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ORIGINAL ARTICLE

Predicted impact of atrial flow regulator on survival in heart failure with reduced and preserved ejection fraction

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Abstract

Aims We aim to assess the theoretical impact of the atrial flow regulator (AFR) on survival in heart failure.

Methods and results The prospective, multicentre, open-label, non-randomised PRELIEVE study (NCT 03030274) assessed the safety and efficacy of the Occlutech AFR device in patients with symptomatic heart failure with reduced ejection fraction (HFrEF) (left ventricular ejection fraction (LVEF) ≥ 15% and <40%) or heart failure with preserved ejection fraction (HFpEF) (LVEF ≥40% and <70%) and elevated PCWP (≥15 mmHg at rest or ≥25 mmHg during exercise). In this analysis, after the first 60 patients completed 12 months of follow-up, the theoretical impact of AFR implantation on survival was assessed by comparing the observed mortality rate with the median predicted probability for one-year mortality. Each subject's risk of mortality was predicted from individual baseline data using the Meta-Analysis Global Group in Chronic HF (MAGGIC) prognostic model. A total of 87 patients (46% female, median age 69 years [IQR 62–74]) had undergone successful device implantation for the treatment of HFrEF (53%) and HFpEF (47%). Sixty patients had a complete 12 month follow-up. The median follow-up was 351 days (interquartile range [IQR] 202–370). Six (7%) patients died during follow-up (8.6 deaths per 100 patient-years; 95% confidence interval [CI] 2.7 to 15.5), all of which had HFrEF. The median predicted mortality rate for the overall study population was 12.2 deaths per 100 patient-years (95% CI 10.2 to 14.7). While the observed mortality rate (0 deaths per 100 patient-years) was significantly lower than the median predicted mortality rate (9.3 deaths per 100 patient-years; 95% CI 8.4 to 11.1) in patients with HFpEF (−9.3 deaths per 100 patient-years; 95% CI −11.1 to −8.4), there was no difference in patients with HFrEF (−3.6 deaths per 100 patient-years; 95% CI −9.5 to 3.0). Four deaths were HF-related deaths (5.7 HF-related deaths per 100 patient-years; 95% CI 1.4 to 11.9; 10.8 HF-related deaths per 100 patient-years; 95% CI 2.5 to 23.1 in the HFrEF subgroup).

Conclusions In patients with HFpEF, the mortality rate following AFR implantation was lower than the predicted mortality rate. Dedicated randomised, controlled trials are needed – and currently ongoing – to investigate whether the AFR improves mortality.

Keywords Device-based therapy; Chronic heart failure; Pulmonary congestion; Exertional dyspnoea

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Introduction

Dyspnoea is a common symptom of chronic heart failure (HF) patients, irrespective of left ventricular ejection fraction (LVEF).[1] Exertional dyspnoea might be caused by acute pulmonary congestion secondary to increased left atrial and ventricular filling pressures.[1] Pharmacological therapy can barely compensate for the underlying rapid volume shifts from the capacitance vessels into the arterial circulation.[2] Various left-to-right interatrial shunt devices are under investigation for left atrial decompression in patients with chronic HF.[3] In open-label studies, interatrial shunt device implantation was feasible and associated with reductions in pulmonary capillary wedge pressure (PCWP), improved submaximal exercise capacity and health-related quality of life.[3] Recently, in the randomised, sham-controlled REDUCE LAP-HF II trial, the implantation of the Corvia IASD II device did not affect the cumulative incidence of cardiovascular death and non-fatal stroke or HF events in patients with symptomatic HF and an LVEF ≥40%.[4] Whether these outcomes are related to the device or the included patient population remains elusive. The multicentre, non-randomised, open-label, single-arm PRELIEVE study investigated a novel Atrial Flow Regulator (AFR, Occlutech International AB, Helsingborg, Sweden) employing an 8 mm or 10 mm interatrial shunt in patients with HF with reduced (HFrEF) and preserved ejection fraction (HFpEF). The implantation of the AFR was feasible and safe in HF patients and associated with reduced PCWP at 3 months and improved 6 min walking distance and health-related quality of life at 1 year in certain patients.[5,6] This analysis aimed to assess the theoretical impact of AFR implantation on mortality by comparing the observed survival rate with the median predicted probability for one-year survival.

Methods

Study design and participants

The PRELIEVE is a multicentre, prospective, non-randomised, open-label, single-arm pilot study assessing the safety, performance, and efficacy of the AFR in patients with symptomatic HFrEF and HFpEF (ClinicalTrials.gov identifier NCT03030274). Patients were recruited at 15 sites in Germany, Turkey, and Belgium between November 2017 and December 2020 and were stratified according to their ejection fraction as having HFrEF (LVEF ≥15% and <40%) or HFpEF (LVEF ≥40% and <70%). This analysis was conducted after the first 60 patients completed 12 months of follow-up. 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 (DSMB) and a clinical event committee were established. The detailed outline of the study and results have previously been published.[5,6] Patients aged ≥18 years with symptomatic (New York Heart Association [NYHA] functional class III or ambulatory class IV) HFrEF (LVEF ≥15% and <40%) or HFpEF (LVEF ≥40% and <70% and plasma level of N-terminal pro-B-type natriuretic peptide [NT-proBNP] > 125 pg/mL) with increased left ventricular fillings pressures (PCWP ≥15 mmHg at rest or ≥25 mmHg during exercise) despite guideline-directed therapy[7] were eligible for study inclusion. Key exclusion criteria were evidence of right HF (tricuspid annular plane excursion <14 mm or severe dilatation), severe pulmonary hypertension (systolic pulmonary artery pressure >60 mmHg), renal insufficiency requiring dialysis, severe valve disease requiring surgery or intervention, a large patent foramen oval or history of an atrial septal defect or repair or closure device in place. Full inclusion and exclusion criteria are listed in the Supporting Information. The study was approved by local ethics committees or institutional review boards.

Procedures

After the patients provided written informed consent, they were consecutively enrolled. We confirmed the presence of trial inclusion and absence of exclusion criteria and gathered baseline information. Detailed study procedures have previously been described.[5] Following right heart catheterisation, the patients underwent balloon atrioseptostomy. Successful balloon atrioseptostomy was required to proceed with the AFR implantation. Patients with a PCWP >15 mmHg at rest received a device with an 8-mm fenestration diameter, while patients with a PCWP <15 mmHg at rest but ≥25 mmHg during exercise received a device with a 10-mm diameter. Patients were followed-up for 12 months (eight visits). A right heart catheterisation was performed at 3 months. Other follow-up procedures included echocardiography, assessment of NYHA functional class, health-related quality of life using the Kansas City Cardiomyopathy Questionnaire (KCCQ), 6-min walking distance and NT-proBNP. Echocardiograms were interpreted by a blinded independent core lab (echo coreLab Black Forest GmbH, Bad Krozingen, Germany).

The primary safety outcome was the incidence of severe adverse device events (SADE) 3 months post-implantation. The secondary safety outcome was SADE incidence between three and 12 months post-implantation. Secondary efficacy outcomes included changes in symptoms and hemodynamic parameters at 3, 6 and 12 months following AFR implantation.

Meta-analysis Global Group in Chronic HF (MAGGIC) predicted survival

We calculated each patient's 1 year predicted survival using the Meta-analysis Global Group in Chronic HF (MAGGIC)

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prognostic model.[8-10] The predicted survival was calculated based on the patients' individual baseline data. Moreover, MAGGIC mortality risk scores were calculated at each follow-up visit with updated values for LVEF, systolic blood pressure, body mass index, creatinine, and NYHA functional class.

Statistical analysis

Continuous variables are summarised as median (interquartile ranges, IQR) or mean (standard deviation [SD]), as appropriate. Categorical variables are presented as numbers (%). Cumulative survival curves were constructed using the Kaplan–Meier method. For incidence rates, we calculated the incidence rate per 100 person-years. The corresponding 95% confidence intervals (95% CI) were estimated using percentile bootstrapping with 1000 bootstrap samples. The paired difference between the observed and predicted mortality rates based on the MAGGIC prognostic model was calculated. The significance of the difference between the observed and predicted mortality rates was established by its CI applying a bootstrapping procedure using 1000 subsamples: if the CI did not contain zero, significance was concluded. A two-sided *P*-value <0.05 was considered statistically significant. All statistical analyses were done using SAS version 9.4 (SAS Institute, Cary, NC, USA). The figures were prepared using STATA version 16 (StataCorp, College Station, TX, USA) and GraphPad Prism version 9.3.1 (GraphPad Software, San Diego, CA, USA).

Results

A total of 87 patients had undergone successful device implantation for the treatment of HFrEF (53%; 46/87) and HFpEF (47%; 41/87). Of these, 72 patients (83%, 87% of the patients with HFrEF, 78% of the patients with HFpEF) received implantation of a device with an 8 mm fenestration diameter, and 15 patients (17%, 13% of the patients with HFrEF, 22% of the patients with HFpEF) had implantation of a device with a 10-mm fenestration diameter. Sixty patients had a complete 12 month follow-up (*Figure S1*). The median follow-up was 351 days (IQR 202–370). As previously reported, three patients were excluded due to transseptal puncture failure (septum >10 mm thickness and elastic septum).[5] At 12 months, shunt patency (left-to-right shunting) was confirmed using transthoracic echocardiography in all patients with sufficient echocardiography data (55/55 [100%]; HFrEF: 26/26 [100%]; HFpEF 29/29 [100%]). In four patients (7%, 7% of the patients with HFrEF, 6% of the patients with HFpEF) the quality of the transthoracic echocardiogram was insufficient to assess shunt patency and in one patient, echocardiography was not performed at 12 months.

Baseline characteristics

Table 1 summarises the patients' baseline characteristics. The patients' median age was 69 years (IQR 62–74), almost half were female (46%), and they frequently had a history of hypertension (66%) and diabetes (44%). All patients were NYHA functional class III (89%) or IV (11%) according to inclusion

Table 1 Baseline characteristics

	Total		HFrEF		HFpEF	
Parameter	Value	*N*	Value	*N*	Value	*N*
Median age, years (IQR)	69 (62–74)	87	68.5 (62–72)	46	71 (62–74)	41
Female, *n* (%)	40 (46)	87	14 (30)	46	26 (63)	41
Median body mass index, kg/m^2 (IQR)	27.7 (25–33)	87	26.5 (24–30)	46	31.9 (26–35)	41
Medical history						
Hypertension, *n* (%)	57 (66)	87	29 (63)	46	28 (68)	41
Diabetes mellitus, *n* (%)	38 (44)	87	18 (39)	46	20 (49)	41
Supraventricular arrhythmias, *n* (%)	35 (40)	87	21 (46)	46	14 (34)	41
Coronary artery disease, *n* (%)	24 (28)	87	10 (22)	46	14 (34)	41
Chronic obstructive pulmonary disease, *n* (%)	11 (13)	87	5 (11)	46	6 (15)	41
Stroke, *n* (%)	3 (3)	87	0 (0)	46	3 (7)	41
Transient ischaemic attack, *n* (%)	2 (2)	87	1 (2)	46	1 (2)	41
Median eGFR, mL/min/1.73 m^2 (IQR)	68.0 (47.0–82.4)	87	69.8 (45.0–83.1)	46	66.0 (48.8–81.1)	41
GFR $<$ 60 mL/min/1.73 m^2, *n* (%)	33 (38)	87	18 (39)	46	15 (37)	41
Cardiac status						
NYHA functional class III, *n* (%)	77 (89)	87	42 (91)	46	35 (85)	41
NYHA functional class IV, *n* (%)	10 (11)	87	4 (9)	46	6 (15)	41
Median 6 min walking distance, m (IQR)	180 (100–300)	87	172.5 (100–285)	46	188 (120–300)	41
Median NT-proBNP, pg/mL (IQR)	648(174–1401)	82	709 (269–1660)	43	363 (128–1151)	39

Data are *n* (%), unless stated otherwise.
eGFR, estimated glomerular filtration rate; 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.

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criteria. The 6 min walking distance was low (median: 180 meters; IQR 100–300). Echocardiographic and hemodynamic data are provided in *Table 2*. In patients with HFrEF, the LVEF was 29 ± 7%. The median systolic pulmonary artery pressure was 29.5 mmHg (IQR 14.7–39.4) in patients with HFrEF and 38.0 mmHg (IQR 27.0–50.0) in HFpEF.

MAGGIC mortality risk score

The median MAGGIC mortality risk score was 22 (IQR 19–27) in the overall study population and 25.5 (IQR 21–29) and 19 (IQR 17–22) for patients with HFrEF and HFpEF, respectively. Post-AFR implantation, the MAGGIC mortality risk score was consistently lower, irrespective of whether patients had HFrEF or HFpEF (*Figure 1*). This effect was maintained between 3 and 12 months after device implantation. In the overall study population, the median predicted mortality rate based on the MAGGIC mortality risk score was 12.2 deaths per 100 patient-years (95% CI 10.2 to 14.7). In patients with HFrEF, the median predicted mortality rate was 16.8 deaths per 100 patients-years (95% CI 14.7 to 19.1) and, in patients with HFpEF, 9.3 deaths per 100 patients-years (95% CI 8.4 to 11.1).

Observed mortality

Of the 87 patients with successful device implantation, six (7%) patients died during follow-up (8.6 deaths per 100 patient-years; 95% CI 2.7 to 15.5), all of which had HFrEF (16.2 deaths per 100 patient-years; 95% CI 5.0 to 30.1) (*Figure 2*). For patients with HFpEF (−9.3 deaths per 100 patient-years; 95% CI −11.1 to −8.4), but not the overall study population (−3.6 deaths per 100 patient-years; 95% CI −9.5 to 3.0) and patients with HFrEF (−0.6 deaths per 100 patient-years; 95% CI −11.9 to 12.5), the observed mortality rate was significantly lower than the predicted mortality rate. Four deaths were HF-related deaths (5.7 HF-related deaths per 100 patient-years; 95% CI 1.4 to 11.9; in the overall population; 10.8 HF-related deaths per 100 patient-years; 95% CI 2.5 to 23.1; in the HFrEF subgroup) (*Figure S2*). One patient died due to liver carcinoma and died due to COVID-19.

Discussion

In this analysis, which is the first assessing the theoretical impact of AFR implantation on survival in HF patients, the

Table 2 Haemodynamic and echocardiographic data

Parameter	Total Value	*N*	HFrEF Value	*N*	HFpEF Value	*N*
Median heart rate, b.p.m. (IQR)	72 (65–83)	84	72 (65–82)	45	73 (63–84)	39
Median systolic blood pressure, mmHg (IQR)	120 (110–135)	87	112 (106–123)	46	130 (112–140)	41
Median diastolic blood pressure, mmHg (IQR)	70 (63–79)	87	70 (60–79)	46	72 (67–79)	41
Left ventricular ejection fraction	39 (13)	87	29 (7)	46	51 (6)	41
Median systolic pulmonary artery pressure, mmHg (IQR)	34.5 (23.5–45)	72	29.5 (14.7–39.4)	38	38 (27–50)	34
Median mean pulmonary capillary wedge pressure, mmHg (IQR)	20 (17–25)	82	20 (17–25)	42	20 (17–24.5)	40
Median cardiac index, (L/min)/m^2 (IQR)	2.25 (2.02–2.74)	82	2.26 (1.93–2.69)	45	2.22 (2.03–2.84)	37

Data are mean (SD) or median (IQR), unless stated otherwise.

Figure 1 MAGGIC score at baseline and each follow-up visit. Data are median (IQR) (black symbol and lines) and individual patients' time courses (grey symbols and lines). MAGGIC scores at baseline and each follow-up visit were calculated with updated values for left ventricular ejection fraction, systolic blood pressure, body mass index, creatinine, and New York Heart Association functional class.

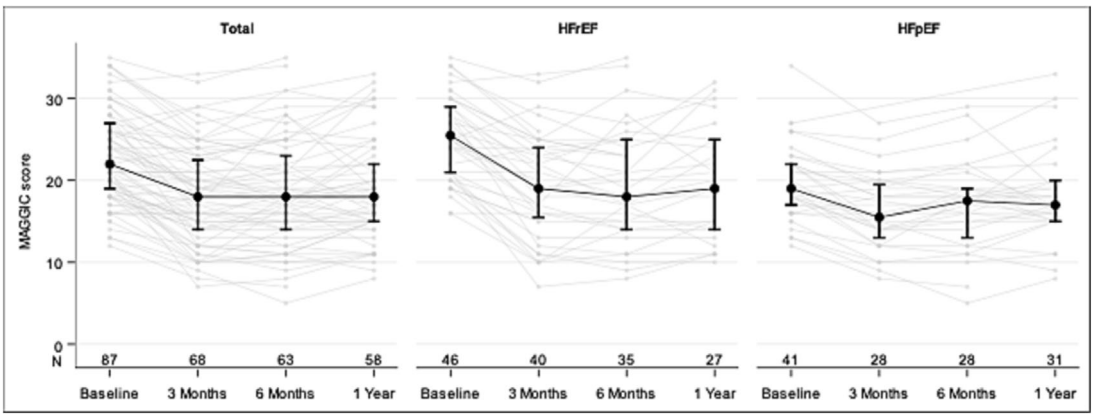

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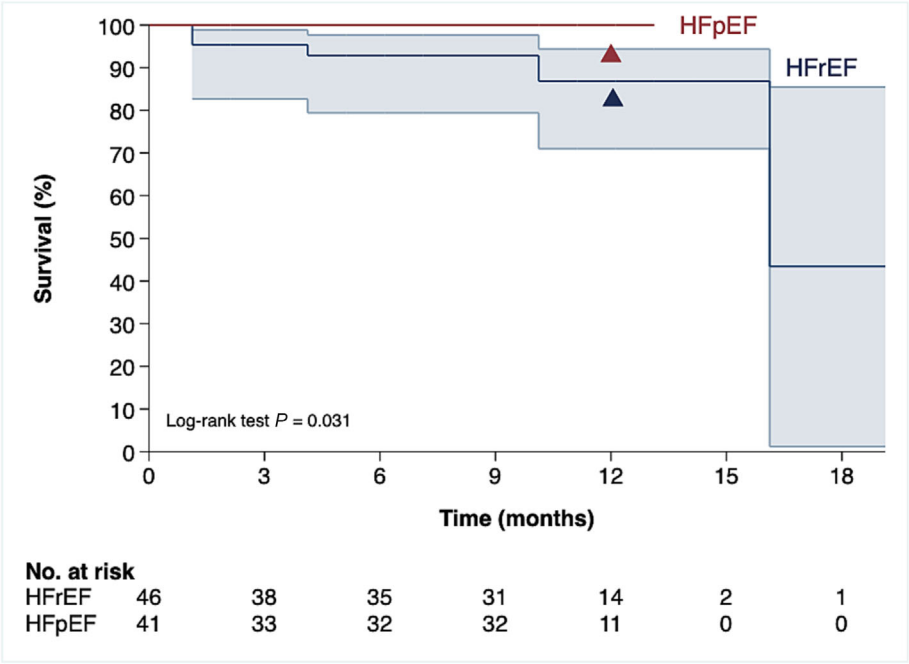
Figure 2 Kaplan–Meier survival curves. The triangles indicate the median predicted survival at 12 months using the MAGGIC prognostic model. Coloured bands around lines represent 95% confidence intervals for survival curves. Log-rank test for the difference between patients with HFrEF and HFpEF.



observed mortality rate in the overall study population was lower than the predicted mortality rate. While there was no difference between the predicted and observed survival rate in HFrEF, the observed mortality was markedly lower than the predicted mortality in patients undergoing AFR implantation for HFpEF.

Pharmacological therapy improves symptoms, cardiac function, and prognosis in patients with HFrEF.[11] In patients with HFpEF, there is no drug or d\evice therapy besides sodium-glucose cotransporter-2 inhibitors that has improved outcomes.[11,12] Several left-to-right interatrial shunt devices are under investigation for left atrial decompression. In a meta-analysis of mostly observational studies, left atrial decompression was feasible and associated with reductions in PCWP, improved submaximal exercise capacity and health-related quality of life.[3] However, data on the effect of left atrial decompression on mortality are scarce and only available for the Corvia IASD II.[3,4] The randomised, sham-controlled REDUCE LAP-HF II trial was the first randomised controlled trial assessing the efficacy of IASD II device placement on a hierarchical composite primary endpoint, including cardiovascular death, in patients with symptomatic HF with elevated left atrial pressures and an LVEF $\geq$40%.[4] There was no difference between the IASD II and sham treatment groups in terms of the primary endpoint (1% in both treatment groups; $P = 0.41$) or incidence of time-to-cardiovascular death at 12 months (1% in both treatment groups; $P = 0.65$).[4] Whether these results are device-specific or related to the included study population remains elusive.[4] Prespecified subgroup analysis showed that men, patients with a pulmonary artery systolic pressure $>$70 mmHg at 20 W of exercise and right atrial volume index $\geq$29.7 mL/m^2 had more HF events with the device than in the sham group. Moreover, post-hoc analyses suggested that patients with a peak exercise pulmonary vascular resistance of $<$1.74 Wood units might represent a group of responders.[4] Of note, the observed cardiovascular mortality rate in the REDUCE LAP-HF II trial[4] was much lower than expected based on data from the REDUCE LAP-HF I trial (which was used for sample size calculation).[13] Moreover, the observed cardiovascular death rates in the active treatment and sham group were far lower than in the current study, despite similar baseline MAGGIC mortality score (23 in REDUCE LAP-HF II vs. 22 in the current study), and large HFpEF trials, such as TOPCAT,[14] PARAGON-HF,[15] or EMPEROR-Preserved.[12] The lack of response could also partly be device-specific so that the results cannot be fully transferred to devices with different designs. While the AFR is available with a fenestration diameter of 8 or 10 mm, the Corvia IASD is only available with 8-mm diameter. Computational models demonstrated that shunt flow increases and PCWP decreases with increasing shunt size.[16] These effects reached a plateau at an 8–9 mm shunt diameter.[16] In line with this, the PCWP at rest was lowered in the PRELIEVE study but not in the REDUCE LAP-HF I trial.[6,17]

In this study, the observed mortality rate was lower than the predicted mortality rate in HFpEF but not HFrEF. Similarly,

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median PCWP dropped significantly at 3 months in HFpEF (−5 mmHg, 95% CI −12.5 to −1.5; P = 0.0004) but not in HFrEF (−4 mmHg, 95% CI −9.0 to 0; P = 0.1).[6] Especially in HFpEF, left atrial pressure increases steeply during exercise[18] and the exercise-induced increase in PCWP is associated with worse survival.[19] One possible underlying mechanism may be an increase in cardiac sympathetic outflow secondary to increased PCWP.[20] In line with a recently published meta-analysis, left atrial decompression improved 6 min walking distance only in patients with preserved LVEF (>40%).[3] However, adequately powered, sham-controlled trials are necessary and planned to identify patients with a high likelihood of benefit from left atrial decompression.

Limitations

Some important limitations of this analysis must be acknowledged. First, the PRELIEVE study is a non-randomised, open-label, single-arm feasibility study without a control group. Therefore, we cannot exclude selection bias and unspecific treatment effects, such as placebo. In contrast to patient-reported outcomes, mortality is not susceptible to placebo effects.[21] Indeed, only adequately powered randomised controlled trials can examine the actual effect of AFR on morbidity and mortality in heart failure; such trial is currently ongoing (NCT03751748). In the absence of data from randomised controlled trials, this analysis, despite its limitations, can provide valuable information and may inform future trial designs. Second, we cannot exclude that the predicted mortality based on the MAGGIC mortality risk score over- or underpredicted the true mortality rate. However, in a large external validation cohort, the MAGGIC mortality risk score performed well, especially in patients with risk scores between 21 and 24.[10] Third, all patients in this study underwent implantation of the AFR. Therefore, these findings are not generalisable to other left-to-right interatrial shunt devices. Fourth, this pilot study was primarily designed to assess the safety and performance of the AFR and was not powered to detect changes in mortality. Fifth, subgroup analyses cannot be performed due to the small study size.[22] Sixth, concomitant medications were not systematically assessed. Therefore, we cannot exclude that pharmacological treatment and medication changes throughout follow-up may have influenced the results. Seventh, in this study, patients with HFrEF (46%) more often had a history of supraventricular arrhythmias, including atrial fibrillation, than patients with HFpEF (34%). We cannot exclude that the higher prevalence of atrial fibrillation in the HFrEF group compared with the HFpEF group might have contributed to the higher mortality rate. Moreover, as atrial fibrillation is associated with LA remodelling, pulmonary hypertension, and RV dysfunction,[2-4] it is conceivable that patients with atrial fibrillation may benefit less from left atrial decompression. However, in a pooled analysis of a different interatrial shunting device, greater reductions in resting pulmonary vascular resistance were observed in patients with a history of AF than in those without.[3]

Conclusions

In patients undergoing AFR implantation in PRELIEVE, the observed mortality rate was lower than the baseline predicted mortality. This result was driven by a significantly lower than predicted mortality rate in patients with HFpEF, while there was no difference between the predicted and observed survival rate in HFrEF. In the absence of data from randomised controlled trials, this exploratory analysis, despite its limitations, provides valuable information and may inform future trial designs. However, larger randomised, controlled trials are needed—and currently ongoing—to investigate whether left atrial decompression using the AFR improves survival.

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Conflict of interest

LL reports speaker honoraria from Medtronic and ReCor Medical, outside the submitted work. MWB declares that he has no conflicts of interest. CP declares that he has no conflicts of interest. RÖ declares that he has no conflicts of interest. CI declares that he has no conflicts of interest. JB has nothing to disclose. AL has nothing to disclose. TK is the owner of ACOMED statistik. ACOMED statistik provides (and has provided) statistical services within a commercial business relationship for Occlutech International AB in a couple of clinical trials investigating medical devices produced by this company. SW is an employee of ACOMED statistik. HS has nothing to disclose. SDA reports receiving fees from Abbott, Actimed, Amgen, Astra Zeneca, Bayer, Bioventrix, Boehringer Ingelheim, Brahms, Cardiac Dimension, Cordio, Impulse Dynamics, Janssen, Novartis, Occlutech, Respicardia, Servier, and Vifor International, and grant support from Abbott and Vifor International. FM is supported by Deutsche Gesellschaft für Kardiologie (DGK), Deutsche Forschungsgemeinschaft (SFB TRR219), and Deutsche Herzstiftung and has received scientific support and speaker honoraria from Astra-Zeneca, Bayer, Boehringer Ingelheim, Medtronic and ReCor Medical.

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Supporting information

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Figure S1. Study flow chart. Abbreviations: FAS, full analysis set; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction.

Figure S2. Kaplan–Meier survival curves for heart failure-related death. Coloured bands around lines represent 95% confidence intervals for survival curves. Log-rank test for the difference between patients with HFrEF and HFpEF.

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