Prospective, controlled, single-arm clinical investigation for the treatment of subjects with severe symptomatic aortic valve stenosis using Valvosoft® Pulsed Cavitational Ultrasound Therapy (PCUT) - First-In-Man.

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Primary Study Objectives:Safety objective: assessment of procedure related mortality up to 30 days post-procedure.Performance objective: demonstration of the ability of Valvosoft to modify the structure of the calcified valve leaflets to improve...

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

Summary

ID

NL-OMON55716

Source
ToetsingOnline

Brief title
VALVOSOFT® FIM-STUDY

Condition

- Cardiac valve disorders

Synonym
severe aortic valve stenosis / severely calcified aortic valve has caused a stenosis

Research involving

Human

Sponsors and support

Primary sponsor: CARDIAWAVE SA.
Source(s) of monetary or material Support: Cardiawave SA. (sponsor of the study)

Intervention

Keyword: Calcified aortic stenosis, non-invasive, ultrasound

Outcome measures

Primary outcome

Safety:

Rate of procedure related mortality up to 30 days post-procedure.

Performance:

1. Level of improvement in leaflet mobility by means of decrease in transvalvular pressure gradient (PG) immediately post procedure compared to baseline (echocardiography).

2. Level of decrease in severity of aortic stenosis by means of increase in aortic valve area (AVA) (echocardiography) immediately post procedure compared to baseline.

Secondary outcome

Safety:

1. Rate of MAEs peri procedural and at 1, 3, 6, 12 and 24 months post procedure.

2. All-cause mortality at 1, 3, 6, 12 and 24 months post procedure.

3. Rate of stroke at 1, 3, 6, 12 and 24 months.

4. Rate of all adverse events up to 24 months.

Performance:

Device usability

1. User handling (questionnaire for operator + procedure duration).

2. Long term maintenance of improvement of AVA and PG at 1, 3, 6, 12 and 24 months. The 6 months assessment being an important secondary endpoint for regulatory purposes.

Effectiveness:

1. Improvement of clinical status assessed by means of NYHA functional class, presyncope/syncope and angina at 1, 3, 6, 12 and 24 months.

2. Improvement of quality of life by means of KCCQ at 1, 3, 6, 12 and 24 months.

Study description

Background summary

Calcific Aortic Stenosis (CAS) affects 2 13% of the population aged 65 and over. It has become a major public health concern because of the ageing western population (by 2030 one person in three will be over the age of 65 in Europe). The mean survival rate is 2 3 years for patients diagnosed with severe symptomatic CAS: about 1.3 million patients in Europe are affected at present. The only medical response to CAS is currently invasive: Surgical Aortic Valve Replacement (SAVR) and Transcatheter Aortic Valve Replacement (TAVR). The morbidity associated with both procedures remains high: 2 5% of patients die during surgery or after 30 days, 17% die within 1 year, 35% within 3 years. These surgeries also cause numerous complications (strokes, infections and infarctions). The cost to the community is ultimately extremely high: e.g. more than 100,000$ per patient in the United States. In Europe and in the US, direct and indirect costs associated with aortic valve disease were over 50 billion$ in 2012.
Moreover, not all patients are eligible for open-heart surgery or TAVR or they refuse surgery (about 10 to 15% of patients).
CARDIAWAVE has developed a new non-invasive, real-time image-guided, therapeutic approach to treat patients suffering from Calcific Aortic Stenosis. CARDIAWAVE*s Valvosoft device is a new ultrasound therapy based on a disruptive technology involving delivering an extremely precise and focused ultrasound

beam to perform a reparative effect on the aortic valve leaflets, softening the valve*s tissues, restoring leaflet mobility, and therefore improving the overall clinical status related to the aortic valve stenosis.

Study objective

Primary Study Objectives:
Safety objective: assessment of procedure related mortality up to 30 days post-procedure.
Performance objective: demonstration of the ability of Valvosoft to modify the structure of the calcified valve leaflets to improve their mobility immediately post-procedure compared to baseline.

Secondary Study Objectives:
Safety assessment of:
1. All-cause mortality and Major Adverse Events (MAEs) peri and post-procedure up to 30 days and then 3, 6, 12 and 24 months post operatively.
MAE defined as:
• Disabling stroke,
• Myocardial infarction or any clinically significant changes in biomarkers (CK, Troponin I - T) that would indicate damage to the heart structure, and,
• Clinically significant conduction disturbances requiring pacemaker implantation or persistent arrhythmias.
2. Non-disabling stroke at 1, 3, 6, 12 and 24 months.
3. Damage to surrounding body structure caused during the procedure.
4. All adverse events (non-device/procedure related; serious and non-serious) throughout the study.
Performance assessment of:
1. Demonstration of the ability of Valvosoft to modify the structure of the calcified valve leaflets to improve their mobility at 1, 3, 6, 12 and 24 months.
2. User handling (questionnaire for operator + procedure duration).
Effectiveness assessment of:
1. NYHA classification, presyncope/syncope and angina at 1, 3, 6, 12 and 24 months.
2. Kansas City Cardiomyopathy Questionnaire (KCCQ) at 1, 3, 6, 12 and 24 months.

Study design

Prospective, controlled, multicenter, single arm clinical investigation, conducted in up to three clinical investigation sites.
Up to thirty (30) subjects can be enrolled and screened simultaneously but will be treated in a consecutive manner: a subsequent subject can only be treated if the previous subject did not experience any SAE after at least 24 hours after the treatment or, in case of an SAE, an independent data safety monitoring board (DSMB) after review of the event has given its approval.

Close proctoring by specialists appointed by Cardiawave will be done for each new investigator starting with the treatment.

This is an exploratory pilot study, and no formal justification of the sample size will be made. A total of up to thirty (30) subjects will be enrolled.

Intervention

Valvosoft PCUT consists in delivering trans-thoracically precisely focused and controlled short ultrasound pulses (<20µsec) at an extremely high acoustic intensity measured in watts per square centimeter (W/cm2), to produce non-thermal mechanical tissue softening of the stiffened calcified aortic valve which is targeted. Echocardiographic live imaging enables to follow valve movements in real-time and thus target the therapeutic ultrasound on the calcified valve with great precision.
Cardiawave's Valvosoft is intended for non-invasive treatment of subjects with severe symptomatic aortic valve stenosis.

Study burden and risks

Animal studies did not show any serious risks. However, since this is a first human study, there are unforeseen risks associated with this study. Valvosoft therapy refers to patients with severe aortic valve stenosis for whom valve replacement is not an option. By means of this non-invasive therapy, these patients may still be able to achieve an improvement in their clinical condition.

Study Duration:
Enrollment: 24 months.
Follow up: discharge, 1, 3, 6, 12 and 24 months.

Study Assessments:
Baseline:
- Demographics, medical history, clinical and neuropsychological assessment, concomitant medication.
- TTE/TEE to determine eligibility and centralized assessment of baseline status of aortic valve, mitral and tricuspid valve.
- Cardiac CT-scan.
- Blood test: CBC, renal function (creatinine), Troponin T, Haptoglobin, LDH, CK.
- NYHA classification.
- KCCQ.
- Concomitant medication.
During procedure:
- TTE/TEE.
- Adverse events and device deficiencies.

- Concomitant medication.
Post-operative/at discharge
- Blood test for safety (CBC and renal function) including Troponin T, CK; to be repeated over the next 4 days if elevated.
- Clinical assessment.
- Neuropsychological assessment.
- TTE/TEE.
- Adverse events and device deficiencies.
- Operator feedback.
- Concomitant medication.
1, 3, 6, 12 and 24 months follow up:
- Clinical assessment.
- Neuropsychological assessment (at 1 month only).
- TTE/TEE.
- NYHA classification.
- KCCQ.
- Adverse events.
- Concomitant medication.

Contacts

Public
CARDIAWAVE SA.

29 rue du Faubourg Saint Jacques c/o Pépinière Paris Santé Cochin
Paris 75014
FR
Scientific
CARDIAWAVE SA.

29 rue du Faubourg Saint Jacques c/o Pépinière Paris Santé Cochin
Paris 75014
FR

Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

1. Subjects suffering from severe symptomatic aortic valve stenosis according to ESC 2017 definition, including subjects with a bicuspid valve.
2. Patient is not eligible for TAVR/SAVR according to local Heart Team.
3. Age >=18 years.
4. Subjects who are willing to provide a written informed consent prior to participating in this clinical investigation.
5. Subjects who can comply with the study follow-up or other study requirements.
6. Patient is eligible for the Valvosoft procedure according to CRC.

Exclusion criteria

1. Subjects with any electrical device implanted.
2. Subjects with unstable arrhythmia not controlled by medical treatment.
3. Subjects with implanted mechanical valve in any position or bio prosthetic valve in aortic position.
4. Subjects with complex congenital heart disease.
5. Chest deformity.
6. Cardiogenic shock.
7. History of heart transplant.
8. Subjects requiring other cardiac surgery procedures (bypass graft surgery, mitral valve procedure, tricuspid valve procedure) within one month after treatment.
9. Thrombus in heart.
10. Acute myocardial infarction, stroke or transient ischemic attack (TIA) within one month prior to enrolment*.
11. Subjects who are pregnant or nursing.
12. Subjects who are participating in another research study for which the primary endpoint has not been reached.

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):	13-03-2019
Enrollment:	15
Type:	Actual

Medical products/devices used

Generic name:	Valvosoft©
Registration:	No

Ethics review

Approved WMO Date:	01-02-2019
Application type:	First submission
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)

Approved WMO Date:	11-05-2020
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)

Approved WMO Date:	29-07-2021
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	NL67939.100.18