ESC European Society of Cardiology

Europace (2020) **22**, 1328–1336
doi:10.1093/europace/euaa101



# Restoration of sinus rhythm by pulmonary vein isolation improves heart failure with preserved ejection fraction in atrial fibrillation patients

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*Received 2 August 2019; editorial decision 1 April 2020; accepted after revision 7 April 2020; online publish-ahead-of-print 25 May 2020*

**Aims** Atrial fibrillation (AF) in patients suffering from heart failure with preserved ejection fraction (HFpEF) is associated with increased symptoms and higher morbidity and mortality. Effective treatment strategies for this patient population have not yet been established.

**Methods and results** We analysed clinical outcomes and echocardiographic parameters of patients with AF and HFpEF who underwent pulmonary vein isolation (PVI). Out of 374 PVI patients, we identified 35 patients suffering from concomitant HFpEF. Freedom from atrial tachyarrhythmia (AT) after 1 year was 80%. Heart failure symptoms assessed by New York Heart Association class significantly improved from 2.7 ± 0.7 to 1.7 ± 0.9 ($P < 0.001$). We observed regression of diastolic dysfunction by echocardiography 12 months after the index procedure. Moreover, 15 patients (42.9%) experienced complete resolution of HFpEF after a single ablation procedure. Multivariate logistic regression revealed absence of AT recurrence as an independent predictor of recovery from HFpEF (hazard ratio 11.37, 95% confidence interval 1.70–75.84, $P = 0.009$). Furthermore, resolution of HFpEF by achieving freedom from AT recurrence by PVI, including multiple procedures, led to a significant reduction of hospitalizations.

**Conclusion** Our results suggest that restoration of sinus rhythm by PVI in HFpEF patients with concomitant AF induces reverse remodelling, improvement of symptoms, resolution of HFpEF and subsequently decrease of hospitalizations. Randomized controlled trials are warranted to confirm our results.

**Keywords** Heart failure with preserved ejection fraction • Atrial fibrillation • Ablation • Pulmonary vein isolation • Cryoballoon • Remodelling

## Introduction

Atrial fibrillation (AF) is the most frequent sustained arrhythmia with a prevalence of approximately 3%, often causing severe symptoms leading to frequent hospitalization and increased morbidity and mortality.[1] Especially in patients suffering from concomitant heart failure the emergence of AF results in aggravating symptoms and worsening of prognosis.[2] Recently, it has been shown that in heart failure patients with reduced ejection fraction (HFrEF) AF ablation reduces heart failure hospitalization and mortality compared to medical therapy.[3] In contrast, the impact of AF ablation on heart failure with preserved ejection fraction (HFpEF) is only poorly understood and has

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## What's new?

- Cryoballoon pulmonary vein isolation is a promising treatment option in patients with atrial fibrillation (AF) and heart failure with preserved ejection fraction (HFpEF).
- Pulmonary vein isolation is able to induce left ventricular reverse remodelling in HFpEF patients with AF.
- Resolution of HFpEF by restoration of sinus rhythm results in significant improvement of heart failure symptoms and decrease of hospitalizations.

yet to be investigated. Heart failure with preserved ejection fraction accounts for approximately half of heart failure diagnoses and prevalence of AF ranges from 30% to 65% in this cohort.[2,4] Interestingly, presence of AF in HFpEF patients leads to a more pronounced increase in heart failure hospitalizations and mortality than in HFrEF patients.[4,5]

Heart failure with preserved ejection fraction typically is accompanied by left ventricular relaxation abnormalities and passive stiffness, leading to impaired diastolic filling.[6] Exposure to greater pulsatility and pressure is believed to result in progressive fibrosis and enlargement of the left atrium, predisposing for development of AF.[6] Vice versa, presence of AF itself is associated with reduced function, progressive enlargement as well as fibrosis of the left atrium and ventricle, contributing to diastolic dysfunction and HFpEF.[6] Pulmonary vein isolation (PVI) as treatment for AF in HFpEF patients has been shown to be feasible and safe.[7–9] However, the impact of PVI on heart failure, hospitalizations, left ventricular remodelling in HFpEF patients suffering from concomitant AF has not been established.

# Methods

## Study population

In this single-centre retrospective study, we included HFpEF patients who underwent ablation of either paroxysmal or persistent AF at our electrophysiology centre.

To be eligible for inclusion, left ventricular diastolic dysfunction as defined by the American Society of Echocardiography (ASE) and the European Association of Cardiovascular Imaging (EACVI) had to be present and HFpEF criteria according to the current European Society of Cardiology (ESC) guidelines had to be fulfilled within 6 months prior to AF ablation.[10,11] In particular, every patient had to have symptoms of heart failure [New York Heart Association (NYHA) Class II–IV] as well as elevated levels of N-terminal pro-B-type natriuretic peptide (NT-proBNP) (>125 pg/mL). Patients with acutely decompensated heart failure or cardiogenic shock were not eligible. Patients with moderate or severe valvular heart disease, in particular aortic stenosis and mitral regurgitation, relevant pulmonary disease, mainly asthma and chronic obstructive pulmonary disease, and severe anaemia (haemoglobin <10 g/dL) were excluded. Left ventricular ejection fraction had to be ≥50%. Moreover, either *E*/*e*′ ratio ≥13 or left ventricular hypertrophy (left ventricular mass index = LVMI: male >115 g/m$^2$, female >95 g/m$^2$) had to be present. Left atrial enlargement was excluded from assessment in order to prevent bias due to the well-established incidence in AF patients even without HFpEF.[6] Echocardiographic assessment was exclusively performed in sinus rhythm. All echocardiographic measurements were re-evaluated by an independent echocardiography expert who was blinded for rhythm and heart failure outcome. Peripheral blood samples were drawn immediately prior to the ablation procedure for measurements of creatinine and NT-proBNP (Roche Diagnostics, Mannheim, Germany). The study complies with the Declaration of Helsinki and was approved by the local ethics committee.

## Preprocedural management and cryoballoon ablation procedure

Preprocedural management was performed as described before.[12,13] In brief, left atrial thrombus was ruled out by transoesophageal echocardiography in all patients prior to PVI. Vitamin K antagonists (VKAs) were administered uninterruptedly to a target INR of 2.0–2.5 at the time of procedure. Patients treated with non-VKA oral anticoagulants were advised to hold their anticoagulant ≤24 h prior to the ablation procedure.

In all patients, the index ablation procedure was performed using the 2nd or 3rd generation cryoballoon (Arctic Front Advance and Arctic Front Advance ST, Medtronic, Minneapolis, MN, USA). The procedure was guided by fluoroscopy only and aside from preprocedural transoesophageal echocardiography to exclude left atrial thrombus no additional pre-procedural or intra-procedural imaging such at computed tomography, magnetic resonance imaging, or intracardiac echocardiography was applied. The cryoballoon ablation procedure was performed under conscious sedation. A 10-polar diagnostic catheter was placed in the coronary sinus. The cryoballoon was advanced to the left atrium via a 12-Fr steerable sheath (Flexcath Advance, Medtronic, Minneapolis, MN, USA) after single transseptal puncture and inflated at the pulmonary vein (PV) ostia. Instead of a guidewire a spiral mapping catheter (20 mm Achieve, Medtronic, Minneapolis, MN, USA) was advanced through the balloon inner lumen and positioned in the PV at the closest achievable proximity to the cryoballoon in order to record real-time PV potentials during PVI. Pulmonary vein occlusion was documented by injection of contrast medium. During PVI, the potentials from the PV were recorded and the ablation was performed using a time-to-isolation based protocol as described before.[12,13]

Patients with recurrent atrial tachyarrhythmia (AT) who received repeat ablation procedures were exclusively treated by irrigated-tip radiofrequency ablation guided by 3D mapping systems (Carto3, Biosense Webster, Irvine, CA, USA or NavX Ensite Velocity, St. Jude Medical, St. Paul, MN, USA) under deep sedation. Operators were encouraged to perform only PV reisolation in case of PV reconduction, however, additional left or right atrial ablation were permitted in case of documented or present focal, micro- or macroreentrant tachycardia or at the operator's discretion. If there were no reconnected PVs and no mappable focal, micro- or macroreentrant atrial tachycardias were present, additional ablation strategies at the discretion of the operator were carried out.

## Postprocedural management and clinical follow-up

Echocardiography was performed in every patient immediately after the procedure and before hospital discharge to rule out pericardial tamponade or pericardial effusion. Oral anticoagulation was resumed on the day of the ablation procedure. Patients were scheduled for outpatient clinic visits including clinical assessment, echocardiography, 12-lead electrocardiogram (ECG), and 7-day-Holter monitoring, or 24 h-Holter monitoring in case of patient's refusal for longer monitoring at 1, 3, and 6 months after the procedure and thereafter every 6 months. Echocardiographic examination was performed at the 12 months of follow-up visit. Diagnosis of HFpEF was re-evaluated according to current ESC guidelines. Resolution of HFpEF was accepted if both, *E*/*e*′ ratio and LVMI, did not meet the ESC criteria. Any documented sustained AT on 12-lead ECG or any tachyarrhythmia of ≥30 s on Holter ECG after the

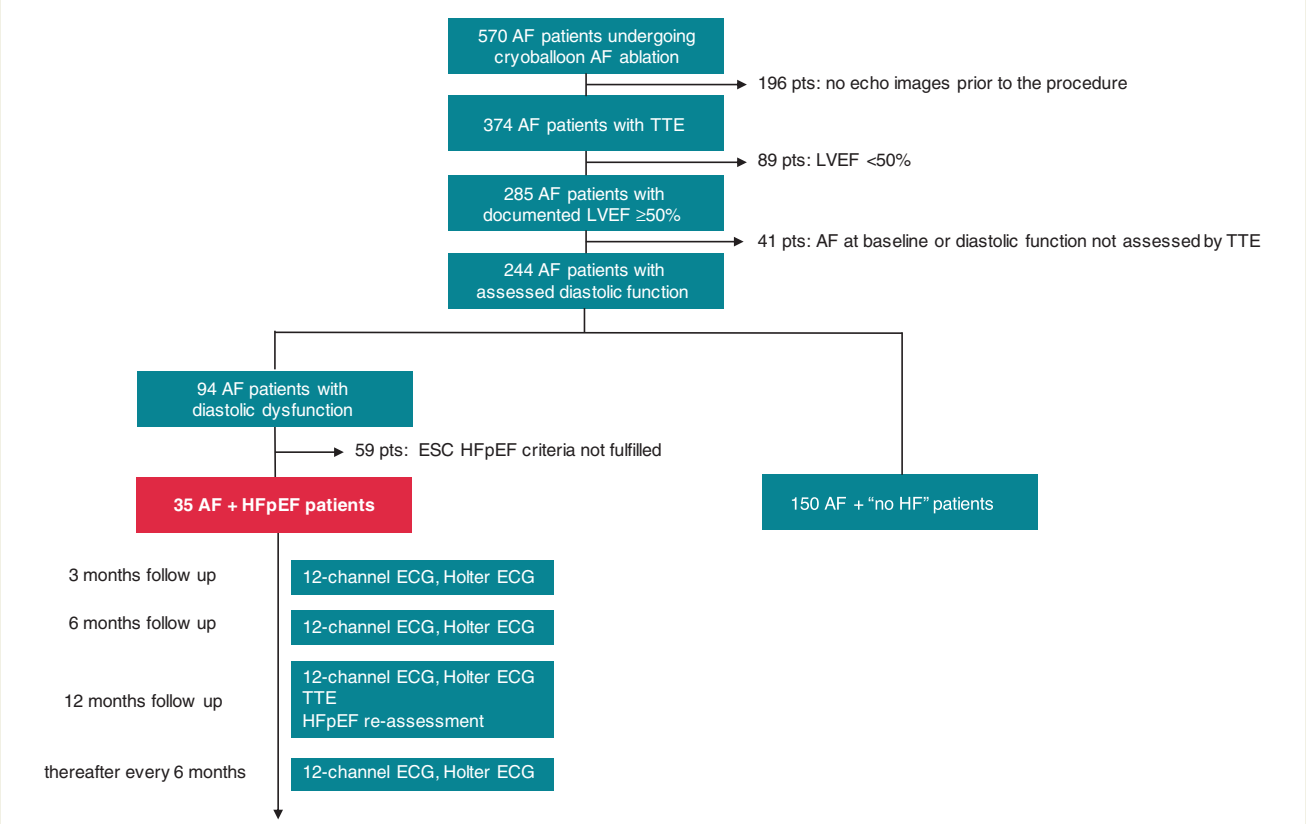


**Figure 1** Study flowchart. AF, atrial fibrillation; ECG, electrocardiogram; ESC, European Society of Cardiology; HFpEF, heart failure with preserved ejection fraction; LVEF, left ventricular ejection fraction; no HF, no heart failure; pts, patients; TTE, transthoracic echocardiography.

3 months blanking period was counted as AT/AF recurrence. Twelve months before the index PVI and 12 months after the last PVI all hospitalizations were assessed.

## Statistical analysis

Significance of differences of numeric values was calculated by *t*-test if normal distribution with equal variance was given. Numeric variables that were not normally distributed were analysed by Mann–Whitney rank-sum test. Categorical variables were analysed by $\chi^2$ test or Fisher's exact test. For identification of independent predictors of HFpEF improvement, baseline characteristics and echocardiographic parameters were analysed by univariate logistic regression. Parameters with $P \leq 0.05$ were further tested for independency by multivariate logistic regression. A *P*-value <0.05 was considered significant. The number needed to treat is the reciprocal of the relative risk reduction. Statistical assessment was performed using SPSS Statistics 25 software (Version 2017, IBM, Armonk, NY, USA). The data underlying this article will be shared on reasonable request to the corresponding author.

# Results

## Study population

We screened 570 patients with AF who received cryoballoon PVI as the first left atrial ablation procedure at our centre between 2013 and 2017 for concomitant HFpEF. Of these 196 patients did not have transthoracic echocardiography prior to the procedure at our institution. Of the remaining 374 patients 89 patients were not eligible because of reduced left ventricular ejection fraction (<50%), thus excluding a diagnosis of HFpEF. The diagnosis of HFpEF can be problematic in patients with AF because of the difficulty in separating symptoms that are due to HFpEF from those due to AF.[1] In addition, natriuretic peptide levels, that are part of the ESC diagnostic criteria for HFpEF, can also be elevated in AF patients.[1] To account for these difficulties, we aimed to only include patients with definite left ventricular diastolic dysfunction in our study. Therefore, patients had to be in sinus rhythm at baseline echocardiographic assessment and diagnostic criteria for diastolic dysfunction according to the recommendations of the ASE and the EACVI had to be fulfilled. Of the remaining 285 patients, 41 had to be excluded due to AF at baseline echocardiography or incomplete echocardiographic assessment, mainly missing *E*/*e*′ ratio. We identified 94 patients that fulfilled echocardiographic criteria of diastolic dysfunction. The remaining 150 patients served as a 'no heart failure (no HF)' control group. Finally, employing the ESC heart failure guidelines on the 94 patients with diastolic dysfunction, we identified 35 patients with a consistent diagnosis of HFpEF (*Figure 1*). Out of 35 patients, 32 (91%) met the LVMI criterion, while 13 (37%) had an initial *E*/*e*′ ratio above 13. Reasons, why patients did not fulfil HFpEF criteria were normal or missing natriuretic peptide levels, normal LVMI, and *E*/*e*′ ratio <13. Baseline characteristics of HFpEF patients in comparison to 'no HF' patients

**Table 1 Demographic and baseline characteristics of HFpEF and 'no HF' patients at baseline prior to pulmonary vein isolation**

| | HFpEF | No HF | *P*-value |
|---|---|---|---|
| Number of patients (*N*) | 35 | 150 | |
| Sex (female) | 21 (60%) | 63 (42.0%) | 0.05 |
| Age at PVI (years) | 69 ± 9 | 64 ± 12 | **0.02** |
| BMI (kg/m$^2$) | 29 ± 6 | 28 ± 5 | 0.88 |
| $CH_2ADS_2$-VASc score | 3.0 ± 1.7 | 2.5 ± 1.7 | 0.08 |
| Paroxysmal AF | 27 (77.1%) | 105 (70.0%) | 0.40 |
| Previous stroke | 2 (5.7%) | 14 (9.3%) | 0.74 |
| Hypertension | 28 (80.0%) | 115 (76.7%) | 0.67 |
| Diabetes | 5 (14.3%) | 18 (12.0%) | 0.78 |
| CAD | 13 (37.1%) | 51 (34.0%) | 0.73 |
| MI | 4 (11.4%) | 11 (7.3%) | 0.49 |
| Dyslipidaemia | 20 (57.1%) | 95 (63.3%) | 0.50 |
| CKD | 9 (25.7%) | 30 (20.0%) | 0.46 |
| ACE-I or ARB | 23 (65.7%) | 86 (57.3%) | 0.22 |
| Beta-blocker | 29 (82.9%) | 125 (83.3%) | 0.95 |
| MCRA | 4 (11.4%) | 6 (4.0%) | 0.10 |
| ASA | 6 (17.1%) | 32 (21.3%) | 0.58 |
| OAK | 29 (82.9%) | 135 (90%) | 0.23 |
| NT-proBNP (pg/mL) | 1839 ± 2114 | 379 ± 620 | **<0.001** |
| NYHA class | 2 (2–3) | 1 (1–1) | **<0.001** |

Boldface denotes significant p-values.
ACE-I, angiotensin converting enzyme inhibitors; AF, atrial fibrillation; ARB, angiotensin II receptor blockers; ASA, acetylsalicylic acid; BMI, body mass index; CAD, coronary artery disease; CKD, chronic kidney disease; HFpEF, heart failure with preserved ejection fraction; MCRA, mineralocorticoid receptor antagonist; MI, myocardial infarction; no HF, no heart failure; NT-proBNP, N-terminal pro B-type natriuretic peptide; NYHA, New York Heart Association; OAK, oral anticoagulants; PVI, pulmonary vein isolation.

are shown in *Table 1*. Patients in the HFpEF group were significantly older, had more heart failure-related symptoms and higher NT-proBNP levels.

## Procedural data

In the 35 HFpEF patients, we identified a total of 138 PVs. All PV's (100%) were isolated successfully with the cryoballoon, without additional touch-up ablations. No additional ablations such as left atrial lines, cavotricuspid isthmus ablation, or substrate modification were applied during the index procedure in any patient. No major complications such as pericardial tamponades or pericardial effusions, no persistent phrenic nerve palsies, no strokes or systemic embolisms, and no fatalities occurred during the procedure and throughout consecutive follow-up. In one case, transient phrenic nerve palsy was present after the ablation procedure, but resolved until the 3 months of follow-up visit. Further procedural data are shown in Supplementary material online, *Table S1*.

## Arrhythmia recurrence

Arrhythmia recurrence was compared between HFpEF patients and our 'no HF' control patients. Mean duration of clinical follow-up was 29 ± 20 months. After a blanking period of 3 months following ablation, single procedure freedom from any AT recurrence >30 s off Class I/III antiarrhythmic drugs (AADs) after 1 year was 80% in the HFpEF and 84% in the 'no HF' group. Freedom from recurrence after 2 years was 63% in the HFpEF and 81% in the 'no HF' group, and 57% in the HFpEF and 79% in the 'no HF' group after 3 years. Recurrence occurred significantly more often in the HFpEF than in the 'no HF' group (log-rank $P = 0.049$; *Figure 2*).

## Heart failure

To evaluate the impact of cryoballoon PVI on heart failure symptoms, we compared HFpEF patients' NYHA class before and 12 months after the index procedure. Initially, all patients suffered from heart failure symptoms. Eighteen patients (51.4%) were in NYHA Class II, 13 patients (37.1%) were in NYHA Class III, and 4 patients (11.4%) were in ambulatory NYHA Class IV before the index procedure. In contrast, 12 months after PVI the majority (20 patients, 57.1%) were free from any heart failure symptoms (NYHA Class I), 9 patients (25.7%) were in NYHA Class II, 4 patients (11.4%) were in NYHA Class III, and only 2 patients (5.7%) were in ambulatory NYHA Class IV. On average NYHA class improved from 2.6 ± 0.7 to 1.7 ± 0.9 ($P < 0.001$, *Figure 3A*). Mean NT-proBNP levels decreased from 1840 ± 2115 pg/mL prior to the procedure to 824 ± 1095 pg/mL 12 months after the procedure ($P = 0.01$). Remarkably, reassessment of HFpEF criteria after 12 months showed complete resolution of HFpEF in 15 patients (42.9%; $P < 0.001$), resulting in a number needed to treat for PVI to resolve HFpEF of 2.3 patients (*Figure 3B*).

## Reverse remodelling

In order to analyse the impact of PVI on echocardiographic parameters of left ventricular reverse remodelling in HFpEF patients with AF, we assessed diastolic interventricular septal thickness, diastolic posterior wall thickness, *E* and *e'* velocity, *E/e'* ratio, *E/A* ratio, and LVMI at baseline and 12 months after the index procedure. *E/e'* ratio decreased from 11.94 to 10.73. However, this reduction was only a non-significant trend ($P = 0.09$). In contrast, assessment of LVMI showed a significant decrease from 128.1 ± 25.2 g/m$^2$ to 108.8 ± 26.4 g/m$^2$ ($P < 0.001$). In addition, intraventricular diastolic septal thickness declined from 11.7 ± 1.7 mm to 11.0 ± 1.7 mm ($P = 0.04$). Detailed results are shown in *Table 2*.

## Predictors of recovery from heart failure with preserved ejection fraction

Next, to identify independent predictors of HFpEF resolution, we performed uni- as well as multivariate logistic regression analysis of several baseline characteristics and echocardiographic parameters. In univariate logistic regression, we identified freedom from atrial arrhythmia recurrence [95% confidence interval (CI) 2.56–88.99, $P = 0.003$] and left atrial diameter at baseline (95% CI 1.03–1.33, $P = 0.04$) as predictors of HFpEF resolution. However, after multivariate analysis, only freedom from atrial arrhythmia recurrence remained independently and significantly associated with resolution of HFpEF (95% CI 1.70–75.84, $P = 0.01$; *Table 3*).

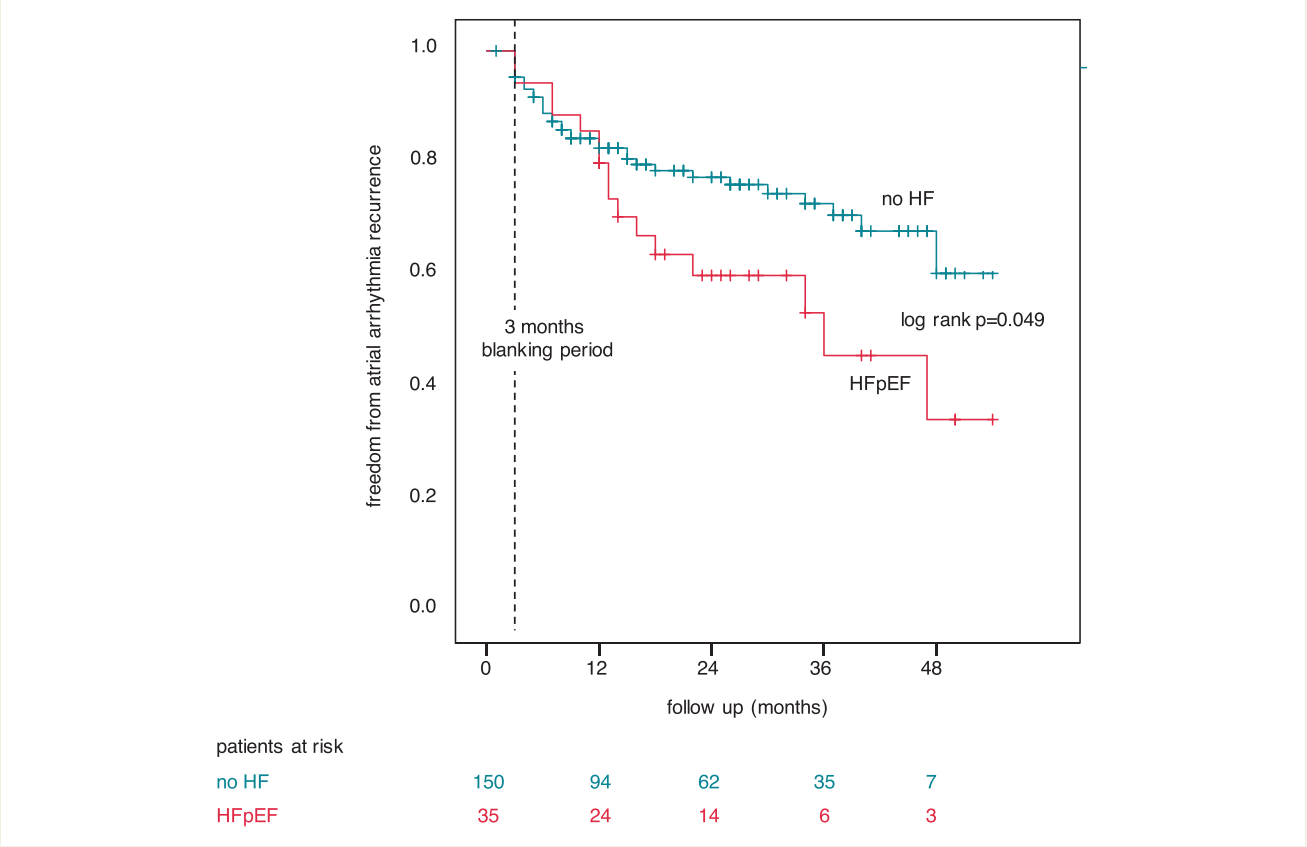


**Figure 2** Kaplan–Meier curves for freedom from atrial tachyarrhythmia recurrence. HFpEF, heart failure with preserved ejection fraction; no HF, no heart failure.

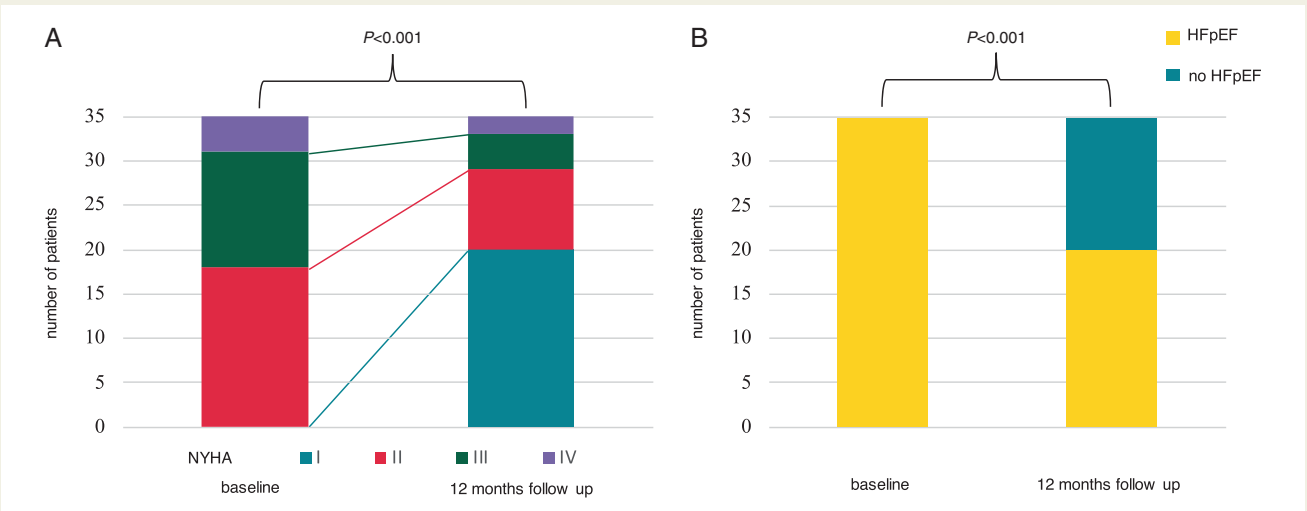


**Figure 3** Symptoms measured by NYHA class and reassessment of HFpEF criteria before and after PVI in HFpEF patients. (*A*) Patients show a significant reduction in heart failure symptoms after PVI. (*B*) Fifteen out of 35 patients (42.9%) show resolution of criteria for HFpEF diagnosis. HFpEF, heart failure with preserved ejection fraction; no HF, no heart failure; NYHA, New York Heart Association; PVI, pulmonary vein isolation.

**Table 2 Echocardiographic Parameters and LVMI before and after PVI**

| | Pre-PVI | Post-PVI | *P*-value |
|---|---|---|---|
| IVSTd (mm) | 11.7 ± 1.7 | 11.0 ± 1.7 | **0.03** |
| PWTd (mm) | 11.4 ± 1.6 | 10.9 ± 2.7 | 0.27 |
| *E*/e′ ratio | 11.9 ± 3.2 | 10.7 ± 4.2 | 0.09 |
| *E*/*A* ratio | 1.21 ± 1.00 | 1.21 ± 0.68 | 0.76 |
| e′ (cm/s) | 8.1 ± 2.9 | 8.1 ± 2.3 | 0.99 |
| *E* (cm/s) | 90 ± 30 | 82 ± 28 | 0.11 |
| LVMI (g/m$^2$) | 128 ± 25 | 109 ± 26 | **<0.001** |
| LVEF (%) | 64 ± 8 | 66 ± 8 | 0.26 |
| LA diameter (mm) | 45 ± 6 | 46 ± 7 | 0.43 |

Boldface denotes significant p-values.
IVSTd, interventricular diastolic septal thickness; LA diameter, left atrial diameter; LVMI, left ventricular mass index; PVI, pulmonary vein isolation; PWTd, posterior diastolic wall thickness.

**Table 3 Identification of predictors of HFpEF improvement**

| Variables | Univariate analysis | | | Multivariate analysis | | |
|---|---|---|---|---|---|---|
| | HR | 95% CI | *P*-value | HR | 95% CI | *P*-value |
| Sex | 3.5 | 0.87–14.30 | 0.08 | | | |
| Age | 1.06 | 0.98–1.06 | 0.15 | | | |
| BMI | 1.03 | 0.91–1.16 | 0.67 | | | |
| No AT/AF recurrence | 15.17 | 2.56–88.99 | **0.003** | 11.37 | 1.70-75.84 | **0.01** |
| Baseline LVEF | 0.91 | 0.83–1.01 | 0.06 | | | |
| Baseline LA diameter | 1.16 | 1.03–1.33 | **0.04** | 1.15 | 0.98-1.35 | 0.09 |
| Hypertension | 1.00 | 0.19–5.33 | 1.00 | | | |
| CAD | 0.81 | 0.20–3.22 | 0.76 | | | |
| Dyslipidaemia | 0.69 | 0.34–5.07 | 0.69 | | | |
| Paroxysmal AF | 2.79 | 0.48–16.35 | 0.26 | | | |

Boldface denotes significant p-values.
AF, atrial fibrillation; AT/AF, atrial tachyarrhythmia/atrial fibrillation; BMI, body mass index; CAD, coronary artery disease; CI, confidence interval; HFpEF, heart failure with preserved ejection fraction; HR, hazard ratio; LA, left atrial; LVEF, left ventricular ejection fraction.

## Reassessment of heart failure with preserved ejection fraction after multiple atrial fibrillation ablation procedures

Suspecting that patients profit from AF ablation only if sinus rhythm can be maintained, we assessed HFpEF criteria in patients with recurrence of AT who underwent one or more redo ablation procedures (*Figure 4*). Out of 35 HFpEF patients in whom PVI with the cryoballoon was performed, 16 patients (45.7%) experienced AT recurrence. Out of these, 11 patients (62.5%) returned to our EP lab for redo AF ablation. All redo procedures were conducted with 3D mapping systems and irrigated radiofrequency ablation. Eight patients (72.7%) showed reconduction of one or more PVs and received re-isolation of reconnected PVs only. Two of the patients without PV reconduction underwent substrate modification, while the remaining patient had sustained left atrial focal tachycardia which was successfully ablated. Four patients (36%) received a second redo procedure. Overall, the 35 HFpEF patients underwent an average of 1.4 ± 0.7 ablation procedures. Mean time from the index procedure to the second ablation procedure was 16 ± 14 months. Total freedom from AT recurrence after multiple procedures was 63%. Resolution of HFpEF was observed in 18 patients (51%), 16 out of 22 (73%) patients without atrial arrhythmia recurrence and 2 out of 13 (15%) patients with atrial arrhythmia recurrence ($P = 0.002$). All HFpEF diagnosis criteria improved significantly after 12 months of follow-up in the absence of AT/AF recurrence (Supplementary material online, *Tables S2* and *S3*).

## Restoration of sinus rhythm by pulmonary vein isolation reduces hospitalizations in heart failure with preserved ejection fraction patients

Mean hospitalizations per patient in all HFpEF patients declined from 1.2 ± 1.3 during the 12 months before the index procedure to 0.3 ± 0.7 during 12 months after the index procedure ($P < 0.001$). To assess if maintenance of sinus rhythm followed by HFpEF resolution drives reduction of hospitalizations, we compared hospitalizations of HFpEF patients 12 months before the index procedure and 12 months after the last ablation procedure. All-cause hospitalization rate of patients with resolved HFpEF decreased significantly from 69% to 25% (11/16 patients before the first procedure vs. 4/16 patients after the last procedure; $P = 0.03$), while hospitalization rate of patients with sustained HFpEF remained high (pre: 5/6 patients, 83%; post: 5/6 patients, 83%; $P = 1$; *Figure 5A*). Similarly, cardiovascular hospitalization rate of patients with resolved HFpEF, showed a trend towards a reduction after the procedure (pre: 63%, post: 25%; $P = 0.07$), while there was no change in patients with sustained HFpEF (pre: 50%, post: 33%; $P = 1$; *Figure 5B*). Mean hospitalizations per patient also decreased from 0.9 ± 0.8 before the procedure to 0.3 ± 0.4 12 months after the procedure in patients with HFpEF resolution ($P = 0.001$), while patients with sustained HFpEF remained similar before and after the procedure (pre: 0.8 ± 0.4, post: 1.0 ± 0.6, $P = 0.363$; *Figure 5C*). Mean cardiovascular hospitalizations per patient also showed a significant decrease after the procedure in patients with resolution of HFpEF (pre: 0.8 ± 0.7, post: 0.3 ± 0.4, $P = 0.006$; *Figure 5D*).

# Discussion

Heart failure and AF often coexist leading to increased morbidity and mortality.[2,5] Catheter ablation of AF has been shown recently to decrease AF burden leading to reduction of heart failure hospitalizations and mortality in HFrEF.[3]

In contrast to HFrEF, treatment options for HFpEF are very limited. Symptoms can be ameliorated by diuretics, however, a prognostic benefit could not yet be established for any medical therapy.[11] AF is even more commonly accompanied by HFpEF than by HFrEF.[2] AF aggravates symptoms and deteriorates prognosis of HFpEF.[14]

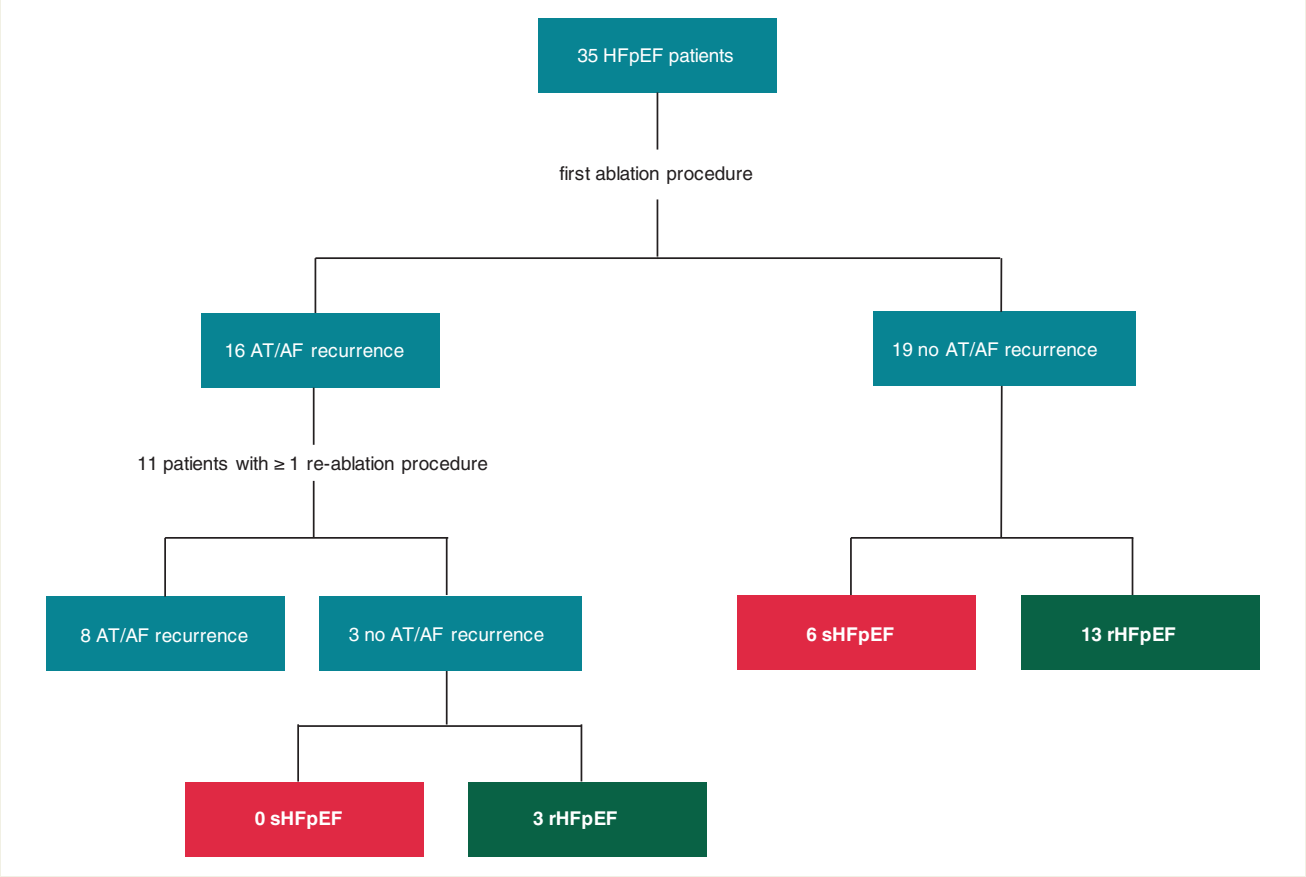


**Figure 4** Flowchart and results of ablation procedures in HFpEF patients. AT/AF, atrial tachyarrhythmia/atrial fibrillation; HFpEF, heart failure with preserved ejection fraction; rHFpEF, resolved heart failure with preserved ejection fraction; sHFpEF, sustained heart failure with preserved ejection fraction.

Diastolic dysfunction, a hallmark of HFpEF, leads to intolerance of tachycardia, explaining why AF has such detrimental effects in these patients.[15] However, AF is not only fostered by HFpEF but also vice versa and there is an unmet need for effective treatment strategies.[6,16] Data on the impact of AF ablation in HFpEF patients is still sparse, and the effect of cryoballoon ablation on HFpEF has not been reported yet.

## Efficacy and safety of cryoballoon ablation of atrial fibrillation in heart failure with preserved ejection fraction patients

Previous studies have shown that radiofrequency ablation of AF can be performed safely in HFpEF patients.[8] To the best of our knowledge, this is the first study systematically analysing cryoballoon PVI in HFpEF patients. Aside from one transient phrenic nerve palsy with complete resolution after 3 months, no major complications occurred in any patient, indicating that—although the number of patients is still limited—cryoballoon PVI can be considered safe in patients with HFpEF.

Catheter ablation for AF has been established as a successful treatment for both paroxysmal and persistent AF, but there is only very limited data on the efficacy in HFpEF patients. A study with 74 patients evaluated the effect of radiofrequency ablation of AF in HFpEF patients and found an overall freedom from atrial arrhythmia recurrence in 72% of patients after a follow-up of 34 ± 16 months after multiple procedures and including long-term Class I or Class III AAD therapy, while only 27% remained free from AF after a single ablation procedure off AAD.[8] The efficacy of cryoballoon PVI-only in HFpEF patients has not been reported previously. We found that single procedure success of cryoballoon PVI-only was 80% after 1 year and 63% after 2 years. However, the higher success rates in our study might be explainable at least partly by a higher proportion of patients with paroxysmal AF (32% vs. 77%). Compared to patients without heart failure, AT/AF recurrence occurs more commonly in HFpEF patients. It should be stressed though, that risk factors for HFpEF such as increased left atrial diameter, female sex and arterial hypertension are also known conditions associated with increased recurrence rates of AF after catheter ablation.

## Impact of cryoballoon ablation on heart failure with preserved ejection fraction

Currently, there is no consensus about treatment of AF in HFpEF patients in both European and American guidelines.[1,11,15,17] Drug-

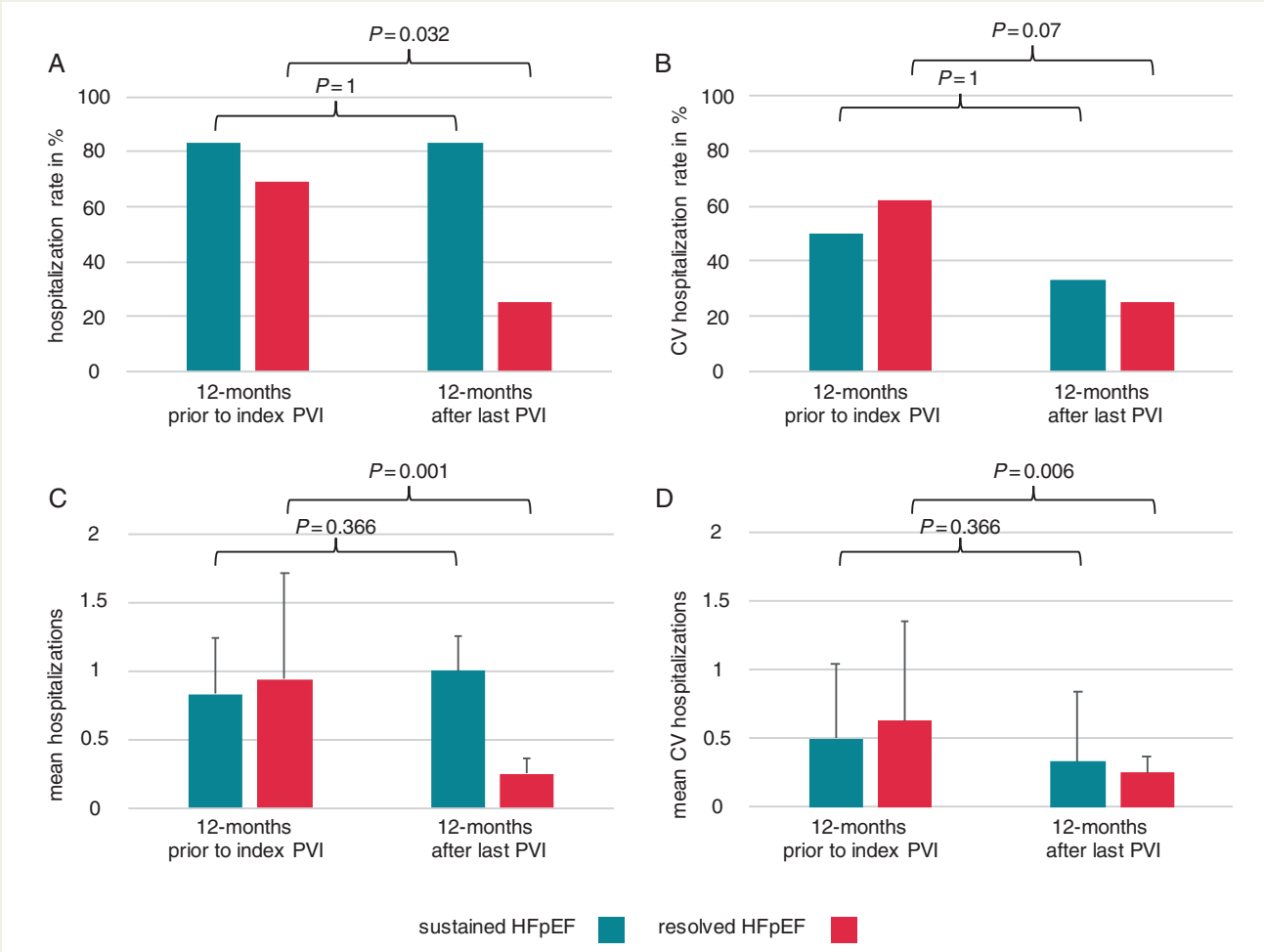


**Figure 5** Hospitalizations 12 months before the index procedure and 12 months after the last ablation procedure in sustained HFpEF and resolved HFpEF patients. (*A*) All-cause hospitalization rate (fraction of patients that had been hospitalized at least once) 12 months before and 12 months after the procedure. (*B*) CV hospitalization rate. (*C*) Mean all-cause hospitalizations per patient. (*D*) Mean CV hospitalizations per patient. CV, cardiovascular; HFpEF, heart failure with preserved ejection fraction; PVI, pulmonary vein isolation.

induced rhythm control seems to be of limited efficacy in HFpEF, moreover harbouring the risk of side effects.[18,19] Evaluating symptomatic improvement of HFpEF in patients suffering from concomitant AF can be challenging, because separation of symptoms of both conditions is difficult.[1] Indeed, we found improvement of NYHA class 12 months after ablation, however, we cannot exclude that this improvement is actually caused by freedom from arrhythmia rather than improvement of HFpEF. For this reason, we also investigated objective HFpEF criteria 12 months after AF ablation. In our study, single procedure cryoballoon PVI resulted in left ventricular reverse remodelling. Intraventricular septal thickness and LVMI significantly improved after the ablation procedure, while *E*/*e*′ ratio showed a non-significant trend towards improvement. Moreover, almost half of the patients had resolution of HFpEF by ESC diagnostic criteria 12 months after the index procedure, resulting in a number needed to treat of 2.3 patients. Analysis of factors influencing regression of HFpEF by multivariate logistic regression identified absence of AT recurrence as the only significant predictor of HFpEF resolution. Therefore, successful AF ablation might evolve as an important therapeutic and disease modifying approach in HFpEF patients. This is also supported by our finding that hospitalization rate decreases in these patients after successful AF ablation.

## Limitations

This is a retrospective, single-centre cohort study, evaluating the effect of AF ablation on HFpEF regarding clinical outcome as well as echocardiographic parameters of left ventricular reverse remodelling. Randomized controlled trials of AF ablation vs. medical therapy are warranted.

# Conclusion

Pulmonary vein isolation in HFpEF patients with concomitant AF is a promising therapeutic option leading to reduction of symptoms, decrease of hospitalizations, and induction of left ventricular reverse remodelling.

# Supplementary material

Supplementary material is available at *Europace* online.

## Acknowledgements

The authors thank Beate Polte, Sylvia Dippmann, Andrea Igel, and Hieronyma Daiber for their excellent support and Sophie Mehner, Romy Bonzheim, and Annika Bacher for their outstanding technical assistance.

## Funding

This work was supported by the Clinician Scientist Program of Ulm University (to A.P.) and was supported by the Hertha-Nathorff-program of Ulm University (to K.W.).

**Conflict of interest:** none declared.

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