CoreValve® ADVANCE Direct Aortic (DA) Study

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This study is intended to collect real-world (post-approval use) data regarding the clinical utility and performance of the Medtronic CoreValve® System for Transcatheter Aortic Valve Implantation (TAVI) in patients with severe symptomatic aortic...

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

Summary

ID

NL-OMON53165

Source
ToetsingOnline

Brief title
CoreValve® ADVANCE DA

Condition

- Cardiac valve disorders

Synonym
aortic stenosis; disease of the heart valves in which the opening of the aortic valve is narrowed

Research involving
Human

Sponsors and support

Primary sponsor: Medtronic B.V.
Source(s) of monetary or material Support: Medtronic Bakken Research Center BV

Intervention

Keyword: Alternative access route, aortic valve stenosis, Performance, TAVI

Outcome measures

Primary outcome

The primary endpoint is defined as all-cause mortality at 30 days post-implant.

Secondary outcome

The following secondary endpoints are defined:

1. All-cause mortality at discharge, 6 months and 12 months.

2. Cardiovascular mortality at discharge, 30 days, 6 months and 12 months.

3. Incidence of Major Adverse Cardiovascular and Cerebrovascular Events (MACCE)-events at discharge, 30 days, 6 months and 12 months.

MACCE is defined as a composite of:

• All-cause mortality

• Myocardial Infarction (MI)

• All stroke

• Reintervention (defined as any cardiac surgery or percutaneous interventional catheter procedure that repairs, otherwise alters or adjusts, or replaces a previously implanted valve (after closure of the thorax of the previous implanted valve)

4. Incidence of individual MACCE components at discharge, 30 days, 6 months and 12 months

5. Incidence of non-disabling and disabling stroke (and ischemic vs hemorrhagic stroke) at discharge, 30 days, 6 months and 12 months

6. Device success at discharge

Device success defined as follows:

• Absence of procedural mortality AND

• Correct positioning of a single prosthetic heart valve into the proper anatomical location AND intended performance of the prosthetic heart valve (no prosthesis-patient mismatch) and mean aortic valve gradient <20 mmHg or peak velocity <3 m/s, AND no moderate or severe prosthetic valve regurgitation).

7. Incidence of life-threatening, disabling or other major bleeding events at discharge, 30 days, 6 months and 12 months.

8. Incidence of major vascular access site and access- related complications at discharge and 30 days.

9. Incidence of implant-related new or worsened conduction disturbances and/or cardiac arrhythmias at discharge, 30 days, 6 months and 12 months.

10. Incidence of conduction disturbances and/or cardiac arrhythmias requiring (intensified) medical intervention at discharge, 30 days, 6 months and 12 months.

11. Indications for pacemaker implantation.

12. Incidence of repeated hospitalization (>30 days after the index procedure) for valve-related issues or cardiac decompensation.

13. Change in NYHA class from baseline at 30 days, 6 months and 12 months.

14. Length of implant procedure.

15. Length of implant hospital stay.

16. Length of fluoroscopy time during implant.

17. Incidence of Acute Kidney Injury at baseline and discharge.

18. Patient health status evaluated by Quality of Life Questionnaires (EQ-5D

and SF-12v2) at baseline, 30 days, 3 months (EQ-5D only), 6 months and 12 months.

19. Patient health status evaluated by Kansas City Cardiomyopathy Questionnaire (KCCQ) at baseline, 30 days, 6 months and 12 months.

20. Prosthetic valve performance evaluated by:

1) Echocardiographic assessment at discharge, 6 months and12 months using the following measures:

• transvalvular mean gradient

• effective orifice area

• degree of prosthetic aortic valve regurgitation (transvalvular and paravalvular).

2) Associated clinical findings indicating impared cardiovascular or valvular function

21. Incidence of aortic valve thrombosis and endocarditis at 30 days, 6 months and 12 months.

22. Incidence of coronary obstruction at 30 days, 6 months and 12 months.

23. Incidence of ventricular perforation at any time resulting in cardiac tamponade, prostatic valve embolization, and acute or delayed valve-in-valve treatment at 30 days, 6 months and 12 months.

24. Clinical efficacy endpoint at 30 days post-implant composed of:

• All-cause mortality

• All stroke

• Requiring hospitalizations for valve-related symptoms or worsening congestive heart failure.

• NYHA class III or IV

• Valve-related dysfunction (mean aortic valve gradient -20 mmHg, EOA - 0.9 - 1.1 cm2 and/or DVI < 0.35 m/s, AND/OR moderate or severe prosthetic valve regurgitation)

In addition the following safety endpoints will be evaluated:

1. Rate of Adverse Device Effects (ADEs) from enrollment through 12 months post valve implantation.

2. Rate of procedure-related Adverse Events (AEs) from enrollment through 12 months post valve implantation.

3. Rate of Serious Adverse Events (SAEs) from enrollment through 12 months post valve implantation.

4. Rate of Serious Adverse Device Events or Unanticipated Serious Adverse Device Events (SADE/USADE) from enrollment through 12 months post valve implantation.

5. Device deficiencies (including device malfunctions, failures, and non-conformance).

6. Combined early safety endpoint at 30 days postimplant composed of:

• All-cause mortality

• All stroke

• Life-threatening bleeding

• Acute kidney injury*Stage 2 or 3 (including renal replacement therapy)

• Coronary artery obstruction requiring intervention

• Major vascular complication

• Valve-related dysfunction requiring repeat procedure (BAV, TAVI, or SAVR)

7. Valve safety at 30 days, 6 and 12 months postimplant:

• Structural valve deterioration:

o Valve-related dysfunction (mean aortic valve gradient -20 mmHg, EOA - 0.9 -

1.1 cm2 and/or DVI < 0.35 m/s, AND/OR moderate or severe prosthetic valve

regurgitation)

o Requiring repeat procedure (TAVI or SAVR)

• Prosthetic valve endocarditis

• Prosthetic valve thrombosis

• Thromboembolic events (e.g. stroke)

• VARC bleeding, unless clearly unrelated to valve therapy (e.g. trauma)

Study description

Background summary

Aortic valve stenosis (AS) is the most prevalent valve disorder in the adult population in developed countries affecting approximately 2% to 4% of people over 65 years of age. This corresponds to approximately 3 million people with AS in Europe alone. One in five will
eventually progress to symptomatic AS representing 600,000 patients.
Patients with severe AS face a grim prognosis once they become symptomatic.Furthermore, mortality is already substantial in the months following the first symptoms. The dismal prognosis of patients with untreated severe, symptomatic aortic stenosis has been recently corroborated in several studies. Based on these studies, both the ESC and ACC/AHA cardiology societies have endorsed guidelines on valvular
heart disease emphasizing the need for surgical aortic valve replacement (SAVR) once symptoms develop or in case of impaired LV function.
Despite these well-established guidelines, one in every three patients with symptomatic AS is considered at too high a risk for surgery mostly because of age, left ventricular dysfunction and co-morbidities. As an alternative for

Surgical Aortic Valve Replacement (SAVR), minimally
invasive transcatheter therapies were developed early this century.
Alain Cribier pioneered the transcatheter aortic valve implantation (TAVI) technology and reported the first in man experience of TAVI in a patient with symptomatic AS who was deemed inoperable in 2002.
Different access routes have been developed for TAVI of which the transfemoral access route is now the most commonly used. Using the transfemoral approach is not always possible however due to peripheral vascular problems like severe peripheral calcification or other
vasculopathies. Alternatives for the transfemoral approach include transapical, subclavian and direct aortic approaches for TAVI. Literature regarding alternative routes for TAVI is currently scarce and the most appropriate access routes are now being selected by multidisciplinary
cardiovascular teams based on patient anatomical and clinical characteristics. Transcathether aortic valve implantation via direct aortic access may be indicated for patients with relatively small vessel diameters, heavy peripheral calcification, excessive tortuosity or subclavian stenosis.
During the 48th Annual Meeting of the Society of Thoracic Surgeons, Moat and Bruschi presented a cohort of patients receiving the CoreValve® system via direct aortic approach. In total 115 patients in 19 centers across Europe received the CoreValve® system via the direct
aortic approach.When the abstract was presented, data were available on 52 patients from 5 centers.
It was concluded that direct aortic access is a feasible approach for TAVI and that these initial and provisional results with this technique are encouraging in a high risk patient cohort. Final results for all patients are still being collected but the drawback of this database is that data are collected in an observational, uncontrolled setting.
Taking the recently published guidelines for the execution of clinical studies from the Valvular Academic Research Consortium (VARC) into consideration, this post-market prospective, interventional, multi-center study would supply the required valid data about the success of the implant technique itself and other clinically relevant safety and performance endpoints. Ultimately the collection of Quality of Life and resource utilization data will determine whether the new treatment strategy is impacting the cost-effectiveness of the therapy in this patient population.

Study objective

This study is intended to collect real-world (post-approval use) data regarding the clinical utility and performance of the Medtronic CoreValve® System for Transcatheter Aortic Valve Implantation (TAVI) in patients with severe symptomatic aortic valve stenosis for which treatment via direct aortic access (DA) is selected. As part of the study analysis, resource utilization together with the Quality of Life questionnaires data will provide an important input into cost effectiveness analysis.

Primary objective
The primary study objective is to further evaluate the clinical outcome of Transcatheter Aortic Valve Implantation (TAVI) via direct aortic access using the Medtronic CoreValve® System in consecutive real world patients with severe Aortic Stenosis (AS).

Secondary objectives
The secondary objective of this study is to assess quality of life, clinical benefit of the therapy and to collect resource utilization data in patients treated with TAVI via a direct aortic approach.

Study design

This study is designed as a prospective, interventional, single arm, multicenter study to collect data regarding the clinical utility, safety and performance of the Medtronic CoreValve® System in patients with severe aortic valve stenosis for which treatment via direct aortic access (DA) route is selected.

One hundred (100) patients will be recruited in up to 15 investigational centers located in Europe. The study may be expanded to include additional geographies based on enrollment rates and identification of qualified centers.

To avoid bias in the study population the following measures will be taken:
• All sponsor and external study personnel will be trained on the Clinical Investigation Plan (CIP) and related study materials.
• Patients will be screened to confirm study eligibility with defined inclusion/exclusion criteria prior to enrollment.
• This study will follow consecutive screening and enrollment.

The CoreValve® Direct Aortic study is a single-arm study. The study will not incorporate blinding techniques and randomization system.

One hundred patients receiving the CoreValve® system and meeting the eligibility criteria will be included. The anticipated enrollment rate is approximately 1 patient per month per center with total enrollment phase of approximately 8-12 months depending on the final number of centers activated. Patients will be followed for 12 months. Enrollments shall not exceed 20% (20 patients) of total implanted patients at any individual site. Enrollment will be competitive across sites, with an initial maximum of 20 patients receiving the CoreValve® system. The per-site enrollment cap of 20 patients receiving a CoreValve® system may be increased upon Sponsor approval. There is no set minimum number of patients to be enrolled per site. At the time when the study-wide enrollment cap of 100 patients receiving the CoreValve® system and meeting the eligibility criteria, has been reached, further enrollment into the study will cease regardless of

whether individual sites have reached their per-site cap.

Intervention

The Medtronic CoreValve® System consists of the following elements:
• Percutaneous Aortic Valve Bioprosthesis (PAV): consisting of a multi-level self expanding frame with porcine pericardial bioprosthesis
• Delivery Catheter System (DCS): designed to house the tissue valve prosthesis in the collapsed position for percutaneous delivery to the patient*s aortic annulus.
• Compression Loading System (CLS): facilitates consistent and trauma-free manual loading of the PAV into the DCS.

CoreValve® Transcatheter Aortic Bioprosthesis Implantation:

The CoreValve® implantation procedure will be performed under general anesthesia. However, the procedure does not require the use of a heart-lung bypass machine.
A catheter will be placed for the purposes of taking x-ray pictures and monitoring of the blood pressure. A small opening is made between the ribs or in the sternum. The CoreValve® is then loaded on a catheter and introduced, via the aorta, into the heart and placed within the native aortic valve.
Following instructions are required prior to use:
1. Carefully inspect the package before opening.
2. Remove the product from the protective package and visually check that it is free of defects.
3. Start the bioprosthesis Rinsing Procedure
4. Start the preparation of the Catheter and CLS
5. Start the bioprosthesis Loading Procedure with CLS
The bioprosthesis loading procedure is performed while immersed in cold, sterile saline (0°C-8°C/ 32°F-46°F).

During the procedure, the doctor will perform angiography (x-ray pictures), echocardiography, and monitor the pressure within the heart to observe the heart function and make sure that the study valve fits and works properly. Doctors from other hospitals who have experience with the implantation procedure may assist the investigator with the procedure. Medtronic staff may assist the physician in the loading of the CoreValve® as needed.
Following instructions are required related to the bioprothesis implantation:
1. Prepare the vascular access site according to standard practice.
2. Predilate the native aortic valve with an appropriate diameter valvuloplasty balloon.
3. Backload the catheter onto the guidewire while maintaining guidewire position across the aortic valve.
4. Under fluoroscopic guidance, advance the catheter over the guidewire to the aortic annulus.
5. Position the catheter so that the top of the first cell of the inflow

portion of the frame is level with the valve annulus.
6. To deploy the bioprosthesis, turn the micro knob clockwise. The outer capsule retracts and exposes the bioprosthesis. Continue deploying the bioprosthesis in a controlled manner; adjust valve position as necessary.
7. Slight repositioning of a partially deployed bioprosthesis (<=2/3 of the bioprosthesis length) can be achieved by carefully withdrawing the catheter.
8. After complete deployment has been achieved, use orthogonal views under fluoroscopy to confirm that the frame loops have detached from the catheter tabs. If a frame loop is still attached to a catheter tab, under fluoroscopy, advance the catheter slightly and, if necessary, gently rotate the handle clockwise (<180°) and counterclockwise (<180°) to disengage the loop from the catheter tab.
9. Close the catheter sheath before withdrawal.
10. Perform routine aortogram to assess the bioprosthesis for proper expansion.

After the procedure, the investigators will continue to monitor the progress and recuperation of the patient.
If the investigator was unable to implant the study valve, the patient will not need to return to the clinic for follow-up visits. Instead he will receive routine medical care.

Study burden and risks

Patients will be followed for 12 months. All patients will undergo follow-up (FU) evaluations at the following time points post implant:
• 30 days in-clinic FU
• 3 months: Quality of Life (EQ-5D) assessment via phone
• 6 months in-clinic FU
• 12 months in-clinic FU
After the patient has completed the 12 month follow-up assessments, the patient is considered to have completed the study. The patient will receive routine care afterwards.

There are possible risks and side effects connected to the Medtronic CoreValve® implant but the risks are similar to those for an implant of the Medtronic CoreValve® bioprosthesis without participation in this study.Currently known adverse events that may result from TAVI include but may not be limited to:
• Access site complications (eg, pain, bleeding, hematoma, pseudoaneurysm)
• Acute coronary closure
• Acute myocardial infarction
• Acute renal failure
• Allergic reaction to antiplatelet agents or contract media
• Ascending aorta trauma
• Arteriavenous fistula
• Bowel ischemia
• Cardiogenic shock
• Conduction system disturbances (atrio-ventricular node block, left-bundle

branch block, asystole)
• Death
• Embolization
• Emergent balloon valvuloplasty
• Emergent percutaneous coronary intervention (PCI)
• Emergent surgery (eg, coronary artery bypass, heart valve replacement)
• Hemorrhage requiring transfusion
• Hypotension or hypertension
• Infection
• Myocardial ischemia
• Mitral valve insufficiency
• Perforation of the myocardium or vessel
• Stroke
• Structural or nonstructural dysfunctions (eg, leak, insufficiency, stenosis)
• Thrombosis
• Tamponade
• Valve migration
• Vessel dissection or spasm
• Ventricular arrhythmias

Contacts

Public
Medtronic Bakken Research Center B.V - CardioVascular, Structural Heart Disease

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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. Severe symptomatic aortic valve stenosis requiring treatment
2. Acceptable candidate for elective treatment with the Medtronic CoreValve® System (according to
the most recent version of the Medtronic CoreValve® Instructions For Use) and in conformity with the local regulatory and medico economic context
3. 21 years of age or older
4. Patient is willing and able to comply with all protocol-specified follow-up evaluations
5. The patient has been informed of the nature of the study and has
consented to participate, and has authorized the collection and release of his/her medical information by signing a consent form (*Patient Informed Consent Form*)
6. Patient will receive the CoreValve® device via direct aortic approach TAVI

Exclusion criteria

1. Known hypersensitivity or contraindication to aspirin, heparin, ticlopidine, clopidogrel, nitinol, or
sensitivity to contrast media which cannot be adequately pre-medicated
2. Sepsis, including active endocarditis
3. Recent myocardial infarction (<30 days)
4. Left ventricular or atrial thrombus by echocardiography
5. Uncontrolled atrial fibrillation
6. Mitral or tricuspid valvular insufficiency (>grade II)
7. Previous aortic valve replacement (mechanical valve or stented bioprosthetic valve)
8. Evolutive or recent (within 6 months of implant procedure) cerebrovascular accident (CVA) or
transient ischemic attack (TIA)
9. Patients with:
a. Vascular conditions that make insertion and endovascular access to the aortic valve impossible, or
b. Symptomatic carotid or vertebral arterial narrowing (>70%) disease, or
c. Thoracic aortic aneurysm in the path of delivery system
10. Bleeding diathesis or coagulopathy
11. Patient refuses blood transfusion
12. Estimated life expectancy of less than 12 months unless TAVI is performed
13. Creatine clearance <20 mL/min

14. Active gastritis or peptic ulcer disease
15. Pregnancy or intent to become pregnant during study follow up
16. Patient is participating in another trial that may influence the results of this study

Study design

Design

Study type: Interventional

Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	13-11-2012
Enrollment:	20
Type:	Actual

Medical products/devices used

Generic name:	Medtronic CoreValve® System for Transcatheter Aortic Valve Implantation (TAVI)
Registration:	Yes - CE intended use

Ethics review

Approved WMO Date:	30-10-2012
Application type:	First submission
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	25-03-2013
Application type:	Amendment

Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	13-06-2013
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)

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
CCMO	NL41409.060.12
Other	The study will be registered on clinicaltrials.gov before inclusion of the first patient: NCT01676727