

Embollic Protection Devices in Transcatheter Aortic Valve Replacement

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Abstract—The initially reported periprocedural neurological events rates associated with transcatheter aortic valve replacement raised concerns that ultimately led to the development and to the clinical research of novel embollic protection devices. Although the reduction of clinical stroke is a desired goal, the current research design of embollic protection devices focuses on surrogate markers of the clinical disease, primarily on silent central nervous system lesions observed in postprocedural diffuse-weighted magnetic resonance imaging and cognitive function testing. As the mere presence of particulate debris in brain matter may not correlate with the extent of brain injury, cognitive function, or quality of life, the clinical significance of embollic protection devices has yet to be determined, and interpretation of study results with regard to real-life clinical use should be viewed accordingly. The purpose of this article is to provide an overview of the updated ongoing clinical research on embollic protection devices and present its major caveats. (*Circ Cardiovasc Interv.* 2016;9:e003284. DOI: 10.1161/CIRCINTERVENTIONS.115.003284.)

Key Words: biomarkers ■ brain injuries ■ embollic protection devices ■ stroke
■ transcatheter aortic valve replacement

The initially reported periprocedural neurological events rates associated with transcatheter aortic valve replacement (TAVR)¹ raised concerns that ultimately led to the development and to the clinical research of novel embollic protection devices (EPD).² Although the reduction of clinical stroke is a desired goal, the current research design of EPD focuses on surrogate markers of the clinical disease, primarily on silent central nervous system (CNS) infarcts observed in postprocedural diffuse-weighted magnetic resonance imaging (DW-MRI). These silent, widespread, small, and mostly temporary CNS lesions have been observed for many other cardiovascular procedures³ and may be regarded as inherent to the procedure. Because the relation of these procedural silent brain infarcts to cognitive decline is still ill defined, their true clinical significance is unknown. It should also be noted that in the cardiac surgical literature, the road leading from the discovery of silent CNS infarcts to EPD development has been previously taken. This road, however, eventually led to the conclusion that EPD lack clinical use and significance.⁴ The purpose of this article is to provide an overview of the updated ongoing clinical research on EPD and present its major caveats.

Neurological Complications in TAVR

Initial neurological complications reported from the first Placement of Aortic Transcatheter Valve (PARTNER) randomized clinical trials ranged between 5.5% and 6.7%.^{5,6} Those rates

were significantly higher as compared with patients randomized to the surgical aortic valve replacement or placebo arms. Since then, new data from large registries have shown lower rates of stroke after TAVR ranging between 1.7% and 3.4%,^{7,8} including the recently published data from the Transcatheter Valve Therapies Registry, indicating a 30-day stroke rate of 2.5%.⁹ In a large meta-analysis of 34 TAVR studies, similar low stroke rates were reported.¹⁰ Finally, in the randomized CoreValve US Pivotal Trial, there was no difference in clinical neurological events between TAVR and surgical aortic valve replacement.¹¹

Cerebral injury during TAVR can result from embollic debris originating from the valve implantation site and the passage of large-caliber catheters through a diseased and calcified aortic arch.¹² Previous reports utilizing DW-MRI, transcranial Doppler, and histopathology studies have revealed that cerebral embolization is common during TAVR.^{13–17} However, the current clinical significance of silent CNS lesions after TAVR on the present patient cohorts referred to the procedure remains to be defined.^{18,19}

Embollic Protection Devices

The currently available EPD designs have been previously described.² Their outline and manufactures are summarized in the Table. Table I in the Data Supplement summarizes the currently available clinical research and development programs for EPD. EPD differ mainly by design and access route, and

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Table. Current Embolic Protection Devices

Device	Manufacturer	Design	Access	Delivery	Deployment
Embrella	Edwards Lifesciences, Irvine, CA	Deflector	Radial/brachial	6F	Aortic arch
TriGuard	Keystone Heart Ltd, Caesarea, Israel	Deflector	Femoral	9F	Aortic arch
Sentinel	Claret Medical Inc., Santa Rosa, CA	Filter	Radial/brachial	6F	2 filters to brachiocephalic trunk and left common carotid
Embol-X	Edwards Lifesciences, Irvine, CA	Filter	Direct aortic	14F	Ascending aorta

the deflectors, represented by the Embrella (Edwards Lifesciences, Irvine, CA) and TriGuard (Keystone Heart Ltd, Caesarea, Israel) devices, are deployed along the outer curve of the aortic arch to provide coverage of the brachiocephalic trunk, the left common carotid artery, and more variably the left subclavian artery by deflecting embolized material into the descending aorta (13–15). The filters are currently represented by the Sentinel (Claret Medical Inc., Santa Rosa, CA) and the Embol-X (Edwards Lifesciences, Irvine, CA). The Sentinel EPD contains filters deployed in the brachiocephalic trunk and left common carotid, and the Embol-X is placed in the ascending aorta through a midsternotomy.

Embrella

The Embrella EPD has been studied in 1 first-in-human (FIH) trial²⁰ and 2 clinical trials,^{21,22} and it received its European CE mark approval in 2010. The initial clinical results of the Embrella EPD were reported in the Feasibility and Exploratory Efficacy Evaluation of the Embrella Embolic Deflector System for the Prevention of Cerebral Emboli in Patients Undergoing Transcatheter Aortic Valve Replacement: the PROTAVI-C pilot study.²¹ This was a multicenter, nonrandomized trial, enrolling 52 patients from 6 centers, of whom 11 were controls, and investigating clinical, neuroimaging, and neurocognitive function outcomes. At 30 days, 3 patients had cerebrovascular events (2 strokes and 1 transient ischemic attack), all from the treatment group. There were also 2 complications related to the device: 1 radial thrombosis with no clinical consequences and 1 pseudoaneurysm of the brachial artery that required surgical repair. The total number of transcranial Doppler high-intensity transient signals during the TAVR procedure was higher in the treatment group than in the control group ($P < 0.001$). In DW-MRI, all patients had new cerebral lesions. There were no differences in total lesion volume per patient between groups; however, patients in the treatment group had a smaller lesion volume per lesion. Neurocognitive function test results were similar in the 2 groups. In another report, Samim et al²² retrospectively compared 15 patients referred to TAVR with the use of the Embrella EPD to 37 patients who had previously undergone TAVR without a protection device. DW-MRI revealed an increase in the number of ischemic lesions in the Embrella group compared with the TAVR-only group (9.0 versus 5.0; $P = 0.044$). The use of the Embrella device was, however, associated with a significant reduction in single-lesion volume. No additional trials are currently ongoing for this device.

Triguard

The Triguard EPD research program included 4 trials, the FIH study,²³ 3 DEFLECT clinical trials,^{24–26} and the upcoming

TriGuard Embolic Deflection Device to Reduced Impact of Cerebral Embolic Lesions After Transcatheter Aortic Valve Implantation (REFLECT, NCT02536196) study. The device received a European CE mark in 2014. REFLECT is a planned prospective, multicenter randomized investigational device exemption approval trial. Onsea et al²³ reported first on the successful placement of the device in all of the 15 TAVR patients enrolled. In a comparison with a historic cohort of TAVR patients ($n = 20$), treatment patients had fewer new cerebral lesions per patient identified in DW-MRI. Baumbach et al²⁴ reported on the results of the SMT Embolic Deflection CE Mark Trial DEFLECT I (DEFLECT I, NCT01448421), a prospective, multicenter, single-arm study in the EU and Brazil, enrolling 37 patients to undergo TAVR with the Triguard device. It was designed to evaluate the device's performance and safety. Its secondary end points included the number of new lesions found with DW-MRI and the total volume and performance on neurocognitive assessment tests. Device success was achieved in 80% of patients, with the composite safety end point occurring in 8% and a major adverse cardiovascular and cerebrovascular event in 16%. The rates of new cerebral lesions in DW-MRI were similar to historic cohorts (82% versus 76%, respectively; $P = \text{NS}$); however, in an exploratory analysis, the per patient total lesion volume was 34% lower than reported from historical data. The DEFLECT II: A Study to Evaluate the Safety and Performance of the TriGuard HDH in Patients Undergoing TAVR (DEFLECT II, NCT02073851) trial was a prospective, single-center, single-arm safety study on 12 patients designed to evaluate device performance as in DEFLECT I, but clinical data are currently not available. The DEFLECT III: A Prospective, Randomized Evaluation of the TriGuard HDH Embolic Deflection Device During TAVI (DEFLECT III, NCT02070731) trial results were recently reported by Lansky et al²⁵ This trial was a multicenter, prospective trial randomizing 85 patients to the EPD plus TAVR ($n = 45$) and to TAVR alone. Technical success was achieved in 88.9% (40/45) of cases. The primary in-hospital procedural safety end point (death, stroke, life-threatening or disabling bleeding, acute kidney injury above stage 1, or major vascular complications) occurred in 21.7% of the treatment group and in 30.8% of control subjects ($P = 0.34$). In the per-treatment population, the device use was associated with greater freedom from assumed new ischemic brain lesions (26.9% versus 11.5%), because baseline MRI was not performed. There were also fewer new neurological deficits detected (3.1% versus 15.4%) and better performance on a delayed memory task ($P = 0.028$) at discharge, with a >2-fold increase in recovery of normal cognitive function (Montreal Cognitive Assessment Memory Index Score >26) at 30 days.

Sentinel

The Sentinel EPD research program included 3 trials, including the FIH study²⁶ and 2 clinical trials: the Claret Embolic Protection and TAVI trial (CLEAN-TAVI, NCT01833052) and Cerebral Protection in Transcatheter Aortic Valve Replacement - The SENTINEL Study (SENTINEL, NCT02214277) were both presented at the 2014 Transcatheter Cardiovascular Therapeutics meeting. The device received a European CE mark in 2014. The prospective, multicenter, randomized SENTINEL clinical trial is ongoing and expected to finish recruitment by the end of 2015. The results of the CLEAN-TAVI trial were reported at the 2014 Transcatheter Cardiovascular Therapeutics meeting. It was a prospective, single-blind, single-center study randomizing 100 patients in a 1:1 ratio to either TAVR with the Sentinel EPD or TAVR alone. The primary end point was the number of lesions in the protected brain region (defined as territories uniquely perfused by the vessels protected by the Sentinel System, namely, the left and right carotid arteries and the right vertebral artery) as determined by DW-MRI at 2 days after TAVR. Secondary end points included the total lesion volume at 2 and 7 days after TAVR and the lesion number at 7 days. The initial trial results presented indicated a device success rate of 96% and a procedural success rate of 94%. Neurological events defined as any new symptoms assessed by a trained specialist were not found to differ in the intention-to-treat or the per protocol analyses, and although not powered for that, the per protocol treatment group showed significantly lower ataxia rates (24% versus 9%). The median number of lesions in the protected regions in the device group was significantly lower than in the control group at 2 days. In addition, the median total lesion volume in the protected area was significantly smaller in the device group than in the control group at 2 and 7 days. The ongoing SENTINEL trial intends to randomize 359 patients in the United States to undergo TAVR with and without the SENTINEL System. Similar to the previous EPD study design, the primary end point was defined as the reduction in the median of the total new lesion volume in protected CNS territories between the imaging arms (test and control group) as assessed by DW-MRI on days 4 to 7 after procedure. The safety end point was defined as the occurrence of all major adverse cardiovascular and cerebrovascular event at 30 days compared with a historical performance goal.

Embol-X

The Embol-X EPD was initially developed for use during open-heart surgery and requires direct access to the ascending aorta. A modified version of the Embol-X EPD with a smaller French sheath has been subsequently used in transaortic TAVR with 3 initial case reports indicating technical success and safety.^{27,28} The Intraprocedural Intra-aortic Embolic Protection With the EmbolX Device in Patients Undergoing Transaortic Transcatheter Aortic Valve Implantation (TAo-EmbolX, NCT01735513) study is a prospective, single-blind, randomized, single-center clinical trial that is currently being studied in the transaortic TAVR population.

Pitfalls in Current EPD Study Design

Brain Infarct, Stroke, and Silent Stroke

The embolic insult during TAVR can vary in relation to the number, volume, type, and temporal profile of the particle shower as well as the condition of the cerebral tissue.²⁹ The mere presence of particulate debris in brain matter may not correlate with the extent of brain injury or clinical function because a slower rate of particle release may have less potential for ischemic injury than the same number of particles delivered in a sudden shower, and given an identical embolic insult, cerebral tissue with reduced perfusion pressure has a greater risk of permanent ischemic injury than cerebral tissue with normal perfusion pressure.

Consistent definitions of stroke, CNS infarction, and silent cerebral infarction are critical for interpretation of clinical research trials. A characteristic clinical presentation occurring at the same temporal context to characteristic imaging changes would ultimately provide a higher sensitivity and specificity for the diagnosis of ischemic stroke. Since the start of EPD trials in about 2010, 2 TAVR-relevant stroke definitions have emerged by the American Heart Association³⁰ and Valve Academic Research Consortium-2.³¹ Although similar in some aspects, the commonly cited Valve Academic Research Consortium-2 definitions published in 2012 have not included a definition of silent stroke, nor do they distinguish sole CNS infarction from clinical stroke. Whereas, the 2013 updated American Heart Association definition of stroke clearly distinguishes CNS infarction, clinical stroke, and silent stroke. The Valve Academic Research Consortium-3 update is currently planned to incorporate stroke imaging and may enable comparison across studies in the future; however, it is not currently incorporated in any of the EPD trial designs. In view of the available data (Table I in the Data Supplement), all major EPD trials, the SENTINEL, DEFLECT III, and EMBOL-X, have assigned DW-MRI new CNS infarcts as their primary end point. A valid surrogate end point allows correct inference to be drawn on the effect of an intervention on the unobserved true clinical end point of interest.³² Because the clinical relevance of silent brain ischemia has not been elucidated yet,¹⁹ choosing such a primary end point might compromise the opportunity to project the results of these trials on future patient populations referred to TAVR. Definitions of stroke in clinical research should reflect the goals of a given research study and should be carefully specified before initiating the trial. Silent infarction implies lack of clear clinical symptoms or signs as well as the inability to define the infarct. Although DW-MRI lesions were previously considered by some as surrogate markers for clinical stroke as a complication of cerebrovascular procedures,²⁹ the current American Heart Association guidelines³⁰ do not define them that way. The American Heart Association recommends avoiding the assignment of clinically silent cerebral infarctions of undetermined onset as primary or secondary outcomes in most stroke studies, unless all study patients undergo standardized imaging at specific time points according to the study protocol. Only in these conditions could new silent infarctions be considered secondary outcomes rather than events equivalent to ischemic strokes, which is the way most current EPD studies define them.

Diffuse-Weighted Magnetic Resonance Imaging

DW-MRI studies in TAVR patients have shown that CNS infarction is inherent to the procedure, and that it occurs in rates above 80% of patients in some reports, with the majority of patients having multiple new foci.^{15,33} Long-term data, however, is lacking. Uddin et al³⁴ reported on 45 patients undergoing TAVR, of whom 36 patients had new embolic lesions on DW-MRI. In a repeat MRI of 17 patients in 6 months, all previously detected microinfarcts had been completely resolved. In the CLEAN-TAVI trial, lesion volume and number were reduced at 7 days, whereas limited data were available from the DEFLECT III trial. The challenges of DW-MRI interpretation include both the preexisting pathology of aged population and the numerous small and widely distributed new CNS lesions needed to be diagnosed as infarcts. Most of the previous reports of DW-MRI in TAVR used 1.5-T imaging, which may have failed to detect showers of smaller emboli and thus missed a potential association. In some of the current EPD trials, 3-T imaging is used. Although 3-T imaging offers improved sensitivity with higher resolution, comparison with previous reports and historic cohorts might not be suitable. Furthermore, enhanced sensitivity might cause over estimation of lesions that might have otherwise been ignored in a real-world setting. Finally, a unified definition of the DW-MRI end point for cardiac procedures has not been defined. Previous EPD studies reported various lesion characteristics, therefore increasing the difficulty of cross-study comparison.¹⁹ Thus, standardized DW-MRI acquisition protocols are needed in future studies.

Neurocognitive Testing

Neurocognitive decline can be detected only with careful neuropsychological testing by a trained and experienced examiner. A meticulous look for characteristic disturbances in memory, psychomotor speed, executive function, visuoconstructional ability, and ability to concentrate is required. As previously mentioned for the DEFLECT III, patients in the intervention arm had better neurocognitive outcomes. However, the association between TAVR and cognition remains unclear because of methodological limitations of previous reports. Currently, there are a wide variety of neurocognitive tests, commonly termed the Neurocognitive Assessment Battery.³⁵ Some of the EPD trials have used these proposed batteries of neurocognitive tests, which have been used in previous clinical trials and have been piloted in the PARTNER II study. Similar studies in older populations have placed neurocognitive function testing as a primary outcome, pointing out that in this population the quality of life is not less important than life itself.³⁶ Nonetheless, the potential implications of using multiple individual tests selected at the investigator's discretion are immense. From an investigator's point of view, the interobserver variability of these tests and their reproducibility between and within study sites have never been examined. Furthermore, the nature of the ischemic insult itself may add to the variability of the cognitive domains covered, as silent CNS infarctions after TAVR are common and diffuse and may impact cognition in ways that would not be diagnosed by certain tests. As in DW-MRI, no standardization is available for neurocognitive testing after TAVR. There are multiple studies

showing the association of new DW-MRI lesions with cognitive impairment after cardiac procedures. However, few studies have investigated their clinical significance in the context of TAVR, all with a relatively low patient number. In a report by Ghanem et al³⁵ on 111 TAVR patients undergoing serial neurocognitive testing, long-term cognitive performance was preserved in the majority (91%) of patients throughout the first 2 years after TAVR. In a recent review on cognitive outcomes after TAVR, Lai et al³⁷ reported on 6 studies assessing the possible link between TAVR and cognitive changes. In reviewing those studies, they conclude that global cognition improves or remains unchanged for 3 months after TAVR, whereas individual cognitive domains remain preserved over time. Although these studies have largely focused on memory, cognitive impairment in this population may be predominantly of vascular origin. Therefore, focusing on domains known to be relevant to vascular cognitive impairment, such as executive function, may be more helpful in elucidating the association between TAVR and cognition in the long term.³⁷

Cardiac Surgery Perspective

Many similarities can be found when comparing the historic development of EPD for surgical patients to those of TAVR patients. As opposed to TAVR, cardiac surgery involves a wide spectrum of neurological injuries, including ischemic stroke, encephalopathy, and neurocognitive decline.³⁸ Embolism is considered the main mechanism of neurological injury,³⁹ and embolic material released into the cerebral circulation has been detected during various aortic manipulations performed in cardiac surgery.⁴⁰ Similar to TAVR patients, an increased risk of silent CNS infarction related to cognitive decline has been reported for cardiac surgery patients.⁴ Sun et al⁴ reported that out of 446 patients included in 13 DW-MRI trials, 127 (29%) had new CNS lesions on postoperative imaging. As is TAVR, these lesions were widespread, multiple, and small, and only few were associated with overt clinical signs of stroke. Also similarly, these lesions were associated with cognitive decline; however, because of the inherent weakness in the reproducibility and objectivity of neurocognitive testing, no firm conclusions could be made.⁴ Importantly, the rates of postoperative neurocognitive decline shows striking variability according to the measurements included, the surgical procedure done, the inclusion and exclusion criteria for a specific study, and the criteria used to define neurocognitive decline or dysfunction.³⁸ Various neuroprotection techniques have been recommended in cardiac surgery patients but not the use of EPD.⁴¹ Banbury et al⁴² reported on 1289 patients undergoing cardiac surgery who were randomized to undergo surgery with or without the Embol-X EPD. Recovery of particulate emboli was found in 96.8% of the filters that were successfully deployed; however, no significant differences in clinical end points, such as mortality, stroke, transient ischemic attack, renal insufficiency, myocardial infarction, gastrointestinal complications, or limb threatening ischemia were observed. Although novel EPD technologies are still being studied for cardiac surgery,⁴³ because the largest EPD trial to date has failed to show any benefit, this method for the reduction of neurological events after cardiac surgery has been currently abandoned clinically.

Long-Term Effects of Silent Brain Infarcts

Currently, there are no data on the relation of silent CNS infarction and cognitive decline in younger and healthier aortic stenosis patients who may ultimately be referred to TAVR. Previous reports from other patient subsets have shown that cumulative cerebral lesions have been correlated with late dementia as well as with ultimate cognitive decline.⁴⁴ DeBette et al⁴⁵ have reported on 2229 participants of the Framingham Offspring Study at a mean age of 62 years. In these patients, MRI-defined brain infarcts predicted an increased risk of stroke, amnesic mild cognitive impairment, dementia, and death independent of vascular risk factors. In the population-based Rotterdam Scan Study, silent brain infarcts have been shown to double the risk of dementia in 1015 participants at a mean age of 72 years.⁴⁶ A similar association between silent brain infarcts and cognitive function has been shown for patients with atrial fibrillation and multiple sclerosis.^{47,48} Thus, the long-term effects of silent brain lesions should be carefully evaluated using validated research tools in the future younger and healthier populations that might be referred to TAVR.

Summary and Implications

Clinical stroke is a devastating event that has an enormous impact on patient's quality of life, morbidity, and mortality. The early reports on high rates of stroke after TAVR as compared with surgical aortic valve replacement raised deep concerns on the procedure's safety and effectiveness. As knowledge has grown, those concerns have been mitigated by research showing lower than previously reported rates of clinical stroke after TAVR. In parallel, new imaging and histopathologic data have also shown that silent CNS infarction is inherent to the procedure. Current trial data indicate that EPD use during TAVR reduces the risk of silent CNS infarction; however, results of ongoing larger clinical trials are pending. In the present populations referred to TAVR, the elderly and the high- and extreme-risk patients, the current rate of cerebral embolization may be high; however, considering the available alternatives, it is currently acceptable.

Clinical trials should be designed to answer clinically relevant questions by using validated and measurable research tools alongside adequate statistical power. With a low event rate of strokes in TAVR, a study design based on clinical stroke rates will require a large sample size. Cognitive end points may be more adequate, but these are regarded as soft end points. Therefore, the major caveats of the ongoing EPD trial design are the use of surrogate disease markers and various definitions for the disease. Using surrogate markers of a disease, not yet clinically proven to cause harm, may be regarded as an inherent limitation of all the current studies. As such, interpretation of their results with regard to real-life clinical use should be viewed with this limitation in mind.

Identifying future subsets of patients that would benefit from EPD is warranted. Because silent CNS lesions occur in almost all patients and EPD up until now have been shown to reduce these lesions, the question is, Should EPD be offered to all patients undergoing TAVR? The answer to that would probably derive from the combination of efficacy, safety, ease

of use, and cost of future EPD. Thus, the risk stratification, usage of accurate definitions of the disease, and the identification of populations at risk that might truly benefit from these devices are something current EPD trials lack. As the mere presence of particulate debris in brain matter may not correlate with the extent of brain injury, cognitive function, or quality of life, the clinical significance of EPD has yet to be determined.

Disclosures

Ron Waksman, MD: Biotronik, Medtronic, AstraZeneca, Boston Scientific, Biosensors International, Abbott Vascular, The Medicines Company, Edwards Lifesciences, St. Jude Medical. The other authors report no conflicts.

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Embolic Protection Devices in Transcatheter Aortic Valve Replacement

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Supplemental Table. Embolic Protection Devices Research and Development Programs

Device	Study reference	Study type	Number of patients	Outcome measures	Results
Embrella	Nietlispach et al. ¹	First in human	n=4. 1 BAV; 3 TAVR	Successful placement of device; New cerebral infarcts	Successful placement achieved in all 4 patients. Infarct detected in MRI of the one BAV patient.
	Rodes-Cabau et al. ²	PROTAVI-C multicenter prospective and non-randomized	Treatment: 41 Controls: 11	Clinical outcomes, TCD HITS, new ischemic lesions in Cerebral DWI MRI, Cognitive function tests.	In the treatment group at 30 days 3 patients had stroke/TIA compared to none in the controls. No difference in cognitive tests. Total number TCD HITS higher in the treatment group. All patients had new lesions in DW MRI – no difference between groups. Lesion volume was lower in the treatment group.
	Samin et al. ³	Retrospective	Treatment : n=15 Historic cohort: n=37	Number of new ischemic lesions in Cerebral DWI MRI	The Embrella group had higher rates of ischemic lesions in DWI MRI (9.0 vs. 5.0, P = .044).
Triguard	Onseal et al. ⁴	First in human with retrospective analysis.	n=15. Historic cohort: n=20.	Successful placement of device. New cerebral infarcts.	Successful placement of device. All patients had new lesions in DW-MRI however in comparison to controls Treatment patients have fewer new lesions per patient.
	Baumbach et al. ⁵	Deflect I prospective, multicentre, single-arm study	Treatment: n=37, comparison to several historical cohorts.	Device success, procedure success, composite safety endpoint, MACCE, TCD HITS, New ischemic lesions in Cerebral DWI MRI, Neuro-Cognitive function tests	Device success in 80%, composite safety endpoint in 8%, MACCE in 16%, new cerebral lesions in DWI not different from historic cohort.
	Deflect II ⁶	Deflect II Prospective, single center, single arm.	N=12	Device performance. New cerebral infarcts.	Study completed. Data not available.
	Lansky et al. ⁷	Deflect III Multicenter prospective and randomized	Treatment: n=45 Controls: n=40	Device success, Procedure success, composite safety endpoint, MACCE, TCD HITS, New ischemic lesions in Cerebral DWI MRI, Neuro-Cognitive function tests	Device success in 88.9%, composite safety endpoint similar in both groups (21% vs. 30.8%, p=NS), new ischemic brain lesion lower in treatment group (11.5% vs. 26.9%), better Neuro-cognitive results for the treatment group.
	REFLECT	Pivotal IDE multicenter prospective randomized			Data not available.

		trial (US and EU)			
Sentinel	Naber et al. ⁸	FIH	Treatment : n=35	Technical success Stroke Rates	Technical success: 60% for the first generation device and 87% for the second-generation device. No procedural TIA, minor or major strokes occurred. One patient had a minor stroke at 30 days.
	Linke et al. ⁹	Clean-TAVI Prospective, single blind, randomized, single center.	Treatment: n=50 Controls: n=50	New cerebral infarcts; new neurological deficits, TCD HITS, neuro-cognitive testing	Device success in 96%, procedural success in 94%, Reduction of total number and volume of new cerebral lesions in DW-MRI, less ataxia reported in the per protocol treatment group.
	Kodali et al. ¹⁰	SENTINEL Pivotal IDE multicenter prospective randomized trial (US and EU)	n=359 (estimated)	Primary endpoint: Reduction in median total new lesion volume as assessed by DW-MRI at Day 4-7 post-procedure Primary safety endpoint: Occurrence of all MACCE at 30 days	On going, data not available.
Embol X	Etienne et al. ¹¹	FIH	n=1	Successful placement of device	Successful placement of device achieved.
	Ye et al. ¹²	FIH	n=2	Successful placement of device	Successful placement of device achieved.
	TAo-EmbolX ¹³	Prospective, single blind, randomized, single center.	n=50 (estimated)	New cerebral infarcts; stroke rates, Neurocognitive function	Data not available.

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