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**Title:** **The AFR-PRELIEVE TRIAL: A prospective, non-randomized, pilot study to assess the Atrial Flow Regulator (AFR) in Heart Failure Patients with either preserved or reduced ejection fraction.**

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# The AFR-PRELIEVE TRIAL

## A prospective, non-randomized, pilot study to assess the Atrial Flow Regulator (AFR) in Heart Failure Patients with either preserved or reduced ejection fraction

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Short Title: Atrial Flow Regulator (AFR) in heart failure patients

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**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-randomized, open-label, multi-center study in patients with symptomatic heart failure NYHA class III or IV and pulmonary capillary wedge pressure (PCWP) ≥ 15mmHg at rest or ≥ 25mmHg at exercise irrespective of left ventricular ejection fraction (EF ≥15%). Here we report on procedural and 3-month follow-up data for a total of thirty-six enrolled patients. Sixteen (44.5%) patients with reduced EF (HFrEF: EF15-39%) 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-procedural and at 3 months) in both patient groups, with 1 SADE in the HFpEF group which completely resolved. Three (3/36, 8.3%) patients were hospitalised for worsening of heart failure (2 HFrEF patients, 1 HFpEF patient). Individual patients from both the HFrEF and HFpEF groups showed symptoms and surrogate parameters of heart failure (NYHA class, 6-minute walking distance, Kansas City Cardiomyopathy Questionnaire, PCWP, NT-proBNP) to improve.

**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 both with HFpEF and HFrEF.

**Keywords:** chronic heart failure, clinical trials, innovation, Atrial septal defect

**Condensed** ABSTRACT

Reducing elevated left atrial pressure with an atrial septum shunt device allowing a left-to-right shunt particularly under exercise is a possible treatment option in symptomatic heart failure patients. AFR-PRELIEVE is a prospective, non-randomized, open-label, multi-center study in patients with symptomatic heart failure NYHA class III or IV and pulmonary capillary wedge pressure (PCWP) ≥ 15mmHg at rest or ≥ 25mmHg at exercise irrespective of left ventricular ejection fraction (EF ≥15%). Patients were subjected to balloon septostomy and implantation of an 8mm or 10mm fenestrated device "ASD-like" device. Implantation success rate and device patency with left-right shunt was 100% (post-procedural and at 3 months) in both patient groups. Individual patients from both the HFrEF and HFpEF groups showed symptoms and surrogate parameters of heart failure to improve.

**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 preserved ejection fraction |
| HFrEF | heart failure 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 |
| PFO | patent foramen ovale |
| PCWP | pulmonary capillary wedge pressure |
| SAE | serious adverse event |
| SADE | serious adverse device event |
| TEE | transoesophageal echocardiography |
| 6MWD | 6-minute walking distance |

## INTRODUCTION

Increased left atrial pressure (LAP) leads to exercise intolerance, 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 HF patients with reduced EF (HFrEF) [2, 3]. Diastolic dysfunction involves several different haemodynamic and molecular mechanisms, leading to impaired 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 left ventricular (LV) filling pressure remains unclear. Reducing LAP and LA volume overload using an atrial septum shunt device emerges 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, 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) in patients with HF and elevated filling pressures. Herein we present the procedural details, periprocedural and safety events, as well as device patency including 3-month results.

## METHODS

### Study Design and Population

AFR-PRELIEVE is a prospective, non-randomized, open-label, multi-center 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 ethical committees before study initiation according to local and national regulations. The study was performed according to

current standards including a clinical event committee. Investigators entered all relevant patient information in a dedicated 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 septum 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 summarized in Table 1. Eligible patients with signed informed consent approved for the study and underwent right-heart catherization at the day of the implantation for haemodynamic measurements. Patients, who met the hemodynamic 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 (8 clinical visits) to evaluate safety and outcome data of the procedure. NYHA class, 6-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 1A. A transoesophageal echocardiography (TEE) and a right heart catherization were pre-specified to be performed at 3 months follow-up. Variables measured by echocardiography are sent to the central reading office for blinded independent validation (echo coreLab Black Forest GmbH, Germany). However, the reported values are electronic case report form (eCRF) entries done 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 3 months and defined as device dislocation/embolization, 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.

**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 the 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.

At the day of implantation, a right-heart catherization was performed to obtain hemodynamic 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 ≥ 15mmHg at rest. Sizing of the AFR device was performed prior to implantation after careful review of the hemodynamic 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 12mm lead to the selection of the current two AFR sizes of 8 and 10mm inner fenestration size. [10] As expected, shunt flow increased with increasing shunt size at rest and during exercise, but reached a plateau at a shunt diameter of 10mm. Furthermore, decrease in PCWP and increase in right atrial pressure also reached a plateau at approximately 9 mm shunt diameter[10].

Patients were sedated and underwent standard TEE. Exemplary 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 of 6 mm larger than the planed fenestration diameter of the AFR device (usually 14mm). The Occlutech® delivery sheath (12 or 14 F 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 served as an anchor for the Pusher (Occlutech® Flex Pusher II). After the AFR device is loaded onto the Pusher grasps and retracted into the loader, the safety-screwing knob secured 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 was confirmed by TEE and angiography. A push and pull manoeuvre confirmed 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 after every implantation by TEE.

### 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 3-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 individual patient level. We compared categorical data with the 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 1B. Baseline characteristics verified the patient stratification in the two groups (HFrEF and HFpEF) and are summarized in Table 2A-B. Both HF groups had multiple comorbidities and all participants were on maximal tolerable HF medication at baseline.

### 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 was no issue 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. The final sizing of the opening once the device was deployed, was performed with TEE. Depending on the inner fenestration diameter of the device, we measured 8-10mm without recoil. Left-right shunt was documented using TEE after implantation in all patients. Furthermore, we calculated postprocedural 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. 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 3 months follow-up (Table 3).

**Patient Follow-up to 90 days**

A summary of all safety events up to 3 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 for the same patient, with temporarily postprocedural disturbance in consciousness, that was considered possibly related to the study device; no action was taken and the event resolved without further sequalae. 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 of HF. SAE rates up to 3 months was 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 3

months of follow-up. All events resolved. No adverse device events were reported in the HFrEF group.

Clinical and hemodynamic variables (paired analysis follow-up vs. baseline on individual patient level) are depicted in Table 5 and Figures 4A-C. Patients improved partially, interpretation of single statistical significant results like change in NYHA class must be done cautiously since the patient numbers are small.

## DISCUSSION

AFR-PRELIEVE is a prospective, non-randomized, multi-centre Phase II pilot study aimed to assess the safety and feasibility of the Atrial Flow Regulator (AFR) in symptomatic HFrEF and HFpEF patients with elevated PCWP ≥ 15mmHg at rest or ≥ 25mmg at exercise. Here, we report the procedural and 3-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 is of 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 lead to the formation of two patient collectives: sixteen patients with HFrEF (EF15-39%) and twenty patients with HFpEF (EF ≥ 40%). Guideline-recommended drug treatment in patients with HFrEF can improve their outcome, however, current treatment strategies fail 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 the 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 characterized 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 are under clinical investigation, namely the IASD (Corvia Medical), and the V-Wave device (V-Wave) [6-9]. The AFR device differs from these devices in several aspects. It has no incorporated valve tissue. The inter-atrial communication is larger than the V-Wave (5mm) and equal or larger compared to the IASD (8mm). The AFR device is uncoated, but 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 postprocedural and at 3-months follow-up) was 100%. The implantation procedure is relatively similar to the placement of an ASD closure device with relatively short device implantation time (<10min). Embolization risk of the device during procedure is low, because it is fully retrievable up to final deployment. No stroke/TIA or thrombus on the device was observed at 3 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. Though, a chronic left-right shunt may hypothetically increase the risk of right heart failure. Of note, adults with smaller ASDs (diameter < 10mm and Qp:Qs ratio < 1.5) are usually not haemodynamically compromised and seldom develop right heart dilatation or failure[21]. The 3-month haemodynamic evaluation in this pilot study showed no significant increase in PAP. Early evaluation of clinical efficacy up to 3 months post-procedural suggests symptom reduction in individual patients. At 3 months follow-up indeed, improvement of 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 3 months post procedure in this report, but the pilot study is ongoing, and 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 lead 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.

## CONCLUSION

Procedural and 3-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 PRACTISE

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 percutaneous 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.

## CONFLICTS OF INTEREST

M.W. Bergmann received lecture fees from Occlutech.

## FIGURE LEGENDS

Figure 1. The AFR-PRELIEVE Trial

A) Flow chart

B) Study participant disposition flow chart

Figure 2. Exemplary haemodynamic and echocardiographic measurements with sizing instructions

Figure 3. Exemplary 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 beginning of the septostomy). Echocardiographic E) and fluoroscopic F) images of the deployment of the left atrial disc, H-J) of the right atrial disc (yellow arrow showes the pull manoeuvre to prove stability before deployment) and J-K) after release. G) Instructions to grip and lock the AFR device on the Pusher and L) for release by opening the locking mechanism.

Figure 4. Secondary clinical efficacy endpoint analysis

A) NYHA class

B) 6-minute walking distance (6MWD)

C) Kansas City Cardiomyopathy questionnaire (KCCQ) score

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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 hemodynamic state |
| 7. | Left ventricular EF ≥15%<br>- in patients with EF ≥ 40%, NT-proBNP-levels > 125 pg/ml |
| 8. | Elevated left ventricular filling pressure documented by<br>- PCWP at rest ≥ 15 mmHg and greater CVP or<br>- PCWP ≥ 25 during exercise and CVP < 20 mmHg |
| 9. | Transseptal catheterization and femoral vein access is determined to be feasible |
| | **Exclusion criteria** |
| 1. | Local or generalized 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):<br>- severe right ventricular dysfunction (TAPSE < 14 mm)<br>- severe right ventricular dilatation<br>- severe pulmonary hypertension (PAPs > 60 mm Hg) |
| 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 thrombocytopenia, thrombocytosis, leukopenia, 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 ischemic 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, PAPs= systolic pulmonary artery pressure, PCWP pulmonary capillary wedge pressure, PFO= patent foramen ovale, TAPSE= tricuspid annular plane systolic excursion | |

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 ischemic) | 0(0) | 2(10) |
| Transitoric ischemic attack | 0(0) | 1(5) |
| Laboratory measurements, mean±SD | | |
| NT-proBNP, pg/ml | 4138±4515 | 909.3±1694.4 |
| 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 enddiastolic diameter, mm | 62.8±9.2 | 52±5.8 |
| Left ventricular endsystolic 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) |
| Aldostorone-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 | | |

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 catherization 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 months follow up and transthoracic echocardiography image quality not adequate to assess shunt patency<br>L->R= left to right, TEE= transoesophageal echocardiography | | | |

Table 4. Safety events up to 3 months 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 |
| Hospitalization 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(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)

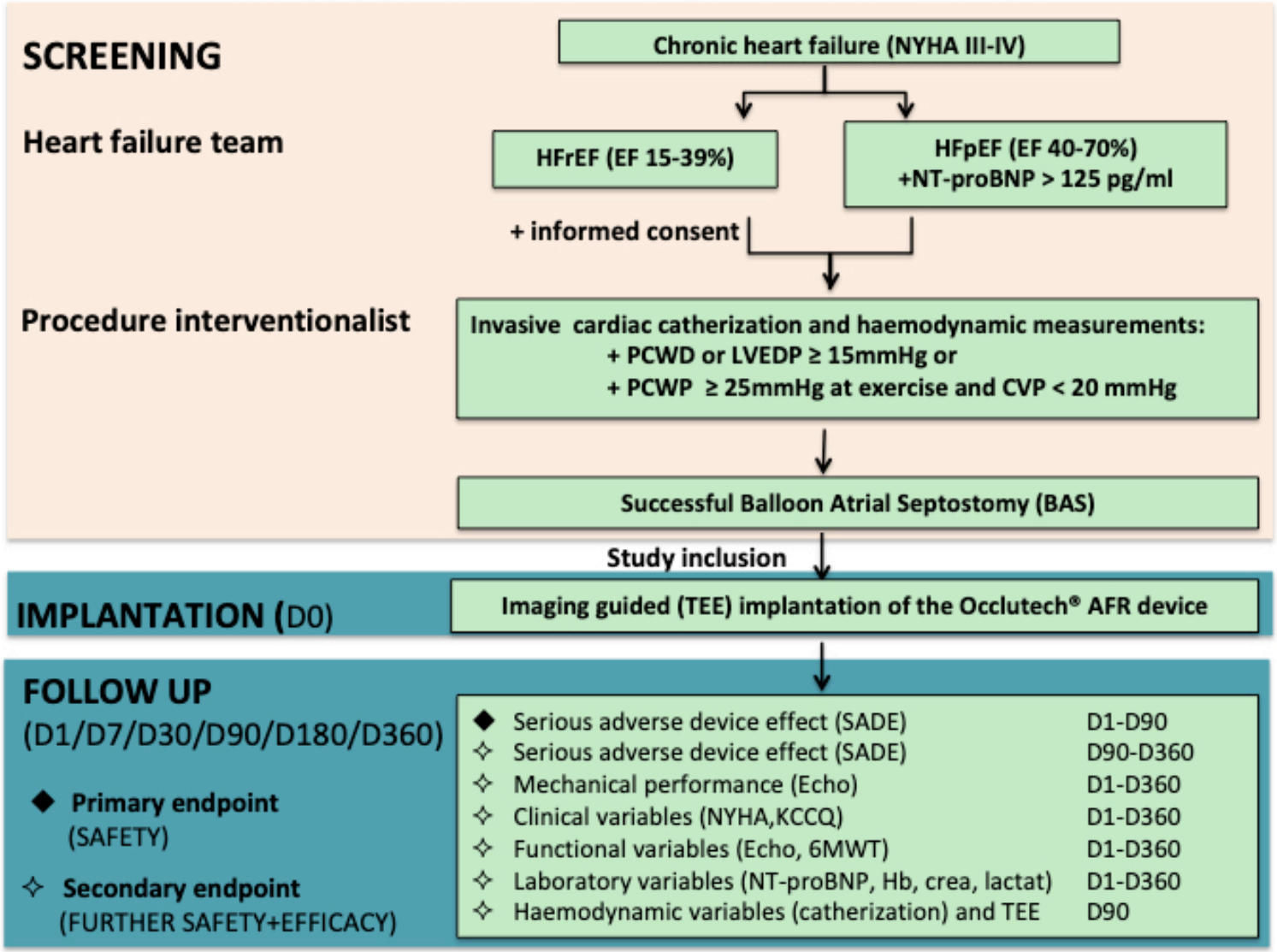
Table 5. Invasive measurements

| Physiological catherization (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 |
| LA= left atrial, LVEDP= left ventricular enddiastolic pressure, ns= not statistically significant, PAP= pulmonary artery pressure, PCWP= pulmonary capillary wedge pressure | | | | |

Fig. 1A

# THE AFR-PRELIEVE TRIAL FLOW CHART



# Study participant disposition flow chart

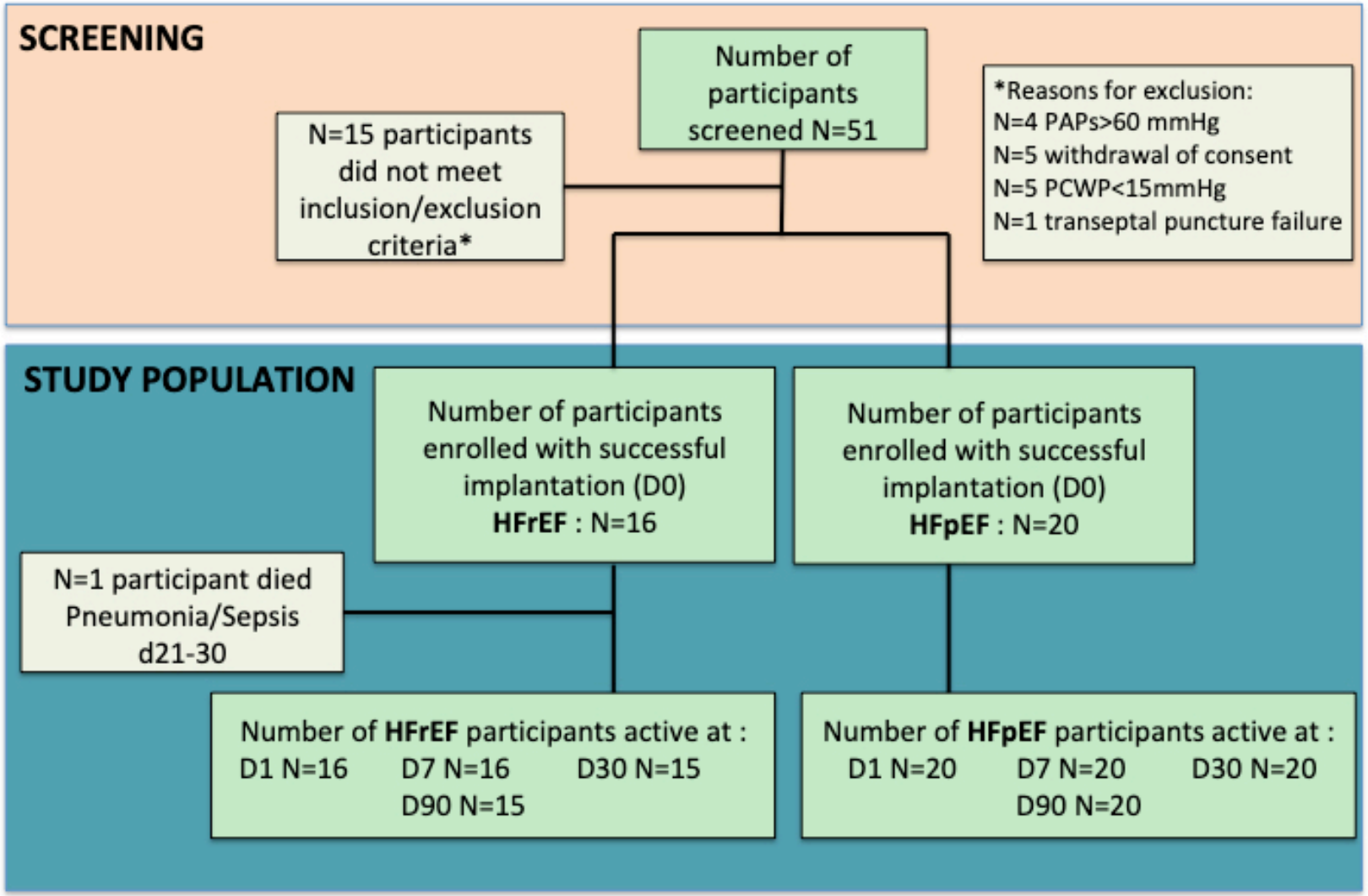
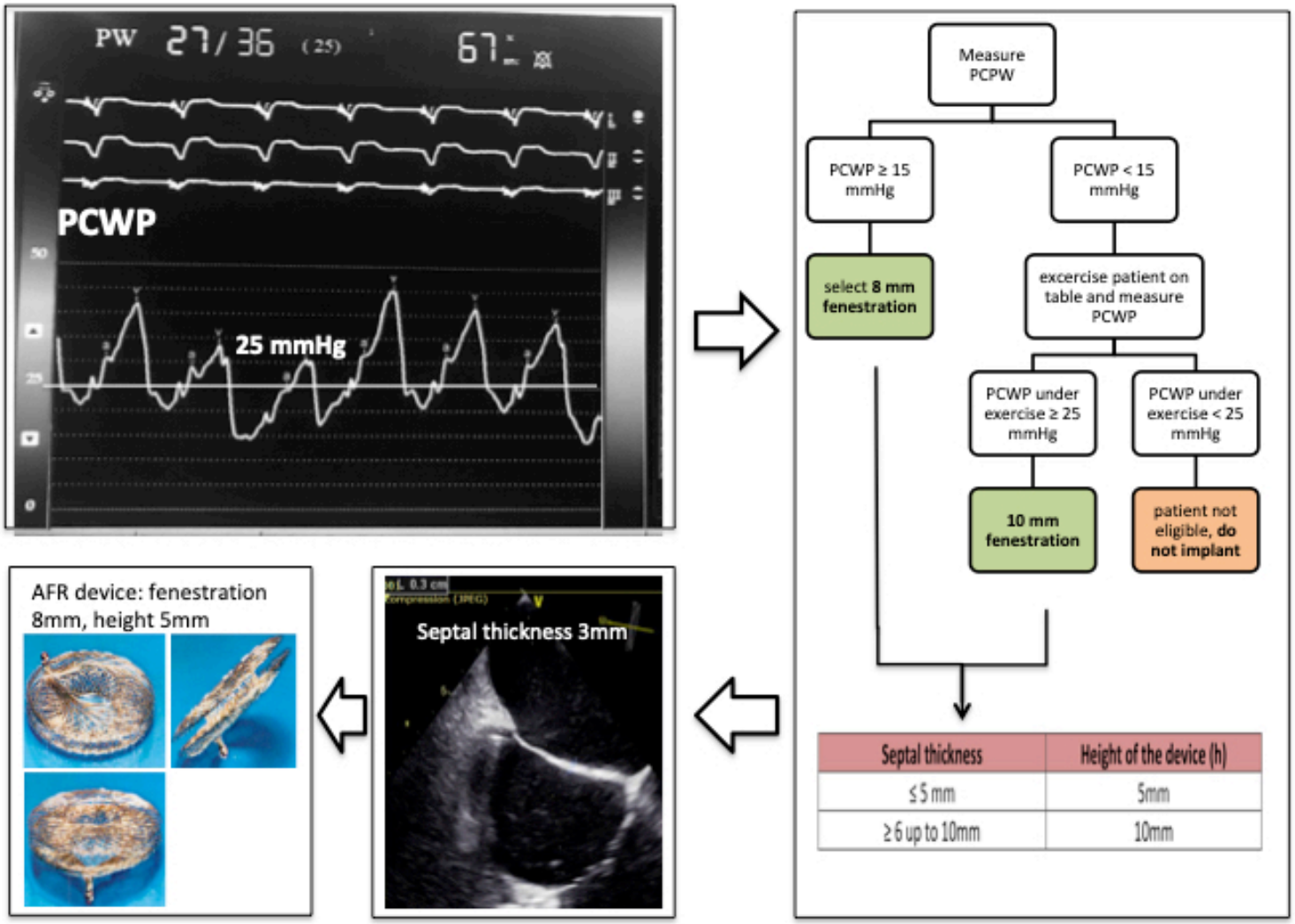


Fig. 2



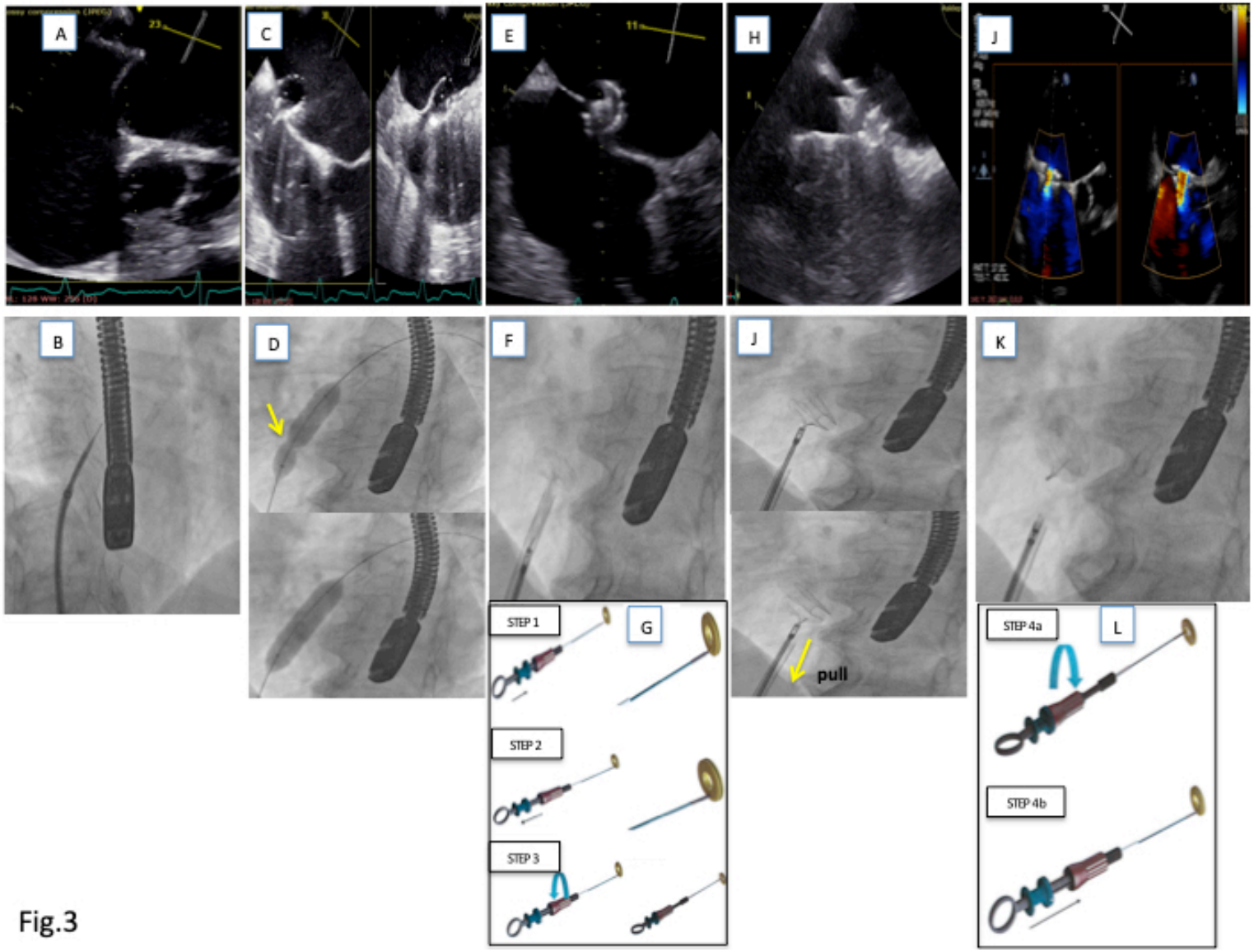



Fig.3

Fig.4