Transcatheter Interatrial Shunt Device for the Treatment of Heart Failure With Preserved Ejection Fraction (REDUCE LAP-HF I [Reduce Elevated Left Atrial Pressure in Patients With Heart Failure])

A Phase 2, Randomized, Sham-Controlled Trial

BACKGROUND: In nonrandomized, open-label studies, a transcatheter interatrial shunt device (IASD, Corvia Medical) was associated with lower pulmonary capillary wedge pressure (PCWP), fewer symptoms, and greater quality of life and exercise capacity in patients with heart failure (HF) and midrange or preserved ejection fraction (EF ≥40%). We conducted the first randomized sham-controlled trial to evaluate the IASD in HF with EF ≥40%.

METHODS: REDUCE LAP-HF I (Reduce Elevated Left Atrial Pressure in Patients With Heart Failure) was a phase 2, randomized, parallel-group, blinded multicenter trial in patients with New York Heart Association class III or ambulatory class IV HF, EF ≥40%, exercise PCWP ≥25 mm Hg, and PCWP-right atrial pressure gradient ≥5 mm Hg. Participants were randomized (1:1) to the IASD versus a sham procedure (femoral venous access with intracardiac echocardiography but no IASD placement). The participants and investigators assessing the participants during follow-up were blinded to treatment assignment. The primary effectiveness end point was exercise PCWP at 1 month. The primary safety end point was major adverse cardiac, cerebrovascular, and renal events at 1 month. PCWP during exercise was compared between treatment groups using a mixed-effects repeated measures model analysis of covariance that included data from all available stages of exercise.

RESULTS: A total of 94 patients were enrolled, of whom 44 met inclusion/exclusion criteria and were randomized to the IASD (n=22) and control (n=22) groups. Mean age was 70±9 years, and 50% were female. At 1 month, the IASD resulted in a greater reduction in PCWP compared with sham control (P=0.028 accounting for all stages of exercise). Peak PCWP decreased by 3.5±6.4 mm Hg in the treatment group versus 0.5±5.0 mm Hg in the control group (P=0.14). There were no peri-procedural or 1-month major adverse cardiac, cerebrovascular, and renal events in the IASD group and 1 event (worsening renal function) in the control group (P=1.0).

CONCLUSIONS: In patients with HF and EF ≥40%, IASD treatment reduces PCWP during exercise. Whether this mechanistic effect will translate into sustained improvements in symptoms and outcomes requires further evaluation.

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Clinical Perspective

What Is New?

- We report a novel therapy for patients with heart failure (HF) with preserved ejection fraction (EF >50%) or midrange EF (40% to 50%) utilizing an implanted device to create an atrial shunt (interatrial shunt device [IASD]).
- The objective of the IASD is to dynamically (at rest and during exercise) decompress left atrial pressure overload associated with HF with preserved EF and HF with midrange EF.
- We conducted a randomized sham-controlled trial to evaluate the mechanistic effect of the IASD on invasively measured pulmonary capillary wedge pressure. At 1 month after randomization, the IASD treatment group had a significantly greater reduction in pulmonary capillary wedge pressure during exercise compared with the control group. In addition, pulmonary capillary wedge pressure during passive leg raise and also during 20 W of exercise decreased to a greater degree in the patients randomized to IASD compared with the sham control.

What Are the Clinical Implications?

- In patients with HF and EF ≥40%, the creation of an interatrial shunt with the IASD unloads the left atrium and reduces pulmonary capillary wedge pressure during exercise.
- This hemodynamic study demonstrates the beneficial mechanistic effect of the IASD.
- The IASD could have beneficial clinical effects in patients with HF with preserved EF and HF midrange EF. A larger trial to examine the effects of the IASD on symptoms, quality of life, exercise capacity, and clinical outcomes such as HF hospitalization is warranted.

Heart failure (HF) with preserved ejection fraction (HFpEF, EF>50%), which is increasing in prevalence and currently accounts for ≈50% of all HF cases, is associated with high morbidity and mortality and lacks effective therapies.[1,2] HF with midrange EF (EF 40% to 50%) is also prevalent and lacks proven therapies, and it was recently highlighted in the European Society of Cardiology HF guidelines.[3,4] Although HFpEF and HF with midrange EF are heterogeneous with respect to etiology and pathophysiology, elevated left atrial (LA) pressure at rest or during exertion represents a central underlying abnormality in all patients with these syndromes.[5]

Patients with HFpEF are known to have left ventricular (LV) diastolic dysfunction (impaired LV relaxation and reduced LV compliance).[6,7] These abnormalities result in elevated LA pressure and volume overload with subsequent elevation in pulmonary venous pressures, particularly during exertion, resulting in symptoms of dyspnea and exercise intolerance.[8] In addition, intrinsic LA mechanical dysfunction is increasingly recognized as potentially important in driving symptoms and poor outcomes in HFpEF.[5,9–11] The inability of the LA to handle increased load during exercise is especially problematic in patients with HFpEF.[5,12] Pulmonary capillary wedge pressure (PCWP) is an invasive hemodynamic parameter that reflects LA and pulmonary venous pressures. Higher peak PCWP during exercise, corrected for workload, has also been associated with reduced exercise capacity[13] and worse outcomes[14] in the HFpEF setting, further underscoring the importance of the LA in the pathogenesis of HFpEF.

Given the importance of LA overload in HF—particularly HFpEF—unloading the LA with the goal of reducing pulmonary venous pressure may lead to improved symptoms and outcomes in these patients.[15] It has long been known that in the setting of mitral stenosis, a condition also associated with elevated LA pressure and LA dysfunction, the coexistence of a congenital atrial septal defect (Lutembacher syndrome) can be associated with fewer symptoms and a more favorable clinical course.[16] It has been hypothesized that an interatrial septal communication can unload the LA in the setting of increased LA pressure (such as during exercise), transferring the excess LA blood volume to the larger reservoir of the right atrium (RA) and systemic veins, thereby limiting the increase in LA pressure and pulmonary venous pressures during exercise. The recognition of this concept led to the development of a novel interatrial shunt device (IASD, Corvia Medical) for the treatment of HF.[17]

Hemodynamic simulations of the IASD have shown LA unloading during exercise without right ventricular (RV) pressure or volume overload.[15] In nonrandomized, open-label, single-arm studies, placement of the IASD has been associated with the lowering of PCWP (a surrogate for LA pressure) during exercise in patients with HF and EF ≥40%.[18–20] In these prior studies, the IASD was also found to be safe and associated with fewer symptoms, better quality of life, and greater exercise capacity, without the development of right-sided HF or pulmonary hypertension. However, these open-label, nonrandomized studies are subject to potential bias and confounding and cannot prove effectiveness of the IASD. We therefore conducted a randomized, blinded, sham-controlled clinical trial to determine the effectiveness of the IASD in HF with EF ≥40%. We hypothesized that the IASD reduces PCWP during exercise in patients with HF and EF ≥40% by unloading the LA.

METHODS

Study Design and Participants

The rationale and design of the REDUCE LAP-HF I trial (Reduce Elevated Left Atrial Pressure in Patients With Heart

Failure) have been described previously.[17] The primary objective of the REDUCE LAP-HF I clinical trial was to evaluate the mechanistic effect of implanting the IASD System II (Corvia Medical) in patients with HF with EF ≥40% and elevated LA pressure who remained symptomatic despite optimal guideline-directed medical therapy. This was a multicenter, prospective, randomized, blinded controlled trial with nonimplant (sham) control group and 1:1 randomization. Patients were recruited between February 3, 2016, and November 23, 2016, at 22 centers in the United States, Europe (Belgium, France, The Netherlands, and United Kingdom), and Australia (Table I in the online-only Data Supplement lists all of the participating sites, principal investigators, and study coordinators for the trial).

A full list of inclusion and exclusion criteria is listed in the online-only Data Supplement. The inclusion and exclusion criteria were designed to ensure that patients had symptomatic HF (New York Heart Association class III or ambulatory class IV), an elevated LA pressure with a pressure gradient between the LA and RA, and no evidence of right-sided HF. Key inclusion criteria included documented chronic symptomatic HF and (1) prior hospitalization for HF (or acute care facility/emergency room intensification of diuretic therapy) within the prior 12 months, or (2) elevated B-type natriuretic peptide (BNP) or N-terminal pro-BNP within the past 6 months (BNP >70 pg/mL in normal sinus rhythm, >200 pg/mL in atrial fibrillation, or N-terminal pro-BNP >200 pg/mL in normal sinus rhythm, >600 pg/mL in atrial fibrillation); EF ≥40%; ≥40 years of age; elevated LA pressure documented invasively by end-expiratory PCWP during supine bike exercise ≥25 mm Hg, and PCWP-RA pressure gradient ≥5 mm Hg. Key exclusion criteria included stage D HF; cardiac index <2.0 L/min/m^2; history of stroke, transient ischemic attack, deep vein thrombosis, or pulmonary embolism within the past 6 months; hemodynamically significant valvular disease; hypertrophic or infiltrative cardiomyopathy; RV dysfunction (>mild RV dysfunction, tricuspid annular plane systolic excursion <1.4 cm, RV size >LV size, or RV fractional area change <35%); resting RA pressure > 14 mm Hg; or pulmonary vascular resistance >4 wood units.

The study protocol was approved by the institutional review board or ethics committee at each of the 22 enrolling sites, and all enrolled patients provided written informed consent. A data safety monitoring committee oversaw the program and reviewed trial data for patient safety at regular intervals. Because of the proprietary nature of the study data, it will not be made publically available at this time. All statistical analyses were performed independently by the Baim Clinical Research Institute.

Randomization and Blinding

Eligible patients were randomized if they met all of the inclusion and exclusion criteria after undergoing the study-related qualification procedures (Figure I in the online-only Data Supplement), including noninvasive screening with echocardiography and supine bicycle exercise right heart catheterization. Immediately after qualification, eligible patients were randomized in a 1:1 ratio to the treatment or control group. Patient randomization was performed via the Interactive Web Response System. Patient blinding included 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. Participants and nonprocedural research staff were blinded to treatment assignment for 1 year after randomization. Each site was assigned blinded and unblinded staff to facilitate unbiased patient assessments through follow-up. The physicians managing the randomized patients clinically (including the treating cardiologist) and research staff involved in conducting selected evaluations after randomization, including the hemodynamic core laboratory, were blinded to the study arm. Treating physicians were also blinded to all right heart catheterization measurements. Research staff members were given explicit instructions to maintain patient blinding throughout the trial (online-only Data Supplement).

Study Procedures

Before enrolling patients into the study, all interventional cardiology investigators and associated investigative staff at each site underwent training to optimize and standardize invasive hemodynamic testing and recording of hemodynamic data, and to ensure proper deployment of the IASD System II device.

Once enrolled into the study, all patients underwent noninvasive screening, including comprehensive echocardiography to ensure EF ≥40%, diastolic dysfunction, and the absence of significant RV dysfunction or valvular disease. Participants meeting echocardiographic criteria underwent further screening with invasive hemodynamic testing. Right heart and pulmonary arterial catheterization was performed from the right internal jugular vein approach using the standard Seldinger technique under fluoroscopic guidance. Using a fluid-filled pulmonary artery catheter, all participants underwent recording of hemodynamics (RA pressure, pulmonary artery pressure, and PCWP) with a properly zeroed and calibrated pressure transducer. Hemodynamic measurements were recorded at rest, with legs up in the exercise bike pedals (equivalent to a passive leg raise procedure, a preload challenge), and during supine bike exercise. All pressure recordings were performed at a 50 mm/second paper speed with adjustment of pressure (mm Hg) scale as needed, and the recordings were saved for blinded measurement by the hemodynamic core laboratory. Cardiac output was measured with the thermodilution method, and pulmonary vascular resistance was calculated as the transpulmonary gradient (mean pulmonary artery pressure—PCWP) divided by cardiac output.

After the baseline right heart catheterization and exercise protocol, all patients who remained eligible by invasive hemodynamic criteria were sedated, blinded using the methods described above, and randomized to IASD treatment or sham control. Patients in both the treatment and control arm underwent femoral venous access after randomization. Patients randomized to the control arm underwent intracardiac or transesophageal echocardiographic examination of the atrial septum and LA appendage (but no transseptal puncture). Patients randomized to the treatment arm underwent a transseptal puncture and IASD System II implantation guided by fluoroscopy and intracardiac or transesophageal echocardiography. The IASD System II consists of a 1-piece, self-expanding metal cage that has a double-disc design with an opening (barrel) in the center (Figure 1A through 1C). The implant is radiopaque and echogenic to allow for imaging during the implantation

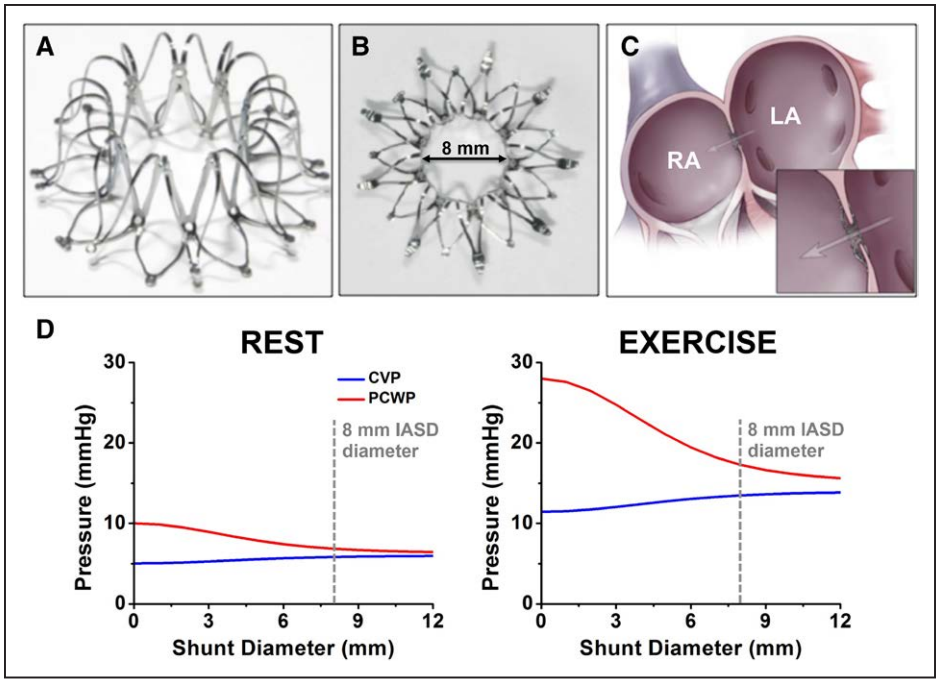

Figure 1. Interatrial shunt device.
A, Corvia Interatrial Shunt Device (IASD) System II. **B,** En face view of the IASD System II (single size, internal diameter = 8 mm). **C,** The IASD creates an interatrial shunt that unloads the left atrium by shunting blood from the higher pressure left atrium to the lower pressure right atrium. **D,** Simulation studies have shown that an 8-mm internal diameter for the shunt device is optimal in maximally reducing left atrial pressure without overloading the right heart (ie, keeping pulmonary-to-systemic flow relatively low at a 1.2–1.3 range). Figure 1D was reprinted from Kaye et al[15] with permission. Copyright ©2014, Elsevier. CVP indicates central venous pressure (right atrial pressure); and IASD, interatrial shunt device.

procedure. The LA side of the implant is flat so the legs rest flush against the LA side of the interatrial septum, thereby minimizing the LA profile of the deployed implant. The RA side is curved to accommodate variable interatrial septal wall thicknesses, with only the leg ends contacting the RA side of the interatrial septum. 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, which corresponds to the optimal interatrial communication size (ie, maximizing the ability to reduce PCWP during exercise while keeping the ratio of pulmonary to systemic blood flow at 1.2–1.3) (Figure 1D).[15] Details regarding medication administration related to the procedure and device are listed in Table II in the online-only Data Supplement. Patients randomized to the IASD who were not previously on an anticoagulant (eg, warfarin, direct oral anticoagulant) were treated with clopidogrel after the procedure. All patients who were on clopidogrel at baseline were kept on clopidogrel after the procedure. All patients in both treatment arms received aspirin after the procedure. The baseline use of these medications (before randomization) is listed in Table III in the online-only Data Supplement.

At 1 month after randomization, all study patients underwent repeat right heart catheterization with hemodynamic measurements at rest, with legs up, and during exercise using the exact same protocol as the exercise study performed at baseline. The primary effectiveness end point was change in PCWP during exercise from baseline to 1 month. All hemodynamic pressure measurements for the trial were made at end expiration using a standardized measurement protocol by the hemodynamic core laboratory, which was blinded to treatment allocation, baseline versus follow-up procedure, and all other clinical data. After initial review, for patients with hemodynamic values that were outside the expected range (eg, PCWP >mean pulmonary artery pressure), a systematic reascertainment of hemodynamic tracings for those patients was conducted by the hemodynamic core laboratory in a blinded fashion as part of their quality assurance process. Secondary effectiveness end points included change in peak exercise PCWP from baseline at 1 month, change in exercise duration at 1 month, and change in peak exercise workload at 1 month. Additional end points included change in New York Heart Association class and change in diuretic use from baseline.

The primary safety end point was periprocedural events and major adverse cardiac, cerebrovascular, and renal events (MACCRE) at 1 month. MACCRE included cardiovascular death, embolic stroke, device- or procedure-related adverse cardiac events, and new-onset or worsening of kidney dysfunction (defined as a decrease in estimated glomerular filtration rate >20 mL/min/1.73 m^2) through 1-month after implant. Additional safety-related end points included the need for implant removal or occlusion of the implant and HF hospitalization. All end points were adjudicated centrally by a blinded, independent clinical events committee.

Statistical Analysis

The statistical analyses for the primary efficacy and safety outcomes (including power calculations and the use of a

mixed-effects model repeated measures, described below) were prespecified a priori and documented in the trial protocol and in our prior publication on the rationale and design of the REDUCE LAP-HF I trial.[17] We assumed a mean change in exercise PCWP of −6.0 mm Hg in the treatment group and 0.0 mm Hg in the control group at each of 20 W, 40 W, 60 W, and 80 W stages, and we assumed a standard deviation in PCWP change of 7.2 mm Hg in each treatment group at each of the exercise stages. Based on these assumptions, a sample size of 20 evaluable participants per treatment arm yielded 82% power at a 2-sided 0.05 level of significance to detect a significant beneficial effect of IASD System II over control when comparing treatment means using a mixed-effects model repeated measures [21] analysis of covariance that included data from all available stages of exercise, assuming the compound symmetry correlation structure where the pairwise correlations among 20 W, 40 W, 60 W, and 80 W stages of exercise are ≤0.8.

The key safety outcome analysis on the end point of MACCRE at 1 month is descriptive (percentage of patients with MACCRE and 2-sided exact confidence interval of the percentage based on the binomial distribution for each treatment group). It was anticipated that the true MACCRE rate in the population would be ≈5%. Under this assumption, there was a 92% chance in a sample of size of 20 that the observed rate would be ≤10%. Sample size calculations were performed using PASS 14 software (NCSS, LLC).

The primary statistical analysis was based on an intention-to-treat (ITT) analysis that included all randomized patients with available data (n=44; n=22 in each treatment arm). Femoral venous access was attempted on all ITT patients; thus, the safety population (n=44) was identical to the ITT population. The per-protocol population consisted of 42 patients (2 of the patient randomized to the treatment arm were excluded from the per-protocol population because they did not receive the IASD implant). All statistical tests were carried out at a 2-sided 0.05 level of significance, and all *P* values were presented as 2-sided. There was no imputation for missing data. For the primary mechanistic end point (change in PCWP during exercise from baseline at 1 month), the 2 treatment groups were compared using the aforementioned prespecified mixed-effects model repeated measures analysis of covariance, which included data from all available stages of exercise. For the primary safety end point (periprocedural and 1-month MACCRE), the 2 treatment groups were compared using a 2-sided exact confidence interval of the percentage of patients who experienced events in the 2 groups based on the binomial distribution for each treatment arm. Given the sample size and low MACCRE rates that were expected, there was no anticipation of a treatment difference on 1-month MACCRE. Mean values of continuous secondary effectiveness outcomes were compared between treatment groups using analysis of covariance with adjustment for the baseline value of the variable of interest. The rate of HF hospitalization was compared between treatments using the Fisher exact test. Mean differences between baseline and 1-month PCWP at rest (legs down), legs up, 20 W, and peak exercise were calculated using paired *t* tests within each treatment group. Analyses were carried out using SAS version 9.4 (SAS Institute).

This trial is registered at ClinicalTrials.gov, NCT02600234.

RESULTS

A total of 94 patients with HF and EF ≥40% underwent screening procedures. Of the 94 enrolled patients, 44 met inclusion/exclusion criteria and were randomized 1:1 to the IASD and control (sham) groups (Figure 2). Baseline demographic, clinical, and invasive hemodynamic characteristics were similar between treatment groups except for more black patients in the control arm (Table 1). Echocardiographic indices of diastolic function were similar between the treatment groups (Table IV in the online-only Data Supplement).

The study participants ranged from 48 to 84 years of age (mean age 70 years), were 50% women, and had multiple comorbidities (including a 50% prevalence of atrial fibrillation). At the time of screening, all but 1 participant were New York Heart Association class III. The vast majority (42/44, 95%) of the participants were on a diuretic at baseline, and 28/44 (64%) had ≥1 hospitalization or emergency department/acute care facility visit for HF within the 12 months before enrollment. All study participants had an EF ≥40% at baseline, and the majority (39/44, 89%) had a baseline EF ≥50%.

Implantation of the IASD System II was attempted in 21 of 22 of the participants randomized to the treatment arm. In 1 participant, RA access could not be established for insertion of the procedure catheters (an occluded inferior vena cava filter was noted); therefore, the procedure was aborted. No subsequent MACCRE events were reported in this participant. Of the 21 remaining participants in whom implantation was attempted, there was 1 participant in whom the device was inadvertently fully deployed in the LA instead of at the interatrial septum. The device was percutaneously retrieved over the guide wire, and the implantation of a second device was not attempted (see Table V in the online-only Data Supplement for further details). The 20 remaining participants randomized to the IASD treatment arm were successfully implanted; 19 participants had 1 implantation attempt, and 1 participant had 2 implantation attempts. Table 2 lists the differences in procedure characteristics between study groups. Total procedure duration, total fluoroscopy duration, and total contrast administered were greater in the treatment group compared to the control group. See Table V in the online-only Data Supplement for further details about the procedural and device characteristics. Of the 20 participants who underwent successful device implantation, 1 refused repeat right heart catheterization at 1 month but remained in the trial and underwent all other follow-up assessments. All 22 patients in the control arm underwent repeat right heart catheterization with invasive hemodynamic testing at 1 month.

The ITT analysis of the key effectiveness end point (PCWP during exercise) was performed on all participants who had PCWP results for ≥1 exercise level (at 20

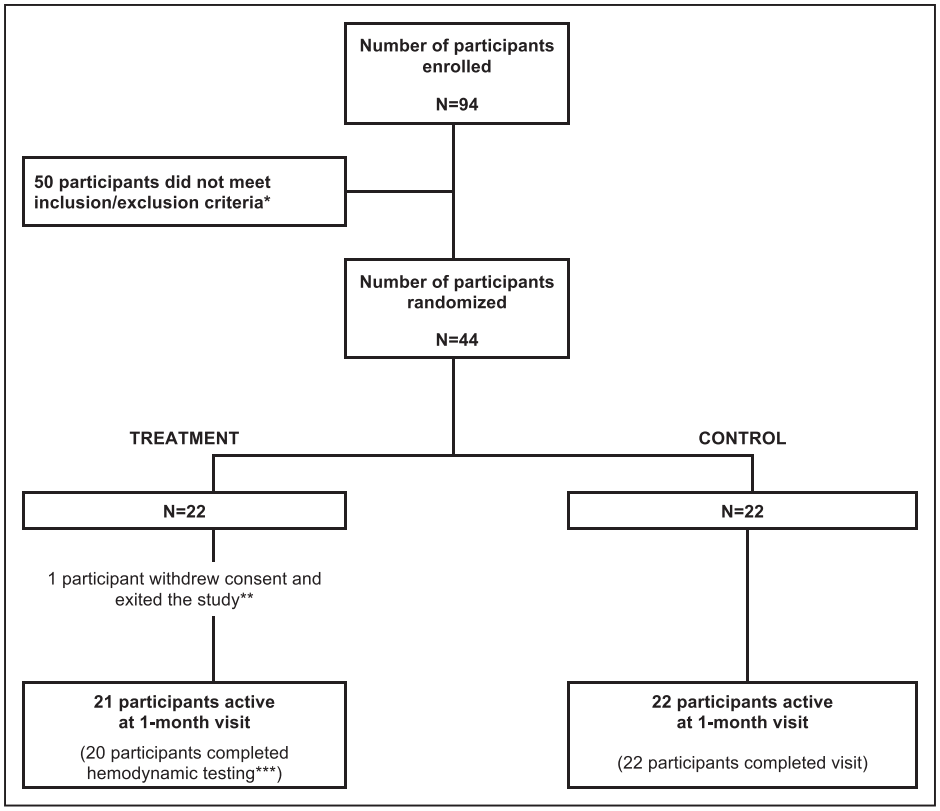

Figure 2. Study participant disposition flow chart.
*Reasons for exclusion included myocardial infarction, percutaneous coronary intervention, or coronary artery bypass grafting within the last 3 months (n=13); known clinically significant unrevascularized epicardial coronary artery disease (n=11); history of stroke, transient ischemic attack, deep vein thrombosis, or pulmonary embolism within the last 6 months (n=5); resting right atrial pressure >14 mm Hg on invasive hemodynamic testing (n=5); not an appropriate participant in the opinion of the investigator (n=5); significant valvular disease (n=4); severe chronic kidney disease (n=2); severe heart failure (n=1); baseline 6-minute walk test outside of acceptable range of 60 to 500 m (n=1); untreated clinically significant carotid stenosis (n=1); right ventricular dysfunction (n=1); significant lung disease (n=1); severe untreated obstructive sleep apnea (n=1); and current immunosuppressive therapy (n=1). In addition, 2 participants could not be enrolled because the study was closed to enrollment during the screening period, and 1 patient was diagnosed with breast cancer and wanted to defer the study while she underwent chemotherapy. Some participants had more than 1 reason for being excluded from the trial. **One participant withdrew consent to participate in the study during the index procedure. Right atrial access could not be obtained for insertion of the intracardiac echocardiography probe, and the participant was unblinded immediately after the attempt. The participant withdrew consent at that point on learning that device placement was not feasible.

W, 40 W, 60 W, or 80 W) at both baseline and 1 month (all participants achieved an exercise level of ≥20 W at 1 month). These results are shown in Table 3. Overall, the IASD treatment group had a greater reduction in PCWP during exercise after 1 month compared with the control group (P=0.028 by mixed-effects model repeated measures analysis of covariance). Thus, the trial met its key effectiveness end point measure. On secondary outcome analysis, the change in peak PCWP at 1 month was −3.5±6.4 mm Hg in the treatment group compared with −0.5±5.0 mm Hg in the control group (P=0.14). As shown in Figure 3, patients randomized to the IASD arm had a reduction in 1-month PCWP at legs up, 20 W, and peak exercise (P<0.05 for all comparisons), whereas the control group did not. From baseline to 1 month, the exercise time increased by a mean of 1.2±3.7 minutes in the treatment group compared with 0.4±3.5 minutes in the control group (P=0.60), and peak supine bike workload increased by a mean of 1.5±14.6 W in the treatment group compared with −1.9±10.8 W in the control group (P=0.35). On exploratory analyses, legs up PCWP and 20 W PCWP decreased to a greater amount in the IASD treatment group compared with the control group (P<0.05 for both comparisons) (Table 3). Results of the per-protocol analyses were similar to the results of the ITT analysis described earlier.

Overall, few periprocedural, MACCRE, or other serious adverse events occurred in either the treatment or control groups at 1 month of follow-up (Table 4). At 1 month, 0/21 (0%) of the participants in the IASD treatment group experienced a MACCRE event, and

Table 1. Baseline Demographic, Clinical, and Invasive Hemodynamic Characteristics of the Treatment Groups

Patient Characteristics	IASD Patients (N=22)	Control Patients (N=22)	*P* Value
Demographics			
Age, y	69.6±8.3 (22)	70.0±9.2 (22)	0.86
Male	63.6% (14/22)	36.4% (8/22)	0.13
Race			0.03
Black	0.0% (0/22)	18.2% (4/22)	
White	86.4% (19/22)	81.8% (18/22)	
Other	13.6% (3/22)	0.0% (0/22)	
Body mass index, kg/m^2	35.2±6.4 (22)	35.1±9.1 (22)	0.98
Comorbidities/risk factors			
Hypertension	81.8% (18/22)	90.9% (20/22)	0.66
Hyperlipidemia	72.7% (16/22)	72.7% (16/22)	1.00
Diabetes	54.5% (12/22)	54.5% (12/22)	1.00
Chronic obstructive pulmonary disease	13.6% (3/22)	31.8% (7/22)	0.28
Ischemic heart disease	22.7% (5/22)	23.8% (5/21)	1.00
Prior myocardial infarction	22.7% (5/22)	19.0% (4/21)	1.00
Prior coronary revascularization	47.6% (10/21)	45.5% (10/22)	1.00
Atrial fibrillation	54.5% (12/22)	45.5% (10/22)	0.76
Atrial flutter	4.5% (1/22)	9.1% (2/22)	1.00
Stroke	9.1% (2/22)	14.3% (3/21)	0.66
Transient ischemic attack	13.6% (3/22)	9.1% (2/22)	1.00
Peripheral arterial disease	13.6% (3/22)	9.1% (2/22)	1.00
Pulmonary embolism	4.5% (1/22)	4.5% (1/22)	1.00
Deep vein thrombosis	13.6% (3/22)	0.0% (0/21)	0.23
Cardiac status			
Left ventricular ejection fraction, site-reported (%)	59.9±9.0 (22)	58.5±6.9 (22)	0.59
NYHA classification			0.32
III	100.0% (22/22)	95.5% (21/22)	
IV	0.0% (0/22)	4.5% (1/22)	
Loop diuretic dose, mg furosemide equivalents	92.7±99.4 (22)	113.2±90.3 (22)	0.48
Hospitalization/emergency room visit/acute care facility visit for heart failure in the past 12 mo	54.5% (12/22)	72.7% (16/22)	0.35
Systolic blood pressure, mm Hg	131±17 (22)	128±22 (22)	0.72
Diastolic blood pressure, mm Hg	68±9 (22)	71±14 (22)	0.53
Mean arterial pressure, mm Hg	89±11 (22)	90±15 (22)	0.84
Heart rate at rest, bpm	65±7 (22)	72±13 (22)	0.05
Heart rate at peak exercise, bpm	102±20 (22)	104±21 (22)	0.78
Increase in heart rate during exercise, bpm	37±21 (22)	32±25 (22)	0.47
Right atrial pressure, mm Hg	10.1±2.3 (22)	9.1±3.7 (22)	0.27
Mean pulmonary artery pressure, mm Hg	30.2±9.5 (22)	28.4±8.6 (22)	0.52
Cardiac output, L/min/m	5.4±1.6 (22)	5.7±2.7 (22)	0.66
Pulmonary vascular resistance, WU	2.19±1.52 (22)	1.74±1.45 (21)	0.32
PCWP, legs down, mm Hg	20.9±7.9 (21)	19.9±7.5 (22)	0.67
PCWP, legs up, mm Hg	26.6±7.1 (21)	24.0±9.3 (22)	0.32
PCWP, peak exercise, mm Hg	37.3±6.5 (19)	37.3±6.7 (19)	1.00
PCWP, right atrial pressure gradient at rest, mm Hg	10.8±5.6 (21)	10.9±7.3 (22)	0.95
Workload-corrected PCWP, mm Hg/W/kg	95.0±49.8 (18)	94.1±45.3 (19)	0.74
Exercise duration, min	7.4±3.1 (22)	8.9±4.0 (22)	0.18
Peak exercise workload, W	42.3±19.5 (22)	41.8±16.2 (22)	0.93

IASD indicates interatrial shunt device; NYHA, New York Heart Association; PCWP, pulmonary capillary wedge pressure; W, watts; and WU, wood units. Values represent mean±SD (N) or % (n/N).

1/22 (4.5%) of the participants in the sham control group experienced a MACCRE event (new onset/worsening kidney function event) (*P*=1.0). At 1 month of follow-up, no deaths, myocardial infarctions, IASD occlusions or removals after the procedure, or strokes or transient ischemic attacks were reported in either of the study arms. Furthermore, during the 1-month follow-up period, none of the study participants in normal sinus rhythm at baseline developed new-onset atrial fibrillation or flutter, and no systemic embolic events or cardiac perforation, cardiac tamponade, or emergency cardiac surgery were reported in either of the study arms.

At 1 month of follow-up, the rate of HF-related hospitalizations or emergency department/acute care facility visits requiring intravenous treatment was 0/21 (0.0%) in the treatment arm compared with 2/22 (9.1%) in the control arm (*P*=0.49). There were no significant differences in loop diuretic dose (furosemide equivalents, in mg) at baseline or at 1 month of follow-up between the 2 treatment groups (mean change from baseline of −0.9±9.7 mg in the IASD treatment group versus 0.9±20.0 mg in the sham control group) (*P*=0.70).

DISCUSSION

The REDUCE LAP-HF I randomized, blinded, sham-controlled trial was designed to test the hypothesis that the implantation of the IASD System II device in the interatrial septum in patients with symptomatic HF and mid-

Table 2. Procedural and Device Characteristics

Procedure/Device Characteristic	IASD Patients (N=22)	Control Patients (N=22)	*P* Value
Device implantation attempted	95.5 (21/22)	N/A	—
Total procedure duration, min	58.1±25.8	12.9±9.0	<0.001
Total fluoroscopy time, min	23.3±13.0	5.3±3.6	<0.001
Total contrast agent administered, mL	19.2±17.4	19.0±15.6	0.986
Femoral venous access*			<0.001
Left only	0.0 (0/22)	4.8 (1/21)	
Right only	18.2 (4/22)	81.0 (17/21)	
Both	81.8 (18/22)	14.3 (3/21)	
Echocardiographic guidance tool used*			0.317
Intracardiac echocardiography	95.2 (20/21)	100.0 (21/21)	
Transesophageal echocardiography	4.8 (1/21)	0.0 (0/21)	
Device deficiency†	4.5 (1/22)	N/A	—
Device malfunction‡	4.5 (1/22)	N/A	—
Device failure	0.0 (0/22)	N/A	—
Device maldeployment without embolization§	4.5 (1/22)	N/A	—
L→R flow observed through device barrel	100.0 (20/20)	N/A	—
R→L flow observed through device barrel	15.0 (3/20)	N/A	—

IASD indicates interatrial shunt device; N/A, not applicable; L, left; and R, right. Values represent mean±SD (N) or % (n/N).

*In 1 patient in the control arm, femoral venous access was attempted but could not be established. Thus, the denominator is 21 for the control arm for both femoral venous access and echocardiographic guidance tool.

†The device did not deploy properly in 1 patient enrolled in the treatment arm (the left atrium legs of the device did not deploy so the device was removed without incident and another device was successfully deployed).

‡In 1 patient enrolled in the treatment arm, a small thrombus was observed on the tip of the device delivery system in the right atrium. The delivery system was removed and exchanged. A new system was then reinserted, and the IASD device was successfully implanted.

§In 1 patient enrolled in the treatment arm, the device was inadvertently maldeployed in the left atrium. The device remained on the guide wire and was percutaneously removed, and the procedure was subsequently aborted.

range or preserved EF (≥40%) results in the lowering of PCWP during exercise. The trial met its primary effectiveness end point, with statistically significant lowering of PCWP during exercise at 1 month of follow-up (*P*=0.028). The 3.5 mm Hg reduction in peak exercise PCWP in the IASD arm at 1 month is similar to the reduction seen in the prior observational study (n=64, all of whom received the IASD) at 6 months.[18,19] Although the decrease in peak exercise PCWP is modest, it was associated with clinically important improvements in exercise duration and quality of life in the prior observational study, which were observed at both 6 and 12 months after IASD implantation.[18,19]

Table 3. Key Effectiveness and Safety Outcome Measures

Outcome at 1 Mo	IASD Patients (N=22)	Control Patients (N=22)	*P* Value
Primary effectiveness outcome, change from baseline to 1 mo			0.028*
PCWP at a workload of 20 W, mm Hg†	−3.2±5.2 (n=14)	0.9±5.1 (n=18)	
PCWP at a workload of 40 W, mm Hg†	−1.0±4.5 (n=10)	−1.9±4.3 (n=10)	
PCWP at a workload of 60 W, mm Hg†	−2.3±4.9 (n=6)	−1.3±4.9 (n=6)	
Primary safety outcome (MACCRE)			1.000
Frequency, n/N (%)	0/22 (0%)	1/22 (4.5%)	
95% confidence interval	(0.0–16.1)	(0.1–22.8)	
Secondary outcomes (change from baseline to 1 mo)‡			
Hemodynamic measures			
PCWP, legs down at rest, mm Hg	−2.2±6.6 (n=18)	−0.5±5.0 (n=21)	0.441
PCWP, legs up at rest, mm Hg	−5.0±5.7 (n=19)	0.0±6.4 (n=21)	0.024
PCWP, peak, mm Hg	−3.5±6.4 (n=17)	−0.5±5.0 (n=17)	0.144
PCWP, workload-corrected, mm Hg/W/kg	−5.7±27.3 (n=16)	10.3±45.9 (n=17)	0.231
Right atrial pressure at rest, mm Hg	0.5±4.0 (n=20)	0.5±3.3 (n=20)	0.673
Mean pulmonary artery pressure at rest, mm Hg	−2.7±5.4 (n=20)	−0.7±4.6 (n=21)	0.111
Cardiac output at rest, L/min§	1.6±1.3 (n=20)	−0.5±1.4 (n=22)	<0.001
Pulmonary vascular resistance at rest, WU	−0.76±1.59 (n=20)	0.17±1.57 (n=21)	0.102
Pulmonary vascular resistance during exercise, WU	−0.29±1.22 (n=19)	0.31±1.64 (n=21)	0.051
Systolic blood pressure at rest, mm Hg	3.8±22.2 (n=20)	6.2±31.6 (n=22)	0.901
Diastolic blood pressure at rest, mm Hg	1.2±11.4 (n=20)	1.6±21.7 (n=22)	0.592
Mean arterial pressure at rest, mm Hg	2.0±14.0 (n=20)	3.2±23.5 (n=22)	0.725
Heart rate at rest, bpm	3.2±10.1 (n=19)	0.6±12.3 (n=22)	0.972
Heart rate at peak exercise, bpm	−2.1±17.6 (n=19)	−3.5±24.0 (n=21)	0.956
Heart rate increase with exercise, bpm	−5.3±19.4 (n=19)	−3.3±24.0 (n=21)	0.880
Functional capacity			
NYHA class	−0.5±0.7 (n=21)	−0.4±0.7 (n=21)	0.538

(*Continued*)

Table 3. Continued

Outcome at 1 Mo	IASD Patients (N=22)	Control Patients (N=22)	*P* Value
Exercise duration, min	1.2±3.7 (n=20)	0.4±3.5 (n=20)	0.603
Peak exercise workload, W	1.5±14.6 (n=20)	−1.9±10.8 (n=21)	0.348
Weight, kg	−0.56±3.20 (n=21)	−0.25±2.33 (n=22)	0.710

ANCOVA indicates analysis of covariance; CI, confidence interval; IASD, interatrial shunt device; MACCRE, major adverse cardiac, cerebrovascular embolic, or renal events; MMRM, mixed effects model repeated measures; NYHA, New York Heart Association; PCWP, pulmonary capillary wedge pressure; W, watts; and WU, wood units. Values represent mean±SD for continuous variables and n/N (%) for categorical variables.

*The *P* value for change in supine exercise PCWP from baseline to 1 mo was computed using MMRM ANCOVA adjusting for the corresponding baseline values of supine exercise PCWP.

†*P*=0.019 at 20 W, *P*=0.990 at 40 W, and *P*=0.822 at 60 W. *P* values were calculated using ANCOVA with adjustment for baseline value.

‡*P* values in this section were calculated using ANCOVA with adjustment for baseline value.

§Right-sided cardiac output, calculated by the thermodilution method.

The REDUCE LAP-HF I trial also showed that the IASD device was safe at 1 month. In 1 patient the IASD was mal-deployed in the left atrium; however, because the device remains on the guide wire after deployment and is fully retrievable, it was safely removed. The key safety outcome measure for the trial was MACCRE at 1 month, defined as the composite of cardiovascular death, embolic stroke, device- or procedure-related adverse cardiac events, and new-onset or worsening kidney dysfunction. Implantation of the IASD appeared to be safe at 1 month, with no MACCRE events reported in the IASD treatment arm compared with a 1-month MACCRE rate of 4.5% in the control arm. In addition, no patients in the treatment arm developed persistent or permanent atrial fibrillation/flutter or complications such as cardiac perforation, cardiac tamponade, emergency cardiac surgery, systemic embolization, or major vascular complications after the procedure. Finally, consistent with prior observational trials of the IASD, none of the patients in the treatment arm experienced device embolization, device occlusion, or device migration, and none of them required a repeat procedure for removal or occlusion of the device.

As shown in Table 1, the patients enrolled in the trial were similar to those in prior studies of patients with HFpEF.[22] Participants were elderly, 50% female, were obese, and had multiple comorbidities. Left ventricular EF was preserved (>50%) in the majority, and most of the participants were on a relatively high dose of diuretics and had a prior HF hospitalization or acute care visit within the last 12 months. On invasive hemodynamic testing, baseline resting PCWP was elevated (mean 20 mm Hg) despite being on a mean dose of diuretics of 103 mg furosemide equivalents per day. Thus, the enrolled patients were symptomatic and had significant HF. Patients enrolled in REDUCE LAP-HF I were generally similar to those enrolled in HFpEF epidemiological studies[23] and contemporary HFpEF clinical trials.[22] However, unlike these prior studies, patients enrolled in the present trial had objective evidence of elevated LV filling pressure (ie, PCWP) at rest and during exercise at baseline, which confirmed the HF diagnosis. Together these findings show that patients enrolled in REDUCE LAP-HF I represent contemporary patients with HFpEF encountered in routine clinical practice.

The findings from the REDUCE LAP-HF I trial are important because they are the first randomized data for this device. In the prior observational, open-label studies of the Corvia IASD in patients with HFpEF, including 75 patients with the IASD implanted,[18–20] were associated with lower PCWP during exercise, greater exercise capacity, and an excellent safety profile, but none of these prior studies were conclusive because they were nonrandomized and therefore subject to potential bias and confounding. In the present trial, randomized evaluation of the IASD confirmed the lowering of PCWP during exercise and demonstrated improvements in workload-corrected PCWP, exercise duration, and peak exercise workload compared with sham control. However, although these latter secondary outcomes were numerically better in the treatment group, the differences did not achieve

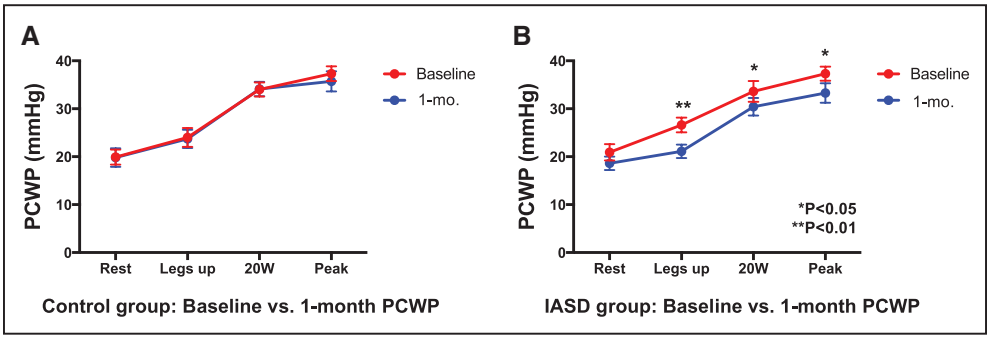

Figure 3. Pulmonary capillary wedge pressure during exercise hemodynamic testing: baseline versus 1-month postrandomization, stratified by treatment group.

A, Control group. **B,** IASD treatment group. IASD indicates interatrial shunt device; and PCWP, pulmonary capillary wedge pressure. *P* values were calculated using paired *t* tests (within-group comparisons of baseline versus 1-month values). Between-group comparison of peak exercise PCWP was not statistically significant (*P*=0.144), as shown in Table 3. *$P<0.05$; **$P<0.01$.

Table 4. Adverse Events (Periprocedural to 1 Mo After Randomization)

Adverse Event	IASD Patients (N=22)	Control Patients (N=22)	*P* Value
MACCRE	0.00 (0/21)	4.55 (1/22)	1.000
Cardiovascular death	0.00 (0/21)	0.00 (0/22)	—
Embolic stroke	0.00 (0/21)	0.00 (0/22)	—
Device-/procedure-related MACE*	0.00 (0/21)	0.00 (0/22)	—
New onset or worsening renal dysfunction	0.00 (0/21)	4.55 (1/22)	1.000
MACE	0.00 (0/21)	0.00 (0/22)	—
Cardiac death	0.00 (0/21)	0.00 (0/22)	—
Myocardial infarction	0.00 (0/21)	0.00 (0/22)	—
Emergency cardiac surgery	0.00 (0/21)	0.00 (0/22)	—
Cardiac tamponade	0.00 (0/21)	0.00 (0/22)	—
Death	0.00 (0/21)	0.00 (0/22)	—
Myocardial infarction	0.00 (0/21)	0.00 (0/22)	—
Stroke or transient ischemic attack	0.00 (0/21)	0.00 (0/22)	—
Systemic embolization	0.00 (0/21)	0.00 (0/22)	—
Cardiac perforation	0.00 (0/21)	0.00 (0/22)	—
Newly acquired atrial fibrillation/flutter	0.00 (0/21)	0.00 (0/22)	—
Major vascular complications	0.00 (0/21)	0.00 (0/22)	—
Device embolization	0.00 (0/21)	0.00 (0/22)	—
Device occlusion	0.00 (0/21)	0.00 (0/22)	—
Device-related repeat procedure	0.00 (0/21)	0.00 (0/22)	—
Heart failure event	4.76 (1/21)	13.64 (3/22)	0.607
Heart failure event requiring intravenous treatment	0.00 (0/21)	9.09 (2/22)	0.488
Cardiogenic shock	0.00 (0/21)	0.00 (0/22)	—

IASD indicates interatrial shunt device; MACCRE, major adverse cardiac, cerebrovascular and renal events; and MACE, major adverse cardiac event. Values represent % (n/N). Events in this table have been adjudicated by the independent, blinded Clinical Events Committee. Denominators indicate the number of patients with at least 23 days of follow-up or an out-of-hospital event through 1 mo.

*Includes MACE events that were determined by the Clinical Events Committee to be definitely, probably, or possibly related to the procedure or device.

statistical significance because the trial was not powered to demonstrate effectiveness in these end points.

Despite the fact that patients with HFpEF have evidence of pulmonary vascular stiffening, in open-label-treated patients with HFpEF enrolled in prior IASD studies,[19] left-to-right shunting through the IASD (which increases flow through the pulmonary vasculature) was not associated with increased pulmonary artery pressure or pulmonary vascular resistance, both of which could be deleterious in HFpEF because of increased RV load, with subsequent right-sided HF. The present randomized trial findings were similar to the prior open-label studies; there was a greater reduction in mean pulmonary artery pressure and pulmonary vascular resistance in the IASD treatment arm compared with the control arm, although these differences did not achieve statistical significance (Table 3). Possible explanations for the seemingly paradoxical trend toward lower PA pressures after IASD placement are 2-fold. First, elevated PCWP can result in augmentation of the reflected pressure wave in the pulmonary artery, which would raise pulmonary artery pressures and can lead to increased pulmonary vascular resistance.[24] Lowering of LA pressure and PCWP would therefore tend to reduce the reflected pressure wave, thereby lowering pulmonary artery pressure. Second, the LA blood that is shunted across the IASD is oxygenated and thus increases pulmonary artery saturation. The higher oxygen content in the pulmonary arterial vasculature, which was also seen in response to the IASD in prior nonrandomized studies, could have a vasodilatory effect that allows for the ability of the pulmonary vasculature to handle increased flow from the IASD-induced left-to-right shunting. This may be especially evident during exercise, as was seen in the present study (Table 3).

Elevated LV filling pressure (ie, increased PCWP) at rest or during exercise is an important determinant of both symptoms and outcomes in patients with HF.[25] Borlaug and colleagues[26] showed that elevated PCWP during exercise can distinguish patients with HFpEF from those with noncardiac dyspnea, and the rise in PCWP during exercise is an important pathophysiologic determinant of HFpEF early in the course of the clinical syndrome. PCWP during exercise also correlates with 6-minute walk test distance and is an important determinant of mortality in patients with HFpEF.[13,14] In addition, implantable hemodynamic sensor-guided lowering of pulmonary artery diastolic pressure (a surrogate for PCWP in left heart failure) has been shown to reduce HF hospitalizations in patients with HF and EF >40%.[27] On this background and in view of the hemodynamic effect of reduced exercise PCWP with the IASD,[18,19] it is expected that treatment with the IASD will result in improved clinical outcomes in patients with HFpEF. However, this hypothesis must be tested in a larger, adequately powered randomized controlled trial.

The importance of testing cardiovascular device therapies against sham control procedures cannot be underestimated. The mere act of having an invasive procedure alone may result in improved symptoms in patients with HF. Although studies of invasive treatments can be difficult to study in a blinded fashion, lack of blinding may overestimate the effectiveness of treatments.[28,29] Thus, the present trial, which evaluated a hemodynamic primary end point in a blinded fashion, is an important step in the development of the IASD as a potential treatment for patients with HF. The finding that the IASD does indeed lower exercise PCWP provides a mechanistic rationale for further randomized

evaluation of the device in a larger pivotal trial that has clinical end points.

Certain limitations should be considered. Although an a priori power calculation was conducted showing adequate statistical power with a sample size of 20 in each treatment group, the overall size of the trial is small. Thus, although the treatment groups were well balanced overall, some demographic and clinical differences occurred between the groups, although only the difference in race/ethnicity was statistically significant. Furthermore, the primary effectiveness end point (PCWP during exercise) can be challenging to measure, even with training of sites and the use of a central hemodynamic core laboratory, as was done in the present study. However, the passive preload increase maneuver (which was done in this trial with legs up in the supine exercise bicycle pedals) does not suffer from the motion artifact of exercise but still provides information on how the LA handles an increased load. In the present trial, PCWP during the legs up maneuver decreased significantly at 1 month in the IASD treatment group but not in the control group (Table 3 and Figure 3), supporting the mechanistic effect of the IASD. Uniform measurement of either BNP or N-terminal pro-BNP at baseline and 1 month in all randomized patients (which was not available in the present study) could have provided additional information on the correlation of changes in natriuretic peptide biomarkers with IASD-induced reduction in exercise PCWP. An additional limitation relates to the use of anticoagulants (ie, clopidogrel) in the IASD-treated patients not previously on a nonaspirin anticoagulant but not in sham-control patients. Although we had specific instructions to maintain blinding throughout the trial (online-only Data Supplement), we did not administer a questionnaire to evaluate the success of blinding at 1 month (the trial does include a questionnaire at the 1-year follow-up visit that will evaluate blinding). A final limitation relates to the relatively short time frame of the study (1-month follow-up). However, the open-label studies show prolonged hemodynamic and symptomatic benefits of the IASD at 1 year.[19]

In summary, we found that in patients with HF and EF ≥40%, implantation of an IASD reduced PCWP during exercise to a greater extent than a sham control procedure, demonstrating that in patients with HF with elevated LA pressure during exercise, the creation of an 8-mm interatrial communication unloads the LA. We also found that the IASD is safe compared with the sham control procedure at 1 month, and it showed favorable but nonsignificant trends in several additional secondary hemodynamic and functional end points. These findings suggest that the IASD could have beneficial effects in patients with HFpEF and HF with mid-range EF, setting the stage for a larger scale randomized clinical trial powered to examine the effects of the IASD on symptoms, quality of life, exercise capacity, and clinical outcomes.

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DISCLOSURES

Dr Feldman has received consulting fees from Abbott, BSC, Edwards, and Gore. Dr Mauri has received research support from Corvia Medical, Inc. Dr Petrie has received speaker fees or consulting honoraria from AstraZeneca, Boehringer Ingelheim, Daiichi-Sankyo, Eli Lilly, Maquet, Novartis, Novo Nordisk, Pfizer, Servier, and Takeda; and has served on clinical events committees for Astellas, AstraZeneca, Bayer, Boehringer Ingelheim, Cardiorentis, GlaxoSmithKline, Reservlogix, Roche, and Stealth Biotherapeutics. Dr Basuray received financial support from Corvia Medical to run the hemodynamic core laboratory and has received consulting fees from Abbott, BackBeat Medical, Boston Scientific, Impulse Dynamics, Medtronic, and Sensible Medical. Dr Shah has received research grants from Actelion, AstraZeneca, Corvia, and Novartis; and consulting fees from Actelion, Amgen, AstraZeneca, Bayer, Boehringer-Ingelheim, Cardiora, Eisai, Ironwood, Merck, Novartis, Sanofi, and United Therapeutics.

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FOOTNOTES

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REFERENCES

1. Oktay AA, Rich JD, Shah SJ. The emerging epidemic of heart failure with preserved ejection fraction. *Curr Heart Fail Rep*. 2013;10:401–410. doi: 10.1007/s11897-013-0155-7.
2. Redfield MM. Heart failure with preserved ejection fraction. *N Engl J Med*. 2016;375:1868–1877. doi: 10.1056/NEJMcp1511175.
3. Lam CS, Solomon SD. The middle child in heart failure: heart failure with mid-range ejection fraction (40–50%). *Eur J Heart Fail*. 2014;16:1049–1055. doi: 10.1002/ejhf.159.
4. Ponikowski P, Voors AA, Anker SD, Bueno H, Cleland JG, Coats AJ, Falk V, Gonzalez-Juanatey JR, Harjola VP, Jankowska EA, Jessup M, Linde C, Nihoyannopoulos P, Parissis JT, Pieske B, Riley JP, Rosano GM, Ruilope LM, Ruschitzka F, Rutten FH, van der Meer P. 2016 ESC guidelines for the diagnosis and treatment of acute and chronic heart failure. *Rev Esp Cardiol (Engl Ed)*. 2016;69:1167.
5. Freed BH, Shah SJ. Stepping out of the left ventricle's shadow: time to focus on the left atrium in heart failure with preserved ejection fraction. *Circ Cardiovasc Imaging*. 2017;10:e006267. doi: 10.1161/CIRCIMAGING.117.006267.
6. Maeder MT, Kaye DM. Heart failure with normal left ventricular ejection fraction. *J Am Coll Cardiol*. 2009;53:905–918. doi: 10.1016/j.jacc.2008.12.007.
7. Zile MR, Baicu CF, Gaasch WH. Diastolic heart failure: abnormalities in active relaxation and passive stiffness of the left ventricle. *N Engl J Med*. 2004;350:1953–1959. doi: 10.1056/NEJMoa032566.
8. Borlaug BA. The pathophysiology of heart failure with preserved ejection fraction. *Nat Rev Cardiol*. 2014;11:507–515. doi: 10.1038/nrcardio.2014.83.
9. Freed BH, Daruwalla V, Cheng JY, Aguilar FG, Beussink L, Choi A, Klein DA, Dixon D, Baldridge A, Rasmussen-Torvik LJ, Maganti K, Shah SJ. Prognostic utility and clinical significance of cardiac mechanics in heart failure with preserved ejection fraction: importance of left atrial strain. *Circ Cardiovasc Imaging*. 2016;9:e003754. doi: 10.1161/CIRCIMAGING.115.003754.
10. Melenovsky V, Hwang SJ, Redfield MM, Zakeri R, Lin G, Borlaug BA. Left atrial remodeling and function in advanced heart failure with preserved or reduced ejection fraction. *Circ Heart Fail*. 2015;8:295–303. doi: 10.1161/CIRCHEARTFAILURE.114.001667.
11. von Roeder M, Rommel KP, Kowallick JT, Blazek S, Besler C, Fengler K, Lotz J, Hasenfuss G, Lucke C, Gutberlet M, Schuler G, Schuster A, Lurz P. Influence of left atrial function on exercise capacity and left ventricular function in patients with heart failure and preserved ejection fraction. *Circ Cardiovasc Imaging*. 2017;10:e005467. doi: 10.1161/CIRCIMAGING.116.005467.
12. Rossi A, Gheorghiade M, Triposkiadis F, Solomon SD, Pieske B, Butler J. Left atrium in heart failure with preserved ejection fraction: structure, function, and significance. *Circ Heart Fail*. 2014;7:1042–1049. doi: 10.1161/CIRCHEARTFAILURE.114.001276.
13. Wolsk E, Kaye D, Borlaug BA, Burkhoff D, Kitzman D, Lam CS, Shah SJ, Gustafsson F. Resting and exercise hemodynamics in relation to 6-minute walk test in patients with heart failure and preserved ejection fraction [published online ahead of print September 26, 2017]. *Eur J Heart Fail*. doi: 10.1002/ejhf.976. http://onlinelibrary.wiley.com/doi/10.1002/ejhf.976/full/.
14. Dorfs S, Zeh W, Hochholzer W, Jander N, Kienzle RP, Pieske B, Neumann FJ. Pulmonary capillary wedge pressure during exercise and long-term mortality in patients with suspected heart failure with preserved ejection fraction. *Eur Heart J*. 2014;35:3103–3112. doi: 10.1093/eurheartj/ehu315.
15. Kaye D, Shah SJ, Borlaug BA, Gustafsson F, Komtebedde J, Kubo S, Magnin C, Maurer MS, Feldman T, Burkhoff D. Effects of an interatrial shunt on rest and exercise hemodynamics: results of a computer simulation in heart failure. *J Card Fail*. 2014;20:212–221. doi: 10.1016/j.cardfail.2014.01.005.
16. Sambhi MP, Zimmerman HA. Pathologic physiology of Lutembacher syndrome. *Am J Cardiol*. 1958;2:681–686.
17. Feldman T, Komtebedde J, Burkhoff D, Massaro J, Maurer MS, Leon MB, Kaye D, Silvestry FE, Cleland JG, Kitzman D, Kubo SH, Van Veldhuisen DJ, Kleber F, Trochu JN, Auricchio A, Gustafsson F, Hasenfubeta G, Ponikowski P, Filippatos G, Mauri L, Shah SJ. 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). *Circ Heart Fail*. 2016;9:e003025. doi: 10.1161/CIRCHEARTFAILURE.116.003025.
18. Hasenfuß G, Hayward C, Burkhoff D, Silvestry FE, McKenzie S, Gustafsson F, Malek F, Van der Heyden J, Lang I, Petrie MC, Cleland JG, Leon M, Kaye DM; REDUCE LAP-HF study investigators. A transcatheter intracardiac shunt device for heart failure with preserved ejection fraction (REDUCE LAP-HF): a multicentre, open-label, single-arm, phase 1 trial. *Lancet*. 2016;387:1298–1304. doi: 10.1016/S0140-6736(16)00704-2.
19. Kaye DM, Hasenfuss G, Neuzil P, Post MC, Doughty R, Trochu JN, Kolodziej A, Westenfeld R, Penicka M, Rosenberg M, Walton A, Muller D, Walters D, Hausleiter J, Raake P, Petrie MC, Bergmann M, Jondeau G, Feldman T, Veldhuisen DJ, Ponikowski P, Silvestry FE, Burkhoff D, Hayward C. One-year outcomes after transcatheter insertion of an interatrial shunt device for the management of heart failure with preserved ejection fraction. *Circ Heart Fail*. 2016;9:e003662.
20. Søndergaard L, Reddy V, Kaye D, Malek F, Walton A, Mates M, Franzen O, Neuzil P, Ihlemann N, Gustafsson F. Transcatheter treatment of heart failure with preserved or mildly reduced ejection fraction using a novel interatrial implant to lower left atrial pressure. *Eur J Heart Fail*. 2014;16:796–801. doi: 10.1002/ejhf.111.
21. Siddiqui O, Hung HM, O'Neill R. MMRM vs. LOCF: a comprehensive comparison based on simulation study and 25 NDA datasets. *J Biopharm Stat*. 2009;19:227–246. doi: 10.1080/10543400802609797.
22. Shah SJ, Heitner JF, Sweitzer NK, Anand IS, Kim HY, Harty B, Boineau R, Clausell N, Desai AS, Diaz R, Fleg JL, Gordeev I, Lewis EF, Markov V, O'Meara E, Kobulia B, Shaburishvili T, Solomon SD, Pitt B, Pfeffer MA, Li R. Baseline characteristics of patients in the treatment of preserved cardiac function heart failure with an aldosterone antagonist trial. *Circ Heart Fail*. 2013;6:184–192. doi: 10.1161/CIRCHEARTFAILURE.112.972794.
23. Owan TE, Hodge DO, Herges RM, Jacobsen SJ, Roger VL, Redfield MM. Trends in prevalence and outcome of heart failure with preserved ejection fraction. *N Engl J Med*. 2006;355:251–259. doi: 10.1056/NEJMoa052256.
24. Dixon DD, Trivedi A, Shah SJ. Combined post- and pre-capillary pulmonary hypertension in heart failure with preserved ejection fraction. *Heart Fail Rev*. 2016;21:285–297. doi: 10.1007/s10741-015-9523-6.
25. Zile MR, Bennett TD, El Hajj S, Kueffer FJ, Baicu CF, Abraham WT, Bourge RC, Warner Stevenson L. Intracardiac pressures measured using an implantable hemodynamic monitor: relationship to mortality in patients with chronic heart failure. *Circ Heart Fail*. 2017;10:e003594. doi: 10.1161/CIRCHEARTFAILURE.116.003594.
26. Borlaug BA, Nishimura RA, Sorajja P, Lam CS, Redfield MM. Exercise hemodynamics enhance diagnosis of early heart failure with preserved ejection fraction. *Circ Heart Fail*. 2010;3:588–595. doi: 10.1161/CIRCHEARTFAILURE.109.930701.
27. Adamson PB, Abraham WT, Bourge RC, Costanzo MR, Hasan A, Yadav C, Henderson J, Cowart P, Stevenson LW. Wireless pulmonary artery pressure monitoring guides management to reduce decompensation in heart failure with preserved ejection fraction. *Circ Heart Fail*. 2014;7:935–944. doi: 10.1161/CIRCHEARTFAILURE.113.001229.
28. Bhatt DL, Kandzari DE, O'Neill WW, D'Agostino R, Flack JM, Katzen BT, Leon MB, Liu M, Mauri L, Negoita M, Cohen SA, Oparil S, Rocha-Singh K, Townsend RR, Bakris GL; SYMPLICITY HTN-3 Investigators. A controlled trial of renal denervation for resistant hypertension. *N Engl J Med*. 2014;370:1393–1401. doi: 10.1056/NEJMoa1402670.
29. Leon MB, Kornowski R, Downey WE, Weisz G, Baim DS, Bonow RO, Hendel RC, Cohen DJ, Gervino E, Laham R, Lembo NJ, Moses JW, Kuntz RE. A blinded, randomized, placebo-controlled trial of percutaneous laser myocardial revascularization to improve angina symptoms in patients with severe coronary disease. *J Am Coll Cardiol*. 2005;46:1812–1819. doi: 10.1016/j.jacc.2005.06.079.

Transcatheter Interatrial Shunt Device for the Treatment of Heart Failure With Preserved Ejection Fraction (REDUCE LAP-HF I [Reduce Elevated Left Atrial Pressure in Patients With Heart Failure]): A Phase 2, Randomized, Sham-Controlled Trial

Ted Feldman, Laura Mauri, Rami Kahwash, Sheldon Litwin, Mark J. Ricciardi, Pim van der Harst, Martin Penicka, Peter S. Fail, David M. Kaye, Mark C. Petrie, Anupam Basuray, Scott L. Hummel, Rhondalyn Forde-McLean, Christopher D. Nielsen, Scott Lilly, Joseph M. Massaro, Daniel Burkhoff and Sanjiv J. Shah

On behalf of the REDUCE LAP-HF I Investigators and Study Coordinators

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Dr. Carolyn Lam: Hello from the American Heart Association meeting in Anaheim. I'm Dr. Carolyn Lam, associate editor from Circulation at National Heart Centre in Duke National University of Singapore and I'm so pleased to be here with the Circulation team led by editor in chief Dr. Joe Hill, as well as with Dr. Laura Mauri, senior editor from Brigham and Women's Hospital, and Dr. Dharam Kumbhani, associate editor from UT Southwestern. Boy, we've got lots to discuss. I mean, I want to just first start with congratulating you, Joe. We have got quite a number of simultaneous publications here at the AHA.

Dr. Joseph Hill: I appreciate that, Carolyn. Don't congratulate me. We have a team that is a privilege to work with. One of the initiatives that we launched right from the start was a desire to foster and shine a bright light on emerging science at the major meetings around the world. Often, that involves simultaneous publication.

I'm proud to say that we have 11 simultaneous publications, a record for us here at AHA. Most of them are clinical trials. A few are clinical science, and two of them are young investigators who are competing in the various different competitions. We reached out to them a few weeks ago and offered them the opportunity to submit to us, of course with no guarantees, and our standard remains the same, but we promised that we would provide them with an external peer review. Two of them made it through the process and they will be simultaneously published with their presentations here in Anaheim.

Dr. Carolyn Lam: Wow, well you heard it. A record 11 simultaneous publications. We've got a lot to talk about. Let me just maybe group the topics a little bit. Let's start with talking about peripheral artery disease. I think there are at least three papers around that area, and then we'll talk about coronary artery disease, and almost focusing more on implementation science, papers, there are two there, and then of course we have to talk about heart failure. Dharam, could you start? Tell us about the FOURIER PAD trial.

Dr. Dharam Kumbhani: Yeah. It's very exciting to have clinical trials in the PAD realm. FOURIER PAD is certainly really well done sub-study of the FOURIER trial. As you remember, this was a landmark trial, which compared a PCSK9 inhibitor Evolocumab in two doses, two placebo. The overall trial was done in about 27,000 patients who were followed for a median of 2.2 years. In this trial, Marc Bonaca and investigators, they looked at the PAD subset, which were about 13% of the total cohort. Now, they specifically set out to look at how patients with PAD, during this trial and very gratifyingly, they also specifically assessed how patients with PAD did as far as limb events, not just cardiovascular events.

At the outset, not surprisingly, patients with PAD had a higher risk of cardiovascular events by, I think it was about 60% higher for the primary end point compared with patients who did not have PAD. There was really no, in fact, modification by PAD in that the benefit of Evolocumab that we saw in the overall trial was preserved among the patients with PAD as well as those

without PAD. However, because patients with PAD had higher event rates, the absolute risk reductions were higher in patients with PAD.

Then, these investigators looked specifically at the incidents of major adverse limb events, which is a composite of acute limb ischemia, urgent revasc, and major amputations. What they show is that in the overall cohort, there is a 42% reduction in the risk of these major adverse limb events with Evolocumab compared with placebo. Obviously, the effect is significantly higher in patients with PAD. Although the benefit wasn't noted in the PAD subset specifically, the overall p-value for interaction was negative.

One of the really exciting things about this paper is that just like investigators have shown a monotonic reduction in cardiovascular event rates with LDL reduction, similarly, the investigators show a reduction in limb events, which is dose related and the same way in a monotonic fashion with Evolocumab. I think this is really exciting and I think this will be a very important paper for the field.

Dr. Carolyn Lam: Yeah. Dharam, that was beautifully summarized but once you start talking about the peripheral artery disease and this lack of interaction on effects and so on, I think of the CANVAS trial results that were reported at this meeting too. If I could maybe briefly summarize what the authors did in this circumstance, they looked at the more than 10,000 patients in the CANVAS trial who were randomized into Canagliflozin versus placebo in diabetic patients but this time they looked at whether or not there was a difference in effect with the primary prevention cohort versus the secondary prevention.

Primary prevention meaning those adults who had diabetes and risk factors but no established cardiovascular disease and the secondary prevention were those with peripheral artery disease, for example, and other established cardiovascular disease. The same thing, a lack of interaction, which I think is really important because it was the same sort of idea that the overall risk of cardiovascular events was lower in the primary prevention group. Looking at them as a subgroup alone, you didn't get the p-value that crossed the limit because the power was less in a lower risk group, but the lack of statistical interaction really gives us additional information, I think, that Canagliflozin and maybe the SGLT2s in general may be effective for primary prevention in diabetic patients. What do you think?

Dr. Dharam Kumbhani: Yeah. I mean, I think certainly, very interesting findings along those lines. As you pointed out, the event rates are much lower in the primary prevention cohort. All the confidence intervals overlap one, but because all the p-values for interaction for the three-point maze, the four-point maze, et cetera, one would say that there really isn't a difference between the primary and the secondary prevention subgroups. You would potentially have the same benefit in that subgroup as well.

Dr. Carolyn Lam: Fortunately or unfortunately, in that same study, they looked at the risk of amputations and there was a lack of interaction too for that meaning there was

a higher risk of amputations with Canagliflozin versus placebo. That of course is a really hot topic now, isn't it? I just wanted to point out though, when you look at it in the primary prevention group, there are only 33 events. What do you think? It spells caution but further look needs to be done? Yeah. Contrast that with the EMPA-REG outcome PAD analysis. You want to tell us about it?

Dr. Dharam Kumbhani: Yeah. Once the Canagliflozin CANVAS findings came out showing a high rate of amputations with Canagliflozin, the Empagliflozin, the EMPA-REG outcome's investigators went back and looked at the PAD subset in EMPA-REG outcomes. This was about 20% of the total cohort. I will say that unlike FOURIER, which we just discussed, the ascertainment of amputations was not prospectively defined for this trial and it was really obtained from the CRF forms.

However, having said that, it did not appear that amputation rates were higher with Empagliflozin. They did not break it down by the different doses but one assumes that the benefit is consistent between the two doses that they study. One would imagine the PAD patients would have a higher rate overall, which it was, but even in that group, it was about 6% over three years and there was really no difference between the patients who received Empagliflozin versus those who got placebo.

Dr. Carolyn Lam: That EMPA-REG outcome paper, I mean, interestingly, it was a research letter. Joe, you've been watching this whole field unfold right now and our journal has published so many good papers, including CVD REAL, all in this space. Could you comment on that a little bit and the research letter concept and the fact that we're publishing so many of these interesting papers in this topic?

Dr. Joseph Hill: Well, Carolyn, as you inferred, this field is evolving very rapidly. Now, the interface between metabolic disease and diabetes and heart disease is blurring. Some of these diabetic drugs are really emerging as heart failure drugs, it looks like and so there's a great deal of interest in exploring that and trying to find underlying mechanisms. It's an incredibly exciting time. In parallel with that, we are publishing research letters now for papers where, again, our bar starts with validity. Our bar doesn't change but if it's a story that can be communicated with really one multi-paneled figure and an 800word text, then that is a nice bite-size piece of information that we can get out to our readership. We're publishing one or two a week now. Overall, it appears to be well received and I think it's an effective vehicle for conveying certain types of our content.

Dr. Carolyn Lam: Frankly, it's such a delight to read, isn't it? It's hard to write. I think the shorter, the harder to write but this just goes to show how equally important they are.

Dr. Joseph Hill: Absolutely.

Dr. Carolyn Lam: That we're discussing it here. Well, let's go on to the next topic then, coronary artery disease. Regionalization of the care. I'll say that again, regionalization of the care. Would you like to comment on the two papers that are simultaneously

being published? One would be the ACCELERATOR-2 trial. That's in the U.S. Then, a second from New Zealand, the ICare-ACS trial. Slightly different but-

Dr. Joseph Hill: Well, that's exactly right. Often, we know what to do but we don't do what we know we need to do in medicine. The implementation of what we already know is an area of hot research and is an area that's evolving rapidly. These two studies, ACCELERATOR-2 here in the United States, focused on regionalization of the interface between EMS systems and EDs, how to get patients identified in the hospital to their device, whether it's a stent or a balloon pump or whatever it is. The first medical contact to device was the metric and by implementing what we already know, the AHA mission lifeline principles, these investigators were able to optimize this regionalization, so there wasn't so much variability across these 12 metropolitan regions. As a consequence, the time to first medical contact to device was shortened, and there was in fact a striking, maybe even surprising, mortality benefit.

Dr. Carolyn Lam: Exactly. That was striking to me too.

Dr. Joseph Hill: From the street to the lab, another paper from New Zealand that you referred to called ICare-ACS focused on doing a better job in the emergency department with serial ECGs and serial high sensitivity troponins, risk stratification algorithms and they found that, again, by developing these clinical pathways within the ED, they were able to shorten the length of stay in the ED and the length of stay in the hospital.

Dr. Carolyn Lam: Yeah. I thought those were amazing and then also from different parts of the world, really strong public health messages as well. Laura, you take care of these ACS patients right on there. What did you think of these papers?

Dr. Laura Mauri: No, I agree. I think that we've, in the past, focused on science and focused on clinical trials but ultimately, none of that matters if we don't deliver the healthcare to the patient. I think this is just a growing field and I'm glad that we're emphasizing it in circulation.

Dr. Carolyn Lam: Absolutely. If we would now go to another area that is really increasing in prevalence throughout the world. Heart failure, and of course, heart failure with preserved ejection fraction.

Dr. Joseph Hill: Your favorite topic.

Dr. Carolyn Lam: Congratulations, Laura on the paper that you're presenting, that is being presented at this meeting, the REDUCE LAP trial. Could you tell us a little bit more about that?

Dr. Laura Mauri: Sure. Yes, as you know, it's a really challenging field, heart failure with preserved ejection fraction. There aren't a lot of therapies that we have. We really don't have great medical therapy. This study actually looks at a medical device to treat

patients. It really is a feasibility study, so it's a relatively small trial, just over 90 patients but it's randomized. We know in the device arena, as in all trials, how important randomization is but also blinding. This was actually a sham-controlled blinded trial really designed to look at this interatrial shunt device in patients who have an elevated wedge pressure.

The REDUCE LAP stands for reduce left atrial pressure. That was the primary endpoint, was pulmonary capillary wedge pressure. This was not only looked at the safety, which showed that the device placement was very safe, but at the same time also looked at the proof of concept that by placing the shunt device, there was actually a reduction in wedge pressure over a period of exercise. It needs to be followed on. It's certainly just the first phase of trials but a pretty good standard with the sham control.

Dr. Carolyn Lam: Yeah, well, congratulations again. I mean, this follows … There was a previous publication of the single arm trial and now, this is the first randomized sham-controlled, and the results are consistent. It's a very difficult trial to carry out. HFpEF patients are notoriously difficult to recruit. Could you tell us a little bit about what it was like successfully completing this trial?

Dr. Laura Mauri: Yeah. Well, we had very enthusiastic centers and principal investigators, Ted Feldman and Sanjiv Shah. I think what it really required in this early phase was sites that were committed to characterizing the exercise physiology. The next stage of rolling this out to a broader number of sites and a larger number of patients to see if there's a clinical effect will really be more focused on the clinical endpoints and quality of life because ultimately that's the goal, is to improve symptoms in these patients.

Dr. Carolyn Lam: What I love about the design and the whole concept, it's so simple and elegant. We almost sometimes forget that HFpEF is heart failure, which means that by definition, there's raised filling pressures. It's hemodynamic at the end and this is just a simple concept of offloading the left atrium. That's so beautiful but it does come with some questions. Every time you mention this to someone, they go, “What about, I don't know, Eisenmenger's syndrome developing later?” The right side, volume overload, pulmonary hypertension, what about atrial fibrillation down the line? How about the safety parts of it?

Dr. Laura Mauri: Right, so the procedural safety was excellent but then I think you raise really important questions and these patients are still in follow-up but looking at the report here at this meeting, there was no pulmonary hypertension in excess in the shunt treated arm. The patient selection was towards patients who had higher wedge compared with right atrial pressure and among those patients, there was no evidence of RV overload. At least at this stage things look good to go on to the next step.

Dr. Carolyn Lam: That's wonderful and exciting. We definitely need a therapy for HFpEF. Joe, would you like to highlight any other trial? We have 11. We've discussed six.

Dr. Joseph Hill: Tonight at the editorial board meeting, we will be saluting these two young investigators who are presenting their work in this competition and simultaneously publishing their work. We've invited these young investigators and their mentor and they will present a short talk to the editorial board dinner. It's an effort to salute and recognize these early career investigators, to congratulate them on outstanding work. We're pleased and privileged to publish it, so I'm particularly excited about that.

Dr. Carolyn Lam: Wow, Joe. That is great. Thank you. I didn't know that was happening either. That's fabulous. Dharam or Laura, any other highlights that you may want to mention in this meeting?

Dr. Laura Mauri: I think that it's just been a wonderful kickoff to the meeting. We've covered, I think, many of the really important trials so it's really exciting to be able to see the work in print.

Dr. Carolyn Lam: That’s great, and to discuss it as well.

Dr. Dharam Kumbhani: Yeah, I agree. This is really exciting and hopefully, we can keep growing from strength to strength every year.

Dr. Carolyn Lam: Yep. You heard it right here everyone. We are going to grow from strength to strength under your leadership and with this great team, so thank you very much for joining us today.

SUPPLEMENTARY MATERIAL

A Transcatheter InterAtrial Shunt Device for the Treatment of Heart Failure with Preserved Ejection Fraction (REDUCE LAP-HF I): *A Phase 2, Randomized, Sham-Controlled Trial*

Inclusion/Exclusion Criteria:

Inclusion Criteria: Participants were included in the study only if all the following conditions were met:

1. Chronic symptomatic 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 months; AND
    b. ≥ One hospital admission for which HF was a major component of the hospitalization, or a healthcare facility (emergency department/acute care facility) treatment with IV or intensification of oral diuresis for HF, within the 12 months prior to study entry; OR an NT-pro-BNP value > 200 pg/mL in normal sinus rhythm, > 600 pg/mL in AF, or a BNP value > 70 pg/mL in normal sinus rhythm, > 200 pg/mL in AF within the past 6 months.
2. Ongoing stable guideline directed medical therapy (GDMT) HF management and management of potential comorbidities according to the 2013 American College of Cardiology/American Heart Association (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 weeks prior to screening) that was expected to be maintained without change for 6 months.
3. Age ≥ 40 years old
4. Site determined left ventricular ejection fraction ≥ 40% within the past 3 months, without previously documented ejection fraction <30% (within the last 5 years).
5. Site determined elevated LAP with a gradient compared to right atrial pressure (RAP) documented by:
    a. End-expiratory PCWP during supine ergometer exercise ≥ 25mm Hg, and greater than RAP by ≥ 5 mm Hg.
6. Site determined echocardiographic evidence of diastolic dysfunction documented by one or more of the following:
    a. LA diameter > 4 cm; *or*
    b. LA volume index > 28 mL/m^2 *or*

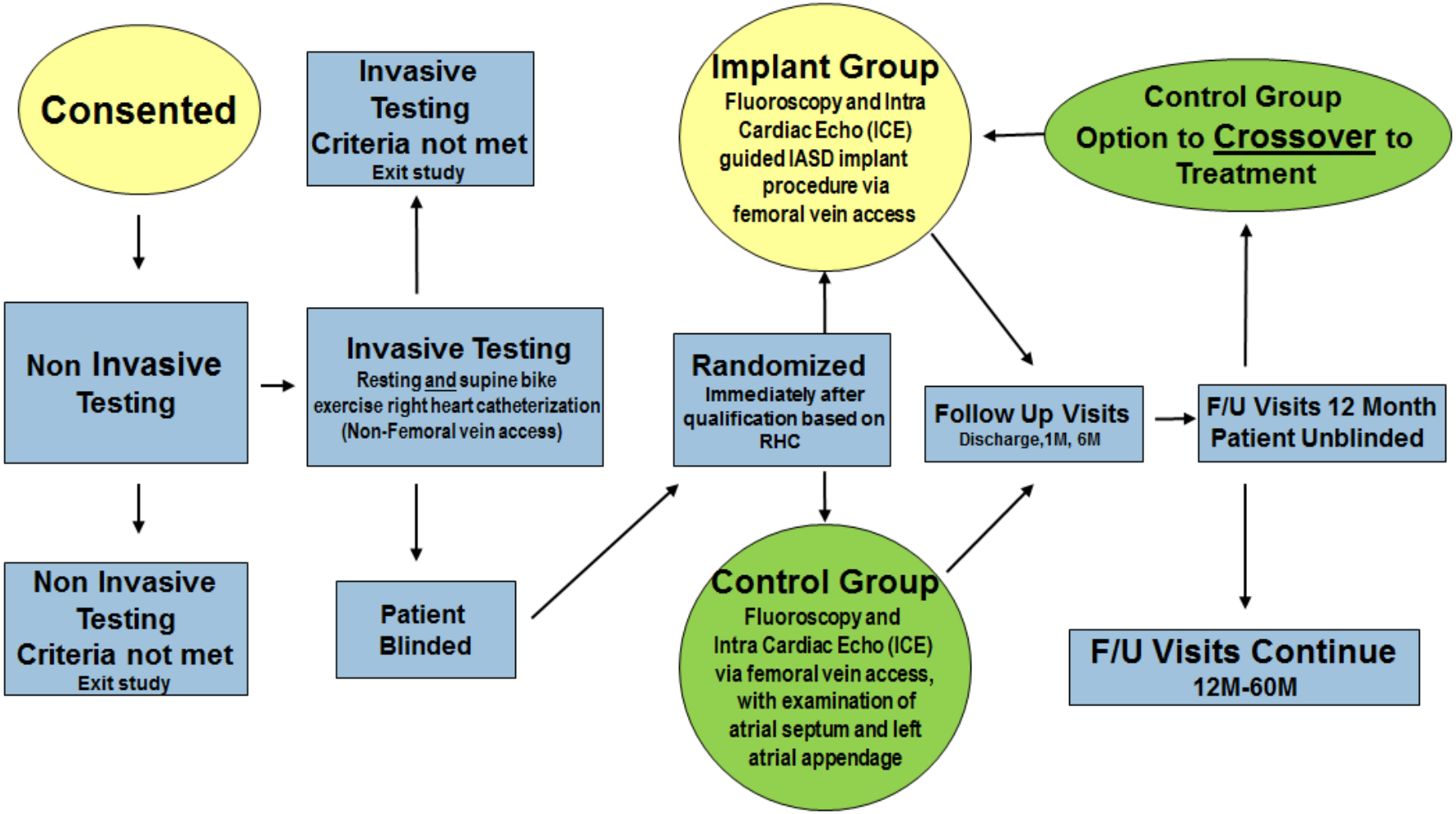
    c. Lateral e' <10 cm/s; *or*
    d. Septal e' <8 cm/s; *or*
    e. Lateral E/e' >10; *or*
    f. Septal E/e' > 15
7. Participant was informed of the nature of the study, agreed to its provisions and provided written informed consent, approved by the Institutional Review Board (IRB) or Ethics Committee (EC)
8. Participant was willing to comply with clinical investigation procedures and agreed to return for all required follow-up visits, tests, and exams
9. Trans-septal catheterization and femoral vein access was determined to be feasible by site principal interventional cardiology investigator

Exclusion Criteria: Participants were excluded from the study if any of the following conditions were present:

1. Myocardial infarction and/or percutaneous cardiac intervention within past 3 months; coronary artery bypass graft (CABG) in past 3 months, or current indication for coronary revascularization
2. Cardiac resynchronization therapy initiated within the past 6 months
3. Severe HF defined as one or more of the below:
    a. ACC/AHA/ESC (American College of Cardiology/American Heart Association/European Society of Cardiology) Stage D heart failure, Non-ambulatory NYHA Class IV HF;
    b. Cardiac Index < 2.0 L/min/m^2
    c. Inotropic infusion (continuous or intermittent) within the past 6 months
    d. Patient is on the cardiac transplant waiting list
4. Inability to perform 6MWT (distance < 50 m), OR 6MWT >600m
5. Known clinically significant un-revascularized coronary artery disease, defined as: epicardial coronary artery stenosis associated with angina or other evidence of coronary ischemia.
6. History of stroke, transient ischemic attack (TIA), deep vein thrombosis (DVT), or pulmonary emboli within the past 6 months
7. Known clinically significant untreated carotid artery stenosis
8. Presence of significant valve disease defined by the site cardiologist as:
    a. Mitral valve regurgitation (MR) defined as grade ≥ 3+ MR
    b. Tricuspid valve regurgitation (TR) defined as grade ≥ 2+ TR;
    c. Aortic valve disease defined as ≥ 2+ aortic valve regurgitation (AR) or > moderate AS
9. Hypertrophic obstructive cardiomyopathy, restrictive cardiomyopathy, constrictive pericarditis, cardiac amyloidosis or other infiltrative cardiomyopathy (e.g. hemochromatosis, sarcoidosis)

10. Participant is contraindicated to receive either dual antiplatelet therapy or warfarin (analogue); or has a documented coagulopathy
11. Atrial fibrillation with resting heart rate > 100 beats per minute (BPM)
12. Arterial oxygen saturation < 95% on room air
13. Significant hepatic impairment defined as 3X upper limit of normal of transaminases, total bilirubin, or alkaline phosphatase
14. Right ventricular dysfunction, defined by the site cardiologist as
    a. More than mild RV dysfunction as estimated by trans-thoracic echocardiogram (TTE); OR
    b. Tricuspid annular plane systolic excursion (TAPSE) < 1.4 cm; OR
    c. RV size ≥ LV size as estimated by TTE; OR
    d. Echocardiographic or clinical evidence of congestive hepatopathy; OR
    e. Evidence of RV dysfunction defined by TTE as an RV fractional area change < 35%;
15. Resting RAP > 14 mmHg
16. Evidence of pulmonary hypertension with pulmonary vascular resistance (PVR) > 4 Woods units
17. Chronic pulmonary disease requiring continuous home oxygen, OR hospitalization for exacerbation in the 12 months prior to study entry, OR significant chronic pulmonary disease defined as forced expiratory volume in 1 second (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 were not considered investigational trials
19. Life expectancy less than 12 months for non-cardiovascular 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 eGFR <25mL/min/1.73 m^2 by CKD-Epi equation
24. Systolic blood pressure >170 mmHg at screening
25. Participants with existing atrial septal defects. Participants with a patent foramen ovale (PFO), who meet PCWP criteria despite the PFO, were allowed
26. Participants on immunosuppression or systemic steroid treatment (>10 mg prednisone/day)
27. Severe obstructive sleep apnea not treated with continuous positive airway pressure (CPAP) or other measures
28. Severe depression and/or anxiety
29. In the opinion of the investigator, the participant was not an appropriate candidate for the study

Supplementary Figure S1. Patient Flowchart – Study Design



Patient and Research Staff Blinding

Patient Blinding

Patients were "blinded" immediately after qualifying in the catheterization lab following supine bike exercise right heart catheterization, and prior to randomization. Blinding is to be maintained through one year follow-up.

a) Study procedure through discharge
   Patient "blinding" after qualification in the catheterization lab was achieved by the use of sedation, earphones and blindfolding (or use of a screen/curtain/drape) to prevent observation of the imaging screens, and strict instructions to all research staff involved in patient management, including the managing heart failure physician.
b) Month 1 follow-up visit
   Patient "blinding" for the 1 month follow-up hemodynamic evaluation was achieved by blocking the patients view to prevent observation of the imaging screens, and strict instructions to the echocardiogram technician and all "un-blinded" research staff involved in patient's visit. Screens will be turned away/out of view from the patient at all imaging follow-up visits through 12 months.
c) Month 6 follow-up visit
   Patient "blinding" at the 6 month follow-up will be achieved by strict instructions to the echocardiogram/cardiac MRI technician and all "un-blinded" research staff involved in patient's visit. Screens will be turned away/out of view from the patient at all imaging follow-up visits through 12 months.
d) Month 12 follow-up visit
   Patients will be "un-blinded" after completion of the 12-month follow-up visit.

Research Staff Blinding (as written in the study protocol)

Research staff involved in patient management were "blinded" immediately after the qualifying event and will remain blinded until the completion of the 12 month visit. All patients (test and control) will have equal interactions with study personnel and similar maintenance of appropriate GDMT throughout the entire study in order to adequately maintain blinding.

The managing HF physician was unaware of the patient's randomization assignment, and qualifying hemodynamic information. The staff was instructed to maintain blinding. During follow-up visits, study staff in the room should not be aware of patient's randomization group (blinded), but because this can be difficult to achieve, a doctor, study nurse, research coordinator or other staff may be present for the purposes of helping to monitor patient safety, etc., but it is critical that they will not be the person performing the tasks, or disclosing treatment assignment to the person performing the blinded task.

The following evaluations are to be conducted by a study team member that is blinded to patients' randomization assignments:

- The NYHA classification
- The 6MWT
- The staff member(s) performing the CPET
- Physical Exam

All involved staff members, including but not limited to the following, are required to maintain the blinding:

- The staff member(s) performing the initial and follow-up catheterization procedures, including the individuals preforming the intracardiac echocardiography (ICE)
- The staff member(s) performing the follow-up Echocardiogram
- The staff member(s) performing the follow-up cardiac MRI.
- The staff member administering the Quality-Of-Life questionnaires The staff member(s) performing the electrocardiogram (ECG) and bloodwork

Supplementary Table S1. Recruiting Sites, Investigators, and Clinical Research Coordinators

Site	Location	Site principal investigator	Clinical research coordinator(s)
Northwestern University	Chicago, Illinois, USA	Mark Ricciardi	Daniel Roshevsky, Hamorabi Mkrdichian
Evanston Northshore Healthcare	Evanston, Illinois, USA	Robert Gordon	Jordan Keller, Lisa Smalley
University of Arizona College of Medicine	Tucson, Arizona, USA	Elizabeth Juneman	Catherine MacDonald, Lizzette Marquez
Mass General Hospital	Boston, Massachusetts, USA	Marc Semigran	Diane Cocca-Spofford, Thomas Cunningham
Medical University of South Carolina	Charleston, South Carolina, USA	Sheldon Litwin	Renee Baxley & Kayla Moses
Vanderbilt University	Nashville, Tennessee, USA	Deepak Gupta	Pamela Williams
Wake Forest University	Winston-Salem, North Carolina, USA	Bharathi Upadhya	Amanda Morgan
Ohio State University College of Medicine	Cambridge, Ohio, USA	Rami Kahwash	Brittany Monk
OhioHealth	Columbus, Ohio, USA	Anupam Basuray	Kitra Hunter
Mayo Clinic	Rochester, Minnesota, USA	Barry Borlaug	Cheryl Wasson, Makinzee Kazeck
University of Michigan	Ann Arbor, Michigan, USA	Scott Hummel	Joanna Wells
Cardiovascular Institute of the South	Houma, Louisiana, USA	Peter Fail	Darla Patrick, Kimberly Arceneaux, Monique Robert
Ochsner Clinic Foundation	New Orleans, Louisiana, USA	Selim Krim	Angela Lala
Yale University	New Haven, Connecticut, USA	Michael Chen	Bemen Habashi, Jackie Gamberdella
University of Pennsylvania	Philadelphia, Pennsylvania, USA	Rhondalyn McLean	Todd Nicklas, Laura Fleszar, Matt Fink
Saint Luke's Hospital	New York, New York, USA	Anthony Magalski	Jackie Smith & Karen Haffey
Mount Sinai Hospital	New York, New York, USA	Srinivas Dukkipati	Sam Cammack, Lissette Rosario-Remigio
University Hospital of Nantes	Nantes, France	Jean-Noel Trochu	Annie Guillard, Manon Pondjikli
Cardiovascular Center Aalst	Aalst, Belgium	Martin Penicka	Hedwig Batjoens
University Medical Center Groningen	Groningen, Netherlands	Pim Van der Harst	Trijntje Steenhuis, B Dorhout
Golden Jubilee National Hospital	Glasgow, UK	Mark Petrie	Sinead McKee, Marion McAdams
Alfred Hospital	Melbourne, Australia	David Kaye	Vivian Mak
St Vincent's Hospital	Sydney, Australia	Christopher Hayward	Clare Coates

Medication Regimen

Concomitant medications are required for the study and are based on the current medication use of each individual participant at the time of study participation. The specific study-required medications are listed in the table below. All medications and dosages for bacterial endocarditis prophylaxis are based on individual physician recommendations.

Supplementary Table S2.

Medication	Patient Population	Pre-Implant Procedure	During Implant and control Procedure	Post-Procedure
Heparin	All participants	N/A	Sufficient for ACT>250 seconds PRIOR to guide wire insertion	N/A
Aspirin AND Clopidogrel	Participants not currently taking an OAC	Per institutional standards	N/A	**Treatment arm**: Clopidogrel for 6 months (dose determined per institutional standards) AND baby Aspirin 75-100 mg orally daily indefinitely **Control Arm:** Baby Aspirin 75-100 mg orally daily for 1 year **Note:** all patients already on clopidogrel prior to the procedure are to continue taking clopidogrel.
OAC	Participants currently prescribed warfarin or an OAC	Per institutional standards	N/A	Continue OAC per institutional standards.
Sub-acute Bacterial Endocarditis Prophylaxis	All participants	Per institutional standards	Per Institutional Standards	Required for a minimum of 6 months. (Drug and dose per institutional standards)

ACT: activated clotting time; N/A: not applicable; OAC: oral anticoagulant

***Note:** Primary heart failure providers and investigators caring for the trial participants were instructed to remain blinded by not directly viewing or asking about medication lists on the study participants; this information was provided in a blinded fashion by the unblinded study coordinator (i.e., by masking anticoagulation treatment assignment).

Supplementary Table S3. Baseline Anticoagulant and Clopidogrel Use in the Treatment Groups

	IASD (N=22 Patients)	Control (N=22 Patients)	All Patients (N=44 Patients)	P-Value
Anticoagulant	40.9% (9/22)	36.4% (8/22)	38.6% (17/44)	1.000
Warfarin	22.7% (5/22)	18.2% (4/22)	20.5% (9/44)	1.000
Apixaban	9.1% (2/22)	9.1% (2/22)	9.1% (4/44)	1.000
Rivaroxaban	9.1% (2/22)	4.5% (1/22)	6.8% (3/44)	1.000
Dabigatran	0.0% (0/22)	4.5% (1/22)	2.3% (1/44)	1.000
Clopidogrel	22.7% (5/22)	4.5% (1/22)	13.6% (6/44)	0.185

Supplementary Table S4. Baseline Echocardiographic Diastolic Function Parameters in the Treatment Groups

Echocardiographic parameter*	IASD (N=22 Patients)	Control (N=22 Patients)	P-Value
LA volume – apical 4-chamber view (ml)	97.7±39.4 (22)	88.6±62.6 (22)	0.566
LA volume – apical 2 chamber view (ml)	94.8±31.3 (19)	96.4±65.4 (21)	0.917
Transmitral E wave velocity (cm/sec)	104.8±43.1 (22)	96.0±21.1 (21)	0.397
Transmitral A wave velocity (cm/sec)	67.9±33.6 (21)	81.3±24.1 (18)	0.165
E deceleration time (msec)	184.6±44.8 (21)	186.9±54.5 (21)	0.883
Lateral e' velocity (cm/sec)	6.9±1.2 (22)	6.5±1.7 (21)	0.391
Septal e' velocity (cm/sec)	6.3±2.0 (21)	6.2±1.5 (21)	0.865
E/e' ratio (average of septal and lateral)	15.9±8.6 (22)	16.2±4.5 (21)	0.890

*Values represent mean±SD (N)

Supplementary Table S5. IASD System II Implantation Details – Treatment Group

IASD System Implantation Details	Treatment (N=22 Patients)
Outcomes of implantation (device based)[1,2]	
Released and properly seated	90.9% (20/22)
Released, improperly seated, left in place	0.0% (0/22)
Released, improperly seated, removed by catheter technique	4.5% (1/22)
Released, improperly seated, removed by open surgery	0.0% (0/22)
Released and mal-positioned or embolized	0.0% (0/22)
Device prepared but not used in patient	0.0% (0/22)
Delivered to target site but not released and removed via delivery catheter	0.0% (0/22)
Mal-positioned or embolized device retrieved by catheter technique	4.5% (1/22)
Embolized device removed by open surgery	0.0% (0/22)
Other[3]	9.1% (2/22)
Participants successfully implanted[4]	90.9% (20/22)
L→R flow observed through device barrel	100.0% (20/20)
R→L flow observed through device barrel	15.0% (3/20)

IASD: interatrial shunt device; TTE: transthoracic echocardiogram
This table is based on site-reported data.
1 More than one outcome may be selected for each implantation attempt.
2 There were 22 implantation attempts in 21 treatment participants as follows:
- Twenty participants had one implantation attempt each.
- One participant had two implantation attempts. The first attempt had the outcome of 'Released, improperly seated, removed by catheter technique' and the second attempt had the outcome of 'Released and properly seated).
- In one participant, the first device was inadvertently fully mal-deployed in the LA. The device was percutaneously retrieved over the guidewire; however, due to temporary hemodynamic instability, implantation of a second device was not attempted. Due to significant blood loss during the retrieval procedure, the participant was transferred to the intensive care unit for monitoring; in addition, 2 units of packed red blood cells were administered, after which her hemoglobin level recovered. She remained hemodynamically stable and was transferred back to the cardiac care unit 1 day post-procedure. Duplex ultrasound of the right groin access site performed 2 days post-procedure did not show any vascular abnormalities and the patient was discharged home in good condition.
- In one participant, right atrial access could not be established for insertion of the ICE probe (occluded IVC filter was noted). The participant was unblinded during the procedure and withdrew consent to participate in the study upon learning that device placement was not feasible.

3 Two participants had one implantation attempt each with two outcomes selected: 'Released and properly seated' and 'Other'. In one participant, the device was released and properly seated and the site commented that the two RA legs were on the muscular septum. In the other participant, the device was released and properly seated and the site commented that a septal balloon was used and after implantation the pacer wire appeared to be touching the implant".
4 A participant is considered to have been successfully implanted if at least one IASD implant was successfully delivered and deployed in the intended treatment location and the delivery catheter successfully and removed intact (regardless of the number of implantations/devices attempted).