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Safety and performance of a novel cerebral embolic protection device for transcatheter aortic valve implantation: the PROTEMBO C Trial

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KEYWORDS

- aortic stenosis
- cerebral protection
- stroke

Abstract

Background: Stroke remains a feared complication associated with transcatheter aortic valve implantation (TAVI). Embolic cerebral injury occurs in the majority of TAVI cases and can lead to cognitive dysfunction.

Aims: The PROTEMBO C Trial evaluated the safety and performance of the ProtEmbo Cerebral Protection System in TAVI patients.

Methods: Forty-one patients were enrolled in this single-arm study conducted at 8 European centres. The primary safety endpoint was the rate of VARC 2-defined major adverse cardiac and cerebrovascular events (MACCE) at 30 days; the primary performance endpoint was the composite rate of technical success versus performance goals (PG). Secondary endpoints included brain diffusion-weighted magnetic resonance imaging (DW-MRI), new lesion volume, and the rate of death or all strokes compared to historical data.

Results: Thirty-seven of 41 enrolled patients underwent TAVI with the ProtEmbo device (intention-to-treat [ITT] population). Both primary endpoints were met. MACCE at 30 days was 8.1% (upper limit of the 95% confidence interval [CI]: 21.3% vs PG 25%; p=0.009), and technical success was 94.6% (lower limit of the 95% CI: 82.3% vs PG 75%; p=0.003). New DW-MRI lesion volumes with ProtEmbo were smaller than in historical data, and 87% of patients completing MRI follow-up had no single lesion >150 mm^3. There was 1 stroke in a patient in whom the device was removed prematurely before TAVI completion.

Conclusions: The PROTEMBO C Trial met its primary safety and performance endpoints compared to prespecified historical PGs. Patients had smaller brain lesion volumes on DW-MRI compared to prior series and no larger single lesions. These results warrant further evaluation of the ProtEmbo in a larger randomised controlled trial (RCT).

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Abbreviations

CEPD	cerebral embolic protection device
DW	diffusion-weighted
IQR	interquartile range
ITT	intention-to-treat
MACCE	major adverse cardiac and cerebrovascular events
MRI	magnetic resonance imaging
NIHSS	National Institutes of Health Stroke Scale
PG	performance goal
PP	per protocol
TAVI	transcatheter aortic valve implantation

Introduction

Transcatheter aortic valve implantation (TAVI) is an established alternative to surgical aortic valve replacement for treatment of severe symptomatic aortic valve stenosis[1,2], with more than 276,000 procedures performed in the United States between 2011 and 2019[3]. Despite the broad adoption of TAVI[4], and the procedure now being performed in low-risk patients[5-8], stroke remains a major complication associated with significant mortality and morbidity[7,9]. The incidence of stroke at 30 days ranges from 3.3%[1] to 12%[10] and is associated with a 6-fold increase in mortality[11], reduced quality of life[12], and significant economic burden[2].

Stroke complicating TAVI primarily results from embolic debris released during TAVI, with embolic material consisting of cholesterol particles, air, atherosclerotic plaque material, thrombus, and calcified valve material[13-16]. Beyond acutely symptomatic stroke, upward of 94% of TAVI patients have evidence of embolic ischaemic brain injury on diffusion-weighted magnetic resonance images (DW-MRI), which has been associated with long-term cognitive dysfunction and motor deficits[1,17-21].

Cerebral embolic protection devices (CEPDs) have been developed to prevent new neuroembolic cerebral events and so-called silent infarctions[1,22]. In the United States, CEPDs are currently available in less than one-third of TAVI centres and used in only 13% of TAVI procedures[23]. The low penetration of CEPDs into clinical practice reflects the ongoing debate (and lack of evidence) regarding the effectiveness of CEPDs in reducing stroke. Recent randomised clinical trials evaluating CEPDs have demonstrated safety without convincing evidence of benefit in reducing stroke or total lesion volume on magnetic resonance imaging (MRI)[9,23], whereas propensity-adjusted real-world data have suggested neurological and mortality benefits[24]. Results of a definitive large-scale randomised trial evaluating a single CEPD are expected in late 2022[25].

The ProtEmbo Cerebral Protection System (Protembis GmbH) is a novel CEPD with a 60 µm pore size designed to protect all 3 cerebral vessels. It is the only left radial access device currently under development. The ProtEmbo was shown to be safe and feasible in the first-in-human PROTEMBO SF Trial (ClinicalTrials.gov: NCT03325283)[26]. The objective of the PROTEMBO C Trial (ClinicalTrials.gov: NCT04618718) was to evaluate the safety and performance of the ProtEmbo for embolic protection during TAVI.

Methods

TRIAL DESIGN AND OVERSIGHT

The PROTEMBO C Trial is an international, multicentre, single-arm, non-inferiority study designed to evaluate the safety and performance of the ProtEmbo System in patients with severe symptomatic native aortic valve stenosis undergoing TAVI **(Supplementary Appendix 1)**. The study was performed in compliance with the Declaration of Helsinki and was approved by the ethics committee of each contributing centre. Each patient provided informed consent. Data collection and monitoring were performed independently by a clinical research organisation (MAXIS Medical). An independent data and safety monitoring board of 2 interventional cardiologists, 1 cardiac surgeon, and 1 neurologist oversaw the safe conduct of the study and adjudicated all clinical events.

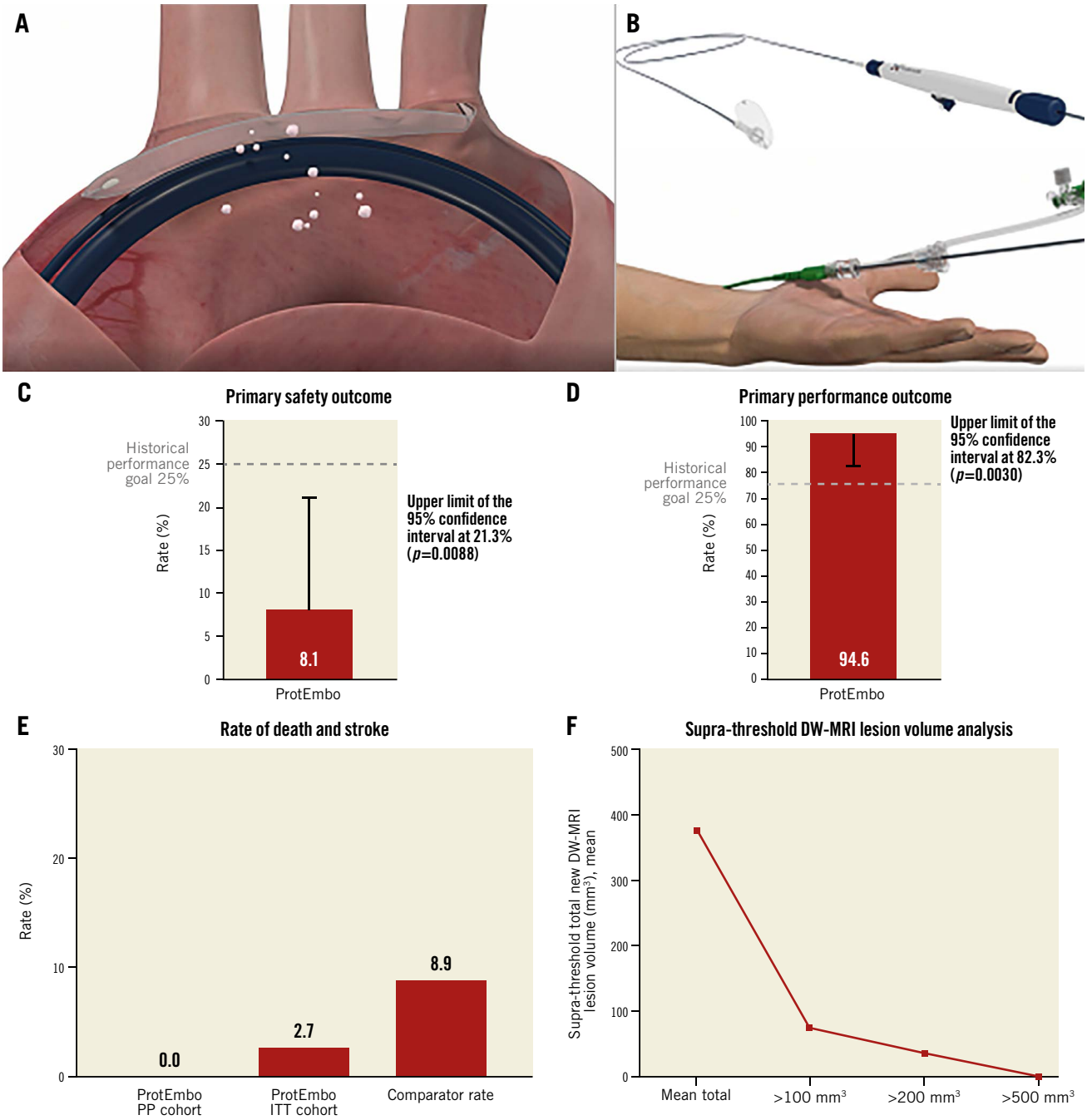
PATIENT POPULATION

Patients with severe symptomatic calcified native aortic valve stenosis who met approved indications for TAVI with commercially available transcatheter aortic valves by transfemoral access were eligible for the study. Patients were excluded if TAVI was planned using access other than transfemoral access or had any of the following: a previously implanted heart valve; evidence of acute myocardial infarction, transient ischaemic attacks, or cerebrovascular accidents within the prior 6 months; blood dyscrasias; contraindications to aspirin, heparin, antiplatelet/anticoagulant therapy, or device materials; renal or hepatic insufficiency; participation in other trials; or any other planned permanent cardiac implant within 30 days of the index procedure. Other exclusion criteria were neurological impairments, a contraindication to MRI, excessive vascular tortuosity or severe peripheral arterial disease, an abnormal aortic arch angulation or anatomy or an inner diameter of the aortic arch <25 mm. Patients meeting all eligibility criteria who signed informed consent and who received a baseline MRI were considered enrolled in the study **(Supplementary Appendix 1-Supplementary Appendix 11)**.

PROTEMBO DEVICE AND TRIAL PROCEDURES

The ProtEmbo device is a temporary, single-use, intra-aortic embolic deflection filter used as an adjunct device during TAVI that is the only available device that can be positioned through a 6 Fr left radial access sheath. The ProtEmbo is inserted at the beginning of the procedure, after administration of heparin with an adequate activated clotting time (ACT) level above 250 seconds, prior to the TAVI device, and removed following the completion of the TAVI procedure. The device consists of (1) a heparin-coated, 60 µm pore size mesh (currently the smallest pore size of CEPDs), (2) a self-expanding nitinol frame that measures 38×70 mm when expanded to ensure sufficient coverage with radiopaque markers for fluoroscopic visualisation and precise device placement, and (3) a delivery unit. The device is delivered unexpanded and deployed by unsheathing the self-expanding filter to cover the orifice of all 3 cerebral vessels (brachiocephalic trunk, left common carotid, and left subclavian arteries) **(Central illustration)**.

CENTRAL ILLUSTRATION ProtEmbo and summary of results.



A) The ProtEmbo deployed in the aortic arch showing the delivery over radial access and coverage of 3 main cerebral vessels with the TAVI catheter, deflecting embolic debris. B) Illustration of the functional parts of the ProtEmbo without handle. The ProtEmbo met (C) the primary safety outcome and (D) the primary performance outcome compared with historical performance goals. E) The secondary efficacy analysis (death or all stroke at 30 days) compared to 9.9% of the SENTINEL trial control arm (N=111)[30] and 7.0% in the REFLECT II trial control arm (N=57)[2]. F) The supra-threshold lesion volume analysis for the ProtEmbo. DW-MRI: diffusion-weighted magnetic resonance imaging; ITT: intention-to-treat; PP: per protocol; TAVI: transcatheter aortic valve implantation

A handle provides a simple user interface for preparation, delivery, deployment, and removal of the device. The device is loaded into a commercially available delivery catheter and placed into the aortic arch using a commercially available guiding sheath via the left radial or brachial artery. TAVI procedures were performed according to institutional standards. Clinical evaluations included assessments at baseline, post-procedure, before discharge, and at 30 days.

Brain DW-MRI scans were acquired at baseline (at least 5 days after any diagnostic cardiac catheterisation) and 2-7 days after TAVI. The timing and acquisition of 1.5 Tesla DW-MRI was standardised across all study centres based on a detailed acquisition protocol. All MRIs were analysed by an independent core laboratory (Buffalo Neuroimaging Analysis Center) using established methods for assessments of ischaemic lesions.

ENDPOINTS AND OUTCOME MEASURES

The primary safety endpoint was major adverse cardiac and cerebrovascular events (MACCE) at 30 days: defined as a composite of all-cause mortality, all stroke, life-threatening or disabling bleeding, major vascular complications in the access vessels or aorta, or acute kidney injury (stage 2 or 3), all according to the Valve Academic Research Consortium-2 (VARC-2) criteria[27]. Secondary safety endpoints included stroke severity, quantified acutely using the National Institutes of Health Stroke Scale (NIHSS) score (NeuroARC)[28], and the occurrence of other serious adverse events reported up to 30 days.

The primary performance endpoint was the rate of technical success: defined as the ability to safely deliver, deploy, and remove the device; the ability to secure and stabilise the position of the device throughout the procedure; and to deflect embolic material, defined by coverage of the 3 cerebral vessels without impeding blood flow. Adequate stability and coverage of the 3 cerebral vessels in the aortic arch was assessed by means of angiographic review by the investigator at each site. Mild-to-moderate interactions (no device displacement) were deemed acceptable, while severe interaction (displacement of the device to the ascending or descending aorta) was considered technical failure.

Secondary efficacy endpoints included a composite of death or VARC-2-defined strokes at 72 hours and 30 days compared to historical data and the median total new lesion volume assessed by brain DW-MRI at 2 to 7 days compared to historical data. The total new lesion volume was defined as the sum of all diffusion-positive new cerebral lesions in the post-procedural DW-MRI relative to the pre-TAVI DW-MRI.

Histological analysis of the ProtEmbo device was conducted by an independent core laboratory (CVPath Institute) to assess the haemocompatibility of the ProtEmbo device surface and to characterise debris captured by the device.

STATISTICAL ANALYSIS

The study prespecified 3 populations for analysis. The safety cohort comprised patients with signed informed consent and completed baseline DW-MRI assessment. The intention-to-treat (ITT) cohort included patients in the safety cohort who met the eligibility criteria with an attempt to use the ProtEmbo (device passed through the skin). The per protocol (PP) cohort included patients in the ITT cohort who received treatment with the ProtEmbo device in accordance with the protocol and completed both MRIs (baseline and follow-up at 2-7 days). The primary safety and performance endpoints were assessed in the ITT cohort and the secondary efficacy endpoints were assessed in the PP cohort.

The primary safety endpoint of 30-day MACCE with the ProtEmbo was compared with a performance goal (PG) of 25% derived from historic data. A sample size of 60 patients would provide 85% power to reject the null hypothesis (the upper limit of the 95% confidence interval [CI] of 30-day MACCE with the ProtEmbo using the Wilson Method was less than the PG) assuming a 30-day MACCE with the ProtEmbo of 10% and a 1-sided alpha=0.025[29].

The primary performance endpoint for the ProtEmbo was compared to an historic PG of 75%. A sample size of 42 patients would provide 85% power to reject the null hypothesis (the lower limit of the 95% CI with the ProtEmbo using the Wilson method was greater than the PG) assuming a success rate for the ProtEmbo of 89% and a 1-sided alpha=0.025[29]. Study success requires both primary endpoints to be met.

The secondary efficacy MRI endpoints are summarised using descriptive statistics[28], using median values when not normally distributed[30]. A multi-threshold, lesion-wise analysis for each patient investigated the supra-threshold new lesion volumes above incremental thresholds from >100 to >1000 mm^3, where lesions below the respective thresholds were excluded from the mean and compared with historical data.

The study was terminated early (with enrolment of 41/60 planned patients) after meeting the primary safety and performance endpoints. Bootstrapping using Stata (StataCorp) was conducted and reviewed by the independent data and safety monitoring board to ensure that the conclusions of the trial were fully justified for both primary endpoints. The bootstrapping analysis for each primary endpoint was performed on 5,000 simulated 60-patient samples and was used to generate the lower 95% CI of the performance endpoint and the upper 95% CI of the safety endpoint, since these are the key determinants of the non-inferiority test.

Results

PATIENT AND PROCEDURAL CHARACTERISTICS

A total of 56 patients were screened for the procedure, and 41 patients were enrolled in the study (safety cohort); 37 patients underwent TAVI using the ProtEmbo device (ITT cohort), of which 31 were treated according to protocol and underwent DW-MRI (PP cohort). Patients were 46% male with a mean Society of Thoracic Surgeons (STS) score of 2.81±1.36%, and 22% were treated with self-expanding valves **(Table 1, Table 2)**.

TAVI was successful in all 37 patients in the ITT cohort using either the Medtronic Evolut R or PRO, Edwards SAPIEN 3, or Meril Myval; 1 patient required 2 TAVIs due to a residual large paravalvular leak. The use of the ProtEmbo was attempted in 37 patients and was successful in 94.6% (35/37). The average time for device deployment was 4.5±4.9 minutes, the average device dwell time in the blood stream was 30.2±13.4 minutes (range 16 to 79 minutes), the amount of mean additional contrast used was 5.9±16.7 mL (the majority of patients [27/37] received no

Table 1. Baseline demographics, clinical presentation, and procedure details.

	Safety cohort (N=41)
Age, years	79±5.7
Male sex, %	46.3 (19)
Body mass index, kg/m^2	28.3±3.9
STS score for mortality, %	2.81±1.36
EuroSCORE II, %	2.79±1.65
Heart failure, %	61.0 (25)
NYHA II, %	22.0 (9)
NYHA III, %	39.0 (16)
Myocardial infarction, %	12.2 (6)
Atrial fibrillation, %	24.4 (10)
Diabetes, %	26.8 (11)
Pulmonary hypertension, %	12.2 (6)
Chronic obstructive pulmonary disease, %	9.8 (4)
Renal insufficiency, %	19.5 (8)
Peripheral vascular disease, %	2.4 (1)
Aortic valve function	
Mean aortic valve gradient, mmHg	42.2±10.7*
Maximum aortic valve gradient, mmHg	68.0±18.1¶
Left ventricular ejection fraction, %	60.2±8.8
Admission medications	
Anticoagulant, %	36.6 (15)
Antiplatelet agent, %	65.9 (27)

Values are mean±standard deviation or % (numbers). *Data missing for 1 patient; ¶data missing for 2 patients. EuroSCORE: European System for Cardiac Operative Risk Evaluation; NYHA: New York Heart Association; STS: Society of Thoracic Surgeons

additional contrast for the use of the ProtEmbo), and the additional fluoroscopy time was 4.3±4.5 minutes **(Table 2)**.

SAFETY OUTCOME

MACCE at 30 days in the ITT cohort was 8.1% (3/37), meeting the predefined PG for the safety endpoint (upper limit 95% CI: 21.3% vs PG 25%; p=0.009) **(Central illustration)**. There were no deaths and no device-related adverse events in this trial. **Table 3** summarises MACCE events, which included a cardiac tamponade unrelated to the ProtEmbo, a thalamic cerebral infarct that developed 12 hours after the TAVI procedure in which the ProtEmbo was retrieved prematurely due to interaction between the TAVI catheter and the ProtEmbo, and an acute kidney injury (stage 3) requiring dialysis in a patient with chronic renal insufficiency prior to TAVI. There was no significant worsening of NIHSS in any of the patients with complete follow-up. Vascular access site-related complications in the radial or brachial artery occurred in 5 of the 37 patients enrolled in the ITT cohort, of which 2 were asymptomatic and 8.1% (3 of the 37 patients) were symptomatic (for 2 events, conservative management was sufficient, and for 1 event, the bleeding was stopped by applying a peripheral balloon).

PERFORMANCE OUTCOME

Technical success was achieved in 94.6% (35 of 37) patients in the ITT cohort, which met the prespecified endpoint compared with the PG (lower 95% CI: 82.3% vs PG 75%; p=0.003) **(Central illustration)**. Complete cerebral vessel coverage was adequate in 94.6% of treated patients, and the ProtEmbo was stable for the duration of the TAVI procedure. Interference with the TAVI procedure by the ProtEmbo device was considered minimal **(Table 2)**.

Histopathological analysis indicated that the majority of the heparin-coated mesh surface remained free of debris, and the filter pores were completely open (thrombus formation score=0). Scanning electron microscope image analysis did not reveal any damage of the heparin coating on the mesh surface, and there was no evidence of device-related thrombogenicity or any significant embolic deposition or accumulation on the device surface. The median area of the ProtEmbo device surface containing debris was 0.121 mm^2, which comprises <0.006% of the filter area (total surface area equals 2,184 mm^2).

EFFICACY OUTCOME

In the PP cohort there were no deaths or strokes **(Central illustration)**. The median total new lesion volume among patients receiving treatment with the ProtEmbo device was 210 mm^3 [137, 456] **(Table 4)**. The largest single lesion volmues in each patient were all <500 mm^3; the largest single lesion volume detected in any of the patients was 402 mm^3; 87% of patients were free of single lesions >150 mm^3; and 97% were free of single lesions >350 mm^3. Supra-threshold lesion volume analysis at lesion volume thresholds of >100 mm^3, >200 mm^3, and >500 mm^3 compared favourably with historical data from the control arm of a previous randomised controlled trial of a CEPD[2].

Discussion

The PROTEMBO C Trial demonstrated that the ProtEmbo System performed as intended, meeting both primary safety and performance endpoints, and can be used safely as an adjunct to TAVI with minimal interaction. The primary safety rate was low in comparison to precedent CEPD studies and in the context of early feasibility studies, with no serious adverse events being adjudicated related to the use of the ProtEmbo. The histopathological evaluation further supported the safety and haemocompatibility of the ProtEmbo for use during TAVI.

The ProtEmbo device was easy to use with a minimal learning curve across 10 different operators performing the investigational device procedure and achieving a high technical success rate of 94.6% in this study, suggesting that the device can easily be adapted into the normal workflow of TAVI procedures. The additional contrast media and fluoroscopy time needed for the use of the ProtEmbo device was negligible. The time to place the device and its stability once in place was without reported undue interference with the TAVI procedure except in 1 patient, in whom the investigational device was shifted during TAVI; however, this did not prolong the TAVI procedure. In addition, the use of the

Table 2. Procedure and device performance.

		ITT cohort (N=37)
TAVI procedure details		
Successful valve deployment		100 (37)
General anaesthesia		49 (18)
Valve-in-valve procedures		1
Number of different THV technologies		3
Number of different operators		10
Self-expanding THV*		22 (8)
Balloon-expandable THV†		78 (29)
Balloon predilatation		51 (19)
Balloon post-dilatation		19 (7)
TAVI procedure time, min		59.3±32.3‡
ProtEmbo procedure characteristics		
Time to place device, min		4.5±4.9§
Vascular access used	Distal radial	13.5 (5)
	Proximal radial	78.4 (29)
	Brachial	8.1 (3)
Dwell time of the device, min		30.2±13.4 (16, 79)§
Additional contrast use for use of ProtEmbo, mL		5.9±16.7
As percentage of total contrast use for TAVI		3.6%
Additional fluoro time for use of ProtEmbo, min		4.3±4.5
As percentage of total fluoro time for TAVI		19.4%
ProtEmbo technical performance		
Technical success (composite)		94.6 (35)
Delivery to target position		100 (37)
Deployment in aortic arch		97.3 (36)$
Stability and coverage of cerebral vessels		94.6 (35)¶
Removal from aortic arch		100 (37)

		ITT cohort (N=37)
ProtEmbo technical performance		
Coverage of side branch vessels	Excellent	86.1 (31/36)
	Good	11.1 (4/36)
	Poor	2.8 (1/36)
Interaction with pigtail	None	88.8 (32/36)
	Mild	8.3 (3/36)
	Moderate	2.8 (1/36)
	Severe	0
	Not applicable	–
Interaction with balloon catheter	None	69.4 (25/36)
	Mild	5.5 (2/36)
	Moderate	0
	Severe	0
	Not applicable	25.0 (9/36)
Interaction with TAVI	None	75.0 (27/36)
	Mild	13.9 (5/36)
	Moderate	8.3 (3/36)
	Severe	2.8 (1/36)
	Not applicable	–
Evidence of impeded blood flow to brain		0
Devices retrieved intact		100 (37)

Values are mean±standard deviation, mean±standard deviation (minimum, maximum), n, or % (n/N). *Medtronic Evolut valve prosthesis; †Edwards SAPIEN 3 and Meril Myval valve prostheses; ‡procedure time was calculated based on 36 patients, as the device could not be placed successfully in 1 patient; §times were collected for 35 patients; $one device not deployed in the aorta – therefore, coverage and interaction is given for 36 patients; ¶stability success was defined as none to moderate interaction (severe would have been a fail), coverage success was defined as excellent or good coverage (poor would have been a fail). ITT: intention-to-treat; TAVI: transcatheter aortic valve implantation; THV: transcatheter heart valve

left radial artery for vascular access seems favourable in comparison with transfemoral CEPDs because interaction between the ProtEmbo and the TAVI procedure was minimal using 3 different transcatheter heart valve (THV) technologies. Adequate coverage of all 3 cerebral vessels was achieved in 94.6 % of patients treated with the ProtEmbo, which may have led to the low new lesion burden observed in patients in this study.

Table 3. Safety outcomes at 30 days.

	ITT cohort (N=37)
Any major adverse cardiovascular or cerebrovascular events	8.1% (3)
All-cause mortality	0% (0)
Stroke	2.7% (1)
Acute kidney injury (stage 2 or 3)	2.7% (1)
Life-threatening or disabling bleeding	2.7% (1)
Major vascular complication	0% (0)

Values are % (n). ITT: intention-to-treat

The efficacy results compare favourably with results from patients in the control groups of randomised controlled trials such as the REFLECT II trial of the TriGuard device[2] (Keystone

Table 4. Secondary efficacy analysis: diffusion-weighted magnetic resonance imaging results.

	PP cohort (N=31)
Time following transcatheter aortic valve replacement, days	4.9±1.4
Total new DW-MRI lesion volume, mm^3	210 [137, 456]
Total new DW-MRI lesion volume, mm^3	376±363
Average new DW-MRI lesion volume, mm^3	34 [24, 45]
Single new DW-MRI lesion volume, mm^3	24 [15, 42]
Number of new lesions	8 [3, 16]
Freedom from brain lesions >150 mm^3	87% (27)
Freedom from brain lesions >350 mm^3	97% (30)

Values are mean±standard deviation, % (n), or median [first quartile, third quartile]. DW-MRI: diffusion-weighted magnetic resonance imaging; PP: per protocol

Heart) and the SENTINEL trial[30]. Although trial-to-trial comparisons should be interpreted with caution, in the REFLECT II trial, patients who did not receive embolic protection had a mean total new lesion volume of 508 mm^3 compared with 376 mm^3 in patients treated with the ProtEmbo. Furthermore, in our series with the ProtEmbo, no patient had a DW-MRI lesion >500 mm^3 (maximum lesion size was 402 mm^3), which compares favourably to the unprotected control patients in REFLECT II and SENTINEL. In the SENTINEL trial, the median total new lesion volume in all territories was 310 mm^3 (interquartile range [IQR] 106-860). The median total new DW-MRI lesion volume in patients treated with the ProtEmbo was 210 mm^3 (IQR 137-456). The favourable performance of the ProtEmbo compared to other CEPDs evaluated in other clinical trials should be interpreted with caution; however, these comparisons are encouraging and provide a useful starting point for the design and analysis of future clinical studies.

Limitations

The PROTEMBO C Trial was a non-randomised, single-arm study, and the results of a relatively small study cannot be directly compared to a randomised control group but do provide initial evidence for the safety and performance of the ProtEmbo device. The comparison with historical data may be affected by bias related to baseline and procedural characteristics of patients in different centres and at different times.

Conclusions

The PROTEMBO C Trial demonstrated that use of the ProtEmbo device during TAVI is safe and that it performs as intended compared to historical PG. The volume of new MRI lesions in patients treated with the ProtEmbo was low compared with historical series. A future randomised controlled trial is planned to evaluate the safety and efficacy of cerebral embolic protection when the ProtEmbo device is used during TAVI.

Impact on daily practice

Despite advancements in TAVI devices and implantation techniques, embolic stroke remains the most frequent ischaemic complication after TAVI. It is associated with significant morbidity and mortality. The ProtEmbo is a novel deflection filter device and the only CEPD that can be used through the left arm arteries. A larger randomised controlled trial is merited to further evaluate the safety and efficacy of the ProtEmbo device when used for cerebral protection during TAVI.

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Conflict of interest statement

D. Jagielak declares proctoring and lecture fees from Meril Life Sciences. M. Abdel-Wahab's hospital receives consultancy fees and/or speaker honoraria on his behalf from Medtronic and Boston Scientific. N. Werner has received proctoring and lecture fees from Edwards Lifesciences and Medtronic. A. R. Witkowski has received proctoring and lecture fees from Edwards Lifesciences and Medtronic. M. Adam has received personal fees from Edwards Lifesciences and Boston Scientific; grants and personal fees from Medtronic; and proctoring fees from Medtronic. F. Gatto reports proctoring fees from Boston Scientific and Medtronic. T. Schmidt has received travel expenses from Protembis. The other authors have no conflicts of interest to declare.

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Supplementary data

Supplementary Appendix 1. Clinical investigation protocol.
Supplementary Appendix 2. Derivation of performance goals.
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The supplementary data are published online at: https://eurointervention.pcronline.com/doi/10.4244/EIJ-D-22-00238

Supplementary data

1.1 Supplementary Appendix 1. Clinical investigation protocol.

The sponsor planned to conduct a clinical trial of the ProtEmbo Cerebral Protection System used as an adjunctive device for embolic protection during Transcatheter Aortic Valve Replacement (TAVR). The study plan was developed according to the guidance given by Medical Device Regulation (EU) 2017/745, Annex XV. The rationale for the trial design, endpoints and variables selected for study are described below.

1.1.1 Study Design

The appropriate safety endpoint for embolic protection devices used during TAVR is defined as Major Adverse Cardiac and Cerebrovascular Events (MACCE) at 30 days defined by VARC-2 including all-cause mortality, all stroke, life-threatening or disabling bleeding, major vascular complications in the access vessels or aorta and acute kidney injury (stage 2 or 3). Previous studies have used a similar definition of safety and, therefore, results of these previous studies provided useful historical comparison data to evaluate the safety of the ProtEmbo System. Similarly, performance was defined as the ability to deliver, deploy, and remove the device successfully, the ability to secure positioning and stability of the position throughout the procedure, and the ability to deflect embolic material, as assessed by adequate coverage, while not impeding blood flow. Results from previous studies of embolic protection devices used during TAVR provided useful historical comparison data against which the performance of the ProtEmbo System can be compared.

1.1.2 Primary Study Endpoints

1.1.2.1 Safety

Major Adverse Cardiac and Cerebrovascular Events (MACCE) at 30 days defined as all-cause mortality, all stroke, life-threatening or disabling bleeding, major vascular complications in the access vessels or aorta and acute kidney injury (stage 2 or 3), all defined by VARC-2.

1.1.2.2 Performance

Technical success, defined as the ability to safely deliver, deploy, and remove a device, the ability to secure positioning and stability of the position throughout the procedure and ability to deflect embolic material, as assessed by adequate coverage of the three vessels in the arch of the aorta supplying blood flow to the brain, while not impeding blood flow.

1.1.3 Secondary Study Endpoints

1.1.3.1 Efficacy

The secondary efficacy endpoints for this clinical investigation were based on magnetic resonance (MR) imaging and a composite of death or strokes, each compared to historical data:

For the MR imaging endpoint, the median new lesion volume in the brain assessed by diffusion weighted magnetic resonance images (DW-MRI) at 2 to 7 days was compared to historical data; The total new lesion volume was defined as the sum of all diffusion-positive new cerebral lesions in post-procedural DW-MRI relative to the pre-TAVR DW-MRI.

For the composite death or stroke endpoint, the rate of death or all strokes according to VARC-2 criteria (to define occurrence and type stroke) within 3 days (72 hours) of the TAVR procedure was compared to historical data.

1.1.4 Number of Patients and Sites

Up to 60 patients were planned to be enrolled at up to 10 clinical study centers.

1.1.5 Study Population

The study population comprised of patients with severe symptomatic calcified native aortic valve stenosis who met the approved indications for TAVR with commercially available transcatheter aortic valves by transfemoral route.

1.1.6 Enrollment Criteria

A potential patient must meet all of the inclusion criteria and none of the exclusion criteria as outlined below in order to be considered eligible to participate in this study.

1.1.6.1 Inclusion Criteria

Patients eligible to participate met all of the following at screening and / or baseline visits:

1. The heart team recommends transcatheter valve aortic valve replacement consistent with the 2017 ESC/EACTS Guidelines for the management of valvular heart.
2. Compatible left subclavian artery (≥ 4 mm diameter) without significant stenosis (> 70%) and distance between the origin of left subclavian artery and valve plain of ≥ 90 mm as determined by Multi-Slice Computed Tomography (MSCT) scan or equivalent imaging modality.
3. The patient and the treating physician agree that the patient will undergo the scheduled pre-procedural testing and return for all required post-procedure follow-up visits.
4. The patient is able to provide informed consent, has been informed of the nature of the trial, agrees to its provisions and has provided written informed consent as approved by the relevant regulatory authority of the respective clinical site.
5. Patient is a minimum of 18 years of age.

1.1.6.2 Exclusion Criteria

Potential patients with one or more of the following were excluded from the study even if they met the inclusion criteria:

1.1.6.3 General Exclusion Criteria

1. Left upper limb vasculature in the left extremity precluding 6 Fr sheath radial / brachial / subclavian access.
2. Inadequate circulation to the left extremity as evidenced by signs of artery occlusion (modified Allen's test) or absence of radial / brachial pulse.
3. Hemodialysis shunt, graft, or arterio-venous fistula involving the upper extremity vasculature.
4. TAVR conducted via other than transfemoral access (subclavian, axillar, transapical, transaortic, carotid or transcaval).
5. Evidence of an acute myocardial infarction ≤ 1 month before the intended treatment.
6. Aortic valve is a congenital unicuspid or bicuspid valve.
7. Mixed aortic valve disease (aortic stenosis and aortic regurgitation with predominant aortic regurgitation >3+).
8. Any therapeutic invasive cardiac procedure resulting in a permanent implant that is performed within 30 days of the index procedure (unless part of planned strategy for treatment of concomitant coronary artery disease).
9. Blood dyscrasias as defined: Leukopenia, acute anemia, thrombocytopenia, history of bleeding diathesis or coagulopathy.
10. Hemodynamic instability requiring inotropic support or mechanical heart assistance.
11. Need for emergency surgery for any reason.
12. Severe hypertrophic cardiomyopathy with or without obstruction.
13. Severe ventricular dysfunction with LVEF ≤ 30%.
14. Echocardiographic evidence of intracardiac or aortic mass, thrombus, or vegetation.

15. Symptomatic or asymptomatic severe (≥ 70%) occlusive carotid disease requiring concomitant CEA / stenting.
16. Patient has undergone carotid stenting or carotid endarterectomy within the previous 6 weeks.
17. Active peptic ulcer or upper GI bleeding within the prior 6 months.
18. A known hypersensitivity or contraindication to aspirin, heparin, ticlopidine, or clopidogrel, device component material, or sensitivity to contrast media, which cannot be adequately pre-medicated.
19. Recent (within 6 months) CVA or a TIA.
20. Renal insufficiency (creatinine > 3.0 mg / dL or GFR < 30) and / or renal replacement therapy at the time of screening.
21. Life expectancy < 12 months due to non-cardiac co-morbid conditions.
22. Patients in whom anti-platelet and / or anticoagulant therapy is contraindicated, or who will refuse transfusion.
23. Patients who have active bacterial endocarditis or other active infections.
24. Currently participating in an investigational drug or another device study.
25. Patients who have a planned treatment with any other investigational device or procedure during the study follow-up period (30 days).
26. Patients with planned concomitant surgical or transcatheter ablation for Atrial Fibrillation during the study follow-up period (30 days).
27. Any patient with a balloon valvuloplasty (BAV) within 30 days of the procedure.
28. Patient is a woman of child-bearing potential.
29. Patient with Heparin-Induced Thrombocytopenia Syndrome.
30. Inner diameter of aortic arch is less than 25mm.
31. Brachiocephalic trunk originating from the aortic arch that splits into the bilateral subclavian arteries and a bicarotid trunk (Origin D).
32. Hepatic failure (defined as liver enzyme elevations two times the upper limit of normal) or active infectious hepatitis.
33. Cardiogenic shock or severe hypotension (systolic blood pressure < 90 mm Hg) at the time of the index procedure.
34. Patients who have a planned concomitant cardiac surgical or interventional procedure (e.g., coronary revascularization) during the TAVI procedure.
35. Patients who have a pre-existing prosthetic heart valve in any position.

1.1.6.4 Neurological Exclusion Criteria

1. Patient had active major psychiatric disease.
2. Patient has severe visual, auditory, or learning impairment and is unable to comprehend English or local language and therefore unable to be consented for the study.
3. Patients with neurodegenerative or other progressive neurological disease or history of significant head trauma followed by persistent neurologic defaults or known structural brain abnormalities.

1.1.6.5 Angiographic Exclusion Criteria

1. Excessive tortuosity or severe peripheral arterial disease in the left radial / brachial / subclavian artery preventing ProtEmbo System access and insertion.
2. Patient whose left radial / brachial / subclavian artery reveals significant stenosis, calcification, ectasia, dissection, occlusion or aneurysm, in particular at or within 3 cm of the aortic ostium.
3. Patient with significant stenosis, ectasia, dissection, or aneurysm in the ascending aorta or in the aortic arch, or with abnormal aortic arch angulation or abnormal anatomical conditions of the aorta.

1.1.6.6 Magnetic Resonance Imaging Exclusion Criteria

1. Patient Body Mass Index (BMI) precluding imaging in scanner.
2. Contraindications to MRI (patients with any implantable temporary or permanent pacemaker or defibrillator, metal implants in field of view, metallic fragments, clips, or devices in the brain or eye before TAVR procedure).
3. Patients who have a high risk of complete AV block after TAVR, with the need of permanent pacemaker (e.g. patients with pre-existing bifascicular block or complete right bundle branch block plus any degree of AV block).
4. Planned implantation of a pacemaker or defibrillator implantation within the first 4 days after TAVR.
5. Claustrophobia precluding MRI scanning.
6. No scanner hardware, software, coil or protocol changes should occur during the course of the study.

1.1.7 Study Procedures

1.1.7.1 Eligibility Assessments

Baseline evaluation was performed after the patient has provided written informed consent in order to ensure that the patient was an appropriate candidate for this study and to obtain baseline values for study endpoint evaluation.

If the patient continued to meet the study's enrollment criteria and continued to be willing and able to participate in the study protocol, the patient was enrolled.

All patients underwent a series of baseline evaluations (if not already available as part of the existing medical records). Baseline visit and data collection could occur anytime within 14 days before the TAVR procedure (unless otherwise indicated).

1.1.7.2 CT/ Angiographic Eligibility

Computed tomographic images of the aorta were reviewed by the angiographic core lab and the aortic angiogram was reviewed to confirm that the patient was eligible for participation in the PROTEMBO C Trial.

1.1.7.3 Sheath Access Eligibility

Computed tomographic images of the aorta were reviewed by the angiographic core lab and an angiogram of the left radial artery was reviewed to confirm that the patient could have a commercially available vascular sheath inserted into the left radial artery and was, therefore, eligible for participation in the PROTEMBO C Trial.

1.1.8 Procedural Treatment and Timing

1.1.8.1 Medication Regimen

Administration of anticoagulation medication and monitoring of activated clotting time (ACT) per institution guidelines was performed throughout the procedure. Anticoagulant therapy was administered pre-, peri- and post-procedure to maintain an Activated Clotting Time of at least 250 seconds for the duration of the procedure.

For those patients who were not under chronic oral anticoagulation prior TAVR, the use of dual antiplatelet therapy (DAPT) before and after the procedure was recommended. Those patients with chronic DAPT continued with acetylsalicylic acid and clopidogrel therapy for at least 1 month after TAVR, as per the standard practice of the institution.

For those patients who were not taking chronic DAPT, it was recommended to administer 300 mg of each acetylsalicylic acid and clopidogrel within 24 hours (and at least 2 hours) before the procedure or the equivalent as per the standard of care at the institution.

1.1.8.2 MRI Timing

Standardization of the timing of scans across study sites was required to maintain integrity of the MRI analysis. The primary evaluation of the MRI scan was performed by the MRI core lab (independent expert).

MRI was performed at baseline and at 2-7 days following TAVR procedure. To avoid imaging any new lesions on the baseline MRI caused by the diagnostic catheterization, the baseline MRI exam took place within two weeks before the TAVR procedure and no sooner than 5 days after any diagnostic catheterization, and there was no diagnostic catheterization in between baseline MRI and TAVR procedure allowed.

1.1.9 TAVR and ProtEmbo Procedure

Study patients were asked to undergo evaluation prior to and during the course of the clinical study. Such tests and procedures are outlined in the Schedule of Events (see Supplemental Appendix Table 1: Schedule of Events) and are consistent with standard of care for TAVR patients.

The ProtEmbo was used strictly as described in the Instructions for Use (IFU), including the preparation, insertion, dwell time and removal of the device. The ProtEmbo was inserted prior to the insertion of the TAVR device and left in place until after the deployment and removal of the TAVR device.

1.1.9.1 Schedule of Events

Supplemental Appendix Table 1: Schedule of Events

	Screening Period		**Treatment Period**	**Post-procedure Period**			
Visit Number	**1**	**2**	**3**	**4**	**5**	**6**	**7**
Study Procedure	**Base-line**	**Base-line MRI**	**TAVR Procedure**	**< 24 Hour Follow-up**	**2-7 Days**	**Dis-charge**	**30 Day (± 7 Days)**
Informed consent	✓						
Inclusion and exclusion criteria	✓						
Medical history/ baseline characteristics	✓						
Medication profile	✓		✓	✓	✓	✓	✓
Physical exam	✓			✓	✓	✓	✓
STS score	✓						
Blood work (Chemistry Panel)	✓					✓	✓
ECG	✓			✓			
Diagnostic Transthoracic Echo-cardiogram within 3 months of TAVR*	✓						
Modified Allen's Test	✓						
NIHSS†	✓				✓		✓
Adverse Event (AE) review			✓	✓	✓	✓	✓

Angiogram			✓		
Multi-Slice or Multi Detector CT‡	✓				
MRI§		✓		✓	
ProtEmbo insertion, dwell and removal times			✓		
ProtEmbo contrast use			✓		
Filter specimen preparation & shipping for histopathology			✓		
Study Exit					✓
Informed consent	✓				

* Conducted as part of the TAVR work up as per institution standard of care and not a dedicated study procedure; †NHISS to be conducted by a neurologist; ‡Conducted as part of the TAVR work up and not a dedicated study procedure**;** §Conducted on a MRI core laboratory certified scanner.
STS = Society of Thoracic Surgeons; ECG = Electrocardiogram; TAVR = Transcatheter aortic valve replacement; NIHSS = National Institutes of Health Stroke Scale; MRI = Magnetic resonance imaging.

1.1.9.2 Study Exit or Premature Withdrawal

Patients were exited from the study by completion of a Study Exit eCRF at the time of study completion provided the patient had not experienced an adverse event that was ongoing and unexplained.

Patients could be prematurely terminated or withdrawn from the study for, including but not limited to, the following reasons:

- Patient death.
- Voluntary withdrawal – meaning that the patient voluntarily chooses not to further participate in the study.
- Preplacement of a 6 Fr. equivalent guiding sheath for radial / brachial / subclavian artery access is attempted but is not possible to complete.
- Lost to follow-up – meaning that the patient is more than 14 days late to a study visit and 3 documented attempts to contact the patient are unsuccessful. A patient who misses a study visit but attends a subsequent visit will no longer be considered lost to follow-up. A missed visit will be considered a protocol deviation and the deviation will be documented and reported.
- In the physician's opinion, it is not in the best interest of the patient to continue study participation.

All patients enrolled (including those withdrawn or lost to follow-up) were accounted for and documented.

1.2 Supplementary Appendix 2. Derivation of performance goals.

1.2.1 Primary Safety Endpoint

The PG for the primary endpoint was established based upon data available in the literature for patients undergoing embolic protection for TAVR using the Sentinel and the TriGuard embolic protection devices.

In the randomized controlled SENTINEL trial (Sentinel device) of 363 patients, the rate of MACCE (defined as death from any cause, any type of stroke, or stage-3 acute kidney injury [AKI]) in the cerebral protection group (7% [17/234]) was not statistically significantly different from that of the control group (10% [11/111]) at 30 days (p=0.40).

In the randomized controlled DEFLECT III trial (TriGuard device) of 85 patients, the rate of in-hospital MACCE (defined as all-cause mortality, all stroke, life-threatening or disabling bleeding, stage-2 or stage-3 AKI, or major vascular complications) was similar in both groups (control TAVR group without TriGuard device versus TAVR plus TriGuard device): 22% compared with 31% (RR 0.71, 95% CI 0.34 to 1.46; p=0.34). The rates of 30-day MACCE were also similar: 26% compared with 31% (RR 0.83, 95% CI 0.37 to 1.84; p=0.62).

The MACCE rate of individuals undergoing TAVR without embolic protection is the appropriate MACCE rate to set the PG for the ProtEmbo System. Based on the number of patients treated in the control groups of both trials, we estimate a weighted MACCE rate of 15% (23/150), 95% CI: 10%, 22%.

To establish the PG for ProtEmbo System, a statistical margin of 10% is added to 15% to obtain a PG of 25% for the primary safety endpoint.

1.2.2 Primary Performance Endpoint

The Performance Goal for the primary performance endpoint was established based upon data available in the literature for patients undergoing embolic protection for TAVR using the TriGuard embolic protection device.

In the randomized controlled DEFLECT III trial of 85 patients, 45 TriGuard devices were used in 44 patients; 2 randomized patients withdrew consent before device introduction, and 1 patient received 2 TriGuard devices over the course of a valve-in-valve procedure. The device was successfully positioned and maintained in position throughout prosthetic-valve deployment, implantation, and retrieval in 89% (40/45, 95% CI [75% to 96%]) of patients. There were no device failures.

The performance success rate of the test arm is the appropriate rate to set the PG for the ProtEmbo System. The comparator rate is therefore set at 90%.

To establish the PG for the ProtEmbo System, a statistical margin of 15% is subtracted from 90% to obtain a PG of 75% for the primary performance endpoint, which is the lower limit of the 95% confidence interval for the DEFLECT III trial.

1.3 **Supplementary Appendix 3. Histological analysis of devices.**

All the devices used in patients were fixed in 10% neutral buffered formalin after the TAVR was completed and shipped in individually labeled plastic containers to the independent histopathology core laboratory. The debris was collected by a Falcon 40-µm Nylon Cell Strainer and photographed before any physical alteration, then the strainer was carefully folded and placed in a biopsy bag. Samples were dehydrated in a graded series of ethanol and xylene and embedded in paraffin by an automated tissue processor. The paraffin blocks were serially sectioned into a total of 12 consecutive sections, with 2 to 3 sections per slide. The slides were stained by hematoxylin and eosin (H&E) and by Movat pentachrome (MP) stains. Some remaining slides were left unstained for future needs, which was determined by the type of material present in the slides examined and the need for identification of the constituent elements of the debris.

The core laboratory randomly selected devices for scanning electron microscope analysis. Specimens were rinsed in 0.1 mmol/L sodium phosphate buffer (pH 7.2 ± 0.1) and then post-fixed in 1% osmium tetroxide for up to 30 minutes. The specimens were then dehydrated in a

graded series of ethanol, critical point dried, and mounted for viewing. After sputter coating with gold, the samples were visualized using scanning electron microscopes. Images were acquired at incremental magnifications of x10 (or x15), x50, x200, and x600. The approximate locations of the higher power images were based on matching [x50, magnification] pictures numerically referenced on the low power [x10 or x15, magnification] montage such that representative regions from the proximal, middle, and distal ends of the device were captured. Thrombus formation was defined as knobby and nodular structures consisting of platelets, fibrin, leukocytes, and red blood cells.

Moreover, a device thrombus formation score was assessed by scanning electron microscope using a semi-quantification scoring system (see Supplemental Appendix Table 2: Semi-quantification of device thrombus formation score as assessed by SEM).

Supplemental Appendix Table 2: Semi-quantification of device thrombus formation score as assessed by SEM

Score	Device Thrombus Formation Score assessed by SEM
0	No to little adherent material covering the device surface
1	Minimal adherent material covering ≤ 10% of the device surface
2	Mild adherent material covering > 10% and ≤ 25% of the device surface
3	Moderate adherent material covering > 25% and ≤ 50% of the device surface
4	Extensive adherent material covering > 50% and ≤ 75% of the device surface
5	Severe adherent material covering > 75% of the device surface

SEM = Scanning electron microscope.

1.4 **Supplementary Appendix 4. MRI and stroke analysis methodology.**

The severity of pre-existing central nervous system lesions on baseline T2-weighted MRI (FLAIR) is an independent predictor of the number of lesions on DW-MRI obtained 3 days after TAVR (31); patients with a large number of vascular / embolic lesions at baseline tend to have a large number of new lesions after TAVR. FLAIR-MRI can be used to account for baseline lesions and has been proposed as a mechanism of differentiating silent cerebral events (regions of increased intensity on the DW-MRI) from silent cerebral lesions (more permanent white matter changes identifiable on FLAIR-MRI) (32).

All of the MRI scans in the study were evaluated at a central MRI Reading Center based at The Buffalo Neuroimaging Analysis Center (BNAC), Buffalo, NY, USA. The BNAC evaluated a test scan of a volunteer from each site as part of the dummy run process to ensure that its scanning techniques are compliant with the requirements of the study. This review took place before the site is permitted to enroll any patients into the study. Subsequently, MRI scans were conducted at baseline and 2-7 days post-TAVR and MRI data was transferred to BNAC directly from the site via a secure web-based transfer system. Alternatively, appropriate media (e.g., DICOM format on CD via courier) was sent to the CRO, and they transferred to BNAC using the web-based transfer system. BNAC provided specific MRI online transfer instructions, and CRO provided shipping instructions prior to the start of enrollment to all sites that opt to transfer the scans on physical media (e.g., DICOM format on CD via courier). MRI exam images were evaluated by physicians/technicians at BNAC according to a pre-specified imaging review protocol. These physicians/technicians were blinded to each patient's treatment. A study-specific case report form (CRF) was used to collect all final data for each patient, and served as the official reading record. This CRF included site identifier, patient identifier, exam timepoint data, BNAC-assigned unique examination identifiers, BNAC-assigned source analysis identifiers linked to locked BNAC database records.

For the analysis of stroke all cerebrovascular events were considered by the medical monitor and independent DSMB as defined by the VARC-2 criteria. In previous studies, such as the SENTINEL US IDE trial, stroke rates of 9.1% have been reported for patients receiving no embolic protection at 30 days (111 patients in control arm and 234 in device arm). All assessments were assessed by neurologists. A patient-level pooled analysis for the SENTINEL US IDE, the CLEAN-TAVI and the SENTINEL-Ulm studies was also conducted (33). A total of 1,066 patients were analyzed in this study (533 with Sentinel versus 533 control). The rate for all-strokes for patients without embolic protection within 3 days was 5.44% (29/533). The rate of all-cause mortality or stroke within 3 days was 6.0% for patients with no embolic protection (32/533).

1.5 **Supplementary Appendix 5. Disposition of patients.**

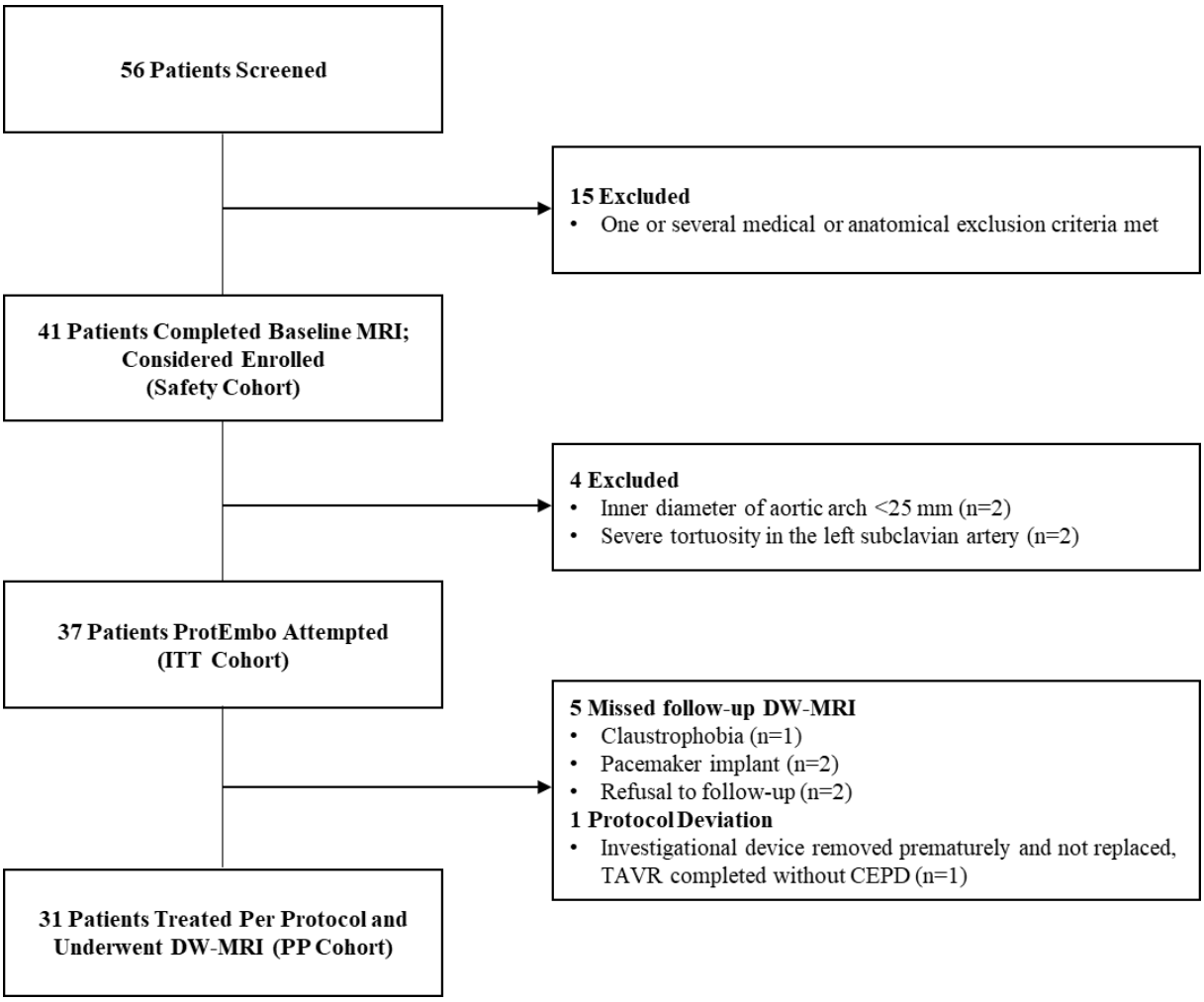
Supplemental Appendix Table 3: Overview Clinical Sites and Enrollment Status

Clinical Site	Site ID	Treating Investigators	Safety Cohort	ITT Cohort	PP Cohort
Gdansk, Poland	003	2	15	15	14
Lübeck, Germany	006	2	7	6	5
Leipzig, Germany	008	1	6	6	5
Trier, Germany	005	1	4	3	2
Poznan, Poland	004	1	4	3	1
Riga, Latvia	001	2	3	3	3
Warsaw, Poland	002	1	1	1	1
Kiel, Germany	010	1	1	0	0
Total number of patients			**41**	**37**	**31**

ITT = intention to treat; PP = per protocol.

1.6 Supplementary Appendix 6. Flow chart patient cohorts.

Supplemental Appendix Figure 1: Flow Chart Patient cohorts



1.7 Supplementary Appendix 7. Patients excluded from ITT cohort.

Supplemental Appendix Table 4: Overview Patients Excluded from ITT cohort

Site ID	Patient ID	Reason for Screen Failure
006	005-HLB	The diameter of the patient's aorta was below the allowed size of 25 mm as stipulated in the protocol (general exclusion criteria no. 30).
005	006-AAB	Patient was found to have severe tortuosity of the left subclavian artery which is an exclusion criterion as stipulated by the protocol (angiographic exclusion criteria no.1).
004	006-ATF	Patient was found to have severe tortuosity of the left subclavian artery which is an exclusion criterion as stipulated by the protocol (angiographic exclusion criteria no.1).
010	002-LKI	The diameter of the patient's aorta was below the allowed size of 25 mm as stipulated in the protocol (general exclusion criteria no. 30).

1.8 Supplementary Appendix 8. Overview of all adverse events in study and adjudication by DSMB.

Supplemental Appendix Table 5: Overview of Adverse Events (Safety Cohort) as adjudicated by DSMB

	Events	Safety Cohort (N = 41)
Overall	36	48.8% (20/41)
Serious Adverse Events	**16**	**26.8% (11/41)**
Device-related	0	0% (0/41)
Procedure-related	2	4.9% (2/41)
Definitely related	*1*	*2.4% (1/41)*
Possibly related	*1*	*2.4% (1/41)*
Unrelated	14	22.0% (9/41)
Adverse Events	**20**	**34.1% (14/41)**
Device-related	0	0% (0/41)
Procedure-related	4	9.8% (4/41)
Definitely related	*4*	*9.8% (4/41)*
Possibly related	*0*	*0% (0/41)*
Unrelated	16	29.3% (12/41)

Values are N, % (n/N), or n (%).

1.9 Supplementary Appendix 9. Serious adverse events.

Supplemental Appendix Table 6: Serious Adverse Event Listings and Descriptions

SAE Description and Resolution	Days to SAE	Device/ Procedure related	Outcome
Radial artery dissection Radial artery dissection due to spasm. Difficulties in sheath removal. Bleeding was stopped by applying a peripheral balloon twice for 5 minutes. A pressure dressing was applied.	0	Definitely Procedure-related	Resolved
Cerebral infarct When the TAVR catheter was withdrawn, the ProtEmbo was pulled out of position (i.e. interaction between TAVR catheter and ProtEmbo) and withdrawn as a consequence. After the ProtEmbo was removed, the patient, who had heavy calcification of the aortic annulus (including the left ventricular outflow track - LVOT), had twice further balloon dilation of the transcatheter heart valve prosthesis without embolic protection in place. In the evening following the TAVR (12 hours after procedure), the patient developed a neurological deficit with left hemiparesis as well as dysarthria due to infarction of the right thalamus.	0	Possibly Procedure-related	Resolved with sequelae
Bradycardia	1	Unrelated	Resolved

One day after TAVR, the patient developed bradycardia for 25 minutes. A temporary pacemaker was inserted. The cardiac rhythm stabilised and the pacemaker could be removed on the same day.			
Cardiac Tamponade, Sternotomy The procedure was complicated by postoperative bleeding. Cardiac tamponade was confirmed clinically and via echocardiogram. An incision was made under the xiphoid process and the pericardium was opened. Blood exited when pressure was being applied. A pericardial drain was placed and the pericardium was closed in layers, and a sterile dressing was applied. However, hemodynamic instability continued to be observed and bleeding increased (a total of 500 ml). The decision was made to perform a full sternotomy to find the source of the bleeding. After opening the pericardium, approximately 200 ml of clots and blood were removed. The pericardium was rinsed with warm saline. Repeated inspection of all potential bleeding sites revealed no significant source. The heart rhythm was a sinus rhythm, and temporary epicardial electrodes were sewn onto the ventricle. The pericardium was partially closed, and drains were placed in the pericardial sac and the mediastinum. Over the subsequent hospitalization, atrial fibrillation was observed, and evidence of inflammation was detected. Therefore, empirical antibiotic therapy was started. No further accumulation of fluid was observed in the x-rays or echocardiogram of the heart.	0	Unrelated	Resolved
Femoral artery dissection After the right femoral artery had been closed with the Proglide and Angioseal systems, artery dissection with decreased peripheral inflow was noticed in the control angiograms. Treatment was performed with a peripheral balloon (8 mm x 4 cm) which was inflated for 5 minutes. Afterwards inflow was sufficient again with only a slight dissection.	0	Unrelated	Resolved
3rd degree AV block requiring pacemaker implantation Third degree atrioventricular block developed 2 days after the procedure. A DDD cardiac device was implanted the next day. The procedure was successful; there were no complications.	2	Unrelated	Resolved
Femoral access site hematoma	1	Unrelated	Resolved

A hematoma (82x33 x130 mm on CT) developed at the femoral access site (including groin and scrotum). There was no active bleeding seen on CT, but as there was a drop in hemoglobin, two units of PRBC were administered the day after.			
Left Bundle Branch Block After the procedure, the ECG showed a left bundle branch block (140 ms). As the left bundle branch block persisted for some days, the decision was made to keep the patient in the hospital for additional observation and to perform a long-term ECG. The average heart rate was 76/min, with a range between 71/min and 106/min. There was no relevant bradycardia, and no sinus pauses during the night of recording. There were also no signs of atrial fibrillation. No further actions were deemed necessary.	0	Unrelated	Stabilized, not expected to resolve (SAE closed)
Fever/ Urinary tract infection Patient developed a less than 24 hour episode of otherwise asymptomatic fever, likely related to a mild urinary tract infection. Patient received 5 days of intravenous Piperacillin/Tazobactam antibiotic therapy which required prolonged hospitalization.	2	Unrelated	Resolved
Sedative circulatory complications Patient experienced drop in blood pressure due to accumulation of sedative during the procedure. Remifentanil was paused and the patient was given norepinephrine and atropine which led to recovery of the patient after the half-life of remifentanil was reached.	0	Unrelated	Resolved
1st degree AV Block and LBB Block After the TAVR procedure, the patient developed a new first-degree AV block and a left bundle branch block and a permanent pacemaker had to be implanted.	0		
Left Bundle Branch Block The patient developed a new left bundle branch block after the TAVR/ProtEmbo procedure. The patient had a history of atrial fibrillation with multiple failed attempts at electrical and medical cardioversion. The patient developed symptomatic atrial fibrillation and required cardioversion again, on May 17, 2021. The cardioversion was initially successful, but two days later recurrent atrial fibrillation was noted with primary arterio-ventricular block with 280 ms PR	0	Unrelated	Resolved

interval and left bundle block as well. Therefore, a permanent pacemaker was implanted on May 19, 2021.			
Drop of HB treated with Blood Infusions The patient experienced a drop in hemoglobin and was administered two units of erythrocyte concentrates, which brought the hemoglobin level close to normal. Pericardial effusion was excluded via echocardiogram post-procedurally at which point a minimal paravalvular insufficiency was noticed. The site provided additional information about the drop in hemoglobin noting that the patient received a large volume of fluid as part of the preparation and execution of the TAVR in the setting of left ventricular hypertrophy to provide adequate preload immediately after the new valve is placed. As there was no source of blood loss identified, the drop in hemoglobin was likely dilutional.	3	Unrelated	Resolved
AV Block III without replacement rhythm Immediately after the procedure the patient developed a complete AV Block III without replacement rhythm. As the placement of the temporary pacer was unstable and the patient had permanent AFIB, a pacemaker was implanted immediately without complications.	0	Unrelated	Resolved
Acute kidney injury Patient, who suffered from chronical renal insufficiency, developed acute kidney injury. On APR/2021 the creatinine level was 4,89 mg/dl and the GFR was 10ml/dl. Patient was put on dialysis from April 18-20.	2	Unrelated	Resolved
Pulmonary Edema Patient had a history of aortic and mitral valve disease, atrial fibrillation, diabetes and ongoing renal insufficiency. Developed pulmonary edema during hospitalization. Pulmonary edema resolved following treatment with non-invasive ventilation and standard treatment.	2	Unrelated	Resolved

SAE = Serious adverse event; TAVR = Transcatheter aortic valve replacement; LVOT = Left ventricular outflow track; AV = Atrioventricular; CT = Computed tomography; PRBC = Packed red blood cells; HB = Hemoglobin; ECG = Electrocardiogram; GFR = Glomerular filtration rate; NIV = Non-invasive ventilatory support; AFIB = Atrial fibrillation.

1.10 **Supplementary Appendix 10. Adverse events.**

Supplemental Appendix Table 7: Procedure-related Adverse Event Listings and Descriptions

AE Description and Resolution	Days to AE	Outcome

Hematoma left brachial access site Forearm hematoma after left brachial access for ProtEmbo. Sense, mobility, and brachial pulse were normal. Vascular surgeon was consulted; no urgent intervention was required. Hematoma to be re-evaluated in 3-4 weeks.	5	Resolved
Hematoma/Pseudoaneurysm left radial access site A small hematoma developed at the left arteria radialis. Sonography was performed, and no further action was required.	2	Resolved
Occlusion of the left Arteria Radialis During the 30 day follow-up closure of the left A. radialis was noticed. As the patient had no symptoms, conservative therapy was chosen.	27	Event stabilized, not expected to resolve
Occlusion of the left Arteria Radialis During the 30 day follow-up closure of the left A. radialis was noticed. As the patient had no symptoms, conservative therapy was chosen.	32	Event stabilized, not expected to resolve

AE = Adverse event; A. radialis = Arteria radialis.

1.11 **Supplementary Appendix 11. Supra-threshold DW-MRI lesion volume analysis.**

Supplemental Appendix Table 8: Supra-Threshold DW-MRI Lesion Volume Analysis

	ProtEmbo* (mm^3)	**No Device† (mm^3)**
Mean total	376	508
Mean >100 mm^3	72	341
Mean >200 mm^3	34	262
Mean >500 mm^3	0	162
Mean >1000 mm^3	0	141

*Patients in per-protocol cohort (N=31) who completed follow-up DW-MRI were considered for secondary efficacy analysis, individual lesions with volume smaller than threshold were excluded from supra-threshold analysis; †Analysis according to REFLECT II trial control arm (N=57) (2).