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

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Abstract

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

ClinicalTrials.gov identifier: NCT02600234 (<https://clinicaltrials.gov/ct2/show/NCT02600234>)

Key words: randomized controlled trial; diastolic heart failure; devices for heart failure; left atrial pressure; intervention

Background

Prevalence of heart failure with preserved left ventricular ejection fraction (HFpEF)

More than one-half of people with heart failure (HF) have a preserved left ventricular ejection fraction (HFpEF).^{1,2} Patients with HFpEF, commonly referred to as diastolic HF, have symptoms and/or signs of HF and a left ventricular ejection fraction (LVEF) >40-50%. The prevalence of HFpEF exceeds 3 million in the US alone and its prevalence appears to be increasing due to factors such as increased diagnostic awareness and greater longevity. The prognosis for patients hospitalized with HFpEF is poor, worsens with increasing age, and has not improved over time.³ Epidemiology studies have shown similar mortality rates in HF with reduced EF (HFrEF) and HFpEF; one-year mortality is 26% in HFrEF compared with 22% in HFpEF.^{4,5} While pharmacological treatments may improve symptoms and reduce mortality in patients with chronic HFrEF,^{6,7} there are currently no approved or evidence based effective pharmacotherapies with similar benefits for HFpEF.⁸⁻¹¹

Pathophysiology of exercise intolerance in HFpEF

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

syndrome, and are largely attributable to elevated pulmonary venous pressure at rest and/or with exercise.

Atrial shunts for left atrial decompression in HFpEF

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

We have therefore developed a novel trans-catheter interatrial shunt device (IASD) for the treatment of HFpEF. The IASD is an implant that creates and maintains an atrial septal communication. Neither the use of transseptal puncture for device delivery, nor the placement of an atrial septal implant are by themselves unusual. Transseptal puncture devices and techniques are widely available and well established.^{19,20} Atrial septal defect closure devices have been in wide use for decades and the techniques for implantation and post implantation management are widely used.²¹

To model the hemodynamic impact of creating such a shunt we reported the theoretical acute hemodynamic effects of this approach using a validated cardiovascular

simulation.²² Rest and exercise hemodynamic data from two previous independent studies of patients with HFpEF were simulated, and the theoretical acute effects of a shunt between the right and left atria were determined. The 8 mm diameter interatrial shunt acutely lowered PCWP by 3 mmHg under simulated resting conditions and by 11 mmHg under simulated peak exercise conditions. The interatrial shunt reduced left-sided cardiac output only slightly with a marked reduction in PCWP. This computer simulation suggested that an IASD approach may reduce PCWP while allowing cardiac output and heart rate to rise during exercise, potentially resulting in ability to exercise longer and reduce the propensity for heart failure exacerbations. This hypothesis is supported by clinical observations in patients with Lutembacher syndrome and the relative absence of adverse long-term effects in patients with small congenital ASD.

Early results from IASD implants in HFpEF patients

The IASD has been evaluated in patients with HFpEF in single-arm, non-blinded clinical trials. A pilot, non-randomized, single-arm evaluation of the Corvia Medical System with permanent implantation in patients with HFpEF has been completed.^{23,24} The primary outcome measure was serious adverse device events through 1-month post implant. The key inclusion criteria were at least one HF hospitalization within the past 12 months, or persistent NYHA Class III for at least 3 months, age ≥ 40 years, LVEF $\geq 45\%$. After patients were discharged from the hospital they were followed-up to 12 months. Eleven patients (6 men and 5 women, mean age 70.5 years) were enrolled and completed the study. The study demonstrated the safety and performance of the device. At one year, NYHA class and quality of life (Minnesota Living with Heart Failure Questionnaire) were improved in 73% and 91% compared to baseline respectively.

There were no deaths, cerebrovascular or systemic embolic events. The rate of HF hospitalization was reduced compared to the prior year. Unidirectional left-to-right flow through the device at rest was demonstrated in all patients in whom analysis was possible (9/9).

After the pilot study, the REDUCE LAP-HF Study was performed.²⁵ This was a prospective, 6-month, open-label, non-randomized, multicenter study to assess the safety and performance of the device in up to 100 HF patients with elevated LA pressure who remained symptomatic despite appropriate medical management. Enrolment has recently been completed. Patients will be followed for three years. The primary safety endpoint is the percentage of subjects who experience MACCE defined as death, stroke, MI, or who require implant removal cardiac surgery at 6 months from day of implant.

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

Randomized evaluation of the mechanistic effect of IASD in HFpEF: the REDUCE

LAP-HF I Trial

Given the unmet needs of patients with HFpEF, and the failure to show effectiveness of several pharmacotherapies for this condition, a novel, device-based treatment to reduce LA pressure could be a major advance in the care of patients with HFpEF.

Accordingly, we have designed a prospective, randomized, placebo-controlled, clinical trial to evaluate a transcatheter interatrial shunt for patients with HF and preserved or mildly reduced LV ejection fraction. Here we describe the device, study design, and inclusion/exclusion criteria for the trial, the REDUCE Elevated Left Atrial Pressure in Patients with Heart Failure I (ClinicalTrials.gov NCT02600234), which will be the first randomized evaluation of a device-based therapy to reduce LA pressure in patients with HFpEF.

IASD Device description

The IASD System II implant (Corvia Medical, Tewksbury, MA) consists of a one-piece self-expanding metal cage that has a double-disc design with an opening (barrel) in the center (Figure 1). It is available in one size. The implant is radiopaque and echogenic to allow for imaging during the implantation procedure. Each side of the implant is multi-legged (9 legs/side), and the LA side has a radiopaque marker at the end of each leg. The LA side of the implant is flat to allow the legs to rest flush against the LA wall, thereby minimizing the LA profile of the deployed implant. The RA side is curved to accommodate variable septal wall thicknesses, with only the leg ends contacting the RA wall. The expanded external diameter of each disc is 19.4 mm. The inner diameter of the barrel in the center of the fully expanded implant is 8 mm.

The delivery system is designed to deploy the implant at the target location across the atrial septum (Figure 2, 3). The implant comes pre-loaded onto the distal tip of the

inner catheter of the delivery system. Implant deployment is achieved by retracting the outer catheter to release the implant legs and barrel in a controlled stepwise manner.

REDUCE LAP-HF I Trial: Study design and objectives

The primary objective of this clinical trial is to evaluate the peri-procedural safety and potential effectiveness (mechanistic effect) of implanting the IASD System II in heart failure patients with an LV ejection fraction >40% and elevated left sided filling pressures who remain symptomatic despite optimal guideline-directed medical therapy (GDMT).²⁶

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

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

with examination of the atrial septum and LA appendage.

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

Patient blinding will include sedation, earphones with music to preclude the patient from hearing the procedural discussions, and blindfolding, or the use of opaque screens to prevent the participant from viewing the imaging screens. Each site will assign blinded and un-blinded staff to facilitate unbiased patient assessments through 12 months of follow-up. Research staff will be instructed to maintain patient blinding. The physicians managing the randomized patients and research staff involved in conducting selected post randomization evaluations, including the hemodynamic and cardiopulmonary exercise testing (CPET) core laboratories, will be blinded to study arm.

After treatment, device implanted patients will be treated with clopidogrel for 6 months (dose determined per institutional standards) and aspirin 75-81 mg p.o. daily indefinitely and control arm patients will be treated with aspirin 75-81 mg p.o. daily for one year. The informed consent states that's patients may receive one or two antiplatelet agents post procedure. Patients with an indication for oral anticoagulation and/or antiplatelet therapy for a pre-existing condition will continue the same regimen following the procedure.

REDUCE LAP-HF I Trial: Patient population

Up to 60 subjects at up to 20 investigational sites in the U.S., and up to 8 investigational sites outside the US, will be enrolled. From the 60 subjects, 40 patients with HFpEF (LVEF >40%) who have elevated left sided filling pressures during exercise and who are symptomatic despite optimal GDMT will be included in the randomized trial (Table 1). The inclusion and exclusion criteria are detailed in Table 2. Key inclusion criteria include documented chronic symptomatic HF; LV ejection fraction $\geq 40\%$; and elevated LA pressure with a gradient compared to RAP documented by end-expiratory PCWP during supine bike exercise ≥ 25 mmHg, and greater than RAP by ≥ 5 mmHg. An elevated resting PCWP has been observed in the majority of patients with HFpEF,²⁷ and a peak exercise PCWP ≥ 25 mmHg at peak exercise has been proposed as a diagnostic criterion for HFpEF.²⁸ Table 3 shows a comparison of the inclusion and exclusion criteria for the REDUCE LAP-HF I trial compared to several other recent or ongoing trials in HFpEF.

REDUCE LAP-HF I Trial: Outcome measures

Patients will be followed for 1 year, and annually every 12 months for a total of 5 years after index procedure and implant.

The key safety outcome measure is major adverse cardiac, cerebrovascular, and renal events (MACCRE) through 1 month post-implant (including peri-procedural) defined as cardiovascular death, embolic stroke, device- and/or procedure-related adverse cardiac or new-onset or worsening of kidney dysfunction (defined as eGFR decrease of > 20 ml/min/1.73 m²) through 1-month post implant.

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

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

REDUCE LAP-HF I Trial: Sample Size Determination

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

$H_0: \mu_{I20W} - \mu_{C20W} = 0, \mu_{I40W} - \mu_{C40W} = 0, \mu_{I60W} - \mu_{C60W} = 0, \mu_{I80W} - \mu_{C80W} = 0$ $H_1:$

At least one of the following is true:

$\mu_{I20W} - \mu_{C20W} \neq 0, \mu_{I40W} - \mu_{C40W} \neq 0, \mu_{I60W} - \mu_{C60W} \neq 0, \mu_{I80W} - \mu_{C80W} \neq 0$

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

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

Assuming a mean change in exercise PCWP of -6.0 mmHg for IASD System II and 0.0 mmHg for control at each of 20W, 40W, 60W and 80W, and assuming a standard deviation in PCWP change of 7.2 mmHg in each treatment group at each of 20W, 40W, 60W and 80W, a sample size of 20 evaluable subjects per treatment group yields 82% power to detect a significant beneficial effect of IASD System II over control when comparing treatment means using a mixed measures repeated model (MMRM) analysis of covariance (ANCOVA), assuming the compound symmetry correlation

structure where the pairwise correlations between 20W, 40W, 60W and 80W are 0.8 or less. Sample size was calculated using the PASS 14 software (NCSS, LLC, Kaysville, Utah).

REDUCE LAP-HF I Trial: Analysis populations

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

REDUCE LAP-HF I Trial: General Statistical Approach

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

Statistical Approach: Key Effectiveness Outcome Measure

The primary effectiveness outcome is the change in supine exercise PCWP from baseline at 1 month at the up to four levels of exercise (at 20W, 40W, 60W, 80W) where baseline and 1 month PCWP measurements are available. Descriptive statistics of the change in PCWP at 1 month will be presented for each treatment group for each of 20W, 40W, 60W, 80W. Treatments will be compared on change in exercise PCWP

across the 4 values using MMRM ANCOVA adjusting for the corresponding baseline exercise PCWPs, using a two-sided 0.05 level of significance.

Statistical Approach: Key Safety Outcome Measure

The key safety outcome measure is the composite incidence of one or more of the following: major adverse cardiac, cerebrovascular embolic, or renal events (MACCRE) at 1 month. The analysis on the endpoint of MACCRE at 1 month will be descriptive (percentage of patients with MACCRE and two-sided exact confidence interval of the percentage based on the binomial distribution for each treatment group). While there is no formal hypothesis testing on this endpoint, note that for the investigational arm, it is anticipated that the true MACCRE rate in the population is approximately 5%. Under this assumption, there is a 92% chance in a sample of size 20 that the observed rate will be 10% or less. This analysis will be carried out on the ITT population in whom an implant of the IADS System II was at least attempted (i.e., the “Safety Population”) with available data (follow-up through one month, or a MACCRE event by 1-month).

Also for each treatment group, Kaplan-Meier curves and estimates of cumulative MACCRE rate at 12 months will be presented for all patients in the ITT population regardless of length of follow-up. A two-sided 95% confidence interval of the difference between treatments with respect to the Kaplan-Meier estimates of cumulative MACCRE rate will be presented. In this analysis, patients not experiencing MACCRE will be censored at one month or at last known follow-up, whichever is earlier.

REDUCE LAP-HF I Trial Substudies

A sub-study will include an optional CPET evaluation and cardiac MRI in eligible patients at baseline and follow up. This sub-study will include selected centers where these evaluations are well established. The data from the CPET and images from the cardiac MRI will be evaluated by independent core laboratories. Participating sites will be provided with detailed instructions from the core labs to standardize the conduct of these studies across sites.

REDUCE LAP-HF I Trial: Data collection

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

REDUCE LAP-HF I Trial: Data safety monitoring board and Clinical Events Committee

The separate data-safety-monitoring board (DSMB) and Clinical Events Committee are managed by the Clinical Research Organization, Harvard Clinical Research Institute, Boston, Massachusetts.

Discussion

HFpEF, with its increasing prevalence and high morbidity and mortality, is a major unmet need in cardiovascular medicine today.^{1,29,30} We hypothesize that creating an appropriately sized left to-right atrial shunt that will allow LA decompression without significantly compromising left ventricular filling and forward cardiac output is a rational strategy for treating patients with HFpEF, potentially improving symptoms (particularly during exertion) and reducing HF hospitalizations. Furthermore, given the device-based nature of the treatment, patient non-compliance and polypharmacy are minimized, which could be beneficial in these patients who are often elderly and have multiple comorbidities. Corvia Medical, Inc. has developed a trans-catheter intracardiac device (the InterAtrial Shunt Device [IASD[®]] System II) that creates an 8 mm permanent opening in the septum between the right and left atria of the heart, designed to maintain a permanent communication. An early unblinded, single-arm pilot study of the IASD in HFpEF has yielded promising results, and a second, larger unblinded, single-arm study is ongoing. Although the prior experience with the IASD has been encouraging, a randomized controlled trial is necessary to provide further evidence of device efficacy and safety. Here we have described the rationale and design of the REDUCE LAP-HF I clinical trial of the IASD in patients with HF and LV ejection fraction $\geq 40\%$, which should advance our understanding of the utility of this device in HF.

There is currently one other device utilizing similar hemodynamic principles of an atrial shunt.³¹ The V-Wave device (V-Wave Medical; Caesarea, Israel) is an hourglass-shaped nitinol frame device with three valve leaflets intended to mechanically maintain a 5 mm sized unidirectional left-to-right shunt at the level of the atrial septum. The V-Wave device was successfully implanted in five patients with chronic HFrEF with a mean LVEF of 25±6%. At three months follow-up all patients showed clinical improvement as evidenced by change to NYHA class II, increased 6-minute walking test, reduction in PCWP and NT-pro-BNP, but there were no changes in LVEF, end-diastolic LV diameter, LA volume, mitral regurgitation grade or right arterial pressure. There were no device-related adverse events.

Strengths

The study described here is the first randomized trial of a device-based therapy for lowering LA pressure in patients with HFpEF. Incorporating a randomized evaluation with a control arm is important given the potential for a placebo effect, as has been demonstrated for other device-based therapies.³² The trial benefits from strict inclusion criteria for the diagnosis of HF (requiring both signs/symptoms of HF; *and* objective evidence of LV diastolic dysfunction or LA enlargement; *and* objective invasive hemodynamic evidence of elevated LA pressure). In addition, the trial includes detailed hemodynamic assessment during exercise, which is critical given the exercise-related symptoms that are so common in HFpEF.

Limitations

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

Conclusions

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

REDUCE LAP-HF I Trial: Sources of Funding

The study is funded entirely by Corvia Medical, Inc. (Tewksbury MA)

Disclosures

JK is an employee of Corvia Medical, Inc., the sponsor of the REDUCE LAP-HF I clinical trial. There are no other disclosures or conflicts of interest.

REFERENCES

1. Oktay AA, Rich JD and Shah SJ. The emerging epidemic of heart failure with preserved ejection fraction. *Curr Heart Fail Rep.* 2013;10:401-10.
2. Oktay AA and Shah SJ. Diagnosis and management of heart failure with preserved ejection fraction: 10 key lessons. *Curr Cardiol Rev.* 2015;11:42-52.
3. Brouwers FP, de Boer RA, van der Harst P, Voors AA, Gansevoort RT, Bakker SJ, Hillege HL, van Veldhuisen DJ and van Gilst WH. Incidence and epidemiology of new onset heart failure with preserved vs. reduced ejection fraction in a community-based cohort: 11-year follow-up of PREVEND. *Eur Heart J.* 2013;34:1424-31.
4. Bhatia RS, Tu JV, Lee DS, Austin PC, Fang J, Haouzi A, Gong Y and Liu PP. Outcome of heart failure with preserved ejection fraction in a population-based study. *N Engl J Med.* 2006;355:260-9.
5. Chun S, Tu JV, Wijeyesundera HC, Austin PC, Wang X, Levy D and Lee DS. Lifetime analysis of hospitalizations and survival of patients newly admitted with heart failure. *Circ Heart Fail.* 2012;5:414-21.
6. Dickstein K, Cohen-Solal A, Filippatos G, McMurray JJ, Ponikowski P, Poole-Wilson PA, Stromberg A, van Veldhuisen DJ, Atar D, Hoes AW, Keren A, Mebazaa A, Nieminen M, Priori SG and Swedberg K. ESC guidelines for the diagnosis and treatment of acute and chronic heart failure 2008: the Task Force for the diagnosis and treatment of acute and chronic heart failure 2008 of the European Society of Cardiology. *Eur J Heart Fail.* 2008;10:933-89.
7. McMurray JJ, Adamopoulos S, Anker SD, Auricchio A, Bohm M, Dickstein K, Falk V, Filippatos G, Fonseca C, Gomez-Sanchez MA, Jaarsma T, Kober L, Lip GY, Maggioni AP, Parkhomenko A, Pieske BM, Popescu BA, Ronnevik PK, Rutten FH, Schwitler J, Seferovic P, Stepinska J, Trindade PT, Voors AA, Zannad F and Zeiher A. ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure 2012: The Task Force for the Diagnosis and Treatment of Acute and Chronic Heart Failure 2012 of the European Society of Cardiology. *Eur Heart J.* 2012;33:1787-847.
8. Edelmann F, Wachter R, Schmidt AG, Kraigher-Krainer E, Colantonio C, Kamke W, Duvinage A, Stahrenberg R, Durstewitz K, Loffler M, Dungen HD, Tschope C, Herrmann-Lingen C, Halle M, Hasenfuss G, Gelbrich G, Pieske B and Aldo DHF. Effect of spironolactone on diastolic function and exercise capacity in patients with heart failure with preserved ejection fraction: the Aldo-DHF randomized controlled trial. *JAMA.* 2013;309:781-91.
9. Massie BM, Carson PE, McMurray JJ, Komajda M, McKelvie R, Zile MR, Anderson S, Donovan M, Iverson E, Staiger C, Ptaszynska A and Investigators IP. Irbesartan in patients with heart failure and preserved ejection fraction. *N Engl J Med.* 2008;359:2456-67.
10. Patel K, Fonarow GC, Kitzman DW, Aban IB, Love TE, Allman RM, Gheorghide M and Ahmed A. Angiotensin receptor blockers and outcomes in real-world older patients with heart failure and preserved ejection fraction: a propensity-

matched inception cohort clinical effectiveness study. *Eur J Heart Fail.* 2012;14:1179-88.

11. Rector TS, Carson PE, Anand IS, McMurray JJ, Zile MR, McKelvie RS, Komajda M, Kuskowski M, Massie BM and Investigators IPT. Assessment of long-term effects of irbesartan on heart failure with preserved ejection fraction as measured by the minnesota living with heart failure questionnaire in the irbesartan in heart failure with preserved systolic function (I-PRESERVE) trial. *Circ Heart Fail.* 2012;5:217-25.

12. Shah SJ, Katz DH and Deo RC. Phenotypic spectrum of heart failure with preserved ejection fraction. *Heart Fail Clin.* 2014;10:407-18.

13. Baumgartner H, Bonhoeffer P, De Groot NM, de Haan F, Deanfield JE, Galie N, Gatzoulis MA, Gohlke-Baerwolf C, Kaemmerer H, Kilner P, Meijboom F, Mulder BJ, Oechslin E, Oliver JM, Serraf A, Szatmari A, Thaulow E, Vouhe PR and Walma E. ESC Guidelines for the management of grown-up congenital heart disease (new version 2010). *Eur Heart J.* 2010;31:2915-57.

14. Feltes TF, Bacha E, Beekman RH, 3rd, Cheatham JP, Feinstein JA, Gomes AS, Hijazi ZM, Ing FF, de Moor M, Morrow WR, Mullins CE, Taubert KA, Zahn EM, American Heart Association Congenital Cardiac Defects Committee of the Council on Cardiovascular Disease in the Y, Council on Clinical C, Council on Cardiovascular R, Intervention and American Heart A. Indications for cardiac catheterization and intervention in pediatric cardiac disease: a scientific statement from the American Heart Association. *Circulation.* 2011;123:2607-52.

15. Warnes CA, Williams RG, Bashore TM, Child JS, Connolly HM, Dearani JA, del Nido P, Fasules JW, Graham TP, Jr., Hijazi ZM, Hunt SA, King ME, Landzberg MJ, Miner PD, Radford MJ, Walsh EP, Webb GD, Smith SC, Jr., Jacobs AK, Adams CD, Anderson JL, Antman EM, Buller CE, Creager MA, Ettinger SM, Halperin JL, Hunt SA, Krumholz HM, Kushner FG, Lytle BW, Nishimura RA, Page RL, Riegel B, Tarkington LG and Yancy CW. ACC/AHA 2008 guidelines for the management of adults with congenital heart disease: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *J Am Coll Cardiol.* 2008;52:e143-263.

16. Lutembacher R. De la stenose mitrale avec commnication interauriculaire. *Arch Mal Coaeur* 1916;9:237.

17. Wiedemann HR. Earliest description by Johann Friedrich Meckel, Senior (1750) of what is known today as Lutembacher syndrome (1916). *Am J Med Genet.* 1994;53:59-64.

18. Ledesma M, Martinez P, Cazares MA and Feldman T. Transcatheter treatment of Lutembacher syndrome: combined balloon mitral valvuloplasty and percutaneous atrial septal defect closure. *J Invasive Cardiol.* 2004;16:678-9.

19. Earley MJ. How to perform a transseptal puncture. *Heart.* 2009;95:85-92.

20. Feldman T and Fisher WG. Transseptal puncture. In: A. Colombo and G. Stankovic, eds. *Problem oriented approaches in interventional cardiology* Boca Raton, FL: Taylor & Francis; 2007.

21. FDA Circulatory System Advisory Panel 2012. Transcatheter ASD Occluders: Clinical Update and Review of Events. <http://www.fda.gov/AdvisoryCommittees/ucm297470.htm>. Accessed December 6, 2015.
22. Kaye D, Shah SJ, Borlaug BA, Gustafsson F, Komtebedde J, Kubo S, Magnin C, Maurer MS, Feldman T and Burkhoff D. Effects of an interatrial shunt on rest and exercise hemodynamics: results of a computer simulation in heart failure. *J Card Fail*. 2014;20:212-21.
23. Malek F, Neuzil P, Gustafsson F, Kaye DM, Walton A, Mates M, Sondergaard L, Ihlemann N, Mariani JA and Reddy V. Clinical outcome of transcatheter treatment of heart failure with preserved or mildly reduced ejection fraction using a novel implant. *Int J Cardiol*. 2015;187:227-8.
24. Sondergaard L, Reddy V, Kaye D, Malek F, Walton A, Mates M, Franzen O, Neuzil P, Ihlemann N and 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.
25. Hasenfuss G, Gustafsson F, Kaye D, Shah SJ, Burkhoff D, Reymond MC, Komtebedde J, Hunlich M and Reduce LAPHFTI. Rationale and Design of the Reduce Elevated Left Atrial Pressure in Patients With Heart Failure (Reduce LAP-HF) Trial. *J Card Fail*. 2015;21:594-600.
26. Yancy CW, Jessup M, Bozkurt B, Butler J, Casey DE, Jr., Drazner MH, Fonarow GC, Geraci SA, Horwich T, Januzzi JL, Johnson MR, Kasper EK, Levy WC, Masoudi FA, McBride PE, McMurray JJ, Mitchell JE, Peterson PN, Riegel B, Sam F, Stevenson LW, Tang WH, Tsai EJ and Wilkoff BL. 2013 ACCF/AHA guideline for the management of heart failure: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. *J Am Coll Cardiol*. 2013;62:e147-239.
27. Shah SJ, Katz DH, Selvaraj S, Burke MA, Yancy CW, Gheorghiade M, Bonow RO, Huang CC and Deo RC. Phenomapping for novel classification of heart failure with preserved ejection fraction. *Circulation*. 2015;131:269-79.
28. Borlaug BA, Nishimura RA, Sorajja P, Lam CS and Redfield MM. Exercise hemodynamics enhance diagnosis of early heart failure with preserved ejection fraction. *Circ Heart Fail*. 2010;3:588-95.
29. Owan TE, Hodge DO, Herges RM, Jacobsen SJ, Roger VL and Redfield MM. Trends in prevalence and outcome of heart failure with preserved ejection fraction. *N Engl J Med*. 2006;355:251-9.
30. 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 and Li R. Baseline characteristics of patients in the treatment of preserved cardiac function heart failure with an aldosterone antagonist trial. *Circ Heart Fail*. 2013;6:184-92.
31. Amat-Santos IJ, Bergeron S, Bernier M, Allende R, Barbosa Ribeiro H, Urena M, Pibarot P, Verheye S, Keren G, Yaacoby M, Nitzan Y, Abraham WT and Rodes-Cabau

J. Left atrial decompression through unidirectional left-to-right interatrial shunt for the treatment of left heart failure: first-in-man experience with the V-Wave device. *EuroIntervention*. 2015;10:1127-31.

32. 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 and Bakris GL. A controlled trial of renal denervation for resistant hypertension. *N Engl J Med*. 2014;370:1393-401.

FIGURE LEGENDS

Figure 1: Corvia Medical, Inc. IASD® System II device.

Figure 2: Corvia Medical, Inc. IASD® System II delivery system.

Figure 3: Implant after placement in the interatrial septum.

Figure 4: Patient flow through the trial.

Table 1: Pharmacological Treatment for Stage C HFpEF—AHA/ACC Guideline Recommendations

CLASS I

Systolic and diastolic blood pressure should be controlled according to published clinical practice guidelines (Level of Evidence: B)

Diuretics should be used for relief of symptoms due to volume overload. (Level of Evidence: C)

CLASS II

Coronary revascularization for patients with CAD in whom angina or demonstrable myocardial ischemia is present despite GDMT (Level of Evidence: C)

Management of AF according to published clinical practice guidelines for HFpEF to improve symptomatic HF (Level of Evidence: C)

Use of beta-blocking agents, ACE inhibitors, and ARBs for hypertension in HFpEF
ARBs might be considered to decrease hospitalizations in HFpEF (Level of Evidence: C)

CLASS III: No Benefit

Nutritional supplementation is not recommended in HFpEF (Level of Evidence: C)

Table 2: Inclusion and exclusion criteria for the REDUCE LAP-HF I trial

Candidates for the study must meet ALL of the following inclusion criteria:

1. Chronic symptomatic heart failure (HF) documented by the following:
 - a. New York Heart Association (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. \geq One hospital admission for which HF was a major component of the hospitalization, or an emergency department visit with IV treatment for HF within the 12 months prior to study entry; OR an NT-pro BNP value > 50 pmol/L (>425 pg/ml) in normal sinus rhythm, >150 pmol/L (>1265 pg/ml) in atrial fibrillation, or a BNP value > 100 pg/ml in normal sinus rhythm, > 250 pg/ml in atrial fibrillation within the past 3 months.
2. Ongoing stable GDMT HF management and management of potential comorbidities according to the 2013 ACCF/AHA Guidelines for the management of Heart Failure (with no significant changes [$>100\%$ increase or 50% decrease], excluding diuretic dose changes for a minimum of 4 weeks prior to screening) that is expected to be maintained without change for 6 months.
3. Age ≥ 40 years old
4. Site determined LV ejection fraction $\geq 40\%$ within the past 3 months, without previously documented ejection fraction $<30\%$.
5. Site determined elevated LA pressure with a gradient compared to right atrial pressure documented by end-expiratory PCWP during supine ergometer exercise ≥ 25 mm Hg, and greater than right atrial pressure by ≥ 5 mm Hg.
6. Site determined echocardiographic evidence of diastolic dysfunction documented by one or more of the following:
 - a. LA diameter > 4 cm; *or*
 - b. LA volume index > 28 ml/m² *or*
 - c. Lateral e' <10 cm/s; *or*
 - d. Septal e' <8 cm/s; *or*
 - e. Lateral E/e' >10 ; *or*
 - f. Septal E/e' > 15

7. Subject has been informed of the nature of the study, agrees to its provisions and has provided written informed consent, approved by the IRB or EC
8. Subject is willing to comply with clinical investigation procedures and agrees to return for all required follow-up visits, tests, and exams
9. Trans-septal catheterization and femoral vein access is determined to be feasible by site principal interventional cardiology investigator

Candidates for this study will be excluded if ANY of the following conditions are present:

1. MI and/or percutaneous cardiac intervention within past 3 months; CABG in past 3 months, or current indication for coronary revascularization
2. Cardiac resynchronization therapy initiated within the past 6 months
3. Severe heart failure defined as one or more of the below:
 - a. ACC/AHA/ESC Stage D heart failure, Non-ambulatory NYHA Class IV HF;
 - b. Cardiac index < 2.0 L/min/m²
 - c. Inotropic infusion (continuous or intermittent) within the past 6 months
 - d. Patient is on the cardiac transplant waiting list
4. Inability to perform 6 minute walk test (distance < 50 m), OR 6 minute walk test > 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 defined as grade \geq 3+ MR
 - b) Tricuspid valve regurgitation defined as grade \geq 2+ TR;
 - c) Aortic valve disease defined as \geq 2+ AR or > moderate AS

9. Hypertrophic obstructive cardiomyopathy, restrictive cardiomyopathy, constrictive pericarditis, cardiac amyloidosis or other infiltrative cardiomyopathy (e.g. hemochromatosis, sarcoidosis)
10. Subject is contraindicated to receive either dual antiplatelet therapy or warfarin (analogue); or has a documented coagulopathy
11. Atrial fibrillation with resting HR > 100 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 TTE; OR
 - b. TAPSE < 1.4 cm; OR
 - c. RV size \geq LV size as estimated by TTE; OR
 - d. Echocardiographic or clinical evidence of congestive hepatopathy; OR
 - e. Evidence of RV dysfunction defined by TTE as an RV fractional area change < 35%;
15. Resting right atrial pressure > 14 mmHg
16. Evidence of pulmonary hypertension with PVR > 4 Wood units
17. Chronic pulmonary disease requiring continuous home oxygen, OR hospitalization for exacerbation in the 12 months prior to study entry, OR significant chronic pulmonary disease defined as FEV1 < 50% predicted, or in the opinion of the investigator
18. Currently participating in an investigational drug or device study. Note: trials requiring extended follow-up for products that were investigational but have since become commercially available are not considered investigational trials
19. Life expectancy less than 12 months for non-cardiovascular reasons
20. Echocardiographic evidence of intra-cardiac mass, thrombus or vegetation
21. Known or suspected allergy to nickel
22. Fertile women

23. Currently requiring dialysis; or estimated-GFR <25ml/min/1.73 m² by CKD-Epi equation
24. Systolic blood pressure >170 mm Hg at screening
25. Subjects with existing s. Subjects with a patent foramen ovale (PFO), who meet PCWP criteria despite the PFO, are allowed.
26. Subjects on immunosuppression or systemic steroid treatment (>10 mg prednisone/day).
27. Severe obstructive sleep apnea not treated with CPAP or other measures
28. Severe depression and/or anxiety
29. In the opinion of the investigator, the subject is not an appropriate candidate for the study

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

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

*In NEAT, alternate criteria besides prior hospitalization for HF or elevated BNP included: (1) elevated LV filling pressures on invasive hemodynamic testing or (2) echocardiographic evidence of diastolic dysfunction, LV hypertrophy, and/or elevated LV filling pressures (at least 2 criteria were required). A complete description of the specific invasive hemodynamic and echocardiographic criteria is listed in Zakeri et al. *Circ Heart Fail* 2015;8:221-228.

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

†In PARAGON, the age cutoff initially was > 55 years but has since been amended to an age cutoff of > 50 years.

HF = heart failure; BNP = B-type natriuretic peptide; NYHA = New York Heart Association; LVEF = left ventricular ejection fraction; AF = atrial fibrillation; NTproBNP = N-terminal pro-B-type natriuretic peptide; LA = left atrial; PCWP = pulmonary capillary wedge pressure; RA= right atrial; CV = cardiovascular

Table 4: Additional outcome measures for safety and effectiveness

Safety related outcome measures:

1. Major adverse cardiac events through 12-months
2. All serious adverse events (SAEs) through 12-months
3. All-cause mortality, CV mortality and heart failure related mortality through 12-months
4. Newly acquired persistent or permanent AF or atrial flutter through 12-months
5. Implant embolization and clinically significant device migration through 12-months.
6. Systemic embolic events through 12-months.
7. Increase in RV size/decrease in RV function through 12-months
8. The need for implant removal or occlusion of the implant.

Efficacy related outcome measures:

1. All-cause, and heart failure related hospitalizations/emergency department visits with IV treatment for HF; and number of hospitalization days, ICU days through 12 months
2. Treatment for outpatient worsening of heart failure
3. Days alive, and not-hospitalized through 12-months
4. Change in blinded Investigator assessed NYHA classification between baseline and 12 months.
5. Change in 6MWT distance between baseline and 12 months
6. Assessment of shunt dimensions and flow at 12 months
7. Changes in resting and exercise PA pressures and CI between baseline and 1 month as assessed by an independent blinded hemodynamic core laboratory.
8. Change in BNP and/or NT-pro-BNP, and MR-ANP between baseline and at 12 months
9. Changes in LA, LV dimensions, volume, and function, between baseline and 12 months assessed by an independent echocardiographic core laboratory
10. Changes in RA, LA, LV and RV dimensions, volume, and function between baseline and 12 months assessed by a cardiac MRI core laboratory (Sub-study only)
11. Change in CPET parameters (including exercise time) between baseline and 12 months as assessed by an independent blinded CPET core laboratory (Sub-study only)
12. Change in diuretic medications between baseline and 12 months

Figure 1: Corvia Medical, Inc. IASD® System II device.



Figure 2: Corvia Medical, Inc. IASD® System II delivery system.

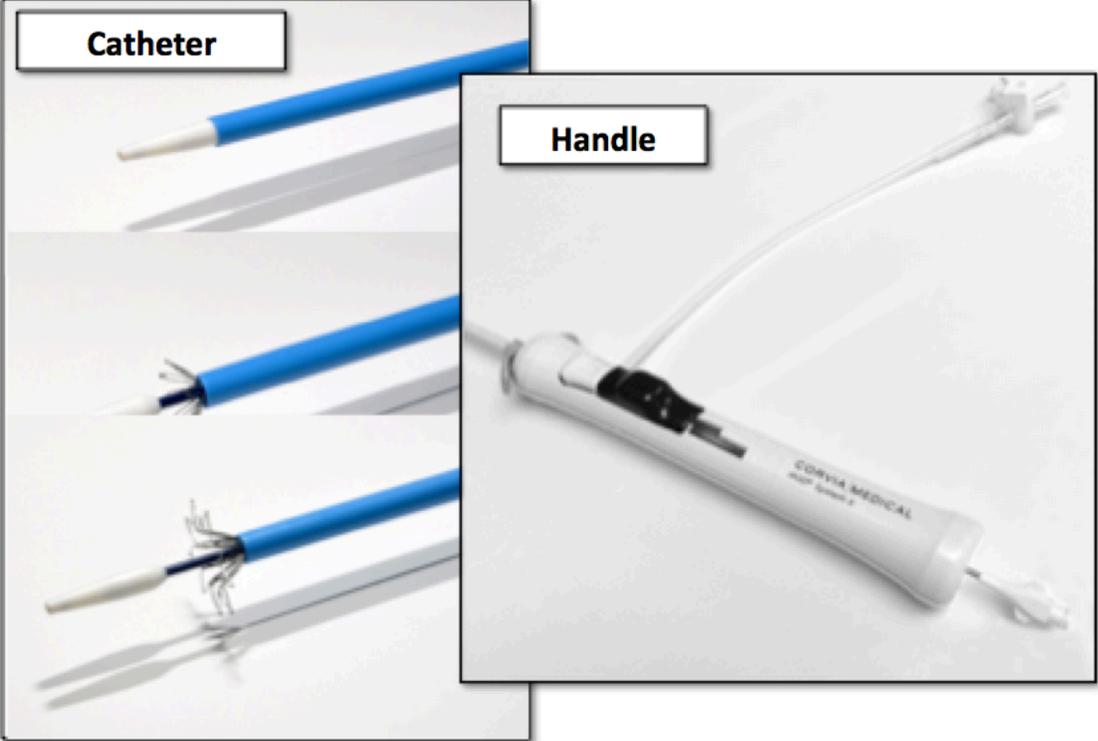


Figure 3: Implant after placement in the interatrial septum.

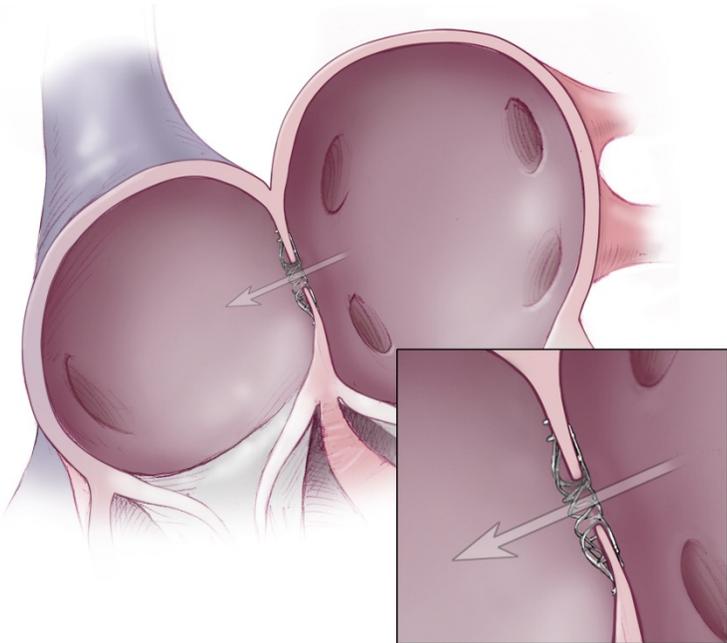


Figure 4: Patient flow through the trial.

