A Randomized Evaluation oF the TriGuard* HDH Embolic Deflection Device to Reduce the Impact of Cerebral Embolic LEsions after TransCatheter Aortic Valve ImplanTation

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To assess the safety and efficacy of the TriGuard HDH embolic deflection device in patients undergoing transcatheter aortic valve implantation (TAVI), in comparison with an active control group of patients undergoing unprotected TAVI.

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Cardiac valve disorders
Study type	Interventional

Summary

ID

NL-OMON46026

Source
ToetsingOnline

Brief title
The REFLECT Trial

Condition

- Cardiac valve disorders

Synonym
brain infarction, stroke

Research involving
Human

Sponsors and support

Primary sponsor: Keystone Heart Ltd.
Source(s) of monetary or material Support: Keystone Heart

Intervention

Keyword: Aortic valve replacement, CVA, Embolic filter, TIA

Outcome measures

Primary outcome

Combined safety endpoint (VARC 2 defined) at 30 days, defined as a composite of death, stroke, life-threatening or disabling bleeding, acute kidney injury (stage 2 or 3), coronary artery obstruction requiring intervention, major vascular complication, and valve-related dysfunction requiring repeat procedure

Hierarchical composite efficacy endpoint, determined by pair-wise comparisons among all subjects according to the following pre-specified hierarchy of adverse outcomes:

*All-cause mortality or any stroke (disabling or non-disabling)[evaluated at 30 days]

*NIHSS worsening (increase from baseline) [evaluated at post-procedure/pre-discharge] or Montreal Cognitive Assessmentworsening (decrease of 3 or more points from baseline) [evaluated at30 days]

*Total volume of cerebral ischemic lesions detected by diffusion-weighted magnetic resonance imaging (DW-MRI) 2 to 5 days post-procedure

In brief, each subject in the trial will be compared with every other subject

based on the above hierarchy according to the Finkelstein-Schoenfeld method.1

For example, if Subject A dies or has stroke and Subject B survives free of stroke to 30 days, Subject B wins (score +1) and Subject A loses (score -1). If both subjects die or have a stroke, it is equilibrium (score 0). If both subjects survive free of stroke to 30 days, the comparison moves to the next tier of the hierarchy.

After all between-subject comparisons have been performed, scores are summed to obtain a cumulative score for each subject, and outcomes between treatment groups are then compared.

Secondary outcome

SECONDARY SAFETY ENDPOINTS

The following safety endpoints will be evaluated in-hospital and at 30 and 90 days, unless otherwise specified. Overall event rates will be reported in both treatment arms. In the Intervention and Roll-In groups, all safety endpoints will be adjudicated for their relationship to the investigational device or the investigational procedure by an independent Clinical Events Committee.

In-hospital procedural safety, defined as the composite of the following Major Adverse Cardiovascular and Cerebrovascular Events (MACCE):

*All-cause mortality

*All stroke (disabling and non-disabling)

*Life threatening (or disabling) bleeding

*Acute kidney injury * Stage 2 or 3 (including renal replacementtherapy)

*Major vascular complications

TAVI device success (VARC), evaluated in-hospital, defined as:

*Absence of procedural mortality AND

*Correct positioning of a single prosthetic heart valve into the

properanatomical location AND

*Intended performance of the prosthetic heart valve (no prosthesis-patient

mismatch (VARC-defined) and mean aortic valve gradient<20 mm Hg or peak

velocity <3 m/s, AND no moderate or severeprosthetic valve regurgitation

(VARC-defined) (site-reported)

General Safety, defined as the composite of the following adverse events:

*All-cause mortality

*All stroke (disabling and non-disabling)

*Acute kidney injury * Stage 3 (including renal replacement therapy)

Mortality:

*All-cause mortality

oCardiovascular mortality

*Neurologic event related mortality

oNon-cardiovascular mortality

Myocardial infarction:

*Peri-procedural MI (*72 hours after the index procedure)

*Spontaneous MI (>72 hours after the index procedure)

Neurological Events (component and composite):

*Stroke (VARC-2 defined)

oIschemic stroke

oHemorrhagic stroke

oUndetermined

*Disabling Stroke (VARC-2 defined)

*Non-disabling stroke (VARC-2 defined)

*Transient ischemic attack (TIA) (VARC-2 defined)

*Overt CNS Injury (NeuroARC defined)

*Covert CNS Injury (NeuroARC defined)

*Neurological dysfunction without CNS injury (NeuroARC defined)

*CNS infarction (NeuroARC defined composite)

*CNS hemorrhage (NeuroARC defined composite)

Bleeding Complications:

*Life-threatening or disabling bleeding

*Major bleeding

*Minor bleeding

Acute Kidney Injury (AKIN Classification):

*Stage 1

*Stage 2

*Stage 3

Vascular Complications:

*Major vascular complications

*Minor vascular complications

*Percutaneous closure device failure

SECONDARY EFFICACY ENDPOINTS

Imaging Efficacy Endpoints

*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 volumedetected by DW-MRI, evaluated 2 to 5 days post-procedure

*Single cerebral ischemic lesion volume (lesion-level analysis)detected by DW-MRI, evaluated 2 to 5 days post-procedure

*Total volume of cerebral ischemic lesions detected by DW-MRI,evaluated 2 to 5 days post-procedure

Neurologic and Cognitive Efficacy Endpoints

*Postoperative cognitive function (overall and by domain) asassessed by a neuropsychological test battery [evaluated in-hospital]

*Change in cognitive function (overall and by domain) frombaseline to post-procedure and 30- and 90-day follow-ups, asassessed by a neuropsychological test battery [evaluated in-hospital and at 30 and 90 days]. The relationship of cognitivefunction to DW-MRI findings will also be evaluated.

*Montreal Cognitive Assessment (MoCA) worsening, definedas a MoCA score decrease of 3 or more points from baseline[evaluated at post-procedure/pre-discharge and at 30 and 90days]

*NIHSS worsening, defined as an NIHSS score increase frombaseline [evaluated at post-procedure/pre-discharge as ahypothesis-driven endpoint, and at 30 and 90 days as anexploratory endpoint]

*New neurologic impairment, defined as NIHSS worsening frombaseline accompanied by the presence of cerebral ischemiclesions [evaluated at post-procedure/pre-discharge]

SECONDARY PERFORMANCE ENDPOINTS

The following performance endpoints will be evaluated post-procedure in the Intervention and Roll-In groups:

*Successful device deployment, defined as ability to access theaortic arch with the TriGuard HDH delivery catheter and deploy thedevice from the delivery catheter into the aortic arch

*Device positioning, defined as ability to position the TriGuardHDH device in the aortic arch to cover all major cerebral arteries,with proper positioning maintained (verified by angiography) untilthe following time points:

oFinal deployment of the first prosthetic valve

oFinal procedure (after any additional post-dilatation oradditional valve implantations have been completed, andthe TAVR delivery system has been removed)

Extent of cerebral artery coverage will be reported as:

oComplete (coverage of all 3 cerebral artery branches)

oPartial (coverage of 1-2 cerebral artery branches)

oNone

Note: Maintenance of device positioning to each time point and extent of cerebral artery coverage will be evaluated by the Angiographic Core Laboratory.

Device positioning with complete cerebral coverage until final deployment of the first prosthetic valve will be considered the primary definition of device positioning for the evaluation of technical success.

*Device interference, defined as interaction of the TriGuard HDHdevice with the TAVI system leading to:

oInability to advance or manipulate the TAVI delivery systemor valve

prosthesis, OR

oInability to deploy the TAVI valve prosthesis, OR

oInability to retrieve the valve prosthesis or delivery system

*Successful device retrieval, defined as ability to retrieve theTriGuard HDH

device and remove the intact TriGuard HDHdelivery system

*Technical success, defined as successful device deployment,device positioning,

and successful device retrieval in the absenceof device interference

*Procedure success, defined as technical success in the absenceof any

investigational device-related or investigational procedure-related in-hospital

procedural safety events

Study description

Background summary

The Keystone Heart TriGuard HDH is an aortic embolism deflection device intended to reduce the amount of embolic material that may enter the carotid, subclavian, and vertebral arteries during transcatheter heart valve implantation.
The TriGuard HDH consists of a temporary, sterile, single use, biocompatible filter, introduced transfemorally through a 9F sheath to the aortic arch. Under fluoroscopic guidance, the device is positioned in the aortic arch to cover all 3 major cerebral arteries (innominate, left carotid, and subclavian arteries), and is held in position by an atraumatic stabilizer in the innominate artery. Once the device is in position, emboli and particulate matter are diverted away from the cerebral circulation and downstream to the descending aorta, where they are either harmless or can be treated effectively.
The TriGuard HDH has received CE Mark and is commercially available in Europe and Israel. Use of the device at European and Israeli sites in the REFLECT study is in accordance with its market approved use.
In the United States, the TriGuard HDH is for investigational use only. The device has received IDE approval for use in the REFLECT study.

Study objective

To assess the safety and efficacy of the TriGuard HDH embolic deflection device in patients undergoing transcatheter aortic valve implantation (TAVI), in comparison with an active control group of patients undergoing unprotected TAVI.

Study design

This prospective, single-blind, randomized, multicenter safety and efficacy trial will enroll up to 285 evaluable subjects and up to 90 roll-in subjects at up to 30 total investigational sites in the United States, Europe, and Israel, including up to 20 sites in the United States. A minimum of 50% of subjects will be enrolled at US sites, and no single site will be permitted to enroll more than 20% of all subjects (maximum 57 evaluable subjects per site). Subjects with indications for TAVI and who meet study eligibility criteria will be randomized 2:1 (stratified by study site) to one of two treatment arms:
*Intervention * TAVI with the TriGuard HDH embolic deflection device
*Control * standard unprotected TAVI
At sites where the investigator does not have prior experience with the TriGuard device (minimum of 2 prior cases), up to 3 roll-in subjects will be enrolled. Roll-in subjects will not be randomized, but will undergo TAVI with the TriGuard HDH device. These cases will be proctored by a Sponsor representative. Investigational sites with *2 prior TriGuard cases may enroll 1 roll-in subject at the discretion of the site principal investigator.
All subjects will be followed clinically in-hospital and at 30 and 90 days, undergo diffusion-weighted MR imaging 2 to 5 days post-procedure, and undergo neurologic and neuropsychological testing pre-procedure, post-procedure, and at 30 and 90 days.
An interim analysis will be performed after 90 subjects total (approximately 60 Intervention group subjects and 30 Control group subjects) who meet the efficacy Intention to Treat (eITT) population definition have completed the 30-day follow-up visit.

Intervention

TAVI will be performed according to standard institutional practice under local or general anesthesia and via the transfemoral or transapical approach at the discretion of the investigator.
In subjects in the Intervention or Roll-in Groups, the TriGuard HDH device will be advanced and deployed across the aortic arch to cover the ostia of the 3 major vessel takeoffs (innominate, left carotid and subclavian arteries) at the initiation of the TAVI procedure and withdrawn at the completion of the procedure. .
Device coverage and positioning must be verified by angiography (a steep left anterior oblique [LAO] view is recommended), with particular attention paid to
1.) Device coverage after initial deployment,
2.) Device positioning after final deployment of the first prosthetic valve,

and
3.) Device positioning after the procedure is complete (i.e., after any additional post-dilatation or additional valve implantations have been completed, and the TAVR delivery system has been removed).

Study burden and risks

The known risks for TAVI are applicable, besieds the potential of local vessel damage due to Manipulation of the device in the aortic arch and manufacturing Problems of the device which may lead to unforeseen complications. The benefit would be the prevention of cerebral embolisms during the TAVI procedure

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

1. The patient is a male or non-pregnant female *18 years of age
2. The patient meets indications for TAVI
3. The patient is willing to comply with protocol-specified follow-up evaluations
4. The patient 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).

Exclusion criteria

1. Patients undergoing TAVI via the trans-axillary, trans-subclavian, or trans-aortic route
2. Patients undergoing TAVI via the transapical approach due to friable or mobile atherosclerotic plaque in the aortic arch
3. Patients with a previously implanted prosthetic aortic valve (i.e., planned valve-in-valve TAVI)
4. Pregnant or nursing subjects and those who plan pregnancy in the period up to 1 year following index procedure. Female subjects of child-bearing potential must have a negative pregnancy test done within 14 days prior to index procedure per site standard test.
5. Patients with known diagnosis of acute myocardial infarction (AMI) within 72 hours preceding the index procedure (according to definition) or AMI >72 hours preceding the index procedure, in whom CK and CK-MB have not returned to within normal limits at the time of procedure, or patients who are currently experiencing clinical symptoms consistent with new-onset AMI, such as nitrate-unresponsive prolonged chest pain
6. Patients with a history of bleeding diathesis or coagulopathy or patients in whom anti-platelet and/or anticoagulant therapy is contraindicated, patients who will refuse transfusion, or patients with an active peptic ulcer or history of upper gastrointestinal (GI) bleeding within the prior 6 months
7. Patients with known mental or physical illness or known history of substance abuse that may cause non-compliance with the protocol, confound the data interpretation, or is associated with a life expectancy of less than one year
8. Patients with severe allergy or known hypersensitivity or contraindication to aspirin, heparin/bivalirudin, clopidogrel, nitinol, stainless steel alloy, and/or contrast sensitivity that cannot be adequately pre-medicated
9. Patients with a history of a stroke or transient ischemic attack (TIA) within the prior 12 months
10. Patients with renal failure (estimated Glomerular Filtration Rate [eGFR] <30 mL/min, calculated from serum creatinine by the Cockcroft-Gault formula)
11. Patients with hepatic failure (Child-Pugh class C)
12. Patients with hypercoagulable states that cannot be corrected by additional periprocedural heparin
13. Patients presenting with cardiogenic shock at the time of the index procedure
14. Patients with severe peripheral arterial disease that precludes delivery sheath vascular access

15. Patients in whom the aortic arch, innominate artery ostium, or proximal innominate artery is heavily calcified, severely atheromatous, or severely tortuous
16. Patients with an innominate artery ostium diameter <10 mm or >25 mm
17. Patients with a transverse aortic diameter >43 mm
18. Patients with anatomic irregularities of the innominate artery that could prevent positioning of the TriGuard upper stabilizer and compromise stability of the device
19. Patients with any other condition that would prevent adherence to the TriGuard HDH Instructions for Use
20. Patients with contraindication to cerebral MRI
21. Patients who have a planned treatment with any other investigational device or procedure during the study period
22. Patients planned to undergo any other cardiac surgical or interventional procedure (e.g., concurrent coronary revascularization) during the TAVI procedure or within 10 days prior to the TAVI procedure. NOTE: Diagnostic cardiac catheterization is permitted within 10 days prior to the TAVI procedure.

Study design

Design

Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Single blinded (masking used)
Control:	Active
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	13-06-2016
Enrollment:	15
Type:	Actual

Medical products/devices used

Generic name:	TriGuard HDH Embolic Deflection Device
Registration:	Yes - CE intended use

Ethics review

Approved WMO Date:	07-12-2016
Application type:	First submission
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	31-05-2017
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
ClinicalTrials.gov	NCT02536196
CCMO	NL55878.041.16

Study results

Date completed:	11-10-2017
Actual enrolment:	9

Summary results
Trial is onging in other countries