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Role Of Embolic Protection In Transcatheter Aortic Valve Replacement: Results From The Deflect I Study

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ROLE OF EMBOLIC PROTECTION IN TRANSCATHETER AORTIC VALVE REPLACEMENT: RESULTS FROM THE DEFLECT I STUDY

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Abstract

Utilization of a cerebral protection device during transcatheter aortic valve replacement (TAVR) will reduce the rate of periprocedural stroke as well as the occurrence and volume of new lesions on diffusion weighted magnetic resonance imaging (DW-MRI), which may serve as a potential surrogate endpoint for clinical studies. The DEFLECT I study is a prospective, multi-center, single arm study that aims to demonstrate the safety and performance of the TriGard™ Embolic Deflection Device (EDD) (Keystone Heart, Caesarea Business Park, Israel), among patients undergoing TAVR. Primary endpoints were device performance and in-hospital device-related safety. A powered secondary endpoint was the number and volume of new DW-MRI brain lesions. Of the 20 consecutive patients enrolled, the device performed as intended with complete vessel coverage until completion of the valve implant in 80% of cases. The hierarchical composite in-hospital procedure-related major adverse cardiac and cerebrovascular (MACCE) event rates was 10% due to 2/20 major disabling strokes, which occurred the day after the procedure following urgent surgery for a failed TAVR implant and a cardiac arrest due to loss of pacer capture. Compared with historical controls, the number of new ischemic brain lesions detected on DW-MRI were similar (70% vs. 76%); however, patients undergoing TAVR with the TriGard™ EDD device demonstrated a 94% reduction in the maximum lesion volume, a 94% reduction in maximum total lesion volume, and a 65% reduction in mean lesion volume compared with historical controls. An angiographic sub-study demonstrated that the only clinical factor associated with the maintenance of device coverage throughout the procedure was anchorage of the upper stabilizer in the innominate artery. The DEFLECT I study established proof of concept of the TriGard™ device and justifies further evaluation in a planned randomized clinical trial.

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INTRODUCTION

Transcatheter aortic valve replacement (TAVR) is increasingly used to treat patients with aortic stenosis deemed high or extreme surgical risk candidates. Since its introduction in 2002, clinical trials have proven its feasibility, safety, and efficacy. Further, the randomized, controlled PARTNER trial demonstrated the superiority of TAVR to standard balloon valvuloplasty in patients at extreme risk and its non-inferiority compared with surgical aortic valve replacement (SAVR) in high surgical risk patients[1]. However, TAVR is not without its complications.

Stroke has emerged as a major source of morbidity and mortality in patients undergoing the procedure[2, 3]. The periprocedural incidence of stroke has been estimated at 1.5% +/- 1.4%[2], but rates as high as 10% have been reported[4]. Stroke is also a known contributor to acute and ongoing mortality rates[5, 6].

In the following, we will define "stroke" and transient ischemic attack (TIA) according to the 2012 VARC-2 definitions[7]. The pathogenesis of stroke or TIA associated with TAVR likely involves cerebral embolization during device positioning and implantation[5]. The nature of the TAVR procedure lends itself to catheter manipulation of the calcified aortic valve and atherosclerotic aorta. Likewise, most studies show a consistent link between both TAVR and SAVR and embolic lesions visualized on diffusion-weighted-magnetic resonance imaging (DW-MRI). Similar clinically silent lesions only identified with neuroimaging have been designated as "silent" strokes[8]. The question of whether these TAVR-related lesions lead to an increased risk of future cerebrovascular events with even longer term cognitive consequences remains open,

but given the large literature on silent strokes and cognition, this association is probable, with significant clinical implications.

We will explore the likely significance of asymptomatic lesions seen on DW-MRI and present data supporting the link between silent stroke and cognitive decline in order to demonstrate the need for cerebral embolic protection during TAVR. Finally, we will discuss potential therapeutic options, including cerebral protection devices currently under investigation, to prevent stroke related to TAVR.

Clinical Significance of DW-MRI Lesions

DW-MRI detects changes in the self-diffusion of water molecules associated with ischemic injury[9]. In conjunction with the apparent diffusion coefficient, it is able to distinguish between cytotoxic edema caused by tissue infarction and vasogenic edema. DW-MRI is highly sensitive for detecting brain ischemia, and widely available, making it a suitable method for detecting neurovascular events acutely following interventional procedures[10].

Early prospective studies investigating the risk of cerebral embolization associated with endovascular cardiac procedures, involving crossing of a stenotic aortic valve, demonstrated new post-procedure DW-MRI lesions in 2-22% of patients[11, 12]. A higher rate is expected with the bulkier devices utilized in balloon valvuloplasty and TAVR, and new foci of restricted diffusion on DW-MRI, consistent with embolic lesions (Fig. 1), have been demonstrated to occur in 68-84% of TAVR patients, with more than 75% of patients enduring multiple new foci[9, 13, 14]. The majority are asymptomatic with neurologic symptoms occurring in less than 10% of

patients[14, 15]. Though few studies have investigated their clinical significance in the context of TAVR, there are multiple studies showing the association of new DW-MRI lesions with cognitive impairment following other cardiac procedures (Table 1).

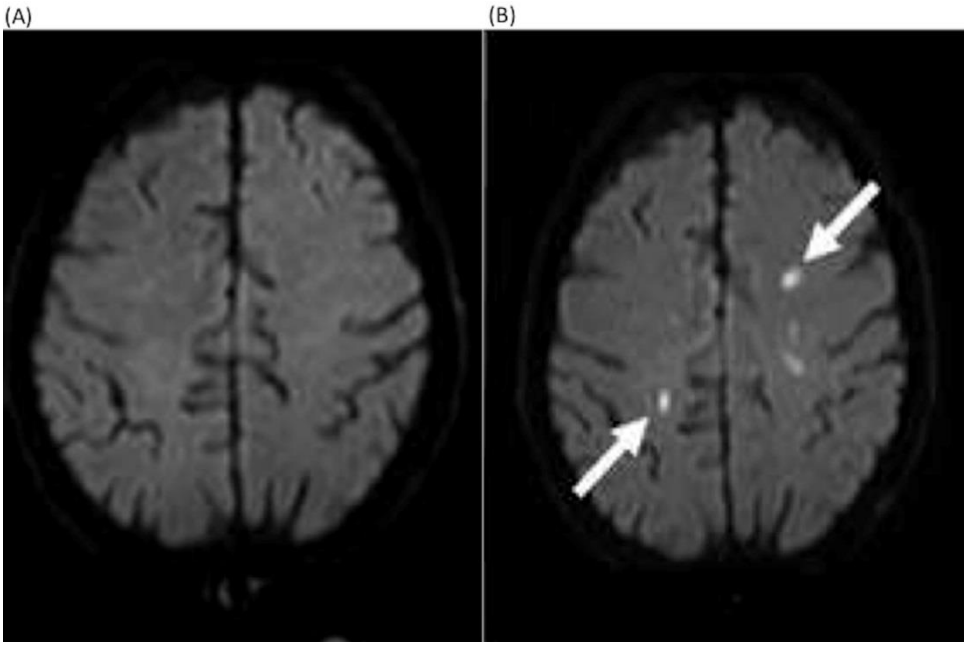

Figure 1. Diffusion weighted-magnetic resonance images: (A) Baseline. (B) Following embolic event. Arrows indicate areas of restricted diffusion.

First, Restrepo et al. demonstrated that in patients undergoing coronary artery bypass grafting, those with new DW-MRI lesions following the surgery had significantly greater declines in cognitive function than those with stable MRI, evident as absolute changes in neuropsychological test performance. In fact, the number of new DW-MRI lesions was correlated with the degree of overall decline as measured within 1 week following surgery[16]. Barber et al. investigated the relationship between post-operative DW-MRI lesions and cognitive decline at 6 weeks, defined as a drop in the Reliable Change Index in at least 1 cognitive measure, following valvular surgery. They found that all patients with postoperative DW-MRI lesions had cognitive decline on at least 1 neuropsychological measure compared with only 35% of those without ischemic change[17].

In patients undergoing left heart cardiac catheterization, more than 16% of patients had post-operative cognitive decline (POCD) following the procedure, defined as a drop of at least 20% on at least 2 of the 12 selected test variables, and patients with DW-MRI lesions failed to show improvement on repeat neuropsychological testing, as compared to those without such lesions[18]. The degree of cognitive decline was related to whether new lesions appeared on DW-MRI post-procedure. In addition, Schwarz et al. compared neuropsychological outcomes in patients undergoing coronary catheterization and coronary artery bypass grafting up to 3 months following the procedure. Indeed, the presence of DW-MRI lesions correlated with POCD in 3 cognitive domains when performed at 3 months as compared to baseline[19].

On the other hand, some studies suggest that DW-MRI lesions may be clinically irrelevant due to apparent reversability[13]. Importantly, DW-MRI lesion reversal may not indicate normalization. Animal studies have shown that even with DW-MRI hyperintensity reversal after ischemia, neurons exhibit structural damage and stress, and histological staining suggests that other non-neuronal cell populations may compensate for the altered fluid balance seen on follow up imaging[20]. Alternatively, the lesions may simply drop below the sensitivity of standard DW-MRI, as high field strength (3 Tesla) imaging has revealed significantly more lesions than 1.5 Tesla studies[21].

There is no data on the long-term consequences of DW-MRI lesions associated with TAVR, however extrapolation from the short-term studies noted above indicates that they cannot be dismissed. A number of studies have concluded that DW-MRI lesions are not predictive of long-term POCD after cardiac surgery[22-24], but the limitations of these individual studies suggest

discrepancies in research methodology that should be improved (Table 1). The studies noted utilized 1.5 Tesla imaging, which may have failed to detect showers of small emboli and thus missed a potential association. In addition, the appropriate DW-MRI endpoint for cardiac procedures has not been defined and these studies reported various lesion characteristics, including mean lesion volume, maximum lesion volume, and number of lesions per patient, therefore increasing the difficulty of cross-study comparison.

Importantly, the neuropsychological testing performed in these studies utilized batteries of multiple individual tests (Table 2). The problem with using multiple individual tests selected at the investigator's discretion is the variability of cognitive domains covered. TAVR-related DW-MRI changes likely impact cognition in subtle ways and this association may be obscured if the cognitive domains most susceptible are not evaluated adequately and/or if neuropsychological instruments that are not sensitive to subtle injury are employed. Further, there is no standard definition for POCD associated with cardiac procedures, suggesting that determination of cognitive decline may vary between studies. There is also no standard neuropsychological battery for cardiac surgery and catheterization, including TAVR. The neuropsychological tests used have been proposed for the detection of vascular dementia, but the selection of tests that may be specific for this diagnosis might not be sensitive to cognitive change following the TAVR intervention[25].

Thus, large, prospective studies with adequate follow-up would help to clarify the association of DW-MRI lesions with clinical outcome following cardiac catheterization procedures, especially

TAVR. A standard neuropsychological battery for measuring cognition after cardiac procedures is also necessary.

Silent Stroke and Cognitive Decline

The relationship between stroke and cognition is well established[26, 27]. Silent stroke is also related to neurodegenerative and psychiatric diseases as well as decline in cognitive and motor abilities in the absence of frank dementia. The prevalence of silent strokes in the elderly population ranges between 13-21%[28, 29] and increases to 30-40% in patients older than 70 years[30]. Although the association of DW-MRI lesions after TAVR with cognitive decline is under debate, there is a growing body of evidence linking silent strokes to poor cognitive outcomes and neurodegenerative diseases.

A "silent" stroke is an area of infarction seen on neuroimaging in the absence of neurological signs or symptoms. Blood flow in silent stroke is compromised and therefore results in neuronal damage, just as in symptomatic infarction. Patients with silent stroke demonstrate "misery perfusion," where there is a decrease in cortical blood flow with an increase in oxygen extraction fraction. They also exhibit diaschisis in which subcortical silent stroke actually causes blood flow to decrease in the superior cortical areas[8].

Evidence for association between silent infarcts and cognitive dysfunction:

The correlation between asymptomatic infarcts and cognitive impairment is convincing. In a prospective study of 1015 elderly people, Vermeer et al. demonstrated that over a 5 year period, the presence of silent brain infarcts at baseline more than doubled the risk of dementia, with

Alzheimer's Disease being the most common type (HR 2.26, 95% CI [1.09-4.70])[28]. The rate of new silent brain infarcts was higher in patients who developed dementia than in those who did not. Further, the presence of silent strokes was associated with significantly worse global cognitive function as well as a steeper rate of cognitive decline. Notably, the presence of multiple silent infarcts was more strongly correlated with cognitive decline than single infarcts[28]. Likewise, Blum et al. studied 658 community-dwelling elderly individuals who received MRI and found that those with any brain infarct had smaller hippocampi than those without. They also found that brain infarcts and smaller hippocampus volumes were independently associated with poorer memory, suggesting that a history of brain infarcts can contribute to a functional state similar to that of early Alzheimer's Disease[31].

It is also known that symptomatic strokes contribute to poorer executive function in patients with Alzheimer's Disease[32]. Similarly, Song et al. found that silent stroke was associated with increased severity of cognitive decline in patients with Alzheimer's Disease[33]. An association between silent stroke and cognitive impairment, self-perceived health status, and independence in community dwelling elderly people has also been shown[29].

In addition to cognition, silent strokes are also associated with depression and motor functional deficits. Fujikawa et al. observed the presence of silent stroke in 51.4% of patients with depression and in 93.7% of those with senile-onset depression[34]. Lastly, in a recent rat model, Faraji et al. demonstrated that repetitive focal ischemic mini-lesions to the sensorimotor cortex resulted in a decreased ability to accurately perform a walking task, indicating that concurrent silent strokes to the cortex can impair motor function[35].

Thus, the accumulation of silent strokes over time likely contributes to cognitive impairment and neurodegeneration. Even 1 silent stroke puts people at risk for cognitive decline and dementia[28]. We suspect that such lesions lower the thresholds for future clinically significant strokes as well as the clinical expression of other neurodegenerative pathologies like Alzheimer's Disease. In addition, silent strokes are associated with steeper cognitive decline in patients with diagnosed dementia. Because TAVR-related microemboli often cause multiple new silent strokes that may contribute to the ischemic burden of the patient, the need for cerebral embolic protection is great.

Embolic Protection in TAVR

Cerebral embolic protection may be accomplished through drugs, such as anti-platelet or antithrombotic regimens, and devices, including capture or deflective devices.

Anti-thrombotic regimens:

The literature is scarce regarding the appropriate anti-thrombotic regimen for TAVR. The only randomized trial to date evaluated the need for dual anti-platelet therapy with aspirin and clopidogrel for 3-6 months after the procedure in 79 patients and found no clinical benefit from the addition of clopidogrel[36]. This finding is important because patients with chronic atrial fibrillation treated with warfarin and aspirin demonstrate a significantly increased bleeding risk with the addition of clopidogrel for catheterization procedures[37]. Larger, prospective studies would be helpful in assessing the need for and type of antithrombotic therapy for patients undergoing TAVR.

Cerebral protection devices:

Given the temporal pattern and arterial distribution of the majority of TAVR-related infarcts[5], peri-procedural cerebral embolization is the most likely mechanism of cerebral infarction. Therefore, anti-thrombotic regimens are unlikely to provide as much benefit as filter-based protection devices, the utility of which has been demonstrated in carotid artery stenting. There are a few devices that have been developed specifically for cerebral protection in TAVR. These include the Claret CE Pro™, the Embrella (Edwards Lifesciences, Irvine, CA, USA) deflection system, and the TriGard™ embolic DEFLECTion device (EDD) (Keystone Heart Ltd., Herzliya, Israel), which vary in their delivery sheath sizes, routes of delivery, and vessel coverage (Table 3).

The Claret CE Pro™ (Fig. 2) is the only device that captures and removes debris from the body. The device uses a 6F transradial or brachial delivery system, a 9-15 mm brachiocephalic artery filter, and a 7-10 mm left common carotid artery filter, with 140-micron pore sizes[38]. The first-in-man trial in 35 patients demonstrated first-generation device and second-generation device success rates of 60% and 87%, respectively. Debris was captured in 54.3% of patients and no procedural cerebrovascular events

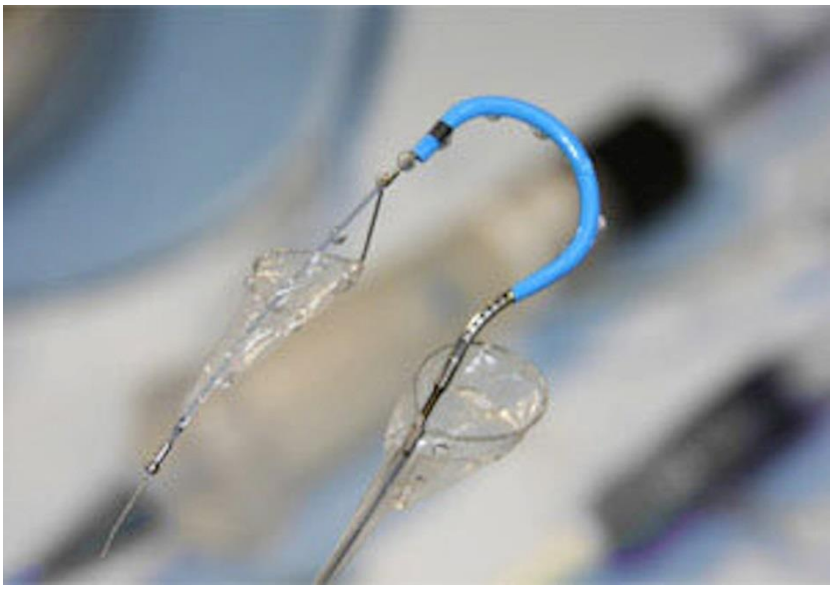

Figure 2. The Claret CE Pro™.

occurred; however 1 patient experienced a minor stroke and 2 patients suffered major strokes within 30 days of the procedure; 1 major stroke occurred within 4 hours of the procedure[38]. This study was limited by the absence of pre- and post-procedural neuroimaging as well as tests of neurocognitive function.

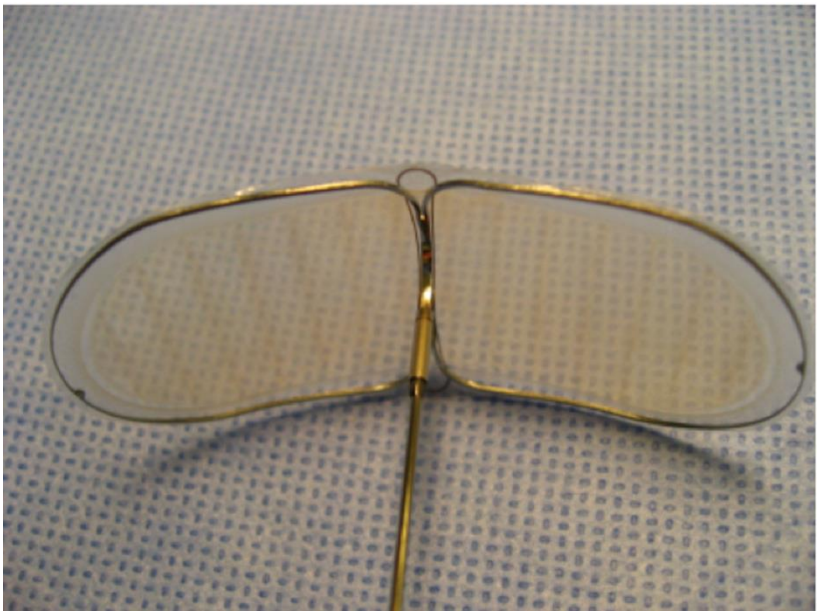

Figure 3. Embrella embolic deflector.

Like the Claret CE Pro™, the Embrella (Fig. 3) only covers the innominate and left carotid arteries, but may also cover the left subclavian artery up to 60% of the time. The device also uses a 6F transradial or brachial delivery system. It consists of 100 micrometer sized pores on a membrane mounted on a Nitinol frame and shaft, with 3 radiopaque markers to aid fluoroscopy-guided delivery. The first-in-human study successfully employed the device in 4 patients without damage to the arteries or interference with the TAVR procedure. None of the TAVR patients exhibited new periprocedural neurologic symptoms or new findings on pre-discharge MRI, however one patient who underwent balloon valvuloplasty alone demonstrated a new 5-mm acute cortical infarct in the right temporal lobe[39].

The TriGard™ EDD (Fig. 4) covers all 3 cerebral inflow vessels and is delivered via the transfemoral route. It uses a larger delivery catheter (9F) via the contralateral transfemoral approach, and a heparin-coated Nitinol mesh to deflect embolic debris. A vertical stabilizer is positioned in the innominate artery and lower feelers anchor the device against the upper wall of the aortic arch. It is the only system that covers all 3 of the great vessels branching off of the aorta, providing the maximal scope of protection[40]. A pilot study of 15 patients demonstrated device safety, and significant reduction in embolic events (average of 3.2 new DW-MRI lesions per patient vs. 7.2 per historical)[40]. The only neurological complication involved 1 patient suffering a TIA within 2 days of the procedure. A 60 patient CE mark trial is currently underway with formal DW-MRI and neuropsychological assessment.

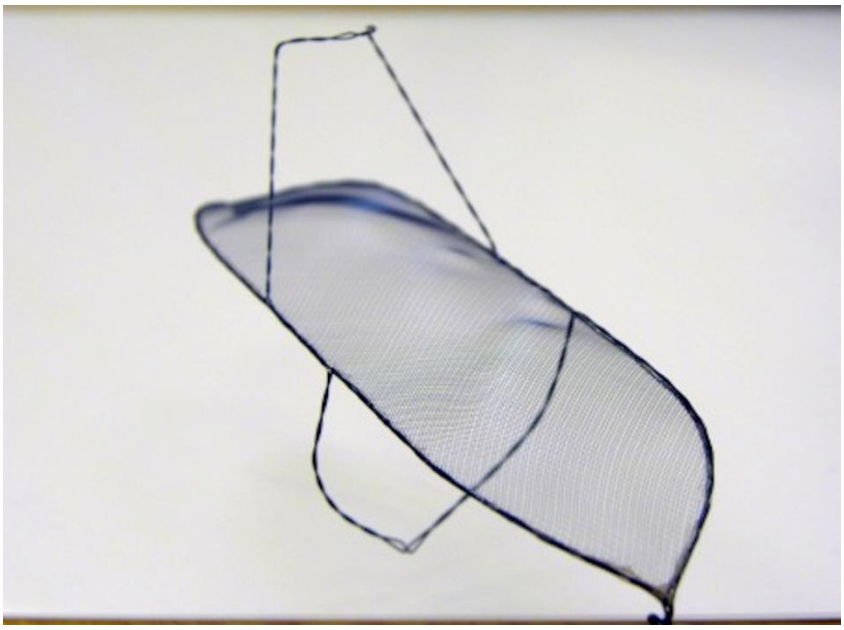

Figure 4. Keystone Heart Triguard™ Embolic Deflection Device.

Embolic protection devices show promise in decreasing the rate of cerebral embolization and stroke in patients undergoing TAVR but their ability to prevent or decrease the long-term occurrence of stroke is unclear. Likewise, cerebral infarction due to procedural hypotension as well as continued embolization from the calcific, degenerated native valve cusps and valve

prosthesis would not be affected by the use of procedural deflection devices. These issues remain to be addressed with further refinement of TAVR.

Neuro-Imaging as an Endpoint Measure

Choosing an appropriate endpoint for a clinical trial can be complex. In fact, up to 10-15% of medical devices that enter the EU regulatory pathway lack relevant endpoints, which is considered grounds for objection. The penetration rate of devices in general, and in TAVR specifically, is significantly delayed in the US compared to Europe mostly due to FDA requirements for reasonable assurance of safety and effectiveness of a device prior to its approval [40].

For clinical trials investigating neuro-protection devices for use in cardiac procedures, the investigators must prove that the device is able to reduce the occurrence and/or severity of cerebral events. Ideally this would be accomplished by reporting an actual reduction in the rate of stroke, transient ischemic attack, and other neurologic events according to Valve Academic Research Consortium-2 definitions [7]. Because the occurrence of TAVR-related stroke is relatively low (<10%), a large sample size would be needed to detect a difference in clinical event rate with versus without a protection device. In addition to sample size requirements, the rising cost of clinical trials limits the feasibility of using relatively uncommon clinical events as trial efficacy endpoints. Further, silent ischemia accounts for the majority of lesions detected on neuro-imaging following TAVR procedures. Using a clinical event endpoint to measure device success would miss the occurrence of these silent lesions, which are associated with cognitive decline and mortality [41, 42].

Neuro-imaging, specifically DW-MRI, may serve as a surrogate endpoint for clinical studies detecting cerebral events in which cost and sample size limitations prohibit the use of clinical outcomes. DW-MRI, which has sensitivity and specificity up to 92% and 97%, respectively, combines features of conventional spin echo and gradient echo techniques to image the freedom of the diffusion of water molecules to identify restriction in diffusion, suggestive of cerebral ischemia [43]. In cytotoxic edema due to hypoxia, the re-distribution of water from the extracellular to the intracellular space is visible within zero to five days of the event (Fig. 1). On DW-MRI, normal tissue appears gray due to the Brownian motion and diffusion of water molecules, whereas restricted diffusion in the case of ischemia prevents the normal loss of MRI signal and thus appears white. A bright signal on DW-MRI and a dark signal on the corresponding apparent diffusion coefficient map is characteristic of acute brain injury within five days.

One important issue to consider is that evidence for long-term consequences of lesions detected by DW-MRI is lacking. Indeed, recent studies have implied that DW-MRI lesions after TAVR are not related to self-sufficiency or mortality one-year post-procedure and that there may even be less cognitive decline post-TAVR compared with surgery, despite a higher incidence of embolic lesions [44, 45]. These studies are limited by small sample sizes but they suggest that there may limitations in utilizing DW-MRI to evaluate TAVR outcomes.

Another major limitation of using DW-MRI in clinical trials is that no clear definition of the endpoint exists. Qualitative measurements include lesion number and vascular territory involved

and quantitative measurements include total lesion volume, average lesion volume, and maximum lesion volume. All are key neuro-imaging endpoint parameters to follow the efficacy of neuro-protection, however, the endpoint must be standardized to allow for cross-study comparison.

Ongoing clinical trials investigating cerebral protection devices for TAVR are utilizing various DW-MRI measures to determine device efficacy. The ongoing Prospective Randomized Outcome Study in Patients Undergoing TAVR to Examine Cerebral Ischemia and Bleeding Complications (PROTAVI) trial, which is randomizing patients eligible for TAVR to undergo the procedure with or without the Embrella deflection device, will analyze the rate of new DW-MRI brain lesions at seven days post-procedure. Likewise, the DEFLECT I trial is a single arm study enrolling up to 60 patients in the EU, Canada, and Brazil to undergo TAVR with the Keystone Heart Trigard^{TM} in place using the presence of new DW-MRI lesions post-procedure compared with a historical control group as a measure of device success.

Although DW-MRI lesion presence and rate of occurrence are being used as endpoints, total lesion volume is the most reproducible measurement when performed in an experienced core laboratory, and along with geographic location, provides the best measure of overall burden of ischemic injury, and may therefore be a more appropriate endpoint measure. Though it fails to identify the functional region of the brain involved, studies have identified DW-MRI lesion volume as an independent predictor of clinical outcome after acute stroke [46, 47]. Specifically, mean lesion volume has been correlated with mental changes and vascular dementia following endovascular procedures [48]. In contrast, the presence and number of DW-MRI lesions are only

likely to be clinically relevant if the individual lesion is large or in an area of functional significance [49]. Therefore, the Yale-University College of London (UCL) summit concluded that DW-MRI lesion volume should be measured by independent core laboratory assessment with validated and reproducible methodology and should be included and reported in all clinical studies using DW-MRI to investigate neuro-protection devices for use in TAVR. We recommend that single lesion volume, number of new ischemic lesions, and total lesion volume be measured.

Lastly, in 2011, the FDA issued draft guidance for clinical trial imaging endpoints for studies intending to confirm drug efficacy, recognizing that the use of imaging may assist in the assessment of safety and efficacy as well as patient eligibility. US regulatory requirements have been an impediment to early clinical testing of new devices, which US investigators have mostly out-sourced overseas. During the Yale-UCL summit, the FDA expressed its goals to encourage medical device innovation, enhance regulatory science, and facilitate early feasibility clinical studies in the US. Consensus from the 2013 Yale-UCL summit called for validation of imaging endpoints in neuro-protection trials involving medical devices and encouraged European regulatory bodies and the FDA to work with the clinical and device industry to support this position [50].

In summation, filter-based embolic protection devices, the utility of which has been demonstrated in carotid artery stenting, show promise as a means of preventing stroke and other neurologic complications following TAVR. Prevention of neurological complications is necessary in order to fully realize the potential of TAVR and optimize the outcomes of patients with severe aortic stenosis. Mean and total lesion volume, as measured on DW-MRI, may be

appropriate surrogate endpoints for clinical studies like DEFLECT I. We report the results of the DEFLECT 1 clinical trial, which was designed to demonstrate the safety and performance of the TriGard™ EDD.

HYPOTHESIS

Patients undergoing TAVR with the Keystone Heart TriGard™ EDD in place will demonstrate a lower rate of periprocedural stroke, as well as a reduction in the number and volume of new brain lesions on DW-MRI.

SPECIFIC AIMS

1. To evaluate the safety and performance of the Keystone Heart TriGard™ EDD in patients undergoing TAVR
2. To determine the risk of clinical stroke with the EDD in place.
3. To evaluate the occurrence and size of new DW-MRI brain lesions with the EDD in place as compared with historical controls.
4. To evaluate the impact of baseline cardiac anatomy and procedural characteristics on device position and function throughout the TAVR procedure.

METHODS

Study Design and patient population

The DEFLECT 1 clinical trial is a prospective, multi-center, single arm study, designed to evaluate the safety and performance of the TriGard™ EDD in patients undergoing TAVR for the purpose of obtaining European Union (CE Mark) approval on the basis of 20 consecutive patients, but allowing extended enrollment of up to 60 patients from up to 10 investigational sites in the European Union, Brazil and Canada.

Patients were included if they were older than 18 years of age, met current indications for TAVR, and were willing to comply with protocol-specified follow-up evaluations. Patients were excluded from the study if they were undergoing TAVR via the trans-axillary, subclavian, or direct aortic route, were in cardiogenic shock, or had a known myocardial infarction (MI) within 72 hours of the procedure, had impaired renal function (Glomerular Filtration Rate <30); bleeding diathesis, coagulopathy, or refusal of blood transfusion, past or pending organ transplantation, known medical illness or history of substance abuse that could interfere with compliance, stroke, TIA, known hypersensitivity or contraindication to aspirin, heparin/ bivalirudin, clopidogrel/ticlopidine, nitinol, stainless steel alloy, and/or contrast sensitivity that could not be adequately pre-medicated, severe peripheral arterial disease precluding delivery sheath vascular access, documented friable or mobile atherosclerotic plaque in the aortic arch, contraindication to cerebral DW-MRI, or had planned treatment with any other investigational device or procedure during the study period. Patients meeting eligibility criteria for TAVR were

enrolled in the study after providing written informed consent. A medical ethics committee/ Institutional Review Board approved the study.

Device description

The TriGard™ EDD (Fig. 4) is intended to be delivered percutaneously via a 9 Fr sheath and positioned in the aortic arch to deflect and reduce embolic material (debris/ thrombus) to the cerebral arteries during endovascular procedures. It is a temporary single use, biocompatible filter, made of fine nitinol #1 (nickel titanium alloy) wires, which is anchored in position by an atraumatic stabilizer, positioned in the ostium of the innominate artery (Fig. 5). The filter portion

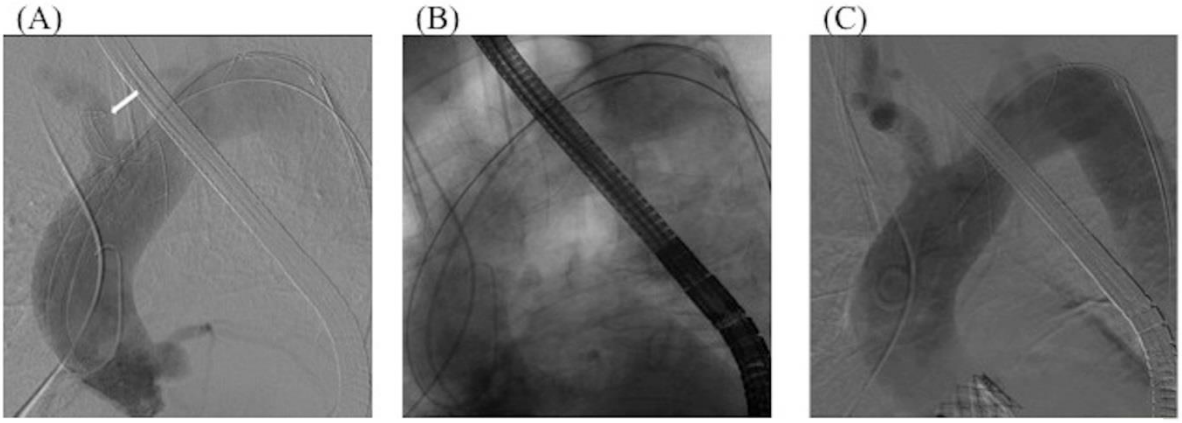

Figure 5. Angiography demonstrating Keystone Heart Triguard™ device position. (A) Before the TAVR procedure. White arrow indicates device upper stabilizer anchorage in innominate artery. (B) During the TAVR procedure. (C) After the TAVR procedure. TAVR, transcatheter aortic valve replacement.

of the device covers all three major cerebral arteries in the aortic arch (innominate, left common carotid and subclavian) and maintains blood flow to the cerebral vessels through 250 μm sized pores, while deflecting larger embolic/particulate matter toward the descending aorta. The filter is coated with an antithrombotic coating (Applause™ Heparin Coating, Surmodics, USA).

Screening and Procedure Description

A series of routine tests were performed to assess general patient eligibility for the study including cardiac biomarkers (CK, CK-MB isoenzyme and troponins) within 24 hours of the procedure to exclude MI and a baseline computed tomography angiogram (CTA) of the left heart, aortic arch and great vessels extending to the peripheral access vessels per standard of care. Patients meeting eligibility criteria signed informed consent prior to enrollment in the study. DW-MRI of the brain was performed within 21 days prior to the procedure. Comprehensive neurological assessments were performed at baseline, including the NIH Stroke Scale, the Modified Rankin Scale and the Montreal Cognitive Assessment (MoCA).[51] These were performed within one week of the procedure by a trained and qualified individual, and repeated by a neurologist or neurology fellow when a stroke or TIA was suspected.

All patients were treated with a 300-325 mg loading dose of aspirin and 75-325 mg of aspirin prior to the procedure, and either 300 mg of clopidogrel 6 hours before the procedure or 600 mg peri-procedurally. Following the procedure, the recommended antiplatelet regimen was ASA 75 mg daily indefinitely and 75 mg daily of clopidogrel for at least 6 months.

TAVR was performed according to standard institutional practice under local or general anesthesia using a transapical or transfemoral approach as indicated. At the start of the procedure, a 9Fr arterial sheath was inserted in the contralateral femoral artery, the EDD device was advanced and deployed across the aortic arch, covering the ostia of the 3 major neck vessels (innominate, left common carotid and subclavian) and withdrawn at the completion of the TAVR

procedure. The procedure was complete once the guiding catheter was removed from the patient and the patient was off the table.

Clinical Follow-up

Follow-up DW-MRI of the brain was performed at 4±2 days (range 2-6 days) post-procedure. A one-month clinical follow-up visit was scheduled for 30±7 days post-procedure for anginal status (Canadian Cardiovascular Society, Braunwald or silent ischemia) and any adverse events. A neurologic evaluation consisting of the NIH Stroke Scale, Modified Rankin Scale, and MoCA, was performed at discharge and 1 month follow-up by an independent qualified individual and repeated by a neurologist or neurology fellow if a stroke or TIA was suspected.

Endpoints and Definitions

Primary Endpoints

The study had two primary endpoints: *The primary device performance endpoint* was defined as the ability to (1) access the aortic arch with the delivery catheter, (2) deploy the EDD, (3) position the device to cover all 3 cerebral inflow vessels (verified by angiography) without obstruction of blood flow or interference during the TAVR procedure, and (4) retrieve the EDD device and delivery system, in the absence of adjudicated device malfunction (Fig. 5). Device malfunction was defined as the failure of the EDD to perform in accordance with its intended use.

The primary safety endpoint was in-hospital device and procedure-related safety, defined as the incidence of investigational device and investigational procedure-related serious adverse events in a composite hierarchical safety endpoint. The components of this safety endpoint included: Valve Academic Research Consortium (VARC) defined as (1) cardiovascular mortality, (2) major stroke disability, (3) life-threatening or disabling bleeding[52], (4) distal embolization (noncerebral) from a vascular source requiring surgery or resulting in amputation or irreversible end organ damage, major vascular or access-related complications and (5) need for acute cardiovascular surgery (defined as immediate transfer from the catheterization lab to the operative room during the initial treatment phase due to the need for emergency coronary artery bypass graft surgery, cardiac valve surgery, or other vascular surgical intervention).

Secondary Endpoints

A major powered secondary efficacy endpoint was the number and volume of new embolic lesions detected by DW-MRI of the brain from pre-procedure to 4±2 days (range 2-6 days) post-procedure compared to a historical control (Table 3).

Additional secondary performance endpoints included: (1) procedure success, defined as successful device performance without the occurrence of the primary composite safety endpoint (defined above); (2) device deployment time (defined as the time elapsed between insertion of the EDD into the delivery sheath and successful deployment into the aortic arch); and (3) total procedural time (defined as the time elapsed between the first arterial access and removal of the last guiding catheter from the arterial access sheath).

Other secondary safety endpoints were measured in hospital and at 30 days and included: (1) device-related safety (component and hierarchical composite), as defined above for the primary

safety endpoint, (2) Major Adverse Cardiac and Cerebrovascular Events (MACCE) defined by a hierarchical composite endpoint of VARC-defined all-cause mortality, major stroke disability, life-threatening (or disabling) bleeding, acute kidney injury – stage 3, peri-procedural MI, major vascular complication, and repeat procedure for valve-related dysfunction[52]; (3) VARC-defined all cause and cardiovascular mortality, periprocedural and spontaneous MI, major and minor vascular complications, acute kidney injury, and neurological events (both component and composite), including stroke and its sub-classifications[52], as well as cerebral infarction (defined as evidence of brain cell death from imaging studies or pathological examination), encephalopathy (defined as altered mental state, e.g., seizures, delirium, confusion, hallucinations), and intracranial hemorrhage (defined as a collection of blood between the brain and skull, subcategorized as epidural, subdural, and subarachnoid bleeds), and cognitive dysfunction as assessed by the MoCA.

Study Conduct and Central Laboratories

Site monitoring was performed for 100% of clinical fields and clinical events (MedPass International, Paris, France). All adverse events were adjudicated by an independent Clinical Events Committee (Yale Cardiovascular Research Group, New Haven, CT) and all neurologic evaluations including NIH Stroke Scale, Modified Rankin Scale and MoCA were independently reviewed by an expert neurologist (AB, Columbia University, New York, NY). Three independent core laboratories were used for independent assessment of imaging data and endpoint measures.

Angiographic Core Laboratory (Yale Cardiovascular Research Group, Yale University, New Haven, CT): All procedural angiograms were sent and reviewed independently by qualified analysts trained in the procedure, the investigational device and its intended use. The angiographic analysis included the first consecutive 20 patients enrolled in the trial. An independent angiographic core laboratory performed comprehensive quantitative coronary angiography of baseline and final angiograms using validated methods (Medis, Leiden, The Netherlands). All EDD performance criteria including successful 1) access of the aortic arch with the delivery catheter, (2) deployment of the EDD, (3) positioning of the device to cover all 3 cerebral inflow vessels without obstruction of blood flow or interference with the TAVR procedure, and (4) removal of the device, were adjudicated by the core laboratory and used for reporting of the primary endpoint. Further angiographic analysis consisted of determining, before, during, and after the TAVR procedure, whether the EDD covered all 3 aortic arch vessels, whether the EDD upper stabilizer was anchored in the innominate artery ostium, and the aortic arch classification. In addition, the innominate artery reference vessel diameter (RVD), take off angle from the innominate artery and aortic arch, take off angle from the EDD after positioning in the aortic arch, and take off angle from the EDD after TAVR were measured. All cases were reviewed for quality control by the laboratory director.

Diffusion-Weighted MRI Core Laboratory (Global Research Institute, Richmond, VA): All baseline and follow-up DW-MRI images were reviewed and analyzed by an independent core laboratory. The analysis was performed blinded to temporal sequence, using validated qualitative and quantitative methods (Vitrea, Version 6.3.2; Olea, NeuroScape; Version 1.2.0). Axial DW-MRI images and corresponding apparent diffusion coefficient (ADC) maps, as well as

corresponding T2-weighted images were reviewed for the presence of lesions with high signal intensity on DW-MRI. Acute ischemic lesions were defined as those areas of high signal intensity on DW-MRI with corresponding areas of low signal intensity on the ADC maps. Corresponding T2-weighted images were also reviewed for T2-shine through. Coronal and sagittal image reformats were also reviewed to determine whether lesions were single or multiple. For each patient, the total number of lesions on the pre-TAVR DW-MRI, the total number of lesions on post-TAVR DW-MRI, and the total number of new lesions were recorded. For each positive lesion on DW-MRI, the number of positive voxels, as measured with the Olea software, and the volume of each lesion were recorded. Lesion volumes were summed across each patient to yield total lesion volume.

CT Angiography Core Laboratory (Global Research Institute, Richmond, VA): All pre-procedural CTAs were forwarded to an independent CT angiographic core laboratory to perform independent assessment of anatomic measures potentially related to device performance and cerebral embolization including vessel tortuosity, presence and extent of valve and vascular calcification and plaque among others. All quantitative measures were performed using validated software (Medis, Leiden, The Netherlands).

Statistical Analysis

The intent to treat population is the primary analysis population for DEFLECT I. Continuous variables are presented as mean ± standard deviation (SD). Binary variables are described as frequencies and percentages. The hypothesis of the powered secondary efficacy endpoint is that the EDD will be superior to the historic control with respect to the number and volume of new

embolic lesions detected by DW-MRI of the brain from pre- to post-procedure. The historic control for new cerebral lesions was derived from a weighted average of 5 clinical trials (Table 1)[9, 13, 15, 53, 54]. These trials were chosen due to similar inclusion/exclusion criteria and similar time points for DW-MRI follow-up. Thus, the control event rate based on contemporary data is assumed to be 76%. The sample size is calculated for the hypothesis of superiority assuming 90% power to detect a 40% reduction in DW-MRI lesions with the EDD. With a two-sided α=0.05, a minimum total of 28 patients treated with the EDD would provide 90% power to conclude that the EDD was superior to historical controls without neuro-protection. The protocol allows continued enrollment of up to 60 patients to account for loss to follow-up or contraindication to a post-procedure DW-MRI (e.g., pacemaker implantation) to meet the efficacy endpoint. For the angiographic sub-study, all statistical analyses were performed using SAS version 8.2 (SAS Institute Inc, Cary, North Carolina). Categorical variables are presented as frequencies and were compared with Pearson chi-square or Fischer's exact test. Continuous variables are presented as mean ± SD and were compared with ANOVA or the Kruskal Wallis test.

Contributions

I participated in protocol development and revision, as well as weekly teleconferences with the trial sponsor and monitor. Patient enrollment and data collection were performed by individual investigators at the international sites. I led the clinical events committee, which served to adjudicate all adverse events. My responsibilities for that role included obtaining source documents from the international sites, writing detailed narratives for each adverse event and angiographic analysis, preparing adverse event and adjudication forms, as well as recruiting a diverse panel of 4 clinical experts from Yale to adjudicate each event. I also assisted with

presentation preparation for the sponsor meetings, performed interim and periodic statistical analyses, drafted the manuscript for publication and am currently participating in revisions. For the angiographic sub-study, I designed the study, collected all of the data, performed the statistical analyses in SAS, wrote the abstract, and gave the oral presentation at EuroPCR.

RESULTS

A total of 20 patients were enrolled in DEFLECT I from 5 actively participating clinical EU sites, including 8 patients from University College of London Hospitals, 2 patients from University Hospitals of Leicester, 2 patients from Brighton and Sussex University Hospital, 7 patients from University Hospitals of Bristol, and 1 patient from Amphia Ziekenhuls Molengracht Breda. The study population is representative of subjects undergoing TAVR with high or extreme risk indications (Table 4). A total of 21 valves were implanted in 20 patients through the transfemoral approach with general anesthesia in 90.0% (18/20); 47.6% (10/21) recieved the Edwards SAPIEN heart-valve system (Edwards Lifesciences, USA) and 52.4% (11/21) the Medtronic CoreValve® system (Medtronic, Inc., USA). Pre-TAVR balloon valvuloplasty was performed in 16/20 (80%) cases. TAVR implantation was successful in 19 out of 20 cases. A single case required urgent conversion to surgical aortic valve replacement after failed implantation of 2 TAVR devices complicated by severe aortic insufficiency.

Primary endpoints

A total of 21 EDD devices were successfully delivered to the aortic arch in 20 patients (100% delivery success). The EDD and delivery sheath accessed the aortic arch, deployed into the aortic arch and were retrieved intact in 100.0% (21/21) of devices used. Coverage of all three cerebral vessels was achieved in 95.0% (19/20) of cases prior to the TAVR procedure; in 1 case, 2 devices were attempted but the investigator was unable to successfully position the device as intended due to poor visualization in an obese patient.

The EDD device performed as intended in 80.0% (16/20) of cases with complete cerebral vessel

coverage from initial EDD positioning, passage of the TAVR delivery system, and positioning and deployment of the TAVR device. The EDD remained in position with full coverage of all cerebral vessels until after removal of the TAVR delivery system in 65.0% (13/20) of cases. Device performance results are reported in Table 5.

The primary safety endpoint of in-hospital EDD and procedure related safety was not met by any patient (0%) as there were no EDD adjudicated device or procedure related cardiovascular deaths, major stroke disability, life-threatening (or disabling) bleeding, distal embolization, major vascular/access site related complications or the need for acute cardiovascular surgery reported (Table 6).

Secondary Endpoints

Procedure success was 80%, mean device deployment time was 16.4±13.8 minutes, and mean total procedure time was 85.6±15.9 minutes. There was no obstruction to cerebral blood flow or interference of the EDD with the valvuloplasty or TAVR procedure reported in any of the cases.

The composite (non-EDD related) in-hospital MACCE was 10% as a result of 2 major stroke disabilities. One stroke occured the day following urgent surgical conversion after a failed TAVR implant, and the second stroke occured in a patient whose procedure was complicated by loss of ventricular capture from a temporary pacing lead in the setting of complete heart block, requiring cardiopulmonary resuscitation. There was one major vascular complication (5.0%); a thoracic aortic dissection occurring in the same patient who underwent 2 failed TAVR attempts with urgent conversion to surgery. The dissection was diagnosed intra-operatively following

manual manipulation of the TAVR device and removal. It was repaired surgically and the patient recovered. There were 2 patients (10.0%) who experienced AKI (stage 1 (n=1), stage 3 (n=1)) related to contrast administration during the study procedure. There were a total of 4 non-EDD related major bleeding events (20.0%), all of which resulted in a drop in hematocrit >15% and 5 minor vascular complications (25.0%), 3 of which (left groin hematoma, bilateral groin hematomas, and bilateral femoral access site oozing) involved the EDD delivery system. All bleeding complications resolved without sequelae.

At 30 days the hierarchical MACCE was 15%; in addition to the 2 in-hospital major stroke disabilities, there was an additional non-cardiovascular death in a patient who developed broncho-pneumonia that occurred after discharge but prior to 30-day follow-up. Primary and secondary safety endpoints are summarized in Table 6.

DW-MRI

DW-MRI results are presented in Table 7. No patients were excluded due to unobtainable or un-interpretable DW-MRI images. New post-procedure DW-MRI lesions were found in 70% (14/20) patients. This rate was not significantly different than the weighted mean of historical control rates from studies reported in unprotected TAVR (70% vs. 76%)[9, 13, 15, 45, 53-55]; however, there was a 94% reduction in maximum single lesion volume (0.39 vs. 6.45 cm^3),[15, 45] a 65% reduction in mean single lesion volume (0.12 vs. 0.34 cm^3),[13, 15, 45, 54, 55] a 57% reduction in mean total lesion volume (0.7 vs. 1.64 cm^3),[13, 15, 45, 54, 55] and a 94% reduction in maximum total lesion volume (3.94 vs. 70.3 cm^3).[15]

Angiographic sub-study

100% of patient angiograms were suitable for complete analysis. 7 patients were classified as aortic arch type I (35%), 9 type II (45%), and 4 type III (20%). Anatomical measurements, presented as mean +/- standard deviation, are as follows: innominate artery RVD (11.49 +/- 1.54), take off angle from innominate artery and aortic arch (73.52 +/- 26.19), take off angle from EDD after positioning (114.72 +/- 30.35), and take off angle from EDD after TAVR (120.28 +/- 26.95). The only angiographic characteristic significantly associated with complete device coverage before, during, and after the TAVR procedure was whether the device upper stabilizer was anchored in the innominate artery at those respective time points (Prior: $p = 0.01$; During: $p = <0.0001$; After: $p = <0.0001$). No baseline anatomical characteristics were associated with the ability of the device to maintain coverage (Table 8).

DISCUSSION

Peri-procedural stroke is a significant contributor to morbidity and mortality in high-risk patients undergoing TAVR. Recent studies have demonstrated an early high-peaking hazard phase in the period immediately following the procedure as well as an arterial distribution of periprocedural cerebral infarcts reflective of typical embolic patterns[5, 56]. These data support embolization of atherosclerotic debris during valve implantation and balloon aortic valvuloplasty as the most likely mechanism for periprocedural stroke in TAVR, and provides the rationale for neuro-protection during the TAVR implant procedure. Neuro protection is not intended to completely eliminate the risk of clinical stroke or neuro embolic events. Though approximately 50-65% of all strokes occur during the procedure, an increased stroke risk is present in the months following the procedure and is likely related to the high-risk profile of the patient population and potentially thrombosis of the implanted valve.[57-59]

The DEFLECT study provides evidence for the feasibility, performance and preliminary efficacy of the TriGard^{TM} EDD. The EDD was placed in the aortic arch and successfully retrieved in all cases, with proper positioning and protection of all cerebral vessels until completion of TAVR in 80% of cases. Thus, in the majority of cases the device was properly positioned to provide neuroprotection during balloon valuvloplasty and valve prosthesis deployment, the period during which the majority of cerebral embolic events have been demonstrated to occur[60, 61]. The EDD was maintained in position until complete retrieval of the TAVR delivery system in 65% of cases. Whether there is incremental benefit in retaining complete neuroprotection until complete removal of the TAVR system remains to be seen. Several studies using TCD have shown that the majority of microembolization occurs during balloon valvuloplasty and TAVR prosthesis

positioning and deployment and not during the retrieval phase of the TAVR delivery system.[60, 61] TCD data gathered throughout the TAVR procedure during each DEFLECT case, will help further clarify the precise period during which the EDD must be in place to provide optimal protection.

It is important to note that most device performance failures (inability to position the EDD and maintain its position) occurred in the first 1-2 cases at the investigational sites. As with any novel device, a learning curve is expected and we did see placement improvement in later cases. We predict further improvement in overall device performance with additional enrollment.

Though the proportion of patients with new ischemic lesions, and the maximum and average number of new lesions were similar in DEFLECT-I as compared with historical controls, maximum and mean single lesion volume were much smaller than the respective averages in the reported literature. Overall, total lesion volume was smaller in DEFLECT-I, which was primarily driven by the reduction in the single lesion volume. These results suggest that the Triguard™ EDD device was successful in deflecting larger emboli away from the cerebral vessels, resulting in significant reductions (up to 94%) in maximum single lesion volume. Similarly, mean lesion volume was 65% lower compared to historical controls. While overall lesion numbers were slightly higher compared to historical data, due to lower single lesion volume, maximum total lesion volume on a per-patient basis was 18-fold smaller compared to the one study in the reported literature, representing a 94% reduction in maximum total lesion volume.

While 2 disabling strokes occurred, they occurred after TAVR and in association with urgent surgical conversion of the failed TAVR procedure in the first case and following cardiac resuscitation in the second case.

It is unlikely that these strokes reflect a failure of neuro-protection. Major stroke event rates reported in similar trials range from 3.8%[62] to 5.0%[1] up to 30 days. We would not expect complete elimination of neurologic events in our study; however, use of the Keystone Heart TriGard™ should result in a decreased peri-procedural stroke rate associated with uncomplicated TAVR as well as a reduction in silent ischemic events. While symptomatic strokes can result in obvious disability, multiple studies have demonstrated the cognitive implications of DW-MRI lesions in cardiac procedures.[16, 17, 41] Further, DW-MRI lesion volume may be a more valuable measure than number of lesions because volume is most indicative of overall ischemic burden and is predictive of clinical outcome after stroke.[46, 47] Following endovascular procedures, mean lesion volume has been associated with vascular dementia and cognitive changes.[48] Thus, the Keystone Heart EDD resulted in large relative reductions in single and total lesion volumes compared with historical controls, suggesting that device utilization can result decreased overall ischemic burden and post-operative cognitive changes. Neurocognitive testing results will lend further support to this finding; however, a randomized trial comparing protected vs. unprotected TAVR is necessary.

Performance of the TriGard™ EDD in this early series appears similar to other neuroprotection devices. The Claret CE Pro™ and the Embrella (Edwards Lifesciences, Irvine, CA, USA) deflection system have been developed to lower the risk of cerebral embolism during the TAVR

procedure. Results of first-in-human experiences with these devices have demonstrated comparable technical success rates[38, 39]; however, the TriGard™ EDD may offer superior protection against cerebral embolism due to its coverage of all three aortic arch vessels, compared with the Claret CE Pro™ and Embrella devices, which lack coverage of the left subclavian artery.

Other complications including vascular and bleeding complications are commensurate with rates seen in association with similar populations undergoing TAVR procedures, which range from 11.0%[62]- 16.2%[1] for vascular complications and from 9.3%[62] - 16.8%[1] for bleeding complications and are not related to the TriGard™. Acute kidney injury was reported in two subjects 10.5% (2/19), one reported as Stage 3 and one reported as Stage 1. While an embolic etiology cannot be excluded, these were likely related to contrast administration during the TAVR procedure; in both cases, no contrast was administered during positioning of the EDD so it is unlikely that use of the TriGard™ device contributed.

Lastly, the ability of the Keystone Heart EDD to maintain full 3-vessel coverage for the entire TAVR procedure correlates with anchorage of its upper stabilizer in the innominate artery and this angiographic marker can assist interventional cardiologists with device positioning. Proper patient selection and upper stabilizer anchoring at procedure initiation can ensure cerebral protection during TAVR.

Study limitations

The DEFLECT study is a safety and feasibility study performed in a limited patient population intended for CE Marking. The study is intended to continue enrollment to establish efficacy compared to historic controls. These early results provide the proof of concept to proceed to a larger prospective randomized clinical trial to establish the benefit of the EDD during the TAVR procedure compared with TAVR alone.

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FIGURE REFERENCES AND LEGENDS

Figure 1. Diffusion weighted-magnetic resonance images: (A) Baseline. (B) Following embolic event. Arrows indicate areas of restricted diffusion.

Figure 2. The Claret CE Pro™.

Figure 3. Embrella embolic deflector.

Figure 4. Keystone Heart Triguard™ Embolic Deflection Device.

Figure 5. Angiography demonstrating Keystone Heart Triguard™ device position. (A) Before the TAVR procedure. White arrow indicates device upper stabilizer anchorage in innominate artery. (B) During the TAVR procedure. (C) After the TAVR procedure. TAVR, transcatheter aortic valve replacement.

TABLES

Table 1. Key studies depicting the relationship between DW-MRI lesions and cognitive decline following cardiac procedures.

Study	Cardiac Procedure	Association with cognitive decline	Number of patients in study	Number of patients developing new DW-MRI lesions	Number of patients with multiple lesions	Mean lesion volume	Minimum/ Maximum lesion volume	Number of lesions per patient (range)
Restrepo et al. [16]	CABG	Yes	13	4 (31%)	3	0.6 cm^3	0.2 cm^3/ 0.8 cm^3	1 to 4
Barber et al.[17]	Valvular replacement surgery ± CABG	Yes	40	15 (41%)	7	<0.2 cm^3	<0.2 cm^3/ 3.0 cm^3	1 to 17
Lund et al.[18]	Left heart catheterization	Yes	47	5 (15.2%)	2	Not available	Not available	1 to 2
Schwarz et al.[19]	Coronary catheterization or CABG	Yes	84	8 (11.6%)	Not available	0.237 cm^3	0.013 cm^3/ 1.75 cm^3	1 to 10
Knipp et al.[22]	Valvular replacement surgery	No	30	14 (47%)	6	Not available	0.05 cm^3/ 1.9 cm^3	1 to 7
Gerriets et al.[23]	CABG	No	106	13 (15.1%)	Not available	0.032 cm^3*	0.016 cm^3/ 0.15 cm^3	Not available
Knipp et al.[24]	CABG	No	39	20 (51%)	10	Not available	0.176 cm^3/ 0.922 cm^3	1 to 7

*Median lesion volume; mean not provided. CABG, coronary artery bypass grafting; DW-MRI, Diffusion Weighted-Magnetic Resonance Imaging.

Table 2. Common neurocognitive tests used.

Cognitive Domains	Tests
Attention	SYNDROM-KURZTEST* TRAIL MAKING A*, †, ‡, §, | | ZIMMERMAN JOINT/DIVIDED ATTENTION TEST§, | | NUMBER/LETTER CANCELLATION*, #, * * SYMBOL DIGIT MODALITIES TEST† BELLS TEST# WAIS-R DIGIT SYMBOL‡, §, | |, * * LETTER-NUMBER SEQUENCING†
Executive Function	SYNDROM-KURZTEST INTERFERENCE LIST*, * * STROOP COLOR-WORD INTERFERENCE*, ‡ TRAIL MAKING B*, †, ‡, | |, #
Language	NAMING, READING# CONTROLLED ORAL ASSOCIATION‡ REGENSBURG WORD FLUENCY* *
Visual Memory	NONVERBAL LEARNING*, * * SYNDROM-KURZTEST PICTORIAL MEMORY*, * * REY-OSTERRIETH'S COMPLEX FIGURE TEST‡ TAYLOR'S COMPLEX FIGURE TEST‡ CORSI BLOCK-TAPPING TEST§, | |
Verbal Memory	VERBAL LEARNING MEMORY*, §, | |, * * REY AUDITORY VERBAL LEARNING†, ‡
Psychomotor	LINE TRACING* GROOVED PEGBOARD TEST†, ‡
Visual-constructive	WAIS BLOCK DESIGN*, ‡ HORN'S PERFORMANCE§, | |

WAIS, Wechsler Adult Intelligence Scale; WAIS-R, WAIS Revised
*Gerriets T, et al.[23]
†Barber P, et al.[17]
‡Lund C, et al.[18]
§Knipp SC, et al.[22]
| |Knipp SC, et al.[24]
#Restrepo L, et al.[16]
* *Schwarz N, et al.[19]

Table 3. New embolic DW-MRI lesions after TAVR.

Study	N	Subjects with Lesions	%	Weight	Contribution to Proportion
Rodes-Cabau 2011[53]	60	41	0.68	0.34	0.24
Astarci 2011[54]	35	32	0.91	0.20	0.18
Kahlert 2010[13]	32	27	0.84	0.18	0.16
Ghanem 2010*[15]	22	16	0.73	0.13	0.09
Arnold 2010[9]	25	17	0.68	0.14	0.10
Total	**174**				**0.76**

* Total study size was N=30. N=22 subjects were imaged. DW-MRI, diffusion-weighted magnetic resonance imaging; TAVR, transcatheter aortic valve replacement.

Table 4. Baseline characteristics.

Subject Characteristics	**DEFLECT 1 (N = 20)**
Age (years)	82.4 ± 6.5
Female	15 (75.0%)
Current smoker (within the last year)	1 (5.3%)
Ex- smoker	7 (36.8%)
Non-insulin Dependent Diabetes Mellitus	2 (10.0%)
Hypertension	15 (75.0%)
Hyperlipidemia	10 (50.0%)
Peripheral Vascular Disease	0 (0.0%)
Prior CVA	1 (5.0%)
Prior MI	3 (15.0%)
COPD	3 (15.0%)
Renal insufficiency	3 (15.0%)
History of left ventricular dysfunction	6 (37.5%)
History of angina pectoris	3 (15.0%)
Current CCS functional classification at time of enrollment	
Class I	18 (90.0%)
Class II	1 (5.0%)
Class III	1 (5.0%)
Class IV	0 (0.0%)
Left ventricular ejection fraction (%)	58.8 ± 15.0
Current NYHA class on enrollment admission	
Class I	3 (15.0%)
Class II	4 (20.0%)
Class III	12 (60.0%)
Class IV	1 (5.0%)
History of prior CABG	3 (15.0%)
History of prior PCI	3 (15.0%)
History of prior aortic valvular surgery	1 (5.0%)

Values reported as mean ± SD or n(%). COPD, chronic obstructive pulmonary disease; CVA, cerebrovascular accident; TIA, transient ischemic attack.
CABG, coronary artery bypass grafting; CCS, Canadian Cardiovascular Society; NYHA, New York Heart Association; PCI, percutaneous coronary intervention.

Table 5. Device performance.

Procedural Angiographic Analysis N = 20	**Prior to TAVR**	**During TAVR Until After Valve Implant**	**After TAVR removal**
EDD Access to Aortic Arch	20 (100%)		
EDD is positioned in the aortic arch	20 (100%)	19 (95.0%)	15 (75.0%)
EDD covers all 3 vessels (innominate, left common carotid, subclavian)	19 (95.0%)	16 (80.0%)	13 (65.0%)
EDD upper stabilizer is anchored in the innominate artery ostium	17 (85.0%)	16 (80.0%)	12 (60.0%)
Able to retrieve the final EDD and remove the delivery system intact	20 (100%)		

Values reported as n (%). EDD, embolic deflection device; TAVR, transcatheter aortic valve replacement.

Table 6. In-hospital and 30 day clinical endpoints.

Clinical Endpoint Events	In Hospital (N = 20)	Two sided 95% CI	30-Day	Two sided 95% CI
Primary safety endpoint: composite in-hospital device and procedure-related safety	0 (0.0%)	[0.0% - 16.8%]	--	--
Secondary safety endpoints				
Device-related safety (component)[a]				
Primary Safety Composite	0.0% (0/20)	[0.0% - 16.8%]	0.0% (0/20)	[0.0% - 16.8%]
Cardiovascular mortality % (n/N)	0.0% (0/20)	[0.0% - 16.8%]	0.0% (0/20)	[0.0% - 16.8%]
Major stroke disability % (n/N)	0.0% (0/20)	[0.0% - 16.8%]	0.0% (0/20)	[0.0% - 16.8%]
Life-threatening (or disabling) bleeding % (n/N)	0.0% (0/20)	[0.0% - 16.8%]	0.0% (0/20)	[0.0% - 16.8%]
Distal embolization (noncerebral) from a vascular source requiring surgery or resulting in amputation or irreversible end organ damage % (n/N)	0.0% (0/20)	[0.0% - 16.8%]	0.0% (0/20)	[0.0% - 16.8%]
Major vascular or access-related complications % (n/N)	0.0% (0/20)	[0.0% - 16.8%]	0.0% (0/20)	[0.0% - 16.8%]
Need for acute cardiovascular surgery % (n/N)	0.0% (0/20)	[0.0% - 16.8%]	0.0% (0/20)	[0.0% - 16.8%]
Procedure-related safety (hierarchical composite MACCE)				
Composite MACCE	10.0% (2/20)	[1.2% - 31.7%]	15.0% (3/20)	[1.2% - 31.7%]
All cause mortality % (n/N)	0.0% (0/20)	[0.0% - 16.8%]	5.0% (1/20)	[0.1% - 24.9%]
Major stroke disability % (n/N)	10.0% (2/20)	[1.2% - 31.7%]	10.0% (2/20)	[1.2% - 31.7%]
Life threatening (or disabling) bleeding % (N/N)	0.0% (0/20)	[0.0% - 16.8%]	0.0% (0/20)	[0.0% - 16.8%]
Acute kidney injury- Stage 3 (including renal replacement therapy) % (n/N)	5.0% (1/20)	[0.0% - 24.9%]	5.0% (1/20)	[0.0% - 24.9%]
Peri-procedural MI % (n/N)	0.0% (0/20)	[0.0% - 16.8%]	0.0% (0/20)	[0.0% - 16.8%]

Major vascular complication % (n/N)	5.0% (1/20)	[0.0% - 24.9%]	5.0% (1/20)	[0.0% - 24.9%]
Repeat procedure for valve dysfunction % (n/N)	0.0% (0/20)	[0.0%-16.8%]	0.0% (0/20)	[0.0%-16.8%]
Neurologic Events				
Stroke	10.0% (2/20)	[1.2% - 31.7%]	10.0% (2/20)	[1.2% - 31.7%]
Ischemic stroke	10.0% (2/20)	[1.2% - 31.7%]	10.0% (2/20)	[1.2% - 31.7%]
Hemorrhagic stroke	0 .0% (0/20)	[0.0% - 16.8%]	0.0% (0/20)	[0.0%-16.8%]
Major stroke disability	10.0% (2/20)	[1.2% - 31.7%]	10.0% (2/20)	[1.2% - 31.7%]
Minor stroke disability	0.0% (0/20)	[0.0% - 16.8%]	0.0% (0/20)	[0.0%-16.8%]
Cerebral infarction	5.0%† (1/20)	[0.1% - 24.9%}	5.0% (1/20)	[0.1% - 24.9%}
Transient ischemic attack	0.0% (1/20)	[0.0% - 16.8%]	0.0% (0/20)	[0.0%-16.8%]
Encephalopathy	0.0% (0/20)	[0.0% - 16.8%]	0.0% (0/20)	[0.0%-16.8%]
Bleeding Complications				
Major bleeding	20.0% (4/20)	[5.7% - 43.7%]	20.0% (4/20)	[5.7% - 43.7%]
Intracranial hemorrhage	0 (0.0%)	[0.0% - 16.8%]	0.0% (0/20)	[0.0%-16.8%]
Life threatening or disabling bleeding	0 (0.0%)	[0.0% - 16.8%]	0.0% (0/20)	[0.0%-16.8%]
Minor bleeding	0 (0.0%)	[0.0% - 16.8%]	0.0% (0/20)	[0.0%-16.8%]
Major bleeding	20.0% (4/20)	[5.7% - 43.7%]	20.0% (4/20)	[5.7% - 43.7%]
Intracranial hemorrhage	0 (0.0%)	[0.0% - 16.8%]	0.0% (0/20)	[0.0%-16.8%]

Values reported as n (%). CI, confidence interval; MACCE, major adverse cardiac and cerebrovascular events; MI, myocardial infarction.
*There were a total of 2 clinical strokes. Both strokes were classified as major stroke disability.
†1 stroke demonstrated an abnormality on neuro-imaging and was also classified as cerebral infarction.

Table 7. Individual subject diffusion-weighted magnetic resonance imaging data.

DW-MRI measure	DEFLECT-I (n=20)	Historical weighted average	Percent reduction (DEFLECT-I vs. historical weighted average)
Proportion of patients with new ischemic lesions	70%	76%[9, 13, 15, 45, 53-55]	-6%
Maximum number of new lesions	28	20[15, 45, 53]	--
Mean number of new lesions ± SD	5.1±7.04	4.4[13, 15, 40, 45, 53-55]	-16%
Maximum single lesion volume (cm^3)	0.39	6.45[15, 45]	-94%
Mean single lesion volume ± SD (cm^3)	0.12±0.13	0.34[13, 15, 45, 54, 55]	-65%
Maximum total lesion volume (cm^3)	3.94	70.3[15]	-94%
Mean total lesion volume ± SD (cm^3)	0.70±0.98	1.64[13, 15, 45, 54, 55]	-57%

*Average single lesion volume was calculated for each patient by dividing total lesion volume by the lesion number in each individual patient. DW-MRI, diffusion-weighted magnetic resonance imaging; SD, standard deviation.

Table 8. Basline demographic and procedural characteristics and successful device coverage.

Variable		Overall	EDD maintained coverage after TAVR		P-value
			Yes	No	
Age		82.4 ± 6.55	81.92 ± 7.02	83.29 ± 5.99	0.67
Gender (female)		15 (75%)	10 (77%)	5 (71%)	0.79
History of smoking		8 (42%)*	6 (46.2%)	2 (33.3%)	0.60
History of diabetes		2 (10%)	1 (7.7%)	1 (14.3%)	0.22
History of hypertension		15 (75%)	9 (69.2%)	6 (85.7%)	0.42
History of hyperlipidemia		10 (50%)	8 (61.5%)	2 (28.6%)	0.16
History of PAD/CAD		0 (0%)	0 (0%)	0 (0%)	N/A
Prior MI		3 (15%)	2 (15.4%)	1 (14.3%)	0.95
History of LV Dysfunction		6 (37.5%)*	4 (40%)	2 (33.3%)	0.79
History of angina		3 (15%)	2 (15.4%)	1 (14.3%)	0.95
LVEF (%)		58.8 ± 15	56.91 ± 15.39	63.00 ± 14.83	0.67
NYHA Class	I	3 (15%)	1 (7.7%)	2 (28.6%)	0.45
	II	4 (20%)	4 (30.8%)	0 (0%)	
	III	12 (60%)	7 (53.9%)	5 (71.4%)	
	IV	1 (5%)	1 (7.7%)	0 (0%)	
Prior CABG		3 (15%)	2 (15.4%)	1 (14.3%)	0.95
Prior PCI		3 (15%)	3 (23.1%)	0 (0%)	0.17
Prior aortic valve surgery		1 (5%)	0 (0%)	1 (14.3%)	0.14
Aortic arch classification	Type I	7 (35%)	5 (38.4%)	2 (28.6%)	0.70
	Type II	9 (45%)	5 (38.4%)	4 (57.1%)	
	Type III	4 (20%)	2 (15.4%)	2 (28.6%)	
Innominate artery RVD		11.49 ± 1.54	11.35 ± 1.63	11.76 ± 1.43	0.58
EDD upper stabilizer maintained anchorage in innominate artery		12 (60%)	12 (92.3%)	0 (0%)	**P < 0.0001**
EDD lower stabilizer in position		17 (89.5%)*	12 (92.3%)	5 (83.3%)	0.55
TAVR device implanted	Medtronic	10 (50%)	6 (46.2%)	4 (57.1%)	0.64
	Edwards	10 (50%)	7 (53.8%)	3 (42.9%)	
Ostial stenosis innominate artery		1 (5%)	1 (7.7%)	0 (0%)	1.00
Take off angle from innominate artery and aortic arch		73.5 ± 26.2	71.23 ± 29.28	77.56 ± 20.61	0.61
Take off angle from EDD after positioning		114.7 ± 30.4*	112.5 ± 33.83	119.5 ± 95.42	0.65
Take off angle from EDD		120.3 ± 27.0*	120.3 ± 27.0	N/A	N/A

after TAVR					
Calcification ascending aorta		7 (35%)	4 (30.8%)	3 (42.9%)	0.80
Degree of calcification in ascending aorta	Mild	4 (20%)	2 (15.4%)	2 (28.6%)	0.35
	Moderate	3 (15%)	2 (15.4%)	1 (14.3%)	
	Severe	0 (0%)	0 (0%)	0 (0%)	
Calcification in aortic arch		15 (75%)	10 (76.9%)	5 (71.4%)	1.0
Location of calcification in aortic arch segment	Proximal	8 (40%)	6 (46.2%)	2 (28.6%)	0.89
	Mid	7 (35%)	4 (30.8%)	3 (42.9%)	
	Distal	0 (0%)	0 (0%)	0 (0%)	
Degree of calcification in aortic arch	Mild	4 (20%)	2 (15.4%)	2 (28.6%)	0.24
	Moderate	10 (50%)	7 (53.9%)	3 (42.9%)	
	Severe	1 (5%)	1 (7.7%)	0 (0%)	

*indicates missing values. CABG, coronary artery bypass grafting; CAD, coronary artery disease; EDD, embolic deflection device; LV, left ventricular; LVEF, left ventricular ejection fraction; MI, myocardial infarction; NYHA, New York Heart Association; PAD, peripheral artery disease; PCI, percutaneous coronary intervention; RVD, reference vessel diameter; TAVR, transcatheter aortic valve replacement.