Cerebral protection devices are still meaningful and necessary

Eberhard Grube MD, FACC, FSCAI
University Hospital, Dept of Medicine II, Bonn, Germany
Stanford University, Palo Alto, California, USA

Disclosure - Eberhard Grube, MD

Physician Name	Company/Relationship
Eberhard Grube, MD	Medtronic, CoreValve: C, SB, AB, OF Direct Flow: C, SB, AB Mitralign: AB, SB, E Boston Scientific: C, SB, AB Biosensors: E, SB, C, AB Cordis: AB Abbott Vascular: AB InSeal Medical: AB, E, Valtech: E, SB, Claret: SB Keystone: AB Shockwave: E, AB

Stroke incidence and mortality after TAVI

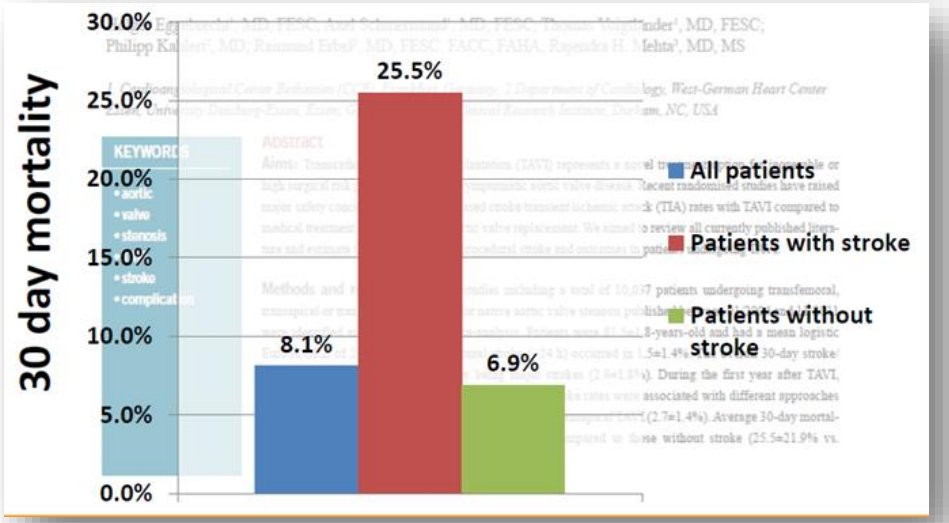
Meta-analysis of 10,037 published patients

Stroke remains a major TAVI complication…

Table 3. Incidence of stroke.

	Number of publica-tions with available data (n)	Overall number of patients with available data (n)	Number of events (n)	Weighted mean±SD
Procedural stroke (<24h)	24	3041	47	1.5±1.4%
30-day stroke/TIA	53	10037	334	3.3±1.8%
30-day major stroke	42	5514	158	2.9±1.8%
30-day minor stroke/TIA	42	5514	53	1.0±1.3%
30-day overall mortality	52	10022	812	8.1±3.9%
30-day mortality in patients suffering stroke	29	4430	41	25.5±21.9%
30-day mortality in patients without stroke	29	4430	312	6.9±4.2%
6-month stroke	9	669	29	4.3±1.6%
12-month stroke	7	1507	78	5.2±3.4%

…which increases 30-day mortality >3 fold



EuroIntervention 2012;8:129-138 publish online ahead of print March 2012
Risk of stroke after transcatheter aortic valve implantation (TAVI): a meta-analysis of 10,037 published patients

TAVI stroke is mostly periprocedural

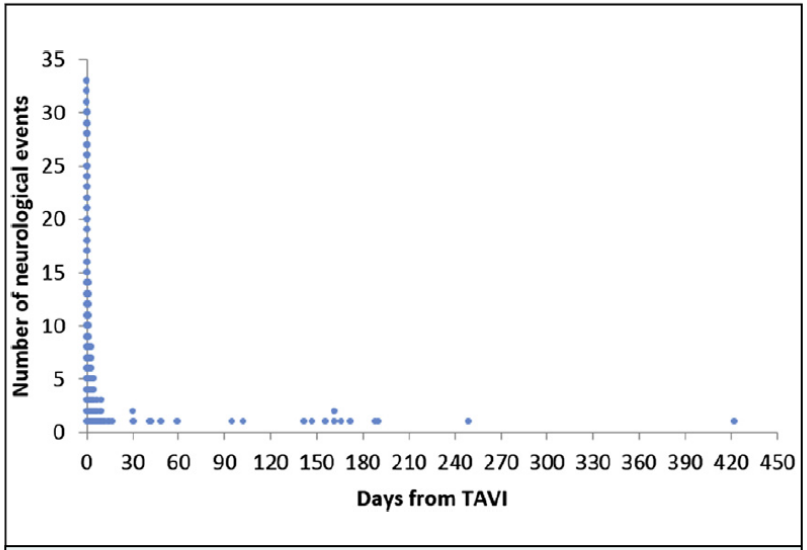


FIGURE 1 Timing of Cerebrovascular Events

Number of days elapsed from the index procedure before the occurrence of a cerebrovascular event.

Timing of Cerebrovascular Events (CVE) in FRANCE-2 Registry (n=3,191)

- CVE most frequently occur day 0-1
- >50% are major strokes
- Median time to major stroke is 1 day

Tchétché et al. *J Am Coll Cardiol Intv* 2014; 7(10)

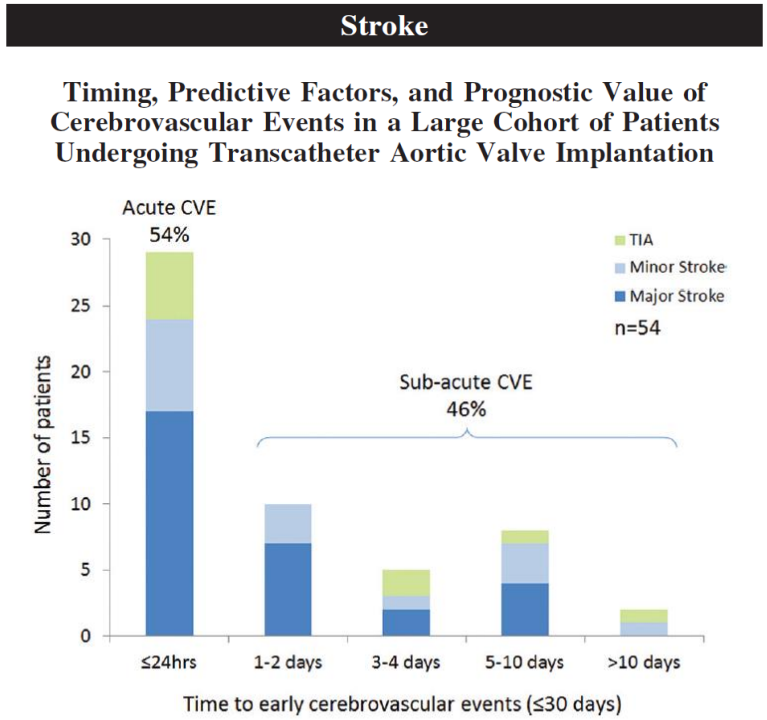


Figure 2. Timing of cerebrovascular events (CVEs) within 30 days after transcatheter aortic valve implantation. TIA indicates transient ischemic attack.

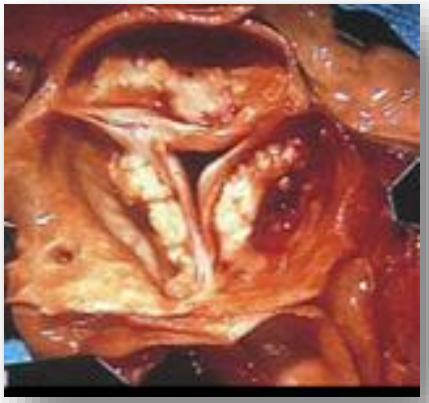
Multi-center cohort of 1,061 TAVI patients

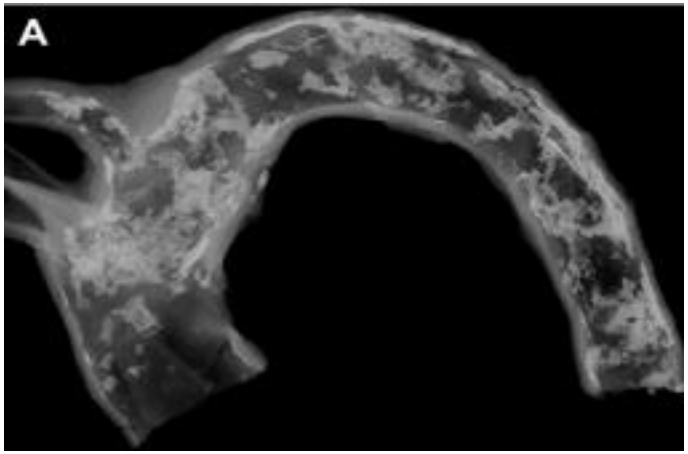
- CVE most frequently occur day 0-1
- >50% are major strokes
- >95% of strokes are ischemic

Nombela-Franco et al., *Circulation* 2012;126:3041-53

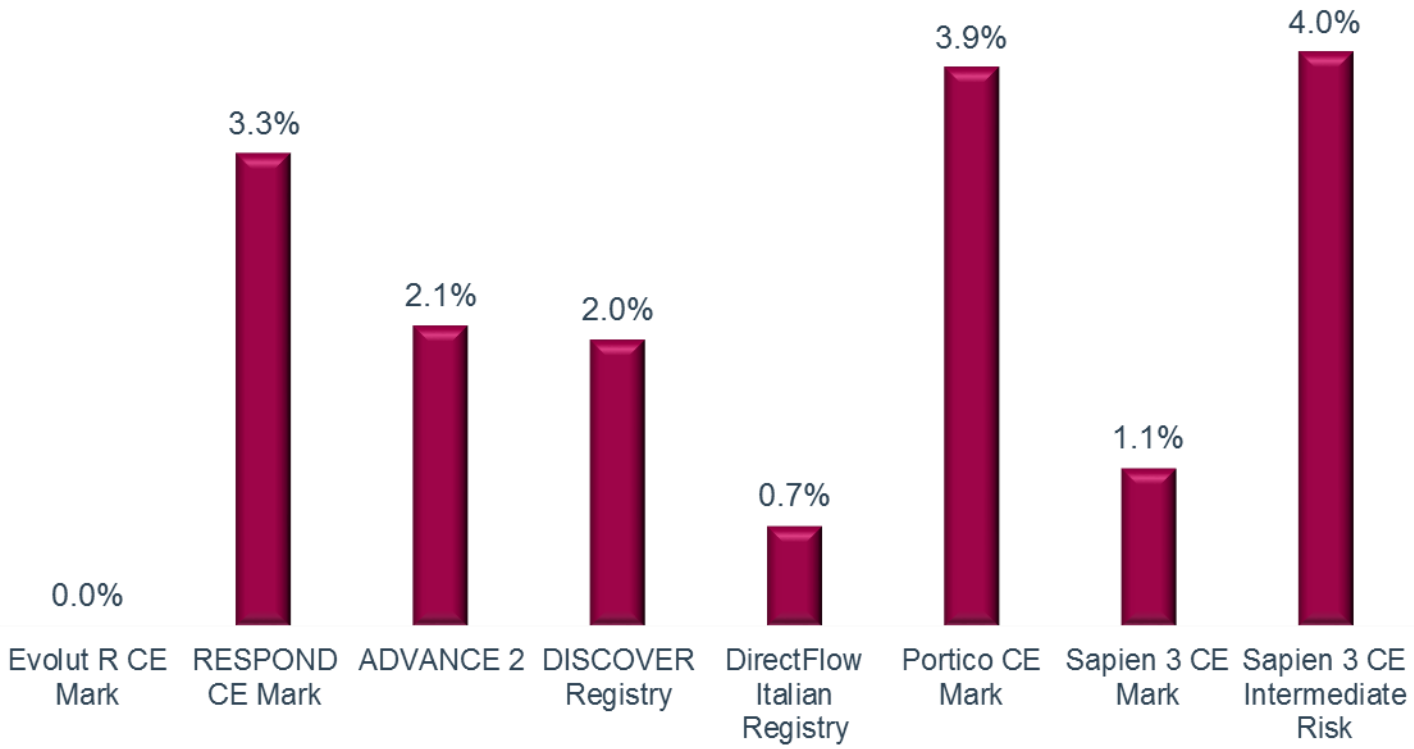
Procedural stroke risk factors

- Presence and location of arch atheroma
- Micro-embolization of calcification and thrombus on valve
- Catheter handling and device placement technique
- Secondary maneuvers
- Procedural duration
- Optimal anti-coagulation and anti-aggregation
- Arrhythmia management



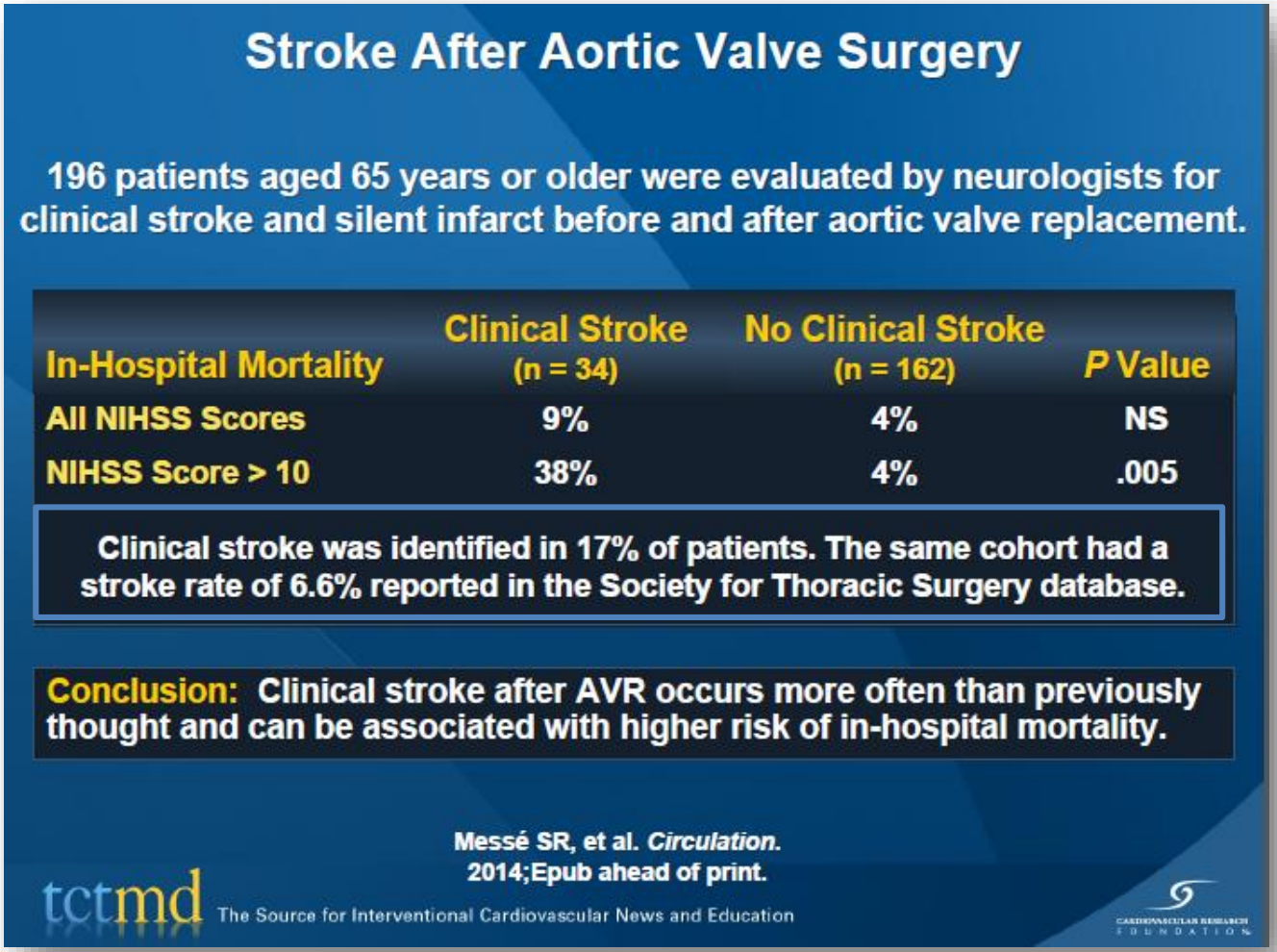


Latest Stroke Data from Studies Presented at EuroPCR 2015



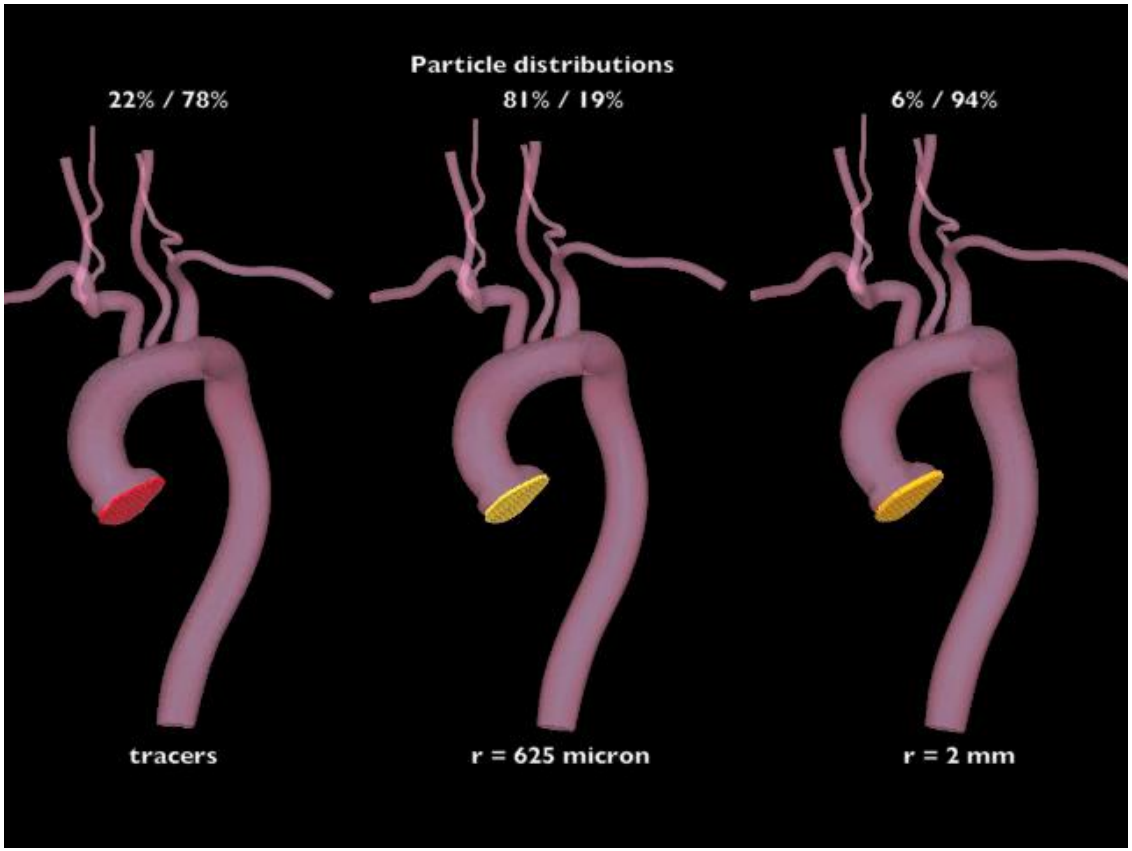
Study	Valve	Patients	FU	NE rate %	Criteria
Corevalve Evolut R CE Mark	Corevalve Evolut	60	30 days	0.0%	Varc 2
Respond CE	Boston Lotus	250	30 days	3.3%	Varc 2
Advance 2	Corevalve Basic	200	30 days	2.1%	Varc 2
Discover Registry	Direct Flow	250	30 days	2.0%	N/A
Ialien DFM Registry	Direct Flow	136	30 days	0.7%	N/A
Biovalve	Biotronik	13	30 days	0.0%	Varc 2
Portico CE Trial	Portico	102	30 days	3.9%	N/A
Sapien 3 CE	Sapien 3	96	30 days	1.1%	Varc 2
Sapien 3 CE (Intermediate Risk)	Sapien 3	101	30 days	4.0%	Varc 2

Under-reporting remains an issue and is even seen in surgical AVR



Messé SR, Acker MA, Kasner SE, et al. *Circulation*. 2014; Epub ahead of print
Stroke after aortic valve surgery: results from a prospective cohort.

Cardiogenic Emboli Distribution

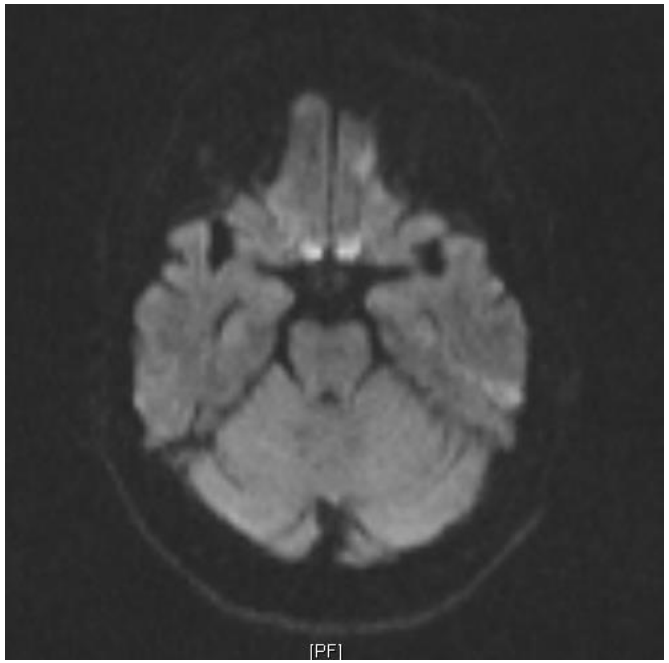


- Emboli distribution to cerebral circulation is not in concordance with volumetric flow assumptions
- Cardiogenic emboli moves preferentially to right hemisphere

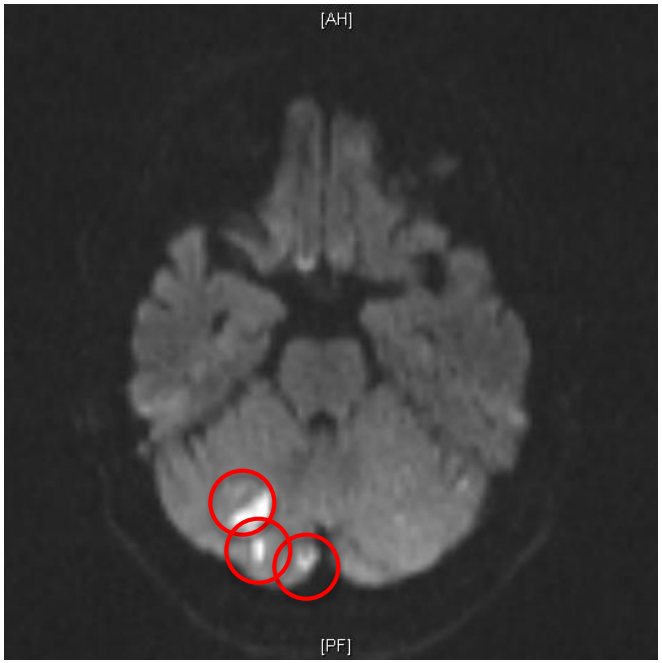
Carr IA et al. Size-dependent predilections of cardiogenic embolic transport, Am J Physiol Heart Circ Physiol. June 21, 2013

Diffusion-weighted MRI shows new lesions

Example of an 82-year-old patient two days after successful TAVR:



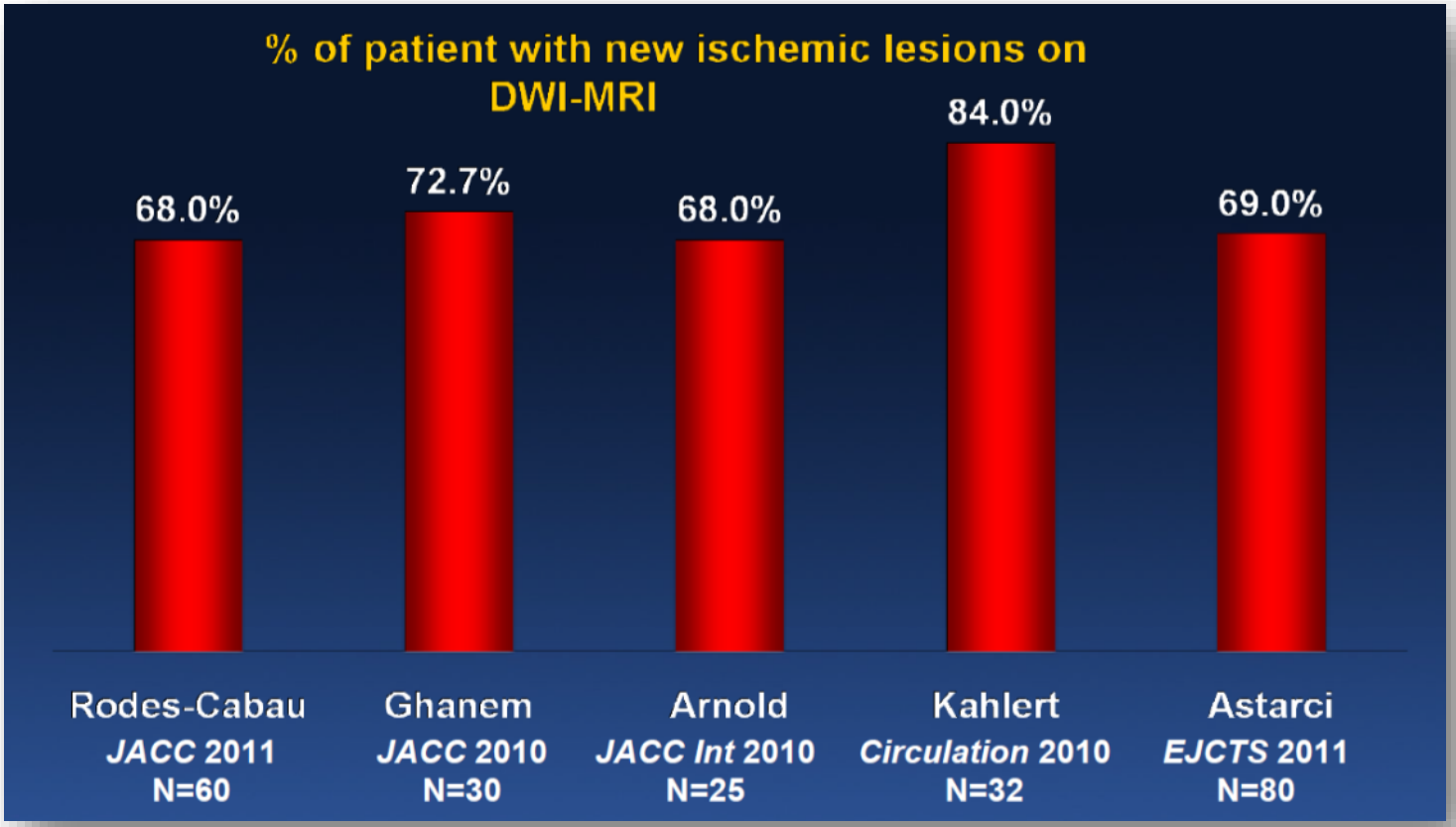
Before TAVR



Two days after TAVR

Treating Physician:
Philipp Kahlert, MD
West German Heart Center Essen
University Duisburg-Essen

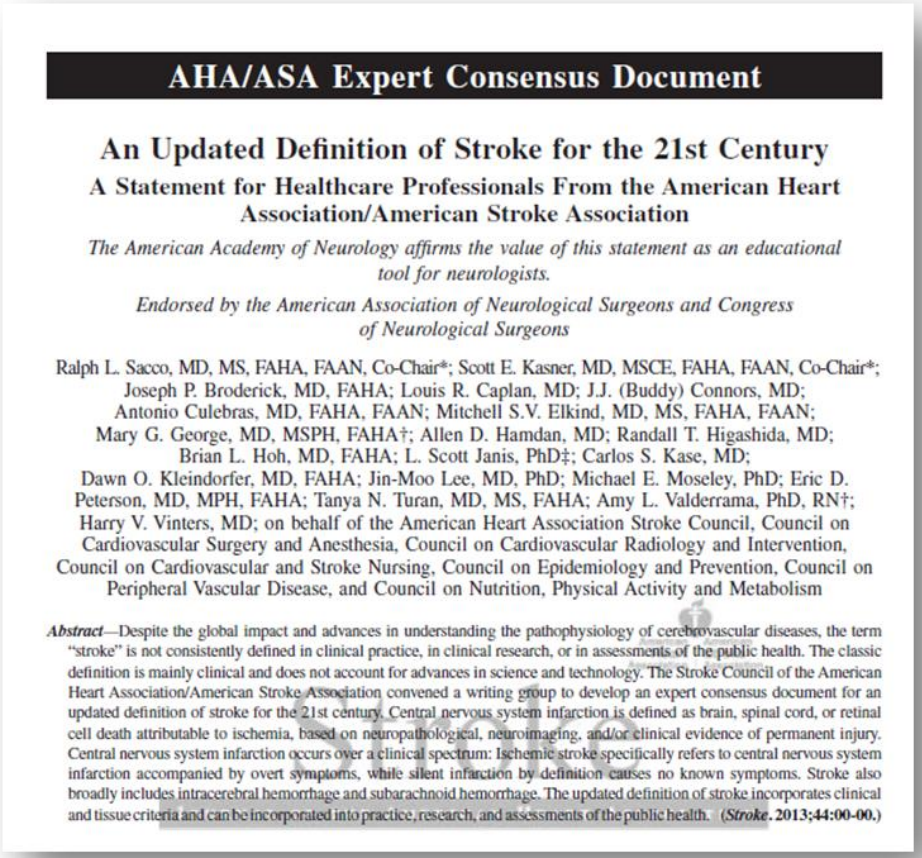
DW-MRI imaging shows “silent lesions” in TAVI



New lesions found in vast majority of diffusion-weighted MR images (DW-MRI) of the brain following TAVI

Daneault et al, JACC 2011;58: 2143-50

Stroke redefined: AHA/ASA consensus



AHA/ASA Expert Consensus Document

An Updated Definition of Stroke for the 21st Century

A Statement for Healthcare Professionals From the American Heart Association/American Stroke Association

The American Academy of Neurology affirms the value of this statement as an educational tool for neurologists.

Endorsed by the American Association of Neurological Surgeons and Congress of Neurological Surgeons

Ralph L. Sacco, MD, MS, FAHA, FAAN, Co-Chair*; Scott E. Kasner, MD, MSCE, FAHA, FAAN, Co-Chair*; Joseph P. Broderick, MD, FAHA; Louis R. Caplan, MD; J.J. (Buddy) Connors, MD; Antonio Culebras, MD, FAHA, FAAN; Mitchell S.V. Elkind, MD, MS, FAHA, FAAN; Mary G. George, MD, MSPH, FAHA†; Allen D. Hamdan, MD; Randall T. Higashida, MD; Brian L. Hoh, MD, FAHA; L. Scott Janis, PhD‡; Carlos S. Kase, MD; Dawn O. Kleindorfer, MD, FAHA; Jin-Moo Lee, MD, PhD; Michael E. Moseley, PhD; Eric D. Peterson, MD, MPH, FAHA; Tanya N. Turan, MD, MS, FAHA; Amy L. Valderrama, PhD, RN†; Harry V. Vinters, MD; on behalf of the American Heart Association Stroke Council, Council on Cardiovascular Surgery and Anesthesia, Council on Cardiovascular Radiology and Intervention, Council on Cardiovascular and Stroke Nursing, Council on Epidemiology and Prevention, Council on Peripheral Vascular Disease, and Council on Nutrition, Physical Activity and Metabolism

Abstract—Despite the global impact and advances in understanding the pathophysiology of cerebrovascular diseases, the term "stroke" is not consistently defined in clinical practice, in clinical research, or in assessments of the public health. The classic definition is mainly clinical and does not account for advances in science and technology. The Stroke Council of the American Heart Association/American Stroke Association convened a writing group to develop an expert consensus document for an updated definition of stroke for the 21st century. Central nervous system infarction is defined as brain, spinal cord, or retinal cell death attributable to ischemia, based on neuropathological, neuroimaging, and/or clinical evidence of permanent injury. Central nervous system infarction occurs over a clinical spectrum: Ischemic stroke specifically refers to central nervous system infarction accompanied by overt symptoms, while silent infarction by definition causes no known symptoms. Stroke also broadly includes intracerebral hemorrhage and subarachnoid hemorrhage. The updated definition of stroke incorporates clinical and tissue criteria and can be incorporated into practice, research, and assessments of the public health. (***Stroke***. 2013;44:00-00.)

- Silent brain infarcts increase the risk of clinical infarction by 2 to 4 times in population-based studies.

- Silent infarcts are well recognized to be associated with several adverse neurological and cognitive consequences:
  - Impaired mobility
  - Physical decline
  - Depression
  - Cognitive dysfunction
  - Dementia
  - Parkinson's disease
  - Alzheimer disease

An Updated Definition of Stroke for the 21st Century : A Statement for Healthcare Professionals From the American Heart Association/American Stroke Association, *Stroke.* published online May 7, 2013

Cerebral protection reduces periprocedural strokes during carotid angioplasty & stenting

Pooled Analysis for Total Stroke Rate Within 30 Days After Protected and Unprotected Carotid Stenting in 134 Studies*

	With Protection (n=82)		Without Protection (n=76)			
	Procedures	Total Strokes	Procedures	Total Strokes	RR	CI
All patients	12,263	324 (2.6%)	11198	474 (4.2%)	0.62†	0.54 to 0.72
Symptomatic	2427	91 (3.8%)	3149	176 (5.6%)	0.67†	0.52 to 0.86
Asymptomatic	2460	41 (1.7%)	2032	56 (2.8%)	0.61†	0.41 to 0.9

RR: relative risk, CI: confidence interval.

* 24 studies included data on both protected and unprotected CAS. Of all studies, only 67 studies reported outcomes on symptomatic patients (34 with protected and 39 with unprotected stenting), while 56 reported outcomes on asymptomatic patients (28 with protected and 30 with unprotected stenting).

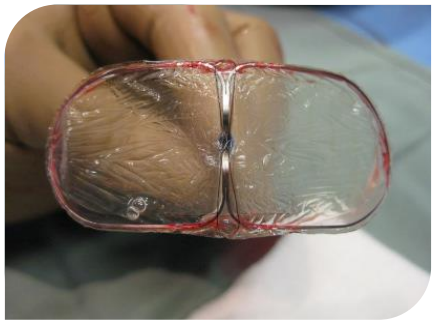
† $P<0.05$.

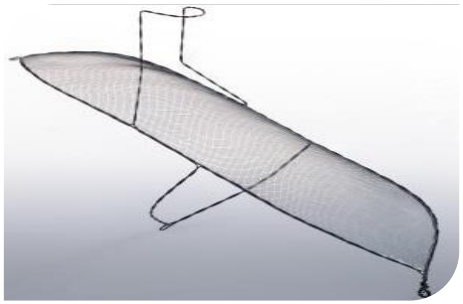
Why should this be different in TAVR?

Garg et al: *J Endovasc Ther*. 2009;16:412-427

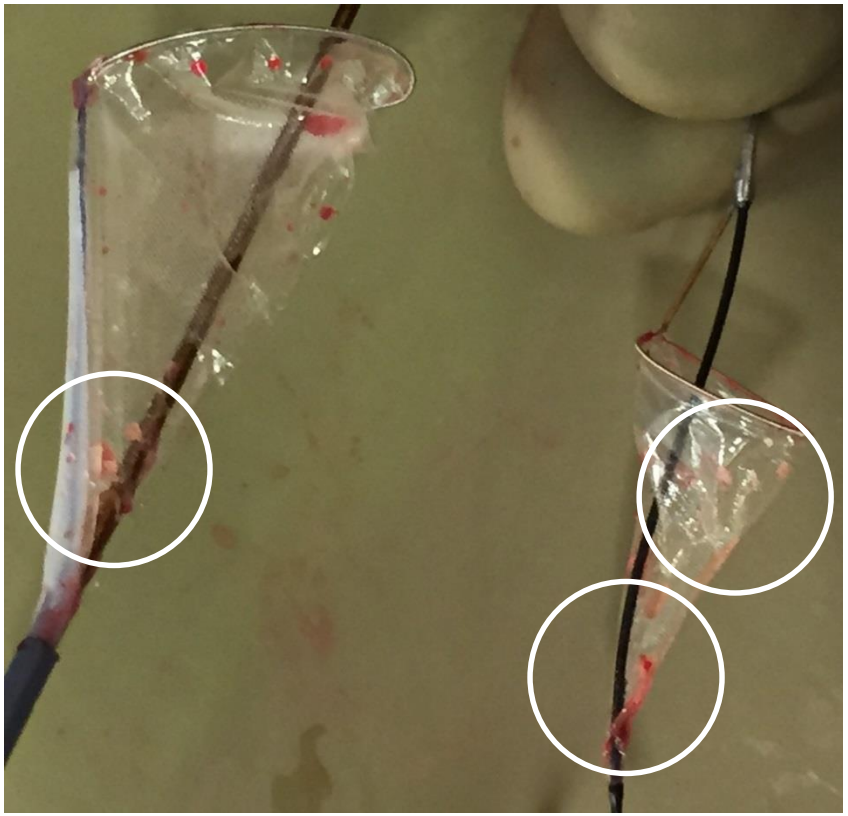
Embolic Protection Devices

Claret Sentinel™ Cerebral Protection System	Edwards Embrella™ Embolic Deflector	TriGuard™ Cerebral Protection Device
Filter capture	Deflector	Deflector
6F (radial)	6F (radial)	9F (femoral)
140 micron pore size	100 micron pore size	130 x 250 micron pore size
Brachiocephalic and LCC	Aortic arch position	Aortic arch position
CE marked and commercialized	CE marked	CE marked

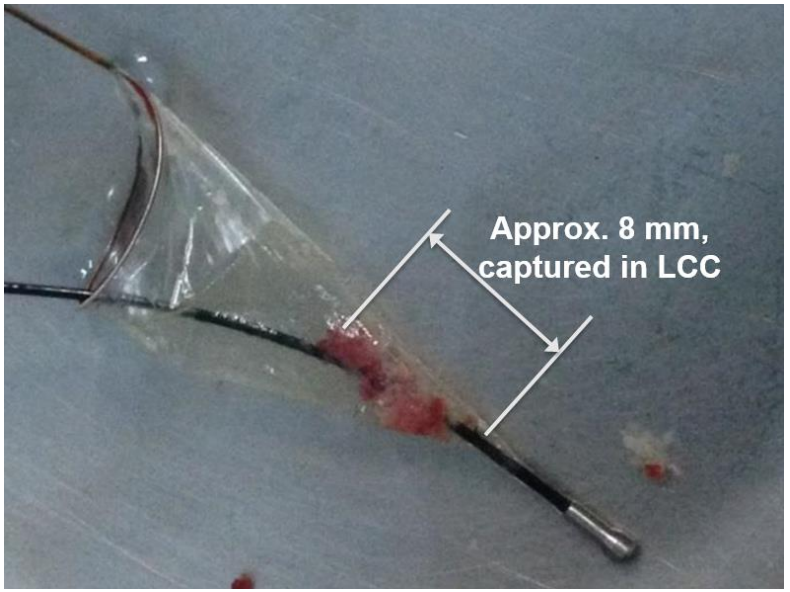




Examples of debris captured with Claret CPS



University of Virginia
Charlottesville, VA, USA
SENTINEL trial 2015



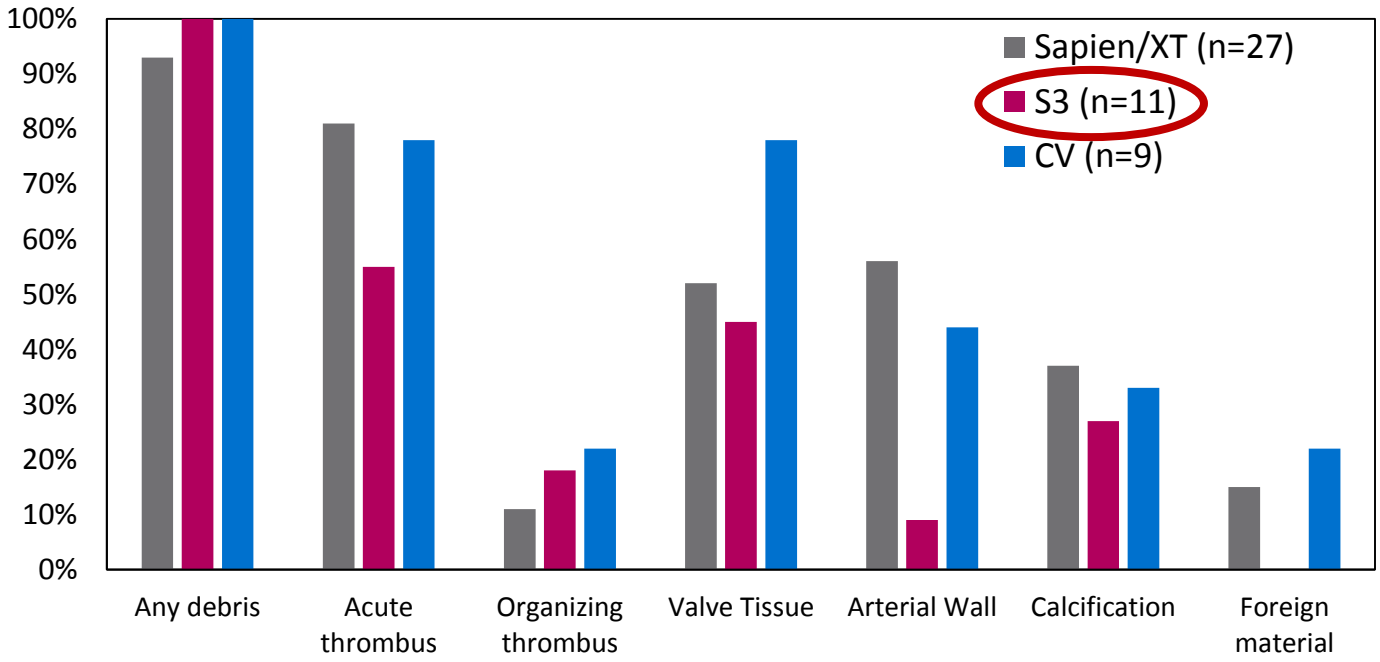
Institute Dante Pazzanese de Cardiologia
São Paulo, Brazil
TCT Live Case 2013

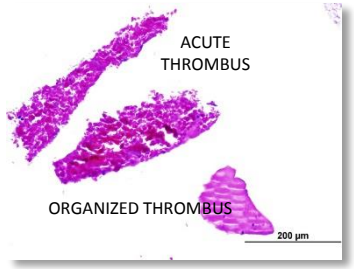
Embolic debris captured by valve type during TAVI procedures at AK St Georg (Hamburg)

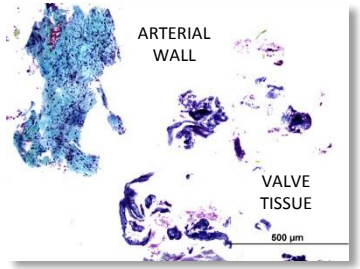
- 52 cases of TAVI using Claret Medical Cerebral Protection System performed at AK St Georg (Hamburg)

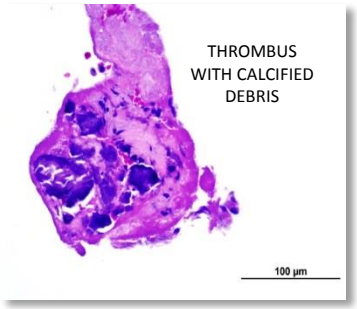
Sapien/XT	S3	CoreValve	Jena	Portico	Centera
27 (52%)	11 (21%)	9 (17%)	2 (4%)	2 (4%)	1 (2%)

- Filter contents subsequently analyzed by CVPath Institute
  - **Debris captured in 96% of patients**









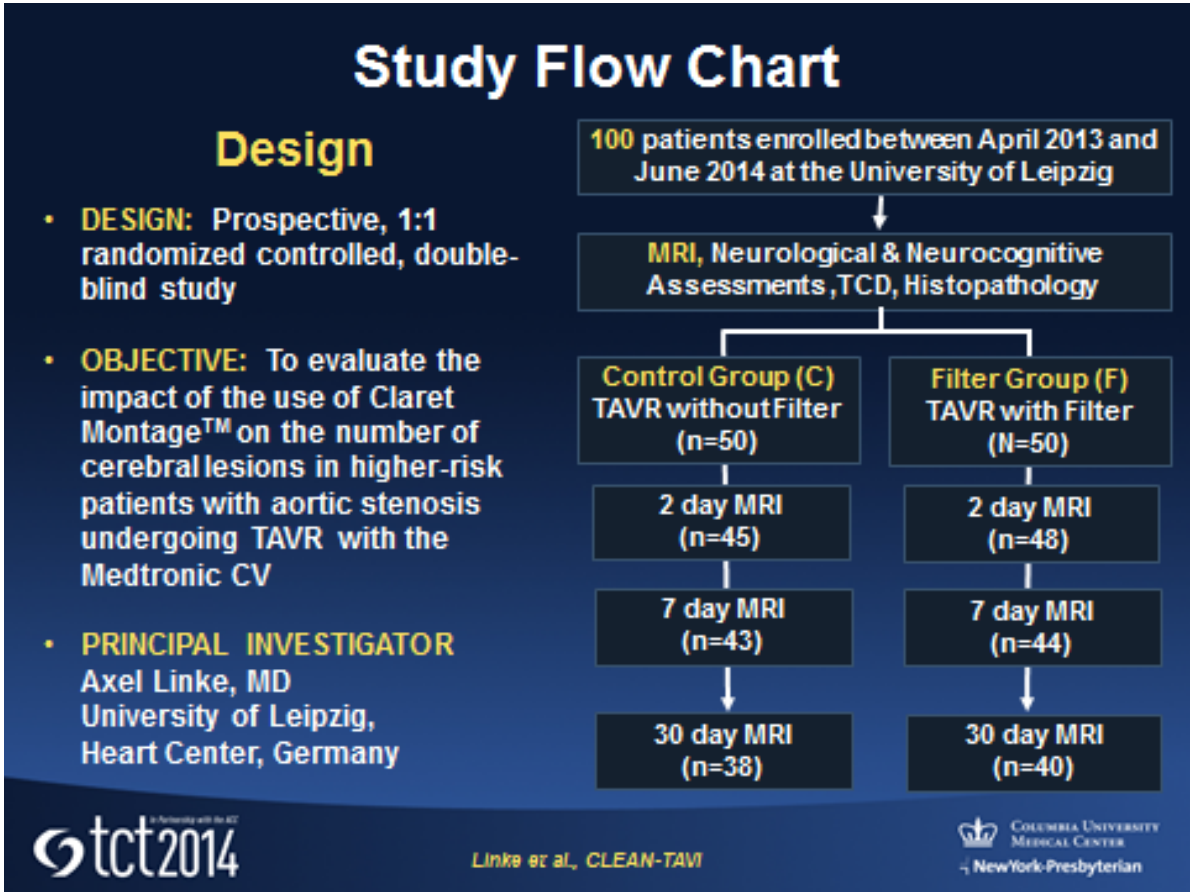
Note: percentages reflect percent of patients in each group in which each particular tissue type was captured. Some filters captured several types of debris, so percentages will not add to 100%

1. Schmidt T, Schaefer U, Sanchez O, et al DGK 2015. CVPath Institute data on file at Claret Medical.

CLEAN-TAVI: First RCT of Cerebral Protection in TAVI

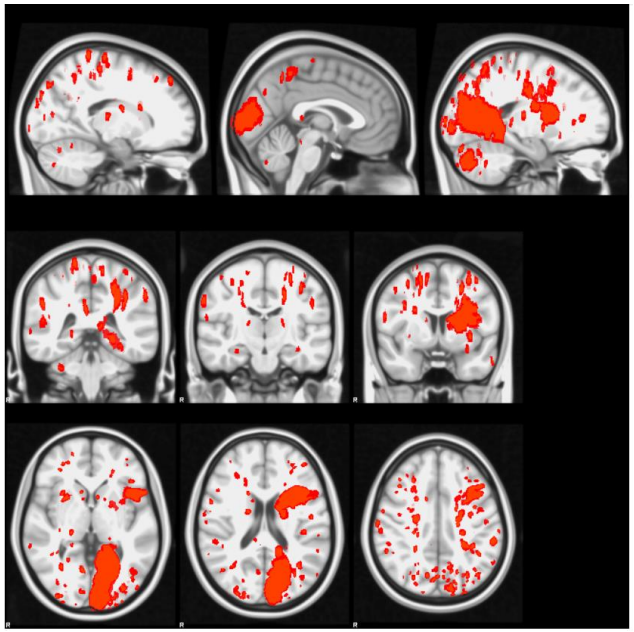
100 higher-risk patients with aortic stenosis undergoing TAVR with CoreValve were randomized 1:1 to TAVR with the Claret Montage™ Cerebral Protection System filters or TAVR without filters.

MRI, neurological and neurocognitive assessments were compared with baseline and between groups.



CLEAN-TAVI shows the problem and the promise

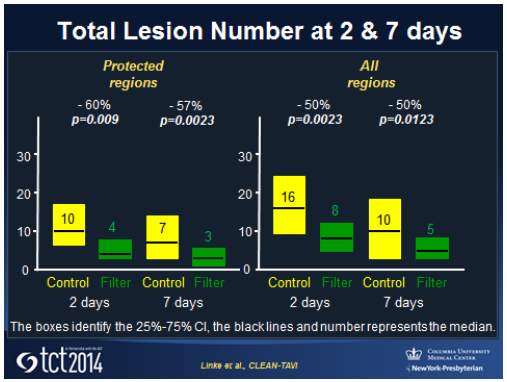
The Problem

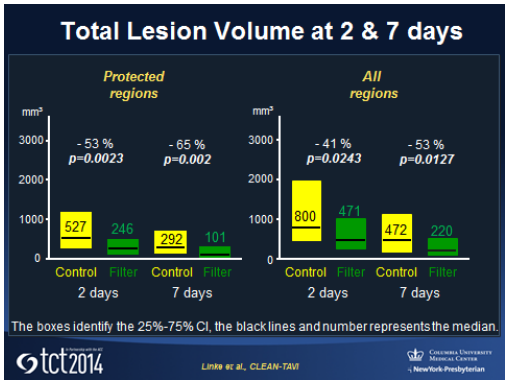


Representative slices from each of the orthogonal planes showing new lesions from **control group** (unprotected, no filters) of CLEAN-TAVI randomized trial

The Promise

Claret Montage Cerebral Protection System significantly reduces new cerebral lesion number and volume at 2 & 7 days, as measured by DW-MRI, and reduces ataxia at 2d





Per Protocol		at 2 days No. (%)
Control (n=50)	any symptom	14 (28%)
	- ataxia	**12 (24%)**
Filter (n=45)	any symptom	6 (13%)
	- ataxia	**4 (9%)**

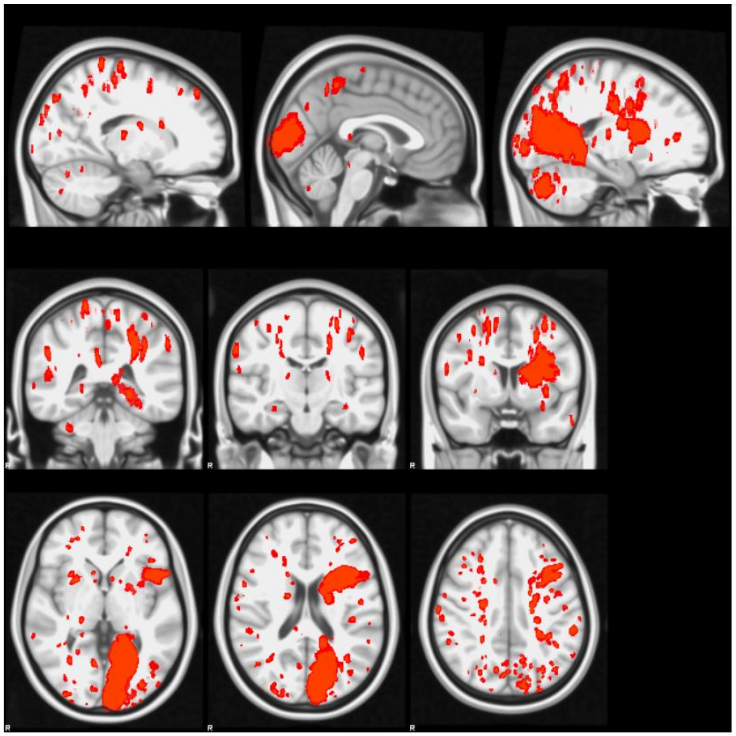
RR 1.559 (1.083 to 2.244), OR 3.2, p<0.05

1. CLEAN-TAVI (manuscript in review)

CLEAN-TAVI shows the promise of protection

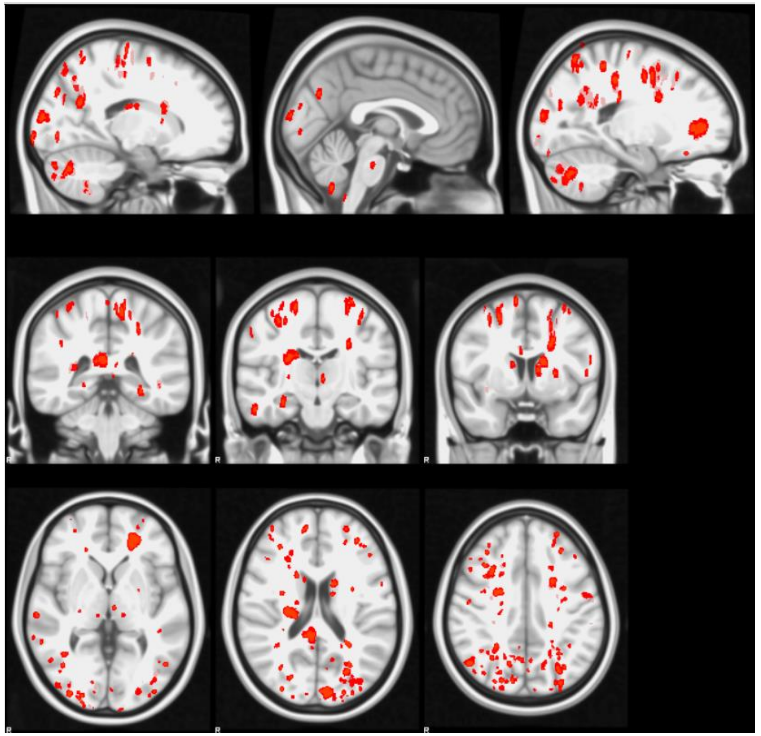
The Problem

Control group (no filters)



The Promise

Test group (filters)



Representative slices from each of the orthogonal planes showing new lesions at 2d from each arm of CLEAN-TAVI randomized trial of cerebral embolic protection in TAVI using Claret dual-filter Cerebral Protection Systems

Claret Montage Cerebral Protection System significantly reduces new cerebral lesion number and volume at 2 & 7 days, as measured by DW-MRI

1. CLEAN-TAVI (manuscript in review)

SENTINEL Study Design

NOW ENROLLING

Pivotal study confirming the therapeutic importance of embolic debris capture and removal during TAVR

Objective: Assess the safety and efficacy of the Claret Medical Sentinel Cerebral Protection System in reducing the volume and number of new ischemic lesions in the brain and their potential impact on neurocognitive function

Primary Investigators:

Samir Kapadia, MD
Cleveland Clinic

Susheel Kodali, MD
Columbia University Medical Ctr

Population: Subjects with severe symptomatic calcified native aortic valve stenosis who meet the commercially-approved indications for TAVR with the Edwards Sapien THV or XT, or Medtronic CoreValve

N=296 subjects
randomized 1:1:1
at 15 sites in the U.S.

- **SAFETY ARM** — TAVR with Sentinel
  - Safety Follow-up
- **TEST ARM** — TAVR with Sentinel
  - Histopathology
  - Safety Follow-up
  - MRI Assessments
  - Neurological and Neurocognitive Tests
- **CONTROL ARM** — TAVR only

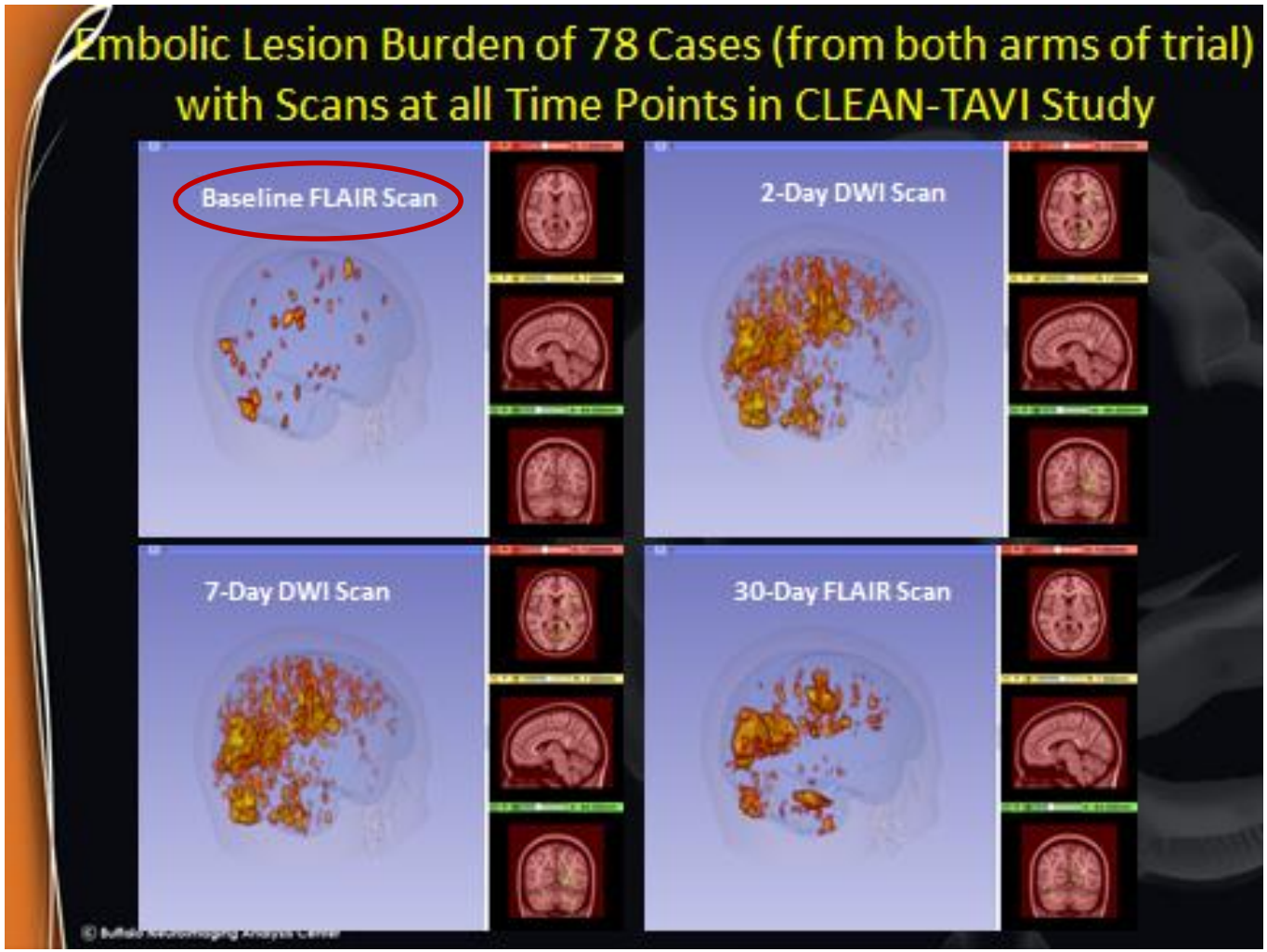
Primary Efficacy Endpoint: Reduction in median total new lesion volume as assessed by DW-MRI.

Primary Safety Endpoint: Occurrence of all MAE at 30 days.

SENTINEL MRI methodology

- **3-Tesla MR scanner standardization for optimal resolution across all study sites**
  - 3.0T is able to resolve smaller lesions, allows shorter acquisition times, and has a higher signal-to-noise ratio than 1.5T MR scanners
- **Diffusion-weighted (DW) and fluid-attenuated inversion recovery (FLAIR) MR sequences**
  - To assess both acute (DW) and chronic (FLAIR) lesions
- **Novel methodology with serial scan acquisition**
  - Baseline mapping must be performed to eliminate over-estimation of existing lesions.
  - Serial co-registration must be performed based on the baseline, otherwise the analysis is not reliable
- **Core lab analysis of all scans**
  - Buffalo Neuroimaging Analysis Center, Buffalo, NY

Composite images of CLEAN-TAVI MRIs

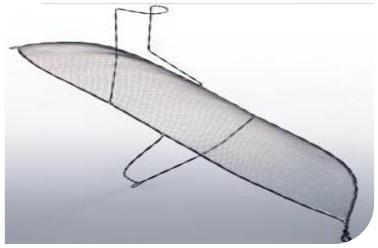


Blinded analysis of first 78 patients

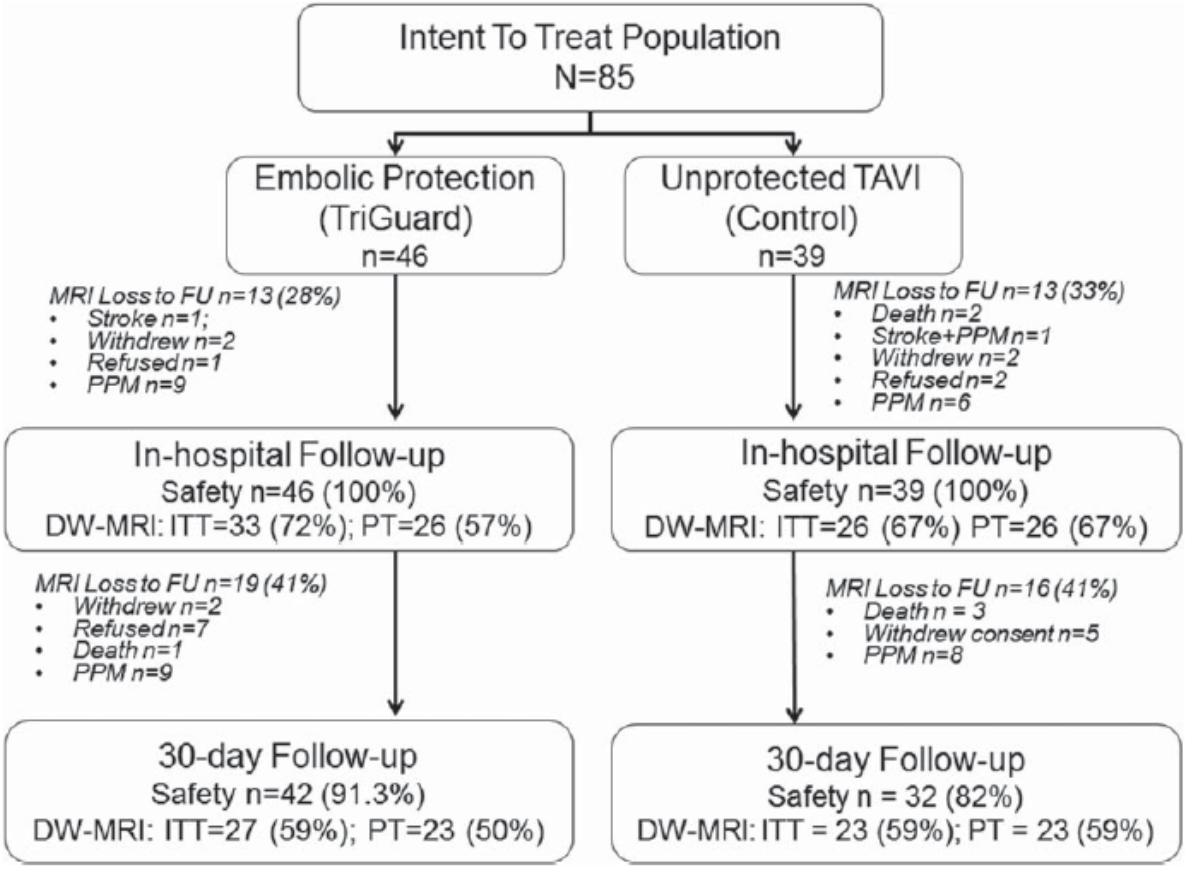
DEFLECT III: Pilot RCT using TriGuard deflection device

euro PCR 2015

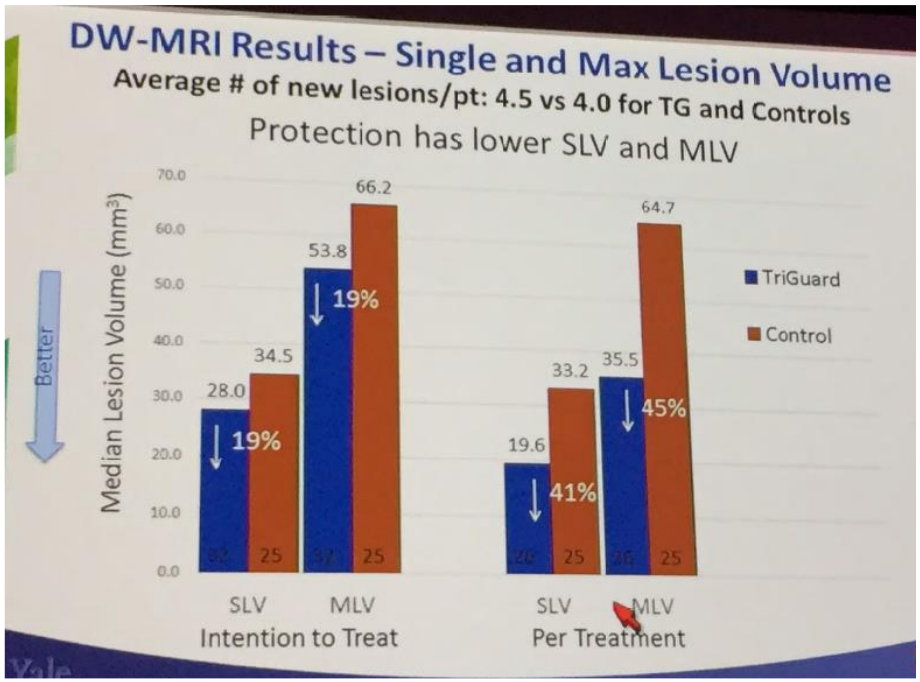
Final 30-day results of the DEFLECT III trial:
a prospective randomised evaluation of the novel embolic protection DEFLECTion device during TAVI

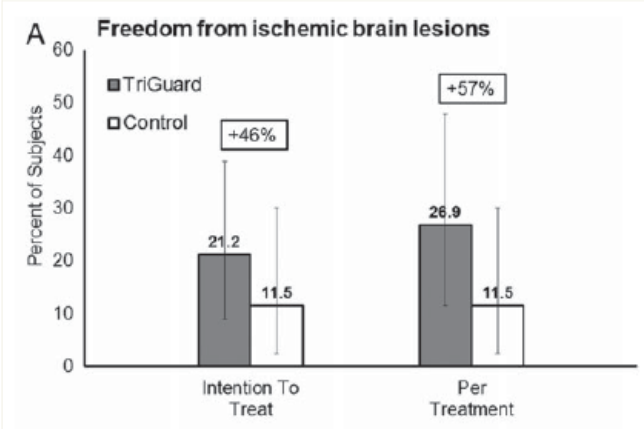


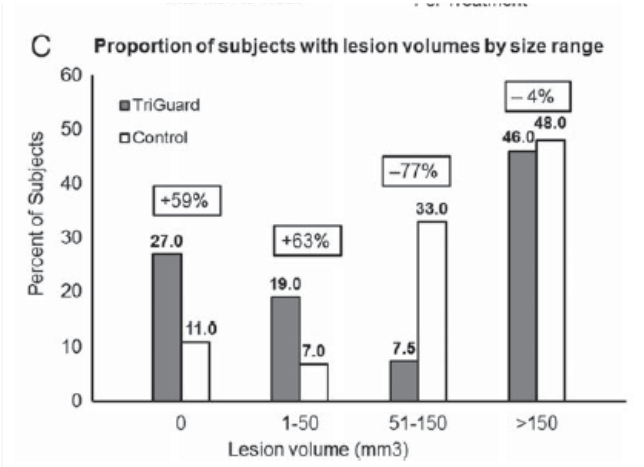
J Schofer, D Tchet
T Cuisset, D Black



DEFLECT III: DW-MRI Results



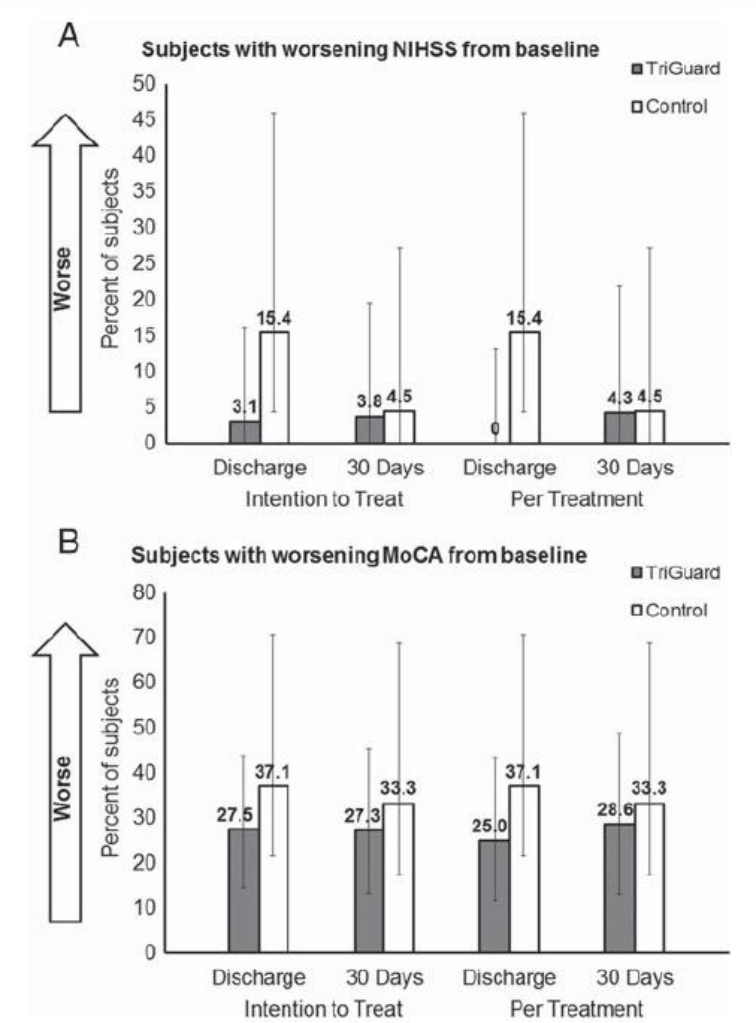




- Trend to lower lesion burden

CAUTION: Investigational device. Limited to investigational use by United States law.

Trend towards improved neurological and neurocognitive outcomes



- Blunt instruments (NIHSS and MoCA) show trends towards improved neurological and neurocognitive outcomes with protection
- Larger trials and more comprehensive neurocognitive batteries (e.g. RECON) will further elucidate benefit

Conclusions

- Stroke remains a devastating complication of TAVR, even with new devices
- Clinical stroke is often under-diagnosed
- Periprocedural subclinical cerebral infarcts are common and increase future risk of events
- Cerebral protection devices show promise in reducing cerebral ischemic burden and improving outcomes for TAVI patients
- Large multicenter randomized trials with detailed MR imaging and neurocognitive assessments will further elucidate potential