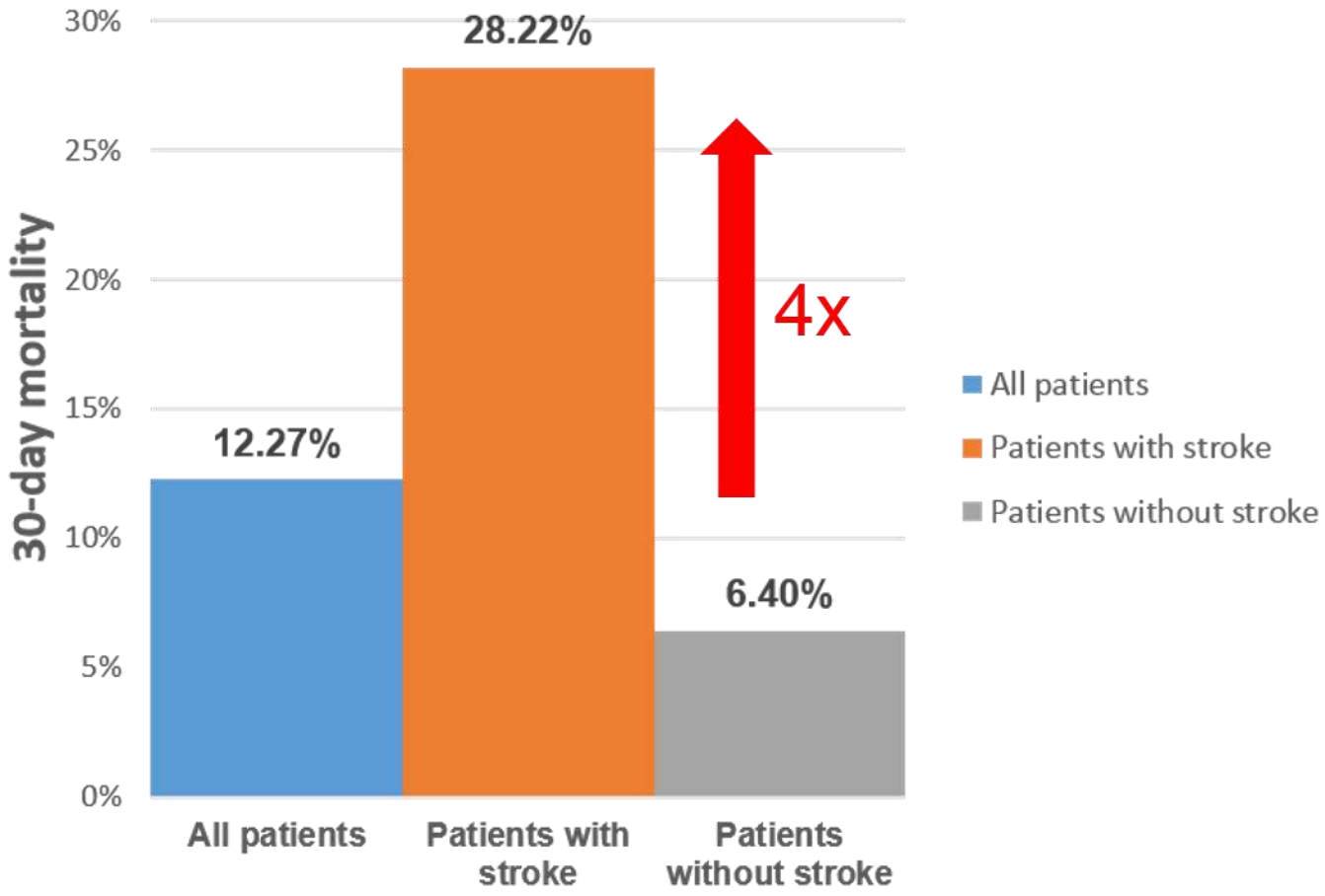
Observed *vs* expected survival after stroke for TF-TAVR

Patients experiencing a stroke or TIA had lower 1-year survival

- With stroke: 47% 1-yr survival vs 82% without for TF-TAVR
- With TIA: 64% 1-yr survival vs. 83% without for TF-TAVR

Meta-Analysis: TAVI Stroke and Mortality

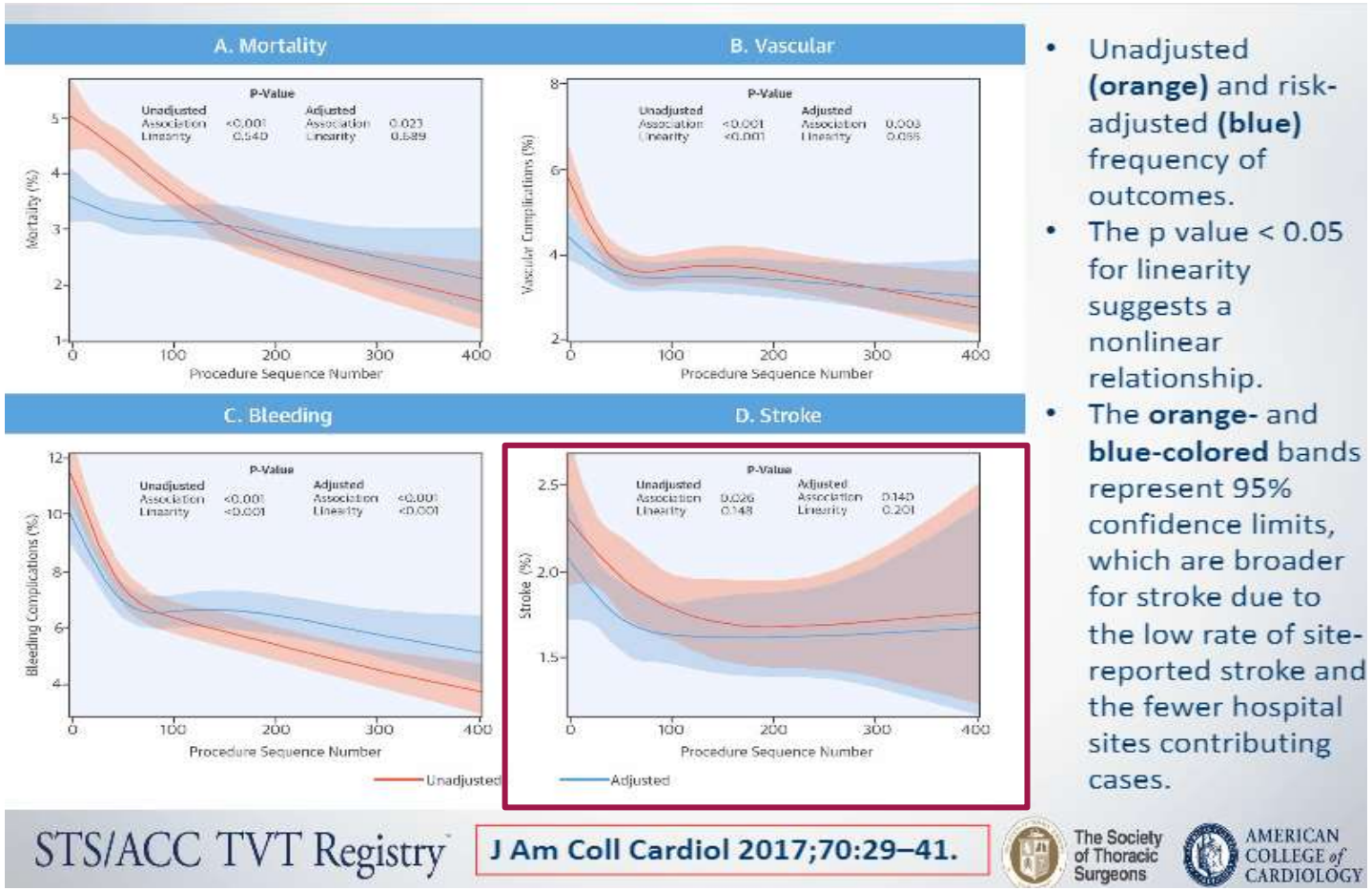
❖ Periprocedural stroke results in an increased 30-day mortality risk.



Stroke Risk is Independent of Experience and Operator Volume

- Increasing TAVI experience was generally associated with better outcomes.
- Increasing site volume was associated with lower in-hospital risk-adjusted outcomes, including mortality, vascular complications, and bleeding *but was not associated with stroke*.

- **TVT Registry**
  - Data from 42,988 commercial TAVI procedures conducted at 395 hospitals
  - Focus on helping sites improve quality of care through national benchmarks
- **Stroke remains a critical problem regardless of increasing TAVI experience.**



- 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.

Peri-procedural Complications Including Stroke Not Different Between Low and High Volume Hospitals

- A retrospective analysis of 9,924 patients who underwent non-emergent TF-TAVI demonstrated higher in-hospital mortality across low volume (<50 procedures/year) sites as compared to sites which perform ≥ 200 procedure/year.
- Major complications including cerebrovascular events were not different between low and high volume hospitals.

Annual number of TF-TAVI procedures	<50	50-99	100-149	150-199	≥200	*p*-value (Welch's test)
Number of hospitals	22	19	25	7	14	–
In-hospital mortality (%)	5.6±5.0	5.0±2.9	4.0±2.6	3.4±1.8	2.4±1.0	<0.001
Cerebrovascular event (%)	2.4±2.9	3.2±1.8	1.9±1.9	2.9±1.9	2.1±0.9	<0.001
Myocardial infarction (%)	0.1±0.5	0.5±1.1	0.3±0.6	0.1±0.2	0.3±0.4	0.1659
Low cardiac output (%)	4.2±6.5	3.0±2.8	2.2±2.2	2.6±2.6	0.9±0.7	<0.001
Resuscitation (%)	3.7±4.5	3.5±2.7	2.5±1.6	2.2±1.4	2.0±1.2	<0.001
Need for transient dialysis (%)	2.6±3.2	2.5±2.7	1.8±1.3	1.2±1.0	1.5±0.8	<0.001
Need for permanent dialysis (%)	1.7±2.7	2.5±3.3	2.0±1.7	0.6±1.0	1.9±1.3	<0.001
Overall length of stay (days)	19±6	20±5	17±3	15±3	14±4	<0.001
Days from TAVI to discharge	11±3	12±2	10±1	10±2	9±2	<0.001
Procedure times (min)	96.2±25.3	98.8±20.6	74.2±19.3	71.2±18.3	78.9±22.9	<0.001

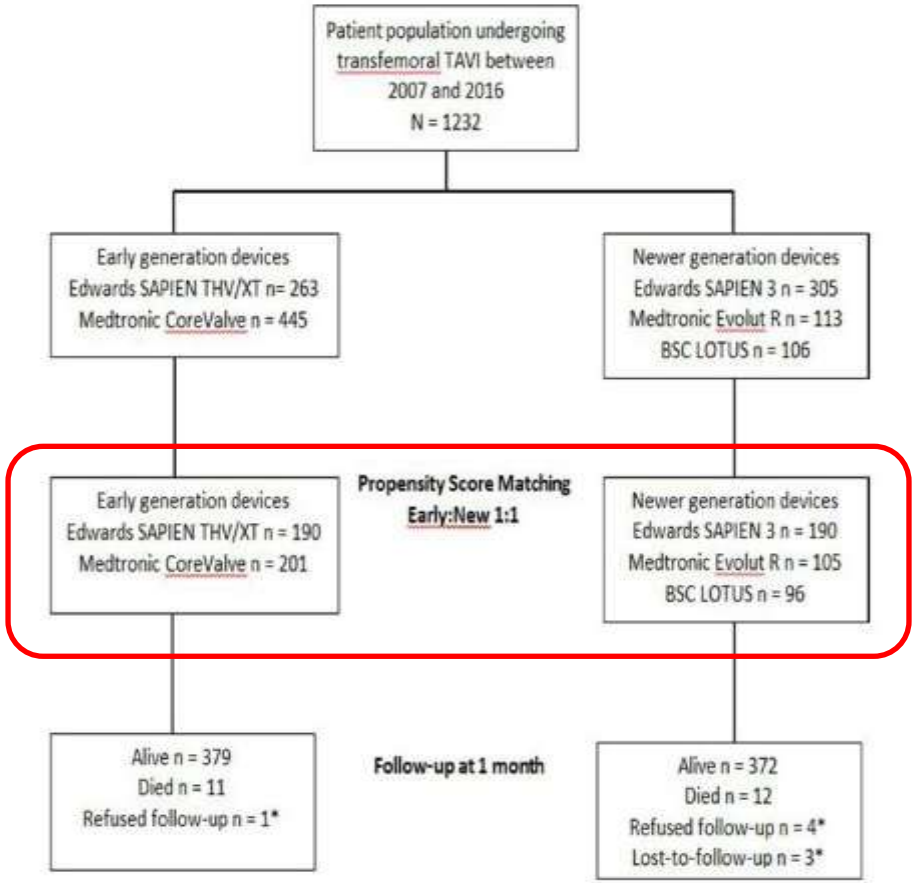
2014 data were compiled from 87 German hospitals via the German Quality Assurance Registry on Aortic Valve Replacement (AQUA).

Stroke Rates Are Not Declining With Newer Generation Valves

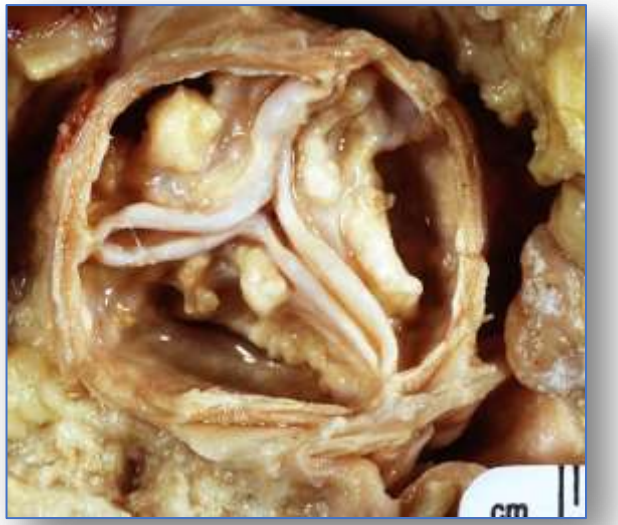
- Prospective, real-world registry with propensity-matched populations, 30-day safety and efficacy study of 782 patients undergoing TAVI via transfemoral access
- Stroke rates of 4.1% and 3.9% of early and newer generation THVs, respectively, were not statistically different.

	Early generation TAVI devices	Newer generation TAVI devices	Newer generation vs early generation	
			Crude	
	n=391	n=391	HR (95% CI)	P value
30-day follow-up				
Early safety composite end point, n (%)	83 (21.2)	81 (20.8)	0.98 (0.72 to 1.33)	0.876
All-cause death, n (%)	19 (4.9)	15 (3.9)	0.80 (0.41 to 1.58)	0.519
Cardiovascular death, n (%)	18 (4.6)	11 (2.8)	0.62 (0.29 to 1.31)	0.210
CVE, n (%)	17 (4.4)	17 (4.4)	1.00 (0.51 to 1.97)	0.989
Stroke	16 (4.1)	15 (3.9)	0.94 (0.47 to 1.91)	0.868
Disabling stroke	14 (3.6)	9 (2.3)	0.64 (0.28 to 1.49)	0.301
Non-disabling stroke	2 (0.5)	6 (1.6)	3.05 (0.61 to 15.09)	0.172
Transient ischaemic attack	1 (0.3)	2 (0.5)	2.02 (0.18 to 22.25)	0.567
Myocardial infarction, n (%)	2 (0.5)	2 (0.5)	1.00 (0.14 to 7.10)	1.000
All-cause death or CVE, n (%)	26 (6.7)	29 (7.5)	1.13 (0.66 to 1.91)	0.661

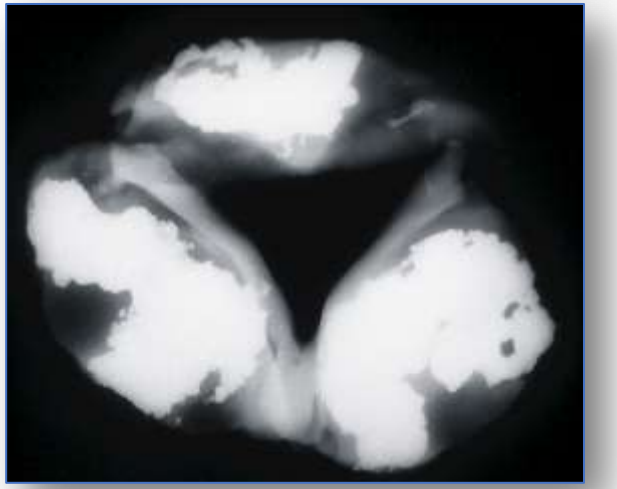
30-day outcomes were adjudicated by an independent CEC.



Cause of Procedural TAVI-Related Strokes – DEBRIS!



Autopsy Specimen of Aortic Valve

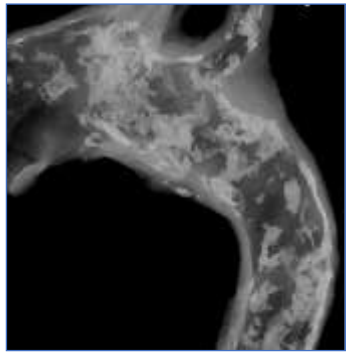


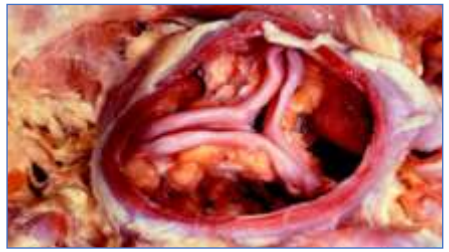
Radiograph of Surgical Specimen

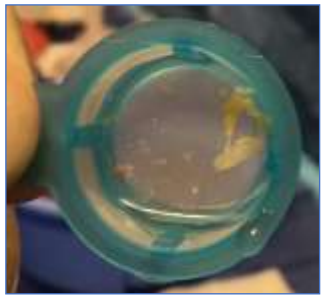
Sources of Debris During TAVI

ASCENDING ARCH
Arterial wall, calcific and atherosclerotic material

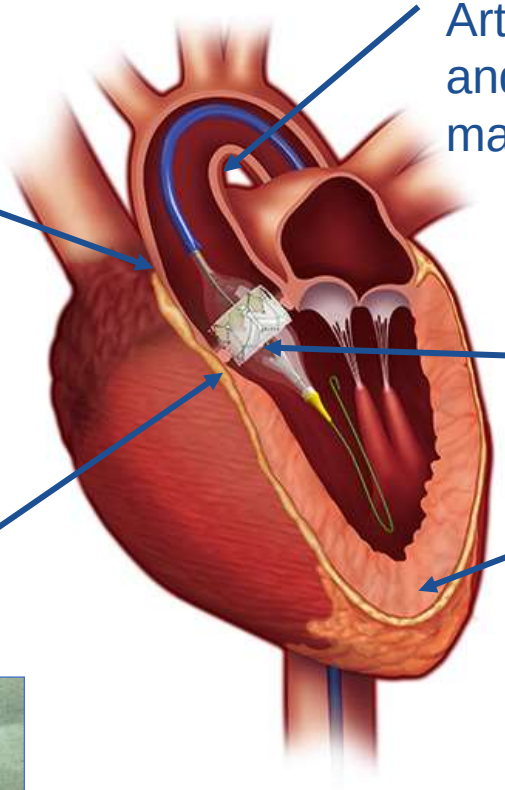
TRANSVERSE ARCH
Arterial wall, calcific and atherosclerotic material





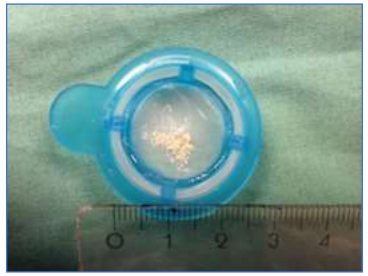


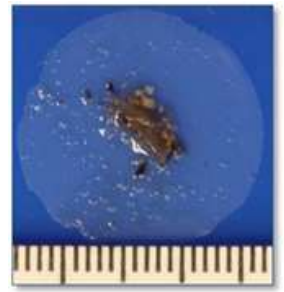
STENOTIC VALVE
Leaflet tissue and calcific deposits

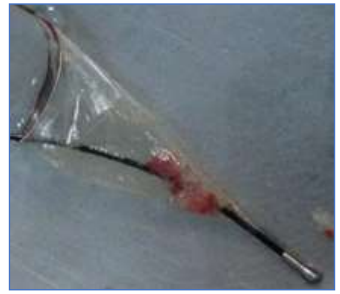


TAVI DEVICES
Foreign material

NATIVE HEART
Myocardium





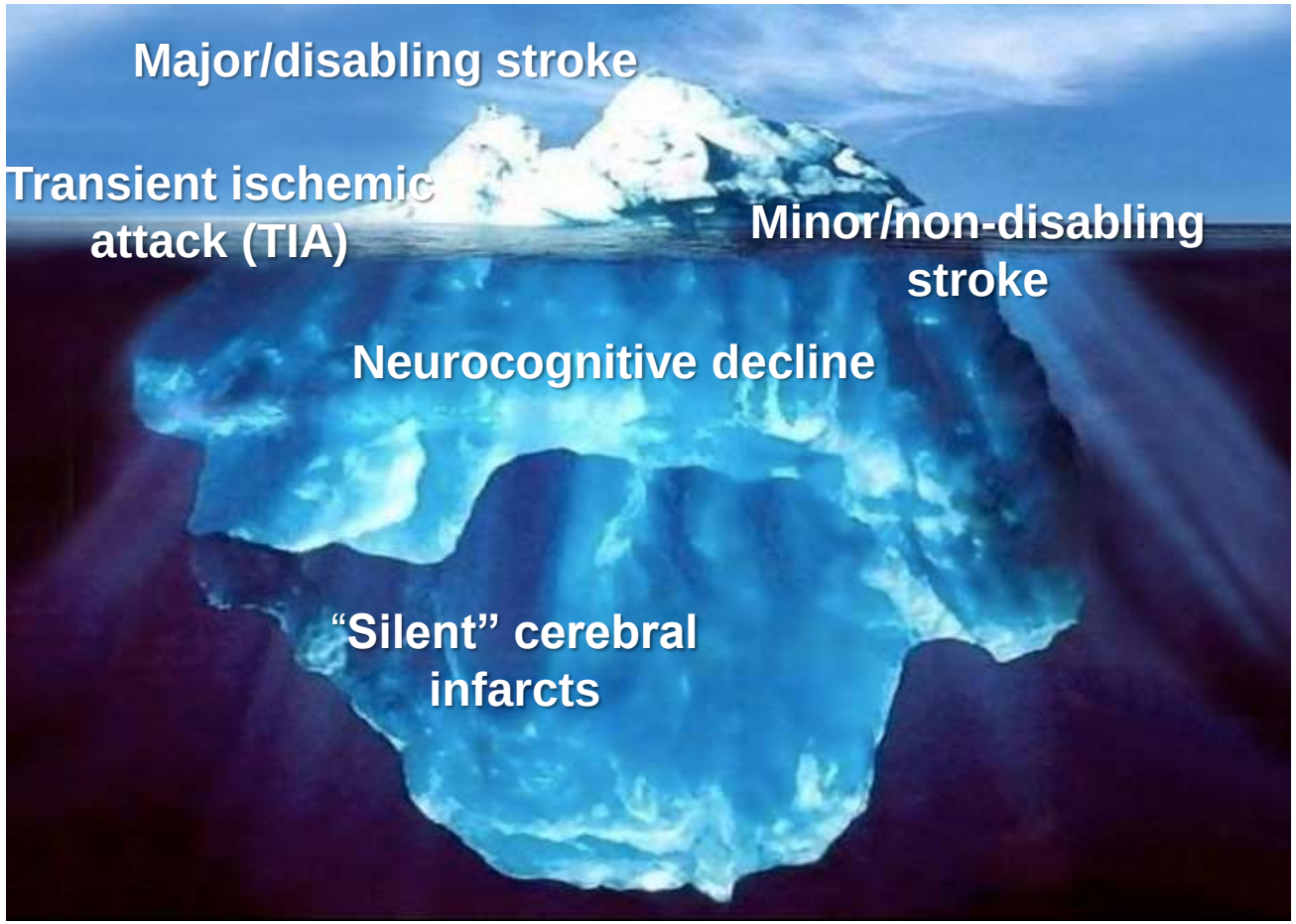


Most cerebral damage in TAVI is unseen

Clinically apparent

Subtle and often undetected

Clinically unrecognized



Clinical exam, NIHSS, mRS

MMSE, MoCA

Neurocognitive test batteries

Neuroimaging

….but can have far-reaching effects

Stroke Prevention

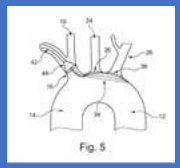
- Current State of Play -

Procedural Stroke Prevention

Optimized Anticoagulation

Embolic Protection

What are Some Options for Cerebral Protection in TAVR?

Company and Product	Claret Medical Sentinel 	Keystone TriGuard 	Edwards Embrella 	ICS Emblok 	Transverse Point-Guard 	Protembis ProtEmbo 
EU Status	CE Mark	CE Mark	CE Mark	FIM first clinical case March 15, 2017	Pre-clinical/prototype	Pre-clinical/prototype
US Status	• SENTINEL IDE completed 2016 • Positive FDA Panel - Feb 23, 2017 • **FDA Cleared - June 2017**	REFLECT IDE trial halted Aug 2017. Planning next trial (TRIFLECT)	No IDE yet	No IDE yet	No IDE yet	No IDE yet
Access	6 Fr Right Radial	9Fr TF	Right Radial	12Fr TF sheath	TF	6F TR
Debris	Captures and removes	Deflects downstream	Deflects downstream	Captures and removes	Deflects downstream	Deflects downstream
Placement and Interaction with TAVR devices	Not in aortic arch, minimizing device interaction	Sits in aortic arch. Devices must pass over and back across	Sits in aortic arch. Devices must pass over and back across	Deployed in ascending aorta. Does not protect during valve delivery and retrieval	Sits in aortic arch. Devices must pass over and back across	Sits in aortic arch. Devices must pass over and back across

Claret Medical™

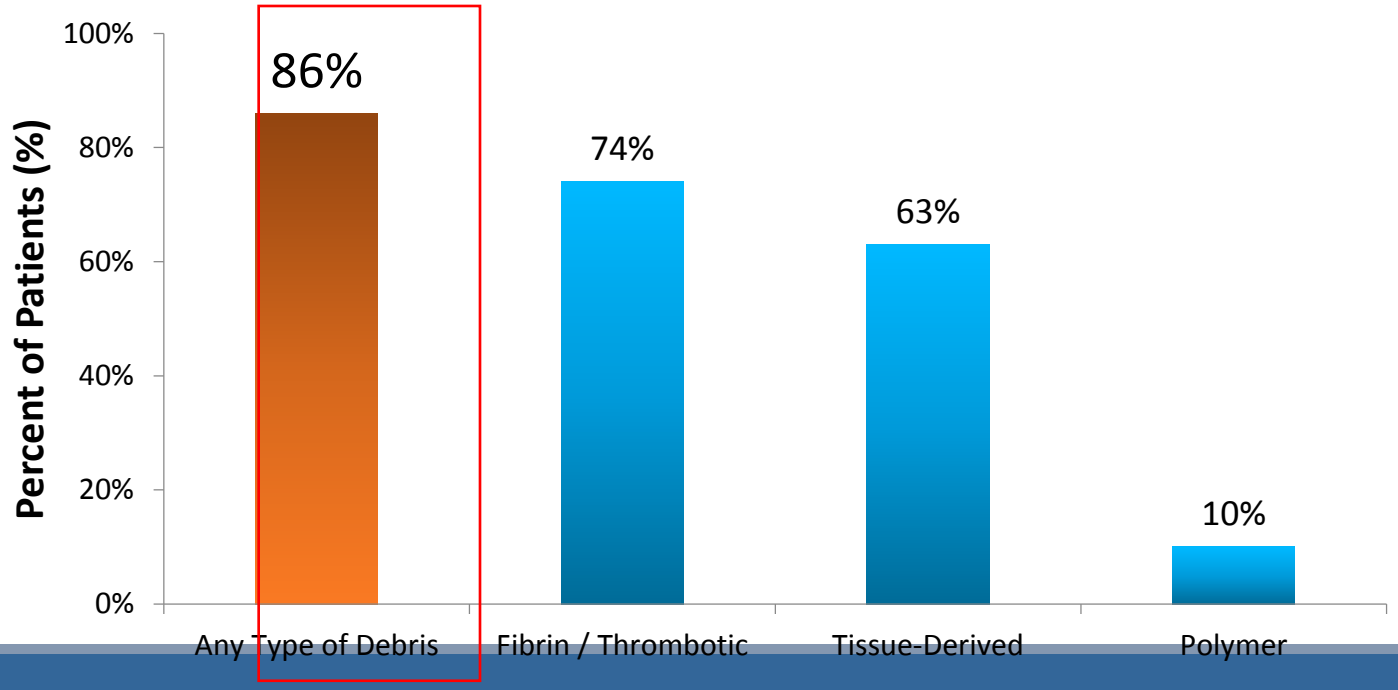
Sentinel™ Cerebral Protection System

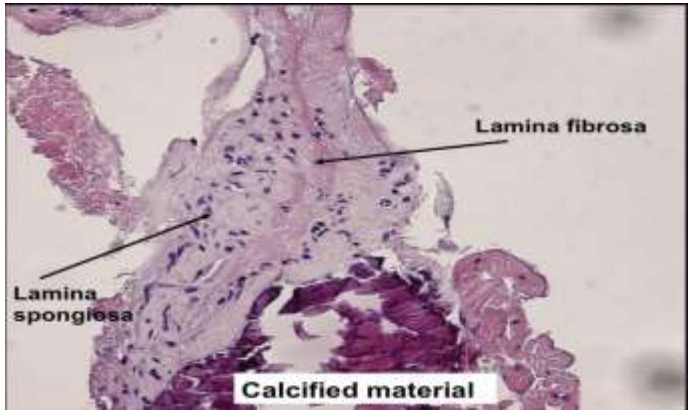
Neurologic Injury
How Does it Happen?

Van Mieghem, et al., placed Claret Montage filters into the brachiocephalic and left common carotid arteries during TAVR, and examined the contents after the procedure.

The key findings:

- ***Macroscopic debris was released into the circulation in ~90% of procedures***
- ***The debris was composed of thrombotic material, fragments of valve leaflet, calcified particles, myocardial tissue, and plastic fragments from interventional tools***





Debris and Fragments of aortic valve leaflet

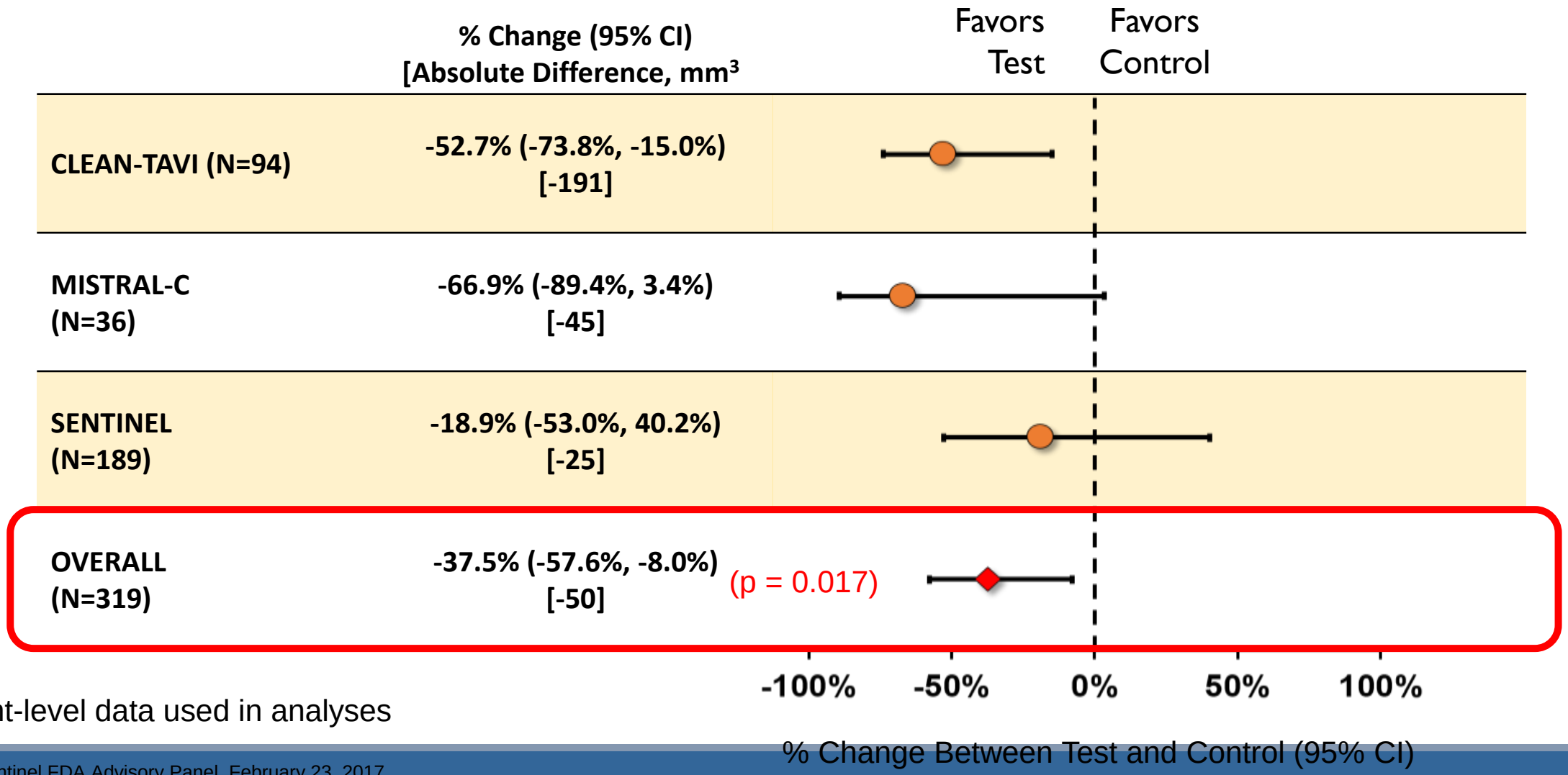
[1]Van Mieghem, et al., *J Am Coll Cardiol Intv* 2015; 8: 718-24

Published Reports on Effectiveness

Leading the Way with Clinical Evidence for Embolic Protection

Study	Principal Investigator	Location	# Patients	Trial Type	Procedure	Data
First in Man	Prof. Christoph Naber	3 centers in Brazil & Germany	40	Registry	TAVR (CoreValve & Sapien)	EuroIntervention March 2012
MISTRAL-I	Dr. Nicolas van Mieghem	Rotterdam, Netherlands	40	Registry	TAVR (CoreValve & Sapien)	Circulation October 2013
CLEAN-TAVI	Prof. Axel Linke	Leipzig University, Germany	100	Randomized	TAVR (CoreValve)	JAMA August 2016
MISTRAL-C	Dr. Nicolas van Mieghem	4 centers in Netherlands	74	Randomized	TAVI (Sapien 3)	Eurointervention June 2016
SENTINEL-H	Prof. Christoph Naber	10 centers in Europe	220	Registry	TAVR (All-comers)	Presented at EuroPCR 2016
SENTINEL IDE	Dr. Susheel Kodali, Dr. Samir Kapadia Dr. Prof. Axel Linke	17 centers in USA & 2 in Germany	363	Randomized	TAVR (Sapien XT, Sapien 3, CoreValve, EvolutR)	JACC Jan 2017
Sentinel-Ulm	Dr Jochen Wörhle	University of Ulm, Ulm, Germany	560	Prospective All-comers	TAVR (all commerc. available)	JACC Intv Sept 2017

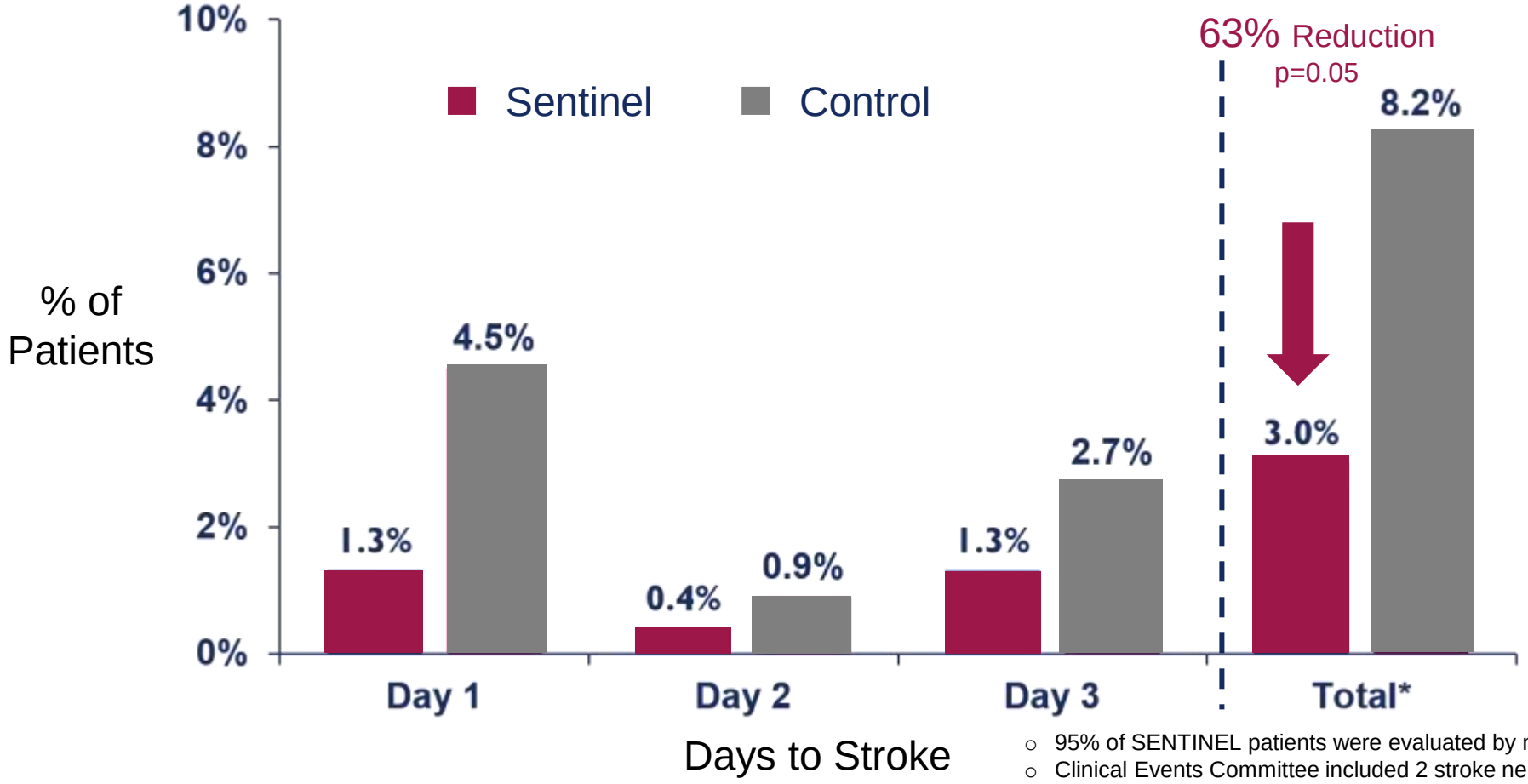
Meta-Analysis of Effectiveness*
Change in Mean New Lesion Volumes (Protected Territories)



*Patient-level data used in analyses

SENTINEL Study Demonstrates Peri-Procedural Stroke Reduction

Statistically significant 63% peri-procedural stroke reduction with Sentinel use

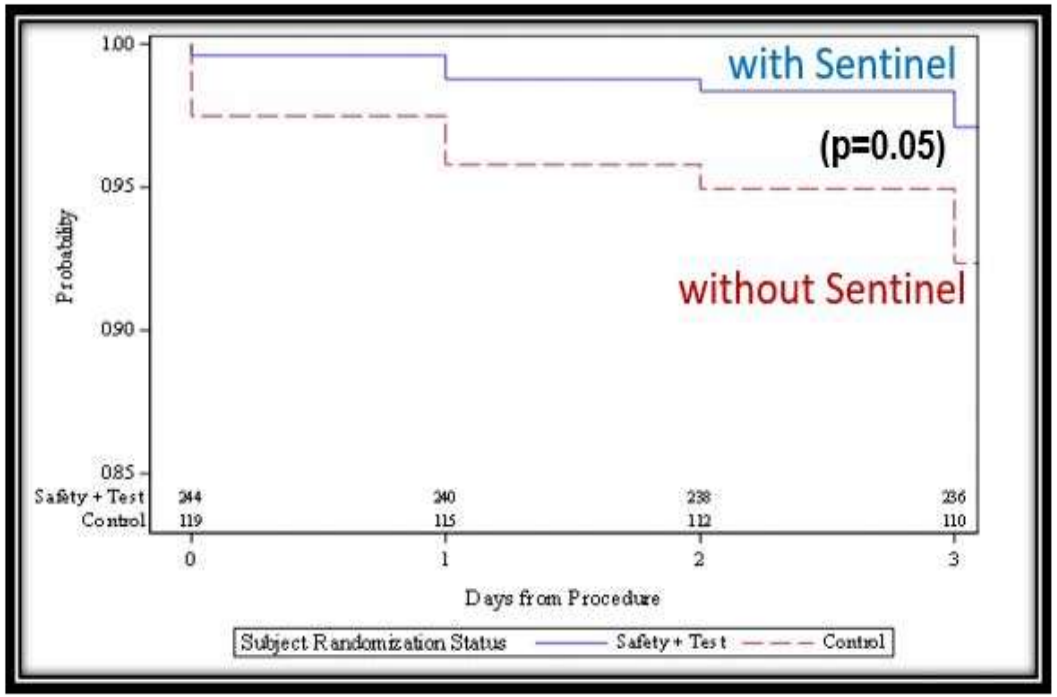


- 95% of SENTINEL patients were evaluated by neurologists
- Clinical Events Committee included 2 stroke neurologists

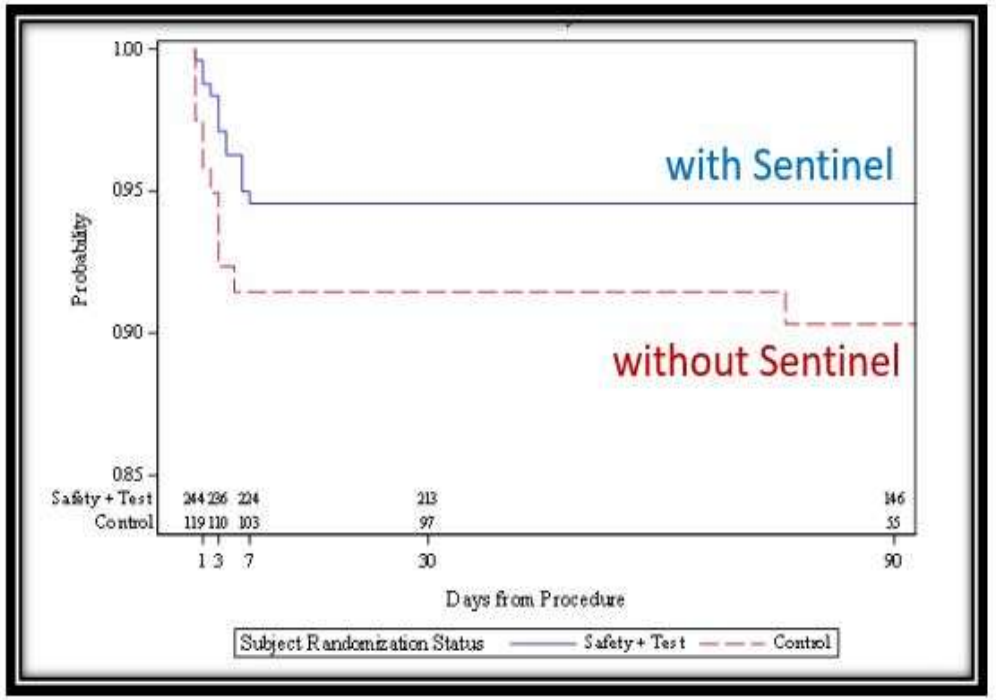
SENTINEL trial. Data presented at Sentinel FDA Advisory Panel, February 23, 2017

SENTINEL Study: Freedom from stroke – Kaplan-Meier curves

- Sentinel provides a significant treatment effect during the critical peri-procedural (≤ 72 hours) period.
- The treatment effect is preserved through 90 days post-procedure.



Through 3 days post-procedure



Through 90 days post-procedure

Data on file from the SENTINEL IDE Trial.

Methods – Meta-Analysis of Cerebral Protection Device (CPD) use in TAVI

- Literature search was conducted of all publications in PubMed and EMBASE databases and meta-analyses were performed, including:

Number of studies and patients included in meta-analysis	Broken out by CPD device as follows:
1225 patients	570 of the 1225 received an embolic protection device (Sentinel, Embrella, TriGuard)
6 total studies	2 prospective observational → **Sentinel Ulm (Sentinel)** PRO-TAVI-C (Embrella Embolic Deflector)
	4 RCTs → DEFLECT III (TriGuard) **MISTRAL-C (Sentinel)** **CLEAN TAVI (Sentinel)** **SENTINEL IDE (Sentinel)**

RCT = randomized controlled trial

Protection offers consistent reductions in new lesion volumes

1. **MISTRAL-C[1] - 65 patients RCT in 5 Dutch Centers**
   - PI: Dr van Mieghem
   - 3T MRI assessment at <u>baseline</u> & 2-5 days
   - 52% reduction in new lesion volume in whole brain


Effect of a Cerebral Protection Device on Brain Lesions Following Transcatheter Aortic Valve Implantation in Patients With Severe Aortic Stenosis
The CLEAN-TAVI Randomized Clinical Trial

2. **CLEAN-TAVI[2] – 100 Patients RCT in Single Center**
   - PI: Prof Linke
   - 3T MRI assessment at <u>baseline</u>, 2 days, 7 days
   - 41% reduction in new lesion volume in whole brain


Filter-based cerebral embolic protection with transcatheter aortic valve implantation: the randomised MISTRAL-C trial

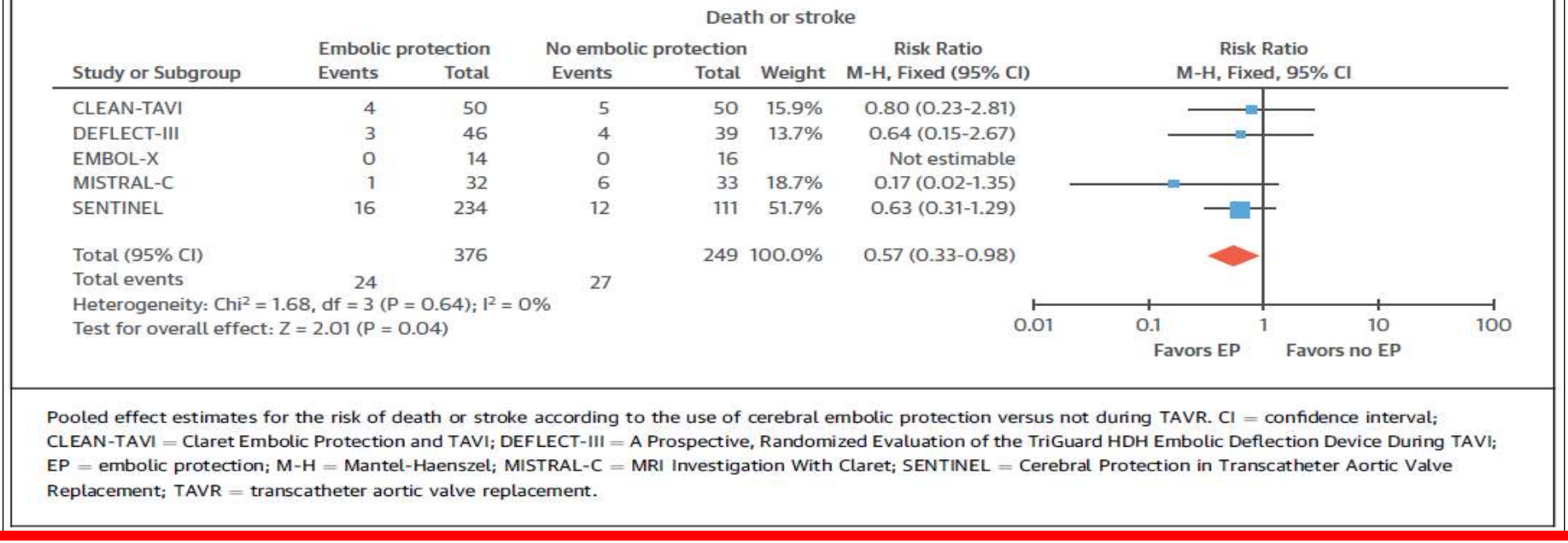
3. **SENTINEL[3] –363 patients RCT in 17 USA & 2 German centers**
   - Co-PIs: Drs Kodali, Kapadia & Linke
   - 3T MRI assessment at <u>baseline</u>, 2-7 days
   - 42% reduction in new lesion volume in whole brain

1. Van Mieghem N, et al. *EuroIntervention* 2016;12:499-507
2. Haussig, S, et al. *JAMA*. 2016;316(6):592-601
3. Kapadia, et al. *JACC*. doi: 10.1016/j.jacc.2016.10.023

Clinical Event Meta-Analysis of Cerebral Embolic Protection RCTs in TAVI

Shows significant >40% reduction in risk of stroke or death with protection

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



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.

- Meta-analysis of 5 randomized controlled trials (RCT) including 625 patients (376 with and 249 without protection)
- >40% reduction in risk of stroke or death (6.4% vs 10.8%; RR: 0.57; 95% CI: 0.33-0.98; p=0.04; I^2 = 0%)
- Number-needed-to-treat (NNT) = 22 patients treated to reduce one stroke or death with cerebral embolic protection

"In conclusion, the totality of the data suggests that use of embolic protection during TAVI appears to be associated with a significant reduction in death or stroke."

RESPOND post-market study: *Impact of embolic protection and repositioning on stroke in patients treated with the Lotus Valve*

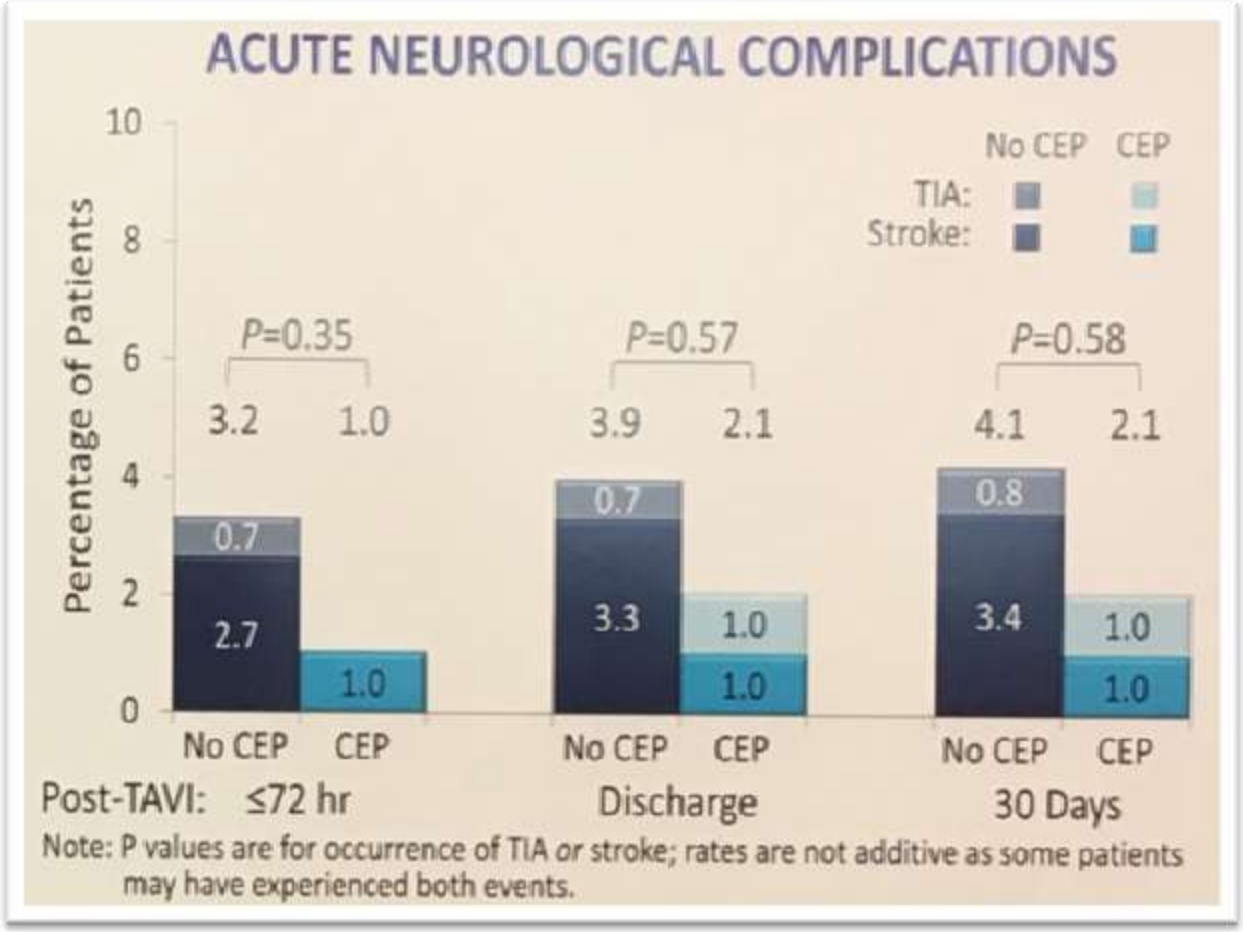
- Cerebral embolic protection (CEP) was associated with a *numerically lower rate of neurological events through 30 days.*
- Valve repositioning did not impact increased risk of stroke regardless of CEP use.

Primary endpoint: All-cause mortality at 30 days & 1 yr

Study Design:

- Prospective, single arm
- 996 patients treated with Lotus Valve
- CEP used in 9.6% (96/996)
- Valve repositioning occurred in 31.4% (313/996)

Strokes adjudicated by an independent medical reviewer



RESPOND post-market study: Zero incidence of stroke in patients treated with embolic protection regardless of valve repositioning

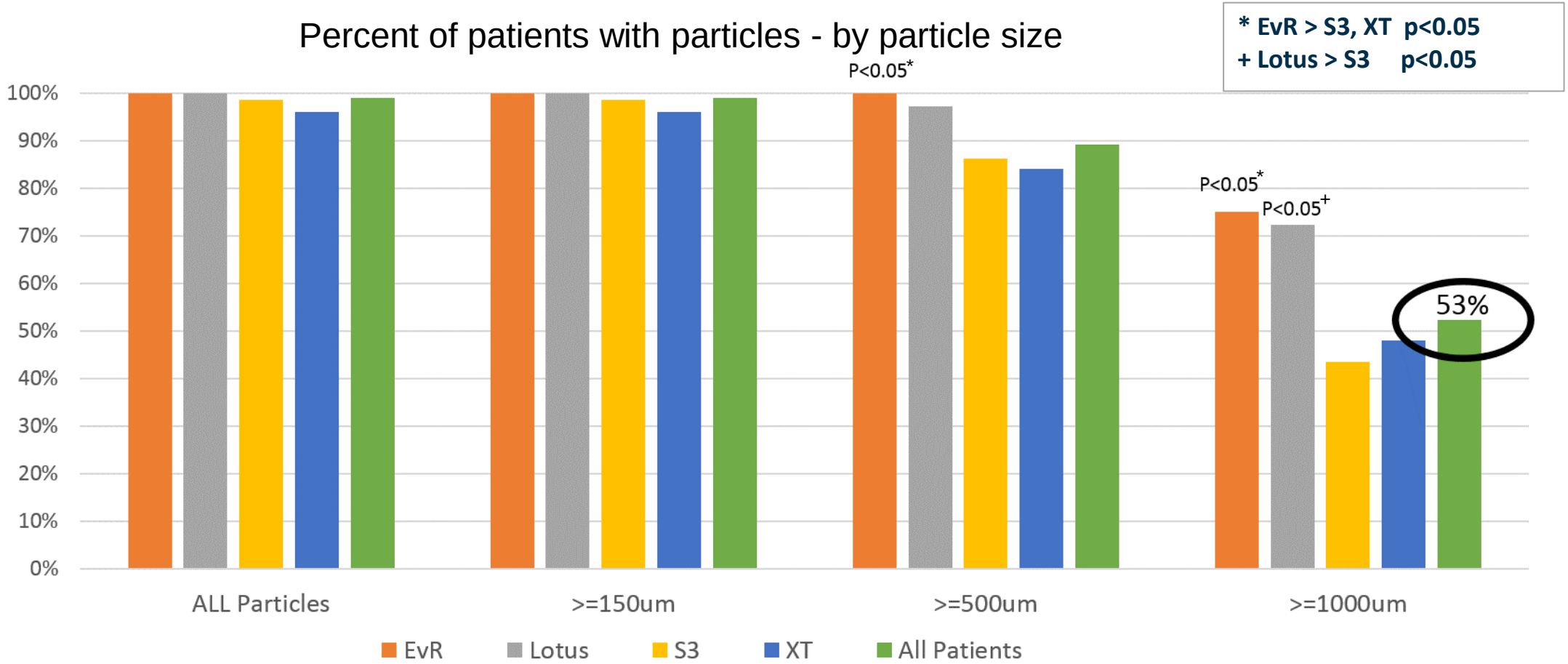
- Cerebral embolic protection (CEP) was associated with a *numerically lower rate of neurological events through 30 days.*
- Stroke rates were numerically higher with repositioning but differences did not reach statistical significance.
- Valve repositioning did not impact increased risk of stroke regardless of CEP use.

PATIENTS WITH CEP (N=96)	No Repositioning (n=64)	Repositioning (n=32)	P Value
≤72 hr, all stroke	1.6% (1)	0.0% (0)	1.00
≤72hr, disabling stroke	0.0% (0)	0.0% (0)	-
Discharge, all stroke	1.6% (1)	0.0% (0)	1.0
Discharge, disabling stroke	0.0% (0)	0.0% (0)	-
PATIENTS WITHOUT CEP (N=900)	**No Repositioning (n=619)**	**Repositioning (n=281)**	P Value
≤72 hr, all stroke	2.6% (16)	2.9% (8)	0.81
≤72hr, disabling stroke	1.8% (11)	2.5% (7)	0.47
Discharge, all stroke	3.2% (20)	3.6% (10)	0.80
Discharge, disabling stroke	2.1% (13)	3.2% (9)	0.32

Wohrle, TCT 2017

Sentinel Captures Debris Regardless of TAVR Valve System

❖ Automated histomorphometry shows debris generated regardless of valve type placed



- Using pooled data from the SENTINEL IDE and SENTINEL H trials, histopathology and histomorphometry measured particle size, count and area of debris captured in 492 filters from 246 patients.

Note: 150µm used as size cut-off as filter pore size is 140µm

Schmidt T et al. TCT 2017, (*manuscript in preparation*)

Shall we wait for conclusive Data before we use CEP routinely?

Let’s use them until Data prove otherwise!

Thank you for your Attention !