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REDUCE LAP-HF II Investigators; Shah, Sanjiv J.; Borlaug, Barry A.; Chung, Eugene S.; Cutlip, Donald E.; Debonnaire, Philippe; Fail, Peter S.; Gao, Qi; Hasenfuss, Gerd; Kahwash, Rami

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Atrial shunt device for heart failure with preserved and mildly reduced ejection fraction (REDUCE LAP-HF II): a randomised, multicentre, blinded, sham-controlled trial

*Sanjiv J Shah, Barry A Borlaug, Eugene S Chung, Donald E Cutlip, Philippe Debonnaire, Peter S Fail, Qi Gao, Gerd Hasenfuß, Rami Kahwash, David M Kaye, Sheldon E Litwin, Philipp Lurz, Joseph M Massaro, Rajeev C Mohan, Mark J Ricciardi, Scott D Solomon, Aaron L Sverdlov, Vijendra Swarup, Dirk J van Veldhuisen, Sebastian Winkler, Martin B Leon, on behalf of the REDUCE LAP-HF II investigators**

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See Comment page 1094

*Investigators are listed in the appendix (pp 4–18)

Northwestern University Feinberg School of Medicine, Chicago, IL, USA (Prof S J Shah MD); **Mayo Clinic, Rochester, MN, USA** (Prof B A Borlaug MD); **The Lindner Research Center at The Christ Hospital, Cincinnati, OH, USA** (E S Chung MD); **Baim Clinical Research Institute, Boston, MA, USA** (Prof D E Cutlip MD, Q Gao MS); **AZ Sint-Jan Brugge-Oostende, Bruges, Belgium** (P Debonnaire PhD); **Cardiovascular Institute of the South, Houma, LA, USA** (P S Fail MD); **Heart Center, University Medical Center, Göttingen, Germany** (Prof G Hasenfuß MD); **Ohio State University, Columbus, OH, USA** (Prof R Kahwash MD); **Alfred Hospital, Melbourne, VIC, Australia** (Prof D M Kaye PhD); **Medical University of South Carolina and Ralph H Johnson Veterans Affairs Medical Center, Charleston, SC, USA** (Prof S E Litwin MD); **Heart Center Leipzig at University Leipzig, Leipzig, Germany** (Prof P Lurz PhD); **Boston University, Boston, MA, USA** (Prof J M Massaro PhD); **Scripps Health, La Jolla, CA, USA** (R C Mohan MD); **Northshore University Health System, Evanston, IL, USA** (Prof M J Ricciardi MD); **Brigham and Women's Hospital, Boston, MA, USA** (Prof S D Solomon MD); **John Hunter Hospital, University of Newcastle, New Lambton**

Summary

Background Placement of an interatrial shunt device reduces pulmonary capillary wedge pressure during exercise in patients with heart failure and preserved or mildly reduced ejection fraction. We aimed to investigate whether an interatrial shunt can reduce heart failure events or improve health status in these patients.

Methods In this randomised, international, blinded, sham-controlled trial performed at 89 health-care centres, we included patients (aged ≥40 years) with symptomatic heart failure, an ejection fraction of at least 40%, and pulmonary capillary wedge pressure during exercise of at least 25 mm Hg while exceeding right atrial pressure by at least 5 mm Hg. Patients were randomly assigned (1:1) to receive either a shunt device or sham procedure. Patients and outcome assessors were masked to randomisation. The primary endpoint was a hierarchical composite of cardiovascular death or non-fatal ischemic stroke at 12 months, rate of total heart failure events up to 24 months, and change in Kansas City Cardiomyopathy Questionnaire overall summary score at 12 months. Pre-specified subgroup analyses were conducted for the heart failure event endpoint. Analysis of the primary endpoint, all other efficacy endpoints, and safety endpoints was conducted in the modified intention-to-treat population, defined as all patients randomly allocated to receive treatment, excluding those found to be ineligible after randomisation and therefore not treated. This study is registered with ClinicalTrials.gov, NCT03088033.

Findings Between May 25, 2017, and July 24, 2020, 1072 participants were enrolled, of whom 626 were randomly assigned to either the atrial shunt device (n=314) or sham procedure (n=312). There were no differences between groups in the primary composite endpoint (win ratio 1·0 [95% CI 0·8–1·2]; p=0·85) or in the individual components of the primary endpoint. The prespecified subgroups demonstrating a differential effect of atrial shunt device treatment on heart failure events were pulmonary artery systolic pressure at 20W of exercise ($p_{interaction}$=0·002 [>70 mm Hg associated with worse outcomes]), right atrial volume index ($p_{interaction}$=0·012 [≥29·7 mL/m², worse outcomes]), and sex ($p_{interaction}$=0·02 [men, worse outcomes]). There were no differences in the composite safety endpoint between the two groups (n=116 [38%] for shunt device *vs* n=97 [31%] for sham procedure; p=0·11).

Interpretation Placement of an atrial shunt device did not reduce the total rate of heart failure events or improve health status in the overall population of patients with heart failure and ejection fraction of greater than or equal to 40%.

Funding Corvia Medical.

Introduction

Dyspnoea due to left atrial pressure overload during exercise is a hallmark of heart failure with preserved or mildly reduced ejection fraction.[1] The potential therapeutic benefit of an iatrogenic interatrial shunt in heart failure is based on the observation that the presence of a congenital secundum atrial septal defect in patients with mitral stenosis (Lutembacher syndrome[2]) appeared to be beneficial due to the ability to decompress the pressure-overloaded left atrium by shunting blood to the lower pressure reservoir of the right atrium and systemic veins. Multiple devices and procedures to accomplish this are in various stages of development in patients with heart failure.[3–10]

A multicentre, open-label study of the Corvia atrial shunt system (IASD System II; n=64) found that the device was safe and associated with improved invasive exercise haemodynamics, health status, exercise capacity, and outcomes in patients with heart failure, an ejection fraction of at least 40%, and elevated pulmonary capillary wedge pressure (PCWP) during exercise.[6,11] Patients were also required to have no evidence of significant pulmonary vascular disease at rest, right-sided heart failure, or moderate or greater tricuspid regurgitation, because each of these would be associated with the potential for inadequate left-to-right interatrial shunting or right-to-left shunting, both of which could worsen symptoms and

Research in context

Evidence before this study

We searched PubMed for papers published between Jan 1, 2015, and Nov 20, 2021, using the search terms "heart failure", "shunt device", "randomised", and "sham", and various combinations of these words with no language restrictions. We aimed to identify randomised clinical trials of interatrial shunt devices and procedures to decompress the left atrium in patients with heart failure. We identified only one previous randomised trial of an interatrial shunt therapy (the Corvia Atrial Shunt Device) in 44 patients with heart failure (REDUCE LAP-HF I; all with ejection fraction ≥40%), which showed a reduction in exercise pulmonary capillary wedge pressure at 1 month (p=0·028) and numerically lower rate of heart failure-related admissions to hospital at 1 year (0·22 *vs* 0·63 in the sham procedure group, p=0·06), but no effect was seen on health status or exercise capacity.

Added value of this study

REDUCE LAP-HF II was an adequately powered, phase 3 pivotal trial of the Corvia Atrial Shunt in patients with heart failure and ejection fraction of at least 40%. It showed no difference between the active treatment and control groups for the hierarchical composite endpoint of cardiovascular death, non-fatal ischaemic stroke, first and recurrent heart failure events, and health status (Kansas City Cardiomyopathy Questionnaire). In prespecified subgroup analyses, individuals with the following had more frequent heart failure events when treated with the atrial shunt device: pulmonary artery systolic pressure greater than 70 mm Hg at 20W bicycle exercise, right atrial volume index greater than 29·7 mL/m², and male sex.

Implications of all the available evidence

REDUCE LAP-HF II is the first phase 3, randomised clinical trial to evaluate an interatrial shunt device in patients with heart failure, with the goal of evaluating the efficacy of shunt-induced lowering of left atrial pressure on cardiovascular death, total heart failure events, and patient-reported outcomes. Despite the reduction of exercise pulmonary capillary wedge pressure in the previously completed REDUCE LAP-HF I trial, there was no improvement in clinical outcomes in this study after atrial shunt device placement compared with sham procedure. However, prespecified analyses showed divergent results in select subgroups.

Heights, NSW, Australia (A L Sverdlov PhD); **Arizona Heart and Rhythm Center, Phoenix, AZ, USA** (V Swarup MD); **University of Groningen, University Medical Center Groningen, Groningen, Netherlands** (Prof D J van Veldhuisen MD); **BG Klinikum Unfallkrankenhaus, Berlin, Germany** (S Winkler MD); **Cardiovascular Research Foundation, New York City, NY, USA** (Prof M B Leon MD)

Correspondence to:
Prof Sanjiv J Shah, Division of Cardiology, Department of Medicine, Northwestern University Feinberg School of Medicine, Chicago, IL 60611, USA
sanjiv.shah@northwestern.edu

See Online for appendix

outcomes.[5,8] Subsequently, a multicentre, phase 2 randomised, sham-controlled trial of the Corvia atrial shunt in patients with heart failure and an ejection fraction of at least 40% (REDUCE LAP-HF I; n=44) showed that the shunt reduced PCWP during exercise at 1 month (p=0·028)[7] and led to a numerically lower rate of heart failure events at 1 year (0·22 *vs* 0·63 in the sham procedure group, p=0·06),[12] but had no statistically significant effect on health status or exercise capacity.

Here, we report the primary efficacy and safety results of the Corvia atrial shunt in patients with heart failure and preserved or mildly reduced ejection fraction enrolled in a phase 3, randomised, double-blind, sham-controlled trial (REDUCE LAP-HF II), designed to determine whether an interatrial shunt would improve outcomes and quality of life.

Methods

Study design and participants

This randomised, international, multicentre, double-blind, sham-controlled REDUCE LAP-HF II trial was conducted in 89 centres in the USA, Canada, Europe, Australia, and Japan (appendix pp 4), and the protocol has been described previously.[8] Eligible participants were aged at least 40 years with symptomatic heart failure and an ejection fraction of at least 40%, and evidence of PCWP during exercise of at least 25 mm Hg while exceeding right atrial pressure by at least 5 mm Hg. Major exclusion criteria included stage D heart failure, cardiac index less than 2·0 L/min/m², previous documented ejection fraction of less than 30%, history of stroke, transient ischaemic attack, deep vein thrombosis, or pulmonary embolism within the past 6 months; haemodynamically significant valve disease (including moderate or greater tricuspid regurgitation); hypertrophic, restrictive, or infiltrative cardiomyopathy; constrictive pericarditis; greater than mild right ventricular dysfunction; resting right atrial pressure more than 14 mm Hg; pulmonary vascular resistance (PVR) of more than 3·5 Wood units; severe obstructive sleep apnoea, chronic pulmonary disease requiring oxygen; body-mass index of more than 45 kg/m²; or an estimated glomerular filtration rate of less than 25 mL/min per 1·73 m². Full inclusion and exclusion criteria are listed in the appendix (pp 26–29).

All participants provided written informed consent before enrolment. The study was approved by local ethics committees or institutional review boards.

Randomisation and masking

Eligible participants were randomly assigned (1:1) to receive the shunt device or a sham procedure. The randomisation sequence was computer-generated and stratified by age (<75 *vs* ≥75 years), geography (within the USA *vs* outside the USA), and the presence or absence of heart failure-related admission to hospital or urgent treatment with intravenous diuretics in a health-care facility in the past 12 months. To maintain masking, participants were sedated and wore headphones during the procedures, and each enrolling centre included masked investigators and study personnel. Patients and masked clinicians involved in follow-up care completed a masking questionnaire at discharge after the index procedure (randomisation) and at follow-up visits. Patients and clinicians involved in follow-up care were unaware of treatment allocation for 24 months after random treatment assignment.

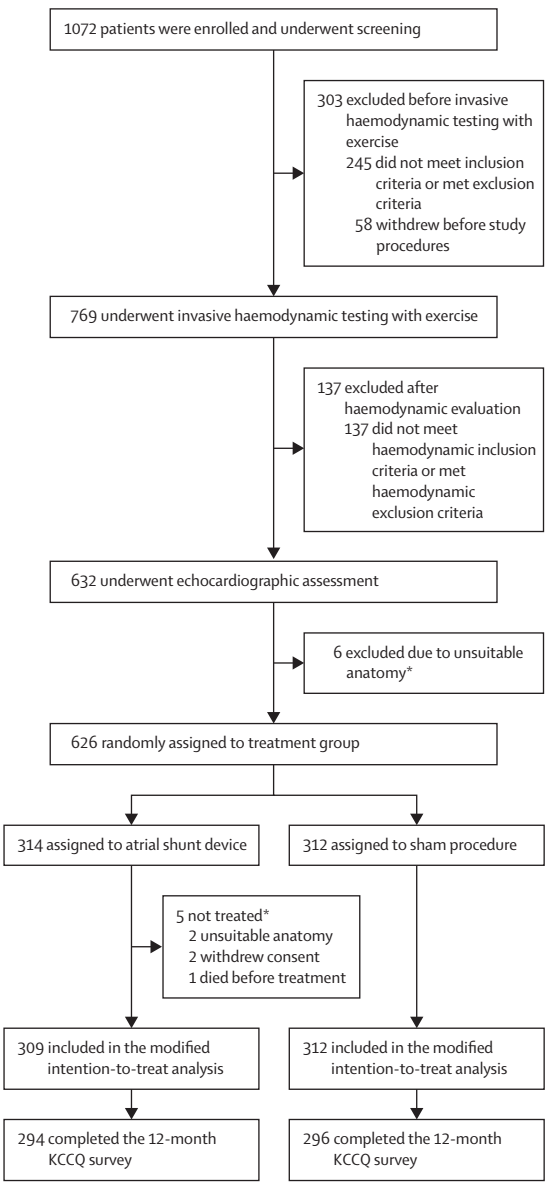

Figure 1: **Trial profile**
KCCQ=Kansas City Cardiomyopathy Questionnaire. *Patients could be excluded from treatment with the atrial shunt device before or after randomisation on the basis of interatrial imaging by echocardiography (either intracardiac echocardiography or transoesophageal echocardiography). Reasons for screen failures are listed in the appendix (p 35).

Procedures

All patients underwent echocardiography and invasive exercise haemodynamic testing before randomisation to confirm they had an ejection fraction of at least 40%, the diagnosis of heart failure (peak exercise PCWP of at least 25 mm Hg), and absence of clinically significant right ventricular dysfunction or pulmonary vascular disease, as described previously.[8] Echocardiograms and invasive haemodynamic pressure tracings were interpreted by independent core laboratories. The InterAtrial Shunt Device System II (Corvia Medical, Tewksbury, MA, USA) was used for placement of the atrial shunt device, as previously reported.[5,8] Briefly, patients randomly allocated to the atrial shunt device underwent imaging of the interatrial septum (via intracardiac echocardiography or transoesophageal echocardiography), followed by placement of the atrial shunt device (self-expanding nitinol cage with double-disk design, with 8-mm diameter opening in its centre; appendix p 45) in the interatrial septum under fluoroscopic guidance via the femoral vein. Patients randomly assigned to the sham control group also underwent femoral venous puncture with sheath placement and imaging of the interatrial septum. Follow-up visits were done at 1, 3, 6, 12, and 24 months, and annually for 5 years. Follow-up procedures consisted of assessment of adverse events, health status (Kansas City Cardiomyopathy Questionnaire [KCCQ][13,14]), New York Heart Association (NYHA) functional class, and echocardiographic evaluations.

Outcomes

The primary efficacy endpoint was a hierarchical composite of cardiovascular death or non-fatal ischaemic stroke up to 12 months post-randomisation; rate of total (first plus recurrent) heart failure events (defined as admissions to hospital or urgent visits to a health-care facility for intravenous diuresis, or intensification of oral diuretics) up to 24 months post-randomisation, analysed when the last randomised patient completed 12 months of follow-up; and change in KCCQ overall summary score between baseline and 12 months. Secondary efficacy endpoints included rate of total (first and recurrent) heart failure events up to 24 months post-randomisation, analysed when the last randomised patient completed 12 months of follow-up; change in NYHA functional class (assessed by a physician unaware of treatment allocation) between baseline and 12 months; and change in KCCQ score between baseline and 12 months.

The prespecified safety endpoint was a composite of (1) cardiovascular death; (2) non-fatal ischaemic stroke; (3) new-onset or worsening kidney dysfunction (defined as an estimated glomerular filtration rate decrease of >20 mL/min per 1·73 m^2); (4) major adverse cardiac events, defined as cardiac death, myocardial infarction, cardiac tamponade, or emergency cardiac surgery; (5) thromboembolic complications (transient ischaemic attack, systemic embolisation); (6) newly acquired persistent or permanent atrial fibrillation or atrial flutter; and (7) at least a 30% increase in right ventricular size or at least a 30% decrease in tricuspid annular plane systolic excursion between baseline and 12 months post-randomisation. All safety endpoint data were measured up to 12 months post-randomisation. All events were adjudicated by a blinded clinical events committee.

Statistical analysis

Sample sizes were calculated based on data from the REDUCE LAP-HF I trial, as described previously.[8] Assuming a combined cardiovascular mortality and nonfatal ischaemic stroke rate of 5·0% in each treatment group at 12 months; a per person-year rate of heart failure events of 0·39 in the shunt device group and 0·5 in the control group; and a mean improvement in KCCQ overall summary score of 13 in the shunt device group and eight in the control group, with an standard deviation of 20 in each treatment group, we calculated that 282 evaluable patients per treatment group would be required for 85% power to demonstrate a significant beneficial effect of the atrial shunt device over sham procedure at a 2-sided 0·05 level of significance using a Finkelstein-Schoenfeld approach.[15] We assumed a premature withdrawal rate of no more than 7·5% before 12 months, resulting in a requirement to enrol at least 304 randomised patients per treatment group.

Analysis of the primary endpoint, all other efficacy endpoints, and safety endpoints was conducted in the modified intention-to-treat (mITT) population, defined as all patients randomly allocated to receive treatment, excluding those found to be ineligible after randomisation. In the mITT analysis, patients with missing information on cardiovascular death, non-fatal ischaemic stroke, heart failure events, or KCCQ before the 12-month time point, primarily due to premature withdrawal from the study, were analysed using available data. We also conducted an analysis of the per-protocol population, defined as patients who were evaluable at 12 months without major protocol violations (appendix p 32) and who were allocated to the shunt device and had an implant or were allocated to sham control and underwent the complete control procedure.

Descriptive statistics of continuous variables were reported as median and IQRs. Treatment differences between groups with respect to the primary endpoint were calculated using the Finkelstein-Schoenfeld approach (appendix p 30).[8] To calculate the Finkelstein-Schoenfeld test statistic, patients are compared with each other in a pairwise manner on the values of the components, in a hierarchical manner, and the Finkelstein-Schoenfeld statistic is an assessment of whether either treatment group has more favourable values of the endpoint components than the other treatment group. The Finkelstein-Schoenfeld method, therefore, provides the ability to combine binary (cardiovascular death or non-fatal ischaemic stroke), recurrent (heart failure events), and continuous (KCCQ) outcomes, as was done here. The null hypothesis was tested at a two-sided 0·05 level of significance.

In addition to the Finkelstein-Schoenfeld p value, two effect sizes were also calculated: the win ratio[16] and the probability that the patients randomly allocated to shunt device treatment have a more favourable distribution of the three primary endpoint components

	Atrial shunt device (n=314)	Sham procedure (n=312)
Demographics		
Median age (IQR), years	73·0 (67·0–77·0)	72·0 (65·0–77·0)
Sex		
Female	64% (200/314)	59% (185/312)
Male	36% (114/314)	41% (127/312)
Race*		
Asian	2% (5/202)	3% (5/198)
Black or African American	6% (13/202)	6% (11/198)
White	90% (181/202)	91% (180/198)
Other	1% (3/202)	1% (2/198)
Hispanic or Latino	3% (5/183)	2% (3/187)
Median body-mass index, kg/m² (IQR)	31·6 (27·5–37·4)	32·2 (28·1–36·8)
Median heart rate, beats per min (IQR)	70·0 (62·0–77·0)	70·0 (62·0–80·0)
Median systolic blood pressure, mm Hg (IQR)	126·5 (116·0–140·0)	127·0 (115·0–139·5)
Comorbidities		
Smoking status		
Current smoker	3% (10/313)	3% (10/312)
Former smoker	42% (131/313)	49% (152/312)
Never smoked	55% (172/313)	48% (150/312)
Hypertension	89% (281/314)	87% (270/310)
Hyperlipidaemia	70% (217/311)	68% (211/311)
Diabetes	37% (115/314)	37% (115/312)
Chronic obstructive pulmonary disease	23% (72/314)	17% (54/311)
Migraines	9% (29/311)	7% (22/308)
Cardiovascular history		
Ischaemic heart disease	13% (41/311)	19% (59/310)
Myocardial infarction	15% (46/312)	12% (37/310)
Prior percutaneous coronary intervention	26% (82/311)	28% (87/310)
Permanent pacemaker	22% (70/314)	17% (53/312)
Atrial fibrillation	50% (158/314)	53% (166/312)
Atrial flutter	11% (33/311)	10% (32/310)
Stroke	7% (23/314)	8% (26/312)
Transient ischaemic attack	9% (28/313)	7% (21/311)
Peripheral vascular disease	12% (36/313)	8% (25/311)
Pulmonary embolism	5% (15/314)	5% (17/311)
Deep vein thrombosis	8% (24/314)	5% (15/310)
Cardiac status		
New York Heart Association classification		
I	0/314	0/312
II	21% (67/314)	21% (65/312)
III	77% (242/314)	78% (242/312)
IV	2% (5/314)	2% (5/312)
Median left ventricular ejection fraction (site-reported), % (IQR)	60·0% (55·0–65·0)	60·0% (55·0–65·0)
Median H2FPEF score (IQR)	6·0 (4·0–7·0)	6·0 (4·0–7·0)
Medications		
Number of diuretics the patient was taking at baseline		
0	1% (3/314)	1% (3/310)
1	50% (158/314)	51% (158/310)
2	42% (131/314)	42% (131/310)
>2	7% (22/314)	6% (18/310)
Loop diuretics	83% (261/314)	81% (253/312)

(Table 1 continues on next page)

	Atrial shunt device (n=314)	Sham procedure (n=312)
(Continued from previous page)		
Thiazides only	4% (13/314)	4% (14/312)
Loop diuretics and thiazides	8% (24/314)	4% (12/312)
Median daily furosemide equivalent dose for patients on loop diuretics, mg/day (IQR)	40·0 (20·0–80·0)	40·0 (20·0–80·0)
Angiotensin converting enzyme inhibitors	24% (74/314)	25% (78/312)
Angiotensin receptor blockers	39% (122/314)	37% (114/312)
Beta-blockers	70% (221/314)	70% (217/312)
Sacubitril–valsartan	2% (5/314)	2% (6/312)
Mineralocorticoid receptor antagonists	53% (166/314)	51% (159/312)
SGLT2 inhibitors	2% (5/314)	4% (11/312)
Digoxin	3% (10/314)	5% (15/312)
Oral anticoagulants	47% (148/314)	52% (161/312)
Aspirin	37% (115/314)	40% (126/312)
Anti-platelet therapy other than aspirin	11% (34/314)	12% (37/312)
Other baseline measurements		
Admission to hospital, emergency room visit, or acute care facility visit for heart failure within 12 months of enrolment	43% (126/292)	43% (128/296)
Admitted to hospital for heart failure in the past 12 months	26% (77/292)	32% (94/296)
Number of admissions to hospital for heart failure in the past 12 months		
1	65% (50/77)	78% (73/94)
2	27% (21/77)	17% (16/94)
3	5% (4/77)	0/94
4	3% (2/77)	1% (1/94)
5	0/77	3% (3/94)
6	0/77	1% (1/94)
Atrial fibrillation or flutter at baseline	14% (45/311)	20% (63/311)
Median BNP with atrial fibrillation, pg/mL (IQR)	240·1 (119·0–380·3)	193·5 (117·1–342·0)
Median BNP without atrial fibrillation, pg/mL (IQR)	95·0 (44·0–154·0)	90·8 (39·0–198·8)
Median NT-proBNP with atrial fibrillation, pg/mL (IQR)	1008·5 (590·5–1683·5)	1223·0 (647·0–1792·0)
Median NT-proBNP without atrial fibrillation, pg/mL (IQR)	300·5 (157·0–615·0)	343·5 (172·1–686·5)
Resting PCWP<15 (core-lab reported), mm Hg	30% (94/314)	28% (88/312)
Resting PCWP≥15 (core-lab reported), mm Hg	70% (220/314)	72% (224/312)
Median tricuspid annular plane systolic excursion, mm (IQR)	20·0 (18·0–23·0)	20·0 (17·0–23·0)
Median MAGGIC risk score (IQR)	23·0 (18·0–26·0)	23·0 (19·0–26·0)
Median CHA_2DS_2-VASc score (IQR)	5·0 (4·0–5·0)	4·0 (4·0–5·0)
Median KCCQ overall summary score (IQR)	45·3 (30·2–61·7)	45·8 (28·0–63·8)
Median estimated glomerular filtration rate, mL/min per 1·73 m^2 (IQR)	58·0 (41·0–68·4)	55·0 (43·0–65·3)

Data are % (n/N), unless stated otherwise. KCCQ=Kansas City Cardiomyopathy Questionnaire. BNP=B-type natriuretic peptide. NT-proBNP=N-terminal pro-B-type natriuretic peptide. PCWP=pulmonary capillary wedge pressure. *Some patients chose not to answer this question.

Table 1: **Baseline demographics of the intention-to-treat population**

than those allocated to the sham procedure. Cumulative incidence curves for the primary endpoint were constructed using the Kaplan-Meier method.

Additional analyses included individual examination of each of the components of the primary efficacy endpoint as follows: comparing treatments on cumulative incidence of cardiovascular death or ischemic stroke using Gray's test where non-cardiovascular death is treated as a competing risk; person-year rate of heart failure events (compared between treatments using zero-inflated Poisson regression analysis); cumulative incidence of at least one heart failure event using Gray's test, where all-cause mortality is treated as a competing risk; and change in KCCQ overall summary score from baseline to 12 months using ANCOVA (adjusted for baseline score). Assumptions for use of the ANCOVA test were confirmed (change in KCCQ was approximately normally distributed in both treatment groups). The incidence of the major secondary safety composite endpoint was compared between treatment groups using logistic regression.

Prospectively planned, prespecified subgroup analyses (appendix p 31) included several categorical variables and continuous variables (divided into tertiles), and treatment by subgroup interactions were evaluated. For each subgrouping, to evaluate homogeneity of treatment effect across the subgroup categories, assessment of treatment-by-subgroup category interaction was done using negative binomial regression for the heart failure events outcome. Treatment, subgroup category, and the treatment-by-subgroup category interaction were included as independent variables in each model. Interaction term significance was defined as $p<0·05$. For continuous variables, the tertile used for the specific cutoff point for further analyses was chosen based on visual inspection of the Forest plot.

We conducted an exploratory post-hoc analysis of additional invasive haemodynamic markers. During exercise, the extent of the increase in pulmonary artery pressure is determined by changes in PCWP, cardiac output, and PVR. Thus, to investigate the meaning of the exercise pulmonary artery pressure interaction effect, we analysed these determinants.

Statistical analyses were done using SAS version 9.4 (SAS Institute, Cary, NC, USA). All statistical analyses were predefined in the protocol or statistical analysis plan unless specifically indicated as being post-hoc analyses. All statistical analyses were conducted independently (Baim Institute for Clinical Research, Boston, MA, USA). An independent data safety and monitoring board reviewed study data approximately quarterly for all enrolled participants.

This trial is registered with ClinicalTrials.gov, NCT03088033.

Role of the funding source

The steering committee designed the protocol with the study sponsor. All data collection, trial monitoring, and data analysis was conducted independently by the Baim Institute for Clinical Research. The funder of the study contributed to the interpretation of the results, but had no role in the writing of the report or the decision to submit the manuscript for publication.

Results

Between May 25, 2017, and July 24, 2020, 1072 participants were enrolled, 626 of whom met eligibility criteria for random assignment and were assigned to receive the atrial shunt device (n=314) or sham procedure (n=312; figure 1).

Baseline characteristics of participants were similar between study groups (table 1; appendix pp 36–37), and were typical for patients with heart failure and preserved ejection fraction (HFpEF) or with heart failure and mildly reduced ejection fraction (HFmrEF). The median age of participants was 72 years (IQR 66–77), 62% were female, most were NYHA class III, and comorbidities were common. Median site-reported ejection fraction was 60% (IQR 55–65) and, of the enrolled patients, 582 (93%) had preserved ejection fraction and 44 (7%) had mildly reduced ejection fraction. Nearly all patients were taking diuretics at baseline. 254 (43%) patients had a history of admission to hospital or acute care facility visit for heart failure exacerbation within the 12 months before enrolment into the study. The median Meta-Analysis Global Group in Chronic Heart Failure mortality risk score[17] was 23 (IQR 18–26), and the median KCCQ overall summary score was 45·8 (29·2–62·5). On invasive haemodynamic testing, 182 (29%) patients had a resting PCWP of less than 15 mm Hg, but were eligible for randomisation on the basis of peak exercise PCWP (≥25 mm Hg).

The primary efficacy endpoint (win ratio 1·0 [95% CI 0·8–1·2]; p=0·85) did not differ between the groups, and there were no differences between groups in the individual components of the primary endpoint (table 2, figure 2). Cardiovascular death and nonfatal ischaemic stroke were uncommon in both groups (six events [four in the atrial shunt device group, and two in the sham procedure group] at 12 months of follow-up). 66 (21%) in the atrial shunt device group and 60 (19%) in the sham control group had at least one heart failure event. Over a median follow-up time of 691 days (IQR 389–809), the total rate of heart failure events was similar between the two groups (0·28 events per patient-year [atrial shunt device] *vs* 0·25 [sham procedure]). Heart failure events did not differ between treatment groups at 3, 6, or 12 months (appendix p 38). The KCCQ overall summary score improved to a similar extent in both groups at 1 year (median change 10·2 [IQR –1·8 to 26·8] in the shunt device group and 9·4 [–2·1 to 22·9] in the sham procedure group). NYHA class improved to a greater extent in the shunt device-treated patients than sham-treated controls (p=0·006; table 2). Results of the per-protocol analysis (appendix p 39) were similar to the mITT analysis. There were no significant differences between treatment groups in uptake of sacubitril–valsartan and SGLT2 inhibitors during 24 months of follow-up in the trial (appendix p 40).

Results of the periodic blinding questionnaire showed that, over the course of the study, 598 (96%) patients remained unaware of their treatment allocation (appendix p 41). The COVID-19 pandemic slowed enrolment into the trial and was associated with a lower rate of heart failure events (0·38 events per patient-year pre-COVID-19 *vs* 0·19 events per patient-year during COVID-19); however, there was no evidence of a differential treatment effect before versus after the COVID-19 pandemic (defined as before *vs* after the first diagnosis of COVID-19 in each geographical location; appendix p 42).

Prespecified subgroup analyses (figure 3; appendix p 46) showed a differential effect of shunt device treatment in the following subgroups: sex ($p_{interaction}$=0·02), right atrial volume index ($p_{interaction}$=0·012), and pulmonary artery

	Atrial shunt device (n=309)	Sham control (n=312)	p value
Primary endpoint			
Finkelstein-Schoenfeld statistic, T (SE)	–780 (3998)	..	0·85
Probability of favourable distribution (95% CI)	0·50 (0·46 to 0·54)	..	..
Win ratio (95% CI)	1·0 (0·8 to 1·2)	..	..
Components of the primary endpoint or secondary endpoints			
Incidence of time-to-cardiovascular death or non-fatal ischaemic stroke at 12 months*	1% (4)	1% (2)	0·41
Cardiovascular death	1% (3)	1% (2)	0·65
Non-fatal ischaemic stroke	<1% (1)	0	0·32
Total rate (first plus recurrent) per patient-year of heart failure events†	0·28	0·25	0·45
Median change in KCCQ-OSS from baseline to 12 months (IQR)	10·2 (–1·8 to 26·8)	9·4 (–2·1 to 22·9)	0·73‡
Median change in NYHA functional class from baseline to 12 months (IQR)	–0·5 (–1·0 to 0·0)	0·0 (–1·0 to 0·0)	0·006§
Safety endpoints (12 months of follow-up)			
Composite safety endpoint¶	38% (116/308)	31% (97/308)	0·11
Cardiovascular mortality	1% (3/308)	1% (2/308)	0·66
Non-fatal ischaemic stroke	<1% (1/308)	0/308	0·96
New onset or worsening of kidney dysfunction	7% (22/308)	8% (25/308)	0·65
Major cardiac events	4% (11/308)	1% (2/308)	0·025
Cardiac death	1% (2/308)	1% (2/308)	1·00
Myocardial infarction	2% (5/308)	<1% (1/308)	0·14
Cardiac tamponade	1% (3/308)	0/308	0·95
Emergency cardiac surgery	<1% (1/308)	0/308	0·96
Thrombo-embolic complications	0/308	0/308	..
Transient ischaemic attack	0/308	0/308	..
Systemic embolic events	0/308	0/308	..
Newly acquired persistent or permanent atrial fibrillation or atrial flutter	1% (4/308)	1% (2/308)	0·42
≥30% increase in right ventricular size or ≥30% decrease in TAPSE	30% (92/308)	25% (76/308)	0·15

SE=standard error. KCCQ-OSS=Kansas City Cardiomyopathy Questionnaire overall summary score. NYHA=New York Heart Association. TAPSE=tricuspid annular plane systolic excursion. *From Kaplan-Meier estimates. Gray's test p values with non-cardiovascular death is treated as a competing risk. †Heart failure events include admissions to or visits to a health-care facility for intravenous diuresis or visits with intensification of oral diuresis for heart failure, with data collected for 24 months. Zero-inflated Poisson regression was used to compare heart failure event rates per patient-year. ‡Computed using ANCOVA, adjusting for baseline score. §Computed using the Wilcoxon rank sum test. ¶The composite safety endpoint is a combination of all of the safety endpoints listed below in the table.

Table 2: **Primary efficacy and safety endpoints in the modified intention-to-treat population**

systolic pressure at 20W exercise ($p_{interaction}$=0·002). Men, patients with right atrial volume index in the highest tertile (>29·7 mL/m²), and patients with pulmonary artery systolic pressure at 20W of exercise in the highest tertile (>70 mm Hg) had worse heart failure event outcomes with the device (favouring sham control). Based on the finding of a significant interaction effect by baseline (pre-randomisation) pulmonary artery systolic pressure at 20W of exercise, we conducted an exploratory post-hoc analysis of additional invasive haemodynamic markers, and found that there was a differential effect of shunt treatment on heart failure events and KCCQ overall summary score based on peak exercise PVR. Patients with a peak exercise PVR of less than 1·74 Wood units (n=382) appeared to benefit from the shunt (win ratio 1·28, p=0·032; incident rate ratio for heart failure events 0·71 [95% CI 0·42–1·20]; change in placebo-corrected KCCQ overall summary score 5·5 [1·6–9·5]; appendix pp 47–48), whereas patients with a peak exercise PVR of at least 1·74 Wood units (n=188) appeared to do worse with the shunt device (incident rate ratio for heart failure events 2·48 [1·23–5·01]; change in placebo-corrected KCCQ overall summary score –6·2 [–11·8 to –0·7], $p_{interaction}$=0·031).

There were no differences in the composite safety endpoint between the two groups (table 2). However, patients treated with the shunt were more likely to have a major cardiac event (cardiac death, myocardial infarction, cardiac tamponade, or emergency cardiac surgery) in the 12 months after the index procedure than were patients who underwent the sham procedure (4% *vs* 1%, p=0·025). Full details are provided in the appendix (pp 33–34). There were also more vascular complications in the shunt device treatment group (18 events in 13 patients, eight [61%] of whom had access site haematomas) than in the sham procedure group (0 events; appendix p 43).

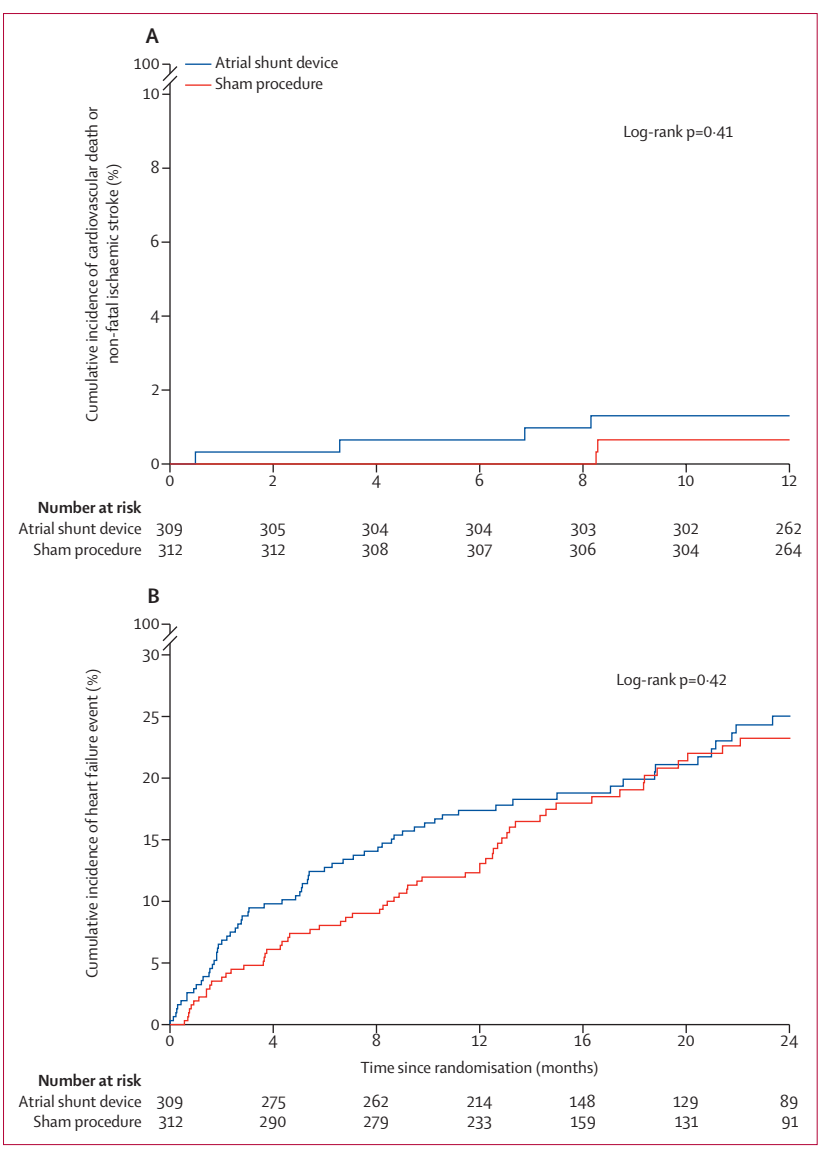

Figure 2: **Kaplan-Meier estimates of primary efficacy outcomes among heart failure with ejection fraction of at least 40% randomly allocated to the atrial shunt device versus sham procedure**
(A) Cardiovascular death or non-fatal ischaemic stroke. (B) Heart failure events requiring treatment.

Discussion

Overall, among patients with heart failure, an ejection fraction of at least 40%, and documented invasive exercise PCWP of at least 25 mm Hg, we found no significant differences between atrial shunt device treatment and sham procedure in terms of cardiovascular death, nonfatal ischaemic stroke, total rate of worsening heart failure events, and health status. However, there were differential treatment effects in some of the prespecified subgroups. Men and patients with pulmonary artery systolic pressure of at least 70W at 20W of exercise or right atrial volume index of at least 29·7 mL/m² appeared to have more frequent heart failure events with the device. Further post-hoc analyses revealed that patients with a peak exercise PVR of less than 1·74 Wood units (which corresponds to the upper limit of normal) might represent a responder group, with improved outcomes and health status with atrial shunt device treatment compared with sham control. The overall composite safety endpoint was similar between treatment groups, although shunt device-treated patients had a higher frequency of vascular complications and major cardiac events than sham-treated patients.

The REDUCE LAP-HF II trial was designed on the basis of the positive results of the REDUCE LAP-HF I trial, which showed that the Corvia atrial shunt device was associated with a reduction in exercise PCWP at 1 month after randomisation compared with sham control, confirming its mechanistic benefit in patients with HFpEF or HFmrEF.[7] In addition, the level of PCWP reduction in the shunt device-treated patients in the REDUCE LAP-HF I trial, though modest, (eg, 5·0 mm Hg mean decrease with legs up; 3·2 mm Hg decrease at 20W exercise at 1 month after device implantation) is likely to be clinically meaningful

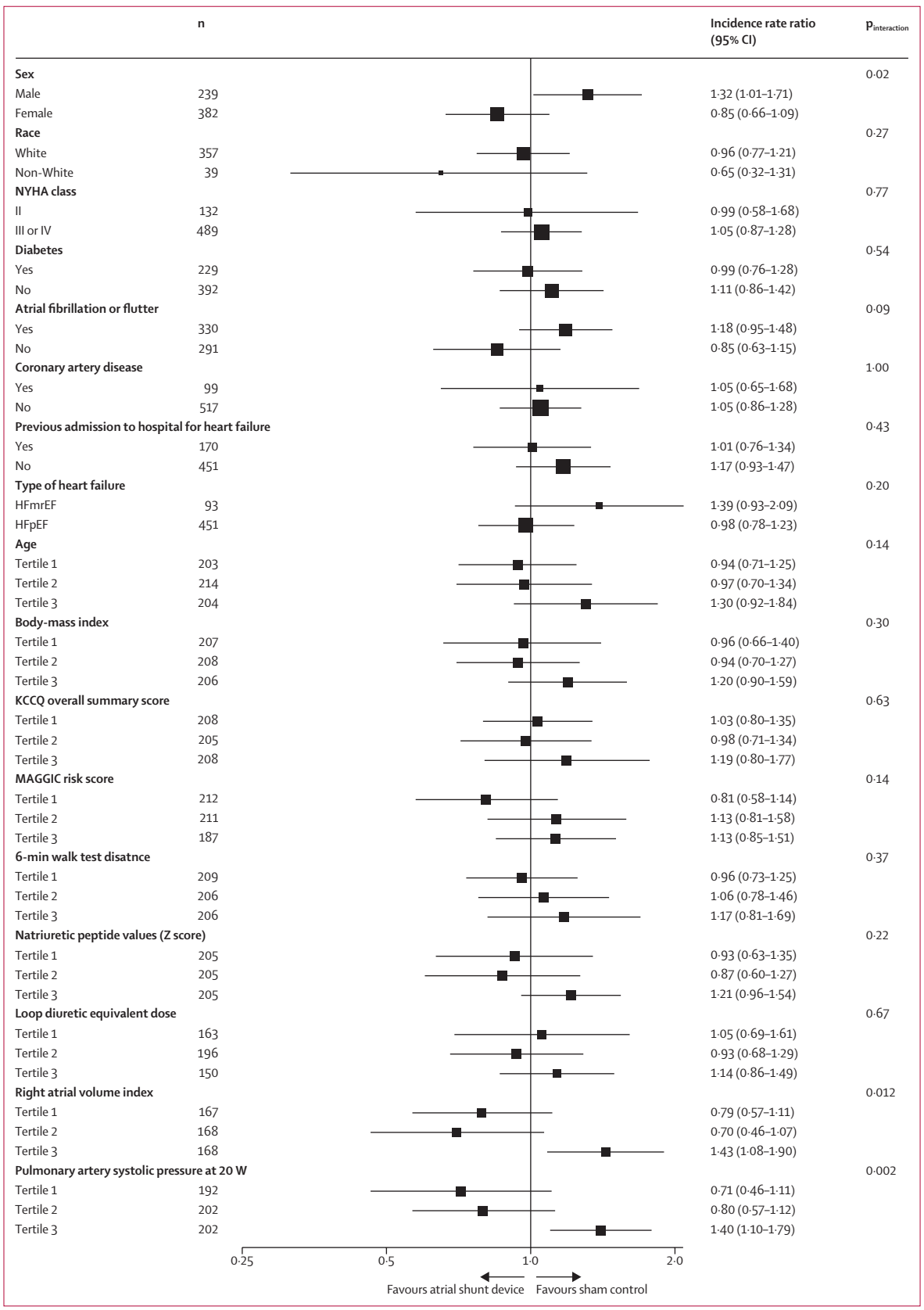

Figure 3: **Forest plot of treatment effect on recurrent heart failure events by prespecified subgroups**
All prespecified echocardiographic and invasive haemodynamic subgroups are shown in the appendix (p 46). NYHA=New York Heart Association. HFmrEF=heart failure and mildly reduced ejection fraction. HFpEF=heart failure and preserved ejection fraction. KCCQ=Kansas City Cardiomyopathy Questionnaire. MAGGIC=Meta-Analysis Global Group in Chronic Heart Failure.

(appendix p 49), based on the association between lower values of legs up and exercise PCWP with lower risk of heart failure events. However, we cannot prove that shunt device-associated lowering of exertional PCWP is associated with improved outcomes based on the design of the present trial, which did not include serial haemodynamic testing.

The REDUCE LAP-HF II trial required each patient to undergo invasive exercise haemodynamic testing to confirm the diagnosis of heart failure in the presence of ejection fraction of at least 40%, which added considerable rigour to the trial. Nevertheless, even in accurately diagnosed patients, HFpEF and HFmrEF can be associated with multiple varying aetiologies and pathophysiologies that underly its heterogeneity.[18] To be beneficial, interatrial shunting requires a specific phenotype: elevated left atrial pressure in the absence of right-sided heart failure or significant pulmonary vascular disease. Indeed, REDUCE LAP-HF II and previous trials of the Corvia Atrial Shunt in essence have all been enrichment trials, a type of precision medicine trial,[19,20] with each documenting elevated exercise PCWP (a surrogate for left atrial pressure) and using comprehensive non-invasive and invasive diagnostics to select patients who were most likely to benefit from the shunt.

The results of REDUCE LAP-HF II highlight a potentially important exclusion criterion for interatrial shunt device treatment—pulmonary vascular disease uncovered during exercise. To restrict enrolment to individuals expected to benefit from shunt device treatment, we excluded patients with resting indicators of right heart failure and pulmonary vascular disease (including significant right ventricular dysfunction, right atrial pressure >14 mm Hg, and PVR >3·5 Wood units). However, our strategy might have been inadequate for excluding pulmonary vascular disease uncovered by exercise, since treatment with the shunt device was associated with worse outcomes in patients with peak exercise PVR of at least 1·74 Wood units, whereas there was a suggestion of a potential beneficial response to shunt device therapy in patients with a normal pulmonary vascular response to exercise. The reason for these differential outcomes requires further investigation. It is known that many patients with HFpEF display elevations in PVR during exercise that are not apparent at rest, which increases afterload on the right ventricle, thereby resulting in increased right atrial pressure,[21] potentially leading to more frequent heart failure events and worse health status. This phenomenon might also impair right-sided ventricular-arterial coupling and further contribute to right ventricular failure.[22] Treatment with atrial shunt device in patients with evidence of pulmonary vascular disease during exercise could also accelerate development of right ventricular dysfunction, which is strongly associated with increased morbidity and mortality in HFpEF.[23,24] The apparent sex difference in response to shunt device treatment also requires further investigation. Men have larger right atrial volumes and worse right ventricular systolic function than women, both of which could have led to worse outcomes with shunt device treatment. Increased right atrial volume, which were also associated with worse outcomes with the device, could be indicative of greater chronic overload of the right heart—which could have hampered left atrial decompression via the shunt device—and subclinical right ventricular dysfunction which might have responded unfavourably to left-to-right shunting.

Although previous randomised trials of angiotensin receptor blockers, sacubitril–valsartan, and spironolactone in patients with HFpEF have shown largely neutral outcomes, prespecified and post-hoc analyses have consistently demonstrated benefits in patients with HFmrEF.[25] Although not statistically significant (based on $p_{interaction}$ values), there was a suggestion of worse outcomes in response to the shunt device in patients with HFmrEF compared with patients with HFpEF (figure 3). In addition, as shown in the appendix (p 46), patients with worse left ventricular global longitudinal strain also appeared to do worse (higher rate of heart failure events), which supports the notion that the worse the left ventricular systolic dysfunction, the worse the patients appear to do with an interatrial shunt device in terms of heart failure events.

Recent trials suggest that SGLT2 inhibitors are beneficial in patients with heart failure across the broader ejection fraction spectrum.[26,27] These trials represent a major advance for HFpEF treatment, given that it now appears that despite its heterogeneity, HFpEF is treatable. However, once fluid overload is adequately managed, it is unclear whether these drugs provide further benefit. In patients with HFpEF and HFmrEF who have normal or near-normal central venous pressure but marked elevation of left atrial pressure with exercise, further diuresis or treatment with neurohormonal modulators might be counterproductive and could result in kidney injury and adverse neurohormonal activation. Thus, a treatment such as the atrial shunt device might be particularly beneficial in patients already on these medications, although further trials are needed to test this hypothesis.

Several other interatrial shunt devices and procedures are currently in various stages of development.[9,10] Given the potential for worse outcomes with interatrial shunting in patients with pulmonary vascular disease uncovered by exercise, current and future trials might benefit from considering more stringent criteria for excluding patients with right ventricular or right atrial dysfunction, significant tricuspid regurgitation, or evidence of pulmonary vascular disease at rest or during exercise. Based on the results of the present trial, excluding patients with a peak exercise PVR of at least 1·74 WU from shunt device trials seems prudent. Additionally, as procedure-related events (particularly

vascular complications) and major cardiac events, though relatively rare, were more common in shunt device-treated patients, these potential adverse effects must be weighed against any potential benefits of left-to-right shunting in subgroups of patients with HFpEF and HFmrEF who might respond favourably to the atrial shunt device.

Several limitations should be considered when interpreting the trial results. Although based on pre-specified subgroup analyses demonstrating a differential treatment effect by presence or absence of significantly elevated pulmonary artery systolic pressure during exercise, the peak exercise PVR subgroup analyses were done post hoc and thus should be considered exploratory. There was a large improvement in the KCCQ score in the control group, which might have made it difficult to show a benefit in health status with the device. However, recent heart failure trials have shown that baseline KCCQ score is inversely related to improvement in KCCQ score in the control group (appendix pp 44, 50); therefore, it is not surprising that there was a large improvement in the control group in the present trial, given the very low KCCQ scores at baseline. The observed mortality rate in the trial was much lower than the predicted mortality rate. However, patients with major risk factors for increased mortality in HFpEF and HFmrEF (such as significant right ventricular dysfunction, overt pulmonary vascular disease, and inability to exercise) were excluded, which could have led to the lower-than-expected mortality rate. Although the long-term efficacy and safety of the atrial shunt device compared with sham control cannot yet be reported, the previous open-label (n=64) and REDUCE LAP-HF I randomised clinical trials (n=44) have demonstrated excellent long-term durability and safety of the device, and all patients in the trial will be followed up for at least 5 years. Our results also only apply to the 8-mm shunt diameter of the Corvia Atrial Shunt Device. Whether similar results would occur with smaller or larger interatrial shunts remains to be determined. It is also possible that patients with atypical forms of heart failure with ejection fraction of at least 40% (eg, infiltrative cardiomyopathy) were inadvertently enrolled in the trial, though unlikely given the requirements for a preserved cardiac index and a difference between PCWP and right atrial pressure of at least 5 mm Hg. Finally, COVID-19 was associated with a lower heart failure event rate during follow-up, an observation which has been well documented in patients with heart failure in the COVID-19 era.[28,29] However, the lower heart failure event rate did not appear to have a significant effect on the primary outcome, and the overall rate of heart failure events (despite COVID) was more than twice as high as recent HFpEF pharmacotherapy trials.[26,30]

In summary, in this adequately powered, sham-controlled, randomised trial of patients with heart failure and ejection fraction of at least 40%, placement of an atrial shunt device did not result in a reduction in total rate of heart failure events or improvement in health status. However, treatment efficacy differed by presence or absence of pulmonary vascular disease unmasked by exercise; patients with no evidence of pulmonary vascular disease during exercise appeared to benefit from the device whereas patients with elevated PVR during exercise had worse outcomes. Additional studies will be required to evaluate the efficacy, safety, durability, and long-term clinical impact of atrial shunt device treatment in patients with heart failure and ejection fraction of at least 40% with no evidence of pulmonary vascular disease during exercise.

Contributors

SJS, MBL, DEC, JMM, SDS, and DJvV designed the study. SJS, BAB, ESC, PD, PSF, GH, RK, DMK, SEL, PL, RCM, MJR, ALS, VS, and SW collected patient data. All authors analysed and interpreted the data. QG and JMM were the independent study biostatisticians responsible for the statistical analyses. SJS wrote the first draft of the report. All authors participated in the writing of the report, agreed on the content of the manuscript, reviewed drafts, and approved the final version. SJS, DEC, QG, and JMM had unrestricted access to and verified the underlying data. Statistical analyses were conducted independently by QG and JMM. All authors had full responsibility for the decision to submit for publication.

Declaration of interests

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Data sharing

Data requests can be submitted to Corvia Medical (info@corviamedical.com). Data will be shared with researchers who submit a detailed research proposal upon approval by the study steering committee. Data will not be made available until after approval of the product in the USA and Japan and not until reporting of the final results, anticipated in 2027. Individual patient data will be shared in datasets in a de-identified and anonymised format.

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