Supplementary Online Content

Haussig S, Mangner N, Dwyer MG; et al. Effect of a cerebral protection device on brain lesions following transcatheter aortic valve implantation in patients with severe aortic stenosis. *JAMA*. doi: 10.1001/jama.2016.10302

This supplementary material has been provided by the authors to give readers additional information about their work.

eTable 1. MRI Regions

Region	Left		Right	
	Code	Protection	Code	Protection
Anterior cerebral artery terminal branches	2	P	22	P
Anterior cerebral artery central branches	3	P	23	P
Middle cerebral artery terminal branches	6	P	26	P
Middle cerebral artery central branches	4	P	24	P
Posterior cerebral artery terminal branches	7	PP	27	PP
Posterior cerebral artery central branches	8	PP	28	PP
Anterior choroidal artery	5	PP	25	PP
Superior cerebellar artery	14	PP	34	PP
Anterior inferior cerebellar artery	13	PP	33	PP
Basilar artery anterior	11	PP	31	PP
Basilar artery anteromedial	10	PP	30	PP
Basilar artery lateral	12	PP	32	PP
Basilar artery dorsal	9	PP	29	PP
Posterior inferior cerebellar artery	15	N	35	P

P - Potentially Protected, PP - Partially Protected, N - Not Protected

eTable 2. Frailty Assessment at Baseline

	Control (n=50)	Filter (n=50)
Grip strength - kg (SD)	21.8 (8.7)	23.4 (9.6)
6 minute walk test - m (SD)	268.8 (120.4)	274.5 (128.8)
Gait speed – m/s (SD)	0.73 (0.36)	0.82 (0.44)
Gait speed < 0,8 m/s - no. (% of total)	26 (57.8%)	22 (46.8%)
Albumin < 3.3 g/dl - no. (% of total)	2 (11.8%)	3 (17.6%)
BMI < 21 kg/m^2 - no (% of total)	3 (6.0%)	2 (4.0%)

Data are reported as number (%) or mean (SD) unless otherwise stated. Albumin of patients in filter and control group was only available for 17 patients, respectively.

eTable 3. Characteristics of the Patients at Baseline for Patients With or Without 2-Day MRI Follow-up

Characteristic	Control Group MRI available at 2 days (n=45)	Control Group No MRI available at 2 days (n=5)	Filter Group MRI available at 2 days (n=49)	Filter Group No MRI available at 2 days (n=1)
Age - yrs (SD)	79.6 (4.0)	75.8 (2.7)	80.0 (5.1)	84 (NA)
Female sex	25 (56%)	3 (60%)	28 (57%)	1 (100%)
NYHA class				
Class I	4 (9%)	1 (20%)	5 (10%)	0 (0%)
Class II	13 (29%)	0 (0%)	13 (27%)	0 (0%)
Class III	25 (56%)	4 (80%)	22 (45%)	1 (100%)
Class IV	3 (7%)	0 (0%)	9 (18%)	0 (0%)
STS PROM estimate				
Mean estimate % (SD)	5.3 (2.7)	3.8 (2.4)	5.4 (3.0)	14.2 (NA)
<4 %	17 (38%)	3 (60%)	19 (39%)	0 (0%)
4-10 %	24 (53%)	2 (40%)	24 (49%)	0 (0%)
>10%	4 (9%)	0 (0%)	6 (12%)	1 (100%)
Logistic EuroScore - % (SD)	14.8 (8.9)	11.8 (5.9)	16.1 (9.9)	29.7 (NA)
Diabetes mellitus				
All	24 (53%)	1 (20%)	19 (39%)	1 (100%)
Controlled by insulin	14 (31%)	1 (20%)	5 (10%)	0 (0%)
Chronic kidney disease				
stage 2 (GFR 60-89)	26 (58%)	2 (40%)	20 (41%)	0 (0%)
stage 3 (GFR 30-59)	9 (20%)	2 (40%)	22 (45%)	1 (100%)
stage 4 (GFR 15-29)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
stage 5 (GFR <15 or dialysis)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
History of hypertension	42 (93%)	5 (100%)	43 (88%)	1 (100%)
Peripheral vascular disease	3 (7%)	1 (20%)	2 (4%)	0 (0%)
Prior stroke or transient ischemic attack	3 (7%)	0 (0%)	1 (2%)	0 (0%)
Cardiac risk factor				
Coronary artery disease	23 (51%)	2 (40%)	25 (51%)	1 (100%)
Prior coronary-artery bypass surgery	2 (4%)	0 (0%)	8 (16%)	0 (0%)
Prior percutaneous coronary intervention	8 (18%)	0 (0%)	5 (10%)	0 (0%)
Preexisting pacemaker or defibrillator	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Prior myocardial infarction	4 (9%)	0 (0%)	6 (12%)	0 (0%)
Congestive heart failure	42 (93%)	4 (80%)	45 (92%)	1 (100%)
Prior atrial fibrillation or atrial flutter	15 (33%)	2 (40%)	16 (33%)	1 (100%)
MRI median lesion number at baseline (IQR) range (minimum-maximum)	0.00 (0.00-1.00) 0.00-5.00	0.00 (0.00-0.00) 0.00-0.00	0.00 (0.00-1.00) 0.00-5.00	1.00 (NA) (NA)
MRI median lesion volume at baseline mm^3 (95% CI) range (minimum-maximum)	0 (0-0) 0-615	0.00 (0.00-0.00) 0.00-0.00	0 (0-36) 0-7604	80 (NA) (NA)

Data are reported as number (%) or mean (SD) unless otherwise stated.
GFR - Glomerular Filtration Rate (mL/min/1.73 m^2).
STS PROM - Society of Thoracic Surgeons Predicted Risk of Mortality, predicts the risk of operative mortality. Values under 3% are generally considered to be low risk, ≥3%-≤8% intermediate risk and >8% high risk.
Logistic EuroScore - system to predict risk of operative mortality with higher accuracy as compared to standard EuroScore. Values under 10% are generally considered to be low risk, ≥10%-≤20% intermediate risk and >20% high risk.
NA - non applicable

eTable 4. Characteristics of the Patients at Baseline for Patients With or Without 7-Day MRI Follow-up

Characteristic	Control Group MRI available at 7 days (n=43)	Control Group No MRI available at 7 days (n=7)	Filter Group MRI available at 7 days (n=45)	Filter Group No MRI available at 7 days (n=5)
Age - yrs (SD)	79.3 (3.8)	78.9 (5.7)	80.0 (5.2)	80.4 (4.7)
Female sex	25 (58%)	3 (43%)	26 (58%)	3 (60%)
NYHA class				
Class I	4 (9%)	1 (14%)	4 (9%)	1 (20%)
Class II	13 (30%)	0 (0%)	12 (27%)	1 (20%)
Class III	23 (54%)	6 (86%)	20 (44%)	3 (60%)
Class IV	3 (7%)	0 (0%)	9 (20%)	0 (0%)
STS PROM estimate				
Mean estimate % (SD)	5.3 (2.7)	4.7 (2.9)	5.5 (3.1)	6.1 (4.6)
<4 %	16 (37%)	4 (57%)	17 (38%)	2 (40%)
4-10 %	23 (54%)	3 (43%)	22 (49%)	2 (40%)
>10%	4 (9%)	0 (0%)	6 (13%)	1 (20%)
Logistic EuroScore - % (SD)	15.1 (9.0)	10.9 (5.0)	16.4 (10.2)	16.5 (8.7)
Diabetes mellitus				
All	24 (56%)	1 (14%)	18 (40%)	2 (40%)
Controlled by insulin	14 (33%)	1 (14%)	5 (11%)	0 (0%)
Chronic kidney disease				
stage 2 (GFR 60-89)	26 (61%)	2 (29%)	17 (38%)	3 (60%)
stage 3 (GFR 30-59)	7 (16%)	4 (57%)	22 (49%)	1 (20%)
stage 4 (GFR 15-29)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
stage 5 (GFR <15 or dialysis)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
History of hypertension	40 (93%)	7 (100%)	39 (87%)	5 (100%)
Peripheral vascular disease	3 (7%)	1 (14%)	2 (4%)	0 (0%)
Prior stroke or transient ischemic attack	3 (7%)	0 (0%)	1 (2%)	0 (0%)
Cardiac risk factor				
Coronary artery disease	22 (51%)	3 (43%)	22 (49%)	4 (80%)
Prior coronary-artery bypass surgery	2 (5%)	0 (0%)	7 (16%)	1 (20%)
Prior percutaneous coronary intervention	8 (19%)	0 (0%)	5 (11%)	0 (0%)
Preexisting pacemaker or defibrillator	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Prior myocardial infarction	4 (9%)	0 (0%)	5 (11%)	1 (20%)
Congestive heart failure	40 (93%)	6 (86%)	42 (93%)	4 (80%)
Prior atrial fibrillation or atrial flutter	14 (33%)	3 (43%)	15 (33%)	2 (40%)
MRI median lesion number at baseline (IQR) range (minimum-maximum)	0.00 (0.00-1.00) 0.00-5.00	0.00 (0.00-0.00) 0.00-0.00	0.00 (0.00-1.00) 0.00-5.00	1.00 (0.00-1.50) (0.00-2.00)
MRI median lesion volume at baseline mm^3 (95% CI) range (minimum-maximum)	0 (0-0) 0-615	0 (0-0) 0-0	0 (0-36) 0-7604	69 (0-119) (0-119)

Data are reported as number (%) or mean (SD) unless otherwise stated.
GFR - Glomerular Filtration Rate (mL/min/1.73 m^2).
STS PROM - Society of Thoracic Surgeons Predicted Risk of Mortality, predicts the risk of operative mortality. Values under 3% are generally considered to be low risk, ≥3%-≤8% intermediate risk and >8% high risk.
Logistic EuroScore - system to predict risk of operative mortality with higher accuracy as compared to standard EuroScore. Values under 10% are generally considered to be low risk, ≥10%-≤20% intermediate risk and >20% high risk.

eTable 5. Procedural TAVI and Filter Deployment Data for Patients With or Without 2-Day MRI Follow-up

Characteristic	Control Group MRI available at 2 days (n=45)	Control Group No MRI available at 2 days (n=5)	Filter Group MRI available at 2 days (n=49)	Filter Group No MRI available at 2 days (n=1)
dose-area product – $cGycm^2$ (95% CI)	17817 (15063-20571)	17378 (10618-24138)	19020 (16072-21967)	8169 (NA)
fluoroscopy time – minutes (95% CI)	14.1 (12.0-16.3)	16.4 (10.0-22.9)	17.5 (14.9-20.1)	11.3 (NA)
amount of contrast medium – ml (95% CI)	130 (120-141)	136 (91-181)	127 (119-136)	145 (NA)
Time – minutes (95% CI)				
From insertion of sheath into Radial artery to insertion of device	NA	NA	21.0 (19.2-22.9)	17.0 (NA)
From insertion of device to device in final position	NA	NA	7.1 (5.5-8.7)	8.0 (NA)
From device in final position to retraction of device	NA	NA	24.0 (21.5-26.6)	19.0 (NA)
Total time from insertion to retraction of device	NA	NA	31.1 (28.0-34.2)	27.0 (NA)
Mean Procedural time – minutes (95% CI)	53.6 (49.4-57.8)	59.2 (31.8-86.7)	72.1 (65.6-78.7)	71.0 (NA)
Device success	NA	NA	45 (92%)	1 (100%)
Procedural success	NA	NA	44 (90%)	1 (100%)
Thoracotomy	0 (0%)	0 (0%)	3 (6%)	0 (0%)

Data are reported as number (%) or mean (95% CI) unless otherwise stated. NA: non applicable.

Device success was defined as successful positioning and deployment of both filters in correct anatomical position.

Procedural success was defined as successful positioning and deployment of both filters in correct anatomical position AND correct position of both filters during TAVI as well as successful retrieval of both filters after TAVI.

eTable 6. Procedural TAVI and Filter Deployment Data for Patients With or Without 7-Day MRI Follow-up

Characteristic	Control Group MRI available at 7 days (n=43)	Control Group No MRI available at 7 days (n=7)	Filter Group MRI available at 7 days (n=45)	Filter Group No MRI available at 7 days (n=5)
dose-area product – $cGycm^2$ (95% CI)	17966 (15084-20848)	16612 (12307-20916)	19009 (15822-22196)	16948 (8160-25737)
fluoroscopy time – minutes (95% CI)	14.2 (12.0-16.4)	15.5 (10.3-20.7)	17.0 (14.3-19.7)	20.1 (7.9-32.3)
amount of contrast medium – ml (95% CI)	132 (121-142)	126 (83-169)	128 (119-137)	124 (80-169)
Time – minutes (95% CI)				
From insertion of sheath into Radial artery to insertion of device	NA	NA	21.3 (19.3-23.3)	18.0 (13.8-22.2)
From insertion of device to device in final position	NA	NA	6.5 (5.1-7.9)	12.6 (1.6-23.6)
From device in final position to retraction of device	NA	NA	23.4 (21.2-25.6)	28.4 (7.0-49.8)
Total time from insertion to retraction of device	NA	NA	29.9 (27.1-32.6)	41.0 (20.7-61.3)
Mean Procedural time – minutes (95% CI)	53.9 (49.6-58.2)	55.2 (37.4-72.9)	71.0 (64.5-77.5)	84.3 (35.5-133.0)
Device success	NA	NA	41 (91%)	5 (100%)
Procedural success	NA	NA	41 (91%)	4 (80%)
Thoracotomy	0 (0%)	0 (0%)	2 (4%)	1 (20%)

Data are reported as number (%) or mean (95% CI) unless otherwise stated. NA: non applicable.

Device success was defined as successful positioning and deployment of both filters in correct anatomical position.

Procedural success was defined as successful positioning and deployment of both filters in correct anatomical position AND correct position of both filters during TAVI as well as successful retrieval of both filters after TAVI.

eTable 7. Imputed Data Sets for the Number and Volume of New Lesions in the Potentially Protected Areas, Partially Protected Areas, and the Entire Brain at 2 and 7 Days

Imputation set	Variable tested Control vs. Filter	n		p potentially fully protected areas	p partially protected areas	p entire brain
		control	filter			
Original data	total new lesion number 2 days	45	49	<.001	.008	0.002
	total new lesion volume 2 days	45	49	.001	.01	0.02
	total new lesion number 7 days	43	45	.003	.02	0.009
	total new lesion volume 7 days	43	45	.002	.008	0.009
1	total new lesion number 2 days	50	50	<.001	.005	0.001
	total new lesion volume 2 days	50	50	<.001	.005	0.006
	total new lesion number 7 days	50	50	.002	.02	0.005
	total new lesion volume 7 days	50	50	.002	.006	0.003
2	total new lesion number 2 days	50	50	.001	.003	0.003
	total new lesion volume 2 days	50	50	.001	.009	0.01
	total new lesion number 7 days	50	50	.006	.02	0.02
	total new lesion volume 7 days	50	50	.002	.007	0.007
3	total new lesion number 2 days	50	50	.001	.02	0.002
	total new lesion volume 2 days	50	50	.001	.004	0.007
	total new lesion number 7 days	50	50	.004	.04	0.02
	total new lesion volume 7 days	50	50	<.001	.06	0.006
4	total new lesion number 2 days	50	50	.001	.009	0.001
	total new lesion volume 2 days	50	50	.001	.003	0.006
	total new lesion number 7 days	50	50	.003	.02	0.008
	total new lesion volume 7 days	50	50	.002	.004	0.003
5	total new lesion number 2 days	50	50	.001	.007	0.002
	total new lesion volume 2 days	50	50	.001	.006	0.009
	total new lesion number 7 days	50	50	.002	.02	0.005
	total new lesion volume 7 days	50	50	.002	.006	0.008
6	total new lesion number 2 days	50	50	<.001	.007	0.001
	total new lesion volume 2 days	50	50	.001	.003	0.007
	total new lesion number 7 days	50	50	.003	.01	0.005
	total new lesion volume 7 days	50	50	.002	.004	0.004
7	total new lesion number 2 days	50	50	.001	.004	0.002
	total new lesion volume 2 days	50	50	.001	.004	0.01
	total new lesion number 7 days	50	50	.004	.02	0.01
	total new lesion volume 7 days	50	50	.005	.003	0.005

***…continued…*eTable 7.**

Imputation set	Variable tested Control vs. Filter	n		p potentially fully protected areas	p partially protected areas	p entire brain
		control	filter			
8	total new lesion number 2 days	50	50	<.001	.01	0.002
	total new lesion volume 2 days	50	50	.001	.005	0.008
	total new lesion number 7 days	50	50	.003	.03	0.009
	total new lesion volume 7 days	50	50	.002	.006	0.02
9	total new lesion number 2 days	50	50	.001	.008	0.002
	total new lesion volume 2 days	50	50	<.001	.003	0.005
	total new lesion number 7 days	50	50	.008	.03	0.01
	total new lesion volume 7 days	50	50	.002	.004	0.003
10	total new lesion number 2 days	50	50	<.001	.002	<0.001
	total new lesion volume 2 days	50	50	.001	.003	0.01
	total new lesion number 7 days	50	50	.003	.01	0.005
	total new lesion volume 7 days	50	50	.002	.004	0.004

eTable 8. Neurological Outcome

Intention-to-treat	Symptom	2 days no (%)	7 days no (%)	30 days no (%)
Control (n=50)	Non-disabling stroke	5 (10%)	5 (10%)	4 (8%)
	disabling stroke	0 (0%)	0 (0%)	0 (0%)
Filter (n=50)	Non-disabling stroke	5 (10%)	5 (10%)	4 (8%)
	disabling stroke	0 (0%)	0 (0%)	0 (0%)

Data are reported as number (%).

New strokes at each time point for 2, 7 and 30 days were reported. A disabling stroke is one that results in a modified Rankin Scale (mRS) score of ≥2 and an increase in >1 mRS category from an individual's pre-stroke baseline. A non-disabling stroke is one that results in a mRS score of <2 or that does not result in an increase in >1 mRS category from an individual's pre-stroke baseline.

In the control group, the following stroke symptoms were recognized: mild dysarthia (in two patients), a mild form of aphasia (in one patient), mild facial nerve paresis (in 2 patients) and slight motoric disability (reduced force development in one patient of the left arm and in one patient of both legs), and homonymic hemianopsia (one patient).

In the filter group, symptoms were the following: mild dysarthria (in 2 patients), paresthesia (in 3 patients), mild facial nerve paresis (in 1 patient) and slight motoric disability (reduced force development of the left leg in 1 patient). The number does not add up to 5 in each group since some patients had more than one symptom.

eTable 9. Neurological and Neurocognitive Outcomes According to NIHSS, mRS, and MoCA

Intention-to-treat analysis	Control	Filter
Patients with overall worsening of NIHSS		
at 2 days	16 (35.6%) (n=45)	17 (38.6%) (n=44)
at 7 days	11 (24.4%) (n=45)	11 (25.0%) (n=44)
at 30 days	9 (22.5%) (n=40)	7 (17.9 %) (n=39)
Patients with overall worsening of mRS		
at 2 days	15 (33.3%) n=45	9 (20.5%) n=44
at 7 days	8 (17.8%) n=45	8 (18.2%) n=44
at 30 days	7 (17.5%) (n=40)	4 (10.3%) (n=39)
Patients with overall worsening of MoCA (%)		
at 2 days	26 (72.2%) (n=36)	18 (50.0%) (n=36)
at 7 days	20 (55.6%) (n=36)	15 (41.7%) (n=36)
at 30 days	12 (38.7%) (n=31)	15 (46.9%) (n=32)

Data are reported as number (%) of patients with a worsening of NIHSS, mRS and MoCA at 2 and 7 days compared to baseline. Worsening is defined as ≥1 point decrease in NIHSS, ≥1 point decrease in MoCA or ≥ 1 point increase in mRS as compared to baseline.

NIHSS - national institute of health stroke scale, MoCA - Montreal Cognitive Assessment,

mRS - modified Rankin Scale

eTable 10. Procedural Outcomes at 30 Days According to VARC 2 Definitions

Outcome	Control Group (n = 50)	Filter Group (n = 50)
Major vascular complications no. (%)	6 (12%)	5 (10%)
Minor vascular complications no. (%)	2 (4%)	3 (6%)
Percutaneous closure device failure no. (%)	2 (4%)	4 (8%)
Bleeding event		
Life-threatening or disabling bleeding no. (%)	1 (2%)	1 (2%)
Major bleeding no. (%)	5 (10%)	5 (10%)
Minor bleeding no. (%)	2 (4%)	4 (8%)
Acute kidney injury no. (%)	5 (10%)	1 (2%)
Cardiogenic shock no. (%)	0 (0%)	1 (2%)
Cardiac perforation no. (%)	0 (0%)	1 (2%)
Permanent pacemaker implantation no. (%)	8 (16%)	12 (24%)
New-onset or worsening atrial fibrillation no. (%)	7 (14%)	7 (14%)

Data are reported as number (%).

Major vascular complications: Any aortic dissection, aortic rupture, annulus rupture, left ventricle perforation, OR new apical aneurysm/pseudo-aneurysm OR access site or access-related vascular injury (dissection, stenosis, perforation, rupture, arterio-venous fistula, pseudoaneurysm, hematoma, irreversible nerve injury, compartment syndrome, percutaneous closure device failure) leading to death, life-threatening or major bleeding, visceral ischemia, or neurological impairment OR distal embolization (non-cerebral) from a vascular source requiring surgery or resulting in amputation or irreversible end-organ damage OR the use of unplanned endovascular or surgical intervention associated with death, major bleeding, visceral ischemia or neurological impairment OR any new ipsilateral lower extremity ischemia documented by patient symptoms, physical exam, and/or decreased or absent blood flow on lower extremity angiogram OR surgery for access site-related nerve injury OR permanent access site-related nerve injury.

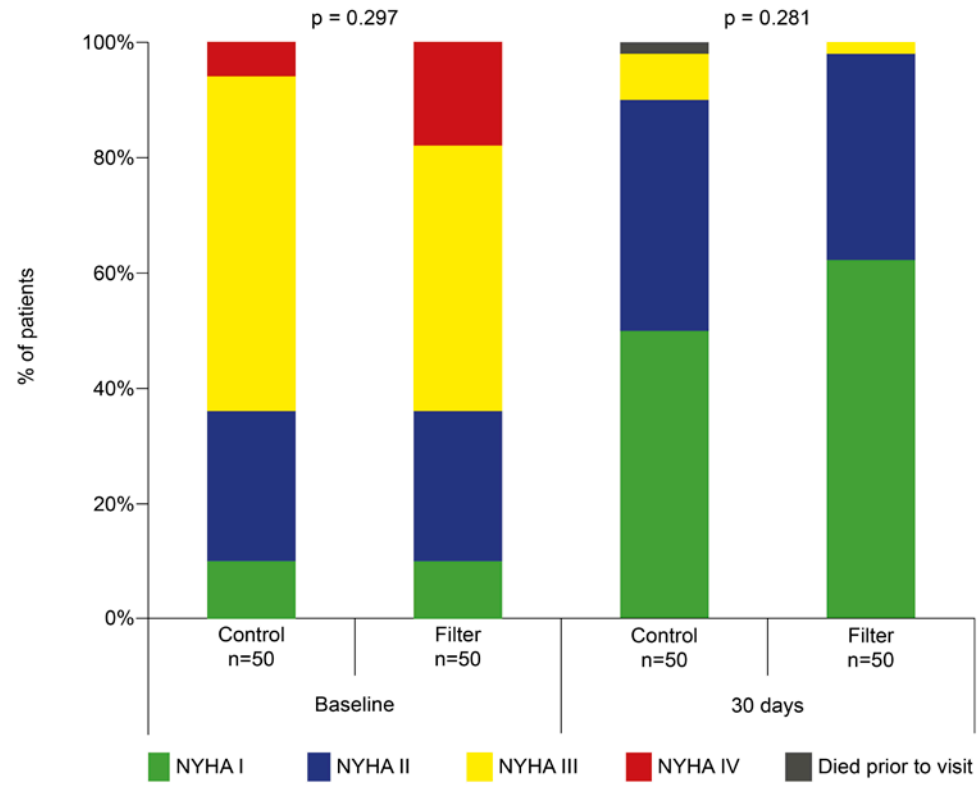
Minor vascular complications: Access site or access-related vascular injury (dissection, stenosis, perforation, rupture, arterio-venous fistula, pseudoaneuysms, hematomas, percutaneous closure device failure) not leading to death, life-threatening or major bleeding, visceral ischemia, or neurological impairment OR distal embolization treated with embolectomy and/or thrombectomy and not resulting in amputation or irreversible end-organ damage OR any unplanned endovascular stenting or unplanned surgical intervention not meeting the criteria for a major vascular complication OR vascular repair or the need for vascular repair (via surgery, ultrasound-guided compression, transcatheter embolization, or stent-graft).

eTable 11. Serial Echocardiography by Treatment Group

	Baseline		Discharge	
	Control	Filter	Control	Filter
Patients - no.	50	50	50	50
Mean aortic gradient - mmHg (SD)	47.1 (15.1)	41.5 (14.7)	9.4 (6.1)	7.9 (3.8)
Effective orifice area - cm^2 (SD)	0.69 (0.18)	0.71 (0.18)	1.98 (0.55)	2.00 (0.54)
Total aortic regurgitation				
None - no. (%)	5 (10%)	5 (10%)	16 (32%)	16 (32%)
Trace - no. (%)	11 (22%)	8 (16%)	19 (38%)	19 (38%)
Mild - no. (%)	28 (56%)	25 (50%)	14 (28%)	14 (28%)
Moderate - no. (%)	6 (12%)	12 (24%)	1 (1%)	1 (1%)
Severe - no. (%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Paravalvular aortic regurgitation				
None - no. (%)	NA	NA	16 (32%)	16 (32%)
Trace - no. (%)	NA	NA	20 (40%)	19 (38%)
Mild - no. (%)	NA	NA	13 (26%)	14 (28%)
Moderate - no. (%)	NA	NA	1 (1%)	1 (1%)
Severe - no. (%)	NA	NA	0 (0%)	0 (0%)
Valvular aortic regurgitation				
None - no. (%)	5 (10%)	5 (10%)	44 (88%)	44 (88%)
Trace - no. (%)	11 (22%)	8 (16%)	1 (2%)	1 (2%)
Mild - no. (%)	28 (56%)	25 (50%)	4 (8%)	5 (10%)
Moderate - no. (%)	6 (12%)	12 (24%)	1 (2%)	0 (0%)
Severe - no. (%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
EF - % (SD)	56.3 (15.6)	57.0 (14.3)	55.7 (11.4)	58.0 (11.7)

Data are reported as number (%) or mean (SD) unless otherwise stated. EF – Ejection fraction.

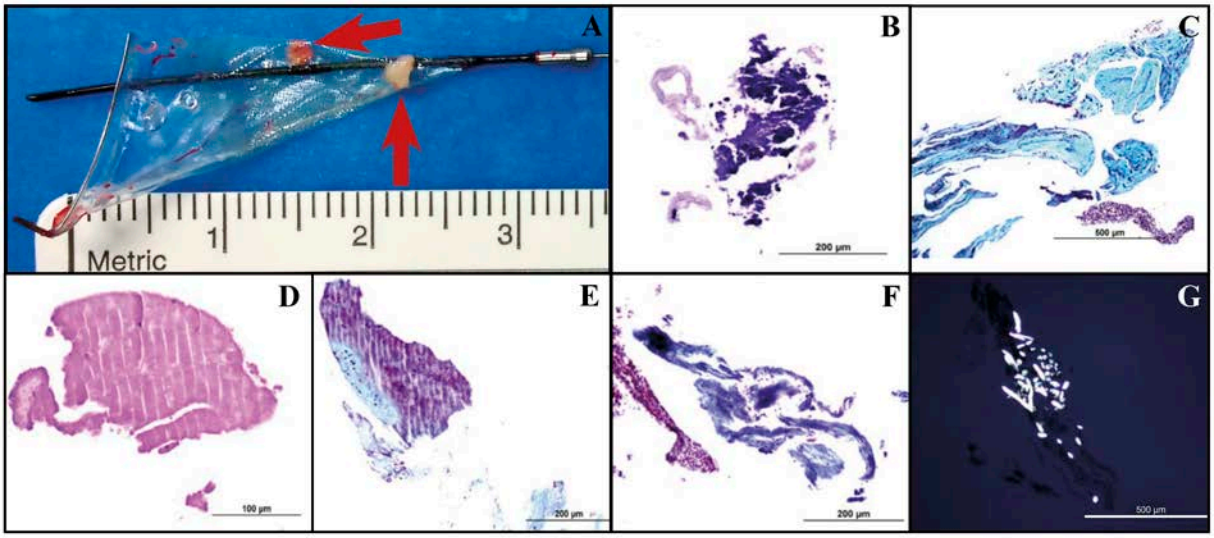
eFigure 1. New York Heart Association Class at Baseline and After 30 Days in the Control and Filter Groups



	Baseline		30 days	
	Control n=50	Filter n=50	Control n=50	Filter n=50
NYHA I	5 (10.0%)	5 (10.0%)	25 (50.0%)	31 (62.0%)
NYHA II	13 (26.0%)	13 (26.0%)	20 (40.0%)	18 (36.0%)
NYHA III	29 (58.0%)	23 (46.0%)	4 (8.0%)	1 (2.0%)
NYHA IV	3 (6.0%)	9 (18.0%)	0 (0.0%)	0 (0.0%)
Died prior to visit	0 (0.0%)	0 (0.0%)	1 (2.0%)	0 (0.0%)

NYHA = New York Heart Association class; Filter = patients treatet with Claret filter; Control = control patients, not treated with Claret filter. Data are reported as number (%). The Chi-square test was used to compare the groups.

eFigure 2. Macroscopic and Microscopic Findings of Captured Debris



Proximal and distal filters of every patient in the filter group containing the captured debris were removed after TAVI. They were fixed in 10% neutral buffered formalin. The collected material was processed in a graded series of alcohol and embedded in paraffin. After cutting the paraffin blocks, the slides were stained using Hematoxylin & Eosin (H&E) and Movat Pentrachrome (MP). Aspirates were then evaluated for the presence of thrombus, calcification, valve tissue, collagenous tissue, arterial wall and foreign material. Representative examples of captured material from various patients are shown in Panel A-G.

Panel A: Filter containing captured debris
Panel B: Calcium
Panel C: Arterial wall
Panel D: Acute thrombus
Panel E: Organizing thrombus
Panel F: Valve tissue
Panel G: Polarized foreign material

eAppendix. Expanded Methods

STUDY DESIGN

The CLaret Embolic protection ANd TAVI (CLEAN-TAVI) trial was a single center, randomized, blinded, clinical trial performed at the Heart Center at the University of Leipzig, Germany. The trial was designed by the senior authors and was approved by the ethics committee of the University of Leipzig. Neither Medtronic Inc. nor Claret Medical, both of which supported the study by unrestricted grants, had any involvement into the study. The analysis of the MRI scans was performed at the Buffalo Neuroimaging Center, Buffalo, New York by an investigator blinded to patients' identity and group assignment. Data were maintained at the University of Leipzig, Heart Center and statistical analysis was performed by independent personnel. The authors vouch for the integrity, completeness and accuracy of the data.

PATIENT SELECTION

Symptomatic patients with severe aortic stenosis were eligible for inclusion in the study if they were considered at increased risk for undergoing surgical aortic valve replacement (SAVR) as determined by the heart team consisting of at least one cardiac surgeon and one interventional cardiologist. The STS PROM and the additive as well as logistic EuroSCORE were calculated as estimates of surgical risk. Computed tomography scans were performed to determine the size of the aortic annulus, the access vessels, the brachiocephalic trunk and the left common carotid artery. The aortic annulus was required to have a size between 20 and 29 mm. Exclusion criteria were an anatomy unsuitable for a safe Medtronic CoreValve implantation, preexisting permanent pacemaker, stroke within the last 12 months, a carotid artery stenosis of more than 70%, significant stenosis of the right subclavian artery or the brachiocephalic trunk, expected non-compliance to follow-up visits, participation in another
clinical study, severe renal failure (GFR < 30 ml/min/1.73m² body surface area) or pregnancy. All the patients provided written informed consent.

RANDOMIZATION AND MASKING

The randomization was performed using an urn model. Patients were randomly assigned (1:1) to the control or filter group using concealed identical envelopes. Before the study, the envelopes (n=100) were deposited in an urn, which was maintained in the study center. The envelopes had a black lamination inside (equivalent to those used by banks when sending credit card PINs) make them non-transparent. The patient was prepared for TAVR on the OR table and immediately before puncture, a study coordinator not involved into this trial was asked to pull an envelope from the urn, bring it to the hybrid suite, open it and present the page inside containing the group assignment to the team, so that the patient remained blinded with regard to the assignment. Using this approach, we were making sure that the investigator could not reach for another envelope. The procedure was continued according to group assignment.

Physicians and nurses performing the neurological and neurocognitive tests, were otherwise not involved into the study or patient treatment and blinded to group assignment. The MRIs were anonymized using the patients study number, and transferred to the central MRI core laboratory for analysis to ensure blinding of the core laboratory. MRI measurements were returned to the statistical expert for analysis, which was performed after looking of the database.

STUDY PROCEDURES

TAVI Treatment

Patients were randomly assigned in a 1:1 ratio into transfemoral aortic valve implantation using the CoreValve (Medtronic Inc., Minneapolis, MN, USA) self-expanding prosthesis without (Control group) or with (Filter group) cerebral protection device (CPD) using the Claret Montage TM Dual Filter System (Claret Medical Inc, Santa Rosa, CA, USA). All of the procedures were performed under conscious sedation by the same heart team. Heparin was given until the target ACT of 250 seconds was achieved. In the filter group, the CPD was deployed as described previously.2,3 Briefly, the proximal filter was deployed in the brachiocephalic trunk and hence covers all areas of the brain supplied by the right vertebral and carotid artery; the distal filter was released in the left carotid artery and protects the areas of the brain supplied by the latter vessel feeding the left side. The left vertebral artery usually originating from the left subclavian artery, and hence the brain areas fed by this vessel, remain unprotected. Based on the structure of the circle of Willis, the brain was separated into 28 segments corresponding to the 14 left and 14 right sided arteries, to provide a detailed map of the territories fed by left and right cerebral tributaries. The volume of the brain that is fully protected, partially protected and unprotected is 74%, 24 % and 2%, respectively. A detailed description of the segmentation of the brain, the respective nutritive support and the level of protection is provided in the Table of the online data supplement. (Table I) Following predilatation in all patients, CoreValve implantation was carried out as described previously as well. The access vessel was closed and the patients transferred to the intensive care unit for further monitoring.

Follow-up assessments were performed at 2 days and 7 days after TAVI and were identical to the preprocedural tests. Besides MRI, it included serial neurological and neurocognitive assessments, NYHA classification, echocardiography, documentation of adverse events and study endpoints.

Magnetic Resonance Imaging

Brain MRI assessments were performed at baseline, 2 and at 7 days. Characteristics of the preexisting lesions before TAVI are provided in Appendix Table VIII. MRI scans were obtained according to a protocol provided by the MRI reading center (Buffalo Neuroimaging Analysis Center, Buffalo, NY, USA) that also performed all MRI analysis. For the majority of subjects, MR images were acquired on a 3 Tesla Siemens Verio system at 0, 2, 7 days. Diffusion weighted images (DWI) were acquired with a 2D echo planar sequence with 3 orthogonal diffusion directions with b values of both 500 and 1000 s/mm^2. Additional parameters were: repetition time (TR) = 13000ms, echo time (TE) = 100ms, slice thickness = 3mm (no gap), acquisition matrix 204 x 156, final voxel size = 1.25mm x 1.25mm x 3.0mm. Fluid attenuated inversion recovery (FLAIR) images were acquired with a 2D spin echo inversion recovery sequence with an inversion time (TI) of 2580ms. Additional parameters were: TR = 9730ms, TE=92ms, slice thickness = 2mm (no gap), acquisition matrix 256 x 186, final voxel size = 0.94mm x 1.17mm x 2.0mm. High resolution T1-weighted images (hires-T1) were acquired with an MP-RAGE sequence. Additional parameters were: TR = 1690ms, TE=2.57ms, flip angle (FA) = 12, TI=1100ms, slice thickness = 1.5mm (no gap), acquisition matrix 256 x 224, final voxel size = 1.00mm x 1.00mm x 1.5mm. Additionally, a manufacturer-based dual-echo GRE sequence was used to acquire B0 field maps (voxel size = 4.00mm x 4.00mm x 5.00mm). A small number of subjects (n=11) were not able to be scanned at 3T due to pacemakers or other 3T-exclusionary criteria. For these subjects, a 1.5T Philips Intera system was used with a similar, adapted MRI protocol.

EPI DWI acquisitions are subject to substantial artifacts, including eddy current distortions and susceptibility-induced warping. Although these do not have a substantial impact on clinical assessment of large lesions associated with stroke or transient ischemic attack (TIA), they are quite large relative to the small embolic lesions resulting from the TAVI procedure – distortions may easily be on the order of 1cm, while lesions may be as small as a few mm. Therefore, a number of pre-processing steps were taken to improve image quality and subsequent analysis. First, the raw DWI images were corrected for eddy current induced distortions using the eddy correct tool from FMRIB's FSL FDT library.[4] Next, the diffusion b=0 (b0) and three corrected b=1000 diffusion-encoded raw images were combined to create trace and apparent diffusivity coefficient (ADC) images. Then, spatial distortions due to field susceptibility effects were corrected with the use of field maps.[5] To accomplish this, the acquired B0 field maps were aligned to the individual T2-weighted DWI b0 images. Then, the FUGUE tool from FSL was used to perform map-based geometric unwarping.[6]

Because the lesions are often so small, subtraction imaging was also employed to increase lesion salience.[7] Baseline DWI and FLAIR images were voxel-wise subtracted from follow-up images to produce direct change maps. To facilitate this subtraction approach, additional pre-processing steps were performed. First, low-frequency spatial intensity inhomogeneities on FLAIR images were corrected using N3.[8] Corrected FLAIR and DWI trace images were further standardized by applying a piecewise-linear histogram adjustment method to compensate for scan-to-scan variability in absolute intensity.[9] Finally, to facilitate direct longitudinal analysis, all within-subject scans were co-registered to each subject's baseline FLAIR image using FLIRT with 6 degrees of freedom.[10]

Lesions were delineated on corrected and aligned 2 and 7 days DWI trace images using a semi-automated contouring technique provided by the JIM software package.[11] Using this approach, a trained operator identified lesions individually, and for each lesion an assistive algorithm delineated a highly reproducible iso-contour at the maximum local gradient. The operator viewed all images and change maps simultaneously to increase confidence, and also coded lesions as new or persistent.

In addition to lesion counts and volumetry, vascular territory was also assessed using an atlas-based technique. For this purpose, a vascular territory atlas was manually created in the standard MNI 152 template space[12] based on existing literature,[13] and including 28 separate regions. Individual hires-T1 images were used to non-linearly align this atlas to individual lesion maps. First, individuals' hires-T1 images were corrected for intensity inhomogeneity using N3, then aligned to the MNI 152 template using a two-stage process consisting of an initial rigid-body co-registration followed by composition with a warp field obtained from a non-linear warping technique.[14] These transforms were then inverted, and applied to the original atlas. Lesion number and volume within each vascular territory were than assessed separately.

For visualization purposes, aggregate lesion maps were also rendered in 3D. First, individual subjects' lesion maps were non-linearly aligned to MNI space as described above. Then, these individual maps were averaged within groups to produce group maps of lesion density. These were rendered using MayaVI,[15] with regions with at least one lesion shown in yellow, and regions with two or more lesions in shown red.

Patients were randomly assigned in a 1:1 ratio into transfemoral aortic valve implantation using the Core Valve (Medtronic Inc., Minneapolis, MN, USA) self-expanding prosthesis without (Control group) or with (Filter group) neuroprotection by the Claret Montage^{TM} Dual Filter System (CMD). Dual antiplatelet therapy with aspirin at dose of 100 mg daily, and clopidogrel 75 mg daily was recommended before the procedure and for 6 months thereafter, followed by aspirin monotherapy at the same dose indefinitely. In case warfarin was indicated, clopidogrel at a dose of 75 mg daily was administered for 6 months in addition, followed by warfarin monotherapy indefinitely.

All of the procedures were performed under conscious sedation by the same heart team. In the filter group, right radial or brachial artery was punctured and a 6 F hydrophilic sheath was introduced. Afterwards, 2500 unit of unfractionated heparin were given iv. Following local anesthesia, femoral venous and arterial access was gained. Heparin was re-administered at a total dosage of 100 units/ kg body weight to reach a target activated clotting time (ACT) above 250 seconds. A balloon-tip pacing lead was positioned in the right ventricle and a 18 F sheath was advanced into the descending aorta as described previously.[1] In patients of the filter group, the CMD was advanced over an extra support wire into the brachiocephalic trunk and the proximal filter deployed. Contrast was given to confirm appropriate filter position and visualize the left common carotid artery. The ADS was flexed and the distal filter deployed in the left common carotid artery followed by angiography to confirm adequate filter position. The stenotic aortic valve was negotiated and an Amplatz superstiff wire positioned into the left ventricle. Following balloon valvuloplasty, the Core Valve implanted. In case of significant paravalvular leakage (AR grade II) a postdilatation was performed. After pull back of all catheters from the ascending aorta and the arch, the distal and proximal filter were recaptured and the CMD was removed. The filters were stored in formaldehyde for histopathological assessment of captured debris. The access sides on the groin were closed and the patients were moved to the intensive care unit for further monitoring.
Follow-up assessments were performed at 2 days and 7 days after TAVI and were identical to the preprocedural tests. They included MRI of the brain, serial neurological and neurocognitive assessment (NIHSS, modified Ranking scale, Montreal cognitive assessment), NYHA classification, echocardiography, documentation of adverse events and study endpoints.

Neurological and neurocognitive assessment
The neurological (NIHSS, mRS) and neurocognitive (MoCA) assessments were performed by an attending physician being currently trained as internists/cardiologist or by an exercise scientist (PhD). Both had a past experience of neurological assessments in studies and where NIHSS and mRS ranking scale certified. They were blinded with regard to group assignment.

STUDY END POINTS
The Claret Montage dual filter system is designed to protect all areas supplied by the right carotid and vertebral artery as well as the left carotid artery. These areas are the ones referred to as “protected areas”. The regions supplied by the left vertebral artery are not protected. The primary endpoint was the numerical reduction in positive post procedure Diffusion Weighted MRI (DW-MRI) perfused brain lesions relative to baseline at 2 days post TAVI in protected territories in the intension-to-treat analysis. Secondary endpoints included serial volumetric and numerical reduction in positive post procedure DW-MRI perfused brain lesions at 2 and 7 days as well as results of serial neurological and neurocognitive assessment (Modified Ranking Scale, NIHSS, Montreal cognitive assessment). Other secondary endpoints included the occurrence of death, stroke, TIA, myocardial infarction or bleeding using the definitions established by the Valve Academic Research Consortium.[16] In addition, echocardiographic outcomes were assessed, including the change in the mean aortic valve gradient and change in the effective orifice area form baseline to discharge. The Valve Academic Research Consortium 2 definitions were used to determine the degree of valvular regurgitation.[16]

STATISTICAL ANALYSIS
The primary endpoint was the number of positive post procedure DW-MRI perfused brain lesions at 2 days relative to baseline between the assignment groups. Astarci and Fairbaim et al. reported a SD of the DW-MRI lesion number of 6.5 and 7.1 after TAVI, respectively.[17,18] However, Astarci et al. used 3T-MRI infrequently and all MRIs in the study by Fairbaim et. al were performed on a 1.5T scanner, which has a lower sensitivity to recognize small lesions.[17,18] Since we applied a methodology that enabled us to detect even very small new lesions and that we were intending to apply 3T-MRI in all cases, we anticipated that the absolute lesion number is higher than reported previously. The primary hypothesis was that the use of the CMD reduces the number of positive post procedure DW-MRI perfused brain lesions at 2 days relative to baseline in protected territories by 50% in patients undergoing TAVI using the CoreValve. Given a standard deviation of 7 for the measure and assuming a drop out rate of 16%, we estimated that a total of 50 patients were required in each group for the study to have a power of 90% at a two-sided alpha level of 0.05. Since the device does not protect the entire brain, primary focus was on the territory where a potential filter effect most reliably could be detected.

The prespecified cohort for the primary analysis was the intension-to-treat population, which included all patients who had undergone randomization. Secondary efficacy endpoints were evaluated and tested for statistical significance, but only if the primary efficacy endpoint has been met. To preserve overall Type I error, a gatekeeping strategy was used, where secondary MRI endpoints were tested in the order in which they are listed here and in the statistical analysis plan (SAP). These endpoints were only tested if the prior one on the list achieved statistical significance. There were 16 secondary endpoints defined: 1) The difference in day 2 DW-MRI median total new lesion volume based on the potentially protected areas, 2) the difference in day 7 DW-MRI median total new lesion number based on the potentially protected areas, 3) the difference in day 7 DW-MRI median total new lesion volume based on the potentially protected areas, 4) the difference in day 2 DW-MRI total new lesion number based on all territories (entire brain), 5) the difference in day 2 DW-MRI median total new lesion volume based on all

territories, 6) the difference in day 7 DW-MRI total new lesion number based on all territories, 7) the difference in day 7 DW-MRI median total new lesion volume based on all territories, 8) the difference in day 30 Flair-MRI total new lesion number based on potentially protected territories, 9) the difference in day 30 day Flair-MRI median total new lesion volume based on potentially protected territories, 10) the differences in day 3 Montreal cognitive assessment and its subcomponents, 11) the differences in day 7 Montreal cognitive assessment and its subcomponents, 12) the difference in day 3 modified Rankin Scale assessment, 13) the Difference in day 7 modified Rankin Scale assessment, 14) the difference in day 3 NIHSS Scale assessment, 15) the difference in day 7 NIHSS Scale assessment, and 16) the difference in periprocedural HITS.

The secondary endpoints Montreal Cognitive assessment (MoCA), modified Rankin scale (mRS) assessment, National Institutes of Health Stroke Scale (NIHSS) and High Intensity Transient Signals (HITS) were considered exploratory and descriptively reported.

Categorical variables are expressed as numbers and/or percentage and were compared with the use of Fishers exact test or the chi-square test, as appropriate. Continuous variables were tested for normal distribution using the Kolmogorov Smironov test. In case of normal distribution, continuous variables were expressed as means±SD and compared with Student's t-test, otherwise they are expressed as median and interquartile range and compared using Mann-Whitney U-test. The odds ratios and 95% CIs were calculated using logistic regression analysis. All echocardiographic measurements were evaluated with the use of a two-sample t-tests or the Wilcoxon rank-sum test for continuous variables, as appropriate. All analysis was performed with the use of SPSS (version 21, IBM, Armonk, New York, USA) or Medcalc software (version 13.1.2.0, MedCalc, Ostend, Belgium).

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