

# Feasibility and efficacy of transcatheter interatrial shunt devices for chronic heart failure: a systematic review and meta-analysis

Lucas Lauder<sup>1\*</sup>, Tiago V. Pereira<sup>2,3</sup>, Markus C. Degenhardt<sup>1</sup>, Sebastian Ewen<sup>1</sup>, Saarraaken Kulenthiran<sup>1</sup>, Andrew J.S. Coats<sup>4</sup>, Michael Böhm<sup>1</sup>, Stefan D. Anker<sup>5</sup>, Bruno R. da Costa<sup>3,6</sup>, and Felix Mahfoud<sup>1</sup>

<sup>1</sup>Department of Internal Medicine III, Cardiology, Angiology, Intensive Care Medicine, Saarland University Medical Center, Saarland University, Saarbrücken, Germany; <sup>2</sup>Ch evening Scholar, Decision Modelling and Evidence Synthesis, University of Leicester, Leicester, UK; <sup>3</sup>Applied Health Research Centre, Li Ka Shing Knowledge Institute of St Michael's Hospital, University of Toronto, Toronto, Canada; <sup>4</sup>Warwick Medical School, University of Warwick, Coventry, UK; <sup>5</sup>Berlin-Brandenburg Center for Regenerative Therapies and Department of Cardiology, German Center for Cardiovascular Research Partner Site Berlin, Charité Universitätsmedizin, Berlin, Germany; and <sup>6</sup>Institute of Primary Health Care (BIHAM), University of Bern, Bern, Switzerland

Received 12 June 2021; revised 28 August 2021; accepted 6 October 2021; online publish-ahead-of-print 5 November 2021

## Aims

To assess the feasibility and efficacy of interatrial shunt devices (IASD) for the treatment of chronic heart failure (CHF).

## Methods and results

MEDLINE and the Cochrane Central Register of Controlled Trials from inception until April 2021 were searched for prospective studies investigating dedicated transcatheter IASD for the treatment of CHF. Standardised mean differences were calculated for the within-group changes before and after implantation of the IASD. The pre-defined primary outcome was change in 6-min walking distance (6MWD) from baseline to 12 months. Other outcomes were change in New York Heart Association class, health-related quality of life (HRQoL), echocardiographic and haemodynamic data, device performance and safety. Subgroup analyses were crude univariable meta-regression analyses. Six studies (five single-arm open-label studies, one sham-controlled trial) were included. In these, 226 patients underwent IASD implantation using four different devices. From baseline to 12 months, 6MWD increased by 28.1 m [95% confidence interval (CI) 10.9–45.3] with no evidence for a difference between devices ( $P$  for interaction = 0.66) and patients with left ventricular ejection fraction (LVEF) >40% or ≤40% ( $P$  for interaction = 0.21). At 12 months, HRQoL improved by 17.7 points (95% CI 10.8–24.6) and pulmonary capillary wedge pressure (PCWP) decreased by 2.0 mmHg (95% CI –3.6 to –0.4). There were no changes in LVEF or N-terminal pro brain natriuretic peptide during follow-up. Shunt patency ranged from 50% for the first-generation v-Wave to 100% for the Corvia IASD II and the second-generation v-Wave system, respectively. The summary risk of serious adverse device-related effects was 8% (95% CI 1–20) at 12 months.

## Conclusions

Interatrial shunt device implantation in CHF is feasible and associates with improved submaximal exercise capacity (measured by 6MWD) and HRQoL, and reductions in PCWP.

## Keywords

Interatrial shunting • Transcatheter • Interventional heart failure treatment

\*Corresponding author: Department of Internal Medicine III, Saarland University Hospital, IMED, Geb. 41, Kirrberger Str. 100, 66421 Homburg, Germany. Tel: +49 6841 1615911, Fax: +49 6841 1615910, Email: lucas.lauder@uks.eu

## Introduction

Pharmacological therapy has shown to reduce cardiac remodelling, ameliorate symptoms, improve cardiac function and prognosis in patients with heart failure (HF) with reduced ejection fraction [HF<sub>r</sub>EF; left ventricular ejection fraction (LVEF)  $\leq 40\%$ ].<sup>1,2</sup> Beside sodium-glucose co-transporter-2 inhibitors,<sup>3</sup> there is currently no pharmacological therapy that has improved morbidity and mortality in patients with chronic HF (CHF) with preserved ejection fraction (HF<sub>p</sub>EF; LVEF  $\geq 50\%$ ).<sup>1,2</sup>

A common symptom of patients with CHF, irrespective of LVEF, is dyspnoea at exertion, which might be caused by an acute development of pulmonary congestion secondary to increased left ventricular and atrial filling pressures.<sup>4</sup> Individual adjustments of HF therapy, particularly diuretics, guided by invasive pulmonary artery pressures using an implantable pressure sensor can reduce HF-related hospitalisations.<sup>5</sup> However, pressure-guided CHF therapy requires patient's adherence, is rather complex and cost-intensive.<sup>6</sup> Moreover, pharmacological therapies can barely counteract rapid volume shifts from the capacitance vessels into the arterial circulation.<sup>6,7</sup>

In analogy to patients with mitral stenosis, where a concomitant small congenital atrial septal defect (Lutembacher's syndrome) associates with fewer symptoms and better outcomes compared with isolated mitral stenosis,<sup>8</sup> various left-to-right interatrial shunt devices (IASD) are currently under investigation for left atrial decompression in patients with CHF.<sup>9</sup>

This systematic review and meta-analysis assessed the feasibility of dedicated catheter-based IASD and their impact on the symptomatology and function in patients with both HF<sub>p</sub>EF and HF<sub>r</sub>EF.

## Methods

This review has been conducted following the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) guidelines<sup>10</sup> and was registered in the International Prospective Register of Systematic Reviews (PROSPERO; CRD42021242168).

## Eligibility criteria, literature search, and study selection

We searched MEDLINE (via PubMed) and the Cochrane Central Register of Controlled Trials Library (CENTRAL) from inception until April 2021 for prospective studies investigating dedicated transcatheter IASD for the treatment of CHF. Online supplementary *Methods S1* provides the details of the search strategy. In addition, conference proceedings, relevant reviews, and editorials were manually searched for further studies. No language restrictions were applied.

We included observational before-after studies and randomised controlled trials investigating dedicated catheter-based IASDs for the treatment of symptomatic [New York Heart Association (NYHA) functional class  $\geq$  II] CHF with preserved or reduced LVEF in adults ( $\geq 18$  years). Studies investigating the diabolical stent configuration or modified (fenestrated) atrial septal occluder were excluded.

After the removal of duplicates, two reviewers independently screened the references identified by the search strategy by title and abstract and discarded obviously irrelevant studies. The full-text

reports of all potentially relevant studies were obtained, and the two review authors independently assessed their eligibility based on the defined inclusion criteria. In case of disagreement between reviewers, a third reviewer was consulted, and disagreement was resolved by consensus.

## Outcomes

The primary outcome was the change in the 6-min walking distance (6MWD) between baseline and 12-month follow-up. Secondary efficacy outcomes were the change in NYHA functional class (dichotomised as NYHA class I–II and NYHA class III–IV), health-related quality of life (HRQoL) assessed by the Kansas City Cardiomyopathy Questionnaire (KCCQ) or Minnesota Living with Heart Failure Questionnaire (MLHFQ), and N-terminal pro brain natriuretic peptide (NT-proBNP) from baseline to 12 months. Additional efficacy outcomes were change in LVEF and tricuspid annular plane systolic excursion (TAPSE) obtained by transthoracic echocardiography and change in pulmonary capillary wedge pressure (PCWP), mean pulmonary artery pressure (mPAP), and mean right atrial pressure (mRAP) at rest assessed by right heart and pulmonary arterial catheterisation. Moreover, we analysed the proportions of patients with successful device implantation and with shunt patency (excluding patients with partial stenosis or total occlusion of the left-to-right shunt) at 12 months. The primary safety outcome was the incidence of serious device-associated adverse events. Additional safety outcomes were hospital admissions for HF, early ( $\leq 30$  days post-procedure), and overall death.

## Data extraction

Two reviewers extracted data independently, and in duplicate. The following information was collected: study design; study size; characteristics of the interventions; type and source of financial support; patient characteristics such as age, sex, and comorbidities; echocardiographic data such as LVEF and TAPSE; haemodynamic data assessed by right heart and pulmonary arterial catheterisation; and follow-up duration of primary and secondary outcomes. If necessary, two reviewers independently approximated means and measures of dispersion from figures in the reports using Digitizelt, version 1.6.1 (Braunschweig, Germany). Final values were based on the average of the independent reviewers. We gave preference to adjusted estimates of change.

## Assessment of study quality

Two reviewers independently assessed the study quality. For observational studies, the methodologic quality was assessed using an adaptation of the Newcastle–Ottawa scale (online supplementary *Methods S2*).<sup>11</sup> We awarded a maximum of seven stars, summed up from three stars for selection criteria (representativeness of the cohort, ascertainment of exposure, and demonstration that the outcome of interest was not present at the start of the study) and two stars each for comparability and outcome assessment. The cohorts were considered comparable if there were only minimal changes in co-interventions (one star) and if outcome data were available for all, or nearly all patients included in the study (one star). Outcome assessment was considered adequate if the patients underwent the 6-min walk test at the study centre and if the follow-up duration was long enough for outcomes to occur (at least 1 month for 6MWD). Randomised controlled trials were

further assessed according to the revised Cochrane risk of bias tool for randomised trials (RoB2).<sup>12</sup>

## Statistical analysis

Continuous outcomes were summarised using mean changes from baseline, with positive values indicating increased values at follow-up relative to baseline. We extracted the standard error (SE) of mean changes directly or approximated it from relevant reported statistics, such as 95% confidence intervals (CI) using established formulae.<sup>13</sup> When necessary, baseline and follow-up means and standard deviations (SD) were converted to mean changes and corresponding SE, assuming a within-group correlation of 0.5. Data reported as sample size, median, the first and third quartiles, or minimum and maximum were transformed to mean and its corresponding SE using recent approaches.<sup>14,15</sup> Results reported on the log scale were converted to the raw scale using the moment-based approach as previously described.<sup>16</sup> HRQoL was assessed using the MLHFQ or KCCQ. As both questionnaires show improvement and worsening of HRQoL on oppositely directed scales, the scores of the MLHFQ were reversed (higher scores indicate better HRQoL) before standardising.

For incidence rates, we calculated the log incidence rate per 100 person-year and computed the corresponding SE for each study. When the actual total time at risk was not reported, we approximated the total person-years at risk by multiplying the mean follow-up time by the number of patients included in the analysis. In case of zero events, we derived the upper end of the 95% CI of the rate as described by Hanley and Lippman-Hand, adding a continuity correction of 0.01 to the numerator, and a continuity correction of 0.02 multiplied by the mean follow-up time to the denominator to derive rates.<sup>17</sup> Pooled estimates were back-transformed and presented as rates per 100 person-years (95% CI) to facilitate the interpretation.

We used the variance-stabilizing Freeman–Tukey double-arcsine transformation to derive pooled incidence proportions. This approach allows asymmetric 95% CI with admissible values around the pooled incidence proportion (95% CI), as well as the inclusion of studies with zero events.<sup>18</sup>

We used a random-effects model to summarize results across trials because it was assumed that the patient's characteristics and the study design could significantly influence the treatment effect. We used the Paule and Mandel method to estimate the between-trial variance for changes from baseline and rates, and the DerSimonian and Laird method for proportions.<sup>19</sup> Statistical significance was defined as 95% CIs that did not include the value 0. We conducted pre-specified subgroup analyses for the primary outcome of 6MWD at 12 months according to the following variables: reduced/preserved LVEF (LVEF  $\leq$  40% and LVEF  $>$  40%), and the implanted device. Subgroup analyses were accompanied by a test for interaction from random-effects meta-regression using the Paule and Mandel method for between-trial variance estimation. In subgroup analyses, a *P*-value  $<$  0.05 was deemed statistically significant. The paucity of trials (i.e. less than 10 trials) precluded proper assessments of small-study bias.<sup>13</sup> We did all analyses with Stata, version 15 (StataCorp, College Station, TX, USA).

## Results

The search strategy identified 95 records, including five single-arm open-label studies and one randomised sham-controlled trial that were eligible for inclusion (online supplementary Figure S1). The

included studies were published between 2014 and 2021 and evaluated four dedicated IASDs: the Corvia IASD II system,<sup>20–22</sup> the first-<sup>23</sup> and second-generation<sup>24</sup> v-Wave system, and the Occlutech Atrial Flow Regulator.<sup>25</sup> Table 1 depicts the main study characteristics.<sup>20–29</sup> Three studies (Corvia Feasibility,<sup>20</sup> REDUCE-LAP HF,<sup>21</sup> and REDUCE-LAP HF I<sup>22</sup>) included patients with CHF with mildly-reduced (41–49%) and preserved LVEF ( $\geq$  50%), two studies (v-Wave first generation<sup>23</sup> and PRELIEVE<sup>25,29</sup>) included patients with an LVEF  $\geq$  15%, and one study included CHF patients irrespective of LVEF.<sup>24</sup> A total of 226 patients underwent IASD implantation. Across studies, the mean age of participants ranged from 66 to 70 years, the mean percentage of females ranged from 8% to 66% and the history of coronary heart disease ranged from 36% to 80%. The study quality of the single-arm open-label studies was assessed using an adaption of the Newcastle–Ottawa scale. One study (20%) was awarded the maximum possible score of seven stars. The other studies scored six (20%) and five (60%) stars (online supplementary Table S1). The REDUCE LAP-HF I trial was judged to be at low risk of bias for all domains of the Cochrane risk of bias tool for randomised trials RoB2 (online supplementary Table S2).<sup>22</sup> Four studies (67%) reported that all events were adjudicated by a blinded, independent clinical event committee.<sup>21–23,25</sup>

## Device performance

In three out of six (50%) studies, the IASDs were successfully implanted in all patients (online supplementary Table S3). In the REDUCE LAP-HF study, IASD implantation was abandoned because of a transseptal puncture complication, which resolved without further sequelae, in one patient, and because of perceived unsuitable atrial septal anatomy in another patient.<sup>21</sup> In the REDUCE LAP-HF I trial, the IASD implantation was impossible in two (9%) patients: in one patient due to an occluded vena cava filter and in one patient in whom the device was inadvertently fully deployed in the left atrium instead of at the interatrial septum.<sup>22</sup> In the PRELIEVE study, two (4%) patients were not included due to transseptal puncture failure and one (2%) patient experienced device dislocation in the left atrium requiring surgical removal.<sup>29</sup> One study did not report shunt patency at 12 months.<sup>26</sup> In the other studies, shunt patency ranged from 50% (14% total shunt occlusion and 36% stenotic valve) for the first generation v-Wave system<sup>23</sup> to 100% for the Corvia IASD II and the second-generation v-Wave system.<sup>24</sup> In the PRELIEVE study, shunt patency could not be confirmed in four of 49 (8%) patients due to inadequate quality of transthoracic echocardiography.<sup>29</sup> It was reported, however, that in these four patients there were no clinical signs of shunt occlusion.<sup>29</sup>

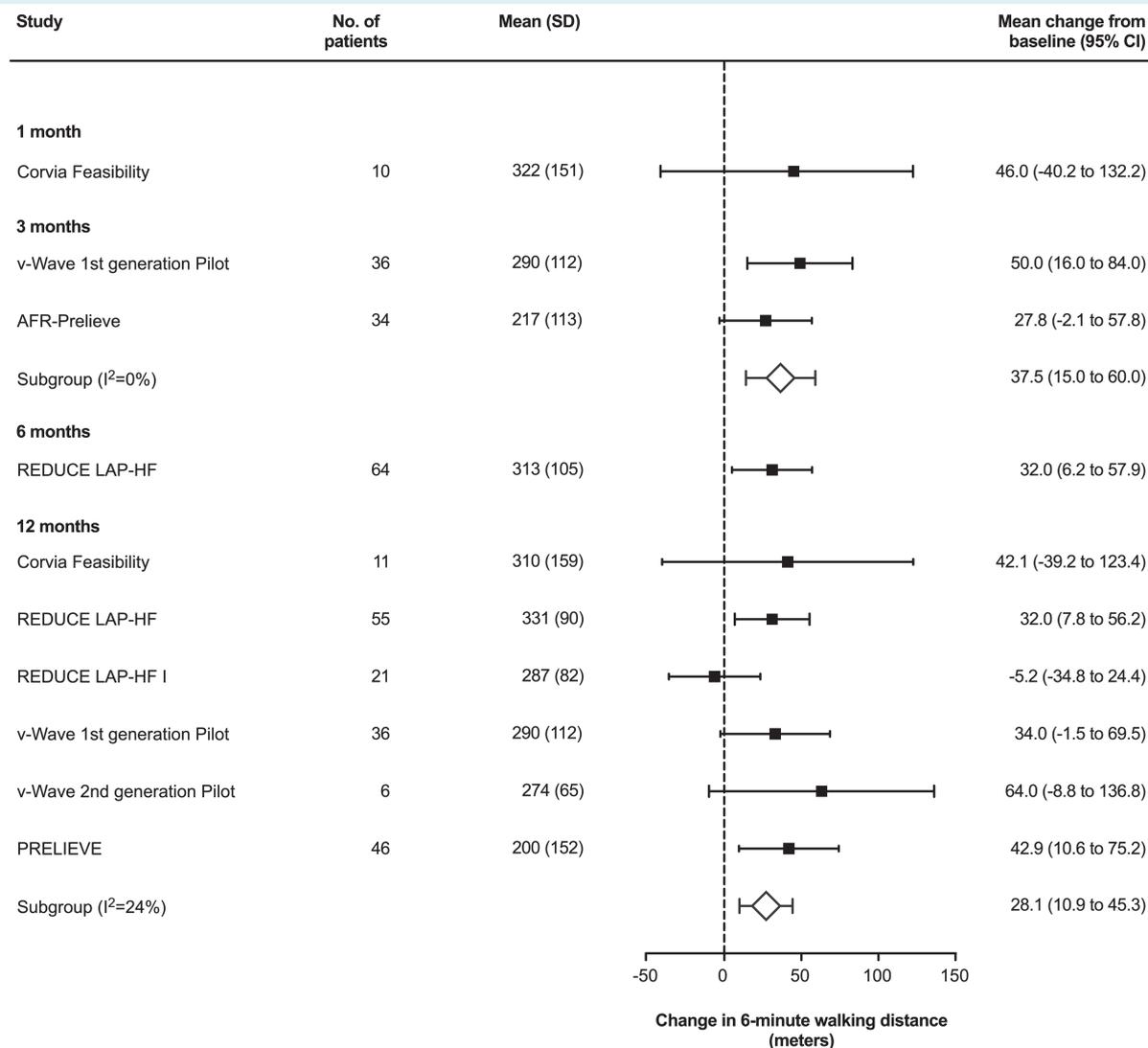
## Submaximal exercise capacity

All six studies assessed the change in submaximal exercise capacity measured by 6MWD between baseline and 12 months. The mean baseline 6MWD ranged from 200 to 331 m. At 12 months, the average mean 6MWD increased by 28.1 m (95% CI 10.9–45.3) (Figure 1). 6MWD increased significantly in patients

**Table 1** Main characteristics of included studies

Study, year	Investigational device	Study design	Main inclusion criteria	No. of patients undergoing IASD implant (proportion of women, %)	Age, years	T2DM, %	AFib, %	CAD, %	LVEF, %	TAPSE, mm
Corvia Feasibility, <sup>20,26</sup> 2014	Corvia IASD II	Open-label, single-arm	LVEF $\geq$ 45%; exercise intolerance; PCWP at rest $\geq$ 15 mmHg ( $\geq$ 25 mmHg during exercise)	11 (55)	70 $\pm$ 12	45	36	36	57 $\pm$ 9	NR
REDUCE LAP-HF, <sup>21,27</sup> 2016	Corvia IASD II	Open-label, single-arm	LVEF $\geq$ 40%; NYHA class II–IV; PCWP at rest $\geq$ 15 mmHg ( $\geq$ 25 mmHg during exercise)	66 (66)	69 $\pm$ 8	33	36	36	47 $\pm$ 7	20 $\pm$ 4
REDUCE LAP-HF I, <sup>22,28</sup> 2018	Corvia IASD II	Randomised, sham-controlled	LVEF $\geq$ 40%; NYHA class III (ambulatory class IV); PCWP $\geq$ 25 mmHg during exercise	22 (36)	70 $\pm$ 8	55	55	48	60 $\pm$ 9	NR
First-generation v-Wave, <sup>23</sup> 2018	v-Wave system	Open-label, single-arm	LVEF $\geq$ 15%; NYHA class III (ambulatory class IV)	38 (8)	66 $\pm$ 9	68	53	79	HFpEF: 50 $\pm$ 9 HFrEF: 26 $\pm$ 7	16 $\pm$ 5
Second-generation v-Wave, <sup>24</sup> 2020	v-Wave system	Open-label, single-arm	CHF; NYHA class $\geq$ III	36 (20)	68 $\pm$ 9	50	60	80	34 $\pm$ 12	16 $\pm$ 4
PRELIEVE <sup>a</sup> , <sup>25,29</sup> 2019	Occlutech Atrial Flow Regulator	Open-label, single-arm	LVEF $\geq$ 15%; NYHA class III (ambulatory class IV); PCWP at rest $\geq$ 15 mmHg ( $\geq$ 25 mmHg during exercise)	53 (41)	70 (63–73)	49	49 <sup>b</sup>	NR	HFpEF: 22 52 (45–55) HFrEF: 20 30 (29–35)	HFpEF: 22 (19–27) HFrEF: 20 (18–23)

Data are mean  $\pm$  standard deviation, median (interquartile range), or relative frequencies (%). AFib, atrial fibrillation; CAD, coronary artery disease; CHF, chronic heart failure; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; IASD, interatrial shunt device; LVEF, left ventricular ejection fraction; NR, not reported; NYHA, New York Heart Association; PCWP, pulmonary capillary wedge pressure; TAPSE, tricuspid annular plane systolic excursion; T2DM, type 2 diabetes mellitus.  
<sup>a</sup>Baseline characteristics of all patients who underwent device implantation as reported in the report of the 1-year outcome data.  
<sup>b</sup>History of supraventricular tachycardia (not further specified).



**Figure 1** Change in 6-min walking test distance. CI, confidence interval.

with LVEF >40% but not in patients with LVEF ≤40%; however, there was no significant difference between LVEF subgroups ( $P$  for interaction = 0.21) (Figure 2). Moreover, there were no significant differences in 6MWD change among different devices ( $P$  for interaction = 0.66).

## Symptomatology and quality of life

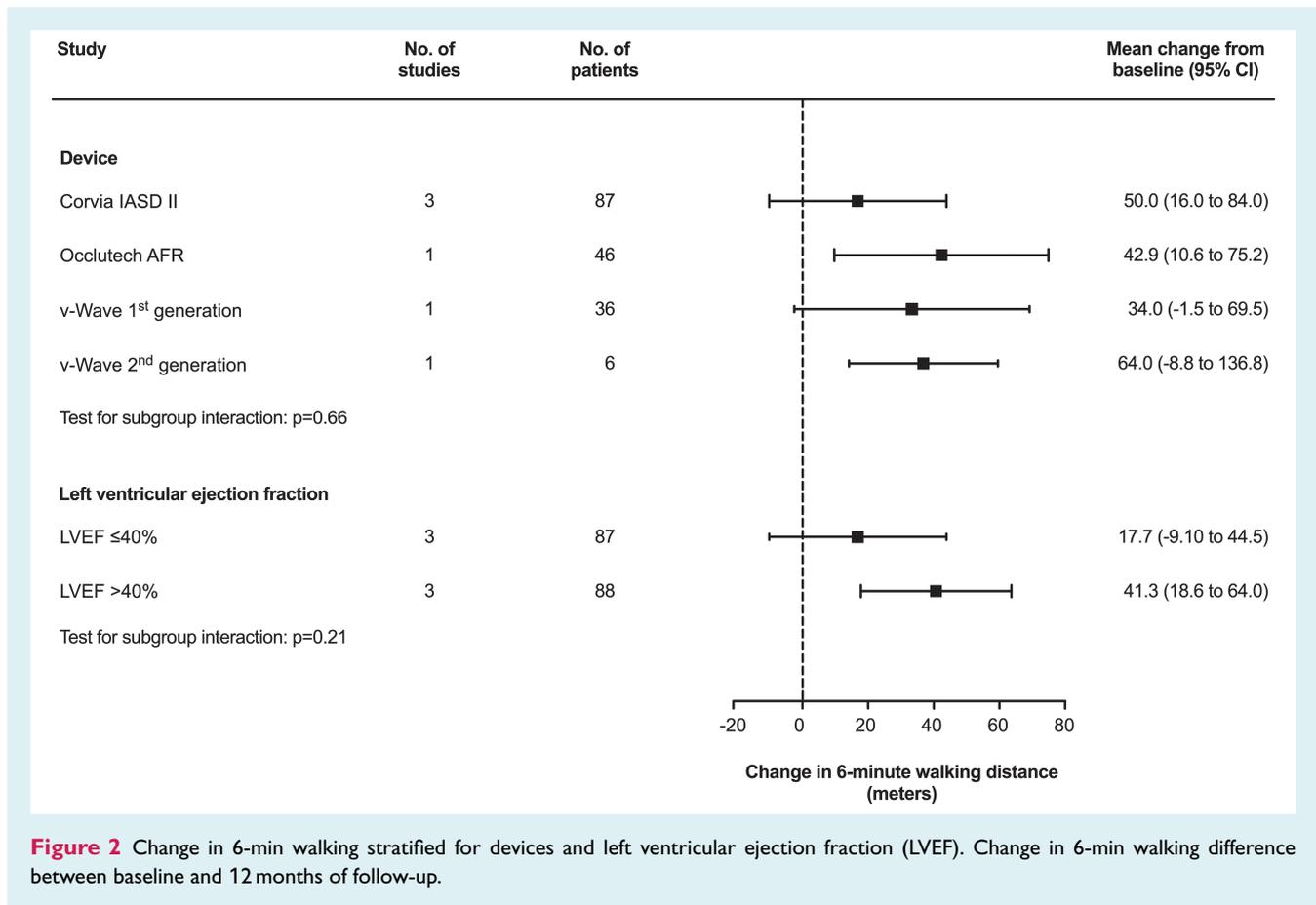
While only the REDUCE LAP-HF study included patients with a baseline NYHA functional class of I–II (9%), the majority (70%) of all patients were in NYHA functional class I–II at follow-up (online supplementary Table S4).

Health-related quality of life was assessed using the MLHFQ and the KCCQ by two and three studies, respectively. One study used either the MLHFQ or the KCCQ and reported the number of patients with a standardised improvement of at least five points. Two studies assessed HRQoL using the MLHFQ. In the two studies

using only the MLHFQ, the baseline score was 54.9 (17.0) and 49.0 (20.0), respectively. The mean baseline KCCQ score ranged from 38.4 to 51.1. In a pooled analysis involving five studies, standardised HRQoL improved significantly at 12 months after IASD implantation by 17.7 points (95% CI 10.8–24.6).

## Haemodynamic and echocardiographic data

In all studies, patients underwent right heart catheterisation at baseline. In five of six (83%) studies, patients also underwent repeat invasive haemodynamic assessments. The haemodynamic data are summarised in Table 2. PCWP at rest was significantly reduced at 1 and 12 months by 3.7 mmHg (95% CI -6.4 to -1.0) and 2.0 mmHg (95% CI -3.6 to -0.4), respectively. PCWP during peak exercise and workload corrected PCPW were measured in two studies. PCWP during peak exercise was significantly reduced



at 1 month ( $-3.5$  mmHg, 95% CI  $-6.5$  to  $-0.5$ ;  $n = 17$ ), but not at 6 ( $n = 59$ ) or 12 months ( $n = 18$ ), whereas workload corrected PCWP decreased only at 6 months ( $-15.0$  mmHg, 95% CI  $-25.9$  to  $-4.1$ ,  $n = 59$ ). mPAP dropped at 1 month ( $-2.8$  mmHg, 95% CI  $-4.8$  to  $-0.7$ ,  $n = 30$ ), but there was no change between baseline and 3 or 12 months of follow-up. mRAP increased at 6 ( $+2$  mmHg, 95% CI  $0.8$ – $3.2$ ,  $n = 60$ ) and 12 months of follow-up ( $+1.4$  mmHg, 95% CI  $0.4$ – $2.4$ ,  $n = 54$ ). Pulmonary vascular resistance decreased at 1 ( $-0.8$  WU, 95% CI  $-1.4$  to  $-0.2$ ) and 6 months ( $-0.2$  WU, 95% CI  $-0.3$  to  $-0.1$ ) of follow-up.<sup>21,22</sup>

The echocardiographic parameters LVEF and TAPSE remained unchanged throughout follow-up (Table 2). Right ventricular end-diastolic volume index (RVEDVI) and diameter (RVEDD) were reported in two studies only: RVEDVI increased by  $6.2$  mL/m<sup>2</sup> (95% CI  $3.4$ – $9.0$ ) after 6 months, whereas there was no significant change in RVEDD between baseline and 12 months (Table 2). Other echocardiographic measures of right heart function were only sporadically and inconsistently reported and therefore not included in this meta-analysis.

## Safety outcome data

Four studies (134 patients) provided information on the incidence of serious device-related adverse events at 12 months. The risk of serious device-related adverse events was 8% (95%

CI 1–20) (Table 3). The most common events were vascular access site complications (five events) and device malpositioning that required catheter-based retrieval which resolved without further sequelae (four events). Online supplementary Table S5 provides further details on the study safety outcomes. Overall, one patient had fatal stroke (CHA<sub>2</sub>DS<sub>2</sub>-VASc score of 6)<sup>27</sup> and one patient had a post-procedural disturbance of consciousness, which resolved without further sequelae.<sup>25</sup> Within 30 days after device implantation, three patients died representing a risk for early all-cause death of 0.2% (95% CI 0.0–2.4;  $I^2 = 12\%$ ). While one of these patients deceased within hours after the procedure due to therapy-refractory electrical storm,<sup>24</sup> the remaining two patients died of pneumonia and worsening of general conditions.<sup>25</sup> In total, 24 patients died resulting in an all-cause mortality rate of 7.5 deaths per 100 patient-years (95% CI 2.7–21.1;  $I^2 = 80\%$ ). A total of 43 patients experienced 103 HF hospitalisations events. Index HF hospitalisations occurred with a rate of 15.0 per 100 patient-years (95% CI 10.2–22.0;  $I^2 = 27\%$ ).

## Discussion

In this meta-analysis of mostly non-randomised, open-label studies investigating four different IASDs comprising 226 symptomatic patients with CHF, the procedural success rates were high (>90%)

**Table 2** Secondary efficacy outcomes

Outcome at follow-up, month	No. of studies	No. of patients	Change from baseline mean (95% CI)	I <sup>2</sup> , %
<b>Cardiac status</b>				
NT-proBNP, pg/mL				
1	1	9	19.0 (−80.6 to 118.6)	–
3	1	36	0.0 (−989.2 to 989.2)	–
6	1	64	36.1 (−116.8 to 189.0)	–
12	3	102	−56.5 (−199.7 to 86.7)	0
Standardised HRQoL score <sup>a</sup>				
3	1	9	34.8 (27.1 to 42.5)	–
6	1	62	13.0 (7.6 to 18.4)	–
12	5	182	17.7 (10.8 to 24.6)	76
<b>Haemodynamic measures</b>				
PCWP, mmHg				
1	2	28	−3.7 (−6.4 to −1.0)	45
3	3	67	−2.3 (−4.7 to 0.1)	36
6	1	60	0.0 (−1.6 to 1.6)	–
12	2	54	−2.0 (−3.6 to −0.4)	0
PCWP, peak exercise, mmHg				
1	1	17	−3.5 (−6.5 to −0.5)	–
6	1	59	−2.0 (−4.0 to 0.0)	–
12	1	18	−3.0 (−7.4 to 1.4)	–
PCWP, workload-corrected, mmHg				
1	1	16	−5.7 (−19.1 to 7.7)	–
6	1	59	−15.0 (−25.9 to −4.1)	–
mPAP, mmHg				
1	2	30	−2.8 (−4.8 to −0.7)	0
3	1	36	−1.0 (−3.5 to 1.5)	–
12	2	54	0.4 (−1.9 to 2.7)	0
mRAP, mmHg				
1	2	29	−0.2 (−1.6 to 1.3)	20
3	2	58	1.1 (−0.2 to 2.5)	0
6	1	60	2.0 (0.8 to 3.2)	–
12	2	54	1.4 (0.4 to 2.4)	0
Pulmonary vascular resistance, WU				
1	2	29	−0.8 (−1.4 to −0.2)	0
3	1	9	−0.6 (−1.2 to 0.0)	–
6	1	59	−0.2 (−0.3 to −0.1)	–
Ratio of pulmonary to systemic blood flow (Qp:Qs)				
6	1	60	0.2 (0.1 to 0.3)	–
12	2	60	0.1 (0.1 to 0.2)	20
<b>Echocardiographic measures</b>				
LVEF, %				
3	2	45	0.9 (−1.5 to 3.4)	0
12	5	166	0.9 (−1.5 to 3.4)	60
LAVI, mL/m <sup>2</sup>				
3	1	36	0.0 (−4.2 to 4.2)	–
6	2	85	1.4 (−2.8 to 5.5)	0
12	3	110	−2.0 (−5.1 to 1.1)	0
TAPSE, cm				
3	1	36	1.0 (−0.3 to 2.3)	–
6	1	64	0.0 (−1.0 to 1.0)	–
12	4	127	0.6 (−0.4 to 1.7)	67
RVEDVI, mL/m <sup>2</sup>				
6	2	86	6.2 (3.4 to 9.0)	46
RVEDD (basal), mm				
12	2	42	2.0 (−1.1 to 5.0)	8

CI, confidence interval; HRQoL, health-related quality of life; LAVI, left atrial volume index; LVEF, left ventricular ejection fraction; mPAP, mean pulmonary artery pressure; mRAP, mean right atrial pressure; NT-proBNP, N-terminal pro brain natriuretic peptide; NYHA, New York Heart Association; PCWP, pulmonary capillary wedge pressure; RVEDD, right ventricular end-diastolic diameter; RVEDVI, right ventricular end-diastolic volume index; TAPSE, tricuspid annular plane systolic excursion; WU, wood units.

<sup>a</sup>As both the Minnesota Living with Heart Failure Questionnaire (MLHFQ) and Kansas City Cardiomyopathy Questionnaire show improvement and worsening of HRQoL on oppositely directed scales, the scores of the MLHFQ were reversed (higher scores indicate better HRQoL) before standardising.

for all IASDs, the procedure improved submaximal exercise capacity (measured by 6MWD) and HRQoL and appeared to be safe in the short term.

Importantly, most shunts were patent with a left-to-right-shunt at 12 months. In the PRELIEVE study, at least 92% of the shunts

(Occlutech Atrial Flow Regulator) were patent. In the remaining patients, shunt patency could not be confirmed due to inadequate quality of transthoracic echocardiography.<sup>25</sup> The first-generation v-Wave devices were patent in all patients at 3 months but became stenotic or occluded in half of the patients within 12 months

**Table 3** Serious adverse device-related effects

Outcome at follow-up, month	No. of studies	No. of patients	Risk (95% CI), %	I <sup>2</sup> , %
1	2	33	9 (1 to 22)	–
3	1	36	3 (0–12)	–
6	1	64	2 (0–7)	–
12	4	134	8 (1–20)	69
36	1	64	2 (0–7)	–

of follow-up.<sup>23</sup> In contrast to patients with occluded shunts, patients with patent first-generation v-Wave devices had improvements in haemodynamic parameters (PCWP decreased from  $23.3 \pm 5.4$  mmHg at baseline to  $18.0 \pm 4.0$  mmHg at 12 months;  $P = 0.011$ ) without worsening of right atrial or pulmonary artery pressures.<sup>23</sup> The key difference between the first-generation v-Wave device and the other IASD is its hourglass-shaped form with a one-way tricuspid bioprosthetic valve. Hence, in the second iteration of the device the valve was removed.<sup>24</sup> Moreover, the v-Wave devices had smaller fenestration diameters (5 mm)<sup>23,24</sup> than the Coriva IASD II (8 mm)<sup>26</sup> and the Occlutech Atrial Flow Regulator (8 or 10 mm).<sup>25</sup> Shunt flow is thought to increase with enlarged shunt size. A computational model demonstrated that as shunt flow increases, there is a progressive decrease in PCWP, increase in right ventricular cardiac output and decrease in left ventricular cardiac output.<sup>30</sup> These effects reached a plateau at a shunt diameter of 8–9 mm.<sup>30</sup> It is therefore conceivable that devices with larger fenestration diameters might translate into more pronounced haemodynamic effects. However, because of the small number of patients and the limited data on the extent of actual shunt flow, a relationship between the different shunt sizes and the resulting shunt flows could not be investigated herein.

After 12 months, the 6MWD (an indicator for submaximal exercise capacity), which was the pre-defined primary efficacy outcome, increased by about 10% (+28.1 m; 95% CI 10.92–45.31). Although the first-generation v-Wave trial reported shunt stenosis or occlusion in half of the patients, which again was associated with a lack of haemodynamic response, and the first- and second-generation v-Wave had smaller shunt diameters, there were no significant differences in 6MWD change across devices. Of note, the number of included studies and patients may have been too small to demonstrate a difference between devices. The importance of patient-centric outcomes, such as functional capacity and HRQoL, is increasingly recognised (also by regulatory agencies) because they provide relevant information beyond mortality and hospitalisation rates in strongly disabling conditions such as CHF.<sup>31</sup> In contrast to the assessment of the NYHA functional class, which is a physician-derived measure and thus subjective and amenable to bias, the 6-min walking test represents an objective measure that correlates well with peak aerobic capacity.<sup>31–33</sup> When compared with resting cardiac function, which weakly correlates with HRQoL and the capacity to perform daily activities (especially in HFpEF), submaximal exercise capacity measured

by 6MWD provides useful prognostic information for all-cause hospitalisation and mortality in HFpEF<sup>34</sup> and HFREF.<sup>35</sup> Changes in 6MWD are commonly assessed as primary outcomes or as part of a composite outcome in clinical trials.<sup>31</sup> For example, mean increases between 19 and 36 m in 6MWD have led to the approval of ambrisentan,<sup>36</sup> bosentan,<sup>37</sup> sitaxsentan,<sup>38</sup> and inhaled iloprost<sup>39</sup> for the treatment of pulmonary hypertension by the Food and Drug Administration. Herein, treatment with IASD increased 6MWD significantly in patients with LVEF >40%, whereas 6MWD did not change in patients with LVEF ≤40%.

The HRQoL is largely reduced in HFpEF and HFREF.<sup>40</sup> In all of the included studies, HRQoL was assessed using the MLHFQ or KCCQ, which are both valid and reliable disease-specific measures for HRQoL.<sup>41,42</sup> HRQoL at baseline ranged between 38 and 58 points, which is lower as, for example, in the PARAGON-HF (KCCQ score  $71 \pm 19$  points) and PARADIGM-HF (KCCQ score  $73 \pm 19$  points) trials comparing sacubitril/valsartan with enalapril in patients with HFpEF and HFREF.<sup>40</sup> Treatment with an IASD significantly improved the standardised HRQoL by 17.7 points (95% CI 10.8–24.6). In general, a change of 5 points is considered a modest but clinically important change<sup>43</sup> whereas changes between 10 and 20 points are interpreted as moderate-to-large.<sup>43</sup> The improvements in HRQoL are larger than for most approved pharmacological CHF therapies. In the DAPA-HF trial, treatment with dapagliflozin increased the KCCQ total symptom score at 8 months by 7.0 points in diabetics and by 5.4 points in non-diabetics.<sup>44</sup> Similarly large improvements were only reported for transvenous edge-to-edge mitral valve repair of secondary mitral regurgitation where KCCQ score improved by 12.5 points.<sup>6,45</sup> One may speculate that the invasiveness of the procedure and lack of a sham control contributed to the relatively large effects on HRQoL seen in the device-based trials.

The shunting of blood from the left atrium to the lower-pressure right atrium resulted in decreases in PCWP at 1 and 12 months, increases in mRAP at 6 and 12 months, and modest decreases in pulmonary vascular resistance at rest. The PRELIEVE study was the only study to report the change in PCWP for patients with HFpEF and HFREF separately. While PCWP significantly dropped in patients with HFpEF (median  $-5$  mmHg, 95% CI  $-12.5$  to  $-1.5$ ;  $P = 0.0004$ ), there was no significant change in patients with HFREF (median  $-4$  mmHg, 95% CI  $-9.0$  to  $0$ ;  $P = 0.1$ ).<sup>29</sup> Of note, invasive haemodynamic measures obtained at rest are not predictive of haemodynamic changes during exercise, but, especially in HFpEF, the steep increase in left atrial pressure during exercise is thought to cause dyspnoea on exertion.<sup>46</sup> Therefore, workload-corrected PCWP was found to significantly correlate with 6MWD in these patients.<sup>46</sup> However, only the REDUCE LAP-HF study and REDUCE LAP-HF I trial provided haemodynamic parameters during exercise.<sup>21,22</sup> There were no consistent changes in PCWP during peak exercise, possibly because of the small number of patients included. The REDUCE LAP-HF study found a significant decrease in workload-corrected PCWP at 6 months ( $-15.0$  mmHg, 95% CI  $-25.9$  to  $-4.1$ ).<sup>21</sup> In the absence of invasive haemodynamic measurements during exercise, the improvements in functional capacity and HRQoL might better

reflect the haemodynamic improvements during exercise than resting haemodynamics.

Despite the positive effects of IASD treatment, especially on functional capacity and HRQoL, the results should be interpreted with caution before confirmed by larger and adequately powered, randomised trials investigating the effects on HF hospitalisation and mortality. In the Corvia Feasibility study, during the year before IASD implantation, 55% of the patients were admitted to the hospital due to worsening of HF<sup>27</sup> whereas herein 15% of the patients had at least one HF hospitalisation event during the first year. Although analyses of the effects of left atrial decompression on mortality are not feasible with the available data, it is reassuring that, in the included studies, the all-cause mortality rate following IASD implantation (7.5 per 100 patient-years) was lower than the predicted mortality rate (10.2 per 100 patient-years; 95% CI 6.1–16.9) calculated using the validated Meta-analysis Global Group in CHF (MAGGIC) prognostic model<sup>47</sup> for patients included in the REDUCE LAP-HF study.<sup>28</sup> Moreover, the available data do not indicate an increased risk of stroke or right HF after IASD implant.

## Limitations

Some limitations of our analysis need to be acknowledged. First, this meta-analysis mainly included small single-arm feasibility studies without control groups and variable short to intermediate follow-up durations. Therefore, we cannot exclude unspecific treatment effects, such as the placebo effect. The small number of studies included could be of concern for the generalisability of our results. Although the improvements in clinical outcomes, such as 6MWD and HRQoL, are promising, they need to be confirmed by adequately powered and ideally sham-controlled trials. Currently, several sham-controlled trials, such as RELIEVE-HF (ClinicalTrials.gov, NCT03499236), REDUCE LAP-HF II (ClinicalTrials.gov, NCT03088033), and FROST-HF (ClinicalTrials.gov, NCT03751748) are ongoing. Second, this study-level meta-analysis is not based on individual patient data. Third, it is important to keep in mind that functional outcomes, including 6MWD, are not solely dependent on cardiopulmonary conditions. Fourth, only four studies (67%) reported that blinded, independent clinical event committees were involved to adjudicate clinical events. In the other two trials clinical event adjudication relied on reports of the investigators. Further trials involving adjudication of centralised events are needed to provide definitive data for the short- and long-term safety of the devices.

## Conclusion

Interatrial shunt device implantation for the treatment of CHF is feasible and associated with significant improvements in patient-centric outcomes, such as the submaximal exercise capacity (measured by 6MWD), and HRQoL improved significantly in both HFrEF and HFpEF. These results need to be confirmed by larger sham-controlled trials.

## Supplementary Information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

## Funding

T.V.P. is funded by the Chevening Scholarship Program (Foreign and Commonwealth Office, United Kingdom).

**Conflict of interest:** T.V.P. is supported by the Chevening Scholarship Program (Foreign and Commonwealth Office, United Kingdom). S.E. has received scientific support and speaker honoraria from Medtronic, ReCor Medical, AstraZeneca, Daiichi Sankyo, Bayer and Novartis. A.J.S.C. reports personal fees from AstraZeneca, Bayer, Boehringer Ingelheim, Menarini, Novartis, Nutricia, Servier, Vifor, Abbott, Actimed, Arena, Cardiac Dimensions, Corvia, CVRx, Enopace, ESN Cleer, Faraday, WL Gore, Impulse Dynamics, and Respicardia. M.B. reports personal fees from Abbott, Amgen, AstraZeneca, Bayer, Boehringer Ingelheim, Bristol-Myers Squibb, Vifor, Servier, Medtronic, and Novartis; and grants from Deutsche Forschungsgemeinschaft (SFB TRR219) and AstraZeneca. S.D.A. reports grants and personal fees from Vifor Int and Abbott Vascular, and personal fees from Bayer, Boehringer Ingelheim, Novartis, Servier, Cardiac Dimensions, Thermo Fisher Scientific, AstraZeneca, Occlutech, Actimed, and Respicardia. F.M. is supported by Deutsche Gesellschaft für Kardiologie (DGK) and Deutsche Forschungsgemeinschaft (SFB TRR219) and has received scientific support and speaker honoraria from Bayer, Boehringer Ingelheim, Medtronic and ReCor Medical. All other authors have nothing to disclose.

## Acknowledgement

Open Access funding enabled and organized by Projekt DEAL.

## References

- Bozkurt B, Coats AJ, Tsutsui H, Abdelhamid CM, Adamopoulos S, Albert N, Anker SD, Atherton J, Böhm M, Butler J, Drazner MH, Felker GM, Filippatos G, Fiuzat M, Fonarow GC, Gomez-Mesa J, Heidenreich P, Imamura T, Jankowska EA, Januzzi J, Khazanie P, Kinugawa K, Lam CSP, Matsue Y, Metra M, Ohtani T, Piepoli MF, Ponikowski P, Rosano GMC, Sakata Y, Seferović P, Starling RC, Teerlink JR, Vardeny O, Yamamoto K, Yancy C, Zhang J, Zieroth S. Universal definition and classification of heart failure: a report of the Heart Failure Society of America, Heart Failure Association of the European Society of Cardiology, Japanese Heart Failure Society and Writing Committee of the Universal Definition of Heart Failure: Endorsed by the Canadian Heart Failure Society, Heart Failure Association of India, Cardiac Society of Australia and New Zealand, and Chinese Heart Failure Association. *Eur J Heart Fail* 2021;**23**:352–380.
- McDonagh TA, Metra M, Adamo M, Gardner RS, Baumbach A, Böhm M, Burri H, Butler J, Čelutkienė J, Chioncel O, Cleland JGF, Coats AJS, Crespo-Leiro MG, Farmakis D, Gilard M, Heymans S. 2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure. *Eur Heart J* 2021;**42**: 3599–3726.
- Anker SD, Butler J, Filippatos G, Ferreira JP, Bocchi E, Böhm M, Brunner-La Rocca HP, Choi DJ, Chopra V, Chuquiure-Valenzuela E, Giannetti N, Gomez-Mesa JE, Janssens S, Januzzi JL, Gonzalez-Juanatey JR, Merkely B, Nicholls SJ, Perrone SV, Piña IL, Ponikowski P, Senni M, Sim D, Spinar J, Squire I, Taddei S, Tsutsui H, Verma S, Vinereanu D, Zhang J, Carson P, Lam CSP, Marx N, Zeller C, Sattar N, Jamal W, Schnaidt S, Schnee JM, Brueckmann M, Pocock SJ, Zannad F, Packer M, EMPEROR-Preserved Trial Investigators. Empagliflozin in heart failure with a preserved ejection fraction. *N Engl J Med*. 2021;**385**:1451–1461.

4. Reddy YNV, Obokata M, Wiley B, Koepf KE, Jorgenson CC, Egbe A, Melonovsky V, Carter RE, Borlaug BA. The haemodynamic basis of lung congestion during exercise in heart failure with preserved ejection fraction. *Eur Heart J* 2019;**40**:3721–3730.
5. Abraham WT, Stevenson LW, Bourge RC, Lindenfeld JA, Bauman JG, Adamson PB. Sustained efficacy of pulmonary artery pressure to guide adjustment of chronic heart failure therapy: complete follow-up results from the CHAMPION randomised trial. *Lancet* 2016;**387**:453–461.
6. Abraham WT. Interatrial shunting for the treatment of heart failure: an on-demand, self-regulating left atrial pressure system. *Eur J Heart Fail* 2021;**23**:811–813.
7. Fallick C, Sobotka PA, Dunlap ME. Sympathetically mediated changes in capacitance. *Circ Heart Fail* 2011;**4**:669–675.
8. Sambhi MP, Zimmerman HA. Pathologic physiology of Lutembacher syndrome. *Am J Cardiol* 1958;**2**:681–686.
9. Griffin JM, Borlaug BA, Komtebedde J, Litwin SE, Shah SJ, Kaye DM, Hoenferd E, Hasenfuß G, Gustafsson F, Wolosk E, Uriel N, Burkhoff D. Impact of interatrial shunts on invasive hemodynamics and exercise tolerance in patients with heart failure. *J Am Heart Assoc* 2020;**9**:e016760.
10. Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *J Clin Epidemiol* 2009;**62**:1006–1012.
11. Deeks J, Dinnes J, D'Amico R, Sowden A, Sakarovich C, Song F, Petticrew M, Altman D. Evaluating non-randomised intervention studies. *Health Technol Assess (Rockv)* 2003;**7**:101–107.
12. Sterne JAC, Savović J, Page MJ, Elbers RG, Blencowe NS, Boutron I, Cates CJ, Cheng HY, Corbett MS, Eldridge SM, Emberson JR, Hernán MA, Hopewell S, Hróbjartsson A, Junqueira DR, Jüni P, Kirkham JJ, Lasserson T, Li T, McAleenan A, Reeves BC, Shepperd S, Shrier I, Stewart LA, Tilling K, White IR, Whiting PF, Higgins JPT. RoB 2: a revised tool for assessing risk of bias in randomised trials. *BMJ* 2019;**366**:i4898.
13. Higgins JPT, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, Welch VA, eds. *Cochrane Handbook for Systematic Reviews of Interventions*, 2nd ed. Chichester, UK: The Cochrane Collaboration; 2019.
14. Wan X, Wang W, Liu J, Tong T. Estimating the sample mean and standard deviation from the sample size, median, range and/or interquartile range. *BMC Med Res Methodol* 2014;**14**:135.
15. Shi J, Luo D, Weng H, Zeng X, Lin L, Chu H, Tong T. Optimally estimating the sample standard deviation from the five-number summary. *Res Synth Methods* 2020;**11**:641–654.
16. Higgins JPT, White IR, Anzueto-Cabrera J. Meta-analysis of skewed data: combining results reported on log-transformed or raw scales. *Stat Med* 2008;**27**:6072–6092.
17. Hanley JA, Lippman-Hand A. If nothing goes wrong, is everything all right? *JAMA* 1983;**249**:1743–1745.
18. Nyaga VN, Arbyn M, Aerts M. Metaprop: a Stata command to perform meta-analysis of binomial data. *Arch Public Health* 2014;**72**:39.
19. Veroniki AA, Jackson D, Viechtbauer W, Bender R, Bowden J, Knapp G, Kuss O, Higgins JP, Langan D, Salanti G. Methods to estimate the between-study variance and its uncertainty in meta-analysis. *Res Synth Methods* 2016;**7**:55–79.
20. Søndergaard L, Reddy V, Kaye D, Malek F, Walton A, Mates M, Franzen O, Neuzil P, Ihlemann N, Gustafsson F. Transcatheter treatment of heart failure with preserved or mildly reduced ejection fraction using a novel interatrial implant to lower left atrial pressure. *Eur J Heart Fail* 2014;**16**:796–801.
21. Hasenfuß G, Hayward C, Burkhoff D, Silvestry FE, McKenzie S, Gustafsson F, Malek F, Van der Heyden J, Lang I, Petrie MC, Cleland JGF, Leon M, Kaye DM. A transcatheter intracardiac shunt device for heart failure with preserved ejection fraction (REDUCE LAP-HF): a multicentre, open-label, single-arm, phase 1 trial. *Lancet* 2016;**387**:1298–1304.
22. Feldman T, Mauri L, Kahwash R, Litwin S, Ricciardi MJ, van der Harst P, Penicka M, Fail PS, Kaye DM, Petrie MC, Basuray A, Hummel SL, Forde-McLean R, Nielsen CD, Lilly S, Massaro JM, Burkhoff D, Shah SJ. Transcatheter interatrial shunt device for the treatment of heart failure with preserved ejection fraction (REDUCE LAP-HF I [Reduce Elevated Left Atrial Pressure in Patients with Heart Failure]). *Circulation* 2018;**137**:364–375.
23. Rodés-Cabau J, Bernier M, Amat-Santos IJ, Ben Gal T, Nombela-Franco L, García del Blanco B, Kerner A, Bergeron S, del Trigo M, Pibarot P, Shkurovich S, Eigler N, Abraham WT. Interatrial shunting for heart failure: early and late results from the first-in-human experience with the V-wave system. *JACC Cardiovasc Interv* 2018;**11**:2300–2310.
24. Guimarães L, Bergeron S, Bernier M, Rodriguez-Gabella T, del Val D, Pibarot P, Eigler N, Abraham WT, Rodés-Cabau J. Interatrial shunt with the second-generation V-wave system for patients with advanced chronic heart failure. *EuroIntervention* 2020;**15**:1426–1428.
25. Paitazoglou C, Özdemir R, Pfister R, Bergmann MW, Bartunek J, Kilic T, Lauten A, Schmeisser A, Zoghi M, Anker S, Sievert H, Mahfoud F. The AFR-PRELIEVE trial: a prospective, non-randomised, pilot study to assess the Atrial Flow Regulator (AFR) in heart failure patients with either preserved or reduced ejection fraction. *EuroIntervention* 2019;**15**:403–410.
26. Malek F, Neuzil P, Gustafsson F, Kaye DM, Walton A, Mates M, Søndergaard L, Ihlemann N, Mariani JA, Reddy V. Clinical outcome of transcatheter treatment of heart failure with preserved or mildly reduced ejection fraction using a novel implant. *Int J Cardiol* 2015;**187**:227–228.
27. Kaye DM, Hasenfuß G, Neuzil P, Post MC, Doughty R, Trochu JN, Kolodziej A, Westenfeld R, Penicka M, Rosenberg M, Walton A, Muller D, Walters D, Hausleiter J, Raake P, Petrie MC, Bergmann M, Jondeau G, Feldman T, Van Veldhuisen DJ, Ponikowski P, Silvestry FE, Burkhoff D, Hayward C. One-year outcomes after transcatheter insertion of an interatrial shunt device for the management of heart failure with preserved ejection fraction. *Circ Heart Fail* 2016;**9**:e003662.
28. Kaye DM, Petrie MC, McKenzie S, Hasenfuß G, Malek F, Post M, Doughty RN, Trochu JN, Gustafsson F, Lang I, Kolodziej A, Westenfeld R, Penicka M, Rosenberg M, Hausleiter J, Raake P, Jondeau G, Bergmann MW, Spelman T, Aytug H, Ponikowski P, Hayward C. Impact of an interatrial shunt device on survival and heart failure hospitalization in patients with preserved ejection fraction. *ESC Heart Fail* 2019;**6**:62–69.
29. Paitazoglou C, Bergmann MW, Özdemir R, Pfister R, Bartunek J, Kilic T, Lauten A, Schmeisser A, Zoghi M, Anker S, Sievert H, Mahfoud F; AFR-PRELIEVE Investigators. One-year results of the first-in-man study investigating the Atrial-Flow-Regulator for left atrial shunting in symptomatic heart failure patients: the PRELIEVE study. *Eur J Heart Fail* 2021;**23**:800–810.
30. Kaye D, Shah SJ, Borlaug BA, Gustafsson F, Komtebedde J, Kubo S, Magnin C, Maurer MS, Feldman T, Burkhoff D. Effects of an interatrial shunt on rest and exercise hemodynamics: results of a computer simulation in heart failure. *J Card Fail* 2014;**20**:212–221.
31. Butler J, Hamo CE, Udelson JE, Pitt B, Yancy C, Shah SJ, Desvigne-Nickens P, Bernstein HS, Clark RL, Depre C, Dinh W, Hamer A, Kay-Mugford P, Kramer F, Lefkowitz M, Lewis K, Maya J, Maybaum S, Patel MJ, Pollack PS, Roessig L, Rotman S, Salsali A, Sims JJ, Senni M, Rosano G, Dunmon P, Stockbridge N, Anker SD, Zile MR, Gheorghiade M. Exploring new endpoints for patients with heart failure with preserved ejection fraction. *Circ Heart Fail* 2016;**9**:e003358.
32. Reddy YNV, Rikhi A, Obokata M, Shah SJ, Lewis GD, AbouEzzedine OF, Dunlay S, McNulty S, Chakraborty H, Stevenson LW, Redfield MM, Borlaug BA. Quality of life in heart failure with preserved ejection fraction: importance of obesity, functional capacity, and physical inactivity. *Eur J Heart Fail* 2020;**22**:1009–1018.
33. Lauder L, da Costa BR, Ewen S, Scholz SS, Wijns W, Lüscher TF, Serruys PW, Edelman ER, Capodanno D, Böhm M, Jüni P, Mahfoud F. Randomized trials of invasive cardiovascular interventions that include a placebo control: a systematic review and meta-analysis. *Eur Heart J* 2020;**41**:2556–2569.
34. Forman DE, Fleg JL, Kitzman DW, Brawner CA, Swank AM, McKelvie RS, Clare RM, Ellis SJ, Dunlap ME, Bittner V. 6-min walk test provides prognostic utility comparable to cardiopulmonary exercise testing in ambulatory outpatients with systolic heart failure. *J Am Coll Cardiol* 2012;**60**:2653–2661.
35. Mangla A, Kane J, Beaty E, Richardson D, Powell LH, Calvin JE. Comparison of predictors of heart failure-related hospitalization or death in patients with versus without preserved left ventricular ejection fraction. *Am J Cardiol* 2013;**112**:1907–1912.
36. Galiè N, Olschewski H, Oudiz RJ, Torres F, Frost A, Ghofrani HA, Badesch DB, McGoon MD, McLaughlin VV, Roecker EB, Gerber MJ, Dufton C, Wiens BL, Rubin LJ. Ambrisentan for the treatment of pulmonary arterial hypertension: results of the ambrisentan in pulmonary hypertension, randomized, double-blind, placebo-controlled, multicenter, efficacy (ARIES) study 1 and 2. *Circulation* 2008;**117**:3010–3019.
37. Galiè N, Rubin L, Hooper M, Jansa P, Al-Hiti H, Meyer G, Chiossi E, Kusic-Pajic A, Simonneau G. Treatment of patients with mildly symptomatic pulmonary arterial hypertension with bosentan (EARLY study): a double-blind, randomised controlled trial. *Lancet* 2008;**371**:2093–2100.
38. Barst RJ, Langleben D, Badesch D, Frost A, Lawrence EC, Shapiro S, Naeije R, Galiè N; STRIDE-2 Study Group. Treatment of pulmonary arterial hypertension with the selective endothelin-A receptor antagonist sitaxsentan. *J Am Coll Cardiol* 2006;**47**:2049–2056.
39. Olschewski H, Simonneau G, Galiè N, Higenbottam T, Naeije R, Rubin LJ, Nikkho S, Speich R, Hooper MM, Behr J, Winkler J, Sitbon O, Popov VV, Ghofrani HA, Manes A, Kiely DG, Ewert R, Meyer A, Corris PA, Delcroix M, Gomez-Sanchez M, Siedentop H, Seeger W; Aerosolized Iloprost Randomized Study Group. Inhaled iloprost for severe pulmonary hypertension. *N Engl J Med* 2002;**347**:322–329.

40. Chandra A, Vaduganathan M, Lewis EF, Claggett BL, Rizkala AR, Wang W, Lefkowitz MP, Shi VC, Anand IS, Ge J, Lam CSP, Maggioni AP, Martinez F, Packer M, Pfeffer MA, Pieske B, Redfield MM, Rouleau JL, Van Veldhuisen DJ, Zannad F, Zile MR, McMurray JJV, Solomon SD; PARAGON-HF Investigators. Health-related quality of life in heart failure with preserved ejection fraction. *JACC Heart Fail* 2019;**7**:862–874.
41. Spertus JA, Jones PG, Sandhu AT, Arnold SV. Interpreting the Kansas City Cardiomyopathy Questionnaire in clinical trials and clinical care. *J Am Coll Cardiol* 2020;**76**:2379–2390.
42. Guyatt GH. Measurement of health-related quality of life in heart failure. *J Am Coll Cardiol* 1993;**22**:A185–A191.
43. Spertus J, Peterson E, Conard MW, Heidenreich PA, Krumholz HM, Jones P, McCullough PA, Pina I, Tooley J, Weintraub WS, Rumsfeld JS. Monitoring clinical changes in patients with heart failure: a comparison of methods. *Am Heart J* 2005;**150**:707–715.
44. Petrie MC, Verma S, Docherty KF, Inzucchi SE, Anand I, Belohlávek J, Böhm M, Chiang CE, Chopra VK, de Boer RA, Desai AS, Diez M, Drozd J, Dukát A, Ge J, Howlett J, Katova T, Kitakaze M, Ljungman CEA, Merkely B, Nicolau JC, O'Meara E, Vinh PN, Schou M, Tereshchenko S, Køber L, Kosiborod MN, Langkilde AM, Martinez FA, Ponikowski P, Sabatine MS, Sjöstrand M, Solomon SD, Johanson P, Greasley PJ, Boulton D, Bengtsson O, Jhund PS, McMurray JJV. Effect of dapagliflozin on worsening heart failure and cardiovascular death in patients with heart failure with and without diabetes. *JAMA* 2020;**323**:1353–1368.
45. Stone GW, Lindenfeld J, Abraham WT, Kar S, Lim DS, Mishell JM, Whisenant B, Grayburn PA, Rinaldi M, Kapadia SR, Rajagopal V, Sarembok J, Brieke A, Marx SO, Cohen DJ, Weissman NJ, Mack MJ; COAPT Investigators. Transcatheter mitral-valve repair in patients with heart failure. *N Engl J Med* 2018;**379**:2307–2318.
46. Wolsk E, Kaye D, Borlaug BA, Burkhoff D, Kitzman DW, Komtebedde J, Lam CSP, Ponikowski P, Shah SJ, Gustafsson F. Resting and exercise haemodynamics in relation to six-minute walk test in patients with heart failure and preserved ejection fraction. *Eur J Heart Fail* 2018;**20**:715–722.
47. Meta-analysis Global Group in Chronic Heart Failure (MAGGIC). The survival of patients with heart failure with preserved or reduced left ventricular ejection fraction: an individual patient data meta-analysis. *Eur Heart J* 2012;**33**:1750–1757.