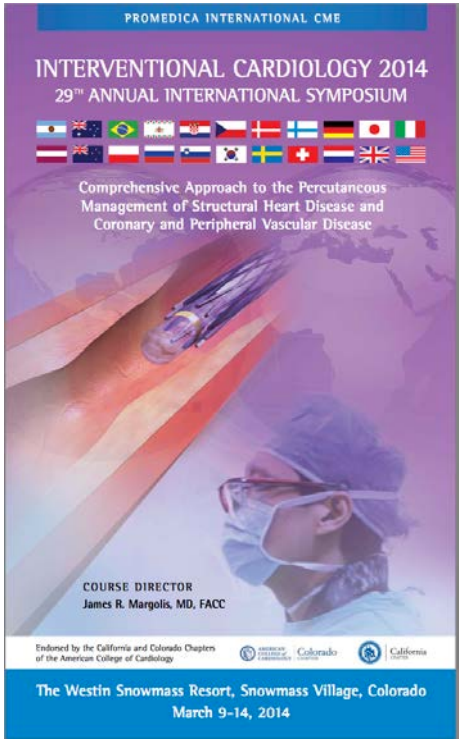
BHI
Bristol Heart Institute

University Hospitals Bristol NHS
NHS Foundation Trust



Neuroprotection: Importance of Covering All Three Cerebral Vessels

Andreas Baumbach, MD, FRCP, FESC
Consultant Cardiologist, hon. Professor of Interventional Cardiology
Bristol Heart Institute
University Hospitals Bristol

Conflicts of Interest

Research support and speaker fees

Keystone Heart

TAVI and Embolic Protection

- Is there a clinically relevant problem with embolic cerebral events ?
- Can we protect the brain with devices ?
- Can we see a difference in cases with partial vs. completely protected cerebral arteries ?

Pathophysiology

Potential Paths of Cerebral Embolism

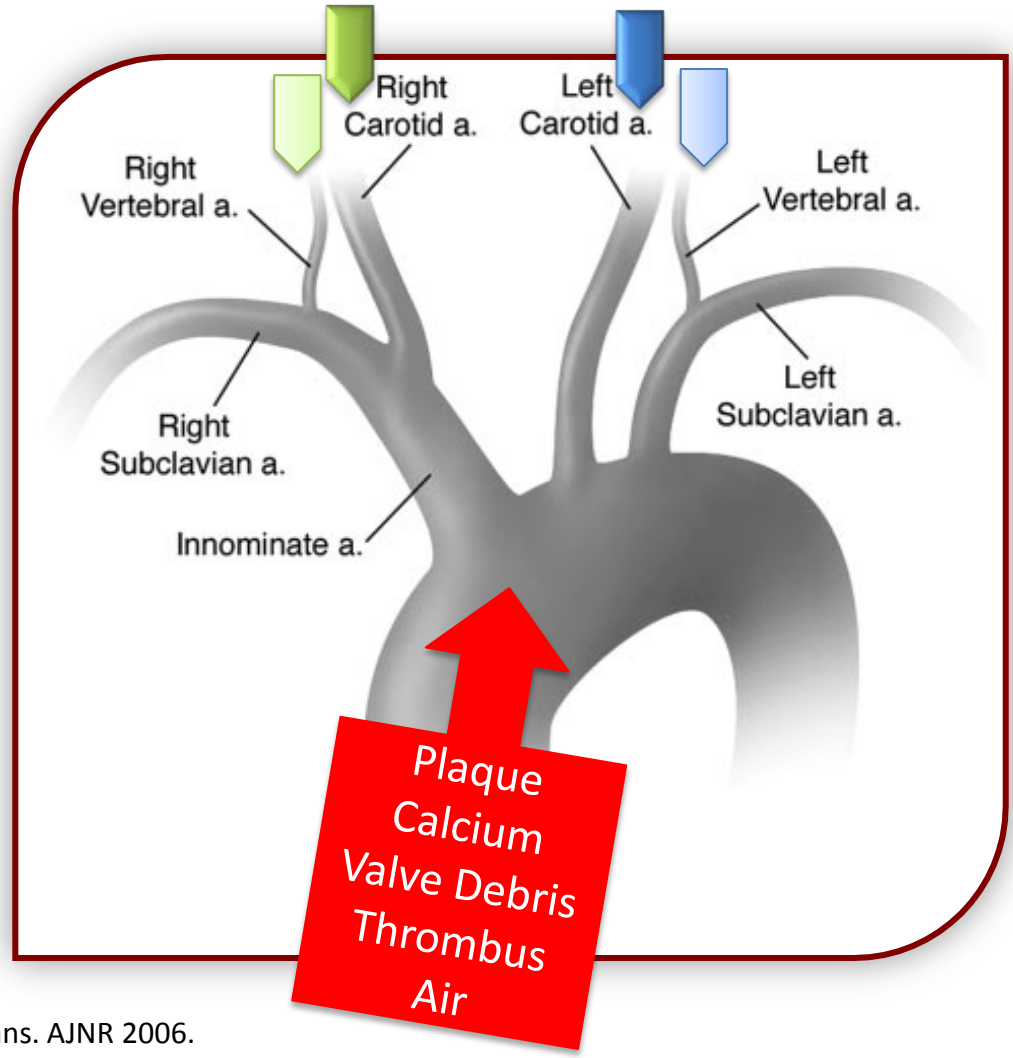
Typical aortic arch anatomy

Right Carotid

Right Vertebral

Left Carotid

Left Vertebral



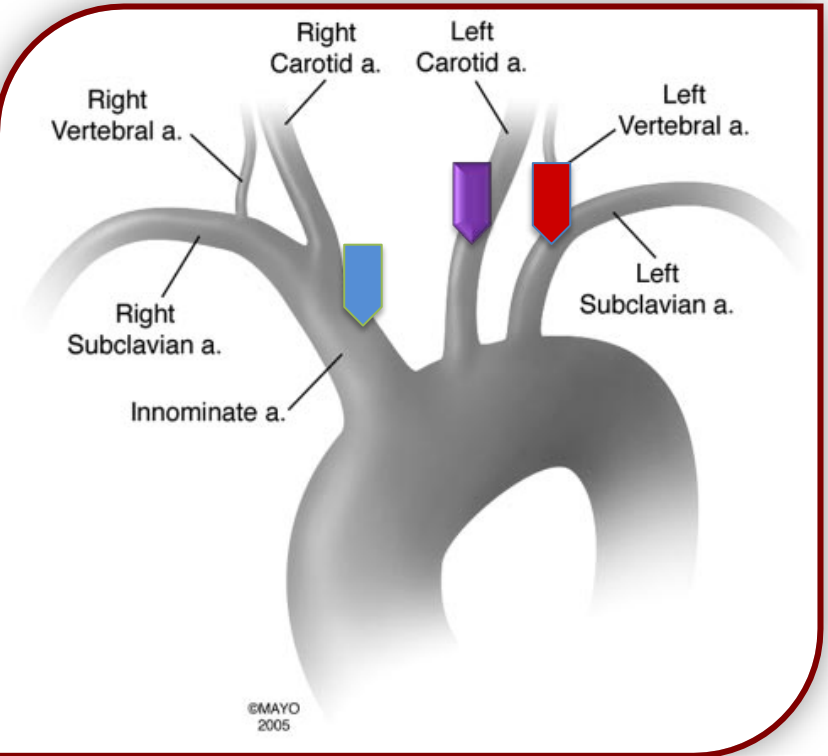
Layton KF et al. Bovine Aortic Arch Variant in Humans. AJNR 2006.

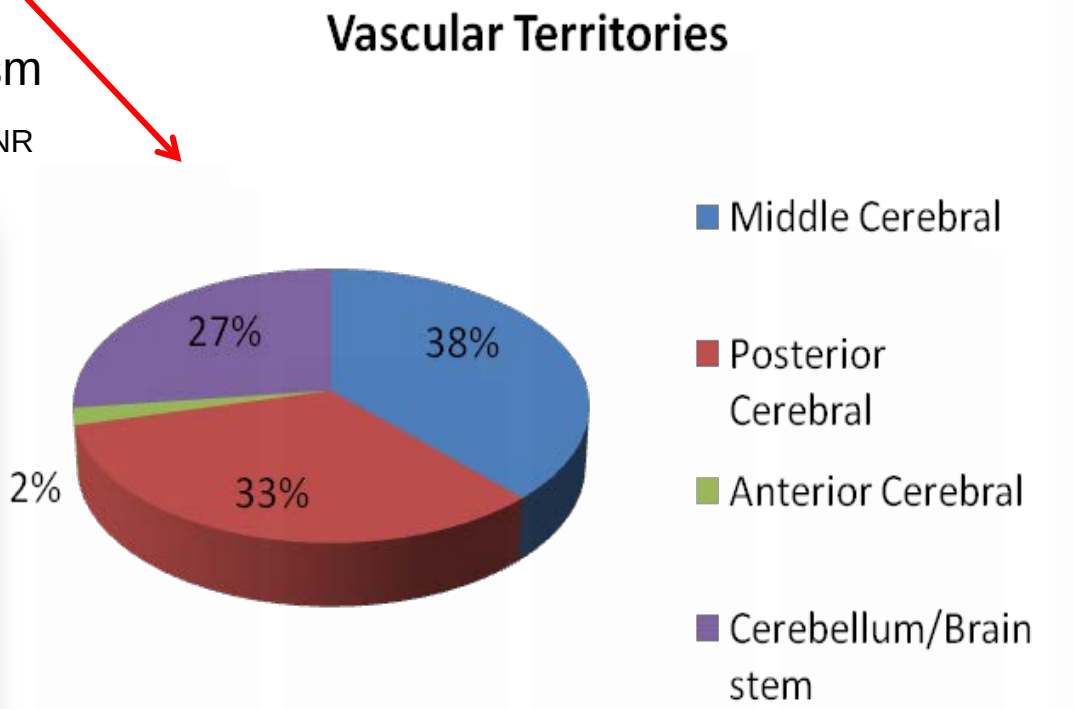
Protecting Left Subclavian Artery - Vital

27% of the DWI MRI Lesions are in the Distribution of the Cerebellum/Brain Stem and 33% in the Posterior Region

Potential Paths of Cerebral Embolism

Layton KF et al. Bovine Aortic Arch Variant in Humans. AJNR 2006.

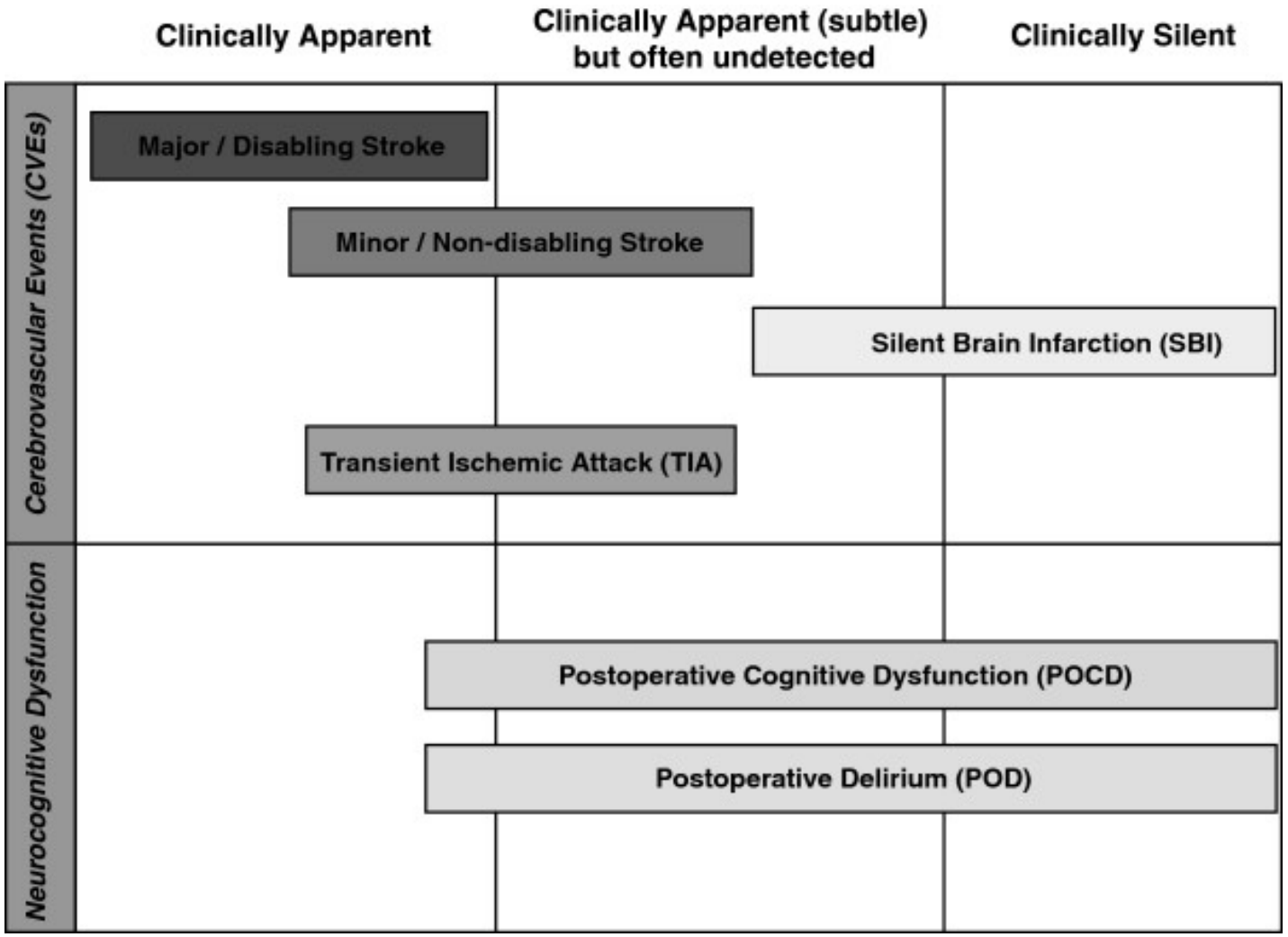




Vertebral Arteries

- Supply **exclusively** the CEREBELLUM and BRAIN STEM
  - BRAIN STEM is critical for sustaining life
    - regulation of cardiac and respiratory function
    - regulates Central Nervous System
    - pivotal in maintaining consciousness and regulating the sleep cycle
  - CEREBELLUM coordinates the motor movements, basic memory and learning processes
    - coordination of voluntary motor movement, balance, equilibrium, and muscle tone
- Provide blood flow to the POSTERIOR CEREBRAL CIRCULATION
  - center for all visual ability
  - involuntary movements, memory defects

Spectrum of Cerebrovascular Events



Reporting Stroke: What if we ask Neurologists ?

Stroke After Aortic Valve Surgery: Results From a Prospective Cohort

Steven R. Messé, Michael A. Acker, Scott E. Kasner, Molly Fanning, Tania Giovannetti, Sarah J. Ratcliffe, Michel Bilello, Wilson Y. Szeto, Joseph E. Bavaria, W. Clark Hargrove, III,, Emile R. Mohler, III, and Thomas F. Floyd
for the Determining Neurologic Outcomes from Valve Operations (DeNOVO) Investigators

Circulation. 2014;129:2253-2261; originally published online April 1, 2014;

- Prospective evaluation of pts undergoing surgical AVR
- Pre and post assessment and DW MRI

- Clinical strokes in hospital: 17%
- Moderate/severe: 4%
- TIA 2%
- Silent infarcts on MRI: 54%

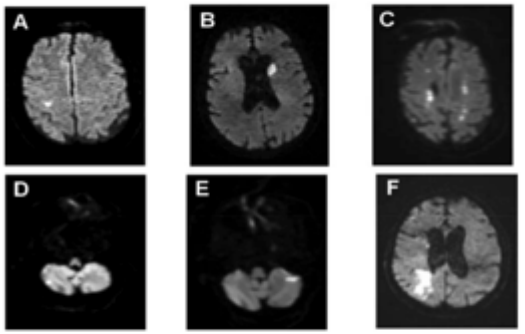


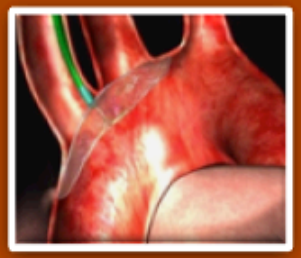
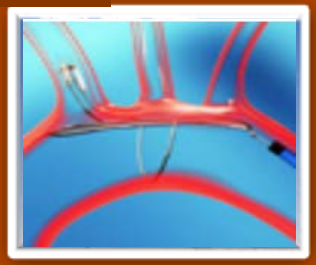
Figure 4. Examples of infarcts on magnetic resonance imaging. **A**, Patient with 14 clinically silent infarcts totaling 3292 mm³. **B**, Patient with 7 clinically silent infarcts totaling 2695 mm³. **C**, Patient with a clinical stroke (National Institutes of Stroke Scale [NIHSS], 15) and 34 infarcts totaling 12033 mm³. **D**, Patient with a clinical stroke (NIHSS, 3), 6 small infarcts totaling 412 mm³. **E**, Patient with a single clinically silent infarct measuring 766 mm³. **F**, Patient with a clinical stroke (NIHSS, 13) and 27 infarcts totaling 55871 mm³.

Postoperative cognitive capacity

cognitive decline
memory
mood disturbances
psychomotor speed
personality changes

THE DATA SO FAR

EMBOLIC PROTECTION DEVICES

Feature	Embrella	Triguard	Claret Medical
			
Access	Radial	Femoral	Radial
Position	Aorta	Aorta	Brachiocephalic Left Common Carotid
Coverage Area	Brachiocephalic & LCC	Brachiocephalic & LCC & LSC	Brachiocephalic & LCC
Mechanism	Deflection	Deflection	Capture
Size	6F	9F	6F
Pore Size	100 microns	~200 microns	140 microns

Embrella Embolic Deflector System

Embolic protection device designed to reduce the amount of embolic material that may enter the carotid arteries during TAVI and valvuloplasty procedures.

- Access: radial, brachial (right). 6F sheath
- The distal end of the deflector consists of an oval shaped nitinol frame (length: 59 mm; width 25.5 mm) covered with a porous polyurethane membrane (100 microns pore size).
- The frame has two opposing petals that are positioned along the greater curvature of the aorta, covering the ostia of both the brachiocephalic and the left common carotid arteries.

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PROTAVI-C

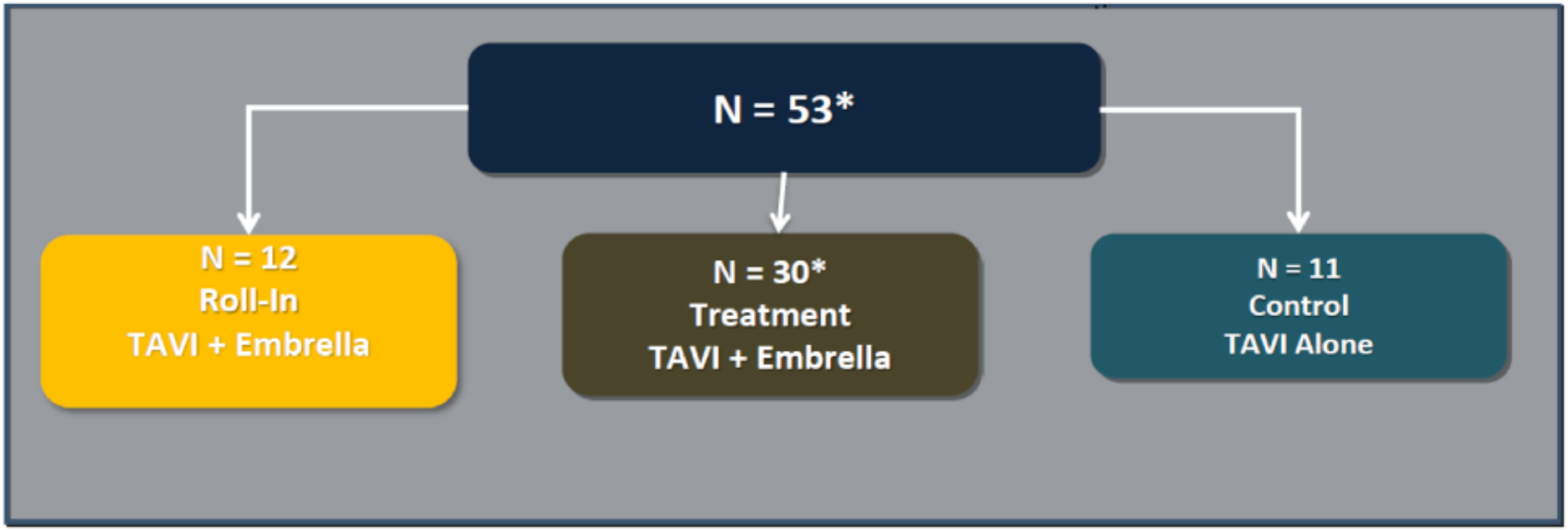
PROTAVI-C Pilot Study

Prospective Randomized Outcome study in patients undergoing TAVI to Examine Cerebral Ischemia and Bleeding Complications

Josep Rodés-Cabau, MD
Quebec Heart & Lung Institute
Quebec City, QC, Canada

on behalf of the PROTAVI-C Pilot Investigators

Study Patient Flow

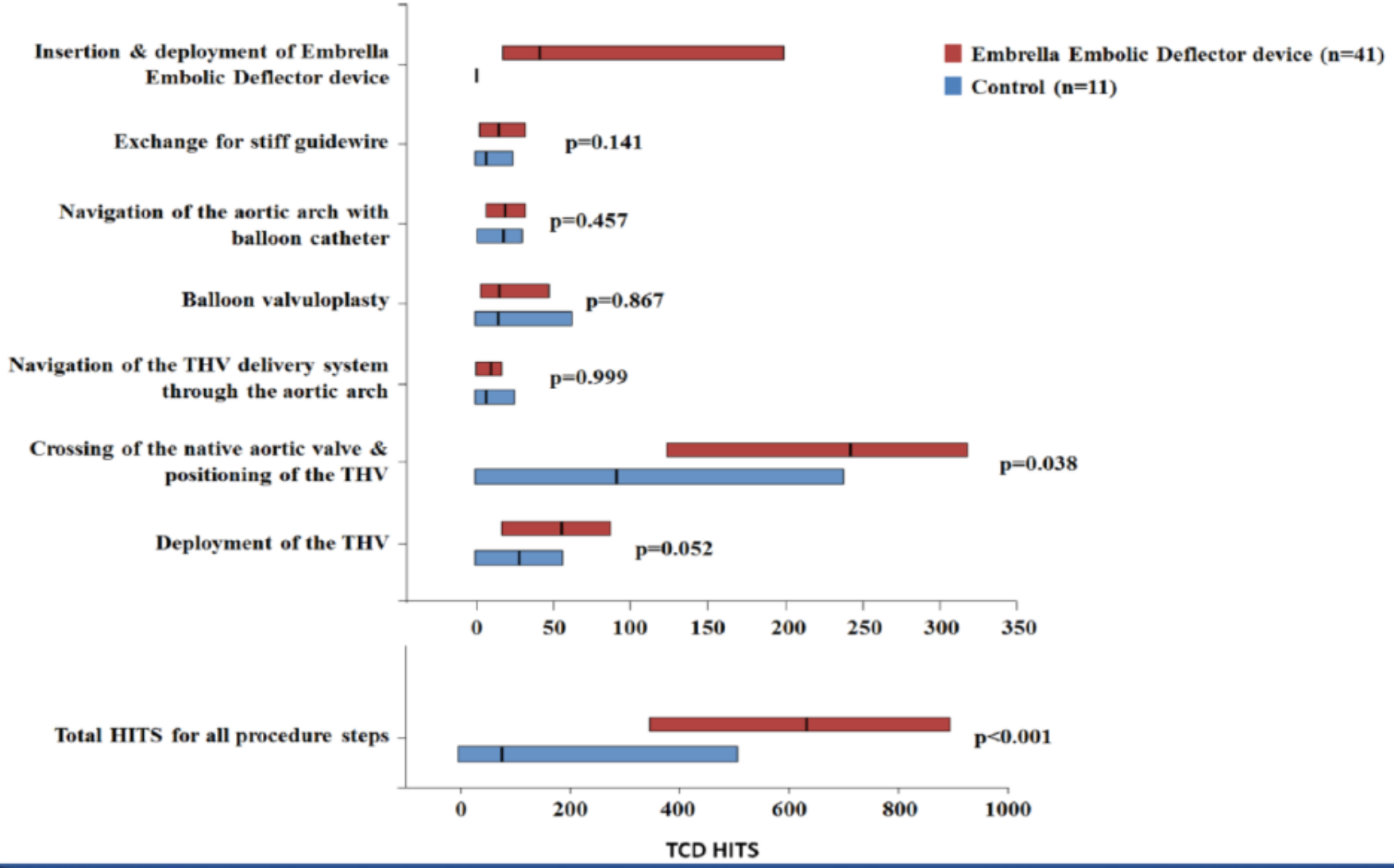


Roll-in and treatment arms will be presented together

•*1 procedure aborted before Embrella insertion

(Rodes-Cabau JACC Cardiovasc Interv In Press)

Transcranial Doppler Findings



(Rodes-Cabau JACC Cardiovasc Interv In Press)

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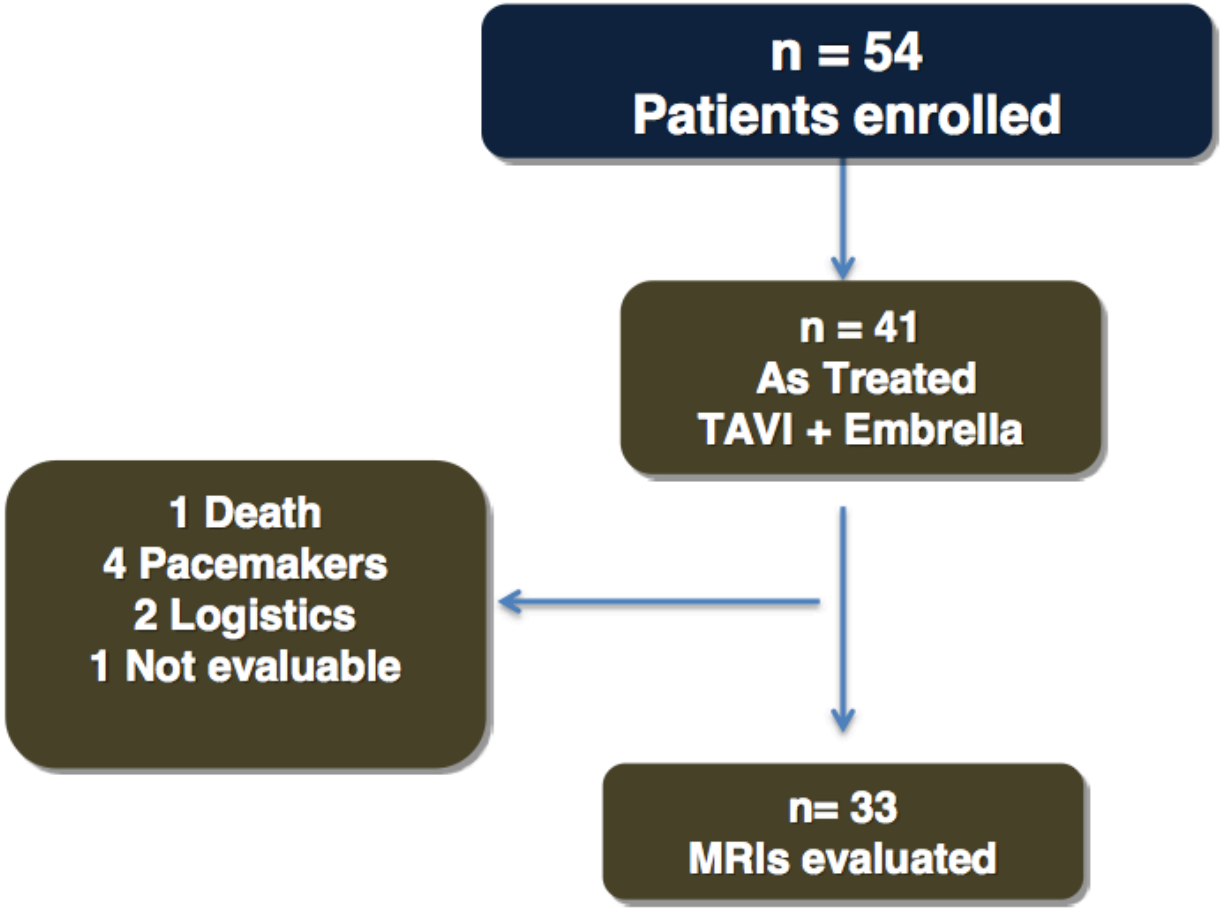
DW-MRI
Within 7 Days After TAVI



PROTAVI-C

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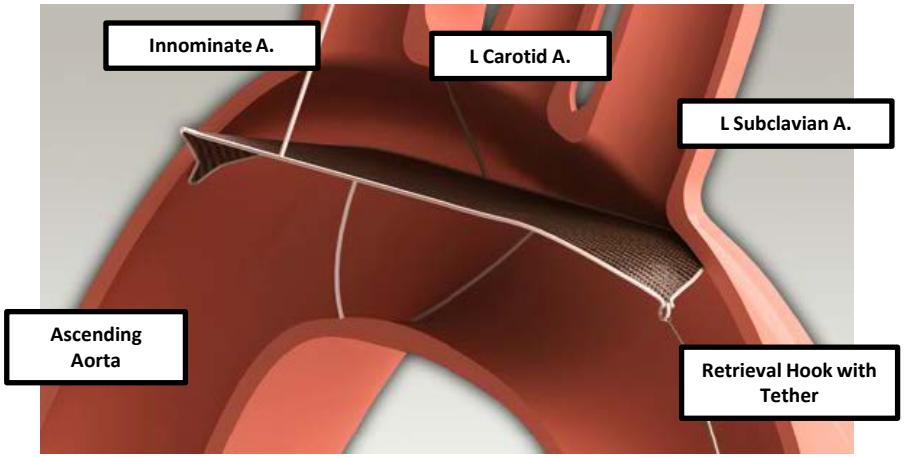
DW-MRI Data

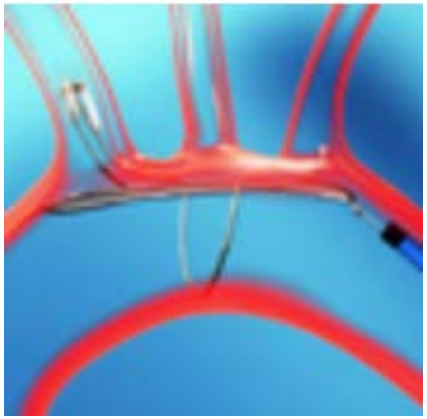
	Treatment TAVI + Embrella (N=33)
Time from TAVI procedure, days, median (min, max)	3 (1-7)
Patients with new lesions	33 (100%)
Lesion location, patients	
Anterior cerebral arte	7 (21%)
Medial cerebral arte	29 (88%)
Posterior cerebral	22 (67%)
Cerebellum	23 (70%)
Border zone	2 (6%)
Patients with single lesions	4 (12%)
Patients with multiple lesions	29 (88%)
Lesions per patient, median (min, max)	8 (1, 70)
Lesion volume (mm^3), median (IQR)	42.3 (27.5, 85.0)

All pts had new lesions
All territories affected
Smaller volume

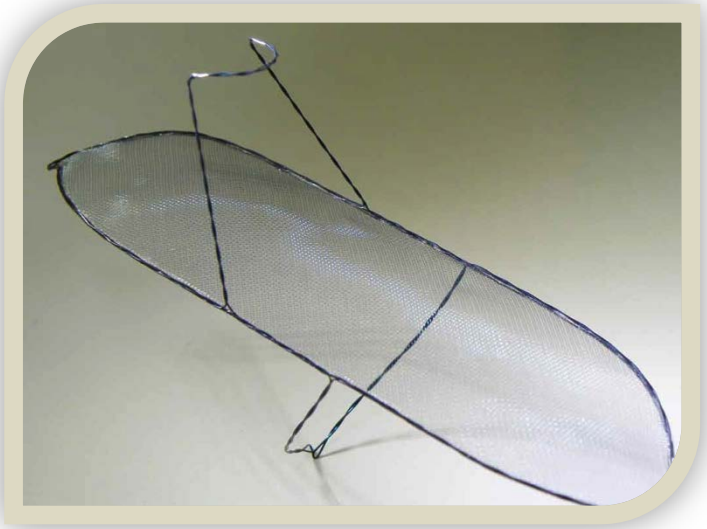
2: Keystone Heart Embolic Deflection Device Triguard



Designed for Coverage of All 3 Take-Offs



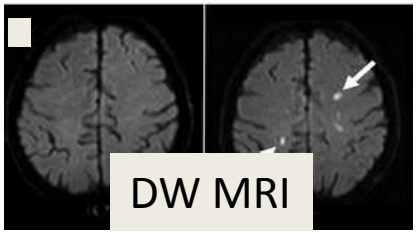
Simple, Fast, Familiar through Femoral access to reduce procedural complexity



Nitinol Frame and Mesh
Self-positioning, with stabilizing atraumatic arms to avoid migration/embolization

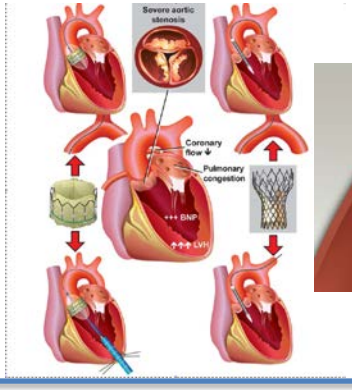
Study Protocol: DEFLECT I

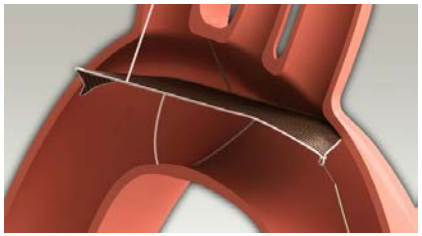
- Pre Procedure

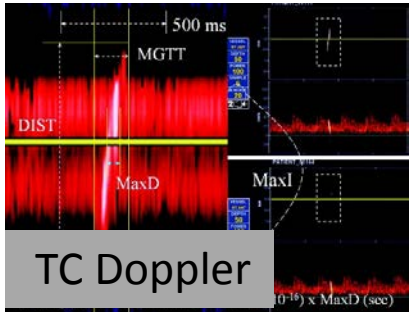


Neurocognitive Assessment

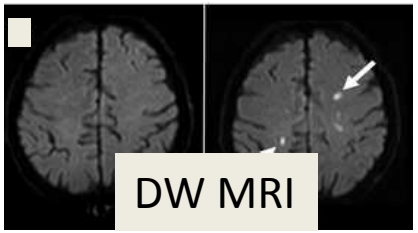
Procedure







Post Procedure



Neurocognitive Assessment

30 Day Follow-up

Neurocognitive Assessment

DW-MRI Results

Lesion Volume Reduction vs. Historic Controls

(Kahlert 2010, Ghanem 2011, Astarci 2011, Stolz 2004, Rodes Cabau 2011)

28 Paired DW-MRI

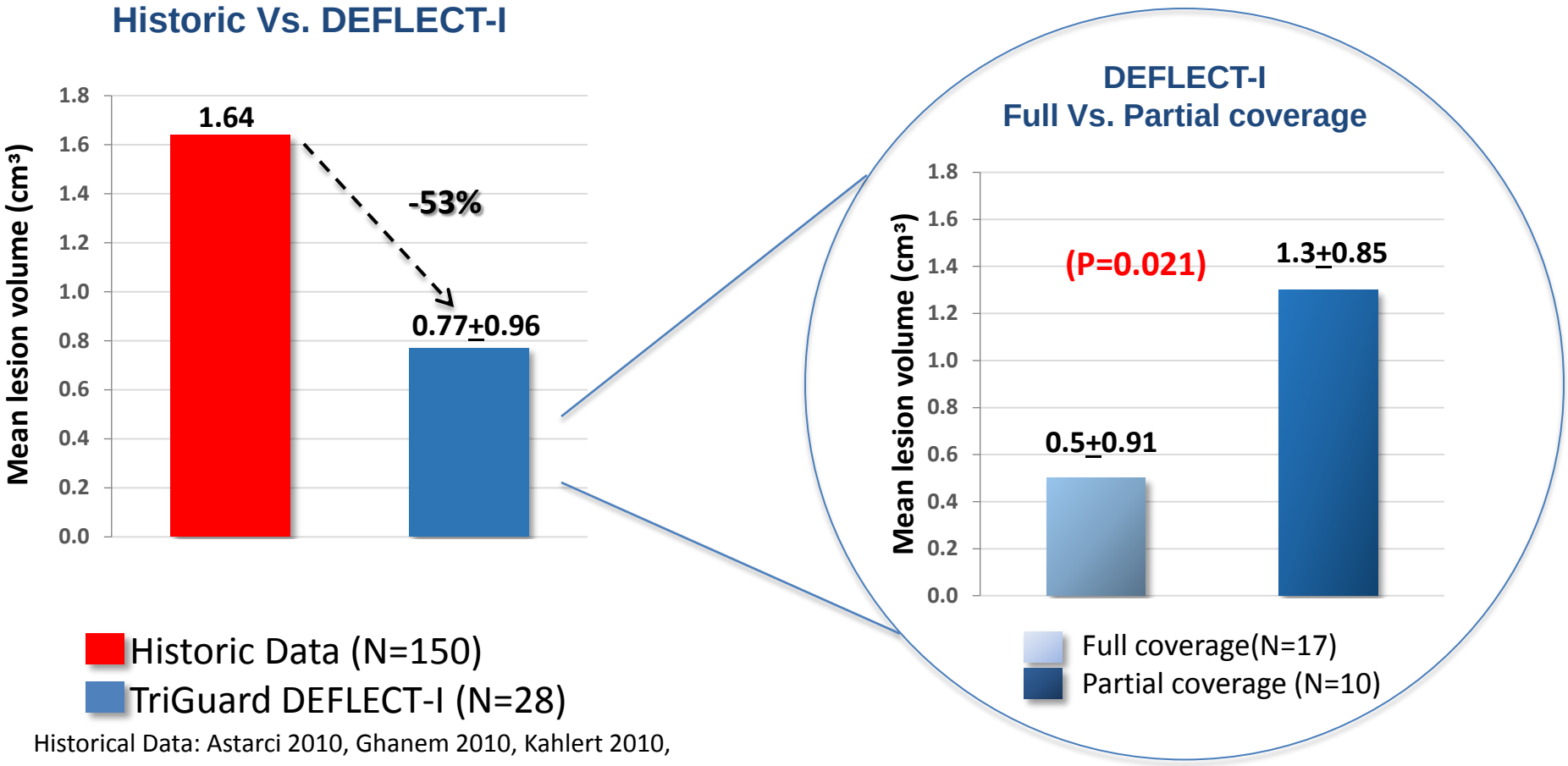
Parameter	DEFLECT-I N=28	Historical Data N=150
Proportion of Patients with New Lesions	78.6%	77%
Number of New Lesions	5.14± 6.10 (0 - 28)	4.60 (0 -36)
Average New Lesion Volume	0.13±0.13 cm^3 (0 – 0.47)	0.33 cm^3
Total New Lesion Volume	0.77±0.96 cm^3 (0 – 3.94)	2.18±4.5 cm^3 (1.65 – 4.3)

Proof of Principle
Complete Coverage

Subgroup analysis of those patients where the device was documented in place throughout the procedure

DW-MRI Results

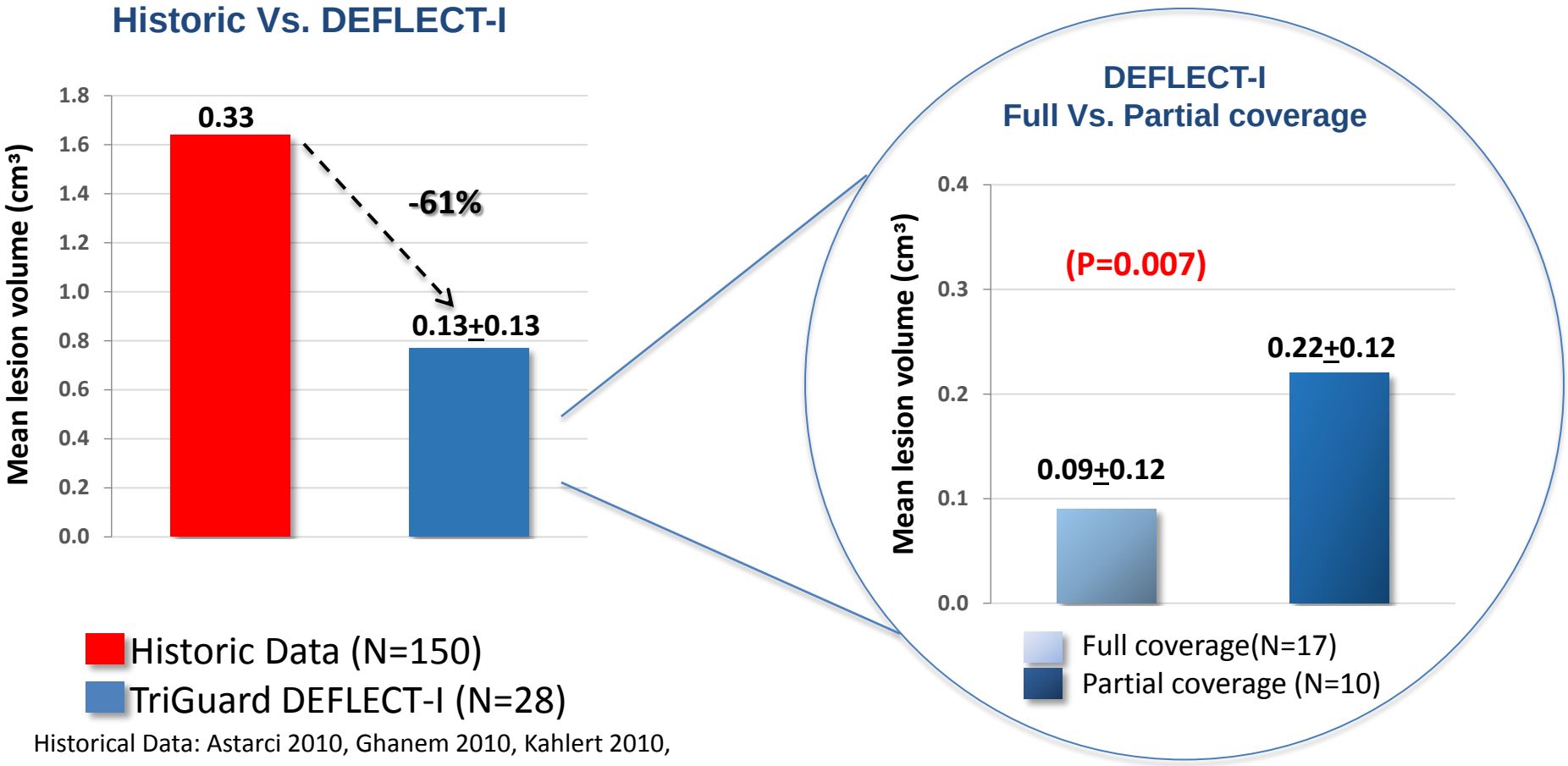
Mean Total New Lesion Volume (cm^3)



Historical Data: Astarci 2010, Ghanem 2010, Kahlert 2010, Fairbarn 2011, Knipp 2012

DW-MRI Results

Mean Single New Lesion Volume (cm^3)

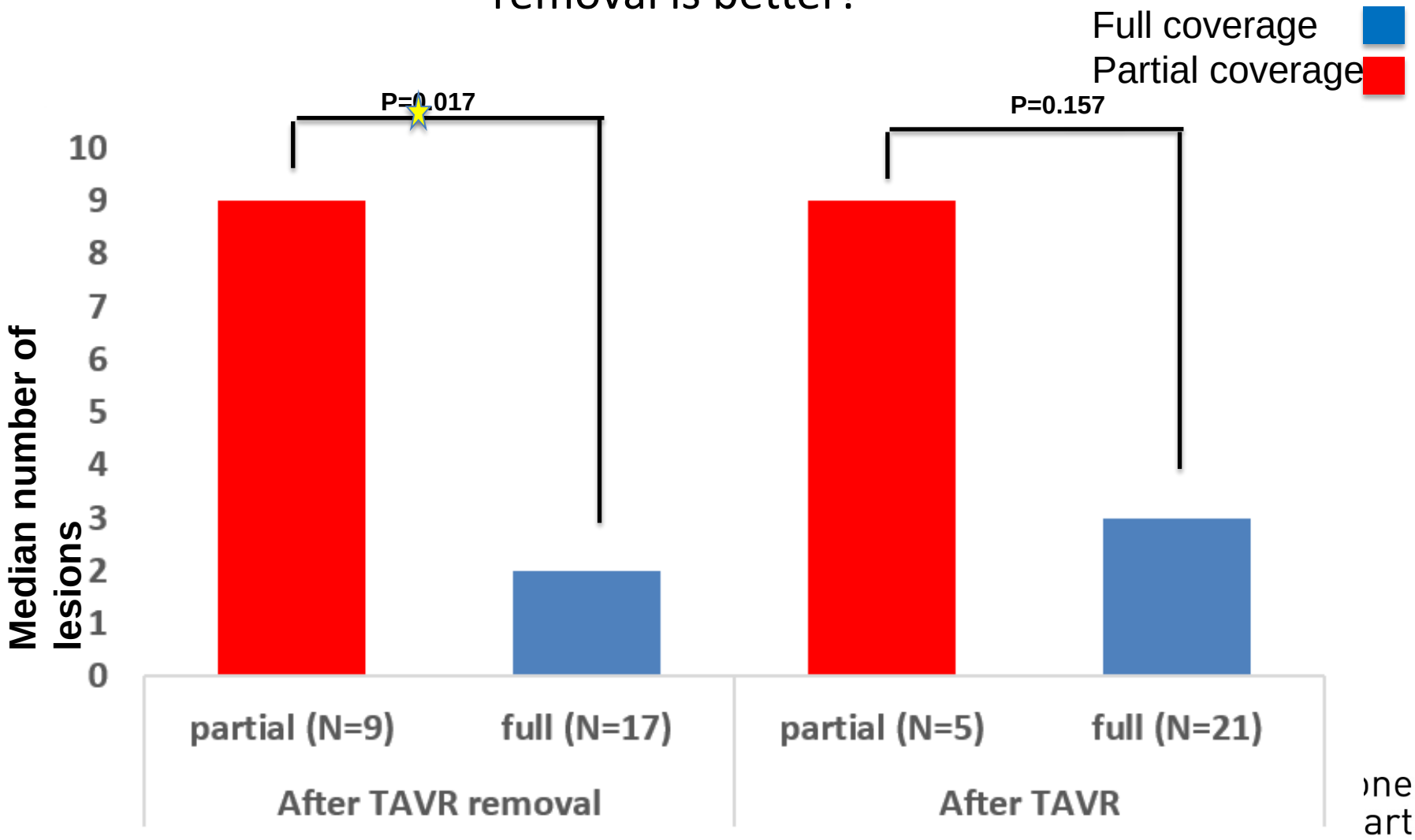


Historical Data: Astarci 2010, Ghanem 2010, Kahlert 2010, Fairbarn 2011, Knipp 2012

Number of lesions

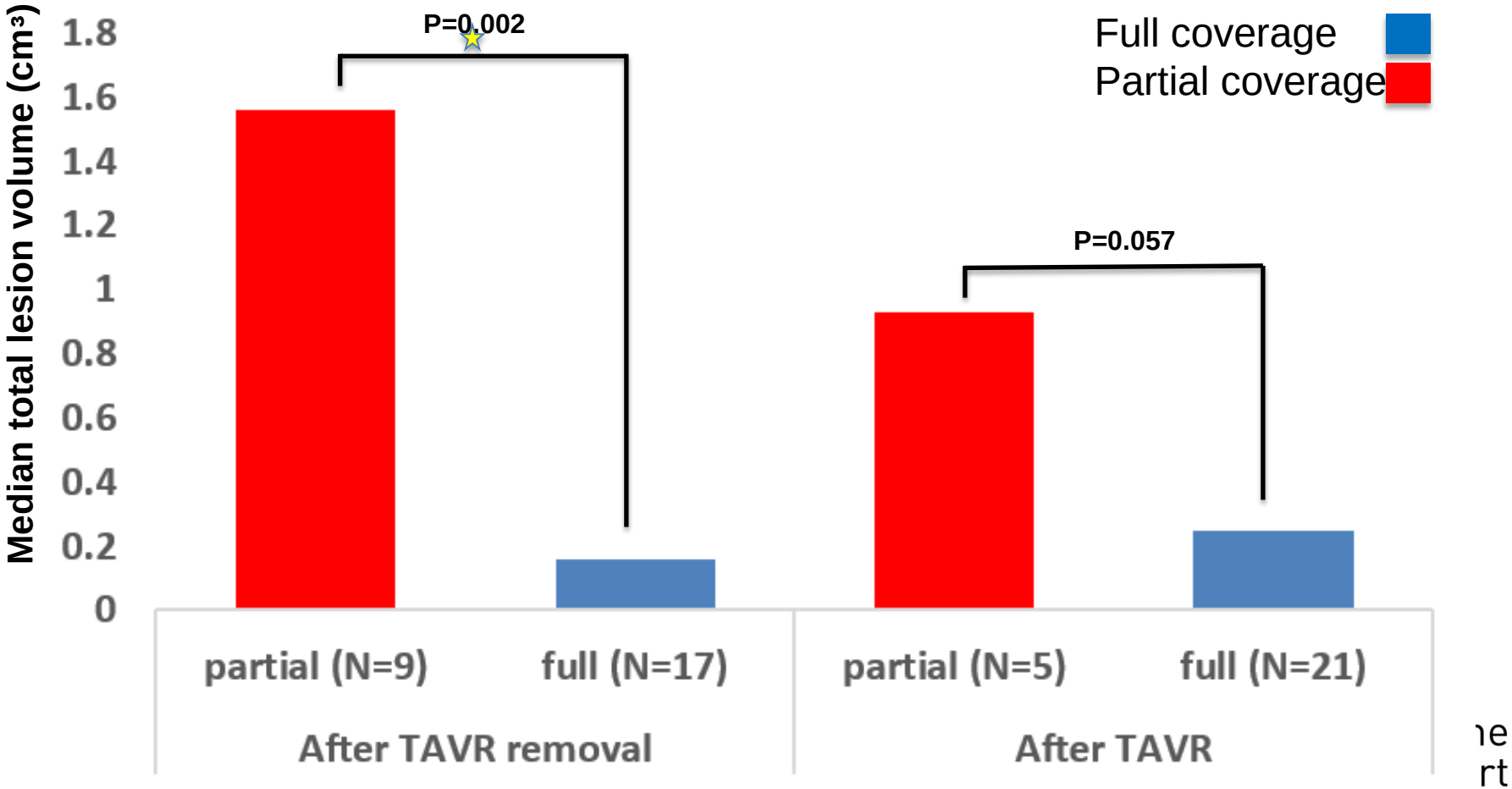
TriGuard full Coverage Vs. Partial Coverage

Protection until after TAVR implant is good but until after TAVR removal is better!

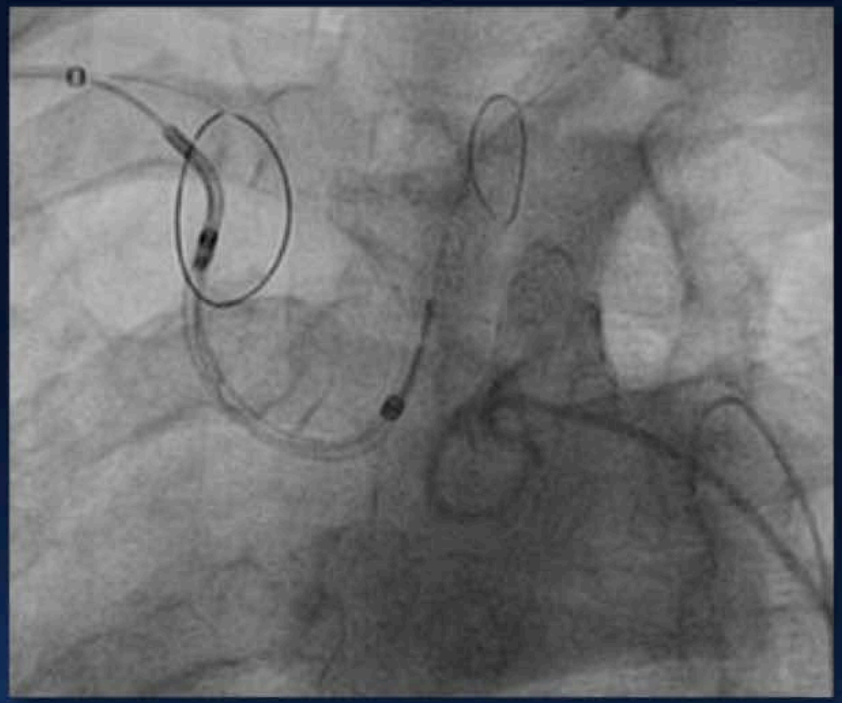


Total lesion volume (cm^3)
TriGuard full Coverage Vs. Partial Coverage

Protection until after TAVR implant is good but until after TAVR removal is better!



3. Claret Montage



- The Claret Montage™ dual-filter Cerebral Protection System was developed to protect the brain from injury caused by embolic debris.
- Randomized controlled trial data showing the efficacy of any embolic protection device in TAVR are missing.

CLEAN-TAVI: A prospective, randomized trial of cerebral embolic protection in high-risk patients with aortic stenosis undergoing transcatheter aortic valve replacement

Axel Linke[1], Stephan Haussig[1], Michael G Dwyer[2], Norman Mangner[1], Lukas Lehmkuhl[1], Christian Lücke[1], Felix Woitek[1], David M Holzhey[1], Friedrich W Mohr[1], Matthias Gutberlet[1], Robert Zivadinov[2], Gerhard Schuler[1]

[1]University of Leipzig, Heart Center, Leipzig, Germany,
[2]University of Buffalo, Buffalo, NY, US

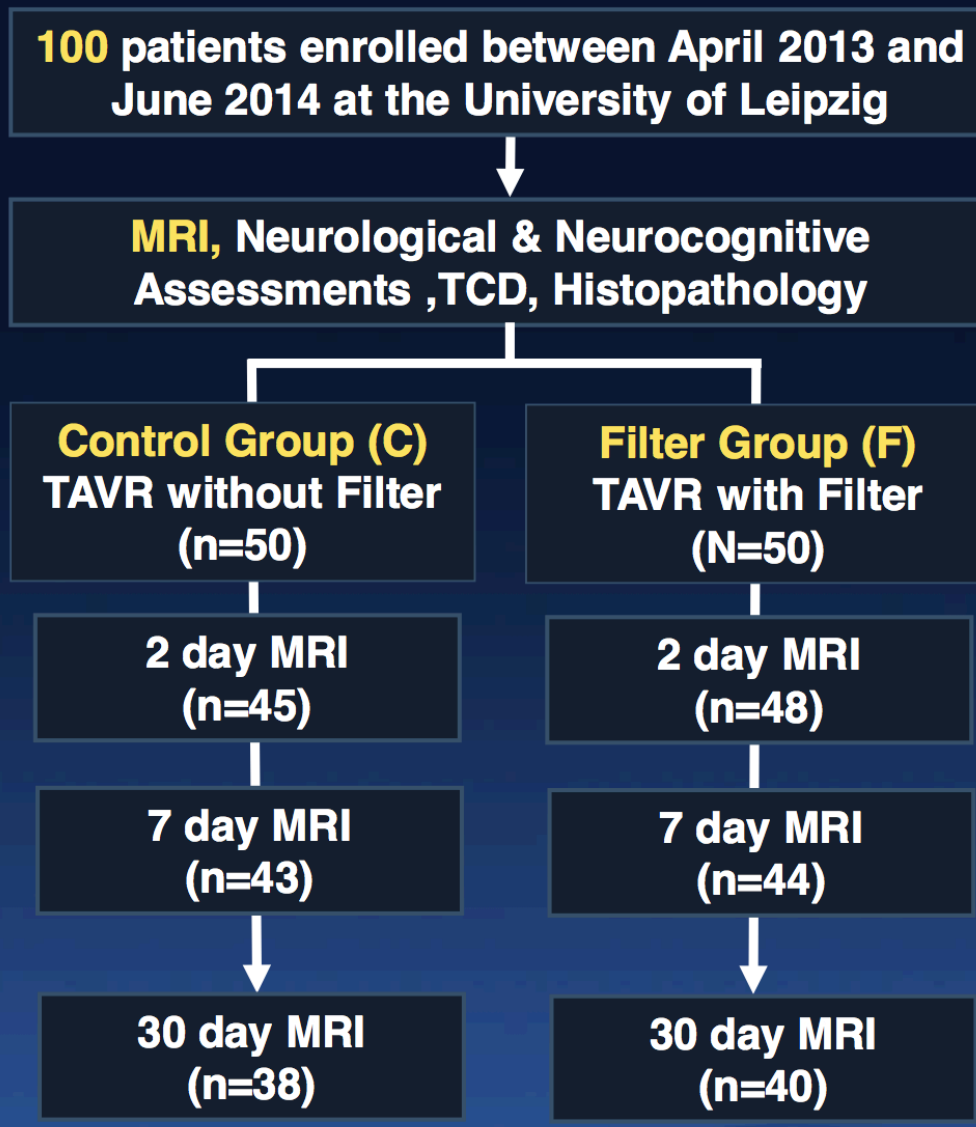
In Partnership with the ACC
tct2014

Columbia University Medical Center
NewYork-Presbyterian

Study Flow Chart

Design

- **DESIGN:** Prospective, 1:1 randomized controlled, double-blind study
- **OBJECTIVE:** To evaluate the impact of the use of Claret Montage™ on the number of cerebral lesions in higher-risk patients with aortic stenosis undergoing TAVR with the Medtronic CV
- **PRINCIPAL INVESTIGATOR**
  Axel Linke, MD
  University of Leipzig,
  Heart Center, Germany

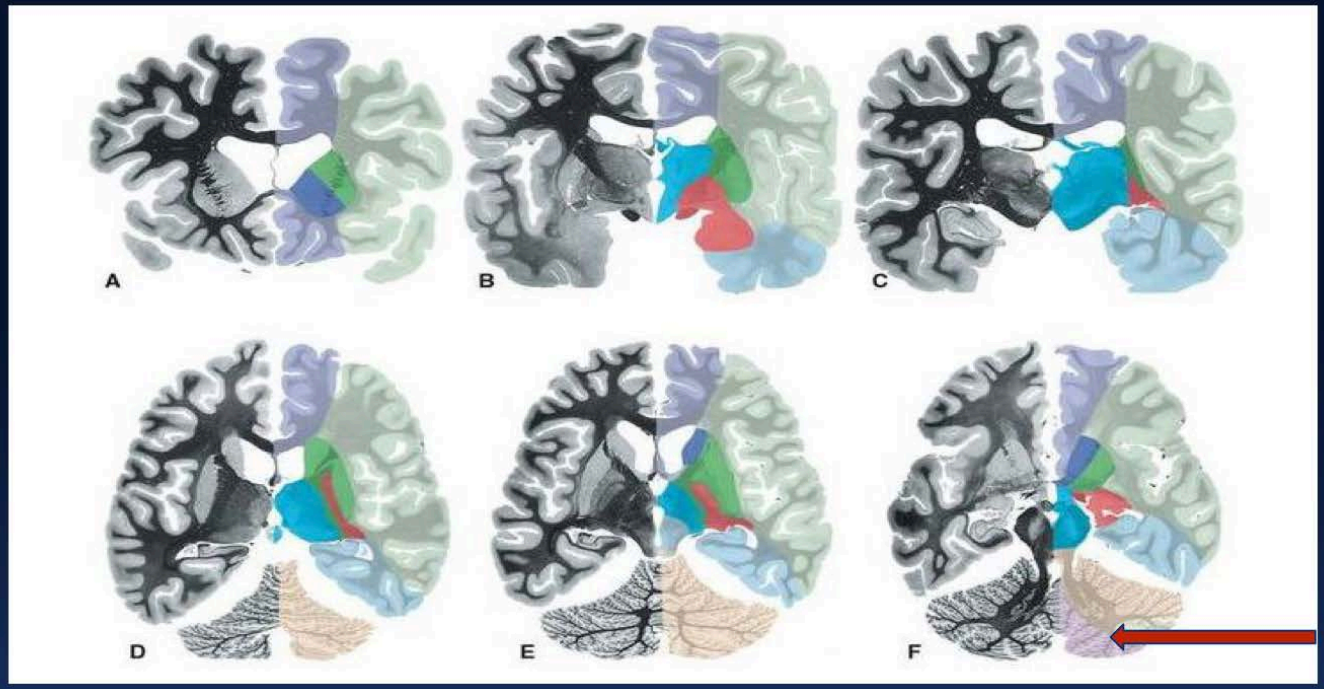


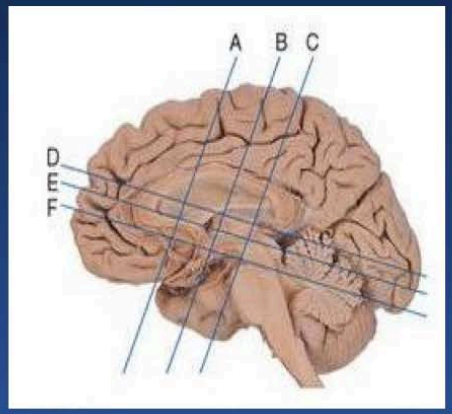
Study Endpoints

- **Primary Endpoint:**
  - Numerical reduction in positive post procedure Diffusion Weighted MRI (DW-MRI) perfused brain lesions relative to baseline at **2 days** in protected territories

- **Secondary Endpoints:**
  - Serial volumetric and numerical reduction in positive post procedure DW-MRI perfused brain lesions at 2, 7, 30, 360 days
  - Serial neurological assessment by NIHSS-trained specialist
  - Serial neurocognitive assessment
  - Peri-procedural Transcranial Doppler assessment

Cerebrovascular Territories





- *Anterior cerebral a.*
- *Middle cerebral a.*
- *Anterior choroidal a.*
- *Posterior cerebral a.*
- *Superior cerebellar a.*
- *Anterior inferior cerebellar a.*
- ***Posterior inferior cerebellar artery***

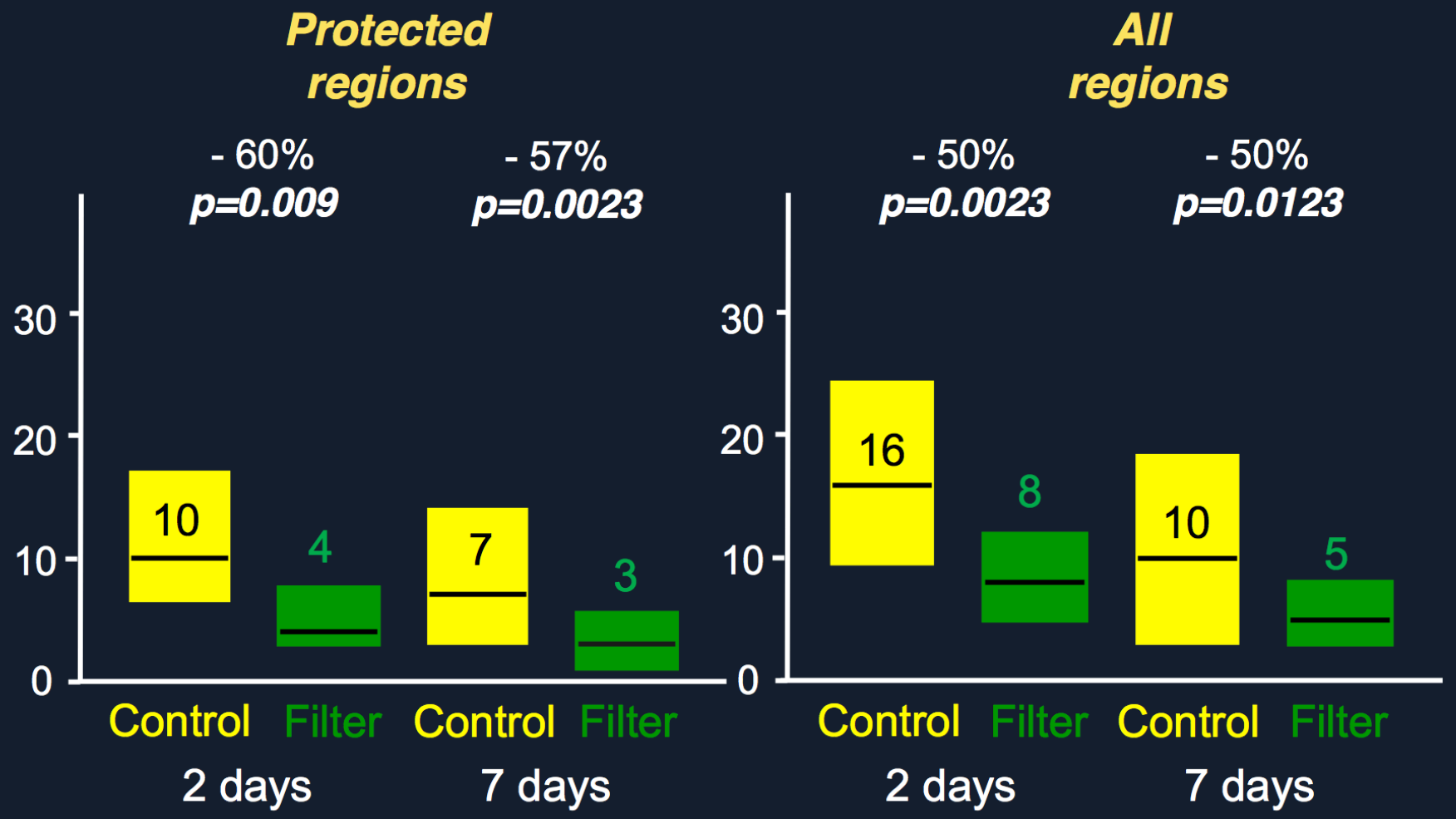
- *Anterior cerebral and anterior communicating aa. (perforating branches)*
- *Middle cerebral a. (perforating branches)*
- *Posterior cerebral and posterior communicating aa. (perforating branches)*

Procedural Results

- **Device Success 48/50 (96%)**
  - Unsuccessful distal filter deployment due to LCC tortuosity, n=1
  - Unsuccessful deployment of both filters due to SC tortuosity, n=1
- **Procedural Success 47/50 (94%)**
  - Accidental dislocation of a correctly deployed filter by pigtail, n=1

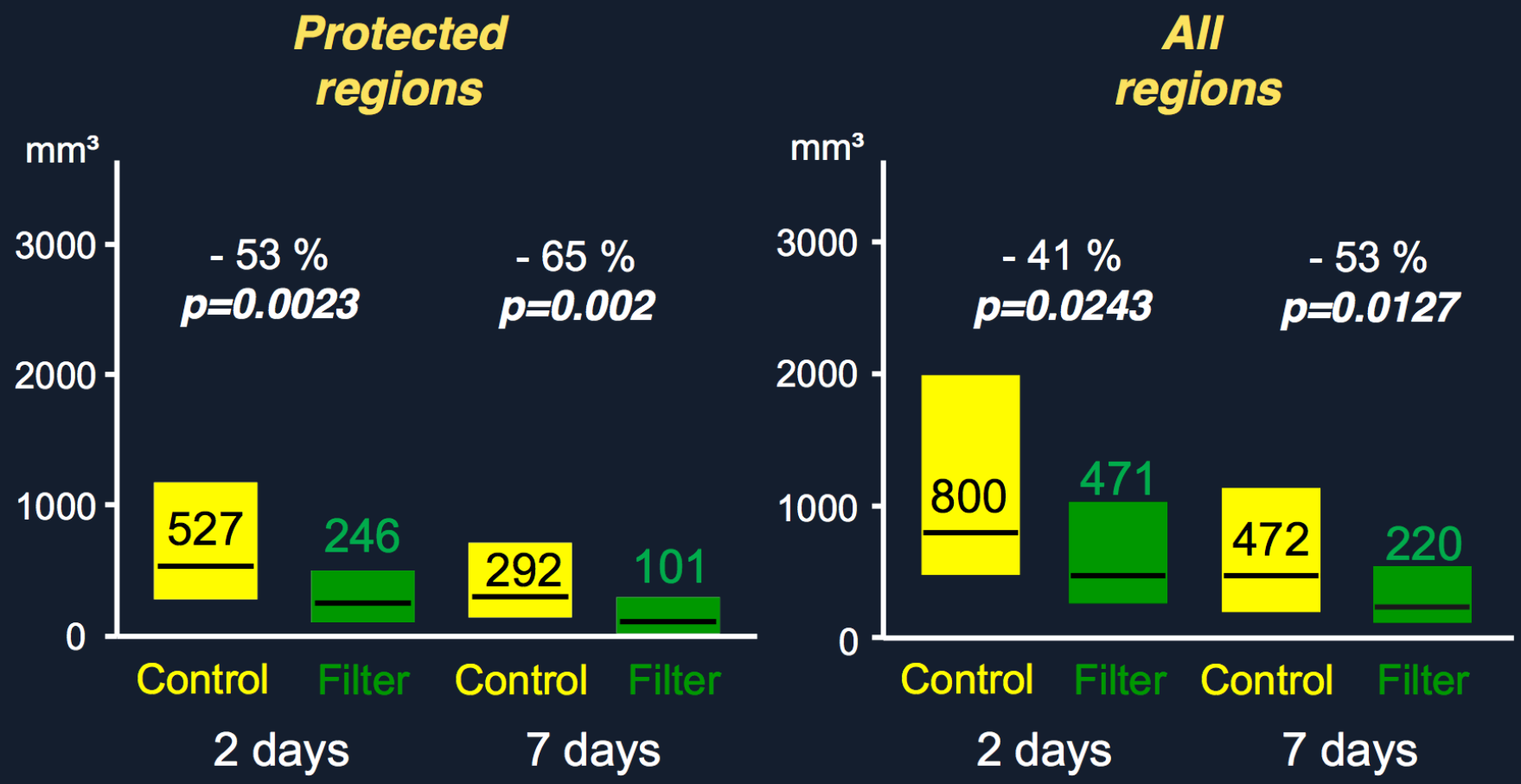
Procedural Outcomes	Control Group (N = 50)	Filter Group (N = 50)	p
Acute kidney injury – no. (%)	5 (10)	1 (2)	0.226
Thoracotomy – no. (%)	0 (0)	3 (6)	0.242
New-onset or worsening atrial fibrillation – no. (%)	7 (14)	7 (14)	1.000
Death at 30 days – no. (%)	1 (2)	0 (0)	1.000
Fluoroscopy time – min.	14.3 ± 6.5	17.0 ± 9.1	0.028
Amount of contrast medium - ml	131 ± 33	125 ± 29	0.613
Lesions positive at 2 days – no. (%)	44/45 (98)	47/48 (98)	1.000

Total Lesion Number at 2 & 7 days



The boxes identify the 25%-75% CI, the black lines and number represents the median.

Total Lesion Volume at 2 & 7 days



The boxes identify the 25%-75% CI, the black lines and number represents the median.

Neurological Outcome

intention-to-treat		cumulative	2 days (No, %)	7 days (No, %)	30 days (No, %)
Control	Any symptom	17 (34 %)	14 (28 %)	5 (10 %)	6 (12 %)
	- Ataxia	16 (32 %)	12 (24 %)	4 (8 %)	5 (10 %)
Filter	Any symptom	14 (28 %)	8 (16 %)	8 (16 %)	6 (12 %)
	- Ataxia	12 (24 %)	6 (12 %)	7 (14 %)	6 (12 %)

RR 1.379 (0.927 to 2.050), OR 2.042, p=0.175

RR 1.439 (0.963 to 2.149), OR 2.316, p=0.118

Neurological Outcome

per protocol		cumulative	2 days (No, %)	7 days (No, %)	30 days (No, %)
Control	Any symptom	17 (34 %)	14 (28 %)	5 (10 %)	6 (12 %)
	- Ataxia	16 (32 %)	12 (24 %)	4 (8 %)	5 (10 %)
Filter	Any symptom	11 (24 %)	6 (13 %)	6 (13 %)	4 (12 %)
	- ataxia	9 (20 %)	4 (9 %)	5 (11 %)	4 (12 %)
	n=45				

RR 1.458 (1.006 to 2.114), OR 2.5, p=0.08

RR 1.559 (1.083 to 2.214), OR 3.2, p<0.05

Neurological Outcomes Summary

- The 'Intent-to-Treat' analysis at 2 days post TAVR shows that neurological deficit was observed in 28% of the control patients when evaluated by a NIHSS-trained specialist.

- The Filter group in 'Per Protocol' analysis at 2 days post TAVR shows a significantly lower ataxia rate (24% vs 9%) than the control group, which supports the notion that the filter has the potential to improve neurological outcome.

Summary

- ‘Silent’ cerebral infarcts are frequent and are likely to impact on cognitive function
- Initial results with cerebral protection devices are promising and need to be validated in powered randomised trials
- Failure to cover all ostia completely (by design or suboptimal positioning) results in increased embolic events compared to full coverage

Postoperative cognitive capacity

The clinical benefit of cerebral protection devices will be measured by cognitive function.