



# A transcatheter intracardiac shunt device for heart failure with preserved ejection fraction (REDUCE LAP-HF): a multicentre, open-label, single-arm, phase 1 trial

Gerd Hasenfuß, Chris Hayward, Dan Burkhoff, Frank E Silvestry, Scott McKenzie, Finn Gustafsson, Filip Malek, Jan Van der Heyden, Irene Lang, Mark C Petrie, John G F Cleland, Martin Leon, David M Kaye, on behalf of the REDUCE LAP-HF study investigators\*

## Summary

**Background** Heart failure with preserved ejection fraction (HFPEF) is a common, globally recognised, form of heart failure for which no treatment has yet been shown to improve symptoms or prognosis. The pathophysiology of HFPEF is complex but characterised by increased left atrial pressure, especially during exertion, which might be a key therapeutic target. The rationale for the present study was that a mechanical approach to reducing left atrial pressure might be effective in HFPEF.

**Methods** The REDUCE Elevated Left Atrial Pressure in Patients with Heart Failure (REDUCE LAP-HF) study was an open-label, single-arm, phase 1 study designed to assess the performance and safety of a transcatheter interatrial shunt device (IASD, Corvia Medical, Tewkesbury, MA, USA) in patients older than 40 years of age with symptoms of HFPEF despite pharmacological therapy, left ventricular ejection fraction higher than 40%, and a raised pulmonary capillary wedge pressure at rest (>15 mm Hg) or during exercise (>25 mm Hg). The study was done at 21 centres (all departments of cardiology in the UK, Netherlands, Belgium, France, Germany, Austria, Denmark, Australia, and New Zealand). The co-primary endpoints were the safety and performance of the IASD at 6 months, together with measures of clinical efficacy, including functional capacity and clinical status, analysed per protocol. This study is registered with ClinicalTrials.gov, number NCT01913613.

**Findings** Between Feb 8, 2014, and June 10, 2015, 68 eligible patients were entered into the study. IASD placement was successful in 64 patients and seemed to be safe and well tolerated; no patient had a peri-procedural or major adverse cardiac or cerebrovascular event or need for cardiac surgical intervention for device-related complications during 6 months of follow-up. At 6 months, 31 (52%) of 60 patients had a reduction in pulmonary capillary wedge pressure at rest, 34 (58%) of 59 had a lower pulmonary capillary wedge pressure during exertion, and 23 (39%) of 59 fulfilled both these criteria. Mean exercise pulmonary capillary wedge pressure was lower at 6 months than at baseline, both at 20 watts workload (mean 32 mm Hg [SD 8] at baseline vs 29 mm Hg [9] at 6 months,  $p=0\cdot0124$ ) and at peak exercise (34 mm Hg [8] vs 32 [8],  $p=0\cdot0255$ ), despite increased mean exercise duration (baseline vs 6 months: 7·3 min [SD 3·1] vs 8·2 min [3·4],  $p=0\cdot03$ ). Sustained device patency at 6 months was confirmed by left-to-right shunting (pulmonary/systemic flow ratio: 1·06 [SD 0·32] at baseline vs 1·27 [0·20] at 6 months,  $p=0\cdot0004$ ).

**Interpretation** Implantation of an interatrial shunt device is feasible, seems to be safe, reduces left atrial pressure during exercise, and could be a new strategy for the management of HFPEF. The effectiveness of IASD compared with existing treatment for patients with HFPEF requires validation in a randomised controlled trial.

**Funding** Corvia Medical Inc.

## Introduction

Many patients with symptoms of heart failure do not have evidence of reduced left ventricular systolic function—a syndrome that has been termed heart failure with preserved ejection fraction (HFPEF)<sup>1,2</sup> to distinguish it from those with heart failure and a reduced ejection fraction (HFREF). Epidemiological studies suggest that the incidence of HFPEF is rising worldwide,<sup>3,4</sup> although whether this increase is mainly attributable to improved recognition, an ageing population, or increases in the prevalence of comorbid diseases such as hypertension, chronic kidney disease, and diabetes, is unclear. Each of these factors probably contributes to the increase.

Although pharmacological treatment has improved symptoms and reduced morbidity and mortality for patients with HFREF, discovery of an effective treatment for patients with the disorder has proved elusive.<sup>5–10</sup> The hallmark of HFPEF is effort intolerance, which is associated with a profound and rapid increase in left atrial pressure during exercise indicating impaired left ventricular diastolic reserve,<sup>11,12</sup> with consequent pulmonary congestion. This disproportionate rise in left atrial pressure is thought to provoke symptoms and contribute to increased morbidity and mortality in HFPEF.<sup>13</sup>

In 1916, Lutembacher<sup>14</sup> described the combination of mitral stenosis, which mimics some of the pathophysiology of HFPEF, and an atrial septal defect. Patients with

Lancet 2016; 387: 1298–304

See Editorial page 1252

See Comment page 1253

\*Investigators listed in appendix

Heart Centre, Georg-August Universität, Göttingen, Germany (Prof G Hasenfuß MD); St Vincent's Hospital, Sydney, NSW, Australia (Prof C Hayward MD); Cardiology Department, Columbia University, New York, NY, USA (D Burkhoff MD); Hospital of the University of Pennsylvania, Philadelphia PA, USA (F E Silvestry MD); The Prince Charles Hospital, Brisbane, Australia (S McKenzie MD); Department of Cardiology, Rigshospitalet, Copenhagen, Denmark (F Gustafsson MD); Na Homolce Hospital, Prague, Czech Republic (F Malek MD); St Antonius Ziekenhuis, Nieuwegein, Netherlands (J Van der Heyden MD); Allgemeines Krankenhaus Universitätskliniken, Vienna, Austria (Prof I Lang MD); Golden Jubilee National Hospital, Glasgow, Scotland, UK (Prof M C Petrie MD); National Heart & Lung Institute, Royal Brompton and Harefield Hospitals, Imperial College, London, UK (Prof J G F Cleland MD); Columbia University Medical Center, New York, NY, USA (Prof M Leon MD); and Alfred Hospital and Baker IDI Heart and Diabetes Institute, Melbourne, VIC, Australia (Prof D M Kaye MD)

Correspondence to: Prof David M Kaye, Department of Cardiology, Alfred Hospital, Commercial Road, Melbourne 3004, VIC, Australia david.kaye@bakeridi.edu.au

See Online for appendix

## Research in context

### Systematic review

We did a search of publicly available sources including PubMed, learned body guidelines (including those published by the American Heart Association, American College of Cardiology, and European Society of Cardiology), and the Cochrane Library using the search terms “diastolic heart failure”, “heart failure with preserved ejection fraction”, and “clinical trials” on Dec 22, 2015. We regarded multicentre, randomised controlled trials as clinically important. We identified a series of studies that focused on the role of angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, and mineralocorticoid receptor antagonists in patients with heart failure with preserved ejection fraction (HFPEF). We also identified a large number of ongoing studies, which is consistent with the substantial unmet clinical need represented by HFPEF.

### Added value of this study

The REDUCe Elevated Left Atrial Pressure in Patients with Heart Failure (REDUCE LAP-HF) study was the first large-scale

trial designed to systematically investigate the effect of placement of an interatrial shunt device (IASD) to decompress the left atrium in patients with HFPEF. Following placement of the shunt, patients had improved quality of life, did better on the 6-min walk test, and had a reduction in exercise pulmonary capillary wedge pressure.

### Implications of all the available evidence

Previous evidence highlights the key role of raised left atrial pressure, especially during exertion, as a key pathophysiological feature in patients with HFPEF. This study reports the effect of a purpose-designed device (IASD) placed in the interatrial septum intended to reduce left atrial pressure. The demonstration of a beneficial effect of the IASD provides further support for the notion that increased left atrial pressure is the fundamental abnormality in patients with HFPEF and that a mechanical approach to reduce left atrial pressure is feasible.

Lutembacher’s syndrome might have fewer symptoms and better outcomes than those with pure mitral stenosis, and closure of their atrial septal defect can trigger a rise in pulmonary artery pressure and pulmonary oedema in some patients. An iatrogenic left-to-right atrial shunt is therefore a potentially attractive intervention that might have therapeutic value. Haemodynamic modelling based on clinical measurements suggests that an appropriately sized iatrogenic atrial septal defect could attenuate exercise-induced increases in left atrial pressure in patients with HFPEF.<sup>15</sup> We postulated that a novel device-based therapy targeting a common pathophysiological feature of HFPEF might succeed where pharmacological therapies have failed. The REDUCe Elevated Left Atrial Pressure in Patients with Heart Failure (REDUCE LAP-HF) study was designed to assess the device performance and safety of a transcatheter, transvenous interatrial shunt device in symptomatic patients with HFPEF.

## Methods

### Study design and participants

The REDUCe LAP-HF study was a multicentre, prospective, non-randomised, open-label, single-arm study designed to investigate the safety and performance of a transcatheter, transvenous interatrial shunt device (IASD system II, Corvia Medical Inc [Tewkesbury, MA, USA]; figure 1). The study design has been described in detail elsewhere.<sup>16</sup>

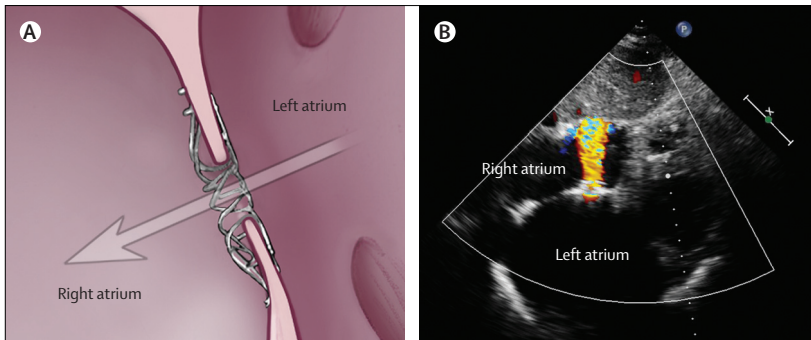
Patients with known HFPEF enrolled from hospital outpatient departments or via referring physicians were eligible for study inclusion if they were adults (aged >40 years) and had evidence of chronic symptomatic heart failure (New York Heart Association [NYHA] functional class II–IV), a left ventricular ejection fraction

higher than 40%, and an increased pulmonary capillary wedge pressure at rest (>15 mm Hg) or during exercise (>25 mm Hg) measured by right heart catheterisation. Patients with substantial right ventricular dysfunction including a central venous pressure higher than 14 mm Hg and tricuspid annular plane systolic excursion below 14 mm were excluded. Other key exclusion criteria included recent (<3 months) myocardial infarction, coronary artery bypass graft, or percutaneous coronary intervention; non-ambulatory NYHA IV heart failure; infiltrative or hypertrophic cardiomyopathy; and moderate or greater aortic stenosis or mitral regurgitation.

The study protocol was approved by the ethics committee at each institution and competent country-specific regulatory authorities. All patients gave written informed consent.

### Procedures

All enrolled patients underwent right heart catheterisation with assessment of cardiac output and central haemodynamics (right atrial pressure, pulmonary artery pressure, and pulmonary capillary wedge pressure) at rest and during supine bicycle exercise, both at baseline (during a separate screening assessment) and 6 months after device implantation. Following baseline haemodynamic measurements, symptom-limited supine bicycle exercise commenced at 20 watts (W) with 20-W increments every 3 min until the patient achieved maximum effort (as defined by symptom limiting dyspnoea or fatigue). Blood samples were collected from the pulmonary artery and vena cavae at baseline and at 6 months’ follow-up to measure oxygen saturation and to assess left-to-right shunting as indicated by the pulmonary to systemic blood flow ratio.



**Figure 1: Interatrial shunt device**  
 (A) Diagram of interatrial shunt device allowing communication between the left and right atria.  
 (B) Echocardiographic image showing Doppler colour flow from the left to right atrium.

Device insertion was done within 45 days of screening. Implantation was performed percutaneously via the femoral vein on a separate occasion to the screening.<sup>17</sup> Standard trans-septal puncture of the interatrial septum was done using the operator’s preferred technique, including fluoroscopy and transoesophageal or intra-cardiac echocardiography, and the device was positioned through the use of an over-the-wire technique. Patients not taking oral anticoagulants were treated with aspirin (75–325 mg daily) indefinitely, and clopidogrel (75 mg daily) for 6 months. Patients treated with oral anti-coagulants continued on their existing oral anticoagulants after the procedure. Endocarditis prophylaxis was advised for a minimum of 6 months post-implantation.

**Outcomes**

The primary objectives of the study were to assess device performance and safety. The primary device performance endpoints were defined as the proportion of patients with successful device implantation, the percentage of patients with a reduction in pulmonary capillary wedge pressure at 6 months either at rest or during exercise compared with baseline, and the presence of persistent left-to-right trans-device blood flow at 6 months. The primary safety endpoints were peri-procedural and 6-month major adverse cardiac and cerebrovascular events, defined as death, stroke, myocardial infarction, or a systemic embolic event (excluding pulmonary thromboembolism), or need for cardiac surgical device removal within 6 months. Echocardiograms done at the implanting site per protocol were analysed at an independent core laboratory at the University of Pennsylvania (PA, USA). Haemodynamic traces were analysed at an independent core laboratory (PVLoops LLC, NY, USA). Secondary outcomes included the incidence of major adverse events, admission to hospital for heart failure during the entire study, and changes in echocardiographic parameters, functional capacity (6-min walk test), natriuretic peptides, and quality-of-life assessments (the Minnesota Living with Heart Failure [MLWHF] questionnaire).

**Statistical analysis**

The study sample size was calculated as that needed to show a device and procedure safety profile similar to other procedures.<sup>16</sup> Normally distributed data are presented as mean (SD) and non-parametric data as median (IQR). We used a paired *t* test or Wilcoxon matched pairs sign-rank test as appropriate to compare follow-up data versus baseline data. The null hypothesis was rejected at  $p < 0.05$ .

This study is registered with ClinicalTrials.gov, number NCT01913613.

**Role of the funding source**

The study was funded by Corvia Medical Inc. Data collection and analysis was done by Medpass International Limited (Windsor House, UK). Interpretation of the results

	All patients (n=64)
Age, years	69 (8)
Sex	
Men	22
Women	42
NYHA functional class	
II	18
III	46
IV	0
Body-mass index, kg/m <sup>2</sup>	33 (6)
eGFR, mL/min per 1.73m <sup>2</sup>	62 (21)
Haemoglobin, g/L	133 (5)
Comorbidities	
Diabetes	21 (33%)
Hypertension	52 (81%)
Atrial fibrillation	23 (36%)
Coronary artery disease	23 (36%)
Echocardiography	
Left ventricular end diastolic volume index, mL/m <sup>2</sup>	68 (13)
Left ventricular ejection fraction, %	47 (7)
Left ventricular mass index, g/m <sup>2</sup>	119 (36)
Left arterial diastolic volume index, mL/m <sup>2</sup>	34 (17)
Right ventricle diastolic volume index, mL/m <sup>2</sup>	22 (9)
Right artery volume index, mL/m <sup>2</sup>	35 (17)
E/A ratio	1.3 (0.8)
E/e' ratio	13.9 (5.9)
TAPSE, mm	20 (4)
NT-proBNP, pg/mL	377 (222–925)
Resting haemodynamics	
Mean right arterial pressure, mm Hg	9 (4)
Mean pulmonary arterial pressure, mm Hg	25 (7)
Mean pulmonary capillary wedge pressure, mm Hg	17 (5)
Cardiac output, L/min	5.5 (1.6)

Data are mean (SD), n (%), or median (IQR). NYHA=New York Heart Association. eGFR=estimated glomerular filtration rate. E/A ratio=ratio of early (E) to late (A) ventricular filling velocities. E/e' ratio=ratio of mitral peak velocity of early filling (E) to early diastolic mitral annular velocity (e'). TAPSE=tricuspid annular plane systolic excursion. NT-proBNP=N-terminal pro b-type natriuretic peptide.

**Table 1: Baseline characteristics**

and preparation of the report was the responsibility of the steering committee (GH, MCP, JGFC, ML, and DMK). Corvia had no role in the collection, analysis, interpretation of data, or the decision to submit for publication. All study authors contributed to data collection and analysis, reviewed the report, read and approved the final version, and endorsed its submission for publication.

## Results

Between Feb 8, 2014, and June 10, 2015, 102 patients were enrolled from 21 centres, of whom 68 met the inclusion and exclusion criteria. The most common reasons for exclusion were failure to meet the haemodynamic inclusion criteria (pulmonary capillary wedge pressure too low in 22 patients, and central venous pressure too high in three patients). One patient was excluded for each of the following reasons: left ventricular ejection fraction below 40%, cardiac index lower than 2.0 L per min/m<sup>2</sup>, renal impairment, cerebrovascular disease, tricuspid regurgitation, mitral regurgitation, coronary disease, raised pulmonary vascular resistance, and pneumonia. Two patients withdrew after enrolment (personal preference). Of the remaining 66 patients, implantation of the IASD system was abandoned in two (in one patient because of a trans-septal puncture complication without further sequelae, and in another because of perceived unsuitable atrial septal anatomy) and was successful in 64 patients. Table 1 shows the baseline demographics of patients who received the implanted device. Consistent with the HFPEF phenotype, the mean pulmonary capillary wedge pressure increased during exercise from 17 mm Hg (SD 5) to 35 mm Hg (SD 8;  $p<0.0001$ ), the mean pulmonary pressure rose from 25 mm Hg (SD 7) to 44 mm Hg (SD 9;  $p<0.0001$ ), and the mean right atrial pressure increased from 9 mm Hg (SD 4) to 18 mm Hg (SD 5;  $p<0.0001$ ). The mean cardiac output rose from 5.6 L/min (SD 1.6) to 8.4 L/min (SD 2.7;  $p<0.0001$ ). The mean exercise time during haemodynamic testing was 7.3 min (SD 3.1) at a mean workload of 43 W (SD 18).

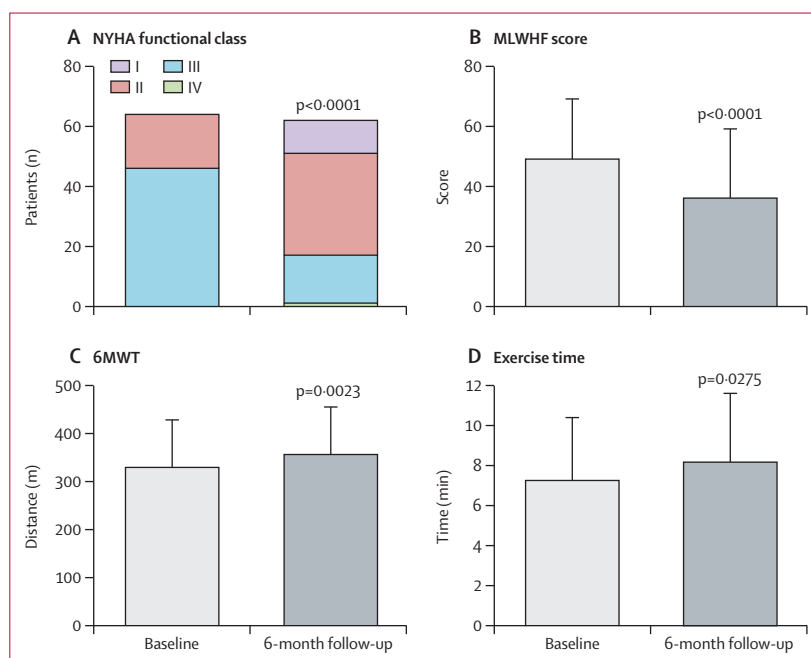
No patient had a peri-procedural or major adverse cardiac or cerebrovascular event, including death, stroke, myocardial infarction, pulmonary or systemic embolism, or need for cardiac surgical intervention for device-related complications, during 6 months of follow-up. One patient declined a final clinical follow-up because of non-cardiovascular illness.

In three patients the initial device was removed because of unsuitable position ( $n=2$ ) or a suspected small mobile thrombus in the right atrium ( $n=1$ ); however, a second device was deployed in all three patients without incident. 60 patients underwent right heart catheterisation for haemodynamic assessment at 6 months, and exercise haemodynamic responses were analysed in 59 patients. At 6 months' follow-up, 42 (71%) of 59 patients met the primary device performance endpoint definition of a reduction in pulmonary capillary wedge pressure either

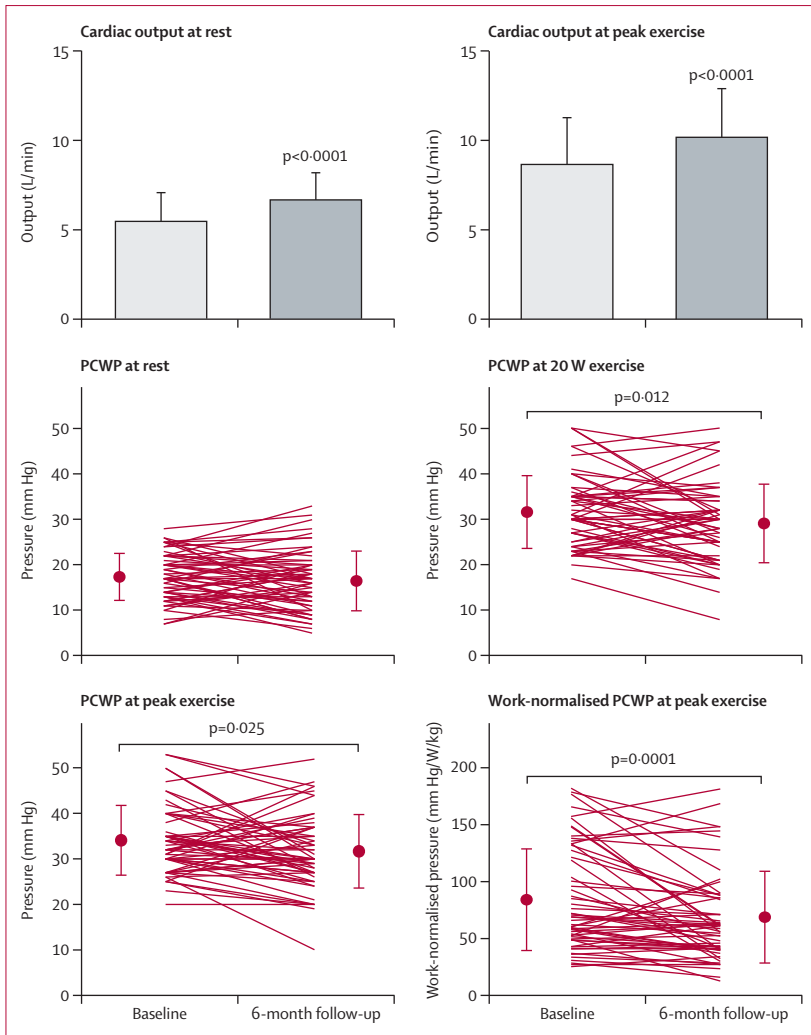
at rest or during exertion compared with their baseline values. 31 (52%) of 60 patients had a reduction in pulmonary capillary wedge pressure at rest, 34 (58%) of 59 had a lower pulmonary capillary wedge pressure during exertion, and 23 (39%) of 59 fulfilled both these criteria. All patients with adequate echocardiographic image quality ( $n=50$ ) had evidence of left-to-right flow through the device by colour flow Doppler flow at 6 months. Right-to-left flow by colour flow Doppler was not observed.

By 6 months, median NYHA functional class had improved from III (IQR II–III) to II (II–III;  $p<0.0001$ ), mean MLWHF score from 49 (SD 20) to 36 (SD 23;  $p<0.0001$ ), mean 6-min walk distance from 313 m (SD 105) to 345 m (SD 106;  $p=0.0023$ ) and supine exercise duration at the time of right heart catheterisation from 7.3 min (SD 3.1) to 8.2 min (SD 3.4;  $p=0.0275$ ) (figure 2).

At the 6-month follow-up assessment, we recorded a modest but statistically significant increase in cardiac output at rest measured by thermodilution, which is consistent with increased right-sided cardiac output due to the interatrial shunt (figure 3). Oximetry was used to estimate left ventricular forward cardiac output at rest, which showed no change from baseline to follow-up (4.6 L/min [SD 1.2] at baseline vs 4.8 L/min [1.3] at 6 months' follow-up;  $p=0.43$ ). The augmentation in thermodilution right-sided cardiac output during exercise was similar at baseline (5.5 L/min [SD 1.6] at rest vs 8.7 L/min [2.6] during exercise;  $p<0.0001$ ) and at



**Figure 2: Symptomatic and functional state at baseline and follow-up**  
(A) NYHA functional class. (B) MLWHF score. (C) 6MWT distance. (D) Exercise time during right heart catheterisation. Error bars are SDs. NYHA=New York Heart Association. MLWHF=Minnesota Living with Heart Failure. 6MWT=6-min walk test.



**Figure 3: Cardiac output and PCWP at rest and exercise at baseline and 6-month follow-up**  
PCWP normalised to workload is also presented. Error bars are SDs. PCWP=pulmonary capillary wedge pressure.

	Baseline	6-month follow-up	p value
Pulmonary vascular resistance, Wood units	1.3 (0.3)	1.1 (0.2)	0.36
Right atrial pressure, mm Hg	9 (4)	11 (5)	0.0270
Gradient between PCWP and right atrial pressure at rest, mm Hg	8 (4)	6 (4)	<0.0001
Gradient between PCWP and right atrial pressure at peak exercise, mm Hg	17 (8)	12 (6)	0.0002
Oxygen saturation, %	69 (6)	75 (5)	<0.0001
Pulmonary:systemic flow ratio	1.06 (0.32)	1.27 (0.20)	0.0004
Left ventricular diastolic volume index, mL/m <sup>2</sup>	68 (13)	62 (17)	0.0004
Right ventricular diastolic volume index, mL/m <sup>2</sup>	22 (9)	27 (11)	<0.0001
Right atrial volume index, mL/m <sup>2</sup>	35 (17)	40 (22)	0.0145
Left atrial volume index, mL/m <sup>2</sup>	34 (17)	35 (22)	0.82
Tricuspid annular plane systolic excursion, mm	20 (4)	20 (4)	0.97

Data are mean (SD). PCWP=pulmonary capillary wedge pressure.

**Table 2: Changes in cardiovascular parameters from baseline to 6 months**

6 months (6.7 L/min [SD 1.5] at rest vs 10.2 L/min [2.7] during exercise;  $p<0.0001$ ). At 6 months, the resting mean pulmonary capillary wedge pressure (17 mm Hg [SD 7]) was similar to that at baseline (17 mm Hg [5];  $p=0.24$ ), whereas exercise pulmonary capillary wedge pressure decreased at 6 months, both at 20 W workload (32 mm Hg [SD 8] at baseline vs 29 mm Hg [9] at 6 months,  $p=0.0124$ ) and at peak exercise (34 mm Hg [SD 8] vs 32 mm Hg [8],  $p=0.0255$ ; figure 3). At peak exertion, pulmonary capillary wedge pressure normalised for workload was lower at follow-up (69 mm Hg/W/kg [SD 40]) than at baseline (84 mm Hg/W/kg [45];  $p=0.0001$ ). Pulmonary vascular resistance did not change between baseline and 6 months (table 2). Right atrial pressure was higher at follow-up than at baseline. The gradient between pulmonary capillary wedge pressure and right atrial pressure decreased from baseline to 6 months' follow-up, both at rest and at peak exercise (table 2). Consistent with the echocardiographic assessment of device patency, measurement of oxygen saturation during cardiac catheterisation confirmed a rise in pulmonary arterial oxygen saturation, with a left-to-right shunt (as shown by an increase in pulmonary/systemic flow from baseline to 6 months; table 2).

Echocardiographic assessment showed small changes in chamber volumes at follow-up compared with baseline (table 2). The mean left ventricular diastolic volume index decreased from baseline to 6 months, whereas the right ventricular end-diastolic volume index increased. The right atrial volume index increased from baseline to 6-month follow-up, whereas the left atrial volume index was unchanged. Tricuspid annular plane systolic excursion was also unchanged from baseline to follow-up (table 2).

Compared with baseline, a small reduction in mean bodyweight was recorded at 6 months (from 90.1 kg [SD 18.3] at baseline to 88.4 kg [18.6] at 6 months;  $p=0.008$ ). Neither N-terminal pro b-type natriuretic peptide level (median 377 pg/mL [IQR 222–925] at baseline vs 382 pg/mL [170–1075] at 6 months) nor mean estimated glomerular filtration rate (62 mL/min/m<sup>2</sup> [SD 21] at baseline vs 61 mL/min/m<sup>2</sup> [20] at 6 months) changed during the study. In the 6 months before trial participation, 13 (20%) of 64 of patients had to be admitted to hospital for heart failure, compared with nine (14%) of 63 in the 6 months following enrolment. The median dose of orally administered furosemide at baseline was 40 mg per day (IQR 0–80). At 6 months, the median dose was 40 mg per day (IQR 0–110); however, this difference between baseline and 6 months was significant (according to paired sign-rank test,  $p=0.0176$ ). The median difference in furosemide dose between 6 months and baseline was 0 mg (IQR 0–15 mg/day), and only eleven patients had an increase in their diuretic dose. Because the difference was small, a change in dose was unlikely to have accounted for the recorded effects.

## Discussion

In this open-label study of a novel transcatheter interatrial shunt device, which was developed for the management of patients with HFPEF, we recorded reductions in left atrial pressure during exercise with improvements in functional capacity and quality of life 6 months after implantation. The procedure was well tolerated, and echocardiographic and oximetric studies showed the presence of continuing device patency and left-to-right shunting at 6 months.

HFPEF is characterised by complex cardiovascular pathophysiology. Originally, attention focused on the role of diastolic dysfunction<sup>11,12</sup> as a cause of a rapid rise in left ventricular diastolic and left atrial pressure during exertion. The underlying myocardial biology of HFPEF is controversial. It has been ascribed to myocardial fibrosis,<sup>18</sup> myocyte hypertrophy, and changed post-translation modification of myocardial proteins such as titin.<sup>19,20</sup> Many other factors contribute to the clinical profile of patients with HFPEF, including hypertension,<sup>4,6</sup> myocardial and systemic microvascular dysfunction,<sup>21,22</sup> and left ventricular long-axis systolic dysfunction,<sup>23</sup> in addition to extra-cardiac comorbidities such as renal insufficiency,<sup>24</sup> anaemia, obesity, and sleep apnoea.<sup>25</sup>

So far, pharmacological management of HFPEF has not reduced morbidity and mortality. Even the effect of pharmacological therapy on symptoms or exercise capacity is uncertain. Therapeutic failure could be attributable to both diagnostic uncertainty and the complexity of the disorder. The identification of a homogeneous patient population with HFPEF has also been challenging.<sup>26</sup> In the present study, we used invasive haemodynamic assessment both at rest and during exertion to reliably identify patients with objective evidence of impaired diastolic reserve. The use of exercise pulmonary capillary wedge pressure as a study endpoint has only been reported once previously to assess the effectiveness of an intervention in patients with HFPEF,<sup>27</sup> although this approach is clearly relevant in view of the dynamic nature of the physiological abnormality in this disorder.<sup>11,12</sup>

This study was an open-label non-randomised trial, so we are unable to exclude a placebo effect. However, reduction in exercise pulmonary capillary wedge pressure is consistent with atrial decompression and the reduction in left ventricular end-diastolic volume consistent with left ventricular decompression. Peak exercise pulmonary capillary wedge pressure was reduced after shunt implantation, despite an increase in exercise capacity; accordingly, pulmonary capillary wedge pressure normalised to workload—a measurement that has predicted mortality in patients with HFPEF<sup>13</sup>—was reduced. Left atrial decompression should lead to a reduction in left atrial volumes but this effect might have been attenuated by the increased venous return to the left atrium as a consequence of the shunt flow. Alternatively, the observation period might

have been too short or a larger sample size might be needed to detect changes, especially in the setting of chronic atrial remodelling and atrial fibrillation. Small increases in right atrial pressure and volume and right ventricular volume were recorded, which could represent the effect of shunting itself or an increase in circulating volume. The latter possibility is unlikely because bodyweight fell during the study period. A modest increase in right-sided cardiac output consistent with volume loading was recorded, whereas left-sided output, as measured from oximetric observations, was unchanged. The long-term sequelae of modest increases in right ventricular output are not known and therefore we excluded patients with substantial right ventricular dysfunction.

Existing guidelines for the diagnosis of HFPEF include evidence of raised levels of natriuretic peptides and echocardiographic measures of increased filling pressures, as indicated by the mitral peak velocity of early filling (E) to early diastolic mitral annular velocity (e') ratio.<sup>28</sup> In this study, device implantation was not accompanied by a decrease in either of these non-invasive measurements. This finding could be explained by the fact that these measures were taken at rest or by the quite modest overall reduction in filling pressures.

Overall, the results of this open-label non-randomised study show that transcatheter transvenous placement of an interatrial shunt device is feasible and might be associated with improvements in exercise haemodynamics, functional capacity, and quality of life. These findings require validation in a randomised controlled masked trial.

### Contributors

GH, DB, FES, JGFC, MCP, ML, and DMK contributed to the analysis of data and preparation of the report. CH, SM, FG, JvdH, FM, DMK, and IL contributed to data collection. All authors read and approved the submission of the final draft of the report.

### Declaration of interests

We declare no competing interests.

### References

- Vasan RS, Larson MG, Benjamin EJ, Evans JC, Reiss CK, Levy D. Congestive heart failure in subjects with normal versus reduced left ventricular ejection fraction: prevalence and mortality in a population-based cohort. *J Am Coll Cardiol* 1999; **33**: 1948–55.
- Yancy CW, Lopatin M, Stevenson LW, De Marco T, Fonarow GC. Clinical presentation, management, and in-hospital outcomes of patients admitted with acute decompensated heart failure with preserved systolic function: a report from the Acute Decompensated Heart Failure National Registry (ADHERE) database. *J Am Coll Cardiol* 2006; **47**: 76–84.
- Steinberg BA, Zhao X, Heidenreich PA, et al. Trends in patients hospitalized with heart failure and preserved left ventricular ejection fraction: prevalence, therapies, and outcomes. *Circulation* 2012; **126**: 65–75.
- 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**: 251–59.
- Massie BM, Carson PE, McMurray JJ, et al. Irbesartan in patients with heart failure and preserved ejection fraction. *N Engl J Med* 2008; **359**: 2456–67.
- Cleland JGF, Tendera M, Adamus J, Freemantle N, Polonski L, Taylor J. The perindopril in elderly people with chronic heart failure (PEP-CHF) study. *Eur Heart J* 2006; **27**: 2338–45.

- 7 Yusuf S, Pfeffer MA, Swedberg K, et al. Effects of candesartan in patients with chronic heart failure and preserved left-ventricular ejection fraction: the CHARM-Preserved trial. *Lancet* 2003; **362**: 777–81.
- 8 Pitt B, Pfeffer MA, Assmann SF, et al. Spironolactone for heart failure with preserved ejection fraction. *N Engl J Med* 2014; **370**: 1383–92.
- 9 Redfield MM, Chen HH, Borlaug BA, et al. Effect of phosphodiesterase-5 inhibition on exercise capacity and clinical status in heart failure with preserved ejection fraction: a randomized clinical trial. *JAMA* 2013; **309**: 1268–77.
- 10 Redfield MM, Anstrom KJ, Levine JA, et al. Isosorbide mononitrate in heart failure with preserved ejection fraction. *N Engl J Med* 2015; **373**: 2314–24.
- 11 Maeder MT, Thompson BR, Brunner-La Rocca HP, Kaye DM. Hemodynamic basis of exercise limitation in patients with heart failure and normal ejection fraction. *J Am Coll Cardiol* 2010; **56**: 855–63.
- 12 Borlaug BA, Nishimura RA, Sorajja P, Lam CSP, Redfield MM. Exercise hemodynamics enhance diagnosis of early heart failure with preserved ejection fraction. *Circ Heart Fail* 2010; **3**: 588–95.
- 13 Dorfs S, Zeh W, Hochholzer W, et al. 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**: 3103–12.
- 14 Lutembacher R. De la sténose mitrale avec communication interauriculaire. *Arch Mal Coeur* 1916; **9**: 237–60 (in French).
- 15 Kaye D, Shah SJ, Borlaug BA, et al. 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.
- 16 Hasenfuss G, Gustafsson F, Kaye D, et al. 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.
- 17 Sondergaard L, Reddy V, Kaye D, et al. 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.
- 18 van Heerebeek L, Borbely A, Niessen HW, et al. Myocardial structure and function differ in systolic and diastolic heart failure. *Circulation* 2006; **113**: 1966–73.
- 19 Hamdani N, Franssen C, Lourenço A, et al. Myocardial titin hypophosphorylation importantly contributes to heart failure with preserved ejection fraction in a rat metabolic risk model. *Circ Heart Fail* 2013; **6**: 1239–49.
- 20 Kruger M, Kotter S, Grutzner A, et al. Protein kinase G modulates human myocardial passive stiffness by phosphorylation of the titin springs. *Circ Res* 2009; **104**: 87–94.
- 21 Borlaug BA, Melenovsky V, Russell SD, et al. Impaired chronotropic and vasodilator reserves limit exercise capacity in patients with heart failure and a preserved ejection fraction. *Circulation* 2006; **114**: 2138–47.
- 22 Poole DC, Hirai DM, Copp SW, Musch TI. Muscle oxygen transport and utilization in heart failure: implications for exercise (IN) tolerance. *Am J Physiol Heart Circ Physiol* 2012; **302**: H1050–63.
- 23 Tan YT, Wenzelburger F, Lee E, et al. The pathophysiology of heart failure with normal ejection fraction: exercise echocardiography reveals complex abnormalities of both systolic and diastolic ventricular function involving torsion, untwist, and longitudinal motion. *J Am Coll Cardiol* 2009; **54**: 36–46.
- 24 Gori M, Senni M, Gupta DK, et al. Association between renal function and cardiovascular structure and function in heart failure with preserved ejection fraction. *Eur Heart J* 2014; **35**: 3442–51.
- 25 Ather S, Chan W, Bozkurt B, et al. Impact of noncardiac comorbidities on morbidity and mortality in a predominantly male population with heart failure and preserved versus reduced ejection fraction. *J Am Coll Cardiol* 2012; **59**: 998–1005.
- 26 Butler J, Fonarow GC, Zile MR, et al. Developing therapies for heart failure with preserved ejection fraction: current state and future directions. *JACC Heart Failure* 2014; **2**: 97–112.
- 27 Borlaug BA, Koepp KE, Melenovsky V. Sodium nitrite improves exercise hemodynamics and ventricular performance in heart failure with preserved ejection fraction. *J Am Coll Cardiol* 2015; **66**: 1672–82.
- 28 Paulus WJ, Tschope C, Sanderson JE, et al. How to diagnose diastolic heart failure: a consensus statement on the diagnosis of heart failure with normal left ventricular ejection fraction by the Heart Failure and Echocardiography Associations of the European Society of Cardiology. *Eur Heart J* 2007; **28**: 2539–50.