

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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Abstract—Heart failure with preserved ejection fraction (HFpEF), a major public health problem with high morbidity and mortality rates, remains difficult to manage because of a lack of effective treatment options. Although HFpEF is a heterogeneous clinical syndrome, elevated left atrial pressure—either at rest or with exertion—is a common factor among all forms of HFpEF and one of the primary reasons for dyspnea and exercise intolerance in these patients. On the basis of clinical experience with congenital interatrial shunts in mitral stenosis, it has been hypothesized that the creation of a left-to-right interatrial shunt to decompress the left atrium (without compromising left ventricular filling or forward cardiac output) is a rational, nonpharmacological strategy for alleviating symptoms in patients with HFpEF. A novel transcatheter interatrial shunt device has been developed and evaluated in patients with HFpEF in single-arm, nonblinded clinical trials. These studies have demonstrated the safety and potential efficacy of the device. However, a randomized, placebo-controlled evaluation of the device is required to further evaluate its safety and efficacy in patients with HFpEF. In this article, we give the rationale for a therapeutic transcatheter interatrial shunt device in HFpEF, and we describe the design of REDUCE Elevated Left Atrial Pressure in Heart Failure (REDUCE LAP-HF I), the first randomized controlled trial of a device-based therapy to reduce left atrial pressure in HFpEF.

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Prevalence of Heart Failure With Preserved Left Ventricular Ejection Fraction

More than one-half of people with heart failure (HF) have a preserved left ventricular ejection fraction (HFpEF).^{1,2} Patients with HFpEF, commonly referred to as diastolic HF, have symptoms and/or signs of HF and a left ventricular ejection fraction (LVEF) >40% to 50%. The prevalence of HFpEF exceeds 3 million in the United States alone, and its prevalence seems

to be increasing because of factors such as increased diagnostic awareness and greater longevity. The prognosis for patients hospitalized with HFpEF is poor, worsens with increasing age, and has not improved over time.³ Epidemiology studies have shown similar mortality rates in HF with reduced ejection fraction (HFrEF) and HFpEF; 1-year mortality is 26% in HFrEF compared with 22% in HFpEF.^{4,5} Although pharmacological treatments may improve symptoms and reduce mortality in

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patients with chronic HFrEF,^{6,7} there are currently no approved or evidence-based effective pharmacotherapies with similar benefits for HFpEF.^{8–11}

Pathophysiology of Exercise Intolerance in HFpEF

The general lack of therapeutic responsiveness to neurohormonal therapies and other lines of evidence indicate that the underlying pathophysiology in HFpEF is different from that of HFrEF. Although HFpEF is a complex clinical syndrome of uncertain pathogenesis with several contributing factors,¹² an increase in left atrial (LA) pressure is a common feature of this syndrome and a central cause of debilitating symptoms. Breathlessness, exercise intolerance, and fatigue are the characteristic symptoms of the chronic HFpEF syndrome and are largely attributable to elevated pulmonary venous pressure at rest and/or with exercise.

Atrial Shunts for LA Decompression in HFpEF

On the basis of clinical experience with naturally occurring interatrial shunts, it has been hypothesized that creating a controlled left-to-right interatrial shunt to allow LA decompression without compromising left ventricular filling or forward cardiac output, is a rational nonpharmacological strategy for alleviating symptoms in patients with HFpEF. Furthermore, reports of the natural history of congenital atrial septal defect suggests that small atrial shunts have no important long-term impact on cardiac function.^{13–15} On the contrary, the protection from LA pressure overload afforded by an incidental atrial septal defect in patients with mitral stenosis is well described as the Lutembacher syndrome^{16,17} and strokes because of paradoxical embolism are rare.¹⁸

We have therefore developed a novel transcatheter interatrial shunt device (IASD) for the treatment of HFpEF. The IASD is an implant that creates and maintains an atrial septal communication. Transseptal puncture devices and techniques are widely available and well established.^{19,20} Atrial septal defect closure devices have been in wide use for decades, and the techniques for implantation and postimplantation management are widely used.²¹

To model the hemodynamic impact of creating such a shunt, we reported the theoretical acute hemodynamic effects of this approach using a validated cardiovascular simulation.²² Rest and exercise hemodynamic data from 2 previous independent studies of patients with HFpEF were simulated, and the theoretical acute effects of a shunt between the right and left atria were determined. The 8-mm-diameter interatrial shunt acutely lowered pulmonary capillary wedge pressure (PCWP) by 3 mmHg under simulated resting conditions and by 11 mmHg under simulated peak exercise conditions. The interatrial shunt reduced left-sided cardiac output only slightly with a marked reduction in PCWP. This computer simulation suggested that an IASD approach may reduce PCWP while allowing cardiac output and heart rate to rise during exercise, potentially resulting in ability to exercise longer and reduce the propensity for

HF exacerbations. This hypothesis is supported by clinical observations in patients with Lutembacher syndrome and the relative absence of adverse long-term effects in patients with small congenital atrial septal defect.

Early Results From IASD Implants in HFpEF Patients

The IASD has been evaluated in patients with HFpEF in single-arm, nonblinded clinical trials. A pilot, nonrandomized, single-arm evaluation of the Corvia Medical System with permanent implantation in patients with HFpEF has been completed.^{23,24} The primary outcome measure was serious adverse device events through 1 month post implant. The key inclusion criteria were at least one HF hospitalization within the past 12 months, or persistent New York Heart Association class III for at least 3 months, age ≥ 40 years, LVEF $\geq 45\%$. After patients were discharged from the hospital, they were followed up for 12 months. Eleven patients (6 men and 5 women, mean age 70.5 years) were enrolled and completed the study. The study demonstrated the safety and performance of the device. At 1 year, New York Heart Association class and quality of life (Minnesota Living with Heart Failure Questionnaire) were improved in 73% and 91% compared with baseline, respectively. There were no deaths and cerebrovascular or systemic embolic events. The rate of HF hospitalization was reduced compared with the previous year. Unidirectional left-to-right flow through the device at rest was demonstrated in all patients in whom analysis was possible (9/9).

After the pilot study, the REDUCE LAP-HF Study was performed.²⁵ This was a prospective, 6-month, open-label, nonrandomized, multicenter study to assess the safety and performance of the device in ≤ 100 HF patients with elevated LA pressure who remained symptomatic despite appropriate medical management. Enrollment has been recently completed. Patients will be followed up for 3 years. The primary safety end point is the percentage of subjects who experience major adverse cardiac and cerebrovascular events defined as death, stroke, myocardial infarction or who require implant removal cardiac surgery at 6 months from day of implant.

These studies have demonstrated the safety and potential efficacy of the device. However, a randomized, placebo-controlled evaluation of the device is now required to further evaluate its safety, effectiveness, and efficacy in patients with HFpEF.

Randomized Evaluation of the Mechanistic Effect of IASD in HFpEF: the REDUCE LAP-HF I Trial

Given the unmet needs of patients with HFpEF and the failure to show effectiveness of several pharmacotherapies for this condition, a novel, device-based treatment to reduce LA pressure could be a major advance in the care of patients with HFpEF. Accordingly, we have designed a prospective, randomized, placebo-controlled, clinical trial to evaluate a transcatheter interatrial shunt for patients with HF and preserved or mildly reduced left ventricular (LV) ejection fraction. Here, we describe the device, study design, and inclusion/exclusion



Figure 1. Corvia Medical, Inc. IASD System II device. Reproduced with permission.

criteria for the trial, the REDUCE Elevated Left Atrial Pressure in Patients with Heart Failure I (ClinicalTrials.gov NCT02600234), which will be the first randomized evaluation of a device-based therapy to reduce LA pressure in patients with HFpEF.

IASD Device Description

The IASD System II implant (Corvia Medical, Tewksbury, MA) consists of a 1-piece self-expanding metal cage that has a double-disc design with an opening (barrel) in the center (Figure 1). It is available in one size. The implant is radiopaque and echogenic to allow for imaging during the implantation procedure. Each side of the implant is multi-legged (9 legs/side), and the LA side 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 deployed implant. The right atrial side is curved to accommodate variable septal wall thicknesses, with only the leg ends contacting the right atrial wall. The expanded external diameter of each disc is 19.4 mm. 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 atrial septum (Figures 2 and 3). The implant comes preloaded onto the distal tip of the inner catheter of the delivery system. Implant deployment is achieved by retracting the outer catheter to release the implant legs and barrel in a controlled stepwise manner.

REDUCE LAP-HF I Trial: Study Design and Objectives

The primary objective of this clinical trial is to evaluate the periprocedural safety and potential effectiveness (mechanistic effect) of implanting the IASD System II in HF patients with an LV ejection fraction $>40\%$ and elevated left sided filling pressures who remain symptomatic despite optimal guideline-directed medical therapy.^{7,26}

The trial is a multicenter, prospective, randomized, controlled, single (patient) blinded trial, with nonimplant control group and 1:1 randomization. Patients are randomized following the study-related qualification procedures (Figure 4), including supine bicycle exercise testing during right heart catheterization, to ensure that patients meet hemodynamic criteria, namely, an elevated PCWP and a gradient between PCWP and right atrial pressure. Afterward, eligible patients will be randomized to the treatment or control group. Patient randomization will be study wide via the Interactive Web Response System. All patients will be sedated, and both treatment and control arm patients will undergo femoral venous access after randomization.

Patients randomized to the treatment arm will undergo a transeptal puncture and IASD System II implantation guided by fluoroscopy and intracardiac echocardiography. Patients randomized to the control arm will undergo intracardiac

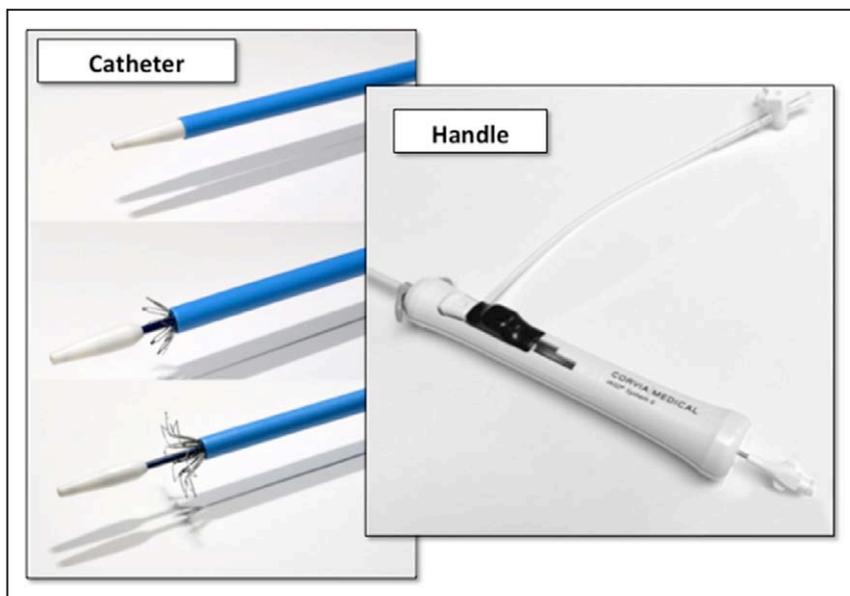


Figure 2. Corvia Medical, Inc. IASD System II delivery system. Reproduced with permission.

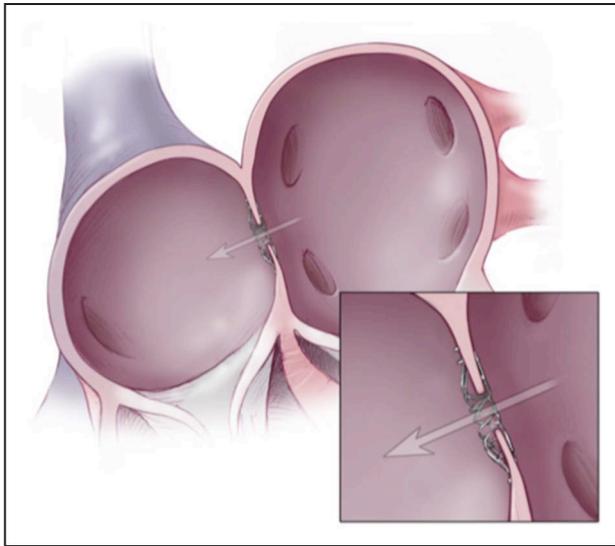


Figure 3. Implant after placement in the interatrial septum.

echocardiography, with examination of the atrial septum and LA appendage.

Patients randomized to the control arm who still meet the inclusion criteria will be allowed to crossover to the treatment arm at ≥ 12 months after the baseline procedure. All patients initially randomized and all patients receiving the device will be followed up for 5 years.

Patient blinding will include sedation, earphones with music to preclude the patient from hearing the procedural discussions, and blindfolding, or the use of opaque screens

to prevent the participant from viewing the imaging screens. Each site will assign blinded and unblinded staff to facilitate unbiased patient assessments through 12 months of follow-up. Research staff will be instructed to maintain patient blinding. The physicians managing the randomized patients and research staff involved in conducting selected postrandomization evaluations, including the hemodynamic and cardiopulmonary exercise testing core laboratories, will be blinded to study arm.

After treatment, device-implanted patients will be treated with clopidogrel for 6 months (dose determined per institutional standards) and aspirin 75 to 81 mg PO daily indefinitely, and control arm patients will be treated with aspirin 75 to 81 mg PO daily for 1 year. Patients may receive 1 or 2 antiplatelet agents post procedure. Patients with an indication for oral anticoagulation and/or antiplatelet therapy for a pre-existing condition will continue the same regimen after the procedure.

REDUCE LAP-HF I Trial: Patient Population

Up to 60 subjects at ≤ 20 investigational sites in the United States and ≤ 8 investigational sites outside the United States will be enrolled. From the 60 subjects, 40 patients with HFpEF (LVEF $>40\%$) who have elevated left-sided filling pressures during exercise and who are symptomatic despite optimal guideline-directed medical therapy will be included in the randomized trial (Table 1).^{7,26} The inclusion and exclusion criteria are detailed in Table 2. Key inclusion criteria include documented chronic symptomatic HF; LV ejection fraction $\geq 40\%$; and elevated LA pressure with a gradient compared with right atrial pressure documented by end-expiratory PCWP during supine bike exercise ≥ 25 mm Hg, and

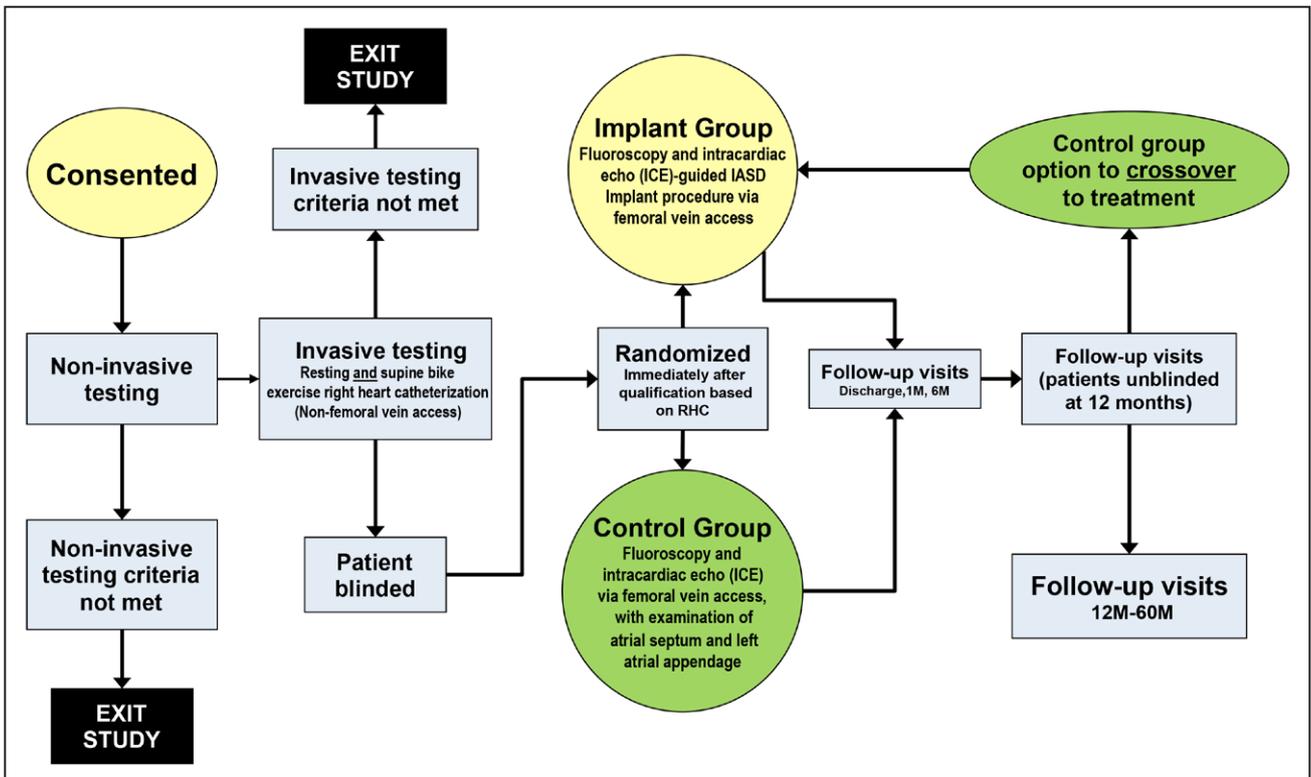


Figure 4. Patient flow through the trial.

Table 1. Pharmacological Treatment for Stage C HFpEF—AHA/ACC and ESC/HFA Guideline Recommendations

AHA/ACC guidelines
Class I
Systolic and diastolic blood pressure should be controlled according to published clinical practice guidelines (level of evidence: B)
Diuretics should be used for relief of symptoms due to volume overload (level of evidence: C)
Class II
Coronary revascularization for patients with CAD in whom angina or demonstrable myocardial ischemia is present despite GDMT (level of evidence: C)
Management of AF according to published clinical practice guidelines for HFpEF to improve symptomatic HF (level of evidence: C)
Use of β -blocking agents, ACE inhibitors, and ARBs for hypertension in HFpEF ARBs might be considered to decrease hospitalizations in HFpEF (level of evidence: C)
Class III: no benefit
Nutritional supplementation is not recommended in HFpEF (level of evidence: C)
ESC/HFA guidelines
Diuretics are used to control sodium and water retention and relieve breathlessness and edema
Adequate treatment of hypertension and myocardial ischemia is also considered to be important
Control of ventricular rate in patients with atrial fibrillation

ACC indicates American College of Cardiology; ACE, angiotensin-converting enzyme; AF, atrial fibrillation; AHA, American Heart Association; ARB, angiotensin receptor blocker; CAD, coronary artery disease; ESC, European Society of Cardiology; GDMT, guideline-directed medical therapy; HF, heart failure; HFA, Heart Failure Association; and HFpEF, heart failure with preserved ejection fraction.

greater than right atrial pressure by ≥ 5 mm Hg. An elevated resting PCWP has been observed in the majority of patients with HFpEF,²⁷ and a peak exercise PCWP ≥ 25 mm Hg has been proposed as a diagnostic criterion for HFpEF.²⁸ Table 3 shows a comparison of the inclusion and exclusion criteria for the REDUCE LAP-HF I trial compared to several other recent or ongoing trials in HFpEF.^{29–31}

REDUCE LAP-HF I Trial: Outcome Measures

Patients will be followed up for 1 year and annually every 12 months for a total of 5 years after index procedure and implant. The key safety outcome measure is major adverse cardiac, cerebrovascular, and renal events (MACCRE) through 1 month post implant (including periprocedural) defined as cardiovascular death, embolic stroke, device- and/or procedure-related adverse cardiac or new-onset or worsening of kidney dysfunction (defined as estimated glomerular filtration rate decrease of >20 mL/min/1.73 m²) through 1 month post implant.

The key effectiveness outcome measure is for a mechanistic effect and is the change in supine exercise PCWP at 1 month, as assessed by an independent blinded hemodynamic

Table 2. Inclusion and Exclusion Criteria for the REDUCE LAP-HF I Trial

Candidates for the study must meet ALL of the inclusion criteria
1. Chronic symptomatic heart failure (HF) documented by the following
a. 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 mo
b. More than one hospital admission for which HF was a major component of the hospitalization or an emergency department visit with IV treatment for HF within the 12 mo before study entry OR an NT-pro-BNP value >50 pmol/L (>425 pg/mL) in normal sinus rhythm and >150 pmol/L (>1265 pg/mL) in atrial fibrillation OR a BNP value >100 pg/mL in normal sinus rhythm or >250 pg/mL in atrial fibrillation within the past 3 mo.
2. Ongoing stable GDMT HF management and management of potential comorbidities according to HF guidelines (eg, 2013 AHA/ACC or 2012 ESC/HFA guidelines), with no significant changes ($>100\%$ increase or 50% decrease)—excluding diuretic dose changes—for a minimum of 4 wk before screening, that is expected to be maintained without change for 6 mo.
3. Age ≥ 40 y
4. Site-determined LV ejection fraction $\geq 40\%$ within the past 3 mo, without previously documented ejection fraction $<30\%$.
5. Site-determined elevated LA pressure with a gradient compared with right atrial pressure documented by end-expiratory PCWP during supine ergometer exercise ≥ 25 mm Hg, and greater than right atrial pressure 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/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. 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. Transseptal catheterization and femoral vein access is determined to be feasible by site principal interventional cardiology investigator
Candidates for this study will be excluded if ANY of the following conditions are present:
1. MI and/or percutaneous cardiac intervention within past 3 mo; CABG in past 3 mo, or current indication for coronary revascularization
2. Cardiac resynchronization therapy initiated within the past 6 mo
3. Severe HF defined as one or more of the below:
a. ACC/AHA/ESC stage D HF, nonambulatory NYHA class IV HF;
b. Cardiac index <2.0 L/min/m ²
c. Inotropic infusion (continuous or intermittent) within the past 6 mo
d. Patient is on the cardiac transplant waiting list
4. Inability to perform 6-min walk test (distance <50 m), OR 6-min walk test >600 m
5. Known clinically significant unvascularized coronary artery disease, defined as: epicardial coronary artery stenosis associated with angina or other evidence of coronary ischemia.
6. History of stroke, TIA, DVT, or pulmonary emboli within the past 6 mo
7. Known clinically significant untreated carotid artery stenosis.

(Continued)

Table 2. Continued

8. Presence of significant valve disease defined by the site cardiologist as:
a. Mitral valve regurgitation defined as grade $\geq 3+$ MR
b. Tricuspid valve regurgitation defined as grade $\geq 2+$ TR
c. Aortic valve disease defined as $\geq 2+$ AR or $>$ moderate AS
9. Hypertrophic obstructive cardiomyopathy, restrictive cardiomyopathy, constrictive pericarditis, cardiac amyloidosis or other infiltrative cardiomyopathy (eg, 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 beats per min
12. Arterial oxygen saturation $<95\%$ on room air
13. Significant hepatic impairment defined as $3\times$ 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 \geq 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 right atrial pressure >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 mo before 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 <12 mo for noncardiovascular reasons
20. Echocardiographic evidence of intracardiac mass, thrombus, or vegetation
21. Known or suspected allergy to nickel
22. Fertile women
23. Currently requiring dialysis; or estimated GFR <25 mL/min/1.73 m ² by CKD-Epi equation
24. Systolic blood pressure >170 mmHg at screening
25. Subjects with existing s. Subjects with a PFO, who meet PCWP criteria despite the PFO, are allowed.
26. Subjects on immunosuppression or systemic steroid treatment (>10 mg prednisone/d).
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

AR indicates aortic regurgitation; AS, aortic stenosis; CKD-Epi, Chronic Kidney Disease Epidemiology Collaboration equation; CPAP, continuous positive airway pressure; DVT, deep vein thrombosis; FEV1, forced expiratory volume in 1 second; GDMT, guideline-directed medical therapy; GFR, glomerular filtration rate; HF, heart failure; HR, heart rate; LV, left ventricle; MR, mitral regurgitation; NT-pro-BNP, N-terminal pro-B-type natriuretic peptide; NYHA, New York Heart Association; PCWP, pulmonary capillary wedge pressure; PFO, patent foramen ovale; PVR, pulmonary vascular resistance; REDUCE LAP-HF, REDUCE Elevated Left Atrial Pressure in Heart Failure; RV, right ventricle; TAPSE, tricuspid annular plane systolic excursion; TIA, transient ischemic attack; TR, tricuspid regurgitation; and TTE, transthoracic echocardiography.

core laboratory, across the 4 exercise workload values (20 W, 40 W, 60 W, and 80 W), measured at both the baseline and 1-month follow-up visit. Key secondary and additional outcome measures for safety, effectiveness, and efficacy are detailed in Table 4.

REDUCE LAP-HF I Trial: Sample Size Determination

The key effectiveness outcome measure is the change in supine exercise PCWP from baseline to 1 month post procedure. At each of baseline and 1 month, 4 supine exercise PCWP values will be measured (at 20 W, 40 W, 60 W, and 80 W). The null and alternative hypotheses of interest across these 4 measurements are

H0: $\mu_{I20W} - \mu_{C20W} = 0$, $\mu_{I40W} - \mu_{C40W} = 0$, $\mu_{I60W} - \mu_{C60W} = 0$, $\mu_{I80W} - \mu_{C80W} = 0$. H1: At least one of the following is true: $\mu_{I20W} - \mu_{C20W} \neq 0$, $\mu_{I40W} - \mu_{C40W} \neq 0$, $\mu_{I60W} - \mu_{C60W} \neq 0$, $\mu_{I80W} - \mu_{C80W} \neq 0$

where μ_{iW} and μ_{cW} are the mean change from baseline to 1-month PCWP at iW for the IASD System II and control, respectively, where $i = 20, 40, 60, \text{ and } 80$.

The assumptions used for the power calculations are generated from historical data and data from the pilot study.

Assuming a mean change in exercise PCWP of -6.0 mmHg for IASD System II and 0.0 mmHg for control at each of 20 W, 40 W, 60 W and 80 W, and assuming a SD in PCWP change of 7.2 mmHg in each treatment group at each of 20 W, 40 W, 60 W and 80 W, a sample size of 20 evaluable subjects per treatment group yields 82% power to detect a significant beneficial effect of IASD System II compared with control when comparing treatment means using a mixed-measures repeated model ANCOVA, assuming the compound symmetry correlation structure where the pairwise correlations between 20 W, 40 W, 60 W, and 80 W are ≤ 0.8 . Sample size was calculated using the PASS 14 software (NCSS, LLC, Kaysville, UT).

REDUCE LAP-HF I Trial: Analysis Populations

The analysis populations in the trial include intent-to-treat (ITT; all randomized patients); per-protocol (subset of ITT with successful implant); and safety (ITT in whom an implant of the IASD System II was at least attempted—this is the primary analysis set for safety).

REDUCE LAP-HF I Trial: General Statistical Approach

All statistical tests will be performed at a 2-sided 0.05 level of significance, and all P values will be presented as 2-sided P values. Analyses will be performed using SAS version 9.4 or higher. Because of the nature of the study, there will be no imputation for missing data; also, it is expected that there will be no dropouts at 1 month, the time at which the key effectiveness and safety outcome measure data are collected.

Statistical Approach: Key Effectiveness Outcome Measure

The primary effectiveness outcome is the change in supine exercise PCWP from baseline at 1 month at the ≤ 4 levels of exercise (at 20 W, 40 W, 60 W, 80 W) where baseline and 1-month PCWP measurements are available. Descriptive

Table 3. Inclusion Criteria of Recent/Ongoing Heart Failure With Preserved Ejection Fraction Trials With Comparison to REDUCE LAP-HF I

Inclusion Criteria	REDUCE LAP-HF I	PARAGON	SOCRATES Preserved ³⁰	NEAT ²⁹	TOPCAT ³¹
Primary inclusion criteria: hospitalization for HF vs BNP	Previous hospitalization for HF or elevated BNP	Previous hospitalization for HF or elevated BNP	Recent hospitalization for HF and elevated BNP	Previous hospitalization for HF or elevated BNP or alternative objective evidence of HF*	Previous hospitalization with HF or elevated BNP†
NYHA class	III or ambulatory IV	II or III	II, III, or IV	II, III, or IV	II, III, or IV
Age	≥40	≥50‡	≥18	≥50	>50
LVEF cutoff	≥40%	>45%	≥45%	≥50%	≥45%
Natriuretic peptides	BNP>100 pg/mL (>250 pg/mL if AF) NT-pro-BNP>425 pg/mL (>1265 pg/mL if AF)	NT-pro-BNP >300 pg/mL (>900 pg/mL if AF)	BNP≥100 pg/mL (≥200 pg/mL if AF) NT-pro-BNP≥300 pg/mL (≥600 pg/mL if AF)	BNP>200 pg/mL NT-pro-BNP>400 pg/mL	BNP>100 pg/mL NT-pro-BNP>360 pg/mL
Echocardiographic criteria	Increased LA size or LV diastolic dysfunction required (multiple possible criteria)	Increased LA size or LV hypertrophy required (multiple possible criteria)	Increase LA size required (multiple criteria including LA volume, LA area, or LA diameter)	Besides LVEF≥50%, echocardiographic criteria were only required as one of the possible eligibility criteria	None besides LVEF≥45%
Invasive hemodynamic criteria	PCWP at rest or with exercise >25 mm Hg required in all patients; PCWP > RA pressure by ≥5 mm Hg	None	None	Invasive hemodynamic criteria were included in eligibility criteria but were not required for enrollment	None
Primary end point	Key effectiveness measure: change in exercise PCWP; key safety measure: major adverse cardiac, cerebrovascular, embolic, or renal events	Composite of CV death and total HF hospitalizations	Co-primary end points: (1) change in NT-pro-BNP and (2) change in LA volume	Accelerometer-assessed physical activity	Composite of CV death, HF hospitalization, or aborted cardiac arrest

AF indicates atrial fibrillation; BNP, B-type natriuretic peptide; CV, cardiovascular; HF, heart failure; LA, left atrial; LV, left ventricular; LVEF, left ventricular ejection fraction; NEAT, Nitrate's Effect on Activity Tolerance in Heart Failure With Preserved Ejection Fraction; NT-pro-BNP, N-terminal pro-B-type natriuretic peptide; NYHA, New York Heart Association; PARAGON, Efficacy and Safety of LCZ696 Compared to Valsartan, on Morbidity and Mortality in Heart Failure Patients With Preserved Ejection Fraction; PCWP, pulmonary capillary wedge pressure; RA, right atrial; REDUCE LAP-HF, REDUCE Elevated Left Atrial Pressure in Heart Failure; SOCRATES, Soluble Guanylate Cyclase Stimulator in Heart Failure Studies; and TOPCAT, Treatment of Preserved Cardiac Function Heart Failure with an Aldosterone Antagonist.

*In NEAT, alternate criteria besides previous hospitalization for HF or elevated BNP included: (1) elevated LV filling pressures on invasive hemodynamic testing or (2) echocardiographic evidence of diastolic dysfunction, LV hypertrophy, and/or elevated LV filling pressures (at least 2 criteria were required). A complete description of the specific invasive hemodynamic and echocardiographic criteria is listed in Zakeri et al.²⁹

†In TOPCAT, heart failure only had to be one of the reasons for hospitalization (not the primary reason for hospitalization).

‡In PARAGON, the age cutoff initially was >55 y but has since been amended to an age cutoff of >50 y. PARAGON trial: <https://clinicaltrials.gov/ct2/show/NCT01920711>.

statistics of the change in PCWP at 1 month will be presented for each treatment group for each of 20 W, 40 W, 60 W, and 80 W. Treatments will be compared on change in exercise PCWP across the 4 values using mixed-measures repeated model ANCOVA adjusting for the corresponding baseline exercise PCWPs, using a two-sided 0.05 level of significance.

Statistical Approach: Key Safety Outcome Measure

The key safety outcome measure is the composite incidence of one or more of the following: major adverse cardiac, cerebrovascular embolic, or renal events (MACCRE) at 1 month. The analysis on the end point of MACCRE at 1 month will be descriptive (percentage of patients with MACCRE and 2-sided exact confidence interval of the percentage based on

the binomial distribution for each treatment group). Although there is no formal hypothesis testing on this end point, note that for the investigational arm, it is anticipated that the true MACCRE rate in the population is ≈5%. Under this assumption, there is a 92% chance in a sample of size 20 that the observed rate will be ≤10%. This analysis will be performed on the ITT population in whom an implant of the IADS System II was at least attempted (ie, the safety population) with available data (follow-up through 1 month, or a MACCRE event by 1 month).

Also for each treatment group, Kaplan–Meier curves and estimates of cumulative MACCRE rate at 12 months will be presented for all patients in the ITT population regardless of length of follow-up. A 2-sided 95% confidence interval of the difference between treatments with respect to the Kaplan–Meier estimates of cumulative MACCRE rate will

Table 4. Additional Outcome Measures for Safety and Effectiveness

Safety-related outcome measures
1. Major adverse cardiac events through 12 mo
2. All serious adverse events through 12-mo
3. All-cause mortality, CV mortality, and heart failure–related mortality through 12 mo
4. Newly acquired persistent or permanent AF or atrial flutter through 12 mo
5. Implant embolization and clinically significant device migration through 12 mo
6. Systemic embolic events through 12 mo
7. Increase in RV size/decrease in RV function through 12 mo
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 mo
2. Treatment for outpatient worsening of heart failure
3. Days alive, and not-hospitalized through 12 mo
4. Change in blinded investigator–assessed NYHA classification between baseline and 12 mo
5. Change in 6MWT distance between baseline and 12 mo
6. Assessment of shunt dimensions and flow at 12 mo
7. Changes in resting and exercise PA pressures and CI between baseline and 1 mo as assessed by an independent blinded hemodynamic core laboratory.
8. Change in BNP and/or NT-pro-BNP, and MR-ANP between baseline and at 12 mo
9. Changes in LA, LV dimensions, volume, and function, between baseline and 12 mo assessed by an independent echocardiographic core laboratory
10. Changes in RA, LA, LV and RV dimensions, volume, and function between baseline and 12 mo assessed by a cardiac MRI core laboratory (substudy only)
11. Change in CPET parameters (including exercise time) between baseline and 12 mo as assessed by an independent blinded CPET core laboratory (substudy only)
12. Change in diuretic medications between baseline and 12 mo

AF indicates atrial fibrillation; BNP, B-type natriuretic peptide; CI, cardiac index; CPET, cardiopulmonary exercise testing; CV, cardiovascular; HF, heart failure; IV, intravenous; LA, left atrial; LV, left ventricular; MR-ANP, mid-regional atrial natriuretic peptide; MRI, magnetic resonance imaging 6MWT, 6-minute walking test; NT-pro-BNP, N-terminal pro-B-type natriuretic peptide; NYHA, New York Heart Association; PA, pulmonary artery; RA, right atrial; and RV, right ventricular.

be presented. In this analysis, patients not experiencing MACCRE will be censored at 1 month or at last known follow-up, whichever is earlier.

REDUCE LAP-HF I Trial Substudies

A substudy will include an optional cardiopulmonary exercise testing evaluation and cardiac magnetic resonance imaging in eligible patients at baseline and follow-up. This substudy will include selected centers where these evaluations are well

established. The data from the cardiopulmonary exercise testing and images from the cardiac magnetic resonance imaging will be evaluated by independent core laboratories. Participating sites will be provided with detailed instructions from the core laboratories to standardize the conduct of these studies across sites.

REDUCE LAP-HF I Trial: Data Collection

All required data for the trial will be collected on standardized case report forms. All protocol-mandated echocardiograms and hemodynamic tracings will be sent to independent core laboratories. The echocardiographic core laboratory for this study is The Center for Quantitative Echocardiography (University of Pennsylvania, Philadelphia, PA) and the hemodynamic core laboratory is Cardiovascular Clinical Studies, Inc (Boston, MA). The exercise testing core laboratory is the Cardiopulmonary Exercise Testing Core Laboratory, Department of Health and Exercise Science (Wake Forest University, Winston Salem, NC), and the magnetic resonance imaging core laboratory is the MRI Core Laboratory, Cardiovascular Clinical Studies, Inc (Boston, MA). Data management is by Harvard Clinical Research Institute, Boston, MA.

REDUCE LAP-HF I Trial: Data Safety–Monitoring Board and Clinical Events Committee

The separate data safety–monitoring board and Clinical Events Committee are managed by the Clinical Research Organization, Harvard Clinical Research Institute, Boston, MA.

Discussion

HFpEF, with its increasing prevalence and high morbidity and mortality, is a major unmet need in cardiovascular medicine today.^{1,32,33} We hypothesize that creating an appropriately sized left to-right atrial shunt that will allow LA decompression without significantly compromising left ventricular filling and forward cardiac output is a rational strategy for treating patients with HFpEF, potentially improving symptoms (particularly during exertion) and reducing HF hospitalizations. Furthermore, given the device-based nature of the treatment, patient noncompliance and polypharmacy are minimized, which could be beneficial in these patients who are often elderly and have multiple comorbidities. Corvia Medical, Inc, has developed a transcatheter intracardiac device (the IASD System II) that creates an 8-mm permanent opening in the septum between the right and left atria of the heart, designed to maintain a permanent communication. An early unblinded, single-arm pilot study of the IASD in HFpEF has yielded promising results, and a second, larger unblinded, single-arm study is ongoing. Although the previous experience with the IASD has been encouraging, a randomized controlled trial is necessary to provide further evidence of device efficacy and safety. Here, we have described the rationale and design of the REDUCE LAP-HF I clinical trial of the IASD in patients with HF and LV ejection fraction $\geq 40\%$, which should advance our understanding of the utility of this device in HF.

There is currently one other device using similar hemodynamic principles of an atrial shunt.³⁴ The V-Wave device (V-Wave Medical, Caesarea, Israel) is an hourglass-shaped nitinol frame device with 3 valve leaflets intended to mechanically maintain a 5 mm sized unidirectional left-to-right shunt at the level of the atrial septum. The V-Wave device was successfully implanted in 5 patients with chronic HFrEF with a mean LVEF of 25±6%. At 3-month follow-up, all patients showed clinical improvement as evidenced by change to New York Heart Association class II, increased 6-minute walking test, reduction in PCWP and N-terminal pro-B-type natriuretic peptide, but there were no changes in LVEF, end-diastolic LV diameter, LA volume, mitral regurgitation grade, or right arterial pressure. There were no device-related adverse events.

Strengths

The study described here is the first randomized trial of a device-based therapy for lowering LA pressure in patients with HFpEF. Incorporating a randomized evaluation with a control arm is important given the potential for a placebo effect, as has been demonstrated for other device-based therapies.³⁵ The trial benefits from strict inclusion criteria for the diagnosis of HF (requiring both signs/symptoms of HF and objective evidence of LV diastolic dysfunction or LA enlargement and objective invasive hemodynamic evidence of elevated LA pressure). In addition, the trial includes detailed hemodynamic assessment during exercise, which is critical given the exercise-related symptoms that are so common in HFpEF.

Limitations

Given the small sample size, the trial presented here will not be definitive; a larger, pivotal trial will be necessary to establish clinical efficacy. However, the rationale for this first randomized evaluation of the IASD system is to establish effectiveness and to inform the design of such a pivotal study; it will provide the impetus to proceed with a larger pivotal trial designed to evaluate clinical outcomes related to HF while avoiding the need for burdensome invasive hemodynamic follow-up evaluation. Finally, although this is designed as a single (patient) blinded study, there is opportunity for inadvertent unblinding which could impact the subjective secondary outcome measures. However, the key effectiveness outcome measure, changes in PCWP across the range of exercise levels, is objective and will be evaluated by a blinded core laboratory.

Conclusions

The initial nonrandomized, single-arm clinical trial using the Corvia transcatheter interatrial shunt supports the safety of the implantation procedure, the safety of the device itself after implantation, and both hemodynamic and clinical improvements. The new trial presently described will be the first prospective, multicenter, randomized, and single blinded trial to test this strategy and has strong potential to provide important data to further advance knowledge of this first-in-class, novel, transcatheter device-based therapy for HFpEF.

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Disclosures

Dr Komtebedde is an employee of Corvia Medical, Inc., the sponsor of the REDUCE LAP-HF I clinical trial. The other authors report no conflicts.

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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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