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Where to with cerebral protection in TAVI?

Horst Sievert,

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Disclosures I

Physician name	Company	Relationship
Horst Sievert	4tech Cardio, Abbott, Ablative Solutions, Ancora Heart, Bavaria Medizin Technologie GmbH, Bioventrix, Boston Scientific, Carag, Cardiac Dimensions, Celonova, Cibiem, CGuard, Comed B.V., Contego, CVRx, Edwards, Endologix, Hemoteq, InspireMD, Lifetech, Maquet Getinge Group, Medtronic, Mitralign, Nuomao Medtech, Occlutech, pfm Medical, Recor, Renal Guard, Rox Medical, Terumo, Vascular Dynamics, Vivasure Medical, Venus, Veryan	Consulting fees, Travel expenses, Study honoraria

Disclosures - II

This is a difficult topic!

If a topic is difficult:

Initiate a debate!

So this will be a debate
Horst Sievert against Horst Sievert

And we will see who will win!

Horst Sievert:

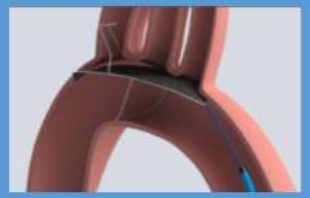
Pro embolic protection during TAVI

Why is embolic protection needed?

- Stroke is an unpredictable and devastating event which is underdiagnosed and underreported in TAVI
  - In the SENTINEL trial, prospective assessment by neurologists revealed a 30-day stroke rate in unprotected TAVI of 9.1%!
- Cerebral embolic debris is generated in at least 99% of TAVI patients[1]
- Capturing and removing this debris with the Sentinel Cerebral Protection System significantly (p=0.05) reduced the risk of periprocedural stroke in TAVI by **63%**[2]
- Patients just deserve “Protected TAVI”
- 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 FDA Advisory Panel 2/23/2017

Cerebral Protection Devices

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

FDA Clears Sentinel for Cerebral Protection During TAVR

Patrice Wendling

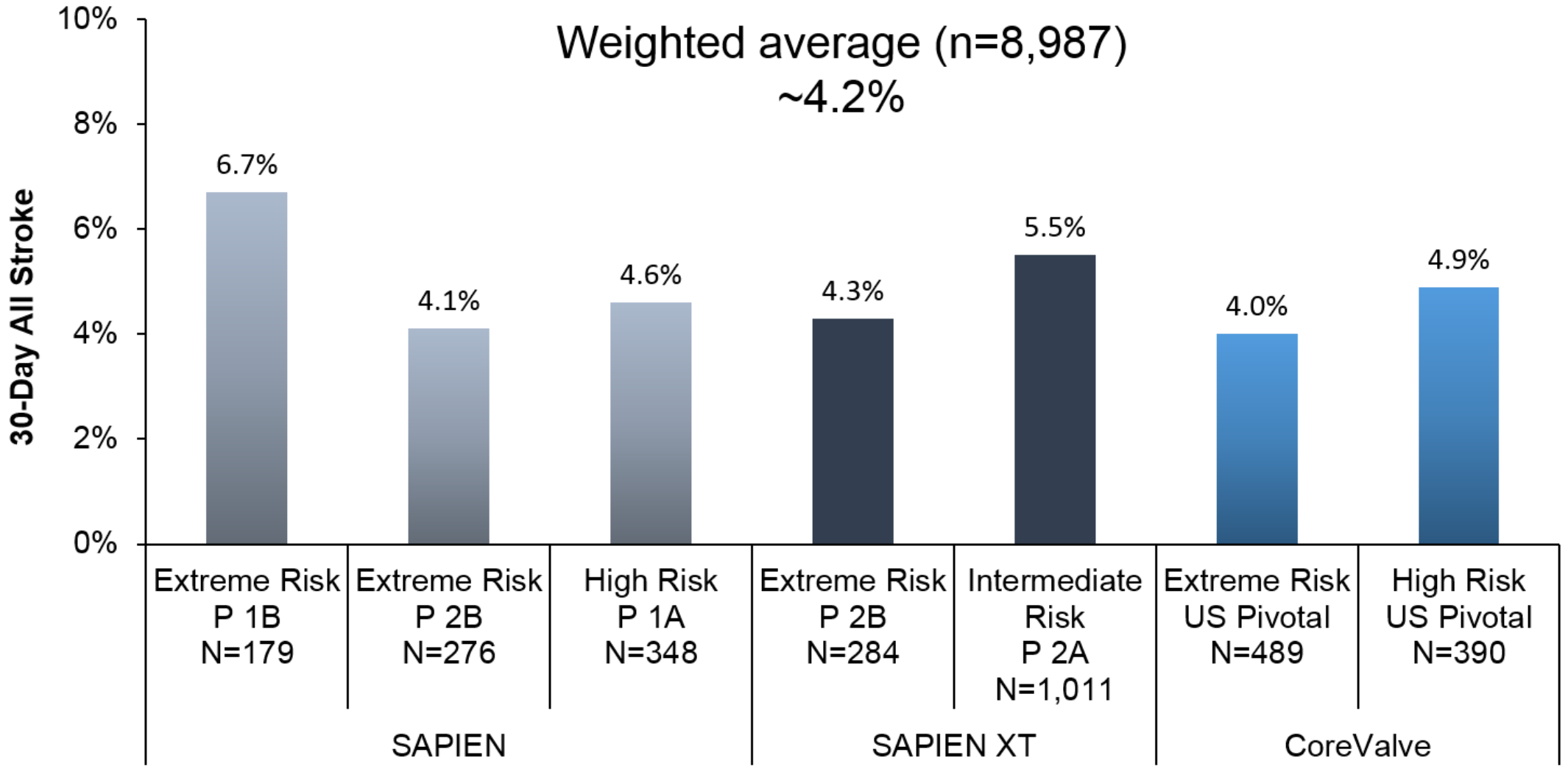
June 05, 2017

SANTA ROSA, CA — The US Food and Drug Administration (FDA) today cleared the first cerebral protection device for use in patients undergoing transcatheter aortic-valve replacement (TAVR), according to the device manufacturer[1].

The *Sentinel Cerebral Protection System* (Claret Medical) contains a proximal and distal filter to capture embolic debris dislodged by the procedure.

Earlier this year, an FDA advisory panel took no formal vote but gave the device a green light after agreeing it carries a low safety risk and that it can't

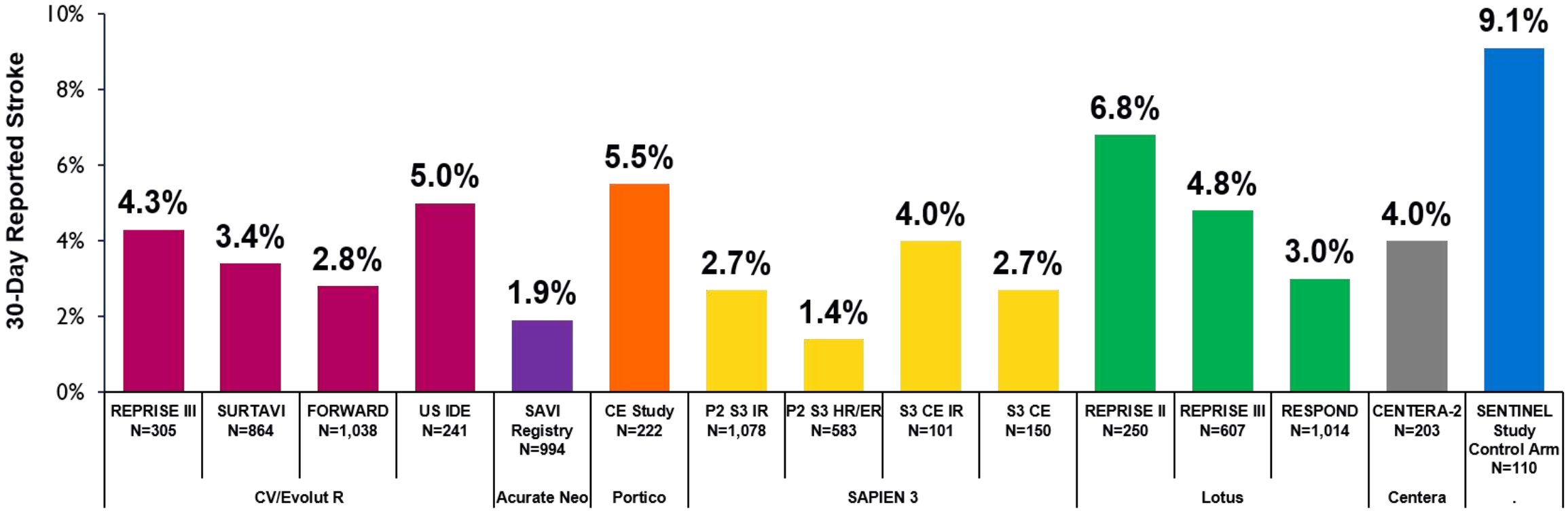
TAVI Stroke Rates with Foundation TAVI Valves



[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;;

Stroke rate did not improve with newer valves!

- TAVR device trials tend to emphasize only the major/disabling stroke rates.
- Even the latest system to obtain CE Mark – CENTERA reports a 4% stroke rate at 30-days.

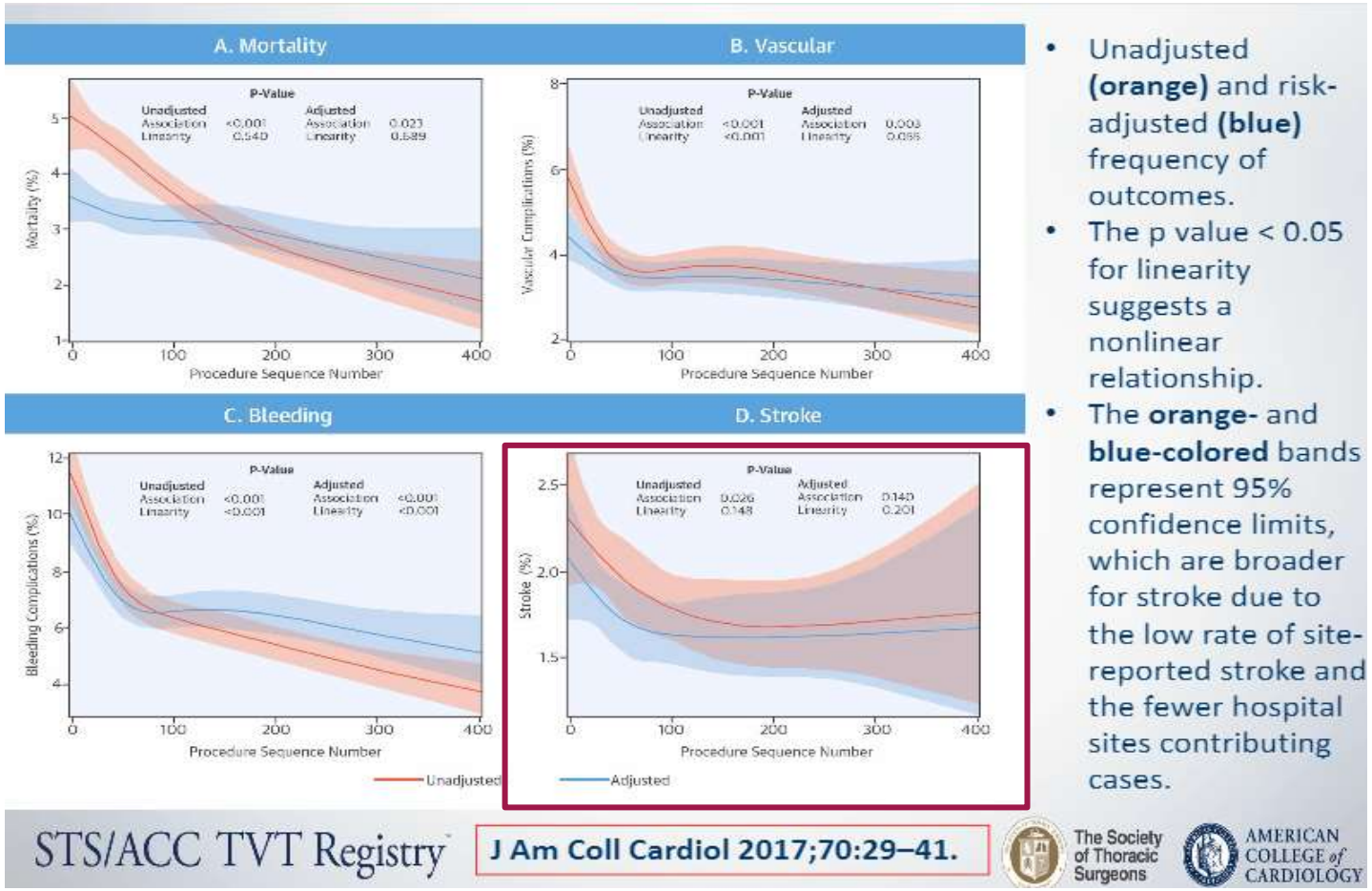


[1] Feldman, et al., EuroPCR 2017; [2]Manoharan, et al., J Am Coll Cardiol Intv 2015; 8: 1359-67; [3]Moellman, et al., PCR London Valves 2015; [4]Grube, et al., EuroPCR 2017; [5]Kodali, et al., Eur Heart J 2016; [6]Vahanian, et al., EuroPCR 2015; [7]Webb, et. al. J Am Coll Cardiol Intv 2015; 8: 1797-806; [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

Stroke Risk is Independent of Experience and Operator Volume

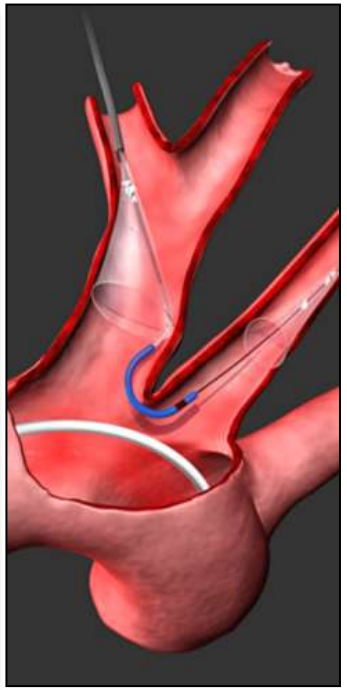
- Increasing site volume was associated with lower in-hospital risk-adjusted outcomes, including mortality, vascular complications, and bleeding *but was not associated with stroke*.

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



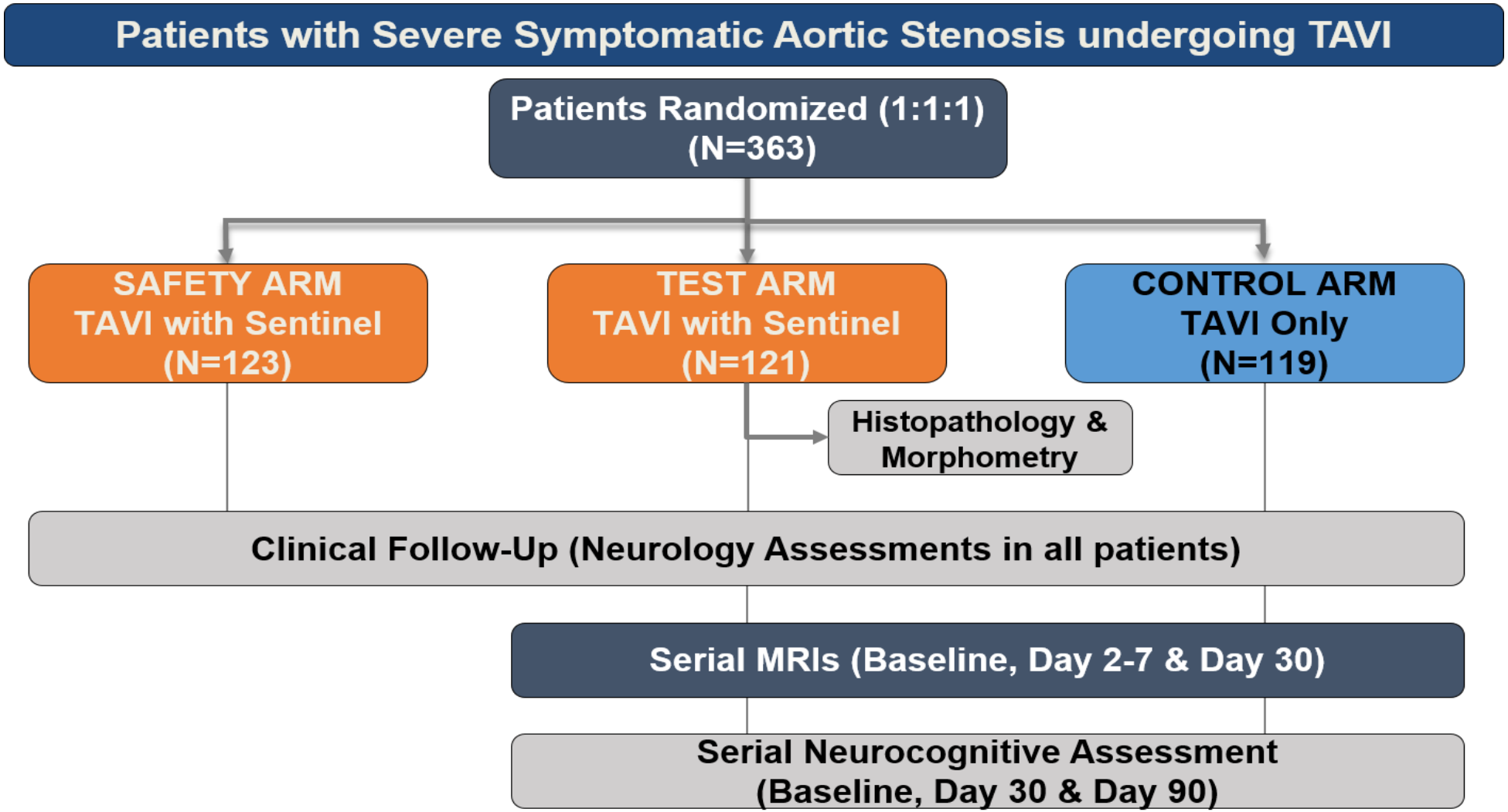
Carroll J, TVT 2017

Sentinel Cerebral Protection System



- Two independent polyurethane filters
  - Brachiocephalic and left common carotid
- Right trans-radial sheath access (6F)
- Minimal profile in aortic arch (little interaction with other devices)

SENTINEL Trial Design Overview

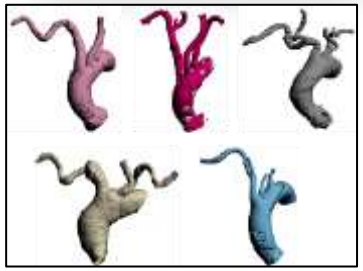


How did the SENTINEL Filter perform?

99% of cases had at least one filter deployed
Both filters deployed: 94.4%

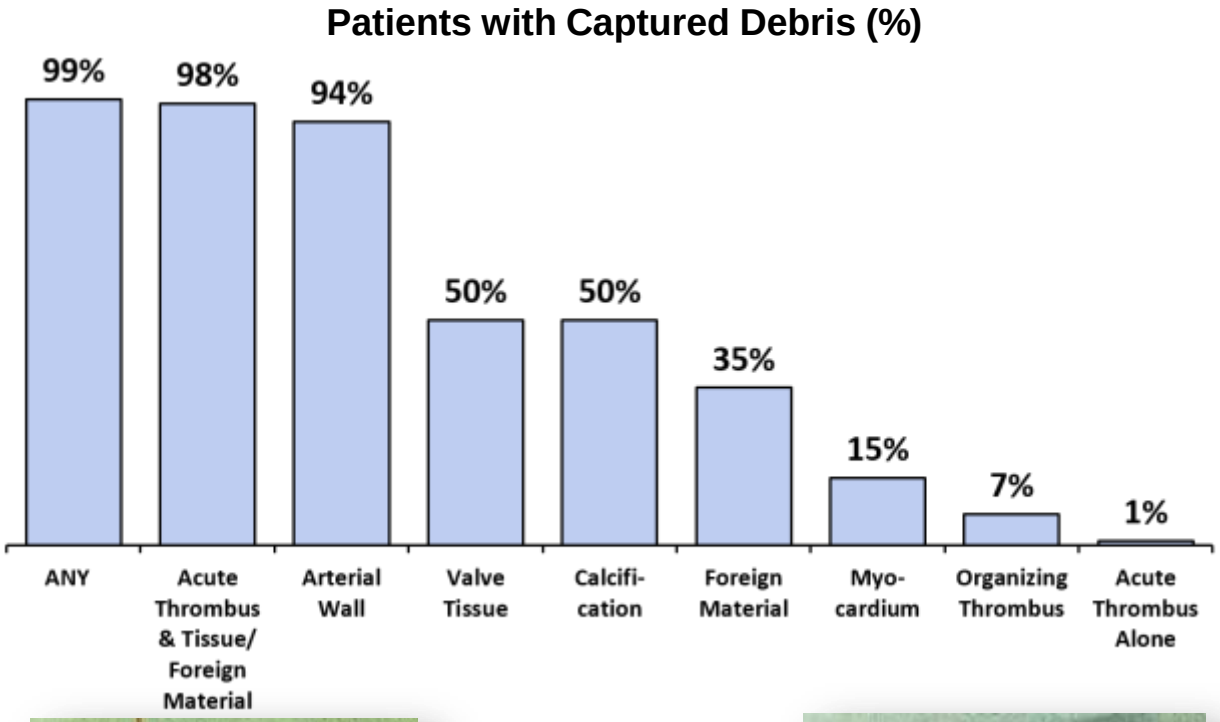
4 Minutes -Median time to deploy the filter

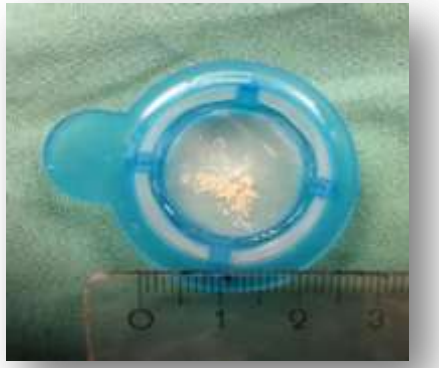
91% of filters deployed in under 10 min

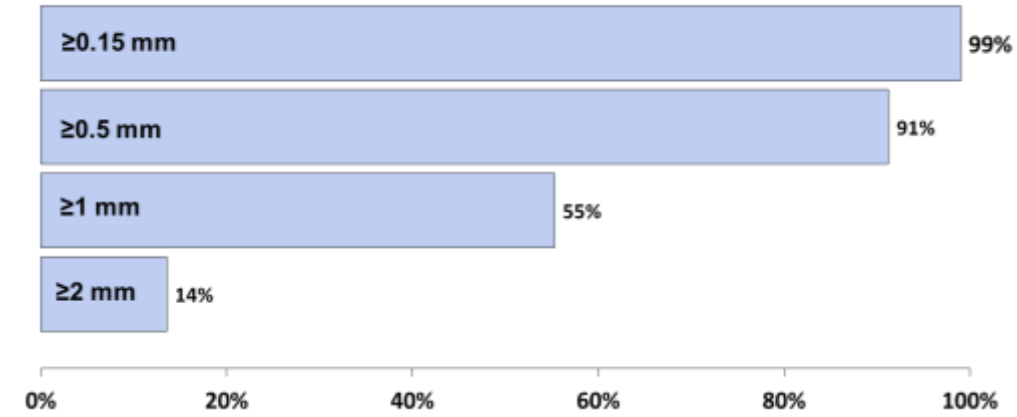


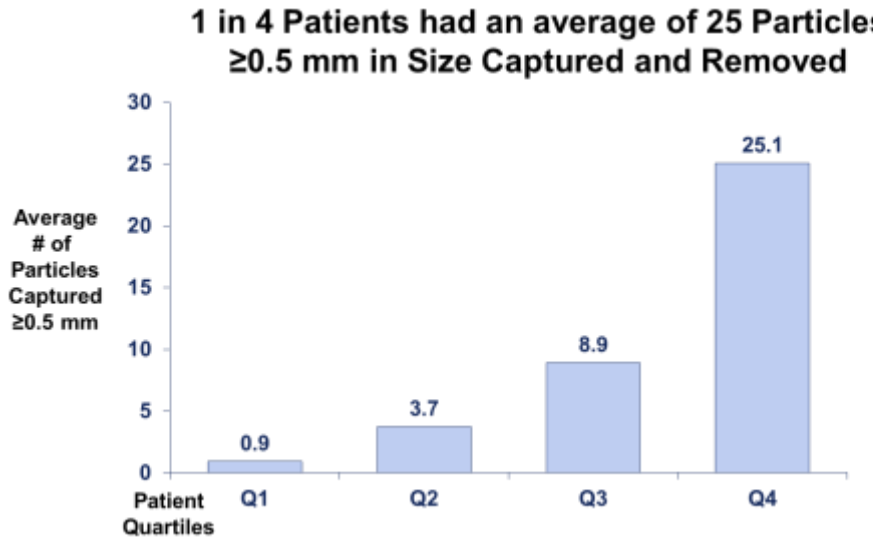
One size accommodates **~90%** of anatomies

Sentinel™ 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

No additional risk of using Sentinel vs. unprotected TAVI

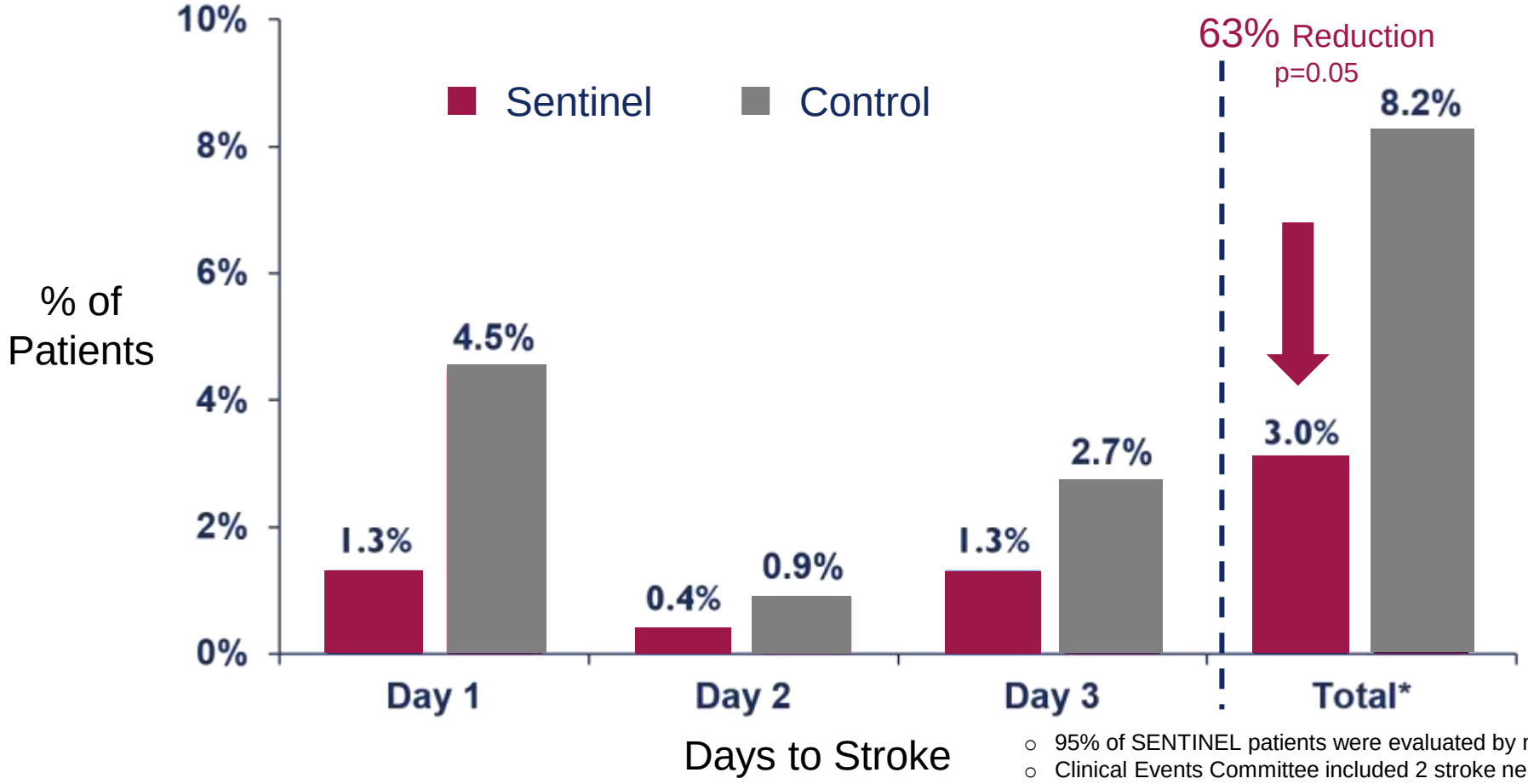
SENTINEL Study: 30-Day Clinical Safety Results (Analyzed Intention to Treat Population)

	Sentinel (Safety + Test) (N=234)		Control (N=111)		P-value
	N	%	N	%	
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 Study Demonstrates Peri-Procedural Stroke Reduction

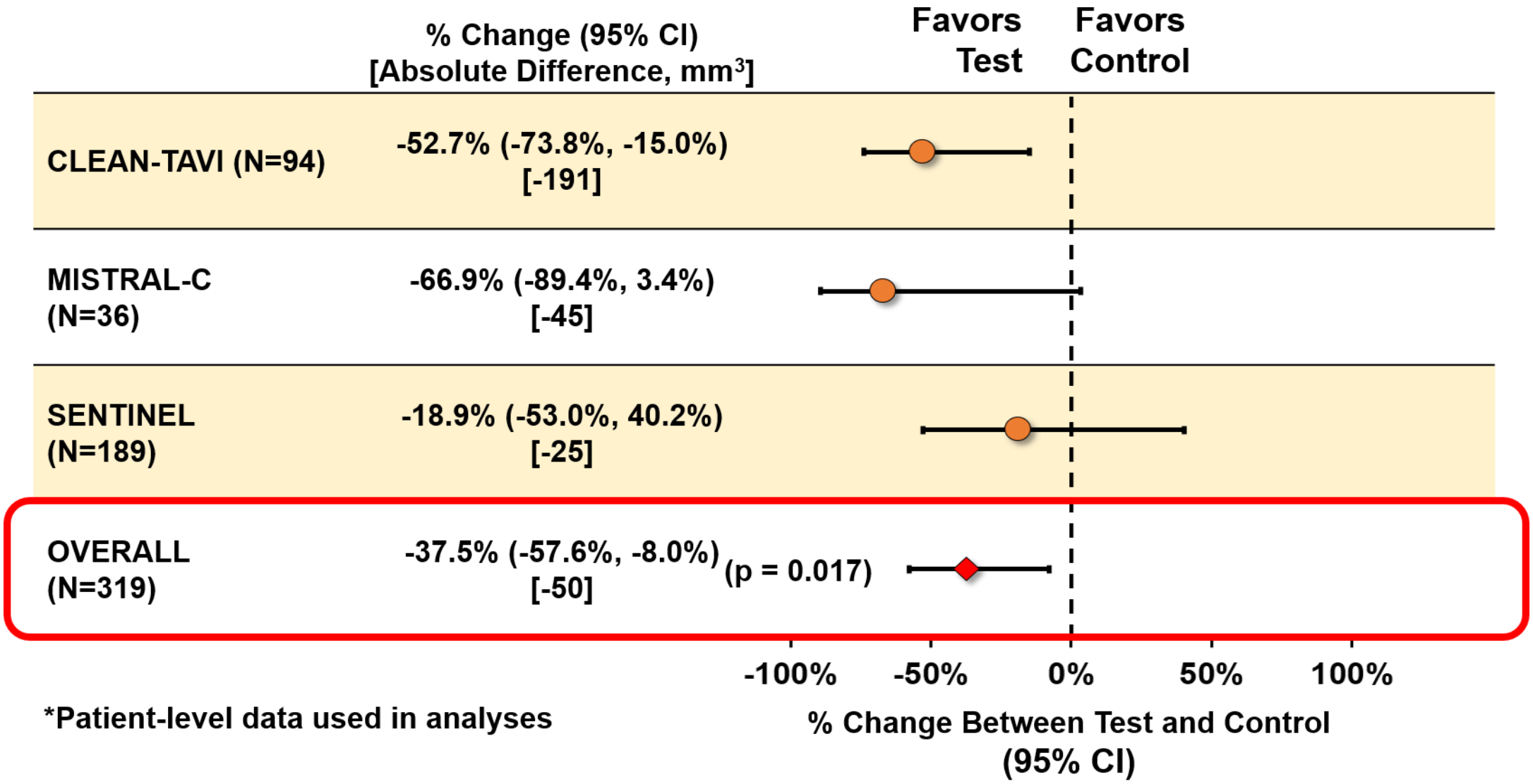
Statistically significant 63% peri-procedural stroke reduction with Sentinel use



- 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

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

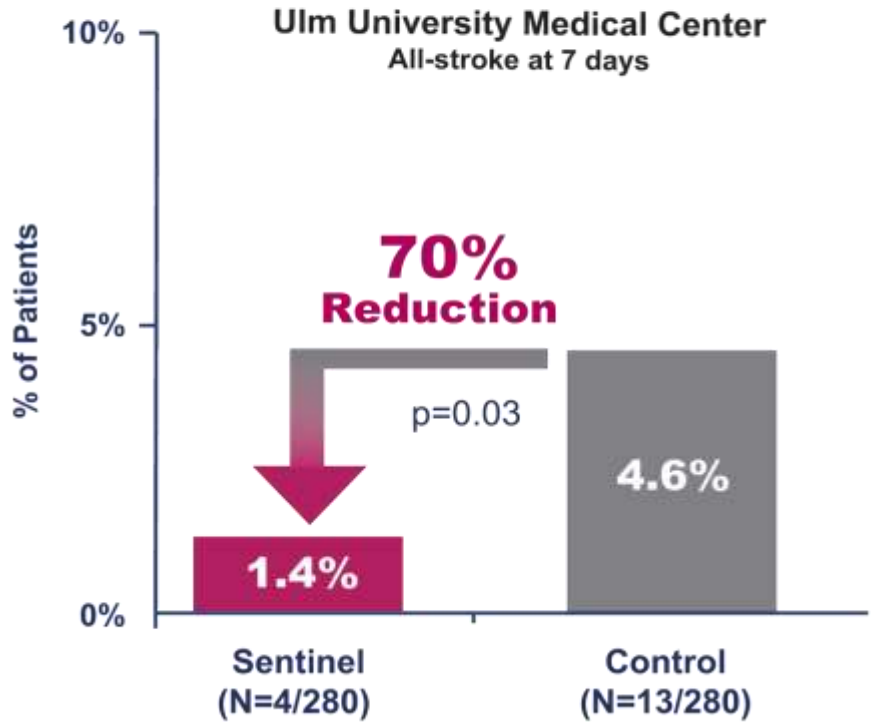


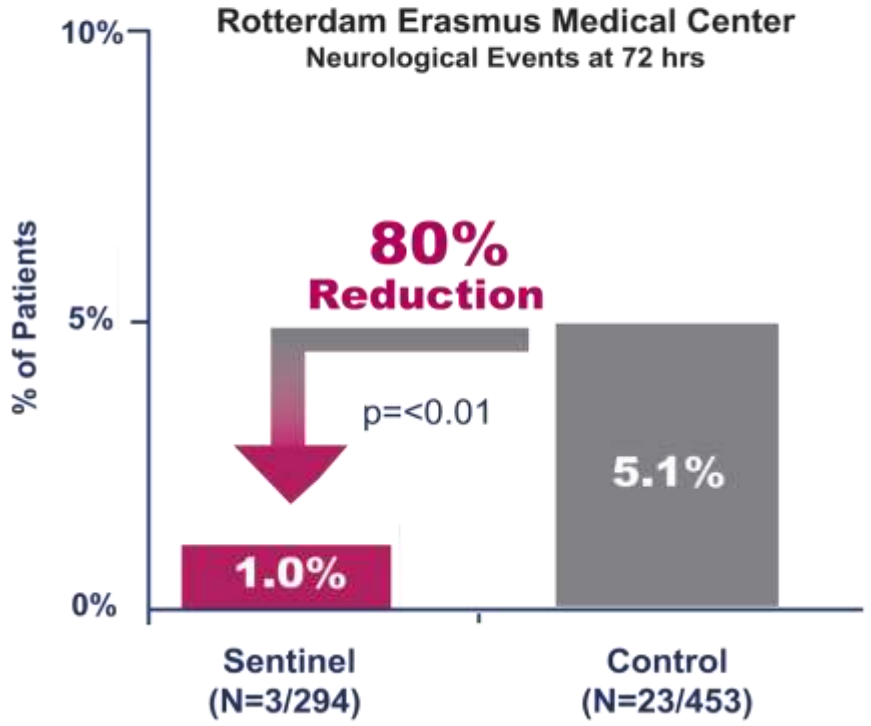
*Patient-level data used in analyses

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

Sentinel Use in Routine Practice from Ulm University and Erasmus Medical Center

Real-world studies continue to demonstrate reduction in peri-procedural neurological events[1,2]





[1] Seeger J, et al. JACC Cardiovasc Inrerv. 2017 Nov 27;10(22):2297-2303
[2] van Mieghem N, et al. presented at JIM 2018 and CRT 2018

The evidence is clear!

- Stroke is a major problem in TAVI
  - Frequent, underdiagnosed and underreported
- Cerebral embolic debris is generated in at least 99% of TAVI patients
- In addition to all clinical stroke, cerebral ischemic damage is also an important risk factor for dementia, cognitive decline, and mortality
- Cerebral protection is safe
- Cerebral protection is effective
- Cerebral protection has to be done in all TAVI procedures

Contra embolic protection during TAVI

That was ridiculous!
You should **not** trust Horst Sievert!

- He is an interventional cardiologist!
- He likes to play with all kind of catheter tools!
- He is completely biased towards any intervention
- He has for sure many conflicts of interest

Currently, there is almost no place for embolic protection!

- It is true, nobody wants to have emboli in the brain!
- Also, everybody agrees that it would be good to prevent emboli
- It seems to be self-evident that emboli can be prevented by embolic protection devices
- However: "There is no free lunch!"
  - Everything has a price: additional complications, time and/or cost
- We are living in the era of evidence based medicine!
  - "seems to be logical" is not enough anymore
  - we need positive randomized trials before we can implement a new therapy into clinical practice
    - and we know that in the view of guideline writers and payers one positive trial may not even be enough!

Are the strokes reported by neurologist and imaging clinically relevant at all?

- Many of us immediately like to believe they are relevant
- However, there are conflicting observations!
- "Silent brain infarctions" occur after many procedures:
  - CABG: 18-42%
  - Surgical AVR: 48%
  - Carotid stenting: 20-70%
  - AF Ablation: 50%
  - Diagnostic cardiac cath: 3-18%

So would you seriously consider embolic protection devices during coronary angiography??

New brain lesions after carotid revascularization are not associated with cognitive performance

Katrin Wasser, MD,[a] Sara M. Pilgram-Pastor, MD,[b] Sonja Schnaudigel, MD,[a] Tomislav Stojanovic, MD,[c] Holger Schmidt, MD,[a,d] Jana Knauf, MD,[a] Klaus Gröschel, MD,[a] Michael Knauth, MD,[b] Helmut Hildebrandt, PhD,[c] and Andreas Kastrup, MD,[a] *Göttingen and Oldenburg, Germany*

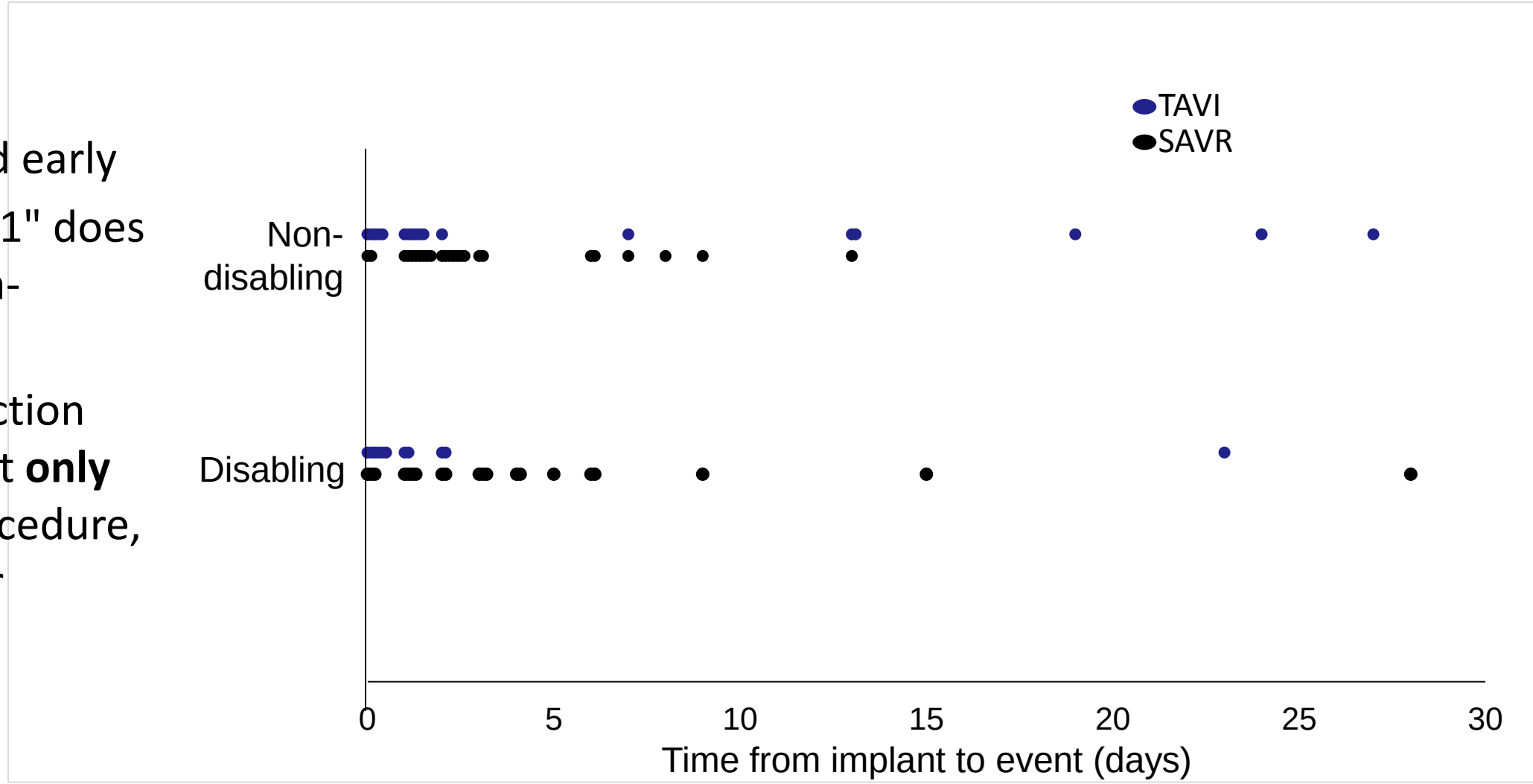
New DWI lesions were detected among 15 of 21 (71%) of the CAS patients immediately after treatment …
The cognitive performance was not significantly different between patients with and without new DWI lesions 3 months after treatment.

Conclusions:
The findings support the assumption that new brain lesions, as detected with DWI after CAS or CEA, do not affect cognitive performance in a manner that is long-lasting or clinically relevant. Despite the higher embolic load detected by DWI, CAS is not associated with a greater cognitive decline than CEA. (J Vasc Surg 2011;53:61-70.)

When do the strokes occur?

SURTAVI TRIAL
Timing of early strokes

- Many occurred early
- But even "day 1" does not mean intra-procedural!
- Embolic protection devices protect **only** during the procedure, not 1 min later

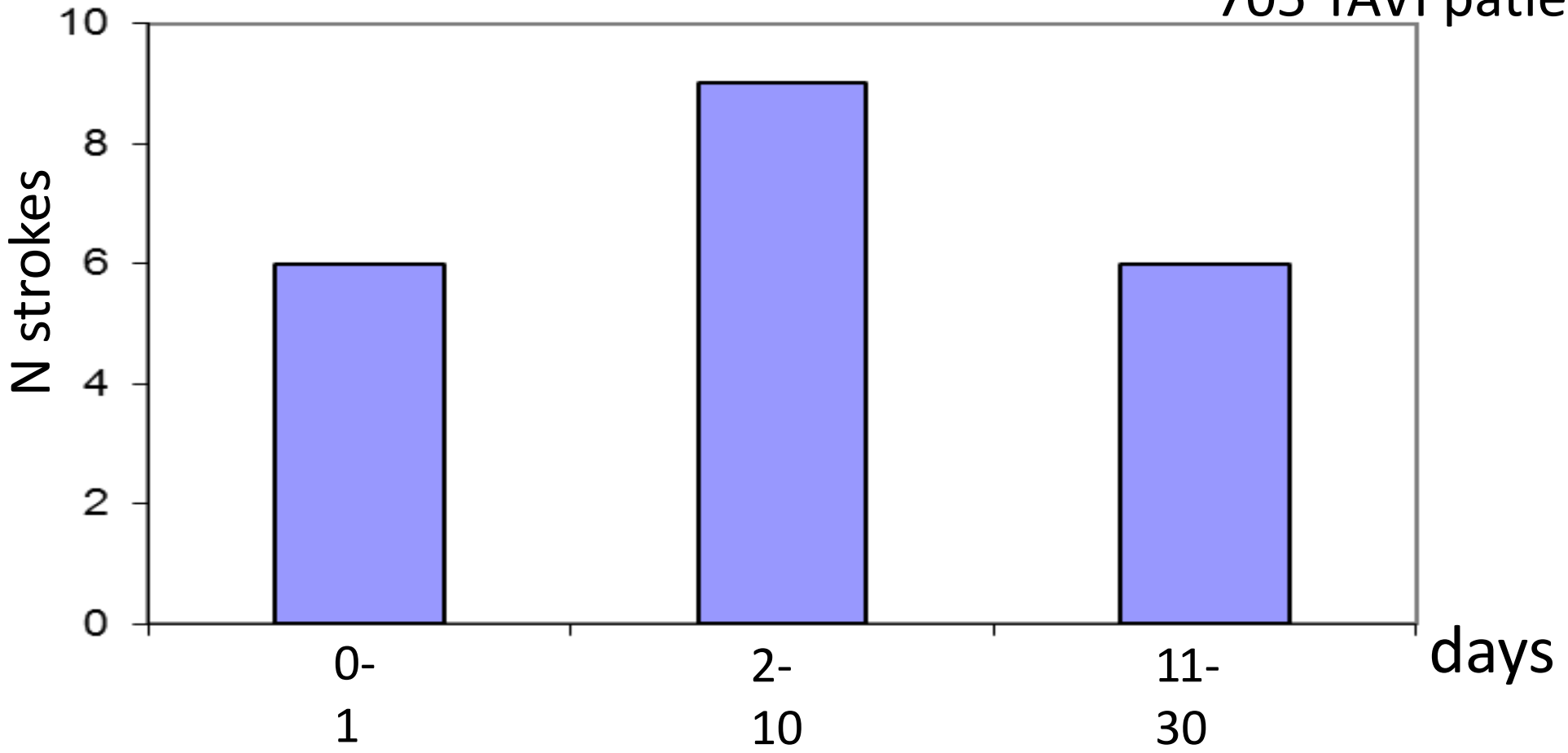


A Pieter Kappetein, TVT 2017

Strokes occur mostly after the procedure

Fateh-Moghadam et al. Tubingen. PCR 2016

705 TAVI patients



It is unknown how many strokes occur really **during** the procedure

Fateh-Moghadam et al.. PCR 2016

For all these reasons, everybody agreed:

"We need randomized trials!"

So now we have a randomized trial:

ELSEVIER

Journal of the American College of Cardiology

Volume 69, Issue 4, 31 January 2017, Pages 367-377

Original Investigation

Protection Against Cerebral Embolism During Transcatheter Aortic Valve Replacement

Samir R. Kapadia MD [a], Susheel Kodali MD [b], Raj Makkar MD [c], Roxana Mehran MD [d], Ronald M. Lazar PhD [b], Robert Zivadinov MD, PhD [e], Michael G. Dwyer MD [e], Hasan Jilaihawi MD [f], Renu Virmani MD [g], Saif Anwaruddin MD [h], Vinod H. Thourani MD [i], Tamim

Do not trust Horst Sievert! He had no time to read it!

Protection Against Cerebral Embolism During Transcatheter Aortic Valve Replacement

Kapadia SR and SENTINEL Trial Investigators

J Am Coll Cardiol. 2017 Jan 31;69(4):367

This trial was as negative as it could be!

- 363 TAVI patients, cerebra
  - Primary safety endpoint: major ad
  - Primary efficacy endpoint: reducti ys
- Debris found within filters in 99% of p
- No difference in the primary safety endpoint: The rate of MACCE (7.3%) was not statistically different from that of the control group (9.9%; p = 0.41)
- Primary efficacy endpoint also faile . New lesion volume was 178.0 mm^3 in control subjects and 102.8 mm^3 in the device arm (p = 0.33)
- No significant difference in strokes at 30 days: 9.1% in control subjects and 5.6% in patients with devices (p = 0.25)
- No difference in neurocognitive function
- **CONCLUSIONS:**
- "Embolic protection was safe and captured embolic debris in 99% of patients"
- "No significant stroke risk reduction and no change in neurocognitive function"
- "Reduction in new lesion volume on MRI was not statistically significant"

Sentinel Trial: > 300 patients randomized

- No significant stroke risk reduction
- No improvement of cognitive function
- No reduction of MRI lesion volume
- Longer procedure time, more contrast dye
- ≈ 2000 US $ additional cost per case
- No shorter stay on the ICU, no shorter stay in the hospital
  - not on average and also not for individual patients
- Probably 1-2 % "asymptomatic radial artery occlusions"
- One false aneurysm at the puncture site

➢ Why should this be of benefit for my next patient?

There is zero evidence for embolic protection!

- My personal cost benefit analysis:
  - > 1000 TAVI, almost all without any sedation, patient fully awake at the end of the procedure
  - 1 procedural stroke, posterior circulation, rescued by catheter intervention
  - If I would have used embolic protection:
    - Longer procedure time, more contrast dye
    - 10 vascular access complications (according to Sentinal trial)
    - 1000 x 2000 US$ = 2 million US$
- What would you tell me as my hospital CEO?

You would tell me:

"Please do not use embolic protection!
I will buy you 2 additional state of the art hybrid cath-labs instead!"

I rest my case!

Thank you for your attention!

Now let's vote!

Thank you!

www.CSI-congress.org