PROTAVI-C Pilot Study

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

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on behalf of the PROTAVI-C Pilot Investigators

Potential conflicts of interest

Consultant for Edwards Lifesciences

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- **TCD Core Laboratory**

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- **DW-MRI Core Laboratory**

  Marc Schlamann, Universitätsklinikum Essen

- **Sponsor**

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  Project Leader: Selma Hadamer

* Neurologist Specialty

Background

- Transcatheter aortic valve implantation (TAVI) represents a novel treatment option for inoperable or high surgical risk patients with severe symptomatic aortic valve disease.
- Randomized trials studies have raised concerns of stroke rates with TAVI compared to medical treatment and aortic valve replacement.
- Several TAVI studies have shown a high rate (>60%) of new cerebral ischemic defects as evaluated by DW-MRI.
- Embolic protection has been successfully used in carotid intervention but its value in the setting of TAVI is still unknown.

Embrella Embolic Deflector System

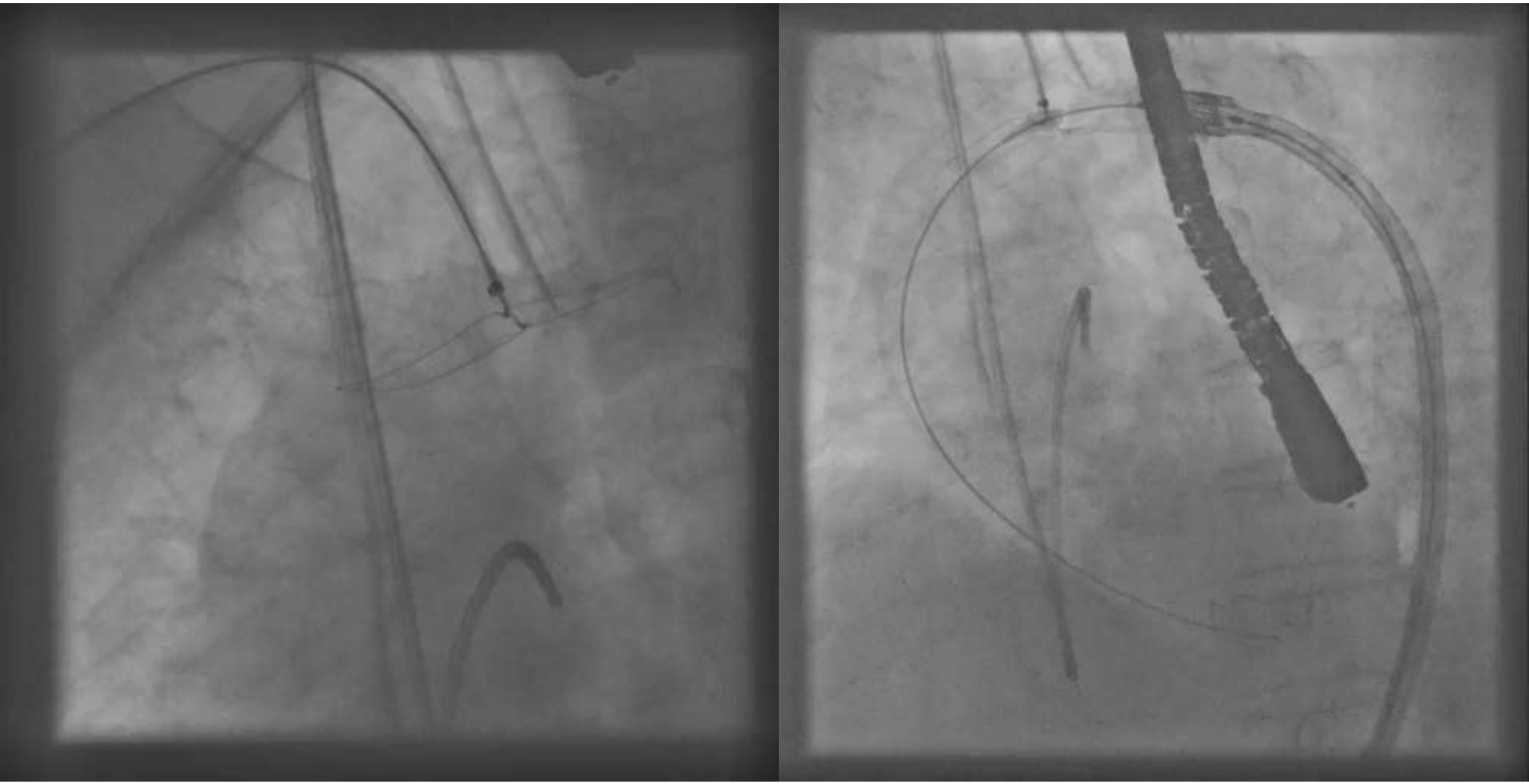
Embolic protection device designed to reduce the amount of embolic material that may enter the carotid arteries during TAVI and valvuloplasty procedures.

- 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.

Embrella Embolic Deflector System



PROTAVI-C Pilot Study

- **The PROTAVI-C Trial** is designed to characterize the neurological complications related to TAVI procedures and to evaluate a novel embolic protection device (*Embrella Embolic Protection System*). The trial consists of a pilot phase followed by a randomized trial evaluating optimal embolic protection and antithrombotic regimens.
- **Objectives of the Pilot Phase**
  - To elucidate the mechanisms and temporal patterns of embolic events during the TAVI procedure.
  - To determine the procedural safety, technical feasibility and exploratory efficacy of the Embrella Embolic Deflector System.

Pilot Study Methods

- Six centers allotted 9 patients each as follows (total 54 patients):
  - First 2 patients “roll-in” group with Embrella
  - Next 5 patients treatment group with Embrella
  - Last 2 patients controls without Embrella
- TAVI procedure by transfemoral approach with the Edwards SAPIEN XT valve (sizes: 23, 26 or 29-mm)
- TAVI Indication consistent with approved CE Mark indication
- Antithrombotic regimen: Aspirin (80 mg) + clopidogrel (75 mg) administered before the procedure. Heparin administered during the procedure (ACT > 300s)

Comprehensive Neurological Outcomes Evaluated in Three Realms

Clinical Outcomes

- Stroke and TIA
- VARC criteria

Neuro-Imaging Per Blinded Core Labs

- Transcranial Doppler (TCD) – procedure
- Cerebral DW-MRI

Neurological, Functional and Cognitive Status

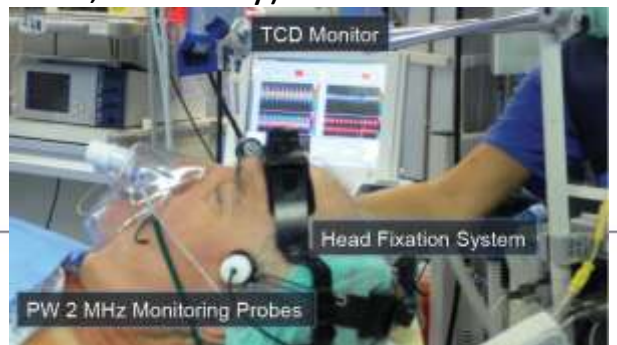
- Modified Rankin Score
- NIHSS
- Montreal Cognitive Assessment
- MMSE
- Barthel Index

Baseline, 1-7 Days and 30 (-7 - +14) Days After TAVI

TCD and MRI Methodology

TCD

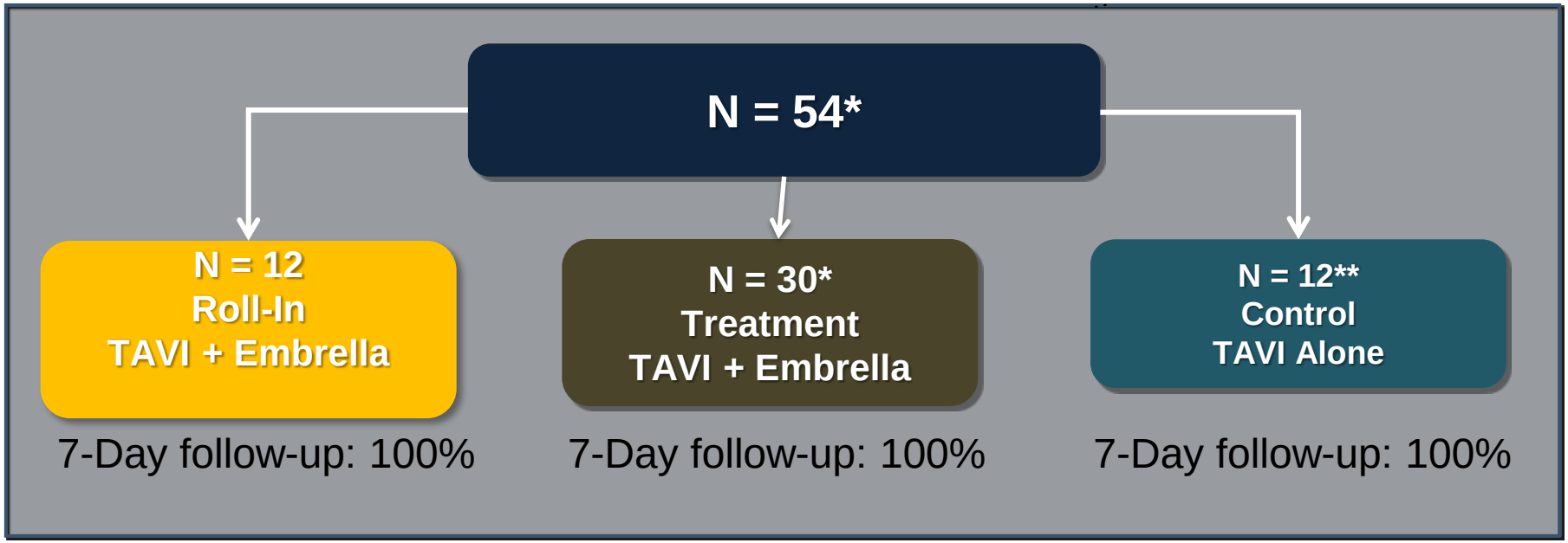
- Simultaneous TCD of both middle cerebral arteries (entire TAVI procedure)
- All procedural events recorded by a member heart team
- Multi-Dop® T digital system (DWL Compumedics, Germany)
- Protocol training and quality oversight with supervision by Dr. Zsolt Garami, Methodist DeBakey Heart and Vascular Center, Houston
- Measurements: presence /number of high-intensity transient signals (HITS) at each step of the TAVI procedure (core lab, Univ. Essen, Germany)



MRI

- MRI protocol incl. 3 sequences:
  - transversal fluid-attenuated inversion recovery (FLAIR)
  - transversal diffusion-weighted MRI (DW-MRI) with ADC maps;
  - transversal SWI (susceptibility weighted imaging)
    - T2* (if SWI is not available)
- Measurements (core lab, Univ. Essen, Germany)
  - Presence of new ischemic lesions
  - Number of lesions
  - Lesion location
  - Lesion size (volume)

Study Patient Flow



Roll-in and treatment arms will be presented together

- *1 procedure aborted before Embrella insertion
- **Enrollment incomplete: 3 control patients pending

Baseline Characteristics

Baseline Characteristics	TAVI+Embrella (N=41)
Age (years)	82 ± 7
Female sex	22 (53.7%)
NYHA III/IV	31 (75.6%)
Diabetes	14 (34.1%)
Hypertension	36 (87.8%)
Coronary Artery Disease	24 (58.5%)
Atrial Fibrillation	4 (9.8%)
Carotid Disease	6 (14.6%)
Peripheral Vascular Disease	6 (14.6%)
Prior Stroke/TIA	7 (17.1%)
STS Score (%)	7.8 ± 7.2
Mean Transaortic Gradient (mmHg)	52.3 ± 16.4
LVEF(%)	57.2 ± 12.9

Procedural Data

Characteristic	TAVI+Embrella (N=41)
Radial access	28 (68.3%)
Time from access site to deployment (min)	2.9±3.61
Successful Embrella deployment	41 (100.0%)
Repositioning required after initial deployment	4 (9.8%)
Device properly seated against aortic arch	41 (100.0%)
Device visualized covering both ostia of brachicephalic and left common carotid arteries	41 (100.0%)
2 Embrella devices used	2 (4.9%)
Device integrity at the end of the procedure (visual examination)	41 (100%)

Procedural Data

	TAVI+Embrella (N=41)
Successful valve implantation	41 (100%)
Cardiac Tamponade	1 (2.4%)
Valve – in – Valve	1 (2.4%)
Valve Embolization	0 (0.0%)
Superior limb ischemia	0 (0.0%)
Brachial/radial access related injury*	2 (4.9%)

* 1 Pseudoaneurysm of the brachial artery
1 right radial artery thrombosis

Clinical Outcomes at 7 Days

Adverse Events	TAVI+Embrella (N=41)
All-cause Mortality	1 (2.4%)
Stroke*	1 (2.4%)
TIA	0 (0.0%)
Life-threatening bleeding	2 (4.9%)
Renal insufficiency	1 (2.4%)

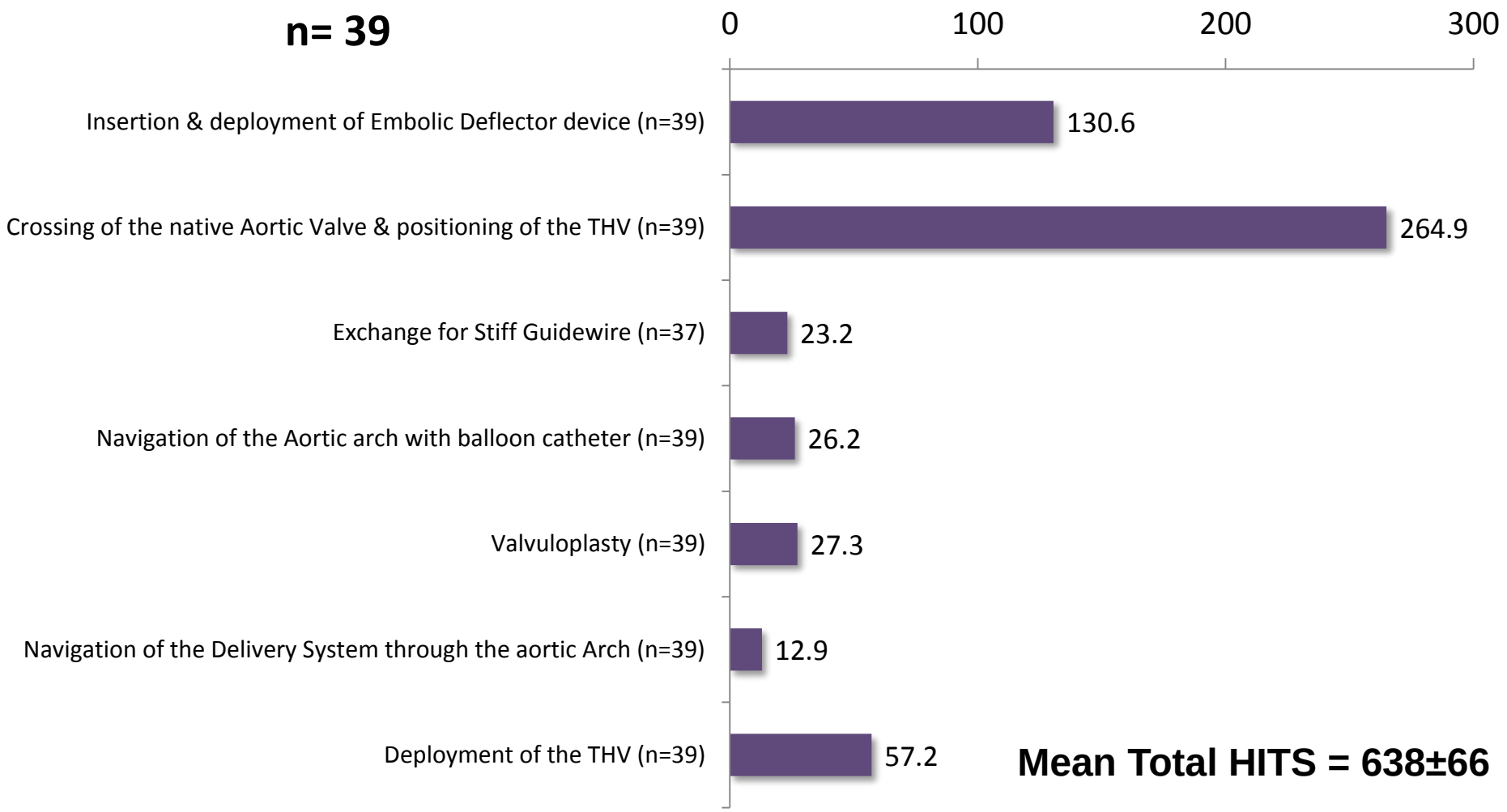
** Day 2, CEC adjudicated as minor; not device related*

* post-procedural

Transcranial Doppler Findings

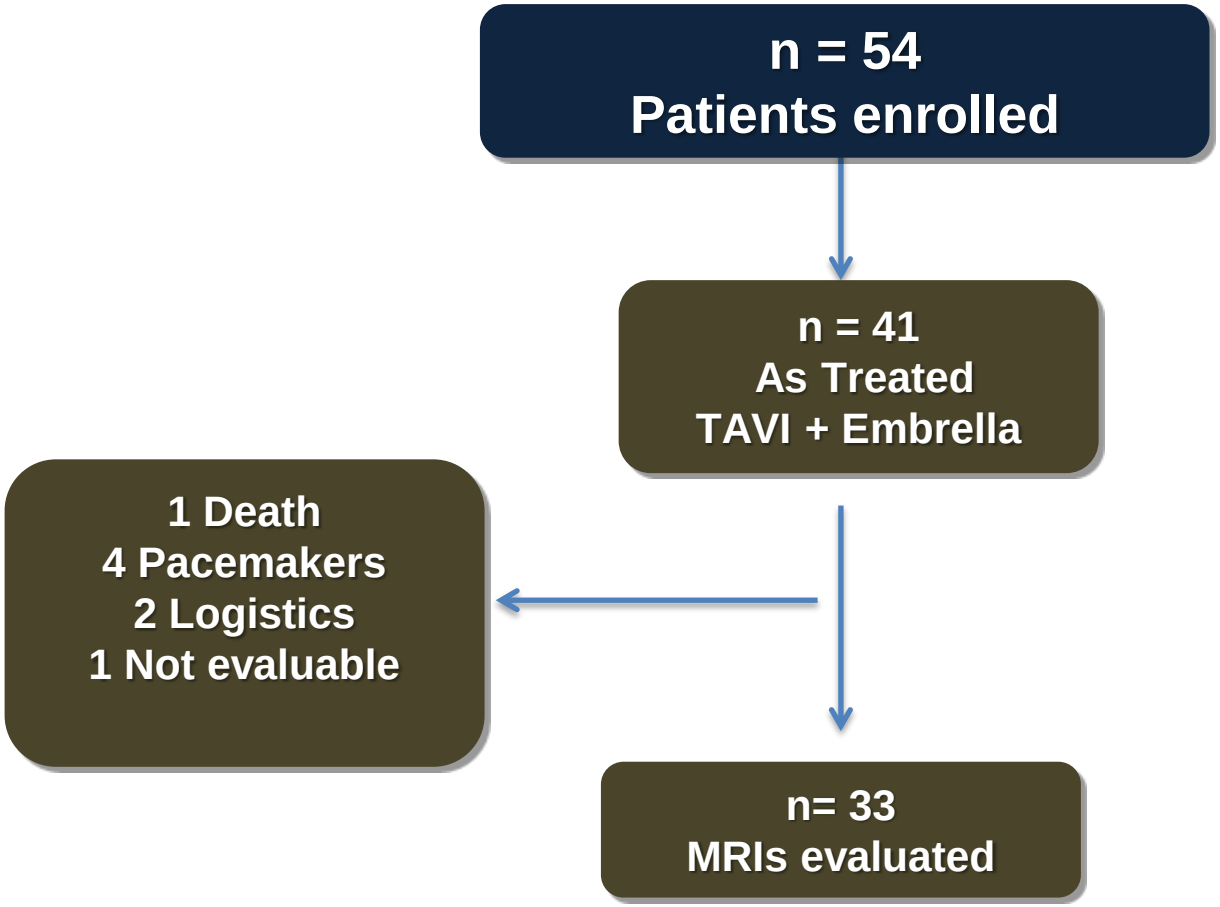
TAVI+Embrella: Mean TCD HITS

n= 39



Mean Total HITS = 638±66

DW-MRI
Within 7 Days After TAVI



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 artery	7 (21%)
Medial cerebral artery	29 (88%)
Posterior cerebral artery	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)

DW-MRI Data

	Roll-In (n=9)	Treatment TAVI + Embrella (n=24)	P Value
Time from TAVI procedure, days, median (min, max)	3 (1,7)	3 (1-7)	NA
Patients with new Lesions	9/9 (100%)	24/24 (100%)	NA
Total No. of lesions, n			
Anterior cerebral artery	1 (11%)	6 (25%)	0.642
Medial cerebral artery	9 (100%)	20 (83%)	0.555
Posterior cerebral artery	6 (67%)	16 (67%)	>.999
Cerebellum	8 (89%)	15 (63%)	0.217
Border zone	0	2 (8%)	>.999
Patients with single lesions	0	4 (17%)	>.999
Patients with multiple lesions	9 (100%)	20	0.555
Lesions per patient, median (min, max)	9 (2, 21)	7 (1, 70)	0.361
Lesion volume (mm^3), median (min, max)	69.4 (25.0, 210.6)	40.0 (10.8, 196.7)	0.897

TAVI – Cerebral MRI Studies

Study	n	Valve Type	New Ischemic Defects	Median Number of Lesions Per Patient	Lesion Volume (Per Lesion, mm^3)
Kahlert et al. ***Circulation 2010***	53	SAPIEN (n=22) CoreValve (n=10) SAVR (n=21)	SAPIEN: 86% CoreValve: 80% SAVR: 48%	SAPIEN: 4 (2.1-6.0) CoreValve: 2.6 (0.3-4.9) SAVR: 1.6 (0.6-2.69)	81 (60-103) 61 (37-86) 224 (111-338)
Ghanem et al. ***JACC 2010***	22	CoreValve	73%	2.5 (1.0-5.5)	NA
Rodés-Cabau et al. ***JACC 2011***	60	SAPIEN/ SAPIEN XT	TF: 66% TA: 71%	TF: 3 (1-7) TA: 4 (2-9)	NA
Fairbairn et al. ***Heart 2011***	31	CoreValve	77%	2 (1-5)	205 ± 350
Arnold et al. ***JACC Intv 2010***	25	SAPIEN	68%	NA	NA
PROTAVI-C Pilot	33	SAPIEN XT	100%	8 (1-70)	42.3 (27.5, 85)

Neurological and Cognitive Test Results

Variables	TAVI+Embrella		
	Baseline evaluation	Post-procedure evaluation	P value
NIHSS (median, min-max)	0.0 (0.0,3.0)	0.0 (0.0,2.0)	0.793
MRS (median, min-max)	0.0 (0.0,3.0)	0.0 (0.0,5.0)	0.979
Barthel Index (median, min-max)	100.0 (65.0,100.0)	97.5 (5.0,100.0)	0.375
MoCa (median, min-max)	24.0 (14.0,29.0)	25.0 (11.0,30.0)	0.162
MMSE (median, min-max)	28.0 (19.0,30.0)	28.5 (15.0,30.0)	0.623

Conclusions

- The PROTAVI-C Pilot study showed that the use of the Embrella Embolic Deflector System during TAVI procedures is feasible and safe with minimal procedural complications.
- There were no procedural strokes; one minor stroke occurred 2 days after the procedure. No impairment of neurocognitive function was observed.
- TCD revealed cerebral microembolization as reflected by HITs in all patients, with the largest number occuring during valve positioning/implantion and Embrella device insertion.
- All patients had new but clinically silent cerebral ischemic defects as evaluated by MRI, usually multiple and located across different cerebral territories.
- While early clinical neurological outcomes are encouraging, this preliminary experience does not suggest a decrease in the occurrence and number of new ischemic defects as evaluated by MRI following TAVI with embolic protection device as compared to historical data. However, the data suggests a potential decrease in cerebral lesion volume that should be further evaluated.

Study Sites

Hôpital Bichat – Claude-Bernard, Paris
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Universtäts Herzzentrum Bad Krozingen
Franz-Josef Neumann

Städtisches Klinikum Karlsruhe
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Universitätsklinikum Essen
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St. Paul's Hospital, Vancouver
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Back up

PROTAVI-C

TCD historical comparison with Essen experience