The Case for and Against Cerebral Embolic Protection During TAVR

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Disclosure Statement of Financial Interest

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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
• Research Support	• Edwards Lifesciences, Medtronic, Direct Flow, Boston Scientific, Abbott, Claret Medical
• Steering Committee	• Edwards Lifesciences, Claret Medical
• SAB (equity)	• Thubrikar Aortic Valve, Inc, Dura Biotech, VS Medtech

Is Cerebral Protection Necessary?

1. Is embolic stroke during TAVI (still) a relevant clinical problem ?
2. Are ‘silent’ microembolic events clinically relevant?
3. Can we improve outcomes with embolic protection devices ?

Stroke is not disappearing with new generation TAVI valves

B Event rate for 30-day major stroke

Study name	Event rate	Lower limit	Upper limit	Total	Event rate and 95% CI
DFM (DISCOVER)	0.040	0.013	0.117	3/75	
Portico (CE mark)	0.029	0.009	0.086	3/103	
Sadra Lotus (REPRISE II)	0.017	0.004	0.065	2/119	
ACURATE TF (CE mark)	0.022	0.006	0.085	2/89	
ACURATE TA (SAVI)	0.028	0.013	0.058	7/250	
JenaValve (JUPITER)	0.011	0.003	0.043	2/180	
JenaValve (CE mark)	0.030	0.008	0.113	2/66	
Engager (CE trial)	0.008	0.001	0.055	1/125	
DFM (FIM)	0.050	0.007	0.282	1/20	
Portico (FIM)	0.023	0.001	0.277	0/21	
Sadra Lotus (REPRISE I)	0.091	0.013	0.439	1/11	
SAPIEN 3 (FIM)	0.019	0.001	0.236	0/26	
CENTERA (FIM)	0.031	0.002	0.350	0/15	
ACURATE TA (FIM)	0.033	0.011	0.098	3/90	
JenaValve (FIM)	0.038	0.002	0.403	0/12	
DFM (SALUS)	0.016	0.001	0.211	0/30	
DFM registry (Naber)	0.019	0.005	0.073	2/105	
DFM (DISCOVER registry)	0.007	0.001	0.045	1/153	
SAPIEN 3 (Webb TF)	0.005	0.000	0.077	0/96	
SAPIEN 3 (Webb TA)	0.069	0.001	0.129	0/54	
Overall event rate	0.024	0.017	0.034		
Fixed effects	0.024	0.017	0.034		

0.00 0.25 0.50

Compare with: PARTNER IA=3.8%, PARTNER IB=5.0%, PARTNER IIB=3.1%, CoreValve High Risk=3.9%, CoreValve Extreme Risk=2.3%.
UK TAVI=4.1%*, FRANCE 2=2.3%, European Sentinel Registry=1.8%.

Meta-analysis of 2nd generation TAVI valves (I^2=36.471, tau^2=0.00)

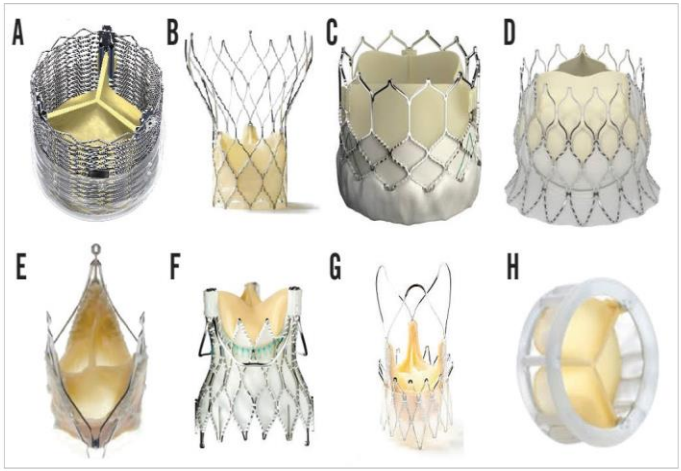


Figure 7. *Second-generation transcatheter aortic valves. A) Sadra™ Lotus Medical valve (Boston Scientific SciMed Inc, Maple Grove, MN, USA); B) Portico® valve (St. Jude Medical); C) Edwards SAPIEN 3 valve (Edwards Lifesciences); D) Edwards CENTERA valve (Edwards Lifesciences); E) JenaValve (JenaValve Technology); F) Engager™ valve (Medtronic Inc.); G) Symetis ACURATE™ valve (Symetis SA); H) Direct Flow Medical® valve (Direct Flow Medical).*

- Meta-analysis of ~20 non-randomized, mostly FIM, valve-company sponsored studies
- 2.4% <u>major</u> stroke at 30-days

Clinical stroke may be under-reported, and as high as 15-28%

AHA/ASA Expert Consensus Document

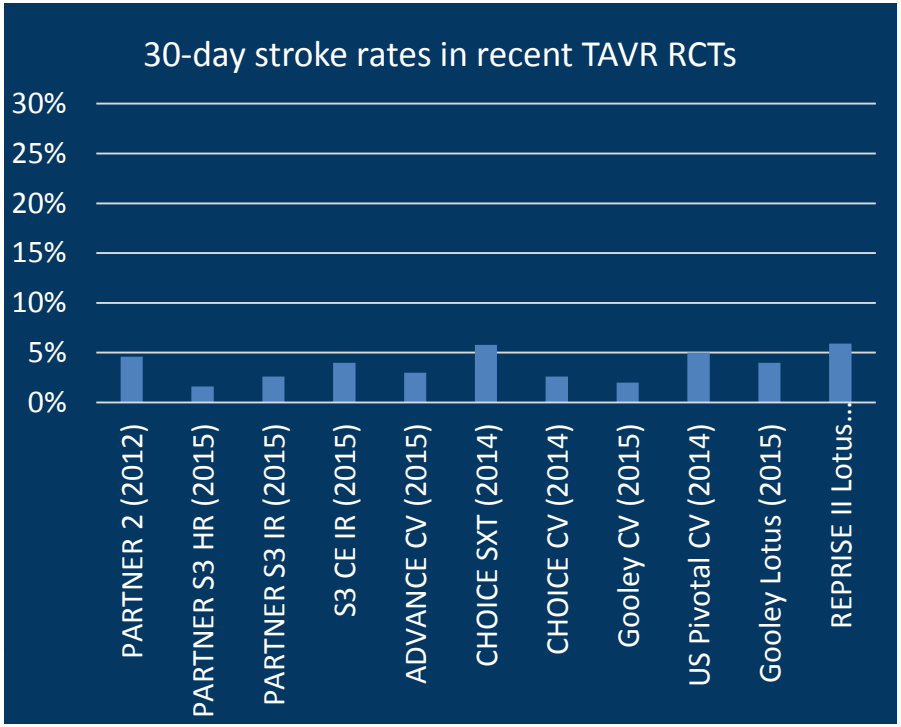
An Updated Definition of Stroke for the 21st Century

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

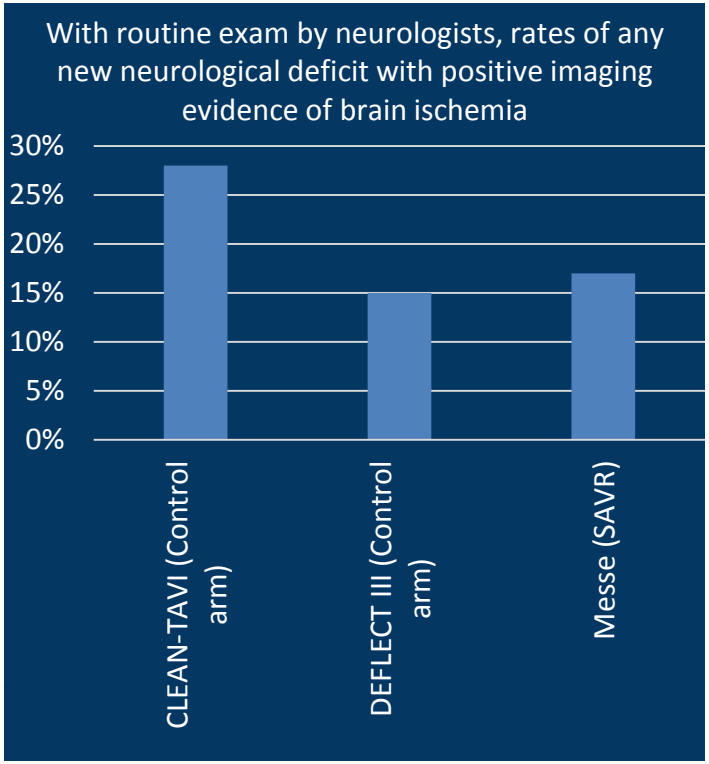
The American Academy of Neurology affirms the value of this statement as an educational tool for neurologists.

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

- AHA/ASA consensus definition of stroke includes imaging evidence of a CNS infarction with or without acute neurological dysfunction
- Most studies do not use routine imaging or routine proactive discharge exams by neurologists
- Studies using *routine discharge exam by neurologists* report much higher clinical stroke rates (Messe, et al, e.g.)

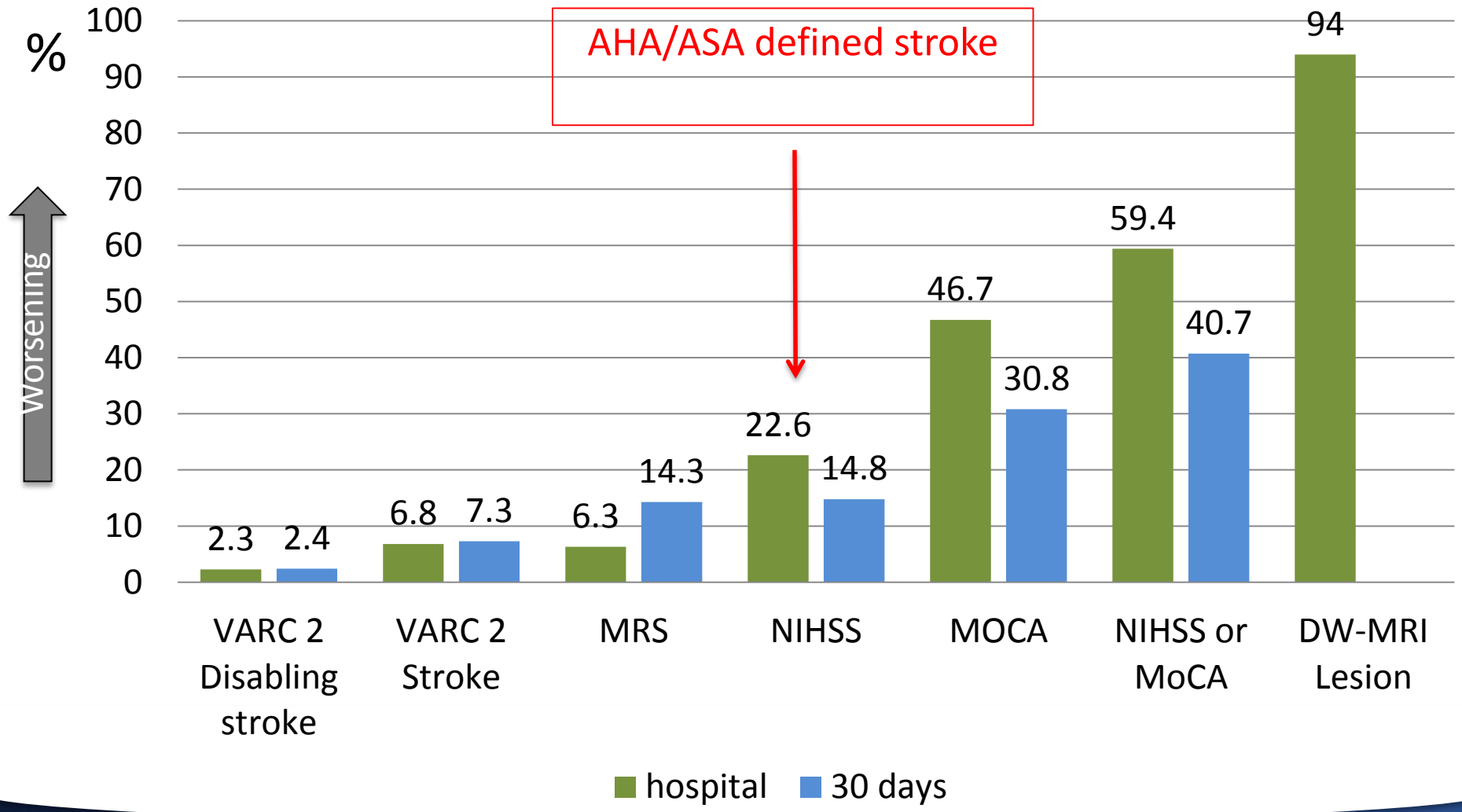


VS.



Neurologic and Cognitive Impairment

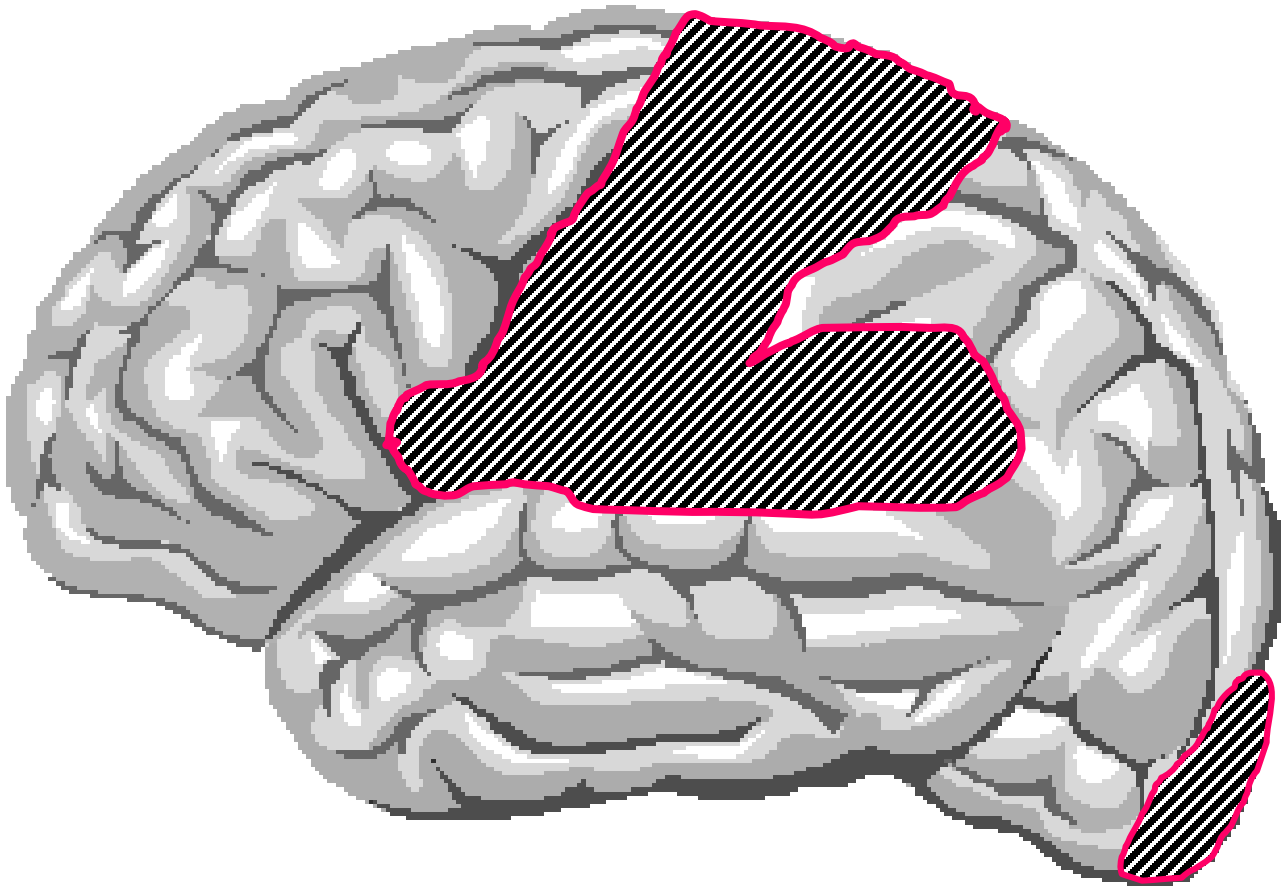
Patients with worsening MRS, NIHSS and MoCA + New Brain Lesions



*AP Kappetein et al. EHJ (2012) 33, 2403–2418;
**Sacco et al. Stroke. 2013;44:2064-2089

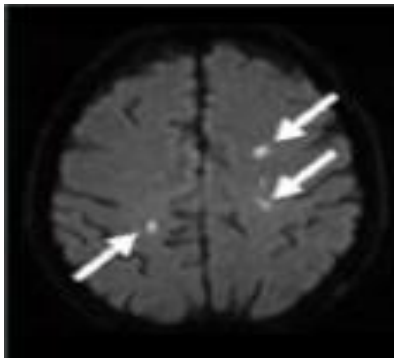
Cognition and TAVR

Brain Regions Assessed by NIH Stroke Scale



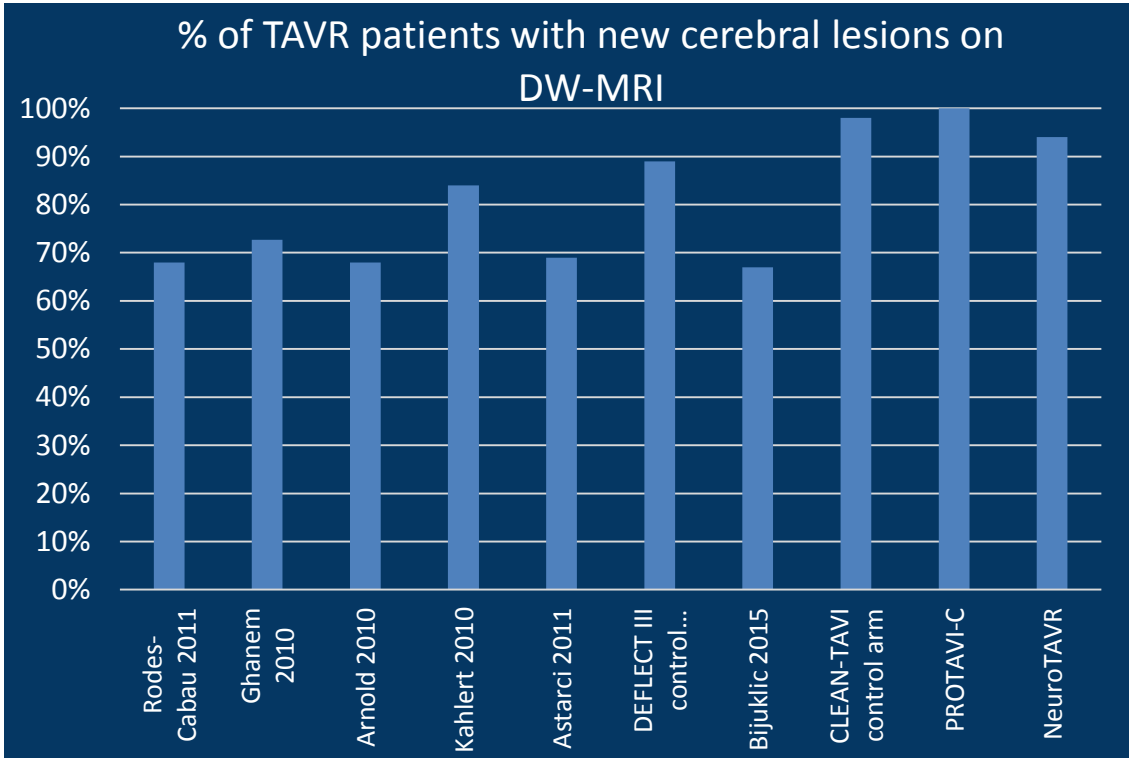
* Courtesy Ronald Lazar

New cerebral lesions are found in the vast majority of patients following TAVI



Ghanem, et. al, JACC 2010

- 68-100% of TAVR patients affected
- Most patients have multiple infarcts
- "Silent" infarcts associated with[1,2,3]
  - 2-4-fold risk of future stroke
  - >3-fold risk of mortality
  - >2-fold risk of dementia
  - Cognitive decline
  - Dementia



TAVI stroke is mostly periprocedural

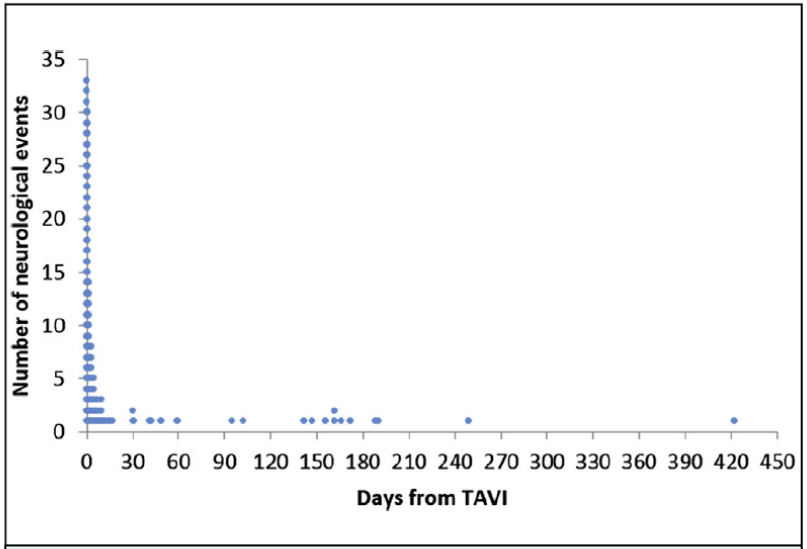


FIGURE 1 **Timing of Cerebrovascular Events**

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

Stroke

Timing, Predictive Factors, and Prognostic Value of Cerebrovascular Events in a Large Cohort of Patients Undergoing Transcatheter Aortic Valve Implantation

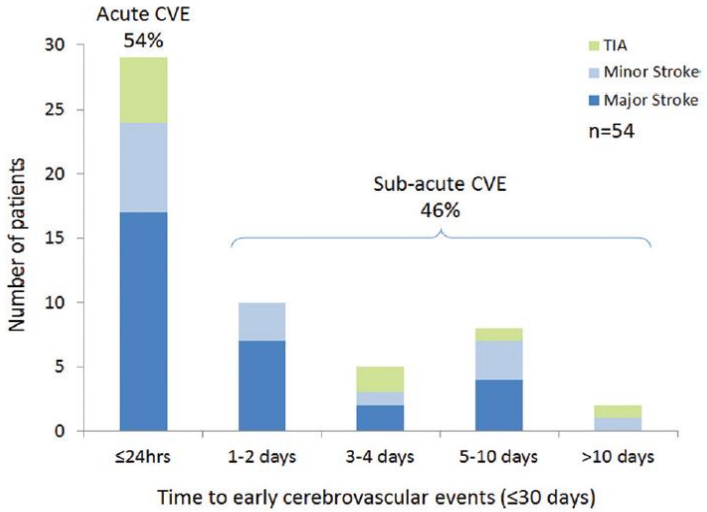


Figure 2. Timing of cerebrovascular events (CVEs) within 30 days after transcatheter aortic valve implantation. TIA indicates transient ischemic attack.

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

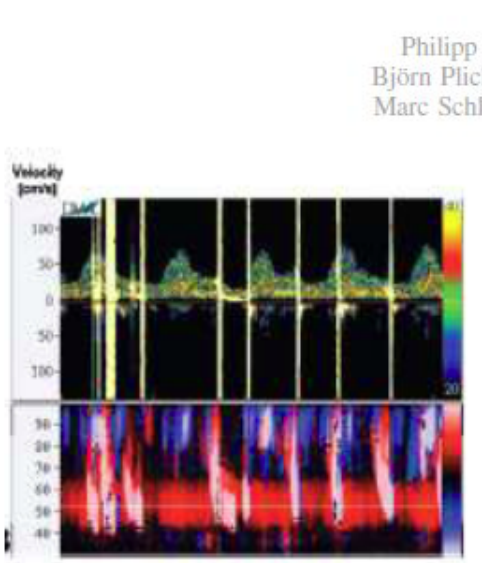
Tchétché et al. J Am Coll Cardiol Intv 2014; 7(10)

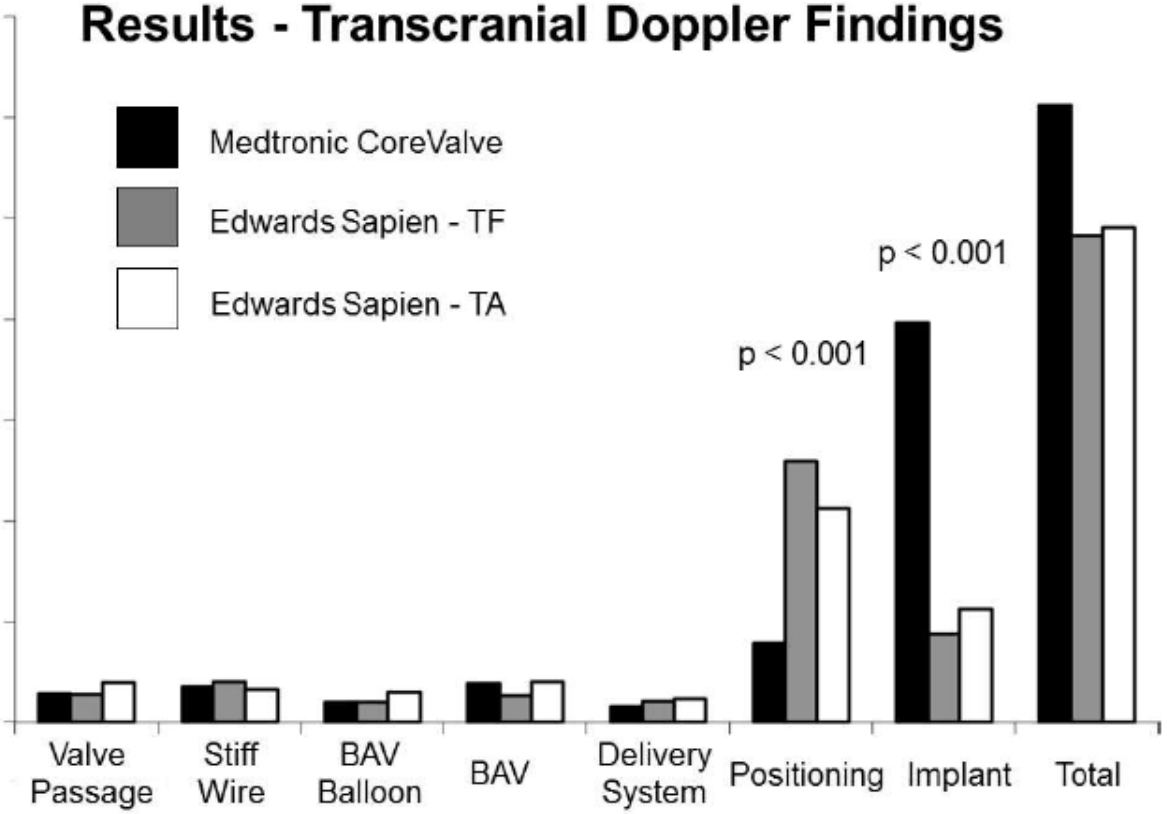
Multi-center cohort of 1,061 TAVI patients

- 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

Embolic events occur with device positioning and deployment





Kahlert P,...,Eggebrecht H, Circulation 2012

1. If embolic events occur, why not prevent them?

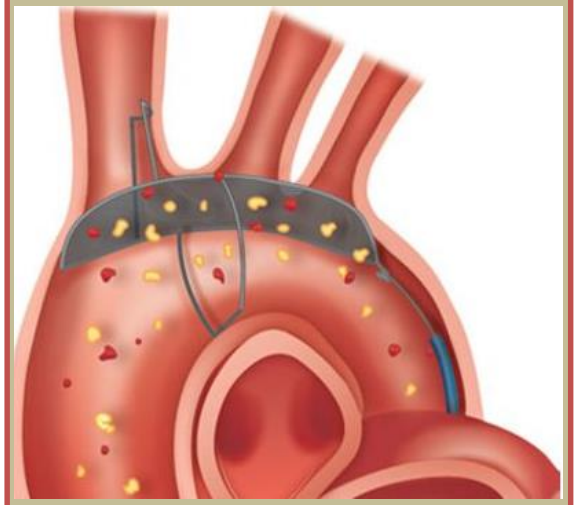
2. Will preventing embolic events improve outcomes?

Ideal Embolic Protection Device

- Easy to use and deploy
- Protects all cerebral vessels
- Captures ***all*** debris
- Doesn't restrict cerebral flow

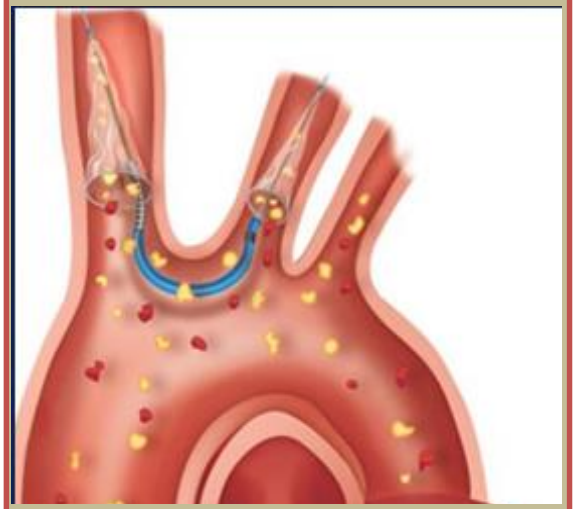
Current Cerebral Protection Devices

TriGuard Embolic Deflection Device (Keystone Heart)[1]



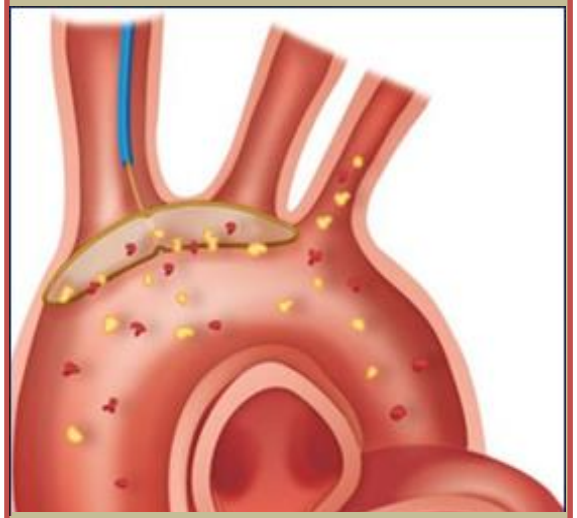
- ✓ Pore Size: 130 µm
- ✓ Delivery Sheath: 9F
- ✓ Access: Transfemoral
- ✓ Mechanism: Debris deflection

Sentinel Cerebral Protection System (Claret Medical)[2]



- ✓ Pore Size: 140 µm
- ✓ Delivery Sheath: 6F
- ✓ Access: Brachial or radial
- ✓ Mechanism: Debris capture and retrieval

Embrella Embolic Deflector System (Edwards Lifesciences)[3]



- ✓ Pore Size: 100 µm
- ✓ Delivery Sheath: 6F
- ✓ Access: Brachial
- ✓ Mechanism: Debris deflection

[1]Lansky, et. al. , presented at TCT 2015; [2]Van Mieghem, et al., presented at TCT 2015; [3]Rodes-Cabau, et al., *J Am Coll Cardiol Intv* 2014;7:1146-55

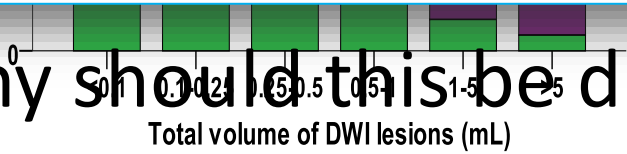
The Case for Embolic Protection

- Carotid stent experience
- MRI abnormalities – "Silent" infarcts are not benign

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.



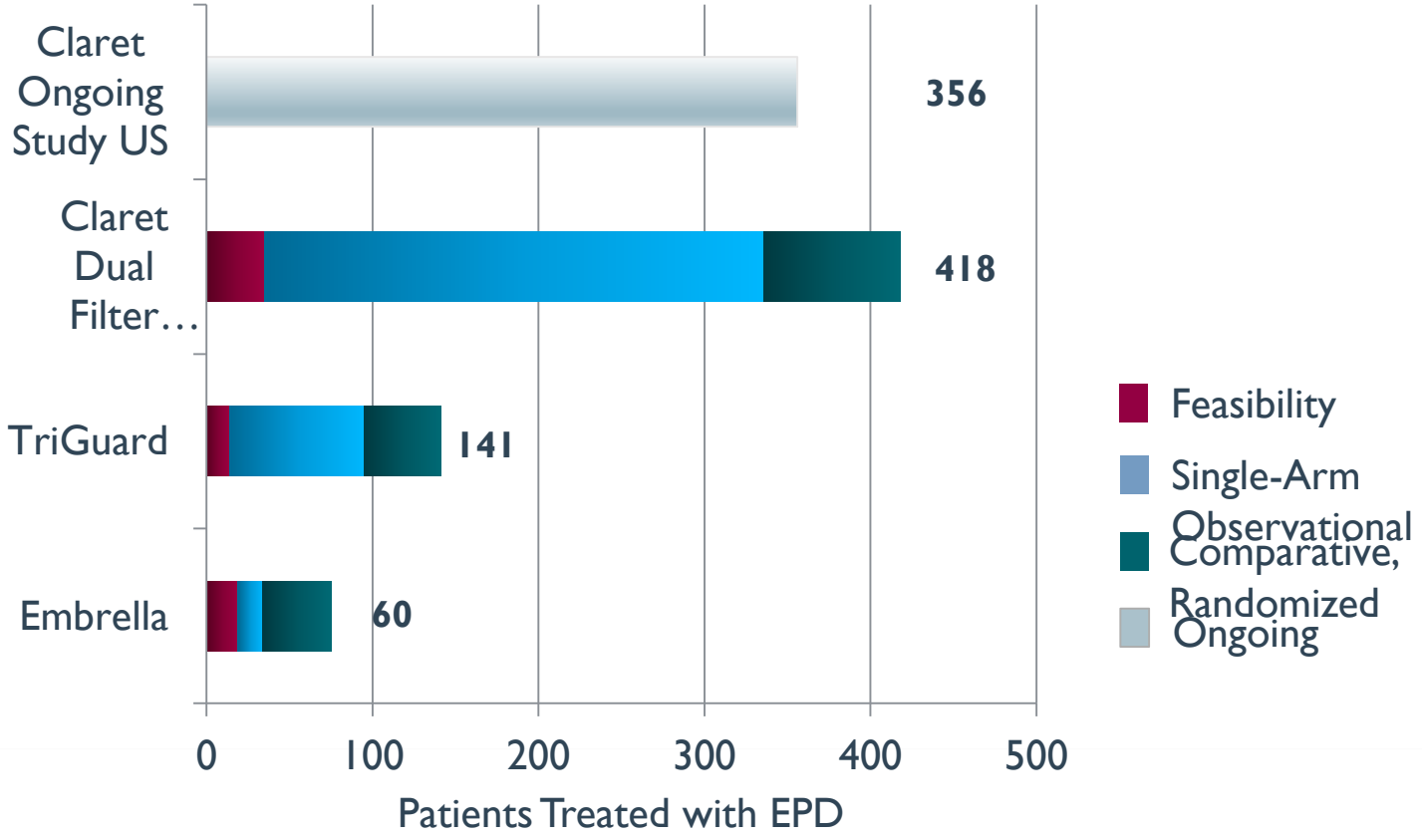
Why should this be different in TAVR?

significantly higher incidence of clinical evident stroke than those without. (p<0.001)

Bernick et al, 2001; Vermeer et al, 2003; Vermeer et al, 2007

Embolic Protection Devices:
Patients under investigation

Embolic protection devices have been under investigation in humans since 2010, however the total number of patients treated with these devices remains limited



[1]Nietlispach, et. al. , *J Am Coll Cardiol Intv* 2010; 3: 1133-8; [2]Samin, et al., *J Thorac Cardiovasc Surg* 2015; 149:799-805; [3]Rodes-Cabau, et al., *J Am Coll Cardiol Intv* 2014;7:1146-55; [4]Naber, et al., *EuroIntervention* 2012; 8: 43-50; [5]Van Mieghem, et al., *J Am Coll Cardiol Intv* 2015; 8: 718-24; [6]Linke, et al., presented at TCT 2014; [7]Van Mieghem, et al., presented at TCT 2015; [8]Onsea, et al., *EuroIntervention* 2012;8:51-6; [9]Baumbach, et al., *EuroIntervention* 2015;11:75-84; [10]Lansky, et al., *Eur Heart J* 2015;36:2070-8; [11]Lansky, et al., presented at London Valves 2015; [12]Nijhoff, et al, presented at EuroPCR 2015; [13]Jensen C, et al., presented at EuroPCR 2016

Embolic Protection Devices

Four studies have looked at EPDs against untreated controls, all had different designs

DEFLECT III N = 85	
Purpose:	Exploratory, benchmark event rates
Device:	Keystone TriGuard
Imaging:	1.5T MRI at day 4, no baseline
Follow-up:	Baseline, day 4, day 30

PROTAVI-C N = 52	
Purpose:	Exploratory safety and efficacy
Device:	Edwards Embrella
Imaging:	MRI
Follow-up:	Baseline, day 7, day 30

CLEAN-TAVI N=100	
Purpose:	Demonstrate reduction in brain lesions at day 2
Device:	Claret Montage
Imaging:	3-T MRI
Follow-up:	Baseline and day 2, 7, 30 , 365

MISTRAL-C N = 65	
Purpose:	Demonstrate reduction in brain lesions at day 5
Device:	Claret Sentinel
Imaging:	3-T MRI, transcranial doppler
Follow-up:	Baseline and day 5

Embolic Protection Devices

The Findings

DEFLECT III N = 85	
Purpose:	Exploratory, benchmark event rates
Achieved?	• Better outcomes with EPD • Stage set for US IDE Trial (REFLECT)

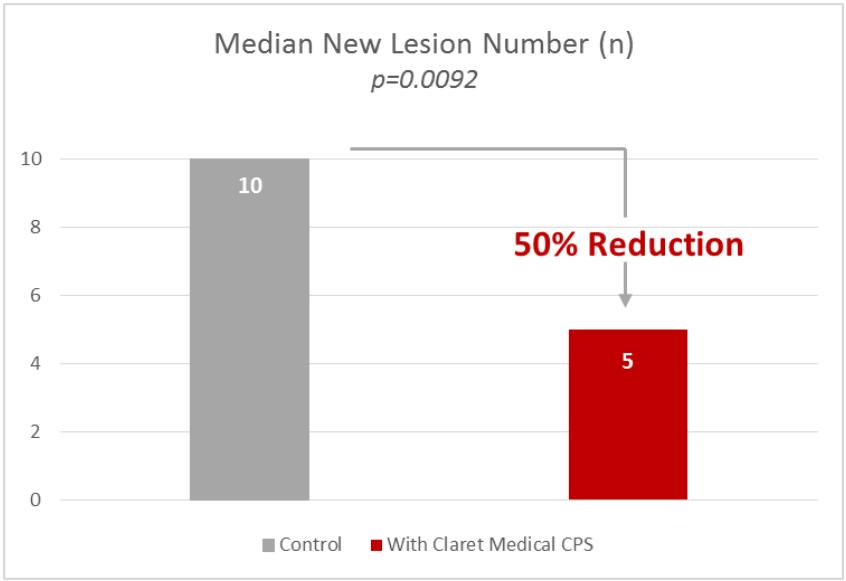
PROTAVI-C N = 52	
Purpose:	Exploratory safety and efficacy
Achieved?	• Better MRI outcomes with EPD, worse with transcranial doppler

CLEAN-TAVI N=100	
Purpose:	Demonstrate reduction in brain lesions at day 2
Achieved?	• Statistically better outcomes with EPD • Stage set for US IDE Trial (SENTINEL)

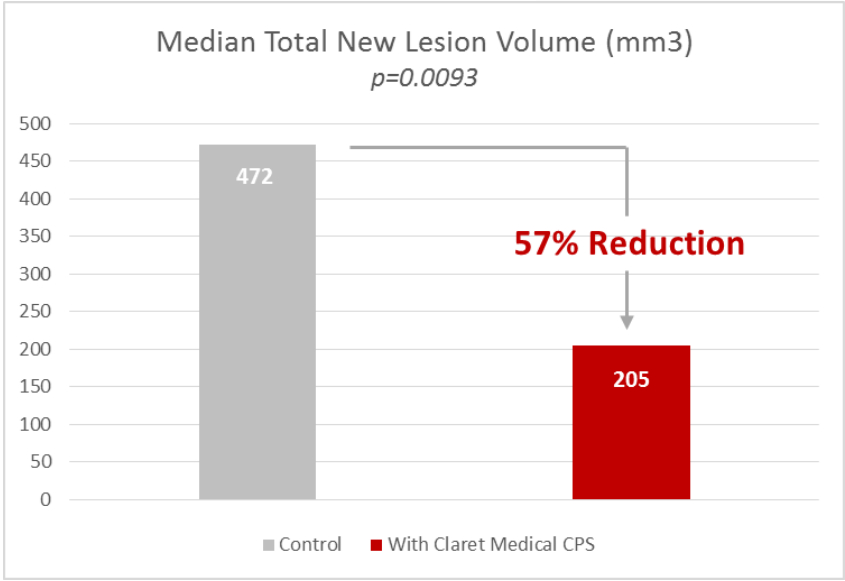
MISTRAL-C N = 65	
Purpose:	Demonstrate reduction in brain lesions at day 5
Achieved?	Better outcomes with EPD, lost statistical power with patients lost to follow up

CLEAN-TAVI shows Claret filters significantly reduce lesion number and volume

Lesion Number per Patient



Total Lesion Volume per Patient

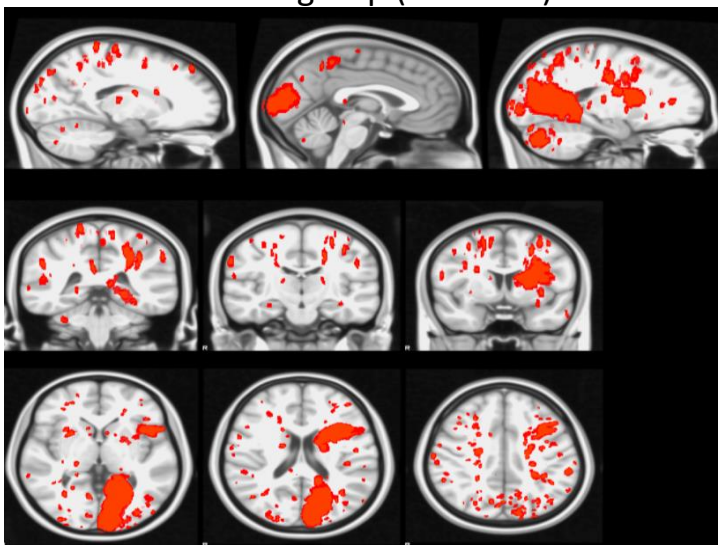


Claret Montage Cerebral Protection System significantly reduces new cerebral lesion number and volume at 7 days, as measured by DW-MRI

CLEAN-TAVI shows the promise of protection

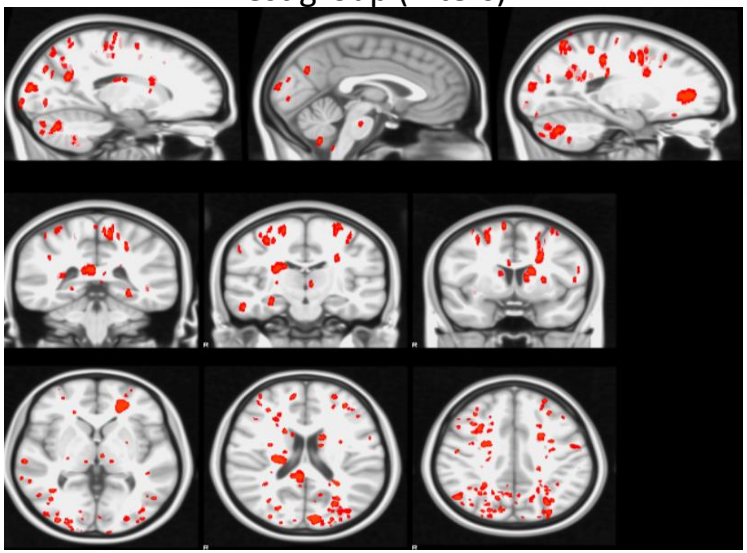
The Problem

Control group (no filters)



The Promise

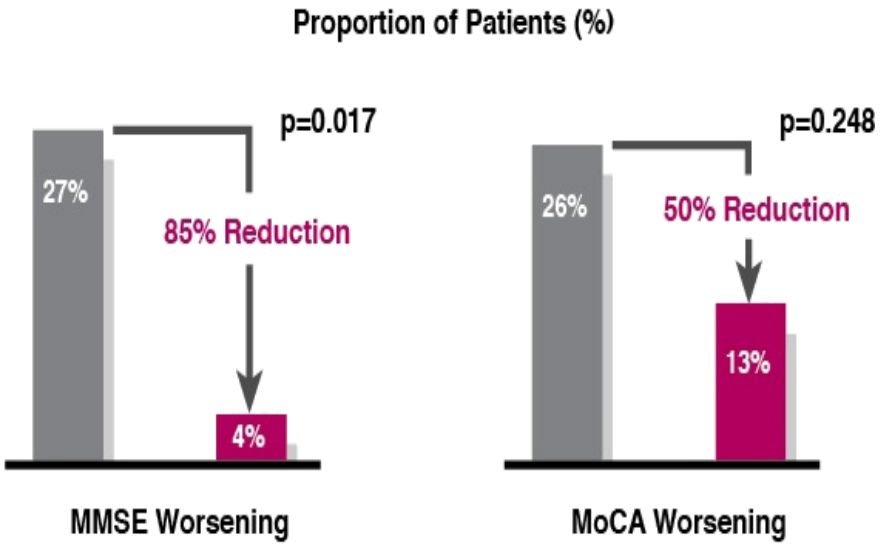
Test group (filters)



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

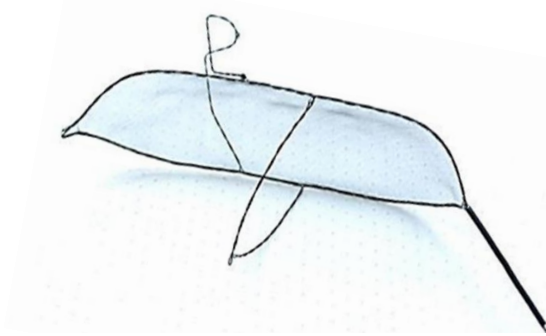
Claret Montage Cerebral Protection System significantly reduces new cerebral lesion number and volume at 2 & 7 days, as measured by DW-MRI

MISTRAL-C RCT shows when Sentinel CPS is used, significantly fewer TAVI patients show worsening neurocognitive changes



Fewer TAVI patients showed worsening neurocognitive changes by MMSE and MoCA at 3 months when filter protection was used

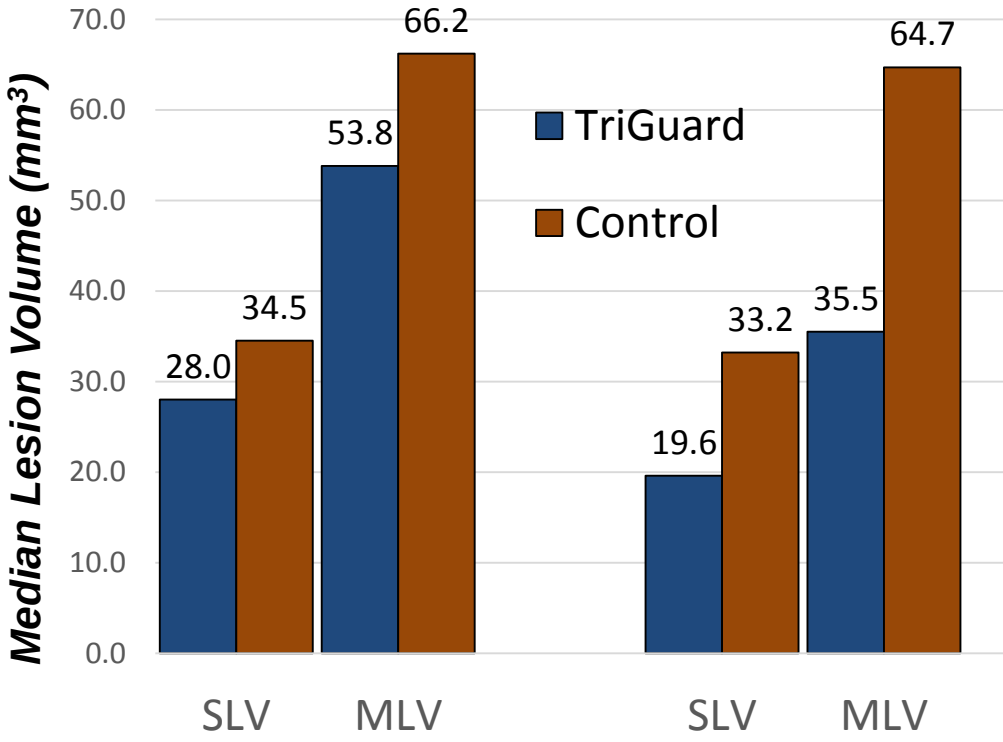
DEFLECT III Study Overview



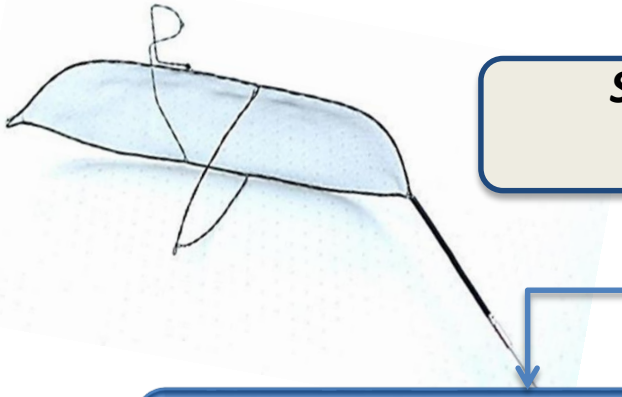
Design: Multicenter prospective single-blind randomized controlled trial at 13 sites (EU/IL)

Objective: To evaluate the safety, efficacy and performance of TriGuard protection compared with unprotected TAVR.

Sample Size: Exploratory study with no formal hypothesis testing (86 patients to set benchmark for pivotal trial).



REFLECT US IDE Trial Design



Subjects with AS undergoing TAVI
N=285

Roll-In
N≤90

2:1 Randomization

TriGuard Embolic Protection
n=190

Unprotected TAVI
n=95

Safety

- *Combined safety endpoint (VARC-2) at 30 days*
- *TriGuard vs. Performance Goal*

Efficacy

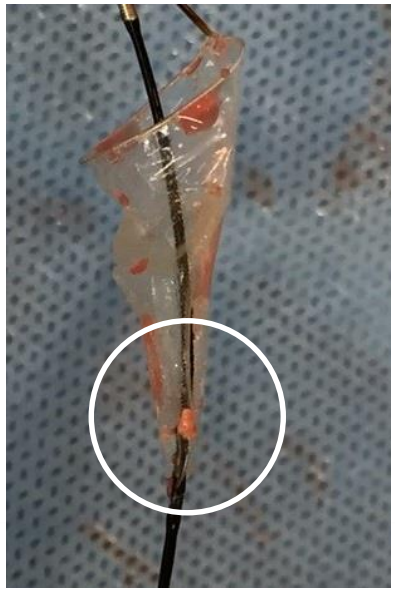
- *Hierarchical composite efficacy endpoint (Finkelstein-Schoenfeld):*
  - *Death or stroke (30 d)*
  - *NIHSS or MoCA worsening (in-hospital)*
  - *Total lesion volume by DW-MRI (post-procedure)*
- *TriGuard vs. Control*

The Case for Embolic Protection

- Carotid stent experience
- MRI abnormalities – "Silent" infarcts are not benign
- Studies have demonstrated that embolic protection devices reduce *MRI abnormalities* after TAVR
  - CLEAN TAVI
  - DEFLECT III
- Potential for clinical benefit beyond stroke – Cognitive improvement
  - How to assess?
  - Who benefits most (older vs younger?)

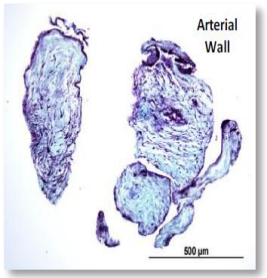
The Case *for* Embolic Protection

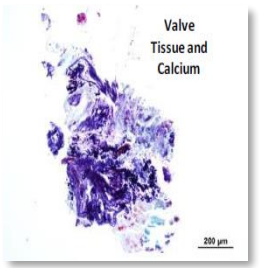
- Carotid stent experience
- MRI abnormalities – "Silent" infarcts are not benign
- Studies have demonstrated that embolic protection devices reduce *MRI abnormalities* after TAVR
  - CLEAN TAVI
  - DEFLECT III
- Potential for clinical benefit beyond stroke – Cognitive improvement
- If we can prevent embolic events, why not do so?

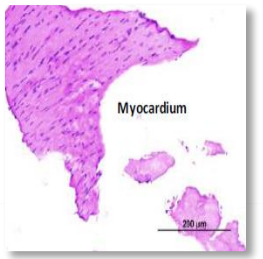


Embolic debris captured in **88%** of patients in CLEAN-TAVI study

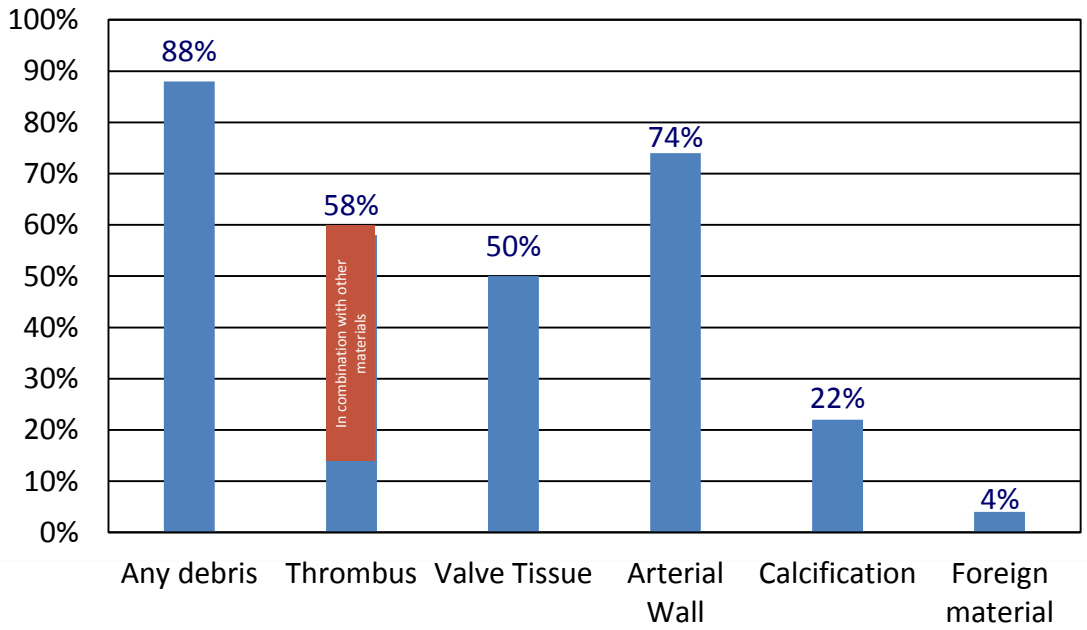
- 50 cases of TAVI using Claret Cerebral Protection System performed at Univ. of Leipzig - Herzzentrum
  - Filter arm of CLEAN-TAVI randomized trial
  - All using Medtronic CoreValve
- Filter contents subsequently analyzed by CVPath Institute
  - **Debris captured in 88% of patients**







Cerebral embolic debris captured in CLEAN-TAVI patients (n=50)

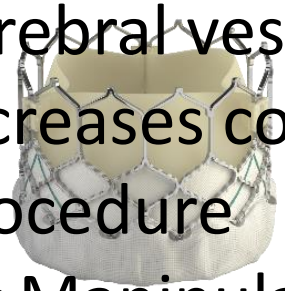


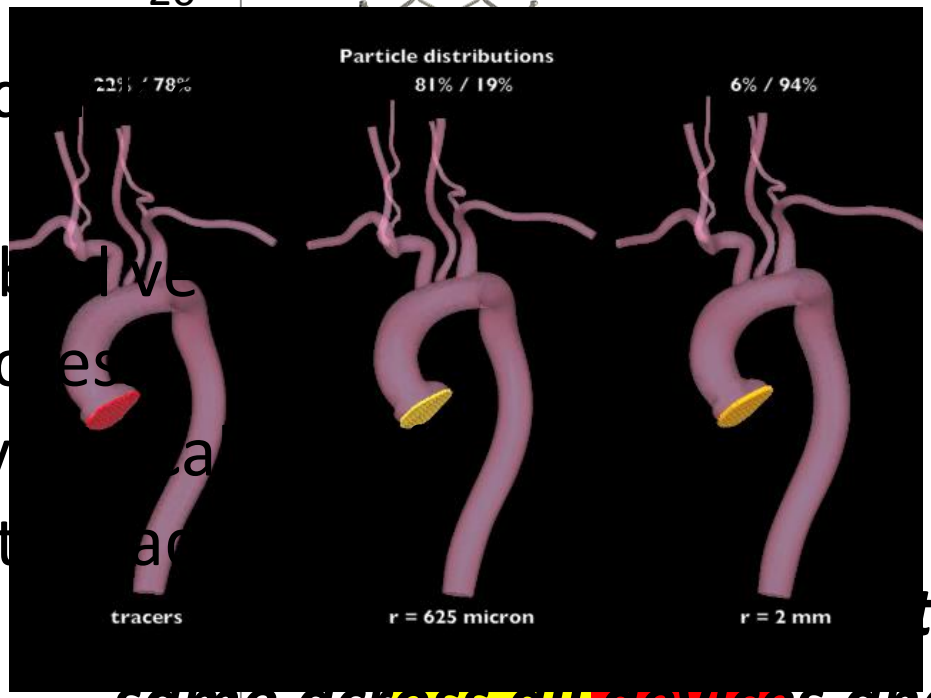
Thrombus was found in combination with other materials in 87% of filters which contained thrombus

1. Unpublished data. CVPath Institute data on file at Claret Medical. CLEAN-TAVI presented by Linke A at TCT 2014

The Case *against* Embolic Protection

- Stroke rates are decreasing
- Current devices don't reliably protect all cerebral vessels
- Increases complexity and procedure
  - Manipulation of cerebral vessels
  - Additional vascular access
- No study has proven any clinical and MRI changes are not surrogate endpoint





the same across all devices and need to studied carefully

- ✓ 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

SENTINEL Study Design

Pivotal trial 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

US Co-PIs:
Samir Kapadia, MD, *Cleveland Clinic*
Susheel Kodali, MD, *Columbia U Med*
German Co-PI:
Axel Linke, MD, Leipzig U

Population: Subjects with severe symptomatic calcified native aortic valve stenosis who meet the commercially-approved indications for TAVR with the Edwards Sapien THV/XT/S3 or Medtronic CoreValve/Evolut-R
N=296 subjects randomized 1:1:1
at sites in the U.S and Germany.

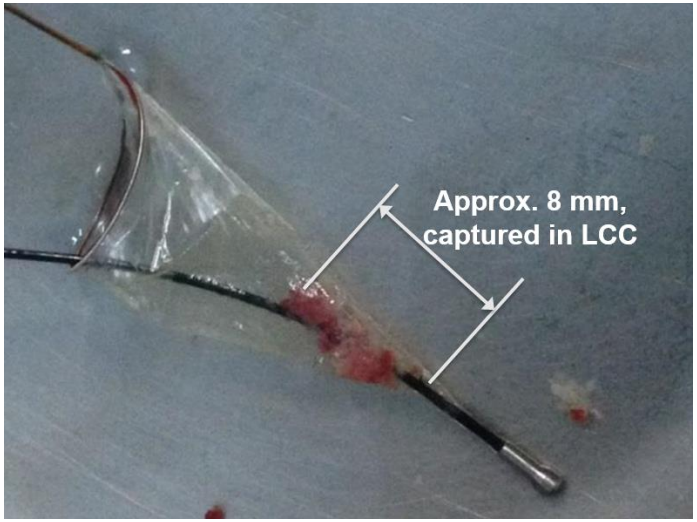
- **SAFETY ARM** — TAVR with Sentinel
  - Safety Follow-up
- **TEST ARM** — TAVR with Sentinel
  - Histopathology
  - Safety Follow-up
  - MRI Assessments
  - Neurological and Neurocognitive Tests
- **CONTROL ARM** — TAVR only
  - Neurological and Neurocognitive Tests

Primary (superiority) Efficacy Endpoint: Reduction in median total new lesion volume assessed by 3T DW-MR by baseline subtraction .
Primary (non-inferiority) Safety Endpoint: Occurrence of all MACCE at 30 days.

The Case *against* Embolic Protection

- Stroke rates are decreasing
- Current devices don't reliably protect all cerebral vessels
- Increases complexity and risk of procedure
  - Manipulation of cerebral vessels
  - Additional vascular access
- No study has proven any clinical benefit and MRI changes are not an adequate surrogate endpoint
- COST!!!

Is Cerebral Protection Necessary?



Would you take a chance and drive without a seatbelt?

You never know when you'll need protection