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

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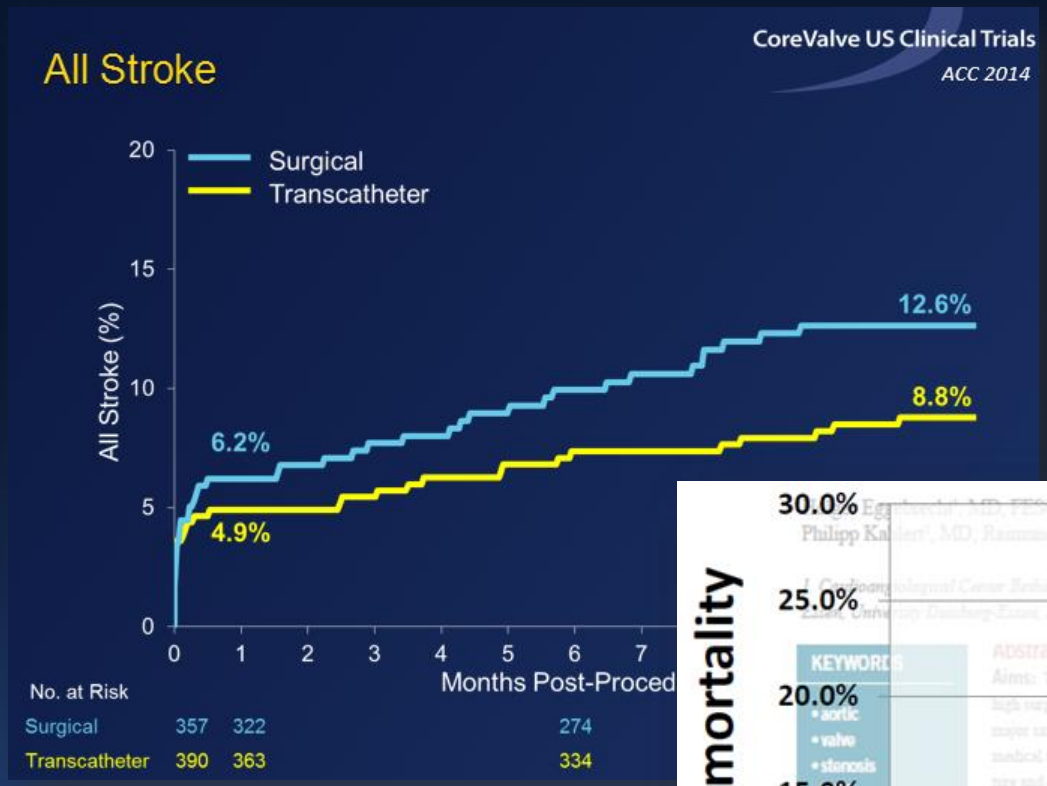
Disclosure Statement of Financial Interest

Within the past 12 months, I or my spouse/partner have had a financial interest/arrangement or affiliation with the organization(s) listed below.

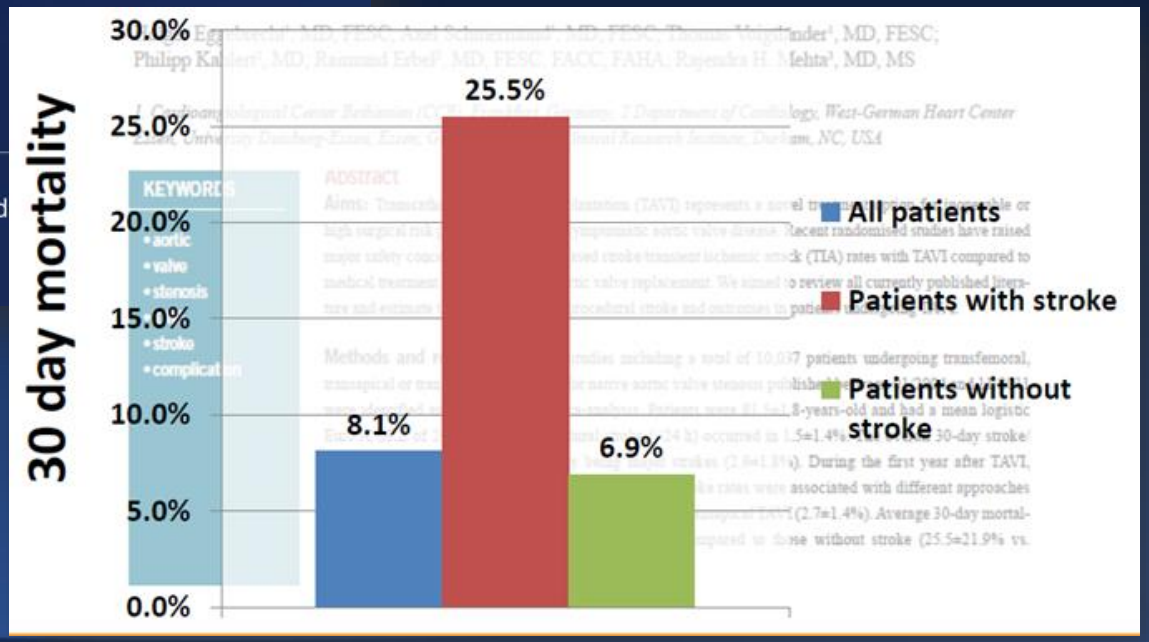
Affiliation/Financial Relationship	Company
• Grant/Research Support	• Medtronic Inc., Claret Medical Inc.
• Consulting Fees/Honoraria	• Medtronic Inc., S. Jude Medical Inc., Claret Medical Inc., Boston Scientific, Edwards Lifesciences
• Major Stock Shareholder/Equity	• none
• Royalty Income	• none
• Ownership/Founder	• none
• Intellectual Property Rights	• none
• Other Financial Benefit	• none

Background



Adams D et al, N Eng J Med 2014, 370(19): 1790-8

- **Stroke remains a major TAVR complication, which increases mortality by 3 fold**
- **Recent SAVR study demonstrated 17% stroke rate with neurologist performing NIHSS assessment***



Eggebrecht H et al, EuroIntervention 2012, 8: 129-138

*Messe SR et al, Circulation 2014;129:2253-2261

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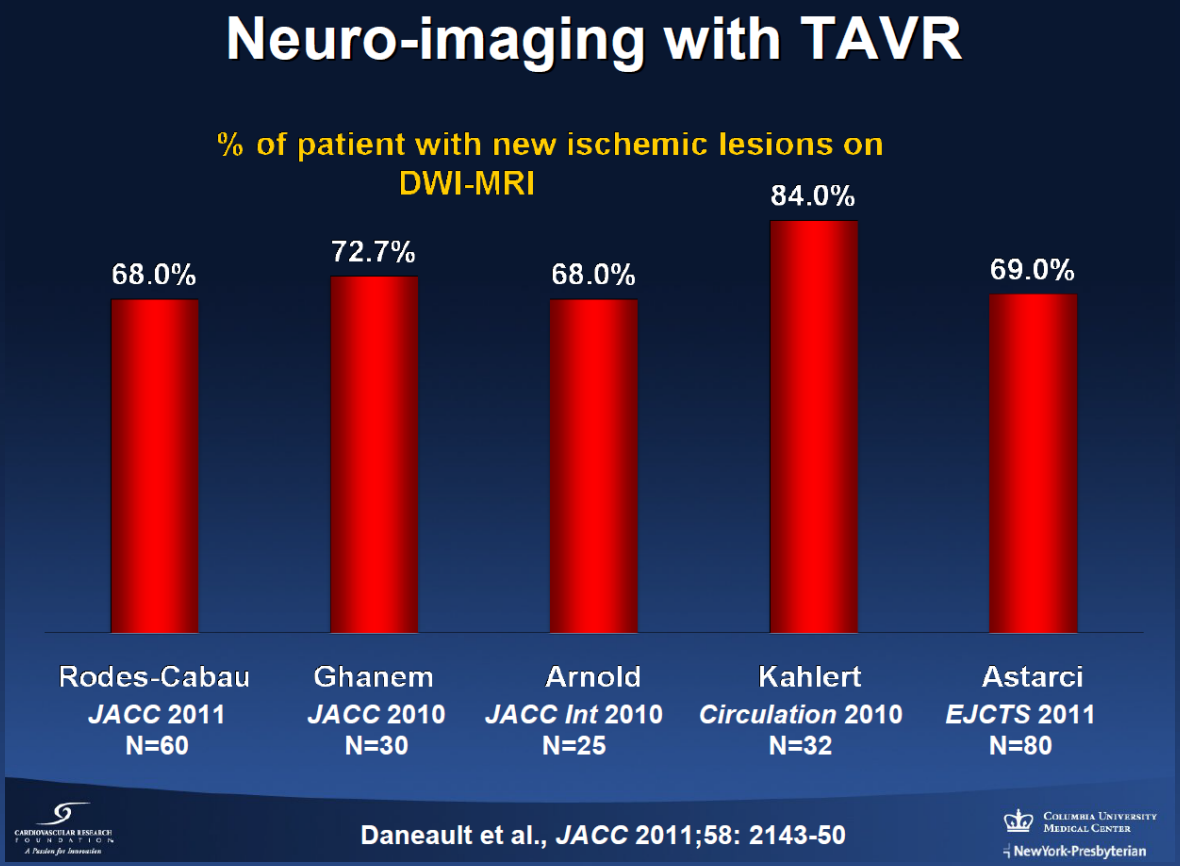
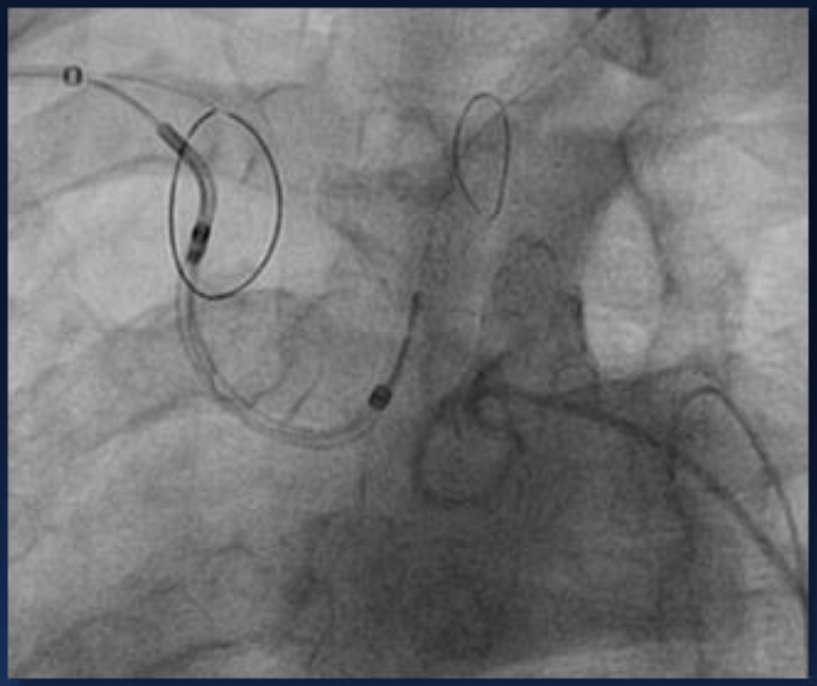
Background



- Ischemic brain lesions are found in more than 2/3 of TAVR patients
- Presence of silent brain infarcts increased the risk of major stroke >3 fold
- Silent infarcts are well recognized to be associated with several adverse neurological and cognitive consequences

Vermeer, SE et al; Stroke. 2003;34:1126-1129

Background

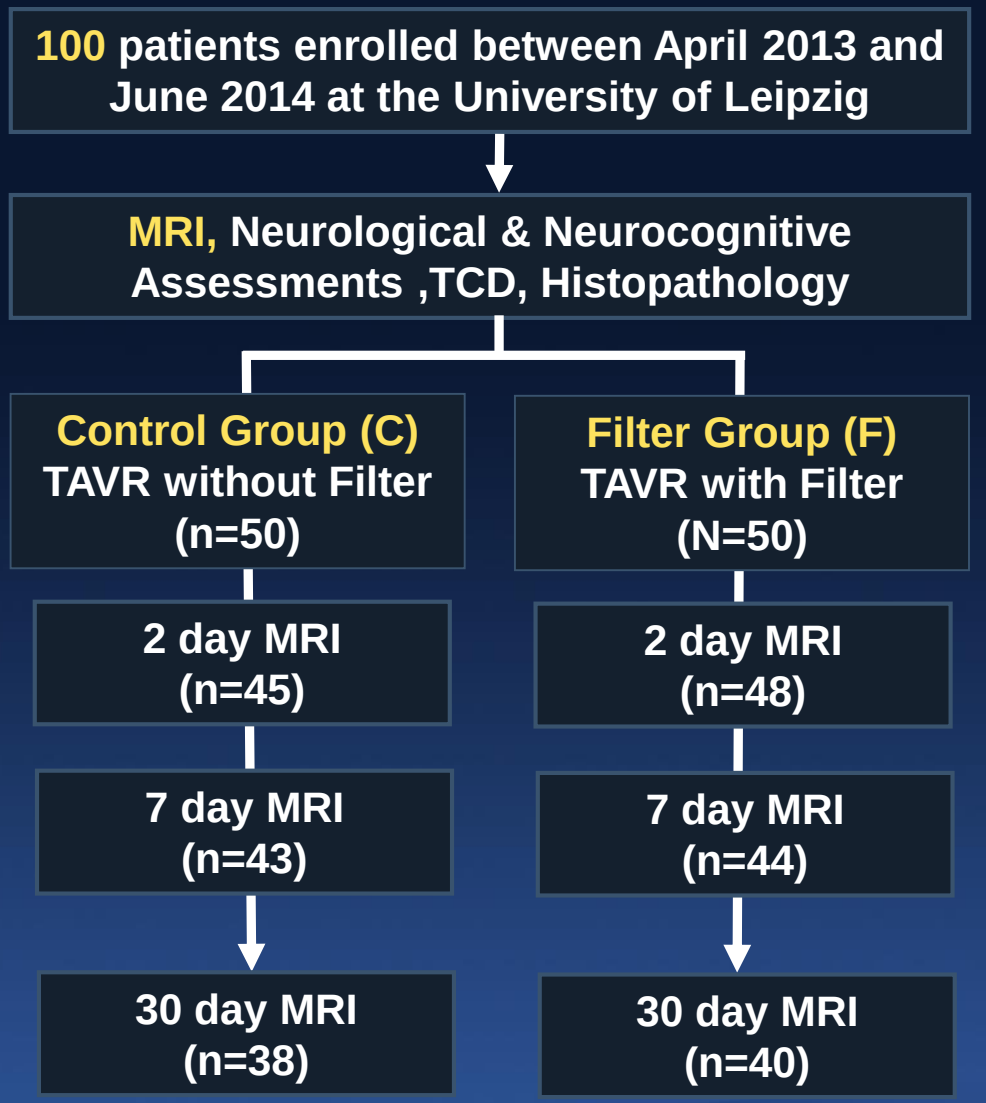


- The Claret Montage™ dual-filter Cerebral Protection System was developed to protect the brain from injury caused by embolic debris.
- Randomized controlled trial data showing the efficacy of any embolic protection device in TAVR are missing.

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

Study Hypothesis

Reduction in number of cerebral emboli by 50 %

at 2 days after TAVR by the use of

the Claret Montage™ dual filter

in patients undergoing transfemoral TAVR using the Medtronic CoreValve™

Sample size analysis: power 0.9, alpha 0.05, SD 7.0, drop-out 16%, n=100 patients

MRI Methodology

Unique challenges:

- Numerous, small, widely distributed lesions
- Lots of pre-existing pathology in aged population

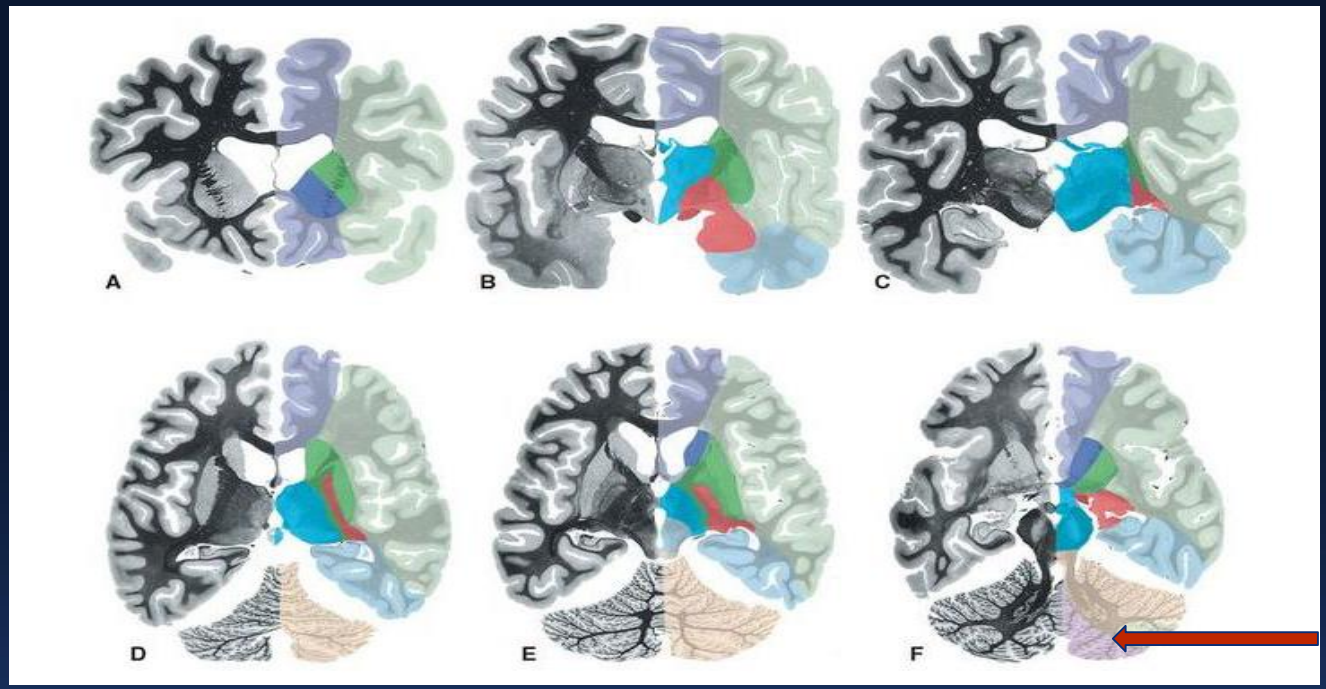
Image acquisition:

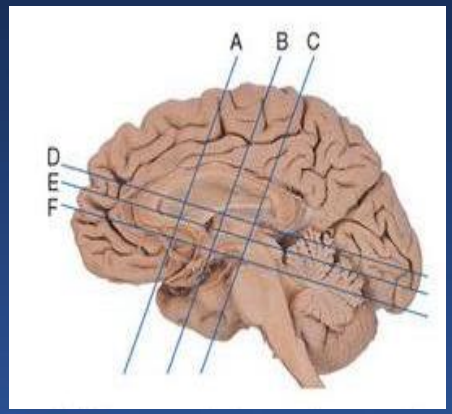
- Improved sensitivity with 3-Tesla scanner
- High-resolution T1-weighted anatomical image
- Diffusion-weighted imaging (DWI) for ischemic lesions

Analysis approach:

- Sub-millimeter longitudinal co-registration for precise lesion tracking of lesion serially over time
- Subtraction imaging technique relative to baseline to focus analysis only on relevant new pathology
- Precise analysis based on 28 pre-specified vascular territories on the right and left hemispheres (one unprotected vascular territory)

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)*

Inclusion and Exclusion Criteria

- **Inclusion criteria:**
  Symptomatic and relevant aortic stenosis with indication for transfemoral aortic valve replacement (TAVR) using Medtronic CoreValve™ (MCV)

- **Exclusion criteria:**
  - Patient unsuitable to undergo TAVR with MCV
  - Pacemaker
  - Stroke within the last 12 month
  - > 70 % stenosis of carotid artery
  - Relevant stenosis of brachiocephalic trunk or subclavian artery

Baseline Characteristics

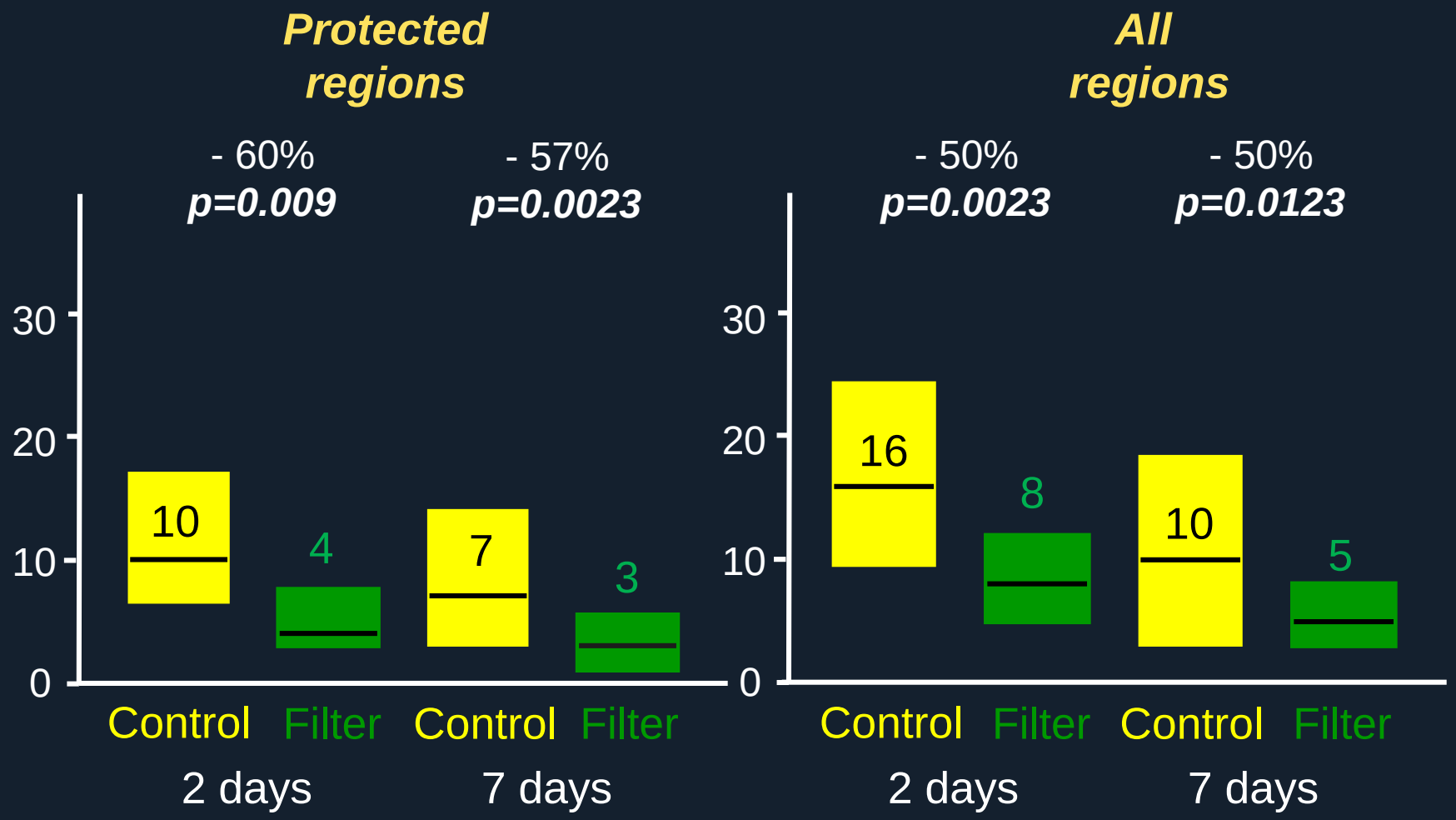
	Control Group (N = 50)	Filter Group (N = 50)	p
Age – yr	79 ± 4	80 ± 5	0.466
Female sex – no. (%)	27 (54)	30 (60)	0.545
STS PROM, mean estimate – %	5.2 ± 2.7	5.6 ± 3.3	0.847
Logistic EuroSCORE – %	14.6 ± 8.6	16.3 ± 10.1	0.478
Diabetes mellitus – no. (%)	25 (50)	20 (40)	0.315
History of hypertension – no. (%)	47 (94)	44 (88)	0.295
Peripheral vascular disease – no. (%)	4 (8)	2 (4)	0.400
Cardiac risk factor:			
-Coronary artery disease – no. (%)	26 (52)	25 (50)	0.841
-Congestive heart failure – no. (%)	47 (94)	45 (90)	0.461
-Prior atrial fibrillation or atrial flutter – no. (%)	18 (36)	16 (32)	0.673

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

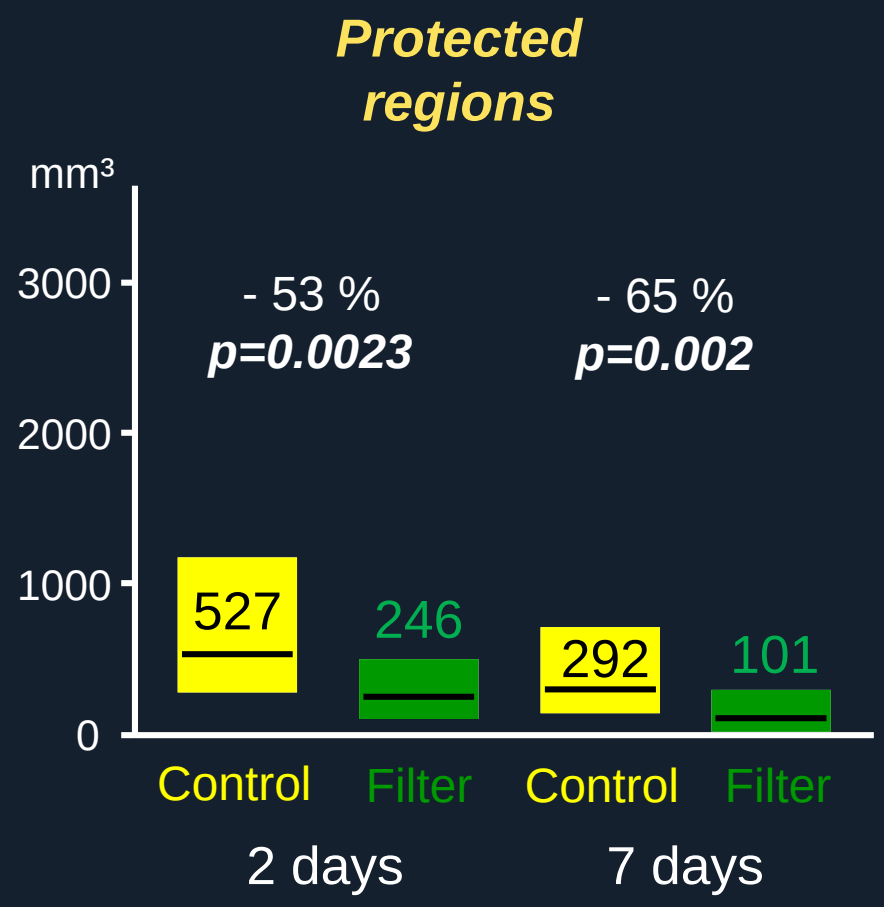
Procedural Outcomes	Control Group (N = 50)	Filter Group (N = 50)	p
Acute kidney injury – no. (%)	5 (10)	1 (2)	0.226
Thoracotomy – no. (%)	0 (0)	3 (6)	0.242
New-onset or worsening atrial fibrillation – no. (%)	7 (14)	7 (14)	1.000
Death at 30 days – no. (%)	1 (2)	0 (0)	1.000
Fluoroscopy time – min.	14.3 ± 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

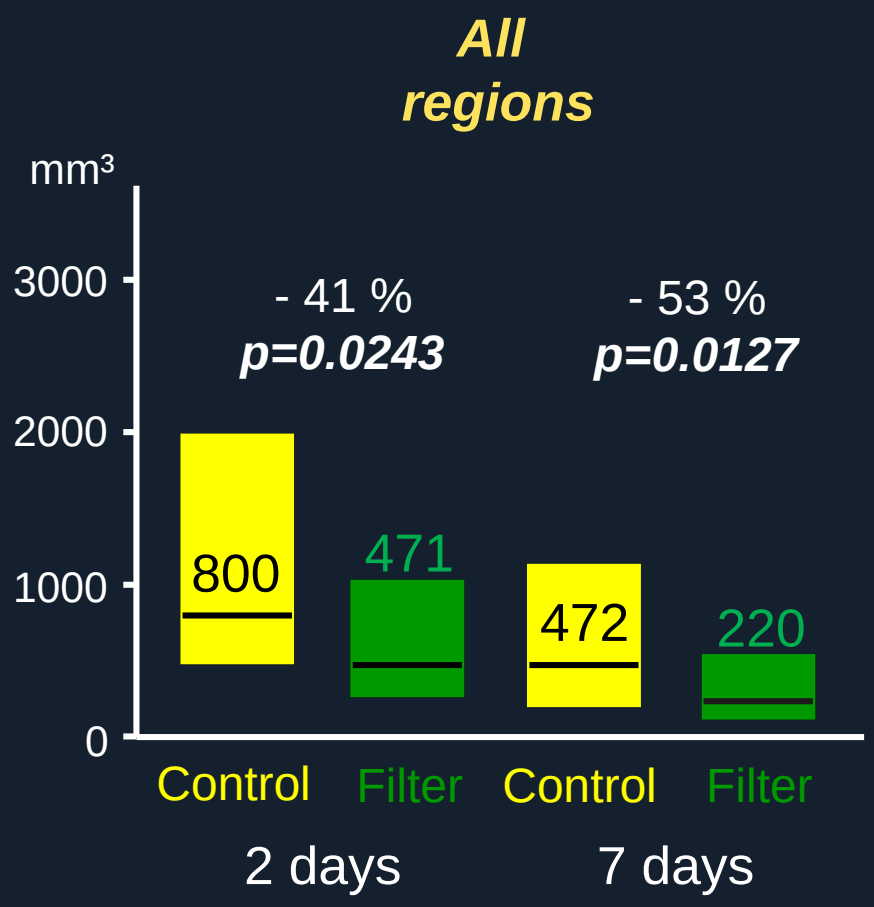
Total Lesion Number at 2 & 7 days



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

Total Lesion Volume at 2 & 7 days





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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

Mechanistic Outcomes Summary

In patients with severe aortic stenosis who are at increased surgical risk, the use of Claret Montage™ dual filter cerebral protection system during TAVR significantly reduces the *number and volume* of cerebral lesions as determined by DW-MRI subtraction at 2 and 7 days after TAVR.

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.

Conclusion

In accordance with recent SAVR* study results, when neurological and MRI assessments are used prospectively, procedure-related cerebral lesions and stroke symptoms are more frequently associated with TAVR than previously thought.

Larger outcomes studies are necessary in order to validate the observed beneficial effects of routine cerebral protection during TAVR in improving acute neurological outcome and reducing stroke rate.

*Messe SR et al, Circulation 2014;129:2253-2261

Linke et al., CLEAN-TAVI

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