Clinical Trials: Methods and Design

Rationale and Design of the Reduce Elevated Left Atrial Pressure in Patients With Heart Failure (Reduce LAP-HF) Trial

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ABSTRACT

Objective: Heart failure with preserved ejection fraction (HFpEF) is characterized by elevated left atrial pressure during rest and/or exercise. The Reduce LAP-HF (Reduce Elevated Left Atrial Pressure in Patients With Heart Failure) trial will evaluate the safety and performance of the Interatrial Shunt Device (IASD) System II, designed to directly reduce elevated left atrial pressure, in patients with HFpEF.

Methods: The Reduce LAP-HF Trial is a prospective, nonrandomized, open-label trial to evaluate a novel device that creates a small permanent shunt at the level of the atria. A minimum of 60 patients with ejection fraction ≥40% and New York Heart Association functional class III or IV heart failure with a pulmonary capillary wedge pressure (PCWP) ≥15 mm Hg at rest or ≥25 mm Hg during supine bike exercise will be implanted with an IASD System II, and followed for 6 months to assess the primary and secondary end points. Safety and standard clinical follow-up will continue through 3 years after implantation. Primary outcome measures for safety are periprocedural and 6-month major adverse cardiac and cerebrovascular events (MACCE) and systemic embolic events (excluding pulmonary thromboembolism). MACCE include death, stroke, myocardial infarction, or requirement of implant removal. Primary outcome measures for device performance include success of device implantation, reduction of PCWP at rest and during exercise, and demonstration of left-to-right flow through the device. Key secondary end points include exercise tolerance, quality of life, and the incidence of heart failure hospitalization.

Conclusion: Reduce LAP-HF is the first trial intended to lower left atrial pressure in HFpEF by means of creating a permanent shunt through the atrial septum with the use of a device. Although the trial is primarily designed to study safety and device performance, we also test the pathophysiologic hypothesis that reduction of left atrial pressure will improve symptoms and quality of life in patients with HFpEF. (*J Cardiac Fail 2015;21:594–600*)

Key Words: Heart failure with preserved ejection fraction (HFpEF), Interatrial Shunt Device (IASD), quality of life, exercise tolerance.

Heart failure with preserved ejection fraction (HFpEF) is defined by signs and symptoms of heart failure, normal or mildly reduced left ventricular ejection fraction in the presence of a nondilated left ventricle, and structural heart disease (left ventricular hypertrophy, left atrial enlargement) and/or diastolic dysfunction.[1]

The prevalence of HFpEF is similar to that of heart failure with reduced ejection fraction (HFrEF), and the prognosis of HFpEF may be only slightly better than that of HFrEF.[2–5] Diastolic dysfunction results in elevated left atrial pressure during rest and/or exercise.[6–8] Elevated left atrial and pulmonary capillary wedge pressure may not only be pathophysiologic substrates of symptoms in patients with HFpEF, they

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may also be direct prognostic markers.[9] Moreover, there is evidence that patients with a Lutembacher syndrome (mitral stenosis with an atrial septal defect) have fewer symptoms and better outcomes compared with patients with pure mitral stenosis.[10] In addition, it has been reported that closure of an atrial septal defect may in some patients result in an increased pulmonary artery pressure and pulmonary edema.[11,12] Ritzema et al recently showed that reduction of left atrial pressure may be associated with improved morbidity and mortality in patients with HFrEF,[13] and Dorffs et al showed a relationship between elevated pulmonary capillary wedge pressure (PCWP) and increased mortality[14]; both studies support the important role of left atrial pressure elevation in heart failure.

Despite several high-quality pathophysiologic investigations and pharmaceutical outcome trials in recent years, there is no available drug therapy to improve morbidity and/or mortality in patients with HFpEF, and guidelines currently recommend control of blood pressure, management of symptoms with the use of diuretics, and management of comorbidities.[1]

Given the critical role of left atrial pressure elevation (at rest and with exercise) as the final common pathway in the pathogenesis of HFpEF, along with the lack of available therapies for HFpEF, a device that could directly lower left atrial pressure in HFpEF may be beneficial to patients. The 30-day results from an 11-patient pilot study with the Interatrial Shunt Device (IASD) were previously reported.[15] Study follow-up was completed through 12 months, and no major adverse cardiac and cerebrovascular events (MACCE) occurred. Here we describe the Reduce Left Atrial Pressure in Patients With Heart Failure (Reduce LAP-HF) trial, a nonrandomized single-arm clinical trial of the IASD System II with the primary goal of determining the safety and device performance of the IASD System II.

Methods

Study Objectives

The primary objectives of this clinical study are to evaluate the safety and performance of the IASD System II (Fig. 1) in the treatment of HFpEF and elevated left atrial pressure in patients who have remained symptomatic despite appropriate medical management.

Inclusion and Exclusion Criteria. Participating trial centers will evaluate consecutive outpatients and inpatients according to the patient selection criteria (Tables 1−3).

Patients who sign informed consent will undergo right heart catheterization with cardiac output and hemodynamic assessment at rest and during supine bike exercise. After recording resting hemodynamics in the screening (ie, baseline) and follow-up tests, patients will undergo supine bicycle exercise. Exercise will be performed in 3-minute stages, starting at 20 W with increases of 20-W increments until the patient reaches maximum effort. If not previously excluded, coronary artery disease will be evaluated by means of simultaneous left heart catheterization. Hemodynamic eligibility requirements are provided in Table 1A, and exclusion criteria are given in Table 3.

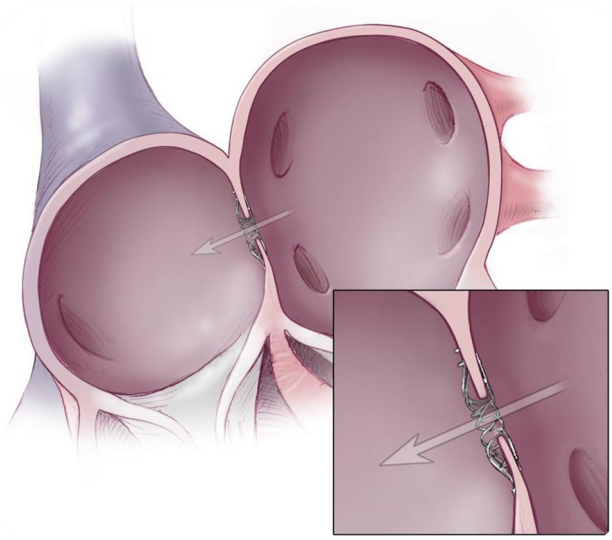

Fig. 1. IASD in position in the atrial septum. The arrow indicates shunt direction and flow over the device.

Independent echocardiographic and hemodynamic core laboratories will evaluate baseline and follow-up data, according to published guidelines for echocardiography core laboratories.[16]

Patients who fulfill all criteria for entry into the study will undergo device implantation.

Study Design

Reduce LAP-HF is a multicenter prospective, nonrandomized, open-label, single-arm trial to evaluate a novel device that creates a small permanent shunt at the level of the atria.

Screening and baseline measurements will be done within 45 days before the implantation procedure. After device implantation, every patient will have follow-up through 36 months. Patients will have an assessment before being discharged from the hospital (or within 2 days after the implantation procedure, whichever occurs first). Follow-up visits will be performed after 1 month (±7 days), 3 months (±15 days), 6 months (±30 days), and 12 months (±30 days). Patients will have annual telephone follow-ups at the 24th month (±30 days), and 36th month (±30 days) time points. Standard clinical follow-up data may be collected at the discretion of the patient and managing clinician (N-terminal pro−B-type

Table 1. Patient Selection Criteria

Candidates for this study must meet all of the following inclusion criteria:

1. Chronic symptomatic heart failure (HF) documented by ≥1 of the following:
   a. New York Heart Association functional class III/ambulatory functional class IV symptoms (paroxysmal nocturnal dyspnea, orthopnea, dyspnea on mild or moderate exertion) at screening visit, or signs (any rales after cough, chest x-ray demonstrating pulmonary congestion) within past 12 months.
   b. One hospital admission for HF within the 12 months before study entry (transient HF in the context of myocardial infarction does not qualify).
   c. On-going management with recommended HF medications and comorbidities for several months according to the guidelines.[1]
2. Age ≥40 years.
3. Left ventricular ejection fraction ≥40% as determined by echocardiography.
4. Hemodynamic inclusion criteria (Table 1A).

Table 1A. Hemodynamic Inclusion Criteria

1. Elevated left ventricular filling pressures with a gradient compared to CVP documented by ≥1 of the following:
   a. PCWP (end-expiratory) or LVEDP (end-expiratory) at rest ≥15 mm Hg and greater than CVP.
   b. PCWP (end-expiratory) during supine bike exercise ≥25 mm Hg, and CVP <20 mm Hg.

LV, left ventricular; CVP, central venous pressure; PCWP, pulmonary capillary wedge pressure; LVEDP, left ventricular end-diastolic pressure.

natriuretic peptide, transthoracic echocardiography, QOL assessment, 6-minute walk test are optional at 24- and 36-month follow-ups). Supplemental Table 1 (online appendix) lists protocol based procedures and assessments.

Device Implantation

The device implantation procedure will be conducted under general anesthesia with endotracheal intubation, or with local anesthesia and conscious sedation. Device implantation will be guided with the use of fluoroscopy and transesophageal or intracardiac echocardiography, the choice of which will be at the discretion of the study investigator. The device will be implanted after puncture of the right femoral vein. After standard transseptal puncture of the atrial septum, a guide wire will be inserted in the left superior pulmonary vein, and the delivery system will be advanced over the wire into the left atrium. First, the left atrial side of the implant will be deployed (Fig. 2). The catheter will be slightly retracted against the atrial septum, and the right atrial side of the implant will be deployed. Thereafter, the guide wire and delivery system will be removed. During the procedure, all patients will receive heparin. Patients not taking oral anticoagulants will be treated with aspirin (75−325 mg orally daily) indefinitely and clopidogrel (75 mg orally daily) for 6 months. Patients on oral anticoagulants before the procedure will continue oral anticoagulation. Endocarditis prophylaxis will be performed per institutional standards for a minimum of 6 months after implantation.

Catheter-Based Invasive hemodynamic Evaluations at Rest and During Stress Testing

At baseline and the 6-month follow-up visit, and optionally at the 12-month follow-up visit, each subject will undergo invasive catheter-based hemodynamic evaluations at rest and during standardized stress testing with the use of a supine ergometer exercise procedure. Pressure tracings (with simultaneous electrocardiography recordings) will be recorded and reported to the core laboratory by fax or e-mail. This will include measurements of right atrial pressure (RAP), pulmonary arterial pressure (PAP), and PCWP and left atrial (measurement, eg, with a multipurpose catheter through the shunt) or ventricular pressures when available. In addition, blood samples will be collected in duplicate and analyzed for oxygen saturations at both rest and peak exercise of the superior vena cava, inferior vena cava, pulmonary artery, and systemic artery.

Table 2. Additional Inclusion Criteria

1. Subject has been informed of the nature of the study, is willing to participate, and has provided written informed consent.
2. Subject is willing to comply with clinical investigational procedures and agrees to return for all required follow-up visits, tests, and exams.
3. Ability to perform a 6-minute walk test.
4. Transseptal catheterization and femoral access is determined to be feasible.

Exercise Capacity Evaluation

Each subject will undergo a 6-minute walk test at baseline and at each follow-up visit.

Quality of Life Evaluation

Each subject will complete the Minnesota Living With Heart Failure Questionnaire (MLWHFQ) at baseline and at each follow-up visit.

Echocardiography

Each subject will undergo transthoracic echocardiography (TTE) with color flow Doppler and tissue Doppler, performed according to echocardiographic and core laboratory standards at baseline, before discharge, and at the 1-, 6-, and 12-month follow-up visits. The TTE will evaluate LV function, RV size and function, estimated systolic PAP, and interatrial flow through the study device.

Telephone Follow-Up

After the 12-month visit, the patients will have an annual telephone follow-up to 36 months to collect information related to symptoms as well as morbidity/mortality information.

Biometric Aspects

An estimated minimum of 50 subjects with 6 months' complete follow-up will be needed for an informative review of the primary safety end point, and a total number of 100 screened patients is foreseen. This number takes into account a withdrawal rate of 10% before 6 months.

Statistical Analysis

Safety end points will be analyzed on patients who undergo the implantation procedure. The number of successful device implantations will be reported, and the number of subjects with reduction of PCWP and demonstration of left-to-right flow through the device at 6 months will be reported for the patients who undergo successful device implantation. For secondary end points that are not safety outcomes, the statistical reporting will be done on the latter population.

Statistical Methods

Quantitative parameters will be described with the use of the following summary descriptive statistics: number of nonmissing values, mean, standard deviation, median, first and third quartiles, and minimum and maximum values. Qualitative parameters will be described overall with the use of frequencies and percentages. Percentages will be calculated on the number of nonmissing observations.

In all cases, the number of missing values will be specified. All confidence intervals will be 2 sided and performed at the 0.05 global significance level. Wilcoxon test or Student test for pairwise comparisons will be used, depending on the normality of the distribution to study evolution in time.

Table 3. Exclusion Criteria

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

1. Myocardial infarction and/or percutaneous cardiac intervention within past 3 months; coronary artery bypass graft 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 ≥1 of the following:
   a. ACC/AHA/ESC stage D heart failure, nonambulatory New York Heart Association functional class IV heart failure.
   b. Cardiac index <2.0 L min^{-1} m^{-2}.
   c. Requiring inotropic infusion (continuous or intermittent) within the past 6 months.
   d. Patient is on cardiac transplant waiting list.
4. Inability to perform 6-minute walk test.
5. Known significant coronary artery disease (stenosis >70%).
6. History of transient ischemic attack, deep-vein thrombosis, or pulmonary emboli within the past 6 months.
7. Known severe carotid artery stenosis (>70%).
8. Presence of significant valve disease defined by echocardiography as ≥1 of the following:
   a. Mitral valve regurgitation, defined as grade >2 + mitral regurgitation.
   b. Tricuspid valve regurgitation, defined as grade ≥2 + tricuspid regurgitation.
   c. Aortic valve disease, defined as ≥2 + aortic regurgitation or ≥moderate AS (AVA ≤1.1 cm^2).
9. Hypertrophic obstructive cardiomyopathy, restrictive cardiomyopathy, constrictive pericarditis, cardiac amyloidosis, or other infiltrative cardiomyopathy (eg, hemochromatosis, sarcoidosis).
10. Subject is contraindicated for receiving either dual antiplatelet therapy or warfarin analogue, or has a documented coagulopathy.
11. Atrial fibrillation with resting heart rate >100 beats/min.
12. Arterial oxygen saturation <95% on room air.
13. Significant hepatic impairment, defined as 3× upper limit of normal of transaminases, total bilirubin, or alkaline phosphatase.
14. Right ventricular dysfunction, defined as ≥1 of the following:
   a. More than mild RV dysfunction as determined by transthoracic echocardiography.
   b. Tricuspid annular plane systolic excursion <1.4 cm.
   c. Right ventricular volume ≥ left ventricular volume on echocardiography estimate.
   d. Echocardiographic or clinical evidence of congestive hepatopathy.
15. Resting central venous pressure >14 mm Hg.
16. Evidence of pulmonary hypertension with PVR >4 Woods Units (mm Hg L^{-1} min^{-1}).
17. Chronic pulmonary disease requiring home O_2, hospitalization for exacerbation within 6 months before study entry, or significant chronic pulmonary disease defined as 1st-second forced expiratory volume <1.
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 to be investigational trials.
19. Life expectancy <12 months for noncardiovascular reasons.
20. Echocardiographic evidence of intracardiac mass, thrombus, or vegetation.
21. Known or suspected allergy to nickel.
22. Fertile women.
23. Currently requiring dialysis or estimated glomerular filtration rate <25 mL/min.
24. Systolic arterial blood pressure >170 mm Hg despite appropriate medical management.
25. Subjects in whom transesophageal echocardiography is contraindicated.
26. Subjects with existing atrial septal defects. Subjects with a patent foramen ovale, who have elevated filling pressure despite the PFO are allowed.
27. Patients who have had cardiac transplantation; patients on immunosuppression or systemic steroid treatment (>10 mg/d prednisone)
28. Subjects who have diagnosed scleroderma.
29. In the opinion of the investigator, the subject is not an appropriate candidate for the study.

AS, aortic stenosis; AVA, aortic valve area.

Ethical Considerations

This trial will be conducted in accordance with national laws and The International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) guidelines for good clinical practice. All persons participating in the conduct of the trial commit themselves to consider the Declaration of Helsinki and all its revisions. The study protocols are submitted for ethical approval by the institutional Review Boards of all participating centers.

Substudies

At selected sites, subjects will have the option to undergo optional substudies at baseline and at the 6- and 12-month follow-up visits. Two optional substudies include cardiac magnetic resonance imaging (MRI) and maximal oxygen consumption (VO_2max) evaluation at baseline and follow-up as described in Supplemental Table 1 (online appendix). The substudy will include selected centers where these evaluations are part of the standard of care for patients, and subject participation at these centers will be optional.

VO_2max. Patients will have the option to undergo a VO_2max measurement at baseline and at the 6- and 12-month follow-up visits. This test may be done during the comprehensive bike or treadmill test with the use of transthoracic echocardiography, during the supine bike exercise right heart catheterization, or as a separate test. Results will be analyzed by an independent core laboratory.

Cardiac MRI. Subjects may undergo an optional cardiac MRI at baseline and at the 6- and 12-month follow-up visits. This evaluation will allow measurement of cardiac chamber dimensions, ventricular function, cardiac output, and flow pattern through the IASD. In particular, it will allow an accurate assessment of changes in these parameters after IASD placement. Results will be analyzed by an independent core laboratory.

Study Organization

The principal investigator and the Coordination Center for Clinical Trials are responsible for all aspects of the study protocol and amendments. A multispecialty external scientific advisory group provides input as required.

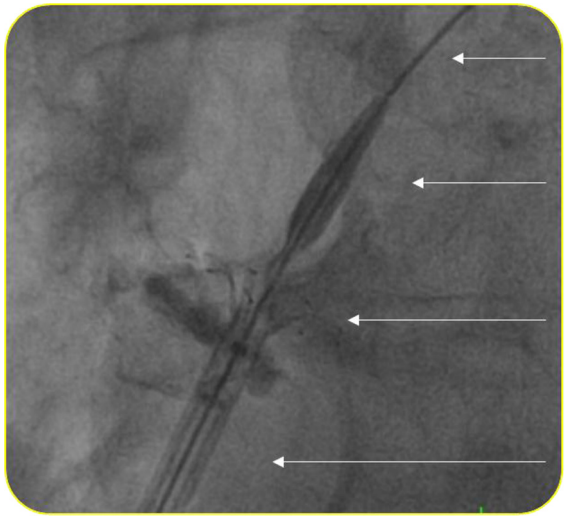

Fig. 2. Fluoroscopy of Interatrial Shunt Device (IASD) deployment immediately earlier the release of the right atrial part of the device. a: Guide wire; b: advance delivery system; c: engaged left atrial legs of the IASD against the septal wall.

An independent Data Safety Monitoring Board (DSMB) will review safety data and risks to subjects at prespecified enrollment milestones. The DSMB is charged with recommending whether the study should be stopped if the data indicate that subjects are at an unacceptable risk of harm because of their study participation.

An independent Clinical Events Committee (CEC) consisting of independent physicians not involved in the study or in the DSMB will serve as an adjudication committee to review all adverse events experienced by study subjects during this trial, and thereby provides valuable information to the sponsor and the investigators. The CEC has been established to assist the sponsor of the study (DC Devices) in the review and adjudication of adverse events that may occur over the course of the study.

End Points

To investigate the study objectives, the following primary end points were chosen:

Safety End Points

The primary safety end points are:

1. Periprocedural and 6-month MACCE.
2. Systemic embolic events (excluding pulmonary thromboembolism).

The primary safety end point is the percentage of patients who experience MACCE, defined as death, stroke, or myocardial infarction, who experience a systemic embolic event (excluding pulmonary embolism), or who require surgical implant removal within 6 months from day of implantation.

Calculation of Incidence Rates

Owing to the fact that incidence rates have been given for each event independently (Table 4), it was not possible to derive "exactly" the number of subjects who experience at least 1 of the MACCE events during the 6-month period in both cases. For that reason, we calculated the exact bilateral confidence intervals associated with all of the events that compose MACCE to define what could be an objective performance criteria (OPC) for the primary end point.

According to the studies considered, the calculated upper bounds vary approximately from 20% to 45%. However, in our calculations, we limited the upper bound for the OPC to $\leq$40% to ensure a reasonable correction.

To evaluate the power of the study for analysis testing, despite the variation of the OPC, we evaluated different scenarios for the OPC estimations, with several simulations of our possible results, with a bilateral alpha level always fixed at 5%.

Table 5, included in the protocol, is a summary of our calculations, with the use of a bilateral exact test for single proportion and Nquery Advisor software. Null and alternative hypotheses are as follows: H_0 P = OPC vs H_a P $\neq$ OPC, where P is the incidence of MACCE with IASD System II.

All of these powers are satisfactory because they are superior to 80% and because they cover a large spectrum of possible situations, with high and low OPC, and optimistic or pessimistic alternative hypotheses. The resulting sample sizes vary from n = 30 to n = 55.

Based on the available pilot study results to date, none of the current subjects included and implanted have experienced MACCE, including those with a complete 6-month follow-up. An MACCE incidence rate of $<$20% with the IASD System II can therefore be expected during this study.

Table 4. Reported MACCE Rates

Complication	Mitraclip Procedures*			Left Atrial Appendage Occlusion†		
	n/N	%	Exact 95% CI	n/N	%	Exact 95% CI
Death	0/27	0	0.0–12.8	2/75	2.7	0.3–9.3
Stroke/TIA	1/27	3.7	0.0–19.0	2/75	2.7	0.3–9.3
Myocardial infarction	0/27	0	0.0–12.7	0/75	0	0.0–4.8
Device failure or embolization	0/27	0	0.0–12.8	3/75	4.0	0.8–11.2
Surgery for implant removal or dysfunction	6/27	22.2	8.62–42.3	1/75	1.3	0.0–7.2
Total	7/27	25.9	11.1–46.3	8/75	10.7	4.7–19.9

TIA, transient ischemic attack.
*Feldman et al. J Am Coll Cardiol 2005;46:2134–40.
†Sick et al. J Am Coll Cardiol 2007;49:1490–5.

Table 5. Power Simulations

Alpha level	5%	5%	5%	5%	5%	5%	5%	5%
Null hypothesis	40%	35%	35%	35%	40%	40%	40%	25%
Alternative hypothesis	15%	15%	15%	15%	10%	20%	20%	10%
Power	84%	87%	88%	88%	97%	81%	82%	81%
N	30	45	50	55	30	50	45	55

Device Performance

The primary device performance end points are:

1. The percentage of patients who have successful device implantation, defined as deployment at the intended location during the index procedure.
2. The percentage of patients with reduction of PCWP of >3 mm Hg. Based on randomized studies with implantable hemodynamic monitors, a 3−5-mm Hg increase or decrease in PCWP (or diastolic PAP) is considered to be clinically meaningful. In the pilot study, a significant decrease was observed. A significant reduction is expected in this study as well.
3. Demonstration of left-to-right flow through the device at 6 months.

In addition, the Reduce LAP-HF trial will investigate a number of secondary end points (Table 6).

Secondary end points include evaluation of the effects of IASD System II on hemodynamic parameters, exercise parameters, quality of life, morbidity, mortality, and adverse cardiac events.

Discussion

The Reduce LAP-HF trial is the 1st study to examine the effect of directly reducing left atrial pressure in patients with HFpEF with the use of a purpose-designed medical device. The trial is based on the hypothesis that a reduction in left atrial pressure will improve symptoms in patients with this syndrome. Moreover, the reduction of left atrial pressure may be relevant to morbidity/mortality in HFpEF. Reduction of left atrial pressure will be achieved with the use of the IASD System II. Primary end points of this trial address safety and device performance, and the latter includes the percentage of patients with a reduction of PCWP and demonstration of left-to-right flow through the device at 6 months.

The rationale behind the IASD System II approach is based on existence of a gradient between the left and the right atrium during rest and more so during exercise in patients with HFpEF. The device would reduce this gradient by an atrial shunt allowing left-to-right flow. Indeed, a recent simulation study suggests that an 8-mm defect induced by the device will reduce left atrial pressure but maintains a small gradient to reduce the likelihood of right-to-left shunting which may be associated with thromboembolic events.[17] Moreover, in a previously published simulation study, it has been calculated that a defect of 8 mm will result in a Qp/Qs ratio of $\sim$1.2−1.3.[18] This degree of left-to-right shunting in the setting of an atrial septal defect (ASD) is below the recommended Qp/Qs ratio of $\leq$1.5 for shunt closure.[19] The decrease in left atrial pressure together with the left-to-right shunt will reduce left ventricular filling, and thus stroke volume may decline. According to the simulation, however, this decline will be $<10\%$ during rest.

It is important to note, in case of unexpected hemodynamic responses in some patients, that the IASD theoretically can be occluded with a commercially available ASD occluder, although this would be considered off-label use, and the long-term safety of closure of the IASD System II device is unknown.

Provided that the Reduce LAP-HF trial demonstrates its safety- and device-related primary end points, the question of whether reduction in left atrial pressure will improve symptoms in patients with HFpEF will remain open, given

Table 6. Secondary End Points

The secondary end points to be measured after implantation include the following:

1. Incidence of major adverse cardiac events through 6 months after implantation.
2. Incidence of all serious adverse events through 6 months after implantation.
3. All-cause and heart failure−related hospitalizations, and number of hospitalization days and intensive care unit days, through 6 months.
4. All-cause mortality, cardiovascular mortality, and heart failure−related mortality through 6 months.
5. Changes in invasive and noninvasive hemodynamic measures (at rest and when performed at baseline, as well as during exercise) assessed compared with baseline at 6 months by a core laboratory.
6. The percentage of patients with reduction of pulmonary capillary wedge pressure below the baseline value at rest and during exercise
7. Changes in pulmonary and systemic cardiac output and in pulmonary arterial pressures.
8. Improvements in B-type natriuretic peptide (BNP) and/or N-terminal pro-BNP assessed at 6 months compared with baseline.
9. Changes in investigatoρ assessed New York Heart Association (NYHA) functional classification assessed at 6 months compared with baseline.
10. Changes in right atrial, left atrial, left ventricular, and right ventricular dimensions, volume, and function as measured with the use of echocardiography, assessed compared with baseline at 6 months by a core laboratory.
11. Improvement in quality of life (QOL) as measured by means of Minnesota Living With Heart Failure Questionnaire assessed at 6 months compared with baseline.
12. Improvement in QOL as measured by Euroqol 5D-3L assessed at 6 months compared with baseline.
13. Incidence of cerebrovascular events through 6 months after implantation.
14. The percentage of subjects with an improvement in exercise tolerance as assessed by 6-minute walk test at 6 months compared with baseline.
15. Incidence of newly acquired atrial arrhythmia through 6 months after implantation.
16. Incidence of new onset or worsening of kidney dysfunction (defined as estimated glomerular filtration rate decrease of >20 mL/min) through 6 months after implantation.
17. Implant embolization and clinically significant device migrations, defined as device migration possibly or probably related to serious adverse event(s).

the nonrandomized nature of the study. Nevertheless, the present trial will provide much needed data, because it will examine a novel therapeutic approach for patients with HFpEF and will provide new important information regarding pathophysiologic mechanisms in HFpEF patients.

The present trial will not change guidelines, because it is not a randomized outcome trial. Nevertheless, it may set the stage for a new treatment option in HFpEF, and provide important input for future clinical studies. Moreover, it may provide new pathophysiologic insight into exercise hemodynamics in the disease, and it will answer the question if reduction of left atrial pressure is associated with improved symptoms and quality of life in patients with HFpEF.

Study Limitations

There are 3 limitations of the trial. First, it is nonrandomized, primarily owing to insufficient data to design a randomized trial. Second, it may be hard to compare results with other studies, because an EF cutoff of 40% was selected. Third, the trial allows enrollment of multiple HFpEF phenotypes.

Conclusion

Current therapeutic options in HFpEF are sparse and ineffective. The results of our IASD pilot study clearly supported further investigations of this device to improve symptoms and potentially even outcome in this underserved population. A positive result of this trial could lead to improved treatment options and may help to design future studies with the technology.

Disclosures

Dr Burkhoff is the director of the hemodynamic core laboratory; Ms Raymond is an employee of the Contract Research Organization, and Mr Komtebedde is an employee of DC Devices. Dr Shah has received consulting fees from DC Devices.

Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.cardfail.2015.05.008.

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