Transcatheter Interatrial Shunt Device for the Treatment of Heart Failure
Rationale and Design of the Randomized Trial to REDUCE Elevated Left Atrial Pressure in Heart Failure (REDUCE LAP-HF I)

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Reference: Feldman T, Komtebedde J, Burkhoff D, et al. Transcatheter Interatrial Shunt Device for the Treatment of Heart Failure. *Circulation: Heart Failure Circ Heart Fail*. 2016;9(7). doi:10.1161/circheartfailure.116.003025.

Background

Heart failure (HF) with preserved ejection fraction (HFpEF) is a major health concern and a therapeutic challenge. Elevated left atrial pressure (LAP) is believed to be a key contributor to dyspnea, exercise intolerance, morbidity and mortality.

Given the lack of success with pharmacological approaches, a device-based approach has been developed, in part based upon the observation that patients with Lutembacher syndrome (ASD + Mitral Stenosis (MS)) are less symptomatic than MS without ASD.

It is hypothesized that the de-compression of the left atrium via a left-to-right, transcatheter, interatrial shunt may minimize symptoms in patients with HFpEF.

The Corvia Medical Inc. (Tewksbury, MA) **Inter-atrial Shunt Device (IASD®) System II** is the device being used in this first randomized trial to investigate reduction of LAP in HFpEF patients using a device-based therapy. It is a self-expanding metal cage with a curved right atrial side to accommodate differences in septal wall thicknesses. It comes preloaded on the inner catheter of the delivery system, which allows for a stepwise release. It is radiopaque and echogenic for imaging purposes.

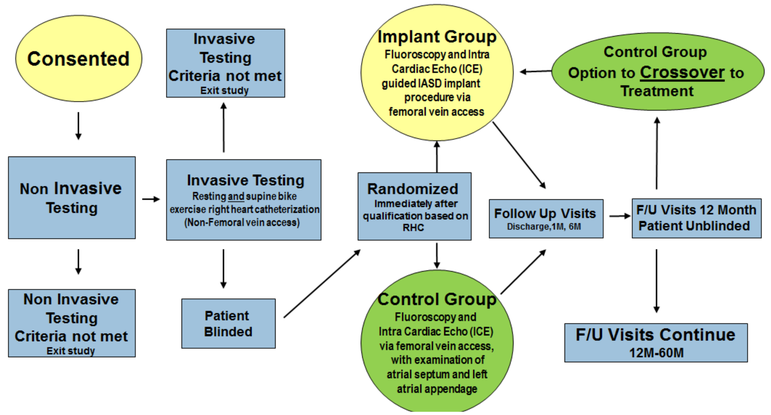
Objective

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 a 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.

Trial 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.
- After qualification, including supine bicycle exercise testing, eligible patients are randomized to either the treatment or control group.
- Patient randomization is via an Interactive Web Response System (IWRS). All patients are sedated, and both treatment and control arm patients require femoral venous access after randomization.
- Patients randomized to the **treatment arm** undergo a fluoroscopically and intra cardiac echocardiography guided trans-septal puncture and IASD® System II implant procedure.
- Patients randomized to the **control arm** undergo fluoroscopy and intra cardiac echocardiography, with examination of the atrial septum and left atrial appendage.
- Patients randomized to the control arm who meet criteria will be allowed to cross-over to the treatment arm at ≥ 12 months post-control procedure. Cross-over patients will then be followed for 5 years after cross-over.
- Patient blinding includes earphones with music to preclude the patient from hearing the procedural discussions, and blindfolding or shielding of the imaging screens in the cardiac catheterization laboratory during the procedure. Research staff are instructed to maintain patient blinding.
- Independent CEC, DSMB, and core laboratories will be utilized for retrospective data analysis and interpretation during this trial.
- The physicians managing the randomized patients, research individuals involved in conducting selected post- randomization evaluations; the Hemodynamic, and CPET core laboratories are blinded to the study arm.
- Up to 80 subjects at 22 investigational sites in the U.S.; and 6 investigational sites outside of the US will be enrolled to randomize 40 patients and obtain 1 month hemodynamic follow-up.*

*The sample size is driven by the mechanistic effect (change in supine exercise PCWP compared to control) using power calculations and based on historical and pilot study data.



Patient Population

40 patients ≥40 years of age with chronic heart failure and a LV ejection fraction ≥40 will be randomized from 22 US sites and 6 sites outside of the US. Eligible patients are symptomatic despite optimal GDMT and meet invasive hemodynamic criteria such as an elevated LA pressure (end expiratory PCWP during ergometer exercise of ≥25mm Hg and greater than RAP by ≥5mm Hg). Patients also have to have site determined echocardiographic evidence of diastolic dysfunction.
Additionally, patients must be able to complete a 6 minute walk test and have no recent history of MI or percutaneous cardiac intervention, stroke, TIA, CABG, or cardiac resynchronization therapy. Patients are also excluded if they have untreated carotid artery stenosis, significant valve disease, a current indication for coronary revascularization, severe heart failure, or require dialysis.

Key Safety Outcome

Patients will be followed for 5 years after index procedure.

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:

- Cardiovascular death through 1-month post implant;
- Embolic stroke through 1-months post implant;
- Device and or procedure related adverse cardiac events through 1-month post implant;
- New onset or worsening of kidney dysfunction (defined as eGFR decrease of > 20 ml/min) through 1-month post implant

Key Effectiveness Outcome

Mechanistic Effect: 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).

Key Secondary Outcomes

- Change in exercise PEAK PCWP from baseline at 1 month;
- Cardiovascular death through 12 months;
- Rate of total (first plus recurrent) HF admissions/emergency clinic visits or acute care facilities for IV diuresis for HF through 12 months;
- Change in QOL (EQ-5D, and KCCQ score) at 12 months

Statistical Considerations

The intent-to-treat population will be used for analysis purposes.
Key Safety Outcome Analysis: The percentage of patients with MACCRE with a 2-sided exact confidence interval will be used. Also for each treatment group, Kaplan-Meier curves and estimates of cumulative MACCRE rate at 12 months will be estimated for the 40 patients.
Key Effectiveness Outcome Analysis: A mixed-measures repeated model ANCOVA test with a two-sided 0.05 level of significance will be used to examine the change in PCWP from baseline to one month.

Discussion

This first randomized trial of a device-based therapy benefits from strict criteria for a HF diagnosis, detailed exercise hemodynamics, and a randomized design to reduce possible placebo effects. The small sample size and potential for unblinding of patients and investigators are limitations but this trial is not intended to be definitive.

CAUTION: Investigational Device. Limited by United States law to investigational use.

Disclosure: Study sponsored by Corvia Medical Inc.