AP Valve 2017
Seoul, August 17, 2017

Cerebral Protection during TAVR: Why and in Whom?

Eberhard Grube, MD, FACC, FSCAI

University Hospital, Dept of Medicine II, Bonn, Germany

Stanford University, Palo Alto, California, USA

Why is Cerebral Protection Needed in TAVI, and in Whom?

- Stroke is an unpredictable and devastating event which is under diagnosed and under reported in TAVI (as well as surgical AVR)
  - In the SENTINEL trial, prospective assessment by neurologists revealed a 30-day stroke rate in unprotected TAVI of 9.1%, encompassing ALL strokes
- Stroke rates are not associated with TAVI case volume
- Stroke rates are similar across the surgical risk spectrum
- Cerebral embolic debris is generated in at least 97% of TAVI patients[1]
- Capturing and removing this debris with the Sentinel Cerebral Protection System significantly reduces the risk of periprocedural stroke in TAVI by **63%**[2]
- Patients deserve “Protected TAVI”, and as TAVI expands to lower surgical risk and less symptomatic populations, the imperative to protect will be even more paramount
- The American Association of Neurological Surgeons has endorsed the key role of Sentinel in the reduction of stroke during TAVI

[1]Kapadia S, et al. *J Am Coll Cardiol* 2017;69:367–77; [2]Sentinel Instructions for Use (US IFU)

- Cerebral embolization detected by DW-MRI in 68-98% of cases[1-3]

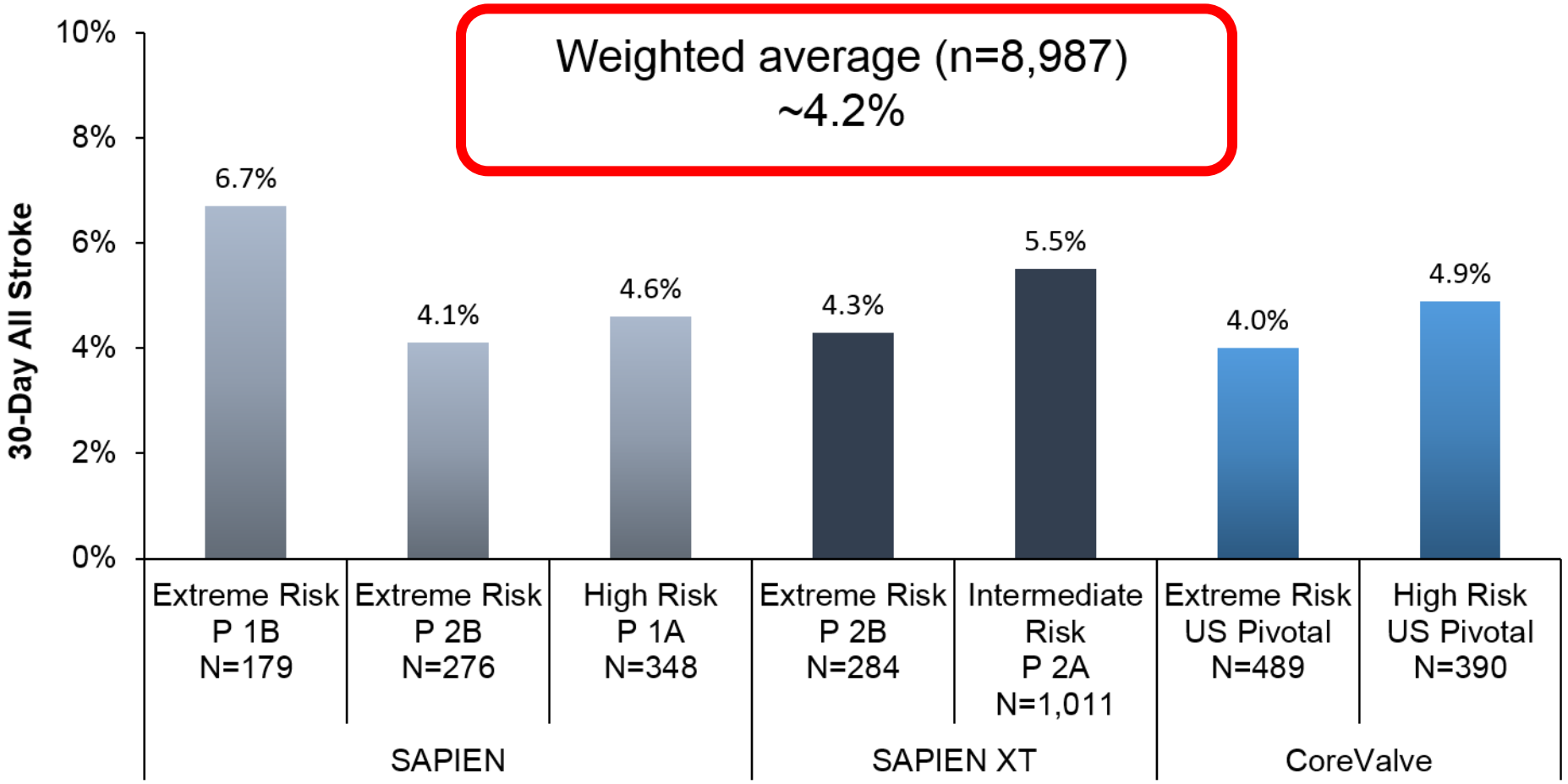
- Cerebral emboli increase risk of clinically overt stroke by 2-4 times
  - Leads to cognitive dysfunction, depression, impaired mobility, dementia, and increased mortality[4-5]

- Increased lesion volume increases long-term risk of cognitive dysfunction and long-term dementia[4-5]

[1]Arnold S, *J Am Coll Cardiol Intv*. 2010 [3]Haussig S, *JAMA*. 2016 [3]Lansky AJ, *Eur Heart J.* 2015 [4]Sacco RL, *Stroke* 2013, [6]Vermeer SE, *Lancet Neurol* 2007

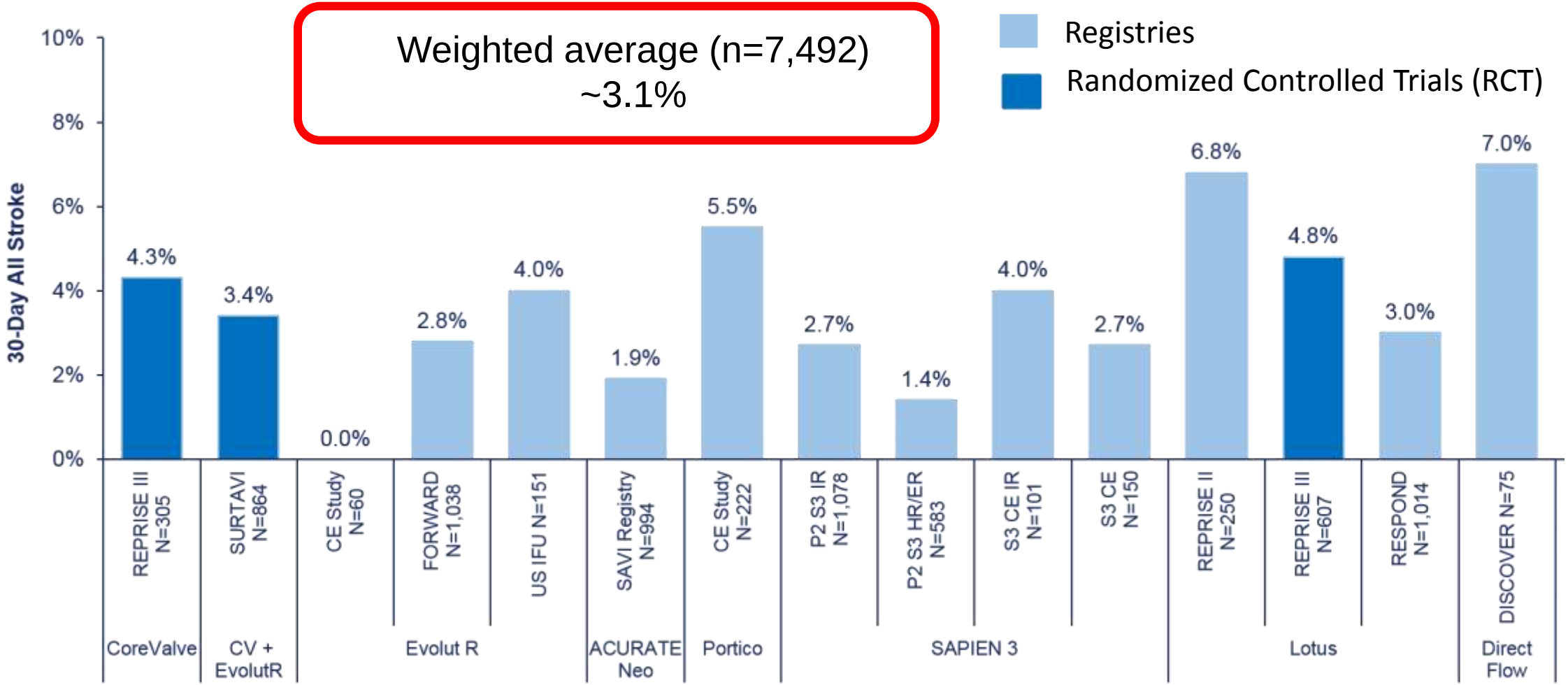
TAVI 30-day All-Stroke Rates with Foundation Devices

When looking at average stroke rates with the foundation valves including SAPIEN, XT, and CoreValve, the early rigorous clinical trials demonstrated a stroke risk of ~4%



[1]Leon, et al., *N Engl J Med* 2010;363:1597-1607; [2]Webb, et al., *J Am Coll Cardiol Intv* 2015;8:1797-806; [3]Smith, et al., *N Engl J Med* 2011;364:2187-98; [4]Leon, et al., *N Engl J Med* 2016;374:1609-20; [5]Popma, et al., *J Am Coll Cardiol* 2014;63:1972-81; [6]Adams, et al., *N Engl J Med* 2014;370:1790-8;;

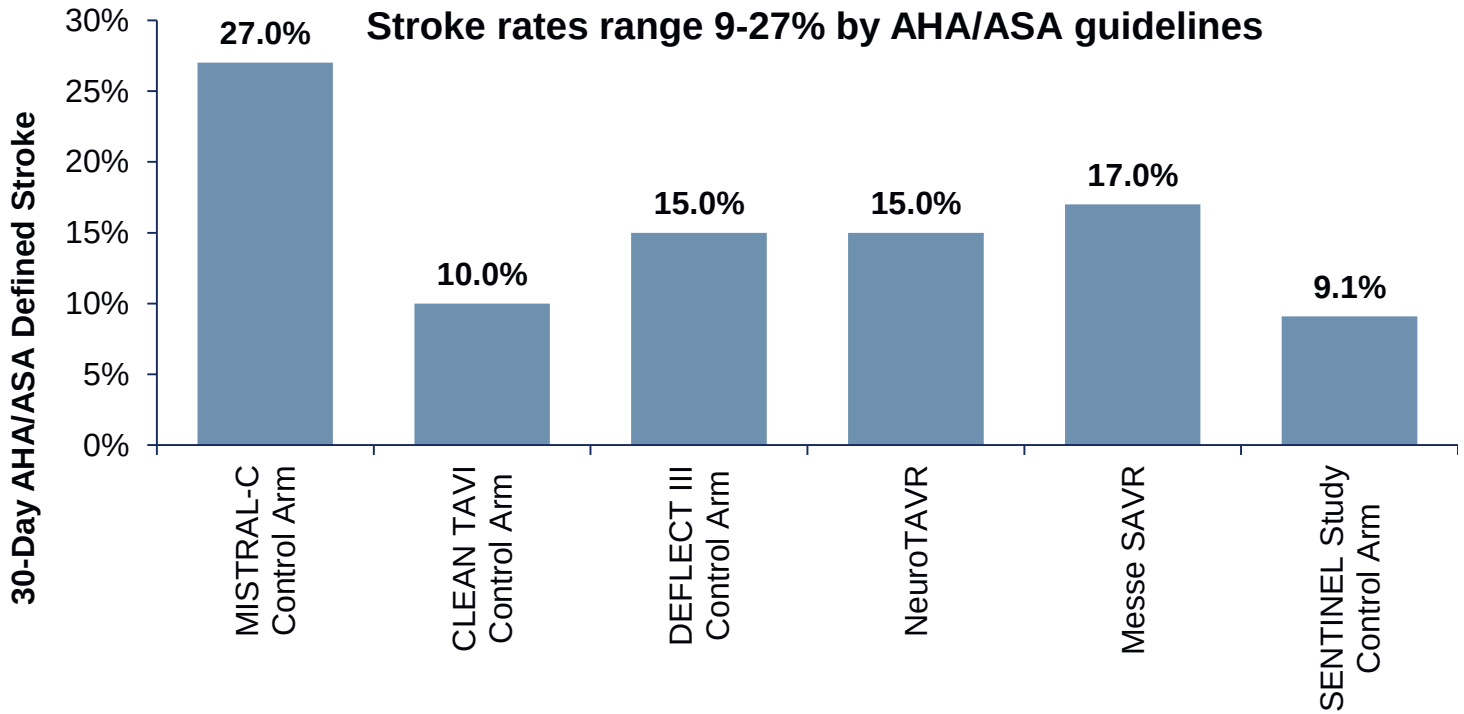
TAVI 30-day All-Stroke Rates with Contemporary Devices



[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., presented at EuroPCR 2016; [11]Kodali, presented at TCT 2016; Reardon, M Published in NEJM March 2017

Strokes Under-Reported

- Stroke classification has changed over time with neuroimaging advances[1]
- AHA/ASA consensus definition includes imaging evidence of CNS infarction with or without acute neurological disfunction[2]
- 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[3]



[1]Mokin, *Expert Review Of Neurotherapeutics*, 2016, [2]Sacco R, et al., *Stroke*. 2013' [3]Messé S, et al., *Circulation*. 2014

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

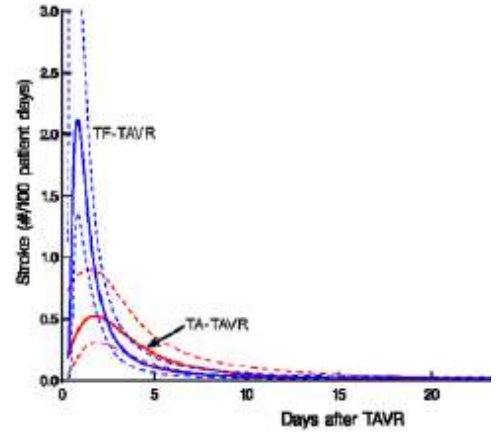
2,621 participants in the PARTNER trial and continued-access registry

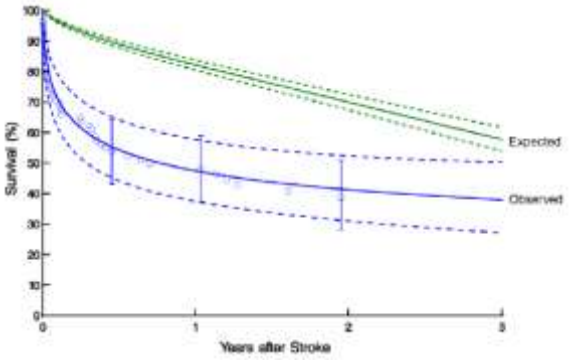
- Stroke incidence was 3.3% at 30d (of which 85% occurred within 1 week, peaking at day 2)

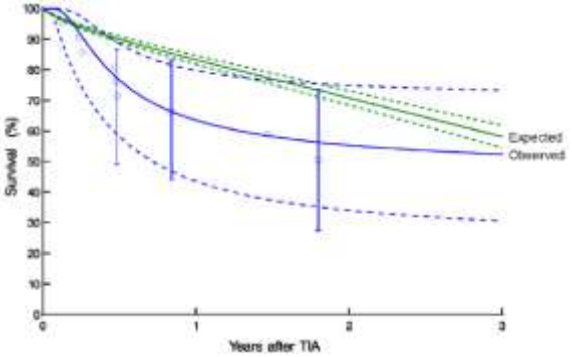
- Patients experiencing a stroke or TIA had lower 1-year survival
  - **With stroke: 47% 1-yr survival vs 82% without for TF-TAVI**
  - With TIA: 64% 1-yr survival vs. 83% without for TF-TAVI

Conclusions from the Author

- Risk of stroke or TIA is highest early after TAVI
- Stroke and TIA after TAVI are associated with increased risk of 1-yr mortality
- This highlights the need for embolic protection devices, anti-platelet therapy, and procedural modifications







Kapadia, et al. *Circ Cardiovasc Interv.* 2016;9:e002981

Recent data presentations under-report true neurological impact. For example: SURTAVI and Swiss Corevalve Experience

Table 3. Clinical Outcomes at 30 Days, 12 Months, and 24 Months (Modified Intention-to-Treat Population).*

Outcome	30 Days			12 Months		
	TAVR	Surgery	95% Credible Interval	TAVR	Surgery	95% Credible Interval
				percent		
Death from any cause or disabling stroke	2.8	3.9	−2.8 to 0.7	8.1	8.8	−3.5 to 2.1
Death from any cause	2.2	1.7	−0.9 to 1.8	6.7	6.8	−2.7 to 2.4
Cardiovascular	2.0	1.7	−1.0 to 1.6	4.8	5.5	−2.9 to 1.5
Valve-related	0.1	0.1	−0.3 to 0.3	0.1	0.3	−0.7 to 0.3
Aortic-valve reintervention	0.9	0.2	−0.1 to 1.4	2.1	0.5	0.4 to 2.7
All stroke and TIA	4.5	6.5	−4.2 to 0.3	8.2	8.6	−3.1 to 2.4
All stroke	3.4	5.6	−4.2 to −0.2	5.4	6.9	−3.9 to 0.9
Disabling	1.2	2.5	−2.6 to 0.1	2.2	3.6	−3.1 to 0.4
Nondisabling	2.2	3.1	−2.5 to 0.6	3.7	3.9	−2.2 to 1.7
TIA	1.5	1.1	−0.7 to 1.5	3.2	2.0	−0.4 to 2.8
Myocardial infarction	0.9	1.0	−1.0 to 0.9	2.0	1.6	−0.9 to 1.8
Hospitalization for aortic-valve–related disease	2.9	4.2	−3.1 to 0.5	8.5	7.6	−1.8 to 3.6
MACCE	5.7	7.4	−4.0 to 0.7	13.2	12.8	−2.9 to 3.7

SURTAVI: Reardon, NEJM March 2017

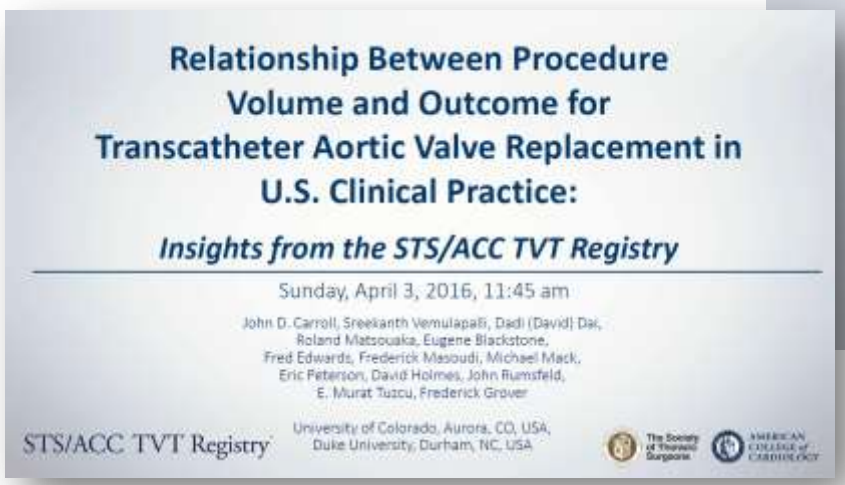
	Evolut R N=317	CoreValve N=678	HR (95% CI)
Mortality, n (%)	10 (3.2)	23 (3.4)	0.94 (0.45-1.97)
Cardiovascular mortality, n (%)	8 (2.5)	22 (3.3)	0.78 (0.35-1.75)
Cerebrovascular accident, n (%)	15 (4.8)	25 (3.7)	1.29 (0.68-2.44)
Disabling stroke, n (%)	6 (1.9)	11 (1.6)	1.17 (0.43-3.15)
Non-disabling stroke, n (%)	8 (2.5)	12 (1.8)	1.43 (0.59-3.51)
Myocardial infarction, n (%)	0 (0.0)	3 (0.4)	0.31 (0.02-5.98)
Periprocedural myocardial infarction, n (%)	0 (0.0)	3 (0.4)	0.31 (0.02-5.98)
Acute kidney injury, n (%)	14 (4.5)	38 (5.7)	0.79 (0.43-1.45)
Stage 3, n (%)	6 (1.9)	16 (2.4)	0.80 (0.31-2.05)
Bleeding, n (%)	59 (18.7)	128 (19.0)	0.99 (0.73-1.35)
Life-threatening or major bleeding, n (%)	40 (12.7)	99 (14.7)	0.86 (0.60-1.24)

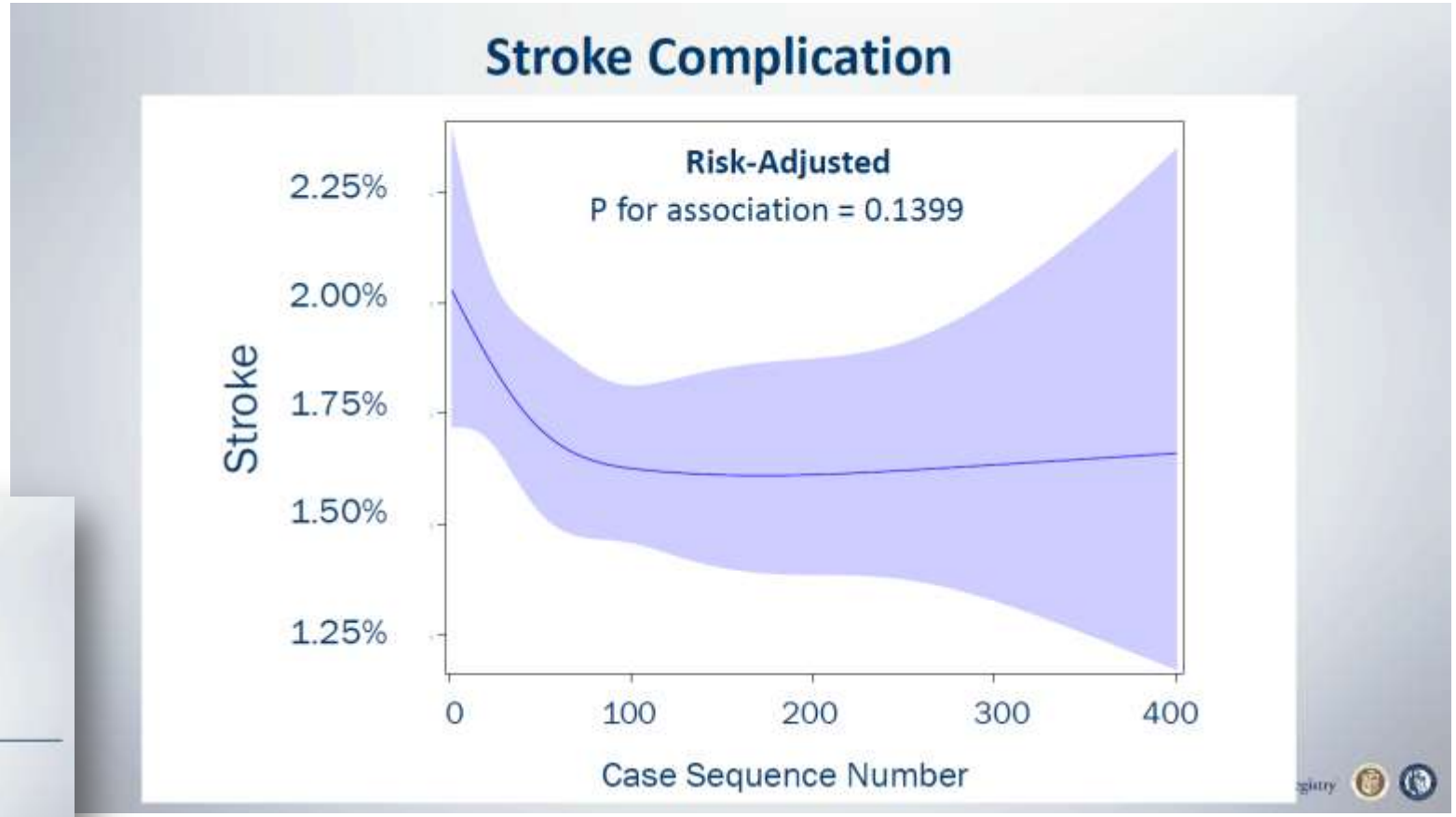
EuroIntervention 2017;12:e2170-e2176 ■ published online

- Two most recent study report publications (March and April 2017)
- Data presentation, press release and published reports usually only mention the Disabling Stroke rates
  - 1.2% and 1.9% disabling stroke rate
  - However, all-stroke rates were **3.4% and 4.4%** in the two studies

TVT Registry shows stroke risk is independent of experience

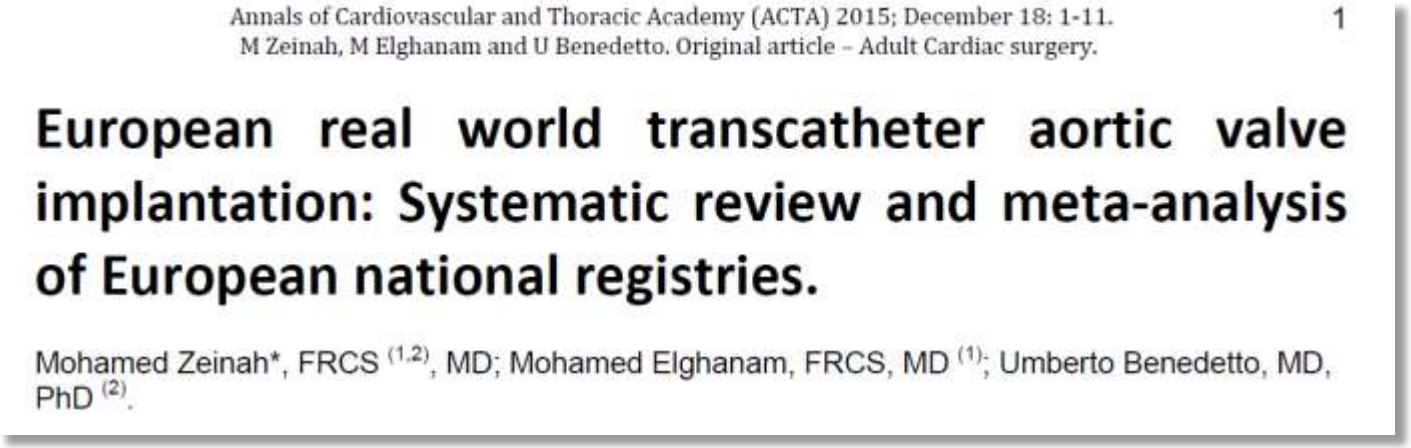
- Over 53,000 US TAVR patients from >350 US centers
- No significant decline in stroke rate as centers gain experience
- Self-reported rates without prospective neurologist exams pre and post-procedure likely underestimate true rates





Carroll J, et al. ACC 2016

TAVI stroke rate not associated with surgical risk score in meta-analysis of 7 European registries (n=9,786)



Annals of Cardiovascular and Thoracic Academy (ACTA) 2015; December 18: 1-11.
M Zeinah, M Elghanam and U Benedetto. Original article – Adult Cardiac surgery.

European real world transcatheter aortic valve implantation: Systematic review and meta-analysis of European national registries.

Mohamed Zeinah*, FRCS [1,2], MD; Mohamed Elghanam, FRCS, MD [1]; Umberto Benedetto, MD, PhD [2].

- 2015 meta-analysis of 7 European national TAVI registries (UK, Swiss, Belgium, Italy, Spain, France, Germany) with a total of n=9,786 patients
- Average logistic EuroSCORE from each registry varied from 16% to 33%
- Pooled estimate for the incidence of 30d stroke was 3.0%
- Patient risk profile assessed by the average logistic EuroSCORE was not associated with the incidence of stroke (p=0.74)

Zeinah, M, et al. Annals of Cardiovascular and Thoracic Academy (ACTA) 2015; December 18: 1-11.

As TAVI expands to lower surgical risk and less symptomatic populations, the imperative to protect will be even more paramount

- Risk of cerebral embolic injury likely similar for <u>all severe AS</u>
  - Most emboli are created during crossing of the stenotic aortic valve, positioning and expanding the new valve[1,2]
  - Patients with severe AS have severely stenotic valves, by definition, regardless of surgical risk score (which has more to do with other health factors)
  - Risk of cerebral embolic injury ≠ surgical operative mortality risk[3]

- Benefit of cerebral protection may <u>increase</u> with lower surgical risk, less symptomatic, younger patients
  - Longer life expectancies over which to benefit from reduced neurological injury (stroke and cognitive decline)
  - Patients with higher cognitive function at baseline may be more likely to show decline[4]

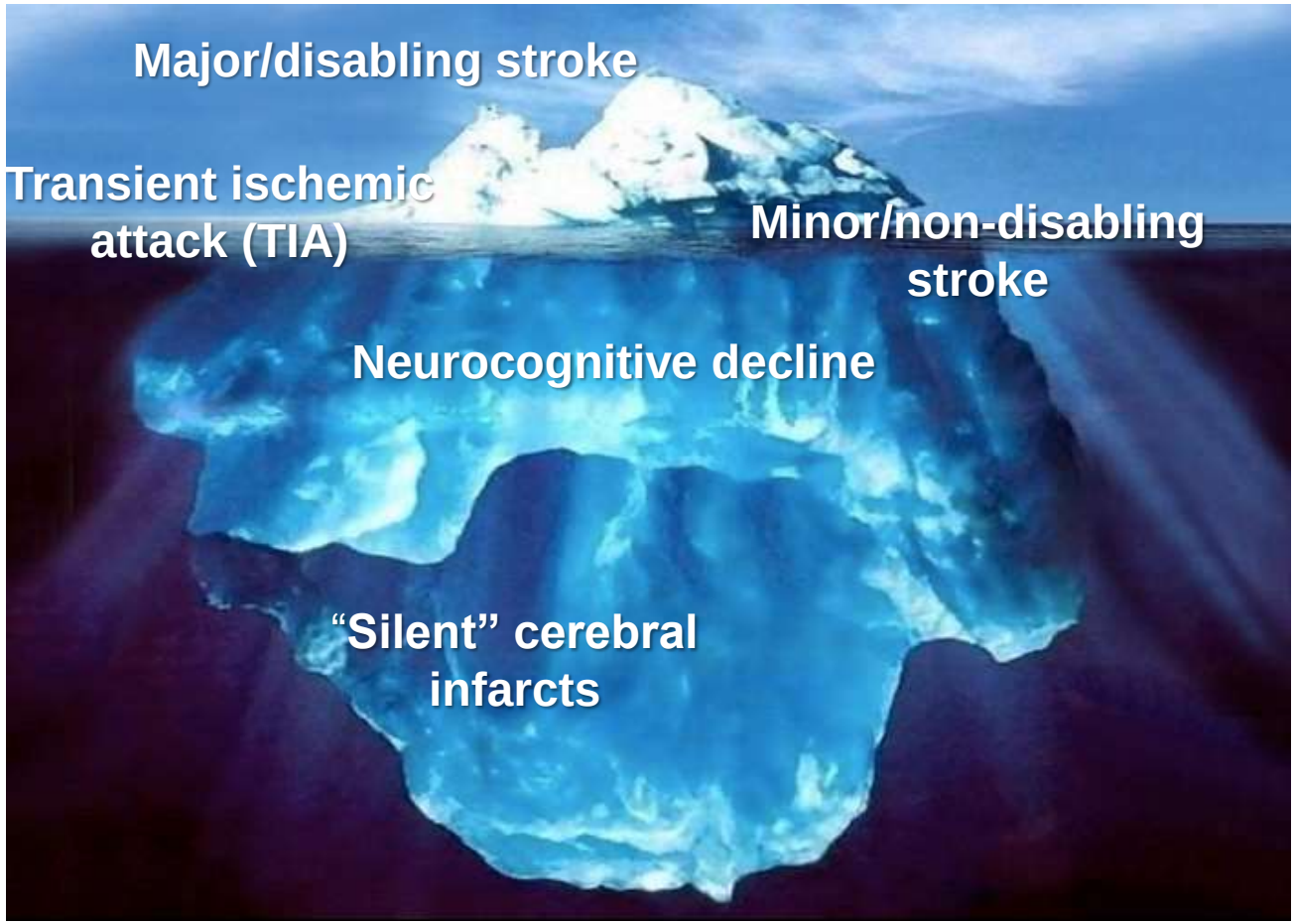
1. Erdoes G, et al Transcranial Doppler-detected cerebral embolic load during transcatheter aortic valve implantation. *EJCTS* 2012; (41): 778-784
2. Kahlert P, et al. Cerebral Embolization During Transcatheter Aortic Valve Implantation: A Transcranial Doppler Study. *Circulation*. 2012;126:1245-1255
3. Zeinah, et al EU TAVI Registry Review and Meta Analysis. *ACTA* 2015
4. Newman M, et al. Longitudinal Assessment of Neurocognitive Function After Coronary-Artery Bypass Surgery. *NEJM* 2001:344:395-402

Most cerebral damage in TAVI is unseen

Clinically apparent

Subtle and often undetected

Clinically unrecognized



Clinical exam, NIHSS, mRS

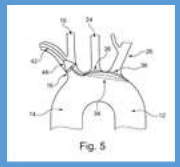
MMSE, MoCA

Neurocognitive test batteries

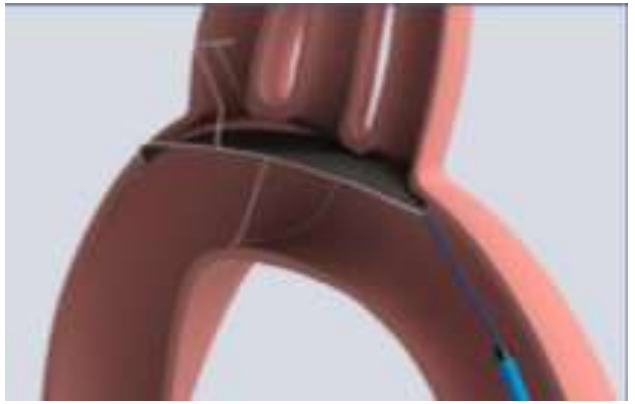
Neuroimaging

….but can have far-reaching effects

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

Keystone Heart TriGuard Study Update



- Aug 1, 2017 Keystone Heart announced that the randomized trial of the TriGuard cerebral protection device for TAVR, REFLECT, has been halted and will not complete enrollment.
- Safety interim analysis announced at TVT 2017
- 300 patients enrolled and remain in follow-up phase
- The company also announced plans to study a new device design in a future study, TRIFLECT.

Ref: PR Newswire Aug 1, 2017 news provided by Keystone Heart Ltd.

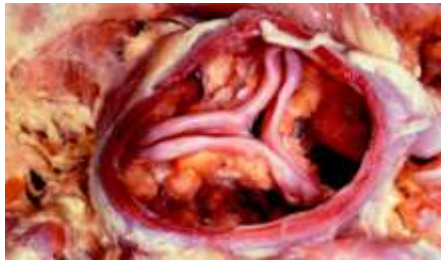
Sentinel Cerebral Protection System – FDA Clearance June 1st 2018

- 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 (brachiocephalic 9-15 mm and left common carotid 6.5-10 mm) and fits ~90% of aortic anatomies
- Deflectable compound-curve catheter facilitates cannulation of LCC
- Minimal profile in aortic arch (little interaction with other devices)

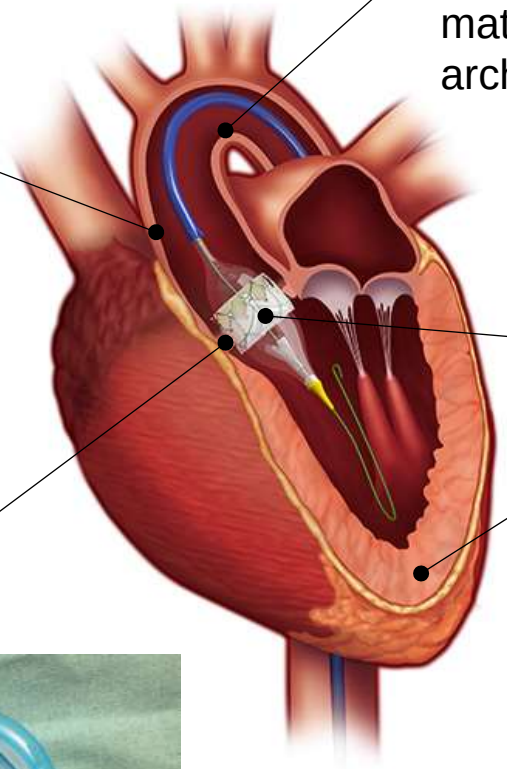
Claret Medical™ Sentinel™ Cerebral Protection System

Captures and Removes Embolic Debris Derived from a Variety of Sources During TAVI

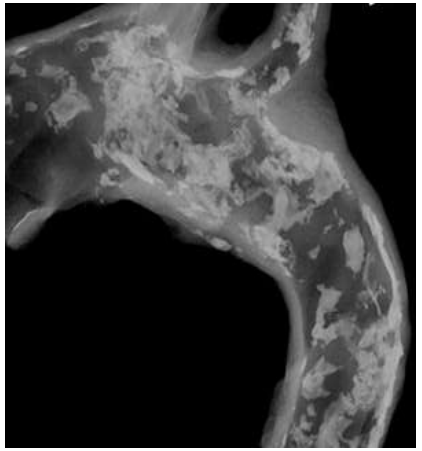
Arterial wall and calcific and atherosclerotic material from ascending arch



Valve leaflet tissue and calcific deposits from stenotic valve

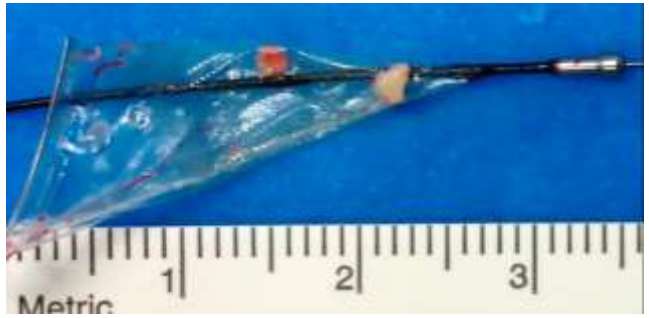


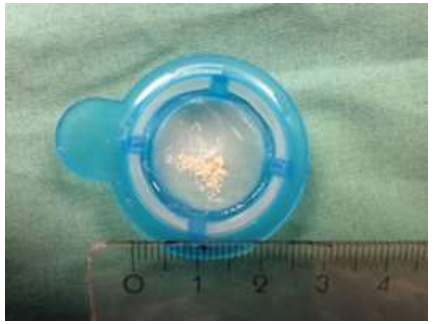
Arterial wall and calcific and atherosclerotic material from transverse arch

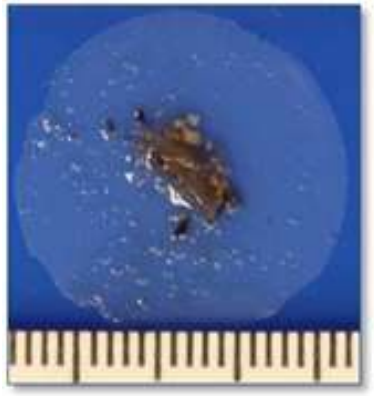


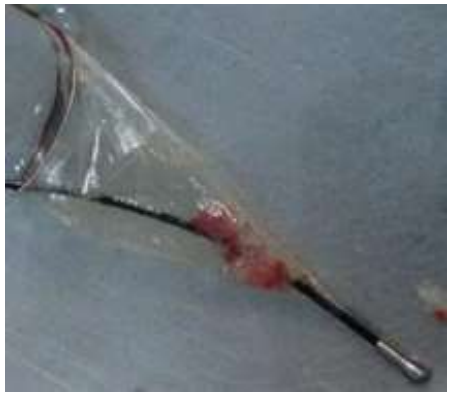
Foreign material from TAVI devices

Myocardium

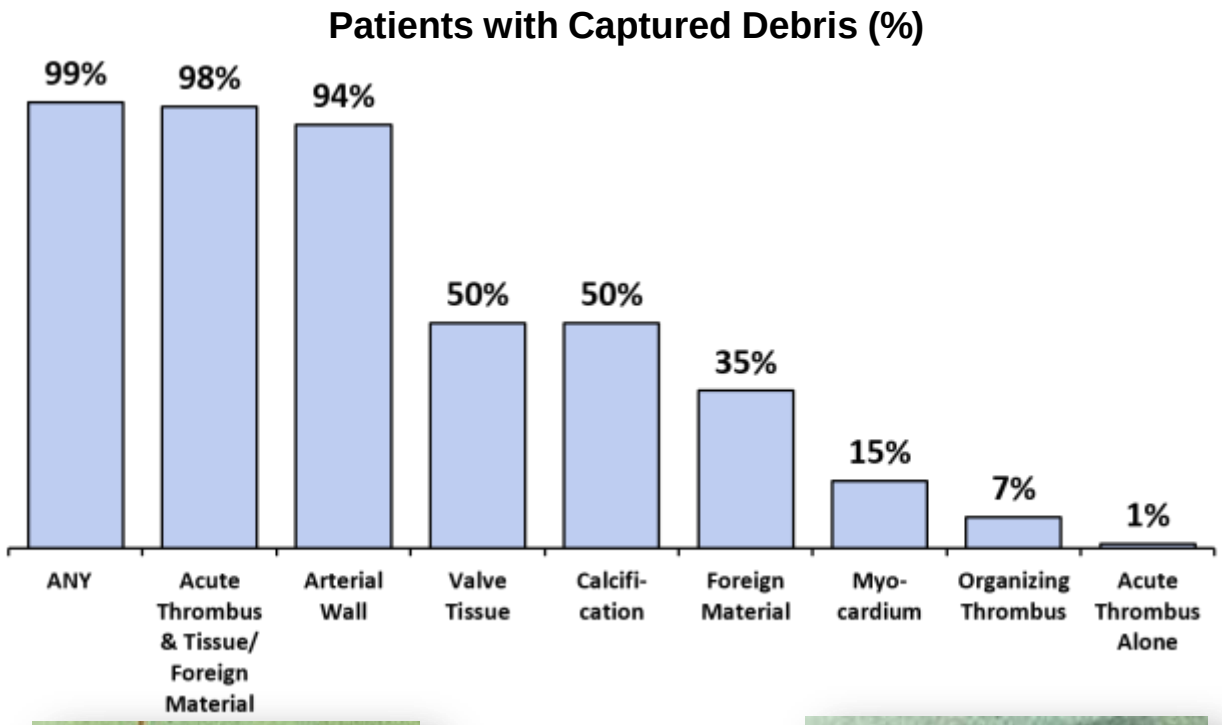


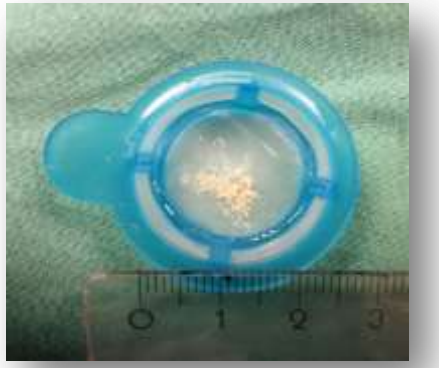


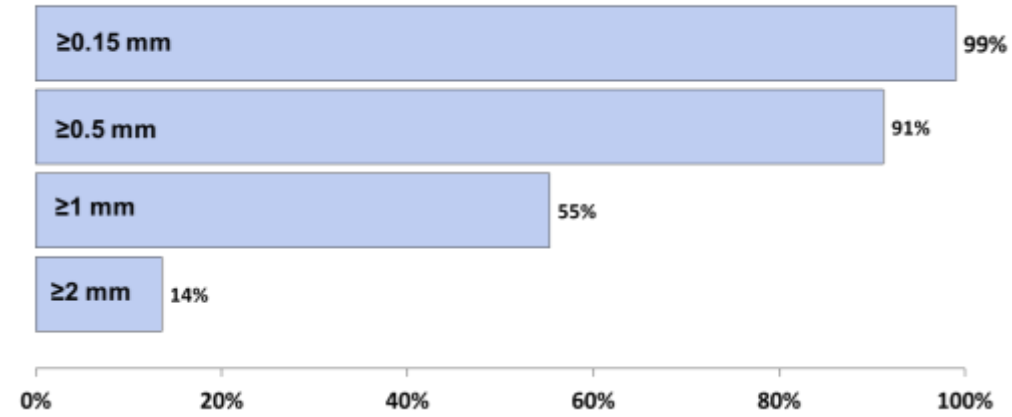


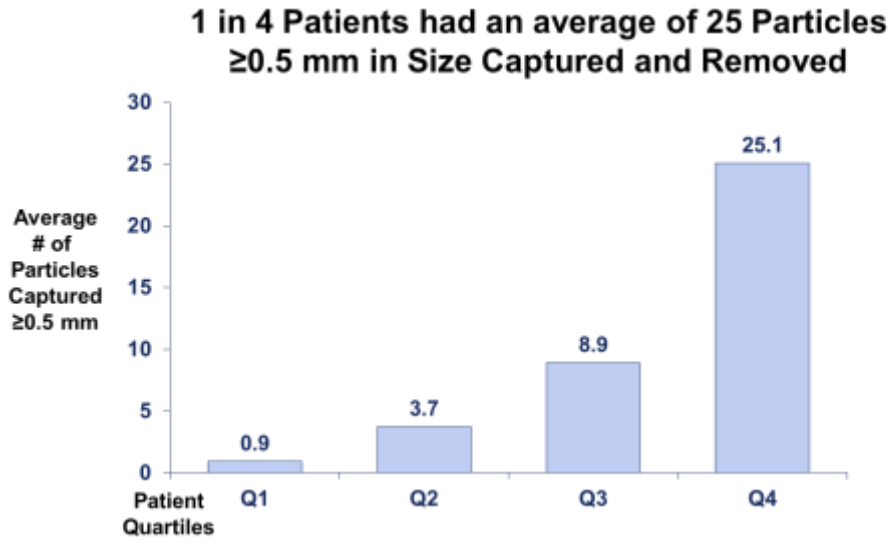


Sentinel™ CPS captured debris in 99% of TAVI patients in SENTINEL



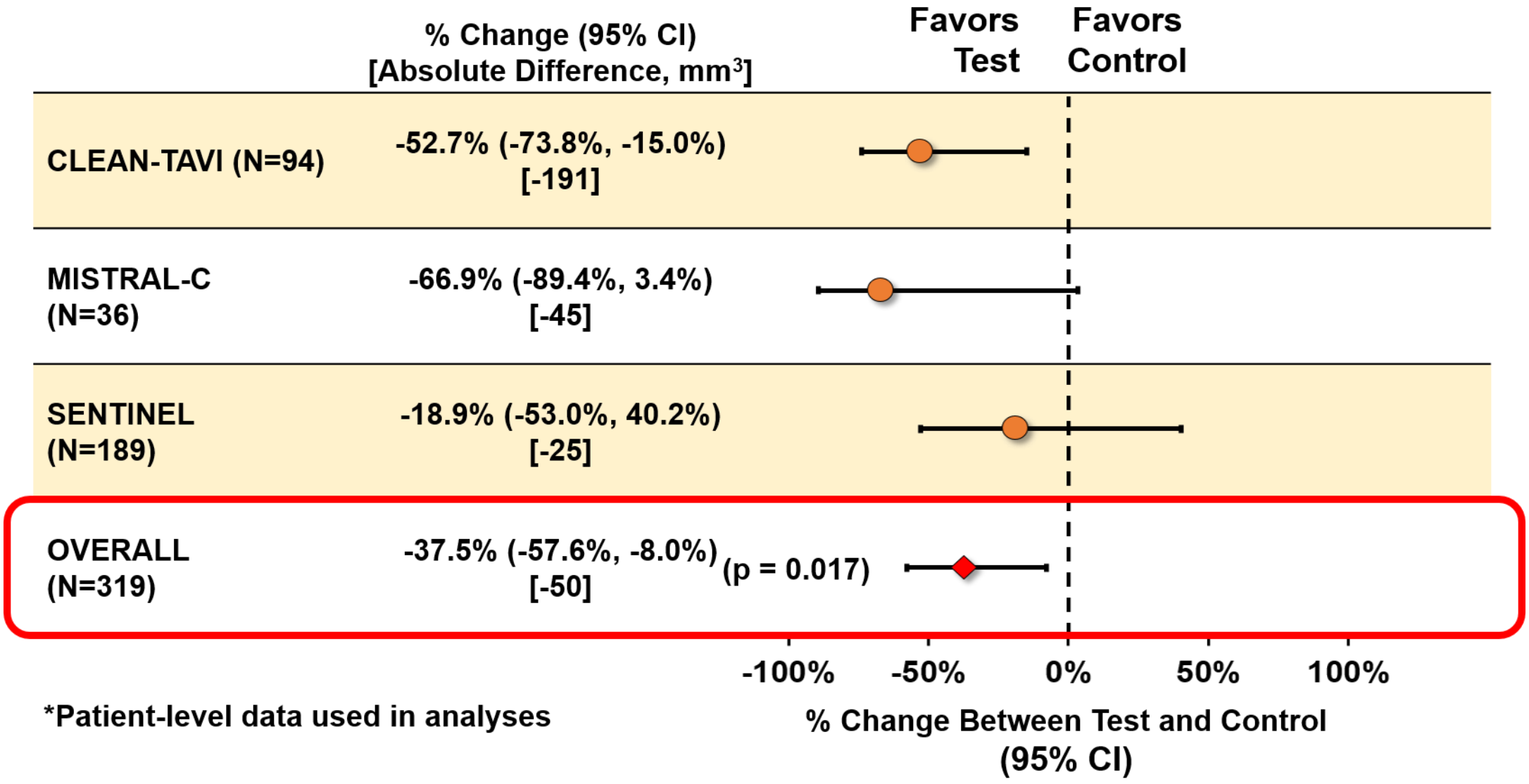






Virmani R, et al. CVPath. SENTINEL trial. Data presented at Sentinel FDA Advisory Panel, February 23, 2017

Meta-Analysis of CLEAN-TAVI, MISTRAL-C, and SENTINEL Randomized Trials* Effectiveness: Change in Mean New Lesion Volumes with use of Claret Filters

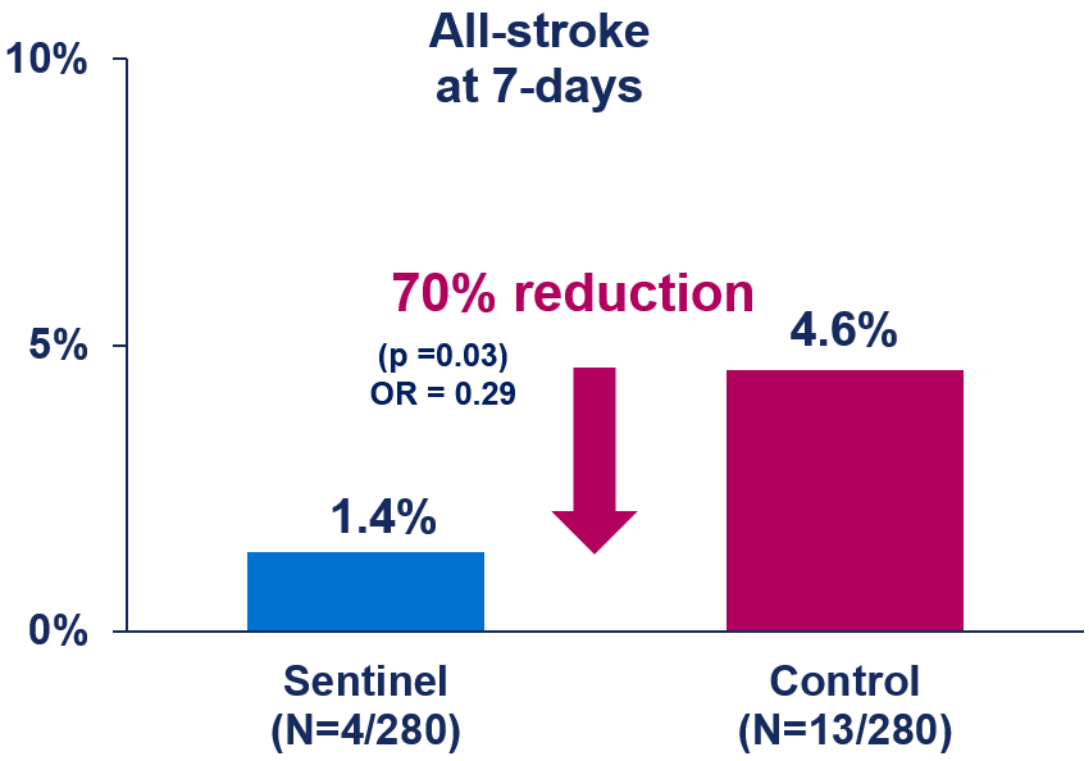


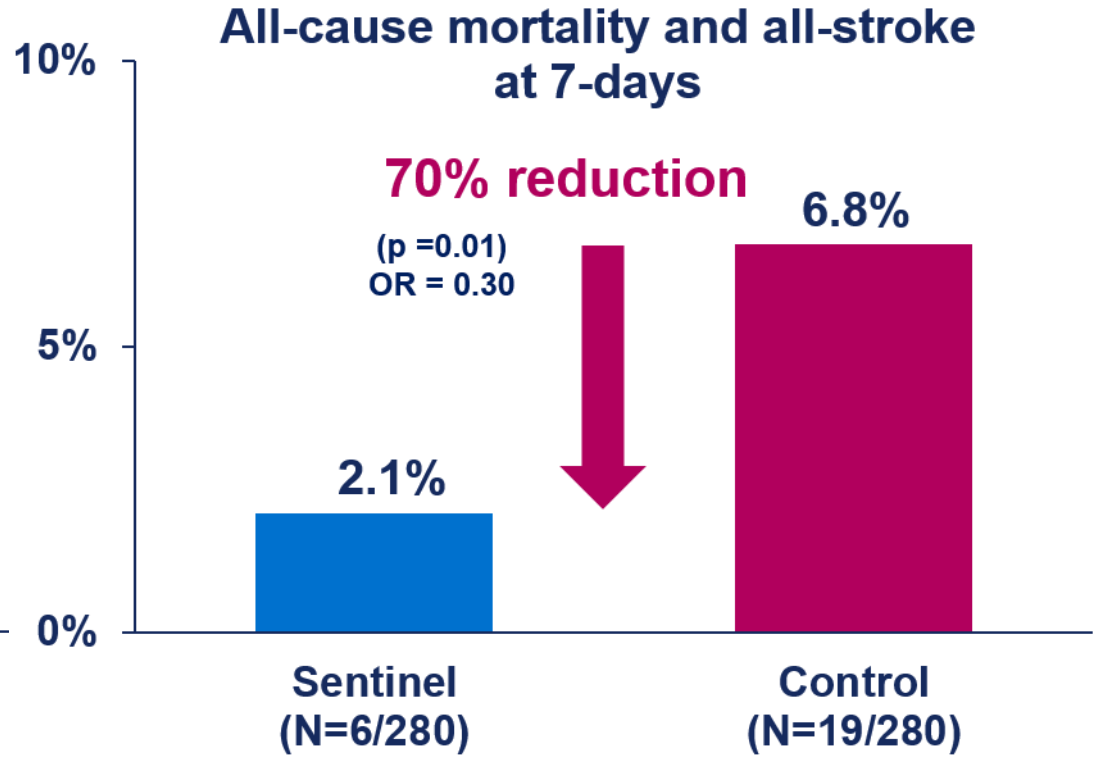
*Patient-level data used in analyses

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

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

Conclusions (1 of 2)

- Stroke is an unpredictable and devastating event which is under diagnosed and under reported in TAVI.
  - SENTINEL trial showed a 30-day stroke rate in unprotected TAVI of 9.1%, encompassing ALL strokes, as revealed by prospective assessment and adjudication by stroke neurologists[1]
  - Stroke rates do not decrease with experience[2,3]; are not associated with surgical risk score[4,5,6] and are not decreasing with new valves[7]

- Cerebral embolic debris is generated in at least 99% of TAVI patients[1]
  - Embolic debris includes pieces of calcium, valve and aortic tissue, myocardium, or other organic or foreign matter[12]
  - One in four patients have an average of 25 pieces of debris $\geq$0.5 mm headed to the brain[12]

- Cerebral ischemic damage occurs in almost all patients undergoing TAVI[1]
  - In addition to all clinical stroke and TIA, cerebral ischemic damage is also an important risk factor for subsequent clinical stroke, dementia, cognitive decline, and mortality[8,9,10,11]

Conclusions (2 of 2)

- Capturing and removing debris with the Sentinel Cerebral Protection System significantly reduces the risk of periprocedural stroke, and stroke or death, in TAVI by up to 70%[12,13]
  - In the SENTINEL RCT, the periprocedural (≤72h) **stroke rate was reduced 63%,** from 8.2% to 3.0% (p=0.05) [1,12]
  - In a propensity-score-matched study from Ulm, the 7d **stroke rate was reduced 70%,** from 4.6% to 1.4% (p=0.03) [13]
  - The same Ulm study showed a **reduction in combined stroke or death at 7d by 70%** from 6.8% to 2.1% (p=0.01) [13]

- Cerebral embolic protection is safe and easy to use
  - In the SENTINEL RCT, 30d MACCE in the protected Sentinel group was 7.3%, lower than the rate of 9.9% in the unprotected control arm[1]
  - >95% deployment success in a median of 4 minutes in SENTINEL[1]
  - One size accommodates ~90% of anatomies[1]

- Patients deserve “Protected TAVI”, and as TAVI expands to lower surgical risk and less symptomatic populations, the imperative to protect will be even more paramount

- The American Association of Neurological Surgeons has endorsed the key role of Sentinel in the reduction of stroke during TAVI

- Safety and efficacy of alternative cerebral protection approaches are beginning to be studied

Routine vs. Selective Use

- Routine use is safest – and ensures smooth integration into a standard TAVR procedure
- We currently can't predict exactly who will benefit exactly how much, so it is best to protect all
  - Future "big data" may allow risk stratification
- Like seatbelts, protection is there for both small and large, predictable and unpredictable "accidents"