AP Valve 2018
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Debate in TAVR: CEP Routine or Selective?
CEP should be Standard of Care!

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Financial Disclosures Eberhard Grube, MD

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The arguments that you always hear…

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

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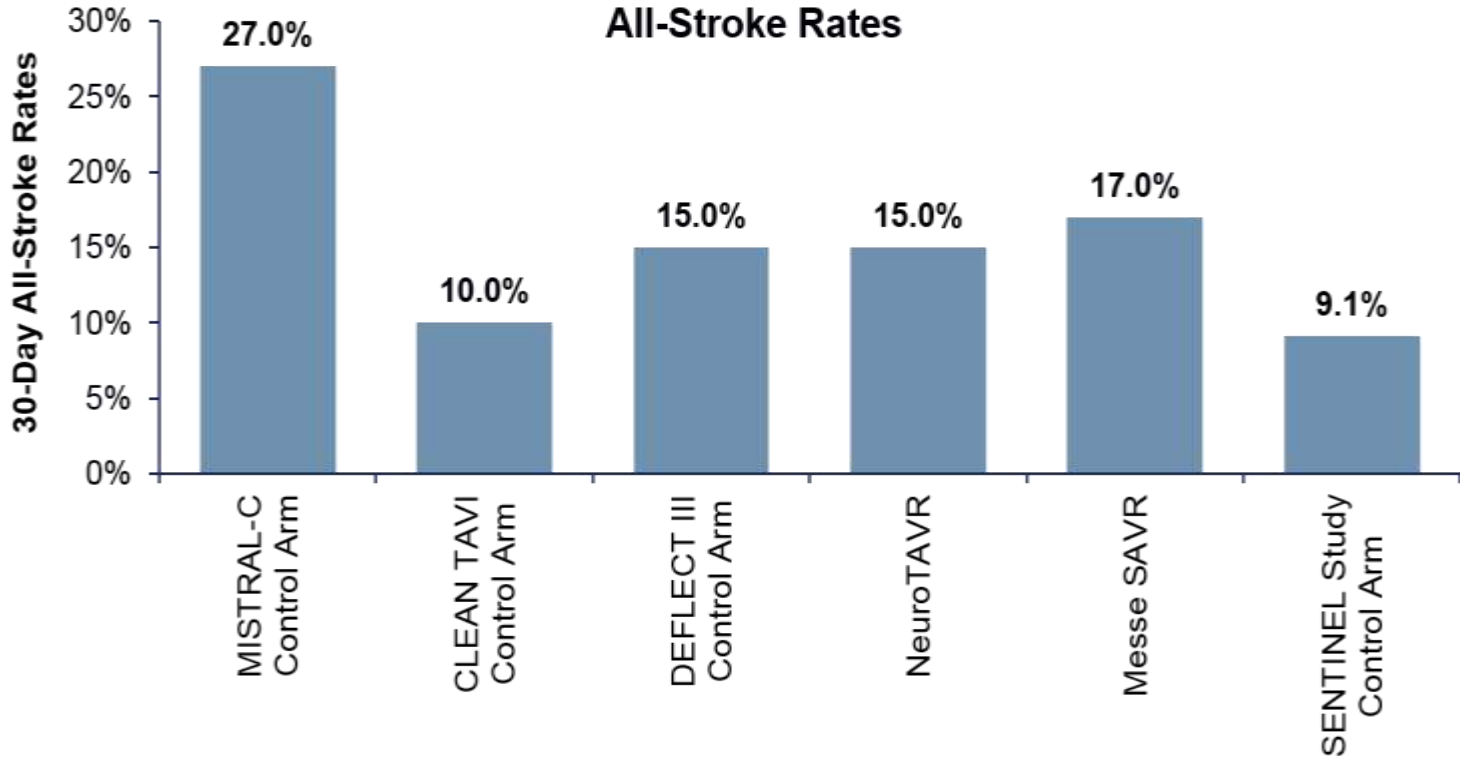
Strokes Often Under-Recognized and Under-Reported in TAVR and SAVR

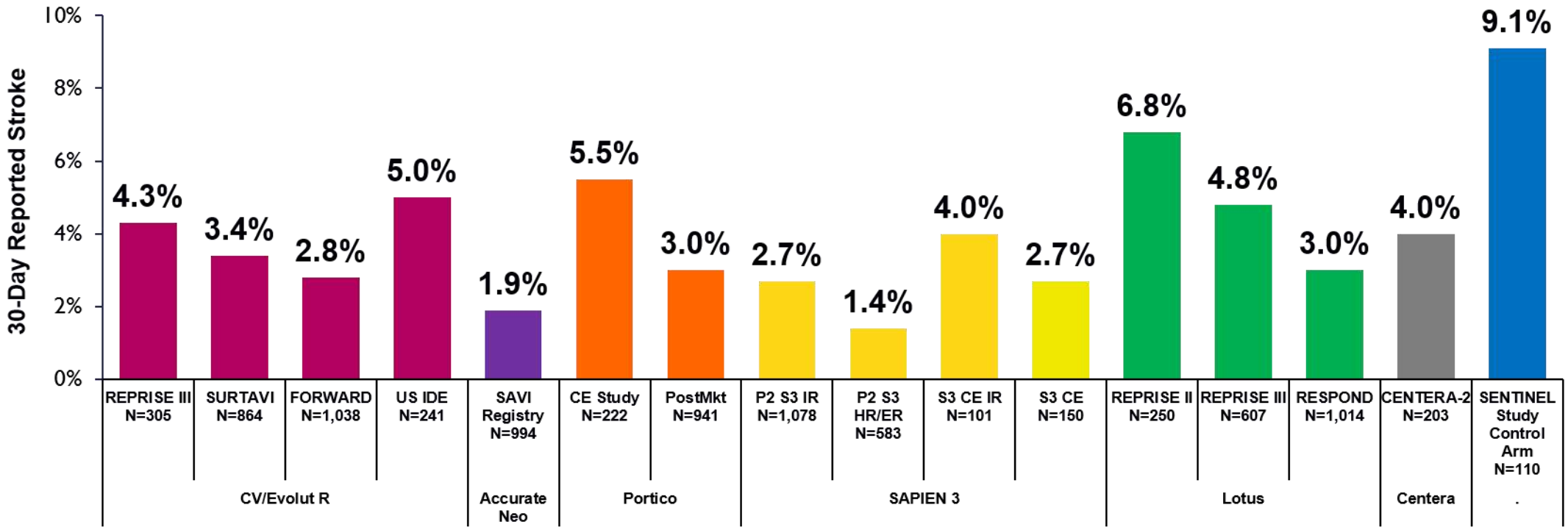
- *True clinical stroke rates in TAVI and SAVR are likely higher than usually recognized and reported.*
- *Stroke definitions and classifications have changed over time with neuroimaging advances.[1-3]*
- *Most studies do not use routine imaging or proactive discharge exam by neurologists.*
- *Studies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

Clinical Stroke Rates with Contemporary TAVR Devices (by Devices)

- *Stroke remains an issue **(4% average rate)** in contemporary TAVI studies*
- *TAVI device trials tend to emphasize only the major/disabling stroke rates*



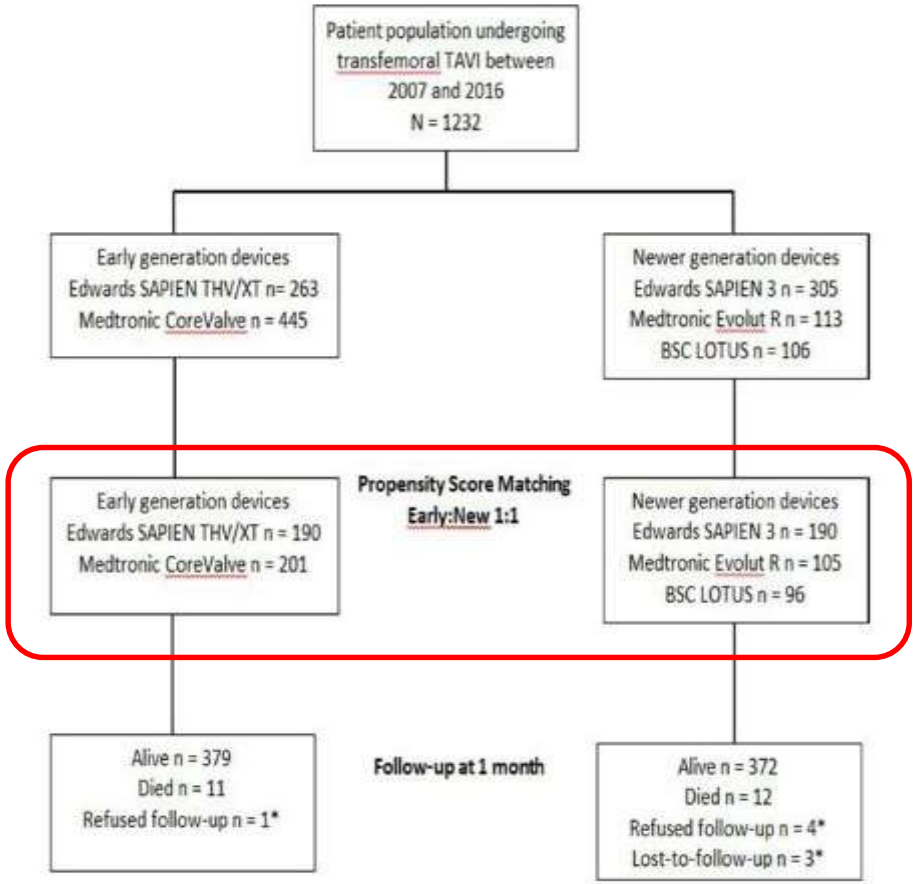
Feldman, et al., EuroPCR 2017; Manoharan, et al., *J Am Coll Cardiol Intv* 2015; 8:1359-67; Moellman, et al., PCR London Valves 2015; Grube, et al., EuroPCR 2017; Kodali, et al., *Eur Heart J* 2016; Vahanian, et al., EuroPCR 2015; Webb, et. al. *J Am Coll Cardiol Intv* 2015; 8:1797-806; DeMarco, et al, TCT 2015; Meredith, et al., PCR London Valves 2015; Falk, et al. Eur Heart J 2017; Kodali, TCT 2016; Reardon, M *NEJM* 2017; Reichenspurner H, et al., *JACC* 2017; Popma et al, JACC:CVInt 2017;10(3):268-75; Maisano F presented at TVT 2018

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.

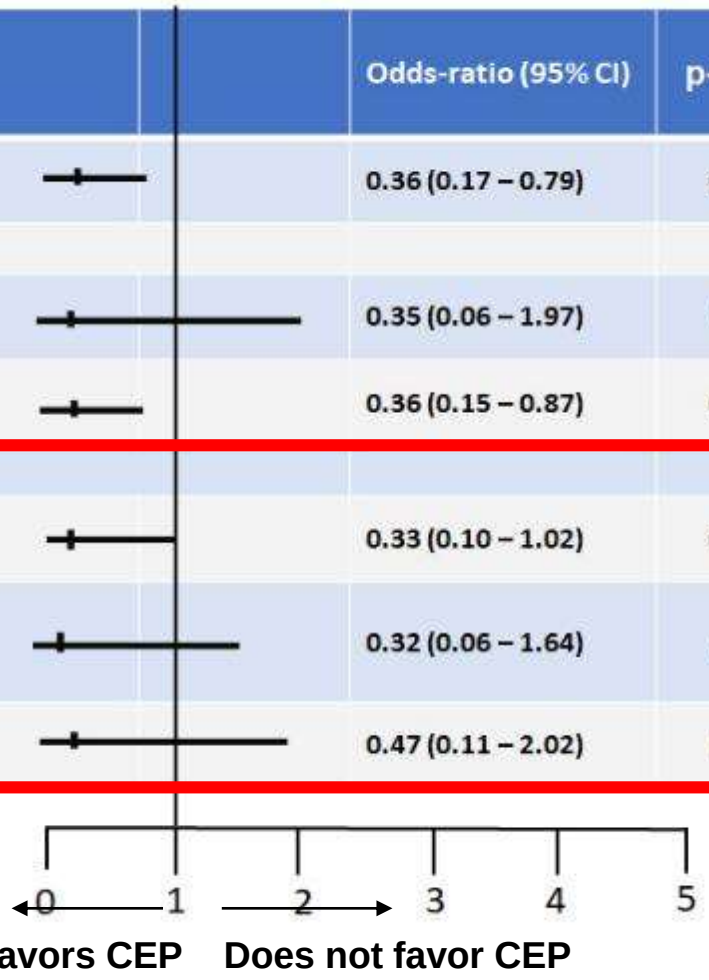


Pilgrim T. *et al. Open Heart* 2018;5:e000695

All-stroke sub-analysis shows peri-procedural (≤ 72 h) reduction in TAVR-related stroke with Sentinel regardless of valve type

- Analysis from Ulm University reveals a significant 62% reduction in TAVR-related stroke (p = 0.010) when Sentinel is used.
- Stroke was reduced regardless of valve type used (balloon, mechanical or self-expandable).

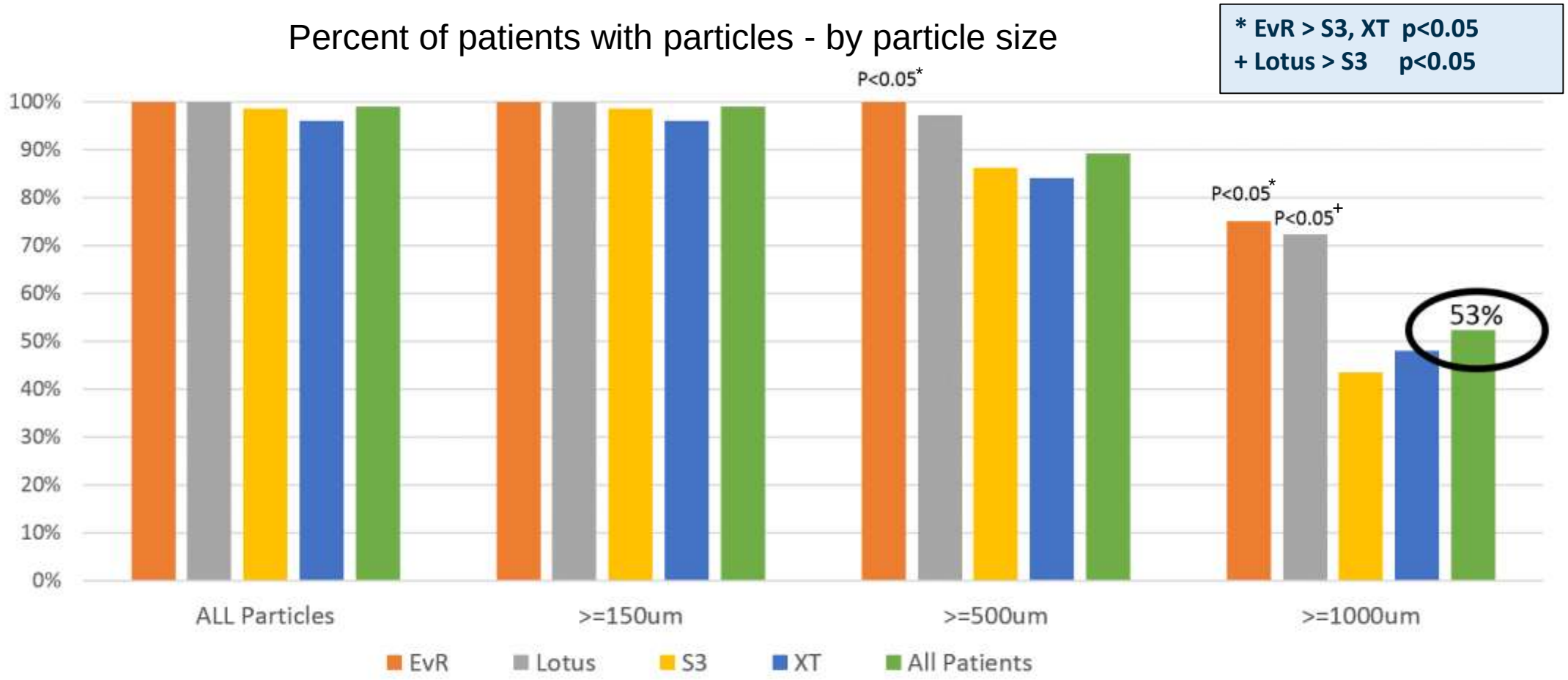
Subgroup	Number of Patients	TAVR + Sentinel (N=485)	TAVR Alone (N=485)	Odds-ratio (95% CI)	p-value
Total population	970	9/485 (1.86%)	24/485 (4.95%)	0.36 (0.17 – 0.79)	0.010
Anesthesia					
General	191/970 (19.7%)	2/111 (1/80%)	4/80 (5.00%)	0.35 (0.06 – 1.97)	0.23
Non-general	770/970 (79.4%)	7/371 (1.89%)	20/300 (5.01%)	0.36 (0.15 – 0.87)	0.023
Valve Type					
Balloon-expandable	674/970 (69.5%)	4/337 (1.19%)	12/337 (3.56%)	0.33 (0.10 – 1.02)	0.053
Mechanically expandable	170/970 (17.5%)	2/85 (2.35%)	6/85 (7.06%)	0.32 (0.06 – 1.64)	0.17
Self-expandable	124/970 (12.8%)	3/62 (4.84%)	6/62 (/9.68%)	0.47 (0.11 – 2.02)	0.31



Seeger J. presented at TVT 2018

Sentinel Captures Debris Regardless of TAVI Valve System

- Automated histomorphometry shows debris generated regardless of valve type placed.



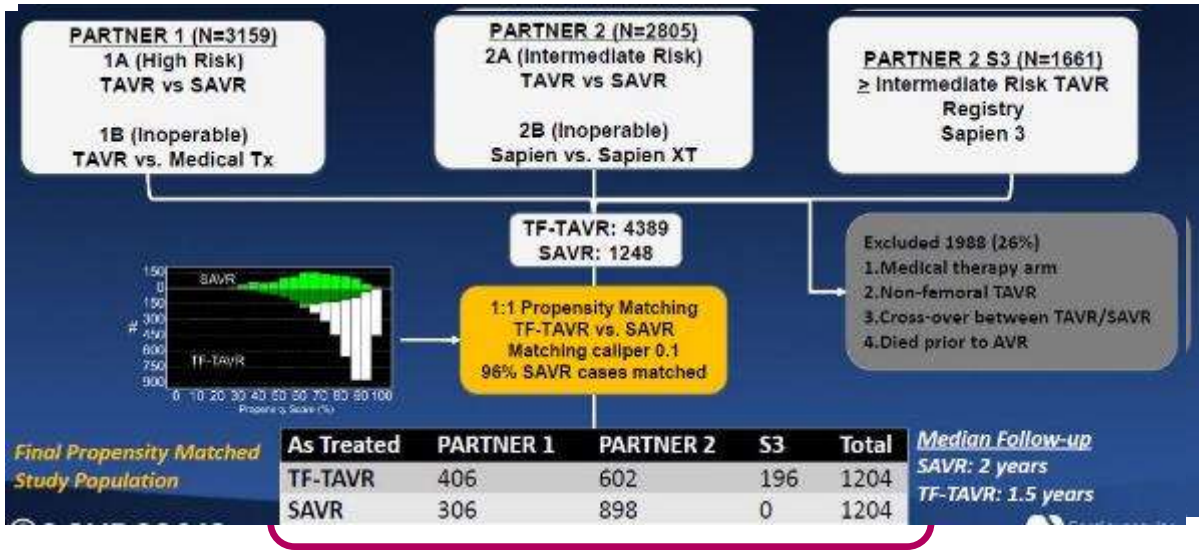
- Using pooled data from the SENTINEL IDE and SENTINEL H trials, histopathology and histomorphometry measured particle size, count and area of debris captured in 492 filters from 246 patients.

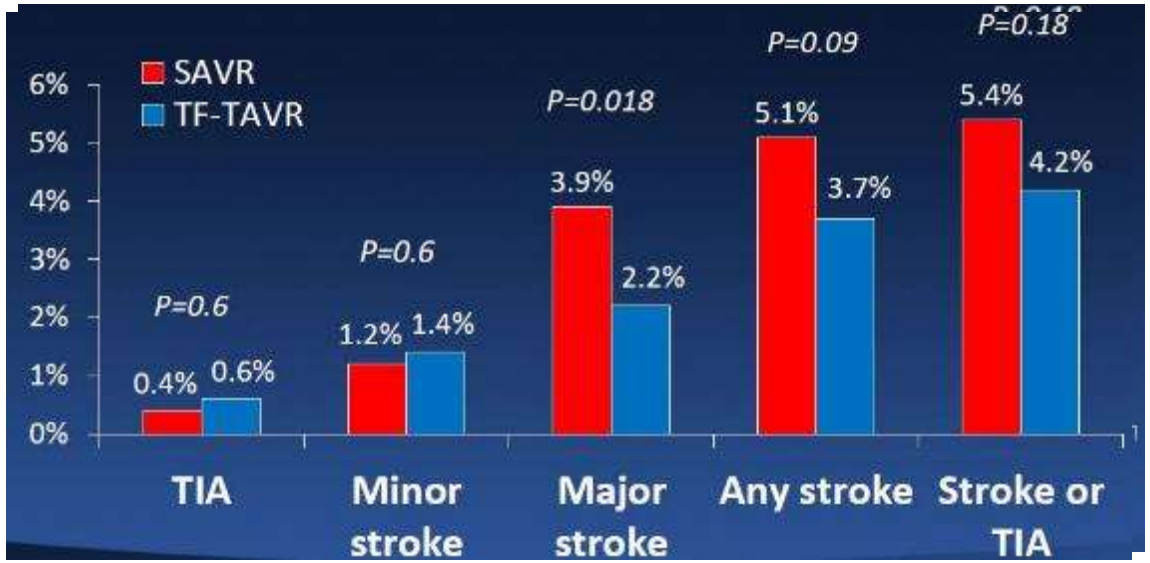
Note: 150µm used as size cut-off as filter pore size is 140µm

Schmidt T et al. 2018. *JACC Cardiovasc Intv.* 11(13):1262-1273

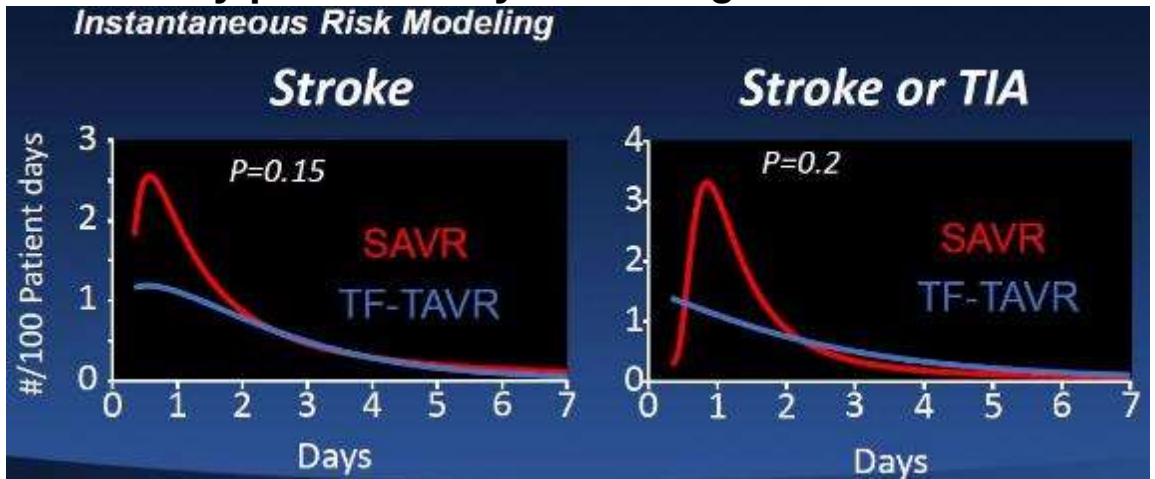
Pooled analysis of the PARTNER trials (1A, 2A, 2 S3) show 3.7% *all*-stroke rates in TAVR

- Neurological event risk was assessed in this large prospective cohort of SAVR vs TF-TAVR (N=2408) in a pooled analysis of the PARTNER trials.
- 30-d neurological events and early phase neurologic risk (<7 days) were assessed with stroke adjudication by an independent CEC committee.





Early phase <7 days neurological events



Post-op neurological assessments were mandatory for PARTNER 2 and 2 S3 cohorts but not PARTNER 1.

Huded C, presented at TVT2018

The arguments that you always hear…

- Stroke in TAVR is declining with every generation of TAVR system
- ***In high volume centers and with experienced operators, stroke has almost disappeared***
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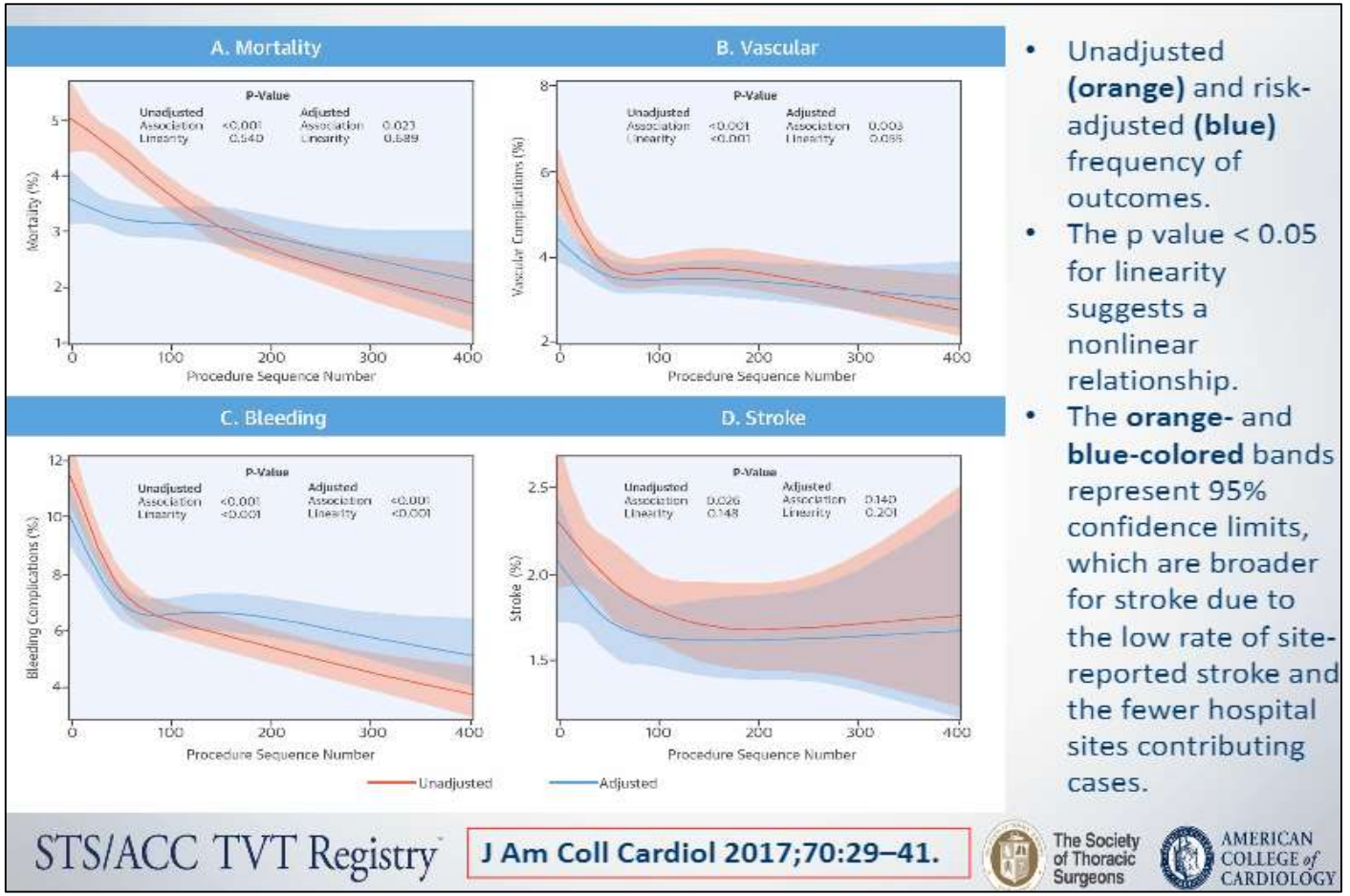
In high volume centers or experienced operators, stroke has almost disappeared

❖ **Increasing TAVR experience** was associated with lower in-hospital risk-adjusted outcomes, including mortality, vascular complications, and bleeding *but* ***was not associated with stroke***.

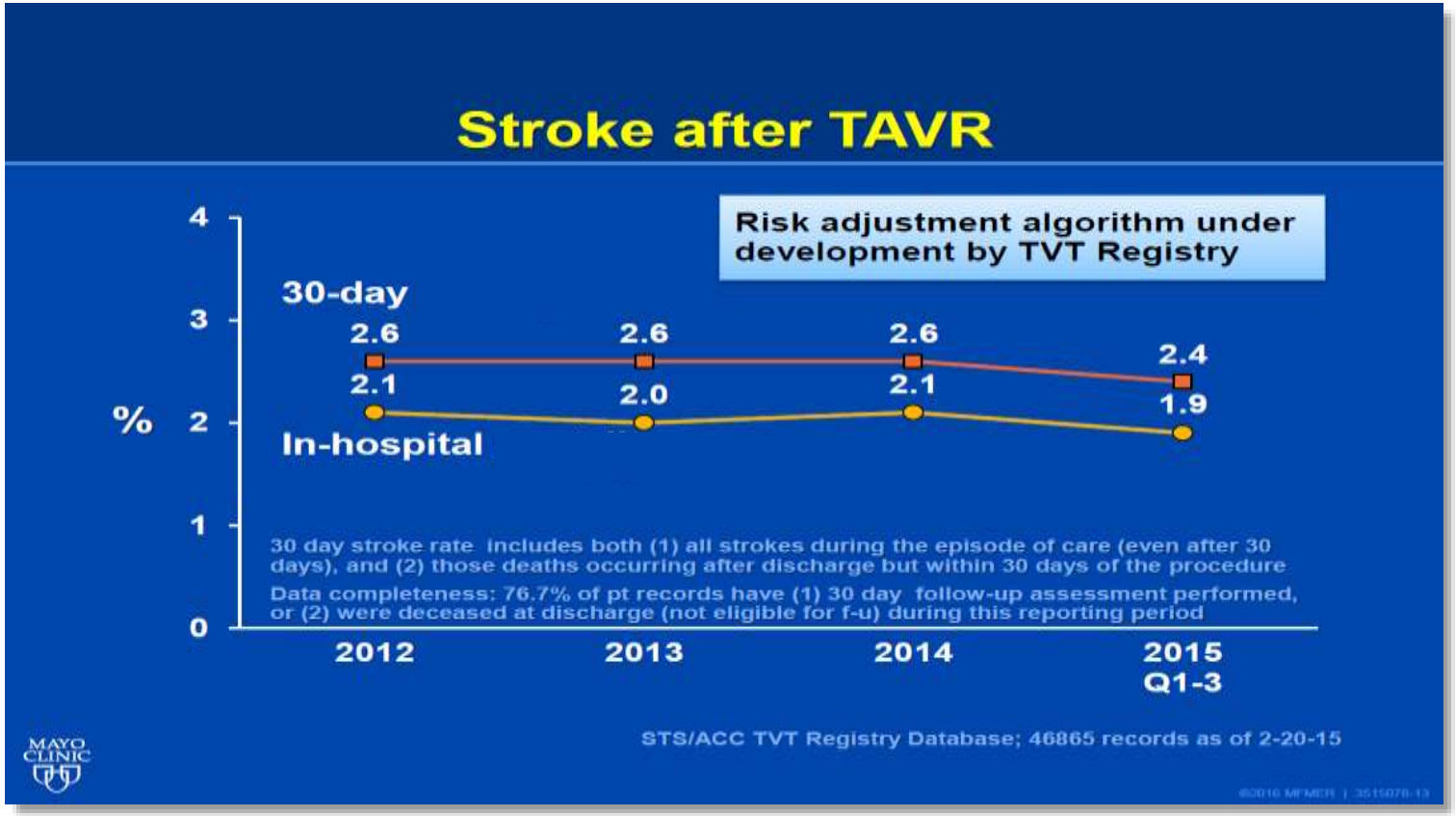
- TVT Registry
  - Data from 42,988 commercial TAVR procedures conducted at 395 hospitals
  - Focus on helping sites improve quality of care through national benchmarks

- *Stroke is independent of operator experience and remains a critical problem*



- 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.

TVT Registry shows no significant decline in stroke rate over time



- *Over 53,000 US TAVR patients*
- *No significant decline in stroke rate over time*

Holmes D, et al. ACC 2016

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).

Bestehorn K. *et al.* 2017 EuroIntervention;13:914-920.

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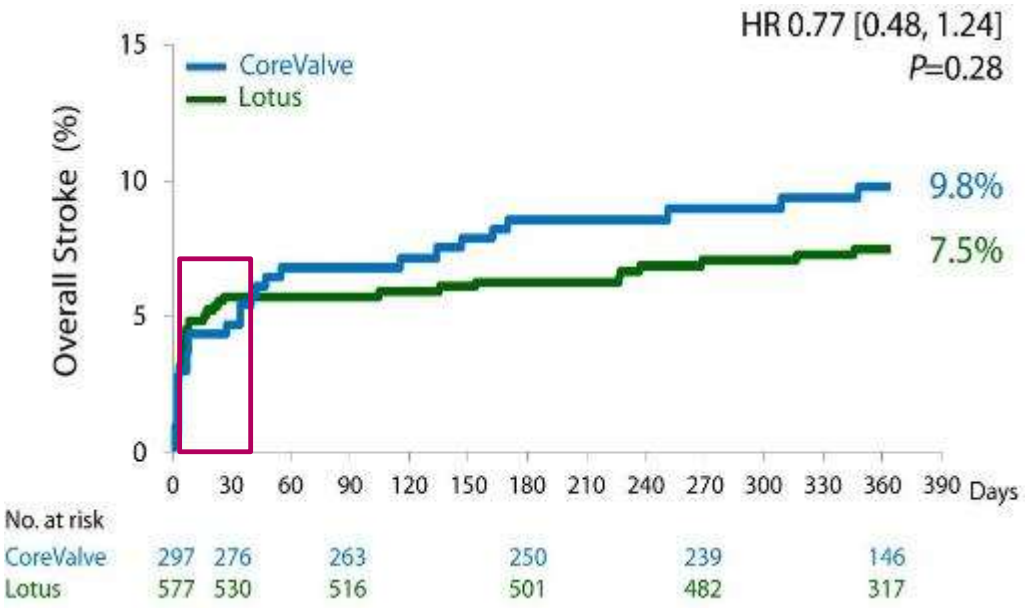
Baseline STS and serum creatinine are weak predictors of early stroke after TAVI: *Data from REPRISE III*

Weak Predictors of Early Stroke [Odds Ratios of >1]

Early Stroke 0-30 days	Univariate Odds Ratio [95% CI]	*P* value	Multivariate Odds Ratio [95% CI]	*P* value
STS Score	1.08 [1.02, 1.14]	0.01	1.07 [1.01, 1.13]	0.03
Serum creatinine (mg/dL)	1.01 [1.00, 1.01]	0.02	1.01 [1.00, 1.01]	0.03
Repositioning performed	2.19 [0.96, 4.99]	0.06		
Procedure time (minutes)	1.01 [1.00, 1.01]	0.07	1.01 [1.00, 1.01]	0.03
Age at time of consent	1.04 [0.99, 1.09]	0.09		
BMI (kg/m^2)	0.96 [0.91, 1.01]	0.11		
History of atrial fibrillation or Flutter	1.50 [0.83, 2.69]	0.18		

Univariate parameters with P<0.02 are shown.

Lotus and CoreValve <30-d Stroke Rates Still ~5%

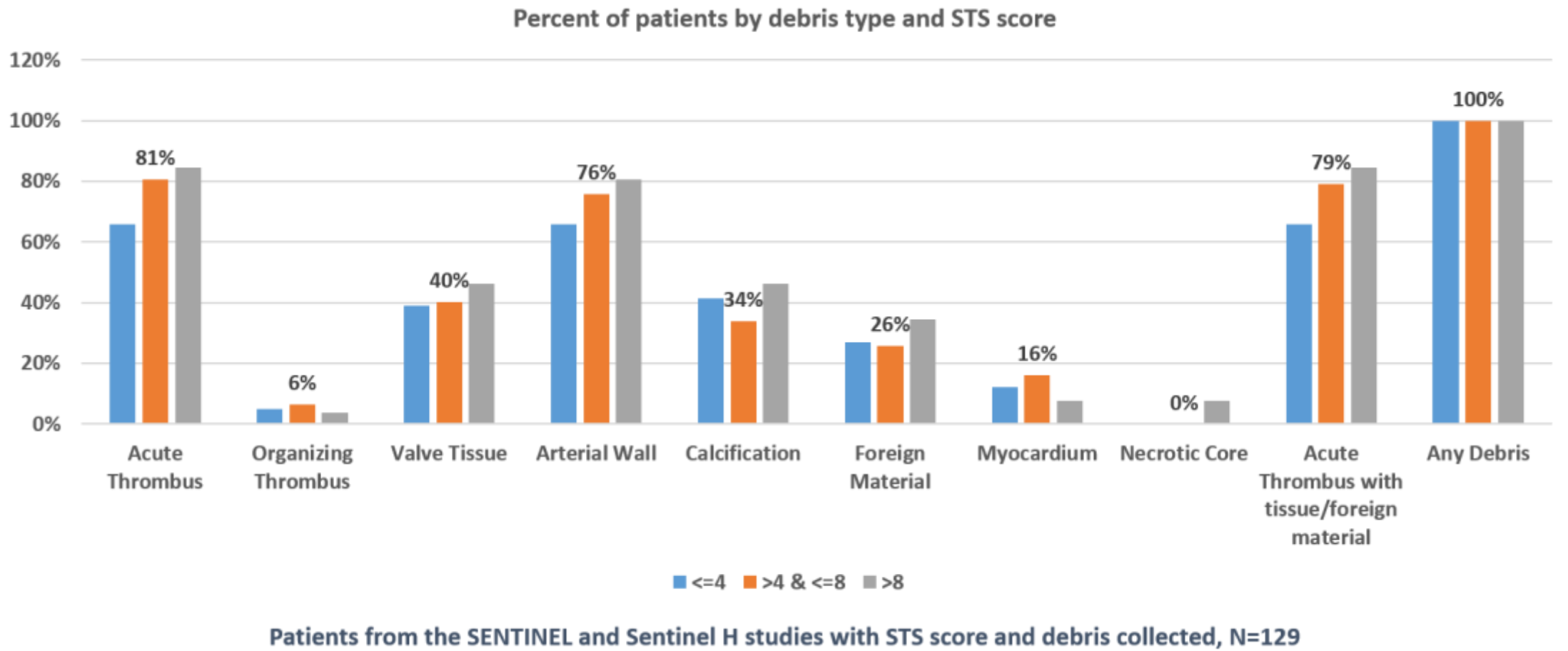


Implanted patient population: CoreValve includes CoreValve Classic and Evolut R;
KM event rate: log-rank P value

- Included are 607 and 305 patients implanted with Lotus and CoreValves, respectively who underwent rigorous VARC-based neurological exams at baseline, discharge, one year and following suspected stroke.
- Predictors of late stroke (31 days – 1 year) were mild PVL at 30 days and EF.
- Device type and EF were predictors of late stroke when only baseline variables were included in analysis.
- Mild or greater PVL at 30 days, EF and SOV area were predictors of late stroke when post-procedural variables were included.

Linke, presented at EuroPCR 2018

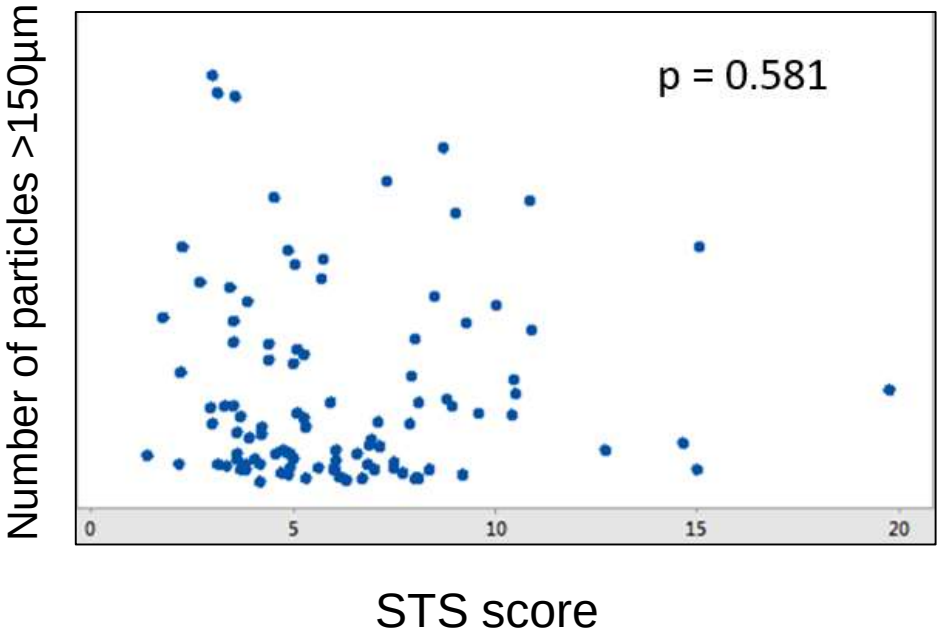
STS score does not predict frequency or type of embolic debris captured by Sentinel®



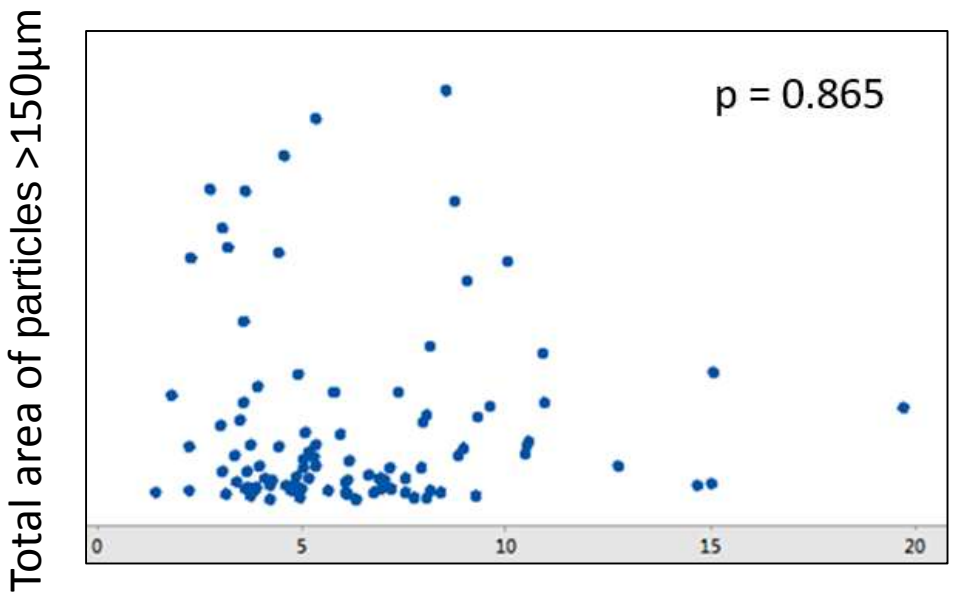
The data above did not reach statistical significance, per Fisher's Exact Test. Claret Medical - data on file for the SENTINEL IDE and SENTINEL H trials.

STS score does not predict total particle count or total area of embolic debris captured by Sentinel®

STS score does not correlate with Number of Particles Captured



STS score does not correlate with Total Area of Particles Captured



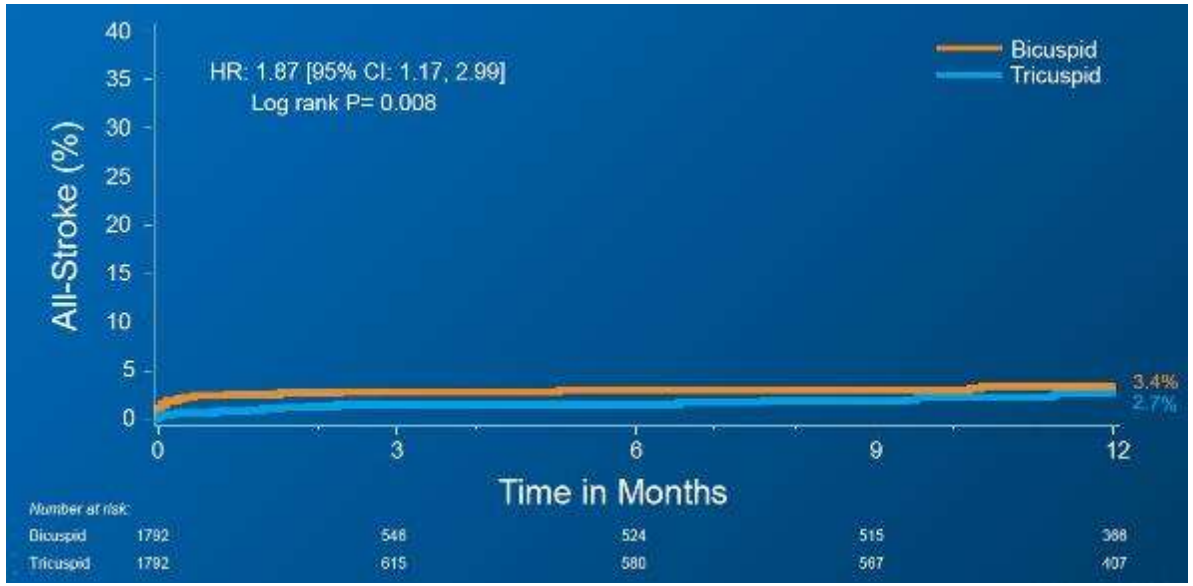
1. Claret Medical. Data on file from patients with histopathology analysis from SENTINEL IDE and Sentinel-H studies

A 2.5-fold higher peri-procedural (≤30 day) stroke rate among bicuspid S3 recipients may warrant consideration for cerebral embolic protection device use

- Data extracted from the STS/ACC TVT Registry were analyzed using a 1:1 propensity-matched approach which compared stroke and mortality outcomes among Edwards S3 recipients with bicuspid aortic stenosis (AS) and tricuspid AS (1792/group).

- Peri-procedural (≤ 30-d) stroke rates were 2.5-fold higher among bicuspid AS S3 patients as compared to the matched tricuspid AS cohort (p<0.0001).

One year all-stroke - Matched



30-day Outcomes – Matched

KM estimate %	Bicuspid	Tricuspid AS	p-value
All-cause mortality	2.9	2.1	0.11
All stroke	2.5	0.9	0.0001
Life-threatening bleeding	0.1	0.1	0.98
Major vascular complication	1.0	0.7	0.35
New pacemaker	9.3	8.4	0.42
Aortic valve reintervention	0.2	0.2	0.71

Makkar R, presented at EuroPCR 2018

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- **Sentinel does not adversely impact cath-lab workflow or timing**
- **In the SENTINEL Study:**

99% of cases had at least one filter deployed (both: 94.4%)

4 minute median time to deploy

91% deployed in under 10 minutes

~90% of anatomies accommodated

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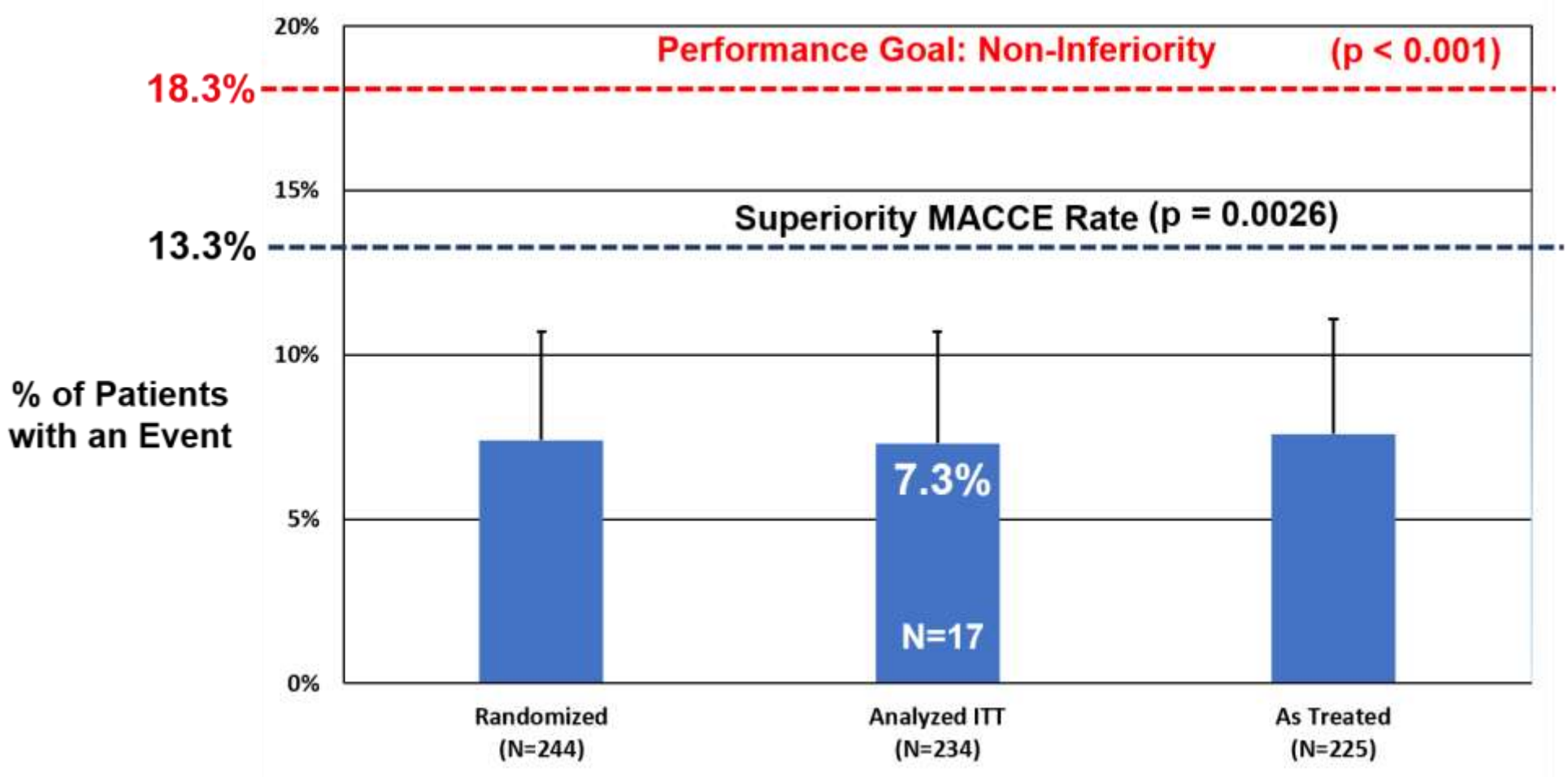
SENTINEL Primary Safety Endpoint : 30 Day MACCE

	Sentinel (Safety + Test) (N=234)		Control (N=111)		
	N	%	N	%	P-value
Any MACCE† patients	17	**7.3**	11	**9.9**	0.40
Events					
Death (all-cause)	3	**1.3**	2	**1.8**	0.65
Stroke	13	**5.6**	10	**9.1**	0.25
Disabling	2	**0.9**	1	**0.9**	1.00
Non-disabling	11	**4.8**	9	**8.2**	0.22
AKI (Stage 3)	1	**0.4**	0	**0**	1.00
TIA	1	**0.4**	0	**0**	1.00
Sentinel-related complications[1]	1	**0.4**	N/A	**N/A**	N/A

[1]Late brachial artery pseudo-aneurysm treated with thrombin injection
†MACCE defined as Death (any cause), Stroke (any), Acute Kidney Injury (Stage 3).
Note: MACCE events adjudicated by independent Clinical Events Committee who were blinded to treatment arm

SENTINEL Primary Safety Endpoint - 30-Day MACCE



Error bars represent upper bound of the one-sided 95% Upper CI

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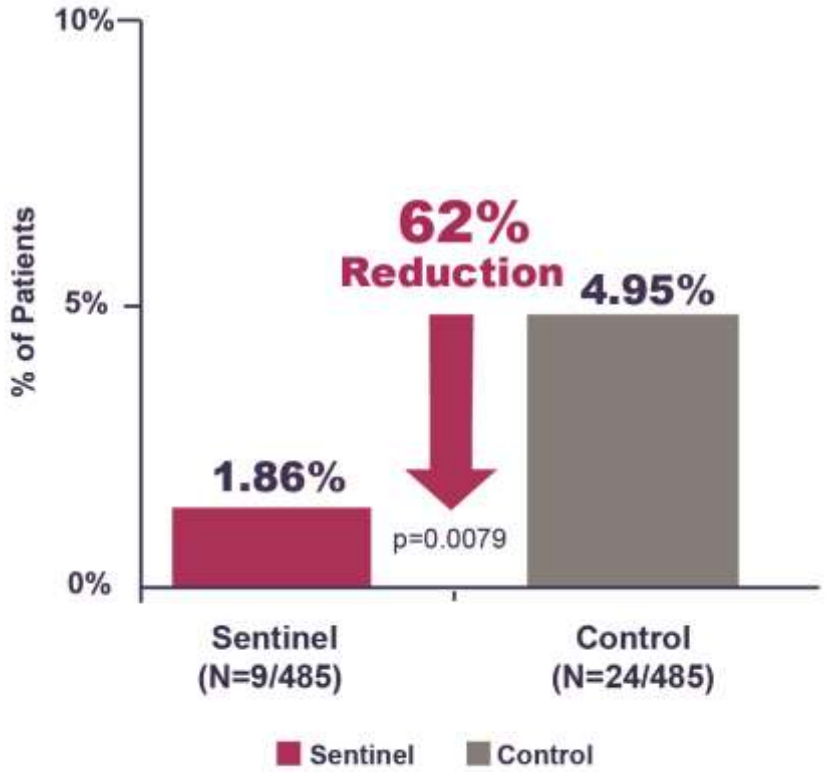
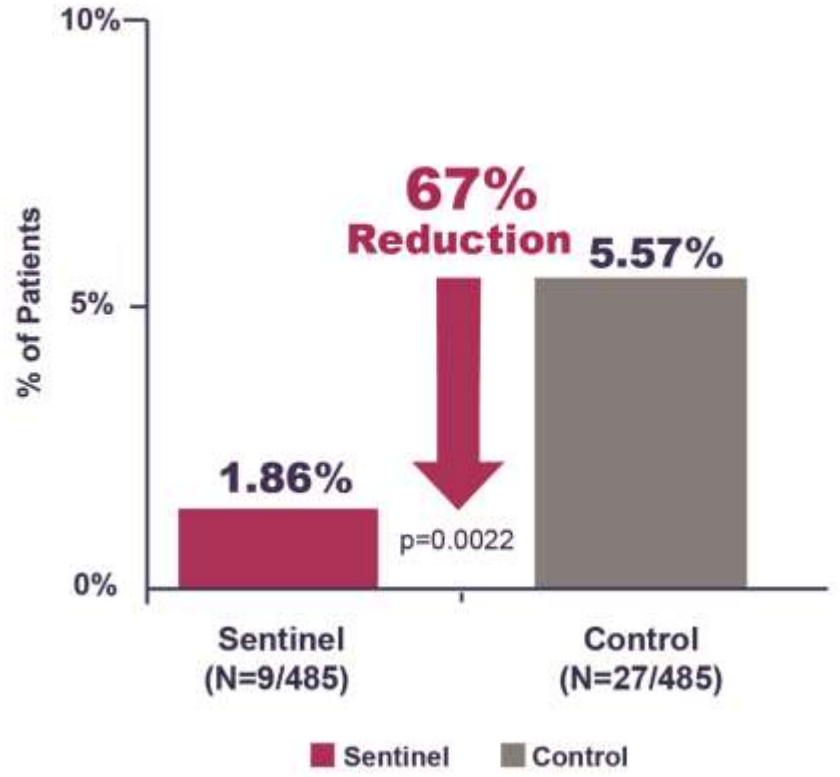
Patient level meta-analysis of 1164 patients demonstrates peri-procedural (≤ 72 h) stroke and mortality *or* stroke reduction with Sentinel use

All procedural stroke



Mortality *or* stroke



- N = 1164 pts combining SENTINEL IDE and Sentinel-Ulm data in a pooled propensity matched analysis.
- Data were matched for valve type, STS score, atrial fibrillation, diabetes mellitus, gender, coronary artery disease and PVD.
- The primary endpoint was all procedural stroke within 72 hours post-TAVI according to VARC-2 criteria.
- Secondary endpoint was the combination of all-cause mortality or all stroke within 72 hours after TAVI.

Seeger J. presented at TVT 2018

Findings from the SENTINEL Trial together with real world outcomes from Ulm, Erasmus and Cedars Sinai Medical Centers demonstrate consistent reductions in stroke among nearly 2,400 patients.

SENTINEL Trial[1]

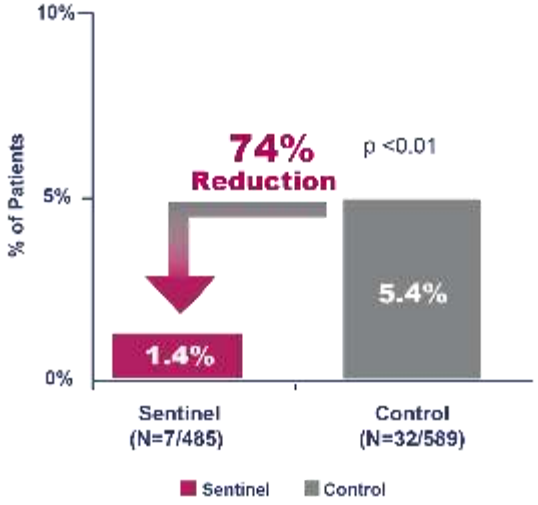
All stroke at ≤ 72 hours post-TAVR

Sentinel Ulm Study[2]

All stroke at 7 days post-TAVR

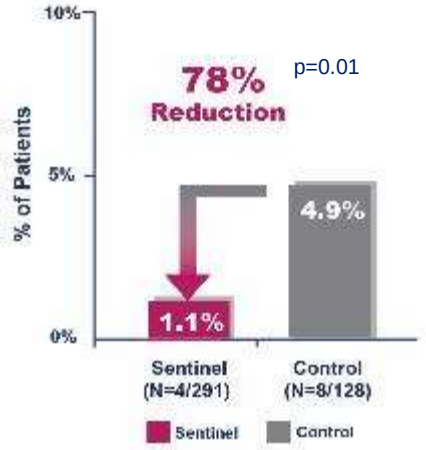
Erasmus and University Medical Centers[3]

All stroke at ≤ 72 hours post-TAVR



Cedars Sinai Medical Center[4]

All stroke at 7 days post-TAVR



[1]Kapadia S, et al. *J Am Coll Cardiol* 2017;69:367–77; [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

Consistent "Real-World" Single Center Experience

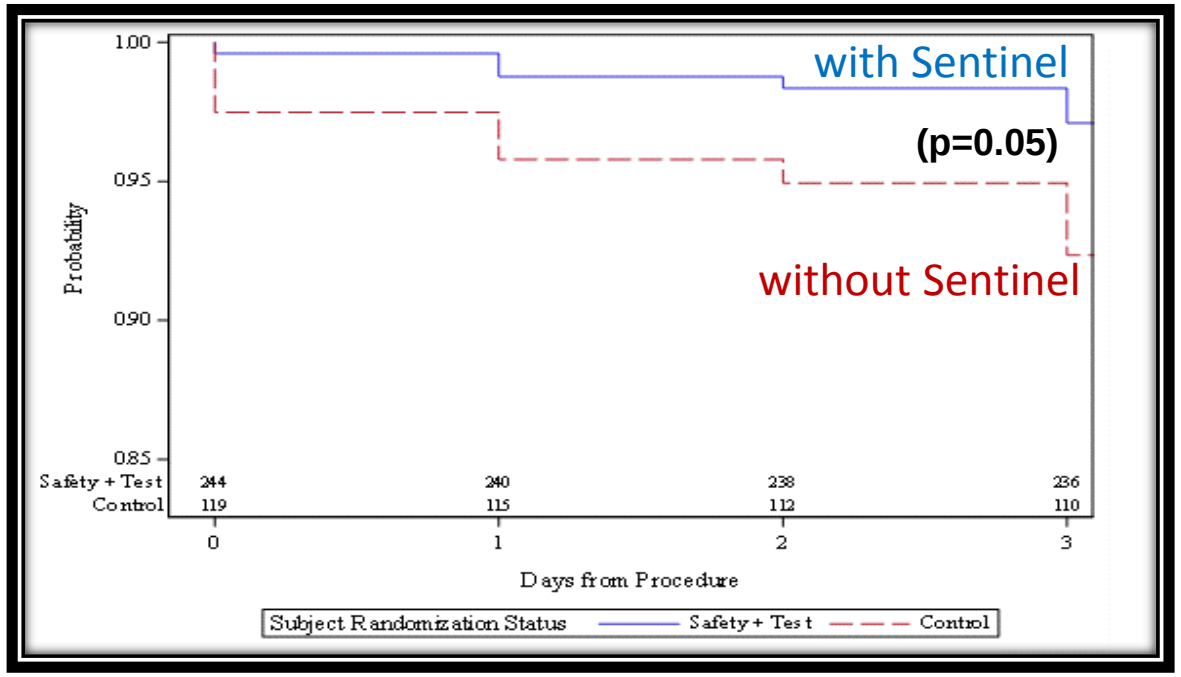
- Sentinel in real-world practice is consistently associated with a reduction in clinically assessed neurological events.
- Data from 2,169 TAVR patients across four independent centers show reproducible results.

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%	22	Propensity-score-matched All-stroke at 7-days
Pinnacle Health[2] • N=122 • Feb 2018	10% (7/69)	0% (0/53)	100%	10	All-stroke at 7-days Length-of-stay reduced from 3.2d without protection to 1.5d with Sentinel
Erasmus and University Med Centers in Rotterdam and Groningen[3] • 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[4] • N=440 • June 2018	4.9% (8/162)	1.1% (3/278)	78%	26	All-stroke at 7-days

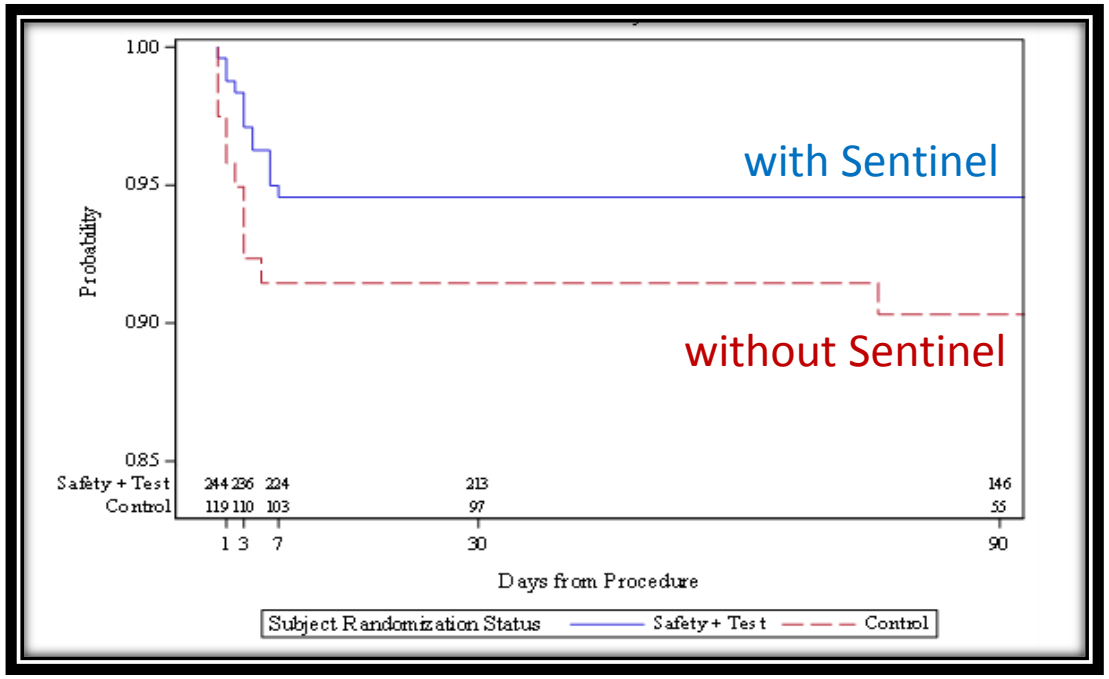
[1]Seeger J, et al. JACC Cardiovasc Interv. 2017 Nov 27;10(22):2297-2303; [2]Gada H, presented at CMS NTAP Town Hall meeting Feb 2018; [3]Van Mieghem N, presented at TVT 2018, manuscript in preparation; [4]Charavarty T, presented at TVT 2018, manuscript in preparation

SENTINEL Study: *Freedom from stroke K-M curves*

Sentinel provides a significant treatment effect during the critical peri-procedural timeframe that is preserved from post-procedure through 90 days.



Through 3 days post-procedure



Through 90 days post-procedure

Data on file from the SENTINEL IDE Trial.

Clinical Event Meta-Analysis of Cerebral Embolic Protection RCTs in TAVI
shows significant >40% reduction in risk of stroke or death with protection

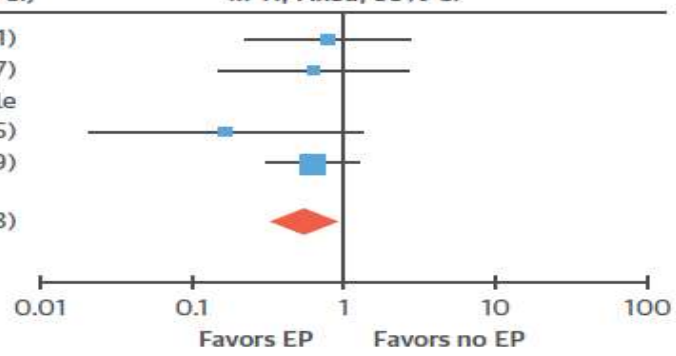
FIGURE 1 Clinical Outcomes in Patients Undergoing TAVR With Versus Without Embolic Protection Devices

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.

- Meta-analysis of 5 randomized controlled trials (RCT) of cerebral protection in TAVI
  - 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."

Giustino, et al. JACC 2017; 69(4):465-6

The arguments that you always hear…

- Stroke in TAVR is declining with every generation of TAVR system
- In high volume centers or experienced operators, stroke has almost disappeared
- Stroke is more prevalent in high-risk patients as low-risk patients will have less debris
- Cerebral Protection is complicated to use and adds time to my procedure
- It adds risk to my procedure
- There is no evidence that it actually reduces stroke
- There is no evidence that strokes are procedural in nature so why not use NOACs post procedure
- ***The only available device (Sentinel) doesn't cover all four arteries supplying blood to the brain***
- It costs too much

The only available device (Sentinel) doesn't cover all four arteries supplying blood to the brain

Surely better to protect the majority of the brain by covering 3 vessels than to leave the entire brain unprotected and wait for a better device!
The next generation will cover all 4 vessels!

PS:
Were the first generation self-expanding and balloon-expandable valves perfect?

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- The only available device (Sentinel) doesn't cover all four arteries supplying blood to the brain
- ***It costs too much!***

Effect of Stroke on Economics of TAVR

PARTNER Trial – major stroke was a contributor to cost related to TAVR

Gada H, presented at TVT2018

It costs too much…?

- ***In the index hospitalization:***
  - Periprocedural stroke could add more than ***$25,000*** to the cost of acute care during the initial post-procedure hospitalization[1]
- ***After discharge:***
  - Ischemic stroke with moderate disability can increase annual health-care costs by up to ***$60,000***, with accrual based on longevity[1]
  - Results in deductions from fee-for-service revenue (Post-Acute Care Transfer Policy)
- ***Longer term:***
  - Transitioning from mild cognitive impairment to mild dementia has been shown to add an annual excess cost of ***$6,000*** per patient.[2]

[1]Freeman JV, *Ann Intern Med*. 2011. [2]Lin PJ, *Alzheimers and Dementia*. 2013

Claret Medical Acquisition

Boston Scientific Closes Acquisition of Claret Medical, Inc., Announces Positive Reimbursement Decision

Aug. 2, 2018, 05:10 PM

Boston Scientific announced a definitive agreement to acquire Claret Medical on July 20, 2018 for **$220 million in up-front cash** with an additional **$50 million payment** for reaching a reimbursement-based milestone, which has been fulfilled with the recent NTAP designation.

"The Sentinel System is an exciting platform technology designed to reduce the risk of procedure-related stroke in TAVR and other left-heart and endovascular procedures, and is an increasingly important consideration for patients and physicians as the TAVR indication expands to treat a younger patient population," **said Kevin Ballinger, president, Interventional Cardiology, Boston Scientific.** "The recent CMS NTAP designation underscores the clinical value of the Sentinel System and will allow for accelerated adoption of this adjunctive therapy amongst structural heart centers."

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

Let's use them in all patients until
Data prove otherwise!

Thank you for your kind Attention !