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Transcatheter InterAtrial Shunt Device for the treatment of heart failure: Rationale and design of the pivotal randomized trial to REDUCE Elevated Left Atrial Pressure in Patients with Heart Failure II (REDUCE LAP-HF II)

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Background A randomized, sham-controlled trial in patients with heart failure (HF) and left ventricular ejection fraction (LVEF) ≥40% demonstrated reductions in pulmonary capillary wedge pressure (PCWP) with a novel transcatheter InterAtrial Shunt Device (IASD). Whether this hemodynamic effect will translate to an improvement in cardiovascular outcomes and symptoms requires additional study.

Study design and objectives REDUCE Elevated Left Atrial Pressure in Patients with Heart Failure II (REDUCE LAP HF-II) is a multicenter, prospective, randomized, sham-controlled, blinded trial designed to evaluate the clinical efficacy of the IASD in symptomatic HF and elevated left atrial pressures. Up to 608 HF patients age ≥ 40 years with LVEF ≥40%, PCWP ≥25 mm Hg during supine ergometer exercise, and PCWP ≥5 mm Hg higher than right atrial pressure will be randomized 1:1 to the IASD versus sham control. Key exclusion criteria include hemodynamically significant valvular disease, evidence of pulmonary arterial hypertension, and right heart dysfunction. The primary endpoint is a hierarchical composite, analyzed by the Finkelstein-Schoenfeld methodology, that includes (1) cardiovascular mortality or first nonfatal ischemic stroke through 12 months; (2) total (first plus recurrent) HF hospitalizations or healthcare facility visits for intravenous diuretics up to 24 months, analyzed when the last randomized patient completes 12 months of follow-up; and (3) change in Kansas City Cardiomyopathy Questionnaire overall summary score from baseline to 12 months. Follow-up echocardiography will be performed at 6, 12, and 24 months to evaluate shunt flow and cardiac chamber size/function. Patients will be followed for a total of 5 years after the index procedure.

Conclusions REDUCE LAP-HF II is designed to evaluate the clinical efficacy of the IASD device in patients with symptomatic HF with elevated left atrial pressure and LVEF ≥40%. (Am Heart J 2020;226:222-31.)

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Heart failure (HF) has a prevalence of >26 million people worldwide[1] and carries with it significant morbidity and mortality.[2,3] An estimated $30.7 billion dollars is spent annually in the United States on HF.[2] More than one half of patients with HF have preserved ejection fraction (HFpEF; EF > 50%), and this proportion has increased over time.[4,5] HF with midrange EF (HFmrEF; EF 40%-50%) is increasingly recognized as an understudied and important subgroup of HF patients that shares characteristics with both HFpEF and HF with reduced EF (HFrEF).

Although a multitude of pharmacologic therapies exist which have been shown to improve mortality and reduce symptoms in patients with HFrEF, there are no such therapies that have been shown to improve outcomes in patient with preserved or midrange EF.[5-7] Therapy consists of treatment of volume overload with diuretics when present and management of coexisting medical

conditions with the goal of improving exercise tolerance and quality of life, and preventing hospitalization.[5] Thus, in patients with HF and EF > 40%, there is a pressing unmet need for novel therapeutics.

Although HFpEF is now considered to be a systemic syndrome that is more complex than simply a disease of left ventricular (LV) hypertrophy and LV diastolic dysfunction, elevated left atrial (LA) pressure is still the primary hemodynamic cardiac abnormality in patients with HFpEF.[4,8] Elevated LA pressure is transmitted to the pulmonary capillary bed, especially during exercise,[9-12] and contributes to symptoms of shortness of breath, fatigue, fluid retention, and mortality.[13-15]Thus, treatment of elevated LA pressure, particularly during exertion, could improve symptoms and outcomes in HFpEF and may do the same for HFmrEF.

Historical experience with mitral stenosis, a condition associated with elevated LA pressure related to obstructed outflow, showed that patients with coexisting atrial septal defects (Lutembacher syndrome, first described in 1916)[16] had fewer symptoms and better outcomes than patients with isolated mitral stenosis.[17,18] Hemodynamic computer modeling has suggested that creation of an interatrial shunt could effectively mitigate increases in LA pressure in patients with HFpEF.[19] This led to postulation that controlled creation of a left-to-right interatrial shunt might be a therapeutic intervention and provided the rationale for the development of a novel InterAtrial Shunt Device (IASD, Corvia Medical Inc, Tewksbury, MA) for the treatment of HF.

This IASD has been evaluated in patients with HF and EF > 40% in 3 separate previous trials. A pilot, open-label, single-arm evaluation of the Corvia IASD in n = 11 patients with EF ≥ 45% demonstrated a decrease in pulmonary capillary wedge pressure (PCWP) at 30 days with improvement in symptoms, New York Heart Association (NYHA) class, and quality of life compared with baseline at 1 year.[20,21]

The REDUCE Left Atrial Pressure in Heart Failure (REDUCE LAP-HF) trial was an open-label, single-arm trial which evaluated the performance and safety of the Corvia IASD in 68 patients (n = 64 received the IASD implant) all of whom had left ventricular ejection fraction (LVEF) ≥ 40%. In this trial, there were no periprocedural or major adverse cardiac or cerebrovascular event through 6 months of follow-up, and 58% of patients had a lower PCWP during exertion at 6 months.[22,23] At 12 months, there were sustained improvements in hemodynamics, NYHA class, quality of life, and 6-minute walk test distance (6MWT).[24] The device has remained patent in all patients in follow-up to date. Although the results of the REDUCE LAP-HF open-label trial were promising from both a therapeutic and safety standpoint, the nonrandomized, nonblinded nature of the trial limited the ability to make causal inferences about the efficacy of the device. Thus, additional properly controlled trials were required to further evaluate the hemodynamic and clinical effectiveness of the device.

The REDUCE LAP-HF I trial was a phase 2, prospective, randomized, blinded, sham-controlled clinical trial that included 44 patients with LVEF ≥ 40% (and no previously documented EF < 30% within 5 years prior to enrollment). Right heart catheterization was used for both baseline and 1-month follow-up assessment of PCWP. Patients were randomized 1:1 to the IASD or sham control procedure. There was a greater reduction in exercise PCWP at 1 month in the IASD group compared with control without any periprocedural or major adverse cardiac, cerebrovascular, or renal events in the IASD group.[25,26] Importantly, protocol-driven echocardiographic follow-up has not identified right-sided HF or pulmonary hypertension associated with the IASD, and the device has remained patent in all patients in follow-up to date. The REDUCE LAP-HF I trial was important because it showed the hemodynamic effectiveness of the device, thereby obviating the need for cumbersome repeated invasive hemodynamic testing in future studies, setting the stage for a larger-scale pivotal trial to determine the clinical effectiveness of the IASD. One-year safety and clinical outcomes of the REDUCE LAP-HF I trial, which have now been published, show that the device remains patent at 1 year in all patients and appears to be safe. In addition, there were nonsignificant trends toward reduced HF hospitalizations in the patients randomized to the IASD.[27]

Here we describe the investigational device, study design, inclusion/exclusion criteria, key end points, and

Figure 1

The Corvia InterAtrial Shunt Device.

Table I. Inclusion and exclusion criteria of the REDUCE LAP-HF II Trial

Inclusion criteria

1. Chronic symptomatic HF documented by the following:
   a. Symptoms of HF requiring current treatment with diuretics for ≥30 d AND
   b. NYHA class II if a prior history of NYHA class > II, or NYHA class III, or ambulatory NYHA class IV symptoms (paroxysmal nocturnal dyspnea, orthopnea, dyspnea on mild or moderate exertion) at screening visit; or signs (any rales post cough, chest radiograph demonstrating pulmonary congestion) within past 12 m AND
   c. ≥1 HF hospital admission (with HF as the primary or secondary diagnosis); or treatment with IV diuretics; or the need for intensification of oral diuresis for HF in
   a health care facility within the 12 m prior to study entry; or an NT-proBNP 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 m
2. Ongoing stable GDMT HF management and management of potential comorbidities according to the 2017 ACC/AHA Guidelines for the Management of HF, with no significant changes (>100% increase or 50% decrease), excluding diuretic dose changes, for a minimum of 4 wk prior to enrollment which is expected to be maintained for 6 m. Stable management includes a minimum period of 4 wk posthospitalization for any cause, including treatment with IV diuretics.
3. Age ≥ 40 y old
4. Site-determined echocardiographic LVEF ≥ 40% within the past 6 m, without documented EF < 30% in the 5 y prior to study entry

Site-determined elevated PCWP with a gradient compared to RAP documented by:

   a. End-expiratory PCWP during supine ergometer exercise ≥25 mm Hg and greater than RAP by ≥5 mm Hg
6. Site-determined echocardiographic evidence of diastolic dysfunction documented by 1 or more of the following:
   a. LA diameter > 4 cm; or
   b. Diastolic LA volume > 50 mL, LA volume index >28 mL/m^2; 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. Patient 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. Patient is willing to comply with clinical investigation procedures and agrees to return for all required follow-up visits, tests, and examinations
9. Transseptal catheterization and femoral vein access are determined to be feasible by site interventional cardiology investigator.

Exclusion criteria

1. MI and/or percutaneous cardiac intervention within past 3 m; CABG in past 3 m or current indication for coronary revascularization; AVR (surgical AVR or TAVR) within the past 12 m; or a planned cardiac interventions in the 3 m following enrollment
2. Cardiac resynchronization therapy initiated within the past 6 m
3. Advanced heart failure defined as 1 or more of the below:
   a. ACC/AHA/ESC Stage D heart failure, nonambulatory NYHA Class IV HF;
   b. Cardiac index <2.0 L/min/m^2
   c. Inotropic infusion (continuous or intermittent) for EF < 40% within the past 6 m
   d. Patient is on the cardiac transplant waiting list.
4. Inability to perform 6MWT (distance <50 m) or 6MWT >600 m
5. The patient has verified that the ability to walk 6 min is limited primarily by joint, foot, leg, hip, or back pain; unsteadiness; dizziness; or lifestyle (and not by shortness of breath and/or fatigue and/or chest pain).
6. Unwilling or unable (per PhysIQ protocol) to wear telemonitoring patch.
7. Known clinically significant unrevascularized coronary artery disease, defined as epicardial coronary artery stenosis with angina or other evidence of ongoing active coronary ischemia.
8. History of stroke, TIA, DVT, or pulmonary emboli within the past 6 m
9. Known clinically significant untreated carotid artery stenosis likely to require intervention.
10. Presence of hemodynamically significant valve disease assessed by the site cardiologist and defined as:
    a. Mitral valve disease defined as grade ≥ 3+ MR or > mild MS; or
    b. Tricuspid valve regurgitation defined as grade ≥ 2+ TR; or
    c. Aortic valve disease defined as ≥2+ AR or > moderate AS.
11. Hypertrophic obstructive cardiomyopathy, restrictive cardiomyopathy, constrictive pericarditis, cardiac amyloidosis, or other infiltrative cardiomyopathy (eg, hemochromatosis, sarcoidosis)
12. Patient is contraindicated to receive either dual antiplatelet therapy or an oral anticoagulant, or has a documented coagulopathy.
13. Atrial fibrillation with resting HR > 100 beats/min
14. Resting arterial oxygen saturation < 95% on room air
15. Significant hepatic impairment defined as 3× upper limit of normal of transaminases, total bilirubin, or alkaline phosphatase
16. Right ventricular dysfunction, assessed by the site cardiologist and defined 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. Ultrasound or clinical evidence of congestive hepatopathy; or
    e. Evidence of RV dysfunction defined by TTE as an RV fractional area change <35%;
17. Resting RAP >14 mm Hg
18. Evidence of significant pulmonary hypertension defined as PVR > 3.5 Woods units at rest or at peak exercise
19. Chronic pulmonary disease requiring continuous home oxygen or significant chronic pulmonary disease defined as FEV1 < 1 L
20. Hemoglobin <10 g/dL

Table I. (*continued*).

21. 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.
22. Life expectancy less than 12 m for known noncardiovascular reasons
23. Echocardiographic evidence of intracardiac mass, thrombus, or vegetation
24. Known or suspected allergy to nickel
25. Women of child bearing potential
26. Currently requiring dialysis; or estimated GFR <25 mL/min/1.73 m^2 by CKD-Epi equation
27. Systolic blood pressure > 170 mm Hg at screening
28. Patients with existing or surgically closed (with a patch) atrial septal defects. Patients with a PFO, who meet PCWP criteria despite the PFO, are not excluded.
29. Patients on significant immunosuppressive treatment or on systemic steroid treatment (>10 mg prednisone/d)
30. Severe obstructive sleep apnea not treated with CPAP or other measures
31. Severe depression and/or anxiety
32. In the opinion of the investigator, the patient is not an appropriate candidate for the study
33. Body mass index >45 kg/m^2

IV, intravenous; *NT-proBNP*, N-terminal pro–brain natriuretic peptide; *ACC*, American College of Cardiology; *AHA*, American Heart Association; *IRB*, institutional review board; *EC*, ethics committee; *CABG*, coronary artery bypass graft; *MI*, myocardial infarction; *AVR*, aortic valve replacement; *TAVR*, transcatheter aortic valve replacement; *ESC*, European Society of Cardiology; *TIA*, transient ischemic attack; *DVT*, deep vein thrombosis; *MR*, mitral regurgitation; *MS*, mitral stenosis; *TR*, tricuspid regurgitation; *AR*, aortic regurgitation; *AS*, aortic stenosis; *HR*, heart rate; *TTE*, transthoracic echocardiography; *TAPSE*, tricuspid annular plane systolic excursion; *PVR*, pulmonary vascular resistance; *FEV1*, forced expiratory volume in 1 second; *GFR*, glomerular filtration rate; *PFO*, patent foramen ovale; *CPAP*, continuous positive airway pressure.

statistical analysis for the REDUCE Elevated Left Atrial Pressure in patients with Heart Failure II (REDUCE LAP-HF II, ClinicalTrials.gov NCT03088033) trial, a multicenter, prospective, randomized controlled, blinded trial with a nonimplant sham procedure control group to evaluate the clinical efficacy of the IASD for patients with HF and preserved or midrange LVEF.

Methods

Device description

The IASD System II Implant (Corvia Medical, Tewksbury, MA) consists of a 1-piece self-expanding nitinol cage with a double-disk design with an opening (barrel) in the center (Figure 1). The implant is radiopaque and echogenic to allow for imaging during the implantation procedure. It is designed to have the necessary structural integrity to maintain device shape and function for long-term use. Each side of the implant is multilegged (9 legs/side), and the LA disk has a radiopaque marker at the end of each leg. The LA side of the implant is flat to allow the legs to rest flush against the LA wall, thereby minimizing the LA profile of the implant. The right atrial side is curved to accommodate variable septal wall thicknesses. The expanded external diameter of each disk is 19.4 mm, and the inner diameter of the barrel in the center of the fully expanded implant is 8 mm.

The delivery system is designed to deploy the implant at the target location across the interatrial septum. The system consists of a delivery catheter with an integrated handle and preloaded implant, with an over the wire design that is 0.035″ guide wire compatible. The implant comes preloaded in a collapsed configuration onto the distal tip of the inner catheter of the delivery system. Implant deployment is achieved by retracting the outer sheath to release the implant legs and barrel in a controlled stepwise manner on the left and the right atrial septal surfaces. The handle has a thumb slide that is used to advance or retract the outer sheath, and is designed with safety features designed to prevent accidental deployment.

Objective and overview of study design

The primary objective of the REDUCE LAP HF II Study is to evaluate the clinical efficacy and safety of the IASD system in symptomatic heart failure patients with an LVEF $\geq$ 40% and elevated left-sided filling pressures despite standard guideline-directed medical therapy (GDMT).

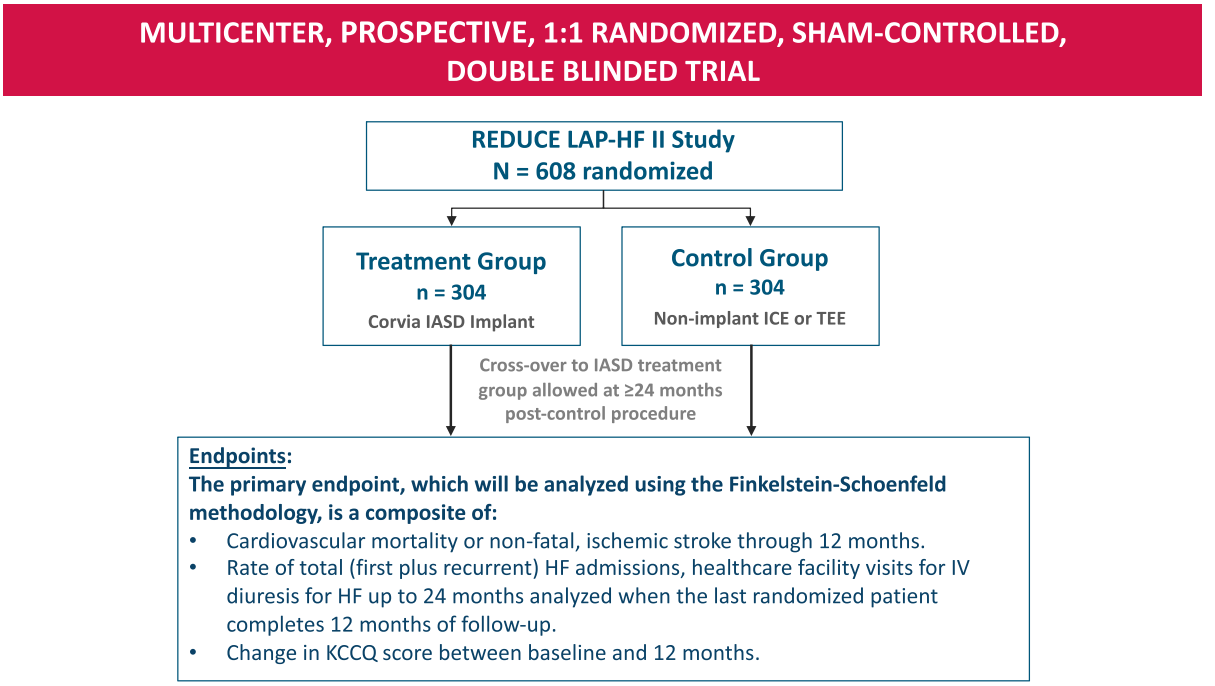
This study is a multicenter, prospective, randomized controlled, blinded trial with a nonimplant sham control procedure group and 1:1 randomization. Patients will be followed for 1 year and annually every 12 months thereafter for a total of 5 years after index procedure and implant.

Study population

The full list of inclusion and exclusion criteria is listed in Table I. Patients age $\geq$ 40 years with NYHA class II or III chronic symptomatic HF with LVEF $\geq$ 40%, with ongoing diuretic therapy and with elevated left-sided filling pressures defined as PCWP $\geq$25 mm Hg during supine ergometer exercise and PCWP greater than right atrial pressure (RAP) by $\geq$5 mm Hg, with echocardiographic evidence of diastolic dysfunction, who are candidates for transseptal catheterization, are eligible for enrollment.

Exclusion criteria include recent myocardial infarction, revascularization, recent stroke, advanced heart failure (NYHA class IV, inotrope therapy, cardiac index < 2.0 L/min, transplant listed), hemodynamically significant valvular disease or cardiomyopathy, existing atrial septal

Figure 2



Study design.

defect (ASD), uncontrolled atrial fibrillation (heart rate > 100 beat/min), known right ventricular (RV) dysfunction, or pulmonary vascular resistance >3.5 Wood units.

Patients will be enrolled at up to 110 sites in the United States, Australia, Austria, Belgium, Canada, Croatia, Denmark, France, Germany, Italy, Japan, Netherlands, Poland, Spain, and the United Kingdom.

Randomization

All enrolled patients who are eligible based on noninvasive evaluation will undergo prerandomization resting and exercise right heart catheterization. Eligible patients who qualify based on invasive hemodynamic criteria will be randomized in a 1:1 fashion within the Electronic Data Capture system to receive the IASD or sham-control procedure (see patient flowchart, Figure 2). Randomization will be stratified by geography (United States vs outside United States), age (age < 75 and ≥ 75), and gender to ensure balanced groups on these factors.

After hemodynamic qualification, all patients will be sedated and will undergo intracardiac echocardiography or transesophageal echocardiography to ensure no previously undetected exclusions are present (including ASD, LA thrombus, or severe septal aneurysm or thickening).

After randomization, both treatment and control arm patients will undergo placement of a femoral venous access sheath. Patients randomized to the treatment arm will undergo fluoroscopy and intracardiac echocardiography or transesophageal echocardiography–guided transseptal puncture and IASD System II implant procedure. Patients randomized to the control arm will undergo fluoroscopy and intracardiac echocardiography from the femoral vein or transesophageal echocardiography for examination of the atrial septum and LA appendage (the sham control procedure consisting of placement of the femoral venous access sheath and the echocardiographic examination). After the procedure, patients who were not previously on oral anticoagluation will receive anti-platelet therapy based on treatment assignment. Patients randomized to the IASD will receive clopidogrel 75 mg and low-dose aspirin (75-100 mg) once daily for 6 months, with continuation of aspirin beyond 6 months based on individual patient circumstances and physician preference; patients randomized to the control arm will receive low-dose aspirin (75–100 mg) once daily for 6 months. Patients in either treatment arm who were previously on oral anticoagulation will continue taking the anticoagulant throughout the study.

Patient blinding will include sedation, earphones with music to prevent the patient from hearing the procedure discussions, and shielding of the patients to prevent viewing the imaging screens during the procedure. The

patients; the physicians managing the randomized patients; research individuals involved in conducting selected postrandomization evaluations; and the hemodynamic, cardiac MRI, echocardiographic, and cardiopulmonary exercise test (CPET) core laboratories (Cardiovascular Clinical Sciences, Boston, MA for hemodynamics and cardiac MRI; The Center for Quantitative Echocardiography, Hospital of the University of Pennsylvania, Philadelphia, PA for echocardiography; Wake Forest University, Winston-Salem, NC for CPET) will be blinded to study arm.

Patients will be followed for 1 year (at 2 weeks and 1, 3, 6, and 12 months postprocedure) and annually every 12 months thereafter for a total of 5 years after the index procedure and implant. Patients and staff will complete questionnaires to determine if blinded staff and patients remained blinded throughout the study. All patients will be unblinded after the 24-month follow-up visit. Patients randomized to the control arm will be allowed to cross over to the treatment arm within 45 days of the 24-month visit provided that the patient inclusion/exclusion criteria are met at that time. Crossover patients will then be followed for 5 years after crossover.

End points

The primary end point is the composite of (*a*) incidence of and time to cardiovascular mortality or first nonfatal, ischemic stroke through 12 months; (*b*) rate (first plus recurrent) of HF admissions or health care facility visits for intravenous diuresis for HF through up to 24 months including time to first HF event, analyzed when the last patient randomized completes 12 months of follow-up; and (*c*) change in baseline Kansas City Cardiomyopathy Questionnaire (KCCQ) total summary score at 12 months. Treatment groups will be compared with respect to the distribution of these components using the Finkelstein-Schoenfeld (F-S) approach as detailed in the next section[28].

The major secondary end points are described in Table II.

Statistical considerations

The primary end point will be compared between treatments using the F-S[27] approach, a nonparametric method that allows for prioritization of more clinically important components when comparing 2 treatments on a composite end point. The null and alternative hypotheses are: H0: $T = 0$ versus H1: $T \neq 0$, where T is the true value of the F-S statistic.[28] The hierarchy in the estimation of the F-S statistic T is CV mortality/nonfatal ischemic stroke component, followed by the HF event component, followed by the KCCQ component. Specifically, the F-S statistic T is estimated from the clinical trial sample as follows: The first patient is compared to every patient, one at a time, and this first patient is assigned a score of 1/0/−1 for *each* comparison if this first patient has a better (did not experience CV death/ischemic stroke and the comparator patient did), same, or worse (experienced CV death/ischemic stroke and the comparator patient did not) outcome, respectively. For every pairwise comparison where the score is 0, the first patient is assigned a score of 1/0/−1 depending on whether he/she has a better (less HF events than the comparator patient), same (same number of HF events as the comparator patient), or worse outcome (more HF events than the comparator patient), respectively. Finally, for every pairwise comparison where the score is still 0, the first patient is assigned a score of 1/0/−1 depending on whether he/she has a better (change in 12-month KCCQ score at least 5 points larger than the comparator), same (change in 12-month KCCQ score within +/−5 points of comparator), or worse (change in 12-month KCCQ 5 at least 5 points lower than the comparator). This algorithm is then repeated for every patient in the study. The F-S T value is the sum of the 1/0/−1 scores across all patients in the IASD group. A T score significantly larger than 0 indicates the IASD group has a more favorable distribution of components than the control group. The null hypothesis will be tested at a 2-sided .05 level of significance.

Table II. Major secondary endpoints in the REDUCE LAP-HF II Trial

1. Composite safety endpoint, defined as follows:
a. Cardiovascular mortality through 12 m
b. Non-fatal, ischemic stroke through 12 months
c. New onset or worsening kidney dysfunction (defined as eGFR decrease of > 20 ml/min/1.73 m2)
d. Major adverse cardiac events through 12 m defined as:
   a. Cardiac death
   b. Myocardial infarction
   c. Cardiac tamponade
   d. Emergency cardiac surgery
e. Thromboembolic complications (transient ischmic attack, systemic embolization) through 12 months
f. Newly acquired persistent or permanent atrial fibrillation or atrial flutter through 12 m
g. ≥30% increase in RV size/decrease in TAPSE through 12 m
2. Rate of total (first plus recurrent) HF admissions, health care facility visits for IV diuresis for HF, or visits with intensification of oral diuresis for HF up to 24 m, analyzed when the last patient randomized completes 12m of follow-up
3. Change in NYHA functional class assessed by a blinded physician between baseline and 12 months
4. Change in KCCQ scroe between baseline and 12 months

To determine sample size to provide adequate power, the following assumptions were made for the components; they were based on data from the REDUCE LAP-HF 1 study: (*a*) The combined CV mortality and nonfatal ischemic stroke rate is 5.0% in each treatment group at 12 months; (*b*) the per person-year rate of HF events is 0.5 in control and 0.39 in IASD; for patients experiencing HF, the median time to first HF admission is 84 days in control and 172 days in IASD; (c) the mean improvement in KCCQ is assumed to be 13 in IASD and 8 in control, with an SD of 20 in each treatment group; (*d*) correlation between probability of death and probability of heart failure events is 0.3 or less; correlation between probability of death and improvement in KCCQ is −0.3 or larger; correlation between probability of heart failure and improvement in KCCQ is −0.3 or larger.

Under these assumptions, an evaluable sample size of 282 patients per treatment group yields 85% power to claim a significant beneficial effect of IASD over control with respect to the combined distribution of the 3 end point components at a 2-sided .05 level of significance using the F-S approach. Power was calculated using 1000 Monte Carlo simulations carried out in SAS Version 9.4. An evaluable patient for this analysis is one who either experienced cardiovascular mortality or nonfatal ischemic stroke before the 12-month time point (and hence can be included in the analysis) or attended the 12-month visit and completed the KCCQ at that visit. Assuming a premature withdrawal rate of no more than 7.5% prior to 12 months, then the 282 evaluable patients per treatment group lead to a requirement of 304 randomized patients per treatment group (304 = 282 divided by [1 − 0.075], where 0.075 or 7.5% is the assumed premature withdrawal rate).

In addition to the F-S *P* value, 2 effect sizes will be presented: the (*a*) win ratio as described by Pocock et al[29] and (*b*) the probability that the IASD patients have a more favorable distribution of the 3 components than control patients.

Also, as supportive analyses, appropriate descriptive statistics of each component (cumulative incidence of CV mortality/ischemic stroke where non-CV death is treated as a competing risk, person-year rate of HF events, and cumulative incidence of at least 1 HF event) will be presented for each randomized treatment group.

Poolability

The primary analysis will combine all study centers. To assess poolability of primary end point results across study centers, assessment of treatment-by-study center interaction will be carried out for the components of the primary end point using Cox proportional hazards regression for 12-month cardiovascular mortality/nonfatal ischemic stroke, zero-inflated Poisson regression for 12-month HF events, and analysis of covariance adjusting for baseline KCCQ for change in KCCQ from baseline to 12 months. Treatment and study center and the treatment-by-study center interaction will be included as effects in each model. A treatment-by-study center interaction that is significant at the .15 level of significance will signal that the treatment difference on the component(s) may differ across study centers; a nonsignificant interaction, or an interaction that is significant but where IASD still yields descriptively better results than control in each center, will support the pooling of results across study centers for the final analyses. If there are too few patients in study centers such that the models do not converge or give unstable results (eg, estimates with very large standard errors), then treatment-*by-region* interaction will instead be assessed in a similar manner as described above, where study centers will be grouped into regions once enrollment is complete and prior to breaking the blind. Currently, the plan is to define regions as United States and outside United States. However, this may change to more than 2 regions depending on enrollment in the various geographic areas. For example, we may consider assigning sites to 4 regions such as United States, Canada, Europe, and New Zealand/Australia/Japan. Again, this will be decided once enrollment is complete. The goal is to have at least 50 randomized subjects in each region.

Descriptive statistics of baseline and outcome variables to be analyzed will be presented by treatment group. Such statistics include sample size, mean, median, SD, and quartiles for continuous variables; counts and percent of patients for categorical variables; and Kaplan-Meier estimates of event rate for time-to-event variables. *P* values will be considered significant at a 2-sided .05 level unless otherwise specified. Analyses will be conducted using SAS Version 9.4 or higher.

Interim analysis

After 250 of the 608 randomized patients reach 12-month follow-up or prematurely withdraw prior to 12 months postrandomization, an interim analysis on the primary end point will be performed using the available evaluable patients to assess if a sample size increase is warranted to maintain a (conditional) power of at least 80% for the study. Given the complexity of the F-S method and given that there is no closed-form equation for power or conditional power, conditional power will be assessed via Monte Carlo simulations in SAS Version 9.4 using a method similar to that used in the overall power calculation above. Specifically, 1,000 Monte Carlo samples of postinterim patients will be simulated. The interim analysis will be performed by an independent statistician; all other members of the trial leadership (principal investigators, steering committee, sponsor) will remain blinded to treatment assignments.

The size of each simulated sample is the number of patients needed postinterim to reach the required final evaluable sample size of 282 patients per group. In these

simulations, the true CV mortality/ischemic stroke incidence, the true per-person-year HF event rate, and the true mean/SD of change in KCCQ for each of the 2 treatment groups will now be assumed to be the same as the values observed in the interim data set.

Each simulated data set will be added to the observed (ie, not simulated) interim analysis evaluable data set to create 1,000 complete data sets with an evaluable sample size of 282 per group. The (simulated) conditional power is the percentage of these 1,000 simulated data sets for which the F-S test statistic is able to reject the null hypothesis. Following the methodology in Mehta and Pocock,[30] if the conditional power is between 38% and 80%, the sample size may be increased to yield a (simulated) conditional power of 80% without paying an α penalty. Otherwise, the study will continue with the planned original enrollment goal of 282 evaluable patients (304 randomized) per treatment group.

Analysis populations

Analysis of the primary end point will be carried out on the intention-to-treat population (ITT) and the modified intention-to-treat (MITT) population. The *ITT population* is defined as all randomized patients; the *MITT* is defined as the ITT population excluding subjects in whom a new, previously unidentified protocol exclusion is discovered before insertion of the investigational device. The MITT population is the primary analysis population. Analyses will also be carried out on the evaluable at 12 months population (MITT patients with 12 months of follow up available), the per-protocol population (patients who were evaluable at 12 months without major protocol violations and who [*a*] were randomized to IASD and had an implant or [*b*] were randomized to control and underwent the complete control procedure). Safety analyses will be carried out on the safety population (subset of ITT in whom an implant of the IASD was attempted or in whom a control procedure was attempted).

Subgroup analyses

Prospectively planned subgroup investigations include the following baseline continuous variables (age, BMI, natriuretic peptide values, TAPSE, left atrial volume index, legs up PCWP, and difference between PCWP-RA pressure at rest) and baseline categorical variables (sex, diabetes status, NYHA class III vs. class II, white vs. non-white race/ethnicity, above vs. below median BMI, atrial fibrillation/flutter vs. sinus rhythm, HF hospitalization within 1 year prior to randomization, and EF 40–49% vs. $\geq$50%). For each subgrouping, to assess homogeneity of treatment effect on the primary end point components across the subgroup categories, assessment of treatment-by-subgroup category interaction will be carried out using Cox proportional hazards regression for 12-month cardiovascular mortality/nonfatal ischemic stroke, zero-inflated Poisson regression for 12-month HF events, and analysis of covariance for change in KCCQ from baseline to 12 months. Treatment and subgroup category and the treatment-by-subgroup category interaction will be included as independent variables in each model. For KCCQ, the baseline KCCQ will also be included as a covariate. The purpose of this analysis is not to assess significance of the treatment difference on the end points within subgroups but to assess consistency of treatment effect on the end points within subgroups.

In addition, homogeneity of treatment effect on the primary end point components will be evaluated across the range of baseline values for each of the continuous variables listed below. Specifically, assessment of the significance of the treatment-by-baseline value interactions will be carried out for each of the variables below using Cox proportional hazards regression for the outcome 12-month cardiovascular mortality/nonfatal ischemic stroke, zero-inflated Poisson regression for 12-month HF events, and analysis of covariance for change in KCCQ from baseline to 12 months. For each of the following variables (peak exercise PCWP, peak exercise RA pressure, peak exercise PCWP-RA gradient, KCCQ overall summary score, 6MWT distance, and eGFR), treatment, baseline value of the variable, and the treatment-by-baseline value interaction will be included as the independent variables in each model. For the KCCQ outcome, the baseline KCCQ will also be included as a covariate.

Missing data

The primary end point analysis will be on the MITT population, with secondary analysis on the PP population. In the MITT analysis, patients may have missing information on cardiovascular death/nonfatal ischemic stroke, HF events, and/or on KCCQ prior to the 12-month time point, primarily due to premature withdrawal from the study. Analyses will be performed on the MITT population with available data. However, as sensitivity analyses, the primary end point analysis will be repeated on the entire MITT population, where missing data for the components of the primary end point will be multiply imputed with 50 imputations using linear regression for KCCQ and the bootstrap imputation approach for time-to-event data as outlined in Jackson et al[31]; there will be no imputation for other end points in the study.

Study administration and management

The local Institutional Review Board or Ethics Committee at each participating institution must approve the study, and all patients must provide written informed consent prior to enrollment. Funding is provided by Corvia Medical, Inc. The Baim Institute for Clinical Research maintains the complete study database and will perform all analyses.

An independent Clinical Events Committee will adjudicate serious adverse events and outcome data. An independent Data Safety Monitoring Board monitoring safety will meet regularly to review adverse events and outcome data. A steering committee will provide strategic leadership for the study. All hemodynamic, echocardiographic, CPET, cardiac magnetic resonance imaging, quality of life, and hemodynamic data will be adjudicated by independent core laboratories to ensure data consistency.

Funding for this study was provided by Corvia Medical. The authors are solely responsible for the design and conduct of this study, all study analyses, the drafting and editing of the paper, and its final contents.

Discussion

Heart failure with both preserved and midrange ejection fraction is associated with significant morbidity and mortality.[2] In patients with HFpEF, elevated LA pressure and, in turn, PCWP have been associated with increased mortality and poorer outcomes.[14,15,32] We hypothesize that lowering LA pressure in patients with symptomatic HF by creating an appropriately sized left-to-right shunt will lead to symptomatic improvement (particularly during exertion), reduced HF hospitalizations, and improved exercise tolerance and quality of life. Additionally, a device-based therapy may avoid some of the difficulties with patient noncompliance and polypharmacy, which are often encountered in older patients with multiple comorbidities.

The REDUCE LAP-HF II study has several key design elements to reliably evaluate the safety and efficacy of the Corvia Medical Inc IASD System II in HF patients with elevated LA pressures. It is the first study involving the IASD that is powered for determining clinical efficacy. Importantly, safety outcomes (composite cardiovascular mortality and stroke) are first in the hierarchical sequence of the primary end point, followed by HF hospitalizations and the KCCQ, which evaluates quality of life. Based on knowledge of the device as well as prior experience, there is no expected effect on either cardiovascular mortality or stroke at 1 year; however, it is important to include these outcomes to further establish the safety of the IASD in a broad group of patients with HF and EF $\geq$ 40%.

The potential effect on HF admissions or health care facility visits for intravenous diuresis, included as the second component in the hierarchical outcome, is important from a patient, caregiver, and resource-utilization perspective. The KCCQ end point is also important to quantify a clinically meaningful improvement in quality of life and has been validated in prior studies.[33] An end point of 12 months will be important to allow for the sustained hemodynamic effect of the IASD on outcomes to be observed. Although REDUCE LAP-HF I demonstrated positive results with short-term (1 month) postprocedural reduction in exercise PCWP and trends to fewer HF hospitalizations and greater improvement in NYHA class in patients in the IASD group, it will be important to determine whether this translates to a clinically meaningful durable effect. Moreover, continued safety monitoring will be paramount at 12 months.

REDUCE LAP-HF I also demonstrated the mechanistic basis for the observed clinical outcomes. Direct, invasive hemodynamic assessment of exercise PCWP demonstrated that IASD results in decreased exercise PCWP.[26] This prior demonstration of the mechanism of the treatment effect of the IASD, reduced PCWP with exercise, will support our understanding of the clinical outcomes in REDUCE LAP-HF II. REDUCE LAP-HF I results at 12 months also demonstrate trends to fewer hospitalizations (P = .064) and greater improvement in NYHA class (.086) in patients assigned to IASD; REDUCE LAP-HF II will be important for further investigation of such trends.

The size of this trial allows exploration of variability across study centers, in the United States and outside, with more diverse center and patient characteristics compared to prior studies. It will also allow for more accurate detection of variations in IASD effectiveness across subgroups, specifically among males/females; patients with greater or less than BMI of 30 kg/m^2; patients with higher-risk features such as hospitalization within the past year; LVEF subgroups; and variations in RV function and tricuspid regurgitation at baseline. Follow-up to 5 years will be important to evaluating continued device safety as well as long-term effect durability.

Conclusions

The REDUCE LAP-HF II trial, the first prospective, multicenter, randomized, double-blinded, sham-controlled trial to evaluate clinical end points in patients treated with the IASD, has the potential to advance our understanding of this first-in-class, novel, transcatheter device-based therapy for HF.

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