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First pilot study with the TriGUARD 3 Cerebral Embolic Protection Device.

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Running title: TriGUARD 3 first pilot study.

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Conflicts of Interest: Pauliina Margolis is Chief Medical Officer at Keystone Heart. AL and PS have served on advisory board for KH in the past.

CLASSIFICATIONS

Aortic stenosis

Cerebral protection

MRI

TAVI

ABREVIATIONS

CEPD	Cerebral embolic protection device
DW-MRI	Diffusion weighted magnetic resonance imaging
MACCE	Major adverse cardiovascular and cerebral event
TAVR	Transcatheter aortic valve replacement
TIA	Transient ischemic attack
TLV	Total lesion volume

INTRODUCTION

A substantial proportion of patients submitted to transcatheter aortic valve replacement (TAVR) continues to be affected by procedure-related neurological events, with 30-day clinical stroke rates in the range of 4-7%. Also, routine neuroimaging studies reveal that ischemic cerebral infarction caused by showers of cerebral emboli during valve instrumentation and placement affect virtually all patients undergoing TAVR [1-3].

In order to prevent these embolic phenomena several cerebral embolic protection devices (CEPD) have been recently developed and their use during TAVR was associated with improved early imaging and clinical neurological outcomes [1].

The TriGUARD and TriGUARD HDH have previously shown reductions in new ischemic brain lesions and total lesion volume (TLV) per-patient in diffusion-weighted magnetic resonance imaging (DW-MRI) in the DEFLECT I and III trials [2,3].

The present study was a prospective, single center, single arm pilot study to evaluate the safety and performance of the newest TriGUARD 3 CEPD in patients undergoing TAVR.

METHODS

Patients were selected if they were eligible for transfemoral TAVR and had no contraindications to cerebral MRI.

The primary performance endpoint was device performance, defined as successful device deployment at the aortic arch, positioning with complete 3-vessel coverage throughout the procedure and retrieval without interference with the TAVR procedure. The primary safety endpoint was in-hospital device related safety, a hierarchical composite of cardiovascular death, ischemic stroke, life-threatening or disabling bleeding and acute kidney injury.

Important secondary safety and imaging efficacy endpoints were also prespecified.

Details are available in the supplementary appendix.

The TriGUARD 3 device

TriGUARD 3 CEPD is a biocompatible single sized deflection device composed of a structural radiopaque nitinol frame and an ultrathin polymer mesh (nominal pore size 115 X 145 μm) that allows maximal blood flow to the brain while diverting emboli towards the descending aorta. (Figure 1 panel C). The device is heparin coated to reduce thrombogenicity and increase lubricity. The full system also includes a delivery subsystem for crimping and loading the device into an 8F sheath introduced transfemorally. Under fluoroscopic guidance, after performing an aortic arch angiogram, the device is positioned in the aortic arch to cover all 3 major cerebral arteries (Figure 1 panels A and B).

RESULTS

A prespecified total of 10 consecutive subjects were enrolled in the study between November and December of 2018.

Baseline patient and procedural characteristics are outlined in Supplementary Tables 1 and 2.

The primary device performance endpoint was met in 90% subjects (Table 1). The TriGUARD 3 device was successfully deployed with correct orientation on the first attempt in all patients (100%). The positioning with complete 3-vessel coverage throughout the TAVR procedure was reported in 90% of subjects (partial coverage was reported in one patient after core-lab analysis). The device was successfully retrieved in all cases (100%) and there was no device interference with the TAVR procedure.

The primary safety endpoint of in-hospital device related safety did not occur in the study population (0%).

A single in-hospital major adverse cardiovascular and cerebral event (MACCE) event occurred (10%), consisting of one vascular complication (hematoma) in a patient who also had a concurrent major bleeding event (not a MACCE event). Both events were related to the TriGUARD 3 vascular access site and considered procedure related.

The cerebral DW-MRI demonstrated new ischemic lesions in all available patients with a median TLV of 200.23 mm^3. Details on the secondary imaging efficacy endpoints are displayed on supplementary table 3.

DISCUSSION

The present study demonstrated an overall efficacy performance of the TriGUARD 3 of 90% with a single case of partial coverage of the cerebral vessels. Although this was not apparent during the procedure, careful core lab analysis concluded that the device was placed too proximal into the ascending aorta with partial coverage of the left vertebrobasilaris artery. Due to design iterations the TriGUARD 3 maintains a stable and correct position in the aortic arch throughout the entire TAVR procedure, without displacement or any interference with the TAVR delivery system, and thus improved performance compared to previous generations (performance success rate of 80% for the TriGUARD in the DEFLECT I study and 89% for the TriGUARD HDH device in the DEFLECT III trial) [2,3].

Importantly, in this study, the use of the TriGUARD 3 device was safe with only one (10%) single vascular complication (device access related groin hematoma) without any other MACCE. These early safety results are also better than the ones from the previous device versions (16.2% overall in-hospital MACCE and 5.4% stroke in the DEFLECT I study and 21.7% overall in-hospital MACCE and 4.3% stroke in the DEFLECT III trial) [2,3].

The cerebral DW-MRI demonstrated new ischemic lesions in all patients, without neurological symptoms, confirming the importance of cerebral embolization prevention. Although speculative, the reasons for these MRI findings might be based on the fact that the pore size of the mesh (115 X 145 μm) still allows small particles to pass and secondly be the result of debris dislodgment shortly after the TAVR procedure. Due to different trials methodologies, changes in MRI acquisition parameters and even evolution of the TAVR procedure over time it is not possible to establish true comparisons with the previous TriGUARD versions or other devices, however the TLV seems reduced compared to previous.

LIMITATIONS

Given the small sample size, no hypothesis testing was performed and no conclusive comparison with unprotected TAVR, the prior generation TriGUARD devices or other CEPD can be made.

CONCLUSION

This pilot study shows that the use of the TriGUARD 3 for cerebral protection during TAVR is feasible and safe. The device was successfully delivered, deployed, and retrieved without interference with the TAVR procedure in 100% of cases, and achieved complete 3-vessel cerebral embolic protection throughout the procedure in 90% of cases.

IMPACT ON DAILY PRACTICE

The TriGUARD 3 enhances and facilitates periprocedural cerebral protection which might represent a step forward regarding this important matter during TAVR

FUNDING

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FIGURE LEGENDS

Figure 1. The TriGUARD 3 after deployment in the aortic arch covering the three major cerebral vessels in schematic representation (A), under fluoroscopy (B) and device details (C).

TABLES

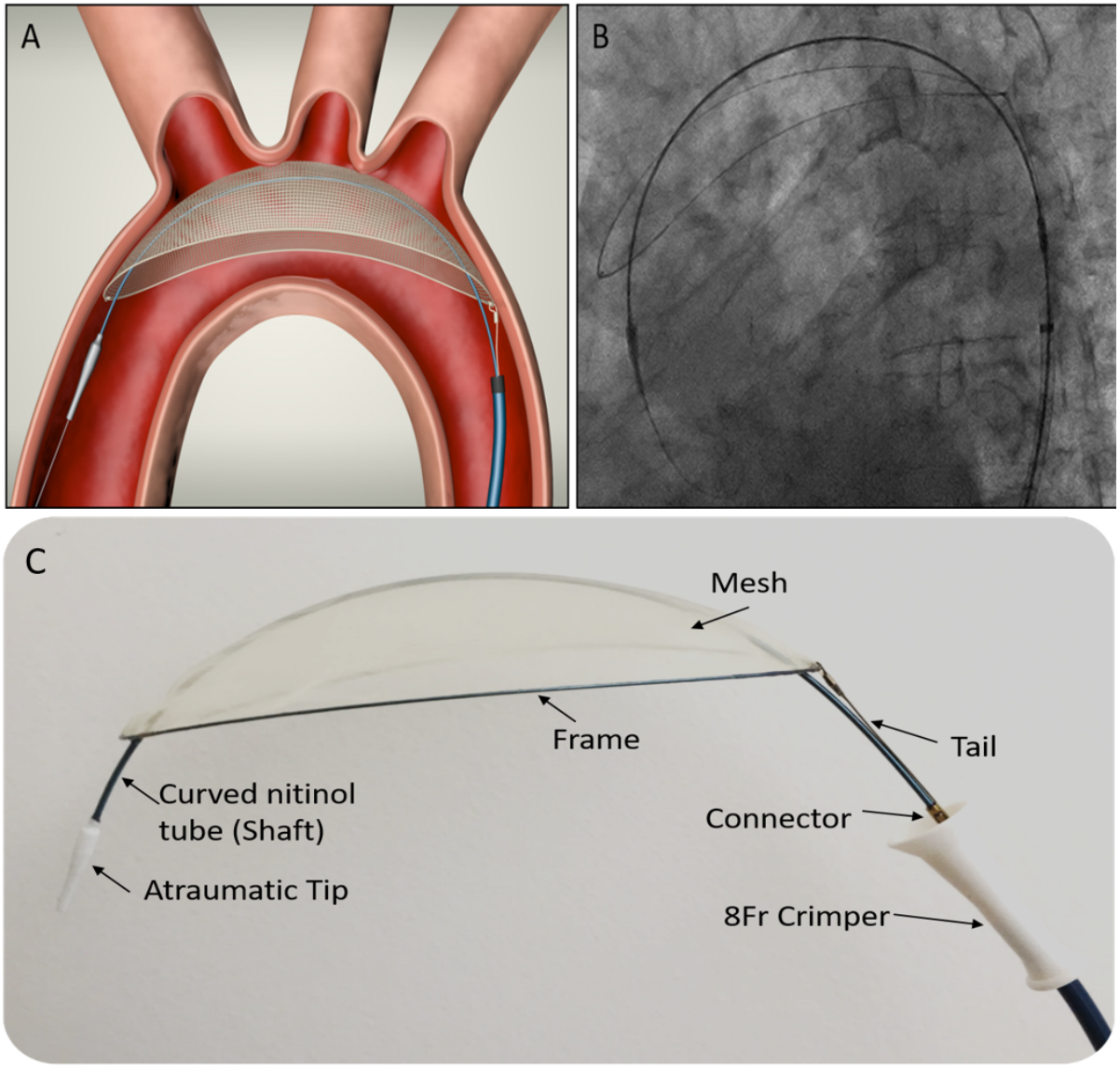
Table I. Primary performance endpoint details.

Ease of preparing the TriGUARD 3	
• No difficulty	10 (100)
• Minimally difficult	0 (0)
• Moderately difficult	0 (0)
• Extremely difficult	0 (0)
• Unable to perform	0 (0)
Success of TriGUARD 3 delivery to the aortic arch	10 (100)
Success of TriGUARD 3 deployment with correct orientation on the first attempt	10 (100)
TriGUARD 3 positioning across all 3 cerebral vessels	
Prior to valve implantation	
• Complete	9 (90)
• Partial	1 (10)
• None	0 (0)
After final valve deployment	
• Complete	9 (90)
• Partial	1 (10)
• None	0 (0)
Until the end of procedure (removal of TAVR delivery system)	
• Complete	9 (90)
• Partial	1 (10)
• None	0 (0)
Interference with the TriGUARD 3 device	0 (0)

Success of TriGUARD 3 retrieval	10 (100)

Data are shown as n (%).

TAVR: transcatheter aortic valve replacement



SUPPLEMENTARY MATERIAL

METHODS

Patients were selected if they were eligible for transfemoral TAVR, had no history of acute myocardial infarction, glomerular filtration rate <30 mL/min, history of stroke or transient ischemic attack (TIA) within the prior 6 months, severe peripheral arterial disease, no contraindications to cerebral MRI and provided written informed consent.

A post-procedure visit was completed at discharge or 3±2 days with neurological status assessment. Subjects underwent DW-MRI imaging 2-5 days post procedure and data analysis was performed by an independent MRI core laboratory. Protocol details have been reported previously [2].

The primary performance endpoint was device performance, defined as successful device deployment at the aortic arch, positioning with complete 3-vessel coverage throughout the procedure and retrieval without interference with the TAVR procedure. The primary safety endpoint was in-hospital device related safety, a hierarchical composite of cardiovascular death, ischemic stroke, life-threatening or disabling bleeding (excluding TAVR side related bleeding), and acute kidney injury (stage 2 or 3).

Important secondary endpoints included in-hospital overall procedural Major Adverse Cardiovascular and Cerebrovascular Events (MACCE) and imaging efficacy endpoints including the presence, number, and volume of cerebral ischemic lesions detected by DW-MRI.

The study was approved by the hospital´s ethics committee.

All analyses were performed with the use of SPSS software (version 20, SPSS Inc, Chicago, IL).

Supplementary table 1. Baseline demographics and clinical characteristics of the patients.

Age (years)	81.2±3.9
Female gender	3 (30)
Hypertension	5 (50)
Dyslipidemia	4 (40)
Diabetes	2 (20)
Smoking history	3 (30)
Previous PCI	4 (40)
Previous CABG	3 (30)
Heart failure	0 (0)
Atrial fibrillation	2 (20)
Porcelain aorta	0 (0)
Carotid disease	0 (0)
Peripheral vascular disease	0 (0)
Prior stroke or TIA	3 (30)
EUROSCORE II	3.19±1.53

Data are shown as mean ± standard deviation or n (%)

CABG: coronary artery bypass grafting; PCI: percutaneous coronary intervention; TIA: transient ischemic attack.

Supplementary table 2. Procedural characteristics

Sedation/anesthesia • General anesthesia • Conscious sedation/local anesthesia	 0 (0) 10 (100)
TriGUARD 3 access side • Right femoral • Left femoral	 0 (0) 10 (0)
TriGUARD 3 devices used • 1 • >1	 10 (100) 0 (0)
Pre-TAVR balloon valvuloplasty performed	1 (10)
TAVR device used • Edwards Sapien 3	 10 (100)
Valve-in-valve implant	0 (0)
Total procedural time	84.8±40
Total fluoroscopy time	18.6±6.2
Total contrast medium given	136±32.4

Data are shown as mean ± standard deviation or n (%)

TAVR: transcatheter aortic valve replacement

Supplementary table 3. Secondary efficacy endpoints (imaging efficacy endpoints).

Number of cerebral ischemic lesions • N • Media [IQR] • Mean ± SD • Range (Min, Max)	 8 4 [14.75] 8.4 ± 7.7 1, 19
Per-patient average single cerebral ischemic lesion volume (mm^3) • N • Median [IQR] • Range (Min, Max)	 8 22.2 [41.5] 7.35, 146.96
Single cerebral ischemic lesion volume (mm^3) • Median [IQR] • Range (Min, Max)	 9.1 [10.77] (3.25, 386.17)
Total volume of cerebral ischemic lesions (mm^3) • N • Median [IQR] • Range (Min, Max)	 8 200.23 [499.8] 7.35, 816.35

IQR: interquartile range; N: number; SD: standard deviation