Re-Evaluation of the Corvia Atrial Shunt Device in a Precision Medicine Trial to Determine Efficacy in Mildly Reduced or Preserved EF Heart Failure

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Ethical review	Approved WMO
Status	Recruiting
Health condition type	Heart failures
Study type	Observational invasive

Summary

ID

NL-OMON53718

Source
ToetsingOnline

Brief title
RESPONDER-HF

Condition

- Heart failures

Synonym
dyspnea on exertion, Heart Failure

Research involving
Human

Sponsors and support

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

Intervention

Keyword: Corvia Atrial Shunt System, Heart failure, InterAtrial Shunt Device (IASD®) System II

Outcome measures

Primary outcome

The primary endpoint is the composite of (a) total rate (first plus recurrent) per patient year of heart failure (HF) admissions or healthcare facility visits for IV diuresis or urgent visits with intensification of oral diuresis for HF through 24 months follow-up, analyzed when the last patient completes 12 months follow-up, and time-to-first HF event; and (b) change from baseline KCCQ total summary score at 12 months. Heart failure events reported by investigators will be adjudicated to the primary endpoint by the CEC. Evaluated through Bayesian technique which borrows treatment effect from the RCT II clinical trial.

Primary Analysis Bayesian statistical analysis of the primary endpoint: Treatment groups from the Modified Intention to Treat (MITT) population will be compared with a Bayesian cumulative logistic proportional odds regression. The analysis utilizes pairwise comparisons from the Finkelstein-Schoenfeld test framework to compare patient outcomes on the primary endpoint. The testing hierarchy is the HF event rate, the time to first HF event followed by the KCCQ component. For each pairwise comparison, patients are assigned a 1, 0, -1 if the patient won, tied, or lost the comparison, respectively. The *F-S score*

for each patient is calculated as the sum of

their pairwise comparison outcomes.

The primary analysis is a Bayesian cumulative logistic proportional odds regression analysis on the F-S scores that facilitates borrowing of information (30%, fixed) on the treatment effect from the previous REDUCE LAP-HF RCT II study within a responder subgroup. The treatment effect will be estimated as the increase or decrease in the odds (odds ratio; OR) of having more wins in the pairwise F-S comparisons in the active treatment group compared to the control group. The null hypothesis will be tested based on the posterior probability that the OR is greater than 1. Significance will be declared if the posterior probability the OR > 1 is greater than 0.975.

Secondary outcome

Major Secondary Endpoint: The major secondary endpoint is the incidence of and

time-to-cardiovascular mortality through 12 months.

Statistical Analysis Secondary Outcome Measures: Listings and descriptive

statistics will be provided and compared for similarity with the

same measures from RCT II.

Study description

Background summary

The Corvia Atrial Shunt System is indicated for the improvement in quality of life and reduction of heart failure related symptoms and events in patients with heart failure with preserved (HFpEF) or mildly reduced ejection fraction (HFmrEF) with elevated left atrial pressures, without latent pulmonary vascular disease and without a cardiac rhythm device, who remain symptomatic despite standard GDMT. The Corvia Atrial Shunt System / InterAtrial Shunt Device

(IASD®) System II bears the CE Mark for medical devices in Europe.

Study objective

The primary objective of this clinical trial is to further evaluate the clinical efficacy of the Corvia Atrial Shunt in symptomatic heart failure patients with a left ventricular ejection fraction (LVEF) >= 40%, and elevated left sided filling pressures despite standard Guideline-Directed Medical Therapy (GDMT); and to confirm the treatment effect observed in the responder group of the REDUCE LAP-HF Randomized Trial II. (Corvia protocol 1601).

Study design

Multicenter, Prospective, Randomized, Sham Controlled, Double Blinded Clinical Trial, with 1:1 randomization
Patients are consented to participate, screened against non-invasive eligibility criteria. Baseline characteristics, demographic, medical history, heart failure medication, echocardiogram, and relevant laboratory data summarized in the Potential Participant Trial Eligibility Committee Evaluation Form, are reviewed by the Trial Eligibility Committee (TEC) to
1) approve the participant for hemodynamic evaluation;
2) to request additional information; or
3) to exclude the participant from further participation the RESPONDER-HF trial.
If the patient does not qualify, then the patient becomes a screen failed patient and is not scheduled for the exercise hemodynamic study and potential randomization.
If the participant is approved, they are scheduled for hemodynamic evaluation including right heart catheterization with hemodynamic measurements at rest and during supine bicycle exercise. Hemodynamically eligible patients will then be blinded and sedated; There will a soft cloth placed to cover the eyes and ear buds used which will be connected to a music player. In addition screens will be used to prevent participants from viewing the imaging screens, which indicate the presence or absence of the device.
All patients will have femoral venous access and will undergo a brief intracardiac echocardiography (ICE) or transesophageal echocardiography (TEE) exam for anatomic suitability. Eligible patients are then randomized to the treatment or control group. Patients randomized to the control group receive additional cardiac imaging and end their intervention with removal of devices. Patients in the treatment arm will undergo an echo
and fluoroscopically guided transseptal puncture and Corvia Atrial Shunt implant procedure. If a previously unknown protocol exclusion is discovered during the index procedure, and prior to the initiation of transseptal puncture, the participant is unblinded, followed for 30 days and then exits the study. All patients receive a physical exam and study medications by an unblinded physician or nurse prior to discharge.

Physicians responsible for managing patient care, research staff involved in conducting follow-up evaluations, and the hemodynamic core laboratory will be blinded to study arm assignment, including baseline hemodynamic data until the patient is unblinded.
Randomized patients will be followed for 30 days, 3, 6, 12, 18 and 24 months and annually for 5 years after the index procedure. In-person visits will take place for the first 24 months. Telephone follow-up and medical chart review will be conducted for years 3-5
Patients and blinded staff will be unblinded following the 24-month follow-up visit.
Patients randomized to the control arm may be offered an opportunity to cross-over to the treatment arm at after 24 months provided patient selection criteria are met at that time.
Crossover patients will then be followed in person for 30 days and 6 and 12 months, and by telephone and chart review annually for 5 years after the crossover procedure.
Independent CEC, DSMB, and core laboratories will be utilized during this trial.

Study burden and risks

Subjects participation in the study will last up to 5-7 years.

The following is out of standard care:
Blood sample collection,
electrocardiogram,
echocardiography,
6-minute walk test,
Invasive exercise hemodynamic evaluation,
Questionnaires and Telephone Follow-Up

Risks associated:
Complications associated with implantation of the Corvia Atrial Shunt and similar procedures in which implants are placed on the atrial septum.
Participation in the study carries additional assessments and imaging above the standard of care.
All other study-specific assessments are clinic and physical assessments that would be within the range of standard follow-up of patients with a this medical history. Additional HF symptom and quality of life assessments with surveys and walking tests.
An additional risk of participating in a clinical study is the risk of a lapse of confidentiality or exposure of personal identifying information.

Risk-benefit analysis:
The risk involved in the clinical study is minimised due to the fact the device being used is CE-marked and the study design falls within the intended use population. Subjects can still receive the same device treatment outside of the

study. The risk of participating in the study is only minimally increased as compared to receiving the device outside the study, as there is a higher degree of imaging and clinical assessment than would be present otherwise. Additionally, there are the risks involved in data collection. These risks, though, have been mitigated by the benefit of additional clinical follow-up and closer care, as well as procedures which have been put in place to protect subjects* personal information.

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. Symptoms of HF requiring current treatment with diuretics if tolerated for >= 30 days AND

b. New York Heart Association (NYHA) class II with prior history of >class II;
OR NYHA class III, or ambulatory
NYHA class IV symptoms; AND
c. >= 1 HF hospital admission (with HF as the primary, or secondary diagnosis); or treatment with intravenous (IV) diuretics; or intensification of oral diuresis within the 12 months prior to study entry; OR an NT-pro BNP value > 150 pg/ml in normal sinus rhythm, > 450 pg/ml in atrial fibrillation, or a BNP value > 50 pg/ml in normal sinus rhythm, > 150 pg/ml in atrial fibrillation within the past 6 months.
2. Ongoing stable GDMT HF management and management of comorbidities according to the 2022 ACC/AHA Guidelines for the Management of Heart Failure. Stable management includes a minimum period of 4 weeks post-hospitalization for any cause, including treatment with IV diuretics.
3. Site determined echocardiographic LV ejection fraction >= 40% within the past 6 months, without documented ejection fraction < 30% in the 5 years prior.
4. Site determined echocardiographic evidence of diastolic dysfunction documented by one or more of the following:
a. LA diameter > 4 cm; or
b. Diastolic LA volume > 50 or LA volume index > 28 ml/m 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
5. Site determined elevated PCWP with a gradient compared to right atrial pressure (RAP) documented by end-expiratory PCWP during supine ergometer exercise >= 25mm Hg, and greater than RAP by >= 5 mm Hg.
6. Resting RAP <= 14 mmHg
7. Site determined hemodynamic evidence of peak exercise PVR < 1.75 Wood units [NEW
inclusion criterion]
8. Age >= 40 years old
9. Participant 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
10. Participant is willing to comply with clinical investigation procedures and agrees to return for all required follow-up visits, tests, and exams
11. Transseptal catheterization and femoral vein access to the right atrium is determined to be feasible by site interventional cardiology investigator.

Exclusion criteria

1. Advanced 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) for EF < 40% within the past 6 months

d. Patient is on the cardiac transplant waiting list.
2. Inability to perform 6 minute walk test (distance < 50 m), OR 6 minute walk test > 600m
3. The patient has verified that the ability to walk 6 minutes is limited primarily by joint, foot, leg, hip or back pain; unsteadiness or dizziness or lifestyle (and not by shortness of breath and/or fatigue and/or chest pain).
4. Right ventricular dysfunction, assessed by the site cardiologist and defined as one or more of the following:
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. Ultrasound or clinical evidence of congestive hepatopathy; OR
e. Evidence of RV dysfunction defined by TTE as an RV fractional area change < 35%.
5. Any implanted cardiac rhythm device [NEW exclusion criterion]
6. Structural heart repair AVR or MVR (surgical or percutaneous) within the past 12 months; planned valve intervention in the next 3 months, or presence of hemodynamically significant valve disease as assessed by the site cardiologist and defined as:
a. Mitral valve disease grade >= 3+ MR or > mild MS; OR
b. Tricuspid valve regurgitation grade >= 2+ TR; OR
c. Aortic valve disease >= 2+ AR or > moderate AS.
7. Echocardiographic evidence of intra-cardiac mass, thrombus or vegetation
8. Participants with existing or surgically closed (with a patch) atrial septal defects.
Participants with a patent foramen ovale (PFO), who meet PCWP criteria despite the PFO, are not excluded.
9. MI and/or percutaneous cardiac intervention within past 3 months; CABG in past 3 months or any planned cardiac interventions in the 3 months following enrollment.
10. Known clinically significant un-revascularized coronary artery disease, defined as:
coronary artery stenosis with angina or other evidence of ongoing active coronary ischemia.
11. Known clinically significant untreated carotid artery stenosis likely to require intervention.
12. Atrial fibrillation with resting HR > 100 BPM
13. Hypertrophic obstructive cardiomyopathy, restrictive cardiomyopathy, constrictive pericarditis, cardiac amyloidosis or infiltrative cardiomyopathy (e.g. hemochromatosis sarcoidosis)
14. History of stroke, transient ischemic attack (TIA), deep vein thrombosis (DVT), or pulmonary emboli within the past 6 months.
15. Participant is contraindicated to receive either dual antiplatelet therapy, or an oral anticoagulant; or has a documented coagulopathy
16. Anemia with Hemoglobin < 10 g/dl
17. Chronic pulmonary disease requiring continuous home oxygen, OR significant chronic pulmonary disease defined as FEV1 <1L.

18. Resting arterial oxygen saturation < 95% on room air, <93% when residing at high altitude
19. Currently requiring dialysis; or estimated GFR < 25ml/min/1.73 m2 by CKD-Epi equation
20. Systolic blood pressure > 170 mm Hg at screening
21. Significant hepatic impairment defined as 3X upper limit of normal of transaminases, total bilirubin, or alkaline phosphatase
22. Participants on significant immunosuppressive treatment or on systemic steroid treatment
23. Life expectancy less than 12 months for known non-cardiovascular reasons
24. Known hypersensitivity to nickel or titanium
25. Women of childbearing potential
26. Severe obstructive sleep apnea not treated with CPAP or other measures
27. BMI > 45; BMI 40 - 45 is also excluded unless in the opinion of the investigator, vascular access can be obtained safely.
28. Severe depression and/or anxiety
29. Currently participating in an investigational drug or device study that would interfere with the conduct or results of this study. Note: trials requiring extended follow-up for products that were investigational but have since become commercially available are not considered investigational
30. In the opinion of the investigator, the Participant is not an appropriate candidate for the study
31. No patients who are unable to give consent will be included in the clinical trial

Study design

Design

Study type:	Observational invasive
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Double blinded (masking used)

Primary purpose: Treatment

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	23-09-2024
Enrollment:	35

Type:	Actual

Medical products/devices used

Generic name:	Corvia Atrial Shunt System / InterAtrial Shunt Device (IASD®) System II
Registration:	Yes - CE intended use

Ethics review

Approved WMO Date:	12-04-2023
Application type:	First submission
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	16-06-2023
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	07-02-2024
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	23-05-2024
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	01-10-2024
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	NCT05425459
CCMO	NL82526.042.22