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

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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 mm³. 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.
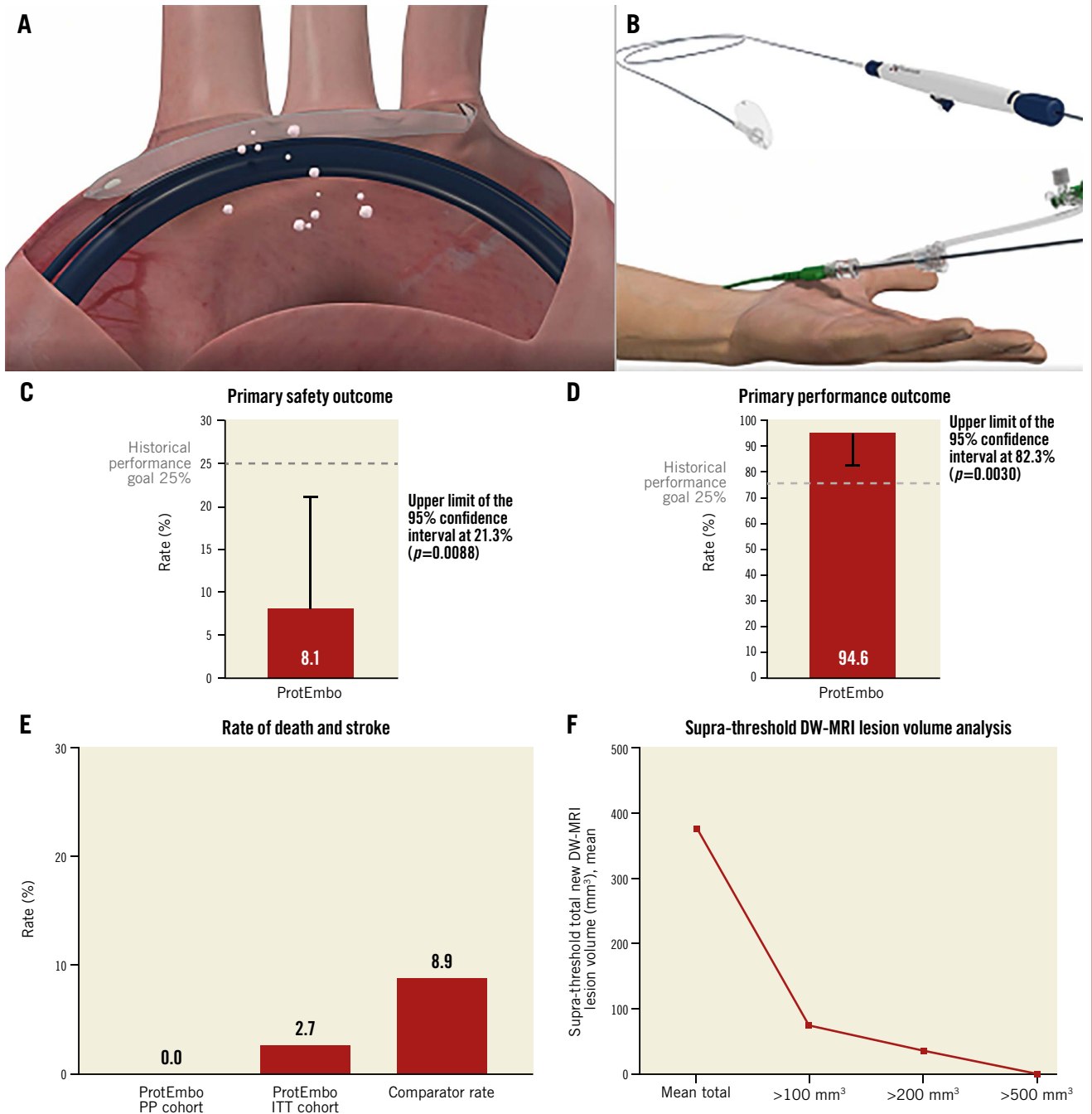
A) The ProtEmbo deployed in the aortic arch showing the delivery over radial access and coverage of 3 main cerebral vessels with the TAVI catheter, deflecting embolic debris. B) Illustration of the functional parts of the ProtEmbo without handle. The ProtEmbo met (C) the primary safety outcome and (D) 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/m²	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 mm², which comprises <0.006% of the filter area (total surface area equals 2,184 mm²).

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 mm³ [137, 456] **(Table 4)**. The largest single lesion volmues in each patient were all <500 mm³; the largest single lesion volume detected in any of the patients was 402 mm³; 87% of patients were free of single lesions >150 mm³; and 97% were free of single lesions >350 mm³. Supra-threshold lesion volume analysis at lesion volume thresholds of >100 mm³, >200 mm³, and >500 mm³ 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, mm³	210 [137, 456]
Total new DW-MRI lesion volume, mm³	376±363
Average new DW-MRI lesion volume, mm³	34 [24, 45]
Single new DW-MRI lesion volume, mm³	24 [15, 42]
Number of new lesions	8 [3, 16]
Freedom from brain lesions >150 mm³	87% (27)
Freedom from brain lesions >350 mm³	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

References

1. Davlouros PA, Mplani VC, Koniari I, Tsigkas G, Hahalis G. Transcatheter aortic valve replacement and stroke: a comprehensive review. *J Geriatr Cardiol.* 2018;15: 95-104.

2. Nazif TM, Moses J, Sharma R, Dhoble A, Rovin J, Brown D, Horwitz P, Makkar R, Stoler R, Forrest J, Messé S, Dickerman S, Brennan J, Zivadinov R, Dwyer MG, Lansky AJ; REFLECT II Trial Investigators. Randomized Evaluation of TriGuard 3 Cerebral Embolic Protection After Transcatheter Aortic Valve Replacement: REFLECT II. *JACC Cardiovasc Interv.* 2021;14:515-27.

3. Carroll JD, Mack MJ, Vemulapalli S, Herrmann HC, Gleason TG, Hanzel G, Deeb GM, Thourani VH, Cohen DJ, Desai N, Kirtane AJ, Fitzgerald S, Michaels J, Krohn C, Masoudi FA, Brindis RG, Bavaria JE. STS-ACC TVT Registry of Transcatheter Aortic Valve Replacement. *J Am Coll Cardiol.* 2020;76:2492-516.

4. Valle JA, Li Z, Kosinski AS, Nelson AJ, Vemulapalli S, Cleveland J, Fullerton D, Messenger JC, Rove JY, Bricker RS, Bradley SM, Masoudi FA, Yeh RW, Armstrong EJ, Waldo SW, Carroll JD. Dissemination of Transcatheter Aortic Valve Replacement in the United States. *J Am Coll Cardiol.* 2021;78:794-806.

5. Mack MJ, Leon MB, Thourani VH, Makkar R, Kodali SK, Russo M, Kapadia SR, Malaisrie SC, Cohen DJ, Pibarot P, Leipsic J, Hahn RT, Blanke P, Williams MR, McCabe JM, Brown DL, Babaliaros V, Goldman S, Szeto WY, Genereux P, Pershad A, Pocock SJ, Alu MC, Webb JG, Smith CR; PARTNER 3 Investigators. Transcatheter Aortic-Valve Replacement with a Balloon-Expandable Valve in Low-Risk Patients. *N Engl J Med.* 2019;380:1695-705.

6. Popma JJ, Deeb GM, Yakubov SJ, Mumtaz M, Gada H, O'Hair D, Bajwa T, Heiser JC, Merhi W, Kleiman NS, Askew J, Sorajja P, Rovin J, Chetcuti SJ, Adams DH, Teirstein PS, Zorn GL 3rd, Forrest JK, Tchétché D, Resar J, Walton A, Piazza N, Ramlawi B, Robinson N, Petrossian G, Gleason TG, Oh JK, Boulware MJ, Qiao H, Mugglin AS, Reardon MJ; Evolut Low Risk Trial Investigators. Transcatheter Aortic-Valve Replacement with a Self-Expanding Valve in Low-Risk Patients. *N Engl J Med.* 2019;380:1706-15.

7. Synnott P, Murphy RP, Judge C, Costello M, Reddin C, Dennehy K, Loughlin E, Smyth A, Mylotte D, O'Donnell MJ, Canavan M. Stroke Severity in Transcatheter Aortic Valve Implantation Versus Surgical Aortic Valve Replacement : A Systematic Review and Meta-Analysis. *J Stroke Cerebrovasc Dis.* 2021;30:105927.

8. Pollari F, Hitzl W, Claes M, Grossmann I, Fischlein T. Machine Learning for Making Aortic Valve Interventions Complementary and Not Competitive. *JACC Cardiovasc Interv.* 2019;12:2112.

9. Yashima F, Briasoulis A, Kuno T, Noguchi M, Ahmad H, Zaid S, Goldberg JB, Malik AH, Tang GHL. Cerebral Embolic Protection During Transcatheter Aortic Valve Replacement. *Cardiovasc Revasc Med.* 2022;36:9-13.

10. Xiong TY, Liao YB, Zhao ZG, Xu YN, Wei X, Zuo ZL, Li YJ, Cao JY, Tang H, Jilaihawi H, Feng Y, Chen M. Causes of Death Following Transcatheter Aortic Valve Replacement: A Systematic Review and Meta-Analysis. *J Am Heart Assoc.* 2015;4: e002096.

11. Vlastra W, Jimenez-Quevedo P, Tchétché D, Chandrasekhar J, de Brito FS Jr, Barbanti M, Kornowski R, Latib A, D'Onofrio A, Ribichini F, Baan J, Tijssen JGP, De la Torre Hernandez JM, Dumonteil N, Sarmento-Leite R, Sartori S, Rosato S,

Tarantini G, Lunardi M, Orvin K, Pagnesi M, Hernandez-Antolin R, Modine T, Dangas G, Mehran R, Piek JJ, Delewi R. Predictors, Incidence, and Outcomes of Patients Undergoing Transfemoral Transcatheter Aortic Valve Implantation Complicated by Stroke. *Circ Cardiovasc Interv.* 2019;12:e007546.

12. Arnold S V, Zhang Y, Baron SJ, McAndrew TC, Alu MC, Kodali SK, Kapadia S, Thourani VH, Miller DC, Mack MJ, Leon MB, Cohen DJ. Impact of Short-Term Complications on Mortality and Quality of Life After Transcatheter Aortic Valve Replacement. *JACC Cardiovasc Interv.* 2019;12:362-9.

13. Schmidt T, Akdag O, Wohlmuth P, Thielsen T, Schewel D, Schewel J, Alessandrini H, Kreidel F, Bader R, Romero M, Ladich E, Virmani R, Schäfer U, Kuck KH, Frerker C. Histological Findings and Predictors of Cerebral Debris From Transcatheter Aortic Valve Replacement: The ALSTER Experience. *J Am Heart Assoc.* 2016;5:e004399.

14. Schmidt T, Leon MB, Mehran R, Kuck KH, Alu MC, Braumann RE, Kodali S, Kapadia SR, Linke A, Makkar R, Naber C, Romero ME, Virmani R, Frerker C. Debris Heterogeneity Across Different Valve Types Captured by a Cerebral Protection System During Transcatheter Aortic Valve Replacement. *JACC Cardiovasc Interv.* 2018;11:1262-73.

15. Seeger J, Virmani R, Romero M, Gonska B, Rottbauer W, Wöhrle J. Significant Differences in Debris Captured by the Sentinel Dual-Filter Cerebral Embolic Protection During Transcatheter Aortic Valve Replacement Among Different Valve Types. *JACC Cardiovasc Interv.* 2018;11:1683-93.

16. Van Mieghem NM, Schipper ME, Ladich E, Faqiri E, van der Boon R, Randjgari A, Schultz C, Moelker A, van Geuns RJ, Otsuka F, Serruys PW, Virmani R, de Jaegere PP. Histopathology of embolic debris captured during transcatheter aortic valve replacement. *Circulation.* 2013;127:2194-201.

17. Arnold M, Schulz-Heise S, Achenbach S, Ott S, Dörfler A, Ropers D, Feyrer R, Einhaus F, Loders S, Mahmoud F, Roerick O, Daniel WG, Weyand M, Ensminger SM, Ludwig J. Embolic cerebral insults after transapical aortic valve implantation detected by magnetic resonance imaging. *JACC Cardiovasc Interv.* 2010;3:1126-32.

18. Fairbairn TA, Mather AN, Bijsterveld P, Worthy G, Currie S, Goddard AJ, Blackman DJ, Plein S, Greenwood JP. Diffusion-weighted MRI determined cerebral embolic infarction following transcatheter aortic valve implantation: assessment of predictive risk factors and the relationship to subsequent health status. *Heart.* 2012;98:18-23.

19. Gass A, Ay H, Szabo K, Koroshetz WJ. Diffusion-weighted MRI for the 'small stuff': the details of acute cerebral ischaemia. *Lancet Neurol.* 2004;3:39-45.

20. Ghanem A, Müller A, Nähle CP, Kocurek J, Werner N, Hammerstingl C, Schild HH, Schwab JO, Mellert F, Fimmers R, Nickenig G, Thomas D. Risk and fate of cerebral embolism after transfemoral aortic valve implantation: a prospective pilot study with diffusion-weighted magnetic resonance imaging. *J Am Coll Cardiol.* 2010;55:1427-32.

21. Kahlert P, Knipp SC, Schlamann M, Thielmann M, Al-Rashid F, Weber M, Johansson U, Wendt D, Jakob HG, Forsting M, Sack S, Erbel R, Eggebrecht H. Silent and apparent cerebral ischemia after percutaneous transfemoral aortic valve implantation: a diffusion-weighted magnetic resonance imaging study. *Circulation.* 2010;121:870-8.

22. Leon MB, Smith CR, Mack M, Miller DC, Moses JW, Svensson LG, Tuzcu EM, Webb JG, Fontana GP, Makkar RR, Brown DL, Block PC, Guyton RA, Pichard AD, Bavaria JE, Herrmann HC, Douglas PS, Petersen JL, Akin JJ, Anderson WN, Wang D, Pocock S; PARTNER Trial Investigators. Transcatheter aortic-valve implantation for aortic stenosis in patients who cannot undergo surgery. *N Engl J Med.* 2010;363:1597-607.

23. Butala NM, Makkar R, Secemsky EA, Gallup D, Marquis-Gravel G, Kosinski AS, Vemulapalli S, Valle JA, Bradley SM, Chakravarty T, Yeh RW, Cohen DJ. Cerebral Embolic Protection and Outcomes of transcatheter Aortic Valve Replacement: Results From the Transcatheter Valve Therapy Registry. *Circulation.* 2021;143:2229-40.

24. Khan MZ, Zahid S, Khan MU, Kichloo A, Ullah W, Sattar Y, Munir MB, Singla A, Goldsweig AM, Balla S. Use and outcomes of cerebral embolic protection for transcatheter aortic valve replacement : A US nationwide study. *Catheter Cardiovasc Interv.* 2021;98:959-68.

25. Sato Y, Kawakami R, Sakamoto A, Cornelissen A, Mori M, Kawai K, Ghosh S, Romero ME, Kolodgie FD, Virmani R, Finn AV. Efficacy and safety of cerebral embolic protection systems during transcatheter aortic valve replacement: a review of current clinical findings. *Expert Rev Cardiovasc Ther.* 2021;19:725-37.

26. Mylotte D, Narbute I, Neylon A, Schäfer U, Werner N, Virmani R, Kolodgie F, Zivadinov R, Erglis A. TCT-43 First-in-human experience of a novel transradial device for embolic deflection during transcatheter aortic valve replacement. *J Am Coll Cardiol.* 2018;72:B19.

27. Kappetein AP, Head SJ, Généreux P, Piazza N, van Mieghem NM, Blackstone EH, Brott TG, Cohen DJ, Cutlip DE, van Es GA, Hahn RT, Kirtane AJ, Krucoff MW, Kodali S, Mack MJ, Mehran R, Rodés-Cabau J, Vranckx P, Webb JG, Windecker S, Serruys PW, Leon MB; Valve Academic Research Consortium-2. Updated standardized endpoint definitions for transcatheter aortic valve implantation: The Valve Academic Research Consortium-2 consensus document. *J Thorac Cardiovasc Surg.* 2013;145:6-23.

28. Lansky AJ, Messé SR, Brickman AM, Dwyer M, van der Worp HB, Lazar RM, Pietras CG, Abrams KJ, McFadden E, Petersen NH, Browndyke J, Prendergast B, Ng VG, Cutlip DE, Kapadia S, Krucoff MW, Linke A, Moy CS, Schofer J, van Es GA, Virmani R, Popma J, Parides MK, Kodali S, Bilello M, Zivadinov R, Akar J, Furie KL, Gress D, Voros S, Moses J, Greer D, Forrest JK, Holmes D, Kappetein AP, Mack M, Baumbach A. Proposed Standardized Neurological Endpoints for Cardiovascular Clinical Trials: An Academic Research Consortium Initiative. *J Am Coll Cardiol.* 2017;69:679-91.

29. Chow S-C, Shao J, Wang H, Lokhnygina Y. Sample Size Calculations in Clinical Research. 2nd ed. New York, USA: Taylor & Francis Group, LLC; 2007.

30. Kapadia SR, Kodali S, Makkar R, Mehran R, Lazar RM, Zivadinov R, Dwyer MG, Jilaihawi H, Virmani R, Anwaruddin S, Thourani VH, Nazif T, Mangner N, Woitek F, Krishnaswamy A, Mick S, Chakravarty T, Nakamura M, McCabe JM, Satler L, Zajarias A, Szeto WY, Svensson L, Alu MC, White RM, Kraemer C, Parhizgar A, Leon MB, Linke A; SENTINEL Trial Investigators. Protection Against Cerebral Embolism During Transcatheter Aortic Valve Replacement. *J Am Coll Cardiol.* 2017;69:367-77.

Supplementary data

Supplementary Appendix 1. Clinical investigation protocol.

Supplementary Appendix 2. Derivation of performance goals.

Supplementary Appendix 3. Histological analysis of devices.

Supplementary Appendix 4. MRI and stroke analysis methodology.

Supplementary Appendix 5. Disposition of patients.

Supplementary Appendix 6. Flow chart patient cohorts.

Supplementary Appendix 7. Patients excluded from ITT cohort.

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

Supplementary Appendix 9. Serious adverse events.

Supplementary Appendix 10. Adverse events.

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

The supplementary data are published online at: https://eurointervention.pcronline.com/ doi/10.4244/EIJ-D-22-00238