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RESEARCH ARTICLE

One-year results of the first-in-man study investigating the Atrial Flow Regulator for left atrial shunting in symptomatic heart failure patients: the PRELIEVE study

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Aims Attenuating exercise-induced elevated left atrial pressure with an atrial shunt device is under clinical investigation for treatment of symptomatic heart failure (HF).

Methods and results PRELIEVE was a prospective, non-randomised, multicentre, first-in-man study in symptomatic HF patients with reduced (HFrEF) or preserved (HFpEF) ejection fraction and pulmonary capillary wedge pressure (PCWP) ≥15 mmHg at rest or ≥25 mmHg during exercise. Here, we provide follow-up data up to 1 year after implantation of the Atrial Flow Regulator (AFR) device. The AFR was successfully implanted in 53 patients (HFrEF $n = 24$ and HFpEF $n = 29$). Two patients were not enrolled due to an unsuccessful transseptal puncture. There was one device embolisation into the left atrium, which required surgical removal. One patient experienced a serious procedure-related adverse event (post-procedural bleeding and syncope). All patients with sufficient echocardiography readout confirmed device patency with left–right shunt both at 3 ($n = 47/51$, 92%) and 12 ($n = 45/49$, 92%) months. At 3 months, rest PCWP decreased by 5 (−12, 0) mmHg ($P = 0.0003$, median Q1, Q3). No patient developed a stroke, worsening of right heart function or significant increase of pulmonary artery pressure. Six (6/53, 11%) patients were hospitalised for worsening of HF and three (3/53, 6%) patients died. We observed improvements in New York Heart Association functional class, 6-min walking distance and quality of life (Kansas City Cardiomyopathy Questionnaire) in certain patients.

Conclusions Implantation of the AFR device in HF patients was feasible. No shunt occlusion, stroke or new right HF was observed during the 1-year follow-up, with clinical improvements in certain patients.

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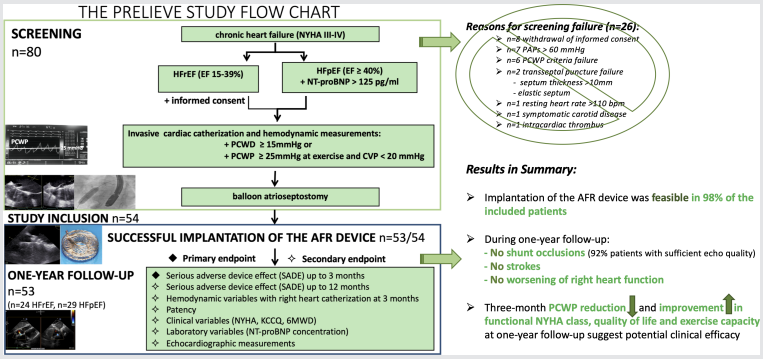
Graphical Abstract



Analysis of the first-in-man PRELIEVE study indicates that implantation of the Atrial Flow Regulator (AFR) device was feasible and associated with improved haemodynamic and clinical outcomes up to 12 months in certain patients with symptomatic heart failure with reduced (HFrEF) and preserved (HFpEF) ejection fraction. 6MWD, 6-min walking distance; CVP, central venous pressure; KCCQ, Kansas City Cardiomyopathy Questionnaire; NT-proBNP, N-terminal pro-B-type natriuretic peptide; NYHA, New York Heart Association; PAPs, systolic pulmonary artery pressure; PCWP, pulmonary capillary wedge pressure.

Keywords Chronic heart failure • Clinical trials • Innovation • Left atrial pressure • Interatrial shunt device

Introduction

Patients with heart failure (HF) suffer from exercise-induced dyspnoea, which is caused by elevated left atrial pressure (LAP) secondary to increased filling pressures of the left ventricle. Elevated LAP may cause pulmonary congestion and is associated with increased mortality and morbidity.[1] Increased filling pressures of the left ventricle are observed in both HF patients with reduced (HFrEF) and preserved (HFpEF) ejection fraction.[2] Current treatment options are limited particularly in HFpEF patients.[3,4]

Observations from the Lutembacher syndrome, describing the congenital anomaly of an atrial septal defect that ameliorates HF symptoms caused by mitral valve stenosis,[5] and findings from a cardiovascular computer simulation, showing that an interatrial shunt lowers LAP without pulmonary artery pressure increase[6] provided the rationale for reducing LAP and left atrial volume overload using an atrial septal shunt device in patients with HF. Medical and interventional therapies that reduce elevated LAP may improve exertional dyspnoea, hospitalisation rates and thereby reduce mortality.[7,8] Studies with haemodynamic modelling of interatrial shunt devices and preliminary data from observational studies suggest feasibility and safety of interatrial shunting in HF patients.[6,9–13]

The present open-label, prospective, non-randomised, first-in-man study (PRELIEVE) investigated the feasibility up to 1-year follow-up after implantation of a novel device (Atrial Flow Regulator, AFR) employing an 8 mm or 10 mm atrial shunt in patients with HFrEF and HFpEF. Study design, procedural and 3-month results of 36 patients have been published previously.[14] Here, we report on the 1-year results of 53 consecutive patients included in this study.

Methods

Study design and population

The detailed outline of the study has been described before.[14] PRELIEVE was a prospective, non-randomised, open-label, multicentre, first-in-man study (ClinicalTrials.gov identifier NCT03030274). Patients were recruited between November 2017 and December 2018 at 12 clinical sites (in Turkey, Germany and Belgium). The study was reviewed and approved by the local and national ethics committees. The study was performed according to current standards. A Data Safety Monitoring Board and a clinical event committee were established. The funding source locked the database after final monitoring and analysed the data together with the authors. The authors of the manuscript had full access to the data.

A full list of inclusion and exclusion criteria is provided in online supplementary *Table S1*. Patients with symptomatic HF [New York Heart Association (NYHA) functional class III or ambulatory class IV], despite optimal therapy as per current guidelines, with HFrEF (ejection fraction 15–39%) or HFpEF [ejection fraction ≥40% and N-terminal pro-B-type natriuretic peptide (NT-proBNP) >125 pg/mL] and a pulmonary capillary wedge pressure (PCWP) ≥15 mmHg at rest or ≥25 mmHg during exercise were included and considered for implantation of the AFR device. Key exclusion criteria included evidence of right HF (tricuspid annular plane systolic excursion <14 mm, severe pulmonary hypertension with systolic pulmonary artery pressure >60 mmHg or severe right heart dilatation), renal insufficiency requiring haemodialysis, severe valve disease requiring surgery or intervention, a large patent foramen ovale or history of an atrial septal defect or repair or closure device in place.

Eligible HFrEF or HFpEF patients with signed informed consent were consecutively enrolled in this study. Patients underwent balloon atrioseptostomy directly after the right heart catherization

and received implantation of the AFR device. A successful balloon atrioseptostomy was required to proceed with implantation of the AFR device.

Patients were followed for 12 months (eight clinical visits). NYHA class, 6-min walking distance (6MWD), quality of life assessed by Kansas City Cardiomyopathy Questionnaire (KCCQ), NT-proBNP concentrations and transthoracic echocardiography (TTE) measurements were assessed during 1-year follow-up according to the protocol. A right heart haemodynamic follow-up evaluation was required once at 3 months.

Variables measured by echocardiography were sent to the central reading office for blinded independent validation (echo coreLab Black Forest GmbH, Germany).

The primary endpoint was feasibility of the AFR device implantation, defined by the rate of serious adverse device-associated effects (SADE) assessed at 3 months: 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 were further SADE up to 12 months and clinical outcome with the rate of all serious adverse events (SAEs) and clinical efficacy variables at 1-year follow-up.

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 12-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 vs. 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 median with the first and third quartile (Q1, Q3). Events are reported as counts of first occurrence. The mortality rate is calculated via the Kaplan–Meier method to account for censoring.

Results

Patient collective

Out of 80 screened patients, 53 HF patients were enrolled, received the AFR device and were followed up to 1 year; 24 (45%) patients with HFrEF (ejection fraction 15–39%) and 29 (55%) patients with HFpEF (ejection fraction ≥40%). Reasons for screening failure and the patient disposition flow chart are depicted in *Figure 1*.

Baseline characteristics are summarized in *Table 1*. Patients had multiple comorbidities and all participants were on maximal tolerated HF medication at baseline. The majority of patients were in NYHA functional class III (49/53, 93%). Natriuretic peptide plasma concentration (NT-proBNP) was highly variable at baseline

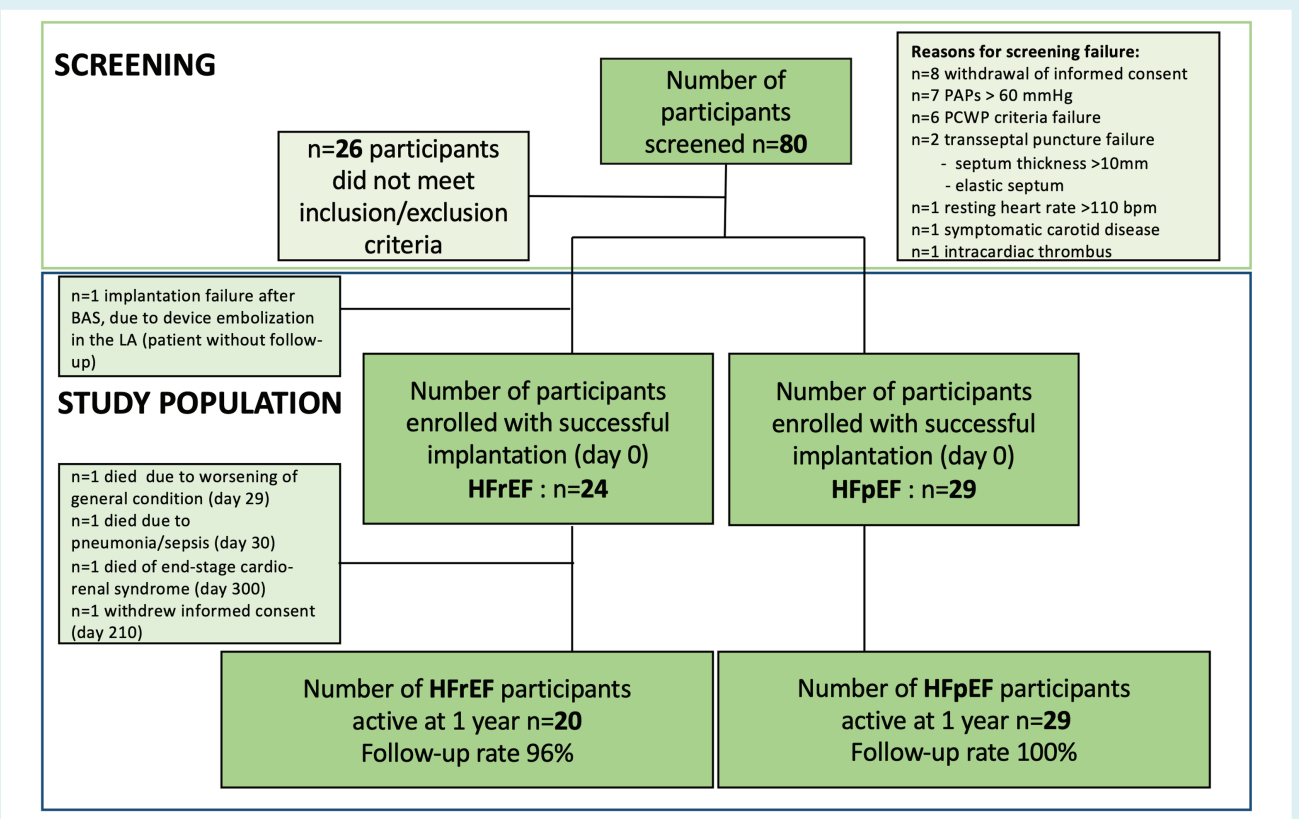


Figure 1 The PRELIEVE study participant disposition flow chart. BAS, balloon atrioseptostomy; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; LA, left atrium; PAPs, systolic pulmonary artery pressure; PCWP, pulmonary capillary wedge pressure.

[all patients (median, (Q1, Q3): 681 pg/mL (228, 1446)]. The 6MWD was reduced [all patients: 200 m (100, 300)], consistent with a class III or IV HF population.

Procedure

Patients (n = 40) with a PCWP at rest of ≥15 mmHg qualified for an 8 mm fenestration device and patients (n = 13) with a PCWP <15 mmHg at rest, but ≥25 mmHg during exercise received a 10 mm fenestration AFR device. Depending on the atrial septal thickness, the device height was chosen (thickness: ≤5 mm, 5 mm height n = 50, and 6–10 mm, 10 mm height n = 3).

Sizing instructions and exemplary images of the AFR implantation procedure are depicted in *Figure 2*. After transseptal puncture, a balloon atrioseptostomy employing a 12 mm or 14 mm low pressure balloon (3–6 bar) was performed. A 12–14 F guiding catheter, serving as the delivery system, was introduced into the left atrium via an exchange wire placed in the upper left pulmonary vein. The left atrial disc was deployed first and attached to the septum, followed by deployment of the right atrial disc under constant pull. Correct positioning of the device was confirmed by a push-and-pull manoeuvre, fluoroscopy and transoesophageal echocardiography (TEE) imaging. Following successful AFR implantation, patency and creation of a left–right shunt was confirmed by TEE.

Implantation of the AFR device was feasible in 53 patients. Procedural characteristics are described in *Table 2*. Procedural data of the first 36 patients were reported previously in the early 3-month report[14] and were now updated for the whole patient collective (n = 53 patients). Two patients were not included in the study, due to transseptal puncture failure (septum >10 mm thickness and elastic septum). There was one periprocedural device embolisation after balloon atrioseptostomy, related to insufficient device loading (training issue). The device was removed surgically, no additional device was implanted. This patient was included in the study population, but received no follow-up as per protocol, due to the unsuccessful AFR implantation (*Figure 1*). There was only one patient with a post-procedural SADE, with temporarily disturbance in consciousness due to post-procedural bleeding, that was considered possibly related to the study device and resolved without further sequela.

One-year safety outcome

The clinical events up to 12 months are shown in *Table 3*. One-year follow-up data assessment were available in 49/53 patients; three (HFrEF) patients (3/53, 6%) died and one patient (HFrEF) withdrew informed consent. One patient died 30 days after implantation, due to pneumonia with septicaemia, one due to worsening of general condition (day 29) and one patient died after 10 months due to end-stage cardio-renal syndrome. Six patients (6/53, 11%, 3 HFrEF and 3 HFpEF) were hospitalised for worsening of HF. Up to 12 months, no patient had undergone device removal and there were no strokes reported. Eleven patients (11/53, 20%, 5 HFrEF and 6 HFpEF patients) had new onset or worsening of supraventricular atrial fibrillation and one patient underwent ablation treatment due to new onset of atrial flutter. Eleven patients (11/53, 20%, 4 HFrEF and 7 HFpEF patients) showed worsening (n = 3) or new impairment (n = 8) of renal function: one patient died (as described above), five recovered and five patients had impaired renal function, without requiring haemodialysis. Kaplan–Meier curves up to 1-year follow-up for mortality, cardiovascular events and hospitalisation rate for HF are provided in online supplementary *Figure 1S*.

Haemodynamic and echocardiographic follow-up data

Both TTE and haemodynamic data confirmed patency of the device at 3-month follow-up, in all patients with available measurements (47/51, 92%). At 12-month follow-up shunt patency maintenance was confirmed by TTE in these patients (45/49, 92%) (*Table 3*). However, assessment of shunt patency by TTE was non-diagnostic in four patients at 3 months (4/51, 8%) and 1-year (4/49, 8%) follow-up, due to inadequate TTE quality. Although there were no clinical signs of shunt occlusion, shunt patency data by echocardiography cannot be provided in these four patients.

Haemodynamic data at 3-month follow-up showed a significant decrease in PCWP by 5 mmHg (−12, 0, P = 0.0003) at rest for the whole patient collective of 53 patients (*Figure 3A*). When analysed separately, the PCWP change was significant for HFpEF patients as compared with HFrEF patients [HFrEF: decrease by 4 mmHg (−9, 0), P = 0.1 vs. HFpEF: decrease by 5 mmHg (−12.5, −1.5), P = 0.0004]. Furthermore, right atrial pressures remained unchanged after 3 months [all patients: 0 mmHg (−4, 4)].

Echocardiographic measurements are detailed in *Table 4*. Echocardiographic data at 12-month follow-up showed that left atrial/ventricular diameter and ejection fraction remained unchanged, with significant improvement of the E/E′ ratio [HFrEF: decrease by 2 (−6, 0.4), P = 0.0443; HFpEF: decrease by 1.9 (−5, 1.4), P = 0.0382]. No patient developed worsening of the right heart function or a significant increase of pulmonary artery pressure values. A mild significant dilatation of right ventricular diameter (long-axis view and right/left ventricle ratio) was observed in the HFpEF collective associated with increased volume, but no deterioration of right ventricular function. Individual patient echocardiographic diameters of the right ventricle during 1-year follow up are depicted in *Figure 3B*.

Symptoms and surrogate variables of heart failure

Patients improved partially, clinical variables (paired analysis follow-up vs. baseline on individual patient level) are shown in *Figures 3C–F*. NYHA class and quality of life improved significantly at 1 year when compared with baseline in all patients [NYHA class decrease by 1 (−1, 0), P < 0.0001; KCCQ overall summary score +14.9 (0.6, 38), P < 0.0001]. Furthermore, the 6MWD improved significantly in the whole patient collective [6MWD at 1 year +50 m (−33, 113), P = 0.0198]. Natriuretic peptide plasma concentrations were highly variable at baseline and during follow-up, without significant changes up to 1 year compared to baseline [all

Table 1 Baseline characteristics

	All patients ($n = 53$)	HFrEF patients ($n = 24$)	HFpEF patients ($n = 29$)
Demographics			
Age, years, median (Q1, Q3)	70 (63, 73)	71 (65, 73)	67 (60, 74)
Male sex, *n* (%)	31 (59)	17 (71)	14 (48)
Relevant medical history, *n* (%)			
Hypertension	38 (72)	17 (71)	21 (72)
Diabetes	26 (49)	8 (33)	18 (62)
Supraventricular arrhythmias[a]	26 (49)	16 (67)	10 (35)
Stroke (haemorrhagic or ischaemic)	3 (6)	1 (4)	2 (7)
Cardiac status			
NYHA class III, *n* (%)	49 (93)	22 (92)	27 (93)
NYHA class IV, *n* (%)	4 (8)	2 (8)	2 (7)
NT-proBNP, pg/mL (all patients), median (Q1, Q3)	681 (228, 1446)	1386 (330, 3908)	395 (188, 1031)
NT-proBNP, pg/mL (patients with atrial fibrillation), median (Q1, Q3)	563 (180, 1739) $n = 24$	678 (213, 3629) $n = 14$	425 (172, 1075) $n = 10$
NT-proBNP, pg/mL (patients with sinus rhythm), median (Q1, Q3)	768 (228, 1435) $n = 29$	1400 (826, 9400) $n = 10$	363 (174, 1031) $n = 19$
6-min walking distance, m, median (Q1, Q3)	200 (100, 300)	190 (100, 271)	200 (125, 300)

HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; NT-proBNP, N-terminal pro-B-type natriuretic peptide; NYHA, New York Heart Association; Q, quartile.
[a]Patients with atrial fibrillation or other supraventricular arrhythmias.

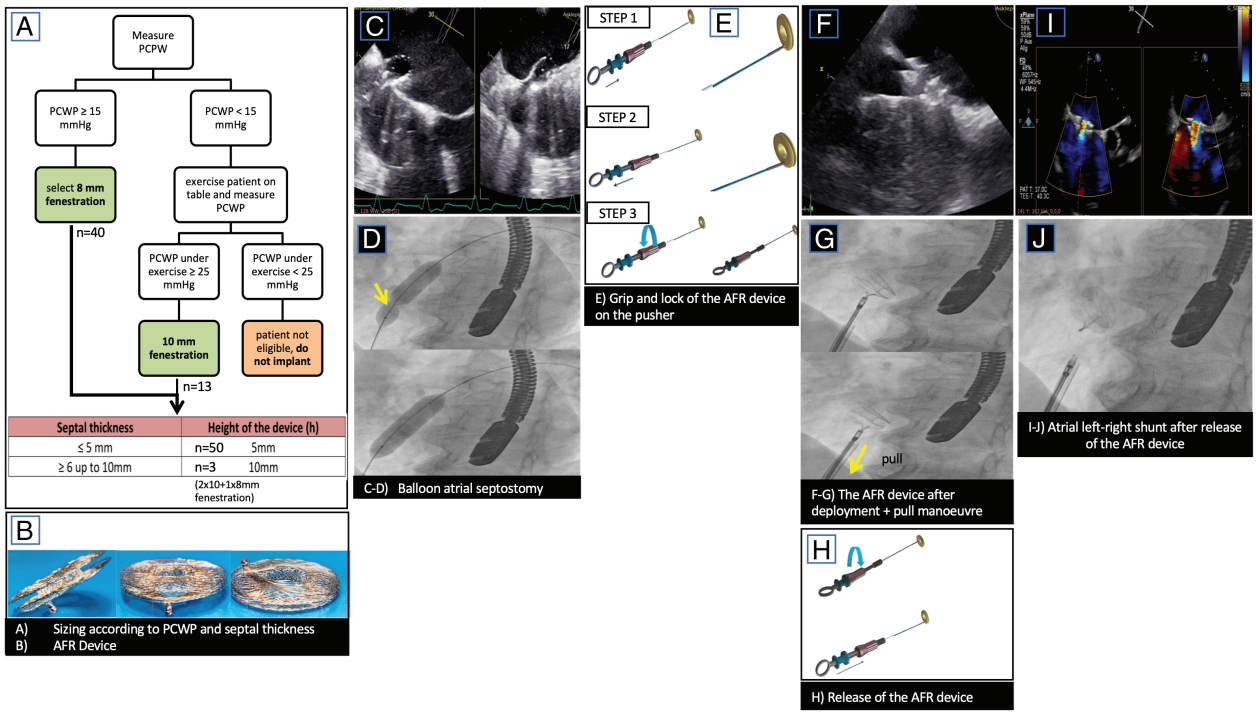


Figure 2 The Atrial Flow Regulator (AFR) implantation procedure step-by-step. PCWP, pulmonary capillary wedge pressure.

Table 2 Procedural characteristics

	All patients ($n = 54$)[a]	HFrEF patients ($n = 25$)[a]	HFpEF patients ($n = 29$)
Balloon atrioseptostomy duration, min	10 (4, 17)	12 (5, 20)	10 (3, 15)
Successful AFR implantation, *n* (%)	53 (98)	24 (96)	29 (100)
AFR implantation duration, min	5 (3, 10)	5 (3, 9)	5 (3, 10)
Overall catherization time, min	80 (70, 95)	80 (70, 90)	80 (70, 100)
Fluoroscopy time, min	21 (16, 26)	23 (19, 28)	17 (14, 23)
Device fenestration diameter, *n* (%)			
8 mm	40 (75)	19 (79)	21 (72)
10 mm	13 (25)	5 (21)	8 (28)
Device waist height, *n* (%)			
5 mm	50 (94)	24 (100)	26 (90)
10 mm	3 (6)	0 (0)	3 (10)
Shunt fraction at end of procedure: Qp/Qs ratio, Fick method	1.2 (0.9, 1.4)	1.4 (1.1, 1.5)	1 (0.8, 1.3)
Shunt fraction at 3 months: Qp/Qs ratio, Fick method	1.2 (1.1,1.4)	1.3 (1, 1.4)	1.2 (1.1, 1.3)

Continuous values are given as median (Q1, Q3).
AFR, Atrial Flow Regulator; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; Q, quintile.
[a] $n = 1$ HFrEF patient with unsuccessful device implantation due to device dislocation in the left atrium and surgical removal, was not part of the collective with 1-year follow-up per protocol.

Table 3 Clinical events up to 1 year

	All patients ($n = 53$)	HFrEF patients ($n = 24$)	HFpEF patients ($n = 29$)
Device removal after implantation, *n* (%)	0	0	0
Death, *n* (%)	3 (6)	3 (13)	0
Stroke, *n* (%)	0	0	0
Myocardial infarction, *n* (%)	1 (2)	0	1 (3)
Worsening of renal function or new impairment (without need for dialysis), *n* (%)	11 (20)	4 (17)	7 (24)
Hospitalisation for heart failure, total events	11	6	5
Hospitalisation for heart failure, *n* of patients with at least one event (%)	6 (11)	3 (13)	3(10)
Atrial fibrillation (new onset or worsening), total events	14	6	8
Atrial fibrillation (new onset or worsening), *n* of patients with at least one event (%)	11 (20)	5 (21)	6 (21)
SADE, *n* of patients (%)	1 (2)	0	1 (3)[a]
SAE rate, total events	64	33	31
Cardiovascular SAE, total events	26	10	16
SAE, *n* of patients with at least one SAE (%)	25 (47)	13 (54)	12 (41)
ADE, total events postoperative	13	1[b]	12[c]
Device patency, *n* (%)			
L -> R shunt flow (TEE) after the procedure	53/53 (100)	24/24 (100)	29/29 (100)
L -> R shunt flow (TTE) at 3 months	47/51 (92)[d]	21/22 (95)[d]	26/29 (90)[d]
L -> R shunt flow (TTE) at 12 months	45/49 (92)[e]	19/20 (95)[e]	26/29 (90)[e]

ADE, adverse device-related event; AE, adverse event; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; L -> R, left right; TEE, transoesophageal echocardiography; SADE, serious adverse device-associated effect; SAE, serious adverse event; TTE, transthoracic echocardiography.
[a] $n = 1$ patient with documented SADE after the procedure with bleeding at the puncture site and loss of consciousness, which resolved without sequela.
[b] $n = 1$ paraesthesia.
[c] 12 ADEs in 8 patients: $n = 3$ puncture site bleeding, $n = 1$ anaemia, $n = 1$ hypoxaemia, $n = 1$ syncope, $n = 1$ groin haematoma, $n = 1$ acute decompensated heart failure, $n = 1$ peripheral oedema, $n = 1$ atrial fibrillation, $n = 1$ non-sustained ventricular tachycardia, $n = 1$ hypotension.
[d] Missing echocardiography data: HFrEF: $n = 2$ patients died, $n = 1$ had inadequate TTE quality to assess patency; HFpEF: $n = 3$ patients had inadequate TTE quality to assess patency.
[e] Missing echocardiography data: HFrEF: $n = 3$ patients died, $n = 1$ withdrew informed consent, $n = 1$ had inadequate TTE quality to assess patency; HFpEF: $n = 3$ patients had inadequate TTE quality to assess patency.

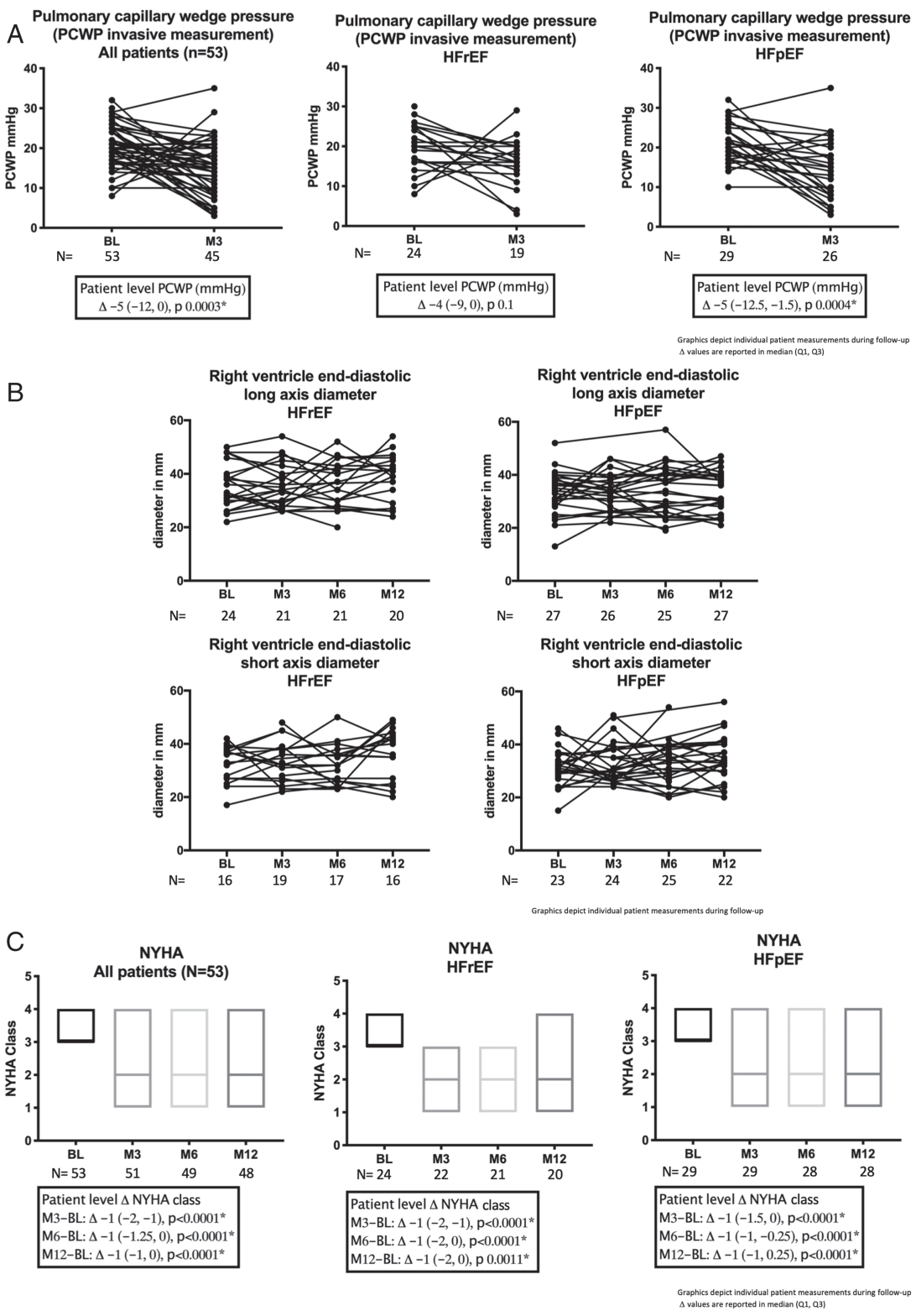


Figure 3 Individual pulmonary capillary wedge pressure (PCWP), right ventricle (RV), New York Heart Association (NYHA) functional class, Kansas City Cardiomyopathy Questionnaire (KCCQ) score, 6-min walking distance (6MWD) and N-terminal pro-B-type natriuretic peptide (NT-proBNP) concentrations. (*A*) Invasive measurement of PCWP. (*B*) Individual echocardiographic diameter of the RV. (*C*) NYHA functional class. (*D*) KCCQ score. (*E*) 6MWD. (*F*) NT-proBNP concentrations. BL, baseline; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; M, months.

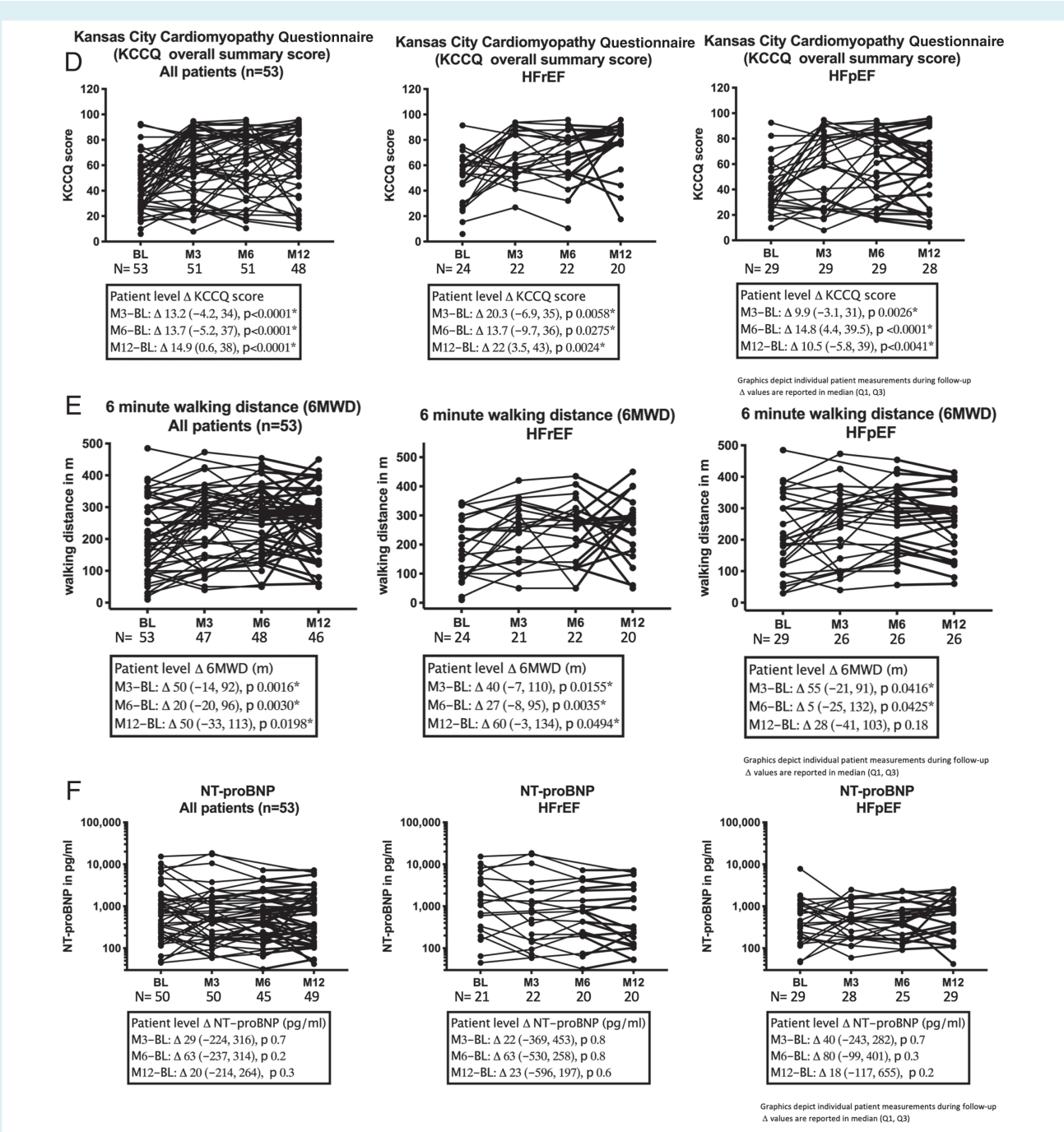


Figure 3 Continued

patients: NT-proBNP +20 pg/mL (−214, 264), $P = 0.3$], also when analysed for the HFrEF and HFpEF collective separately.

Discussion

The 12-month analysis of the PRELIEVE study indicates that AFR device implantation was feasible and associated with improved haemodynamic and clinical outcomes in certain patients with symptomatic HF with reduced and preserved ejection fraction. The study flow chart and a summary of the results are depicted in the *Graphical Abstract*.

Around 100 patients have been treated worldwide with the AFR device as compassionate use for pulmonary arterial hypertension, severe HF and congenital heart disease, mostly to create a right-to-left shunt.[15,16] This study provides evidence for the feasibility of AFR device implantation in a highly symptomatic HF patient population. Fifty-three patients with elevated left ventricular filling pressures were enrolled, consisting of 24 patients with

Table 4 Echocardiographic measurements at 1 year

	HFrEF patients			HFpEF patients		
	Baseline ($n = 24$)	12 months ($n = 20$)	Individual patient level Δ12 months vs. baseline	Baseline ($n = 29$)	12 months ($n = 29$)	Individual patient level Δ12 months vs. baseline
Left heart measurements, median (Q1, Q3)						
LA diameter (mm)	43 (38, 49)	44 (42, 49)	2 (−1, 3)	43 (40, 47)	42 (40, 47)	−1.5 (−4, 4)
LV end-diastolic diameter (mm)	62 (57, 66)	59 (55, 68)	−0.5 (−7, 5)	51 (48, 56)	52 (45, 59)	−1.4 (−5, 2)
Mitral valve E/E′	11 (8, 15)	7 (6, 11)	−2 (−6, 0.4)[a] ($P = 0.0443$)	15 (12, 20)	12 (9, 16)	−1.9 (−5, 1.4)[a] ($P = 0.0382$)
MAPSE (cm)	1.3 (1.1, 1.8)	1.5 (1.2, 1.9)	0.2 (−0.2, 0.3)	1.6 (1.4, 1.8)	1.6 (1.2, 2.1)	0.02 (−0.4, 0.5)
LV ejection fraction (%)	30 (29, 35)	36 (31, 50)	3 (−2, 20)[a] ($P = 0.0481$)	52 (45, 55)	51 (45, 58)	−1 (−5, 5)
Right heart measurements, median (Q1, Q3)						
PAP systolic (mmHg)	28 (18, 40)	26 (21, 38)	7 (−5, 10)	37 (27, 50)	35 (26, 46)	−1.5 (−9, 9)
TAPSE (cm)	2 (1.8, 2.3)	2.2 (1.9, 2.5)	0.07 (−0.1, 0.3)	2.2 (1.9, 2.7)	2.2 (1.8, 2.8)	−0.05 (−0.6, 0.2)
RV/LV size ratio (mm)	0.6 (0.5, 0.7)	0.6 (0.5, 0.9)	0.03 (−0.1, 0.2)	0.7 (0.5, 0.7)	0.7 (0.5, 0.8)	0.09 (0, 0.2)[a] ($P = 0.068$)
RV end-diastolic diameter long-axis (mm)	36 (31, 40)	42 (29, 45)	3 (−5, 8)	33 (28, 38)	37 (28, 40)	2 (−1, 7)[a] ($P = 0.0121$)
RV end-diastolic diameter short-axis (mm)	33 (27, 38)	40 (27, 44)	2.4 (−1.3, 6.2)	31 (27, 34)	33 (30, 41)	3 (−5, 6)
Tricuspid regurgitation mild, *n* (%)	2 (8)	12 (60)	N/A	8 (28)	12 (41)	N/A
Tricuspid regurgitation moderate, *n* (%)	7 (29)	4 (20)	N/A	3 (10)	5 (17)	N/A
Tricuspid regurgitation severe, *n* (%)	0 (0)	0 (0)	N/A	0 (0)	2 (7)[b]	N/A

HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; LA, left atrium; LV, left ventricle; MAPSE, mitral annular plane systolic excursion; N/A, not applicable; PAP, pulmonary artery pressure; Q, quintile; RV, right ventricle; TAPSE, tricuspid annular plane systolic excursion.

[a]Values are statistically significant.

[b]One patient had moderate and one patient had mild tricuspid valve insufficiency at 6-month follow-up.

HFrEF (ejection fraction 15–39%) and 29 patients with HFpEF (ejection fraction ≥40%). AFR implantation requires a balloon atrioseptostomy, which was feasible in all 53 enrolled patients. Two patients were not enrolled, due to unsuccessful transseptal puncture and there was one periprocedural device embolisation in the left atrium after balloon atrioseptostomy, related to a deviation from the instructions for use. To avoid any future deviations, the device handle has thereafter been redesigned to ensure easiness of use and adherence to the instructions. While not formally designed to address safety, the device safety profile in this pilot experience was favourable with only one patient experiencing a SADE (post-procedural bleeding and syncope), which resolved without sequela. During the 1-year follow-up, none of the 53 patients with successful AFR implantation experienced a device dislocation or repeated intervention with device removal or occlusion.

Shunt patency with unidirectional left–right shunting was proven post-procedurally in all patients and at 3 months in 92% of the patients. The AFR device remained patent in these patients up to 1-year follow-up. In the remaining 8% of patients, however, TTE quality was insufficient to assess shunt patency. In turn, there were no clinical or echocardiographic signs of shunt occlusion in these patients. Though not being predefined in the study protocol, alternative evaluation ideally by TEE, could have been considered to rule out unequivocally shunt occlusion. Note, the single-arm, open-label, first-in-man study of the V-Wave device, with an incorporated V-trileaflet porcine tissue valve, demonstrated initial safety and early improvement in outcomes in HFrEF patients, though the benefits appeared to be compromised by impaired shunt patency over time,[12,13] leading to redesigning the second generation V-Wave device without a valve. The Corvia IASD device showed patency at 6 months in the REDUCE LAP-HF trial and at 12 months in the REDUCE LAP-HF I trial in all patients.[11,17]

The rate of 1-year hospitalisation and all-cause mortality in the present cohort was 11% and 6%, respectively. Total cardiovascular SAE rate was high (around 50%) and within the expected range of a NYHA class III/IV HF population. Randomised controlled studies are required to finally assess the safety of the AFR in patients with HF. Large Phase III trials (RELIEVE-HF, NCT03499236 with the V-Wave and REDUCE LAP-HF II NCT03088033 with the IASD) in symptomatic refractory HF patients are ongoing, aiming to assess the efficacy and impact of interatrial shunting on cardiovascular mortality. Recently, Kaye *et al.*[8] compared in an observational study the theoretical impact of the IASD device in HFpEF patients on mortality to the predicted survival and suggested that interatrial shunting was associated with a 33% reduction in all-cause mortality.

Pulmonary capillary wedge pressure decreased at rest after 3 months significantly in the whole patient cohort. Yet when analysed separately, the decrease remained significant only in patients with the HFpEF phenotype. This is of interest as, in the REDUCE LAP-HF I trial after implantation of the Corvia IASD device in similar patients, the decrease in PCWP was not significant during peak exercise, but over the entire spectrum of exercise workloads at 1-month follow-up.[7] In contrast to our findings in HFrEF patients, Del Trigo *et al.*[12] reported a significant PCWP decrease of 6 mmHg at rest in HFrEF patients after implantation of the V-Wave device.

Several clinical observations are noteworthy with regard to future prospective clinical validation of the AFR device. First, a chronic left–right shunt may hypothetically increase the risk of right HF due to volume overload. The measured left–right shunt

fraction after AFR implantation at 3 months was low [Qp:Qs ratio 1.2 (1.1, 1.4)]. Additionally, echocardiographic measurements of right ventricular function remained stable with no increase in pulmonary artery pressure values at 1-year follow-up. However, a mild dilatation of the mean right ventricular diameter was documented in the HFpEF collective. This is in line with the REDUCE LAP-HF I trial, where a small (but significant) increase in right ventricular size was observed in the IASD group compared with the control group, without further increase up to 12 months.[17] Taken together, long-term clinical data of large trials are needed to provide more evidence on the potential impact of interatrial shunts on right ventricular function.

Additionally, implantation of an atrial shunt device may raise concerns about the potential for thromboembolic complications. The post-procedural antithrombotic therapy herein consisted of: (i) continuation of oral anticoagulation in patients with atrial fibrillation, or (ii) dual antiplatelet treatment for 3 months, followed by aspirin monotherapy. There were no strokes or major systemic embolism reported during 1-year follow-up and in line with other studies.[10,17] The optimal antithrombotic/anticoagulation regimen after shunt implantation, however, needs to be defined. Careful patient selection with haemodynamic baseline measurements favouring left-to-right shunt remains certainly key to this therapy.

Finally, clinical evaluation up to 12 months suggested symptom relief in certain patients. At 1-year follow-up, an improvement in NYHA functional class, quality of life (KCCQ) and the 6MWD was documented. The NT-proBNP concentrations were highly variable and remained unchanged after shunting. Similarly, changes in NT-proBNP concentrations did not significantly differ from baseline to 3 months after implantation of the V-Wave device[12] or after implantation of a LAP monitor (HOMEOSTASIS trial).[18]

The current study has limitations inherent to its small sample size, the open-label, non-randomised observational nature without a control group. Follow-up has been limited to 12 months post-procedure. Some secondary clinical outcome variables, obtained through subjective testing (NYHA class, quality of life) by unblinded participants and investigators, may be subject to unintentional bias. The haemodynamic results, though significant compared with baseline measurements, should be interpreted with caution as there was no control group in this study.

Implantation of the AFR device in HF patients with reduced and preserved ejection fraction was feasible. There were no shunt occlusions, strokes or new right HF observed during the 1-year follow-up. Three-month PCWP reduction and improvement in symptomatology, quality of life and exercise capacity at 1-year follow-up suggest potential clinical efficacy for this novel treatment in certain patients with HF. Future studies are needed to finally determine the efficacy and safety of this approach and the role of left atrial shunting in the treatment of patients with HF.

Supplementary Information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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