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Interatrial shunting for heart failure: current evidence and future perspectives

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KEYWORDS

- acute heart failure
- chronic heart failure
- pulmonary hypertension

Abstract

The creation of an interatrial shunt in order to decompress the right or left atrium in patients with right and left ventricular failure, respectively, has been used as an alternative therapy to improve symptoms and clinical outcomes in patients with pulmonary hypertension-right heart failure and left heart failure refractory to optimal medical therapy. If ongoing randomised clinical trials further substantiate these beneficial effects in patients with chronic HF, interatrial shunting will represent an important new approach for treating this population.

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Abbreviations

6MWT	6-minute walk test
AFR	atrial flow regulator
AS	atrial septostomy
BDAS	balloon dilation atrial septostomy
CI	cardiac index
HF	heart failure
HFpEF	heart failure with preserved ejection fraction
HFrEF	heart failure with reduced ejection fraction
IASD	interatrial shunt device
LA	left atrial
LV	left ventricular
LVEF	left ventricular ejection fraction
NYHA	New York Heart Association
PAH	pulmonary arterial hypertension
PAP	pulmonary artery pressure
PCWP	pulmonary capillary wedge pressure
PH	pulmonary hypertension
RAP	right atrial pressure
RV	right ventricular
TEE	transoesophageal echocardiography
TTE	transthoracic echocardiography
VA-ECMO	veno-arterial extracorporeal membrane oxygenation
WHO-FC	World Health Organization functional class

Introduction

The creation of an interatrial shunt in order to decompress the right or left atrium in patients with right ventricular (RV) and left ventricular (LV) failure, respectively, has been used as an alternative therapy in patients with pulmonary hypertension (PH)-right heart failure (HF) and left HF[1-3]. This review aims to provide an updated overview and clinical perspective on interatrial shunting for treating different HF conditions, as well as highlighting the potential challenges and future directions of this therapy. A computerised search was performed to identify all relevant studies from PudMed and EMBASE databases. The following terms were used: "interatrial shunt", "atrial shunting", "balloon septostomy", "atrial septostomy", "atrial decompression", "interventional therapy pulmonary hypertension", and "interventional therapy heart failure". Databases were last accessed in November 2018. In addition to the computerised search, we manually reviewed the bibliography of all included articles to ensure complete inclusion of all possible studies.

INTERATRIAL SHUNTING FOR PULMONARY ARTERIAL HYPERTENSION – RIGHT HEART FAILURE

In Europe, the prevalence and incidence of pulmonary arterial hypertension (PAH) has been estimated at 15-60 cases per million and five to 10 cases per million/year, respectively[4].

The response to medical treatment in PAH remains somewhat unpredictable, and lung transplantation, with a high number of contraindications and a very limited access, remains the very last recourse for such patients[5]. Right ventricular dysfunction in patients with PAH is associated with poor short-term prognosis and remains the main cause of death in this population[6].

In an animal PAH model, the presence of an atrial septal defect was associated with improved exercise performance and survival[7]. Also, PAH patients with congenital heart disease and septal defects have a better life expectancy[8]. The presence of a patent foramen ovale has also been consistently associated with better clinical outcomes in patients with idiopathic PAH[9]. Also, the presence of an atrial septal defect in patients with mitral stenosis (Lutembacher syndrome) seems to be associated with fewer symptoms and improved outcomes compared to pure mitral stenosis[10]. In 1983, Rich and Lam performed the first atrial septostomy (AS) to treat refractory PAH using a blade septostomy catheter[11]. After an initial experience was associated with a high rate of periprocedural complications[12,13], the procedure was modified to balloon dilation atrial septostomy (BDAS) which allows a better control of the final atrial septal defect size and has been associated with a significant reduction in procedural complications[14,15].

TECHNIQUE

Following transseptal puncture, a balloon dilation of the interatrial septum using a non-compliant balloon is performed[14] **(Supplementary Figure 1A)**. The final balloon size is usually ~10 mm (ranging from 4-20 mm), and the decision about the maximum balloon diameter should be based on the avoidance of a massive shunt leading to refractory hypoxaemia and/or acute pulmonary oedema. Avoiding either a drop >10% in SaO_2% compared with baseline and/or an increase in left ventricular end-diastolic pressure exceeding 18 mmHg is recommended. Thus, a progressive balloon dilation technique, with small increases in balloon size, checking haemodynamics and SaO_2 values after each balloon dilation, should be used. Chronic anticoagulation has been recommended following the procedure[3].

HAEMODYNAMIC RESULTS

Table 1 summarises the main results from the largest series on AS in PAH. The immediate haemodynamic effect of AS includes a small but significant reduction in right atrial pressure (RAP) and SaO_2 along with an increase in cardiac index (CI)[3,12,14,16-20]. Pulmonary artery pressure (PAP) and systemic pressure usually remain stable following AS. The degree of haemodynamic change post-AS is mainly related to baseline RAP values and AS size.

CLINICAL OUTCOMES

Following an initial experience of AS for PAH patients with very high periprocedural mortality rates, there has been a subsequent progressive decrease in procedural mortality (2-7%), mainly related to better patient selection, increased experience of the operators and technical/procedural improvements[3,21]. Refractory hypoxaemia has been identified as the most common cause of death following AS in PAH patients. Four factors have been identified as potential contraindications for AS: 1) RAP >20 mmHg,

Table 1. Baseline, procedural characteristics and outcomes of patients with pulmonary hypertension undergoing atrial septostomy.

		Kerstein et al[12]	Sandoval et al[14]	Reichenberger et al[20]	Micheletti et al[19]	Law et al[18]	Sandoval et al[3]	Kuhn et al[17]	Chiu[16]
N (patients)		15	15	17	20	43	34	16	32
N (procedures)		16	22	20	22	46	50	23	46
Baseline characteristics									
Age, years		24.9±11.3	33±9	35.9±14.2	8.4±5.6	12 (0.3–30)*	35.0±10	47.6±11.3	23*
Female (%)		86.6	87.0	70.6	55.0	81.0	85.0	75.0	74.0
NYHA class		3.5±0.5	3.6±0.6	3.7±0.5	3.5±0.5	3-4	3.5±0.6	3.9±0.3	
IPAH/CTD/CHD/CTEPH/others		15	13/1/0/1/0	13/2/0/1/1	19/0/0/0/1	29/2/10/0/2	29/1/1/3/0	7/1/0/0/8	20/2/6/0/4
Symptoms	Syncope/RVF/both	7/0/8	4/8/3	4/10/3	12/7/1	18/22/3	9/14/11	0/11/5	
Procedural characteristics									
Blade/BDAS/Blade+BDAS		4/0/12	0/22/0	0/20/0	2/17/3	30/5/11	0/50/0	0/23/0	0/46/0
Size, mm		4-18	10±3	10.6±1.6	6.9±2.4	12.2±2.9	8.5±2.5	4-20	NA
Haemodynamic outcomes									
RAP (mmHg)	Baseline	11.2±7.1		12.2±6.2	9.3 (3–19)	9.9±6.3	14.5±6.0	16.6±6.7	13.0±7.0
	Post-procedure	10.0±4.3			NA	8.3±4.8¶	10.7±5.9¶	17.1±5.8	11.6±5.0
PAP (mmHg)	Baseline	69.6±22.9	59.0±11.0	54.8±10.7	62.6 (25–80)	73.0±20.0	66.0±13.0	62.0±13.2	59.0±19.0
	Post-procedure	71.9±23.7	52.0±8.0¶	51.1±10.6	NA	71.0±21.0	61.0±16.0¶	69.5±10.8	62.0±17.0
PWP (mmHg)	Baseline	NA		NA	NA		NA	13.0±6.1	NA
	Post-procedure	NA		NA	NA		NA	16.8±4.8	NA
CI (L/min/m^2)	Baseline	2.1±0.7	2.2±0.5	1.7±0.5	NA	2.3±0.8	2.26±0.43	2.1±0.6	2.6±1.0
	Post-procedure	3.9±1.1¶	3.0±0.8¶	2.2±0.5¶	NA	2.9±1.1¶	2.97±0.83¶	2.4±0.6	2.7±1.3
SaO_2%	Baseline	98.0±2.0	92.0±3.0	93.2±4.3	NA	93.0±5.0	91.7±3.8	90.7±4.3	94.0±4.0
	Post-procedure	85.0±6.0¶	83.0±8.0¶	87.4±5.6¶	NA	86.0±10.0¶	84.0±6.3¶	82.5±5.6	91.0±5.0¶
Clinical outcomes									
6MWT (m)	Baseline	305±116	107±127	NA	326 (160-432)	NA	106±115	NA	NA
	Post-procedure	358±76	217±108¶	NA	NA	NA	214±99¶	NA	NA
Procedural death (<24 hrs)		2	1	3	0	2		1	0
Early death (24 hrs–30 d)				2		8	1	3	4
Late death (>30 d)		4	1	1	2	9	21	2	8
Follow-up		2-45 months	2-35 months	5-17 months	Mean 2.1 years	Median 36 months	Mean 58.5 months	Mean 39.4 months	Median 17.5 months

Values are mean±SD or median (IQR). * Median (range). ¶ statistically significant. BDAS: balloon dilation atrial septostomy; CHD: congenital heart disease; CI: cardiac index; CTD: connective tissue disease; CTEPH: chronic thromboembolic pulmonary hypertension; IPAH: idiopathic pulmonary artery hypertension; NYHA: New York Heart Association; PAP: pulmonary artery pressure; PWP: pulmonary wedge pressure; RAP: right atrial pressure; RVF: right ventricle failure; 6MWT: 6-minute walk test

2) SaO_2 <90% without supplemental oxygen, 3) left ventricular end-diastolic pressure >18 mmHg, and 4) severe RV failure on cardiorespiratory support[21-23].

A significant functional class improvement of at least one degree was observed in about 70% of patients and better exercise capacity (mean increase of ~90 metres during 6-minute walk test [6MWT]) have been demonstrated following AS in PAH patients[3,12,14,21] **(Supplementary Figure 2)**.

The impact of AS on long-term survival of PAH patients is difficult to establish due to the lack of randomised controlled studies. Some studies comparing AS-PAH recipients with historical series or estimated survival rates have suggested a survival benefit of AS at one- to three-year follow-up[3,12,14,16,18] **(Supplementary Figure 3)**. Thus, AS may be considered in patients who are still in World Health Organization functional class (WHO-FC) III or IV despite optimal medical therapy or with severe syncopal symptoms.

SHUNT PATENCY AND PERMANENT DEVICES

The rate of shunt occlusion following BDAS has been close to 20% after a mean follow-up of 15 months[3,12,14,17,18,20]. Redo AS has been shown to be feasible and safe[3,20], and several permanent interatrial shunt devices have been tested in patients with PAH to improve shunt patency and maintain shunt size.

The modified stent, with a diabolo or butterfly shape **(Figure 1A)**, is made by a loop of a pre-defined diameter created with suture or pacing wires placed over the mid portion of

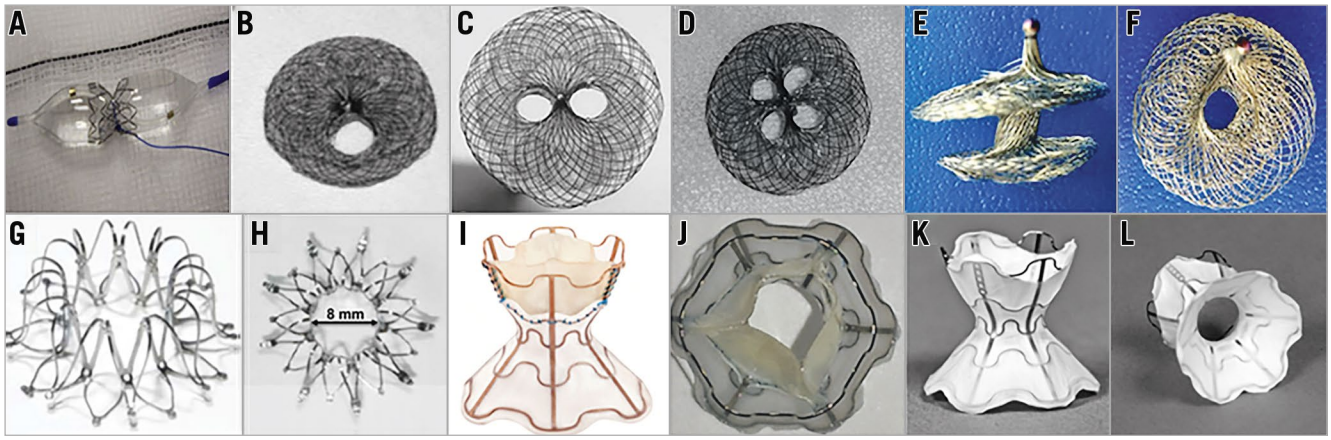

Figure 1. *Interatrial shunt devices. A) Diabolo stent. B), C) & D) AMPLATZER Atrial Septal Occluder (ASO) with modified fenestration and different configurations. E) & F) Atrial Flow Regulator (AFR; Occlutech). G) & H) InterAtrial Shunt Device (IASD; Corvia Medical Inc.). I) & J) V-Wave device (V-Wave Inc.). K) & L) Second-generation (valveless) V-Wave device (V-Wave Inc.).*

the balloon, and a stent mounted and crimped with the loop in the centre of the stent. A series including 12 patients has shown haemodynamic results similar to those obtained with BDAS; no evidence of shunt occlusion was observed after a mean follow-up of two years[24].

Some studies have shown the feasibility and preliminary efficacy of the AMPLATZER™ Atrial Septal Occluder (St. Jude Medical/Abbott Vascular, Abbott Park, IL, USA) with modified fenestration, including different configurations **(Figure 1B-Figure 1D)**. Contradictory data have been reported regarding midterm to long-term patency[25-27], and an occlusion rate of up to 40% was reported after a mean follow-up of about one year in a series including 10 patients.

A new device, the Atrial Flow Regulator (AFR; Occlutech, Jena, Germany), consists of a double disc device made of a nitinol wire mesh and a central orifice **(Figure 1E, Figure 1F)**. The fenestration diameter varies from 4 to 10 mm, and there are three waist sizes (2, 5, and 10 mm) to suit the atrial septal thickness. The most important difference between the AFR and the fenestrated AMPLATZER devices is the absence of fabric. A recent study including 12 patients who had AFR implantation and a mean follow-up of about six months showed immediate haemodynamic and clinical improvements similar to BDAS. The permeability of the shunt was demonstrated by contrast echocardiography and oximetry after exercise in all patients[28].

ONGOING AND FUTURE STUDIES

Supplementary Table 1 summarises ongoing and future studies.

Interatrial shunting for left heart failure

Despite decades of major advances in medical and device treatment, left HF morbidity and mortality remain high, regardless of aetiology. In patients with chronic HF, increased left atrial (LA) pressure leading to pulmonary congestion is the common mechanism precipitating symptom worsening and acute decompensation[29]. An interatrial shunt may relieve the volume excess from the left atrium, regulated by the interatrial pressure gradient.

DEVICES

The InterAtrial Shunt Device (IASD®; Corvia Medical Inc., Tewksbury, MA, USA) consists of a nitinol mesh with multiple legs and radiopaque markers, and a central hole for creating the interatrial septal defect **(Figure 1G, Figure 1H)**. When fully expanded, the external and inner diameters are 19 mm and 8 mm, respectively[30].

The V-Wave device (V-Wave Inc., Caesarea, Israel) is an hourglass-shaped device made of nitinol with expanded polytetrafluoroethylene encapsulation, and three porcine pericardial leaflets sutured inside to ensure an unidirectional left-to-right shunt **(Figure 1I, Figure 1J)**. The lumen diameter of the V-Wave device is 5 mm[1]. The newer-generation device is similar but without valve leaflets (valveless device) **(Figure 1K, Figure 1L)**.

The AFR device (previously described and initially tested in patients with PAH) **(Figure 1E, Figure 1F)** will be tested soon in patients with heart failure with reduced ejection fraction (HFrEF) and heart failure with preserved ejection fraction (HFpEF).

Overall, shunt device size in HF patients has ranged from 5 to 8 mm. Congenital data showed the lack of negative haemodynamic effects among patients with atrial septal defects <10 mm and, in a validated cardiovascular simulation model, Kaye et al[31] showed the lack of increase in right atrial and PA pressures with an 8-9 mm shunt. However, further studies are needed to determine the optimal shunt size for patients with left HF.

TECHNIQUE

Following transseptal puncture, a sheath (14 to 16 Fr) is advanced into the LA cavity, and the device deployed using a dedicated delivery system. Of note, balloon predilation is recommended before the implantation of some devices (e.g., AFR device). The left side of the device is initially opened, and the entire system is pulled back ensuring back tenting at the level of the interatrial

septum. Then, the right side of the device is deployed, and the device finally released **(Supplementary Figure 1B)**.

Aspirin (75-325 mg daily) indefinitely associated with a $P2Y_{12}$ inhibitor or anticoagulant therapy (warfarin or a direct-acting oral anticoagulant) for six months has been recommended (empirically) post-procedure.

CLINICAL AND HAEMODYNAMIC RESULTS

The main results of interatrial shunt studies in patients with HFrEF and HFpEF are summarised in **Table 2**. The first experience using the IASD was in 11 patients with LVEF >45% and NYHA Class III/IV. The device was successfully implanted in all patients and there was a significant decrease in pulmonary capillary wedge

Table 2. Baseline, procedural characteristics and clinical outcomes of patients with chronic heart failure undergoing interatrial shunting with a permanent device.

		Sondergaard et al[30]	Hasenfuss et al REDUCE LAP-HF[32]	Feldman et al REDUCE LAP-HF I[2]	Del Trigo et al[1]	Rodés-Cabau et al[36]
N		11	64	22	10	38
Baseline characteristics						
Age (years)		70±12	69±8	70±8	62±8	66±9
Male sex (%)		5 (45.4)	22 (34.4)	14 (63.6)	9 (90)	35 (92)
HFpEF/HFrEF		11/0	64/0	22/0	0/10	8/30
LVEF		57±9	47±7	60±9	25±8	–
Procedural characteristics						
Device		IASD	IASD	IASD	V-Wave	V-Wave
Procedural success		11/11	–	20/21	10/10	38/38
Haemodynamic outcomes						
RAP (mmHg)	Baseline	12±3	9±4	10.1±2.3	9.5±4.0	8±4
	Post-procedural	11±3	11±5¶	10.6±4.0	8.0±5.0	9±4
PAP (mmHg)	Baseline	30±7	25±7	30.2±9.5	29±7	30±7
	Post-procedural	27±6	–	27.5±5.4	26±11	30±10
PWP at rest	Baseline (mmHg)	19±5	17±5	20.9±7.9	23±5	21±5
	Post-procedural	14±3¶	17±7	18.7±6.6	17±8¶	19±7
PWP at exercise	Baseline (mmHg)	–	32±8	37.3±6.5	–	–
	Post-procedural	–	29±9¶	33.8±6.4	–	–
CI (L/min/m^2)	Baseline	2.4±0.4	–	–	2.1±0.3	2.2±0.4
	Post-procedural	–	–	–	2.4±0.7	2.3±0.5
Clinical outcomes						
NT-proBNP	Baseline	193±153	377 (222-925)	–	2,485±3,318	2,640±2,301
	Post-procedural	212±152	382 (170-1,075)	–	2,473±2,984	–
6MWT (m)	Baseline	322±151	313±105	–	249±106	–
	Post-procedural	368±123¶	345±106¶	–	319±134¶	–
MLWHF score	Baseline	53±17	49±20	–	–	290±112
	Post-procedural	18±19¶	36±23¶	–	–	324±105¶
KCCQ	Baseline	–	–	–	44.8±9.4	–
	Post-procedural	–	–	–	79.1±13.0¶	–
DASI	Baseline	–	–	–	12.4±6.2	–
	Post-procedural	–	–	–	24.8±12.9¶	–
NYHA	Baseline	3.2±0.4	3 (2-3)	3	3	3.0±0.2
	Post-procedural	2.4±0.8	2 (2-3)¶	2.5±0.7	2.0±0.5¶	–
Device occlusion/stenosis (%)		1#	0	0*	0**	19/36 (52.8)***
Immediate death (<24 hrs)		0	0	0	0	0
Late death (>30 days)		–	0	–	1	2
Follow-up		1 month	6 months	1 month	3 months	Median 28 months

Values are mean±SD or median (IQR). ¶ statistically significant. #10 patients presented shunt patency, in one patient the shunt patency was unable to be assessed. * 1-month follow-up. ** 3-month follow-up. *** median follow-up of 28 months (range: 18-48 months). CI: cardiac index; DASI: Duke Activity Status Index; HFpEF: heart failure with preserved ejection fraction; HFrEF: heart failure with reduced ejection fraction; KCCQ: Kansas City Cardiomyopathy Questionnaire; LVEF: left ventricular ejection fraction; MLWHF: Minnesota Living with Heart Failure; PAP: pulmonary artery pressure; PWP: pulmonary wedge pressure; RAP: right atrial pressure; 6MWT: 6-minute walk test

pressure (PCWP) with no changes in RAP or PAP and significant improvements in 6MWT distance, quality of life, and NYHA class at 30-day follow-up[30].

The REDUCE LAP-HF trial[32], included 64 patients with symptomatic HFpEF treated with the IASD device with no major periprocedural complications. At six-month follow-up, there were no significant changes in PCWP at rest; a significant decrease in PCWP at peak exercise was observed (p=0.01). Furthermore, improvements in NYHA class, quality of life and exercise capacity were observed at six months[32] and maintained at one-year follow-up[33].

A randomised controlled trial[2] included 44 patients with LVEF >40% and NYHA Class III-IV. At one-month follow-up, patients in the IASD group exhibited a reduction of PCWP values during exercise compared to a lack of changes in the control (no device) group (p=0.01) **(Supplementary Figure 4, Table 2)**. However, these haemodynamic differences between groups did not translate into differences in functional status or exercise capacity at one-month follow-up. Recently, Shah et al[34] reported the one-year results, with no evidence of device occlusion over time. Some degree of RV dilation was observed at six months in the group which received the IASD device, with no further RV dilation and no decrease in RV function up to one year. The improvement in quality of life and exercise capacity was similar in both groups, and the IASD group exhibited a tendency towards a better NYHA class improvement (p=0.08) and fewer heart failure hospitalisations (p=0.06). Finally, major adverse cardiac, cerebrovascular or renal events were similar between the groups, with a survival rate of 95% at 12 months (one death in each group)[34].

The V-Wave device was the first interatrial shunt device implanted in patients with HFrEF[35]. Del Trigo et al[1] reported the initial experience in 10 patients with HFrEF and functional class III/IV despite optimal medical/device therapy **(Table 2)**. Recently, the results of multicentre initial experience with the V-Wave device[36] including 38 patients (HFrEF: 30; HFpEF: 8; NYHA Class III-IV in all of them) were reported. The V-Wave device was successfully implanted in all cases with only one major periprocedural complication (cardiac tamponade resolved with pericardiocentesis). Significant improvements in functional class, exercise capacity and quality of life were observed early after the procedure (within the first three months) and maintained at one-year follow-up. There were no changes in haemodynamic parameters (as determined at rest) at one-year follow-up **(Table 2)**. After a median follow-up of 28 months, 10 patients (26%) had died (eight from cardiovascular causes), one patient received a left ventricular assist device as destination therapy at 15 months, and another underwent heart transplantation at 27 months.

AS has demonstrated clinical benefits and may be considered in patients who remain symptomatic despite optimal medical/device therapy based on current guidelines. Patients with severe RV dysfunction or severe pulmonary hypertension exhibit a higher risk of periprocedural and midterm complications and have been excluded from trials.

SHUNT PATENCY

One of the potential concerns for permanent interatrial shunt devices is shunt patency over time. Kaye et al[33] reported shunt patency data at one-year follow-up as evaluated by TTE in 64 patients with HFpEF following the implantation of the IASD device. TTE images were not considered adequate for determining shunt patency in 16 patients (25%), highlighting the potential difficulties in appropriately evaluating the interatrial shunt by TTE. The shunt was patent in all patients with appropriate TTE images (48 patients).

The patency of the V-Wave device was evaluated by TEE at one to three months and at one year after device implantation[36]. All shunts were fully patent at one to three months, and shunt occlusion was observed in 14% of patients at one-year follow-up. Additionally, some degree of shunt stenosis at the valve level occurred in 36% of patients, leading to an incidence of shunt stenosis or occlusion of 50% at one year. The potential cause of stenosis or occlusion was suggested from a stenotic shunt that was explanted during cardiac transplantation two years after the procedure. The bioprosthetic leaflets were thickened and stenotic with neoendocardial hyperplasia (pannus). These data along with the lack of thrombus suggested intra-shunt valve deterioration as the main mechanism of shunt stenosis-occlusion. This is the reason why a newer generation of the V-Wave device has been developed.

Comparative analysis of haemodynamic and clinical outcomes between patients with and without shunt stenosis or occlusion showed that patients with fully patent shunts exhibited significant improvements in haemodynamic parameters compared to a lack of changes in the shunt stenosis-occlusion group. Also, those patients with patent shunts had improved late clinical outcomes, with lower rates of death/left ventricular assistance/transplantation or heart failure rehospitalisation at three-year follow-up **(Supplementary Figure 5)**[36].

FUTURE STUDIES

Supplementary Table 1 summarises the ongoing and future studies.

Clinical implications and future directions

Current evidence for interatrial shunting is based on observational studies and small randomised trials showing the feasibility, safety and preliminary efficacy in patients with PAH and left HF. These data seem to be insufficient to modify current clinical practice but support the use of interatrial shunting as a palliative therapy in selected patients with PAH and left HF who remain symptomatic despite optimal treatment based on current guidelines. Several ongoing randomised trials will provide definite evidence about the exact role of this therapy for the treatment of HF patients. If further substantiated and associated with improved clinical outcomes, device-mediated left-to-right atrial shunting would offer an important new approach to treatment of this population.

Conclusions

In PAH patients, AS can be considered as a palliative therapy in non-responders to available therapies. Careful patient selection and

limiting the size of the atrial septal defect appear to be key in order to avoid major periprocedural complications and death. Also, new permanent devices are currently being evaluated in order to ensure shunt patency over time. In left HF patients, interatrial shunting with different permanent devices has been shown to be a feasible and safe therapy in patients with chronic left HF who remain symptomatic despite optimal medical/device therapy. Also, preliminary efficacy data, with significant improvements in functional status, exercise capacity and quality of life, have provided the rationale for designing large randomised trials (currently ongoing) in order to determine further the efficacy of this new therapy for reducing major cardiovascular events in patients with chronic HF.

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Conflict of interest statement

J. Lindenfeld, A. Bayés-Genis, and J. Rodés-Cabau are consultants for V-Wave Inc. The other authors have no conflicts of interest to declare.

References

1. Del Trigo M, Bergeron S, Bernier M, Amat-Santos IJ, Puri R, Campelo-Parada F, Altisent OA, Regueiro A, Eigler N, Rozenfeld E, Pibarot P, Abraham WT, Rodés-Cabau J. Unidirectional left-to-right interatrial shunting for treatment of patients with heart failure with reduced ejection fraction: a safety and proof-of-principle cohort study. *Lancet.* 2016;387:1290-7.

2. 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; REDUCE LAP-HF I Investigators and Study Coordinators. 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]): A Phase 2, Randomized, Sham-Controlled Trial. *Circulation.* 2018;137:364-75.

3. Sandoval J, Gaspar J, Pena H, Santos LE, Cordova J, del Valle K, Rodriguez A, Pulido T. Effect of atrial septostomy on the survival of patients with severe pulmonary arterial hypertension. *Eur Respir J.* 2011;38:1343-8.

4. Peacock AJ, Murphy NF, McMurray JJ, Caballero L, Stewart S. An epidemiological study of pulmonary arterial hypertension. *Eur Respir J.* 2007;30:104-9.

5. de Perrot M, Granton JT, McRae K, Pierre AF, Singer LG, Waddell TK, Keshavjee S. Outcome of patients with pulmonary arterial hypertension referred for lung transplantation: a 14-year single-center experience. *J Thorac Cardiovasc Surg.* 2012;143:910-8.

6. Hoeper MM, Granton J. Intensive care unit management of patients with severe pulmonary hypertension and right heart failure. *Am J Respir Crit Care Med.* 2011;184:1114-24.

7. Austen WG, Morrow AG, Berry WB. Experimental Studies of the Surgical Treatment of Primary Pulmonary Hypertension. *J Thorac Cardiovasc Surg.* 1964;48:448-55.

8. Hopkins WE, Ochoa LL, Richardson GW, Trulock EP. Comparison of the hemodynamics and survival of adults with severe primary pulmonary hypertension or Eisenmenger syndrome. *J Heart Lung Transplant.* 1996;15:100-5.

9. Rozkovec A, Montanes P, Oakley CM. Factors that influence the outcome of primary pulmonary hypertension. *Br Heart J.* 1986; 55:449-58.

10. Bashi VV, Ravikumar E, Jairaj PS, Krishnaswami S, John S. Coexistent mitral valve disease with left-to-right shunt at the atrial level: clinical profile, hemodynamics, and surgical considerations in 67 consecutive patients. *Am Heart J.* 1987;114:1406-14.

11. Rich S, Lam W. Atrial septostomy as palliative therapy for refractory primary pulmonary hypertension. *Am J Cardiol.* 1983;51: 1560-1.

12. Kerstein D, Levy PS, Hsu DT, Hordof AJ, Gersony WM, Barst RJ. Blade balloon atrial septostomy in patients with severe primary pulmonary hypertension. *Circulation.* 1995;91:2028-35.

13. Rich S, Dodin E, McLaughlin VV. Usefulness of atrial septostomy as a treatment for primary pulmonary hypertension and guidelines for its application. *Am J Cardiol.* 1997;80:369-71.

14. Sandoval J, Gaspar J, Pulido T, Bautista E, Martinez-Guerra ML, Zeballos M, Palomar A, Gomez A. Graded balloon dilation atrial septostomy in severe primary pulmonary hypertension. A therapeutic alternative for patients nonresponsive to vasodilator treatment. *J Am Coll Cardiol.* 1998;32:297-304.

15. Klepetko W, Mayer E, Sandoval J, Trulock EP, Vachiery JL, Dartevelle P, Pepke-Zaba J, Jamieson SW, Lang I, Corris P. Interventional and surgical modalities of treatment for pulmonary arterial hypertension. *J Am Coll Cardiol.* 2004;43:73S-80S.

16. Chiu JS, Zuckerman WA, Turner ME, Richmond ME, Kerstein D, Krishnan U, Torres A, Vincent JA, Rosenzweig EB. Balloon atrial septostomy in pulmonary arterial hypertension: effect on survival and associated outcomes. *J Heart Lung Transplant.* 2015;34:376-80.

17. Kuhn BT, Javed U, Armstrong EJ, Singh GD, Smith TW, Whitcomb CJ, Allen RP, Rogers JH. Balloon dilation atrial septostomy for advanced pulmonary hypertension in patients on prostanoid therapy. *Catheter Cardiovasc Interv.* 2015;85:1066-72.

18. Law MA, Grifka RG, Mullins CE, Nihill MR. Atrial septostomy improves survival in select patients with pulmonary hypertension. *Am Heart J.* 2007;153:779-84.

19. Micheletti A, Hislop AA, Lammers A, Bonhoeffer P, Derrick G, Rees P, Haworth SG. Role of atrial septostomy in the treatment of children with pulmonary arterial hypertension. *Heart.* 2006;92:969-72.

20. Reichenberger F, Pepke-Zaba J, McNeil K, Parameshwar J, Shapiro LM. Atrial septostomy in the treatment of severe pulmonary arterial hypertension. *Thorax.* 2003;58:797-800.

21. Keogh AM, Mayer E, Benza RL, Corris P, Dartevelle PG, Frost AE, Kim NH, Lang IM, Pepke-Zaba J, Sandoval J.

Interventional and surgical modalities of treatment in pulmonary hypertension. *J Am Coll Cardiol.* 2009;54:S67-77.

22. Bhamra-Ariza P, Keogh AM, Muller DWM. Percutaneous interventional therapies for the treatment of patients with severe pulmonary hypertension. *J Am Coll Cardiol.* 2014;63:611-8.

23. Sandoval J, Rothman A, Pulido T. Atrial septostomy for pulmonary hypertension. *Clin Chest Med.* 2001;22:547-60.

24. Stümper O, Gewillig M, Vettukattil J, Budts W, Chessa M, Chaudhari M, Wright JG. Modified technique of stent fenestration of the atrial septum. *Heart.* 2003;89:1227-30.

25. Althoff TF, Knebel F, Panda A, McArdle J, Gliech V, Franke I, Witt C, Baumann G, Borges AC. Long-term follow-up of a fenestrated Amplatzer atrial septal occluder in pulmonary arterial hypertension. *Chest.* 2008;133:283-5.

26. O'Loughlin AJ, Keogh A, Muller DW. Insertion of a fenestrated Amplatzer atrial septostomy device for severe pulmonary hypertension. *Heart Lung Circ.* 2006;15:275-7.

27. Lammers AE, Derrick G, Haworth SG, Bonhoeffer P, Yates R. Efficacy and long-term patency of fenestrated amplatzer devices in children. *Catheter Cardiovasc Interv.* 2007;70:578-84.

28. Rajeshkumar R, Pavithran S, Sivakumar K, Vettukattil JJ. Atrial septostomy with a predefined diameter using a novel occlutech atrial flow regulator improves symptoms and cardiac index in patients with severe pulmonary arterial hypertension. *Catheter Cardiovasc Interv.* 2017;90:1145-53.

29. Ritzema J, Troughton R, Melton I, Crozier I, Doughty R, Krum H, Walton A, Adamson P, Kar S, Shah PK, Richards M, Eigler NL, Whiting JS, Haas GJ, Heywood JT, Frampton CM, Abraham WT; Hemodynamically Guided Home Self-Therapy in Severe Heart Failure Patients (HOMEOSTASIS) Study Group. Physician-directed patient self-management of left atrial pressure in advanced chronic heart failure. *Circulation.* 2010;121:1086-95.

30. Sondergaard 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.

31. 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;20:212-21.

32. Hasenfuss G, Hayward C, Burkhoff D, Silvestry FE, McKenzie S, Gustafsson F, Malek F, Van der Heyden J, Lang I, Petrie MC, Cleland JG, Leon M, Kaye DM; REDUCE LAP-HF study investigators. 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;387:1298-304.

33. 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, 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 Dec;9(12).

34. Shah SJ, Feldman T, Ricciardi MJ, Kahwash R, Lilly S, Litwin S, Nielsen CD, van der Harst P, Hoendermis E, Penicka M, Bartunek J, Fail PS, Kaye DM, Walton A, Petrie MC, Walker N, Basuray A, Yakubov S, Hummel SL, Chetcuti S, Forde-McLean R, Herrmann HC, Burkhoff D, Massaro JM, Cleland JGF, Mauri L. One-Year Safety and Clinical Outcomes of a Transcatheter Interatrial Shunt Device for the Treatment of Heart Failure With Preserved Ejection Fraction in the Reduce Elevated Left Atrial Pressure in Patients With Heart Failure (REDUCE LAP-HF I) Trial: A Randomized Clinical Trial. *JAMA Cardiol.* 2018;3:968-77.

35. Amat-Santos IJ, Bergeron S, Bernier M, Allende R, Barbosa Ribeiro H, Urena M, Pibarot P, Verheye S, Keren G, Yaacoby M, Nitzan Y, Abraham WT, Rodés-Cabau J. Left atrial decompression through unidirectional left-to-right interatrial shunt for the treatment of left heart failure: first-in-man experience with the V-Wave device. *EuroIntervention.* 2015;10:1127-31.

36. Rodes-Cabau J, Bernier M, Amat-Santos IJ, Ben Gal T, Nombela-Franco L, Garcia 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.

37. Sandoval J. Interventional Therapies in Pulmonary Hypertension. *Rev Esp Cardiol (Engl Ed).* 2018;71;565-74.

Supplementary data

Supplementary Figure 1. Interatrial shunt technique.

Supplementary Figure 2. Clinical changes after AS in patients with PAH.

Supplementary Figure 3. Survival after atrial septostomy (AS) in PAH patients.

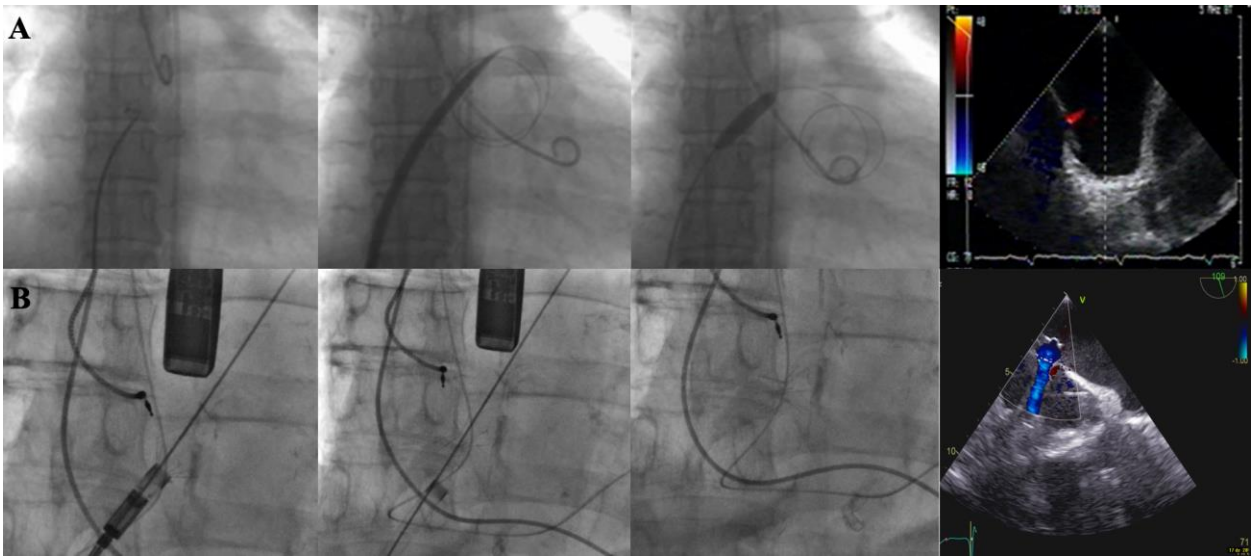
Supplementary Figure 4. Pulmonary capillary wedge pressure during exercise haemodynamic testing: baseline vs. 1-month post randomisation, stratified by treatment group.

Supplementary Figure 5. Clinical events up to three-year follow-up, according to shunt patency.

Supplementary Table 1. Ongoing and future studies on interatrial shunting.

The supplementary data are published online at: https://eurointervention.pcronline.com/doi/10.4244/EIJ-D-18-01211

Supplementary data



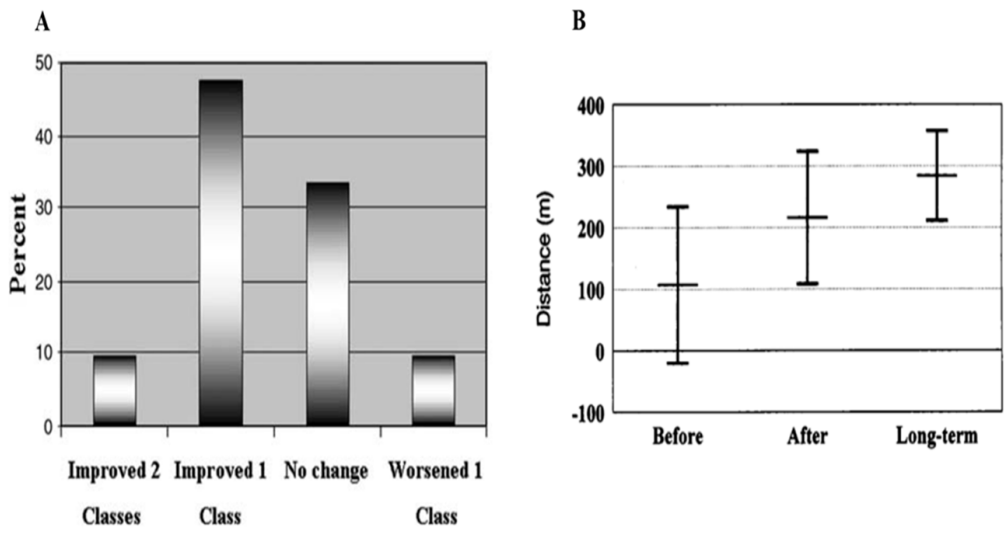
Supplementary Figure 1. Interatrial shunt technique.

A) Balloon atrial septostomy technique.

Mullins dilator with the Brockenbrough needle, following transseptal puncture; an Inoue circular-end guidewire is positioned in the left atrium and concluded with 8 mm balloon dilation. Transoesophageal echocardiography view of the atrial septal defect post balloon dilation. Reproduced from Sandoval et al[37], with permission.

B) Implantation technique of the V-Wave device.

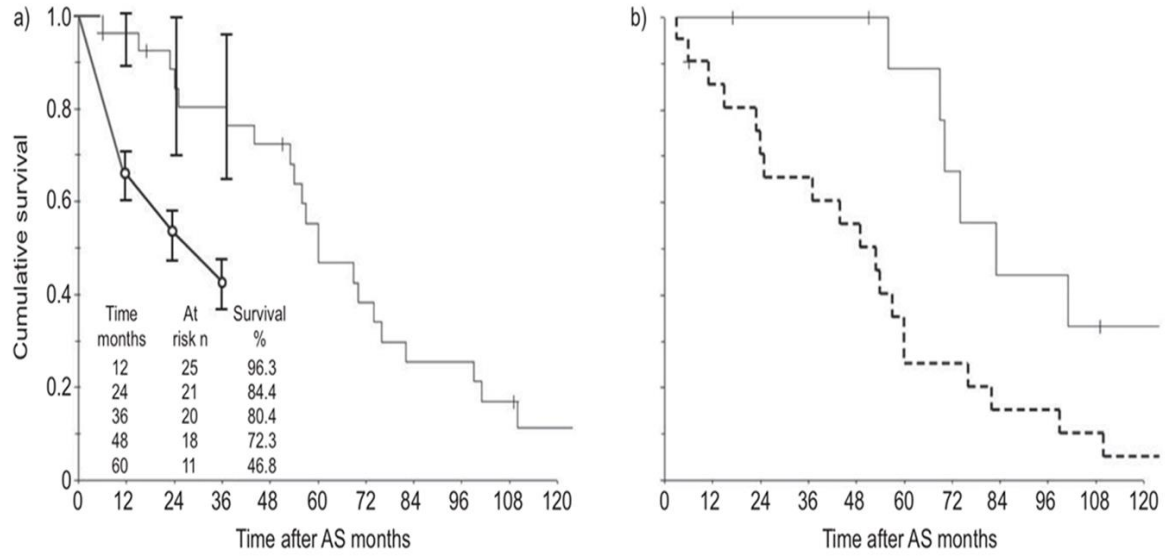
V-Wave device with the left side deployed, followed by both sides deployed (right and left) with the guidewire through the central hole and finally V-Wave completely deployed. Transoesophageal echocardiogram showing left-to-right shunt through V-Wave device.



Supplementary Figure 2. Clinical changes after AS in patients with PAH. Reproduced from Law et al[18] and Sandoval et al[14], with permission.

A) Changes in functional class over time.

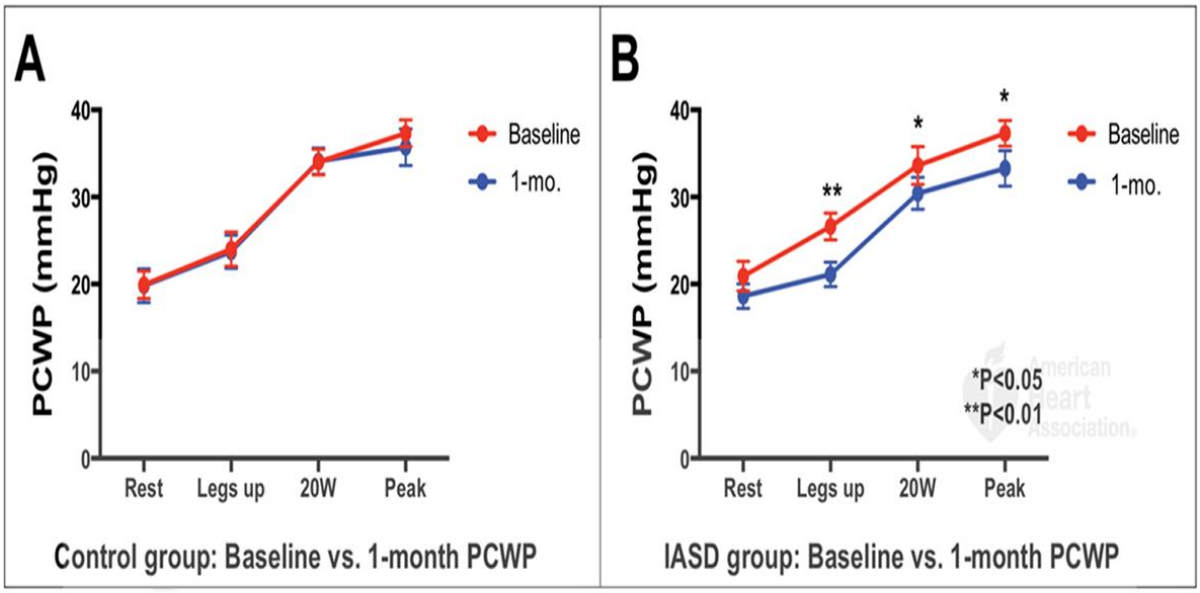
B) Changes in exercise capacity over time.



Supplementary Figure 3. Survival after atrial septostomy (AS) in PAH patients.
Reproduced from Sandoval et al[3], with permission.

A) Kaplan-Meier survival estimates following AS in a group of patients with pulmonary arterial hypertension (PAH). The mean survival of the group was 60 months (95% CI: 43–77 months). A predicted survival curve (o) is plotted for comparison. Error bars indicate 95% confidence intervals.

B) The survival estimates for PAH patients with AS + PAH-specific pharmacological treatment (—) were better than those in patients with AS alone (---) (median survival 83 months [95% CI: 57–109 months] versus 53 months [95% CI: 39–67 months], respectively; chi-squared log-rank 6.52; p=0.01).



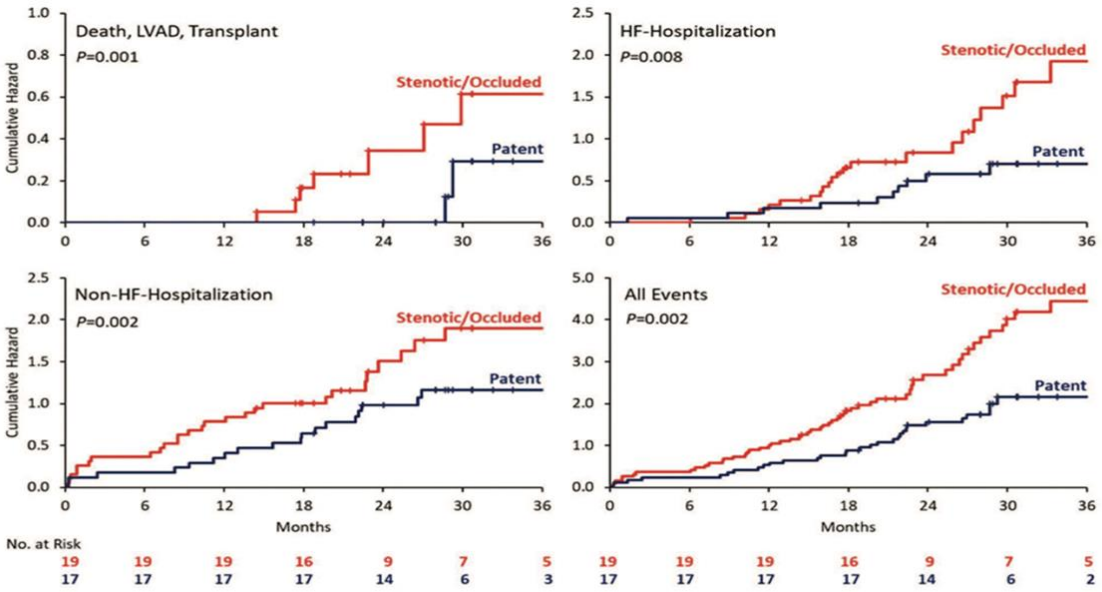
Supplementary Figure 4. Pulmonary capillary wedge pressure during exercise haemodynamic testing: baseline vs. 1-month post randomisation, stratified by treatment group.

Reproduced from Feldman et al[2], with permission.

A) Control group; B) IASD treatment group.

p-values were calculated using paired t-tests (within-group comparisons of baseline vs. 1-month values). *p<0.05; **p<0.01.

PCWP: pulmonary capillary wedge pressure



Supplementary Figure 5. Clinical events up to 3-year follow-up, according to shunt patency. Reproduced from Rodés-Cabau et al[36], with permission.

A) Death, heart transplant, LVAD.

B) Heart failure hospitalisation.

C) Non-heart failure hospitalisation.

D) All events.

Supplementary Table 1. Ongoing and future studies on interatrial shunting.

	Condition	Device	Study design	Number of participants	Primary endpoints
Prophet (NCT03022851)	Pulmonary hypertension	Occlutech AFR device	Prospective, non-randomised	30	Absence of Serious Adverse Device Effects (SADES) within 3 months following implantation, including deaths, systemic embolism or device embolisation.
REDUCE LAP-HFrEF (NCT03093961)	HFrEF	IASD System II (Corvia Medical)	Prospective, non-randomised	10	Periprocedural, and 6-month major adverse cardiac and cerebrovascular events (MACCE) and systemic embolic events in patients implanted with the IASD. The percent of subjects who have successful device implantation and the percent of subjects with left to right flow through the device assessed by an echocardiographic core laboratory.
REDUCE LAP HF II (NCT03088033)	HFpEF	IASD System II (Corvia Medical)	Multicentre, prospective, randomised controlled, blinded trial	380	Cardiovascular mortality or non-fatal ischaemic stroke up to 6 months; change in baseline KCCQ at 6 months.
REDUCE LAP HF III (NCT03191656)	HFpEF or HFmrEF	IASD System II (Corvia Medical)	Observational registry	100	Device and or procedure-related serious adverse cardiac events. Improvement in quality of life using KCCQ score and EQ5D score; improvement in functional NYHA class.
RELIEVE-HF (NCT03499236)	HFpEF or HFrEF	V-Wave Interatrial Shunt System	Multicentre, prospective, randomised controlled, blinded trial	500	Safety: percentage of treated patients experiencing major device-related major adverse cardiovascular or neurological events (MACNE) during the first 30 days after randomisation, compared to a pre-

					specified performance goal. Effectiveness: hierarchical composite of death, heart transplant or left ventricular assist device (LVAD) implantation, HF hospitalisations, and change in 6-minute walk test (6MWT).
PRELIEVE (NCT03030274)	HFrEF or HFpEF	Occlutech AFR device	Prospective, non-randomised	30	Incidence of serious adverse device effects (SADE) following implantation such as: device dislocation/embolisation, damage to the tricuspid or mitral valve caused by the device, intractable arrhythmias caused by the device and any circumstances that require device removal.

AFR: atrial flow regulator; HFrEF: heart failure with reduced ejection fraction; IASD: InterAtrial Shunt Device; HFpEF: heart failure with preserved ejection fraction; KCCQ: Kansas City Cardiomyopathy Questionnaire; HFmrEF: heart failure with mid-range ejection fraction; NYHA: New York Heart Association