Keystone Heart
Executive Summary

TriGUARD 3™ Cerebral Embolic Protection Device Designed to Minimize the Risk of Cerebral Damage by Deflecting Embolic Debris Away from the Cerebral Circulation During Transcatheter Valve Replacement

SUBMITTED TO THE CIRCULATORY SYSTEM DEVICES PANEL OF THE FOOD & DRUG ADMINISTRATION FOR THE 03 AUGUST 2021 MEETING

AVAILABLE FOR PUBLIC RELEASE

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List of Abbreviations

Abbreviation	Definition
AE	Adverse event
AT	As Treated (efficacy analysis population)
BNAC	Buffalo Neuroimaging Center
CEC	Clinical Events Committee
CEP	Cerebral embolic protection
CFR	Code of Federal Regulations
CI	Confidence interval
CT	Computed tomography
DMC	Data Monitoring Committee
DW-MRI	Diffusion-weighted magnetic resonance imaging
eITT	Efficacy endpoint intention-to-treat (analysis population)
EU	European Union
F	French (catheter scale system)
FDA	Food and Drug Administration
IFU	Instructions for Use
MACCE	Major adverse cardiovascular and cerebrovascular events
MI	Myocardial infarction
MRI	Magnetic resonance imaging
NIHSS	National Institutes of Health Stroke Scale
PEEK	Polyether ether ketone
PC	Partial coverage
PMA	Premarket Approval
PT	Per Treatment (analysis population)
SCIL	Supra-threshold cerebral ischemic lesion
SP(AT)	As Treated safety population (analysis population)
TAVR	Transcatheter aortic valve replacement
TIA	Transient ischemic attack
VARC	Valve Academic Research Consortium
VARC-X	Valve Academic Research Consortium – version X
US	United States

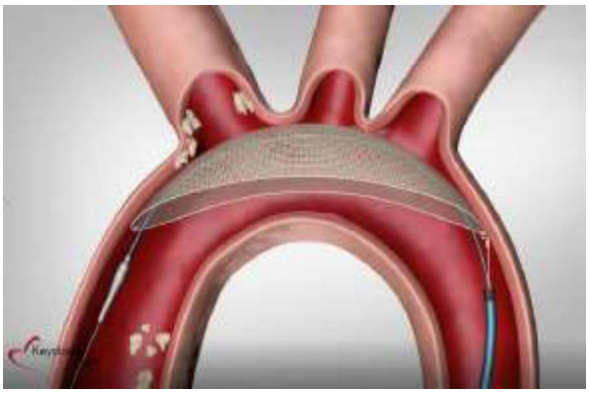
1 SYNOPSIS

1.1 Introduction

Cerebral embolic protection (CEP) devices are accessory devices that provide minimally invasive treatment for cerebral protection during transcatheter aortic valve replacement (TAVR). CEP devices protect the brain during TAVR procedures by deflecting or capturing dislodged emboli which may travel to cerebral branches and potentially result in stroke or other serious brain damage (Haussig et al 2020; Lansky et al 2016; Nazif et al 2021).

The Keystone Heart TriGUARD 3™ Cerebral Embolic Protection Device (TriGUARD 3) is a new femoral access CEP device, designed to protect all 3 cerebral branches of the aortic arch to deflect stray emboli from entering the brain during TAVR procedures (Figure 1).

Figure 1: TriGUARD 3 Device Positioned in Aortic Arch



Keystone Heart has submitted a 510(k) Premarket Notification to the United States Food and Drug Administration (US FDA) seeking clearance of the TriGUARD 3 based on a demonstration of substantial equivalence to the SENTINEL® Cerebral Protection System, the legally marketed predicate device.

1.2 Regulatory History and Clinical Development Overview

The regulatory requirements to legally market the TriGUARD device have evolved throughout the course of its clinical development program:

- The pivotal study for TriGUARD 3, REFLECT, was initially designed in consultation with the FDA to meet the requirements of Premarket Approval (PMA), which requires demonstration of safety and effectiveness in an independent and absolute sense.
- In 2017, while the REFLECT pivotal study was underway, the FDA held a meeting of the Circulatory System Devices Panel to obtain input on critical aspects of the supporting clinical data for the Sentinel device.

  - Even though the primary effectiveness endpoint was not met in the pivotal study for the Sentinel device, the FDA 24-hour summary stated that the Panel concluded 1) that the post hoc analysis concerning debris trapped by the system provided sufficient evidence of benefit given that the device was used in an adjunctive procedure, and 2) that preventing some debris from reaching the cerebral circulation is better than allowing all of the debris to reach the cerebral circulation (FDA 2017a).
  - This rationale transcended, with practicality, the technicality of the missed efficacy endpoint.

- Following the Circulatory System Devices Panel (CSDP) meeting, FDA concluded that the Sentinel was a moderate-risk device that did not require approval through the PMA pathway, which is designed for high-risk devices. Therefore, FDA granted De Novo classification (approval) for the Sentinel device, which created a new classification regulation (Code of Federal Regulations Title 21, Section 870.1251 [21 CFR 870.1251]) and set precedent for similar devices to be cleared though the 510(k) pathway using Sentinel as a predicate (FDA 2014; FDA 2017b).
  - As a result, the Sentinel device can now serve as predicate device for clearance of other temporary catheters for cerebral embolic protection during transcatheter intracardiac procedures.
  - A 510(k) submission requires a subject device (TriGUARD 3) to be "substantially equivalent" to a predicate device (Sentinel); Class II 510(k) devices are considered moderate risk, not high risk by FDA.
- Based on these new regulations, Keystone was allowed to seek clearance through the 510(k) pathway.
  - Additionally, when a De Novo approval is granted, Special Controls are created by FDA. A subject device (TriGUARD 3) claiming substantial equivalence to a predicate device (Sentinel) must meet the Special Controls established by FDA to allow for that comparison.
  - For the TriGUARD 3, the Special Control requirements for clinical performance testing must demonstrate:
    - The ability to safely deliver, deploy, and remove the device;
    - The ability of the device to filter embolic material while not impeding blood flow;
    - Secure positioning and stability of the position throughout the transcatheter intracardiac procedure; and
    - Evaluation of all adverse events including death, stroke, and vascular injury.

- A complete list of Special Controls is provided in Appendix 12.1.

- Therefore, while clinical data collected from the REFLECT study support the clearance of the TriGUARD 3 device, meeting the predefined effectiveness endpoint is no longer the regulatory burden required to market the device.
- During the Pre-Submission meeting for the TriGUARD 3, the FDA confirmed that the Sentinel CPS was the appropriate predicate for determining substantial equivalence.

1.3 510(k) Pathway Overview and Determination of Substantial Equivalence

As stated in the FDA 2014 Guidance for Industry, the regulatory standard for a 510(k) clearance is that the new device to be marketed must be "substantially equivalent" to a legally marketed predicate device. Substantial Equivalence to a predicate device means both devices have:

- Same Intended Use (ie, "to filter blood in a manner that may prevent embolic material [thrombus/debris] from the transcatheter intracardiac procedure from traveling towards the cerebral circulation")

  AND

- Same technological characteristics OR different technological characteristics that do not raise different questions of safety and effectiveness

  AND

- Performance data demonstrates that the device is as safe and effective as a legally marketed device.

1.4 Substantial Equivalence Summary – Comparison of the TriGUARD 3 to the Sentinel Predicate Device

As described throughout this document, and in Table 1 below, the TriGUARD 3 is substantially equivalent to (as safe and effective as) the legally marketed predicate device, the Sentinel Cerebral Protection System, meeting the requirements for clearance under the 510(k) regulatory pathway.

Table 1: Substantial Equivalence Conclusions

Identification as per 21 CFR 870.1251	TriGUARD 3	Sentinel
This device is a single-use percutaneous catheter system	Yes – single-use percutaneous system	Yes – single-use percutaneous system
that has (a) blood filter(s) at the distal end	Yes – single filter that spans all 3 arteries	Yes – 2 filters covering 2 arteries
This device is indicated for use while performing transcatheter intracardiac procedures.	Yes	Yes
The device is used to filter blood in a manner that may prevent embolic material (thrombus/debris) from the transcatheter intracardiac procedure from traveling towards the cerebral circulation	Yes – demonstrated through MRI and clinical evidence that it may prevent embolic material from going to the brain	Yes – demonstrated through visual filter inspection that it may prevent embolic material from going to the brain
21 CFR 870.1251 Section 7 Special Controls		
(i) The ability to safely deliver, deploy, and remove the device;	Yes – 100%	Yes – 94%
(ii) The ability of the device to filter embolic material while not impeding blood flow;	Yes – Demonstrated via DW-MRI and imaging endpoints in eITT and PT Population in total brain	Yes – Demonstration of debris in baskets and in TLV in protected areas*
(iii) Secure positioning and stability of the position throughout the transcatheter intracardiac procedure; and	Yes – 82.7% - Complete + partial 59.3% - all three	No data available (Comparison not possible)
(iv) Evaluation of all adverse events including death, stroke, and vascular injury	Yes – MACCE**: 9.6% (SP/AT) 7.6%(eITT)	Yes – MACCE**: 7.6% (AT) 7.3% (ITT)

AT: As treated; CFR: Code of Federal Regulations; DW-MRI: diffusion-weighted magnetic resonance imaging; eITT: efficacy intent-to-treat; ITT: intent-to-treat; MACCE: major adverse cardiovascular and cerebral events; PT: per treatment; TLV: total volume

*While the ITT population of the predicate was used, the effectiveness results were based on protected areas of the brain, not the whole brain. This removed 26% of the comparable brain area from the assessments as the Sentinel device only provides 2-vessel coverage.

**As per the Sentinel predicate study, MACCE is defined as the composite of death, stroke, and acute kidney injury (stage 3)

The REFLECT pivotal study has demonstrated effectiveness of the TriGUARD 3 at a level that is clinically meaningful and meets the Special Controls. By meeting the Special Controls, Keystone Heart has met the burden of substantial equivalence of the TriGUARD 3 to the predicate Sentinel device under the 510(k) regulatory pathway.

1.5 FDA Topics for Circulatory System Devices Panel

In advance of the CSDP meeting, FDA provided Keystone proposed high level topics for discussion at the meeting. Sections 2–8 of this document provide background information on the TriGUARD 3 device and relevant analyses to support 510(k)

clearance of the device. The FDA topics are addressed by Keystone Heart in Section 10.

2 BACKGROUND ON TAVR, STROKE, AND MARKETED ACCESSORY DEVICES

Summary

- Stroke is a known and devastating risk of TAVR caused by emboli dislodged during the procedure.
- Cerebral protection systems have been developed as adjunctive devices to minimize the risk of cerebral damage by preventing embolic debris from entering the brain during TAVR procedures.
- The Sentinel device provides 2 of 3 vessel coverage, with one filter placed in the brachiocephalic trunk and a second filter in the left common carotid artery to capture particles in the blood stream.
- In a study by Voss et al, approximately 39% of TAVR patients are not eligible to receive Sentinel (Voss et al 2020).

2.1 Overview of Transcatheter Aortic Valve Replacement and Stroke

Aortic stenosis remains one of the most significant valvular diseases and can manifest in dyspnea, angina, syncope, sudden cardiac death, and congestive heart failure. TAVR has rapidly replaced standard surgical procedures as the standard of care for the replacement of stenotic aortic heart valves on account of its lower risk profile. However, one of the most important drawbacks of TAVR is the potential for cerebral insult. These injuries can lead to short-term and long-term consequences, including transient ischemic attack (TIA), stroke, dementia, depression, Parkinson's disease, Alzheimer's disease, and neuro-cognitive decline. In addition, clinically silent brain infarcts are associated with a more than 2-fold increase in the risk for developing dementia and a more than 3-fold increase in the risk for a clinically evident stroke (Knipp et al 2008; Lund et al 2005; Restrepo et al 2002; Schwarz et al 2011; Vermeer et al 2003a; Vermeer et al 2003b).

One in twenty patients who undergo TAVR can experience one of these devastating clinical events (Muntane-Carol et al 2020; O'Riordan 2020). Further, diffusion-weighted magnetic resonance imaging (DW-MRI) has demonstrated that 94% of patients have new brain lesions post TAVR (Claret Medical 2017). New brain lesions can alter the neurocognitive profile of patients and are associated with a 2-fold increase in risk for the development of dementia (Prins et al 2004). In addition, elderly patients are at higher risk for progressive neurocognitive deterioration because of other concomitant factors, such as previous cerebrovascular accidents, atrial fibrillation, and neurodegenerative diseases (De Carlo et al 2020).

The risk of embolic stroke increases in more complex cardiovascular procedures and in patients with aortic stenosis, in whom valvular calcification is an additional contributor to cerebral embolic load. In patients with aortic stenosis, retrograde catheterization of the aortic valve is associated with a 3% rate of clinically apparent neurological complications (Omran et al 2003). When combined with the larger (22F) catheters required for modern catheter-based valve interventions such as TAVR, aortic arch atherosclerotic and aortic valve calcific debris have combined to produce stroke rates of 2% to 9% (Haussig et al 2020; Lansky et al 2016; Nazif et al 2021).

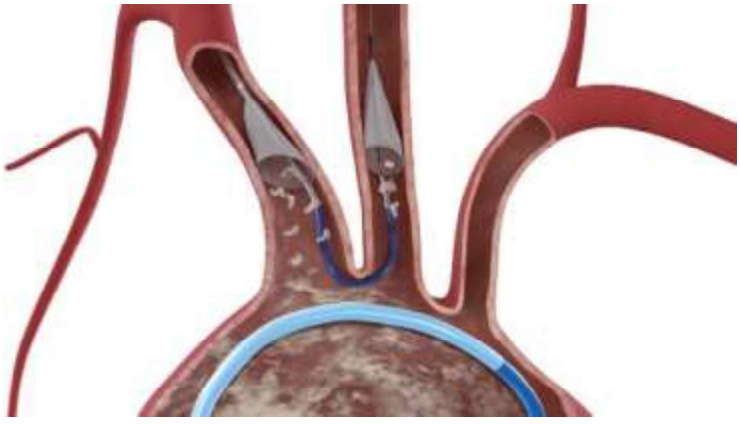
Cerebral protection systems such as the Sentinel CEP have been developed as adjunctive devices to minimize the risk of cerebral damage by preventing embolic debris from entering the brain during TAVR procedures.

2.1.1 Particle-Trapping Filters

The majority of the emboli during TAVR are released during valve preparation and replacement leading to the dislodgment of plaque, leaflet and vessel wall particles, thrombus formation, and calcific nodule fragmentations (Messika-Zeitoun et al 2020). Therefore, the use of cerebral protection devices offers an opportunity to reduce the embolic burden of the brain. The clinical need for cerebral protection devices continues to grow as the number of catheter-based aortic valve replacement increases, and such procedures are increasingly being performed in younger and lower-risk patients.

Particle-trapping filters, such as the Sentinel Cerebral Protection System, take the form of miniature nets, which are inserted into arteries branching from aortic arch (Figure 2). The Sentinel consists of 2 interconnected filters, placed in the brachiocephalic trunk and the left common carotid artery to capture particles in the blood stream, which are then withdrawn along with the filter. In addition to the TAVR access and contralateral pigtail, the Sentinel device requires a 3rd access site at the right radial or brachial artery during the TAVR procedure.

Figure 2: Sentinel Cerebral Protection System



Source: image from https://vascularnews.com/boston-scientific-to-buy-cerebral-protection-system-company/

2.2 Need for the TriGUARD 3 Cerebral Embolic Protection Device

As described in the Sentinel Indications for Use, the diameters of the arteries at the site of filter placement should be between 9 – 15 mm for the brachiocephalic and 6.5 – 10 mm in the left common carotid. Therefore, not all patients are eligible for the Sentinel device based on vessel size.

In a recent article by Voss et al (Voss et al 2020), multi-slice computed tomography and data analysis showed Sentinel-CPS compatibility in 61.5% of patients (n = 195). In the population studied by Voss et al, 38.5% (n = 122) had anatomic considerations outside of the indications in the Sentinel IFU due to one or more of the following: (i) (95%) measured diameters of the filter-landing zones (as defined in the indication) < 9 or > 15 mm in the brachiocephalic artery and < 6.5 or > 10 mm in the left common carotid artery (n = 116; 88 with carotid dimensions too small); (ii) (5.7%) significant subclavian artery stenosis (n = 4) or an aberrant subclavian artery (n = 3) precluding Sentinel-CPS implantation and (iii) (5.8%) clinical characteristics including hypersensitivity to nickel–titanium (n = 1), radial artery occlusion (n = 1) or previous left common carotid artery interventions (n = 5).

Additionally, Sentinel does not cover the left vertebral artery – which originates from the left subclavian artery and supplies blood to the circle of Willis through the basilar artery. Accordingly, approximately 24% of the brain is left unprotected.

3 TRIGUARD 3 (SUBJECT DEVICE) DESCRIPTION

Summary

- The TriGUARD 3 Cerebral Embolic Protection Device is an accessory device that provides 3-vessel coverage (the innominate, left carotid, and left subclavian arteries) during TAVR to minimize the risk of cerebral damage.
- TriGUARD 3 deflects particles away from the upwards-branching blood vessels in the aortic arch, protecting the blood supply to the brain.
    - The deflection filter is made of a polymer mesh that allows for blood flow to the cerebral arteries while diverting emboli downstream toward the descending aorta.
- Leveraging the existing TAVR access points, the TriGUARD 3 is introduced trans-femorally into the contralateral pigtail access point through an 8F sheath to the aortic arch prior to the TAVR deployment and is removed after the TAVR procedure.

3.1 Proposed Intended Use

The TriGUARD 3 Cerebral Embolic Protection Device is designed to minimize the risk of cerebral damage by deflecting embolic debris away from the cerebral circulation during TAVR.

Proposed product labeling is provided in Appendix 12.2.

3.2 Device Description

The Keystone Heart TriGUARD 3 Cerebral Embolic Protection Device is a temporary, retrievable, sterile, single-use, biocompatible deflection filter, introduced trans-femorally through an 8F sheath to the aortic arch as an accessory device during TAVR procedures (Figure 1). Under fluoroscopic guidance, the device is positioned in the aortic arch to cover all 3 major cerebral arteries (covering the innominate, left carotid, and left subclavian arteries) and is held in position by circumferential apposition and the support of the nitinol shaft (external communicating device) in the aortic arch. Once the device is in position, emboli and particulate matter are either trapped in the filter or diverted away from the cerebral circulation and downstream to the descending aorta.

Design verification tests for the TriGUARD 3 device were conducted against industry standards and in accordance with 21 CFR 820.30 and ISO 13485.

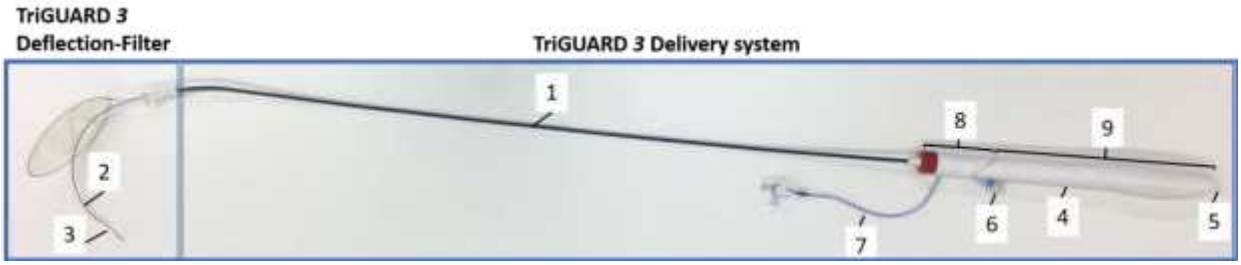
3.2.1 Component Descriptions

3.2.1.1 TriGUARD 3 Delivery System

The TriGUARD 3 delivery system (Figure 3) is an 8F sheath that is compatible with a 0.035” guidewire. The design allows for relative movements of the sheath and guidewire to enable the TriGUARD *3* to be pulled into the delivery sheath or de-sheathed for deployment.

The handle incorporates a Luer connected to the shaft to allow guidewire insertion and flushing of the shaft as well as a Tuohy-Borst adapter to allow pigtail insertion and a flushing tube for the 8F sheath. The proximal end of the delivery shaft is connected to a control handle, which includes a Y-connector hemostasis valve, permitting the introduction of the TAVR pigtail catheter through the TriGUARD *3* delivery sheath.

Figure 3: TriGUARD 3 System Overview

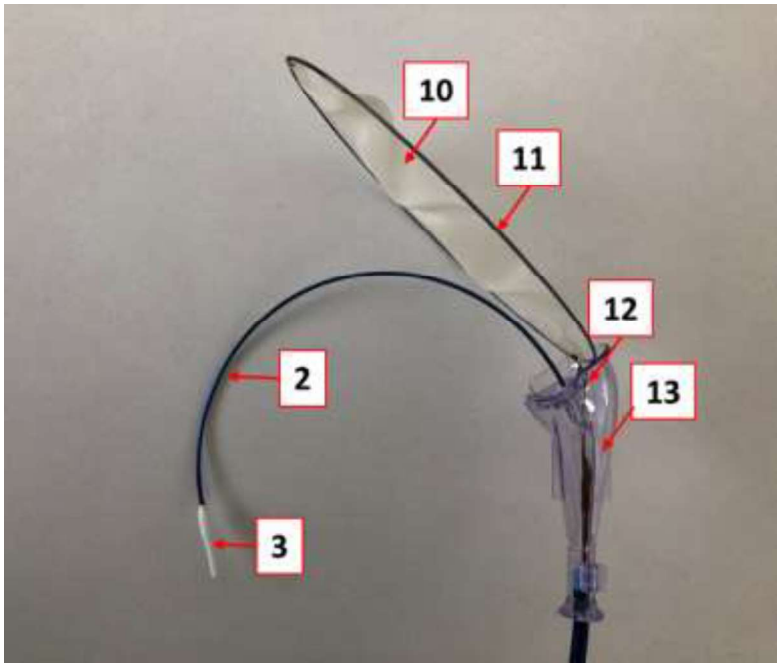


1) 8F sheath; 2) nitinol curved shaft; 3) traumatic tip; 4) two-part handle; 5) Luer - ports for the guidewire; 6) Tuohy-Borst adapter (pigtail); 7) heparinized saline flushing tube for the 8F sheath; 8) front part connected to the delivery system sheath; 9) rear part connected to the shaft

3.2.1.2 TriGUARD 3 Deflection Filter

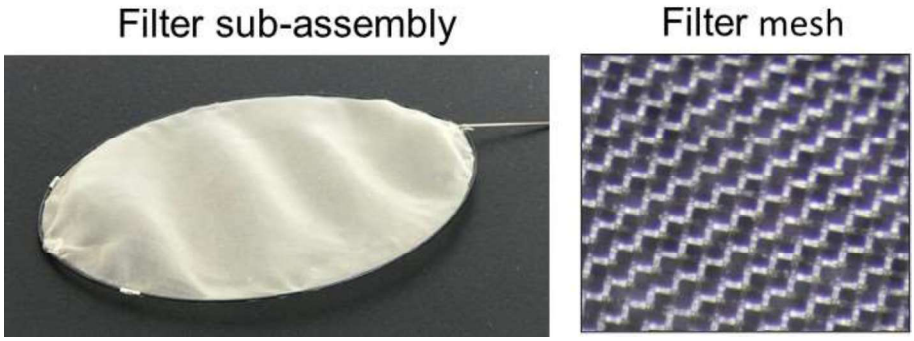
The TriGUARD 3 deflection filter (Figure 4) is composed of a polymer mesh and an oval-shaped structural nitinol frame. The mesh is constructed of 0.00149’’ diameter Polyether Ether Ketone (PEEK) fibers in a flat-weave configuration with a proprietary dome shape (Figure 4). The mesh has a nominal pore size of 115 × 145 µm, which allows for blood flow to the cerebral arteries while diverting emboli downstream toward the descending aorta. The frame and mesh are coated with a hydrophilic heparin coating intended to reduce the risk of thrombogenicity and increase the deflection filter lubricity (PhotoLink® HP01 Photo-Heparin; SurModics, Eden Prairie, MN).

Figure 4: TriGUARD 3 Filter



PEEK: polyether ether ketone
2) Nitinol shaft 3) atraumatic tip; 10) PEEK Mesh (filter); 11) Nitinol Frame; 12) nitinol connector; 13) crimper

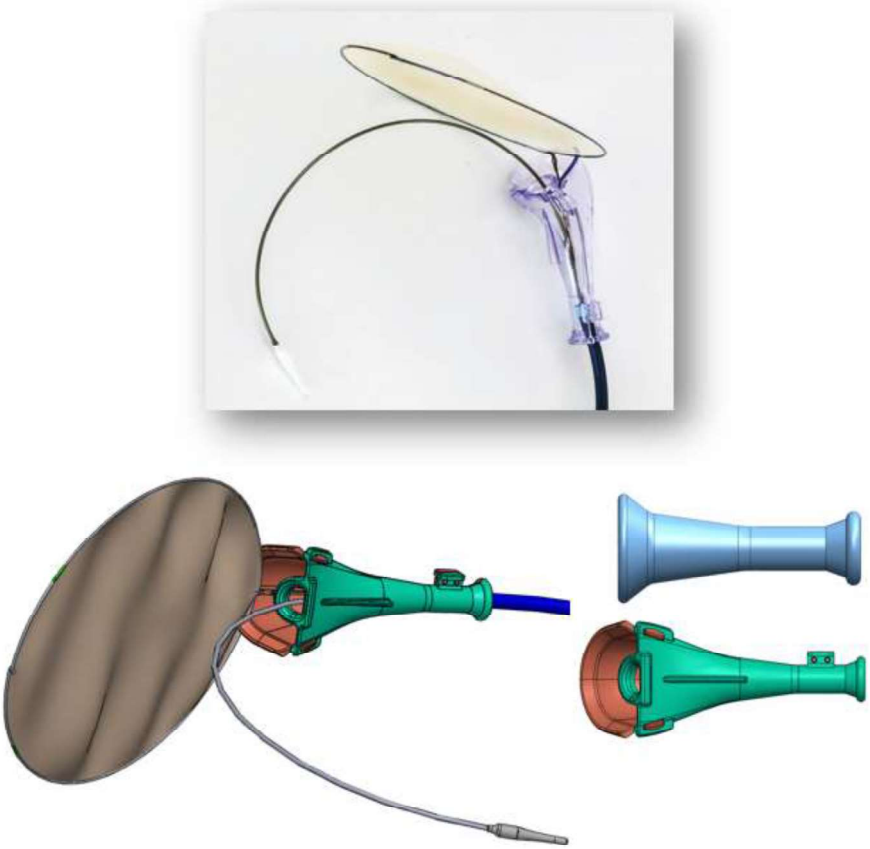
Figure 5: TriGUARD 3 Filter Sub-Assembly and Mesh



The deflection filter frame ends with a nitinol tail, which is connected via a nitinol connector to a nitinol curved tube (shaft) that has an atraumatic tip at its front end. The shaft runs underneath the deflection filter to provide stability and enhanced positioning of the deflection filter against the upper wall of the aortic arch.

The TriGUARD 3 shaft is pre-loaded onto the delivery system, which includes a dedicated crimper (Figure 6) for loading of the filter into the supplied commercially available delivery sheath (8F Adelante Breezeway delivery sheath [Oscor, Inc., Palm Harbor, FL], length 79 cm).

Figure 6: TriGUARD 3 Crimper



3.2.1.3 Hydrophilic Coating

The TriGUARD 3 is coated with heparin in order to prevent thrombogenicity. This coating has been used on many cardiac devices for 20 years and has demonstrated that it was successful in preventing clot formation, thus enhancing its hemocompatibility. Patients undergoing interventional cardiac procedures receive anticoagulation treatment including injection of heparin sodium at doses that are 1000 times greater than the total amount of heparin bound (not released to the blood stream) to the TriGUARD 3 mesh.

3.2.2 Component Dimensions and Materials

The TriGUARD 3 component dimensions and materials are described in Appendix 12.3.

4 REGULATORY AND DEVELOPMENT HISTORY

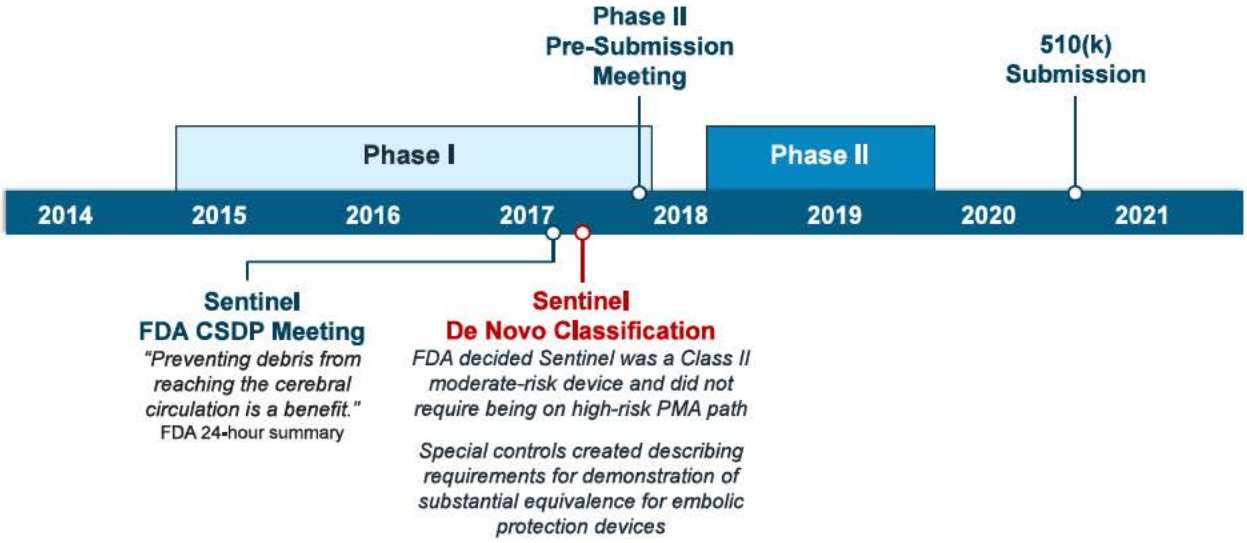
Summary

- The clinical development program for TriGUARD 3 was originally developed to support a PMA submission.
- After the Sentinel device was granted De Novo classification, TriGUARD 3 was submitted for 510(k) clearance, using Sentinel as the predicate device.

4.1 Regulatory History

The TriGUARD 3 device has been CE Marked in Europe since 4 March 2020. Commercial activity in Europe began in July 2020 using the identical device that is the subject of this panel meeting.

Figure 7: Regulatory Timeline for TriGUARD 3 and REFLECT Clinical Trial



CSDP: Cardiovascular System Devices Panel; FDA: Food and Drug Administration; PMA: Premarket Approval

4.2 Agreement on 510(k) Pathway

At the Phase II Pre-Submission meeting and again at the Pre-Submission prior to the 510(k) submission, the FDA confirmed that TriGUARD 3 could follow the 510(k) pathway and that the Sentinel device was the appropriate predicate. Sentinel was classified as a moderate risk device. In some cases, for moderate risk devices, Special Controls (see Appendix 12.1) are also required to establish substantial equivalence to the predicate device.

5 CLINICAL DEVELOPMENT PROGRAM

Originally, Keystone was planning to follow the PMA pathway to market the TriGUARD 3 and designed a pivotal clinical study called REFLECT to support the planned PMA application (details of the study design can be found in the Section 6).

The REFLECT study consisted of 2 phases. Phase I was conducted in patients undergoing TAVR and evaluated an earlier iteration of the TriGUARD 3 device. Keystone Heart revised the device design for Phase II of the study, which is the design of the device being considered for FDA clearance. The data presented in this Executive Summary and supporting the 510(k) submission include control patients from Phase I.

5.1.1 Suspension of REFLECT Study

During Phase II, a series of events led to FDA requesting study suspension as outlined in Table 2. Pertinent meeting minutes are provided in Appendix 12.4.

Table 2: Summary of Key Events Leading to REFLECT Study Suspension

Date	Description
29 January 2019	Following a routine data audit by a data manager, Keystone was notified of a potential data tabulation error by the trial CEC (Columbia Research Foundation) where 4 patients randomized to the Control Group were included in the Treatment Group analysis by the CEC.
30 January 2019	Keystone informed the DMC of the situation and hired Yale University to independently review all trial data. Keystone remained blinded to the data and Yale University reported findings to the DMC.
30 January 2019 to 10 February 2019	Yale University conducted their independent review and confirmed that 4 patients were in fact improperly tabulated.
11 February 2019	DMC recommended a temporary pause in study enrollment while a more extensive independent review of data by Yale University be performed.
12 February 2019	**Keystone sent a notice to all sites regarding the temporary pause in study enrollment.**
28 February 2019	Keystone Heart asked the regulatory consultant (Yale University) to begin compiling of the pause notification to the FDA.
19 March 2019	FDA contacted Yale University regarding information pertaining to the temporary pause in study enrollment.
22 March 2019	**After completion of Yale University data review, DMC recommended resumption of enrollment of the study.**
28 March 2019	Keystone informed FDA of both temporary enrollment pause and resumption of study.
05 April 2019	FDA holds teleconference with Keystone and recommends a suspension on all enrollment and treatment of patients until further notice.
08 April 2019 and 11 April 2019	FDA holds calls with the DMC. Keystone is not privy to the details of those conversations.
16 April 2019	**After FDA interaction, the DMC reverses position and recommends study suspension.**

17 April 2019	**Keystone suspended the study as requested by the FDA.**
16 June 2019	Last patient follow-up.
05 March 2020	Keystone provides FDA with notice of formal study completion.
24 July 2020	Keystone submits Clinical Study Report from REFLECT to FDA.

CEC: Clinical Events Committee; DMC: Data Monitoring Committee; FDA: Food and Drug Administration

6 CLINICAL DATA – REFLECT STUDY

Summary

- In the REFLECT study, successful deployment and retrieval of TriGUARD 3 was achieved in 100% of patients.
- TriGUARD 3 met the primary safety endpoint. The observed rate of primary safety events at 30 days was significantly lower than the prespecified performance goal.
- The REFLECT study was not powered to demonstrate safety differences between treatment groups; however, when used as an accessory device in a high-risk procedure, there were no clinically meaningful increased risks with TriGUARD 3.
    - Few events were Clinical Events Committee (CEC) adjudicated as related to the TriGUARD 3 device.
    - Most strokes occurred more than 24 hours after the TAVR procedure
- The prespecified primary effectiveness endpoint in REFLECT was not met. However, post hoc imaging analysis demonstrated that TriGUARD 3 effectively diverts large, more dangerous embolic debris, from entering the brain – representing a clinically meaningful level of protection for patients undergoing a TAVR procedure.
- TriGUARD 3 effectively reduced total lesion volume by 26.1% when complete coverage was achieved in at least 2 of 3 procedural timepoints.
    - MRI analyses showed that there were clinically meaningful reductions in larger lesions with a reduction of 82.9% in lesions > 1000 mm^3.
- Overall, the study results suggest that TriGUARD 3 minimizes the risk of cerebral damage during a high-risk TAVR procedure by deflecting embolic debris away from the cerebral circulation.

6.1 REFLECT Study Design

6.1.1 Design Overview – Study Objective

Originally intended to support a PMA submission (see Section 4), the REFLECT study Phase II was designed to evaluate the effects of the use of the TriGUARD 3 in patients undergoing TAVR, in comparison with a control group of patients undergoing unprotected TAVR.

Patients who met study eligibility criteria were randomized 2:1 (stratified by study site and implanted valve type [Medtronic or Edwards]) to one of 2 treatment arms:

- Intervention – TAVR with the TriGUARD 3
- Control – standard of care unprotected TAVR.

The REFLECT study (Phase II) was designed to enroll up to 50 roll-in patients and 225 randomized patients (up to 295 if interim sample size re-estimation was warranted) at up to 25 sites in the US. Roll-in patients were not randomized but underwent TAVR with the TriGUARD 3 device. These cases were proctored by a Sponsor representative as part of investigator training.

All patients were followed clinically in-hospital and at 30 days, underwent diffusion-weighted MR imaging 2 to 5 days post-procedure, and underwent neurologic testing pre-procedure (National Institutes of Health Stroke Scale [NIHSS]), post-procedure (2-5 days post-procedure), and at 30 days. A follow-up phone call to assess the occurrence of death or stroke was conducted at 90 days. The study was prospectively designed to leverage previously collected data from Control patients (treated with standard unprotected TAVR) who were enrolled in Phase I of the REFLECT study of the prior generation TriGUARD device.

6.1.2 Enrollment Criteria

The target population included patients ≥ 18 years of age with severe symptomatic aortic stenosis meeting indications for TAVR via the transfemoral approach.

Key exclusion criteria included:

- valve-in-valve TAVR
- planned concurrent procedure (eg, coronary revascularization)
- recent (< 72 hours) myocardial infarction, prior stroke or TIA within 6 months,
- bleeding diathesis or coagulopathy or recent GI bleed (< 3 months),
- renal or hepatic failure,
- cardiogenic shock,
- contraindication to cerebral MRI, or life expectancy of less than 1 year.

Device-specific exclusion criteria included allergy to device components, severe peripheral or aortic disease that precluded delivery sheath access, or severe aortic arch atheroma, calcification, or tortuosity.

6.1.3 Endpoints

6.1.3.1 Safety Endpoints

The primary safety endpoint was a composite of the following events at 30 days as defined by VARC-2 (“TAVR early safety”) (Kappetein et al 2012):

- death
- stroke

- life-threatening or disabling bleeding
- acute kidney injury (stage 2 or 3)
- coronary artery obstruction requiring intervention
- major vascular complication
- valve-related dysfunction requiring repeat procedure.

Secondary endpoints included components of the primary safety endpoint, as well as in-hospital procedural outcomes, assessments of MACCE and MACCE components, VARC-defined TAVR device success and an analysis of neurologic events.

6.1.3.2 Effectiveness Endpoints

The primary effectiveness endpoint was a hierarchical composite endpoint, determined by pair-wise comparisons among all patients according to the following pre-specified hierarchy of adverse outcomes:

- All-cause mortality and/or any stroke (fatal and non-fatal, disabling or non-disabling) evaluated at 30 days
    - If both had a death/stroke a time to event analysis by days will determine a win
    - If both patients had a death or stroke at the same day the comparison moves to the next tier. Note: there were no deaths on the same day during the REFLECT study.
- NIHSS worsening (increase from baseline) evaluated at 2 to 5 days post-procedure
    - If both patients had the same degree of NIHSS worsening, then a score of 0 was assigned and the lesion status was not considered; if both patients did not have NIHSS worsening, then lesion status was considered.
- Freedom from any cerebral ischemic lesions detected by DW-MRI 2 to 5 days post-procedure
- Total volume of cerebral ischemic lesions detected by DW-MRI 2 to 5 days post-procedure

Each patient in the analysis population intervention group was compared with every other patient in the analysis population based on the hierarchy outlined above according to the Finkelstein-Schoenfeld method (Finkelstein and Schoenfeld 1999). For example, if Patient A died or had a stroke and Patient B survived free of stroke to 30 days, Patient B was declared a success (score +1) and Patient A was declared a non-success (score -1). If both patients died or had a stroke, the patient with the later event was considered the success. If both had death/stroke on same day, the comparison moved to the next tier of the hierarchy (NHISS worsening). If both patients were alive and had a

stroke on the same day, the comparison moved to the next tier of the hierarchy (NIHSS worsening). If both patients survived free of stroke to 30 days, the comparison also moved to the next tier of the hierarchy. After all between-patient comparisons were performed, scores were summed to obtain a cumulative score for each patient, and outcomes between treatment groups were then compared.

The Finkelstein-Schoenfeld method is to compare every patient to every other patient in the population, and this was done for calculating the hierarchical scores and the p-values. The win-ratios and the win percentages were calculated by comparing every patient in the treatment group to every patient in the control group using the method described by Pocock.

Secondary imaging effectiveness endpoints were conducted using DW-MRI and included:

- Presence of cerebral ischemic lesions detected by DW-MRI, evaluated 2 to 5 days post-procedure
- Number of cerebral ischemic lesions detected by DW-MRI, evaluated 2 to 5 days post-procedure
- Per-patient average single cerebral ischemic lesion volume detected by DW-MRI, evaluated 2 to 5 days post-procedure
- Single cerebral ischemic lesion volume (lesion-level analysis) detected by DW-MRI, evaluated at 2 to 5 days post-procedure
- Total volume of cerebral ischemic lesions detected by DW-MRI, evaluated 2 to 5 days post-procedure

6.1.4 Statistical Methods

6.1.4.1 Primary Safety and Effectiveness Hypotheses

The primary safety hypothesis was that the rate of the primary safety endpoint in the TriGUARD 3 group would be significantly less than a performance goal based on historical outcomes of patients undergoing unprotected TAVR. The performance goal was based on a historical control event rate of 25% and a 37.5% relative margin (absolute delta 9.4%), so the performance goal was set at 34.4% (25% + 9.4%).

The null hypothesis was tested at the one-sided $\alpha=0.05$ level of significance using the one-sample z-test of proportions in the SP(AT) population (see Section 6.1.4.2).

The primary efficacy hypothesis was that the TriGUARD 3 system was superior to standard unprotected TAVR for the primary hierarchical composite efficacy endpoint based on pair-wise comparisons between all patients. The null hypothesis was to be tested at one-sided $\alpha=0.025$ confidence level according to the method described by Finkelstein and –Schoenfeld (Finkelstein and Schoenfeld 1999) and further explored and recommended for cardiovascular trials by Pocock et al (Pocock et al 2012).

The primary efficacy analysis population was prespecified as the efficacy intention-to-treat (eITT) population (Section 6.1.4.2).

6.1.4.2 Analysis Populations

Analysis population included:

- **Intention-to-Treat Analysis (ITT) Population**: All patients enrolled in the study, by assigned treatment, regardless of the treatment actually received.
- **Efficacy Intention-to-Treat (eITT) Analysis Population**: Patients who are enrolled in the study and randomized to a treatment group, regardless of treatment actually received AND who do not have conversion to surgery or prolonged cardiac arrest (> 3 minutes) prior to the post-procedure DW-MRI.
- **As Treated (AT) Analysis Population:** Defined by the treatment actually received, rather than the treatment assigned.
- **Per Treatment (PT) Population:** Patients in the Intervention group in whom device positioning is maintained until final procedure with complete cerebral coverage, and all Control group patients. This analysis was undertaken by the angiographic core laboratory to evaluate those patients who had verifiable complete 3 vessel coverage at 2 of 3 timepoints during the procedure.
- **Roll-in Patients:** all patients who undergo TAVR with the TriGUARD device prior to enrollment of the first evaluable patient at each investigational site; a patient is considered enrolled in the roll-in phase of the study when:
    - The patient has been judged to meet all inclusion and no exclusion criteria, and has signed a Patient Informed Consent form; and
    - The TriGUARD 3 device has been introduced into the patient's bloodstream.
- **Safety Population (SP):** randomized patients (AT or ITT as identified in the applicable analysis) and roll-in patients.
- **Pooled Control Group:** patients randomized to the Control group in Phase II of the study and patients randomized to the Control group in Phase I of the study.

6.1.4.3 Control Group Pooling

In accordance with the protocol and presubmission meeting prior to Phase II, poolability of the Phase I and Phase II control patients was assessed at the time of the primary analysis, and the results were used to determine the control population used for the primary analysis of the primary efficacy endpoint. The specific methods of poolability assessment were not predefined in the protocol. In the final analysis, poolability of the control patients was assessed using 7 baseline characteristics that were chosen based on differences in these baseline characteristics between the Phase II TriGUARD 3 group (randomized and roll-ins) and the Phase II Control group that were identified via

statistical comparisons. These variables were compared between the Phase I and Phase II control groups using two-sided Fisher's exact tests or t-tests, as appropriate.

The pre-specified procedure was that the Phase I and Phase II control groups would be poolable if there were no significant differences between the two control groups (at the significance level of $p < 0.15$) on all 7 baseline characteristics. This pooling procedure was a statistical oversight due to the fact that the binomial probability of observing at least 1 p-value < 0.15 for 7 independent tests by chance alone is approximately 68%.

Given that the Control patients in both phases were treated under the same treatment procedure and the baseline characteristics that were significant at the 0.15 significance level were small and not clinically relevant (Table 3), the Control groups were treated as poolable for efficacy analyses.

Table 3: Poolability of Phase 1 and Phase 2 Control Patients, Baseline Characteristics (eITT Population)

Baseline Characteristics (from Propensity Modeling)	Phase I Control Group (N=62)	Phase II Control Group (N=57)	p-value [2]
Age (yrs)			
Mean±SD (n)	81.6 ± 7.2 (62)	78.1 ± 8.2 (57)	0.01
Median, Range (Min,Max)	82.0, (56.0, 94.0)	79.0, (59.0, 93.0)	
Sex (Male)	67.7% (42/62)	61.4% (35/57)	0.57
Ethnicity (Not Hispanic or Latino)	100.0% (60/60)	90.6% (48/53)	0.02
Smoker Status (Never)	54.8% (34/62)	42.1% (24/57)	0.34
Diet-controlled diabetes mellitus	9.7% (6/62)	7.0% (4/57)	0.75
History of coronary artery disease	10.3% (6/58)	23.2% (13/56)	0.08
History of COPD	16.9% (10/59)	21.4% (12/56)	0.64
History of renal disease	18.0% (11/61)	29.8% (17/57)	0.19
Prior cerebral vascular attack	6.7% (4/60)	3.5% (2/57)	0.68
Prior TIA	6.7% (4/60)	3.5% (2/57)	0.68
History of prior percutaneous coronary intervention (PCI)	30.0% (18/60)	26.3% (15/57)	0.69
History of severe pulmonary hypertension	1.7% (1/60)	5.3% (3/57)	0.36
NIHSS (NIHSS=0)	83.9% (52/62)	81.5% (44/54)	0.81
T2 Lesion Volume [1]			
Mean±SD (n)	8951.0 ± 13107.5 (56)	6447.7 ± 10804.5 (49)	0.07
Median, Range (Min,Max)	4860.5, (199.7, 72758.3)	2870.5, (55.0, 52073.4)	

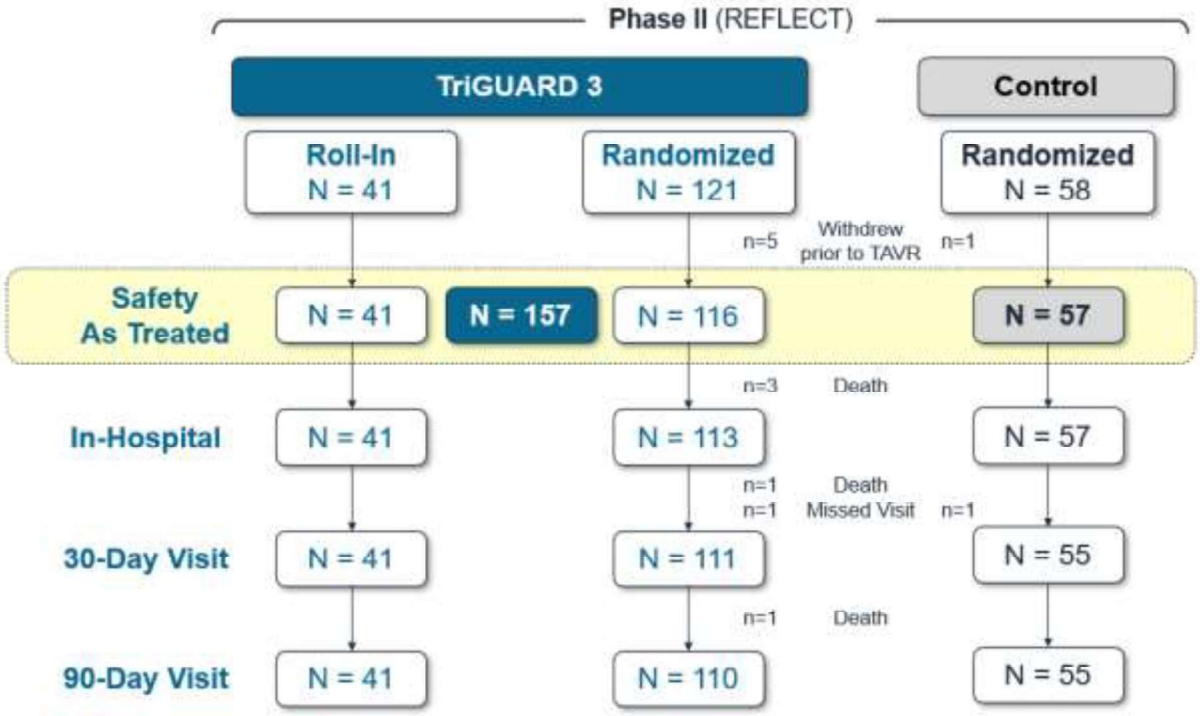
SD: Standard deviation; COPD: Chronic obstructive pulmonary disease; TIA: Transient ischemic attack; NIHSS: National Institutes of Health Stroke Scale
[1] Total volume of T2 cerebral lesions is transformed with a cubic-root prior to analysis.
[2] P-values are from two-sided Fisher's exact tests or t-tests, as appropriate.

6.2 Enrolled Populations

6.2.1 Disposition

The REFLECT study enrolled 179 randomized patients and 41 roll-in patients at 18 sites in the United States. Among the randomized patients, 121 were randomized to TriGUARD 3 and 58 were randomized to Control (Figure 8). Six randomized patients did not have the procedure resulting in a total of 173 treated patients (n=116 TriGUARD 3, n=57 Control) in the As Treated population. Effectiveness populations are described in Section 6.5.1.

Figure 8: Patient Disposition – Safety Population/As Treated (SP[AT])



SP(AT): as treated safety population (analysis population)

6.2.2 Demographics and Baseline Characteristics

Baseline patient characteristics were comparable between the 2 treatment arms with the exception of a notably higher proportion of patients with a prior history of cerebral vascular attack or TIA in the TriGUARD group (17.2% vs 5.3%; Table 4). These are notable given that prior strokes correlate with a higher risk of another clinical stroke and with a risk of larger DWI lesions (Baird et al 2000; Ederle et al 2013; Staff et al 2004).

Demographics and medical history of the PT Population are provided in Appendix 12.5.

Table 4: Demographic Characteristics and Medical History (SP[AT] Population)

Patient Characteristics	TriGUARD 3 (N=157)	Control Group (N=57)
Demographics		
Age (yrs)		
Mean±SD (n)	80.31 ± 7.73 (157)	78.05 ± 8.19 (57)
Median	81.00	79.00
Range (Min,Max)	(55.0, 98.0)	(59.0, 93.0)
Male	54.8% (86/157)	61.4% (35/57)
Hispanic or Latino Ethnicity	4.5% (7/157)	8.8% (5/57)
Medical History, % (n/N)		
Smoking/Tobacco Usage		
Current within last year	3.2% (5/157)	7.0% (4/57)
Ex-Smoker	37.6% (59/157)	50.9% (29/57)
Never	59.2% (93/157)	42.1% (24/57)
Diabetes Mellitus (DM)	39.1% (61/156)	40.4% (23/57)
Insulin Dependent (IDDM)	5.8% (9/156)	10.5% (6/57)
Diet-controlled	18.6% (29/156)	7.0% (4/57)
Oral hypoglycemic controlled	28.2% (44/156)	28.1% (16/57)
History of Hypertension	93.6% (146/156)	91.2% (52/57)
History of Hyperlipidemia	82.8% (130/157)	85.7% (48/56)
History of Peripheral Vascular Disease	12.9% (20/155)	19.3% (11/57)
History of aortic artery disease (aneurysm)	2.5% (4/157)	1.8% (1/57)
History of prior treatment/repair	0.0% (0/4)	0.0% (0/1)
Carotid artery disease	19.9% (30/151)	23.2% (13/56)
Prior cerebral vascular attack (CVA)	10.8% (17/157)	3.5% (2/57)
Prior transient ischemic attack (TIA)	7.8% (12/154)	3.5% (2/57)
Prior CVA or TIA	17.2% (27/157)	5.3% (3/57)
History of anemia requiring transfusion	7.9% (12/152)	5.7% (3/53)
History of renal disease	22.9% (36/157)	29.8% (17/57)
LVEF assessed	96.8% (152/157)	96.5% (55/57)
History of congestive heart failure	54.8% (86/157)	58.9% (33/56)
History of atrial fibrillation/atrial flutter	28.0% (44/157)	29.8% (17/57)
History or presence of intracardiac mass, thrombus or vegetation	0.6% (1/157)	0.0% (0/57)
History of prior coronary artery bypass graft(s) (CABG)	18.5% (29/157)	19.3% (11/57)
History of prior percutaneous coronary intervention (PCI)	31.2% (49/157)	26.3% (15/57)
Chronic Lung disease/ COPD	17.8% (28/157)	21.4% (12/56)

In home Oxygen Use	2.5% (4/157)	3.5% (2/57)
Severe Pulmonary hypertension	7.6% (12/157)	5.3% (3/57)

COPD: Chronic obstructive pulmonary disease; LVEF Left ventricular ejection fraction; SD: standard deviation:

6.3 Device Performance

The TriGUARD 3 was deployed and retrieved in 100% of the cases, and the aortic arch was successfully accessed in 100% of the cases in the SP(AT) Population (Table 5).

Complete 3 cerebral vessel coverage as defined in the protocol (2 of 3 procedural timepoints [pre, during, and post TAVR] with verified 3 vessels coverage) was achieved in 61.2% of randomized patients in the SP(AT) Population. The verification of the device positioning during the TAVR procedure was not feasible for all timepoints in all patients due the angiographic focus on the TAVR procedure.

In REFLECT, successful device positioning and coverage at specified procedural time points was assessed by the angiographic core laboratory. TriGUARD 3 maintained secure positioning and stability in 80.9% of the cases (defined as full or partial coverage of the 3 cerebral branches) throughout the TAVR procedure (Table 5). Full 3 vessel coverage in at least 2 of 3 procedural timepoints was achieved in 61.2% of the cases. Notably, 75% of patients had complete 3-vessel coverage during the TAVR procedures (Figure 9).

During the course of REFLECT, the angiographic core laboratory reported incomplete 3-vessel coverage in some cases. Through bench testing Keystone Heart determined that if the catheter is twisted or torqued during advancement the filter may not be properly deployed or positioned.

Based on this information, the TriGUARD 3 training program was enhanced to emphasize proper delivery technique (see Section 8). Effectiveness of proper delivery technique has been demonstrated by Dr. Pieter Stella in 50 sequential and consecutive cases (Jimenez-Rodriguez et al 2021a). Dr. Stella has imaging for all cases demonstrating full 3 vessel coverage at the most critical timepoint during the TAVR procedure, which is during deployment when the vast majority of emboli are dislodged. It is clear from these images that the TriGUARD 3 was stable and provides the 3-vessel coverage.

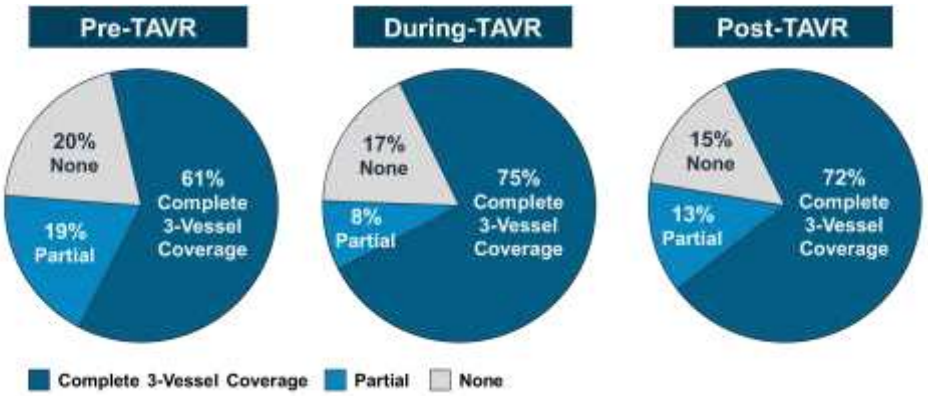
These data of the first 50 patients have recently been presented at Cardiovascular Research Technologies (CRT) conference 2021 (Jimenez-Rodriguez et al 2021a), and the first 75 patients have been presented at Euro PCR (Jimenez-Rodriguez et al 2021b). The initial 100 patients are being submitted for publication in the American Journal of Cardiology and are also being entered into the Dutch National Cardiovascular Registry.

Table 5: Analysis of Device Performance Endpoints (SP[AT] TriGUARD Patients)

Secondary Performance Endpoints	TriGUARD 3 Randomized Group (N=116)	TriGUARD 3 Roll-In Group (N=41)	TriGUARD 3 All Patients (N=157)
Successful device deployment [1]	**100.0% (116/116)**	**100.0% (41/41)**	**100.0% (157/157)**
Number of attempts needed to successfully deploy TriGUARD device (device-level)			
1	98.3% (114/116)	97.6% (40/41)	98.1% (154/157)
2	1.7% (2/116)	2.4% (1/41)	1.9% (3/157)
Aortic arch successfully accessed	**100.0% (116/116)**	**100.0% (41/41)**	**100.0% (157/157)**
Device interference [5]	8.6% (10/116)	12.2% (5/41)	9.6% (15/157)
Successful device retrieval [6]	**100.0% (116/116)**	**100.0% (41/41)**	**100.0% (157/157)**
Technical success [3, 7]	69.5% (73/105)	75.0% (30/40)	71.0% (103/145)
Procedure success [3, 8]	67.6% (71/105)	75.0% (30/40)	69.7% (101/145)

[1] Successful device deployment: Ability to access the aortic arch with the TriGUARD delivery catheter and deploy the device into the aortic arch.
[2] Device positioning: Ability to position the TriGUARD device in the aortic arch to cover all major cerebral arteries, with proper positioning maintained (verified by angiography) until specified.
[3] Patients with Coverage=N/A (due to indiscernible angiograms) are not included in the denominator.
[5] Device interference: Interaction of the TriGUARD device with the TAVR system leading to (1) inability to advance or manipulate the TAVR delivery system or valve prosthesis, OR (2) inability to deploy the TAVR valve prosthesis, OR (3) inability to retrieve the valve prosthesis or delivery system.
[6] Successful device retrieval: Ability to retrieve the TriGUARD device.
[7] Technical success: Successful device deployment, device positioning for complete coverage during TAVR and successful device retrieval in the absence of device interference.
[8] Procedure success: Technical success in the absence of any investigational device-related or procedure-related in-hospital procedural safety events.

Figure 9: TriGUARD 3 Device Positioning and Vessel Coverage at Specified Procedural Time Points as Assessed by Angiographic Core Laboratory (SP[AT]) Population)



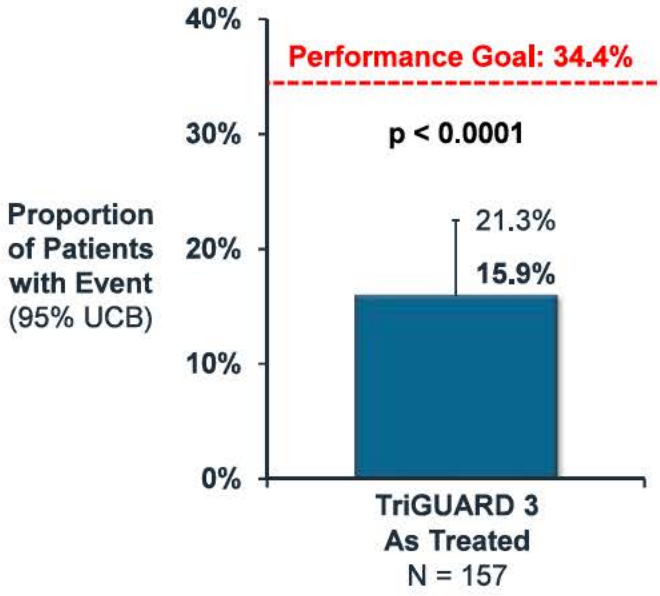
SP(AT): as treated safety population (analysis population); TAVR: Transcatheter aortic valve replacement

6.4 Safety Results

6.4.1 Primary Safety Endpoint

The composite primary safety endpoint of the study was met in the SP(AT) Population. The rate of primary safety endpoint events in the TriGUARD group was 15.9% with a one-sided 95% upper confidence bound of 21.3%, which was lower than the performance goal of 34.4% ($p < 0.0001$; Figure 10).

Figure 10: Primary Safety Endpoint at 30 Days (SP[AT] Population)



CI: confidence interval; SP(AT): as treated safety population (analysis population)
Primary Safety Endpoint includes all-cause mortality, all stroke, life-threatening or disabling bleeding, acute kidney injury, coronary artery obstruction requiring reintervention, major vascular complication or valve-related dysfunction requiring repeat procedure

It is important to recognize that the REFLECT study was not designed to demonstrate a statistically significant difference in the rate of primary safety events compared with control. Rather, the purpose of the study was to demonstrate that TriGUARD 3 did not increase the risks associated with a TAVR procedure. The rate of primary safety events observed with TriGUARD 3 and Control demonstrate that the risks for both groups are in line with what would be expected with a TAVR procedure, as demonstrated by the prespecified performance goal (Table 6). While numerical imbalances exist, they must be interpreted with caution as the design of the study and small sample sizes limit the ability to draw definitive conclusions on the significance of between group comparisons.

Table 6: Analysis of the Primary Safety Study Endpoint to 30 days Phase II Treated SP(AT) Patients

Primary Safety Endpoint within 30 days	TriGUARD 3 N=157		Control N=57	
	% (n)	95% CI [2]	% (n)	95% CI [2]
Combined Safety Endpoint[1]	15.9% (25)	[11.0, 22.5]	7.0% (4)	[1.9, 17.0]
All-Cause Death	2.5% (4)	[1.0, 6.4]	1.8% (1)	
Stroke (Disabling and Non-Disabling)	8.3% (13)	[4.9, 13.7]	5.3% (3)	
Life-Threatening or Disabling Bleeding	5.7% (9)	[3.0, 10.5]	0	
Acute Kidney Injury (Stage 2/3)	2.5% (4)	[1.0, 6.4]	0	
Coronary Artery Obstruction Requiring Intervention	0.6% (1)	[0.1, 3.5]	0	
Major Vascular Complication	7.0% (11)	[4.0, 12.1]	0	
TriGUARD Access Site-Related	1.9% (3)	[0.7, 5.5]	0	
TAVR or Other Access Site-Related	4.5% (7)	[2.2, 8.9]	0	
Secondary Access Site-Related	0	[0.0, 2.4]	0	
Aortic Vascular Injury	1.3% (2)	[0.4, 4.5]	0	
Valve-Related Dysfunction Requiring Intervention	0	[0.0, 2.4]	0	

CI: confidence interval; SP(AT): as treated safety population (analysis population); TAVR: Transcatheter aortic valve replacement
[1] Events defined for the period of 30 days post-procedure follow up are reported for patients with at least 23 days of follow-up or with a composite primary safety endpoint to 30 days post-procedure.
[2] Confidence interval is the Wilson-Score CI.
[3] Exact binomial test.

6.4.1.1 Relatedness Assessment of Individual Components of Primary Endpoint

The risk of any accessory device during the main procedure should be assessed independently from the main index procedure to fully understand the risk that is attributable to the accessory device. Therefore, a pre-specified relatedness assessment was conducted by the CEC (Table 7).

While the sample sizes in REFLECT were small, particularly in the control group (N=57), there was a numerically higher proportion of primary safety endpoint events in the TriGUARD 3 group. This was predominantly due to major vascular events, which occurred at rates of 7% vs 0%. In the CEC's adjudication of the relatedness of the major vascular events in the TriGUARD 3 group, 7 events were TAVI or other access site-related, and 2 were aortic vascular injury (both adjudicated as related to the TAVI device and procedure); 3 events were at the contralateral access site (TriGUARD 3) but related to the closure device. Narratives for these cases are provided in Appendix 12.6.

Table 7: Primary Safety Endpoint – By TriGUARD 3 Relationship (SP[AT] Population)

	TriGUARD 3 Group (N=157) CEC-Adjudicated Relationship to TriGUARD 3 Device or Procedure[1]					
Primary Safety Endpoints, % (n)	**Overall[3]**	**Not Related**	**Unlikely to be Related**	**Possibly Related**	**Probably Related**	**Related**
Combined Safety Endpoint at 30 Days [2]	**15.9% (25)**	**10.2% (16)**	**0**	**6.4% (10)**	**0**	**1.3% (2)**
All-Cause Death	2.5% (4)	2.5% (4)	0	0	0	0
Stroke (Disabling and Non-Disabling)	8.3% (13)	3.2% (5)	0	5.7% (9)	0	0
Life-Threatening or Disabling Bleeding	5.7% (9)	5.1% (8)	0	0.6% (1)	0	0
Acute Kidney Injury (Stage 2/3)	2.5% (4)	2.5% (4)	0	0	0	0
Coronary Artery Obstruction Requiring Intervention	0.6% (1)	0.6% (1)	0	0	0	0
Major Vascular Complication	7.0% (11)	5.1% (8)	0	0.6% (1)	0	1.3% (2)
TriGUARD Access Site-Related	1.9% (3)	0	0	0.6% (1)	0	1.3% (2)
TAVR or Other Access Site-Related	4.5% (7)	4.5% (7)	0	0	0	0
Secondary Access Site-Related	0	0	0	0	0	0
Aortic Vascular Injury	1.3% (2)	1.3% (2)	0	0	0	0
Valve-Related Dysfunction Requiring Intervention	0	0	0	0	0	0

SP(AT); as treated safety population (analysis population)
[1] If the relationship to TriGUARD 3 Device is different than the relationship to TriGUARD 3 Procedure, then the most related of the 2 is considered for evaluation.
[2] Events defined for the period of 30 days post-procedure follow up are reported for patients with at least 23 days of follow-up or with a composite primary safety endpoint to 30 days post-procedure.
[3] Number of patients who experienced the respective safety endpoint at least once.

6.4.2 Secondary Safety Endpoints Through 30 Days

Secondary safety endpoints through 30 days are summarized in Table 8.

Table 8: Secondary Safety Endpoint – By TriGUARD 3 Relationship (SP[AT] Population)

Endpoints to 30 days post-procedure,% (n)	TriGUARD 3 Group (N=157)	Control Group (N=57)
All-cause death	2.5% (4)	1.8% (1)
Cardiovascular death	2.5% (4)	1.8% (1)
Neurologic event related death	0	0
Non-cardiovascular death	0	0
Myocardial infarction	0	1.8% (1)
Peri-procedural MI (≤ 72 hours after the index procedure)	0	0
Spontaneous MI (> 72 hours after the index procedure)	0	1.8% (1)
General Safety event	9.6% (15)	7.0% (4)
All-cause mortality	2.5% (4)	1.8% (1)
All stroke (disabling and non-disabling)	8.3% (13)	5.3% (3)
Acute kidney injury - Stage 3 (including renal replacement therapy)	1.9% (3)	0
Neurological Events		
Stroke (VARC-2 defined)	8.3% (13)	5.3% (3)
Ischemic	7.6% (12)	5.3% (3)
Hemorrhagic	0	0
Undetermined	0.6% (1)	0
Disabling Stroke (VARC-2 defined)	2.5% (4)	1.8% (1)
Non-disabling Stroke (VARC-2 defined)	5.1% (8)	3.5% (2)
Transient ischemic attack (TIA) (VARC-2 defined)	1.3% (2)	1.8% (1)
Overt CNS Injury (Type 1)	8.3% (13)	5.3% (3)
Covert CNS Injury (Type 2)	68.8% (108)	63.2% (36)
Neurological dysfunction without CNS injury (Type 3)	1.9% (3)	5.3% (3)
CNS infarction (NeuroARC defined)	77.1% (121)	68.4% (39)
CNS hemorrhage (NeuroARC defined)	0	1.8% (1)
Bleeding Complications		
Life-threatening or disabling bleeding (VARC-2)	5.7% (9)	0
Major bleeding	7.6% (12)	1.8% (1)
Minor bleeding	6.4% (10)	8.8% (5)
Acute Kidney Injury (AKIN Classification)		
Acute kidney injury - Stage 2	0.6% (1)	0
Acute kidney injury - Stage 3 (including renal replacement therapy)	1.9% (3)	0
Vascular Complications		
Major vascular complications	7.0% (11)	0

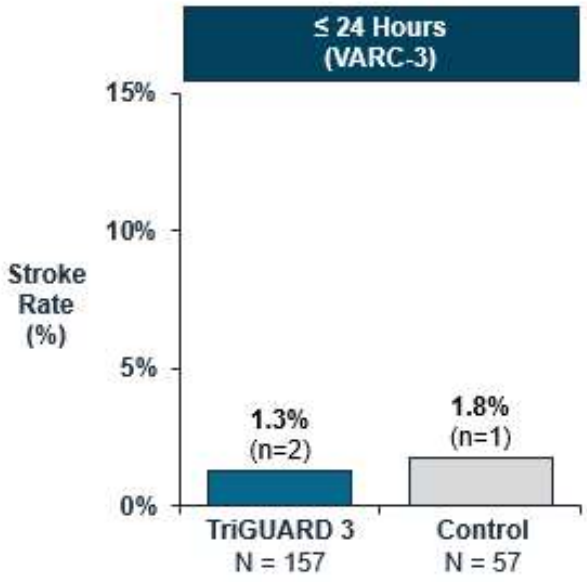
TriGUARD access site related	1.9% (3)	0
TAVR or other access site related	4.5% (7)	0
Secondary access site-related	0	0
Aortic vascular injury	1.3% (2)	0

SP(AT): as treated safety population (analysis population); CNS: central nervous system; TAVR: transcatheter aortic valve replacement; VARC: Valve Academic Research Consortium

In April 2021, the Valve Academic Research Consortium (VARC) published updated guidelines (VARC-3) to standardize endpoints used in aortic valve clinical research endpoints (Varc-3 Writing et al 2021). The VARC noted that “periprocedural neurological events could be further sub-classified as acute (occurring within 24 h of the index procedure) or sub-acute (occurring between 24 h and 30 days following the index procedure).”

In line with VARC-3 guidelines, Keystone performed a post hoc analysis of acute strokes at 24-hr in the SP(AT) Population. In the TriGUARD 3 treatment group, 2 patients (1.3%) experienced stroke events within 24 hours compared with 1 (1.8%) in the control group (Figure 11). These data are important to the assessment of the overall safety profile given that TriGUARD 3 is an accessory device to a high-risk procedure, and the majority of strokes occurred in patients after the TriGUARD device was removed.

Figure 11: Stroke Rate with TriGUARD 3 within 24-Hours Post-Procedure (SP[AT] Population)



SP(AT): as treated safety population (analysis population); VARC: Valve Academic Research Consortium

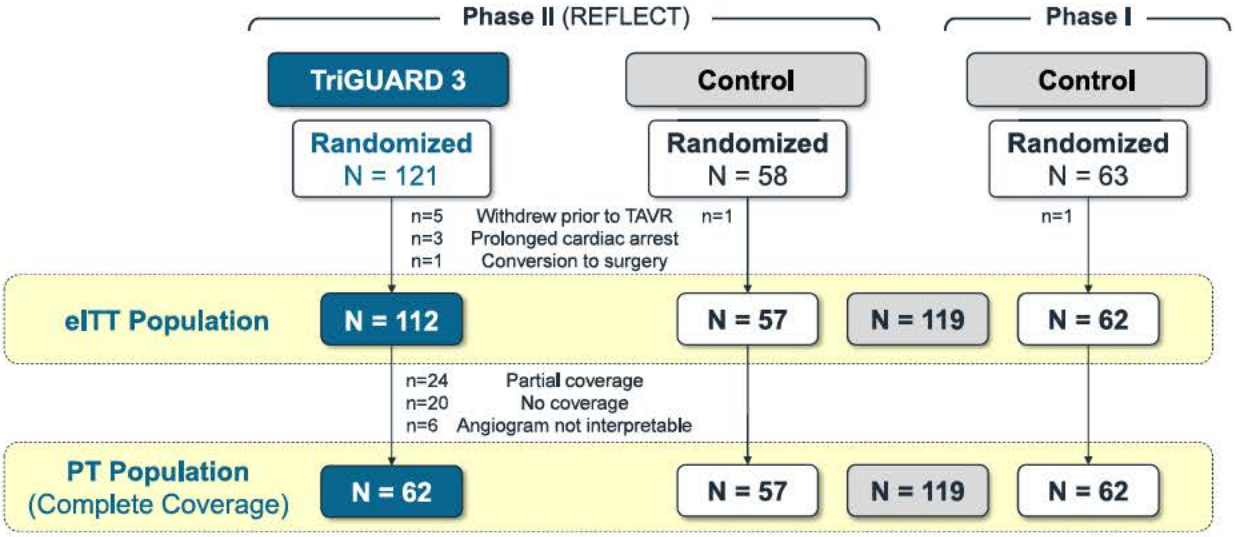
6.5 Effectiveness Results

6.5.1 Effectiveness Patient Populations

The primary effectiveness assessment in REFLECT was conducted in eITT population and includes 112 patients randomized to TriGUARD 3 and 119 Control patients (Figure 12). As described in Section 6.1.4.3, Control patients from Phase 1 and Phase 2 were pooled for a total of 119 patients in the control group.

Effectiveness analyses were also conducted in the PT Population which includes all patients with complete 3-vessel coverage (N=62 and N=119), as described in Section 6.1.4.2. The PT Population represents best population to demonstrate the effectiveness of the TriGUARD 3 when the device is used as intended. Therefore, analyses in this population are important to the overall assessment of TriGUARD 3 effectiveness.

Figure 12: eITT and PT Effectiveness Population



eITT: efficacy intent-to-treat; PT: per treatment

6.5.2 Primary Effectiveness Endpoint

6.5.2.1 eITT Population

For the hierarchical primary effectiveness endpoint, there were no significant differences in the eITT population between treatment and control groups (Table 9).

Table 9: Primary Effectiveness Endpoint (eITT Population)

	TriGUARD 3 (N=112)	Control (N=119)	p-value [4]
Primary Effectiveness Hierarchical Endpoint Score [1]			
Mean ± SD (n)	-8.58 ± 120.76 (112)	8.08 ± 116.51 (119)	0.857
Range (Min, Max)	(-226.00, 183.00)	(-230.00, 183.00)	
Median	13.00	21.00	
(Q1, Q3)	(-104.00, 84.00)	(-87.00, 110.00)	
Win-ratio [2]	0.84	1.19	
Win-percentage [2]	45.7%	54.3%	
All-cause mortality or any stroke at 30 days	9.8% (11/112)	6.7% (8/119)	
NIHSS worsening [3]	14.1% (14/99)	7.6% (8/105)	
Cerebral ischemic lesions	85.0% (85/100)	84.9% (90/106)	
Total volume of cerebral ischemic lesions (cubic mm)			
Mean ± SD (n)	587.80 ± 1028.42 (100)	508.22 ± 1123.96 (106)	
Range (Min, Max)	(0.00, 5681.26)	(0.00, 8133.60)	
Median	215.39	188.09	
(Q1, Q3)	(68.13, 619.71)	(52.08, 453.12)	

eITT: efficacy intent-to-treat; NIHSS: National Institutes of Health Stroke Scale; SD: standard deviation

[1] Hierarchical endpoint score is the sum of the number of wins minus the number of losses in patient pairs based on the hierarchical algorithm comparing death/stroke, NIHSS worsening and cerebral ischemic lesions as described in Finkelstein and Schoenfeld (1999).
[2] Win-ratio is the ratio of the number of wins to the number of losses in treatment v control pairs as described by Pocock et al. (2011). Win percentage is defined as the number of wins divided by the sum of the number of wins and losses.
[3] Worsening of NIHSS score is defined as a higher NIHSS score at pre-discharge (2-5 days after procedure) than at baseline.
[4] p-value for the primary endpoint is based on a one-sided test described by Finkelstein and Schoenfeld (1999).

6.5.2.2 PT Population

The results from the PT Population are important to the overall effectiveness assessment for TriGUARD 3 as they are representative of the device performance when used as intended (3-vessel coverage achieved). In the PT Population, the win % in the hierarchical primary efficacy endpoint was similar for TriGUARD 3 and controls (50.1% vs 49.9%; Table 10).

Table 10: Analysis of Primary Effectiveness Endpoint PT Population

Primary Efficacy Endpoint	TriGUARD 3 (N=62)	Control (N=119)	p-value [4]
Primary Efficacy Hierarchical Endpoint Score [1]			
Mean ± SD (n)	0.29 ± 94.21 (62)	-0.15 ± 90.75 (119)	0.488
Range (Min, Max)	(-171.00, 140.00)	(-180.00, 140.00)	
Median	20.00	12.00	
(Q1, Q3)	(-78.00, 70.00)	(-72.00, 78.00)	
Win-ratio [2]	1.01	0.99	
Win-percentage [2]	50.2%	49.8%	
All-cause mortality or any stroke at 30 days	6.5% (4/62)	6.7% (8/119)	
NIHSS worsening [3]	13.8% (8/58)	7.6% (8/105)	
Cerebral ischemic lesions	79.6% (43/54)	84.9% (90/106)	
Total volume of cerebral ischemic lesions (mm^3)			
Mean ± SD (n)	375.80 ± 617.69 (54)	508.22 ± 1123.96 (106)	
Range (Min, Max)	(0.00, 3519.00)	(0.00, 8133.60)	
Median	145.71	188.09	
(Q1, Q3)	(43.75, 444.44)	(52.08, 453.12)	

PT: per treatment; SD: standard deviation; NIHSS: National Institutes of Health Stroke Scale

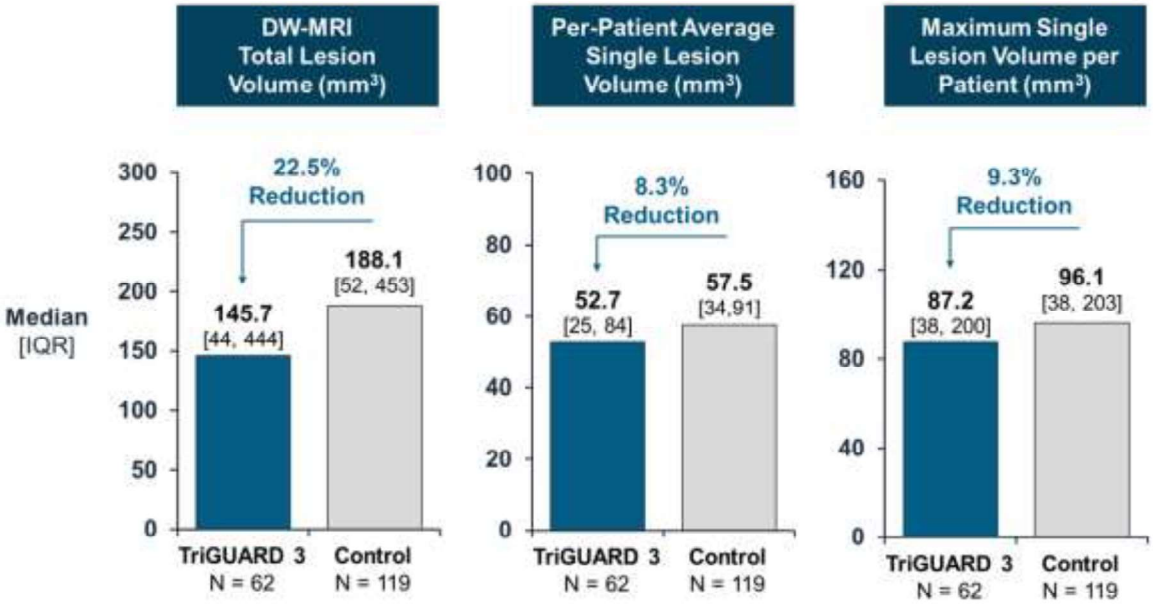
[1] Hierarchical endpoint score is the sum of the number of wins minus the number of losses in patient pairs based on the hierarchical algorithm comparing death/stroke, NIHSS worsening and cerebral ischemic lesions as described in Finkelstein and Schoenfeld (1999).
[2] Win-ratio is the ratio of the number of wins to the number of losses in treatment v control pairs as described by Pocock et al. (2011). Win percentage is defined as the number of wins divided by the sum of the number of wins and losses.
[3] Worsening of NIHSS score is defined as a higher NIHSS score at pre-discharge (2-5 days after procedure) than at baseline.
[4] P-value for the primary endpoint is based on a one-sided test described by Finkelstein and Schoenfeld (1999).

6.5.3 Secondary Effectiveness Endpoints

Because the primary effectiveness endpoint was not met, hypothesis-driven secondary endpoints were not formally tested.

Several additional secondary imaging endpoints were conducted in the PT Population to evaluate the benefit of TriGUARD 3 in preventing debris from reaching the cerebral circulation. In the PT Population, which includes only patients with complete coverage in at least 2 of 3 procedural timepoints, TriGUARD 3 treated patients had a reduction in total lesion volume by DW-MRI, per-patient average single lesion volume, and maximum single lesion volume compared to control (Figure 13).

Figure 13: Secondary Effectiveness Imaging Endpoints (PT Population)



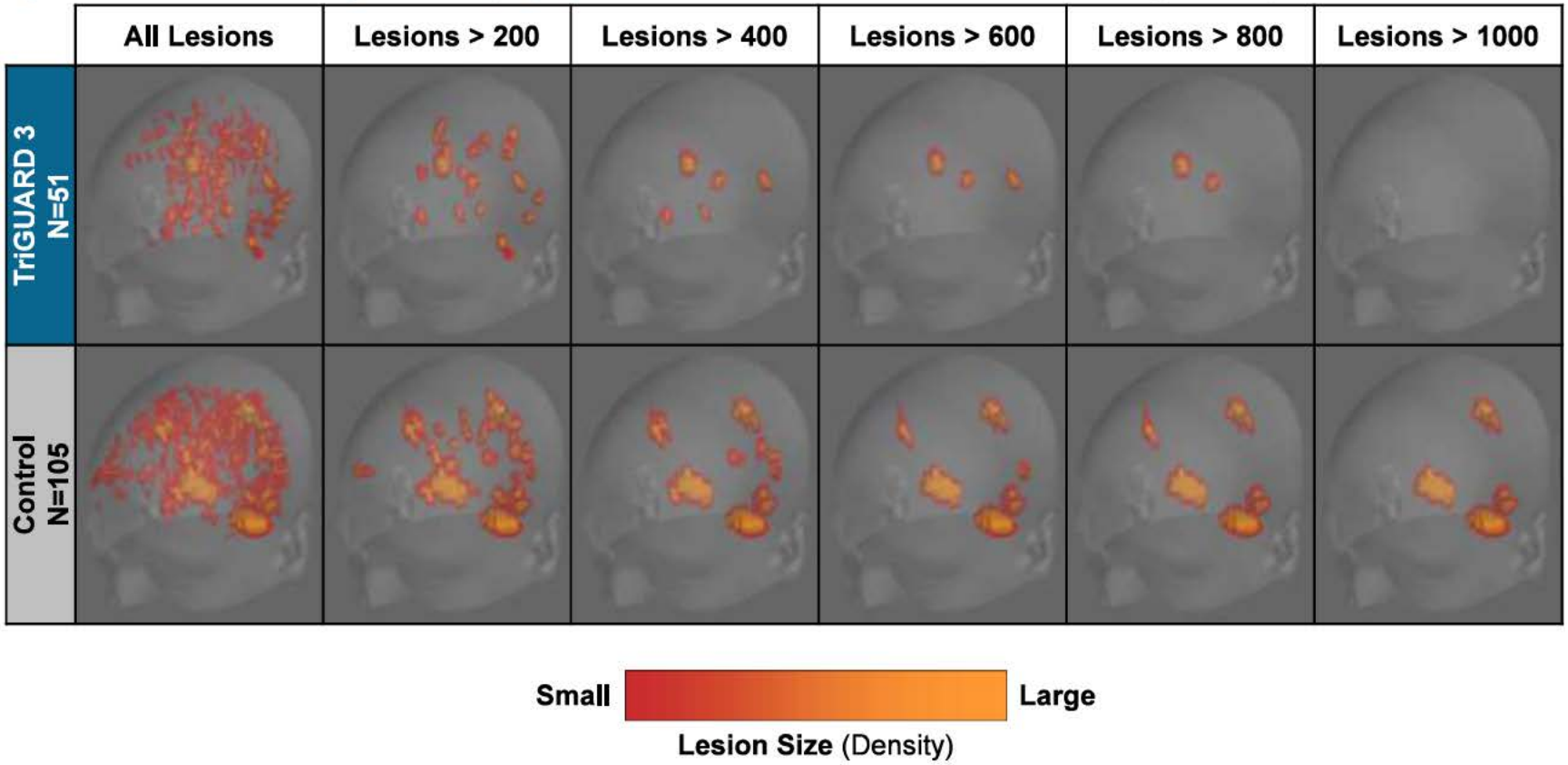
DW-MRI: diffusion-weighted magnetic resonance imaging; IQR: interquartile range; PT: per treatment

6.5.4 Additional Effectiveness Analyses - Imaging (3D Rendering and SCIL)

In addition to the pre-planned analyses performed to evaluate the effectiveness of the TriGUARD device in the REFLECT study, imaging-specific analyses were performed to understand the dynamics of the device and treatment efficacy more fully.

These post hoc analyses support the premise that TriGUARD 3 provides a clinically meaningful level of protection through a reduction in total lesion volume. In addition, lesion size-based MRI analysis visually support TriGUARD 3 effectiveness as the threshold of the lesions increased progressively from small to clinically dangerous larger lesions (Figure 14). This mapping demonstrates that when all 3 branches are covered, there is a noticeable difference in the size of the DWI lesions in the control group and the TriGUARD 3 treatment group. Data are internally consistent and are illustrative of the mechanism of the device.

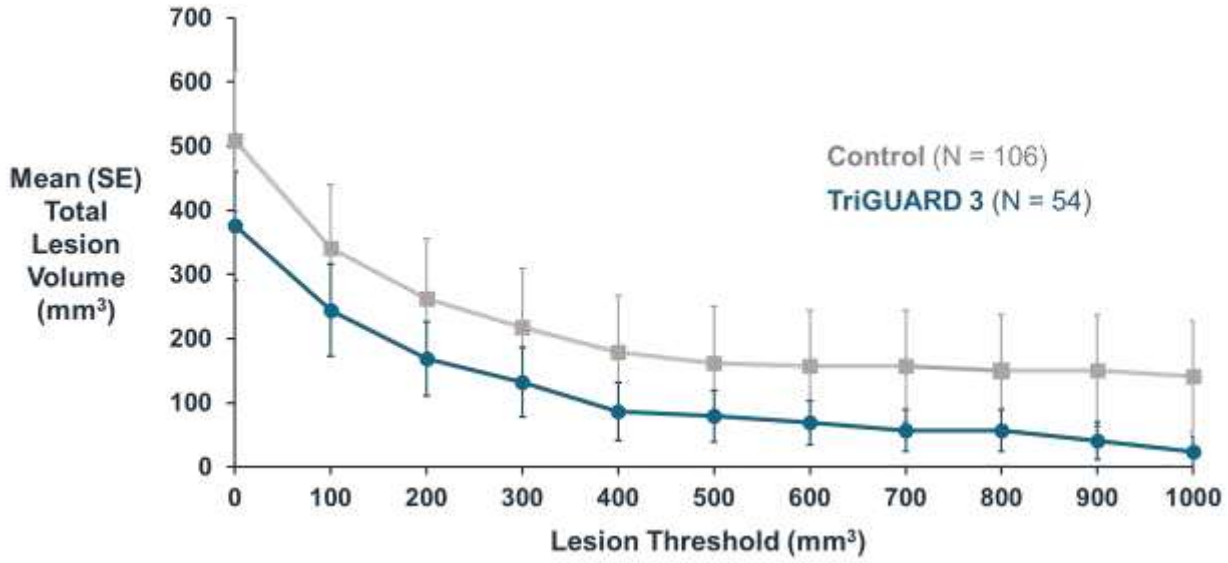
Figure 14: 3D Rendering of the Topographical Lesion Size and Distribution (PT Population)



PT: per treatment

Assessments of average new supra-threshold cerebral ischemic lesions (SCIL) volume were also conducted. These data demonstrate a consistent benefit of the TriGUARD device as the lesion size threshold increases (Figure 15).

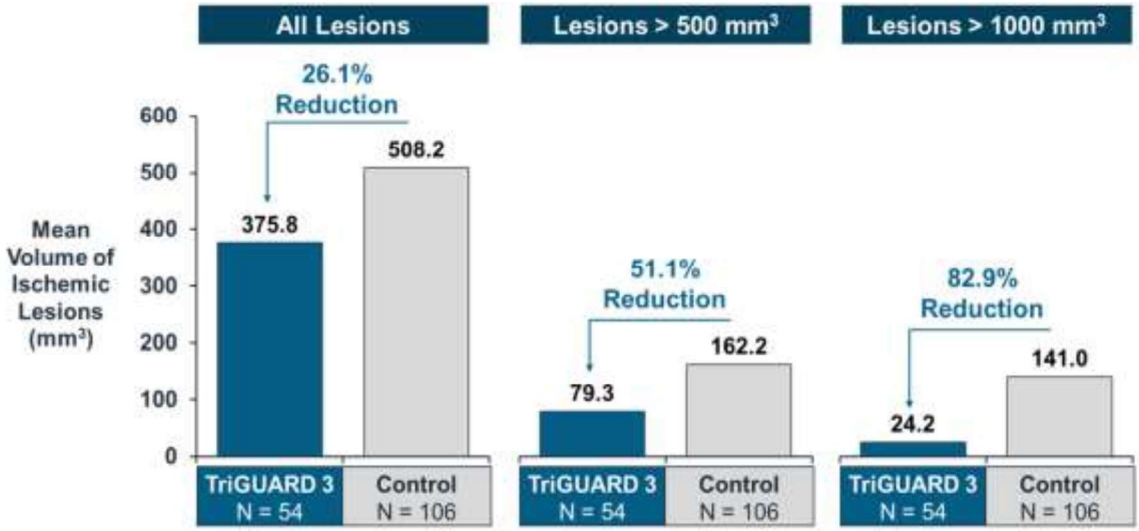
Figure 15: Total New Supra-Threshold SCIL (PT Population)



PT: per treatment; SCIL: supra-threshold cerebral ischemic lesions; SE: standard error
Note: confidence intervals presented for descriptive purposes and are not adjusted for multiplicity.

Reductions were consistently observed in all lesions and in larger lesions (ie, > 500 mm^3 and > 1000 mm^3; Figure 16).

Figure 16: TriGUARD 3 Filtration by Lesion Size (PT Population)



PT: per treatment (complete coverage)

6.6 Clinical Study Conclusions

This multi-center, randomized, controlled study demonstrated that the safety profile of the TriGUARD 3 was consistent with TAVR and is sufficient to prove the safety of the device in clinical use. MRI analysis concluded that there was a numerically and clinically meaningful although non-statistically significant reduction in lesion volume. The primary safety endpoint was met with significance. Effectiveness results also demonstrated that when all 3 cerebral branches were covered, there was a consistent numerical reduction in cerebral lesions and lesion volume.

An analysis of DW-MRI lesion sizes revealed that, for all lesion sizes, TriGUARD 3 patients with 3-vessel coverage in at least 2 of 3 procedural timepoints had numerically smaller size of individual lesions, with the greatest effect seen in the largest (and most clinically meaningful) lesion size ranges.

Overall, the study results suggest that TriGUARD 3 minimizes the risk of cerebral damage during a high-risk TAVR procedure by deflecting embolic debris away from the cerebral circulation.

7 SUBSTANTIAL EQUIVALENCE OF THE TRIGUARD 3 DEVICE TO THE PREDICATE SENTINEL DEVICE

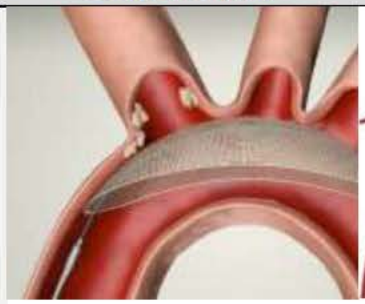
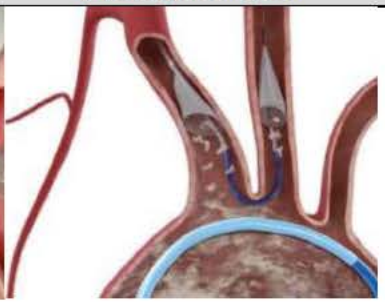
Summary

- The totality of evidence supports that TriGUARD 3 is "as safe and effective as" the predicate Sentinel device and meets all Special Controls and the burden of substantial equivalence as outlined by the 510(k)-regulatory pathway.
- Similar to the predicate device, TriGUARD 3 has shown substantial reductions in lesion volume.

The FDA Guidance Document, "The 510(k) Program: Evaluating Substantial Equivalence in Premarket Notifications [510(k)]", including the FDA Decision-Making Flowchart (see Figure 22 in Appendix 12.7), was used to determine substantial equivalence of the proposed TriGUARD 3 device to the predicate Sentinel device (FDA 2014).

Table 11 summarizes similarities and differences of the TriGUARD 3 and the Sentinel devices. Overall, the devices have similar design characteristics and intended uses, meeting the requirements for substantial equivalence.

Table 11: Summary of Device Characteristics

	Subject Device	Predicate Device	Summary of Similarities and Differences
			
Device Name	TriGUARD 3 Cerebral Embolic Protection Device	Sentinel Cerebral Embolic Protection Device	*Not applicable*
510(k) Number	TBD	DEN160043	*Not applicable*
Manufacturer	Keystone Heart, Ltd.	Boston Scientific (formerly Claret)	*Not applicable*
Regulation Number	870.1251	870.1251	*Same*
Device Classification Name	**Temporary catheter for embolic protection during transcatheter intracardiac procedures.** This device is a single-use percutaneous catheter system that has (a) blood filter(s) at the distal end. This device is indicated for use while performing transcatheter intracardiac procedures. The device is used to filter blood in a manner that may prevent embolic material (thrombus/debris) from the transcatheter intracardiac procedure from traveling towards the cerebral circulation.	**Temporary catheter for embolic protection during transcatheter intracardiac procedures.** This device is a single-use percutaneous catheter system that has (a) blood filter(s) at the distal end. This device is indicated for use while performing transcatheter intracardiac procedures. The device is used to filter blood in a manner that may prevent embolic material (thrombus/debris) from the transcatheter intracardiac procedure from traveling towards the cerebral circulation.	*Same*
Product Code	PUM	PUM	*Same*
Intended Use/ Indications for Use	The TriGUARD 3 Cerebral **Embolic Protection Device** is designed to minimize the risk of cerebral damage by deflecting embolic debris away from the cerebral circulation during trans-catheter heart procedures.	The Sentinel Cerebral Protection System is indicated for use as an **embolic protection device** to capture and remove thrombus/debris while performing transcatheter aortic valve replacement procedures. The diameters of the arteries at the site of filter placement should be between 9 – 15 mm for the brachiocephalic and 6.5 –	*Similar. Use of the predicate Sentinel is restricted based on target vessel size. The proposed TriGUARD 3 does not have any anatomical restrictions with regard to treated vessels.*

		10 mm in the left common carotid.	
Intended User	Physician	Physician	*Same*
Indicated Patient Population	Indicated for TAVR	Indicated for TAVR	*Same*
Prescription Device for Physician Use Only	Yes	Yes	*Same*
Single Patient Use	Yes	Yes	*Same*
Vessel Coverage	Yes; all 3 cerebral vessels	Yes; brachiocephalic artery (Proximal Filter), and a second filter delivered to the left common carotid artery (Distal Filter)	*Similar. The TriGUARD provides coverage for the entire brain as opposed to coverage of select portions provided by the predicate.*
Principle of Operation	Filters and deflects embolic debris	Filters and captures and removes embolic debris	*Similar*
Time for deployment	4 Minutes	4 Minutes	*Same*
Cerebral Blood Flow Impedance	Not to exceed 15%	Not to exceed 15%	*Same*
Deployment / Retrieval Forces	Not to exceed 25N (5.62 lbs)	Not to exceed 6 lbs.	*Similar*
Use Environment	Cardiac catheterization lab	Cardiac catheterization lab	*Same*
Device Design			
Filter Size	Width 74 mm; Length 98 mm	Proximal Filter- 15 mm; Distal Filter- 10 mm	*Different. Devices are designed appropriately for target anatomy.*
Pore Size	115 x 145 µm	140 µm	*Similar. Both devices have demonstrated that they do not impede blood flow.*
Filter Material(s)	Nitinol frame with PEEK mesh	Nitinol frame with polyurethane film	*Different. However, both leverage well known biocompatible materials. Biocompatibility and performance testing have been completed to demonstrate substantial equivalence.*
Delivery Method	8F contralateral femoral artery groin access site	6F Radial artery	*Similar. Size is based on access anatomy (radial artery for Sentinel versus femoral artery for TriGUARD 3)*
Working Length	76 cm	95 cm	*Similar. Working length is based on patient size and location of access point (radial artery for Sentinel versus femoral artery for*

			TriGUARD 3)
Guidewire Compatibility	Super stiff 0.035"260 cm long with 1 cm floppy end	0.014" (0.36 mm) diameter floppy tip coronary guidewire, 175 cm minimum length	*Similar.*
Radiopaque Features	Nitinol frame	Articulating Sheath tip, Proximal Sheath tip, Proximal Filter hoop, Distal Filter hoop and Distal Filter tip	*Similar. Both meet requirements for radiopaque features for visualization during procedure.*

TAVR: transcatheter aortic valve replacement; TBD: to be determined; PEEK: polyether ether ketone

7.1 Technological Differences

While the TriGUARD 3, definitionally speaking, has the same general technological characteristics as Sentinel, it does have some design differences. The most important difference between the devices is the fact that the TriGUARD 3 device is designed to cover all 3 cerebral branches whereas the Sentinel device is only designed to cover 2.

The second design difference is the fact that the Sentinel device is a capture filter whereas the TriGUARD 3 device is a deflection filter. While the TriGUARD 3 device can trap debris, it is also positioned in the aortic arch in such a way that debris can also flow to the peripheries.

The access point is also different between the 2 devices. The Sentinel device uses radial access whereas the TriGUARD 3 device uses femoral access. Femoral access allows for the TAVR access point to be used to advance the pigtail catheter to enable the TAVR procedure.

Overall, as acknowledged by the FDA, these differences do amount to different technological characteristics for purposes of the 510(k) pathway but do not raise different questions of safety or effectiveness. This allows for a claim of substantial equivalence to the predicate device.

7.2 Performance Testing

Clinical and nonclinical performance testing was performed to demonstrate that the subject TriGUARD 3 Cerebral Embolic Protection Device is substantially equivalent to the predicate device. The technical characteristics between the subject device and the predicate device have been evaluated through design, material and dimensional comparison, bench, and biocompatibility tests to provide evidence of substantial equivalence. The TriGUARD 3 is substantially equivalent to the predicate device based on comparison of the device functionality, compatibility, technological characteristics, clinical performance and indications for use.

7.2.1 Special Controls Under Section 7 of 21 CFR 870.1251

As described in Section 4, the clinical performance testing must demonstrate:

i. The ability to safely deliver, deploy, and remove the device;

ii. The ability of the device to filter embolic material while not impeding blood flow;

iii. Secure positioning and stability of the position throughout the transcatheter intracardiac procedure; and

iv. Evaluation of all adverse events including death, stroke, and vascular injury.

Each of the above criteria are evaluated below with substantiating data from the clinical study.

7.2.1.1 (i) Ability to safely deliver, deploy and remove the device

The clinical data from REFLECT demonstrate that the TriGUARD 3 device was successfully deployed, the aortic arch was accessed, and the device was successfully retrieved in 100% of patients, satisfying the conditions set forth in the first special control. The clinical equivalence to the predicate with regards to this clinical control is shown in Table 12.

Table 12: Clinical Equivalence for Safe Delivery, Deployment and Retrieval

	TriGUARD 3 (N=157)	Sentinel [1] (N=231)
Delivery / Retrieval successful, % (n)	100% (157)	94.4% (218)
Vascular complication (related), % (n)	1.3% (2)	0.4 % (1)

[1] (Claret Medical 2017)

Safety data presented in Section 6.4, coupled with the fact that the REFLECT study met the primary endpoint with significance, further support the safety aspect of this clinical control and the safety of the device operation as required by the Special Controls.

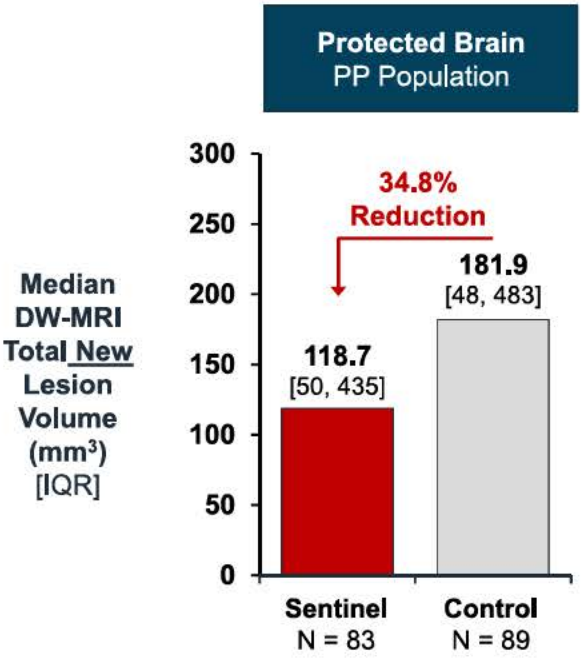
7.2.1.2 (ii) Ability to filter embolic material while not impeding blood flow

At the purely biomechanical level, the TriGUARD 3 device has comparable pore size (TriGUARD 3 115 x 145 µm) to the predicate Sentinel device (140 x 140 µm). Similarly, neither device has had reported events related to blood flow or drop in pulsatile pressures. For the TriGUARD device, this is also supported by the Good Laboratory Procedure animal testing.

In the Sentinel study, total new lesion volume in protected territories was assessed as the primary effectiveness endpoint **in the ITT and Per Protocol populations. The Sentinel study's ITT population, the pre-specified primary analysis population, includes patients who were out of window for MRI analysis and a patient who was not treated as per randomized assignment. As such, Keystone believes the appropriate analysis population for cross-study comparison of the Sentinel study and the REFLECT study is the Sentinel Per Protocol population. The REFLECT populations (eITT or PT) respect the comparative MRI windows and do not have any incorrect patient assignments. In the REFLECT clinical protocol, MRI was**

required to be performed at 2 to 5 days (≥48 to <144 hours) post procedure. However, the clinical study report included all MRI data collected between 1- and 7-days post-procedure (inclusive). In addition, in support of Substantial Equivalence and to maximize available data, Keystone Heart used to the *same MRI windows as the Sentinel device in the PP population* which excluded improper patient treatment assignments and out of window scans that would be unlikely to provide a valid assessment of peri-procedural neurologic injury. As shown in Figure 17, a 42% reduction in total new lesion volume was observed with the predicate device in the Per Protocol Population. It is important to recognize that this assessment required both pre- and post-procedure MRI data, and therefore patients without imaging data prior to the TAVR procedure were excluded from the analysis. In addition, this assessment is limited as it does not distinguish between the size of lesions that enter the cerebral circulation.

Figure 17: DW-MRI Total New Lesion Volume – Sentinel vs Control

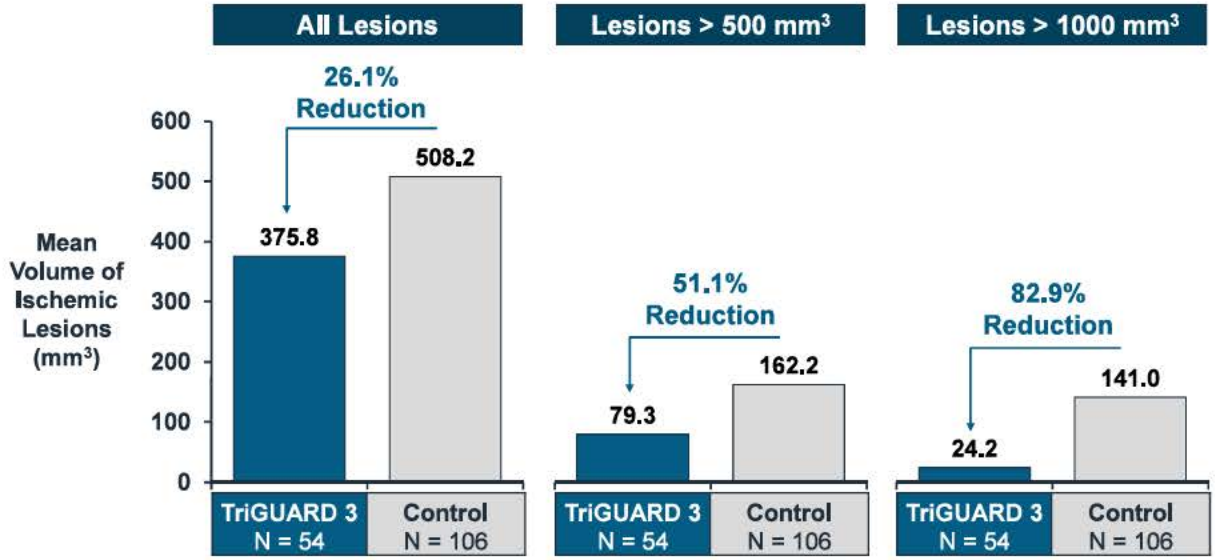


DW-MRI: diffusion-weighted magnetic resonance imaging;
Per Protocol Population: Patients in whom the investigational study procedure was attempted, as prescribed by their treatment arm, and whose follow-up assessments were in the pre-specified window
IQR: interquartile range
Source: **Data from FDA Presentation at 2017 CSDP Meeting for Sentinel Device (Video Recording)**

In an effort to include more patients in the primary effectiveness endpoint evaluation in the REFLECT study, an analysis of total new lesion volume that required MRI pre and post TAVR procedure was not performed. Instead, effectiveness endpoints included an

assessment of total lesion volume by DW-MRI. In the PT Population, a 22.5% reduction in total lesion volume was observed in TriGUARD-treated patients compared to control patients (Figure 13). A reduction was also observed when looking at the lesion size analysis described in Section 5.5.4 and summarized below in Figure 18. TriGUARD 3 effectively diverted, large more dangerous, embolic material from entering cerebral circulation thus satisfying the second clinical control (ii).

Figure 18: TriGUARD 3 Filtration by Lesion Size (PT Population)



PT: per treatment (complete coverage)

The clinical data captured in REFLECT indicate that there was no global hypoperfusion of the brain, which demonstrates that the device does not impede blood flow to the brain.

7.2.1.3 *(iii) Secure positioning and stability of the position throughout the transcatheter intracardiac procedure*

The clinical data demonstrate that the TriGUARD device was able to be secured and stable within the aortic arch if used in accordance with the Instructions for Use. As previously noted, 100% of devices were successfully deployed. As a result of the analysis of the REFLECT study, Keystone made a minor modification to the crimper to ensure that the hypotube is positioned underneath the filter during deployment. Additional training and clarifications to the IFU will also assist with ensuring complete coverage with the marketed device with the resulting improvements in overall effectiveness.

From a substantial equivalence perspective, it is not possible to make a direct comparison within the clinical study as these data are not available for the predicate.

In terms of real-world evidence, under commercial use in Europe, all available physician reports indicated that the TriGUARD 3 held its position during the TAVR procedure (N=376). See Section 8.

7.2.1.4 (iv) Evaluation of all adverse events including death, stroke, and vascular injury

The primary safety endpoint of the study was met with significance ($p < 0.0001$), 15.92% in the TriGUARD group as compared to the performance goal of 34.4%. In addition to meeting the safety endpoint, an analysis of relatedness to the TriGUARD device or procedure was conducted. Seven of the 11 major vascular complication events were at the TAVR access site, and 3 events were at the contralateral access site and related to the closure device.

The risk related to any accessory device during the main procedure should be assessed independently from the main index procedure to fully understand the risk that is attributable to the accessory device. Any additional risk of the TriGUARD 3 device would take place at specific time points as enumerated below:

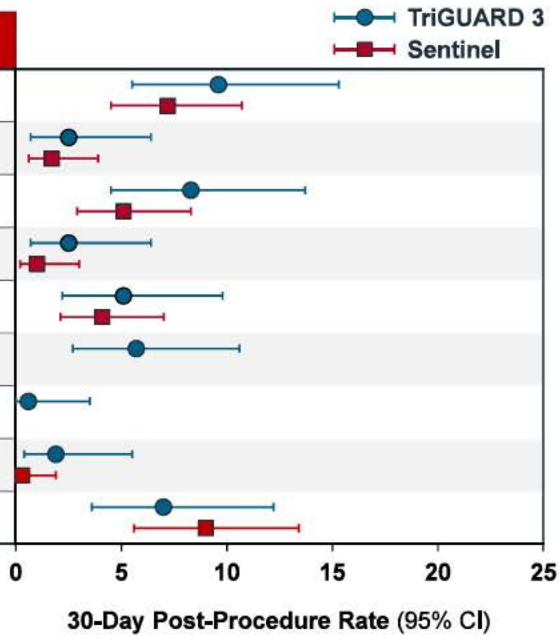
1) when the TriGUARD 3 is advanced and deployed,
2) when the possible pre-balloon system is advanced,
3) when the TAVR system is advanced,
4) when the TAVR system is retrieved,
5) when the possible post balloon system is advanced and retrieved, and
6) when the TriGUARD 3 system is retrieved.

At all other timepoints, the TriGUARD 3 device is in place, not touched or moved, and does not interfere with the overall TAVR procedure. In the REFLECT study, to truly assess the additional risk of the TriGUARD 3 device, the CEC was asked to assess the relatedness of all serious adverse events (AEs) and AEs to the TriGUARD 3 procedure/device and to the TAVR procedure/device.

The complexity of TAVR-related complications (such as aortic ring ruptures, dissections of ascending aorta, arrhythmias/complete heart block/ventricular tachycardias) leading to resuscitation efforts requires that any adverse outcome be assessed carefully to avoid misleading conclusions on the safety of the cerebral protection devices. Even though rare, any SAE during TAVR can also be misleading in small clinical studies when each event can have a major impact on any statistical conclusions and comparison for other relevant historical other data may warranted. Although there were higher rates of these early safety endpoints in the TriGUARD 3 than the control group, this is outweighed by the benefits associated with reduced lesion volume and the impact long-term significant safety events. For the purposes of the REFLECT study and to add perspective, a summary of the TriGUARD 3 data in comparison to the Sentinel data is provided in Figure 19.

Figure 19: Safety Comparison of TriGUARD 3 and Sentinel

	TriGUARD 3 (N=162)	Sentinel (N=309)
MACCE (as per Sentinel Study)	9.6%	7.2%
All-Cause Death	2.5%	1.7%
All Stroke	8.3%	5.1%
Disabling	2.5%	1.0%
Non-Disabling	5.1%	4.1%
Life-Threatening Bleeding	5.7%	*NR*
Acute Kidney Injury – Stage 2	0.6%	*NR*
Acute Kidney Injury – Stage 3	1.9%	0.3%
Major Vascular Complications	7.0%	9.0%



CI: confidence interval; MACCE: major adverse cardiovascular and cerebrovascular events; NR: not reported
Note 1: MACCE definition from SENTINEL study used for comparison (composite of death, stroke, and acute kidney injury [stage 3]).
Note 2: confidence intervals presented for descriptive purposes and are not adjusted for multiplicity.
Note 3: Sample sizes reflect SP(ITT) Population for TriGUARD 3 (Roll-in + ITT) and Roll-In + ITT Population for Sentinel.
Source:(Claret Medical Inc 2017)

Approximately 50% of all strokes post TAVR have been shown to take place peri-procedurally (Smith et al 2011) and related to the TAVR procedure as emboli and debris are dislodged to the brain circulation. Since the cerebral protection devices are in place only during the TAVR procedure, the true safety of any cerebral protection devices to protect the brain is therefore best assessed before discharge. As described in Section 6.4.1.1, there were only 2 strokes reported in the TriGUARD 3 group within 24 hours of the TAVR procedure.

7.3 Substantial Equivalence Conclusions

The totality of evidence support that TriGUARD 3 is “as safe and effective as” the predicate Sentinel device and meets all Special Controls under 21 CFR 870.1251 and therefore meets the burden of substantial equivalence as outlined by the 510(k) pathway (Table 1). Similar to the predicate device, TriGUARD 3 has shown substantial reductions in lesion volume, including in large lesions.

8 REAL-WORLD EXPERIENCE – COMMERCIAL DATA FROM EUROPE

8.1 Post-Marketing Experience

Due to the pandemic, a data sharing agreement was executed with several European centers in order to gather data. Patient demographics were collected regarding prior stroke, history of diabetes, hypertension, and atrial fibrillation. Physicians also reported coverage data. A summary of the 94 patients whose data has been collected under structured data gathering process (see Appendix 12.8) is shown in Table 13. While some summary data has been presented, there has been no detailed data submitted to the FDA. No strokes have been reported since the start of commercialization in July 2020. Data collection is continuing for vigilance purposes.

Table 13: Summary of Real-Word Data

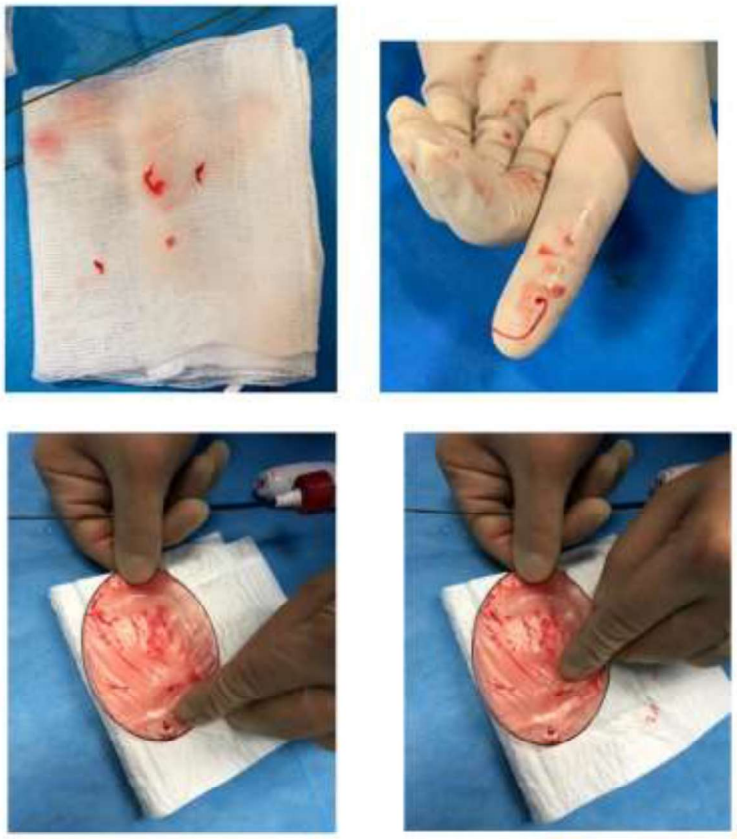
# Sites	30
# Patients	94
Avg. Age	81 years
Physician Reported Coverage	
Pre-Tavi	93 3 Vessel 1 not reported
During Tavi	87 3 Vessel 4 2 Vessel 3 not reported
Male	61%
Valve Types	Accurate Neo: 11
	Evolute: 25
	MyVal: 7
	Sapien: 41
	Occluder and Portico: 2 each
	Allegra: 1

Commercial activity of the TriGUARD 3 in the EU began in July 2020. As of 18 June 2021, a total of 376 cases have been performed in 57 sites throughout 9 countries, with procedures spread equally across 5 commercially available valves in the EU. In respect of General Data Protection Regulation in the EU, the data that has been collected demonstrated that all cases maintained 3 vessel coverage throughout the cardiac procedure, which provides evidence that the changes to the TriGUARD 3 crimper and training materials have been successful in ensuring that the device is properly place. All index procedures have completed successfully, and importantly, no neurological events, including no disabling stroke, have been reported.

8.2 TriGUARD 3 Debris Capture

Photographs taken of the TriGUARD 3 in commercial use also provide real-world evidence that, in addition to deflecting debris, the TriGUARD 3 captures debris (Figure 20). Additional images are provided in Appendix 12.9.

Figure 20: Clinical Evidence of TriGUARD 3 Debris Capture



9 TRAINING

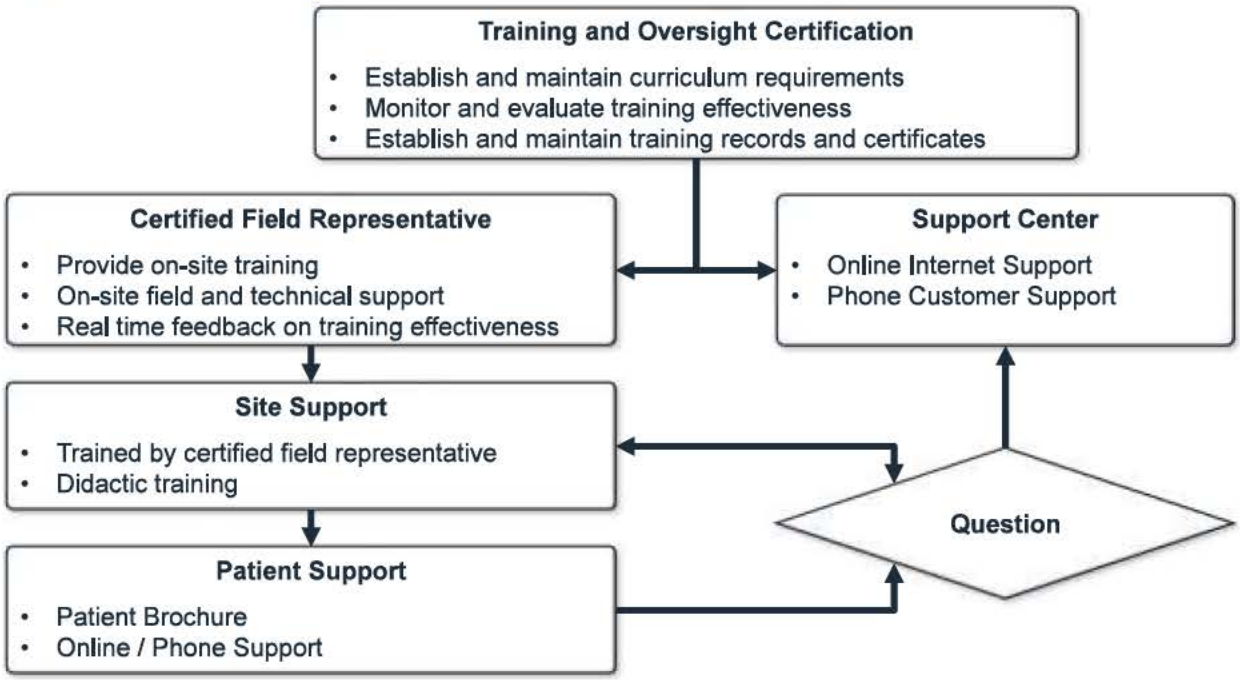
9.1 Training Overview

Keystone Heart has utilized its international commercial experience and US pivotal study experience to develop an enhanced training program and with additional educational materials (Figure 21). All physicians and staff will be educated and trained by Keystone Heart, with certification required prior to using the TriGUARD 3 device. Additionally, sites will be monitored by trained Keystone Heart field staff.

A separate and dedicated in-house training manager will be responsible for developing, tracking and updating training materials and plans for both physicians and Keystone Heart field personnel.

Training materials are provided in Appendix 12.2.3.

Figure 21: Training Overview



9.2 Keystone Heart Field Personnel Training

An extensive pre-training and self-study module will be developed and provided to all field personal prior to their in-person didactic and hands-on training, and a pre-test will be administered on those materials. Subsequently, all field personnel will attend a multi-day didactic and hands-on training course that will include written, oral, and practical testing for verification of training effectiveness prior to certification of a Keystone Heart

Field Representative. The primary training modules and topics will be consistent with those utilized for the Pivotal Trial and include:

- Cardiac anatomy and physiology
- Indications, precautions, warnings and appropriate patient selection
- TriGUARD 3 design, components and operation
- TriGUARD 3 preparation, operation and retrieval
- Avoiding actual and potential adverse events
- Trouble shooting (learning from international and US trial experiences)
- Comprehensive computed tomography (CT) and angiographic case review training
- Pre-case planning and post-case debrief review training
- Hands-on device simulation training
- Tips and tricks – Best practice training

Upon successful completion of training and certification, all new field personnel will be mentored through their initial customer training and procedures by a Keystone Heart employee with actual, practical procedure experience prior to doing so on their own. Initially, the mentors will be the Field Clinical Engineer team and Research and Design Engineers who trained and supported the physicians and staff at the pivotal study sites.

9.2.1 Site Physician and Staff Training

A primary physician at each site will be identified and designated as responsible for ensuring physicians and staff involved in using the TriGUARD 3 are adequately qualified and trained.

Certified Keystone Heart Field Trainers (as described above) will conduct training consisting of both didactic and hands-on methodologies. Training will be documented for all physician and staff attending.

The didactic section will include:

- Cardiac anatomy and physiology
- Indications, precautions, warnings and appropriate patient selection
- TriGUARD 3 design, components, and operation
- TriGUARD 3 preparation, operation, and retrieval
- Avoiding actual and potential adverse events
- Troubleshooting (learning from international and US trial experiences)
- Review of clinical data, including thorough review of AEs

- Comprehensive CT and angiographic case review training
- Pre-case planning and post-case debrief review training
- Tips and tricks – Best practice training

The hands-on session will include the deployment of an actual TriGUARD 3 in a simulated aortic arch and practice TriGUARD removal utilizing a simulator module that was utilized for training the Field Personnel.

9.2.2 Product Launch

The TriGUARD 3 device will only be distributed to sites that have undergone the training. Users are intended to be interventional cardiologists with cardiac catherization capabilities. Keystone Heart will closely monitor results, especially related to safety, and adjust the rate of site expansion appropriately.

10 KEYSTONE HEART'S POSITIONS ON TOPICS IDENTIFIED BY FDA

In advance of the CSDP meeting, FDA provided Keystone proposed high level topics for discussion. Keystone's reposes to these topics are provided below.

10.1 FDA Topic 1

The TriGUARD 3 failed to meet the prespecified primary effectiveness endpoint. The sponsor performed analyses using secondary imaging endpoints including, but not limited to, 'per-patient average single cerebral ischemic lesion volume' and 'maximum single cerebral ischemic lesion volume' to support substantial equivalence in terms of effectiveness. FDA plans to ask the panel to comment on the clinical significance of these analyses.

As described by Choi et at and Asdaghi et al, larger ischemic lesions are more likely to have a negative clinical impact on cognitive function (Asdaghi et al 2014; Choi et al 2000), as illustrated by REFLECT data in Table 14. Further, many TAVR-related cerebral lesions are very small with unknown clinical impact. These smaller lesions are frequently seen to reverse at later timepoints (Nagaraja et al 2020), and, in contrast to the size of conventional stroke related lesions, there is no accepted minimum "clinically meaningful" lesion volume. Therefore, including very small lesions in total lesion volume measures may actively confound meaningful association with clinical outcomes. As such, per-patient average single cerebral ischemic lesion volume and maximum single cerebral ischemic lesion volume are clinically relevant endpoints to evaluate the effectiveness of the TriGUARD 3 device.

Table 14: NIHSS and Lesion Number Comparison

	Case 1: A few large lesions, high NIHSS	Case 2: Many small lesions, low NIHSS change
Total Lesion Volume	6558.59 mm^3	5681.26 mm^3
Lesion Number	7	51
NIHSS Change pre / post TAVR	11 (0 to 11)	3 (1 to 4)

NIHSS: National Institutes of Health Stroke Scale; TAVR: transcatheter aortic valve replacement

In the Sentinel study, total new lesion volume was assessed and required both pre and post-procedure MRI data, and therefore was only evaluated in 65% of patients. Although this assessment does allow for evaluation of lesions formed post TAVR, total volume does distinguish between the impact of multiple small lesions (potentially a more benign situation) and single large lesions (potentially more damaging) and can only be assessed in patients with imaging data available.

In an effort to include more patients in the primary effectiveness endpoint evaluation, MRI pre and post TAVR procedure was not performed. Instead, secondary effectiveness endpoints included per patient average single cerebral ischemic lesions

volume and maximum single cerebral ischemic lesion volume. As presented in Section 6.5.3, in the PT Population, TriGUARD 3 was shown to provide substantial reductions compared with control in total lesion volume, per patient average single cerebral ischemic lesion volume, and maximum single cerebral ischemic lesion volume (Figure 13).

Furthermore, imaging analyses from the REFLECT study suggest that embolic protection devices may have a differential effect on the size of the lesions they can protect against. TriGUARD 3 was shown to reduce the amount of large, clinically more relevant lesions than smaller, clinically less dangerous lesions, as described in Section 6.5.4.

10.2 FDA Topic 2

The primary safety composite endpoint was met; however, individual components of the composite were numerically in favor of the control group. FDA plans to ask the panel to comment on the clinical significance of the primary safety composite endpoint, as well as specific components of the primary safety endpoint.

Similar to the Sentinel study, the REFLECT study was designed to evaluate safety as a composite endpoint compared to a clinical performance goal based on historical TAVR studies to demonstrate that TriGUARD 3 did not increase the risks associated with a TAVR procedure (see Section 6.1). The study was not designed or powered to draw statistical inferences between the study groups on safety endpoints. Furthermore, the sample size was limited as a result of the study suspension with only 57 control patients in the safety analyses (see Section 5.1.1). Comparing observed rates of infrequent adverse events across groups may lead to spurious conclusions on account of the limited precision with the sample sizes in the study.

With these considerations in mind, the study met its primary safety endpoint; therefore, the TriGUARD 3 group had a safety profile consistent with the expected safety profile of TAVR procedures. There was a numerically higher proportion of primary safety endpoint events in the TriGUARD 3 group, which was predominantly due to a higher proportion of major vascular events in the TriGUARD 3 group (7% vs 0%).

The CEC adjudicated 9 of the 11 major vascular events to be related to TAVR or aortic injury and not related to the device. Additionally, the 7% rate of major vascular complications in the TriGUARD 3 group is consistent with rates reported in recent TAVR studies.

Overall, the REFLECT study shows that the added risks associated with this adjunctive procedure are minimal, consistent with the predicate Sentinel device.

10.3 FDA Topic 3

The REFLECT study investigational plan analysis cohorts included inclusion of roll-in subjects in the safety analysis, pooling of Phase I and II controls groups for the

effectiveness analysis, and the Per Treatment population for additional analyses of the primary and secondary effectiveness endpoints. FDA plans to ask the panel to comment on the clinical significance of analysis populations, including which patient population should be used to evaluate substantial equivalence.

Inclusions of roll-in patients in the safety analysis

All roll-in patients received the TriGUARD 3 device and were therefore assessed for safety events and device performance. However, because TriGUARD use in roll-in patients were proctored cases as part of training, no efficacy information was collected.

Pooling of Phase 1 and II patients in the control group for effectiveness analysis

Keystone Heart acknowledges that it was a statistical oversight to specify in the Statistical Analysis Plan that the poolability of the Phase I and Phase II control patients required that the p-value on each significance test for 7 variables needed to be > 0.15. As previously described, the binomial probability that at least one of 7 variables would be different at the 0.15 significance level by chance alone was approximately 68%. Importantly, none of the observed differences in baseline characteristics between the Phase 1 and Phase II control patients were clinically meaningful. Given the relatively modest sample size of the Pooled Control patients (ie, N=57), Keystone considers it clinically and statistically appropriate to evaluate efficacy endpoints using the totality of data from the Pooled Control population.

Per Treatment (PT) population for effectiveness endpoints

The PT Population (patients with complete 3-vessel coverage in at least 2 of 3 procedural timepoints) is the most appropriate analysis population to evaluate the effectiveness of the TriGUARD 3 device when used as intended. Effectiveness analyses in the PT Population are equivalent to the analyses of “protected territories” that were the primary focus of the effectiveness analyses in the pivotal study for the predicate Sentinel device. The effectiveness results for the predicate device excluded areas of the brain not protected by the 2-vessel coverage design. Thus, the PT Population for the REFLECT study is the appropriate analysis population to evaluate substantial equivalence with the predicate device.

10.4 FDA Topic 4

The sponsor proposes to demonstrate substantial equivalence in part by using adverse event rates calculated from events adjudicated as related to the device. The predicate’s DeNovo petition was granted based on event rates computed from all events (regardless of device-relatedness). FDA plans to ask the panel to comment on the clinical significance of device relatedness when considering adverse events.

The REFLECT study was designed to evaluate safety as a composite endpoint compared to a clinical performance goal to demonstrate that TriGUARD 3 did not increase the risks associated with a TAVR procedure (see Section 6.1). Importantly, the study met its primary safety endpoint.

Given that the TriGUARD 3 is an accessory device to a high-risk index procedure, it is important to assess relatedness of events determined by CEC adjudication. Overall, few events were adjudicated as related to the TriGUARD 3 device (see Section 6.4.1.1).

10.5 FDA Topic 5

The TriGUARD 3 is introduced through an 8-F access sheath located contralateral to Transcatheter Aortic Valve Replacement (TAVR) device access. Although standard TAVR also commonly utilizes a contralateral sheath to accommodate pressure catheters,a smaller 6-F sheath is typically employed for this use. FDA plans to ask the panel to comment on the clinical significance of an increased risk of vascular complications fromthe 8-F puncture.

It was anticipated that the larger access sheath might be associated with an increase in vascular complications. However, the benefits of leveraging the contralateral access site and not exposing the frail patient population to an additional (ie, third) access site for potential opportunistic infection were anticipated to outweigh the potential increase in risk for vascular complications. Ultimately, the rate of major vascular complications related to the TriGUARD 3 was low (2/157; 1.3%).

The narratives, provided in Appendix 12.6, further suggest that while the TriGUARD 3 was used in the contralateral site, these events could also have been expected given the rate of the events noted with the closure device used in isolation (6 – 10% Perclose SSED [P960043/S080]). Vascular complications most commonly occur at the access site, and bleeding and/or hematoma formation occurs most frequently. Interestingly, studies consistently show that failure of a closure device (adopted to prevent vascular access complication) is the most common cause of a major vascular complication (Scarsini et al 2019).

10.6 FDA Topic 6

Data presented by the sponsor indicated that three-vessel coverage throughout the TAVRprocedure was obtained in approximately 60% of patients. FDA plans to ask the panel tocomment on the clinical significance of stable positioning rates as they relate to risk of stroke.

In REFLECT, successful device positioning and coverage at specified procedural time points was assessed by the angiographic core laboratory. TriGUARD 3 maintained secure positioning and stability in 80.9% of the cases (defined as full or partial coverage of the 3 cerebral branches) throughout the TAVR procedure (Table 5). Full 3-vessel coverage in at least 2 of 3 procedural timepoints was achieved in 61.2% of the cases, including roll-in patients. Notably, 75% of patients had complete 3-vessel coverage in at least 2 of 3 procedural timepoints during the TAVR procedures (Figure 9).

During the course of REFLECT, the angiographic core laboratory reported incomplete 3-vessel coverage in some cases. Keystone Heart conducted thorough bench testing to interrogate potential causes for these observations and determined that twisting or

torquing the catheter during advancement could lead to incomplete filter deployment or positioning. Based on this information, the TriGUARD 3 training program was enhanced to emphasize proper delivery technique (see Section 9).

Effectiveness of proper delivery technique has been demonstrated by Dr. Pieter Stella in 50 sequential and consecutive cases. Confirmatory imaging available from 34 of 50 cases was submitted to the FDA on 19 Feb 2021. Dr. Stella has imaging for all cases demonstrating complete 3 vessel coverage at the most critical timepoint during the TAVR procedure, which is during deployment and the time when the vast majority of emboli are dislodged. It is clear from these images that the TriGUARD 3 was stable and provides the 3 vessel coverage.

These data have recently been presented at CRT (Jimenez-Rodriguez et al 2021a), and the first 100 patients will be submitted for publication in the American Journal of Cardiology and are also being entered into the Dutch National Cardiovascular Registry.

10.7 FDA Topic 7

Differences in baseline characteristics were observed between the TriGUARD 3 and Control patient groups including prior stroke or TIA and Insulin-Dependent Diabetes Mellitus (IDDM). FDA plans to ask the panel to comment on the clinical significance of the impact of observed differences on study results.

Keystone Heart agrees and acknowledges that there were some numeric differences between the study groups on certain baseline characteristics. For example, the prevalence of prior stroke or TIA was 17.2% in the TriGUARD 3 group compared with 5.3% in the Control group. However, in the context of a randomized controlled trial with relatively modest sample sizes in each group, such numeric imbalances are not uncommon and are almost certainly due to chance. It is not possible to accurately quantify the impact that these observed differences in baseline characteristics may have had on the results. Nonetheless, the REFLECT study showed that the TriGUARD 3 has an overall favorable benefit-risk ratio for its intended use, and, more importantly, TriGUARD 3 meets the regulatory requirements of substantial equivalence to the predicate device under the 510(k) regulatory pathway.

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12 APPENDICES

12.1 Special Controls for TriGUARD 3 (21 CFR 870.1251)

(1) Non-clinical performance testing must demonstrate that the device performs as intended under anticipated conditions of use. The following performance characteristics must be tested:

(i) Simulated-use testing in a clinically relevant bench anatomic model to assess the following:

(A) Delivery, deployment, and retrieval, including quantifying deployment and retrieval forces, and procedural time; and

(B) Device compatibility and lack of interference with the transcatheter intracardiac procedure and device.

(ii) Tensile strengths of joints and components, tip flexibility, torque strength, torque response, and kink resistance.

(iii) Flow characteristics.

(A) The ability of the filter to not impede blood flow.

(B) The amount of time the filter can be deployed in position and/or retrieved from its location without disrupting blood flow.

(iv) Characterization and verification of all dimensions.

(2) Animal testing must demonstrate that the device performs as intended under anticipated conditions of use. The following performance characteristics must be assessed:

(i) Delivery, deployment, and retrieval, including quantifying procedural time.

(ii) Device compatibility and lack of interference with the transcatheter intracardiac procedure and device.

(iii) Flow characteristics.

(A) The ability of the filter to not impede blood flow.

(B) The amount of time the filter can be deployed in position and/or retrieved from its location without disrupting blood flow.

(iv) Gross pathology and histopathology assessing vascular injury and downstream embolization.

(3) All patient contacting components of the device must be demonstrated to be biocompatible.

(4) Performance data must demonstrate the sterility of the device components intended to be provided sterile.

(5) Performance data must support the shelf life of the device by demonstrating continued sterility, package integrity, and device functionality over the identified shelf life.

(6) Labeling for the device must include:

(i) Instructions for use;

(ii) Compatible transcatheter intracardiac procedure devices;

(iii) A detailed summary of the clinical testing conducted; and

(iv) A shelf life and storage conditions.

(7) Clinical performance testing must demonstrate:

(i) The ability to safely deliver, deploy, and remove the device;

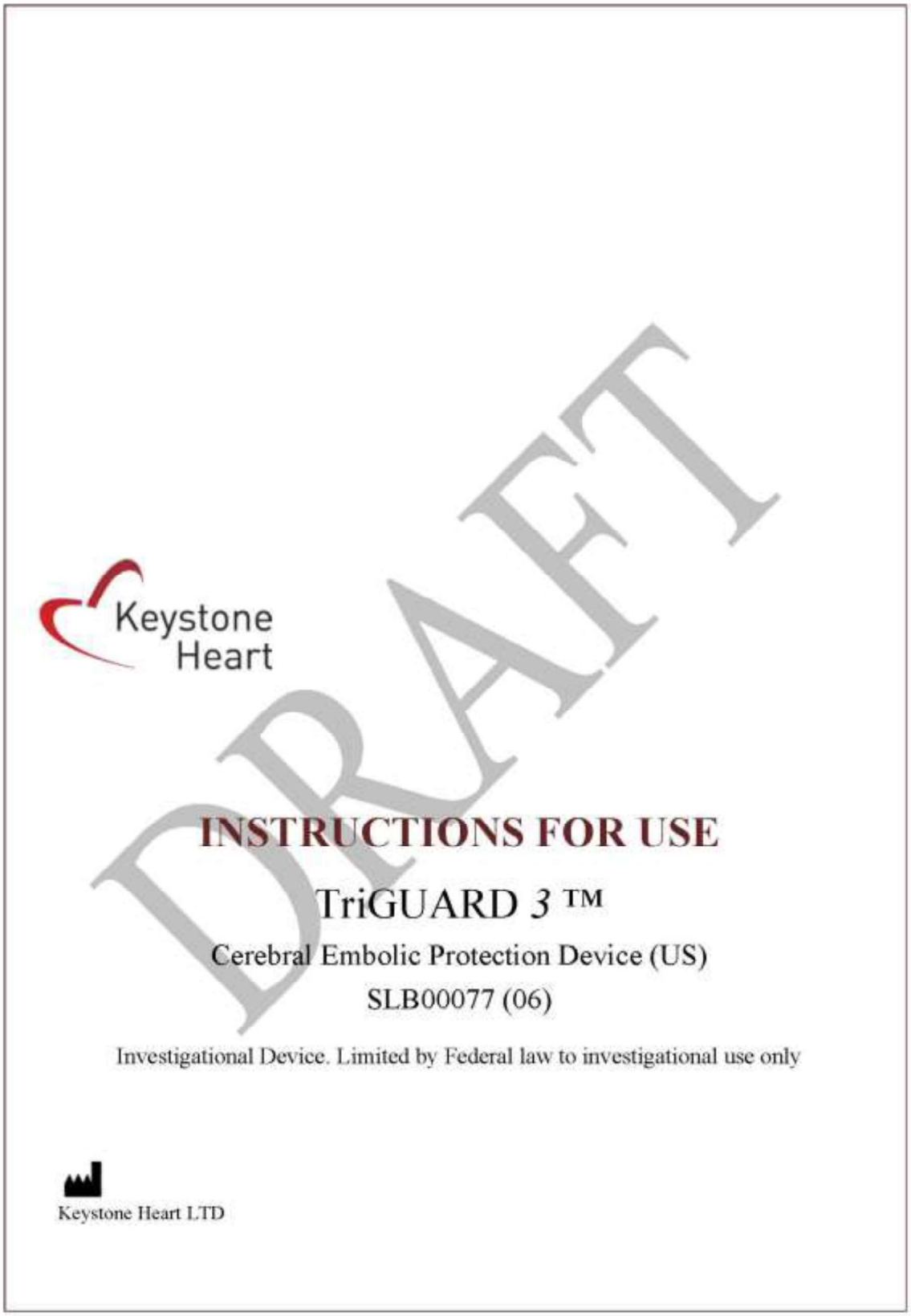
(ii) The ability of the device to filter embolic material while not impeding blood flow;

(iii) Secure positioning and stability of the position throughout the transcatheter intracardiac procedure; and

(iv) Evaluation of all adverse events including death, stroke, and vascular injury.

12.2 Proposed Labeling for TriGUARD 3

12.2.1 Draft Instructions for Use


Keystone
Heart
DRAFT
INSTRUCTIONS FOR USE
TriGUARD 3 ™
Cerebral Embolic Protection Device (US)
SLB00077 (06)
Investigational Device. Limited by Federal law to investigational use only
Keystone Heart LTD

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Caesarea Business Park
Caesarea 3088900
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CE 0123

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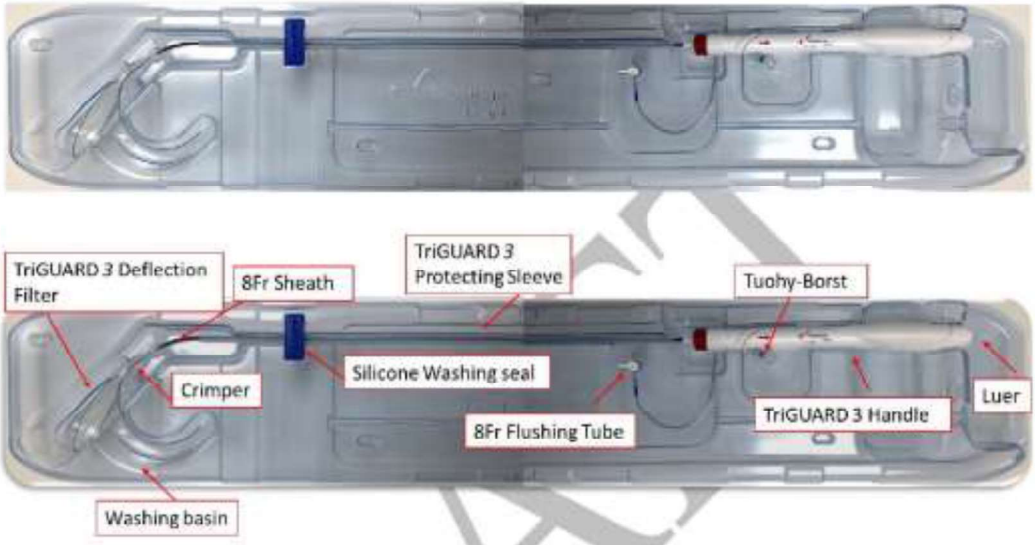
Figure 1: Keystone Heart TriGUARD *3* ™ Cerebral Embolic Protection Device



Recommended Supplies

Not provided in the TriGUARD *3* ™ Cerebral Embolic Protection Device kit

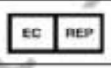
- **Guidewire** - Super stiff 0.035", 1 cm floppy end, 260 cm long. Ensure curve is added to the straight tip.
- **Angio Catheter** - 5Fr at least 125cm long, pigtail, or J shaped angio-catheter.
- **Pressurized heparinized[1] saline bags**

Warning	Use only Keystone Heart or procedural recommended components! Use of non-recommended components with the TriGUARD *3* system may result in patient injury, system damage, or loss of efficacy.

Product Labels

The information provided below is an explanation of reference symbols that can be found on product labels.

	Consult Instructions for Use
	Reference part number
	Lot number
	Serial Number
	Sterilized using Ethylene oxide (EO).
	Caution, consult accompanying documents
	Do not reuse
	Date of manufacture
	Temperature limitations
	CE Marked

	Use-by-date YYYY-MM-DD
	Manufacturer address
	Authorized representative in the European community
	Do not re-sterilize
	Do not use if package is damaged
	Non pyrogenic
	Keep away from sunlight
	Keep dry
	Prescription only device restricted to use by or on the order of a physician

[1] Heparinized saline concentration per hospital practice

TriGUARD *3* Cerebral Embolic Protection Device deflection-filter

The TriGUARD *3* Cerebral Embolic Protection Device deflection-filter (**Figure 3**) is comprised of a frame and mesh. The mesh ***(10)*** is made of a polymer with a dome shape. The mesh has a nominal pore size of 115 * 145 µm, which allows for adequate blood flow to the cerebral arteries while diverting emboli downstream toward the descending aorta. The frame and mesh are coated with Hydrophilic Heparin coating.

The nitinol frame ***(11)*** provides the structural stability of the deflection-filter and is radiopaque for visual confirmation via fluoroscopy. The frame self-expands in the desired location, adapts to the aortic arch anatomy, and provides stability in the aortic arch by inducing radial forces on the aortic arch walls.

The deflection-filter frame ends with a nitinol tail ***(12)***. The tail is connected via a nitinol connector to a nitinol curved tube (hypotube shaft) ***(2)*** that has an atraumatic tip at its front end ***(3)***. The hypotube shaft crosses underneath the deflection-filter to provide stability and enhanced positioning of the deflection-filter towards the upper part of the aortic arch (passing a stiff guidewire through the hypotube shaft enhances the positioning).

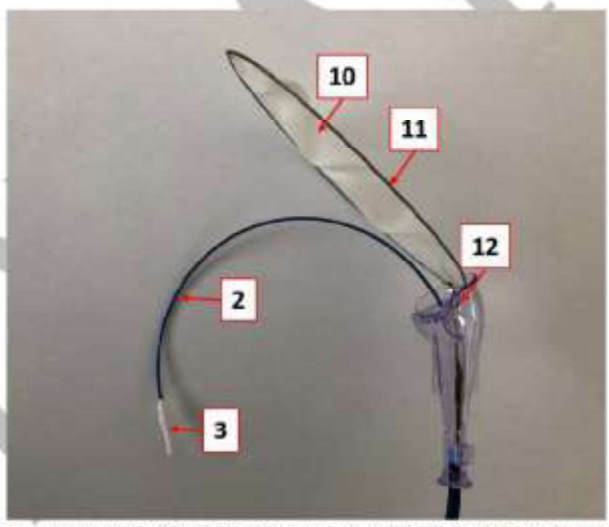


Figure 3: Keystone Heart TriGUARD *3* Cerebral Embolic Protection Device deflection-filter

Procedure Overview

The TriGUARD *3* Cerebral Embolic Protection Device is introduced through an 8Fr sheath inserted in one of two femoral arteries at the groin level. Under fluoroscopy, the TriGUARD *3* Cerebral Embolic Protection Device delivery system is inserted over a guide wire and positioned in the ascending arch distal to the innominate artery. Upon deployment from the 8Fr sheath, the deflection-

filter unfolds and conforms to the aortic arch anatomy. The frame shape provides apposition to the aortic arch walls to enhance full cerebral vessels coverage (**Figure 4**). Once deployed, the TriGUARD *3* Cerebral Embolic Protection Device can be retrieved into the sheath to allow for repositioning during the procedure or removal at the end of the procedure. The TriGUARD *3* Cerebral Embolic Protection Device is the first system introduced and last system to be removed after the index procedure is completed.

The TriGUARD *3* is supplied sterile and should not be re-sterilized.

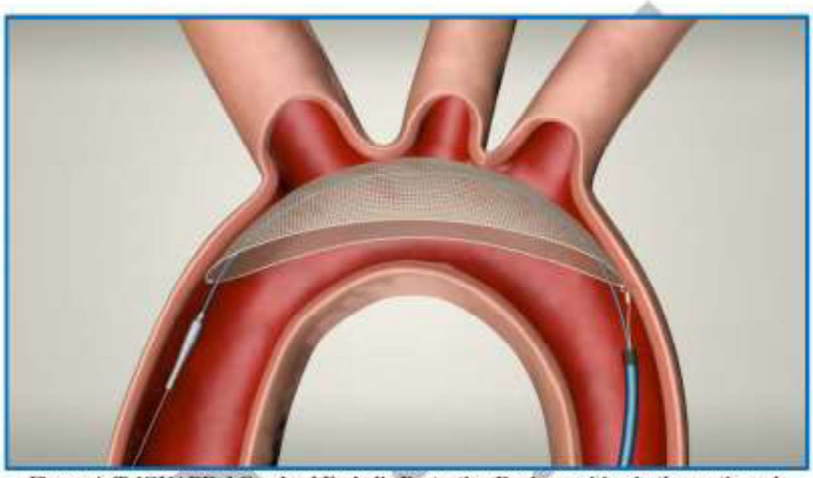


Figure 4: TriGUARD *3* Cerebral Embolic Protection Device position in the aortic arch

Contraindications

DO NOT USE IN THE FOLLOWING CIRCUMSTANCES:

- Hypercoagulable states that cannot be corrected by additional periprocedural heparin.
- Renal failure with plasma creatinine > 4 mg/dl.
- Hepatic failure.
- Patients with allergy to nitinol or heparin
- Patients with history of thrombocytopenia

Warnings

- Only physicians trained in the use of the device should use it.
- The appropriate antiplatelet and anticoagulation therapy should be administered pre- and post-procedure to minimize the risk of embolism and thrombosis.
- Porcine material as porcine allergens other than porcine heparin could be present
- Failure to follow recommended device preparation and use of dry pad to wipe the filter may damage the hydrophilic coatings and potentially cause serious injuries to patients.

- Introduce and advance devices slowly to prevent air embolism or trauma to the vasculature.
- Do not attempt to move the handle without observing the resultant deflection-filter response.
- Visualization of device position is essential for proper deployment. In procedures where visualization of the device via fluoroscopy is impeded by patient obesity or other reasons, do not attempt to deploy the device in the aortic arch.
- Ensure visualization of the device when attempting to cross the aortic arch with any device. Uncontrolled interaction between the TriGUARD 3 Cerebral Embolic Protection Device and any other device may lead to undesirable movement of the deflection-filter, resulting in incomplete coverage of the ascending arteries.
- To avoid damage to the device or injury to the patient, do not pull excessively on the device handle or the Introducer Sheath.
- Rotation of the device handle may result in rotation or flipping of the device. Do not attempt to rotate or torque the device using any accessory tool or the device handle.
- Single use device. Do not reuse or re-sterilize. Reusing the device may impose risk of inter-patient contamination, improper cleaning, and compromised performance of the device.
- In case of redeployment, first pull back the device into the sheath and then advance the sheath over the wire to the desired location. Once in the desired location, deploy per the instructions for use.
- The safety and effectiveness of the device has not been evaluated in patient populations with the following conditions:
    - Variant angina pectoris, unstable angina or recent acute coronary syndrome including myocardial infarction (in the past three months).
    - Stroke, TIA - Transient Ischemic Attack (in the past 6 months).
    - Hypotension (systolic blood pressure of below 90mm Hg).
    - Active peptic disease or history of upper GI bleeding.
    - Spastic bronchitis, Chronic Obstructive Lung Disease, Asthma.
    - Complex ventricular arrhythmia or history thereof.
    - Major psychiatric disorder in the present or past.
    - Bleeding diathesis such as hemophilia, ITP, aplastic anemia, TTP etc.
    - Diabetes mellitus with peripheral vascular and/or neurologic changes.
    - Any proliferative disease with patient life-span less than 6 months.
    - Pregnancy.
    - Pediatric use.

Adverse Events

There are risks associated with any endovascular intervention and complications may develop. The following anticipated events have been identified as possible complications of trans-catheter procedures and these and others may be associated with the device:

- Acute cardiovascular surgery (need for)
- Acute coronary artery occlusion
- Acute myocardial infarction
- Acute neurological events such as: Stroke, transient ischemic attack (TIA), encephalopathy
- Allergic reaction to contrast, antiplatelet therapy or device component materials
- Angina pectoris
- Anesthesia reactions
- Aneurysm or pseudoaneurysm
- Arteriovenous fistula
- Ascending or descending aorta trauma
- Atrial or ventricular arrhythmias or fibrillation, Heart Palpitations (sustained requiring therapy)
- Bleeding complications such as hematoma and hemorrhage
- Bleeding at access site
- Blood loss requiring transfusion
- Coronary artery or other vascular injury, dissection, or perforation which may need repair
- Blue toe syndrome or blue discoloration of a toe
- Bowel ischemia
- Embolism (air, tissue, device, or thrombus)
- Fever
- Femoral nerve damage
- Fluoroscopy related harm
- Hemodynamic changes
- Hypertension or hypotension (sustained requiring therapy)
- Infection, including endocarditis and septicemia
- Pain (at femoral puncture site, abdominal, back or other)
- Percutaneous coronary intervention (need for)
- Peripheral ischemia, peripheral nerve damage
- Pulmonary edema
- Pyrogenic reaction
- Renal complications, injury, or failure
- Unstable angina
- Vascular complications which may require vessel repair
- Vessel spasm (sustained, not responding to therapy)

In addition to the risks listed above, the potential risks specifically associated with the Keystone Heart TriGUARD *3* Cerebral Embolic Protection Device procedure includes, but may not be limited to, the following:

- Dislodgement or migration of the TriGUARD *3* Cerebral Embolic Protection Device or its delivery system, due to passage of other instrumentation, e.g.: balloon, stent, catheter, wire.
- Femoral bleeding at the access site.
- Local trauma to the aortic wall due to device movement.

Technical Specifications

Deflection-filter	Frame width	74 mm
	Frame length	98 mm
Delivery hypotube	Inner diameter	Accommodates 0.035" Guide-wire
	Total length	127.5 cm
8Fr Sheath	Inner diameter	8 Fr
	Effective length	76 cm
Device effective length	Strain relief to atraumatic tip (during over the wire advancement)	78cm

SHELF LIFE: 6 months

How Supplied

Packaging

The kit is pre-assembled and packed in an inner blister tray with a blister cover. The blister is placed in a sealed Tyvek pouch. The set is placed in a cardboard box. The entire set is Ethylene Oxide (EtO) sterilized. Only the blister Tray should be placed in the sterile field.

Inspect packaging prior to use. Do not use if there is damage to the packaging, the package is open, or if there are any other defects.

Ensure appropriate labeling and that the device is used prior to device expiration.

Storage

Store at room temperature in a dry, dark (away from sunlight) place.

Physician Training

Only physicians trained in percutaneous intravascular techniques and procedures should use the Keystone Heart TriGUARD *3* Cerebral Embolic Protection Device System.

Keystone Heart TriGUARD *3* Cerebral Embolic Protection Device System training is required and may include on-site training and proctoring of initial cases.

Instructions for Use

Device Preparation

1. Inspect the package sealing and verify product sterility and integrity. An opened or damaged item should not be used and should be returned to Keystone Heart.
2. Open the TriGUARD *3* Cerebral Embolic Protection Device carton box.
3. Open the TriGUARD *3* Cerebral Embolic Protection Device sealed Tyvek pouch and place the sterile blister tray in the sterile zone.
4. Remove the blister tray cover.
5. Tighten the handle nut to the front part of the handle to a full closure (**Figure 5-5A**).
6. Fill in the flushing basin with saline (or heparinized saline) until the TriGUARD *3* deflection-filter is fully immersed.
7. Flush the hypotube shaft with saline (or heparinized saline) through the luer located at the rear part of the device handle (**Figure 5-5B**).
8. Flush the delivery system sheath with saline (or heparinized saline) through the flushing tube located at the front part of the device handle then close rotating the tuohy-borst adaptor on handle (**Figure 5-5C**).
9. Once saline (or heparinized saline) is dripping out of the Tuohy-Borst, screw it to full closure (**Figure 5 - 5D**).
10. Immerse the TriGUARD *3* deflection-filter in the flushing basin for approximately 1-minute in saline (or heparinized saline) solution to hydrate the heparinized hydrophilic coating.
11. After 1 minute of immersion,no air bubbles should be visible, Gently tap on the deflection filter to remove remaining air bubbles.
12. While maintaining the handle orientation, pull back the rear part of the handle while holding the **front part** stationary until the Deflection-Filter is fully crimped into the delivery system..
13. Ensure that the atraumatic tip is not fully inside the sheath or extending beyond the tip of the sheath. If a gap is noted between the atraumatic tip and the sheath, address by advancing the sheath over the atraumatic tip.
14. Flush the 8Fr sheath via the flushing tube with saline (or heparinized saline), while TriGUARD *3* Cerebral Embolic Protection Device tip is immersed completely, until no bubbles are released.
15. Pull back the device delivery system until delivery sheath is totally out of the protecting sleeve.

Figure 5: Flushing the hypotube via the Luer and the 8Fr sheath via the flushing tube

Note	Handle orientation should be kept while crimping the deflection filter into the delivery system by: Tuohy and flushing tube are facing toward the left side, as indicated in Figure 5. The delivery system tip is inserted into the crimper.
Warning ⚠	Avoid wiping the TriGUARD 3 Cerebral Embolic Protection with dry gauze as this may damage the device coating.

Deployment

Warning ⚠	**Perform all steps under fluoroscopic guidance. Do not make any movements of the delivery system or components without adequate visualization. All steps that reference delivery system movements assume fluoroscopic guidance!**
Warning ⚠	**Failure to maintain an ACT level >250 may increase the risk of thrombus formation on the device and in the 8Fr delivery sheath.**

1. Maintain an ACT>250 seconds throughout device deployment and dwell time, in line with routine hospital practice.
2. Insert a guidewire in the ascending Aorta in the vicinity of native aortic annulus.
3. In a wide LAO projection, perform an angiogram to demonstrate the anatomy of the aortic arch and cerebral vessels. If possible, superimpose the aortic arch image on top of the live fluoroscopic image for reference purposes. It is recommended to obtain the best anatomical view of the arch and cerebral vessels. Remove angiogram catheter once completed.

Note	Before insertion of the delivery system into the introducer groin, it is recommended to inject Heparinized saline to the delivery system through the flushing tube until the tip of the delivery system drips.

4. Before insertion of the delivery system into the introducer/groin, inject HS through the flushing tube until the tip of the delivery sheath drips (use 5-10cc syringe).
5. Advance the TriGUARD 3 Cerebral Embolic Protection Device delivery system (loaded with the TriGUARD 3 Cerebral Embolic Protection Device), over the guidewire, to approximately 4

cm distal to the Innominate branch in the ascending aorta (based on the initial angiogram) using fluoroscopic guidance in the same reference plane as the angiogram (**Figure 6**).

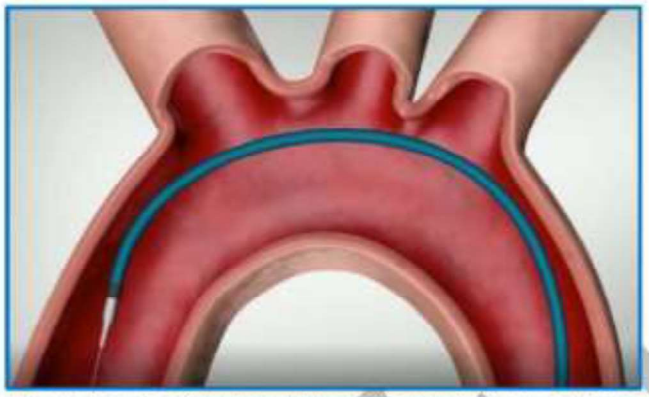


Figure 6: The delivery sheath is positioned 4 cm distal to the Innominate branch in the ascending aorta

Note	Insertion of the TriGUARD 3 Cerebral Embolic Protection Device into the femoral access should be made by advancing the 8Fr sheath only.
Warning ⚠	Avoid manually rotating the TriGUARD 3 Cerebral Embolic Protection Device deflection-filter either while inside the delivery sheath or at the deployment site.
Warning ⚠	Advance the TriGUARD 3 Cerebral Embolic Protection Device, over the wire, while avoiding torqueing.
Warning ⚠	allow the handle to rotate freely according to vessel trajectory during the insertion of the delivery system.

6. Pull the guidewire back to the descending aorta to assure that the hypotube is under the mesh and to allow the mesh to fully expand across the aortic arch.
7. Hold the rear part of the handle stationary and slowly pull back the front part of the handle until the TriGUARD *3* Cerebral Embolic Protection Device deflection-filter is fully deployed from

the delivery sheath (**Figure 7**). Re-advance the guidewire to the vicinity of the native aortic annulus.

Figure 7: The TriGUARD *3* Cerebral Embolic Protection Device is deployed in the Aortic arch

8. Connect a continuous, pressurized heparinized saline bag to the delivery-sheath flushing tube located in the TriGUARD *3* Cerebral Embolic Protection Device handle. Another option is to perform a heparinized saline flush (every 20 min) through the flushing tube to maintain the sheath free from blood clots.
9. Maintain forward pressure on the guide-wire of the TriGUARD *3* Cerebral Embolic Protection Device at the annulus. This will provide support for the mesh and keep the atraumatic tip on the outer curvature of the arch.

Note	Following deployment, pull & push the GW in order to verify that the hypotube is underneath the deflection filter and to allow the deflection filter to self-position.
Note	User may control the hypotube shaft curvature by pulling/pushing the GW in the hypotube: Pushing the guidewire will push the hypotube shaft toward the upper curvature of the arch providing better support for the deflection filter and moving the tip away from mid-stream.

Warning ⚠	**Leave sufficient guidewire distal to the atraumatic tip to avoid any potential damage to the vessel wall from the guidewire or tip.**

Note	If the guidewire is pulled out from the TriGUARD *3* Cerebral Embolic Protection Device delivery system, it is recommended to connect the Luer, at the rear part of device's handle, to a continuous pressurized dripping system, to maintain the hypotube shaft free from blood clots.

Aortic Valve and Arch Angiogram

Note	It is recommended to perform an angiogram using a pig-tail angiography catheter.

1. Advance the pigtail catheter through the rotating tuohy-borst adapter at the front part of the TriGUARD *3* Cerebral Embolic Protection Device handle. Use fluoroscopy to assure its position

underneath the deflection-filter by verifying that it does not alter the position of the deflection-filter during tracking.

Note	It is best to introduce the pigtail with the curled end leading under the deflection-filter Mesh. It is recommended to use at least two views to ensure crossing underneath the deflection-filter.

2. After passing the deflection-filter, advance the pigtail catheter into ascending aorta. It is recommended to perform an angiogram to evaluate device position in the aortic arch. If needed, fine adjustments of device position may be made for optimal coverage.

Trans-Catheter Heart procedures

When an attempt is made to pass the aortic arch with any additional device (e.g. guide-wire, TAVR, balloon) make sure that:

- The deflection-filter front side is facing the ascending aorta and the rear side is facing the descending aorta (**Figure 8**).
- The deflection-filter covers the aortic branches with its front and backend opposing the aortic walls.
- The deflection-filter is stable (no major tilting).
- The hypotube shaft with the atraumatic tip at its distal part is under and opposing the center of the deflection-filter.

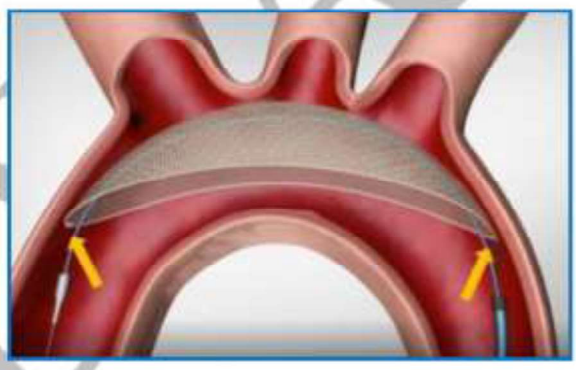


Figure 8: Deflection-filter optimal coverage and apposition

1. Advance the guidewire (ipsilateral access) using fluoroscopy to verify that the guidewire is below the deflection-filter and does not alter its position.
2. At physician discretion, complete the main index procedure.

Note	When advancing instrumentation (balloons, guidewires, valve delivery systems or other devices) around the arch and under the deflection-filter, counterpull the guidewire while pushing the delivery system forward. This will prevent tension build-up and will allow smoother passage of the instrumentation under the TriGUARD *3*.

Warning ⚠	**Always visualize TriGUARD 3 during the entire procedure to ensure the TAVR catheter does not get tangled with deflection filter potentially causing dislodgement. (22 words)Uncontrolled interaction between the TriGUARD *3* Cerebral Embolic Protection Device and any other device may lead to inadvertent movement of the deflection-filter.**
Warning	Trying to manipulate/ crossing underneath the TriGUARD 3 deflection filter with a bare wire is forbidden.
Warning ⚠	**When TAVR or any other delivery system is retrieved (pulled back), make sure it does not entangle with the TriGUARD 3 Cerebral Embolic Protection Device deflection-filter.**

Retrieval

Note	For best results, the TriGUARD *3* Cerebral Embolic Protection Device should be First-in Last Out (FILO) to be sure that full vessel coverage and protection is maintained throughout the procedure.
Note	There is an option to remove the TriGUARD 3 Cerebral Embolic Protection Device while leaving the delivery sheath in the artery for other purposes. Release the handle nut and pull back the rear part of the device handle, while holding the 8Fr sheath stationary, until the TriGUARD 3 Cerebral Embolic Protection Device is completely removed from the sheath.

1. Remove the trans-catheter devices used during the procedure and the pigtail catheter from the TriGUARD *3* Cerebral Embolic Protection Device delivery system.

Note	User shall retrieve the pigtail catheter over a guide wire to avoid entanglement with the deflection-filter.

2. Pull back the handle from its rear part, while holding the front handle front part stationary, until the TriGUARD 3 deflection filter is fully crimped into the delivery sheath (**Figure 9**).
3. Pull back the delivery sheath, with the crimped TriGUARD 3 Until the delivery sheath is fully removed from the patient's body.
4. Close femoral access point.

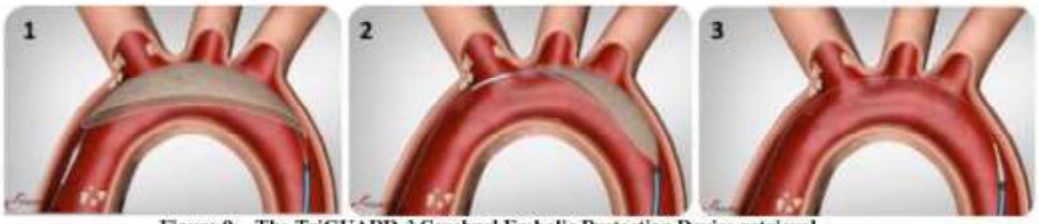


Figure 9: The TriGUARD *3* Cerebral Embolic Protection Device retrieval

Note	The TriGUARD 3 Device must be disposed of in accordance with local biohazard waste disposal and hospital procedures.

Troubleshooting and Tips

Note	Events described below may take place during the procedure and can be handled using the following trouble shooting tips.

1. TriGUARD *3* Cerebral Embolic Protection Device malpositioned during deployment or migration in the transverse arch.

Retrieve the deflection-filter into the delivery sheath by pulling back the rear part of the TriGUARD *3* Cerebral Embolic Protection Device deflection-filter handle while holding its front part stationary until the TriGUARD *3* Cerebral Embolic Protection Device deflection-filter is fully crimped into the delivery sheath and the device tip meets the sheath tip. Reposition the delivery sheath, over the guide wire, to the correct location and then redeploy as described above.

Note	Only one additional attempt of complete redeployment of the same device is permitted.
Note	Make sure both the introducer sheath and the delivery sheath are secured in position.

2. The position of the guidewire or pigtail catheter underneath the TriGUARD *3* Cerebral Embolic Protection Device is not clear.

Using fluoroscopy (RAO view), slightly pull and push guidewire or pigtail catheter while observing its peak location. If this manipulation causes the guidewire or pigtail catheter to be in the same plane as the hypotube shaft then guidewire or pigtail catheter is underneath the TriGUARD *3*. If it is NOT in the same plane, remove the guidewire or pigtail and re-navigate it below the deflection-filter Mesh.

3. Deflection-filter is out of position during maneuvering of other devices in the aortic arch.

Check if the introducer sheath and the delivery sheath are secured in position and slowly advance index procedure hardware. If deflection-filter fails to return to its position, remove it before continuing with the index procedure *or*

At physician discretion, it may be attempted to retract the index procedure hardware to the descending aorta and reposition the deflection-filter.

4. Interaction between the TriGUARD 3 and TAVI delivery system.

Slightly pull back (~1 cm) the TAVI delivery system and the TAVI wire which will disengage the TAVI tip from the TriGUARD 3 device frame. Then push the TAVI delivery system forward while holding stationary the TAVI wire which will lower the tip of the TAVI delivery system to allow free passage underneath the TriGUARD 3 device frame.

TriGUARD 3™ clinical study summary

Cerebral protection in transcatheter Aortic Valve Implantation, the REFLECT study

Purpose: To evaluate the safety and effectiveness of the TriGUARD *3* Cerebral Embolic Protection Device (CEPD) in patients undergoing TAVR, in comparison with a control group of subjects undergoing TAVR without CEPD.

Design: The REFLECT Trial was a prospective, single-blind, randomized, multicenter trial using the TriGUARD *3* CEPD (Keystone Heart Ltd.) in patients with severe symptomatic calcified native aortic valve stenosis indicated for TAVR via the transfemoral approach. The REFLECT Trial was designed to enroll up to 50 Roll-In subjects and up to 295 randomized subjects (randomized 2:1 to TriGUARD or Control) at up to 25 sites in the United States.
Subjects who met the commercially approved indications for TAVR and complied with the study inclusion/exclusion criteria were enrolled.
All subjects (Test and Control Arms) followed clinically in-hospital and at 30 days, undergo diffusion-weighted magnetic resonance imaging (DW-MRI) 2 to 5 days post-procedure, and underwent neurologic testing pre-procedure, 2 to 5 days post-procedure, and at 30 days. A follow-up telephone contact assessed the occurrence of death or stroke at 90 days.
Commercially approved TAVR devices implanted during the REFLECT Study included SAPIEN XT, SAPIEN 3, CoreValve®, and CoreValve® Evolut R®.
A Clinical Events Committee (CEC) remained blinded throughout the trial and adjudicated all MACCE event endpoints. Independent blinded MRI and Angio core labs analyzed all the endpoint data.

Primary Endpoints:
1) Safety: (Test Vs Control); The primary safety endpoint was combined safety at 30 days (VARC-2 "TAVR early safety"), defined as the composite of all-cause mortality, all stroke (disabling and non-disabling), life-threatening or disabling bleeding, acute kidney injury stage 2 or 3, coronary artery obstruction requiring intervention, major vascular complication, or valve-related dysfunction requiring repeat procedure.
2) Efficacy: (Test Vs Control); The primary efficacy endpoint was a hierarchical composite efficacy endpoint, determined by pair-wise comparison between all subjects according to the following pre-specified hierarchy of adverse outcomes:

- All-cause mortality or any stroke at 30 days
- NIHSS worsening (increase from baseline) at 2 to 5 days post-procedure
- Freedom from any cerebral ischemic lesions detected by DW-MRI 2 to 5 days post-procedure
- Total volume of cerebral ischemic lesions detected by DW-MRI 2 to 5 days post-procedure

Several hypothesis-driven secondary endpoints were prespecified, to be tested sequentially if both primary endpoints were met.

Secondary Endpoints: Secondary endpoints consisted of the following:
1) Safety: (Test Vs Control); Secondary safety endpoints included in-hospital procedural safety (major adverse cardiovascular and cerebrovascular events [MACCE] composite of all-cause mortality, all stroke, life-threatening or disabling bleeding, acute kidney injury [AKI] stage 2 or 3,

and major vascular complications), MACCE components, VARC-defined TAVI device success, and detailed reporting of neurologic events by VARC-2 and Neuro ARC definitions.
2) Efficacy: Efficacy endpoints included NIHSS worsening from baseline, new neurologic impairment (NIHSS worsening and new cerebral ischemic lesions by DW-MRI), and DW-MRI cerebral ischemic lesion measures including presence, number, average single lesion volume (patient-level and lesion-level), and total lesion volume (TLV).
3) Performance: Performance endpoints included successful device deployment, successful device positioning (complete 3-vessel coverage maintained throughout the procedure by Angiographic Core Laboratory analysis), device interference, and successful device retrieval. Technical success was defined as successful deployment, positioning (3-vessel-coverage), and retrieval in the absence of device interference, and procedure success was defined as technical success without TriGUARD-related in-hospital MACCE.

Eligibility Criteria Summary: The study population consisted of male and female patients, at least 18 years of age.
Key inclusion criteria included the following:

- Patients with severe symptomatic aortic stenosis meeting indications for TAVI via the transfemoral approach.
- The patient is willing to comply with protocol-specified follow-up evaluations
- The patient, or legally authorized representative, has been informed of the nature of the study, agrees to its provisions, and has provided written informed consent, approved by the appropriate Institutional Review Board (IRB) or Ethics Committee (EC).

Key exclusion criteria included the following:

- Patients undergoing TAVI via the trans-apical, trans-axillary, trans-subclavian, or trans-aortic route.
- Patients with a previously implanted prosthetic aortic valve (i.e., planned valve-in-valve TAVI).
- Recent (<72 hours) myocardial infarction.
- Prior stroke or TIA within 6 months.
- Bleeding diathesis or coagulopathy or recent GI bleed (<3 months).
- Physical illness or known history of substance abuse.
- Renal or hepatic failure.
- Patients with hypercoagulable states that cannot be corrected by additional periprocedural heparin
- Cardiogenic shock.
- Patients with severe peripheral arterial, abdominal aortic, or thoracic aortic disease that precludes delivery sheath vascular access.
- Patients in whom the aortic arch is heavily calcified, severely atheromatous, or severely tortuous.
- Contraindication to cerebral MRI.
- Planned concurrent procedure (e.g., coronary revascularization).
- Device-specific exclusion criteria included:
    - Allergy to device components.
    - Severe peripheral or aortic disease that precluded delivery sheath access.
    - Severe aortic arch atheroma, calcification, or tortuosity.

Accountability: In the Roll-in group, all 41 subjects underwent TAVI and no subjects died or withdrew prior to 90 days. In the randomized cohort, 5 subjects in the TriGUARD group and 1 subject in the Control group died prior to the final 90-day follow-up assessment. In addition, 5 of the 121 subjects (4.1%) in the TriGUARD group and 1 of 58 (1.7%) subjects in the Control group withdrew prior to TAVI.

Table 1. provides details of all **subject's compliance, by visit by population**. Compliance is defined as subjects with expected visits who completed all required forms.

Disposition	TriGUARD 3 Roll-In Group (N = 41) n/N (%)	TriGUARD 3 Randomized Group (N = 121) n/N (%)	Control Group (N = 58) n/N (%)
Subjects Randomized	-	121/121 (100.0%)	58/58 (100.0%)
Subjects with Procedure	41/41 (100.0%)	116/116 (100.0%)	57/57 (100.0%)
Early Withdrawal [a]	0	5 (4.1%)	1 (1.7%)
Post-Procedure/In-Hospital Visit [b]	41/41 (100.0%)	113/113 (100.0%)	57/57 (100.0%)
Death	0	3 (2.6%)	0 (0%)
30-Day Follow-Up [b]	41/41 (100.0%)	111/112 (99.1%)	55/56 (98.2%)
Missed Follow-Up	0/41 (0.0%)	1/112 (0.9%)	1/56 (1.8%)
Death	0	1 (0.9%)	1 (1.8%)
90-Day Follow-Up [b]	41/41 (100.0%)	110/111 (99.1%)	56/56 (100.0%)
Missed Follow-Up	0/41 (0.0%)	0/111 (0.0%)	0/56 (0.0%)
Lost to Follow Up	0/41 (0.0%)	1/111 (0.9%)	0/56 (0.0%)
Death	0	1 (0.9%)	0 (0%)

a. Reasons for Early Withdrawal include subject refusing to continue/withdrawing consent or order from investigator due to subject's health/safety.
b. Percentages are based on the number of subjects having at least one required assessment completed at the respective time point.

Demographics: The control subjects from Phase I and Phase II of the study were pooled to one group (N=119).

The **efficacy Intention To Treat (eITT)** population was defined as randomized subjects, by assigned treatment, excluding subjects with conversion to surgery or prolonged cardiac arrest (>3 minutes) prior to the post-procedure DW-MRI.

The **Per Treatment (PT)** population was defined as subjects in the Intervention group in whom device positioning is maintained until final procedure with complete cerebral coverage, and all Control group subjects.

The **As Treated (AT)** Population was defined by the treatment actually received, regardless of the assigned treatment. In the AT population, all subjects in whom vascular access in the contralateral femoral artery has been established for the intended deployment of the TriGUARD *3* device will be assigned to the intervention group.

The **Safety Population As Treated** (SP(AT)) was defined as the primary safety analysis population (consisting of TriGUARD 3 randomized and Roll-in subjects versus Phase II Control subjects).

Table 2. **Demographic Characteristics** and **Medical History** of TriGUARD 3 (ITT Population) and control group.

Subject Characteristics	TriGUARD 3 ITT Group (N=112)	Pooled Control Group (N=119)
Demography		
Age (yrs)		
Mean±SD (n)	79.71 ± 7.96 (112)	79.88 ± 7.84 (119)
Median	80.00	81.00
Range (Min, Max)	(55.0, 98.0)	(56.0, 94.0)
Male gender	55.4% (62/112)	64.7% (77/119)
Hispanic or Latino Ethnicity	5.4% (6/112)	4.2% (5/119)
Medical History		
Smoking/Tobacco Usage		
Current within last year	1.8% (2/112)	7.6% (9/119)
Ex-Smoker	40.2% (45/112)	43.7% (52/119)
Never	58.0% (65/112)	48.7% (58/119)
Diabetes Mellitus (DM)	34.8% (39/112)	35.3% (42/119)
Insulin Dependent (IDDM)	15.8% (6/38)	40.0% (16/40)
Diet-controlled	44.7% (17/38)	29.4% (10/34)
Oral hypoglycemic controlled	76.9% (30/39)	57.9% (22/38)
History of Hypertension	93.7% (104/111)	89.9% (107/119)
History of Hyperlipidemia	83.0% (93/112)	79.7% (94/118)
History of Peripheral Vascular Disease (PVD)	13.5% (15/111)	16.5% (19/115)
History of aortic artery disease (aneurysm)	1.8% (2/112)	0.8% (1/119)
History of prior treatment/repair	0.0% (0/2)	0.0% (0/1)
Carotid artery disease	17.6% (19/108)	16.7% (19/114)
Prior cerebral vascular attack (CVA)	10.7% (12/112)	5.1% (6/117)
Prior transient ischemic attack (TIA)	8.3% (9/109)	5.1% (6/117)
Prior CVA or TIA	17.9% (20/112)	8.5% (10/117)
History of anemia requiring transfusion	6.5% (7/107)	4.5% (5/112)
History of renal disease	20.5% (23/112)	23.7% (28/118)
LVEF assessed	96.4% (108/112)	95.8% (114/119)
History of congestive heart failure (CHF)	56.3% (63/112)	47.9% (56/117)
History of atrial fibrillation/atrial flutter	28.6% (32/112)	28.0% (33/118)
History or presence of intracardiac mass, thrombus or vegetation	0.9% (1/112)	0.0% (0/119)
History of prior coronary artery bypass graft(s) (CABG)	18.8% (21/112)	17.6% (21/119)
History of prior percutaneous coronary intervention (PCI)	32.1% (36/112)	28.2% (33/117)
Chronic Lung disease/ COPD	15.2% (17/112)	19.1% (22/115)
In home Oxygen Use	3.6% (4/112)	2.6% (3/117)
Severe Pulmonary HTN	6.3% (7/112)	3.4% (4/117)

Results:

Primary safety endpoint:

The primary safety endpoint to 30 days in TriGUARD 3 (including Roll-in subjects) and control group is provided in Table 3.

Table 3. **Primary Safety Endpoint** to **30 Days** in TriGUARD 3 (SP(AT) including Roll-in subjects) and control group.

Primary Safety Endpoints	TriGUARD 3 SP(AT) & Roll-in Groups (N=157)	Control Group (N = 57)
Combined Safety Endpoint within 30 Days [3]	15.9% (25/157)	7.0% (4/57)
All-Cause Death	2.5% (4/157)	1.8% (1/57)
Stroke (Disabling and Non-Disabling)	8.3% (13/157)	5.3% (3/57)
Life-Threatening or Disabling Bleeding	5.7% (9/157)	0.0% (0/57)
Acute Kidney Injury (Stage 2/3)	2.5% (4/157)	0.0% (0/57)
Coronary Artery Obstruction Requiring Intervention	0.6% (1/157)	0.0% (0/57)
Major Vascular Complication	7.0% (11/157)	0.0% (0/57)
TriGUARD Access Site-Related	1.9% (3/157)	0.0% (0/57)
TAVI or Other Access Site-Related	4.5% (7/157)	0.0% (0/57)
Secondary Access Site-Related	0.0% (0/157)	0.0% (0/57)
Aortic Vascular Injury	1.3% (2/157)	0.0% (0/57)
Valve Related Dysfunction Requiring Intervention	0.0% (0/157)	0.0% (0/57)

Table 4. **Primary Safety Endpoint** to **30 Days by Relatedness** in TriGUARD 3 (SP(AT) including Roll-in subjects) and control group.

	TriGUARD 3 Group Relationship to TriGUARD 3 Device or Procedure CEC Adjudicated						
Primary Safety Endpoints	Number of Subjects	Not Related	Unlikely to be Related	Possibly Related	Probably Related	Related	Control Group All Events
Combined Safety Endpoint within 30 Days	25	10.2% (16/157)	0.0% (0/157)	6.4% (10/157)	0.0% (0/157)	1.3% (2/157)	7.0% (4/57)
All-Cause Death	4	2.5% (4/157)	0.0% (0/157)	0.0% (0/157)	0.0% (0/157)	0.0% (0/157)	1.8% (1/57)
Stroke (Disabling and Non-Disabling)	13	3.2% (5/157)	0.0% (0/157)	5.7% (9/157)	0.0% (0/157)	0.0% (0/157)	5.3% (3/57)
Life-Threatening or Disabling Bleeding	9	5.1% (8/157)	0.0% (0/157)	0.6% (1/157)	0.0% (0/157)	0.0% (0/157)	0.0% (0/57)
Acute Kidney Injury (Stage 2/3)	4	2.5% (4/157)	0.0% (0/157)	0.0% (0/157)	0.0% (0/157)	0.0% (0/157)	0.0% (0/57)
Coronary Artery Obstruction Requiring Intervention	1	0.6% (1/157)	0.0% (0/157)	0.0% (0/157)	0.0% (0/157)	0.0% (0/157)	0.0% (0/57)
Major Vascular Complication	11	5.1% (8/157)	0.0% (0/157)	0.6% (1/157)	0.0% (0/157)	1.3% (2/157)	0.0% (0/57)
TriGUARD Access Site-Related	3	0.0% (0/157)	0.0% (0/157)	0.6% (1/157)	0.0% (0/157)	1.3% (2/157)	0.0% (0/57)
TAVI or Other Access Site-Related	7	4.5% (7/157)	0.0% (0/157)	0.0% (0/157)	0.0% (0/157)	0.0% (0/157)	0.0% (0/57)
Secondary Access Site-Related	0	0.0% (0/157)	0.0% (0/157)	0.0% (0/157)	0.0% (0/157)	0.0% (0/157)	0.0% (0/57)
Aortic Vascular Injury	2	1.3% (2/157)	0.0% (0/157)	0.0% (0/157)	0.0% (0/157)	0.0% (0/157)	0.0% (0/57)
Valve Related Dysfunction Requiring Intervention	0	0.0% (0/157)	0.0% (0/157)	0.0% (0/157)	0.0% (0/157)	0.0% (0/157)	0.0% (0/57)

Primary efficacy endpoint:

The control group consists of control subjects from Phase I and Phase II of the study (N=119).

Table 5. **Primary Efficacy Endpoint** in TriGUARD *3* (eITT and PT populations) and pooled control groups.

Primary Efficacy Endpoint	TriGuard 3 eITT Group (N=112)	TriGuard 3 PT Group (N=62)	Control Group (N=119)
Primary Efficacy Hierarchical Endpoint Score [a]			
Mean ± SD (n)	-8.58 ± 120.76 (112)	0.29 ± 94.21 (62)	8.08 ± 116.51 (119)
Range (Min, Max)	(-226.00, 183.00)	(-171.00, 140.00)	(-230.00, 183.00)
Median	13.00	20.00	21.00
(Q1, Q3)	(-104.00, 84.00)	(-78.00, 70.00)	(-87.00, 110.00)
All-cause mortality or any stroke at 30 days	9.8% (11/112)	6.5% (4/62)	6.7% (8/119)
NIHSS worsening [c]	14.1% (14/99)	13.8% (8/58)	7.6% (8/105)
Cerebral ischemic lesions	85.0% (85/100)	79.6% (43/54)	84.9% (90/106)
Total volume of cerebral ischemic lesions (mm^3)			
Mean ± SD (n)	587.80 ± 1028.42 (100)	375.80 ± 617.69 (54)	508.22 ± 1123.96 (106)
Range (Min, Max)	(0.00, 5681.26)	(0.00, 3519.00)	(0.00, 8133.60)
Median	215.39	145.71	188.09
(Q1, Q3)	(68.13, 619.71)	(43.75, 444.44)	(52.08, 453.12)

a. Hierarchical endpoint score is the sum of the number of wins minus the number of losses in subject pairs based on the hierarchical algorithm comparing death/stroke, NIHSS worsening and cerebral ischemic lesions as described in Finkelstein and Schoenfeld.
b. Win-ratio is the ratio of the number of wins to the number of losses in treatment vs. control pairs as described by Pocock et al. Win percentage is defined as the number of wins divided by the sum of the number of wins and losses.
c. Worsening of NIHSS score is defined as a higher NIHSS score at pre-discharge (2-5 days after procedure) than at baseline.

Secondary safety endpoint:

Table 6. In-hospital secondary safety endpoint in TriGUARD 3 (SP(AT) population including Roll-in subjects).

	TriGUARD 3 Group (N=157) Relationship to TriGUARD 3 Device or Procedure [a]					
Events in-hospital	Number of Subjects [b]	Not Related	Unlikely to be Related	Possibly Related	Probably Related	Related
MACCE	22	8.9% (14/157)	0.0% (0/157)	5.1% (8/157)	0.0% (0/157)	1.3% (2/157)
All-cause mortality	3	1.9% (3/157)	0.0% (0/157)	0.0% (0/157)	0.0% (0/157)	0.0% (0/157)
All stroke (disabling and non-disabling)	10	1.9% (3/157)	0.0% (0/157)	4.5% (7/157)	0.0% (0/157)	0.0% (0/157)
Life threatening (or disabling) bleeding	9	5.1% (8/157)	0.0% (0/157)	0.6% (1/157)	0.0% (0/157)	0.0% (0/157)
Acute kidney injury - Stage 2 or 3	4	2.5% (4/157)	0.0% (0/157)	0.0% (0/157)	0.0% (0/157)	0.0% (0/157)

	TriGUARD 3 Group (N=157) Relationship to TriGUARD 3 Device or Procedure [a]					
Events in-hospital	**Number of Subjects [b]**	**Not Related**	**Unlikely to be Related**	**Possibly Related**	**Probably Related**	**Related**
Major vascular complications	11	5.1% (8/157)	0.0% (0/157)	0.6% (1/157)	0.0% (0/157)	1.3% (2/157)
All-cause mortality	3	1.9% (3/157)	0.0% (0/157)	0.0% (0/157)	0.0% (0/157)	0.0% (0/157)
Cardiovascular mortality	3	1.9% (3/157)	0.0% (0/157)	0.0% (0/157)	0.0% (0/157)	0.0% (0/157)
Neurologic event related mortality	0	0.0% (0/157)	0.0% (0/157)	0.0% (0/157)	0.0% (0/157)	0.0% (0/157)
Non-cardiovascular mortality	0	0.0% (0/157)	0.0% (0/157)	0.0% (0/157)	0.0% (0/157)	0.0% (0/157)
Myocardial infarction	0	0.0% (0/157)	0.0% (0/157)	0.0% (0/157)	0.0% (0/157)	0.0% (0/157)
Peri-procedural MI (≤ 72 hours after the index procedure)	0	0.0% (0/157)	0.0% (0/157)	0.0% (0/157)	0.0% (0/157)	0.0% (0/157)
Spontaneous MI (> 72 hours after the index procedure)	0	0.0% (0/157)	0.0% (0/157)	0.0% (0/157)	0.0% (0/157)	0.0% (0/157)
General safety event	12	3.2% (5/157)	0.0% (0/157)	4.5% (7/157)	0.0% (0/157)	0.0% (0/157)
All-cause mortality	3	1.9% (3/157)	0.0% (0/157)	0.0% (0/157)	0.0% (0/157)	0.0% (0/157)
All stroke (disabling and non-disabling)	10	1.9% (3/157)	0.0% (0/157)	4.5% (7/157)	0.0% (0/157)	0.0% (0/157)
Acute kidney injury - Stage 3	3	1.9% (3/157)	0.0% (0/157)	0.0% (0/157)	0.0% (0/157)	0.0% (0/157)
Neurological Events						
Stroke (VARC-2 defined)	10	1.9% (3/157)	0.0% (0/157)	4.5% (7/157)	0.0% (0/157)	0.0% (0/157)
Ischemic	9	1.3% (2/157)	0.0% (0/157)	4.5% (7/157)	0.0% (0/157)	0.0% (0/157)
Hemorrhagic	0	0.0% (0/157)	0.0% (0/157)	0.0% (0/157)	0.0% (0/157)	0.0% (0/157)
Undetermined	1	0.6% (1/157)	0.0% (0/157)	0.0% (0/157)	0.0% (0/157)	0.0% (0/157)
Disabling Stroke (VARC-2 defined)	1	0.0% (0/157)	0.0% (0/157)	0.6% (1/157)	0.0% (0/157)	0.0% (0/157)
Non-disabling stroke	7	0.6% (1/157)	0.0% (0/157)	3.8% (6/157)	0.0% (0/157)	0.0% (0/157)
Transient ischemic attack (TIA) (VARC-2 defined)	1	0.6% (1/157)	0.0% (0/157)	0.0% (0/157)	0.0% (0/157)	0.0% (0/157)
Overt CNS Injury (Type 1)	10	1.9% (3/157)	0.0% (0/157)	4.5% (7/157)	0.0% (0/157)	0.0% (0/157)

	TriGUARD 3 Group (N=157) Relationship to TriGUARD 3 Device or Procedure [a]					
Events in-hospital	**Number of Subjects [b]**	**Not Related**	**Unlikely to be Related**	**Possibly Related**	**Probably Related**	**Related**
Covert CNS Injury (Type 2)	74	0.0% (0/157)	0.0% (0/157)	47.1% (74/157)	0.0% (0/157)	0.0% (0/157)
Neurological dysfunction without CNS injury (Type 3)	2	1.3% (2/157)	0.0% (0/157)	0.0% (0/157)	0.0% (0/157)	0.0% (0/157)
CNS infarction (NeuroARC defined)	84	1.9% (3/157)	0.0% (0/157)	51.6% (81/157)	0.0% (0/157)	0.0% (0/157)
CNS hemorrhage (NeuroARC defined)	0	0.0% (0/157)	0.0% (0/157)	0.0% (0/157)	0.0% (0/157)	0.0% (0/157)
Bleeding Complications						
Life-threatening bleeding (VARC-2)	9	5.1% (8/157)	0.0% (0/157)	0.6% (1/157)	0.0% (0/157)	0.0% (0/157)
Major bleeding	12	3.2% (5/157)	0.0% (0/157)	0.6% (1/157)	0.0% (0/157)	3.8% (6/157)
Minor bleeding	8	3.8% (6/157)	0.0% (0/157)	0.6% (1/157)	0.0% (0/157)	1.9% (3/157)
Acute Kidney Injury (AKIN Classification)						
Stage 2	1	0.6% (1/157)	0.0% (0/157)	0.0% (0/157)	0.0% (0/157)	0.0% (0/157)
Stage 3	3	1.9% (3/157)	0.0% (0/157)	0.0% (0/157)	0.0% (0/157)	0.0% (0/157)
Vascular Complications						
Major vascular complications	11	5.1% (8/157)	0.0% (0/157)	0.6% (1/157)	0.0% (0/157)	1.3% (2/157)
TriGUARD access site-related	3	0.0% (0/157)	0.0% (0/157)	0.6% (1/157)	0.0% (0/157)	1.3% (2/157)
TAVI or other access site-related	7	4.5% (7/157)	0.0% (0/157)	0.0% (0/157)	0.0% (0/157)	0.0% (0/157)
Secondary access site-related	0	0.0% (0/157)	0.0% (0/157)	0.0% (0/157)	0.0% (0/157)	0.0% (0/157)
Aortic vascular injury	2	1.3% (2/157)	0.0% (0/157)	0.0% (0/157)	0.0% (0/157)	0.0% (0/157)

a. If the relationship to TriGUARD 3 Device is different than the relationship to TriGUARD 3 Procedure, then the most related of the two is considered for evaluation.
b. Number of subjects who experienced the respective safety endpoint at least once.

Secondary efficacy endpoint:

Table 7. Secondary efficacy (imaging) endpoint in TriGUARD 3 (PT and eITT populations) and control groups.

Endpoints	TriGuard 3 PT Group (N=62)	TriGUARD 3 eITT Group (N=112)	Control Group (N=119)
Presence of cerebral ischemic lesions	79.6% (43/54)	85.0% (85/100)	84.9% (90/106)
Number of cerebral ischemic lesions [c]			
Mean±SD (n)	3.9 ± 4.8 (54)	6.0 ± 8.3 (100)	4.6 ± 5.9 (106)
Median (Q1, Q3)	2.5 (1.0, 5.0)	3.0 (1.5, 7.0)	2.0 (1.0, 7.0)
Range (Min, Max)	(0, 23)	(0, 51)	(0, 32)
Per-patient average single cerebral ischemic lesion volume, mm³ [d]			
Mean±SD (n)	66.9 ± 63.7 (54)	72.8 ± 63.7 (100)	83.3 ± 112.9 (106)
Median (Q1, Q3)	52.7 (25.0, 83.9)	59.9 (35.7, 90.5)	57.5 (34.0, 90.6)
Range (Min, Max)	(0.0, 273.2)	(0.0, 341.4)	(0.0, 936.9)
Single cerebral ischemic lesion volume, mm³ [d]			
Mean±SD (n)	73.3 ± 135.1 (277)	74.9 ± 161.1 (785)	81.4 ± 328.3 (662)
Median (Q1, Q3)	35.7 (18.8, 76.5)	31.3 (18.8, 71.4)	35.8 (0.0, 71.4)
Range (Min, Max)	(0.0, 1304.3)	(0.0, 2037.5)	(0.0, 6894.9)
Total volume of cerebral ischemic lesions, mm³ [d]			
Mean±SD (n)	375.8 ± 617.7 (54)	587.8 ± 1028.4 (100)	508.2 ± 1124.0 (106)
Median (Q1, Q3)	145.7 (43.8, 444.4)	215.4 (68.1, 619.7)	188.1 (52.1, 453.1)
Range (Min, Max)	(0.0, 3519.0)	(0.0, 5681.3)	(0.0, 8133.6)

Secondary performance endpoint:

Table 8. **Secondary performance endpoint** in TriGUARD 3 SP(AT), Roll-in population and the combined populations (All subjects).

Secondary Performance Endpoints	TriGUARD 3 SP(AT) group (N = 121) [a]	TriGUARD 3 Roll-In (N = 41)	TriGUARD 3 All Subjects (N = 162) [a]
Successful device deployment [b]	100.0% (116/116)	100.0% (41/41)	100.0% (157/157)
Number of attempts needed to successfully deploy TriGUARD 3 device (device-level)			
1	98.3% (114/116)	97.6% (40/41)	98.1% (154/157)
2	1.7% (2/116)	2.4% (1/41)	1.9% (3/157)
Aortic arch successfully accessed with the TriGUARD 3 delivery catheter	100.0% (116/116)	100.0% (41/41)	100.0% (157/157)
Device positioning at: [c,d]			
Pre-TAVI:			
Complete	62.1% (59/95)	58.8% (20/34)	61.2% (79/129)
Partial	15.8% (15/95)	26.5% (9/34)	18.6% (24/129)
None	22.1% (21/95)	14.7% (5/34)	20.2% (26/129)
Final deployment of the first prosthetic valve (during TAVI):			
Complete	72.4% (76/105)	80.0% (32/40)	74.5% (108/145)
Partial	8.6% (9/105)	7.5% (3/40)	8.3% (12/145)
None	19.0% (20/105)	12.5% (5/40)	17.2% (25/145)
Final procedure (post-TAVI): [e]			

Secondary Performance Endpoints	TriGUARD 3 SP(AT) group (N = 121) [a]	TriGUARD 3 Roll-In (N = 41)	TriGUARD 3 All Subjects (N = 162) [a]
Complete	71.4% (80/112)	72.5% (29/40)	71.7% (109/152)
Partial	12.5% (14/112)	15.0% (6/40)	13.2% (20/152)
None	16.1% (18/112)	12.5% (5/40)	15.1% (23/152)
Comprehensive Coverage:			
Complete and Partial	80.9% (89/110)	87.5% (35/40)	82.7% (124/150)
Complete	58.2% (64/110)	62.5% (25/40)	59.3% (89/150)
Partial	22.7% (25/110)	25.0% (10/40)	23.3% (35/150)
None	19.1% (21/110)	12.5% (5/40)	17.3% (26/150)
Device interference [f]	8.6% (10/116)	12.2% (5/41)	9.6% (15/157)
Successful device retrieval [g]	100.0% (116/116)	100.0% (41/41)	100.0% (157/157)
Technical success [d,h]	69.5% (73/105)	75.0% (30/40)	71.0% (103/145)
Procedure success [d,i]	67.6% (71/105)	75.0% (30/40)	69.7% (101/145)

a. Five (5) TriGUARD 3 randomized subjects did not undergo the TAVI procedure and were not followed, and therefore are not included in the denominators.
b. Successful device deployment: Ability to access the aortic arch with the TriGUARD 3 delivery catheter and deploy the device into the aortic arch.
c. Device positioning: Ability to position the TriGUARD 3device in the aortic arch to cover all major cerebral arteries, with proper positioning maintained (verified by angiography) until specified.
d. Subjects with Coverage = N/A (due to indiscernible angiograms) are not included in the denominator.
e. Final procedure: After any additional post-dilatation or valve implantations have been completed, and the TAVI delivery system has been removed.
f. Device interference: Interaction of the TriGUARD 3 device with the TAVI system leading to (1) inability to advance or manipulate the TAVI delivery system or valve prosthesis, OR (2) inability to deploy the TAVI valve prosthesis, OR (3) inability to retrieve the valve prosthesis or delivery system.
g. Successful device retrieval: Ability to retrieve the TriGUARD 3 device.
h. Technical success: Successful device deployment, device positioning for complete coverage during TAVI, and successful device retrieval in the absence of device interference.
i. Procedure success: Technical success in the absence of any investigational device-related or procedure-related in-hospital procedural safety events.

Table 9: Percentage Reduction in Lesion volume with Complete Coverage

Imaging Endpoint	TriGUARD	Control	% Reduction
Phase 1	N=78	N=62	
average single lesion volume	100.4 mm^3	104.8 mm^3	4.2%
maximum single lesion volume	320 mm^3	400 mm^3	20%
mean total lesion volume	614 mm^3	651 mm^3	5.7%
Phase 2	N=62	N=119	
average single lesion volume	66.9 mm^3	83.3 mm^3	19.7%
maximum single lesion volume	73.3 mm^3	81.4 mm^3	10%
mean total lesion volume	375.8 mm^3	508.2 mm^3	26.1%

Conclusions:

The REFLECT Trial met the primary safety endpoint with significance, demonstrating that the TriGUARD 3 cerebral embolic protection device was safe in comparison with historical TAVR data. The primary hierarchical efficacy endpoint in comparison with the active Control arm was not met

but demonstrated a numerical reduction in means and in the median per patient lesion volume and the average single lesion volume
The TriGUARD 3 device demonstrated reliable aortic arch access, deployment, and retrieval.
Subjects in the Per Treatment population (complete TriGUARD 3 cerebral vessel coverage without conversion to surgery or prolonged cardiac arrest) experienced a numerical 26% relative reduction in mean total lesion volume, suggesting a possible benefit of TriGUARD 3 cerebral protection when complete 3-vessel coverage is achieved.

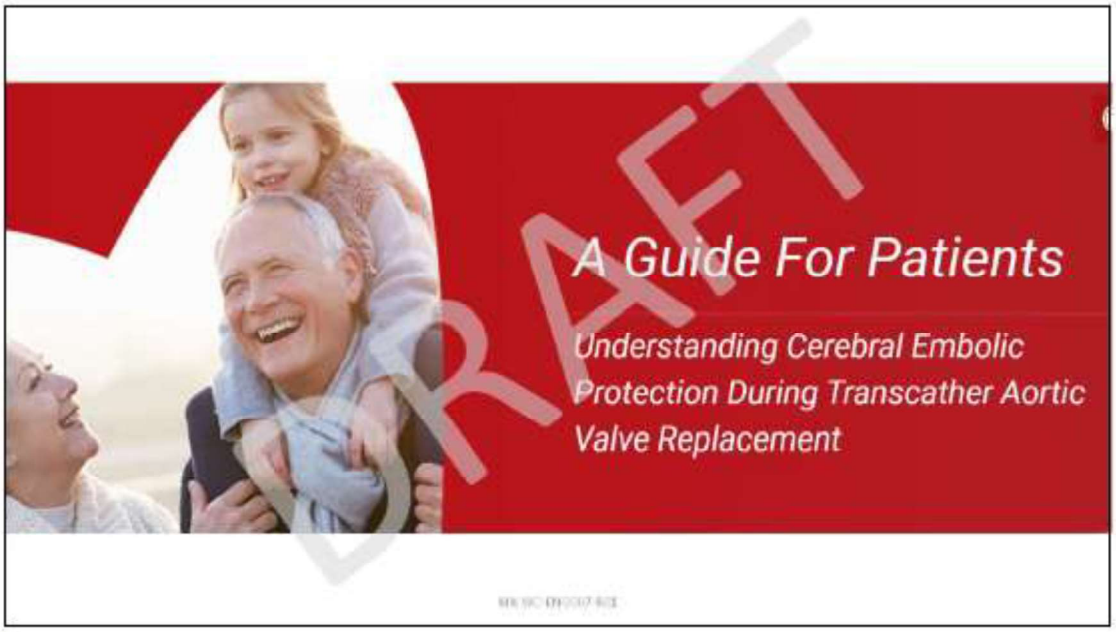
Warranty

Keystone Heart warrants that reasonable care has been used in the design and manufacture of this instrument. The foregoing warranty is in lieu of and excludes all other warranties not expressly set forth herein, whether express or implied, by operation of law or otherwise, including, but not limited to, any implied warranties of merchantability or fitness for a particular purpose.

Handling, storage, cleaning and sterilization of this instrument, as well as other factors relating to the patient, diagnosis, treatment, surgical procedures and other matters beyond Keystone Heart's control directly affect the instrument, its performance and the results obtained from its use.

Keystone Heart's obligation under this limited warranty is strictly limited to the replacement of the instrument. In no event will Keystone Heart be liable for any indirect, incidental or consequential loss, damage or expense directly or indirectly arising from the use of the instrument. Keystone Heart neither assumes nor authorizes any other person to assume for it any other or additional liability or responsibility in connection with the instrument. Keystone Heart assumes no liability with respect to any re-use, re-processing or re-sterilization of the instrument, and disclaims all warranties, express or implied, including but not limited to merchantability or fitness for a particular purpose, with respect to such instruments.

12.2.2 Draft Patient Brochure



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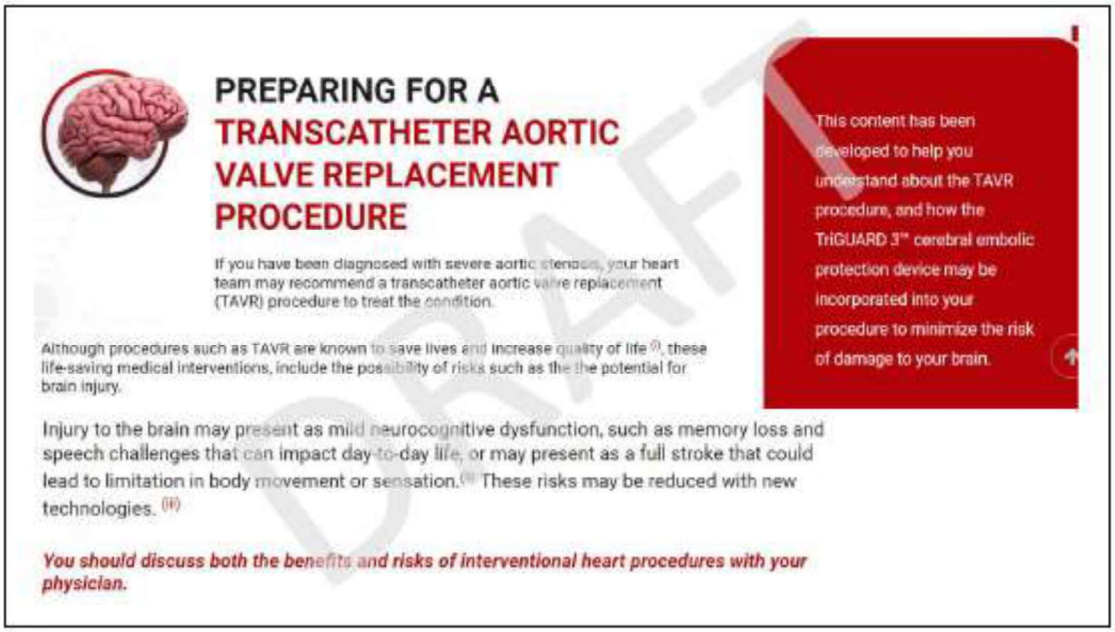

2


DID YOU KNOW?
WHAT DOES YOUR BRAIN HAVE TO DO WITH YOUR HEART?
Twenty percent of the blood pumping through your heart travels to the brain.[iv] When you have a heart procedure, what happens in the heart can impact the brain.[v]
There is a direct connection between your heart and your brain through the body's vascular system.[vi]
During a heart procedure, pieces of calcium, blood clots, parts of vessel walls or other intraluminal matter may break off from your heart chambers, valve, and/or blood vessels.[vii]
There is potential that this debris may travel in your blood stream up to your brain and cause damage, which is referred to as a brain lesion.[viii]
The clinical consequences of brain lesions depend on the size, location and through which of the three cerebral branches the debris travels to the brain.[ix]
It may seem strange to discuss a neurological event like stroke with your cardiologist, but the heart and the brain are physically connected.
The TriGUARD 3™ device is designed to deflect the debris from traveling to your brain by protecting all three major vessels that supply blood to your brain during trans-catheter procedures. In doing so, it can potentially reduce
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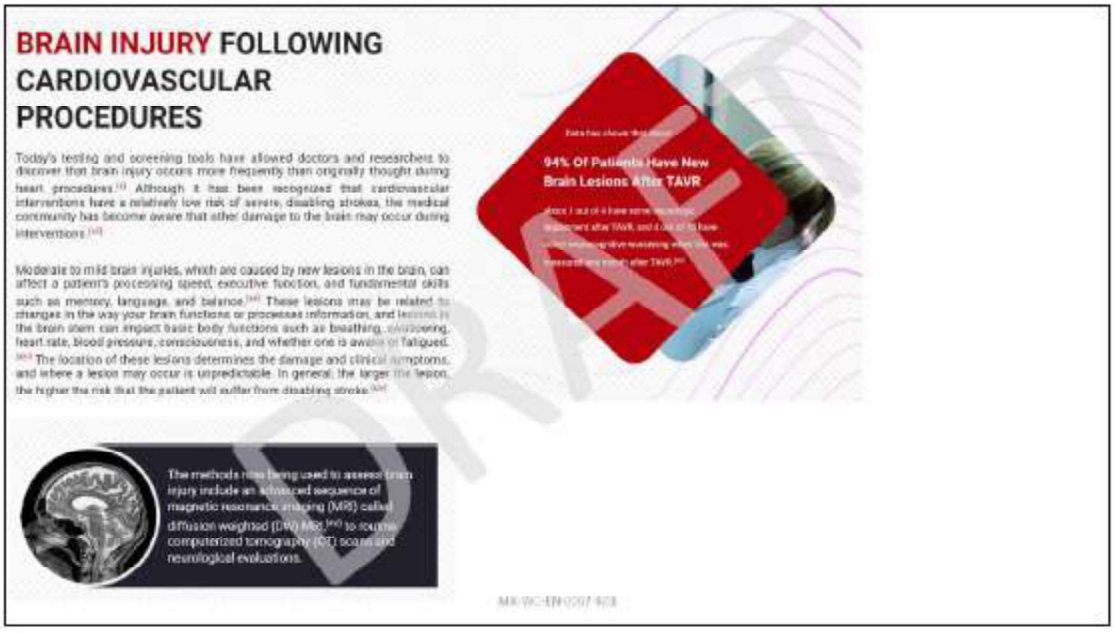
BRAIN INJURY FOLLOWING CARDIOVASCULAR PROCEDURES
Today's testing and screening tools have allowed doctors and researchers to discover that brain injury occurs more frequently than originally thought during heart procedures.[i] Although it has been recognized that cardiovascular interventions have a relatively low risk of severe, disabling strokes, the medical community has become aware that other damage to the brain may occur during interventions.[ii][iii]
Moderate to mild brain injuries, which are caused by new lesions in the brain, can affect a patient's processing speed, executive function, and fundamental skills such as memory, language, and balance.[iv] These lesions may be related to changes in the way your brain functions or processes information, and lesions in the brain stem can impact basic body functions such as breathing, swallowing, heart rate, blood pressure, consciousness, and whether one is awake or fatigued.[v][vi] The location of these lesions determines the damage and clinical symptoms, and where a lesion may occur is unpredictable. In general, the larger the lesion, the higher the risk that the patient will suffer from disabling stroke.[vii][viii]
94% Of Patients Have New Brain Lesions After TAVR
The methods now being used to assess brain injury include an advanced sequence of magnetic resonance imaging (MRI) called diffusion weighted (DW) MRI,[ix][x] to routine computerized tomography (CT) scans and neurological evaluations.
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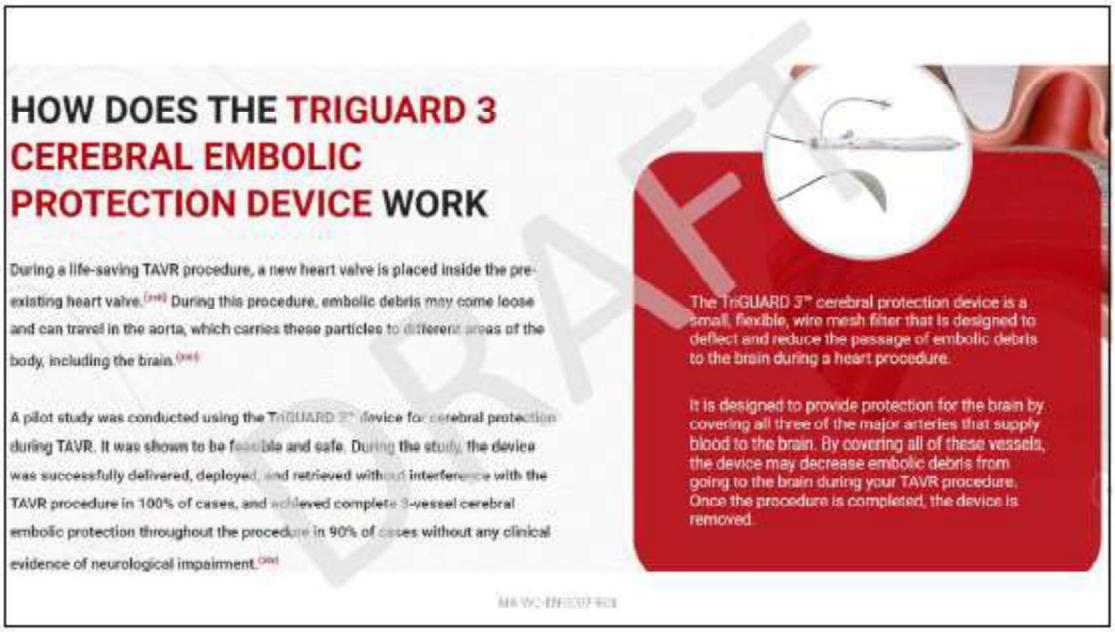
4


HOW CAN WE KEEP EMBOLIC DEBRIS FROM TRAVELING TO THE BRAIN
There is a growing body of evidence that shows if we can reduce embolic debris going to the brain, we can decrease the risk of brain injury during life-saving procedures such as TAVR. If your physician recommends that you consider TAVR, you may be a candidate to receive a new cerebral embolic protection device called TriGUARD 3™, which is a device to provide protection for the brain during a heart procedure.

5


HOW DOES THE TRIGUARD 3 CEREBRAL EMBOLIC PROTECTION DEVICE WORK
During a life-saving TAVR procedure, a new heart valve is placed inside the pre-existing heart valve.[xvii] During this procedure, embolic debris may come loose and can travel in the aorta, which carries these particles to different areas of the body, including the brain.[xvii]
A pilot study was conducted using the TriGUARD 3™ device for cerebral protection during TAVR. It was shown to be feasible and safe. During the study, 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 without any clinical evidence of neurological impairment.[xviii]
The TriGUARD 3™ cerebral protection device is a small, flexible, wire mesh filter that is designed to deflect and reduce the passage of embolic debris to the brain during a heart procedure.
It is designed to provide protection for the brain by covering all three of the major arteries that supply blood to the brain. By covering all of these vessels, the device may decrease embolic debris from going to the brain during your TAVR procedure. Once the procedure is completed, the device is removed.

6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4. http://dx.doi.org/10.1016/j.amjcard.2016.08.013
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7. http://dx.doi.org/10.1016/j.amjcard.2016.08.013
8. https://www.ncbi.nlm.nih.gov/pubmed/21087747
9. https://www.ncbi.nlm.nih.gov/pubmed/21087747
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11. http://dx.doi.org/10.1016/j.amjcard.2016.08.013
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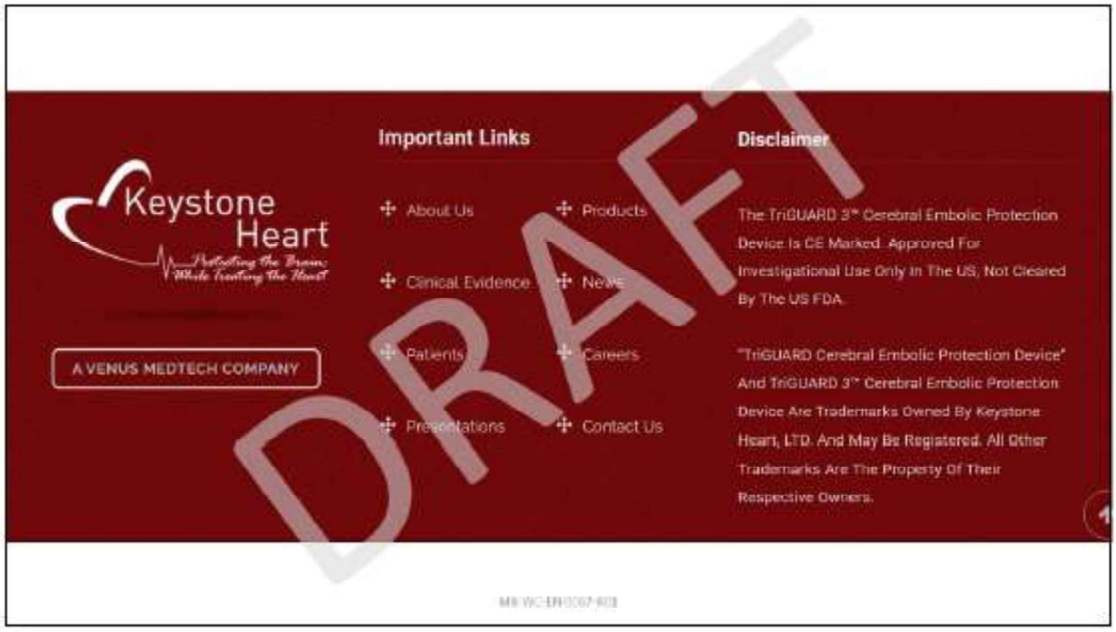
Keystone Heart
Protecting The Brain. While Treating The Heart
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Disclaimer
The TriGUARD 3™ Cerebral Embolic Protection Device Is CE Marked. Approved For Investigational Use Only In The US, Not Cleared By The US FDA.
"TriGUARD Cerebral Embolic Protection Device" And TriGUARD 3™ Cerebral Embolic Protection Device Are Trademarks Owned By Keystone Heart, LTD. And May Be Registered. All Other Trademarks Are The Property Of Their Respective Owners.
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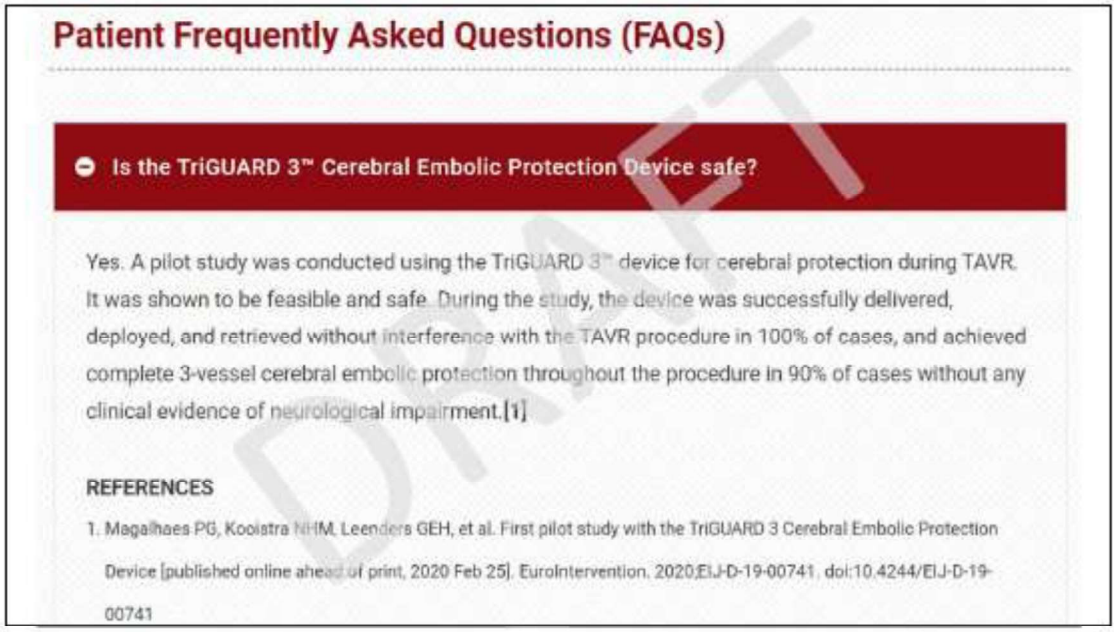

Patient Frequently Asked Questions (FAQs)

Is the TriGUARD 3™ Cerebral Embolic Protection Device safe?

Yes. A pilot study was conducted using the TriGUARD 3™ device for cerebral protection during TAVR. It was shown to be feasible and safe. During the study, 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 without any clinical evidence of neurological impairment.[1]

REFERENCES

1. Magalhaes PG, Koolstra NHM, Leenders GEH, et al. First pilot study with the TriGUARD 3 Cerebral Embolic Protection Device [published online ahead of print, 2020 Feb 25]. EuroIntervention. 2020;EIJ-D-19-00741. doi:10.4244/EIJ-D-19-00741

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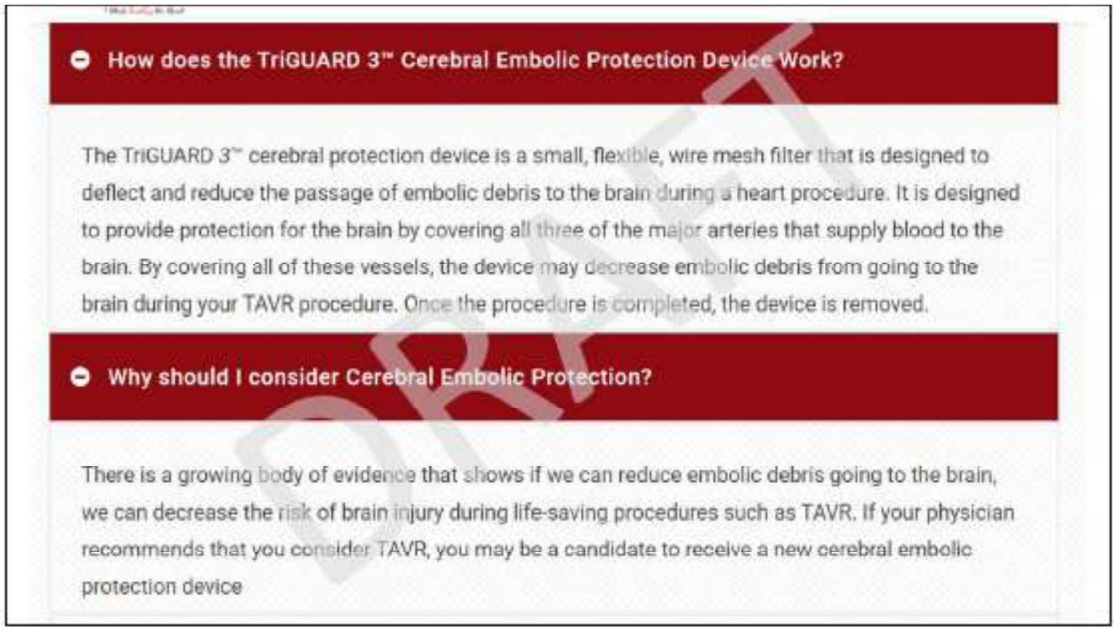

How does the TriGUARD 3™ Cerebral Embolic Protection Device Work?

The TriGUARD 3™ cerebral protection device is a small, flexible, wire mesh filter that is designed to deflect and reduce the passage of embolic debris to the brain during a heart procedure. It is designed to provide protection for the brain by covering all three of the major arteries that supply blood to the brain. By covering all of these vessels, the device may decrease embolic debris from going to the brain during your TAVR procedure. Once the procedure is completed, the device is removed.

Why should I consider Cerebral Embolic Protection?

There is a growing body of evidence that shows if we can reduce embolic debris going to the brain, we can decrease the risk of brain injury during life-saving procedures such as TAVR. If your physician recommends that you consider TAVR, you may be a candidate to receive a new cerebral embolic protection device

10


How do physicians assess brain injury after TAVR?
The methods now being used to assess brain injury include an advanced sequence of magnetic resonance imaging (MRI) called diffusion weighted (DW)-MRI,[1] to routine computerized tomography (CT) scans and neurological evaluations.
REFERENCES
1. Gress D. J Am Coll Cardiol. 2012 Oct 23;60(17):1614-6
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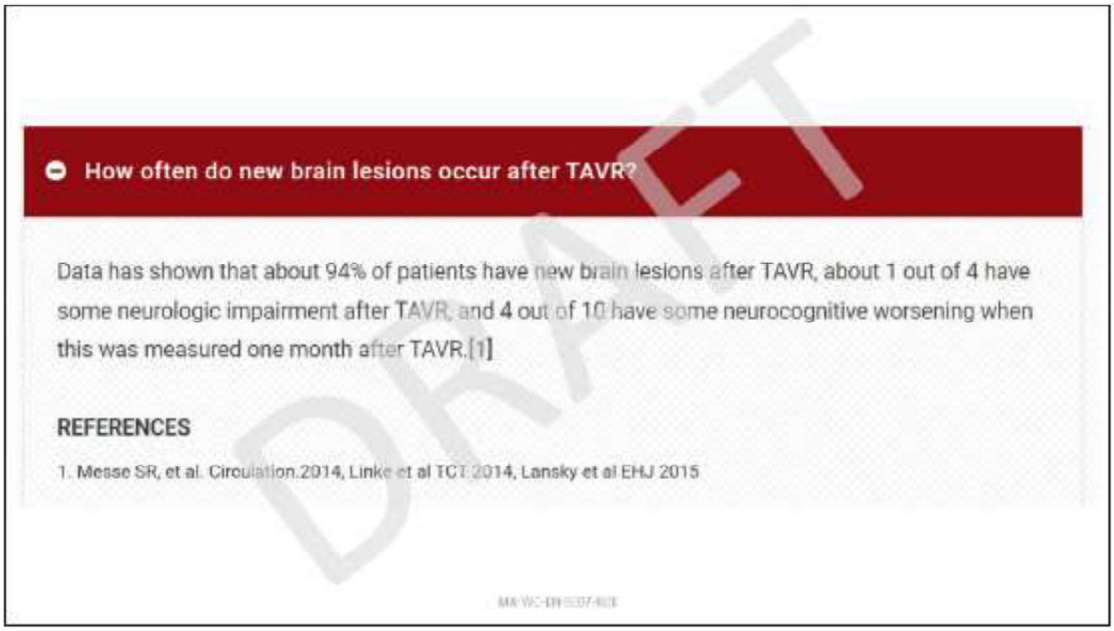
How often do new brain lesions occur after TAVR?
Data has shown that about 94% of patients have new brain lesions after TAVR, about 1 out of 4 have some neurologic impairment after TAVR, and 4 out of 10 have some neurocognitive worsening when this was measured one month after TAVR.[1]
REFERENCES
1. Messe SR, et al. Circulation.2014, Linke et al TCT 2014, Lansky et al EHJ 2015
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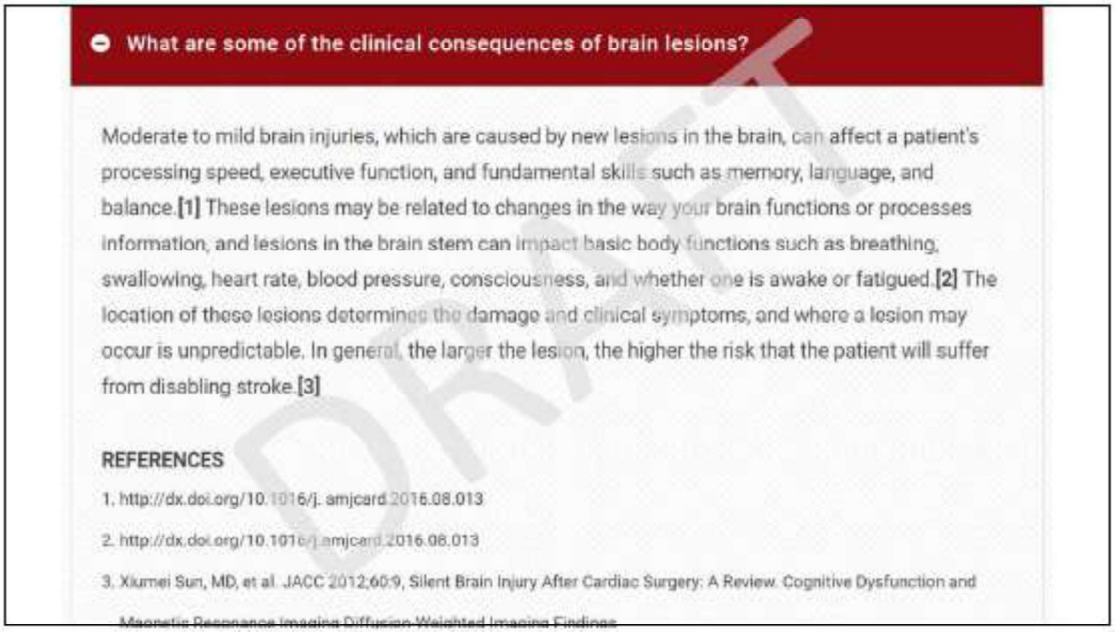

What are some of the clinical consequences of brain lesions?

Moderate to mild brain injuries, which are caused by new lesions in the brain, can affect a patient's processing speed, executive function, and fundamental skills such as memory, language, and balance.[1] These lesions may be related to changes in the way your brain functions or processes information, and lesions in the brain stem can impact basic body functions such as breathing, swallowing, heart rate, blood pressure, consciousness, and whether one is awake or fatigued.[2] The location of these lesions determines the damage and clinical symptoms, and where a lesion may occur is unpredictable. In general, the larger the lesion, the higher the risk that the patient will suffer from disabling stroke.[3]

REFERENCES

1. http://dx.doi.org/10.1016/j.amjcard.2016.08.013
2. http://dx.doi.org/10.1016/j.amjcard.2016.08.013
3. Xiumei Sun, MD, et al. JACC 2012;60:9, Silent Brain Injury After Cardiac Surgery: A Review. Cognitive Dysfunction and Magnetic Resonance Imaging Diffusion-Weighted Imaging Findings

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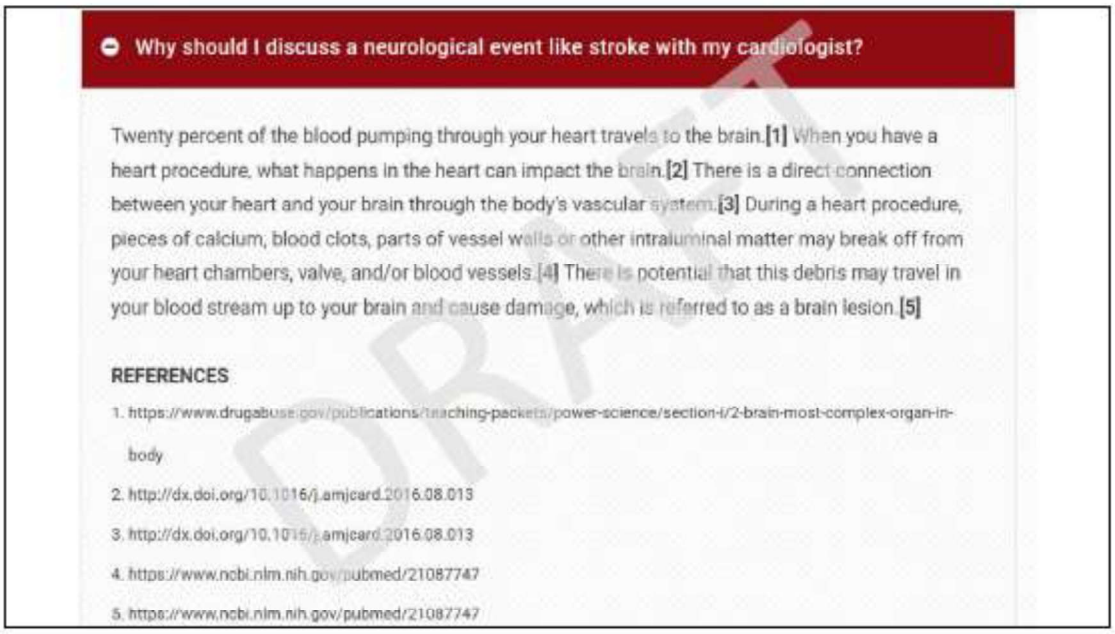

Why should I discuss a neurological event like stroke with my cardiologist?

Twenty percent of the blood pumping through your heart travels to the brain.[1] When you have a heart procedure, what happens in the heart can impact the brain.[2] There is a direct connection between your heart and your brain through the body's vascular system.[3] During a heart procedure, pieces of calcium, blood clots, parts of vessel walls or other intraluminal matter may break off from your heart chambers, valve, and/or blood vessels.[4] There is potential that this debris may travel in your blood stream up to your brain and cause damage, which is referred to as a brain lesion.[5]

REFERENCES

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3. http://dx.doi.org/10.1016/j.amjcard.2016.08.013
4. https://www.ncbi.nlm.nih.gov/pubmed/21087747
5. https://www.ncbi.nlm.nih.gov/pubmed/21087747

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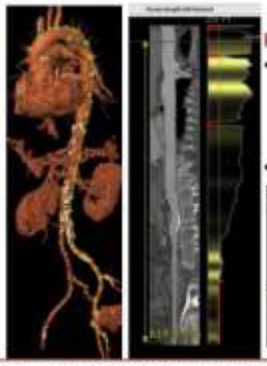
12.2.3 Draft Training Materials

12.2.3.1 Anatomical Requirements for using TriGUARD 3

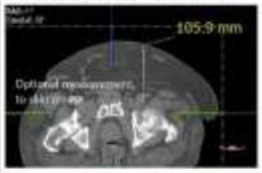
Access Length:

- **Place a centerline on the outer (longer) curve** of aortic arch to Innominate;
- **If >76 cm ->Exclude**



Puncture Length

- May be necessary to consider excessive pannus and the ability to pull this back.
- Note: average needle is

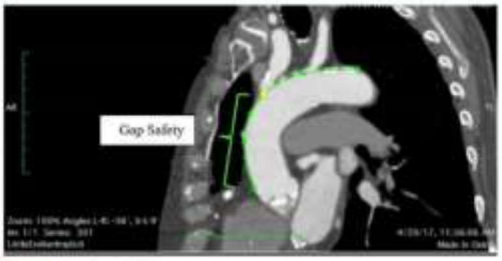


Access Length – Femoral head to front of IA + 3-4cm (error factor for placing sheath) + skin to femoral artery at the head
Distance > 76 cm (exclusion consideration)

Safety Gap:

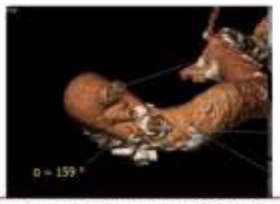
Measure the length from the Innominate Ostia to the Sinotubular junction (STJ) along the outer arch

Distance from Innominate to STJ ("safety gap") < 6 cm (exclusion consideration)



Keystone Heart

Aortic Arch Tortuosity:



- Measure tortuosity at inflection point of aortic arch
- Inflection point viewed from superior view in the arch

Tortuosity of the aortic arch – **Exclude Severe**

- Nominal (>170)
- Mild (150-169)
- Moderate (130-149)
- Severe (<129) – Exclude

- Multi-factorial decision (location, aortic diameter) - images, measurements, and video will be utilized

Keystone Heart

Aortic Arch Tortuosity:

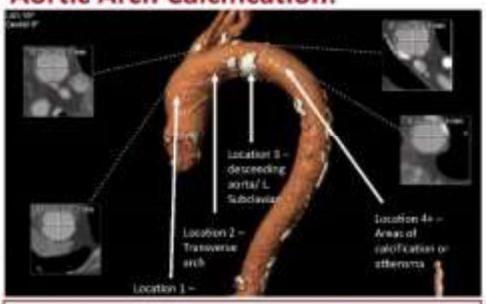
- Determining the tortuosity grade of the Aortic arch artery.

For criterion, use the angle tangent to the centerline before the curvature and tangent to the centerline after curvature, irrespective of the arch type.

- Four grades are used:
  - Grade 0 (No tortuosity): Aortic arch with > 170° angulation (A)
  - Grade 1 (Mild): Aortic arch with 150° < Angle < 169° angulation (B)
  - Grade 2 (Moderate): Aortic arch with 130° < Angle < 149° angulation (C)
  - **Grade 3 (Severe): Aortic arch with < 129° angulation (D)**

Keystone Heart

Aortic Arch Calcification:



- Diameter measurement:
- 3 locations:
  - Infront of IA,
  - Mid transverse arch,
  - Descending aorta (t
- Cross section images of any area of calcifications or atheroma

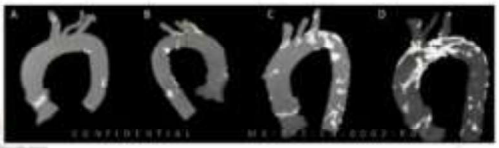
Exclude heavily calcified or severely atheromatous aortic arch - Grade 3 (Severe): Circumferential calcification or areas of intraluminal thrombus/calcification (protrusion) including atheroma

Keystone Heart

Aortic Arch Calcification:

Aortic arch calcification is graded by visual estimation of the proportion of the surface area and divided into 4 grades.

- Grade 0 (None): No visible calcification (A)
- Grade 1 (Mild): Small spots or a single thin area of calcification (B)
- Grade 2 (Moderate): One or more areas of thick calcification (C)
- **Grade 3 (Severe): Circumferential calcification or areas of intraluminal thrombus/calcification (protrusion) including atheroma (D)**

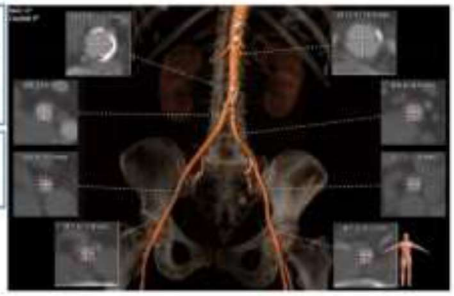


Keystone Heart

Abdominal Aorta and Ilio-femoral:

Ilio-femoral Artery Diameter –from the access point to the aorto-iliac junction (left and right) to demonstrate compatibility with 8Fr sheath.
If< 3.7mm- Exclude

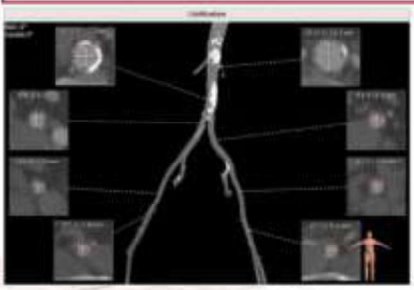
Abdominal Aorta Diameter – Measure the abdominal aorta diameter
If <10mm- Exclude

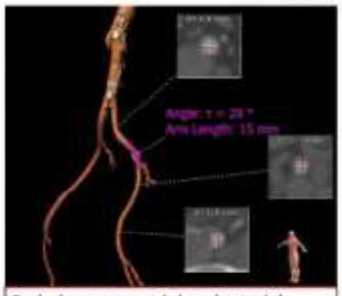


Femoral Tortuosity and Calcification:

Iliac-femoral tortuosity
Exclude Severe (**<90° angulation**)

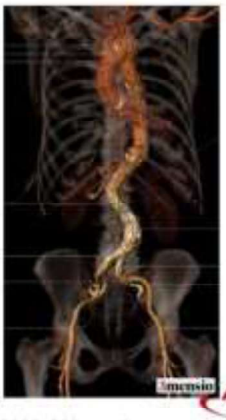
Iliac-femoral calcification
Exclude Severe (**>50% of vessel length**)



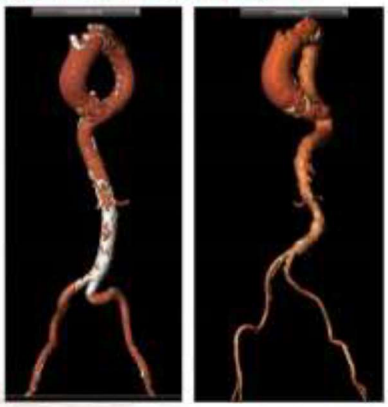


Exclude severe peripheral arterial, abdominal aortic, or thoracic aortic disease that precludes delivery sheath vascular access

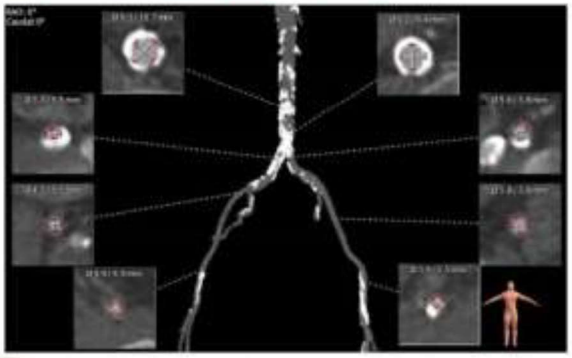
Rejected cases from REFLECT phase 2



Rejected cases from REFLECT phase 2



Rejected cases from REFLECT phase 2



Thank You
for
Making a Difference

Anatomical requirements

- **Access Length**
  - Consideration for tall subjects (>1.85 cm) OR with excess tissue/pannus
- **Aortic Arch Tortuosity**
  - Measure at inflection point in the transverse aorta
  - Inflection point determined from superior view
- **Arch calcifications/measurements**
  - 3 standard measurement (in front of innominate, mid arch, distal to subclavian
  - Cross section views of calcification or atheroma present (most significant)
- **Abdominal aorta**
  - **If< 10 mm>>Exclude**
  - If any abdominal aorta tortuosity, show images (kinks, etc)
- **Femoral arteries**
  - **If< 3.7 mm>>Exclude**

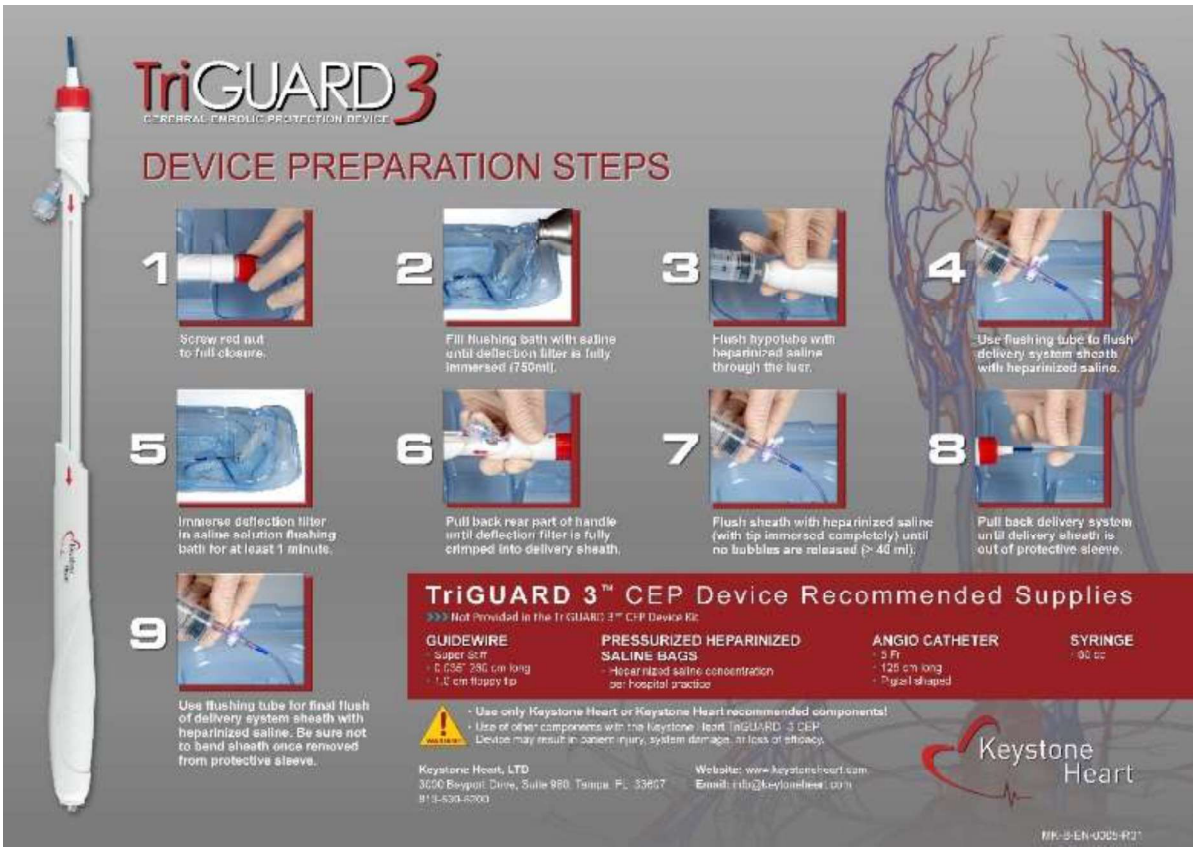
Keystone Heart

Delivery Sheath Vascular Access:

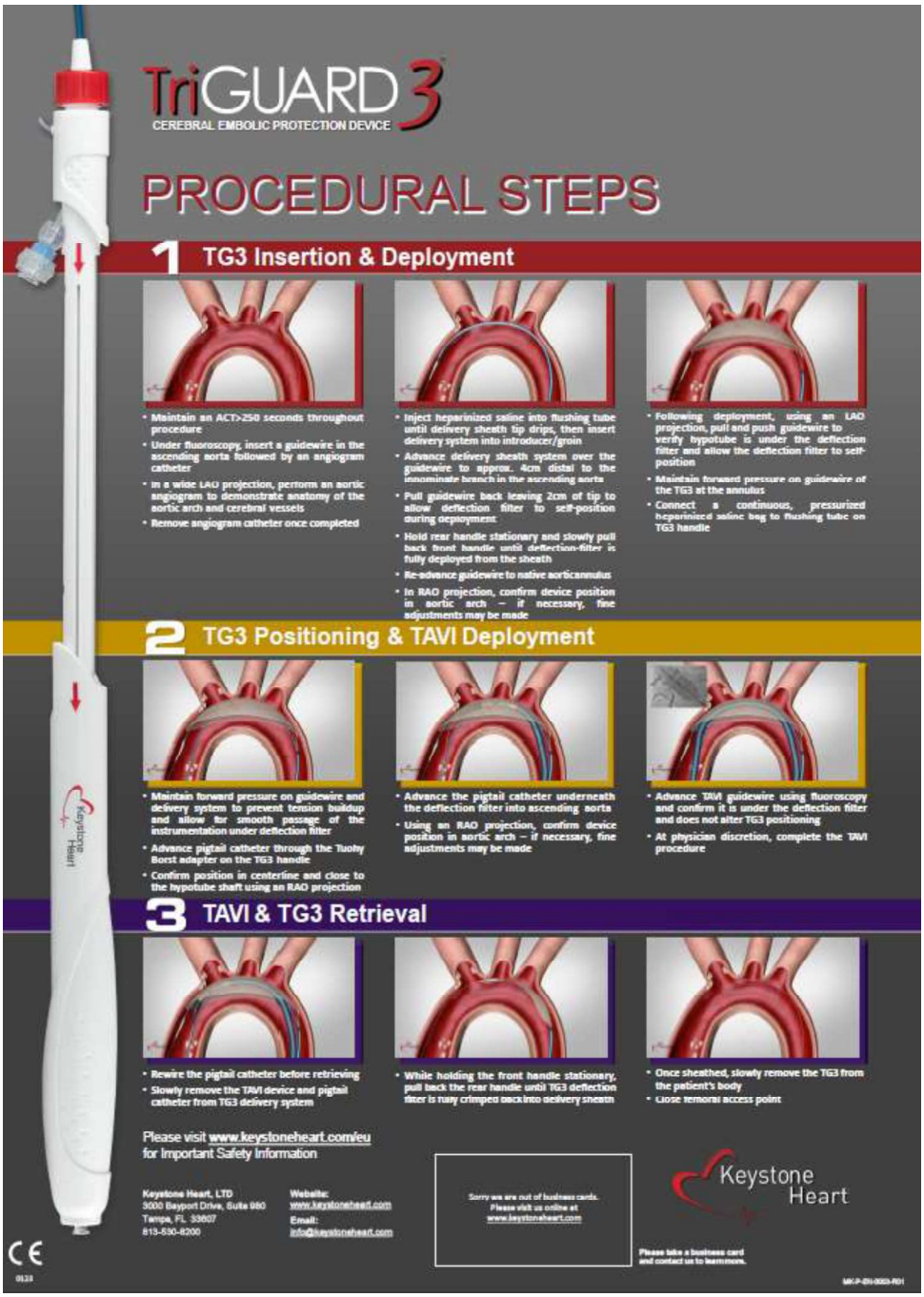
- **Abdominal Aorta Diameter** – Measure the abdominal aorta diameter to demonstrate compatibility with an 8F sheath and 18F Delivery System.
- **Iliofemoral Artery Diameter** – Measure the diameters of iliofemoral arteries from the access point to the aorto-iliac junction to demonstrate compatibility with 8Fr sheath.
- **Iliofemoral Tortuosity** – Assess the tortuosity grade of both iliofemoral arteries from the access point to the aorto-iliac junction.
- **Iliofemoral Calcification** – Assess the calcification grade of both iliofemoral arteries from the access point to the aorto-iliac junction.
- **Distance Measurement** – Measure the distance from 4 cm beyond the BCA to the location of the femoral head on the left side. Measure the perpendicular distance from the femoral artery at the location of the femoral head to the skin.

Keystone Heart

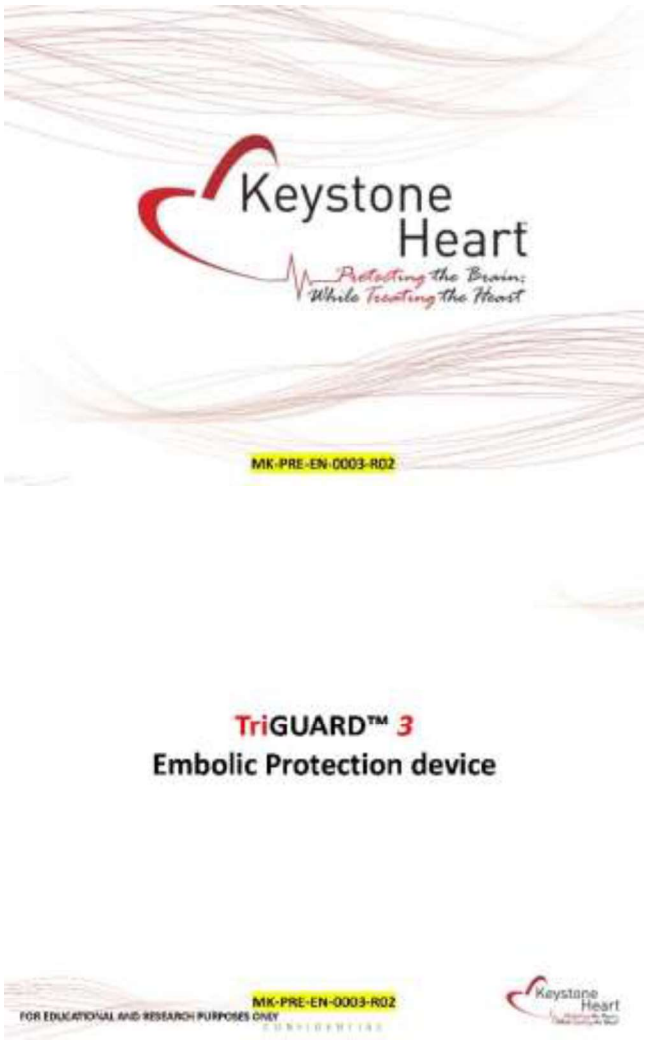
12.2.3.2 Device Preparation Brochure



12.2.3.3 Procedural Poster



12.2.3.4 Training for Medical Staff



TriGUARD 3 Components & Structure

* **Tuohy-borst**, connected to the sheath, allows for PT catheter insertion

** **Luer**, connected to the hypotube shaft, allows for guidewire insertion and flushing

Delivery Hypotube shaft	Inner diameter	Accommodates 0.035" Guide-wire
	Total length	127.5 cm
Delivery Sheath	Inner diameter	8 Fr
	Effective length	76 cm

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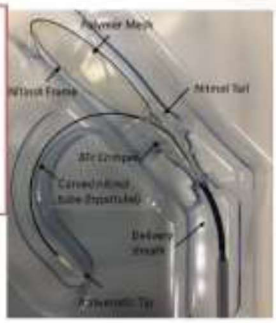
TriGUARD 3 Deflection-Filter

- Dome-shaped polymer mesh – 74mm x 98mm, Filtration area = 68.3 cm²
- Mesh Dimensions : (pore size: 115 x 145 µm); Porosity: 60%
- Hydrophilic coating with covalently bonded heparin
- Frame: Self-positioning, radiopaque nitinol frame
- Over-the-wire delivery
- Atraumatic distal tip



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TriGUARD 3 Device

Main characteristics:

- Single use device
- EtO Sterilization
- Device crimps into 8Fr delivery sheath
- Over the wire deployment (compatible with 0.035, super stiff GW)
- Applies radial force on the aortic arch walls for sealing and structural stability
- DF is supported, throughout procedure, by the hypotube shaft & G.W.

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TriGUARD *3* – Device Iteration

- **Safety:**
  - **8 Fr introducer sheath, OTW delivery, atraumatic tip, fully visible via fluoroscopy, prevents tissue-TAVI/accessories interaction due to DF mesh.**
- **Efficacy:**
  - **Circumferential apposition, large filtration area, small pore size.**
- **Ease of Use:**
  - **System:** **Ergonomic handle, OTW delivery, simplified and predictable delivery and deployment, improved visualization**
  - **Procedure:** **frame apposition (stability) and dome shaped mesh all designed to minimize device- tissue interactions, fast and simplified preparation, position, deployment and retrieval, common practice in interventional cardiology.**

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TriGUARD 3 Procedure Ancillary products

Warning Use only Keystone Heart or procedural recommended components! Use of non-recommended components with the TriGUARD *3* system may result in patient injury, system damage, or loss of efficacy

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TriGUARD *3* - Device preparation

1. Inspect the package sealing and verify product sterility and integrity. An opened or damaged item should not be used and should be returned to Keystone Heart.
2. Open the TriGUARD *3* Cerebral Embolic Protection Device carton box.
3. Open the TriGUARD *3* Cerebral Embolic Protection Device sealed Tyvek pouch and place the sterile blister tray in the sterile zone.
4. Remove the blister tray cover.
5. Tighten the handle nut to the front part of the handle to a full closure (**Figure 5-5A**).
6. Fill in the flushing basin with saline (or heparinized saline) until the TriGUARD *3* deflection-filter is fully immersed.
7. Flush the hypotube shaft with saline (or heparinized saline) through the luer located at the rear part of the device handle (**Figure 5-5B**).
8. Flush the delivery system sheath with saline (or heparinized saline) through the flushing tube located at the front part of the device handle (**Figure 5-5C**).
9. Once saline (or heparinized saline) is dripping out of the Tuohy-Borst, screw it to full closure (**Figure 5-5D**).

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TriGUARD *3* - Device preparation

10. Immerse the TriGUARD *3* deflection-filter in the flushing basin for more than 1-minute in saline (or heparinized saline) solution to hydrate the heparinized hydrophilic coating.
11. After 1 minute of immersion, no air bubbles should be visible. Gently tap on the deflection filter to remove remaining air bubbles.
12. While maintaining the handle orientation, pullback the rear part of the handle while holding the front part stationary until the Deflection-Filter is fully crimped into the delivery system.
13. Pull back the device delivery system until delivery sheath is totally out of the protecting sleeve.
14. Flush the 8Fr sheath via the flushing tube with saline (or heparinized saline), while TriGUARD *3* Cerebral Embolic Protection Device tip is immersed completely, until no bubbles are released.

Note	**Handle orientation should be kept while crimping the deflection filter into the delivery system by:** **Tuohy and flushing tube are facing toward the left side.** **The delivery system tip is inserted into the crimper.**
Note	**Flush the TriGUARD *3* delivery system with HS via the flushing tube.**
Warning	**Avoid wiping the TriGUARD *3* Cerebral Embolic Protection with dry gauze as this may damage the device coating.**

TriGUARD *3* - Device preparation:
Tuohy & flushing tube are toward the **left side**

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Keystone Heart

TRIGUARD *3* PROCEDURE

During TAVI

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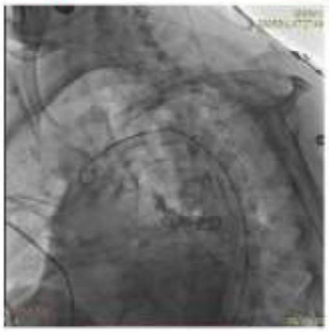
TriGUARD *3* Anatomy mapping

- LAO widest view (at least 40°, use PT to identify widest view)
- Position PT catheter just below the cerebral arteries and inject contrast to identify cerebral arteries and arch outer wall.
- ACT>250sec
- Identify landmarks for positioning of TG3.



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Inserting the delivery sheath into femoral arteries

- Orient the TriGUARD 3 distal curve towards the left side (distal curve, flushing tube and Thuy- Borst facing left).
- Just before insertion of the delivery system into the introducer/groin, inject HS through the flushing tube until the tip of the delivery sheath drips (use 5-10cc syringe).
- Advance the TriGUARD 3, over the wire, while avoiding corkscrewing.
- Allow the handle to rotate freely according to vessel trajectory.

TriGUARD 3 distal curve

Tuohy-Borst and flushing tube

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TriGUARD *3* Insertion

Warning	Perform all steps under fluoroscopic guidance. Do not make any movements of the delivery system or components without adequate visualization. All steps that reference delivery system movements assume fluoroscopic guidance!
Warning	Failure to maintain an ACT level >250 may increase the risk of thrombus formation on the device and in the 8Fr delivery sheath.

1. Insert a guidewire up to the ascending Aorta in the vicinity of native aortic annulus.
2. In a wide LAO projection, perform an angiogram to demonstrate the anatomy of the aortic arch and cerebral vessels. If possible, superimpose the aortic arch image on top of the live fluoroscopic image for reference purposes.

It is recommended to obtain the best anatomical view of the arch and cerebral vessels. Remove angiogram catheter once completed.

Warning	Before insertion of the delivery system into the introducer/groin, inject Heparinized saline to the delivery system through the flushing tube until the tip of the delivery system drips

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TriGUARD 3 Insertion

3. Before insertion of the delivery system into the introducer/groin, inject HS through the flushing tube until the tip of the delivery sheath drips (use 5-10cc syringe).
4. Advance the TriGUARD 3 Cerebral Embolic Protection Device delivery system (loaded with the TriGUARD 3 Cerebral Embolic Protection Device), over the guidewire, to approximately 4 cm distal to the Innominate branch in the ascending aorta.
5. Pull the guidewire back to reveal few cm (~2) of guidewire outside the tip to confirm the hypotube shaft is under the mesh and to allow the mesh to fully expand across the aortic arch.

Warning	To avoid air bubbles, just before and during the insertion of the delivery system into the introducer/groin inject Heparinized Saline to the delivery system through the flushing tube until the tip of the delivery system drips.
Warning	Advance the TriGUARD 3 Cerebral Embolic Protection Device, over the wire, while avoiding torquing.

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Positioning the delivery sheath in the Aortic arch

Under fluoroscopy:

- Position the TriGUARD 3 **~3-4 cm distal to the Innominate artery**, at the ascending aorta.
- Pull back the GW from leaning against the valve annulus when the TriGUARD 3 tip reaches the ascending Aorta

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TriGUARD 3 Deployment

Under fluoroscopy:

6. Hold the **rear part** of the handle stationary and slowly pull back the **front part** of the handle until the deflection filter is fully deployed from the delivery sheath.
7. Re-advance the guidewire to the vicinity of the native aortic annulus.
8. Connect a continuous, pressurized heparinized saline bag to the flushing tube.

Note	Insertion of the TriGUARD 3 Cerebral Embolic Protection Device into the femoral access should be made by advancing the 8Fr sheath only.
Warning	Throughout the procedure, avoid manually rotating/ torqueing either the handle or the TriGUARD 3 delivery sheath.

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TriGUARD 3 Deployment

Accurate, fully visible under fluoroscopy allows for full coverage of the cerebral arteries in various anatomies.

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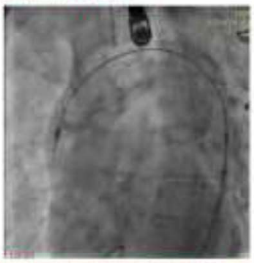
Confirming the position of the hypotube shaft relative to the deflection-filter:

Under fluoroscopy (LAO view):

- Slightly **pull and push** GW while observing the movements of the deflection filter.
- If this manipulation causes movements to the deflection filter, **beware** the hypotube is **above.**



Note User may control the hypotube shaft curvature by pulling/pushing the GW in the hypotube:
Pushing the guidewire will push the hypotube shaft toward the upper curvature of the arch providing better support for the deflection filter and moving the tip away from mid-stream.

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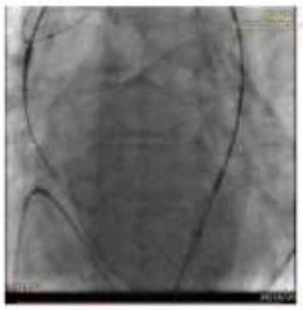
Pigtail insertion

- Advance **5Fr** PT **(125 cm)** trough the **Tuohy-Borst** access.
- Make sure the PT is inserted underneath the TG3 device by maintaining the front part of PT in midstream.
- Slow, cautious advancement



Warning Trying to manipulate/ crossing underneath the TriGUARD 3 deflection filter with a bare wire is forbidden.

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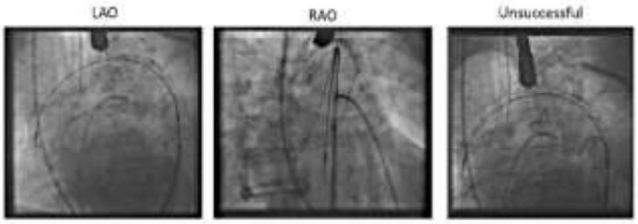
Pigtail Insertion



DF tail - emerge from sheath **left of hypotube shaft and rear frame**
DF body - cross under TG3
DF nose - cross to the **right of front frame**

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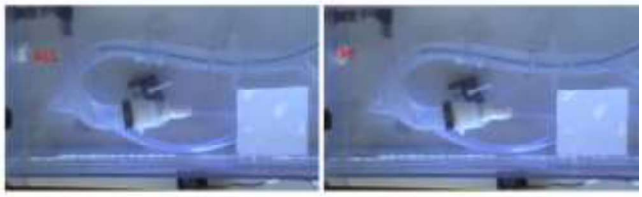
TAVI GW Insertion

The crossing trough the abdominal artery, up to the descending Aorta, should be **fully visualized under fluoroscopy**.

Instruction: Maintain AL1/PT tip orientation throughout insertion including the passage underneath deflection filter.



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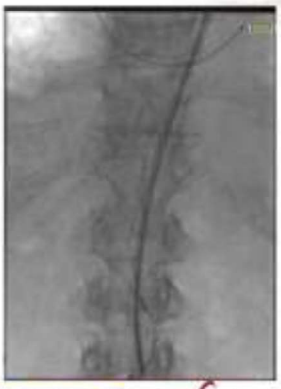
TAVI GW Insertion

Instruction: Maintain AL1/PT tip orientation throughout insertion including the passage underneath deflection filter.



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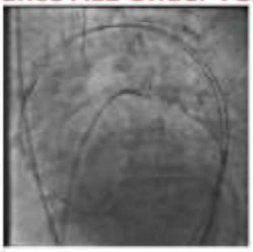
Advance AL1 Under TG3:



DF tail - left of hypotube shaft, left of rear frame

DF body - cross at the inner curve, direct catheter curve towards the inner curve

DF nose - ensure AL1 crosses to the right of the front frame in a wide LAO and confirm in RAO

TAVI GW / PT crossing

Confirmation that the position of the GW/PT catheter is underneath the TriGUARD 3 deflection filter

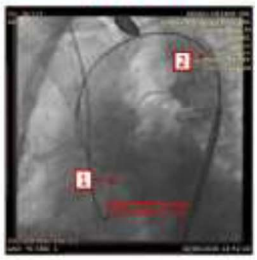
Under fluoroscopy (LAO view):

- Slightly **pull and push** GW/PT catheter while observing its location underneath the rear frame.
- Make sure that the GW/PT catheter is underneath the TriGUARD *3* rear frame.

Before crossing of the TAVI delivery system

Position the deflection filter against the upper part of the aortic arch by:

1. **Push forward the TriGUARD 3 wire to lean against the valve annulus** (hypotube shaft is pushed towards the upper wall.
2. **Push forward the TriGUARD 3 delivery system** (Close any gap between the device tail and the hypotube shaft).

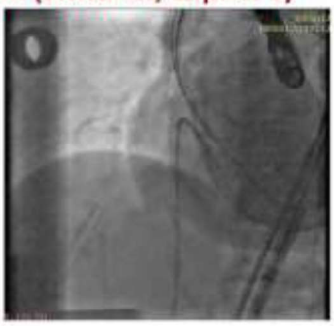


These maneuvers will help:

- **Stabilizing** the device
- **Maintain** cover of cerebral arteries
- **Prevent potential interaction** between TriGUARD *3* and index procedure instrumentations

Crossing underneath the TriGUARD *3* device: TAVI-insertion (Edwards, Sapien 3)

Advance slowly, less flexion is required to gently slide underneath the deflection-filter



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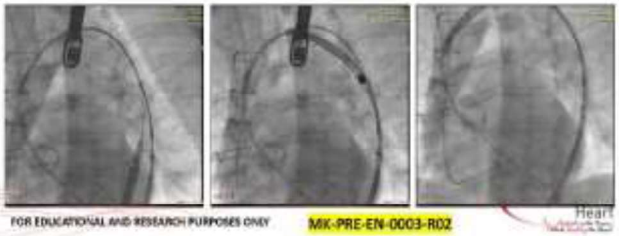
Crossing underneath the TriGUARD *3* device: TAVI-insertion (Medtronic, Evolut)

Advance slowly, slightly pull back the TAVI wire as the TAVI delivery system crosses underneath the Deflection filter

DF tail - keep TAVI system to the left of the hypotube shaft and rear engine
DF body - minimize interaction by pulling TAVI wire to reduce tension
DF nose - go slowly past front engine.



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Interaction between the TriGUARD *3* front frame and TAVI delivery system

Instruction: Slightly pull back TAVI DS and wire, Pin the wire and push forward the TAVI DS

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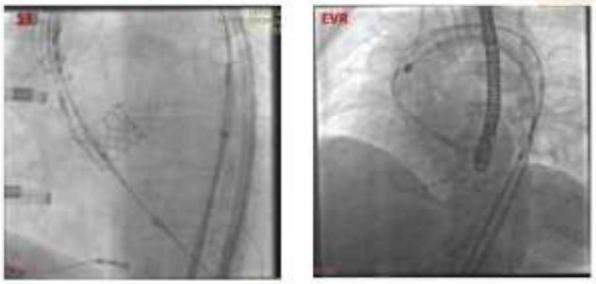
TAVI delivery system retrieval:



- Use wide LAO view
- Go slowly and monitor process
- Ensure there is no interaction with DF front/ rear frame of TG3

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TriGUARD 3 Retrieval

Under fluoroscopy:

1. Remove the trans-catheter devices used during the procedure and the pigtail catheter from the TriGUARD 3 Cerebral Embolic Protection Device delivery system.
2. Pull back the **rear part** of the handle, while holding the **front part** stationary, until the deflection filter is **fully** collapsed into the delivery sheath.

Note	Rewire the pigtail catheter before retrieving it out.

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TriGUARD 3 Retrieval

Under fluoroscopy:

3. Pull back the delivery sheath, with the crimped TriGUARD 3, until the delivery sheath is fully removed from the patient's body.
4. Close femoral access point

Note	The TriGUARD 3 should be First-in Last Out (FILO) to provide maximal protection throughout the procedure.
Note	The TriGUARD 3 Device must be disposed of in accordance with local biohazard waste disposal and hospital procedures.

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TriGUARD 3 Retrieval

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Main instructions:

Step	
Device deployment	• Avoid rotating the delivery sheath, during insertion of the TriGUARD 3 into the patient body • Ensure handle rotates freely while advancing delivery sheath into patient body • Position the device tip ~3-4 cm distally to the LA to avoid entering the LA • Before deployment, pull back the G/W in order to allow the hypotube shaft to bow down during deployment • Following deployment, pull & push the G/W in order verify that the hypotube is underneath the deflection-filter and to allow the deflection filter to self position
Crossings	
Before any crossing, position the deflection filter against the upper part of the aortic arch by: 1. Push forward the **TriGUARD 3 wire** to lean against the valve annulus (hypotube shaft is pushed towards the upper wall). 2. Push forward the **TriGUARD 3 delivery system** (Close any gap between the device tail and the hypotube shaft.	
Pigtail	• Advance to the left of rear frame (LAO view) • Cross on the inner curve of the arch (LAO view) • Confirmation (RAO view) in centerline and close to the hypotube shaft
ALI	• Monitor ALI while crossing the abdominal artery, so it doesn't loop around the TG3 delivery system • Advance to the left of rear frame (LAO view) • Avoid advancing into rear frame tail area (LAO view) • Cross on the inner curve of the arch (LAO view)
TAVI	• Advance slowly • Release tension on wire, if necessary
Device retrieval	• Remove TAVI delivery system slowly • Rewire pigtail

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Angio Procedure Workflow

Best LAO arch projection should be used for all assessments (keep angulation consistent at all time).

1. **Arch Anatomy** - Angiography of the innominate artery
2. **Delivery System positioning** - 3-4 cm past innominate
3. **Device Deployment** - Controlled deployment
4. **Place PT under the TG3** - Full angiography of arch for evaluation of TG3 position
5. **TAVI/Balloon GW - pass under TG3**
6. **TAVI Delivery insertion / TAVI Delivery retrieval**
7. **Final TG3 assessment** - In best LAO arch projection
8. **PT out** - Rewire PT before retrieval to avoid entanglement
9. **TG3 Retrieval**

If the TriGUARD 3 device has changed position at any time, arch angiography with contrast is strongly recommended.

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12.3 TriGUARD 3 Component Dimensions and Materials

Table 15: TriGUARD 3 Component Dimensions

Component	Patient Contact	Description	Dimension
Deflection Filter	Transient, direct blood circulation	Frame Width	74 mm
		Frame Length	98 mm
Delivery Shaft	Transient, direct blood circulation	Inner diameter	Accommodates . Guide-wire
		Total Length	127.5 cm
8F Sheath	Transient patient contact	Inner diameter	8 F
		Effective Length	76 cm
Device Effective length		Strain relief to atraumatic tip (during over the wire advancement)	78 cm

F: french

Table 16: TriGUARD 3 Component Materials

Component	Length of Patient Contact	Material
Deflection Filter	Up to 4 hours	Nitinol
		PEEK
		Acrylated urethane
		Polyurethane film with acrylic adhesive
		Surmodics Heparin
Delivery System	Up to 4 hours	Nitinol
		Stainless Steel 304
		Oscor sheath
	Indirect; Outside circulation	Stainless Steel 316
		Makrolon
		Silicone
		PTFE
		Ethyl cyanoacrylate
		Acrylated urethane
		Stainless Steel 304
		HDPE
		PC+ABS
TriGUARD 3 Tip	Up to 4 Hours	PEBAX

HDPE: high-density polyethylene; PC+ABS: polycarbonate/acrylonitrile butadiene styrene
PEBAX: polyether block amide; PEEK: polyether ether ketone; PTFE: polytetrafluoroethylene

12.4 DMC Meeting Materials

Keystone Heart

Protecting the Brain; While Treating the Heart

Keystone Heart appreciates FDA's availability to discuss the recent "Notice of Significant New Information" regarding the REFLECT Trial, and would like to convey to FDA the following additional considerations as a prelude to tomorrow's discussion:

- Keystone Heart appreciates FDA's feedback that they should have been notified promptly upon study enrollment suspension. There was never an intent to withhold any information from the FDA. Due to the Sponsors blinding and the identification of potential data integrity concerns, we believed a thorough investigation should be conducted prior to any communication in order to present the facts, not speculation. The Sponsor believed that because the DMC was involved throughout the entire process and the recommendation to suspend enrollment was based on the data quality issues that were proactively raised by the Sponsor, no FDA notification was necessary at that time until all the facts could be provided. We apologize if this conclusion was incorrect, and sincerely regret the error.
- As you have been informed, immediately after we became aware of possible data integrity issues, Keystone Heart began a thorough investigation, which included recommendations by the REFLECT trial PI's and Executive Committee, the DMC, and independent experts. As described in the submission, this investigation uncovered significant concerns related to the quality and integrity of the CEC adjudication process, as well as statistical services from the same vendor. We immediately engaged Yale and the prior CEC to re-adjudicate all SAEs and AEs per protocol, and also engaged the Phase I statistical group to re-evaluate those aspects of trial activities.
- Keystone Heart has been extremely open and responsive to the DMC providing safety oversight of the study, and assures FDA that that the proactive steps to re-evaluate the CEC data, and to suspend enrollment while this evaluation was pending, were taken in the interest of fulfilling the highest standards of patient protection and study integrity. At no time has KSH received information from investigators or the DMC indicating that the study should be interrupted on the basis of safety concerns.
- We have been made aware that FDA wishes to more fully evaluate the information that has been provided before drawing conclusions on appropriate next steps for trial conduct. KSH would like to emphasize that the DMC has been very closely involved throughout Phase I and II of the trial, and encourages FDA to speak to them directly to understand the DMC's rationale for the recommendation that study enrollment should be permitted to resume immediately.
- Finally, Keystone Heart would like to note that enrollment in the REFLECT Trial is 80% complete. Because the study is not powered for individual event components, and in the absence of frank safety concerns (none of which have been identified by the DMC), we request that we be permitted to complete enrollment of the remaining 29 TriGUARD 3 and 17 Control subjects in order to allow a complete evaluation of the totality of fully adjudicated and QC'ed data, rather than a preliminary snap shot.

Sincerely,

Christopher L Richardson

Chris Richardson
President and CEO

Keystone Heart

Keystone Heart, LTD
3000 Bayport Drive, Suite 980
Tampa, FL 33607
813-309-8577
chris.richardson@keystoneheart.com

Yale Cardiovascular Research Group

RE: A Randomized Evaluation of the TriGuard™ HDH Embolic Deflection Device and the TriGUARD™ 3 Cerebral Embolic Protection Device to Reduce the Impact of Cerebral Embolic Lesions after Transcatheter Aortic Valve Implantation

The REFLECT Trial

Data Monitoring Committee (DMC) Meeting Minutes

Date: March 22, 2019

Location: Teleconference

DMC Members Present: (b)(6)

DMC Management Team (b)(6)

This meeting was commenced at 6:00 PM EDT

Minutes

The purpose of this meeting was to review the recent information received from the Sponsor on March 20, 2019 regarding the Sponsor's decision to not conduct the pre-specified interim conditional powering analysis for the REFLECT Trial.

(b)(6) opened the meeting with a review of recent communications with and from the Sponsor, including the fact that an ad hoc conference call had been conducted on March 20, 2019 between the Sponsor, Sponsor representatives and the Chair of the DMC. He informed the committee that the Sponsor had communicated that they had no intention of expanding the number of randomized subjects to be enrolled into the trial, and therefore no plans to perform the conditional power analysis originally planned for in the adaptive trial design. He informed the committee members that with less than 50 randomized subjects left to enroll, the Sponsor was asking the committee to consider their request regarding a recommendation to allow the trial to complete enrollment.

(b)(6) informed the committee that no recommendation or decision was communicated to the Sponsor during this ad hoc meeting other than the fact that he wanted to call for a convened meeting with full committee membership present.

(b)(6) noted that the participants in this call had included the individual responsible for regulatory submissions and representation on behalf of the Sponsor with FDA. He noted that this individual had commented on the fact that FDA would prefer to review a complete set of data to evaluate the trial.

(b)(6) informed the committee he had requested a commitment in writing from the Sponsor that they had no intention of going beyond the original 225 randomized subjects and written confirmation documenting the Sponsor had no plans for conducting the conditional power analysis. He informed the committee that a letter stating such had been received from the Sponsor.

(b)(6) noted that this written communication had been distributed to all committee members.

(b)(6) asked the committee to consider the current data provided since the initiation of event re-adjudication and asked the committee if the possibility of recommending continued enrollment could be made given the fact that the comparison of key event rates between the intervention and control arms was reported to be not statistically significant. He also noted that the number of events and event rates were still fluid as the data was still under review and events were in the process of collection, reporting and adjudication.

(b)(6) agreed noting that the differences between the two groups had been reported to be not significant.

(b)(6) noted that from a statistical point of view, if one did an assessment of the p-value with the data provided, the differences did not appear to approach borderline significance. She commented that had the data which was recently presented originally been provided to the committee, the committee would not have had the series of recent discussions and considerations.

(b)(6) noted that he was more comfortable making a recommendation with this information. He asked the committee if they were comfortable in allowing the trial to complete enrollment of 225 randomized subjects.

(b)(6) stated he was comfortable in allowing the trial to complete enrollment.

(b)(6) stated she was comfortable in allowing the trial to complete enrollment.

(b)(6) summarized what was to be communicated to the Sponsor as follows:

- A statement that the committee was now aware of the Sponsor's intention to not perform the conditional power analysis as specified in the investigational plan, and their intention to not expand the study sample size
- A statement that based upon the most recent data provided, the committee recommends that the trial may continue enrollment to the pre-specified 225

randomized subjects as planned under the current protocol.

(b)(6) requested this communication to the Sponsor be completed as soon as possible.

(b)(6) assured the committee this correspondence would be ready for signature this evening.

With no further comments and consensus of opinion regarding the recommendation to be made to the Sponsor expressed by the committee, this meeting of the REFLECT DMC was adjourned at 6:25 PM EDT.

Minutes submitted by:

(b)(6)

March 15, 2019
Date

March 25, 2019
Date

Meeting Minutes

FDA Discussion via Teleconference – Clarification Call re: (b) (4)

RE: IDE (b) (4)
TriGUARD™ 3 Cerebral Embolic Protection Device

Date: April 5, 2019

Time: 9:00AM – 9:40AM ET

Location: Teleconference

ATTENDEES

US Food and Drug Administration

- (ST) Sadaf A. Toor, M.S. (Lead Reviewer)
- (DB) Donna Buckley, MD, MS (Medical Officer)
- (JR) Jaime Raben, PhD (Senior Lead Reviewer, Structural Heart Devices Branch)
- (NI) Nicole Ibrahim, PhD (Deputy Director, Division of Cardiovascular Devices)

Keystone Heart, Ltd.

- (CR) Chris Richardson (President and CEO, Keystone Heart)
- (PM) Paulina Margolis, PhD (VP and CMO, Keystone Heart)
- (AL) Alexandra Lansky, MD (Yale School of Medicine, REFLECT Trial US Co-PI)
- (CP) Cody G. Pietras (Yale School of Medicine, US Regulatory Correspondent)

BACKGROUND, AGENDA, AND REFERENCED DOCUMENTS

In response to informal feedback on the (b) (4) submission (submitted March 28, 2019) that was communicated by FDA (ST) to CP via telephone on April 3, the Sponsor requested a clarification conference call for discussion with FDA, which is the subject of these minutes. Prior to the conference call, the Sponsor submitted a letter via email to FDA in preparation for the conference call (refer to "Keystone Communication to FDA 2019-04-04").

SUMMARY OF DISCUSSION

TBD

- (ST) What is the blinding status of those on the call, so we can be sure to avoid any unblinding during this discussion?

- (CP) Everyone on this call is fully blinded to aggregate data and individual subject treatment group assignments and outcomes, therefore any discussion of actual clinical data from the study should be had with the DMC.
- (CR) [Provides summary of events as described in the "Notice of Study Suspension" submission.]
- (ST) When were you were initially notified that there may be an issue, and when did you suspend enrollment?
- (CP) The delay between the Jan 29 notification of the issue, and the February 12 suspension of enrollment was because the DMC was evaluating whether ongoing oversight could be conducted using site-reported data. Ultimately they concluded that the site-reported data was not adequate for this purpose.
- (DB) Why didn't you notify FDA when you suspended enrollment?
- (CR) We were not sure whether or not there was a real issue or not, explains, and wanted to get the facts before presenting them to FDA.
- (NI) Regardless of whether or not there is a safety concern or not, FDA should be notified whenever sites are instructed to suspend enrollment. We should be part of the discussion and understand the events that occurred.
- (CR) Understood, we apologize.
- (DB) This decision contributed to why we are where we are because we are playing catch-up. I'm not sure that we have reached the same level of confidence as you that there are no safety issues and that all study conduct problems have been resolved. We have also offered the DMC a lot of leeway in study oversight in order to maintain blinding, and want to make sure that we are properly evaluating that. What is the nature of the problem with the CEC data?
- (CP) Initially it was inconsistencies in the CEC-adjudicated data that were unable to be resolved through dialogue between the Data Management CRO and the CEC CRO. This led the Data Management CRO to recommend an independent audit of the CEC process. After blinded comparison by independent third party of narratives for the same events by the Yale CEC and the CRF CEC, it was determined that the CRF narratives were less supportive of CEC's ability to appropriately adjudicate events. In addition, while we are blinded to the specific events and details, the Yale CEC and the Data Management group identified issues with the process of identifying events that were sent for adjudication, the source data that was obtained in order to provide a basis for a decision by the DMC, and consistency in how the protocol definitions were applied.
- (DB) How did you come to the conclusion there are no safety issues if you are blinded?
- (CR) We have never heard a safety issue from DMC, we have never had issues from sites. The majority of the reason for this statement is that the DMC continued to recommend that enrollment proceed as planned until we notified them of a data quality issue. After we provided the corrected data, they re-approved us to enroll. If there was a safety issue we would want to know about it and we would stop the trial.

- (ST) We appreciate your explanation and the time to discuss today. Our recommendation hasn't changed, and we need a little bit more time to gather more information and address the concerns that we have. Are there more patients planned for immediate enrollment (in the next week or so)?
- (CR) We have one patient already enrolled, 3 patients who have consented and approved by the PRC and are scheduled to be randomized next week, and 3 more patients who have been submitted to the PRC but are not yet scheduled.
- (ST) We recommend no further enrollment at this time, so is it possible that you can postpone those cases for the next week?
- (AL) Can we operationally prevent enrollment while FDA continues to evaluate the data and talk to (b)(6) to see if that can alleviate your concerns, rather than formally suspending enrollment at this time, which would be very disruptive?
- (DB) Our goal is to fill in our gaps in understanding. We don't want to penalize enrollment because of how things rolled out. If you can provide assurances that you can informally prevent further enrollment while we talk to DMC, that would be acceptable to FDA.

Action Items

- CP will facilitate conference call between FDA and REFLECT Chair (b)(6) via (b)(6) at Yale.
- Keystone Heart will operationally ensure that no subjects are enrolled over the next week while FDA deliberates.
- FDA will discuss with DMC and try to make a quick decision whether enrollment can proceed, or if it needs to be formally suspended while further evaluation is conducted.

Yale Cardiovascular Research Group

RE: A Randomized Evaluation of the TriGuard™ HDH Embolic Deflection Device and the TriGUARD™ 3 Cerebral Embolic Protection Device to Reduce the Impact of Cerebral Embolic Lesions after Transcatheter Aortic Valve Implantation

The REFLECT Trial

Data Monitoring Committee (DMC) Meeting Minutes

Date: April 15, 2019

Location: Teleconference

DMC Members Present: (b)(6)

DMC Management Team (b)(6)

This meeting was commenced at 6:00 PM EDT

The purpose of this meeting was to review recent communications with FDA regarding the REFLECT Trial and to inform committee members on recent discussions held between FDA and the DMC Chair.

Minutes

(b)(6) opened the meeting by informing the committee that the point of the meeting was to inform all committee members of recent communications with FDA held at the agency's request. (b)(6) informed those present that the previous week FDA had reached out to (b)(6) and indicated that the agency wanted to speak with the DMC Chair (b)(6) A call had taken place on Tuesday April 9, 2019 with several FDA members involved in the review and oversight of the REFLECT Trial.

During this conference call members of FDA had asked (b)(6) several questions regarding the committee' s thought process and decisions made regarding trial enrollment and conduct of the study (b)(6) noted that he had informed FDA during the discussion

that although the data showed a strong trend in the wrong direction during Phase I limiting a chance for success for the study, there was no clear indication that the study was not going to be positive until the point in time that the interim analysis was performed. (b)(6) informed his colleagues that FDA had recently been looking at the same data tables that the DMC had reviewed.

(b)(6) informed the committee members that during the initial call with FDA the agency members wanted to ask questions to better understand the committee's thoughts during their oversight of the trial. (b)(6) noted that FDA had been informed that the first recommendation for suspension of enrollment and the information communicated to the Sponsor had been made to allow the Sponsor a chance to decide what steps they wanted to take next.

(b)(6) reviewed the background and timelines of decisions and noted that the second recommendation by the committee for a temporary pause in enrollment had been generated at a time when the data reviewed in January 2019 had shown event rates which were 10% for stroke in one arm and 0% for stroke in the second arm of the study which had caused concern on the behalf of all. Very quickly following this review the committee had been informed that the Sponsor had no confidence in the data which led to the committee's recommendation to the Sponsor to implement a pause in enrollment for Phase 2 of the study until the committee had the opportunity to review the re-adjudicated data for stroke and death.

(b)(6) then informed that committee members that a second request for a call with the DMC Chair had been made and this meeting had occurred Friday April 12, 2019. Members from FDA present on this call included Dr. Bram Zuckerman. (b)(6) noted that the discussion during this session included the committee's thoughts and decisions made in March. (b)(6) noted that he had informed FDA that at the time, the committee had been interested in making sure the Sponsor performed the conditional power analysis specified in the investigational plan as a means of getting a better understanding of any potential futility. He also noted that the committee had taken a look at some of the narratives used for the re-adjudication process. He noted that if one took out two stroke events, one occurring the setting of an annular rupture and the second occurring in a subject with multiple episodes of ventricular arrhythmias leading to multiple rounds of CPR, that clearly occurred when the device had no chance of protecting against a neurological event, the differences in event rates (stroke) changed.

(b)(6) informed the committee that it was Dr. Zuckerman's opinion that there was a trend in the wrong direction seen in Phase I and there was a continued trend in the wrong direction being seen in Phase II of the study. (b)(6) informed the committee that he felt that FDA had come to a decision to recommend stopping the trial and he asked the committee if they wished to reconsider their decision to recommend resuming enrollment. (b)(6) noted that this was a decision to be made by the committee and not a unilateral decision and let the committee know that he had informed FDA that this needed to be taken to committee for a full review.

(b)(6) next posed the question and asked the committee if they still thought the trial

could continue when it appeared that FDA was planning on recommending that the trial be stopped. He asked the committee members how they felt about this aspect and opened the meeting up for discussion. He noted there were pros and cons to both positions and noted that one could make an argument that either way the likely outcome is that there would be no difference between the two groups in efficacy, and it was likely that one would see more vascular complications in the treatment arm. He noted that the potential increase in vascular complications in the treatment arm was a known possibility at the onset of the trial.

He noted that one item to consider was the fact that this was a new method of incorporating imaging data into the adjudication process and there could be value in completing the data that has been acquired and could be acquired if the enrollment was completed.

(b)(6) posed the question as to how it would work for the committee to reverse their opinion.

(b)(6) noted that it would look odd, but the communication to the Sponsor should be very succinct indicating that after further review and discussion with FDA the committee had reversed their decision that enrollment into the trial should continue.

(b)(6) commented that all members, and the committee as a whole, had gone back and forth and still felt that there is not a clear picture of what the data is despite all of the effort that has been put forth in the re-adjudication process. She noted that the conditional power analysis would have been helpful and probably would have shown a sign of futility which could have helped in the decision-making process. She noted that the totality of evidence indicates a recommendation to stop the trial is not unwarranted. However, even though there is a signal, there is no clear evidence to say stop the trial.

(b)(6) noted that Dr. Zuckerman had acknowledged that point, but he had expressed that he clearly did not feel comfortable allowing additional human subjects to be enrolled into the trial.

(b)(6) asked for a vote from the committee members and for each to state their position.

(b)(6) stated that he felt comfortable with making the decision to reverse the DMCs previous recommendation. He noted that there had been concerns with the trends in the data but there had not been a clear signal of harm to lead the committee to making a recommendation for stopping the trial.

(b)(6) stated she felt comfortable in making the decision to reverse the committee's previous recommendation noting that although the committee had thought about recommending stopping enrollment, there really had been no clear signal of harm.

(b)(6) stated he agreed with his colleagues. He noted that a brief, clear statement should be drafted for delivery to the Sponsor and the discussions occurring during this meeting should be documented on the internal DMC meeting minutes.

(b)(6) informed the committee that a request for provision of the minutes from this meeting to FDA had already been made earlier in the day. (b)(6) noted that operationally there was a priority to getting the minutes from this meeting out to the committee members for their review and then getting the minutes from the meeting to FDA as soon as possible. She asked about timelines for communications to the Sponsor and asked if the DMC should allow FDA to communicate with the Sponsor and not pre-empt the opportunity for that communication to happen.

(b)(6) stated the communications could occur in parallel.

(b)(6) informed the committee that the draft minutes of FDA and DMC Chair calls were under review by the FDA team present on those calls to assure mutual agreement on the content and detail and informed the committee she would distribute these documents to all once they had been returned to her.

(b)(6) asked if communication from the committee to the Sponsor, separately or other, should include encouragement from the committee for the Sponsor to complete adjudication of the data already acquired.

(b)(6) agreed that the Sponsor should be encouraged to complete the adjudication but also noted that the DMC was not in a position to impose this, just encourage it.

With no further comments and consensus of opinion regarding the recommendation to be made to the Sponsor expressed by the committee, this meeting of the REFLECT DMC was adjourned at 6:25 PM EDT.

Minutes submitted by:

(b)(6)

April 16 2019
Date

4/16/2019
Date

The REFLECT Trial

12.5 PT Population Demographics and Medical History

Table 17: Demographic Characteristics and Medical History (PT Population)

Patient Characteristics	TriGUARD 3 (N=62)	Control (N=57)
Demography		
Age (yrs)		
Mean±SD (n)	79.47 ± 7.86 (62)	78.05 ± 8.19 (57)
Median	80.00	79.00
Range (Min,Max)	(55.0, 96.0)	(59.0, 93.0)
Male	54.8% (34/62)	61.4% (35/57)
Hispanic or Latino Ethnicity	9.7% (6/62)	8.8% (5/57)
Medical History		
Smoking/Tobacco Usage		
Current within last year	3.2% (2/62)	7.0% (4/57)
Ex-Smoker	43.5% (27/62)	50.9% (29/57)
Never	53.2% (33/62)	42.1% (24/57)
Diabetes Mellitus (DM)	32.3% (20/62)	40.4% (23/57)
Insulin Dependent (IDDM)	1.6% (1/62)	10.5% (6/57)
Diet-controlled	9.7% (6/62)	7.0% (4/57)
Oral hypoglycemic controlled	24.2% (15/62)	28.1% (16/57)
History of Hypertension	96.7% (59/61)	91.2% (52/57)
History of Hyperlipidemia	80.6% (50/62)	85.7% (48/56)
History of Peripheral Vascular Disease	14.8% (9/61)	19.3% (11/57)
History of aortic artery disease (aneurysm)	0.0% (0/62)	1.8% (1/57)
History of prior treatment/repair	0.0% (0/0)	0.0% (0/1)
Carotid artery disease	16.9% (10/59)	23.2% (13/56)
Prior cerebral vascular attack (CVA)	9.7% (6/62)	3.5% (2/57)
Prior transient ischemic attack (TIA)	11.5% (7/61)	3.5% (2/57)
Prior CVA or TIA	19.4% (12/62)	5.3% (3/57)
History of anemia requiring transfusion	6.8% (4/59)	5.7% (3/53)
History of renal disease	14.5% (9/62)	29.8% (17/57)
LVEF assessed	96.8% (60/62)	96.5% (55/57)
History of congestive heart failure	58.1% (36/62)	58.9% (33/56)
History of atrial fibrillation/atrial flutter	25.8% (16/62)	29.8% (17/57)
History or presence of intracardiac mass, thrombus or vegetation	0.0% (0/62)	0.0% (0/57)
History of prior coronary artery bypass graft(s)	22.6% (14/62)	19.3% (11/57)
History of prior percutaneous coronary intervention	32.3% (20/62)	26.3% (15/57)
Chronic Lung disease/COPD	12.9% (8/62)	21.4% (12/56)

In home Oxygen Use	1.6% (1/62)	3.5% (2/57)
Severe Pulmonary HTN	6.5% (4/62)	5.3% (3/57)

PT: per treatment; SD: standard deviation; LVEF: Left ventricular ejection fraction; COPD: Chronic obstructive pulmonary disease; HTN: hypertension

12.6 Adverse Events Vignettes and Narratives

12.6.1 Vignettes for Major Vascular Complication Events at Access Site

Patient A: The TAVR procedure was successful and TriGUARD 3 was deployed successfully into position on first attempt. The TriGUARD 3 device was successfully removed as well as the TAVR delivery sheath. A Perclose vascular closure device was deployed in the left femoral artery, but closure was unsuccessful. At this point oozing from around the left 8 Fr arterial sheath insertion site was noted. An attempt to close the left femoral arterial access with another Perclose device was made which was unsuccessful. Manual pressure was applied and conversion to surgical repair of the artery was performed.

The event was CEC adjudicated as possibly related to the TriGUARD 3 device.

Patient B: Both the TriGUARD 3 deployment and valve placement were successful. Post hemostatic closure, the patient developed progressive hypotension and tachycardia. There was concern for a bleed in the pelvis or retroperitoneal space, so 2 units of blood were administered as access was re-established in the left femoral artery using micropuncture technique under ultrasound guidance. Once access was obtained, selective left iliofemoral was performed via the arterial sheath and a RIM catheter was re-introduced to perform selective right ilio-femoral angiography followed by introduction of a pigtail catheter to perform selective abdominal aortography. Flow in both vessels appeared to be uncompromized. The patient's hemodynamics began to stabilize, and it was thought that there had been a bleed which had stopped causing transient instability. The right femoral venous sheath was removed under manual pressure to achieve hemostasis.

The event was CEC adjudicated as possibly related to the TriGUARD 3 device.

Patient C: Two TriGUARD 3 devices were used. The first was deployed but unable to be positioned, the second was deployed and positioned on first attempt. The TAVR procedure was successful, and the patient was discharged. Post procedure day 1, the investigator reported an AE termed right iliac retroperitoneal hematoma with an onset date of 15-Aug-2018. This event was reported to be severe in presentation, unlikely to be related to the TAVR procedure, not related to the TAVR device, unlikely to be related to the TriGUARD 3 procedure and not related to the TriGUARD 3 device. This was noted to be a new finding post-TAVR and post cardiac catheterization.

12.6.2 Narratives for Stroke Events

Stroke 1

Stroke Class: Non-disabling Event Date: 18-Dec-2018

Type: Type 1a ischemic

Clinical Notes: Index NIHSS/mRS 0/0. CAD, HT, prior colon Ca, 2 x hip replacement. TAVR Nov 8th, Nov 9 physiotherapist noted neurological symptoms, MRI Nov 10th. Syncope Nov 11th due to hypertensive meds, NIHSS/mRS 0/3. pre discharge, no AE report from the investigator or the neurologists - no change in the NIHSS score. Discharged Nov 12. Event reported Dec 18th (40 days later), change in NIHSS score. Patient had fallen at home and hurt her leg week before, NIHSS/mRS 2/3 due to drift in the left leg

CEC Notes: Adjudicated outcome: Event name: Stroke, Ischemic stroke, Non-disabling stroke, Focal stroke (VARC); Overt CNS Injury- Ischemic stroke; Acute Stroke Severity- Mild neurological dysfunction; Stroke Disability- Non-disabling stroke; Stroke Recovery- Incomplete recovery

CEC Comment: Physical therapist description of symptoms and memory impairment, problem solving and physical performance deficits post-procedure in association with numerous acute ischemic lesions on MRI felt to be indicative of CNS injury manifested at 1 month neuro assessment.

Adjudicated Time to Event: Adjudication based on symptoms and positive MRI findings. There was no post-event follow-up so the CEC cannot adjudicate stroke recovery.

Other Adjudicated Outcome: Event name: Syncope**, Event Date**: 11-Nov-2018

Stroke 2

Stroke Class: Non-disabling **Event Date:** 25 Feb 2019 (67 days post TAVR)

Type: Type 1a ischemic

Clinical Notes: Index prior PCI, NIDDM, prior ischemic stroke, NIHSS/mRS 0/2. Prior ischemic cererovascular attack. 2 days post TAVR NIHSS 0 and mRS 1. Discharged Dec 23. At 67 days post TAVR submitted to acute care facility due to stroke symptoms. CEC adjudicated the event as non-disabling stroke, covert CNS infarction due to study mandated MRI findings post TAVR. Event adjudicated to have happened >72 hours and post discharge

CEC Notes: Adjudicated outcome: Event name: Stroke- Ischemic stroke, Focal, Non-disabling (VARC); Overt CNS Injury- Ischemic stroke; Acute Stroke Severity- Mild neurologic dysfunction; Stroke Disability- Non-disabling (NeuroARC). Was the subject in atrial fibrillation? No

CEC Comment: Adjudication based on symptoms and positive MRI findings. There was no post-event follow-up so the CEC cannot adjudicate stroke recovery

Adjudicated Time to Event: Adjudication based on symptoms and positive MRI findings. There was no post-event follow-up so the CEC cannot adjudicate stroke recovery

Post-hoc Neurologist Assessment: most likely not disabling however unable to say for sure as there is no mention of mRS assessment after the stroke on the narrative

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Stroke 3

Stroke Class: Not Adjudicated by CEC Event Date: 23-Oct-2018

Type: Type 1e Symptomatic Hypoxic-Ischemic Injury

Clinical Notes: TAVR Oct 23rd. Annular disruption/dissection originating from the TAVR valve. VF during TAVR, defibrillation, echo on the table showed the dissection. Patient died Oct 29th. Also AKI 3, coronary art obstruction, cardiogenic shock and major vasc compl on TAVR side. -- day 2 post surgery. On physical examination she was noted to move all extremities, open her eyes but did not follow commands prior to re-sedation. Life threatening bleeding during resuscitation

CEC Notes: Adjudicated outcome: Event name: Stroke- Undermined stroke, Global stroke (VARC); Overt CNS Injury- Symptomatic hypoxic-ischemic injury; Acute Stroke Severity- Severe neurological dysfunction (NeuroARC)

CEC Comment: Unable to adjudicate stroke disability and stroke recovery as the subject expired less than 30 days post-procedure

Post-hoc Neurologist Assessment: unless neuroimaging showed a new ischemic event, no neuroimaging was given in the case description

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Stroke 4

Stroke Class: Stroke severity not adjudicated since no 30 day follow-up **Event Date:** 28-Dec-2018

Type: Type 1.e Symptomatic Hypoxic-Ischemic Injury

Clinical Notes: Index: CAD, CABG, severe PH, NIDDM, NIHSS/mRS 1/0. TAVR Dec 27. During TAVR complete heart block and several CPR. At CCU On physical examination his pupils were 2-3 mm bilaterally with sluggish reactivity. It was noted he was still on propofol, remained sedated and Dec 28 VT, cardioversion x 3, CPR x 6. Alveolar oedema, septic shock, severe AKI, dialysis, neurologist assessment anoxic brain injury. CT chr microvasc ischemia. Anemia of unknown origin. Jan 2 "do not rescue". Jan 6 family decided to stop care and passed away the same evening

CEC Notes: Anoxic Brain Injury. The investigator reported an adverse event termed anoxic brain injury with an onset date of 28-Dec-2018. Adjudicated outcome: Event name: Stroke- Ischemic stroke, Global stroke (VARC); Overt CNS Injury- Symptomatic Hypoxic-Ischemic Injury; Acute Stroke Severity- Severe neurological dysfunction (NeuroARC)

CEC Comment: Unable to determine stroke disability or stroke recovery as the subject expired within less than 30 days due to multiple causes. Note: The adjudicated date of event was likely >24 hours but <48 hours post-procedure and prior to discharge

Adjudicated Time to Event: ≤24 hours post-procedure, prior to discharge

Other Adjudicated Outcome: Acute Kidney Injury, Stage 3 Event Date: 29-Dec-2018

Other Adjudicated Outcome: Death, Cardiac Event Date: 06-Jan-2019 CEC **Comment:** Cardiac death Note: This event occurred >72 hours post-procedure and prior to discharge **Adjudicated Time to Event:** >72 hours post-procedure, prior to discharge

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Stroke 5

Stroke Class: Non-disabling **Event Date:** 28-Oct-2018

Type: Type 1a Ischemic Stroke

Clinical Notes: Index AF, chronic kidney disease, IDDM. TAVR Oct 25. Discharged stable Oct 26. 2 days later patient felt fogginess, aphasia, memory impairment. Blood sugar levels were in the 400s (symptoms patient has had also before when patient had forgotten to take insulin). Day 5 at study mandated examination symptoms had resolved and NIHSS was 0 and mRS also 0

CEC Notes: Adjudicated outcome: Event name: Stroke- Ischemic Stroke, Focal Stroke, Non-disabling Stroke (VARC); Overt CNS Injury- Ischemic Stroke; Acute Stroke Severity- Mild Neurological Dysfunction; Stroke Disability- Non-disabling; Stroke Recovery- Complete Recovery

CEC Comment: Subject has a history of atrial fibrillation but was reported to be in sinus rhythm

Post-hoc Neurologist Assessment: assuming neuroimaging was negative for acute ischemic events and therefore his transient symptoms were due to hyperglycemia

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Stroke 6

Stroke Class: Disabling Event Date: 07 July 2018

Type: Type 1a Ischemic Stroke

Clinical Notes: Prior CVA with residual hemiparesis, seizer disorder. NIHSS 0 and mRS 1 (no significant disability despite symptoms). TAVR July 5. July 7 (day 2 post op) NIHSS (due to inattention and extinction) from 0 at index to 1. MRS 1 (in spite of symptoms no significant issue with walking noted). Discharge July 13 with no focal neurological symptoms. At 30 days slight disability when walking (able to walk himself) but mRS was reported now 2 and NIHSS back to 0.

CEC Notes: NIHSS worsening from Baseline. Event name: Stroke- Ischemic, Focal, Disabling (VARC), ≤72 hours post-procedure, prior to discharge; Overt CNS Injury- Ischemic Stroke; Acute Stroke Severity- Mild neurologic dysfunction; Stroke Disability- Disabling stroke; Stroke Recovery- Incomplete recovery (NeuroARC); ≤72 hours post-procedure, prior to discharge

Other: Surgical Closure **Event Name:** Major Vascular Complication, TAVI access site-related

Post-hoc Neurologist Assessment: review of neuroimaging could help in this case. I am assuming the NIHSS was done correctly and the 1 point for inattention/ neglect was unilateral / which side? The narrative doesn't clarify. If he has a stroke on neuroimaging that could explain this finding this would reinforce adjudication of stroke. If inattention / neglect is not focal/unilateral and the neuroimaging is negative this could be changed to no stroke. Also, duration of the deficit is not mentioned on the narrative. I am assuming that it lasted >24 hours

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Stroke 7

Stroke Class: Non-disabling Event Date: 29-Jul-2017

Type: Type 1a Ischemic Stroke

Clinical Notes: Prior paroxysmal AF. Index NIHSS 0 and mRS 1 (no significant disability despite symptoms). TAVR June 28. Same day complete heart block leading to temp pace maker. Day 2 post op NIHSS 1 mRS 1 due to drift in right upper extremity. MRI was not done. Discharged July 3rd. At 30 day follow-up NIHSS was 0 and mRS 1 (as pre TAVR). CEC adjudicated non-disabling stroke, predischarge.

CEC Notes: Event name: Covert CNS Injury- Covert CNS infarction; Acute Stroke Severity- Mild neurologic dysfunction (NeuroARC). Adjudication category: Category 2

Post-hoc Neurologist Assessment: assuming neuroimaging did not show a hemorrhagic lesion

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Stroke 8

Stroke Class: Non-disabling Event Date: 17-Aug-2018

Type: Type 1a Ischemic Stroke

Clinical Notes: Prior PCI and TIA. NIHSS 0 and mRS 0. TAVR Aug 7. UTI Aug 7. Aug 9th MRI and right upper extremity drift, NIHSS from 0 to 1. Sept 11 (day 34) stroke. On CT intracranial and vertebral atherosclerosis. Sep 26 (30 day study follow-up done at 50 days post TAVR) NIHSS 2 due to stroke on the 11th (lower extremity weakness). Oct 29 ER due to right TIA (45 min)

CEC Notes: Adjudicated outcome: Event name: Stroke- Ischemic stroke, Focal stroke, Non-disabling stroke (VARC); Overt CNS Injury- Ischemic stroke; Acute Stroke Severity- Moderate neurological dysfunction; Stroke Disability- Non-disabling stroke; Stroke Recovery- Incomplete recovery

CEC Comment: Note: Prior date of adjudication would be post-procedure day 1 and therefore <48 hours post-procedure and prior to discharge from the TAVI hospitalization

Adjudicated Time to Event: ≤72 hours post-procedure, prior to discharge

Post-hoc Neurologist Assessment: [1] Patient had 3 events. Of note there were some inconsistencies in the documentation. At times patient is reported to have nihss of 2 and mRS of 0, this is impossible as at a minimum patient would be a mRS of 1 with new neurologic deficits. [2] assuming neuroimaging was performed and that it was negative for hemorrhage[3] assuming neuroimaging was performed after the first event of right arm weakness

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Stroke 9

Stroke Class: Non-disabling Event Date: 17-Aug-2018

Type: Type 1a Ischemic Stroke

Clinical Notes: Prior atherosclerosis everywhere. NIHSS and mRS 0. TAVR Aug 16th, stroke Aug 17th (left side hemiparesis). Aug 22 discharged to rehab center, 48 post TAVR (30 day follow-up) NIHSS/MRs 1/1, Nov 2nd (90 day follow-up) NIHSS and mRS back to 0

CEC Notes: Adjudicated outcome: Event name: Stroke- Ischemic stroke, Focal stroke, Non-disabling stroke (VARC); Overt CNS Injury- Ischemic stroke; Acute Stroke Severity- Moderate neurological dysfunction; Stroke Disability- Non-disabling stroke; Stroke Recovery- Incomplete recovery

CEC Comment: Note: Prior date of adjudication would be post-procedure day 1 and therefore <48 hours post-procedure and prior to discharge from the TAVI hospitalization

Adjudicated Time to Event: ≤72 hours post-procedure, prior to discharge

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Stroke 10

Stroke Class: Disabling Event date: 08-Sep-2018

Type: Type 1a Ischemic Stroke

Clinical Notes: Pre NYHA IV, sever LVDD. NIHSS 0 and mRS 0. TAVR Sept 4, surgeon cut down on the 4th, NIHSS worsening sept 8 (NIHSS 4 and mRS 3, left side weakness), rehab sept 20, fem abscess and cellulitis, TIA Oct 8th, Watchman, 30 day follow-up (at 64 days) NIHSS worsening 5 and mRS 3

CEC Notes: Adjudicated outcome: Event name: Stroke, Ischemic stroke, Disabling stroke, Focal stroke (VARC); Overt CNS Injury- Ischemic stroke; Acute Stroke Severity- Mild neurological dysfunction; Stroke Disability- Disabling stroke; Stroke Recovery- Incomplete recovery (NeuroARC)

CEC Comment: Note: The adjudicated date of event places this event >72 hours post-procedure but prior to discharge from the TAVI hospitalization

Adjudicated Time to Event: >72 hours post-procedure, prior to discharge

Other Adjudicated Outcome: Event name: Stroke, Ischemic stroke, Disabling stroke, Focal stroke (VARC); Overt CNS Injury- Ischemic stroke; Acute Stroke Severity- Mild neurological dysfunction; Stroke Disability- Disabling stroke; Stroke Recovery- Incomplete recovery (NeuroARC) Event Date: Event date: 07-Nov-2018. Adjudicated Time to Event: >72 hours post-procedure, post discharge

Other Adjudicated Outcome: Transient Ischemic Attack (VARC); Neurologic Dysfunction without CNS Injury- Transient Ischemic Attack (NeuroARC), Event Date: 08-Oct-2018

Post-hoc Neurologist Assessment: [1] however no neuroimaging was provided for this event. I am assuming it was performed and that it was negative for hemorrhage

Stroke 11 (same patient as Stroke 10)

Stroke Class: Disabling Event Date: see above

Type: Type 1d Stroke not otherwise specified

Clinical Notes: see above

CEC Notes: see above

Stroke 12

Stroke Class: Non-disabling Event Date: 23-Aug-2018

Type: Type 1a Ischemic Stroke

Clinical Notes: AT index NIHSS 0 and mRS 0/. TAVR Aug 21st. Surgical closure of the right groin due to severe calcification and bleeding complication requiring blood transfusion. Hypertensive episode the night of the 21st, extubated on the 22nd feeling good. Study MRI Aug 23rd and NIHSS 1 (left lower extremity drift). Discharged on the 24th, no neurological deficits. Aug 25 ER due to shortness of breath, pulmonary oedema. 30 day follow-up NIHSS and mRS 0/0. Non disabling stroke

CEC Notes: Adjudicated outcome: Event name: Stroke- Ischemic stroke, Focal stroke, Non-disabling stroke (VARC); Overt CNS Injury- Ischemic stroke; Acute Stroke Severity- Mild neurological dysfunction; Stroke Disability- Non-disabling stroke; Stroke Recovery- Complete recovery (NeuroARC)

CEC Comment: ANOTHER Surgical Closure requiring Blood Transfusion (1 unit pRBC)

Adjudicated Time to Event: ≤72 hours post-procedure, prior

Post-hoc Neurologist Assessment: [1] There are some inconsistencies in the documentation. By definition a patient cannot have a new change in the NIHSS with a score of 1 and a mRS of 0, mRS would have to be at least a 1. [2] I have no neuroimaging available but I am assuming it was performed and that it was negative for hemorrhage. Duration of symptoms was not described on the narrative. I am assuming therefore it was >24 hours

---

Stroke 13

Stroke Class: Non-disabling Event Date: 29-Sep-2018

Type: Type 1a Ischemic Stroke

Clinical Notes: Baseline NIHSS 0 and mRS 2 (slight walking disability). TAVR Sept 27 2018. NIHSS 0 to 2 Sept 29 (motor drift left leg). At 30 day follow-up NIHSS 0 and mRS 2

CEC Notes: Adjudicated outcome: Event name: Stroke- Ischemic stroke, Focal stroke, Non-disabling stroke (VARC); Over CNS Injury- Ischemic stroke; Acute Stroke Severity- Mild neurologic dysfunction; Stroke Disability- Non-disabling stroke; Stroke Recovery- Complete recovery (NeuroARC)

CEC Comment: Note: The adjudicated date of event and time of assessment place this event as >48 but <72 hours post-procedure and prior to discharge from the TAVI hospitalization

Adjudicated Time to Event: ≤72 hours post-procedure, prior to discharge

Post-hoc Neurologist Assessment: [1] This adjudication is tricky. The NIHSS does not take into account new or old deficits. The evaluator scores what they see. The baseline was 0 and then she developed a score of 2 lasting >24 hours. Furthermore she later returned to a 0. In the absence of other etiology for her leg weakness in the narrative (such as new radiating back pain, etc.) I have to assume her deficit was due to

a new stroke. [2] neuroimaging results are not provided, but I am assuming it does not show a hemorrhage

---

Stroke 14

Stroke Class: Non-disabling Event Date: 26-Oct-2018

Type: Type 1a Ischemic Stroke

Clinical Notes: TAVR Oct 26. Oct 30 scattered recent infarcts on MRI with visual changes and note of neurologic deficit as sensory loss involving the face >24 hours. NIHSS repeatedly 0 mRS 3-1-0

CEC Notes: Adjudicated outcome: Event name: Stroke, Ischemic stroke, Non-disabling stroke, Focal stroke (VARC); Overt CNS Injury- Ischemic stroke; Acute Stroke Severity- Mild neurological dysfunction; Stroke Disability- Non-disabling stroke; Stroke Recovery- Complete recovery (NeuroARC)

CEC Comment: Note: The adjudicated event date corresponds to the date of the procedure, therefore <24 hours post-procedure and prior to hospital discharge

Adjudicated Time to Event: ≤24 hours post-procedure, prior to discharge

Post-hoc Neurologist Assessment: [1] I do not have access to neuroimaging in her case. I am assuming any neuroimaging that was performed failed to reveal an ischemic event that could worsen vision or produce facial numbness (the side of facial numbness is not described on the narrative)

Stroke 15

Stroke Class: Non-disabling Event Date: 31-Oct-2018

Type: Type 1a Ischemic Stroke

Clinical Notes: Prior CHF, prior PCIs (2112, 16, 18), IDDM, NIHSS/mRS 1/1. TAVR Oct 30. Oct 31 weak right hand grip. Neurology NIHSS/mRS 5/2. Nov 4 complete heart block. 30D follow-up NIHSS/mRS 1/1 and 90D no stroke symptoms

CEC Notes: Adjudicated outcome: Event name: Stroke- Ischemic stroke, Focal stroke, Non-disabling stroke (VARC); Overt CN Injury- Ischemic stroke; Acute Stroke Severity- Mild neurological dysfunction; Stroke Disability- Non-disabling stroke; Stroke Recovery- Incomplete recovery (NeuroARC)

CEC Comment: Note: The adjudicated date of event and time of neurological assessment places this event as >48 but <72 hours post-procedure and likely prior to hospital discharge

Adjudicated Time to Event: ≤72 hours post-procedure, prior to discharge

Post-hoc Neurologist Assessment: [1] I have no access to neuroimaging but I am assuming it was negative for hemorrhage

---

Stroke 16

Stroke Class: Disabling Event Date: 14-Dec-2018

Type: Type 1a Ischemic Stroke

Clinical Notes: Index; parox AF. SSS, prior TIA, chr renal disease, left hip arthroplasty, prior fractured hip and ankle, attention deficit disorder. NIHSS/mRS 0/0. TAVR Dec 11. Discharged Dec 13. Study MRI Dec 13. Dec 18th (day 7 post TAVR) NIHSS/mRS 2/1 (each for mild facial palsy, extinction, inattention). Worsening SSS and permanent pace maker. Jan 15 pericardial effusion post chest pain and pneumonia. 30 D study follow-up Jan 17, NIHSS 1 and mRS 4

CEC Notes: Adjudicated outcome: Event name: Stroke- Ischemic stroke. Focal stroke, Disabling stroke (VARC); Overt CNS Injury- Ischemic stroke; Acute Stroke Severity- Mild neurological dysfunction; Stroke Disability- Disabling stroke; Stroke Recovery- Incomplete recovery

CEC Comment: Note: This imaging study was performed at 09:32 AM (>48 hours but <72 hours post-procedure). The evidence for this event occurred following discharge from the TAVI hospitalization.

Adjudicated Time to Event: ≤72 hours post-procedure, prior to discharge

Post-hoc Neurologist Assessment: [1] There is no 90 day mRS only 30 day mRS provided. [2] I don't have access to neuroimaging results but assume it was negative for hemorrhage. [3] patient has atrial fibrillation, unclear if she was on anticoagulants or what was the anticoagulant strategy following TAVR

Stroke 17

Stroke Class: Disabling Event Date: 11-Jan-2019

Type: Type 1a Ischemic Stroke

Clinical Notes: CAD, R carotid stenosis s/p endarterectomy, ischemic CVA 2013, paroxysmal AF. NIHSS/mRS 1/1 for partial hemianopia (Wrong in the CEC notes 0)/1. TAVR Jan 8. Discharged Jan 9. Jan 11 (>48 but <72 hours) study MRI. Jan 11 NIHSS 4 (1 for mild facial palsy, 2 for visual, and 1 for dysarthria) and mRS 1. 30 D follow-up Feb 14 NIHSS 4/mRS 2 (1 for mild facial palsy, 2 for visual, and 1 for dysarthria) (wrong in the notes 5/3, table says 4/2

CEC Notes: Adjudicated outcome: Event name: Stroke- Ischemic stroke, Focal stroke, Disabling stroke (VARC); Overt CNS Injury- Ischemic stroke; Acute Stroke Severity-

Mild neurological dysfunction; Stroke. Disability: Disabling stroke; Stroke Recovery- Incomplete recovery (NeuroARC)

CEC Comment: Note: Neurological imaging and a neurological assessment were performed >48 but <72 hours post-procedure and subsequent to hospital discharge

Adjudicated Time to Event: ≤72 hours post-procedure, prior to discharge

Post hoc Neurologist Assessment: [1] There is no 90 day mRs only 30 day mRS. Also, it is unclear when the patient's stroke symptoms started, it only mentions when the neurologist assessment was made. [2] I don't have neuroimaging but assume it was negative for hemorrhage. [3] not directly. Unclear what the post TAVR anticoagulation strategy was in this patient with AF and on Xarelto before surgery

---

Stroke 18

Stroke Class: Non-disabling Event Date: 31-Jan-2019

Type: Type 1a Ischemic Stroke

Clinical Notes: Index NIHSS/mRS 1/0 (facial paralysis). TAVR Jan 29. Right FA "closure device vessel pinch" leading to 90% stenosis and PCI. Groin hematoma and reduced Hb. Jan 31 NIHSS/mRS 4/2 (2 points for LOC questions, 1 point for visual [partial hemianopia] and 1 point for facial paralysis noted as old) and a mRS score of 2. 30 D follow-up Feb 21st 2/1

CEC Notes: Adjudicated outcome: Event name: Stroke- Ischemic stroke, Focal stroke, Non-disabling stroke (VARC); Overt CNS Injury- Ischemic stroke; Acute Stroke Severity- Mild neurological dysfunction; Stroke Disability- Non-disabling stroke; Stroke Recovery- Incomplete recovery (NeuroARC)

CEC Comment: Note: Neurological imaging and neurological assessment occurred <48 hours post-procedure and prior to hospital discharge

Adjudicated Time to Event: ≤48 hours post-procedure, ≤72 hours post-procedure and prior to discharge

Other Adjudicated Outcome: Minor Vascular Complication, TAVI access site-related Event Date: 29-Jan-2019 CEC Comment: Right femoral artery balloon dilatation due to stenosis following vessel closure

Other Adjudicated Outcome: Major Bleeding Event Date: 29-Jan-2019

Post-hoc Neurologist Assessment: [1] I am assuming neuroimaging was obtained and that it was negative for hemorrhage

---

Stroke 19

Stroke Class: Disabling Event date: 06-Feb-2019

Type: Type 1a Ischemic Stroke

Clinical Notes: Index chr AF, NIHSS/mRS 0/2. TAVR Feb 1st. Immediately post TAVR right groin bleed, manual compressions. Same evening after toilet visit left groin bleed, man compression. Feb 2 US showed left common artery pseudoaneurysm, thrombin injection. Feb 4 Hemoglobin from 10 to 4.9 g/dL, MRI with multiple lesions and NIHSS/mRS 1 (consciousness questions)/4 l(cranial nerves, arm and leg) on right side. Discharged Feb 5. Back to ER Feb 6 due to severe clinical stroke. CT evolving infarction on occipital lobe, considered fatal. Feb 7th new MRI with evolving situation. Death Feb 10th

CEC Notes: Adjudicated outcome: Event name: Stroke- Ischemic, Focal stroke, Disabling stroke (VARC); Overt CNS Injury- Ischemic stroke; Acute Stroke Severity- Severe neurologic dysfunction; Stroke Disability- Fatal stroke; Stroke Recovery- Incomplete recovery (NeuroARC)

CEC Comment: NIHSS not available from the time of this event but assessed as ≥15 by symptom presentation review. Note: Timing of this event is >72 hours post-procedure and following the date of hospital

Other Adjudicated Outcome: Death, cardiac Event Date: 10-Feb-2019 Note: Timing of this event is 9 days post-procedure and following discharge from the TAVI hospitalization Adjudicated Time to Event: >72 hours post-procedure, post discharge

Stroke 20 (same patient as Stroke 19)

Stroke Class: Non-disabling Event Date: 04-Feb-2019

Type: Type 1a Ischemic Stroke

Clinical Notes: see above

CEC Notes: Event name: Stroke- Ischemic, Focal, Non-disabling (VARC); Overt CNS Injury- Ischemic stroke; Acute stroke Severity- Mild neurological dysfunction; Stroke Disability- Non-disabling stroke (NeuroARC)

CEC Comment: CEC cannot assess stroke recovery as the subject suffered a second stroke two days later. Neurological Event

Adjudicated Outcome: Event name: Stroke- Ischemic, Focal stroke, Non-disabling (VARC); Overt CNS Injury- Ischemic stroke; Acute Stroke Severity- Mild neurologic dysfunction; Stroke Disability- Non-disabling stroke (NeuroARC) CEC Comment: CEC cannot assess stroke recovery as the subject suffered a second stroke two days later. Note: The timing of the neurological imaging and neurological assessment were both >72 hours post-procedure and prior to hospital discharge. Adjudicated Time to Event: >72 hours post-procedure, prior to discharge.

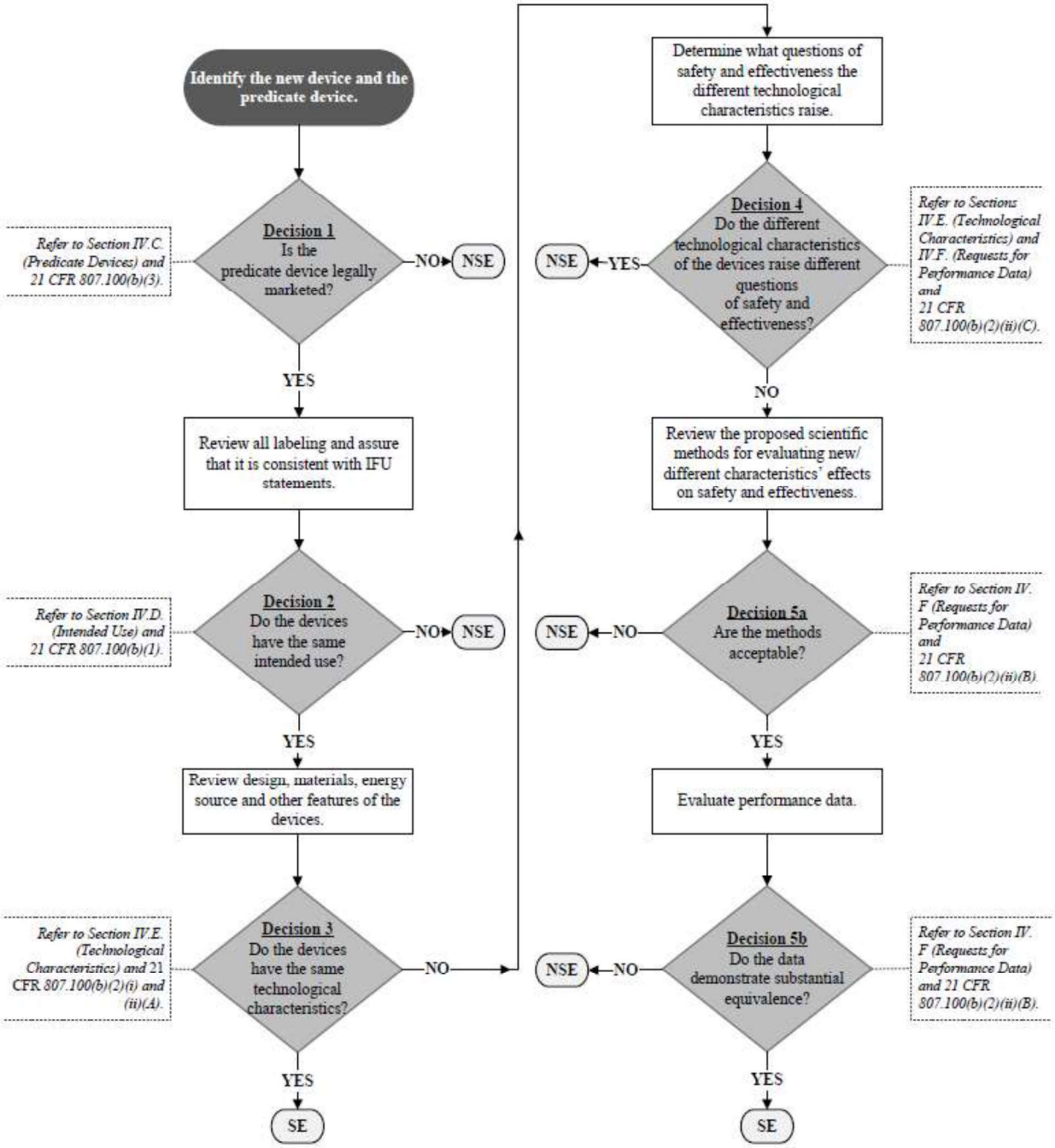
Other Adjudicated Outcome: Major Bleeding Event date: 01-Feb-2019 CEC Comment: Subject experienced significant bleeding at the right groin access site (TAVI)

and smaller bleeding at the left groin access site (TriGUARD). Adjudicated Outcome: Event name: Minor Vascular Complication, TriGUARD access site-related Event date: 02-Feb-2019 CEC Comment: LCFA pseudoaneurysm

Post-hoc Neurologist Assessment: [1] not directly. But it might have been related to being off anticoagulation in this patient with AF (if this was the case; I have no access to the medication list during and after admission)

12.7 FDA Substantial Equivalence Decision-Making Flowchart

Figure 22: SE Decision-Making Flowchart from FDA Guidance



SE="Substantially Equivalent" NSE="Not Substantially Equivalent" IFU="Indications For Use"
Source: The 510(k) Program: Evaluating Substantial Equivalence in Premarket Notifications [510(k)], FDA Guidance for Industry (FDA, 2014)

12.8 Post-Market Surveillance Data Collection Form

TriGUARD 3™ Post-Market Surveillance Data Collection Form	Patient Identifier (Do not include PHI)			

Basic Demographics and Medical History		
1. Sex: ☐ Male ☐ Female		
2. History of the following (check all that apply): ☐Stroke/TIA ☐Diabetes ☐Hypertension ☐Atrial Fibrillation ☐ Other notable history, describe:		
3. Any relevant medical history, current medical condition, or anatomy for which the TriGUARD 3 could not be used in accordance with the IFU? ☐No ☐Yes, describe:		
Procedural Information and Device Performance (NOTE: If available, please upload de-identified angio images to the eCRF supporting the questions below)		
4. Valve Type:	5. Valve Size:	6. Valve in Valve: ☐Yes ☐No
7. Aortic Arch Type (circle): Type 1 Type 2 Type 3 Unk	8. Arch Tortuosity: (circle): None Mild Moderate Severe	9. Femoral Tortuosity (circle): None Mild Moderate Severe
10. Pre-dilatation ☐Yes ☐No	11. Post-dilatation ☐Yes ☐No	12. Bicuspid ☐Yes ☐No
13. During device preparation, was the hypo tube oriented beneath the deflection filter as it entered the sheath crimping mechanism? ☐Yes ☐No ☐Not assessed		
14. Was anatomy mapping performed? ☐Yes ☐No Coverage: 15. Pre-TAVI Positioning: Full coverage ☐Yes ☐No ☐Not assessed		16: TAVI delivery system Crossing: Full coverage ☐Yes ☐No ☐Not assessed
Safety Information		
17. Was discharge data available for this patient to adequately assess TriGUARD *3* safety? ☐Yes ☐No		
18. Did the patient have any of the following (check all that apply, refer to definitions in the Data Collection Plan): ☐ Death: ☐ Cardiovascular ☐ Non-Cardiovascular ☐ Stroke (meets VARC-2 definitions, select classifications below) ☐ Disabling ☐ Non-Disabling ☐ Ischemic ☐ Hemorrhagic ☐ Undetermined ☐ Bleeding Event (TG3 or TG3 access site related): ☐ Life Threatening or Disabling Bleed (BARC) ☐ Major Bleeding (VARC-2 defined) ☐ Major Vascular Complication (VARC-2 defined, TG3 or TG3 access site related) Was this related to a closure device failure? ☐ Yes ☐ No ☐ Stage 3 Acute Kidney Injury		
If Yes to any of the above, please detail with supporting information below or attached to the eCRF (i.e. stroke confirmed with MRI, other neurological assessment such as mRS increase >2):		

I hereby attest that this information is true, accurate and complete to the best of my knowledge.

_____ _____

Institution Representative Date

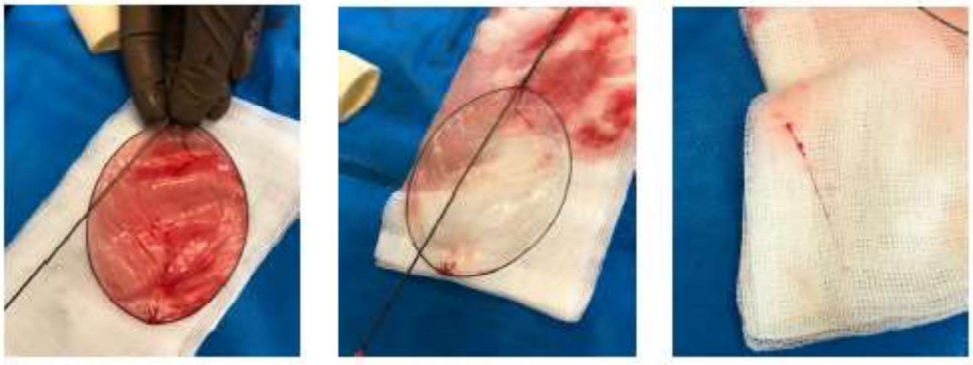
12.9 Evidence of TriGUARD 3 Debris Capture

PHOTOGRAPHS OF DEBRIS FROM COMMERCIAL CLINICAL CASES CONDUCTED IN EUROPEAN SITES SINCE CE MARK APPROVAL OF TRIGUARD 3™ CEREBERAL EMBOLIC PROTECTION DEVICE

Hospital: Helios Herzzentrum- Universitätsklinik
Location: Leipzig

LEI-002, 7. OCT 2020, Evolut R - 29

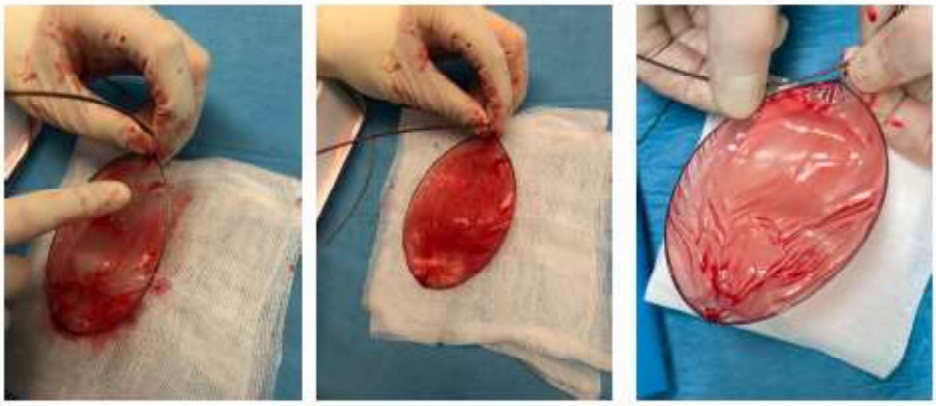
LEI-005, 8. OCT 2020, S3 - 2



1

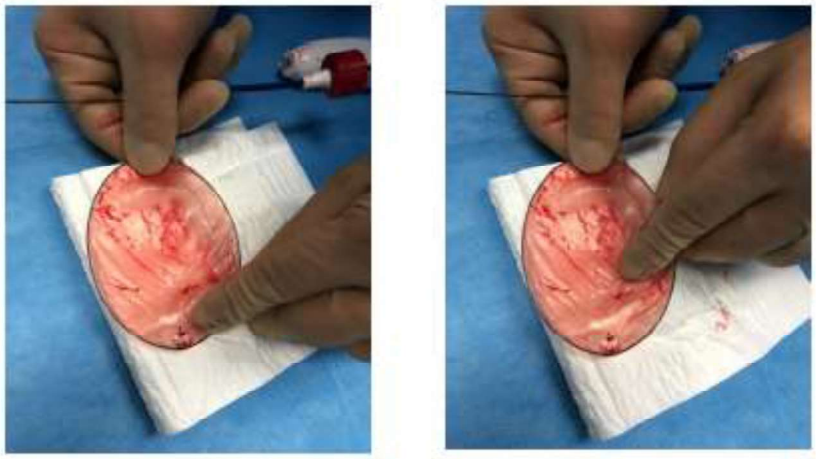
SEG-002, 10. NOV 2020, Evolute R - 29

Hospital: Segeberger Kliniken
Location: Bad Segeberg



Hospital: Westdeutsches Herz- und Gefäßzentrum Essen - Universitätsklinkum Essen
Location: Essen

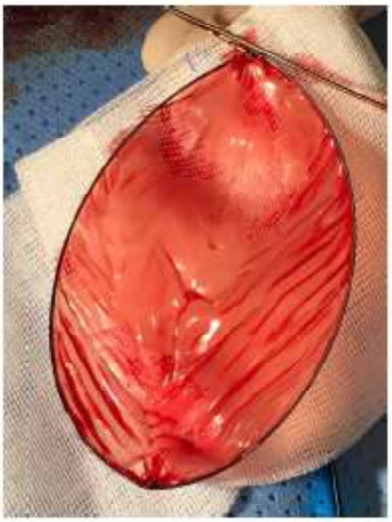
ESS-003, 09. NOV 2020; S3 - 26

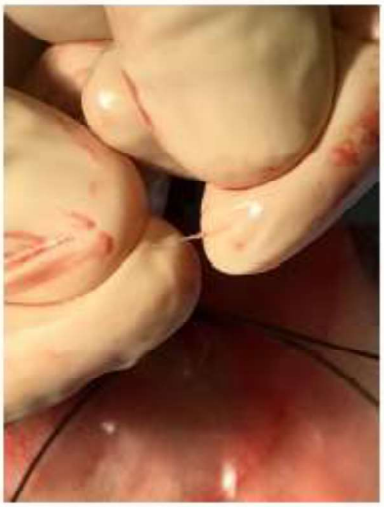


2

Hospital: Universitätsmedizin der Johannes Gutenberg-Universität Mainz
Location: Mainz

UMZ-001, NOV 12, 2020; S3 Ultra – 26

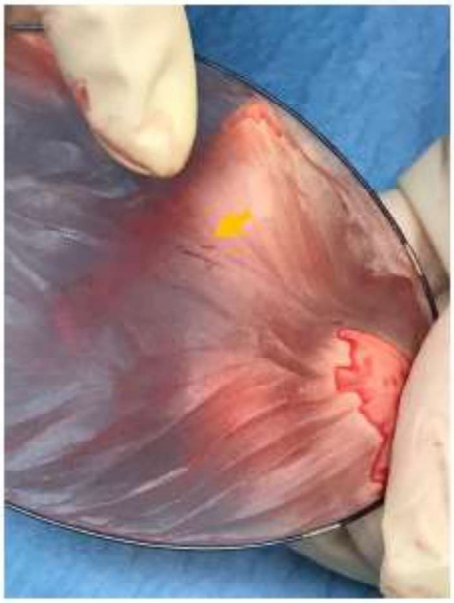


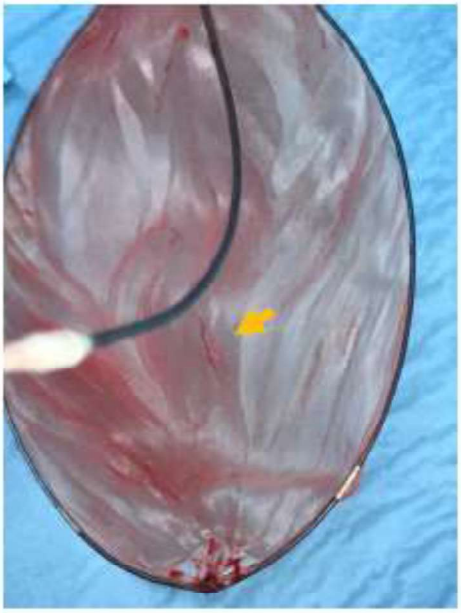


3

Hospital: Universitätsklinikum Münster - Klinik für Kardiologie
Location: Münster

UKM-002 Nov. 9, 2020, S3-26





4

Hospital: Amphia Breda
Location: Molengracht 21

Myval, Sept. 3, 2020

5

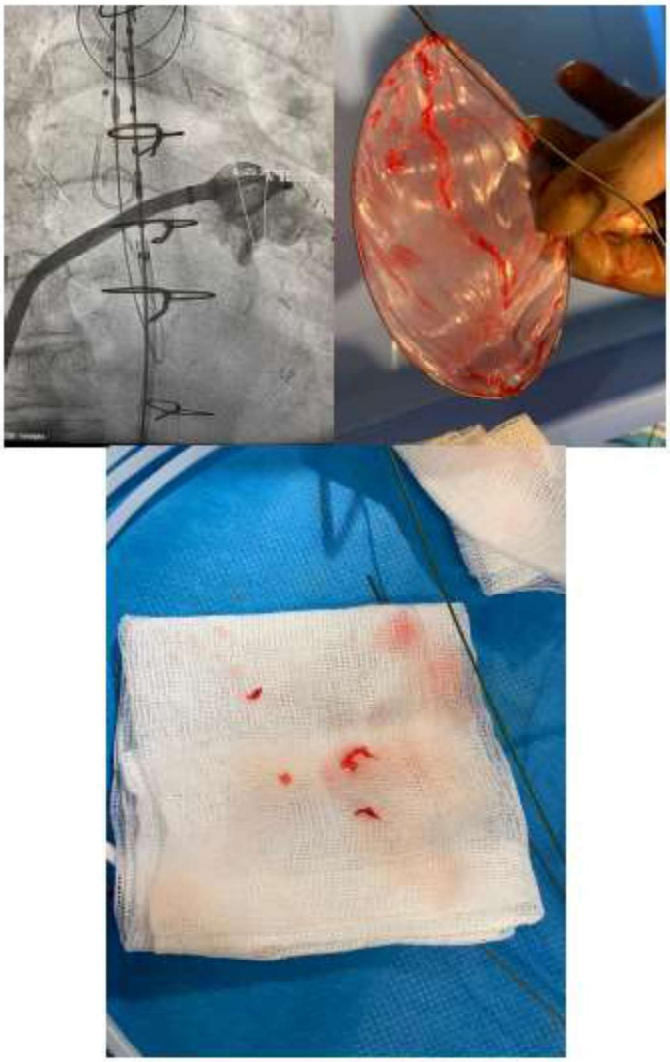
Hospital: Bresica Hospital
Location: Piazzael Spedali Civil 1

Evolut case, Oct. 23, 2020

6

Hospital: University Dijon Hospital
Location: Dijon

LAA Watchman case, Sept. 4, 2020



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