

**Investigation of cerebral damage
using a cerebral protection
device in patients undergoing
transfemoral Aortic Valve
Implantation using the Medtronic
CoreValve System –
The CLaret Embolic protection
ANd TAVI (CLEAN-TAVI) trial**

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1 Investigators

1.1 Principal Investigator

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3 Description of the Research Project

3.1 Subject

Investigation of cerebral damage using a cerebral protection device in patients undergoing transfemoral aortic valve implantation using the Medtronic Core Valve System.

3.2 Study Design

Prospective, randomized, single blind, monocentric trial.

3.3 Acknowledgement of Informed Consent of the Patients

The informed consent is or will be obtained in accordance with the rules of GCP (Good Clinical Practice) and the Declaration of Helsinki. The informed consent is attached. The study is a prospective, randomized, monocentric trial to compare the effects of using a cerebral protection device (Claret Montage™ Dual Filter System) during transfemoral aortic valve implantation (Medtronic CoreValve® System) vs. conservative TAVI treatment of the aortic valve stenosis without using a cerebral protection device.

3.4 Documentation

All data will be collected in a data base. Data acquisition will be prospective. Data analysis will be blinded and performed with a computer. Privacy protection will be achieved anonymizing the data sets. The privacy protection will be warranted by the PI.

3.5 Patient Insurance

The general risk of the procedure is covered by the patient insurance of the hospital. Additional risk and possible harm to the patient which may be caused by the study design will be covered by an additional patient insurance for the trial. The insurance will be:

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A copy of the insurance and the general terms will be available in the study folder. A copy of the general terms and the insurance company will be handed out to the patient during informed consent. A proof of insurance is attached.

3.6 Evidence

3.6.1 Aortic Valve Stenosis

The aging society and the increasing numbers of patients with severe aortic stenosis represents a huge challenge for our health system. The development of increasing systolic gradients between the left ventricle and the ascending aorta is mainly caused by the senile aortic stenosis which is predominately a disease of the elderly. Looking at the current guidelines: treatment by surgical aortic valve replacement should be considered when patients develop symptoms.¹⁻² Surprisingly a large number of patients would not be referred to conventional surgery due to their age and additional risk factors.³⁻⁵

3.6.2 Percutaneous Aortic Valve Implantation

The transcatheter aortic valve implantation (TAVI) utilizing a transapical or transarterial access (direct aortic, transfemoral, transsubclavian) represents an alternative to conventional surgical aortic valve replacement. Feasibility and safety of several TAVI devices and percutaneous treatment of severe aortic valve stenosis in high-risk patients has been shown in several studies. The Medtronic CoreValve® Revalving System, which will be treatment device for the aortic valve stenosis but not investigational during the current study, and the Edwards SAPIEN XT tissue heart valve (THV) are available in Europe since several years for routine therapy of high-risk patients with severe aortic stenosis. The Accurate Valve (Symmetis Inc.) as well as the JenaValve (Jena Valve) received the CE mark for transapical treatment of patients with severe aortic stenosis.

The Medtronic CoreValve® Revalving System, the JenaValve and the Accurate Valve are composed of a self-expanding nitinol frame which carries the biological heart valve. The prosthesis will be loaded onto a special catheter, advanced to the aortic valve and will be passively expanded until a certain pre-defined configuration is reached when the outer catheter sheath is retracted. The valve material of the EdwardsSAPIEN XT THV consists of a pericardial tissue heart valve with is sewn in a cobalt-chrome-stent. The prosthesis is fixed onto a balloon using a specific crimping device and implanted in aortic position inflating the carrier balloon under rapid ventricular pacing.

Beside the initial feasibility trials more reliable randomized trials are available now. One trial compared the interventional aortic valve replacement with the conservative treatment of aortic stenosis or the conventional surgical aortic valve replacement. The study was conducted in a two armed fashion.^{6,7} Cohort A represented an operable high-risk group of patients with severe aortic stenosis suitable for TAVI or surgical aortic valve replacement. A 1:1 randomization for surgical aortic valve replacement vs. transfemoral access TAVI was performed. Patients with inadequate transfemoral access were randomized between surgical aortic valve replacement and transapical Edwards SAPIEN THV TAVI. A non-inferiority-hypothesis was applied for this Cohort A of the PARTNER trial, postulating that TAVI (transfemoral or transapical) is not inferior to surgical aortic valve replacement in high risk patients with severe aortic stenosis.⁷

Out of the 492 patients with possible transfemoral access, 244 received a transfemoral TAVI treatment and 246 underwent conventional surgical aortic valve replacement; the group with possible transapical access was divided in 104 patients receiving a transapical TAVI and 103 patients for conventional surgical aortic valve replacement. Age of the groups was 83.6 ± 6.8 vs. 84.5 ± 6.4 years, the EuroSCORE $29.3 \pm 16.5\%$ vs. $29.2 \pm 15.6\%$ and the STS Score 11.8 ± 3.3 vs. $11.7 \pm 3.5\%$. The primary endpoint of the study was the one year mortality, which was in Cohort A: 24.2 % in the TAVI (transfemoral and transapical) vs. 26.8 % in the surgery group.⁷ The sub group analysis showed even lower one year mortality in the transfemoral TAVI arm (22.2 %) vs. the conventional surgery arm (26.4 %). The one year mortality was higher in the transapical arm (29.0 %) vs. 25.3 % in the surgical group ($p=n.s.$).⁷

There was an increased number of bleeding complications in the surgery group and an **increased number** of vascular and neurological **complications in the TAVI group**. However there was no significant difference between the TAVI and the surgical group applying the combined endpoint of death of any cause and major stroke (26.5 vs. 28.0 %, $p=n.s.$). Fortunately the rate of implantation of new pacemakers and significant bradycardias was below 4% and comparable in both groups.

In summary: TAVI represents a superior treatment option vs. conservative treatment in patients which are inoperable and not suitable for conventional surgery. TAVI is a non-inferior treatment option in high risk patient with severe aortic stenosis.^{6,7}

3.6.3 Stroke and Detection of Micro Embolizations

Patients receiving transfemoral aortic valve implantation experience in 2.5% (Source Registry 30 day⁸) and up to 6.7 %⁶ any stroke or TIA. Additionally almost all patients (66-86%) have silent ischemic cerebral lesions detected by MRI. The impact of these lesions on cognitive function has not been evaluated yet.⁹⁻¹¹

Data from a trial conducted by Ghanem et al.¹² showed an occurrence of silent cerebral lesions in 73% of the patients whereas the rate of symptomatic cerebral embolizations was only 3.6%. Kahlert et al. found as well an increased number (84%) of silent cerebral ischemic lesions in TAVI patients in 2010¹³. Concerning these "silent" lesions it has to be noted that the impact of these lesions has only be studied by questionnaires and neurological tests which are not meant to investigate the full neurological impact of these microembolic lesions especially possible cognitive

decline. Parts of the assumable silent lesions might be due to insufficient neurological examination of the patients. This problem is gaining especially importance if percutaneous aortic valve implantation is performed more and more in a younger patient population where the cognitive power and capacity if even more important.

3.6.4 Protection Devices

The cerebral protection device (Claret Montage™ Dual Filter System) will be placed in the brachiocephalic artery and the left carotid artery peri-interventionally. It represents the only available protection device which can collect embolic material with filters. Feasibility and safety of the device has been shown by Naber et al in 2012¹⁴.

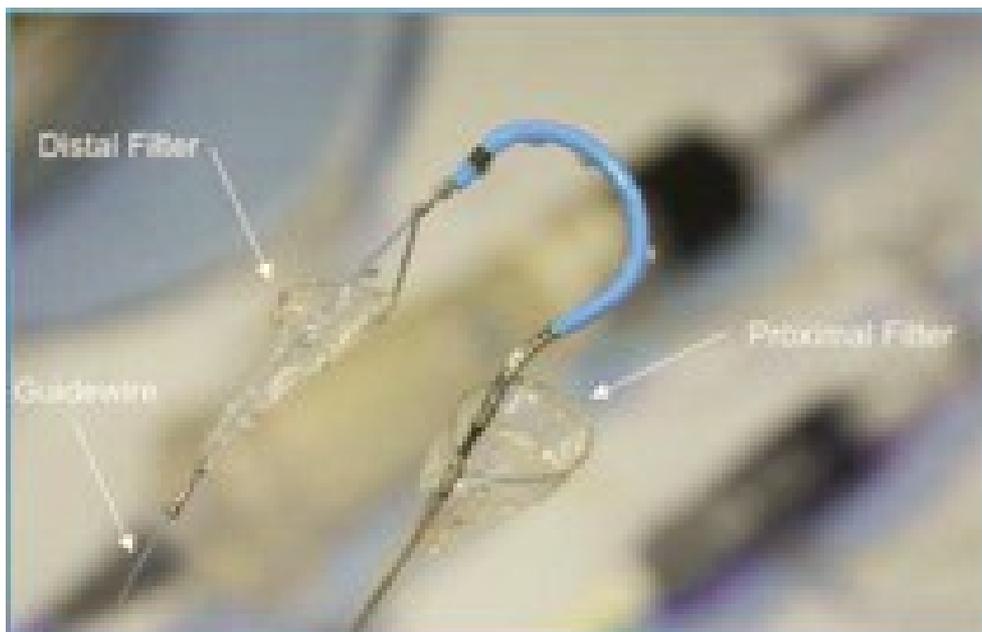


Figure 1 - Claret Montage™ Dual Filter System

3.6.5 Transfemoral Aortic Valve Implantation and Implantation Protection Device Procedure

Preparation, disinfection and covering of the patient is performed in the usual manner as for a conventional aortic valve replacement surgery that emergency thoracotomy and surgical aortic valve replacement are possible in case of rare severe complications. This makes the attendance of a perfusionist and the availability of a heart lung machine obligatory. The procedure is performed under conscious sedation and local anesthesia. Intubation and mechanical ventilation are only necessary in

rare special cases. At first a 0.035In wire is placed in the right femoral vein to be prepared for an emergency connection of the venous cannula of the heart lung machine. Then the right femoral artery is punctured and a closure device which allows closure of the puncture site after the procedure, usually the Prostar XL (Abbott Vascular, Wiesbaden, Germany) is inserted into the artery. This is followed by the insertion of the application sheath for the percutaneous valve over a rigid wire up to the ascending aorta. The right jugular vein is used to insert a venous sheath and for placement of a MRI-compatible pacemaker for the rapid pacing of the right ventricle and as back-up pacemaker in case of high degree AV-blocks during valvuloplasty and valve replacement. Before the Medtronic CoreValve® is implanted the right radial or brachial artery is punctured and the Claret Montage™ Dual Filter system is advanced over a guide wire into the aorta. The filter covering the brachiocephalic artery is opened first and then the wire is advanced to the left carotid artery to open the second filter (attached movie). After these preparations a pigtail catheter is advanced through the femoral artery to the aortic sinus. The aortic valve is passed retrograde and a pre-formed rigid wire is placed in the left ventricle. The balloon valvuloplasty of the valve is performed under rapid ventricular pacing whereas the balloon size should be smaller than the aortic annulus. The Medtronic CoreValve® System is then slowly released retrieving the outer catheter sheath after selection of the right vertical projection of the annulus. This is performed under fluoroscopic guidance and beating heart conditions. Final angiography of the ascending aorta is performed to document the right position of the valve, to identify and quantify possible para-valvular or trans-valvular regurgitation and to semi-quantify coronary perfusion. Post-dilatation of the valve might be necessary in single cases. Peri-interventional embolic material and debris will be collected by the Claret Montage™ Dual Filter system. Angiography of the access route is performed before the femoral puncture site is closed with the closure device since vessel dissections and perforations occur from time to time due to the large sheath size and the generalized arteriosclerosis of these patients. Suitable stents for the treatment of such complications are always available in the surgical hybrid suite and the team is experienced in using them. Uncomplicated transfemoral case are performed within 30min (time of puncture till closure of the access site).

After the Medtronic CoreValve® System has been implanted the Claret Montage™ Dual

Filter system is re-captured in reverse order, whereas the collected debris is removed too. The radial puncture site is closed and a pressure bandage applied. (A movie showing the protection device and placement has been attached to this application)

3.7 Necessity of the Study

Strokes and TIA are representing frequent complications during and after percutaneous aortic valve replacement and are causing higher co-morbidity. Eggebrecht et al.¹⁵ have shown that patients experiencing a stroke during TAVI have a 3.5-fold increased mortality compared to patients not suffering from any neurological complication. A cerebral protection device could decrease the number and burden of peri-interventional embolizations but this has never been shown in a randomized clinical trial. Thus a positive results of the study could lead consequent use of cerebral protection devices and subsequently to a reduction of peri-interventional strokes and TIAs to reduce morbidity of the patients.

3.8 Hypothesis

The number of cerebral lesions in TAVI patients can be reduced by approximately 50% with the peri-interventional use of the Claret Montage™ Dual Filter System.

Please see Appendix A “Statistical analysis plan (SAP)” for detailed information.

4 Aim of the Study

The aim of the study is to investigate if the use of a cerebral protection device (Claret Montage™ Dual Filter System) during implantation of a percutaneous aortic valve prosthesis (Medtronic CoreValve® System) can decrease the rate of cerebral micro-embolizations and subsequently the occurrence of cerebral perfusion deficit. The use of the Claret Montage™ Dual Filter Systems and the Medtronic CoreValve® System is performed only with the indication and line with the CE mark.

4.1 Study Endpoints

Please see Appendix A “Statistical analysis plan (SAP)” for detailed information.

4.1.1 Primary Endpoint

The rate and the size of cerebral embolizations detectable with MRI up to two days after TAVI.

4.1.2 Secondary Endpoints

Secondary endpoints are applied from the VARC2 definitions¹⁶ and cover a combined endpoint of death, stroke, TIA MI and major after 48 ± 24 hours, 7 ± 3 days, 30 ± 15 days and one year. Additional secondary endpoints are changes in the neurological and cognitive status of the patients (Montreal Cognitive Assessment, NIHHS, Mini-Mental Status, Modified Ranking Scale, Gait-Speed (Figure 2), Grip-Strength (Figure 3), Eyeball-Test,), changes in quality of life estimated with the EQ5D questionnaire, the independence during daily life measured by the Barthel-Index as well as the occurrence of micro-embolic HITS in the perfusion area of the medial cerebral artery during percutaneous valve implantation.

4.2 Study Protocol

4.2.1 Inclusion Criteria

- Patients with an increased peri-operative risk for conventional aortic valve replacement due to their co-morbidities which have the indication for a percutaneous aortic valve implantation and a transfemoral Medtronic CoreValve® System implantation.

4.2.2 Exclusion Criteria

- Risk factors and/or anatomical conditions do not allow percutaneous valve replacement with the Medtronic CoreValve® System
- Permanent Pacemaker
- Stroke within the last 12 months
- Significant carotid stenosis > 70 % or
- Significant stenosis of the brachiocephalic or the right subclavian artery.
- Expected non-compliance concerning follow-up-examinations due to social, psychological or other medical reasons
- Participation in another clinical trial
- Severe kidney disease with a GFR < 30 ml/min/1,73m²
- Pregnancy

4.2.3 Randomization

Randomization is performed in two groups, group 1 and group 2 after fulfilling the inclusion criteria without the exclusion criteria:

- Group 1 (Medtronic CoreValve® with Claret Montage™ Dual Filter System)
- Group 2 (Medtronic CoreValve® without Claret Montage™ Dual Filter System)

The randomization is executed by a computer-based algorithm – urn model without reverse draws. Power analysis was performed with Sigmastat 32 with a power of 0.9 and an alpha of 0.05 with the hypothesis that the event rate of ischemic lesions that are detectable on MRI up to two days after the procedure can be reduced 50 %. This analysis revealed a patient number of 86. Acknowledging a drop-out-rate of 16% would justify a total of 100 patients. Fifty patients per group are supposed to be included and randomized during the study period.

4.2.4 Magnetic Resonance Imaging (MRI)

Brain MRI assessments will be performed at baseline, two and at seven days. MRI scans will be obtained at a or according to a standardized protocol provided by the MRI core lab (Buffalo Neuroimaging Analysis Center, Buffalo, NY, USA) that also will perform all MRI analysis in a blinded fashion. The MRI protocol includes diffusion weighted images (DWI) acquired with a 2D echo planar sequence, high resolution T1-weighted images (hires-T1) acquired with an MP-RAGE sequence and B0 field maps acquired with a manufacturer-based dual-echo GRE sequence.¹⁷⁻¹⁹ All exams will be acquired on a 3T scanner (Magnetom Verio™, Siemens, Erlangen, Germany), except for subjects that are pacemaker-dependent post TAVI. For these subjects, a 1.5T system (Intera™, Philips, Best, The Netherlands) will be used. The MRI outcomes include calculation of number and volume of new DWI hyperintensities (two and seven days) in the whole brain and within predefined vascular territories. The brain will be separated into 28 different cerebral vascular territories based on the supplying artery: left anterior cerebral artery terminal branches (vascular territory code 2), left anterior cerebral artery central branches (vascular territory code 3), left middle cerebral artery terminal branches (code 6), left middle cerebral artery central branches (code 4), left posterior cerebral artery terminal branches (code 7), left posterior cerebral artery central branches (code 8), left anterior choroidal artery (code 5), left superior cerebellar artery (code 14), left anterior inferior cerebellar artery (code 13), left basilar artery anterior (code 11), left basilar artery anteromedial (code

10), left basilar artery lateral (code 12), left basilar artery dorsal (code 9), left posterior inferior cerebellar artery (code 15), right anterior cerebral artery terminal branches (code 22), right anterior cerebral artery central branches (code 23), right middle cerebral artery terminal branches (code 26), right middle cerebral artery central branches (code 24), right posterior cerebral artery terminal branches (code 27), right posterior cerebral artery central branches (code 28), right anterior choroidal artery (code 25), right superior cerebellar artery (code 34), right anterior inferior cerebellar artery (code 33), right basilar artery anterior (code 31), right basilar artery anteromedial (code 30), right basilar artery lateral (code 32), right basilar artery dorsal (code 29), right posterior inferior cerebellar artery (code 35). The “entire brain analysis” contains the number and volume of lesions in all vascular territory codes. The “protected areas” analysis contains the number and volume of lesions in the vascular territories that are definitely protected by the CMD: 2, 3, 4, 6, 22, 23, 26, 24, and 35, respectively. The vascular territories 5, 7, 8, 9, 10, 11, 12, 13, 14, 25, 27, 28, 29, 30, 31, 32, 33, 34, 35 are only partially protected, area 15 is not protected at all. However, all of these segments are included in the “entire brain analysis”. Please see Appendix A ‘Statistical Analysis Plan (SAP)’ for further analysis details.

4.2.5 Pre-Interventional Procedures

Standardized tests, questionnaires and neuro-cognitive examinations are performed after inclusion into the study and group 1 and group 2 (NIHHS-Score, Montreal Cognitive Assessment, Activity of daily life - Katz, Mini-Mental Status, Gait-Speed (Figure 2), Grip-Strength (Figure 3), Eyeball-Test, Rankin-Score). Additionally Brain-MRI and blood sampling to determine NSE, S100, CK, CKMB, Troponin T, Creatinine, urea, ASAT, ALAT, Bilirubin, Gamma-GT is done on the day before the procedure. These examinations are an addition to the usual pre-interventional work up which include coronary catheterization, CT-Angio/CT-Cor, TTE, TOE, chest X-Ray and ultrasound of the cervical vessels and which are not part of the trial.

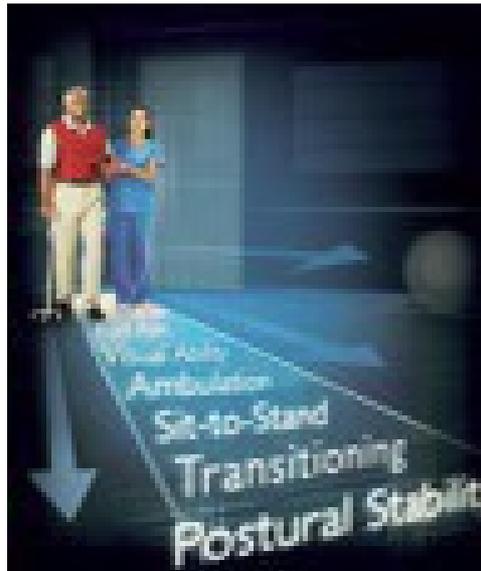


Figure 2 - Gait speed – Test



Figure 3 - Grip strength - Test

4.2.6 Acquisition of Peri-Interventional Data

The trans-cranial ultrasound test to measure HITS, the occurrence of microembolic events in the perfusion area of the medial cerebral artery is taken out in addition to the usual monitoring and acquisition of interventional data such as for example invasive hemodynamics.

4.2.7 Post-interventional Data

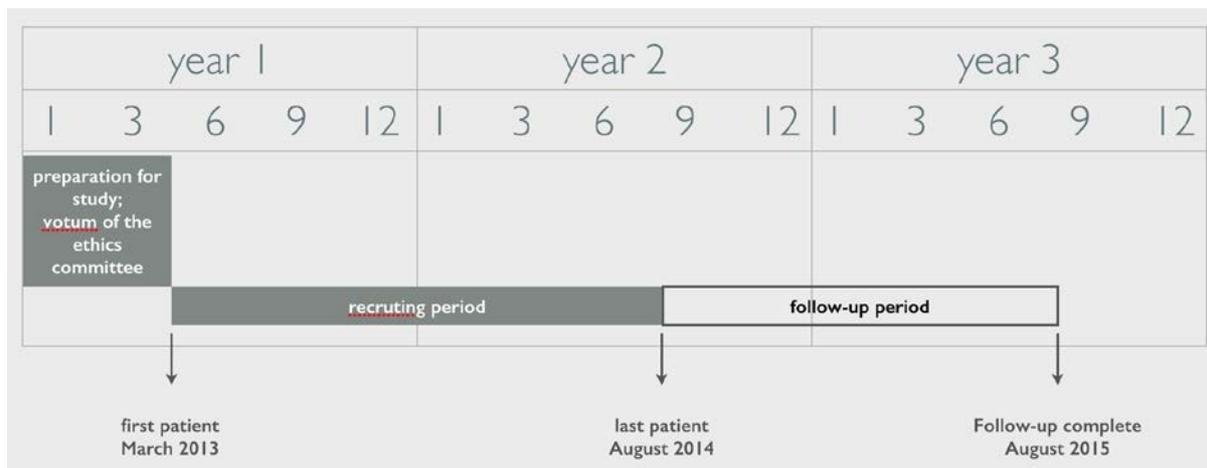
The standardized tests, questionnaires and neuro-cognitive examinations are performed after inclusion into the study and group 1 and group 2 (NIHHS-Score, Montreal Cognitive Assessment, Activity of daily life - Katz, Mini-Mental Status, Gait-Speed (Figure 2), Grip-Strength (Figure 3), Eyeball-Test, Rankin-Score) are

performed at 48 ± 24 hours, 7 ± 3 days, 30 ± 15 days and one year after the index procedure. Additionally the study MRI and blood sampling is repeated (NSE, S100, CK, CKMB, Troponin T, Creatinine, Urea, ASAT, ALAT, Bilirubin, Gamma-GT). These samples are drawn additionally directly after the procedure as well as three and ten days after the procedure.

Patients who receive a permanent pacemaker after the TAVI due to significant bradycardia, which can be up to 20%, will receive a MRI-compatible device (Leads: atrial leads CapSure Fix MRI 5086-52cm, ventricular leads CapSure Fix MRI 5086-58cm or anchor lead CapSure Sense MRI 4074-58cm, Device: Advisa MRI (A3DR01) or Ensura MRI(ENDR01)).

Report and notification for adverse events and serious adverse events is performed in compliance with the governmental directives and the GCP guidelines.

4.3 Time Frame of the Study



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Appendix

A) Statistical Analysis Plan (SAP)

B) Signature Page

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Statistical Analysis Plan (SAP)

Version: 1

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ABBREVIATIONS

ANOVA	analysis of variance
CMD	Claret Montage dual filter system
DW-MRI	diffusion-weighted magnetic resonance imaging
GFR	Glomerular filtration rate
HITS	high-intensity transient signals
IQR	interquartile range
MI	Myocardial infarction
MOCA	Montreal cognitive assessment
MRI	magnetic resonance imaging
NIHSS	National Institutes of Health stroke scale
NYHA	New York Heart Association (functional classification)
SAVR	surgical aortic valve replacement
SD	standard deviation
TAVI	transcatheter aortic valve implantation
TCD	Transcranial doppler
TIA	Transient ischemic attack
VARC	valve academic research consortium

1 INTRODUCTION

Transcatheter aortic valve implantation (TAVI) has been shown to be feasible, safe and superior to standard medical therapy in inoperable patients and to be non-inferior to surgical aortic valve replacement (SAVR) in high-risk patients.¹⁻³ Results of TAVI improved considerably during the last decade.^{4,5} However, stroke remains a major predictor of mortality after transcatheter aortic valve implantation (TAVI).⁶⁻¹¹

Cerebral protection devices (e.g. Claret Montage dual filter system [CMD]) might reduce brain damage as determined by diffusion-weighted magnetic resonance imaging (DW-MRI). However, randomized controlled trial data showing the efficacy of any embolic protection device in TAVR are missing.

2 OBJECTIVES/ENDPOINTS

2.1 Study objectives

The aim of this blinded, randomized controlled, CLaret Embolic protection AND TAVI (CLEAN-TAVI) trial is to investigate the impact of cerebral protection using CMD on the number and volume of cerebral lesions in patients with significant calcified aortic stenosis undergoing TAVI.

2.2 Endpoints

The primary efficacy endpoint is the rate of positive post procedure DW-MRI perfused brain lesions relative to baseline at two days in protected territories. A primary safety endpoint was not defined for this study. The statistical methods proposed for this study will determine if the total new lesion number from the protected territories at 2 days post procedure is significantly less in subjects randomized to the CMD compared to the control group. Study success is defined as a significant difference ($p < 0.05$) in the mean new lesion number from the protected territories between the CMD and the control group, where the CMD group has lower mean new lesion numbers. In addition, a 50% lower mean new lesion number from the protected territories in the CMD compared to control was defined as a clinically significant success.

2.2.1 Primary Efficacy endpoint (Superiority)

The primary efficacy endpoint of this study is to show a reduction in mean new lesion number in protected territories between the CMD and the control group assessed by DW-MRI at day 2

post TAVI, where protected territories are defined as areas uniquely perused by the vessels protected by the CMD, namely the left and right carotid arteries and the right vertebral artery. Diffusion-weighted magnetic resonance imaging is a powerful tool to characterized ischemic lesions early after an embolic event and can be considered an established method to quantify brain damage after TAVI. Recent studies suggest that silent brain infarcts determined by DW-MRI precede clinically relevant strokes and are predictors of inferior neurological outcome. Given that even small brain infarcts – depending on their location – can result in devastating neurological outcome, it was decided to use the lesion number as the primary outcome variable. However, there are also studies linking the total lesion volume to neurological outcome, therefore this measure was considered as a secondary endpoint.

Given that numerous factors will affect the MRI output, a predefined protocol (defining time points of MRI assessment, machine settings, magnetic field strength (3 Tesla, and 1.5 T in those patients with contraindication for a 3 Tesla scan) etc.) will be used in all subjects at all time points. MRI measure will include number and location of lesions, volume and density, respectively. All of the MRIs will be analyzed in a blinded manner by the MRI corelab (Buffalo Neuroimaging center, Buffalo, New York, USA).

Protected vs. unprotected territories:

Arterial territories will be analyzed based on a stereotaxic atlas and placed in the standard MNI152 space. For each subject, a combination of affine registration and non-linear spatial normalization will be used to map the MNI152 space onto subject specific scan. Territory labels will be applied in a discrete fashion, assigning each subject-space voxel to the nearest territory, and covering 100% of the parenchymal volume. The brain will be separated into 28 different cerebral vascular territories based on the supplying artery: left anterior cerebral artery terminal branches (vascular territory code 2), left anterior cerebral artery central branches (vascular territory code 3), left middle cerebral artery terminal branches (code 6), left middle cerebral artery central branches (code 4), left posterior cerebral artery terminal branches (code 7), left posterior cerebral artery central branches (code 8), left anterior choroidal artery (code 5), left superior cerebellar artery (code 14), left anterior inferior cerebellar artery (code 13), left basilar artery anterior (code 11), left basilar artery anteromedial (code 10), left basilar artery lateral (code 12), left basilar artery dorsal (code 9), left posterior inferior cerebellar artery (code 15), right anterior cerebral artery terminal branches (code 22), right anterior cerebral artery central branches (code 23), right middle cerebral artery terminal branches (code 26), right middle cerebral artery central branches

(code 24), right posterior cerebral artery terminal branches (code 27), right posterior cerebral artery central branches (code 28), right anterior choroidal artery (code 25), right superior cerebellar artery (code 34), right anterior inferior cerebellar artery (code 33), right basilar artery anterior (code 31), right basilar artery anteromedial (code 30), right basilar artery lateral (code 32), right basilar artery dorsal (code 29), right posterior inferior cerebellar artery (code 35). The “entire brain analysis” will contain the number and volume of lesions in all vascular territory codes. The “protected areas” analysis contains the number and volume of lesions in the vascular territories that are definitely protected by the CMD: 2, 3, 4, 6, 22, 23, 26, 24, and 35, respectively. The vascular territories 5, 7, 8, 9, 10, 11, 12, 13, 14, 25, 27, 28, 29, 30, 31, 32, 33, 34, 35 are only partially protected, area 15 is not protected at all. However, all of these segments will be included in the “entire brain analysis”.

3 STUDY METHODS

3.1 General study design and plan

The CLaret Embolic protection ANd TAVI (CLEAN-TAVI) trial is a randomized, controlled and blinded trial investigating the impact of cerebral protection using CMD on the number and volume of cerebral lesions in patients undergoing TAVI.

The patients are randomly (1:1) assigned to TAVI with (filter group, n=50) or without CMD protection (control group, n=50). Therefore, a dataset of 100 patients will be created and analysed. MRI analysis will be performed by an independent core lab in a blinded fashion. A study flowchart is attached to this SAP.

3.2 Inclusion criteria

Symptomatic patients with severe aortic stenosis were eligible for inclusion in the study if they were considered to be at increased risk for undergoing surgical aortic valve replacement as determined by the heart team consisting of at least one cardiac surgeon and one interventional cardiologist.

3.3 Exclusion criteria

Exclusion criteria are an anatomy unsuitable for a safe CoreValve™ System (Medtronic Inc., Minneapolis, MN, USA) implantation, preexisting permanent pacemaker, stroke within the last 12 months, a carotid artery stenosis of more than 70%, significant stenosis of the right subclavian artery or the brachiocephalic trunk, expected non-compliance to follow-up visits,

participation in another clinical study, severe renal failure (GFR <30 ml/min/1.73m² body surface area) or pregnancy.

3.4 Randomisation and blinding

Randomization is performed 1:1 into two groups, group 1 and group 2 after fulfilling the inclusion criteria without the exclusion criteria:

- Group 1 (Medtronic CoreValve® with Claret Montage™ Dual Filter System)
- Group 2 (Medtronic CoreValve® without Claret Montage™ Dual Filter System)

The randomization is executed by a urn model without reverse draws.

MRI analysis will be performed by an independent core lab in a blinded fashion. A NIHSS trained specialist will perform neurological assessment in a blinded fashion.

3.5 Key Study variables

	Baseline	Procedure	2 days	7 days	30 days
History and examination	X		X	X	X
MRI	X		X	X	X
TCD		X			
NIHSS	X		X	X	X
MOCA	X		X	X	X
Modified Rankin Scale	X		X	X	X
Blood samples	X		X	X	X

4 STATISTICAL METHODS and ANALYSES

Determination of Sample Size

The primary hypothesis is that the CMD reduces the number of positive post procedure DW-MRI brain lesions at two days relative to baseline in protected territories by 50% in patients undergoing TAVI using the Medtronic CoreValve™ System. Assuming a normal distribution of the data, a dropout rate of 16%, we estimated that a total of 50 patients were required in each group for the study to have a power of 90% at a two-sided alpha level of 0.05 (t-test, Medcalc software, version 13.1.2.0, MedCalc, Ostend, Belgium).

Handling of missing values

Patients in poor clinical condition may not be able to undergo MRI or neurocognitive assessments. On the other hand there may be patients in a good clinical condition willing to

leave hospital earlier and unwilling to undergo follow-up MRIs or neurocognitive assessments. With assumption of same numbers of patients in each of both scenarios, a complete-subject analysis could be performed, so subjects with missing values are deleted from the analysis.

Population of Analysis and Statistical Methodology

The primary efficacy analysis will be on the modified intention-to-treat population (ITT), composing of all randomized subjects in whom the investigational study procedure is attempted and MRIs are available at baseline and 2 day follow-up.

Primary efficacy analysis: Analysis of the rate of positive post procedure DW-MRI perfused brain lesions relative to baseline at two days in protected territories compared to control group will be performed by Student's t-test. In this case, data will be reported as mean and standard deviation (SD). Given that there is some uncertainty regarding the distribution of the primary endpoint data, in case of non-normal distribution or extreme outliers, analysis will be performed using the Mann-Witney U-test. In this case, results will be presented as median and interquartile range (IQR).

Primary efficacy success is predicated on detecting a significant difference ($p < 0.05$) with a lower total new lesion number in the CMD group in the protected territories as compared to the control arm at 2 days post TAVI. A new DWI lesion is defined as one present on a post-treatment scan that was not visible on the baseline scan. Total new lesion number from the protected territories is defined as the sum of all DW-MRI positive brain lesions from the protected territories in post-procedure MRI as compared to baseline MRI scans; protected territories are brain territories uniquely perfused by the vessels protected by the CMD.

The null and alternative hypotheses are:

$$H_0: \mu_{\text{CMD}} = \mu_{\text{control}}$$

$$H_A: \mu_{\text{CMD}} \neq \mu_{\text{control}}$$

μ_{CMD} = day 2 DW-MRI total new lesion number based on the protected areas from the CMD group.

μ_{control} = day 2 DW-MRI total new lesion number based on the protected areas from the control group.

No interim analysis is scheduled.

Secondary efficacy analyses: Secondary efficacy endpoints will be evaluated and will be tested for statistical significance, but only if the primary efficacy endpoint has been met. To preserve overall Type I error, a gatekeeping strategy will be used, where secondary MRI endpoints will be tested in the order in which they are listed below, but the endpoints will only be tested if the prior one on the list achieved statistical significance. Each MRI endpoint will be evaluated using the modified ITT population. Secondary non-MRI endpoints will be considered exploratory.

Secondary Efficacy Endpoint No 1:

Difference in day 2 DW-MRI median total new lesion volume based on the protected territories.

$$H_0: \mu_{\text{CMD}} = \mu_{\text{control}}$$

$$H_A: \mu_{\text{CMD}} \neq \mu_{\text{control}}$$

μ_{CMD} = day 2 DW-MRI median total new lesion volume based on the protected areas from the CMD group.

μ_{control} = day 2 DW-MRI median total new lesion volume based on the protected areas from the control group.

Secondary Efficacy Endpoint No 2:

Difference in day 7 DW-MRI total new lesion number based on the protected territories.

$$H_0: \mu_{\text{CMD}} = \mu_{\text{control}}$$

$$H_A: \mu_{\text{CMD}} \neq \mu_{\text{control}}$$

μ_{CMD} = day 7 DW-MRI total new lesion number based on the protected areas from the CMD group.

μ_{control} = day 7 DW-MRI total new lesion number based on the protected areas from the control group.

Secondary Efficacy Endpoint No 3:

Difference in day 7 DW-MRI median total new lesion volume based on the protected territories.

$$H_0: \mu_{\text{CMD}} = \mu_{\text{control}}$$

$$H_A: \mu_{\text{CMD}} \neq \mu_{\text{control}}$$

μ_{CMD} = day 7 DW-MRI median total new lesion volume based on the protected areas from the CMD group.

μ_{control} = day 7 DW-MRI median total new lesion volume based on the protected areas from the control group.

Secondary Efficacy Endpoint No 4:

Difference in day 2 DW-MRI total new lesion number based on all territories.

H0: $\mu_{\text{CMD}} = \mu_{\text{control}}$.

HA: $\mu_{\text{CMD}} \neq \mu_{\text{control}}$.

μ_{CMD} = day 7 DW-MRI total new lesion number based on the all areas from the CMD group.

μ_{control} = day 7 DW-MRI total new lesion number based on the all areas from the control group.

Secondary Efficacy Endpoint No 5:

Difference in day 2 DW-MRI median total new lesion volume based on all territories.

H0: $\mu_{\text{CMD}} = \mu_{\text{control}}$.

HA: $\mu_{\text{CMD}} \neq \mu_{\text{control}}$.

μ_{CMD} = day 2 DW-MRI median total new lesion volume based on all areas from the CMD group.

μ_{control} = day 2 DW-MRI median total new lesion volume based on all areas from the control group.

Secondary Efficacy Endpoint No 6:

Difference in day 7 DW-MRI total new lesion number based on all territories.

H0: $\mu_{\text{CMD}} = \mu_{\text{control}}$.

HA: $\mu_{\text{CMD}} \neq \mu_{\text{control}}$.

μ_{CMD} = day 7 DW-MRI total new lesion number based on all areas from the CMD group.

μ_{control} = day 7 DW-MRI total new lesion number based on all areas from the control group.

Secondary Efficacy Endpoint No 7:

Difference in day 7 DW-MRI median total new lesion volume based on all territories.

H0: $\mu_{\text{CMD}} = \mu_{\text{control}}$.

HA: $\mu_{\text{CMD}} \neq \mu_{\text{control}}$.

μ_{CMD} = day 7 DW-MRI median total new lesion volume based on all areas from the CMD group.

μ_{control} = day 7 DW-MRI median total new lesion volume based on all areas from the control group.

Secondary Efficacy Endpoint No 8:

Difference in day 30 Flair-MRI total new lesion number based on protected territories.

H0: $\mu_{\text{CMD}} = \mu_{\text{control}}$.

HA: $\mu_{\text{CMD}} \neq \mu_{\text{control}}$.

μ_{CMD} = day 30 Flair-MRI total new lesion number based on protected areas from the CMD group.

μ_{control} = day 30 Flair-MRI total new lesion number based on protected areas from the control group.

Secondary Efficacy Endpoint No 9:

Difference in day 30 day Flair-MRI median total new lesion volume based on protected territories.

H0: $\mu_{\text{CMD}} = \mu_{\text{control}}$.

HA: $\mu_{\text{CMD}} \neq \mu_{\text{control}}$.

μ_{CMD} = day 30 Flair-MRI median total new lesion volume based on protected areas from the CMD group.

μ_{control} = day 30 Flair-MRI median total new lesion volume based on protected areas from the control group.

Secondary Efficacy Endpoint No 10:

Difference in day 3 Montreal cognitive assessment and its subcomponents

H0: $\mu_{\text{CMD}} = \mu_{\text{control}}$.

HA: $\mu_{\text{CMD}} \neq \mu_{\text{control}}$.

μ_{CMD} = value of the day 3 Montreal cognitive assessment in the CMD group.

μ_{control} = value of the day 3 Montreal cognitive assessment in the control group.

Secondary Efficacy Endpoint No 11:

Difference in day 7 Montreal cognitive assessment and its subcomponents

H0: $\mu_{\text{CMD}} = \mu_{\text{control}}$.

HA: $\mu_{\text{CMD}} \neq \mu_{\text{control}}$.

μ_{CMD} = value of the day 7 Montreal cognitive assessment in the CMD group.

μ_{control} = value of the day 7 Montreal cognitive assessment in the control group.

Secondary Efficacy Endpoint No 12:

Difference in day 3 Modified Rankin Scale assessment

H0: $\mu_{\text{CMD}} = \mu_{\text{control}}$.

HA: $\mu_{\text{CMD}} \neq \mu_{\text{control}}$.

μ_{CMD} = value of the day 3 modified Rankin Scale assessment in the CMD group.

μ_{control} = value of the day 3 modified Rankin Scale assessment in the control group.

Secondary Efficacy Endpoint No 13:

Difference in day 7 Modified Rankin Scale assessment

H0: $\mu_{\text{CMD}} = \mu_{\text{control}}$.

HA: $\mu_{\text{CMD}} \neq \mu_{\text{control}}$.

μ_{CMD} = value of the day 7 modified Rankin Scale assessment in the CMD group.

μ_{control} = value of the day 7 modified Rankin Scale assessment in the control group.

Secondary Efficacy Endpoint No 14:

Difference in day 3 NIHSS Scale assessment

H0: $\mu_{\text{CMD}} = \mu_{\text{control}}$.

HA: $\mu_{\text{CMD}} \neq \mu_{\text{control}}$.

μ_{CMD} = value of the day 3 NIHSS assessment in the CMD group.

μ_{control} = value of the day 3 NIHSS assessment in the control group.

Secondary Efficacy Endpoint No 15:

Difference in day 7 NIHSS Scale assessment

H0: $\mu_{\text{CMD}} = \mu_{\text{control}}$.

HA: $\mu_{\text{CMD}} \neq \mu_{\text{control}}$.

μ_{CMD} = value of the day 7 NIHSS assessment in the CMD group.

μ_{control} = value of the day 7 NIHSS assessment in the control group.

Secondary Efficacy Endpoint No 16:

Difference in periprocedural HITS

H0: $\mu_{\text{CMD}} = \mu_{\text{control}}$.

HA: $\mu_{\text{CMD}} \neq \mu_{\text{control}}$

μ_{CMD} = number of HITS in the CMD group.

μ_{control} = number of HITS in the control group.

Other secondary endpoints will include the occurrence of death, stroke, TIA, myocardial infarction or bleeding after 48 ± 24 hours, 7 ± 3 days, 30 ± 15 days and one year using the definitions established by the Valve Academic Research Consortium, they will be reported as descriptive statistics only. Safety issues will be carefully monitored.

Summary tables (descriptive statistics and/or frequency tables) will be provided for all baseline variables and procedural data, categorical variables will be compared by chi-squared test or Fisher's exact test, as appropriate. Frequency counts and percentage of subjects within each category will be provided for categorical data. Odds ratios or risk ratios with 95% confidence intervals will also be provided, as appropriate. Continuous variables will be tested for normal distribution using the Kolmogorov Smirnov test. In case of normal distribution, continuous variables will be expressed as means \pm SD and compared with Student's t-test, otherwise they are expressed as median and interquartile range and will be compared using Mann-Whitney U-test. All echocardiographic measurements will be evaluated with the use of a two-sample t-tests or the Wilcoxon rank-sum test for continuous variables, as appropriate. All analysis will be performed with the use of SPSS (version 21, IBM, Armonk, New York, USA) or Medcalc software (version 13.1.2.0, MedCalc, Ostend, Belgium).

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