REDUCE LAP-HF Dutch RANDOMIZED TRIAL I:
A study to evaluate the Corvia Medical, Inc. IASD® System II to REDUCE Elevated Left Atrial Pressure in Patients with Heart Failure

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The primary objective of this randomized controlled clinical study is to evaluate the peri-procedural safety and potential effectiveness (mechanistic effect) of implanting the IASD System II in heart failure patients with an LV ejection fraction...

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Heart failures
Study type	Interventional

Summary

ID

NL-OMON42917

Source
ToetsingOnline

Brief title
REDUCE LAP-HF Dutch RANDOMIZED TRIAL I

Condition

- Heart failures

Synonym
Heart failure, Heart Failure with preserved ejection fraction

Research involving

Human

Sponsors and support

Primary sponsor: Corvia Medical, Inc.
Source(s) of monetary or material Support: Corvia Medical;Inc.

Intervention

Keyword: Heart failure, Medical device, Randomised, Safety and effectiveness

Outcome measures

Primary outcome

Safety

Peri-procedural, and 1 month Major Adverse Cardiac, Cerebrovascular, and Renal Events (MACCRE)

The primary safety outcome measure is the incidence of one or more of the following major adverse cardiac, cerebrovascular embolic, or renal events (MACCRE) defined as:

1. Cardiovascular death through 1-month post implant;

2. Embolic stroke through 1-months post implant;

3. Device and or procedure related adverse cardiac events through 1-month post implant;

4. New onset or worsening of kidney dysfunction (defined as eGFR decrease of > 20 ml/min) through 1-month post implant

Effectiveness

1. Change in supine exercise PCWP at 1 month, as assessed by an independent blinded hemodynamic core laboratory, across the four

values measured at each visit (values at 20W, 40W, 60W and 80W).

Secondary outcome

1. Change in exercise PEAK PCWP from baseline at 1 month.

2. Cardiovascular death through 12 months;

3. Rate of total (first plus recurrent) HF admissions/emergency clinic visits

or acute care facilities for IV diuresis for HF through 12 months;

4. Change in QOL (EQ-5D, and KCCQ score) at 12 months

Additional Outcome Measures

Safety related outcome measures:

1. Major adverse cardiac events through 12-months

2. All serious adverse events (SAEs) through 12-months

3. All-cause mortality, CV mortality and heart failure related mortality

through 12-months

4. Newly acquired persistent or permanent AF or atrial flutter through

12-months

5. Implant embolization and clinically significant device migration through

12-months.

6. Systemic embolic events through 12-months.

7. Increase in RV size/decrease in RV function through 12-months

8. The need for implant removal or occlusion of the implant.

Efficacy related outcome measures:

1. All-cause, and heart failure related hospitalizations/emergency department

visits with IV treatment for HF; and number of hospitalization days, ICU days through 12 months

2. Treatment for outpatient worsening of heart failure

3. Days alive, and not-hospitalized through 12-months

4. Change in blinded Investigator assessed NYHA classification between baseline and 12 months.

5. Change in 6MWT distance between baseline and 12 months

6. Assessment of shunt dimensions and flow at 12 months

7. Changes in resting and exercise PA pressures and CI between baseline and 1 month as assessed by an independent blinded hemodynamic core laboratory.

8. Change in BNP and/or NT-pro-BNP between baseline and at 12 months. MR-ANP is optional.

9. Changes in LA, LV dimensions, volume, and function, between baseline and 12 months assessed by an independent echocardiographic core laboratory

10. Changes in RA, LA, LV and RV dimensions, volume, and function between baseline and 12 months assessed by a cardiac MRI core laboratory (Sub-study only)

11. Change in CPET parameters (including exercise time) between baseline and 12 months as assessed by an independent blinded CPET core laboratory (Sub-study only)

12. Change in diuretic medications between baseline and 12 months

Study description

Background summary

Heart failure is defined as a disorder of the heart pump function with associated symptoms. Symptoms can be very different, but include at least his fatigue and / or dyspnea.
Mortality is high and depending on the severity of the heart failure. Fifty percent of patients deceased within five years (with severe heart failure, within one year) after diagnosis.

The prevalence of heart failure among the population is 2-2.5%. Currently there are 200,000 patients with heart failure in the Netherlands. The prevalence increases sharply with increasing age.
With increasing aging population combined with improved medical techniques of cardiac and non-cardiac diseases, the prevalence of heart failure is increasing.
This study is evaluating a new device (Inter-atriale septum Device (IASD) System II) that is permanently implanted in the heart and is designed to reduce the increased pressure due to heart failure, by creating a small permanent opening between the two upper chambers in the heart. The relief of this pressure by the study device may reduce some or all of the symptoms a subject is experiencing.

Study objective

The primary objective of this randomized controlled clinical study is to evaluate the peri-procedural safety and potential effectiveness (mechanistic effect) of implanting the IASD System II in heart failure patients with an LV ejection fraction >=40%, elevated left sided filling pressures, and who remain symptomatic despite optimal Guideline Directed Medical Therapy (GDMT). Clinical outcomes will also be evaluated. A subset of the results of this study will be used to facilitate design of the U.S. pivotal trial.

Study design

Multicenter, Prospective, Randomized Controlled, Single (patient) Blinded Trial, with Non-implant Control group; 1:1 randomization. Patients will be followed for 1 year, and annually every 12 months for a total of 5 years after index procedure and implant.

Intervention

Percutaneous implantation (permanent) of the IAS System II.

Study burden and risks

Heart Catheterization Risks

The main risks of a heart catheterization include but are not limited to :
• pain at the catheter insertion site,
• abnormal heart rate,
• excessive collection of blood at insertion site (4 cases in previous studies of excessive collection of blood at insertion site),
• fever after the procedure,
• significantly increased or decreased blood pressure sometimes requiring medication,
• blood loss sometimes requiring blood replacement,
• allergic reaction to the dye used to take pictures of the heart,
• temporary stoppage of breathing,
• reaction to the anesthesia medications,
• accidental creation of an abnormal passage between an artery and vein,
• obstruction of a blood vessel by an air bubble,
• blockage of a blood vessel by a blood clot,
• injury to a nerve at the insertion site, appearance of a bulge in a blood vessel,
• and the tearing or poking of a hole through a blood vessel or heart (2 cases in previous studies of tearing or poking of a hole through a blood vessel).
These risks are uncommon. This procedure will be performed 2 times within approximately 1 month. To reduce the likelihood of these risks, the study sponsor carefully selects and supports study doctors that have significant experience with similar types of procedures.

Intra-cardiac Echocardiography Risks
The main risks of an intra-cardiac echo include but are not limited to irregular heart rhythms, which may require treatment, bleeding where the catheter was put into your blood vessel, a blood clot could form, and the catheter may damage a blood vessel, for example, where the catheter was inserted. Other potential risks of intra-cardiac echo are puncture of a blood vessel as it travels to the heart or puncture of the heart, both of which may be life threatening and may require urgent surgery to correct. While uncommon, a heart attack or stroke might be triggered by the test. To reduce the likelihood of these unlikely risks, specially trained doctors perform these procedures.

Investigational Device and Implantation Procedure Risks
The main risks of having the investigational device implanted are similar to the risks listed above for heart catheterization. In addition, small clots may form on the implant itself and be released into the blood circulation. There is also a risk of paradoxical embolism, where the blood clot moves directly from the right side of the heart to the left through the hole made by the device. If clots like these happen, stroke, heart failure, heart attack or death may occur. The study doctor will give the patient medications before the procedure, (anticoagulation also called blood thinner), after the procedure and during the study follow up period to

reduce this risk. Some preclinical testing without anticoagulation suggested that thrombus (clot) formation might occur. Therefore, this device should not be used in patients who cannot be anticoagulated (e.g., with heparin or another type of anticoagulant).

Another potential risk is that, once implanted in the heart, the investigational device does not stay in place and floats away into another part of
the heart or into a blood vessel. If this happens, stroke, heart failure, heart attack or death may occur. To reduce the risk of this happening, the study doctor uses special imaging equipment during the procedure to see the investigational device and make sure it is placed in the correct position in the heart. In addition, the investigational device shape and materials were selected to hold it in place. If the device does move out of place during the implant procedure, the study doctor may use a catheter to retrieve and remove it (in previous studies, 2 of 75 were not in the correct position during procedure. The devices were removed and a new device successfully implanted during the same procedure). If the device moves out of place after the subject is discharged from the hospital, the investigational device may need to be removed during open heart surgery (this has not yet occurred in previous studies).

Another potential risk is that one or more of the investigational device arms rubs or erodes or pokes a hole into a blood vessel or part of the heart, also referred to as perforation or erosion. If this happens, urgent surgery may be required to remove the device and repair the tear or hole.

Another potential risk is a break of one of the investigational device arms once it is in the heart. If this happens, the broken arm could rub against the wall of the heart causing a callous, blood clot and/or infection. In the unlikely event that the investigational device breaks into several pieces, a piece of it could potentially break off and float away to another place in the body. Depending on its final location, surgery may be required to remove the piece and the remaining broken device. To reduce the risk of this happening, the investigational device is made of materials that were specifically selected because of their strength and resistance to wear.

Another potential risk is that the heart failure does not improve during the study, or worsens. The procedure may involve risks which are currently unforeseeable.

Side effects are usually temporary and manageable. However, it is possible they could cause serious injury or death. The patient's condition may not get better or may become worse during this study. If we learn of any new risks while this study is ongoing, the study doctor will make

the patient aware of them as soon as possible.

Exercise Testing Risks
The peak oxygen test can be exhausting. The risks of these exercise stress tests include brief light-headedness, severe shortness of breath, fatigue (tiredness) from walking on the treadmill or pedaling the exercise bike, muscle soreness, irregular heartbeat, chest pain, sudden heart attack, stroke, or death. To minimize these risks trained medical professionals will be present during this procedure. In addition, the patient will have his/ her heart rate monitored continuously throughout the testing. The patient will also have his/ her blood pressure and his/ her rate of perceived exertion monitored throughout the testing.

Blood Draw Risks
There are some side effects that can happen when the patient has his/ her blood drawn. This includes excessive bleeding, fainting or feeling light-headed, hematoma (blood pooling under the skin), infection (a slight risk any time the skin is broken).

Pregnant women
This treatment may have unforeseeable risks to your embryo or foetus if you are pregnant at the moment of the procedure. Woman of childbearing age and fertile are not authorized to take part of this clinical trial.

Risks of Antiplatelet Medication
The medications used to reduce the chance of developing a blood clot do carry certain risks. Sometimes the medications can cause bleeding problems, headaches, dizziness, pain, and discomfort. Other risks include bruises, swelling, blood in the urine or stool or stools that look like coffee grounds, more bleeding than normal during your period, purple toes, a sign of purple toes syndrome, a serious condition; and pain, change in temperature, or noticeable blackish areas in your extremities.

Cardiac MRI Risks
The magnetic resonance imaging (MRI) machine uses a strong magnet to take images of the heart. Due to the use of the strong magnet, special precautions must be taken to perform an MRI on people with certain implanted devices such as pacemakers or cochlear implants, or other internal metal objects, such as surgical clips, plates, screws, or wire mesh. The MRI magnet may cause any metal in the body to move. The patient will be screened carefully beforehand to make sure you can have an MRI. There are no other known risks of MRI. Some individuals with claustrophobia (fear of closed spaces) may find the MRI equipment too confining. In that case, the patient can request to be removed from the scanner and this will be done immediately. The MRI scanner makes a loud thumping sound. The patient can ask to wear

protective earplugs during the scanning.

Benefits
There is no guarantee that the subject will benefit from participation in this study.
Potential benefits to patients implanted with the study device include the following:
• Reduction in shortness of breath
• Reduction in the number of hospitalizations and/or hospital days
• Reduction in the number of emergency room visits
• Reduction in medications
• Improved exercise tolerance
• Improved quality of life
• Improved life expectancy
By participating in this study, the subject will help others by providing information that may be used to develop new treatments for patients with similar conditions.

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. Chronic symptomatic heart failure (HF) documented by the following:
a. New York Heart Association (NYHA) class III/ambulatory class IV symptoms (Paroxysmal nocturnal dyspnea, orthopnea, dyspnea on mild or moderate exertion) at screening visit; or signs (Any rales post cough, chest x-ray demonstrating pulmonary congestion,) within past 12 months; AND
b. >= One hospital admission for which HF was a major component of the hospitalization, or a healthcare facility (emergency department/acute care facility) treatment with intravenous (IV) or intensification of oral diuresis for HF, within the 12 months prior to study entry; OR an NT-pro BNP value > 200 pg/ml in normal sinus rhythm, > 600 pg/ml in atrial fibrillation, or a BNP value > 70 pg/ml in normal sinus rhythm, > 200 pg/ml in atrial fibrillation within the past 6 months.
2. Ongoing stable GDMT HF management and management of potential comorbidities according to the 2013 ACCF/AHA Guidelines for the management of Heart Failure (with no significant changes [>100% increase or 50% decrease], excluding diuretic dose changes for a minimum of 4 weeks prior to screening) that is expected to be maintained without change for 6 months.
3. Age >= 40 years old
4. Site determined LV ejection fraction >= 40% within the past 3 months, without previously documented ejection fraction <30%.% (within the last 5 years).
5. Site determined elevated left atrial pressure with a gradient compared to right atrial pressure (RAP) documented by:
a. End-expiratory PCWP during supine ergometer exercise >= 25mm Hg, and greater than RAP by >= 5 mm Hg.
6. Site determined echocardiographic evidence of diastolic dysfunction documented by one or more of the following:
a. LA diameter > 4 cm; or
b. LA volume index > 28 ml/m2 or
c. Lateral e* <10 cm/s; or
d. Septal e* <8 cm/s; or
e. Lateral E/e* >10 ; or
f. Septal E/e* > 15
7. Subject has been informed of the nature of the study, agrees to its provisions and has provided written informed consent, approved by the IRB or EC
8. Subject is willing to comply with clinical investigation procedures and agrees to return for all required follow-up visits, tests, and exams
9. Trans-septal catheterization and femoral vein access is determined to be feasible by site principal interventional cardiology investigator

Exclusion criteria

1. Myocardial infarction and/or percutaneous cardiac intervention within past 3 months; CABG in past 3 months, or current indication for coronary revascularization
2. Cardiac resynchronization therapy initiated within the past 6 months
3. Severe heart failure defined as one or more of the below:
a. ACC/AHA/ESC Stage D heart failure, Non-ambulatory NYHA Class IV HF;
b. Cardiac index < 2.0 L/min/m2
c. Inotropic infusion (continuous or intermittent) within the past 6 months
d. Patient is on the cardiac transplant waiting list
4. Inability to perform 6 minute walk test (distance < 50 m), OR 6 minute walk test > 600m
5. Known clinically significant un-revascularized coronary artery disease, defined as: epi-cardial coronary artery stenosis associated with angina or other evidence of coronary ischemia.
6. History of stroke, transient ischemic attack (TIA), deep vein thrombosis (DVT), or pulmonary emboli within the past 6 months
7. Known clinically significant untreated carotid artery stenosis.
8. Presence of significant valve disease defined by the site cardiologist as:
a) Mitral valve regurgitation defined as grade >= 3+ MR
b) Tricuspid valve regurgitation defined as grade >= 2+ TR;
c) Aortic valve disease defined as >= 2+ AR or > moderate AS
9. Hypertrophic obstructive cardiomyopathy, restrictive cardiomyopathy, constrictive pericarditis, cardiac amyloidosis or other infiltrative cardiomyopathy (e.g. hemochromatosis, sarcoidosis)
10. Subject is contraindicated to receive either dual antiplatelet therapy or warfarin (analogue); or has a documented coagulopathy
11. Atrial fibrillation with resting HR > 100 BPM
12. Arterial oxygen saturation < 95% on room air
13. Significant hepatic impairment defined as 3X upper limit of normal of transaminases, total bilirubin, or alkaline phosphatase
14. Right ventricular dysfunction, defined by the site cardiologist as
a. More than mild RV dysfunction as estimated by TTE; OR
b. TAPSE < 1.4 cm; OR
c. RV size >= LV size as estimated by TTE; OR
d. Echocardiographic or clinical evidence of congestive hepatopathy; OR
e. Evidence of RV dysfunction defined by TTE as an RV fractional area change < 35%;
15. Resting RAP > 14 mmHg
16. Evidence of pulmonary hypertension with PVR > 4 Wood units
17. Chronic pulmonary disease requiring continuous home oxygen, OR hospitalization for exacerbation in the 12 months prior to study entry, OR significant chronic pulmonary disease defined as FEV1 < 50% predicted, or in the opinion of the investigator
18. Currently participating in an investigational drug or device study. Note: trials requiring extended follow-up for products that were investigational but have since become commercially available are not considered investigational trials
19. Life expectancy less than 12 months for non-cardiovascular reasons
20. Echocardiographic evidence of intra-cardiac mass, thrombus or vegetation

21. Known or suspected allergy to nickel
22. Fertile women
23. Currently requiring dialysis; or estimated-GFR <25ml/min/1.73 m2 by CKD-Epi equation
24. Systolic blood pressure >170 mm Hg at screening
25. Subjects with existing atrial septal defects. Subjects with a patent foramen ovale (PFO), who meet PCWP criteria despite the PFO, are allowed.
26. Subjects on immunosuppression or systemic steroid treatment (>10 mg prednisone/day).
27. Severe obstructive sleep apnea not treated with CPAP or other measures
28. Severe depression and/or anxiety
29. In the opinion of the investigator, the subject is not an appropriate candidate for the study

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):	03-02-2016
Enrollment:	5
Type:	Actual

Medical products/devices used

Generic name:	IASD® System II
Registration:	Yes - CE intended use

Ethics review

Approved WMO Date:	19-07-2016
Application type:	First submission
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	07-11-2016
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	27-02-2017
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	25-04-2017
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)

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	NCT02600234
CCMO	NL57357.042.16

Study results

Date completed:	23-11-2021
Actual enrolment:	4