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Review Article

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Transcatheter Implantation of Interatrial Shunt Devices to Lower Left Atrial Pressure in Heart Failure

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ABSTRACT

Patients with heart failure with preserved ejection fraction (HFpEF) constitutes a considerable sized population like that of subjects with heart failure with reduced ejection fraction. The symptoms include exercise induced dyspnoea and fatigue besides an increased mortality rate when compared to the general population. There is limited evidence of benefit from pharmacological therapy. A main pathophysiological mechanism is a left ventricular filling pressure that might be near to normal during resting conditions but increases during exercise leading to pulmonary congestion. Based on observations like the apparent lesser symptomatology in patients with combined mitral valve stenosis and atrial septal defect (Lutembacher syndrome) when compared to patients with isolated mitral valve stenosis, several Inter-Atrial Shunt Devices (IASD) have been developed with the intent to unload the pressure in the left atrium by creating a shunt into the right atrium. Smaller studies have found that the IASDs reduce the left ventricular filling pressure during exercise and increase the functional status of patients both subjectively and objectively with reported low rates of complications. These devices are undergoing further investigations and might prove to be a new paradigm in the treatment of patients with HFpEF.

Keywords: Heart failure; Left ventricle; Investigatoinal therapies; Haemodynamics

INTRODUCTION

Heart failure (HF) is a complex clinical syndrome categorised into with HF with reduced ejection fraction (HFrEF; left ventricular ejection fraction [LVEF] <40%); HF with mildly reduced ejection fraction (HFmrEF; LVEF 41–49%), and HF with preserved ejection fraction (HFpEF; LVEF ≥50%. The syndrome consists of dyspnoea, fatigue, and oedema due to structural or functional cardiac abnormalities.[1] Depending on geography, approximately 1–2% of the population have HF and the prevalence increases with older age, reaching >10% in patients older than 85 years of age.[1)2] Although the incidence of HF is reported to decrease over time, the prevalence is still increasing in absolute numbers due to a larger ageing population.[3] Patients with HFpEF accounts for approximately 50% of patients with HF.[1)4)5]

The aetiologies of HFpEF are numerous and heterogenous and include both cardiovascular diseases such as valvular heart disease, atrial fibrillation, right ventricle heart failure,

pericardial diseases, systemic hypertension and dilated left atrium; as well as non-cardiovascular diseases including obesity, ageing, chronic pulmonary obstructive disease and chronic kidney disease.[1)4)6)7)]

When compared to the general population patients with HFpEF have reduced survival with a 5-year mortality rate of 54–74%.[7)8)] The risk of cardiovascular death is reported to be lower in patients with HFpEF when compared to patients with HFrEF.[4)9)10)] Thus, the risk of all-cause mortality for patients with HFpEF when compared to patients with HFrEF showed an adjusted hazard ratio of 0.68 (95% confidence interval [CI], 0.64–0.71) during 3 years of follow-up.[9)]

Despite heterogenous aetiologies of HFrEF, several pharmacological and cardiac devices have been found to improve outcome for these patients, likely due to similar pathophysiological adaptation of failing of the systolic left ventricular function. However, no pharmacological therapy has been found to reduce mortality or morbidity for patients with HFpEF effectively. Thus, randomised clinical trials have failed to demonstrate effect of ACE-inhibitor (perindopril), angiotensin-receptor blocker (irbesartan or candesartan) or mineralocorticoid-receptor blockers (spironolactone) in reducing the risk of mortality and/or HF hospitalisation in patients with HFpEF.[11-15)] Still, the Guidelines recommend control of blood pressure and volume status depending on signs of congestion.[1)16)] Recently, the EMPEROR-preserved trial reported a reduction of the primary combined end-point of cardiovascular death or heart failure hospitalisation for patients with HFpEF treated with empagliflozin compared to placebo. However, the prespecified isolated primary endpoint of cardiovascular death and other prespecified secondary endpoints including all-cause mortality, re-hospitalisation for any cause and change in quality-of-life scores where all neutral between the two groups.[17)]

Due to the paucity of pharmacological therapies targeted at patients with HFpEF, attention has turned to decreasing the left atrial pressure and left ventricular filling pressure through interatrial shunts.

LEFT ATRIAL PRESSURE AND HF

In healthy individuals, exercise results in an increased heart rate, as well as ventricular stroke volume and ejection fraction (EF) by increased end-diastolic volume and reduced end-systolic volume. The increase in heart rate, EF and stroke volume has been reported to be blunted during exercise in patients with HFpEF when compared to healthy controls, despite similar heart rate, EF and stroke volume at rest.[18)] When changing from rest to exercise, the pulmonary capillary wedge pressure (PCWP) increased from a mean of 14–19 mmHg to 31–33 mmHg in HFpEF patients compared with 7–9 mmHg to 14 mmHg in healthy controls. The increase in left ventricular filling pressure results in increased pulmonary artery pressure (PAP) and impaired increase in cardiac output[18-21)] leading to increased perceived dyspnoea, higher New York Heart Association (NYHA) class, and lower peak exercise capacity—likely due to pulmonary congestion.[19)]

In HFpEF patients with an implantable hemodynamic monitor, diastolic PAP increases prior to episodes of acute decompensated HF.[22)] Importantly, body weight did not change prior to events of acute decompensated HF indicating it may be an unreliable method of monitoring. The diastolic PAP can function as an estimate of the PCWP and left ventricular filling

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pressure and is detected to start increase at a mean of 19.3 days in advance of the episode with acute decompensated HF and returned to baseline levels after therapy. In patients with HFpEF who did not develop episodes of acute decompensated HF, the diastolic PAP is stable during the 75 days of follow-up.[22] The CHAMPION trial showed, that the risk of HF hospitalisation is reduced in HFpEF patients on vasodilator and diuretics therapy guided by wireless continuous PAP monitoring when compared to HFpEF patients without continuous monitoring (incidence rate ratio, 0.54; 95% CI, 0.35–0.70).[23]

This underscores the importance of controlling the left ventricular filling pressure, although, many patients with HFpEF have normal filling pressures at rest. In these patients the primary symptom burden is exercise-induced and pharmacological reduction of preload can lead to hypotension at rest.

Patients with combined mitral valve stenosis and atrial septal defect (Lutembacher syndrome) seem less symptomatic when compared to patients with mitral valve stenosis alone. Similar, patients with atrial septum defects and left ventricular dysfunction can develop pulmonary oedema in case of closure of the atrial septum defect. Based on these and other similar observations, a computer simulated study investigated the effect of creating an interatrial shunt on resting and exercise haemodynamics.[24] The study found that a shunt diameter of 8 mm creates a unidirectional left-to-right flow, lowering PCWP by 3 mmHg during rest (from 10 to 7 mmHg) and by 11 mmHg during exercise (from 28 to 17 mmHg), with a Qp/Qs ratio of 1.3 to 1.4, respectively.[24] Considering the appealing effect on auto-regulation of shunting and left ventricular filling pressure in relation to rest and exercise, several inter-atrial shunt devices (IASD) have been developed in order to control the shunt diameter and keep the shunt patent (**Figure 1**).

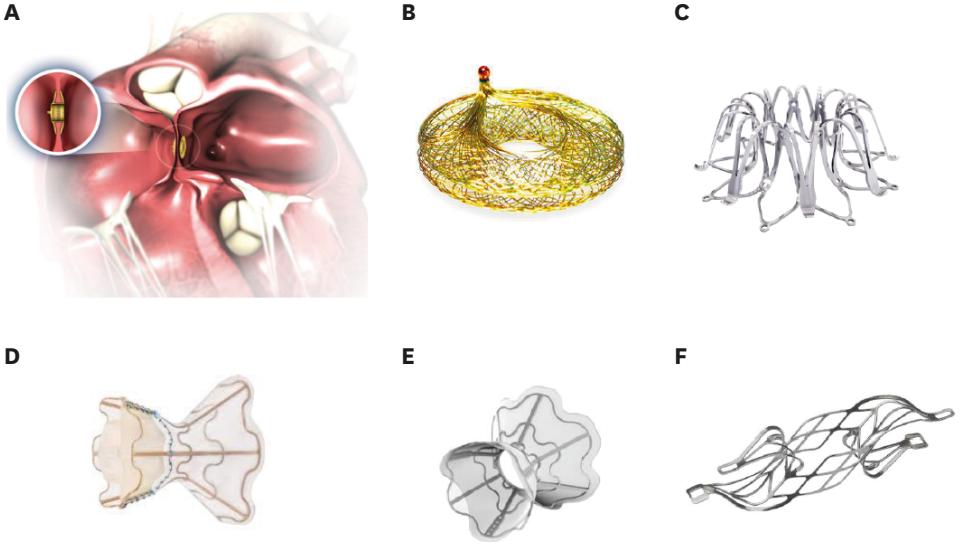

Figure 1. Interatrial and coronary sinus-to let atrium shunt devices.
(A) IASD placement, shown the Occlutech atrial flow regulator. (B) Occlutech Atrial flow regulator. (C) Corvia. (D) First generation V-Wave. (E) Second generation V-Wave Ventura (valve-less). (F) Edwards Transcatheter Atrial Shunt System.
IASD = inter-atrial shunt devices.

IASD

Technical aspects

The Corvia IASD (Corvia Medical, Tewksbury, MA, USA), V-wave (V-Wave Ltd., Caesarea, Israel) and Occlutech atrial flow regulator (Occlutech AG, Schaffhausen, Switzerland) are all implanted through the femoral vein guided by fluoroscopy and echocardiography. Heparinization to activated clotting time >250 or 300 seconds is encouraged in most trials. A transseptal puncture is performed and the device is advanced from the right to left atrium and deployed over the both sides of the created atrial septal defect (**Figure 1F**).

Currently no international guideline have recommendations for the indication of IASDs and invite further investigations.[1)16)] Listed contraindications include obstructive cardiomyopathy, right ventricular dysfunction, existing atrial septal defect or surgical closure hereof, recent venous thrombus, significant valvular disease or contraindication to antithrombotic therapy. Further, interaction with intracardiac pace leads should be avoided due to the risk of embolization of thrombus from the surface of the pace lead; tricuspid regurgitation due to tension on the pace lead; dysfunction of the pacemaker or difficulty of future pace lead replacement.

No consensus on antithrombotic therapy exists yet. For patients without need for oral anticoagulation most trials administered clopidogrel and aspirin for 3 to 6 months followed by lifelong single platelet inhibitor. Patients with indication for oral anticoagulation continue the same regime post-procedure with or without adding a single platelet inhibitor.[25-28)]

Corvia

The Corvia IASD (Corvia Medical) (**Figure 1A**) consists of a nitinol mesh formed into a double disc (20 mm diameter) with an open barrel (8 mm diameter). The Corvia IASD has been investigated in several studies (**Table 1**). The pilot single-arm study from 2014 enrolled 11 patients with EF >45%; baseline PCWP ≥15 mmHg at rest or ≥25 mmHg during exercise; NYHA class ≥III or HF hospitalisation within the last year.[29)] The PAP was stable, whereas PCWP and NYHA class was reduced during 30 days of follow-up.[29)] At one year follow-up the NYHA class was still reduced when compared to baseline, the mean distance of a 6 minute walk test was 43 meters (13%) longer than at baseline, and the patients had a reduction in the rate of HF hospitalisation from 1.36 to 0.73 per 10 patient-years from prior to following IASD implantation.[30)]

The REDUCE LAP-HF single-arm study followed in 2015, designed to evaluate safety and device performance.[36)] The trial enrolled 66 patients with similar inclusion criteria as the pilot trial. Device implantation could not be completed in two patients; one due to complication of the trans-septal puncture and another with unsuitable septal anatomy, resulting in 64 patients with the Corvia IASD implanted (**Table 1**).[31)] The PCWP during rest was unchanged from baseline to after 6 months of follow-up, but was reduced during peak exercise from a mean of 34 to 32 mmHg. Further, NYHA class was reduced and 6 minute walk test increased by 32 meters (10%) at follow-up when compared to baseline.[31)] The REDUCE LAP-HF 12 months follow-up study reported clinical data on 60 patients and invasive measurement in 18 of the originally included patients, and found that NYHA class and PCWP was still reduced and 6 minute walk test longer when compared to baseline measurements.[32)]

The REDUCE LAP-HF I was a placebo-controlled randomised trial evaluating the safety and efficacy of the Corvia IASD. The trial included patients with LVEF ≥40%, NYHA class ≥III, exercise PCWP ≥25 mmHg or PCWP-to-right atrial pressure (RAP) gradient ≥5 mmHg.[37)]

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Table 1. Previous trials with interatrial shunt devices

Study	Author	Number (Incl./ Succ.)	Follow-up (months)	Age (years)	Ejection fraction (%)	PCWP at rest (mmHg)		PCWP during peak exercise (mmHg)		PAP (mmHg)		6MWT (m)		NYHA class	
						Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post
Corvia															
Pilot trial	Søndergaard et al.[29]	11/11	1	70 (12)	57 (9)	19 (5)	14 (3)			30 (7)	27 (6)	322 (151)	368 (123)	3.2 (0.4)	2.5 (0.8)
	Malek et al.[30]		12										352 (79)		2.5 (0.5)
REDUCE LAP-HF	Hasenfuß et al.[31]	66/64	6	69 (8)	47 (7)	17 (5)	17 (7)	34 (8)	32 (8)	25 (7)	23 (7)	313 (105)	345 (106)	3 (2, 3)	2 (2, 3)
	Kaye et al.[32]		12				17 (6)		33 (10)		26 (8)		363 (93)		
REDUCE LAP-HF I	Feldman et al.[25]	22/20	1	70 (9)	60 (9)	21 (8)	19 (7)	37 (7)	34 (6)	30 (10)	28 (5)	300 (231, 334)		3 (0)	2.5 (0.7)
V-wave															
1st generation	Del Trigo et al.[33]	10/10	3	62 (8)	25 (8)	23 (5)	17 (8)			29 (7)	26 (11)	244 (112)	318 (134)	3 (0)	2.0 (0.5)
	Rodés-Cabau et al.[34]	38/38	28	66 (9)		21 (5)	19 (7)			30 (7)	30 (10)	289 (112)	324 (105)	3.0 (0.2)	
2nd generation Ventura	Guimarães et al.[26]	10/10	12	68 (9)	34 (12)	24 (11)				35 (16)		255 (68)	338 (104)	3 (0)	
Occlutech atrial flow regulator															
AFR-PRELIEVE	Paitazoglou et al.[35]	20/20	3	66 (10)	52 (6)	21 (6)	Δ−5 (9)			43 (12)	Δ3 (18)	233 (118)	Δ24 (22)	3.1 (0.3)	Δ−1.1 (0.2)
PRELIEVE	Paitazoglou et al.[27]	54/53	12	70 (63, 73)								200 (100, 300)	Δ50 (−33, 133)	3 (3, 4)	Δ−1 (0, −1)
Edwards Transcatheter Atrial Shunt System															
Pilot trial	Simard et al.[28]	11/8	7 (5, 9)	78 (72, 81)	55 (49, 60)	22 (19, 24)	Δ−9 (−8, −10)			26 (21, 29)	27 (20, 31)	243 (198, 316)		3.1 (0.4)	1.9 (0.6)

Values are presented as numbers (standard deviation) or (interquartile range).
Δ = difference from baseline; PCWP = pulmonary capillary wedge pressure; PAP = pulmonary artery pressure; 6MWT = 6-minute walk test; NYHA = New York Heart Association.

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After randomisation, 22 patients had IASD implantation and 22 controls underwent sham-procedure with invasive measurements. After one month of follow-up the PCWP during exercise had decreased by 3.5±6.4 mmHg in the IASD group compared to 0.5±5.0 mmHg in the control group (p=0.14) and the change in NYHA class, exercise duration and peak exercise workload was similar between the 2 groups. However, in intergroup comparison from baseline to one-month follow-up, the PCWP during peak exercise was statistically reduced by 3.2±5.2 mmHg in the treatment group whereas the PCWP increased by 0.9±5.1 mmHg in the control group.[25] In the one-year follow-up study, the IASD was patent in all patients and the one year rate of HF hospitalisation was 0.22 in the treatment group compared to 0.63 in the control group (p=0.06), and NYHA had decreased by a median of one class in the treatment arm compared to zero in the control group (p=0.08).[38]

V-wave

The V-wave IASD (V-Wave Ltd.) was initially designed as an hour-glass shaped nitinol device covered with polytetrafluoroethylene with three porcine pericardial leaflets sutured together centrally in the barrel to only allow left-to-right shunting.[33] A Canadian special access programme pilot-study included ten patients with NYHA class ≥III and HFrEF. From baseline to three months of follow-up the patients had a reduction in NYHA class and in PCWP from 23 to 17 mmHg at rest, higher quality-of-life scores and an increase in 6-minute walk test distance of 74 meters (30%) from baseline. The device was patent at follow-up as assessed by transthoracic echocardiography in all patients alive at three months.[33] A larger multi-centre international pilot study included 38 (30 with HFrEF and 8 with HFpEF) patients to have the first-generation V-wave IASD implanted and followed for 1 year. All patients had successful implantation of the V-wave IASD, however at 1-year follow-up the shunt had become either stenotic or occluded in 50% of the patients.[34]

This led to modifications of the device by removing the central valve in expectations to promote long-term patency. The second-generation V-Wave Ventura IASD was tested and reported in a pilot study including 10 patients with NYHA class ≥ III, chronic HFrEF and HFpEF. Six of these patients were alive and followed for 12 months, all with patency of the IASD (**Table 1**).[26]

Occlutech

The Occlutech atrial flow regulator (Occlutech AG) is a self-expanding nitinol wire mesh formed into two discs connected by a central fenestration with a diameter of either 8 or 10 mm (**Figure 1D**). In a multicentre pilot study 36 patients (16 with HFrEF and 20 with HFpEF) with NYHA class ≥III, PCWP ≥15 mmHg at rest or ≥25 mmHg during exercise were included. Patency and left-to-right shunt were present in all patients after three months of follow-up. During follow-up the HFpEF population had a reduction in NYHA class and mean PCWP during rest, and an increase in quality-of-life scores, while the PAP remained unchanged.[35] After the initial trial the inclusion continued and 53 patients (24 with HFrEF and 29 with HFpEF) were followed for 12 months in the PRELIEVE trial. Patency was confirmed by transthoracic echocardiography in 45 of 49 eligible patients (92%), and non-diagnostic due to poor imaging quality in the remaining four patients. NYHA class and 6-minute walk test distance was improved in the total and HFpEF population after 12 months follow-up (**Table 1**). Invasive measurements were not repeated at 12 months.[27]

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Edwards Transcatheter Atrial Shunt System

The Edwards left atrium to coronary sinus shunt (LA-to-CS) system (Edwards Lifesciences, Irvine, CA, USA) uses a different approach by creating a shunt through a nitinol frame implanted into the left atrium through the coronary sinus, keeping the atrial septum intact (**Figure 1E**). The inner diameter is 7 mm and the frame is anchored by 4 arms, 2 in the left atrium and 2 in the coronary sinus. Access is gained through the jugular vein and a 24 Fr introducer sheath is inserted. The systems allows for assessment of correct positioning and is fully recapturable up until the point of final arm deployment and is compatible with an occluder device in case of excessive shunting.[28] An international pilot study including 11 patients reported successful implantation in 8 patients with a reduction in NYHA class and a decrease in PCWP of 9 mmHg as well as HF hospitalisations when compared to baseline rates (**Table 1**).[28]

IASD IN HFrEF

Data specifically on patients with HFrEF is sparse. In the abovementioned PRELIEVE trial, 24 of the 53 included patients had HFrEF and after one year of follow-up these patients had statistically significantly improved NYHA Class, quality of life score and 6 minute walk test distance.[27] However, the PCWP measured at three months was not different from baseline.

In the pilot trial of the first generation V-wave including ten patients with HFrEF the PCWP decreased by 6 mmHg at rest.[33] The RELIEVE-HF trial is planned to randomise 500 symptomatic patients with HFrEF and HFpEF to either implantation of the second generation V-wave or standard medical therapy (**Table 2**).

COMPLICATIONS IN RELATION TO IASD IMPLANTATIONS

Only few complications during implantation of IASDs have been reported in the currently literature. Of the collective 95 patients included in the Corvia IASD pilot, REDUCE LAP-HF and REDUCE LAP-HF I trials one patient had a trans-septal complication without further complications; in one patient the device did not fully deploy, and five patients had successful implantation of a second device peri-procedurally due to unsuitable positioning (n=4) or suspected small thrombus in the right atrium (n=1).[25][29][31] During one-year follow-up all patients had survived without cerebral adverse events reported in the Corvia pilot trial.[30] A clinical three-year follow-up study reported a lower observed mortality rate (3.4 per 100 patient-years (95% CI, 1.52–7.54)) for the included patients in the REDUCE LAP-HF trial when compared to a predicted mortality rate (10.2 per 100 patients-years (95% CI, 6.1–16.9).[40] Cause of death was HF-related (n=3); not directly related to HF (n=2) and one patient experienced a fatal stroke. The presence of a patent atrial shunt might be the cause for paradoxical embolism, although left-to-right shunting was reported in all patients at one year follow-up a temporary right-to-left shunt cannot be excluded to occur during Valsalva.[32][40] After one-year follow-up in the sham-controlled randomised clinical REDUCE LAP-HF I trial, there was no statistical difference in the risk of all-cause mortality (4.8% vs. 13.6%) or the composite risk of major cardiac, cerebrovascular or renal events (9.5% vs. 22.7%) between patients with IASD implantation and the control group, respectively. Further, no stroke or events of systemic embolization occurred in either group.[38]

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Table 2. Future trials with interatrial shunt devices

Trial	Design	No. of patients	Expected completion	Inclusion	Primary outcome
Corvia					
REDUCE LAP-HF II (NCT03088033)[39]	- Multicentre - Prospective - Blinded - Randomised clinical trial - 1:1; Treatment with Corvia IASD vs control group	608	July 29, 2021	- Symptoms of HF - NYHA class ≥III - ≥1 HF hospital admission within the last 12 months - Age ≥40 years - LVEF ≥40% - Exercise PCWP ≥25 mmHg, and greater than RAP by ≥5 mmHg	*12 months incidence:* - Composite cardiovascular mortality and first non-fatal ischemic stroke - Total rate of recurrent HF events - Time-to-first HF event - Change in quality-of-life scores
REDUCE LAP-HF III (NCT03191656)	- German registry on consecutively treated patients	500	July 31, 2023	- Age ≥40 years	- Serious adverse device and cardiac events - NYHA class - Quality of life scores
REDUCE LAP-HF IV (NCT04632160)	- Multicenter - Prospective - Open Label - Single Arm - Comparator is treatment arm of REDUCE LAP-HF II	150	January 1, 2022	- Symptomatic heart failure - Age ≥40 years - LVEF ≥40%	- Similar to REDUCE LAP-HF II
V-Wave					
RELIEVE-HF (NCT03499236)	- Multicentre - Prospective - Blinded - Randomised clinical trial - 1:1; Treatment with V-wave IASD vs control group	500	December 31, 2022	- HFrEF and HFpEF patients - NYHA class ≥II - ≥1 HF hospital admission	*30 days incidence:* - Major device-related adverse events *12–24 months incidence:* - Composite rate of death, heart transplant or left ventricular assist device implantation; HF hospitalizations - Change in quality-of-life scores
Edwards Transcatheter Atrial Shunt System					
Alt-FLOW US (NCT03523416)	- Feasibility trial - Single Arm - Open Labe	40	July 2021	- NYHA class ≥III - ≥18 years old - ≥1 HF hospital admission - PCWP >15 mmHg at rest or >25 mmHg during exercise AND exceeding RAP by >5 mmHg at rest or >10 mmHg during exercise	*30 days incidence:* - Composite of major adverse cardiac, cerebrovascular, or renal events - Re-intervention due to study device related complications

PCWP = pulmonary capillary wedge pressure; RAP = right atrial pressure; NYHA = New York Heart Association; HF = heart failure; HFrEF = heart failure with reduced ejection fraction; HFpEF = heart failure with preserved ejection fraction.

Implantation of the first-generation V-wave was reported successful in all 38 investigated patients. In the hours following the procedure one patient had cardiac tamponade treated with pericardiocentesis. During 12 months of follow-up serious adverse events included death in two patients, one of which had ventricular storm leading to terminal HF at two months post-procedure. Additionally, admission for gastrointestinal bleeding (n=2), acute coronary syndrome (n=5) acute decompensated HF (n=9) and vascular access complications in four patients were reported. No stroke was reported.[26)33)] In the second-generation Ventura V-wave pilot trial the IASD was successfully implanted in all 10 included patients. One patient died in the hours following the procedure due to electrical storm and during one-year follow-up another three patients died (2 with pneumonia; 1 with terminal HF).

In the Occlutech PRELIEVE trial transseptal puncture was unsuccessful in two of the 53 included patients, one patient experienced device embolisation into the left atrium requiring surgical removal and one patient had severe post-procedural bleeding with syncope but the event was self-limiting.[27)35)] During one-year follow-up, four patients died (All from the HFrEF group) (one due to pneumonia; two due to end-stage cardio-renal syndrome, and one due

to deterioration of general condition). No events of stroke or myocardial infarction were reported. New or worsening atrial fibrillation occurred in 11 patients and new or worsening of renal function was reported in 11 patients.[27]

Finally, in the Edwards LA-to-CS shunt system pilot trial the percutaneous atriotomy was unsuccessful due to inability to track the guidewire in the coronary sinus in 3 of the 11 included patients. After the first three failures implementation of pre-procedural computed tomographic three-dimensional model printing was performed as part of patient evaluation process and no further failures to achieve atriotomy occurred. No further procedural complications were reported. During follow-up two patients died with unknown cause of death.[28]

FUTURE PERSPECTIVES

To date several small randomised clinical trials have demonstrated the feasibility and safety of IASDs but are insufficient in providing a clear therapeutical indication.[1][16] Ongoing randomised clinical trials are investigating the use of IASDs in larger scale and might provide much needed answers (**Table 2**). In a sub-study of the REDUCE LAP-HF trial, it was reported that patients with higher pressure gradient between the PCWP and central venous pressure (CVP) (the driving pressure for shunt flow) at baseline had a greater reduction of PCWP-CVP due to lower PCWP and a small increase in CVP during peak exercise after six months of follow-up.[41] In the REDUCE LAP-HF trial the reduction in peak exercise PCWP from 36.3 mmHg at baseline to 33.4 mmHg after 6 months was modest. However, the investigators highlighted that peak exercise tolerance is limited when PCWP raise beyond a threshold during exercise. This threshold is not changed with IASD implantation, however the peak exercise workload tolerated increased from 47.8 W at baseline to 57.8 W at 6 months of follow-up. Therefore, the work and weight normalised PCWP was reduced from 84.3 mmHg/W/kg at baseline to 59.7 mmHg/W/kg after six months of follow-up. The investigators speculate that patients with greater PCWP-CVP gradient during baseline exercise might be good responders to IASD and aids in patient selection.[41]

However, the lower PCWP-CVP gradient would result in an increased RAP/PCWP ratio. In subsequent analyses of the ESCAPE trial including 188 patients with LVEF ≤30%, systolic blood pressure ≤125mmHg and signs of congestion an increased RAP/PCWP ratio was associated with an increased risk of death or hospitalisation.[42] The patient group with the highest risk of adverse events in the ESCAPE trial had a mean RAP of 20 mmHg, a higher pulmonary vascular resistance (PVR) and lower right ventricle stroke volume when compared to the other groups with lower RAP/PCWP ratios.[42] A pooled analysis of the REDUCE LAP-HF and the REDUCE LAP-HF I trials found that although RAP increased the pulmonary blood flow and oxygen saturation increased and had favourable effects on pulmonary vascular tone with a decrease in PVR while also maintaining stable systemic blood flow and oxygen saturation. Although the authors emphasize that patients with right ventricular dysfunction and severe pulmonary disease where excluded and that patients with greater pulmonary compliance might gain greater benefit from IASD implantation.[19] Interestingly, they also reported that patients with atrial fibrillation showed reduction in resting PVR when compared to those without speculating they may gain benefit from IASDs.[19]

Several questions remain unanswered including: which patients are good responders to IASD implantation, effect of arrhythmias such as atrial fibrillation without the atrial kick, effect in

patients with HFrEF and further understanding of short and long term complications as well as anticoagulation regimes. Several feasibility and larger trials are recruiting and will provide crucial information regarding the use of IASD implantation.

CONCLUSIONS

HFpEF like HFrEF is a frequent heart disease with debilitation symptoms and an increased risk of all-cause mortality and little benefit has been found from pharmacological therapy so far. Although only investigated in smaller trials the implantation of IASD appears to reduce the PCWP with no reported increase in the pulmonary artery pressure and no detrimental effect on the right ventricle but with an increase the functional status both subjectively and objectively. Besides one feasibility trial with a LA-to-CS shunt two larger randomised trials with different IASDs are ongoing as to evaluate the effect of this novel therapy on HF hospitalisation, mortality, quality of life and exercise tolerance (**Table 2**). The interatrial and LA-to-CS shunt devices will likely remain investigational until these trials demonstrate an appropriate safety and consistent efficacy for the relevant population of patients with HFpEF.

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