Comprehensive Review of the Sentinel Cerebral Embolic Protection Program

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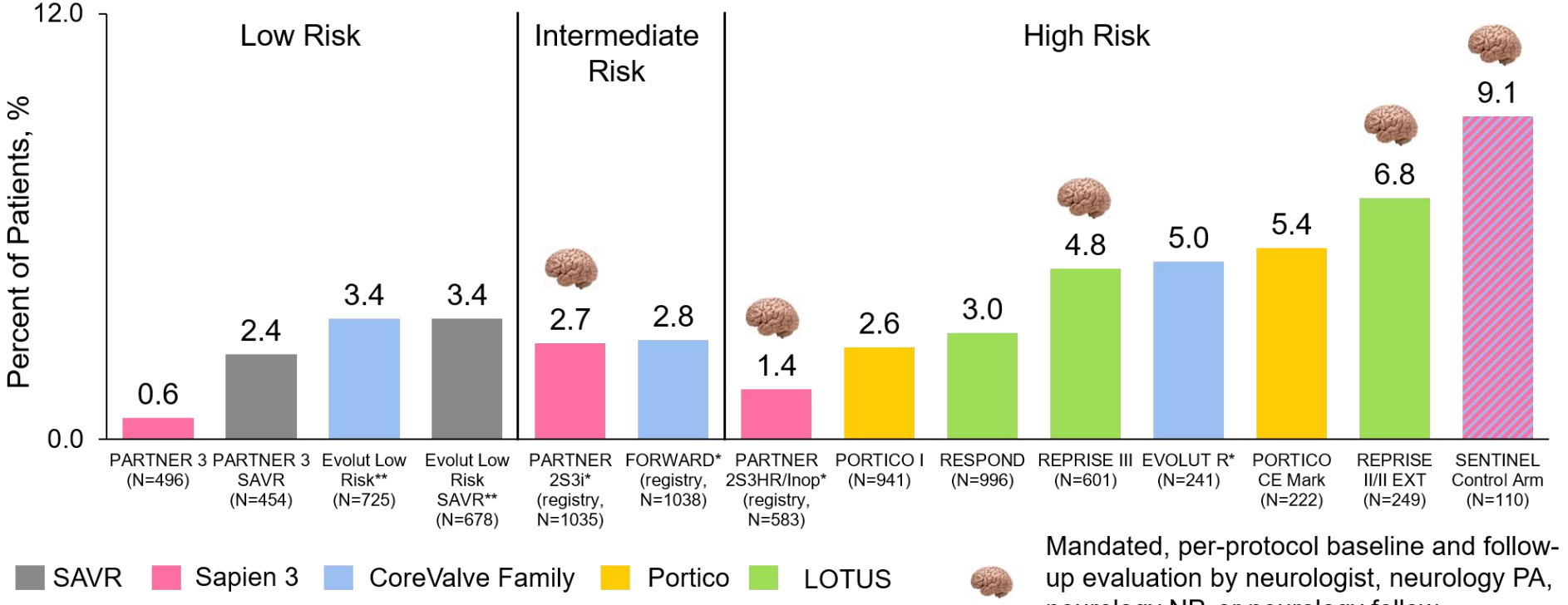
Disclosure Statement of Financial Interest

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**
Speakers´Honoraria	Boston Scientific

Stroke remains an issue in contemporary TAVR trials



*Kaplan Meier estimates; **Bayesian estimate; PA=physician assistant; NP=nurse practitioner; SENTINEL: Kapadia JACC 2017 (95% of patients were evaluated pre- and post-TAVR by neurologists, and stroke neurologists were on the CEC); Evolut Low Risk: Popma NEJM 2019 (<2% of TAVR patients received an embolic protection device); PARTNER 3: Mack NEJM 2019; PORTICO CE Mark: Linke, Circ Cardiovasc Interv 2018 (Supplement); ; PORTICO I: Sondergaard JACC 2018; EVOLUT R: Popma, JACC Cardiovasc Interv 2017; FORWARD: Grube, JACC 2017 (an embolic protection device was used in 4.1% of patients); PARTNER 2S3i: Thourani, Lancet 2016; PARTNER 2S3HR/Inop: Kodali Eur Heart J 2016; REPRISE II/II Ext: Meredith, EuroIntervention 2017; REPRISE III: Feldman JAMA 2018; RESPOND: Van Mieghem, JACC Cardiovasc Interv 2019; Results from different studies are not directly comparable. Information provided for educational purpose only.

Most Stroke is Related to the Procedure

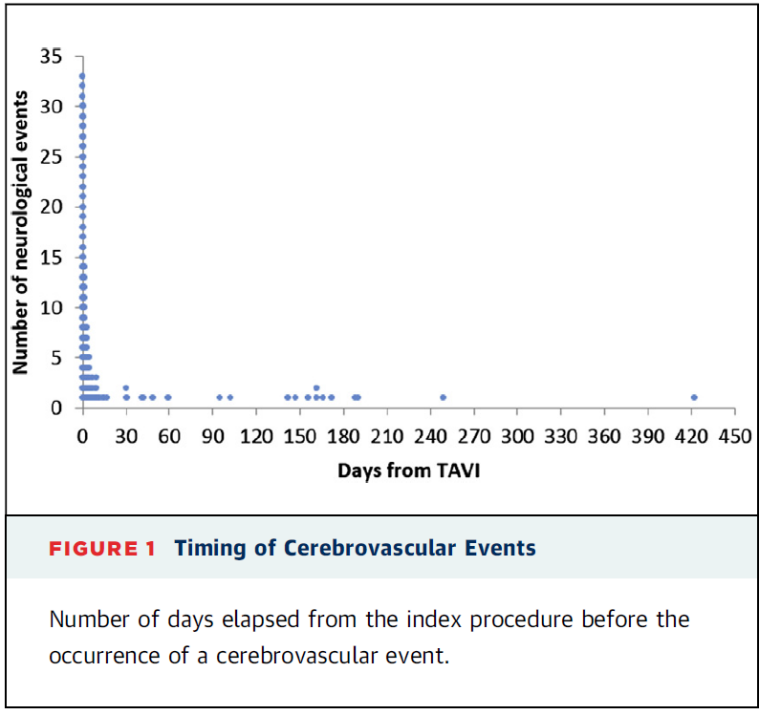


FIGURE 1 Timing of Cerebrovascular Events

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

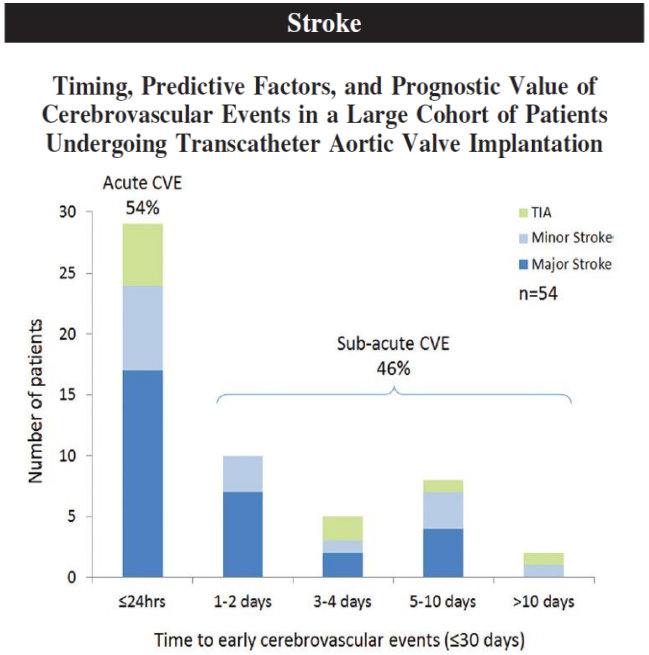


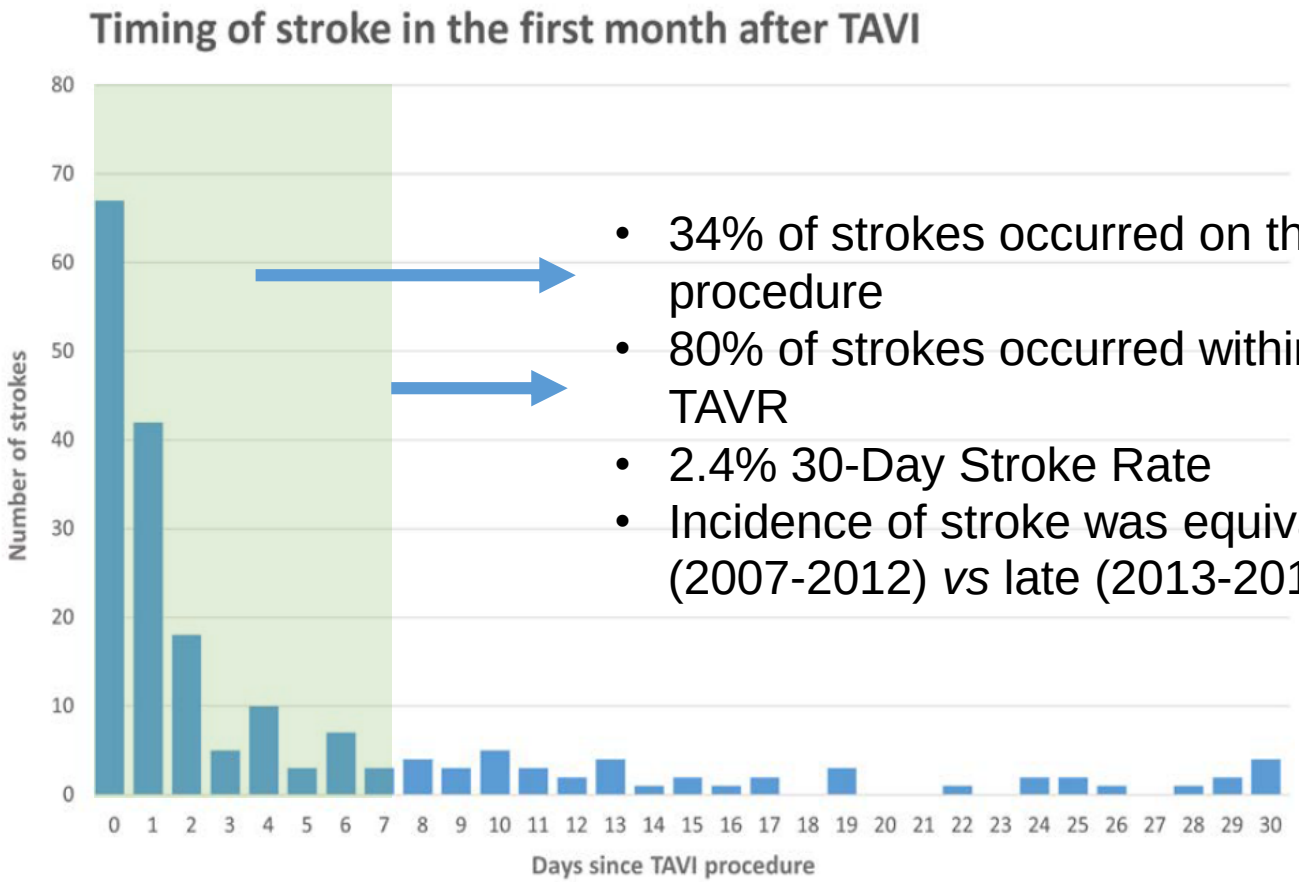
Figure 2. Timing of cerebrovascular events (CVEs) within 30 days after transcatheter aortic valve implantation. TIA indicates transient ischemic attack.

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

80% of TAVR-Related Stroke Occurred in the First Week After TAVR

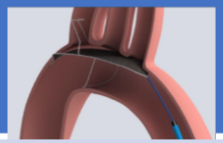
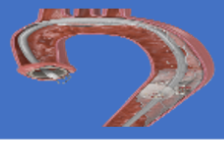


- 34% of strokes occurred on the day of the TAVR procedure
- 80% of strokes occurred within the first week after TAVR
- 2.4% 30-Day Stroke Rate
- Incidence of stroke was equivalent in early (2007-2012) *vs* late (2013-2018) years

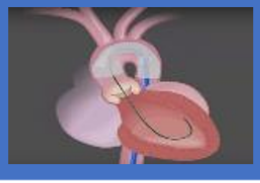
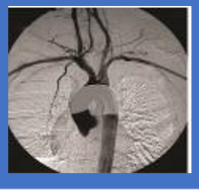
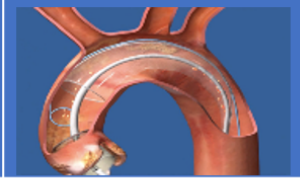
N=10982 patients undergoing TF-TAVR with Edwards' balloon-expandable valves or Medtronic self-expanding valves between 2007-2018 from 3 national registries and 7 local registries or prospective clinical trials

Vlastra, W. et al. *Circ Cardiovasc Interv* 2019; 12:e007546

Landscape of cerebral protection devices

Company and Product	Boston Scientific Sentinel CPS	Keystone TriGuard	Protembis ProtEmbo CPS	ICS Emblok	Filterlex Medical Filterlex	Emboline Emboliner
						
EU Status	CE Mark	CE Mark	FIM Q3'18	FIM Q3 2018 EU Feasibility study underway Q1 2019	Pre-clinical/prototype	CE Mark study FIM Q2 2018
US Status	FDA Clearance June 2017	Reflect II Trial underway, Q2 2019	No IDE yet	IDE planned for Q3'19	No IDE yet	No IDE yet
Access	6 Fr Right Radial	9Fr TF	6 Fr Left Radial	11Fr TF sheath	TF	6Fr TF
Debris	Captures and removes	Deflects downstream	Deflects downstream	Captures and removes	Dual deflector/capture system	Dual deflector/capture system
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. Device must pass over and back across	Sits in aortic arch. Device must pass over and back across

Landscape of cerebral protection devices continued

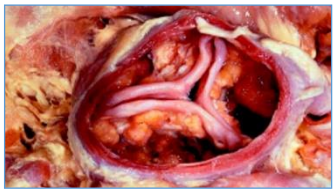
Company And Product	Transverse Medical PointGuard	Edwards Embrella	CardiOptis Embolisher	Capricon	TransAortic Capture System
					
EU Status	No CE Mark	CE Mark	Pre-clinical/prototype	Pre-clinical/prototype	Pre-clinical/prototype
US Status	No IDE yet	No IDE planned	No IDE yet	No IDE yet	No IDE yet
Access	TF	Right Radial	TF	TF - no other data avail	TF – no other data avail
Debris	Deflects downstream	Deflects downstream	Captures and removes	Deflector? Capture system?	Deflector?
Placement and interaction with TAVR devices	Sits in aortic arch. Devices must pass over and back across	Sits in aortic arch. Devices must pass over and back across	Placed in in aortic arch; device must pass over and back across	Appears to sit in the arch. Device must pass over and back across	Sits in aortic arch. Device must pass over and back across

SENTINEL Cerebral Protection System (CPS)

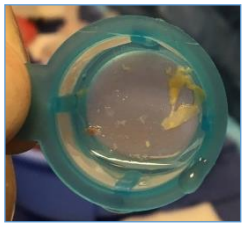
- Two independent filters capture & remove embolic material
- Polyurethane filter, pore size = 140 µm
- Standard right trans-radial sheath access (6F)
- One size accommodates most vessel sizes; fits ~90% of anatomies
- Deflectable compound-curve catheter facilitates cannulation of LCC
- Minimal profile in aortic arch (little interaction with other devices)

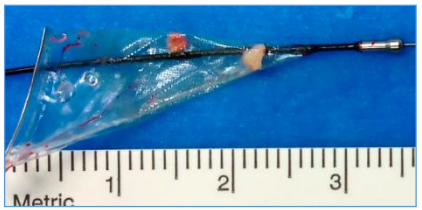
Sources of Debris During TAVR

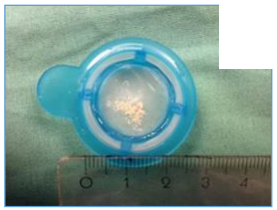
ASCENDING ARCH
Arterial wall, calcific and atherosclerotic material

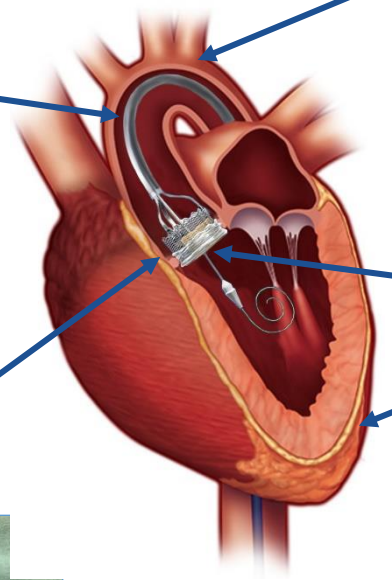


STENOTIC VALVE
Leaflet tissue and calcific deposits

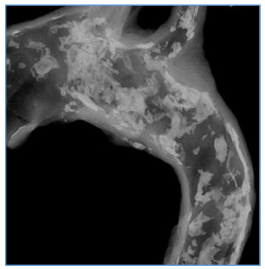






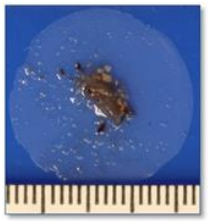


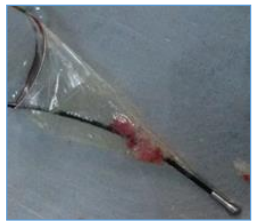
TRANSVERSE ARCH
Arterial wall, calcific and atherosclerotic material



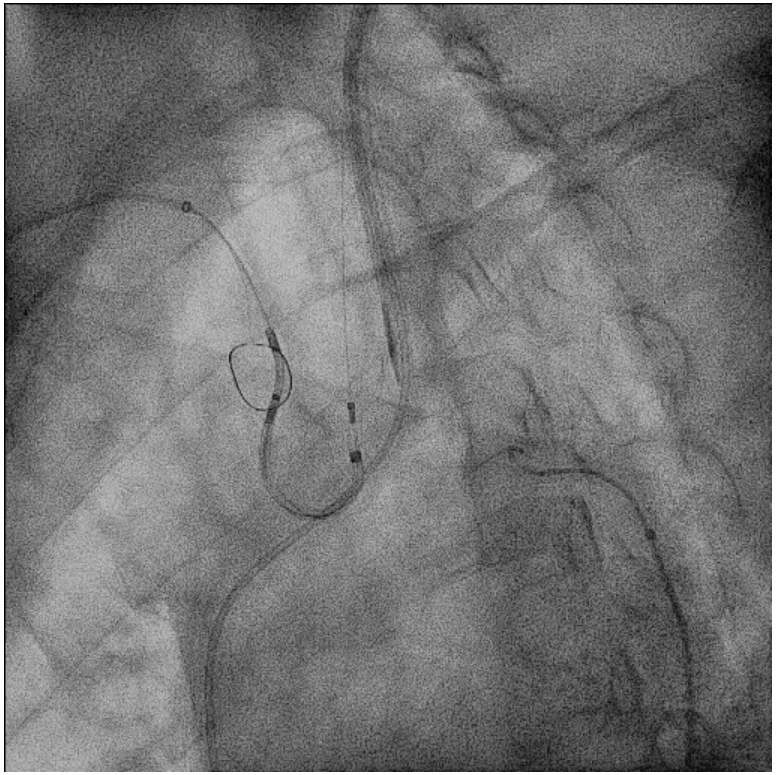
TAVR DEVICES
Foreign material

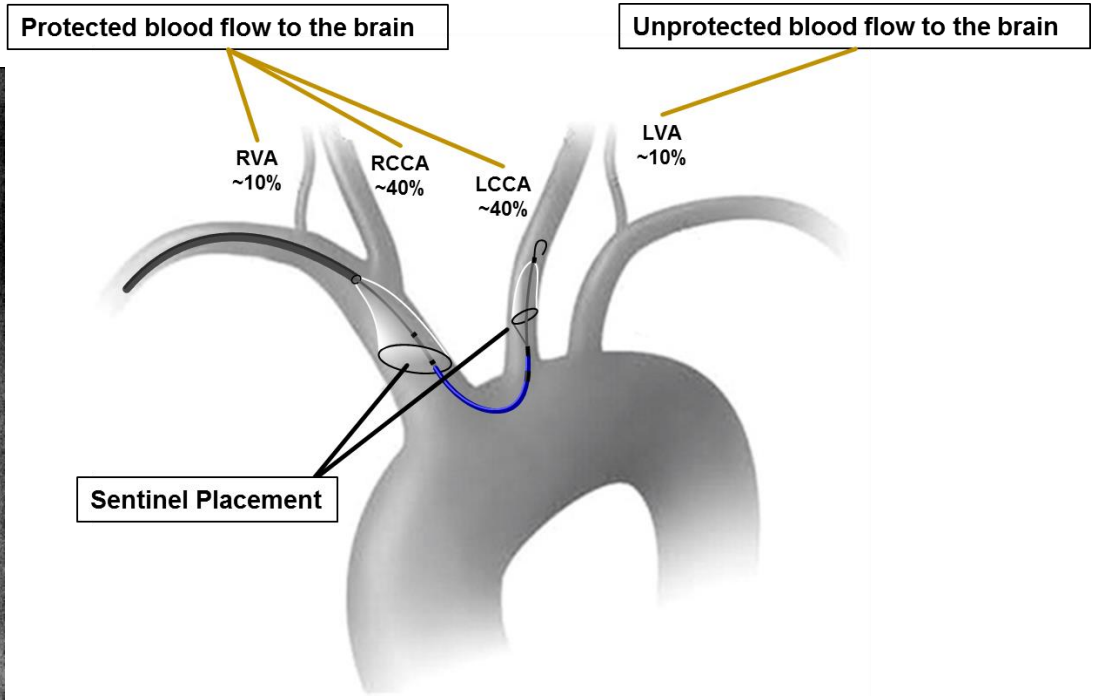
NATIVE HEART
Myocardium





SENTINEL CPS Filters >90% of Blood Flow to Brain





Zhao M, et al. *AJNR* 2007

SENTINEL CPS leads the way with clinical evidence for embolic protection in TAVR

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	TAVR (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 Prof. Axel Linke	17 centers in USA & 2 in Germany	363	Randomized	TAVR (Sapien XT, Sapien 3, CoreValve, EvolutR)	JACC Jan 2017
SENTINEL-Ulm	Prof. Jochen Wöhrle	University of Ulm	560	Registry Propensity-Score Matched	TAVR (All-comers)	JACC: CVInt 2017
Patient-level Meta-analysis	PD Dr. Julia Seeger	19 centers world-wide	1306	Propensity – score matched	TAVR (All-comers)	European Heart Journal 2019

Consistent “Real-World” Single Center Experience

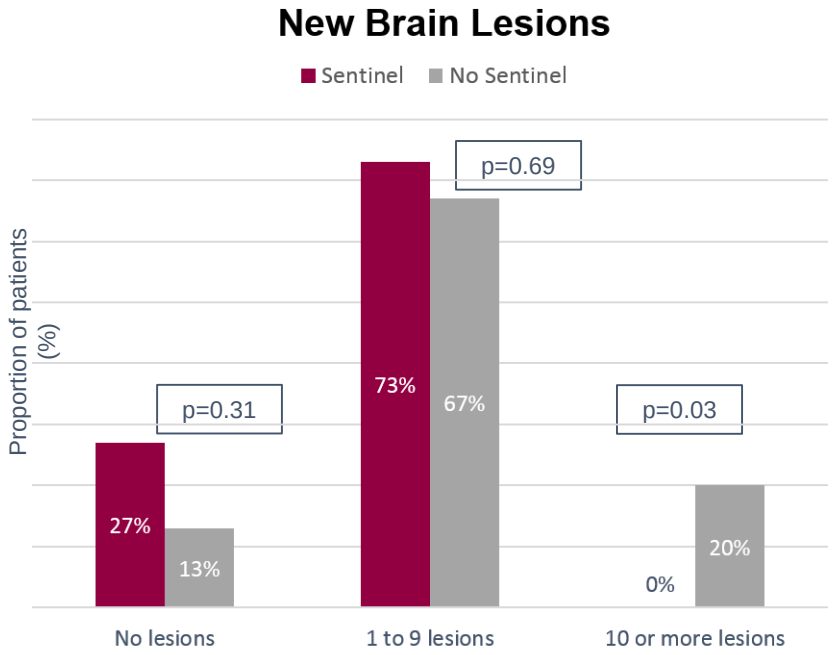
- SENTINEL CPS in real-world practice is consistently associated with a reduction in clinically assessed neurological events.
- Data from more than 2,000 TAVR patients across three independent centers show reproducible results.

Study Center • Total N • Timing	Unprotected TAVR Patients Neurological Event Rate % (n/N)	SENTINEL TAVR Patients Neurological Event Rate % (n/N)	Relative Risk Reduction (RRR)	Number-needed-to-treat (NNT) to avoid one event	Notes
Ulm University[1] • N=560 • May 2017	4.6% (13/280)	1.4% (4/280)	70%	21	Propensity-score-matched All-stroke at 7-days
Erasmus and University Med Centers in Rotterdam and Groningen[2] • N=1047 • June 2018	5.4% (32/589)	1.4% (7/485)	74%	25	All-stroke + TIA at 3-days
	3.6% (21/589)	0.8% (4/485)	78%	36	Disabling stroke at 3-days
Cedars Sinai[3] • N=618 • Sep 2018	4.9% (8/162)	1.1% (5/456)	78%	26	All-stroke at 7-days

[1]Seeger J, et al. *JACC Cardiovasc Interv.* 2017 Nov 27;10(22):2297-2303; [2]Van Mieghem N, presented at TVT 2018, manuscript in preparation; [3]Chakravarty T, presented at TCT 2018, manuscript in preparation

When SENTINEL is used, twice as many patients had no new lesions and zero patients had 10 or more lesions

- In **MISTRAL-C**, twice as many SENTINEL CPS-protected patients had zero new lesions *vs* patients not protected with SENTINEL CPS (27% vs 13%).
- When SENTINEL CPS was NOT used, 20% of patients had 10 or more lesions compared to 0% when SENTINEL CPS was used.

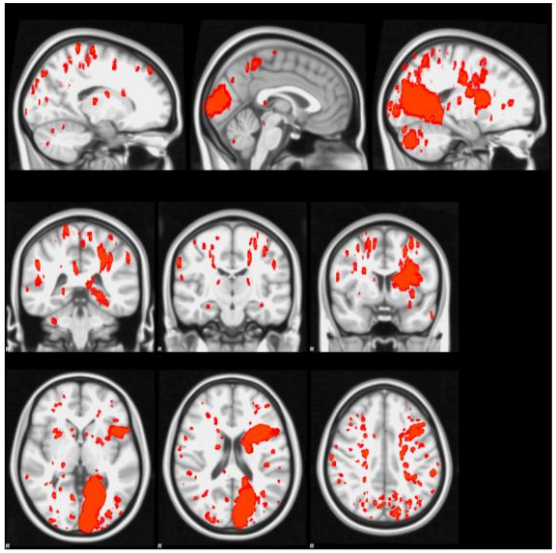


SENTINEL CPS: n = 22
No SENTINEL CPS:n = 15

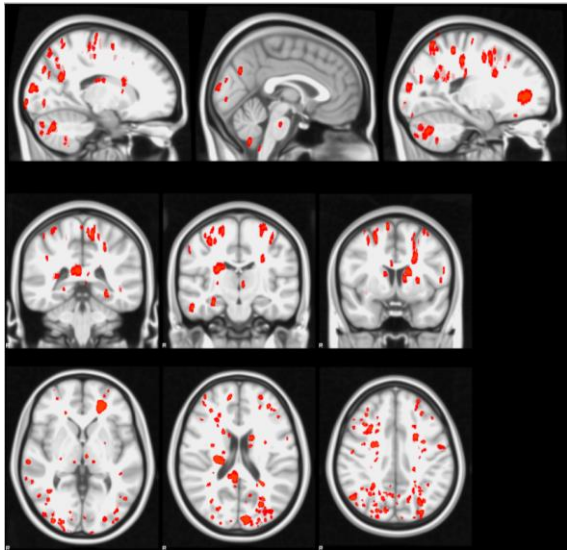
Van Mieghem N, et al. *EuroIntervention* 2016;12:499-507

CLEAN-TAVI: Effective protection

Control group (no filters)



Test group (filters)



Representative slices from each of the orthogonal planes showing new lesions at 2d from each arm of the CLEAN-TAVI randomized trial which evaluated use of the SENTINEL™ Cerebral Protection System in TAVR.

Haussig et al. *JAMA* 2016. 316(9):592-601.

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

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

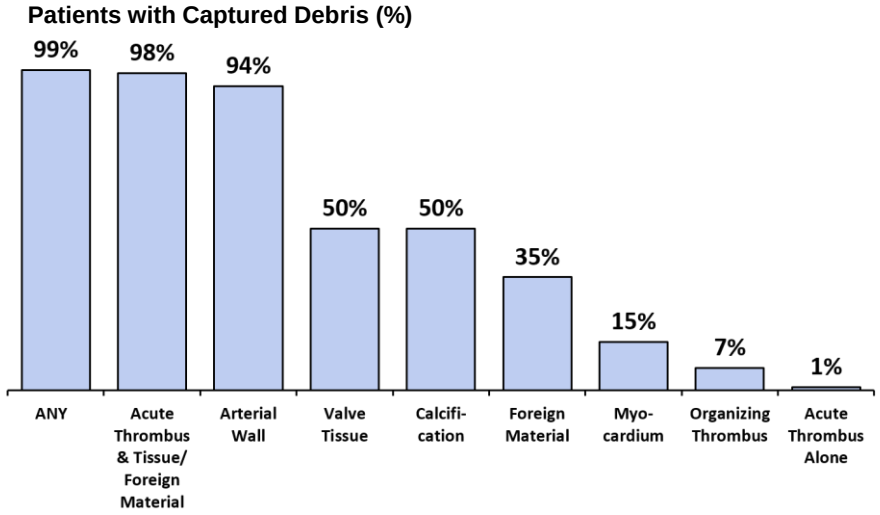
3. **SENTINEL[3] –363 patients RCT in 17 USA & 2 German centers**
   - Co-PIs: Drs Kodali, Kapadia & Linke
   - 3T MRI assessment at <u>baseline</u>, 2-7 days
   - 42% reduction in new lesion volume in whole brain

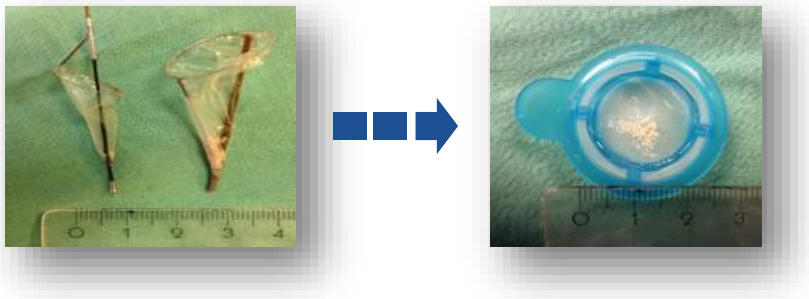

Effect of a Cerebral Protection Device on Brain Lesions Following Transcatheter Aortic Valve Implantation in Patients With Severe Aortic Stenosis
The CLEAN-TAVI Randomized Clinical Trial

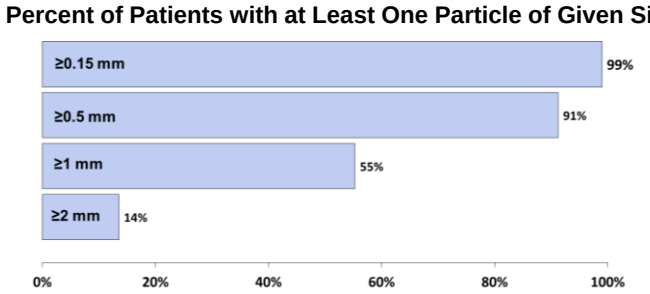

Filter-based cerebral embolic protection with transcatheter aortic valve implantation: the randomised MISTRAL-C trial

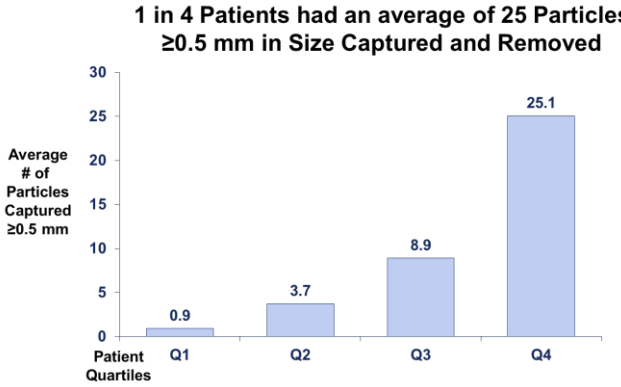
1. Van Mieghem N, et al. *EuroIntervention* 2016;12:499-507
2. Haussig, S, et al. *JAMA*. 2016;316(6):592-601
3. Kapadia, et al. *JACC*. doi: 10.1016/j.jacc.2016.10.023

Debris Captured in 99% of TAVR Patients in the SENTINEL IDE



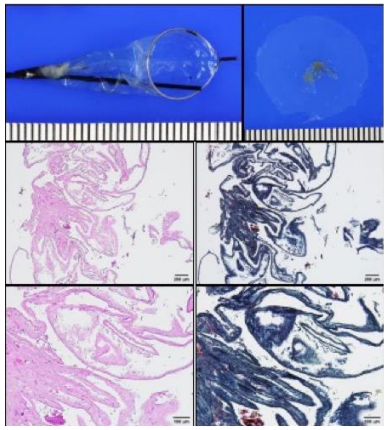




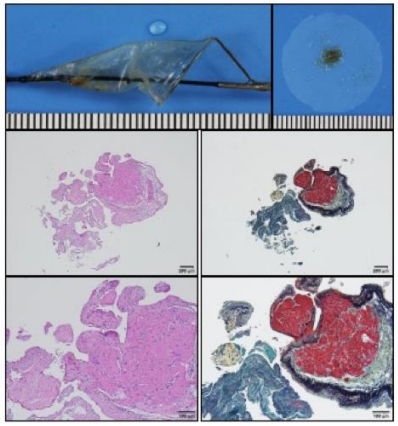


Virmani R, et al. CVPath. SENTINEL IDE Trial. Data presented at SENTINEL FDA Advisory Panel, February 23, 2017

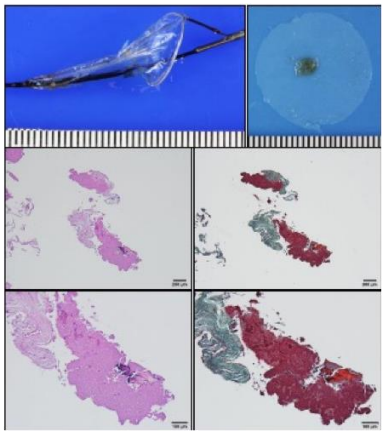
Histopathology of captured debris



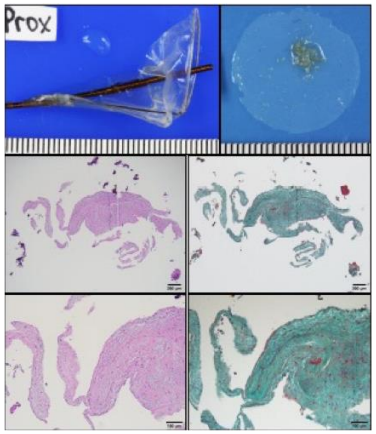
Valve tissue



Myocardium and valve tissue



Acute thrombus with tissue and some calcification

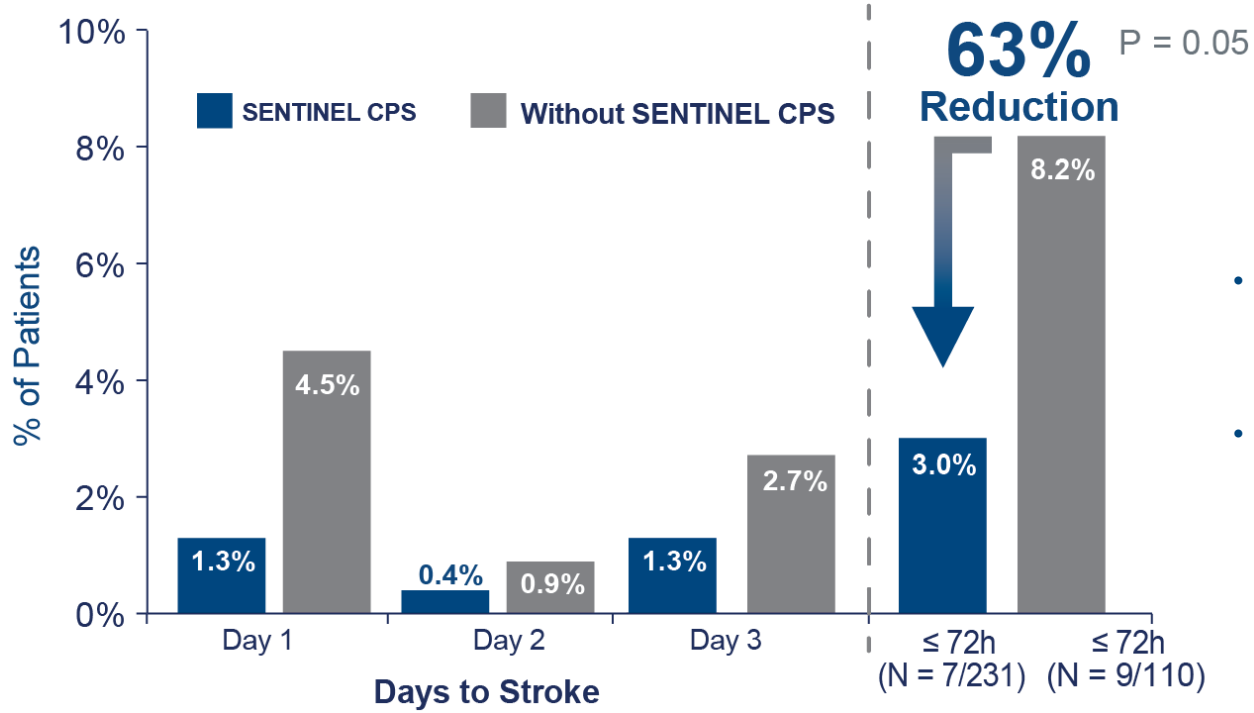


Arterial wall

top –left: Gross images of the distal filter
top – right: debries collected by the cell strainer
mid/bottom – left: scanned images of H&E-stained slides
mid/bottom – right: scanned images of Movat pentachrome-stained slides

SENTINEL IDE Trial – Peri-procedural Stroke Reduction

- 63% peri-procedural (≤ 72 hours) stroke reduction with SENTINEL™ CPS.

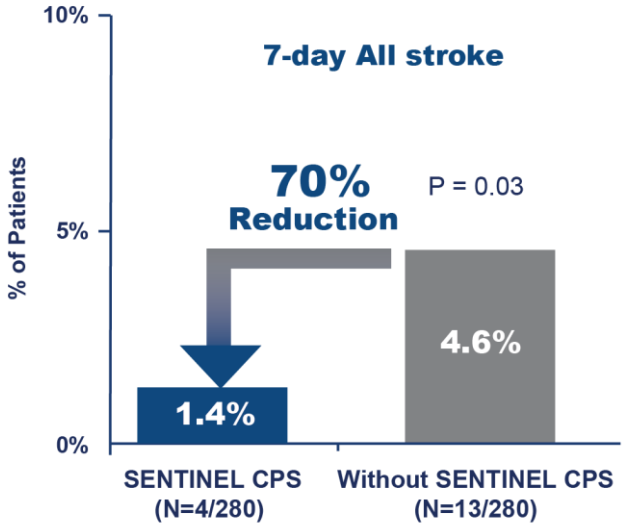


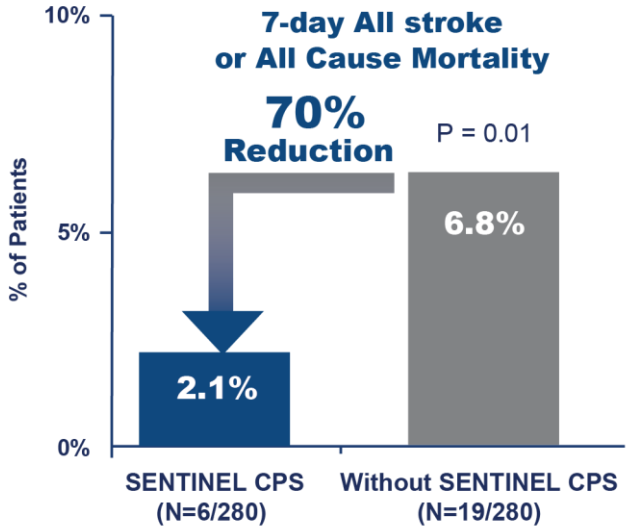
- 95% of SENTINEL CPS patients were evaluated by neurologists
- Clinical Events Committee included 2 stroke neurologists

SENTINEL IDE Trial. Data presented at SENTINEL FDA Advisory Panel, February 23, 2017

Independent Real-World All-Comers Study Shows Significant Peri-Procedural (7 day) Stroke Reduction

- SENTINEL-all-comers Study of Cerebral Embolic Protection demonstrated a 7-day 70% reduction in stroke, and stroke or death, in 560 patient prospective propensity-score matched all-comers study.





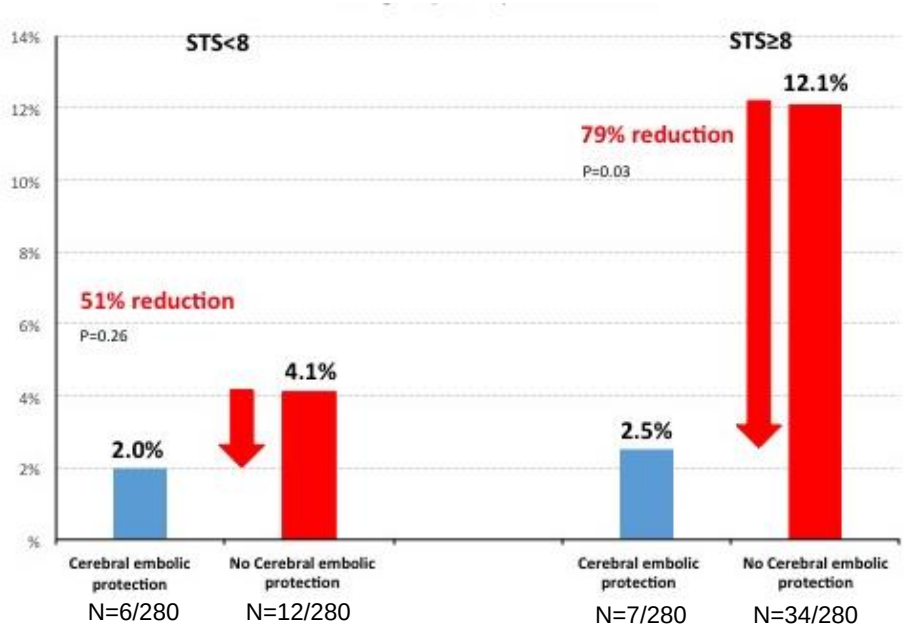
Number-needed-to-treat (NNT) = 22 patients to reduce one stroke or death with cerebral embolic protection

Seeger J *et al.* 2017. *JACC Cardiovasc Interv*. 10(22):2297-2303

Sub-group analysis demonstrates embolic protection system (SENTINEL CPS) is the only independent predictor of being stroke-free

- By multivariable analysis, use of SENTINEL CPS was the only independent predictor of being stroke-free.

P value	Stroke	Mortality and stroke
Gender	0.387	0.640
Diabetes mellitus	0.421	0.224
Valve calcification (mod/sev)	0.412	0.867
Atrial fibrillation	0.437	0.864
STS score (<8 vs. ≥8)	0.572	**0.021**
Embolic protection system	**0.044**	**0.028**



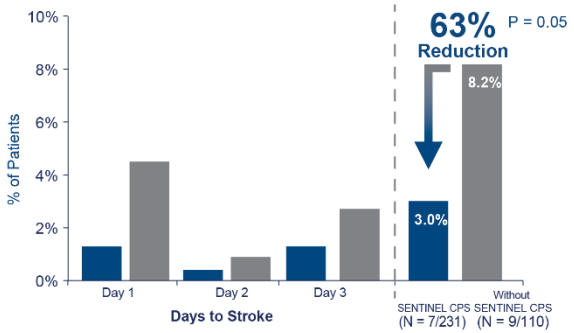
Seeger J *et al.* 2017. *JACC Cardiovasc Interv*. 10(22):2297-2303

Findings from the SENTINEL IDE Trial Together with Real World Outcomes from Demonstrate Consistent Reductions in Stroke

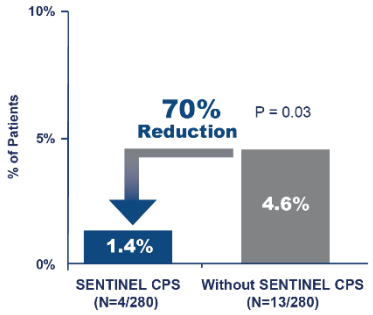
ARR ~ 3-5%
(Absolute Risk Reduction)

NNT ~ 20-30
(Number Needed to Treat to avoid one event)

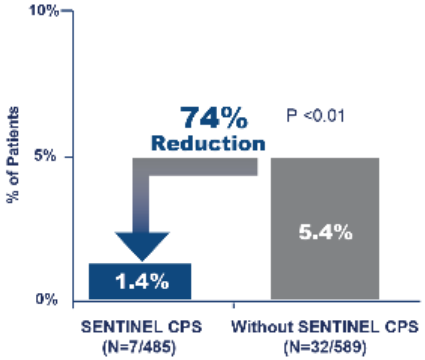
SENTINEL IDE Trial[1]
All stroke at ≤ 72 hours post-TAVR



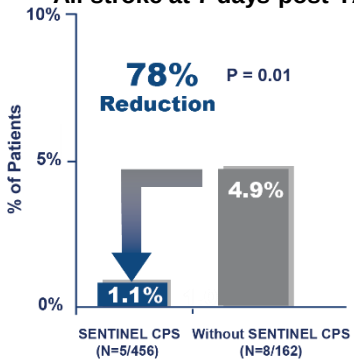
SENTINEL Ulm Study[2]
All stroke at 7 days post-TAVR



Erasmus and University Medical Centers[3]
All stroke at ≤ 72 hours post-TAVR

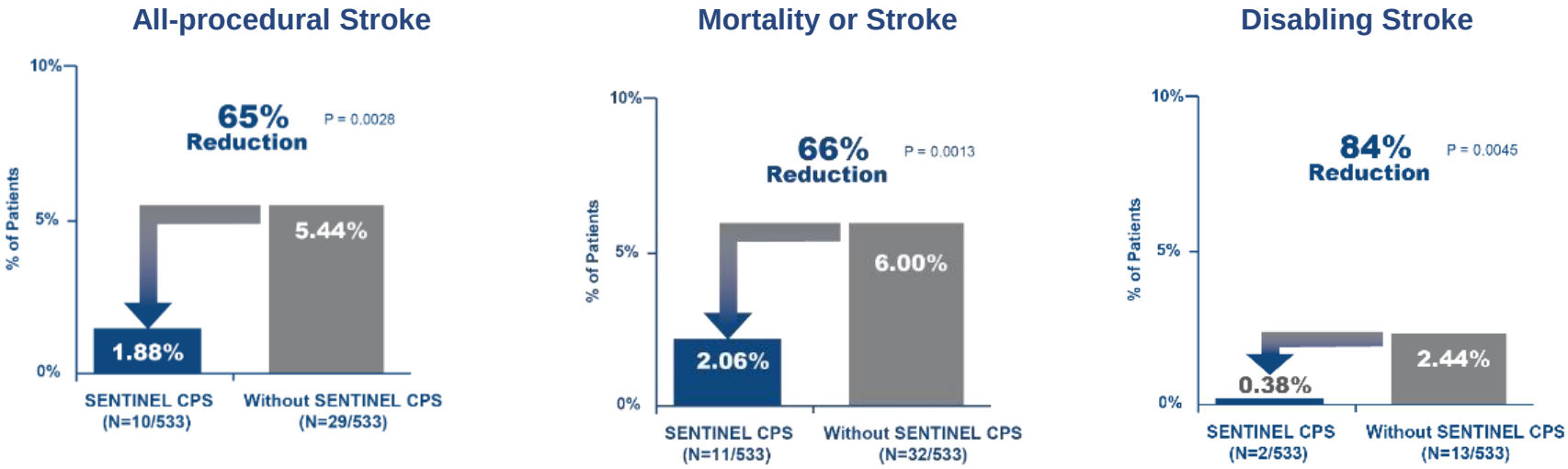


Cedars Sinai Medical Center[4]
All stroke at 7 days post-TAVR



[1]Data presented at SENTINEL FDA Advisory Panel, February 23, 2017; [2]Seeger J et al. 2017. *JACC Cardiovasc Interv*. 10(22)2297-2303; [3]Van Mieghem N. presented at TVT 2018; [4]Chakravarty T. presented at TVT 2018

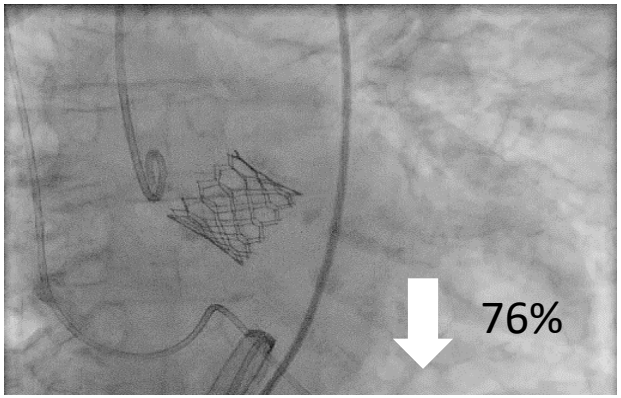
Largest Patient-level Pooled Propensity-Matched Analysis to Date Demonstrates Reductions in Peri- procedural (≤ 72 h) Stroke, Mortality *or* Stroke and Disabling Stroke with Routine SENTINEL CPS Use

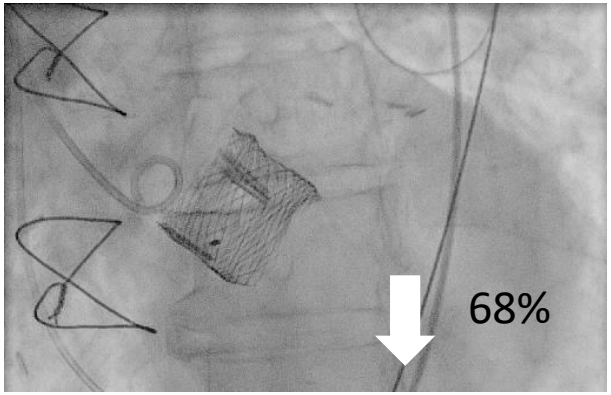


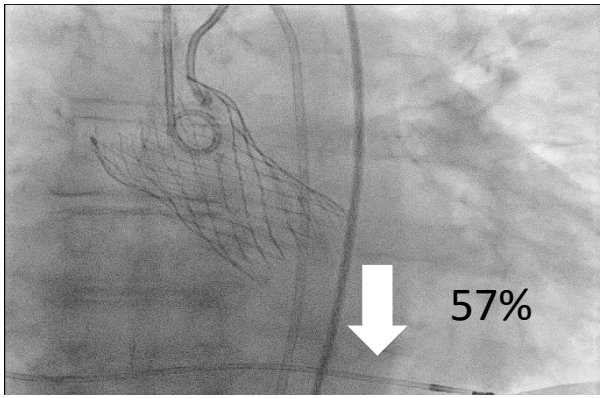
- Patient level meta-analysis demonstrates a reduction in -related (≤ 72 h) stroke with SENTINEL CPS, using VARC-2 criteria.
- Analysis was based on **n=1306** patients with severe aortic stenosis from the SENTINEL IDE RCT Trial (n=363), CLEAN-TAVI RCT (n=100) and SENTINEL all-comers study (n=843).
-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

Seeger J. Eur Heart J. 2019;40(17):1334-1340

Reductions in Stroke Favor Routine SENTINEL CPS Use in TAVR Regardless of Valve Type







- Data were propensity score-matched for valve type, STS score, A-fib, gender, diabetes mellitus, CAD and PVD.
- Patient level meta-analysis based on n=1306 TAVI patients with severe aortic stenosis from the SENTINEL IDE Trial (n=363), CLEAN-TAVI (n=100) and SENTINEL Ulm (n=843).

Seeger J. Eur Heart J. 2019;40(17):1334-1340

Largest Stroke Meta-Analysis to Date with SENTINEL CPS Favors Cerebral Embolic Protection Among Sub Groups

- Patient level meta-analysis demonstrates a 66% reduction in TAVR-related (≤ 72 h) mortality or stroke, p =0.0013 with SENTINEL CPS.

Subgroup	Number of Patients	Odds ratio (95% CI)	p-value
Total population	1066	0.34 (0.17 – 0.68)	0.0013
Anesthesia			
General	200/1066 (18.8%)	0.49 (0.11 -2.26)	0.36
Non-general	860/1066 (80.8%)	0.29 (0.13 – 0.68)	0.0045
Valve Type			
Balloon-expandable	672/1066 (63.0%)	0.24 (0.07 – 0.82)	0.029
Mechanically expandable	170/1066 (15.9%)	0.32 (0.06 – 1.64)	0.17
Self-expandable	224/1066 (21.0%)	0.43 (0.14 – 1.29)	0.13

- Analysis was based on **n=1306** patients with severe AS from the SENTINEL IDE Trial (n=363), CLEAN-TAVI (n=100) and SENTINEL Ulm (n=843).
- Data were propensity score-matched for valve type, STS score, A-fib, gender, diabetes mellitus, CAD and PVD.

Seeger J. Eur Heart J. 2019;40(17):1334-1340

Summary

- Largest body of evidence for the Sentinel CPS
- Imaging data from 3 RCTs on Sentinel CPS in TAVR showed a 41-52% reduction in new lesion volume on cMRI
- Histopathological analysis reveal debris captured in 99% of filters with 55% of debris being larger than 1mm
- Data of one randomized trial (SENTINEL-IDE) showed a strong trend towards a lower periprocedural stroke rate within 72 hours after TAVR
- Several large registries as well as a patient level-meta analysis based on 1306 patients demonstrated a significant benefit with use of Sentinel CPS in TAVR patients compared to unprotected procedures with a NNT of 22 to avoid one stroke.