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STATE OF THE ART REVIEW
Heart failure and cardiomyopathies

Therapeutic left-to-right shunting in heart failure

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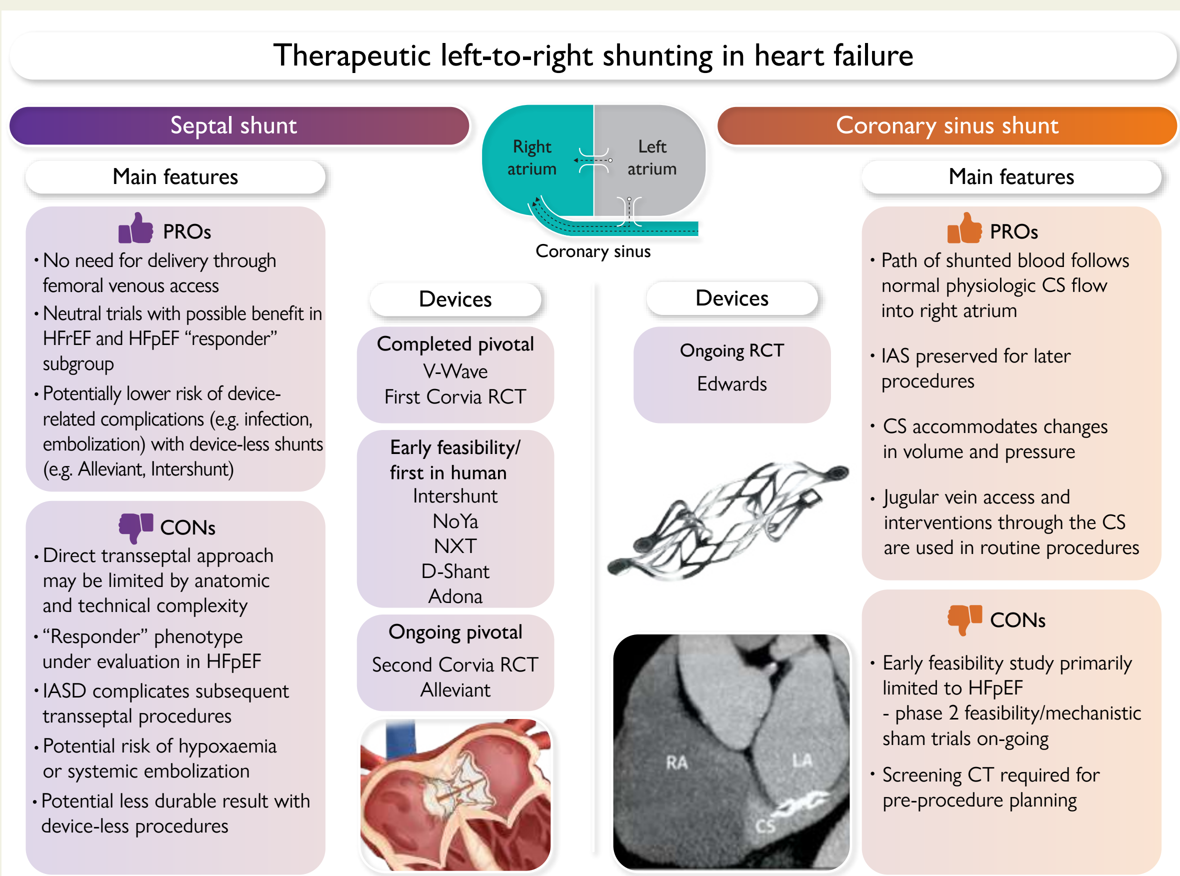
Graphical Abstract



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Therapeutic left-to-right shunting in heart failure. CS, coronary sinus; CT, computed tomography; HF, heart failure; HFpEF, heart failure with preserved ejection fraction; IAS, interatrial septum; IASD, interatrial shunt device; LA, left atrium; LAP, left atrial pressure; RA, right atrium; RCT, randomized controlled trial.

Abstract

Heart failure with reduced or preserved ejection fraction is associated with elevated left atrial pressure at rest due to fluid overload or during exercise, leading to pulmonary venous congestion. Even with available treatments, heart failure hospitalizations remain high, and improvements in quality-of-life scores and functional capacity are modest. Thus, there is growing interest in non-pharmacological methods to decompress the left atrium and improve heart failure symptoms and outcomes. Left-to-right shunts have emerged as a potential therapeutic option to reduce left atrial hypertension, improve quality of life, and impact long-term outcomes. This nascent field carries both potential therapeutic promise and many unanswered questions. Recent data have questioned whether the effects of this therapy vary based on the left ventricular ejection fraction, pulmonary vascular resistance, and/or right ventricular structure and function. This review discusses the basis for left-to-right shunt therapies, synthesizes past and ongoing clinical trials, and offers future directions.

Keywords Heart failure • Atrial shunt • Interatrial shunt device • Coronary sinus • Exercise haemodynamic testing • Pulmonary vascular disease

Introduction

Heart failure (HF) affects over 64 million people worldwide.[1] Despite advances in medical therapy, these patients remain at high risk for mortality and hospitalizations and suffer from impaired functional capacity and quality of life. For example, in the EMPEROR-Reduced (Empagliflozin Outcome Trial in Patients with Chronic Heart Failure and a Reduced Ejection Fraction) trial, patients with HF with reduced ejection fraction (HFrEF) were enrolled in the outpatient setting and ∼70% had New York Heart Association (NYHA) Class II symptoms, and yet, the annualized rate of hospitalization for HF or cardiovascular death in the empagliflozin arm was 15.8/100 person-years.[2]

A central hallmark of HF is elevated cardiac filling pressures.[3,4] Elevated left atrial (LA) pressure (LAP) often precedes the progression of symptoms and overt decompensation. Interventions aimed at lowering LAP may present an option to alleviate HF symptoms and improve outcomes.[5] Several left-to-right shunt devices to alleviate LA hypertension in patients with HF are under investigation. Herein, we provide an updated review of the pathophysiology as well as recent and ongoing research in this field of device innovation.

Left atrial hypertension and left atrial myopathy

Left atrial dysfunction is a hallmark of HF. The LA performs several functions: it is a reservoir, a conduit for left ventricular (LV) filling, and a pump in the active filling phase of the LV.[6] In patients with HF, the LV develops progressive systolic and diastolic dysfunction leading to elevated LV end-diastolic pressure and LAP. To compensate for the loss in LV relaxation and compliance, LA contractility becomes essential for diastolic filling.[7] Eventually, compensatory adaptations lead to remodelling and dysfunction of the LA, termed 'LA myopathy', that has been associated with pulmonary venous hypertension, right ventricular (RV) dysfunction, and diminished exercise tolerance.[8] Left atrial myopathy and impaired conduit function are associated with impaired early ventricular filling, as potential mechanism leading to impaired oxygen uptake, independent of incremental to abnormalities of LV diastolic dysfunction.[9]

Several studies have demonstrated that LA myopathy is also associated with an increased risk of mortality and HF hospitalizations. Khan *et al.*[10] identified LA reservoir strain as a negative prognostic factor in HF. An acute increase in LAP leads to lung congestion, while a sustained increase leads to long-term sequelae in the pulmonary vasculature.[4,11] In patients with HF with preserved ejection fraction (HFpEF) suffering from exertional dyspnoea, LA hypertension correlates with increased pulmonary artery (PA) pressures at rest and exercise and decreased cardiac output during exercise.[12] Sustained increases in PA pressures result in vascular remodelling leading to pulmonary hypertension (PH) and increased pulmonary vascular resistance (PVR). Patients with HF and PH have reduced exercise cardiac output and peak exercise oxygen consumption compared with those without PH.[11,12]

Right ventricular function impacts prognosis in HFrEF and HFpEF.[13,14] Increased PVR might be a consequence of longstanding LA hypertension, potentially contributing to increased RV afterload. Right ventricular diastolic dysfunction may be present early in the course of HFpEF and might also be associated with impairment in RV reserve.[15] Although resting RV function may be normal, exercise may unmask RV-PA uncoupling secondary to limited RV contractile reserve in the setting of increased afterload.[16] On echocardiography, RV-PA uncoupling may be measured as a low tricuspid annular plane systolic excursion (TAPSE) to PA systolic pressure (PASP) ratio and has been identified as a risk factor for adverse outcomes in HFpEF.[17] The RV-PA uncoupling has also been identified as a prognostic risk factor in patients with HFrEF and severe mitral regurgitation.[18] Sugimoto *et al.*[19] demonstrated that abnormal changes in LA strain, reflecting loss of reservoir function during exercise, correlate with abnormal ventilatory parameters measured by cardiopulmonary exercise testing and to RV-PA uncoupling. Therapies that enhance outcome and functional status in HF, such as sodium-glucose cotransporter-2 inhibitors, also improve RV-PA coupling during exercise.[20]

Decompression of the LA by creating a left-to-right shunt leads to the shifting of volume from the LA to the right atrium (RA), thus lowering LAP more than increasing systemic venous pressures.[21,22] Left-to-right shunts offer potential additional advantages that include (i) avoidance of complications associated with diuretic therapy including dehydration, renal insufficiency, and electrolyte imbalances; (ii) absence of resting or orthostatic hypotension; (iii) circumventing polypharmacy[23]; (iv) the fact that they are 'always active', instantaneously responding to changes in gradient from the LA to the RA, without delays requiring for drug absorption and metabolism; and (v) they are variably responsive, affording minimal left-to-right shunting when LAP is within normal limits, yet allowing increased shunting under conditions of elevated LAP, such as during physical exertion.

Conceptual framework

Much like in HFpEF, mitral stenosis symptomology is largely driven by elevated LAP. In 1916, Réné Lutembacher documented that the combination of mitral stenosis alongside a congenital atrial septal defect attenuated and delayed the onset of symptoms from the stenotic valve depending on the size of the defect.[24] The concept of an artificially created left-to-right shunt was proposed based on this principle. A small permanent opening would allow left-to-right shunting, thereby counteracting the elevated LAP that emerges during exertion, preventing pressure transmission to the pulmonary circulation. Utilizing computational modelling, Kaye *et al*. illustrated that an interatrial shunt (IAS) diameter up to 12 mm could lower pulmonary capillary wedge pressure (PCWP) by 3 mmHg at rest and 11 mmHg at peak exercise. At an optimal IAS diameter of 8 mm, a balance could be achieved between the need for a substantial reduction in LAP and the risk to the right heart and pulmonary circulation, limited within a pulmonary to systemic flow (Qp:Qs ratio) of 1.3–1.4:1.[25] Left-to-right shunt reduces PCWP by redistributing blood from the high-pressure LA to the lower-pressure right heart, resulting in a 25% increase in pulmonary blood flow.[26] Effects of left-to-right shunt on LA and RA haemodynamic parameters at rest and during exercise are shown in *Figure 1*.[25]

Left-to-right septal shunt devices

Main shunt devices and procedural landscape are reported in *Table 1*.

Corvia device

The IAS device (IASD), made by Corvia (Tewksbury, MA, USA), is a 19 mm wide self-expanding nitinol-based device with an 8 mm orifice diameter (*Table 1*).[27] The device legs are designed to remain flat on the LA side, reducing the risk of thrombus formation, while the RA side of the shunt includes legs to ensure the device stability. The device is deployed via a right femoral vein access and positioned in the fossa ovalis following an atrial septal puncture. Dual antiplatelet therapy is prescribed for 6 months, followed by lifelong aspirin. Patients previously on oral anticoagulants are advised to continue their oral anticoagulants, and endocarditis prophylaxis is initiated for a minimum of 6 months.[28,29]

Initial experience (NCT01570517)

The Corvia IASD was initially evaluated in 11 patients with LV ejection fraction (LVEF) > 45% (*Table 2*). The device was implanted successfully in all patients. The resting LV filling pressures were reduced at 30 days by 5.5 mmHg (19.7 ± 3.4 vs. 14.2 ± 2.7; $P = .005$), and there were improvements in NYHA class, 6-min walk distance (6MWD), and quality of life. No significant change was seen in the PA and RA pressures.[30] The PCWP response to exercise, expressed as the ratio of PCWP at peak exercise to effort normalized to body weight (mmHg/W/kg), demonstrated a decrease from 89.1 to 70.5 mmHg/W/kg.[22,31] Cardiac output did not change significantly at rest (4.8 vs. 5.1 L/min), alleviating concerns for an excessive decrease in systemic flow due to shunting. Favourable effects on pulmonary vascular elastance and compliance were observed, suggested to be related to enhanced pulmonary vascular recruitment with the shunt flow, with no impairment in systemic cardiac output responses at rest or exercise.[26] At 1 year, all patients survived, and beneficial effects on symptoms (NYHA class III/IV 45%/0% vs. 82%/18% at baseline; $P = .017$), functional capacity (baseline 6MWD 315 ± 152 m to 1 year 343 ± 76 m; $P =$ NS), and quality of life (Minnesota Living With Heart Failure score at baseline 53 ± 17 to 1 year 37 ± 17; $P = .057$) were sustained.[32] Furthermore, survival free from HF hospitalization requiring intravenous diuretics, with improved quality of life, was 73%.[32]

REDUCE LAP-HF study (NCT01913613)

The REDUCe Elevated Left Atrial Pressure in Patients with Heart Failure (REDUCE LAP-HF) was a multicentre (in Europe and Australia), open-label, single-arm, Phase 1 study designed to assess the performance and safety of the Corvia IASD in 64 patients with symptomatic HF despite pharmacological therapy, LVEF > 40%, and a raised PCWP at rest (>15 mmHg) or during exercise (>25 mmHg). All enrolled patients underwent right heart catheterization at rest and during exercise, both at baseline and 6 months after device implantation. In all patients, IASD placement was successful and showed to be safe and well tolerated during 6 months of follow-up. At 6 months, 52% of patients had a reduction in PCWP at rest, 58% had a lower PCWP during exertion, and 39% both criteria. It was observed a lower mean exercise PCWP at 6 months than at baseline, both at 20 W workload (32 mmHg at baseline vs. 29 mmHg at 6 months, $P = .0124$) and at peak exercise (34 mmHg vs. 32 mmHg, $P = .0255$), and a sustained device patency at 6 months confirmed by left-to-right shunting (Qp:Qs ratio 1.06 at baseline vs. 1.27 at 6 months, $P = .0004$).[22] At 1 year, reductions in PCWP were sustained, and Qp:Qs values remained stable.[33]

REDUCE LAP-HF I trial (NCT02600234)

The Reduce Elevated Left Atrial Pressure in Patients with Heart Failure (REDUCE LAP-HF I)[28] study was a Phase 2, sham-controlled, randomized study in 44 patients with LVEF ≥ 40%, NYHA Class III–IV symptoms, exercise PCWP ≥ 25 mmHg and PCWP-RA pressure gradients ≥ 5 mmHg. At 1 month, the IASD group showed to significantly reduce exercise PCWP at a workload of 20, 40, and 60 W compared with sham control group ($P = .028$), and also peak PCWP decreased by 3.5 ± 6.4 mmHg in the treatment group vs. 0.5 ± 5.0 mmHg in the control group ($P = .14$).[28] At 1 year, shunt patency was maintained among all patients, and there was a trend for decreased hospitalization with IASD. There were no appreciable differences in NYHA class, 6MWD, or quality of life.[34]

REDUCE LAP-HF II (NCT03088033)

The Study to Evaluate the Corvia Medical, Inc. IASD System II to Reduce Elevated Left Atrial Pressure in Patients with Heart Failure (REDUCE LAP-HF II) was a Phase 3, randomized, sham-controlled trial in 626 patients with HF and an ejection fraction > 40% and a PCWP of ≥25 mmHg with exercise while exceeding RA pressure by 5 mmHg. The primary endpoint was a hierarchical composite of cardiovascular death or non-fatal ischaemic strokes at 12 months, total HF events (defined as hospitalizations for HF, urgent visits for intravenous diuretics, or escalation of oral diuretics) up to 24 months, and a change in Kansas City Cardiomyopathy Questionnaire overall summary score (KCCQ-OSS) at 12 months. This trial failed to show a benefit on the primary endpoint [win ratio 1.0, 95% confidence interval (CI) 0.8–1.2, $P = .85$] or its individual components.[35] Despite a numeric excess in cardiovascular events in the IASD arm during the first year of the trial,

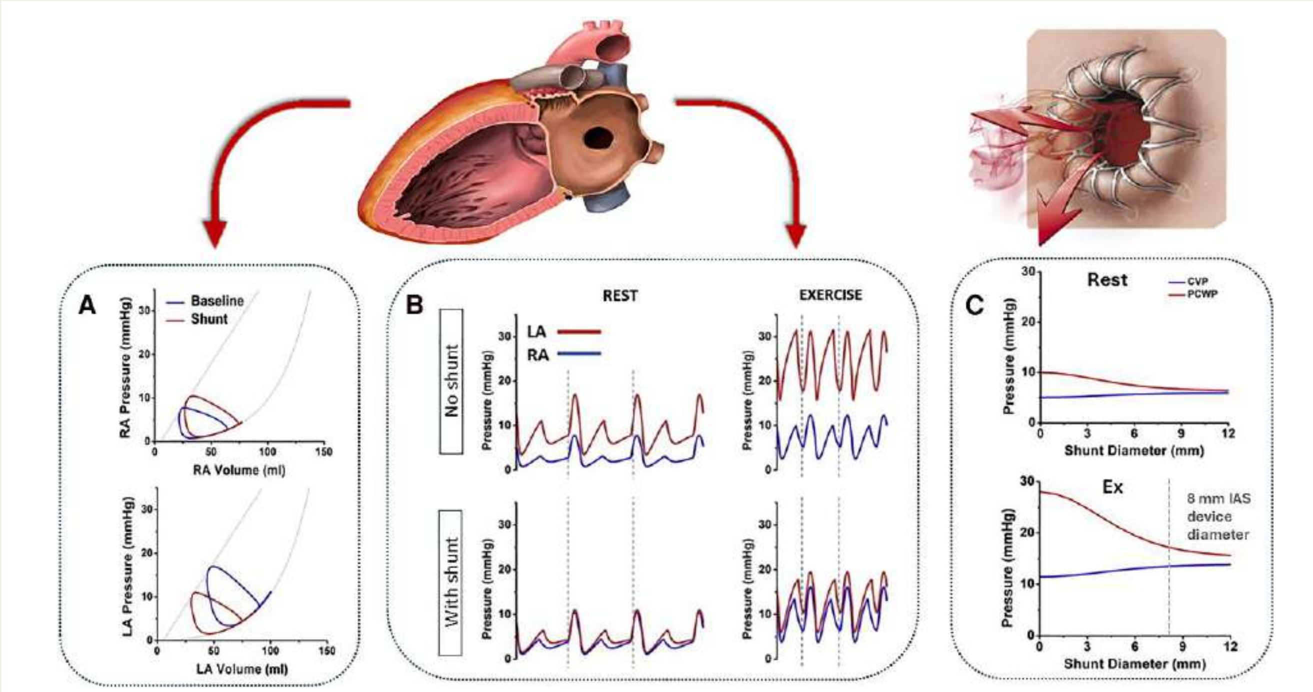


Figure 1 Changes in haemodynamic parameters in left atrium and right atrium at rest and during exercise, with and without interatrial shunt. (*A*) Pressure-volume loops of the left atrial and right atrial chambers under simulated resting conditions before (blue) and after (red) simulated introduction of an 8 mm interatrial shunt. (*B*) Right atrial and left atrial pressure tracings at rest (left column) and during exercise (right column). Without the shunt (top), both at rest and during exercise, there is a gradient between the left atrial and right atrial pressures (more pronounced during exercise); in both cases, the gradient was reduced after the shunt, although the pressure is always greater in the left atrium than in the right atrium. Dashed vertical lines indicate start of each beat. (*C*) Changes in haemodynamic parameters of left atrial and right atrial chambers observed varying shunt size from 1 to 12 mm at rest (top) and during exercise (bottom). A majority of the haemodynamic effects are seen with shunt sizes of 8–9 mm in diameter. Modified from Kaye *et al.*[25] CVP, central venous pressure; Ex, exercise; IAS, interatrial shunt; LA, left atrium; PCWP, pulmonary capillary wedge pressure; RA, right atrium

there was no difference in the composite safety endpoint between the two groups (38% vs. 31%; $P = .11$). In a prespecified analysis, patients with PASP > 70 mmHg at 20 W exercise or RA enlargement (volume index > 29.7 mL/m^2) and male sex were associated with worse outcomes. Patients with HF with mildly reduced ejection fraction (HFmrEF), pacemaker implantation, and significant LA enlargement also trended towards greater adverse events with left-to-right shunt therapy.[36]

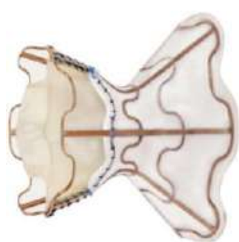
Responder analysis

In a *post hoc* analysis from REDUCE LAP-HF II, Borlaug *et al*. reported that the presence of latent pulmonary vascular disease (PVD), defined as an exercise PVR ≥ 1.74 WU, resulted in worse outcomes [win ratio 0.60 (95% CI 0.42–0.86); $P = .005$]. Patients with latent PVD ($n = 188$) were more likely to be older and to have atrial fibrillation, elevated resting LAP, and right heart dysfunction.[36] Patients with latent PVD had similar elevations in PCWP to those without latent PVD, but the rise in PA pressure with exercise was greater with an attenuated increase in cardiac index. Resting PVR did not accurately predict exercise-associated latent PVD. In patients without latent PVD or pacemakers [$n = 313$ (50%) of 626 randomized], left-to-right shunt therapy was associated with benefit [win ratio 1.51 (95% CI 1.14–2.00); $P = .004$]. Patients with a normal PCWP in whom exercise-induced LA hypertension occurs represent a subgroup of potential responders as they demonstrated lower PVR and an absence of pacemakers.[37] Accounting for 29% of the patients enrolled in REDUCE LAP-HF II, this subgroup of patients had lower LA volumes, natriuretic peptide levels, and incidence of atrial fibrillation, compared with patients with resting LA hypertension. This subgroup had similar symptom severity and significant PCWP increase with exercise. Diuretic therapy may reduce resting PCWP and lead to hypotension in the phenotype with normal resting PCWP and exercise-induced LA hypertension resulting in renal insufficiency, hypotension, and neurohormonal activation. Thus, left-to-right shunt therapy may be a promising alternative in this population.[37] Also, both the improvement in the responder group and worsened adverse outcomes in the non-responder group noted at 1 year were sustained at 2 years of follow-up.[38]

RESPONDER-HF (NCT05425459)

The short- and long-term benefits with the Corvia IASD in patients with HFmrEF and HFpEF remain uncertain. An ongoing trial, the Re-Evaluation of the Corvia Atrial Shunt Device in a Precision Medicine Trial to Determine Efficacy in Mildly Reduced or Preserved Ejection Fraction Heart Failure (RESPONDER-HF) trial, is being conducted in 260–750 patients (adaptive with a Bayesian design) with an LVEF > 40% with elevated exercise LAP but without latent PVD or right HF. This trial is specifically examining patients who meet the 'responder criteria' [i.e. no pacemaker/implantable cardioverter

Table 1 Shunt device and procedural landscape

Device type and description		Shunt diameter	Shunt type	Patient population	Current status
CORVIA Permanent implant Nitinol stent		8 mm	Atrial septum shunt	HFmrEF, HFpEF	**REDUCE LAP-HF II trial**: completed • $N = 621$, sham-controlled • LVEF $\geq$ 40% • 2-year outcomes available At 2 years: • No difference in the primary endpoint • Shunt patency at 24 months: 98% • In responders: shunt superior to sham, with 51% fewer HF events. In non-responders shunt inferior to sham **RESPONDER-HF confirmatory RCT**: enrolling • $N = 260$, sham-controlled • LVEF $\geq$ 40% • Peak exercise PVR < 1.75, no CIED
V-WAVE Permanent implant Nitinol/PTFE hourglass		5 mm [functionally 6.5 mm (Venturi effect)]	Atrial septum shunt	HFrEF, HFmrEF, HFpEF; PAH	**RELIEVE-HF pivotal RCT**: completed • $N = 508$, sham-controlled • All LVEFs • No exercise RHC • 2-year outcomes available At 2 years: • No primary safety events after shunt implantation • No difference in 2-year primary effectiveness outcome between shunt and placebo • Stratified randomized subgroups: harmful in HFpEF, effective in HFrEF
Occlutech Permanent implant Nitinol braid with central orifice		6 or 8 mm (10)	Atrial septum shunt	HFrEF, HFpEF, PAH	**FROST-HF pivotal RCT**: HALTED • $N = 588$, sham-controlled • All LVEFs • No exercise RHC • 6 mm vs. 8 mm shunt vs. sham

Continued

Table 1 ***Continued***

Device type and description		Shunt diameter	Shunt type	Patient population	Current status
Edwards Permanent implant Tubular nitinol device with retention arms		7 mm	Coronary sinus shunt	HFrEF, HFmrEF, HFpEF, ±PVD	**ALT-FLOW II RCT (phase 2)**: enrolling • *N* = 100, sham-controlled • LVEF ≥ 40% • Exercise RHC but no exercise PVR or CIED exclusions
Alleviant No implant: RF or excision to create shunt Coring catheter		6 mm	Atrial septum shunt	Variable	**ALLAY-HF RCT**: enrolling • *N* = 400–700, sham-controlled • LVEF ≥ 40% • Peak exercise PVR < 1.8, no CIED
NoYA No implant RF catheter		4–12 mm	Atrial septum shunt	HFrEF, HFmrEF, HFpEF	**RAISE-II study**: currently enrolling • *N* = 120 • LVEF ≥ 15% • No exercise RHC • Open-label
InterShunt No implant Cutting catheter		6 mm	Atrial septum shunt	HFmrEF, HFpEF	**EASE-HF study**: completed • *N* = 10 • LVEF ≥ 40% • Exercise RHC • Open-label

CIED, cardiac implantable electronic device; HFmrEF, heart failure with mildly reduced ejection fraction; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; LVEF, left ventricular ejection fraction; PAH, pulmonary arterial hypertension; PTFE, expanded polytetrafluoroethylene; PVD, pulmonary vascular disease; PVR, pulmonary vascular resistance; RF, radio frequency; RHC, right heart catheterization.

Table 2 Main clinical trials evaluating different interatrial shunt devices in heart failure

Device	CORVIA					V-Wave			Occlutech	
Trial	**Pilot**	**REDUCE LAP-HF**	**REDUCE LAP-HF-I**	**REDUCE LAP-HF-II**	**RESPONDER-HF**	**FIH**	**FIH Next Gen**	**RELIEVE-HF**	**AFR-PRELIEVE**	**FROST-HF**
Study design	Feasibility Single-arm	Single-arm Open-label	1:1 with sham procedure Crossover at 1 year	Randomized 1:1 to shunt vs. non-implant sham control Crossover at 2 years	Sham-controlled Unblinded at 2 years	Single-arm Open-label	Single arm	Randomized 1:1 to shunt vs. non-implant sham Crossover at 2 years allowed	Prospective	Randomized 6 mm, 8 mm, or sham
Subjects	11	64	44	626	260	38	6	508 randomized 97 roll-ins	108	698
Key inclusion/ exclusion criteria	• HHF within 12 months, or • NYHA Class III/ IV • LVEF ≥ 45%	• ≥40 years • LVEF > 40% • NYHA Class III • PCWP >14 mmHg (rest) or >25 mmHg (ex)	Inclusion: • LVEF ≥ 40% • NYHA II, III, IVa • PCWP ≥ 25 mmHg (ex) and >RAP by 5 mmHg Exclusion: • Severe HF • Dialysis or eGFR <25	Inclusion: • Same of REDUCE LAP-HF I Exclusion: • Significant VHD • Evidence of PAH • RV dysfunction	Inclusion: • Same of REDUCE LAP-HF I & II • Peak exercise pulmonary vascular resistance (PVR) < 1.75 Wood units Exclusion: • Cardiac rhythm management device • RV dysfunction	• LVEF > 15% • NYHA III or IV • on optimal GDMT • PCWP ≥15mmHg	• Same of FIH study	Inclusion: • Any LVEF • NYHA II, III, ambulatory IV • on optimal GDMT Exclusion: • PASP >70 mmHg, • PVR >4 WU, • ≥ moderate RV dysfunction	Inclusion: • HFrEF (LVEF >15% and <40%) or • HFmrEF and HFpEF (LVEF >40%–70%) • PCWP ≥15 (rest) or ≥25 mmHg (ex) Exclusion: • RV failure	Inclusion: • NYHA ≥Class II • If LVEF > 55%, PCWP ≥ 15 mmHg (rest), LA enlargement, or LVEDP ≥ 15 mmHg
Primary endpoint	Serious adverse device events	• Successful device implantation, • Reduction in PCWP (%) • Shunt patency • MACCE	• PCWP at 1 M • MACCE and renal events	• CV mortality or non-ischaemic stroke • HF events • Change in KCCQ	• Total HF events • Change in KCCQ	• MACNE at 3 months	• MACNE • HHF	• Safety: MACNE at 30 days • Effectiveness: Hierarchical composite: o Death o Heart transplant or LVAD o All HHF o All worsening HF events o Change in KCCQ	SADE within 3 months	• MACE • Composite: o CV death o Heart transplant or LVAD o HHF o HF treatment intensification o Change in KCCQ

Continued

Table 2 *Continued*

Device	CORVIA					V-Wave			Occlutech	
Trial	**Pilot**	**REDUCE LAP-HF**	**REDUCE LAP-HF-I**	**REDUCE LAP-HF-II**	**RESPONDER-HF**	**FIH**	**FIH Next Gen**	**RELIEVE-HF**	**AFR-PRELIEVE**	**FROST-HF**
Follow-up duration	30 days	1 year	1 month	24 months	12–24 months	12 months	3 months	24 months	12 months	12 months
Key findings/ notes	• Evidence of procedural safety • PCWP at rest ↓5 mmHg • Improvement in NYHA, QoL, and functional capacity	• Exercise PCWP at 20 W ↓3 mmHg and at peak exercise ↓2 mmHg • Sustained device patency • Significant and sustained improvement NYHA, QoL and functional capacity through 1 year	• ↓ PCWP with IASD • No effect on primary endpoint • Benefit with normal exercise PVR and without pacemaker.	At 24 months: • No differences in primary and safety endpoints • Shunt patency: 98% • PASP at 20 W of exercise > 70 mmHg, RAVi ≥ 29.7 mL/m^2, and men → worse outcomes • In responders: shunt superior to sham, with 51% fewer HF events, in non-responders shunt inferior to sham	Ongoing • Excludes patients with pacemaker/ ICD or peak exercise PVR 1.75 WU	• 2.6% MACE • NYHA Class I or II in 62% • KCCQ 73% improved >5 point • 6MWD ↑28 m • No significant change in PCWP	• Improvement in LVEF • NYHA Class I or II in 83% • KCCQ ↑32 • 6MWD ↑64 m	Roll-in data: • HFrEF: significantly improved RV and LV structure and function • HFpEF: improvement in RV size Final results: • MACNE rate = 0% • No difference for primary endpoint and KCCQ By baseline LVEF (stratified randomization): • HFrEF: improved clinical outcomes. • HFpEF: worse clinical outcomes.	• Increased CV mortality in HFrEF vs. HFpEF • 100% shunt patency • No worsening RV function	Currently on hold Active treatment group: 2 shunt sizes (6 and 8 mm) depending on resting PCWP

Device	Alleviant		APTURE			NoYA		InterShunt
Trial	**ALLEVIATE-HF I & II**	**ALLAY-HF**	**FIH**	**ALT-FLOW EFS (US)/Exploratory (CA)**	**ALT-FLOW II**	**RAISE Trial**	**RAISE-II**	**EASE-HF**
Study design	Feasibility	Randomized 1:1 Non-implant control Adaptive	Feasibility	Randomized	Randomized 1:1 Sham procedure	FIH Non-randomized Self-controlled	Objective performance criteria study Open-label	Open-label, pilot study
Subjects	15 + 13	500	11	100+	100	10	120	10
Key inclusion/ exclusion criteria	HFmrEF and HFpEF	HFmrEF and HFpEF	• HF • NYHA III or ambulatory IV • PCWP ≥ 15 mmHg (rest)	Inclusion: • LVEF ≥ 20% • PCWP ≥15 (rest) or ≥25 mmHg (ex) • PCWP > RAP by	Inclusion: • LVEF > 40% • NYHA Class II to IVa, • ≥1 prior HHF AND/ OR high NPs values	Inclusion: • HFpEF or HFmrEF • NYHA Class ≥II • ≥1 prior HHF AND/ OR high NPs values	Inclusion: • LVEF ≥ 15% • NYHA Class II to IVa, • ≥1 prior HHF • On optimal GDMT.	Inclusion: • Any LVEF • NYHA Class II to IVa,

Continued

Table 2 *Continued*

Device	Alleviant		APTURE			NoYA		InterShunt
Trial	**ALLEVIATE-HF I & II**	**ALLAY-HF**	**FIH**	**ALT-FLOW EFS (US)/Exploratory (CA)**	**ALT-FLOW II**	**RAISE Trial**	**RAISE-II**	**EASE-HF**
			and >RAP by 5 mmHg	>5 mmHg at rest or >10 mmHg (ex) Exclusion: • Severe HF • VHD • RV dysfunction	• ex PCWP 20 W ≥ 25 mmHg and PCWP 20 W > RAP 20 W by≥8 mmHg Exclusion: • Sever HF • VHD • ≥moderate RV dysfunction • Mean rest RAP > 15 mmHg • PVR ≥ 5.0 WU • CS lead or CRT	• Mean LAP > 15 mmHg Exclusion: • Severe RV dysfunction • CHD • VHD. • PASP > 70 mmHg.	• mLAP or end-expiratory resting PCWP ≥ 15 mmHg, and mLAP or PCWP-RA pressure ≥ 5 mmHg. Exclusion: • 6MWD <100 or >450 m. • Prior atrial septum implantation or inferior vena cava filter. • CRT/CRT-D or ICD • RV failure • PASP > 70 mmHg	• Resting RHC only
Follow-up duration	6 months	12 months	30 days	6 months	6 months	1–3 months	12 months	6 months
Primary endpoint	• MACCE, and thromboembolic events	• Composite: o Mortality o HHF o KCCQ	Procedural results	• MACCRE • Re-intervention at 30 days	• MACCRE: at 30 days • Change in ex PCWP at 20W	• Death or MACCE • Shunt performance (success and patency)	• Composite: o Cardiac death o HHF	• Safety and shunt patency
Key findings/ notes	• 100% patency • ↓ ex PCWP • ↑ 6MWD	Ongoing Excludes patients with pacemaker/ ICD or peak exercise PVR 1.75 WU	• PCWP: ↓8 mmHg • 73% device success	• ex PCWP at 20 W: ↓7 mmHg • Shunt patency: 100% • No RV dysfunction	Ongoing	• No major safety events • 3/10 shunts closed • ↓ NT-proBNP • ↑ 6MWD • ↓ NYHA class in 8/10	Ongoing	• Favourable safety at 30 days • Durability of shunt at 90 days

ASD, atrial septum defect; CHD, congenital heart disease; CRT/CRT-D, cardiac resynchronization therapy/-defibrillator; CV, cardiovascular; CVP, central venous pressure; eGFR, estimated glomerular filtration rate; ex, exercise; FIH, first-in-human; GDMT, guideline-directed medical therapy; HF, heart failure; HFmrEF, heart failure with mildly reduced ejection fraction; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; HHF, hospitalization for heart failure; IASD, interatrial shunt device; ICD, implantable cardioverter defibrillator; KCCQ, Kansas City Cardiomyopathy Questionnaire; LA, left atrium; LAP, left atrial pressure; LVAD, left ventricular assist device; LVEDP, left ventricular end-diastolic pressure; LVEF, left ventricular ejection fraction; MACCRE, major adverse cardiac, cerebrovascular, and renal events; MACE, major adverse cardiovascular events; MACCE, major adverse cardiac and cerebrovascular events; mLAP, mean left atrial pressure; NYHA, New York Heart Association; NPs, natriuretic peptides; NT-proBNP, N-terminal B-type natriuretic peptide; PAH, pulmonary arterial hypertension; PASP, pulmonary artery systolic pressure; PCWP, pulmonary capillary wedge pressure; PVR, pulmonary vascular resistance; QoL, quality of life; RA, right atrium; RAP, right atrial pressure; RAVi, right atrial volume index; RHC, right heart catheterization; RCT, randomized controlled trial; RV, right ventricle; SADE, Serious Adverse Device Effects; 6MWD, 6-min walking distance; TAPSE, tricuspid annular plane systolic excursion; VHD, valvular heart disease.

defibrillator (ICD) and with exercise PVR < 1.75 WU]. All patients have to undergo review by trial eligibility committee, which reviews resting echo and all of inclusion and exclusion criteria, clinical history, and prior haemodynamics (if available). The primary endpoint of this study is a composite of HF event rates and KCCQ scores initially at 12 months and then up to 5 years.

V-Wave device

The Ventura shunt (made by V-Wave Ltd, Caesarea, Israel) is a 5.1 mm diameter prosthesis with a self-expanding, hourglass-shaped nitinol stent frame. The device is placed in the fossa ovalis. The device length is 12 mm and the effective orifice diameter is 6.5 mm.[39,40] Patients are treated with dual antiplatelet therapy for 6 months post-device placement if not otherwise on oral anticoagulation.[41]

Initial experience

In early investigations, a version of the V-Wave shunt was tested that included a porcine pericardial leaflet valve within the neck of the shunt to prevent right-to-left shunting and paradoxical emboli. A cohort study enrolled 10 patients with LVEF < 40%, NYHA Class III–IV, and PCWP > 15 mmHg with no evidence of RV dysfunction. The shunt was successfully implanted in all patients, and echocardiography demonstrated shunt patency at 3 months. There was an improvement in NYHA class and 6MWD and a significant reduction in PCWP at 3 months.[39] A prospective single-arm open-label study was then conducted and included 38 patients (30 with HFrEF and 8 with HFpEF) without significant RV dysfunction or PH (PASP > 70 mmHg). At 3 and 12 months, improvements in NYHA class, quality-of-life measures, and 6MWD were observed.[42] At 12 months, however, shunt occlusion or stenosis occurred in 50% of patients with 5 of 36 having complete occlusion due to pannus infiltration of the valve. After 28 months, 10 deaths were reported (eight cardiovascular), and one patient each required LV assist device (LVAD) and transplant. In *post hoc* analysis, patients with shunt patency had lower rates of death, LVAD placement, cardiac transplantation, and hospitalizations for HF compared with those with shunt stenosis. Due to concerns about reduced long-term device patency, the second-generation V-Wave Ventura shunt was redesigned to be valveless. This second-generation V-Wave device was subsequently tested in 10 patients and had no shunt stenosis at 1 year.

RELIEVE-HF (NCT03499236)

The Reducing Lung Congestion Symptoms using the V-Wave shunt in advanced HF (RELIEVE-HF) trial evaluated the Ventura V-Wave shunt in both HFpEF and HFrEF patients with no upper or lower LVEF limits. Severe PH (PASP ≥ 70 mm/Hg or PVR > 4 WU) and moderate or greater RV dysfunction were key exclusions. Exercise haemodynamics were not assessed. Stratified randomizations were performed in patients with LVEF ≤40% and >40%. The primary safety endpoint was the incidence of device- or procedural-related major adverse cardiac or neurologic events (MACNE) at 30 days. The primary effectiveness endpoint, assessed at 24 months when the last randomized patient reached 12-month follow-up, was a hierarchical composite ranking of all-cause death, cardiac transplantation or LVAD implantation, all hospitalizations for HF, all outpatients worsening HF events, and change in KCCQ-OSS of at least 5 points at 12 months.

An open-label roll-in cohort included 97 treated patients and at 12 months demonstrated a reduction in LV end-systolic and end-diastolic volumes ($P = .02$ and .04, respectively) and an improvement in LVEF ($P = .009$), RV fractional area change ($P < .001$), and TAPSE ($P < .001$).[43]

The randomized cohort included 508 patients including 206 with LVEF ≤ 40% and 302 with LVEF > 40%. No patient developed a device or procedural-related MACNE through either 30-day or 2-year follow-up. There was no difference in the 2-year primary effectiveness outcome (win ratio 0.86, 95% CI 0.61–1.22; $P = .20$). However, the occurrence of adverse cardiovascular outcomes was sensitive to the baseline LVEF according to the stratified randomization: HFrEF patients showed fewer cardiovascular events with shunt treatment [annualized rate 49.0% vs. 88.6%; relative risk (RR) 0.55, 95% CI 0.42–0.73; $P < .0001$] compared with HFpEF patients, who showed more cardiovascular events (annualized rate 60.2% vs. 35.9%; RR 1.68, 95% CI 1.29–2.19; $P = .0001$; $P_{interaction} < .0001$). The better prognosis in shunt-treated HFrEF patients during 2-year follow-up was driven by a two-fold reduction in hospitalizations for HF [hazard ratio (HR) 0.52; 95% CI 0.31–0.86; $P = .01$], whereas the worse prognosis in shunt-treated HFpEF was driven by a three-fold increased rate of mortality (HR 3.24; 95% CI 1.38–7.59; $P = .004$) and a two-fold increase in HF hospitalizations (HR 2.05; 95% CI 1.35–3.10; $P = .0008$). An increasingly better prognosis after shunt treatment with progressively lower LVEF was shown in an assessment of the continuous relationship between LVEF and total cardiovascular events with an ≈40% cut-off. Finally, the KCCQ-OSS improved from baseline to 12 months to a similar degree in both the placebo and treatment arms among patients with either HFrEF or HFpEF, demonstrating a significant placebo effect. The discordant effects of the shunt on cardiovascular events and KCCQ in patients with HFrEF and HFpEF question the interpretation and utility of this quality-of-life metric in this trial.[44]

Atrial Flow Regulator

The Atrial Flow Regulator (AFR) device made by Occlutech (Helsingborg, Sweden) is a self-expandable double-disc nitinol-based device with a central fenestration, with manufactured diameters that could vary from 4 to 10 mm. The device is repositionable and retrievable.

Early data

A pilot study tested the 8 and 10 mm diameter AFR devices in HFrEF and HFpEF patients. Shunt patency was confirmed at 3 months and improvement in PCWP was demonstrated in the HFpEF cohort.[45]

AFR-PRELIEVE

The Pilot Study to Assess Safety and Efficacy of a Novel AFR in Heart Failure Patients (AFR-PRELIEVE) was an open-label, Phase 2 study of the AFR in patients with both HFpEF and HFrEF with PCWP ≥ 15 mmHg at rest or ≥25 mmHg with exercise. Patients with a resting PCWP ≥ 15 mmHg qualified for the 8 mm AFR and those with PCWP < 15 mmHg at rest but ≥25 mmHg with exercise qualified for the 10 mm AFR. In an early report, at 3 months, there was 100% device patency with haemodynamic and symptomatic improvement in 36 patients (16 with HFrEF and 20 with HFpEF). Three (8.3%) patients were hospitalized for HF (two HFrEF and one HFpEF).[45] One-year follow-up was reported from 53 patients (24 with HFrEF and 29 with HFpEF). At 12 months, there were two deaths and one patient withdrawal. Among 49 patients, shunt patency was demonstrated in 45 patients while 4 others had suboptimal imaging to assess the shunt. There was a 5 mmHg decrease in PCWP, but this was only significant in the HFpEF cohort. Although RV dilation was observed by echocardiography, there was no deterioration of RV function. New York Heart Association class, quality-of-life, and 6MWD were improved at 1 year.[46]

Alleviant system

The Alleviant (Austin, TX, USA) system uses radiofrequency energy to excise a 7 mm core of atrial septal tissue allowing for a precise left-to-right shunt without the need for an implant, potentially avoiding the risks from a permanent implant and facilitating future trans-septal procedures, e.g. atrial fibrillation ablation or mitral valve repair.

Early experience (NCT04583527 and NCT04838353)

The Evaluation of the Safety and Feasibility of a Percutaneously Created Interatrial Shunt to Alleviate Heart Failure Symptoms in Patients with Chronic Heart Failure and Preserved or Mid-Range Left Ventricular Ejection Fraction Studies 1 and 2 (ALLEVIATE-HF-1 and ALLEVIATE-HF-2) enrolled 28 patients with LVEF ≥ 40%. The patients had exercise PCWP ≥ 25 mmHg with a PCWP to RA pressure gradient of >5 mmHg. All 28 procedures were successful, and the average shunt diameter was 7.1 ± 0.9 mm. At 1 month, the peak exercise PCWP decreased by 5.4 ± 9.6 mmHg without significant change in RA pressures. Shunt patency was confirmed at 6 months. There were significant improvements in 6MWD, NYHA class, KCCQ scores, and natriuretic peptide levels.[47]

ALLAY-HF (NCT05685303)

The randomized, double-blind, sham-controlled Safety and Efficacy of the Alleviant System for No-Implant Interatrial Shunt Creation in Patients With Chronic Heart Failure (ALLAY-HF) trial is currently enrolling 400–700 patients with HF and LVEF ≥ 40%, exercise PCWP ≥ 25 mmHg, peak exercise PVR < 1.8 WU, and no cardiac implanted electronic devices who remain symptomatic despite medical therapy.[48]

NoYA system (ChiCTR1900027664)

Radiofrequency ablation has also been evaluated via a separate technique using an adjustable IAS system (NoYa, Hangzhou, China). The radiofrequency ablation-based shunt consists of a self-expanded flower-like nitinol stent fixed within the delivery sheath. The device was evaluated in 11 domestic pigs and 7 showed continuous shunting at 6 months. Subsequent 10 patients with LVEF > 40% with PCWP > 15 mmHg were assessed. An average shunt size of 5 mm was created, which remained patent in seven patients at 6 months. There were associated improvements in NYHA, 6MWD, and natriuretic peptide levels.[49]

RAISE II (NCT05375110)

NoYA is currently conducting the Radiofrequency Ablation-Based Interatrial Shunt for Heart Failure (RAISE II) trial, which is an open-label study of 120 patients with LVEF ≥ 15%, resting PCWP 15 mmHg, and PCWP-RA pressure gradient 5 mmHg. The primary endpoint is a composite of cardiovascular mortality and hospitalization for HF.[50]

InterShunt (NCT05403372)

The InterShunt (St Louis, MO, USA) percutaneous atrial shunt catheter system is device-less atrial shunt procedure that excises a 6 mm circular section of tissue in the atrial septum. An open-label study of 10 patients demonstrated favourable safety at 30 days and durability of left-to-right shunting at 90 days.[51]

Other devices

RiVet Shunt

RiVet Shunt (NTX Biomedical) is a novel shunt that provides a 'right-to-right' or 'pre-capillary' shunt. This 4 mm shunt is placed between right PA and superior vena cava, with the PA-RA gradient driving flow, creating a pulmonary-to-venous shunt with a Qp:Qs of 1.2–1.3 and without increasing pulmonary flow. As a consequence, all oxygenated blood contributes to the systemic output.[52] An early feasibility study in patients with HFpEF and Group 2 PH was started but was withdrawn due to logistic reasons.[53,54]

D-Shant

D-Shant interatrial septal device (Wuhan Vickor Medical Technology Co., Ltd) is a double disc and buckle-shaped mesh plug designed in four sizes (4, 6, 8, and 10 mm).[55] The first application of the D-Shant in six patients with chronic HF showed good safety and symptoms improvement.[56] Another study with the D-Shant device in 34 patients showed an improvement in functional status 6 months post-implantation.[56] Further studies are warranted in a larger cohort of patients with HF.

Adona Medical

Adona Medical device consists of an adjustable IAS design with biatrial pressure sensors that can adapt atrial shunt orifice size allowing for adjustment of shunt flow according to haemodynamic needs. The built-in haemodynamic sensors on both the LA and RA sides allow for biatrial pressure measurements without the need for patient involvement.[52] Recently, the company announced the initiation of first-in-human study in patients with HF.[57]

Coronary sinus shunt devices

Septal shunting vs. coronary sinus shunting

While traditional approaches to achieve increased blood flow from the left to right heart involve creating a shunt (with or without a permanent implant) in the interatrial septum, the alternative approach is a shunt from the LA to the coronary sinus (CS) (*Graphical Abstract*). The atriotomy formed directs flow from the LA to the CS and subsequently into the RA via the natural flow path of the CS.[58] Importantly, the normal entry of blood to the RA via its two anatomically offset and opposing inflow channels—the superior vena cava and the inferior vena cava together with entrained CS inflow—promotes the formation of a dominant vortex in the RA, which can be visualized by 4D magnetic resonance imaging. This critically preserves continuous organized motion of RA blood throughout the entire cardiac cycle, avoiding flow deceleration and preserving momentum and kinetic energy for efficient transfer to the RV.[59] The resultant flow distribution through the tricuspid valve in diastole creates similar basilar RV vortical flow patterns, which redirect high velocity RV inflow directly to the RV outflow tract for efficient systolic ejection.[60] Therapeutic shunt locations where entry of shunted blood into the RA is via natural flow paths such as the CS may be better able to offset the harmful effects of chronic volume overload on right heart size and function by better preserving blood flow momentum and energy transfer through the RA and RV. Furthermore, this procedure preserves the interatrial septum for future transcatheter procedures and minimizes the risk of right-to-left shunting/embolization due to the directional and continuous flow of the CS into the RA making paradoxical right-to-left embolization unlikely. Pressurization of the CS could enhance coronary perfusion,[61] as shown in patients with refractory angina[62] and microvascular angina. The latter were enrolled in a mechanistic trial in which an acute increase in CS pressure led to a decrease in microvascular resistance and an increase in blood flow, thus hypothesizing that the venous vasculature may be leveraged to improve coronary resistances.[63] However, increasing pressure in the coronary venous system has also been shown to be associated with myocardial oedema, contractile dysfunction, and fibrosis involving both LA and LV.[64,65] These potential effects need to be studied further. Access is obtained via the right internal jugular vein favourably impacting logistics of the procedure. Furthermore, the compliance of the CS accommodates changes in volume and pressure.[66] So far, this approach is being tested with the APTURE system, even though further evidence is needed to clarify the safety and effectiveness profile of this approach compared with IAS on clinical outcomes in HF.

APTURE system

The APTURE shunt (Edwards Lifesciences, Irvine, CA, USA) is an alternative to an IAS that involves a percutaneous atriotomy to establish a LA to CS connection that is maintained via a nitinol-based shunt.

ALT FLOW (NCT03523416)

The Early FeasibiLity Study of the Edwards Transcatheter Atrial Shunt System (ALT FLOW) enrolled over 100 HF patients with LVEF ≥ 20% and PCWP ≥ 15 mmHg at rest or ≥25 mmHg with exercise and with PCWP > RAP by >5 (rest) or >10 mmHg (exercise), whose 87 completed the 1-year follow up.[67] There was no PVR exclusion and baseline PVR was used to dichotomize the analysis for PVR ≤ 3 or >3 WU. Major adverse cardiac, cerebrovascular, and renal events or re-intervention for device-related complications at 30 days occurred in 2.3% of patients. At 6 months, two late neurologic events occurred; both were not related to the device. At 6 months, 100% shunt patency was observed. The mean 20 W exercise PCWP decreased by 7 mmHg without a change in RA pressures. Similar mean reductions in PCWP at 20 W exercise were observed in both PVR cohorts. There were also significant improvements of NYHA class, 6MWD, and KCCQ score.[66]

ALT-FLOW II (NCT05686317)

A prospective, randomized, double-blind, sham-controlled trial to compare outcomes of the APTURE device vs. sham treatment in participants who remain symptomatic with HFmrEF or HFpEF, the Randomized, Sham-controlled Clinical Trial for Evaluation of the Edwards APTURE Transcatheter Shunt System (ALT-FLOW II) trial, is now enrolling.[68]

Are shunts harmful in patients with heart failure and preserved ejection fraction?

Clinical trials on left-to-right shunt currently have produced mixed results. The prespecified stratified analysis of the RELIEVE-HF trial suggested that IAS was beneficial in patients with HFrEF (LVEF ≤ 40%) and harmful in those with HFmrEF or HFpEF (LVEF > 40%).[69] Furthermore, a recent echocardiographic sub-analysis from Zile *et al.*[70] also showed that in HFrEF patients, IAS treatment was tolerated without increased RV preload or afterload. However, in those with HFmrEF and HFpEF, LV stiffness and RV stiffness were already present at baseline and persisted after IAS without adapting to nor tolerating shunt flow, providing a mechanistic basis for the difference in clinical outcomes seen in RELIEVE-HF.[70] These findings are in line with a previous invasive study from Rommel *et al.*[15] in which diastolic abnormalities with intrinsic RV stiffness and prolonged RV relaxation were already present in compensated stages of the HFpEF syndrome, even though systolic RV function was preserved. Conversely, the neutral results of REDUCE LAP-HF II trial in patients with HFpEF/HFmrEF (LVEF > 40%) led to the identification of a potential responder subgroup, defined by peak exercise PVR < 1.74 WU and no pacemaker/ICD, in whom a 50% reduction in HF events and a KCCQ improvement of 5.9 points were shown.[52] The REDUCE LAP-HF II longitudinal echocardiographic analysis over 2 years showed that in the responder group, there was an improved left heart unloading and LA function and a reduction in RV enlargement associated with improved RV function, leading to an increased delivery of blood through the lungs, preserving LV cardiac output and improving HF outcomes.[71] These observations led to the proposed three HFpEF phenotypes defined by invasive haemodynamic testing who may or may not improve with an IASD (*Figure 2*).[52]

Analysing patients enrolled in the RELIEVE-HF roll-in HFpEF cohort and comparing them with the REDUCE LAP-HF II responder subgroup, it is noted that RELIEVE-HF had fewer females (30% vs. 63%), whereas ischaemic heart disease (45% vs. 17%) and atrial fibrillation (63% vs. 41%) were more frequent. Moreover, the RELIEVE-HF cohort had higher levels of N-terminal pro-B-type natriuretic peptide levels (mean 1736 vs. 617 ng/L), a lower TAPSE (16 vs. 21 mm), cardiac index (2.3 vs. 3.0 L/min/m^2), and higher PVR (2.5 vs. 1.3 WU) compared with the REDUCE LAP-HF II responder subgroup.[43] The REDUCE LAP-HF II population had lower rates of hospitalization for HF during the 12 months prior to study enrolment (27% vs. 58%), and the REDUCE LAP-HF II control group exhibited low event rates at 1-year follow-up. These data demonstrate a progressively increasing risk profile from REDUCE LAP-HF II responders to RELIEVE-HF. This highlights the need to better characterize patients with HFpEF into specific phenotypes (*Figure 2*).

Differences in shunt size may also have contributed to outcomes; the Corvia shunt has an 8 mm orifice diameter that may transmit >2 times the flow for a given pressure gradient compared with the smaller 5.1 mm V-Wave shunt, which may present less volume overload to the RV.[43]

In REDUCE LAP-HF II, the frequency of HF events during 2-year follow-up was similar in patients who received the IASD and a placebo procedure.[38] The responder subgroup (i.e. no pacemaker/ICD and with exercise PVR < 1.75 WU) was characterized by low-risk features.[36,38] As a consequence, although RESPONDER-HF is designed to show a clinical benefit, the eligibility criteria will be applicable to a smaller population of patients with HFpEF and the lower expected event rate in the trial may make it difficult to show meaningful clinical benefits. The study design of ALLAY-HF is similar to RESPONDER-HF, so the same considerations apply.

Further studies focusing on specific HFpEF phenotypes are needed to discern the potential therapeutic role of left to right shunt in these patients.

Optimal size of the shunt

An important issue in therapeutic shunts was to identify an optimal size of the shunt to provide an effective LA unloading and avoid excessive right heart overload. Computer simulation to model the effect of an atrial shunt on haemodynamics in HFpEF showed that shunt flow increases with increasing shunt size at rest and during exercise. Under resting condition, increasing shunt size is associated with a progressive decline in PCWP and a little increase in RA pressures, with a corresponding increase in RV cardiac output and decrease in LV cardiac output. However, these effects plateau with an atrial shunt diameter of 8 mm. Although exercise makes those haemodynamic effects become prominent, the effect on shunt flow still reaches a plateau at atrial shunt diameter

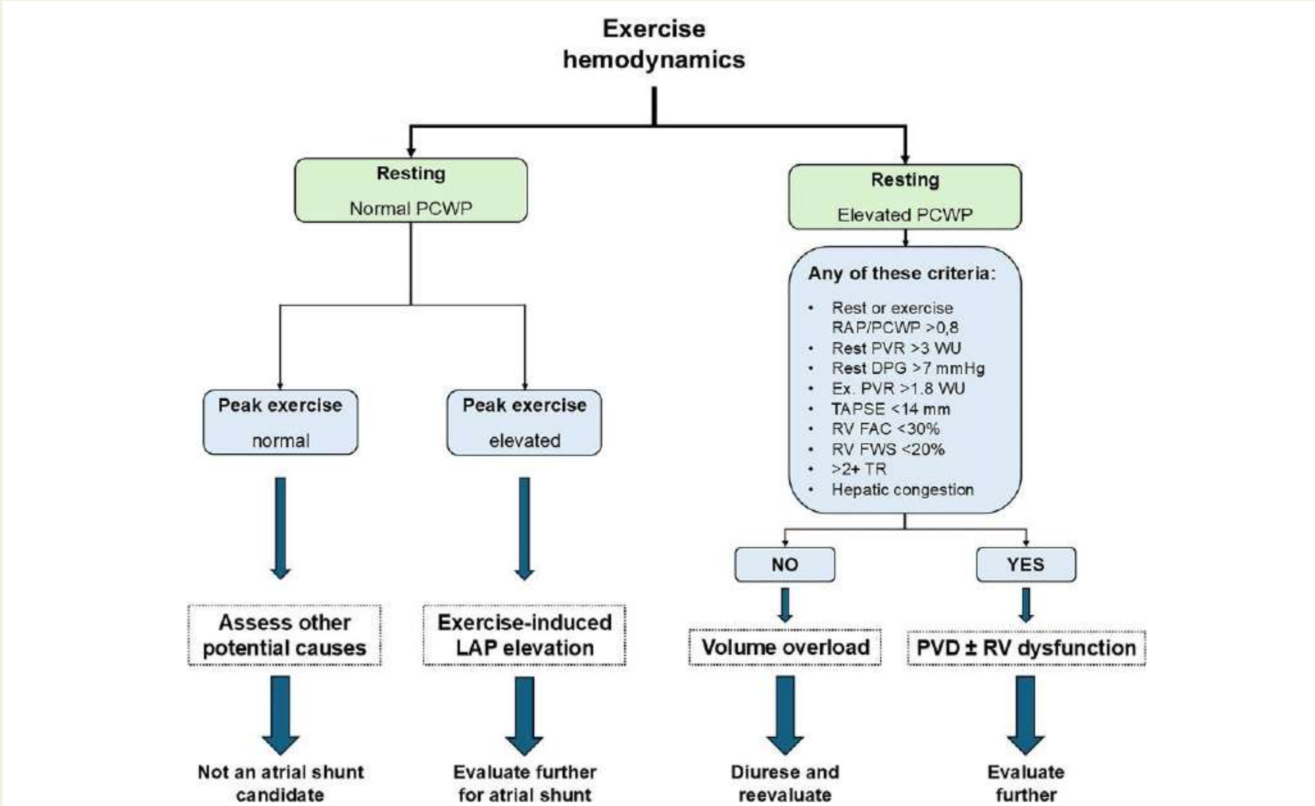


Figure 2 Potential algorithm to identify heart failure with preserved ejection fraction phenotypes by invasive haemodynamic testing to recognize atrial shunt candidates. Modified from Jagadeesan *et al.*[52] DPG, diastolic pulmonary gradient; FAC, fractional area change; FWS, free-wall strain; LAP, left atrial pressure; PCWP, pulmonary capillary wedge pressure; PVD, pulmonary vascular disease; PVR, pulmonary vascular resistance; RAP, right atrial pressure; RV, right ventricle; TAPSE, tricuspid annular plane systolic excursion; TR, tricuspid regurgitation

of 10 mm (*Figure 1C*). Therefore, 8 mm atrial shunt size, with a Qp:Qs ratio of ~1.3–1.4, appears to be the optimal size.[25] Accordingly, the first atrial shunt tested in humans (Corvia) was designed as an 8 mm orifice, but clinical trials showed mixed results. Other novel devices were subsequently developed with different shunt sizes and currently under evaluation (*Table 1*). Whether one-size-fits-all, or whether multiple sizes are needed, remains an open question.

Need for invasive exercise haemodynamic testing

Invasive exercise haemodynamic testing provides information about dynamic changes in haemodynamic parameters. In REDUCE LAP-HF II, 29% of patients had PCWP < 15 mm Hg at rest who would have been excluded if only resting haemodynamic testing had been performed,[37] and it is known that one-third of patients with HFpEF in the community have normal PCWP at rest and require exercise stress to elicit the haemodynamic perturbations of HF.[72] Invasive haemodynamic exercise testing may help to identify patients with HFpEF unresponsive to LA-to-RA shunt therapy, such as those with latent PVD, wherein PVD becomes apparent only during exercise.[36] Importantly, this is a new concept in clinical practice, and the scalability of its reproducible assessment needs to be demonstrated. However, there are logistic concerns as invasive haemodynamic testing remains underutilized in many across cardiac catheterization laboratories.

Future directions

The specific patient characteristics that predict a positive outcome with a LA shunt remain to be determined. Both HFrEF and HFpEF are characterized by increased LAP and pulmonary venous congestion at rest or with exertion directly causing exercise intolerance, and LAP rising during exercise may be difficult to regulate pharmacologically. A communication between the LA and RA may provide an autoregulatory mechanism to decrease LAP and ventricular filling pressures, also providing symptomatic relief and functional improvement. Though, while IAS treatment in HFrEF was shown in RELIEVE-HF[45] to be tolerated without significant increase in RV preload or afterload (reflecting a compliant LV and RV), the LV and RV are less compliant (stiffer) in HFpEF and may be unable to tolerate shunt flow from the LA to the RA, contrasting the potentially varying effects of an IAS according to cardiac structure and function. Furthermore, the results of two Phase 3 trials question the utility of the device for unselected patients with HFpEF, especially if the PVR is elevated, at rest or with exercise. The potential for adverse events in HFpEF patients with PH is evidence of the importance of pathological pulmonary vascular remodelling and RV dysfunction.[73,74] Exercise haemodynamics can unveil latent PVD, although the feasibility of widely translating this new concept to clinical practice must be demonstrated.[16] Pulmonary artery pressures, PVR, PA compliance, and elastance, have all been correlated with mortality in a broad spectrum of PH patients including patients with HF.[75–77] This finding is in line with data showing reduction in stress-induced PH and right heart remodelling with closure of atrial septal defects.

Therefore, exercise pulmonary circulation testing may play a crucial role in appropriate patient population selection for left-to-right shunt. However, whether exercise-assessed haemodynamics are reproducible and feasible in most catheterization laboratories requires further study. Although yet to be proven, the route by which shunted blood enters the RA (i.e. transeptal vs. CS) may also be an important factor for minimizing perturbations in right-sided physiologic blood flows and preserving momentum and kinetic energy.[78] Ultimately, the narrative of PCWP reduction to mitigate pulmonary vascular congestion and improve outcomes may need to shift to a more complex paradigm that includes consideration of underlying left heart pathology across the spectra of LVEF, PVR, and RV function and tailors the choice of shunt based on underlying physiology and potential future needs. Trials focused on patients with HFmrEF and HFpEF without significant PVD will be critical to determine if there is a HFpEF subgroup that will respond to left-to-right shunt.

Conversely, the RELIEVE-HF trial spline analysis showed that the lower the LVEF, the greater the relative reduction in cardiovascular events during 2-year follow-up, with an LVEF of ∼40% signifying the inflection point below which harm with IAS shifted to benefit. However, these outcomes were derived from a non-powered subset, and while the marked reduction in events makes a false positive finding unlikely, these results need further confirmation. Nonetheless, given the safety profile of the IAS in this trial, the potential has been demonstrated for shunt therapy to safely and substantially improve outcomes in patients with HFrEF who remain symptomatic despite guideline-directed medical therapy. These results should be interpreted carefully in light of conflicting data from studies of iatrogenic atrial septal defect closure following mitral valve transcatheter edge-to-edge repair in patients with functional mitral regurgitation showing some evidence of haemodynamic improvement,[79] but without a clear clinical benefit or harm.[80] A confirmatory randomized trial of atrial shunt therapy in patients with HFrEF using the Alleviant device will soon begin.

Left-to-right shunt therapy is a nascent field. These devices aim to provide haemodynamic improvement, symptomatic relief, quality-of-life enhancement, and ultimately decreased morbidity and mortality in patients with HF. Amid several devices, identification of the optimal shunt type and size/configuration and patient population(s) most likely to derive benefit from this approach is essential. Adaptive trial designs with patient selection based on HF subtype and phenotype, presence of PVD, and other comorbid conditions will be important to achieve therapy success. Ongoing trials will provide additional insights into the efficacy, safety, and long-term outcomes with these devices. Advances in device design, improved patient selection, and optimal combination with existing HF therapies hold promise for optimizing patient outcomes.

Supplementary data

Supplementary data are not available at *European Heart Journal* online.

Declarations

Disclosure of Interest

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