EuroIntervention 2019;15:403-410 published online May 2019

euro PCR 2019 LATE BREAKING TRIALS

The AFR-PRELIEVE trial: a prospective, non-randomised, pilot study to assess the Atrial Flow Regulator (AFR) in heart failure patients with either preserved or reduced ejection fraction

Christina Paitazoglou[1], MD; Ramazan Özdemir[2], MD, FESC; Roman Pfister[3], MD, FESC; Martin W. Bergmann[1]*, MD, FESC; Jozef Bartunek[4], MD; Teoman Kilic[5], MD, FESC; Alexander Lauten[6], MD, FESC; Alexander Schmeisser[7], MD, FESC; Mehdi Zoghi[8], MD; FESC; Stefan Anker[6], MD, FESC; Horst Sievert[9], MD, FESC; Felix Mahfoud[10], MD, FESC; on behalf of the AFR-PRELIEVE Investigators

1. Interventional Cardiology, Cardiologicum Hamburg, Hamburg, Germany; 2. Department of Cardiology, Bezmiâlem Vakıf University, Istanbul, Turkey; 3. Department of Cardiology, Pulmonology, Angiology and Intensive Care Medicine, Heart Center University Clinic Cologne, Cologne, Germany; 4. Cardiovascular Center, Onze-Lieve-Vrouwziekenhuis Hospital Aalst, Aalst, Belgium; 5. Department of Cardiology, Kocaeli University Medical Faculty, Kocaeli, Turkey; 6. Department of Cardiology, Charité University Clinic Berlin, Berlin, Germany; 7. Department of Cardiology and Angiology, University Clinic Magdeburg A.ö.R., Magdeburg, Germany; 8. Department of Cardiology, Ege University Medical Faculty, Bornova/Izmir, Turkey; 9. Cardiovascular Center Frankfurt, Frankfurt, Germany; 10. Department of Internal Medicine, Cardiology, Angiology and Intensive Care Medicine, University Clinic Saarland, Homburg, Germany

KEYWORDS

- atrial septal defect
- chronic heart failure
- clinical trials
- innovation

Abstract

Aims: Reducing elevated left atrial pressure with an atrial septum shunt device is a possible treatment option in symptomatic heart failure patients. This study aimed to investigate the safety and feasibility of the Atrial Flow Regulator (AFR) in heart failure patients.

Methods and results: AFR-PRELIEVE is a prospective, non-randomised, open-label, multicentre study in patients with symptomatic heart failure NYHA Class III or IV and pulmonary capillary wedge pressure (PCWP) ≥15 mmHg at rest or ≥25 mmHg at exercise irrespective of left ventricular ejection fraction (EF ≥15%). Here we report on procedural and three-month follow-up data for a total of thirty-six enrolled patients. Sixteen (44.5%) patients with reduced EF (HFrEF: EF 15-39%) and twenty (55.5%) patients with preserved EF (HFpEF: EF ≥40%) were enrolled. Implantation success rate and device patency with left-right shunt was 100% (post procedure and at three months) in both patient groups, with one SADE in the HFpEF group which completely resolved. Three (3/36, 8.3%) patients were hospitalised for worsening of heart failure (two HFrEF patients, one HFpEF patient). Individual patients from both the HFrEF and HFpEF groups showed improvement in symptoms and surrogate parameters of heart failure (NYHA class, six-minute walking distance, Kansas City Cardiomyopathy Questionnaire, PCWP, NT-proBNP).

Conclusions: Implantation of the AFR device in heart failure patients is feasible and safe; shunt patency at three months was confirmed in the study. The atrial shunt improved symptoms and surrogate parameters of heart failure in some but not all patients in both the HFpEF and HFrEF groups.

**Corresponding author: Interventional Cardiology, Cardiologicum Hamburg, Schloßgarten 3-7, 22401 Hamburg, Germany. E-mail: docbergmann@mac.com*

© Europa Digital & Publishing 2019. All rights reserved.

SUBMITTED ON 30/03/2019 - REVISION RECEIVED ON 1st 12/05/2019 / 2nd 18/05/2019 - ACCEPTED ON 20/05/2019

DOI: 10.4244/EIJ-D-19-00342

Abbreviations

AE	adverse event
AFR	Atrial Flow Regulator
CRT	cardiac resynchronisation therapy
CVP	central venous pressure
eCRF	electronic case report form
EF	ejection fraction
HF	heart failure
HFpEF	heart failure with preserved ejection fraction
HFrEF	heart failure with reduced ejection fraction
KCCQ	Kansas City Cardiomyopathy Questionnaire
LA	left atrium
LAP	left atrial pressure
LV	left ventricle
LVEDP	left ventricle end-diastolic pressure
PAP	pulmonary artery pressure
PCWP	pulmonary capillary wedge pressure
PFO	patent foramen ovale
SADE	serious adverse device (-related) effect
SAE	serious adverse event
TEE	transoesophageal echocardiography
6MWD	6-minute walking distance

Introduction

Increased left atrial pressure (LAP) leads to exercise intolerance and exertional dyspnoea, and predicts mortality in patients with heart failure (HF)[1]. Morbidity and mortality rates in HF patients with preserved ejection fraction (HFpEF) are similar to those in HF patients with reduced EF (HFrEF)[2,3].

Diastolic dysfunction involves several different haemodynamic and molecular mechanisms, leading to impaired left ventricular (LV) relaxation, development of left atrial (LA) volume overload and pulmonary venous congestion[2].

Evidence-based treatments in patients with HFrEF have improved their prognosis[4]; however, the role of dedicated approaches to reduce elevated LV filling pressure remains unclear. Reducing LAP and LA volume overload using an atrial septum shunt device has emerged as a novel treatment option to improve HF symptoms. Two different devices have been clinically investigated. Implantation of the interatrial shunt device (IASD), tested in HFpEF patients, was proven to be safe and associated with lower pulmonary capillary wedge pressure (PCWP) in a pilot trial, an open-label Phase I and a prospective Phase II trial[5-7]. The first-in-man study of the V-Wave device (V-Wave Ltd, Caesarea, Israel), with an incorporated V-trileaflet porcine tissue valve, demonstrated initial safety and early beneficial clinical and haemodynamic outcomes in patients with HFrEF, though the benefits appeared to be compromised by impaired shunt patency in a single-arm, open-label study[8,9].

The present open-label, prospective pilot study (the AFR-PRELIEVE trial) investigated the safety of the Atrial Flow Regulator (AFR; Occlutech, Helsingborg, Sweden) in patients with HF and elevated filling pressures. Herein we present the procedural details, periprocedural and safety events, as well as device patency including three-month results.

Editorial, see page 398

Methods

STUDY DESIGN AND POPULATION

AFR-PRELIEVE is a prospective, non-randomised, open-label, multicentre pilot study. Patients were recruited between November 2017 and December 2018 in 10 clinical sites (Germany, Turkey and Belgium). The study was reviewed and approved by the local and national ethics committees before study initiation according to local and national regulations. The study was performed according to current standards including a clinical events committee. Investigators entered all relevant patient information in a dedicated electronic case report form (eCRF). A data safety monitoring board (DSMB) was established. The study was monitored; each site was visited at least once. The funding source as well as the authors analysed the data; the funding source locked the database after final monitoring. The authors of the manuscript had full access to all data. This pilot study has been started on the background of the vast clinical experience with the Occlutech® patent foramen ovale (PFO) and atrial septal defect (ASD) occluder devices, as well as a limited number of compassionate use cases for this particular shunt device implanted in patients with pulmonary hypertension creating a right-to-left shunt.

Inclusion and exclusion criteria are summarised in **Table 1**. Eligible patients with signed informed consent were approved for the study and underwent right heart catheterisation on the day of the implantation for haemodynamic measurements. Patients who met the haemodynamic study criteria received the Occlutech AFR device. Patients with symptomatic HF (HFpEF or HFrEF) were enrolled consecutively without initial stratification.

Patients are followed for 12 months (eight clinical visits) to evaluate safety and outcome data of the procedure. NYHA class, six-minute walking distance (6MWD), quality of life assessed by Kansas City Cardiomyopathy Questionnaire (KCCQ) and transthoracic echocardiography parameters are assessed during follow-up according to the protocol, as presented in **Figure 1**.

Transoesophageal echocardiography (TEE) and a right heart catheterisation were pre-specified to be performed at three-month follow-up. Variables measured by echocardiography (echo) are sent to the central reading office for blinded independent validation (coreLab Black Forest GmbH, Bad Krozingen, Germany). However, the reported values are eCRF entries carried out by the local investigators. Each site had to submit a validation echo at the beginning of the study for eligibility.

The primary safety endpoint is the rate of serious adverse device-associated effects (SADEs), assessed at three months and defined as device dislocation/embolisation, damage to the tricuspid or mitral valve caused by the device, intractable arrhythmias caused by the device and any circumstance that requires device removal. Secondary endpoints are the rate of all serious adverse events (SAEs) and further clinical efficacy variables.

EuroIntervention 2019;15:403-410

Table 1. Inclusion and exclusion criteria.

No.	Inclusion criteria
1.	Age ≥18 years
2.	NYHA functional Class III or ambulatory IV
3.	Ongoing management of heart failure according to ESC guidelines during previous ≥6 months
4.	Control of arrhythmia with heart rate <110 bpm
5.	Life expectancy ≥1 year
6.	Undergone successful balloon atrial septostomy procedure and in a stable haemodynamic state
7.	Left ventricular EF ≥15% – in patients with EF ≥40%, NT-proBNP levels >125 pg/ml
8.	Elevated left ventricular filling pressure documented by – PCWP at rest ≥15 mmHg and greater CVP or – PCWP ≥25 during exercise and CVP <20 mmHg
9.	Transseptal catheterisation and femoral vein access is determined to be feasible
	Exclusion criteria
1.	Local or generalised sepsis or other acute infection(s)
2.	Renal insufficiency requiring haemodialysis
3.	History of ASD and/or ASD repair or closure device in place
4.	Intracardial thrombus
5.	Evidence of right heart failure defined as (by echocardiography): – severe right ventricular dysfunction (TAPSE <14 mm) – severe right ventricular dilatation – severe pulmonary hypertension (sPAP >60 mmHg)
6.	Resynchronisation therapy initiated within the last 6 months
7.	Severe valve disease requiring surgery or intervention, or implanted mechanical valve prosthesis
8.	Congenital heart defect
9.	Large PFO with significant atrial septal aneurysm
10.	Clinically relevant thrombocytopaenia, thrombocytosis, leukopaenia, or anaemia
11.	Myocardial infarction or percutaneous intervention or coronary bypass surgery (all within the last 3 months) or indication for a coronary intervention
12.	Systolic blood pressure of >170 mmHg, despite medical therapy
13.	Severe lung disease
14.	Transitory ischaemic attack or stroke within the last 6 months
15.	Candidates to heart transplant or mechanical circulatory support

ASD: atrial septal defect; CVP: central venous pressure; EF: ejection fraction; PCWP: pulmonary capillary wedge pressure; PFO: patent foramen ovale; sPAP: systolic pulmonary artery pressure; TAPSE: tricuspid annular plane systolic excursion

PROCEDURE AND AFR DEVICE DESCRIPTION

Before enrolling patients into the study, all interventional cardiology investigators and associated investigative staff at each site underwent training on AFR device implantation and the required medical assessments. Only interventional cardiologists with experience in interventional transcatheter techniques for placement of a PFO or ASD occluder device performed the implantation.

On the day of implantation, a right heart catheterisation was performed to obtain haemodynamic data and provide confirmation of study eligibility. Right atrial, left atrial, pulmonary artery, left ventricular end-diastolic and aortic (systolic and diastolic) pressures, as well as PCWP and cardiac output at rest were measured. PCWP during exercise was measured only in patients who did not reach PCWP ≥15 mmHg at rest. Sizing of the AFR device was performed prior to implantation after careful review of the haemodynamic and anatomical parameters and according to the device sizing instructions **(Figure 2)**. Results from computational predicted haemodynamic pressures in a real-time model of the cardiovascular system to simulate pressure effects at rest and during exercise with an interatrial shunt up to 12 mm led to the selection of the two current AFR sizes of 8 and 10 mm inner fenestration[10]. As expected, shunt flow increased with increasing shunt size at rest and during exercise, but reached a plateau at a shunt diameter of 10 mm. Furthermore, decrease in PCWP and increase in right atrial pressure also reached a plateau at approximately 9 mm shunt diameter[10].

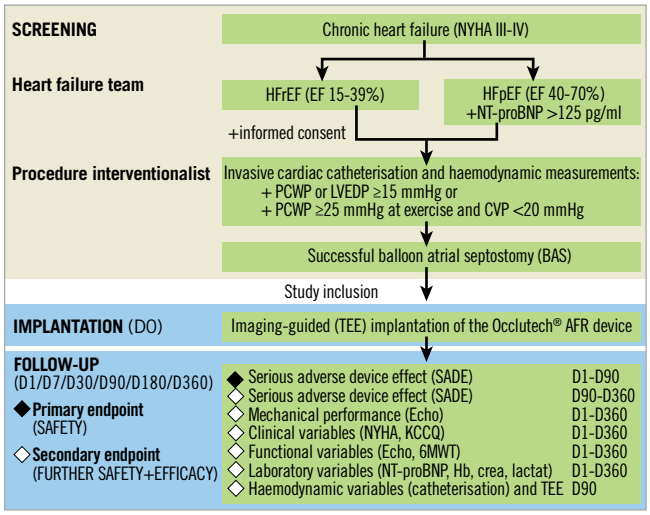

Figure 1. *Flow chart of the AFR-PRELIEVE trial.*

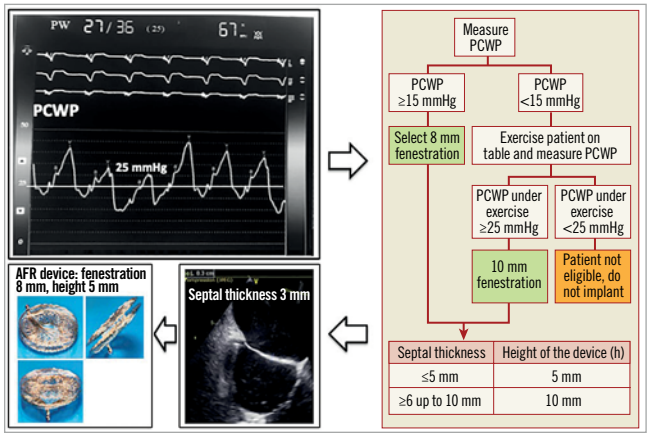

Figure 2. *Examples of haemodynamic and echocardiographic measurements with sizing instructions.*

Patients were sedated and underwent standard TEE. Examples of intraprocedural images are shown in **Figure 3**. Following transseptal puncture, a stiff wire was placed into the upper left pulmonary vein. A balloon-based atrial septostomy was performed in all patients; the balloon had a diameter 6 mm larger than the planned fenestration diameter of the AFR device (usually 14 mm). The Occlutech delivery sheath (12 or 14 Fr depending on the AFR device size) was inserted together with a dilatator across the septum into the pulmonary vein over the stiff wire. The Occlutech AFR is a double-disc, circular device made of self-expanding, nitinol wire mesh. A flexible waist in the centre connects the two discs and has a centrally located shunt. A welded ball structure located on the right atrial disc serves as an anchor for the pusher (Flex-II Pusher; Occlutech). After the AFR device is loaded onto the pusher grasps and retracted into the loader, the safety screwing knob secures loading of the device preventing accidental device release. The whole system is advanced through the delivery sheath into the left atrium. Following positioning of the AFR in the LA, the left atrial disc is deployed and positioned at the left side of the septum, similar to PFO or ASD closure devices. Next, the right atrial disc is deployed under constant pull and the correct left/right positioning of the device is confirmed by TEE and angiography. A push and pull manoeuvre confirms stability of the device prior to activation of the release mechanism. Release is performed by unscrewing the security knob at the handle and deployment of the device. Device patency with left-right shunt was documented by TEE after every implantation.

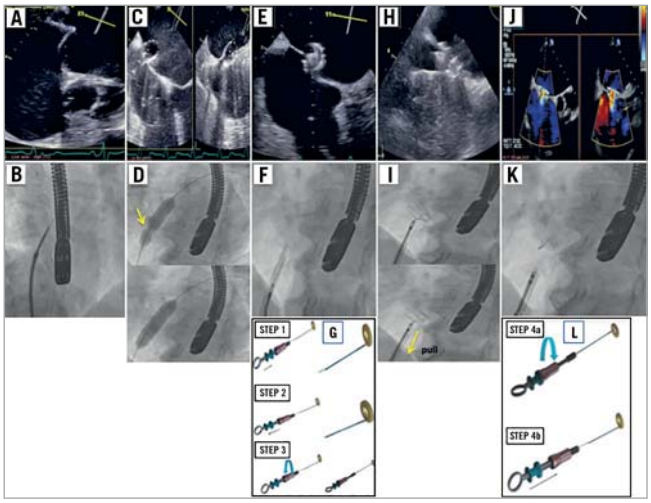

Figure 3. *Examples of implantation procedure images of the AFR. Echocardiographic (A) and fluoroscopic (B) images of the transseptal puncture. Echocardiographic (C) and fluoroscopic (D) images of the balloon atrial septostomy (yellow arrow shows the hourglass balloon formation at the start of the septostomy). Echocardiographic (E) and fluoroscopic (F) images of the deployment of the left atrial disc, of the right atrial disc (yellow arrow shows the pull manoeuvre to prove stability before deployment) (H & I), and after release (J & K). Instructions to grip and lock the AFR device on the pusher (G) and for release by opening the locking mechanism (L).*

STATISTICAL ANALYSIS

Statistical analysis was performed using GraphPad Prism, version 8 (GraphPad Software, Inc., San Diego, CA, USA). We analysed changes in continuous variables from baseline to three-month follow-up using the paired t-test or Wilcoxon signed-rank test, where appropriate. Haemodynamic and clinical variables were analysed by paired comparison of follow-up versus baseline on an individual patient level. We compared categorical data with Fisher's exact test. A p-value <0.05 was considered to be statistically significant. Results are reported as mean±standard deviation (SD). NYHA class, 6MWD and KCCQ score analysis results are reported as mean±standard error of the mean (SEM).

Results

ENROLMENT AND BASELINE CHARACTERISTICS

The patient disposition flow chart is presented in **Figure 4**. Baseline characteristics determined the patient stratification in the two groups (HFrEF and HFpEF) and are summarised in **Table 2A** and **Table 2B**. Both HF groups had multiple comorbidities and all participants were on maximal tolerable HF medication at baseline.

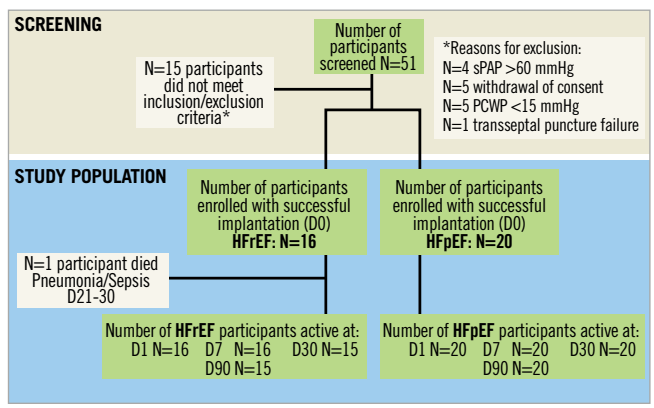

Figure 4. *Study participant disposition flow chart of the AFR-PRELIEVE trial.*

PROCEDURAL RESULTS

Procedural details are summarised in **Table 3**. The device has less radial force compared to other devices in the field; therefore, as the stiffness of the septum varies by patient, balloon atrial septostomy is recommended to secure sufficient lumen gain. In this study, as well as previously in the compassionate use cases, there were no issues related to the balloon septostomy.

Implantation of the AFR device was successful in all patients with only one placement attempt. In the majority of procedures (HFrEF: 87.5% and HFpEF: 70%), a device with an inner fenestration diameter of 8 mm and a device height of 5 mm (HFrEF: 100% vs. HFpEF: 95% patients) was implanted. Once the device was deployed, the final sizing of the opening was performed with TEE. Depending on the inner fenestration diameter of the device, we measured 8-10 mm without recoil. Left-right shunt was documented

EuroIntervention 2019;15:403-410

Table 2A. Baseline characteristics.

	HFrEF patients N=16	HFpEF patients N=20
Demographics, mean±SD		
Age, years	69.2±6.5	65.8±9.9
Gender male, n (%)	11 (68.8)	10 (50)
Body mass index, kg/m^2	28.1±7.1	32.8±5.8
Medical history, n (%)		
Hypertension	11 (68.8)	13 (65)
Hyperlipidaemia	5 (31.3)	6 (30)
Diabetes	6 (37.5)	13 (65)
Supraventricular arrhythmias	10 (62.5)	7 (35)
Chronic obstructive pulmonary disease	2 (12.5)	3 (15)
Coronary artery disease	9 (56.3)	11 (55)
Peripheral vascular disease	2 (12.5)	3 (15)
Stroke (haemorrhagic and ischaemic)	0 (0)	2 (10)
Transient ischaemic attack	0 (0)	1 (5)
Laboratory measurements, mean±SD		
NT-proBNP, pg/ml	4,138±4,515	909.3±1,694.4
Estimated GFR, ml/min	61.2±19.6	62.1±20.5
Creatinine, mg/dl	1.2±0.5	1.2±0.5
Hb, g/dl	12.2±1.9	12.5±1.3

Table 2B. Baseline characteristics.

Patient characteristics	HFrEF patients N=16	HFpEF patients N=20
Cardiac status and vital signs, mean±SD		
NYHA Class III, n (%)	15 (93.8)	18 (90)
NYHA Class IV, n (%)	1 (6.3)	2 (10)
Systolic blood pressure, mmHg	115.1±17	129.2±15.6
Diastolic blood pressure, mmHg	70.6±12.5	72.3±7.4
Heart rate at rest, bpm	67.7±11.8	71.8±13.4
Left ventricular ejection fraction, %	31.9±7	51.5±6.0
6-minute walking test distance, m	199.3±108.2	232.8±117.6
Left atrial diameter, mm	45.9±8.8	44.7±7.9
Mitral valve E/E´, ratio	15.3±10.6	15.7±4.9
Left ventricular end-diastolic diameter, mm	62.8±9.2	52±5.8
Left ventricular end-systolic diameter, mm	51.7±9.6	36±6.4
Tricuspid annular plane systolic excursion, cm	1.8±0.3	4.1±5.8
Medication, n (%)		
Diuretics	15 (93.7)	16 (80)
Aldosterone antagonist	13 (81.2)	10 (50)
ACE/AT1 inhibitors	10 (62.5)	8 (40)
Beta-blocker	15 (93.7)	16 (80)
Sacubitril/valsartan	2 (12.5)	1 (5)
Ca channel blocker	3 (18.7)	8 (40)

ACE: angiotensin-converting enzyme; AT1: angiotensin receptor 1

using TEE after implantation in all patients. Furthermore, we calculated post-procedural pulmonary to systemic flow ratio (Qp:Qs) to determine the left to right shunt, based on the Fick principle. To provide accurate information, measurements were performed, without providing oxygen-enriched gas. The Qp:Qs ratio was 1.3±0.2, 1.1±0.4 and 1.2±0.3 in the HFrEF, HFpEF and total patient collective, respectively. Both TEE and haemodynamic data calculation confirmed patency of the device at three-month follow-up **(Table 3)**.

PATIENT FOLLOW-UP TO 90 DAYS

A summary of all safety events up to three months is shown in **Table 4**. In one patient with HFpEF, a procedure-related SAE was documented, i.e., inguinal bleeding after the procedure, no transfusion or surgical intervention needed. One SADE was reported in the same patient, with temporary post-procedural disturbance in consciousness, which was considered possibly related to the study device. No action was taken, and the event resolved without further sequelae. No strokes/TIAs or myocardial infarctions were reported after implantation. One patient (1/36, 2.7%) with HFrEF died 30 days after implantation, due to pneumonia with septicaemia. Three patients (3/36, 8.3%) were hospitalised for worsening

Table 3. Procedural characteristics.

	HFrEF patients N=16	HFpEF patients N=20	All patients N=36
Implantation success, n (%)	16 (100)	20 (100)	36 (100)
Device fenestration diameter			
8 mm, n (%)	14 (87.5)	14 (70)	28 (77.8)
10 mm, n (%)	2 (12.5)	6 (30)	8 (22.2)
Device waist height			
5 mm, n (%)	16 (100)	19 (95)	35 (97.2)
10 mm, n (%)	0 (0)	1 (5)	1 (2.8)
Procedural duration, mean±SD			
Balloon atrial septostomy duration, min	17.1±9.4	14.4±11.8	15.6±10.7
Device implantation duration, min	5.6±3.9	9.6±8.5	7.8±7.1
Overall catheterisation time, min	82.7±19.3	94.9±25.2	89.7±23.4
Fluoroscopy time, min	23±6.5	20.5±12.6	21.6±10.4
Shunt fraction at end of procedure: Qp/Qs ratio, Fick method	1.3±0.2	1.1±0.4	1.2±0.3
Shunt fraction at three months: Qp/Qs ratio, Fick method	1.3±0.2	1.2±0.1	1.2±0.2
Periprocedural TEE, n (%)	16 (100)	20 (100)	36 (100)
L→R shunt flow (TEE) after the procedure, n (%)	16 (100)	20 (100)	36 (100)
L→R shunt flow (TEE) at 3 months, n (%)	14*(100)	17*(100)	31*(100)

*missing TEE data, patency 100% in TEE procedures at 3-month follow-up and transthoracic echocardiography image quality not adequate to assess shunt patency. L→R: left to right; TEE: transoesophageal echocardiography

Table 4. Safety events up to 3-month follow-up.

	HFrEF patients N=16	HFpEF patients N=20	All patients N=36
SADE, n (%)	0 (0)	1 (5)	1 (2.7)
Procedure-related SAE, n (%)	0	1 (5)	1 (2.7)
Device removal, n (%)	0	0	0
Death, n (%)	1 (6.2)	0	1 (2.7)
Stroke, n (%)	0	0	0
Myocardial infarction, n (%)	0	0	0
Hospitalisation for heart failure, n (%)	2 (12.5)	1 (5)	3 (8.3)
SAE rate, total number of events	5	7	12
Patients with SAE, n (%)	5 (31.2)	6 (30)	11 (30)
AE rate, total number of events	28	37	65
Patients with AE, n (%)	9 (56.3)	14 (70)	23 (63)
ADE, total number	0	8	8
Patients with ADE*, n (%)	0	5 (25)	5 (13)

*ADE: 2 catheter site reactions, 1 oedema, 1 anaemia, 1 supraventricular arrhythmia, 1 heart failure symptoms, 1 abnormal respiratory gas exchange, 1 disturbance in consciousness. ADE: adverse device event(s); AE: adverse event(s); SADE: serious adverse device event(s); SAE: serious adverse event(s)

Table 5. Invasive measurements.

Physiological catheterisation (rest) parameter	HFrEF patients N=16 baseline	HFrEF patients N=16 Individual patient level Δ3 months vs baseline	HFpEF patients N=20 baseline	HFpEF patients N=20 Individual patient level Δ3 months vs baseline
RA pressure (mean), mmHg	11.4±5.4	0±8.0 (n=4) p>0.99	9.7±4.6	2.1±7.8 (n=18) p=0.3
LA pressure (mean), mmHg	23±8	–5.5±5.3 (n=6) p=0.13	20.2±9.3	–1.75±10.4 (n=8) p=0.5
PAP (systolic), mmHg	45.5±13.1	–1.3±13.5 (n=14) p=0.96	42.7±12.4	3.4±17.8 (n=17) p=0.75
Cardiac output, L/min	4.5±1.5	–0.4±1.5 (n=13) p=0.31	5.4±1.6	0.1±1.5 (n=14) p=0.75
PCWP (mean), mmHg	19.9±5.1	–2.2±8.2 (n=13) p=0.07	21±5.9	–5.2±8.8 (n=18) p=0.03*
LVEDP, mmHg	15.9±8.4	–3.5±9.7 (n=14) p=0.16	17.8±10.6	–2.6±9.6 (n=15) p=0.4
Aortic pressure systolic, mmHg	110.9±25.5	25.2±48.2 (n=14) p=0.048*	144.2±25.7	5.2±30.2 (n=18) p=0.28
Aortic pressure diastolic, mmHg	64.5±15.4	5.8±23.5 (n=14) p=0.53	69.5±15.7	2.6±18.7 (n=17) p=0.4

*: statistically significant difference. LA: left atrial; LVEDP: left ventricular end-diastolic pressure; PAP: pulmonary artery pressure; PCWP: pulmonary capillary wedge pressure

of HF. SAE rates up to three months were low in both groups. Five patients (5/36, 13%) had adverse device events, all in the HFpEF group: catheter site reaction, oedema, anaemia, supraventricular arrhythmias and an abnormal respiratory gas exchange were observed during three months of follow-up. All events resolved. No adverse device events were reported in the HFrEF group.

Clinical and haemodynamic variables (paired analysis, follow-up vs baseline, on individual patient level) are depicted in **Table 5** and **Figure 5A-Figure 5C**. Patients improved partially; interpretation of single statistically significant results such as change in NYHA class should be cautious since the patient numbers are small.

Discussion

AFR-PRELIEVE is a prospective, non-randomised, multicentre Phase II pilot study aiming to assess the safety and feasibility of the Atrial Flow Regulator (AFR) in symptomatic HFrEF and HFpEF patients with elevated PCWP ≥15 mmHg at rest or ≥25 mmHg at exercise. Here, we report the procedural and three-month results. Implantation of the AFR was feasible and safe in all patients. The shunts remained patent at three months.

Diastolic dysfunction with impaired LV relaxation and increased LV stiffness leads to elevated LV filling pressures, atrial volume overload and pulmonary congestion causing dyspnoea symptoms[3]. It is observed in patients with HFpEF and HFrEF[11]. According to the "single syndrome" hypothesis of HF, diastolic LV dysfunction has a similar mechanism across the entire HF spectrum[12-14]. An excessive rise of PCWP during exercise, despite normal PCWP at rest in patients with HFpEF, is associated with increased mortality[1]. In patients with HFrEF, diastolic dysfunction remains impaired despite adequate medical therapy and is highly predictive of worse outcome[11,15]. The pilot study included patients with elevated LV filling pressures irrespective of the EF, which led to the formation of two patient collectives: sixteen patients with HFrEF (EF 15-39%) and twenty patients with HFpEF (EF ≥40%).

Guideline-recommended drug treatment in patients with HFrEF can improve their outcome; however, current treatment strategies have failed to reduce morbidity or mortality convincingly in patients with HFpEF[16]. The lack of efficient treatment options in HFpEF prompted the evaluation of new device-based approaches. Device-based reduction of increased LAP is under investigation in patients with symptomatic HF and high filling pressures. The presence of an ASD in patients with mitral valve stenosis, known as Lutembacher syndrome, is associated with fewer symptoms and improved outcomes compared to pure mitral stenosis[17]. Furthermore, progression to HF following ASD closure has been observed in adult patients and is characterised by acute pulmonary congestion, which is manifested by acute atrial volume overload[18]. Continuous, invasive measurement of LAP to guide medical therapy in patients with HFrEF was associated with reduced LAP and improved symptoms[19].

Currently, there are two devices under clinical investigation, namely the InterAtrial Shunt Device (IASD®; Corvia Medical, Tewksbury, MA, USA), and the V-Wave device[6-9]. The AFR device differs from these devices in several aspects. It has no

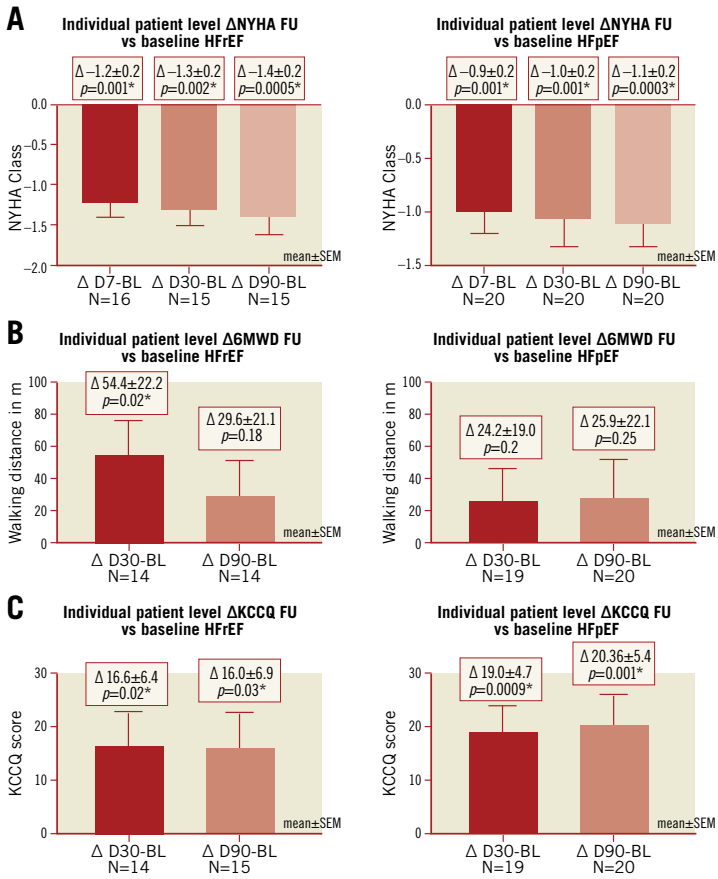

Figure 5. *Secondary clinical efficacy endpoint analysis. A) NYHA class. B) Six-minute walking distance (6MWD). C) Kansas City Cardiomyopathy Questionnaire (KCCQ) score. *p<0.05: significant change.*

incorporated valve tissue. The interatrial communication is larger than the V-Wave (5 mm) and equal to or larger than the IASD (8 mm). The AFR device is uncoated, made of nitinol mesh. A procedural difference is the necessity to perform a balloon atrial septostomy prior to AFR implantation, which was performed safely in all cases. Procedural success rate and patency of the device (confirmed by TEE post procedure and at three-month follow-up) was 100%. The implantation procedure is relatively similar to the placement of an ASD closure device with a relatively short device implantation time (<10 min). The embolisation risk of the device during the procedure is low, because it is fully retrievable up to final deployment. No stroke/TIA or thrombus on the device was observed at three months using TEE.

One hundred patients have been treated worldwide with the AFR device as compassionate use for pulmonary arterial hypertension, severe heart failure and congenital heart disease, mostly to create a right-to-left shunt[20].

Outcome and long-term effects of LA decompression remain incompletely understood. In line with the pathophysiology of diastolic HF, the creation of a controlled left-right shunt may reduce LAP and improve HF symptoms, although a chronic left-right shunt may hypothetically increase the risk of right heart failure. Of note, adults with smaller ASDs (diameter <10 mm and Qp:Qs ratio <1.5) are usually not haemodynamically compromised and seldom develop right heart dilatation or failure[21]. The three-month haemodynamic evaluation in this pilot study showed no significant increase in pulmonary artery pressure (PAP).

Early evaluation of clinical efficacy up to three months post procedure suggests symptom reduction in individual patients. Indeed, at three-month follow-up, improvement in NYHA class and quality of life (KCCQ) as well as 6MWD was observed in some patients of both collectives. Future studies will need to determine parameters that allow identification of patients who will benefit from this novel approach.

Study limitations

This study is limited by its small sample size, the open-label, non-randomised nature and the absence of a control group. Follow-up is limited to three months post procedure in this report, but the pilot study is ongoing. The study is expected to provide continued insights with additional data collection and analysis. We analysed data separately for HFrEF and HFpEF patients, because the broad inclusion criteria led to clinical differences in the enrolled patient collective. Some secondary clinical outcome parameters are obtained through subjective tests (NYHA class, quality of life) by unblinded participants and investigators; however, additional endpoints not subject to bias (haemodynamic and laboratory measurements, echocardiographic parameters evaluated by a blinded central core lab) are also being investigated.

Conclusions

Procedural and three-month follow-up data indicate that implantation of the AFR device is feasible and safe. Individual patients show improved symptom control and surrogate parameters of heart failure.

Impact on daily practice

HFrEF patients have a poor prognosis even with currently available guideline-recommended therapy. So far, no effective treatment for HFpEF has been identified. Reducing LAP and LA volume overload with a percutaneously delivered atrial septum device is a novel therapeutic approach for HF patients with elevated filling pressures. The first report of the AFR-PRELIEVE pilot study indicates that the implantation of the AFR shunt device is feasible and safe for HF patients.

Funding

The study was funded by Occlutech S.A.

Conflict of interest statement

M.W. Bergmann has received lecture fees from Occlutech. The other authors have no conflicts of interest to declare.

References

1. Dorfs S, Zeh W, Hochholzer W, Jander N, Kienzle RP, Pieske B, Neumann FJ. Pulmonary capillary wedge pressure during exercise and long-term mortality in patients with suspected heart failure with preserved ejection fraction. *Eur Heart J.* 2014;35:3103-12.

2. Lam CSP, Voors AA, de Boer RA, Solomon SD, van Veldhuisen DJ. Heart failure with preserved ejection fraction: from mechanisms to therapies. *Eur Heart J.* 2018;39:2780-92.

3. Borlaug BA, Paulus WJ. Heart failure with preserved ejection fraction: pathophysiology, diagnosis, and treatment. *Eur Heart J.* 2011;32:670-9.

4. Maggioni AP, Dahlström U, Filippatos G, Chioncel O, Crespo Leiro M, Drozdz J, Fruhwald F, Gullestad L, Logeart D, Fabbri G, Urso R, Metra M, Parissis J, Persson H, Ponikowski P, Rauchhaus M, Voors AA, Nielsen OW, Zannad F, Tavazzi L; Heart Failure Association of the European Society of Cardiology (HFA). EURObservational Research Programme: regional differences and 1-year follow-up results of the Heart Failure Pilot Survey (ESC-HF Pilot). *Eur J Heart Fail.* 2013;15:808-17.

5. 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.

6. 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.

7. 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.

8. 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.

9. Rodés-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;11:2300-10.

10. 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.

11. Nagueh SF, Smiseth OA, Appleton CP, Byrd BF 3rd, Dokainish H, Edvardsen T, Flachskampf FA, Gillebert TC, Klein AL, Lancellotti P, Marino P, Oh JK, Popescu BA, Waggoner AD. Recommendations for the Evaluation of Left Ventricular Diastolic Function by Echocardiography: An Update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. *J Am Soc Echocardiogr.* 2016;29:277-314.

12. Burlew BS, Weber KT. Cardiac fibrosis as a cause of diastolic dysfunction. *Herz.* 2002;27:92-8.

13. Paulus WJ, Tschöpe C, Sanderson JE, Rusconi C, Flachskampf FA, Rademakers FE, Marino P, Smiseth OA, De Keulenaer G, Leite-Moreira AF, Borbély A, Edes I, Handoko ML, Heymans S, Pezzali N, Pieske B, Dickstein K, Fraser AG, Brutsaert DL. How to diagnose diastolic heart failure: a consensus statement on the diagnosis of heart failure with normal left ventricular ejection fraction by the Heart Failure and Echocardiography Associations of the European Society of Cardiology. *Eur Heart J.* 2007;28:2539-50.

14. Schellings MW, Pinto YM, Heymans S. Matricellular proteins in the heart: possible role during stress and remodeling. *Cardiovasc Res.* 2004;64:24-31.

15. Dokainish H, Rajaram M, Prabhakaran D, Afzal R, Orlandini A, Staszewsky L, Franzosi MG, Llanos J, Martinoli E, Roy A, Yusuf S, Mehta S, Lonn E; Echocardiographic Substudy of the OASIS-6 Trial Investigators. Incremental value of left ventricular systolic and diastolic function to determine outcome in patients with acute ST-segment elevation myocardial infarction: the echocardiographic substudy of the OASIS-6 trial. *Echocardiography.* 2014;31:569-78.

16. Ponikowski P, Voors AA, Anker SD, Bueno H, Cleland JG, Coats AJ, Falk V, Gonzalez-Juanatey JR, Harjola VP, Jankowska EA, Jessup M, Linde C, Nihoyannopoulos P, Parissis JT, Pieske B, Riley JP, Rosano GM, Ruilope LM, Ruschitzka F, Rutten FH, van der Meer P; Authors/Task Force Members; Document Reviewers. 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: The Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC). Developed with the special contribution of the Heart Failure Association (HFA) of the ESC. *Eur J Heart Fail.* 2016;18:891-975.

17. Sambhi MP, Zimmerman HA. Pathologic physiology of Lutembacher syndrome. *Am J Cardiol.* 1958;2:681-6.

18. Masutani S, Senzaki H. Left ventricular function in adult patients with atrial septal defect: implication for development of heart failure after transcatheter closure. *J Card Fail.* 2011;17:957-63.

19. 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.

20. Patel MB, Samuel BP, Girgis RE, Parlmer MA, Vettukattil JJ. Implantable atrial flow regulator for severe, irreversible pulmonary arterial hypertension. *EuroIntervention.* 2015;11:706-9.

21. Webb G, Gatzoulis MA. Atrial septal defects in the adult: recent progress and overview. *Circulation.* 2006;114:1645-53.