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ORIGINAL RESEARCH

Cryoballoon Ablation for the Treatment of Atrial Fibrillation in Patients With Concomitant Heart Failure and Either Reduced or Preserved Left Ventricular Ejection Fraction: Results From the Cryo AF Global Registry

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BACKGROUND: Heart failure (HF) and atrial fibrillation (AF) often coexist; yet, outcomes of ablation in patients with AF and concomitant HF are limited. This analysis assessed outcomes of cryoablation in patients with AF and HF.

METHODS AND RESULTS: The Cryo AF Global Registry is a prospective, multicenter registry of patients with AF who were treated with cryoballoon ablation according to routine practice at 56 sites in 26 countries. Patients with baseline New York Heart Association class I to III (HF cohort) were compared with patients without HF. Freedom from atrial arrhythmia recurrence ≥30 seconds, safety, and health care utilization over 12-month follow-up were analyzed. A total of 1303 patients (318 HF) were included. Patients with HF commonly had preserved left ventricular ejection fraction (81.6%), were more often women (45.6% versus 33.6%) with persistent AF (25.8% versus 14.3%), and had a larger left atrial diameter (4.4±0.9 versus 4.0±0.7 cm). Serious procedure-related complications occurred in 4.1% of patients with HF and 2.6% of patients without HF (P=0.188). Freedom from atrial arrhythmia recurrence was not different between cohorts with either paroxysmal AF (84.2% [95% CI, 78.6–88.4] versus 86.8% [95% CI, 84.2–89.0]) or persistent AF (69.6% [95% CI, 58.1–78.5] versus 71.8% [95% CI, 63.2–78.7]) (P=0.319). After ablation, a reduction in AF-related symptoms and antiarrhythmic drug use was observed in both cohorts (HF and no-HF), and freedom from repeat ablation was not different between cohorts. Persistent AF and HF predicted a post-ablation cardiovascular rehospitalization (P=0.032 and P=0.001, respectively).

CONCLUSIONS: Cryoablation to treat patients with AF is similarly effective at 12 months in patients with and without HF.

REGISTRATION: URL: https://www.clinicaltrials.gov; Unique Identifier: NCT02752737.

Key Words: atrial fibrillation ■ catheter ablation ■ heart failure

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CLINICAL PERSPECTIVE

What Is New?

- Evidence on the outcome of cryoballoon ablation in patients with atrial fibrillation (AF) who have concomitant heart failure (HF) is limited. In the Cryo AF Global Registry, 318 (24%) patients had HF with concomitant AF and were treated with cryoablation in a standard-of-care practice.
- This analysis reconfirmed that cryoballoon ablation for the treatment of AF is similarly safe and effective in patients with AF with and without concomitant HF, despite patients with HF having higher rates of comorbidities at baseline.
- The population in this analysis was primarily composed of patients who had HF with preserved ejection fraction, and 30% of patients were treated with first-line cryoablation.

What Are the Clinical Implications?

- These findings add new insights in the management of patients with AF who have HF in a standard-of-care practice.
- Future controlled trials are needed to evaluate cryoablation as a treatment for AF in patients with concomitant HF in a relative early stage of AF disease.

Nonstandard Abbreviations and Acronyms

AAD	antiarrhythmic drug
AE	adverse event
AFL	atrial flutter
AT	atrial tachycardia
HFpEF	heart failure with preserved ejection fraction
HFrEF	heart failure with reduced ejection fraction
MACE	major adverse cardiovascular events
NYHA	New York Heart Association
PAF	paroxysmal atrial fibrillation
PsAF	persistent atrial fibrillation
PV	pulmonary vein

Atrial fibrillation (AF) and heart failure (HF) often comanifest.[1] AF and HF independently increase the risk of hospitalization, morbidity, mortality, and symptoms that reduce quality of life (QOL) and the risk of deterioration of health is intensified by the coexistence of these conditions.[1–3] The reciprocal relationship between HF and AF has challenged the treatment in these patients.

Long-term pharmacological rhythm control in patients with AF and HF has not markedly improved mortality and rehospitalization outcomes.[4,5] Catheter ablation to achieve pulmonary vein (PV) isolation is the cornerstone treatment for patients with AF, and it has been identified as a reasonable treatment for selected patients who have AF with concomitant HF in recently updated guidelines.[6,7] The randomized CASTLE-AF (Catheter Ablation Versus Standard Conventional Therapy in Patients With Left Ventricular Dysfunction and Atrial Fibrillation) trial identified an improvement in mortality and HF-related rehospitalization after radiofrequency ablation for the treatment of AF in a highly selected cohort of patients with HF and reduced left ventricular ejection fraction (LVEF).[8] Subsequently, small evaluations of cryoballoon ablation for the treatment of patients with AF and HF have been reported.[9–11] However, clinical reports of cryoablation in a large cohort of patients with AF and HF who have either reduced or preserved LVEF (HF with reduced ejection fraction [HFrEF] and HF with preserved ejection fraction [HFpEF], respectively) are limited. The aim of this analysis was to evaluate the safety, efficacy, and health care utilization after cryoablation for the treatment of patients with AF and HF in a global, postmarket setting.

METHODS

The data, analytic methods, and study materials will not be made available to other researchers. Specifically, patient data privacy within the Cryo AF Global Registry does not allow nor consent to data sharing with outside parties.

Study Design

The Cryo AF Global Registry (ClinicalTrials.gov registration: NCT02752737) is an ongoing, prospective, postmarket data collection of AF ablation procedures and outcomes conducted with Medtronic ablation products. Data for this analysis were collected from cryoballoon ablation procedures conducted at 56 centers by 139 investigators in 26 countries around the world (Table S1). Data collection milestones, data quality, clinical questions, data analysis, and potential publications for the registry are overseen by a global steering committee of international physicians, and the registry is sponsored by Medtronic, Inc. Data collection adhered to Good Clinical Practice guidelines and the principles outlined in the Declaration of Helsinki. This study was approved by each site's institutional review board and local ethics committees, and each patient provided written informed consent for participation in

the study. The objective of this analysis was to assess patient characteristics, outcomes of cryoballoon ablation, and health care utilization in patients with HF with concomitant AF.

Patient Population

All patients aged 18 years and older (or minimum age per local regulations) with a planned cryoballoon catheter ablation were eligible for inclusion. Patients were not excluded from the registry for any preexisting baseline characteristics, including medical history. For the current analysis, all consecutively enrolled patients who completed the required 12-month follow-up after a cryoablation procedure through January 2020 were included, except: (1) patients diagnosed with long-standing persistent AF (continuous AF >12 months) and/or (2) patients treated with a prior cardiac ablation for the treatment of an atrial arrhythmia. During the baseline visit, each center identified patients as having HF and the New York Heart Association (NYHA) class in accordance to the 2016 European Society of Cardiology AF management guidelines (as the presence of left ventricular systolic or diastolic dysfunction).[12] Moreover, the cardiovascular history of the patient was analyzed in order to report previous cardioembolic events, HF, and cardiovascular disease. Patients with an NYHA classification of I to IV at baseline were included in the HF cohort. Patients who were reported to have no HF at baseline comprised the no-HF group. HFrEF was defined as HF with LVEF ≤40%, HFpEF was defined as HF with LVEF ≥50%, and HF midrange LVEF was defined as HF with LVEF between 40% and 50%. Patients with AF episodes of AF <7 days in duration were classified with paroxysmal AF (PAF) and patients with episodes of ≥7 days and ≤12 months were classified with persistent AF (PsAF).

Cryoballoon Ablation Procedure

The cryoablation procedure was performed according to each local center's standard-of-care. Typical procedural techniques are outlined below and have been previously described.[13] After transseptal puncture, a dedicated 15-F outer diameter steerable sheath (FlexCath or FlexCath Advance Steerable Sheath; Medtronic) was used to guide a 23- or 28-mm cryoballoon ablation catheter (Arctic Front Advance; Arctic Front Advance Pro; Medtronic, Inc.) into the left atrium. A J-tip wire or dedicated inner-lumen octopolar/decapolar circular mapping catheter (Achieve or Achieve Advance; Medtronic, Inc.) was used to position the sheath and cryoballoon catheter at the antrum of the targeted PVs. The number and duration of cryoapplications for each PV and any non-PV ablation adjunctive to PV isolation were determined by physician. PV isolation was demonstrated by entrance and/or exit block following the ablation. Phrenic nerve monitoring was recommended during right-sided cryoablation by pacing with a diagnostic catheter at the level of the right subclavian vein. The cryoapplication was terminated immediately upon detection of reduced diaphragmatic function. Adjunctive imaging, monitoring, and/or focal catheter ablation tools were used at the operator's discretion. Intraprocedural testing of acute PV isolation, periprocedural anticoagulation, and antiarrhythmic drug (AAD) prescription was determined by physician. Patients were discharged from the hospital according to standard-of-care procedures.

Patient Follow-Up

Patients were followed according to each site's standard-of-care protocols by telephone visits and/or in-person visits. Arrhythmia monitoring was not protocol required and was conducted according to the center's standard-of-care practice when completed, inclusive of but not limited to the following methods: Holter monitoring, ECG, transtelephonic monitoring, implantable cardiac monitor, pacemaker, and/or implantable cardioverter-defibrillator. Patients were asked to provide any other Holter or ECG results since the previous visit. Patients were required by protocol to have an annual follow-up visit 12 months after the cryoablation.

End Points

The primary end point of this analysis was the 12-month freedom from a ≥30-second recurrence of AF/atrial flutter (AFL)/atrial tachycardia (AT) following a

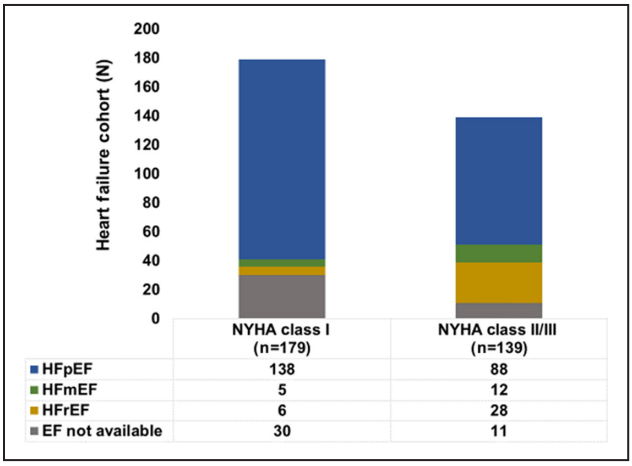

Figure 1. Baseline characteristics of the heart failure (HF) cohort.
The HF cohort stratified by New York Heart Association (NYHA) class status and left ventricular ejection fraction (LVEF). Patients had an NYHA class of I to III, and most patients had preserved LVEF. EF indicates ejection fraction; HFmEF, HF with mild reduced ejection fraction; HFpEF, heart failure with preserved ejection fraction; and HFrEF, heart failure with reduced ejection fraction.

90-day blanking period during which patients were managed per standard-of-care. The primary safety end point was the serious procedure-related adverse event (AE) rate. Serious procedure-related AEs were classified by physician and included all events related to the ablation procedure that led to death or a serious deterioration of health. Arrhythmias classified by the physician as a serious adverse event related to the procedure but with arrhythmia onset postdischarge were not included in the primary safety end point for this analysis. All patients were followed until AE resolution, no further actions were planned, or the patient exited the study. QOL was measured by the 3-level EuroQol 5-dimensional questionnaire (EQ-5D-3L) (score of 1 represents maximal QOL) at baseline and 12-month follow-up. The following ancillary objectives were also evaluated in the HF and no-HF cohorts: (1) baseline patient demographics; (2) procedural outcomes; (3) AAD usage at postablation discharge and 12 months; (4) change in AF-related symptoms between baseline and 12 months; and (5) freedom from repeat ablation, all-cause rehospitalization, and cardiovascular-related rehospitalization at 12 months after the cryoballoon ablation procedure. Rehospitalization events were defined as nonprocedure-related hospitalizations after the cryoablation procedure.

Statistical Analysis

Kaplan-Meier methods were used to estimate 12-month freedom from atrial arrhythmia recurrence, freedom from repeat ablation, and freedom from all-cause

Table 1. Baseline Patient Characteristics

Patient characteristics	HF (n=318)	No HF (n=985)	*P* value**
Women, n (%)	145 (45.6)	331 (33.6)	<0.001
Age, mean±SD, y	64±11	60±12	<0.001
Body mass index, mean±SD, kg/m^2*	28±5	27±5	0.002
CHA_2DS_2-VASc score, mean±SD	3.4±1.6	1.6±1.4	<0.001
Paroxysmal AF, n (%)	236 (74.2)	844 (85.7)	<0.001
Years diagnosed with AF†			
Mean±SD	3.3±4.4	3.3±5.1	0.954
Median (IQR)	1.5 (0.4–4.3)	1.2 (0.4–4.3)	
History of AFT, n (%)	8 (2.5)	50 (5.1)	0.060
History of AT, n (%)	3 (0.9)	12 (1.2)	1.000
Left atrial diameter, mean±SD, cm‡	4.4±0.9	4.0±0.7	<0.001
LVEF, mean±SD, %§	58±13	62±7	<0.001
Preserved LVEF ≥50%, n (%)	226 (81.6)	816 (97.5)	
Midrange LVEF 40%–50%, n (%)	17 (6.1)	15 (1.8)	
Reduced LVEF ≤40%, n (%)	34 (12.3)	6 (0.7)	
No. of failed AADs, mean±SD	0.8±0.7	0.8±0.7	0.800
First-line cryoablation, n (%)¶	89 (28.0)	306 (31.1)	0.326
Hypertension, n (%)	216 (67.9)	484 (49.1)	<0.001
Prior cardiac device implant, n (%)#	29 (9.1)	33 (3.4)	<0.001
Prior myocardial infarction, n (%)	12 (3.8)	17 (1.7)	0.046
Prior stroke/TIA, n (%)	24 (7.5)	56 (5.7)	0.229
Coronary artery disease, n (%)	46 (14.5)	60 (6.1)	<0.001
Diabetes, n (%)	54 (17.0)	100 (10.2)	0.002
Sleep apnea, n (%)	14 (4.4)	31 (3.1)	0.291

AFT indicates atrial flutter; AT, atrial tachycardia, CHA_2DS_2-VASc, congestive heart failure, hypertension, age (2 points); diabetes, previous stroke/transient ischemic attack (2 points), vascular disease; IQR, interquartile range; and TIA, transient ischemic attack.

*A total of 1299 patients with body mass index reported; 316 with heart failure (HF) and 983 without HF.

†A total of 1254 patients with atrial fibrillation (AF) diagnosis date reported; 312 with HF and 942 without HF.

‡A total of 862 patients with left atrial diameter reported; 277 with HF and 837 without HF.

§A total of 1114 patients with left ventricular ejection fraction (LVEF) reported; 277 with HF and 837 without HF.

¶No prior failed antiarrhythmic drug (AAD) or not taking an AAD at enrollment.

#Prior cardiac device includes implantable pulse generator, implantable cardioverter-defibrillator, cardiac resynchronization therapy pacemaker, cardiac resynchronization therapy defibrillator, and insertable cardiac monitor.

**Statistical tests comparing the HF cohort versus the no-HF cohort. Continuous variables compared with t test and binary variables compared with exact test.

and cardiovascular-related rehospitalization. Standard error was calculated with the Greenwood formula. Cox regression models were utilized to assess the hazard of AF/AFL/AT recurrence, repeat ablation, all-cause rehospitalization, and cardiovascular-related rehospitalization between HF and no-HF cohorts. Separate regression models were utilized for each end point. Because of the strong association of baseline AF classification with efficacy outcomes postablation, the imbalance in baseline AF classification was controlled for by including baseline AF type (PAF versus PsAF) as a covariate in all Cox regression models. Procedural complication rate was compared between cohorts with exact methods, and McNemar test was used to compare change in arrhythmia-related symptoms from baseline to 12 months. *P* values of <0.050 were considered significant. Statistical analyses were completed using SAS software version 9.4 (SAS Institute Inc).

RESULTS

Patient and Procedural Characteristics

Of the 1303 patients who completed 12-month follow-up during this analysis window, 985 did not have HF and 318 had HF. The HF cohort was characterized by an NYHA class of I to III and included patients with HFpEF, HF with mild reduced ejection fraction, and HFrEF (Figure 1). Baseline characteristics are presented in Table 1. Compared with patients without HF, those with HF were more often women (45.6% versus 33.6%), older (64±11 versus 60±12), with PsAF (25.8% versus 14.3%), and larger left atrial diameters (4.4±9 versus 4.0±7 cm) (all *P*<0.010). Patients with HF also had higher rates of hypertension (67.0% versus 49.1%), diabetes (17.0% versus 10.2%), prior myocardial infarction (3.8% versus 1.7%), and history of coronary artery disease (14.5% versus 6.1%) (all *P*<0.050). Procedural characteristics are detailed in Table 2. See Table S2 for baseline differences between no-HF, HF NYHA class I, and HF NYHA class II or III groups.

Procedure-Related Safety

The primary safety end point, serious cryoballoon procedure–related AEs, occurred in 13 (4.1%) patients with HF and 26 (2.6%) patients without HF (*P*=0.188; Table 3). Of those events, 1 (0.3%) in patients with HF and 4 (0.4%) in patients without HF were attributable to supraventricular arrhythmia recurrence onset during the index procedure hospitalization. Of the 8 serious phrenic nerve injuries observed, all but 1 asymptomatic

Table 2. Procedural Characteristics

Procedural characteristics	HF (n=318)	No HF (n=985)	*P* value[#]
Total procedure time, mean±SD, m[*]	85±32	78±34	0.001
Left atrial dwell time, mean±SD, m[†]	55±23	50±23	0.001
Total fluoroscopy time, mean±SD, m[‡]	19±18	16±15	0.002
Total cryoapplication duration, mean±SD, m[§]	19±6	18±7	0.001
No. of applications per vein, mean±SD	1.6±0.9	1.4±0.8	<0.001[**]
Duration of cryoapplication, mean±SD, s	189±51	196±52	0.012[**]
Cryoballoon nadir temperature, °C	−47±8	−48±7	0.112[**]
Sedation method, n (%)			<0.001
General anesthesia	79 (24.8)	378 (38.4)	
Nongeneral anesthesia	239 (75.2)	606 (61.5)	
Preprocedural imaging (CT and/or MRI)	47 (14.8)	187 (19.0)	0.093
PV ablation acute success, n (%)[¶]	303 (95.3)	930 (94.4)	0.667
PV isolation touch-up with focal cryocatheter, n (%)	4 (1.3)	0 (0.0)	0.003
PV isolation touch-up with focal radiofrequency catheter, n (%)	6 (1.9)	20 (2.0)	1.000
Additional ablation lesions			
CTI line with focal radiofrequency catheter, n (%)	8 (2.5)	142 (14.4)	<0.001
Other non-PV isolation ablation, n (%)	6 (1.9)	27 (2.7)	0.538

CT indicates computed tomography; CTI, cavotricuspid isthmus; MRI, magnetic resonance imaging; and PV, pulmonary vein.
*A total of 1297 of 1303 patients reported procedure time; 318 of 318 patients with heart failure (HF) and 979 of 985 patients without HF.
†A total of 1296 of 1303 patients reported left atrial dwell time; 318 of 318 patients with HF and 978 of 985 patients without HF.
‡A total of 1284 of 1303 patients reported fluoroscopy time; 316 of 318 patients with HF and 968 of 985 patients without HF.
§A total of 1300 of 1303 patients reported total cryoablation time; 318 of 318 patients with HF and 982 of 985 patients without HF.
¶All targeted pulmonary veins isolated after cryoballoon ablation and focal touch-up.
#t Test for continuous variables and exact test for binary variables.
**Repeated-measures mixed model accounting for multiple veins treated within a patient.

event resolved before 12 months. A post hoc analysis completed on major adverse cardiovascular events (MACE) showed that the rate of MACE events in patients with HF was higher than the patients without HF (2.5% versus 0.8%, *P*=0.034). The events included 1 stroke/transient ischemic attack, which occurred in both the HF and no-HF cohorts (0.3% versus 0.1%); myocardial infarction or ischemic cardiac events, which were observed only in the HF cohort (0.9% versus 0.0%); cardiac tamponade/pericardial effusion and postoperative hypotension, which was observed in both the HF and no-HF cohorts (1.3% versus 0.5%, respectively); and pericarditis, which occurred only in the no-HF cohort. In subanalysis of the HF cohort, there was no statistical difference in the safety end point between patients without HF, HF NYHA class I, and HF NYHA class II/III (*P*=0.265). No deaths related to the cryoablation procedure occurred during 12-month follow-up. The all-cause mortality rate was 1.3% and 0.3% in the HF and no-HF cohorts, respectively. Of the 3 deaths observed in the no-HF group, 1 was cardiac related, occurring 104 days following the procedure. Of the 4 deaths in the HF group, 2 were cardiac related, occurring >200 days after the cryoablation.

Efficacy and Patient Follow-Up

During follow-up, 72 (5.5%) patients exited before completing a 12-month visit; 1 patient was withdrawn by the investigator, 46 were lost to follow-up, 21 requested withdrawal, and 2 withdrew for other reasons. Patients were followed according to local standard-of-care protocols. Compared with patients without HF, patients with HF were seen at clinic visits more often (3.9±2.3 and 2.9±1.8, respectively; *P*<0.001) and received arrhythmia monitoring (eg, 12-lead ECG and Holter) more frequently (3.2±3.3 versus 2.5±2.3, respectively; *P*<0.001) on average over 12-month follow-up. The Kaplan-Meier estimate of 12-month freedom from a ≥30-second recurrence of AF/AFL/AT after the 90-day blanking period was 84.2% (95% CI, 78.6%–88.4%) and 86.8% (95% CI, 84.2%–89.0%) in patients with PAF and HF versus no HF, respectively. The 12-month freedom from a ≥30-second recurrence of AF/AFL/AT was 69.6% (95% CI, 58.1%–78.5%) and 71.8% (95% CI, 63.2%–78.7%) in patients with PsAF and HF versus no HF, respectively (Figure 2). A Cox regression model identified a significant difference in the freedom from atrial arrhythmia recurrence between patients with PAF versus PsAF (hazard ratio [HR], 0.45; 95% CI, 0.33–0.61 [*P*<0.001]). HF was not a predictor of AF/AT/AFL recurrence after cryoablation (HR, 0.86; 95% CI, 0.63–1.16 [*P*=0.319]). In subanalyses of the HF cohort, 12-month atrial arrhythmia recurrence tended to be higher in patients with HF NYHA class II/III versus those with HF NYHA class I and no HF, although this difference was not statistically significant (*P*=0.079; Figure S1). Similarly, arrhythmia recurrence rate was slightly higher in patients with LVEF <50%, but, overall, the primary efficacy end point was not statistically different between patients without HF versus those with HFpEF versus HFrEF (*P*=0.233; Figure S2).

QOL and Health Care Utilization

AF-related symptom burden was higher at baseline in the HF versus no-HF cohort, with 39.5% versus 16.6% of patients experiencing ≥3 symptoms, respectively. Both HF and no-HF cohorts reported significant reductions in the number of AF-related symptoms experienced at 12 months (*P*<0.001, Figure 3A). AF-related symptoms reduced >70% from baseline to 12 months in both groups (Figure 3B). Likewise, patient-reported QOL as measured by the EQ-5D-3L significantly improved from baseline to the 12-month visit in both groups (HF cohort: *P*=0.001; no-HF cohort: *P*<0.001 [Table 4]). The no-HF cohort had a small but statistically greater improvement in EQ-5D-3L from baseline to 12 months than the HF cohort (*P*=0.017).

Health care utilization after the cryoablation was evaluated by AAD usage, repeat ablations, and rehospitalizations after the cryoablation (Figure 4). AAD prescription was higher in patients with PsAF (66.2% HF and 63.2% no HF) than patients with PAF (46.1%

Table 3. Serious Procedure-Related AEs

Serious procedure-related complications	No. of events (n, % of patients)	
	HF (n=318)	No HF (n=985)
Total	14 (13, 4.1)	27 (26, 2.6)
Supraventricular arrhythmia recurrences*	1 (1, 0.3)	4 (4, 0.4)
Groin-site complication†	2 (2, 0.6)	4 (4, 0.4)
Phrenic nerve injury	1 (1, 0.3)	7 (7, 0.7)
Cardiac tamponade or pericardial effusion	3 (3, 0.9)	4 (4, 0.4)
Pulmonary or bronchial complication‡	1 (1, 0.3)	3 (3, 0.3)
Myocardial infarction or ischemic cardiac event§	3 (3, 0.9)	0 (0, 0.0)
Pericarditis	0 (0, 0.0)	2 (2, 0.2)
Stroke or TIA¶	1 (1, 0.3)	1 (1, 0.1)
Postoperative hypotension	1 (1, 0.3)	1 (1, 0.1)
Face injury#	0 (0, 0.0)	1 (1, 0.1)
Sepsis	1 (1, 0.3)	0 (0, 0.0)

AEs indicates adverse events; HF, heart failure; and TIA, transient ischemic attack.

*Atrial fibrillation or sinus bradycardia occurring during the index procedure hospitalization.

†Hematoma, vascular pseudoaneurysm, or vessel puncture site discharge.

‡Hematemesis, hypercapnia, pneumonia, or pleurisy.

§Angina pectoris or myocardial infarction.

¶Cerebral infarction or cerebrovascular accident.

#Caused by a postablation fall.

HF and 47.6% no HF) at procedure discharge irrespective of HF diagnosis and decreased between discharge and 12-months in all groups (Figure 4A). Freedom from repeat ablation was 94.3% (95% CI, 92.4%–95.7%) and 92.4% (95% CI, 88.1%–95.2%) in the PAF no-HF versus the PAF HF groups, respectively. Freedom from repeat ablation in patients with PsAF was 87.1% (95% CI, 80.1%–91.8%) and 87.2% (95% CI, 77.5%–92.9%) for those with no HF and HF, respectively (Figure 4B). Patients with PsAF had a significantly higher risk of a reablation than patients with PAF (P=0.001), but HF diagnosis at baseline did not predict reablation over 12 months (P=0.439). Freedom from all-cause and cardiovascular-related rehospitalization after the cryoablation are displayed in Figure 4C through 4D. Freedom from cardiovascular-related rehospitalization in patients with PAF was 87.1% (95% CI, 81.9%–90.8%) and 92.4% (95% CI, 90.4%–94.1%) in the HF and no-HF cohorts, respectively. Freedom from cardiovascular rehospitalization in patients with PsAF was 78.7% (95% CI, 68.0–86.2) and 89.5% (95% CI, 83.0–93.7) in the HF and no-HF cohorts, respectively. Baseline AF type did not predict all-cause rehospitalization (P=0.179), but HF status was a significant predictor of all-cause rehospitalization (P<0.001). Similarly, HF status most strongly predicted a cardiovascular-related rehospitalization event after the cryoablation (P<0.001), and AF baseline classification also increased the risk of a cardiovascular-related hospitalization after cryoablation (P=0.032). In total, 83 cardiovascular-related rehospitalizations were reported in 74 patients without HF, and 61 cardiovascular-related rehospitalizations were observed in 46 patients with HF. AF/AFL/AT recurrence was the predominant cause of rehospitalization, and, in total, 57 (5.8%) patients without HF and 37 (11.6%) patients with HF were rehospitalized for AF/AFL/AT recurrences over 12-month follow-up.

DISCUSSION

HF and AF often coexist and together can worsen patient QOL and increase the risk of morbidity and mortality.[1–3] In this evaluation of standard-of-care practice, 24% of patients treated with cryoablation had HF with concomitant AF. Although patients with HF had more comorbidities, there was no statistical difference in the rate of the predefined study safety end point, serious procedure-related AEs, between patients with HF and those without HF (4.1% versus 2.6%, respectively; P=0.188). A post hoc analysis was completed on a subset of the primary safety end point events, MACE. A statistically different rate in MACE events was observed between patients with HF and those without

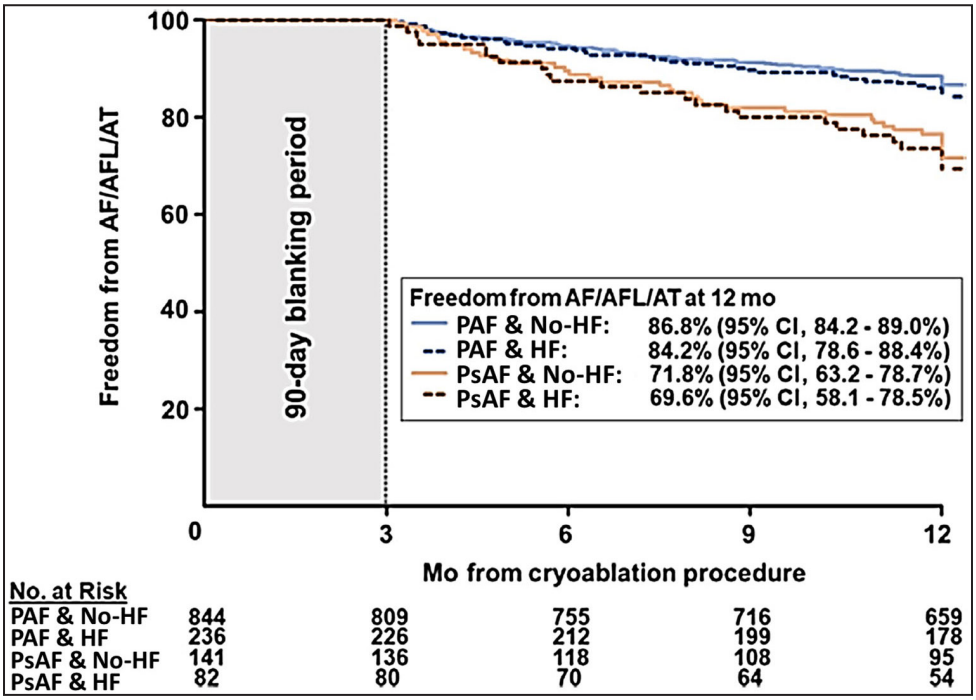

Figure 2. Freedom from atrial arrhythmia recurrence over 12 months.
Kaplan–Maier estimate of 12-month freedom from a ≥30-second recurrence of atrial fibrillation (AF)/atrial flutter (AFL)/atrial tachycardia (AT) in patients with paroxysmal AF (blue) and persistent AF (red) with (dashed line) and without (solid line) heart failure (HF). Persistent AF at baseline predicted atrial arrhythmia recurrence (P<0.001), but HF status did not predict arrhythmia recurrence over the 12-month follow-up (P=0.319). PAF indicates paroxysmal atrial fibrillation; and PsAF, persistent atrial fibrillation.

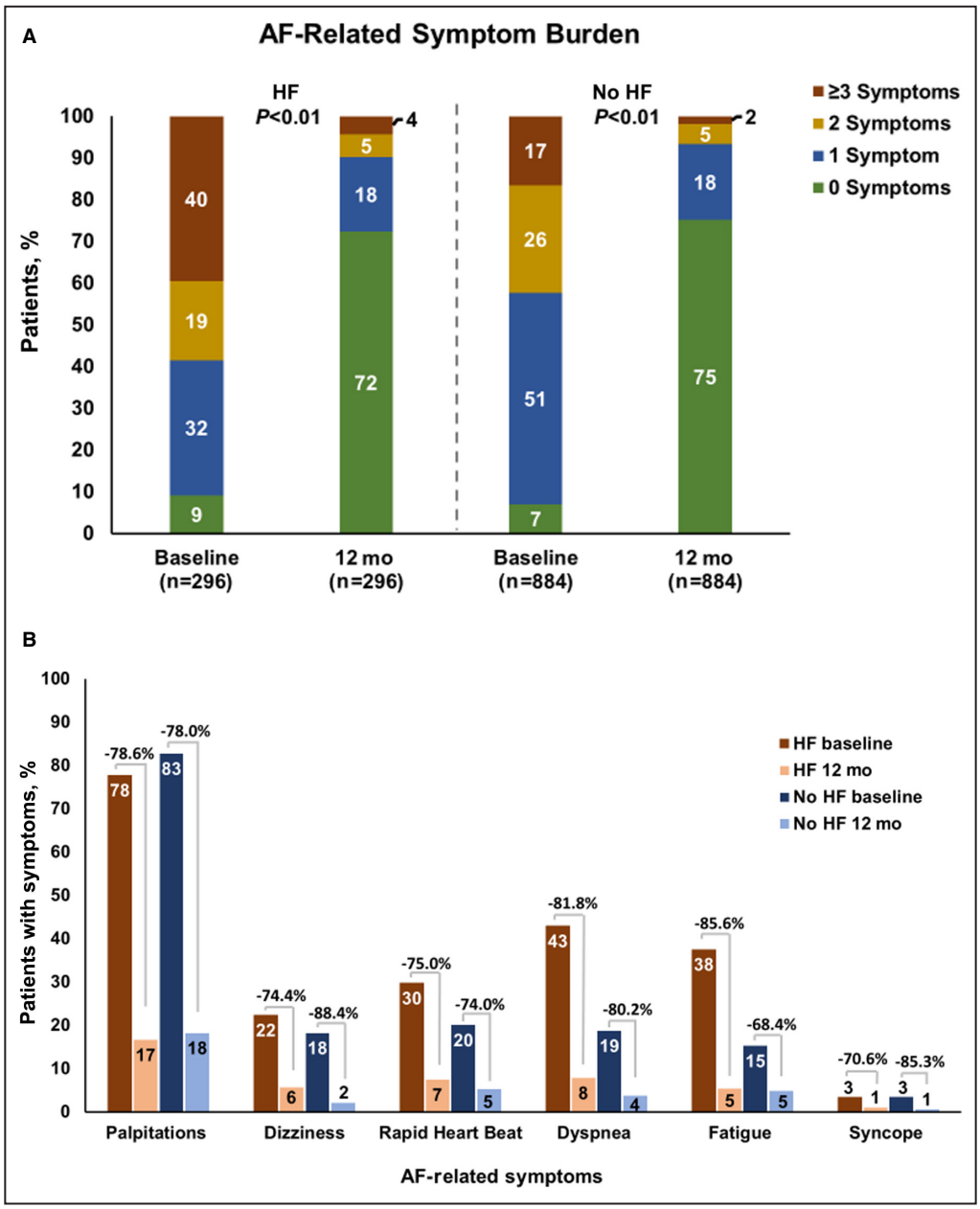

Figure 3. Change in atrial fibrillation (AF)–related symptoms after cryoballoon ablation.
A, The percentage of patients with heart failure (HF) and patients without HF with 0 (green), 1 (blue), 2 (yellow), and ≥3 AF-related symptoms (red) at baseline and 12-month follow-up is depicted. AF-related symptom burden was higher in the HF cohort at baseline, and AF symptom burden significantly reduced from baseline to 12 months in both the HF and no-HF cohorts (P<0.001). **B**, AF-related symptoms after cryoballoon ablation were significantly reduced between baseline and the 12-month follow-up (P<0.001 for all except syncope in the HF group, P=0.052).

HF (2.5% versus 0.8%, respectively). However, both the rate of MACE and overall periprocedural events in our HF population was similar, and even slightly lower, to those recorded in previous studies on AF catheter ablation of patients with both preserved and reduced ejection fraction.[14,15] HF status did not increase the risk of arrhythmia recurrence at 12 months (P=0.319) despite a higher frequency of clinic visits reported during follow-up. A significant reduction in AF-related symptoms and AAD use after the cryoablation was observed in both groups, and freedom from repeat ablation at 12 months was not different between the HF and no-HF cohorts. Atrial arrhythmia recurrence was the predominant cause of cardiovascular-related rehospitalization events and reinforces the importance of AF management in the AF and HF population.

Table 4. Changes in QOL as Measured by EQ-5D-3L

(n=1101*)	No HF (n=815)	HF (n=286)	*P* value†
Baseline	0.90±0.14	0.88±0.14	0.017
12 mo	0.93±0.12	0.90±0.13	
Absolute difference	0.034±0.15	0.026±0.14	

QOL indicates quality of life.

*A total of 1101 of 1303 patients completed a 12-month visit and the 3-level EuroQol 5-dimensional questionnaire (EQ-5D-3L) at baseline and 12 months.

†Linear regression model: outcome=EQ-5D-3L change, covariates=baseline EQ-5D-3L, baseline atrial fibrillation type, and heart failure (HF).

An increased mean number of follow-up visits (over a 1-year period) was reported in the HF cohort as compared with the no-HF cohort (3.9 versus 2.9, respectively), and this difference could be explained, in part, by the observation that patients with HF were considered at higher risk and were seen more often in routine clinical follow-up care.

Previous studies have demonstrated that catheter ablation is more effective than medical therapy in reducing major clinical events in patients with HF who have concomitant AF.[16,17] Moreover, restoration of sinus rhythm by catheter ablation in patients with HF leads to significant and sustained improvements in LVEF.[18,19] Published studies have focused on outcomes of radiofrequency AF ablation for the treatment of patients with HFrEF, but AF may incur even greater morbidity and mortality in patients with HFpEF. The population in this analysis was primarily composed of patients with HFpEF, and 30% of patients were treated with first-line cryoablation. Therefore, the findings add new insights in the management of these patients. This HF cohort had a higher rate of preexisting baseline cardiovascular comorbidities than patients without HF, and a statistically significant but small increase in procedure time was used to treat patients with HF. Despite these

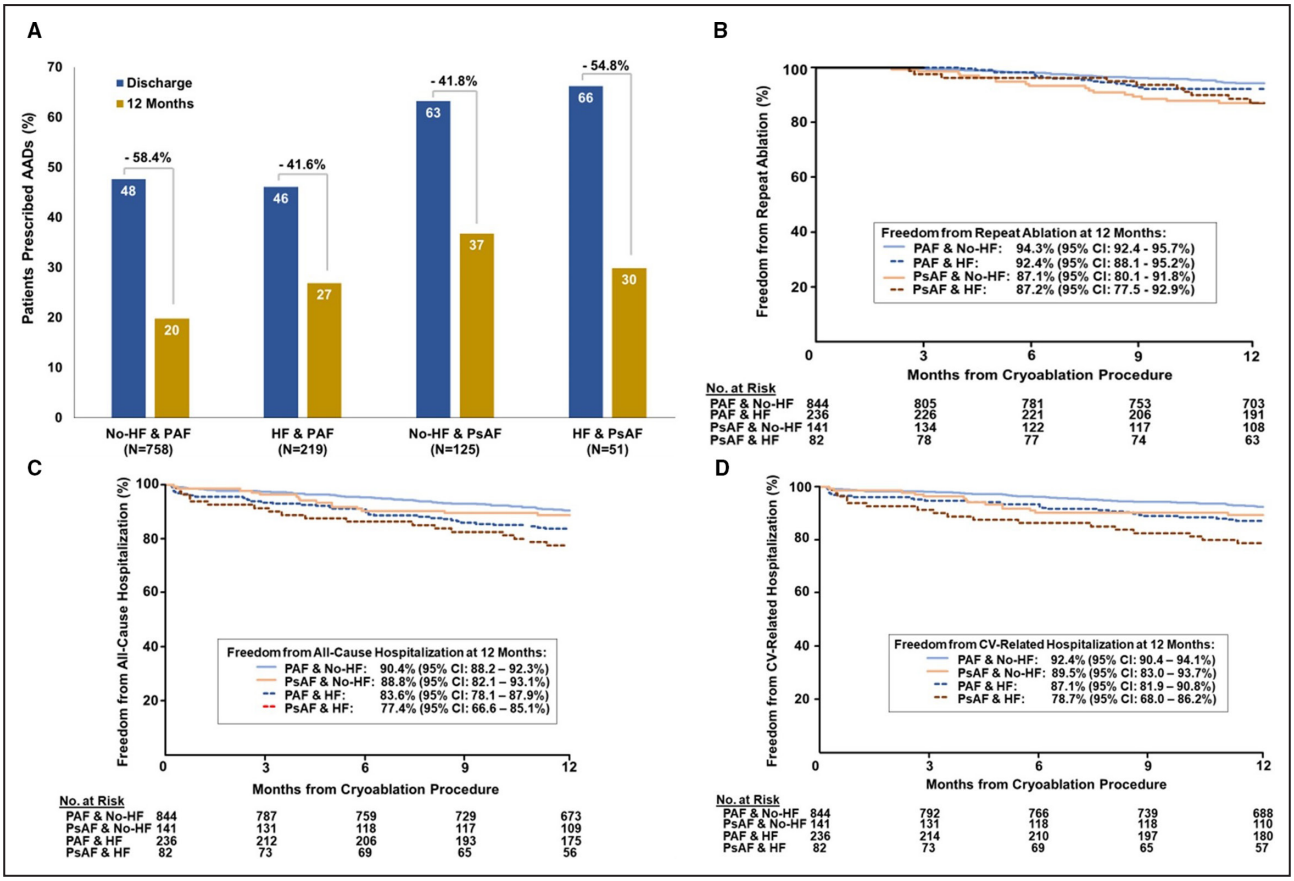

Figure 4. Health care utilization after cryoballoon ablation.
A, Antiarrhythmic drug utilization decreased between discharge (blue) and 12 months (yellow) among patient subgroups. **B**, Kaplan-Meier estimate of freedom from reablation over 12 months is displayed. Persistent atrial fibrillation (AF), but not heart failure (HF) status (*P*=0.439), predicted reablation (*P*=0.001) over follow-up. Kaplan–Meier estimates of (**C**) freedom from all-cause and (**D**) cardiovascular-related rehospitalization over 12-month follow-up are presented. HF predicted both all-cause (*P*<0.001) and cardiovascular-related (*P*<0.001) rehospitalization. Persistent AF did not predict all-cause hospitalization (*P*=0.179) but did predict cardiovascular-related rehospitalization (*P*=0.032) over follow-up. AAD indicates antiarrhythmic drug; PAF, paroxysmal atrial fibrillation; and PsAF, persistent atrial fibrillation.

baseline comorbidities in patients with HF, cryoablation was similarly effective in treating AF in patients with and without HF. Cryoablation was recently found to have a superior efficacy/safety profile than radiofrequency as a first-option ablation technique,[20] and future controlled trials should evaluate cryoablation as a treatment for AF in patients with concomitant HF in a relative early stage of AF disease.

A recent pooled analysis of randomized data on patients with AF and HF showed that catheter ablation (as compared with medical therapy) significantly reduced rates of mortality and rehospitalization.[21] Accordingly, catheter ablation has been advocated as cost-effective for the management of patients with AF and HF.[22] Our study showed that rates of reablation and both all-cause and cardiovascular-related rehospitalization were relatively low in both cohorts, and recurrence of atrial arrhythmias was the primary cause of rehospitalization for patients both with and without HF. Overall, AF/AFL/AT recurrence rates were similar between patients with HF and those without HF. Therefore, the higher rate of cardiovascular rehospitalization in the HF group may be attributable to: (1) more serious effects of an arrhythmia recurrence in patients with HF, and/or (2) the additional cardiovascular comorbidity burden in patients with HF. Additionally, the use of AADs significantly decreased at 12 months after ablation similarly in patients with and without HF. Although hospitalization rates before ablation were unavailable, these data indicate a positive effect of catheter ablation on health care resource utilization in patients with AF and HF. In agreement with previous studies,[21] these data demonstrated a significant improvement in AF-related symptoms and QOL in patients treated with cryoablation irrespective of HF status. These consistent findings reinforce the importance of a rhythm control strategy by means of catheter ablation to improve QOL in patients with AF and HF.

Study Limitations

This is an observational study of cryoablation; therefore, no comparisons to other therapies were possible. Nevertheless, these data are representative of global clinical practice and are useful to confirm the safety and efficacy of cryoablation in specific populations. The rate of hospitalization before catheter ablation was not collected and prevented assessment of change in rates after ablation. Although all serious AEs were required by protocol to be reported, it is possible that delayed AEs were not identified, and there may have been insufficient statistical power to detect a difference in the risk of an AE after cryoablation between the HF and no-HF cohorts. While our subanalysis did not show a difference in outcomes, the sample size was not large enough to draw definite conclusions on the safety and effectiveness of cryoablation in different subgroups of patients with HF (eg, HFrEF, HFpEF, and NYHA class). Similarly, multiple end points and subgroups were assessed but no adjustment for multiple testing was used.

Moreover, HF status was defined by the enrolling physicians based on patients' symptoms and clinical history, but diagnostic testing (ie, biomarkers and imaging) was not required to confirm the HF diagnosis. Last, as per the observational nature of this registry, no protocol was provided to the participating centers in terms of follow-up and intensive monitoring of AF recurrence. Thus, some asymptomatic AF episodes could be missed. However, for comparative data assessment, it is important to recognize that the HF cohort was (on average) more often seen in routine follow-up care, and, hence, these patients had more opportunity to record an AF episode compared with the cohort without HF in this study.

CONCLUSIONS

In this large, multicenter, international registry, cryoablation of AF was found to be safe and effective in the treatment of patients with AF and HF. Cryoablation for patients in an early stage of AF with a concomitant diagnosis of HF resulted in high rates of freedom from arrhythmia recurrence and low rates of hospital utilization after treatment.

ARTICLE INFORMATION

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Disclosures

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Supplemental Material

Appendix S1
Tables S1–S2
Figures S1–S2

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SUPPLEMENTAL MATERIAL

Appendix S1. List of Study Group Investigators, Cryo AF Global Registry Investigators

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Sonia Busch	Klinikum Coburg GmbH, Germany
Sascha Stiller	Oberschwaben-Klinik GmbH Krankenhaus St. Elizabeth, Germany
Christian Drephal	Sana Klinikum Lichtenberg, Germany
Georgios Kourgiannidis	Hellenic Airforce 251 General Hospital, Greece
Zoltan Csanadi	Debreceni Egyetem, Hungary
Csaba L. Földesi	Gottsegen György Országos Kardiovaszkuláris Intézet, Hungary
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Massimo Tritto	Humanitas Mater Domini, Italy
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Maria Grazia Bongiorni	Universitaria Pisana - Stabilimento di Cisanello, Italy
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Masaomi Kimura	Hirosaki University Hospital, Japan
Osamu Inaba	Japanese Red Cross Saitama Hospital, Japan
Takashi Kurita	Kindai University Hospital, Japan
Atsushi Kobori	Kobe City Medical Center General Hospital, Japan
Kenji Ando	Kokura Kinen Hospital Japan
Satoshi Shizuta	Kyoto University Hospital, Japan
Masahiko Goya	Tokyo Medical and Dental University, Japan
Yasuteru Yamauchi	Yokohama City Minato Red Cross Hospital, Japan
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Arisara Suwanagool	Siriraj Hospital, Thailand
Derick Todd	Liverpool Heart and Chest Hospital, United Kingdom
Richard Schilling	St Bartholomew's Hospital, United Kingdom
Mark Gallagher	St George's University Hospitals - NHS Trust, United Kingdom
Ewan Shepherd	The Newcastle upon Tyne Hospitals - Freeman Hospital, United Kingdom

Table S1: List of participating centers

Country	Center	Number of Patients
Total number of subjects		**1303**
Argentina	Hospital Universitario Fundacion Favaloro	67
	Instituto Cardiovascular de Buenos Aires (ICBA)	93
Austria	Kepler Universitatsklinikum Med Campus III.	20
Belgium	Centre Hospitalier Regional de la Citadelle	83
	Onze-Lieve-Vrouwziekenhuis-Campus Aalst	2
Brunei Darussalam	Gleneagles Jerudong Park Medical Centre	1
Colombia	Fundacion Clinica Shaio	1
Czech Republic	Nemocnice Na Homolce	24
Germany	Cardioangiologisches Centrum Bethanien	47
	Herz- und Gefasszentrum Bad Bevensen	19
	Kliniken Maria Hilf GmbH Monchengladbach -KH St. Franziskus	28
	Klinikum Coburg GmbH	11
	Oberschwaben-Klinik GmbH Krankenhaus St. Elizabeth	4
	Sana Klinikum Lichtenberg	46
Greece	Hellenic Airforce 251 General Hospital	11
Hungary	Debreceni Egyetem	9
	Gottsegen György Országos Kardiovaszkuláris Intézet	63
Iceland	Landspitali - National hospital of Iceland	1
Italy	Fondazione IRCCS Policlinico San Matteo	9
	Humanitas Mater Domini	10
	Ospedale Santa Maria della Misericordia di Perguia	15
	Universitaria Pisana - Stabilimento di Cisanello	24
Japan	Fukuoka Sanno Hospital	36
	Hirosaki University Hospital	29
	Japanese Red Cross Saitama Hospital	39
	Kindai University Hospital	35

Country	Center	Number of Patients
	Kobe City Medical Center General Hospital	29
	Kokura Kinen Hospital	30
	Kyoto University Hospital	35
	Tokyo Medical and Dental University	26
	Yokohama City Minato Red Cross Hospital	38
Kuwait	Salman Al Abdallah Al Dabbous Cardiac Center	25
Malaysia	Cardiac Vascular Sentral Kuala Lumpur	3
	Hospital Serdang	3
	Institut Jantung Negara	22
Mexico	Hospital San Angel Inn Universidad	18
Poland	Centralny Szpital Kliniczny Uniwersytetu Medycznego w Lodzi	52
	Krakowski Szpit.Specjalist.im.J.Pawla II	18
	Spital Wojewodzki nr 2	4
Portugal	Centro Hospitalar de Vila Nova de Gaia/Espinho - Unidade I	4
Saudi Arabia	King Fahad Medical City (KFMC)	29
Serbia	Insitute for Cardio Vascular Disease Dedinje	18
Singapore	National Heart Centre Singapore	6
Slovakia	NUSCH a.s. Bratislava	14
	Stredoslovensky ustav srdcovych a cievnych chorob a.s	26
	Vychodoslovensky ustav srdcovych a cievnych chorob, a.s	47
South Africa	Netcare Sunninghill Hospital	27
Spain	Hospital Universitario Moncloa	17
Taiwan, Republic of	Mackay Memorial Hospital-Tamsui Branch	4
	Taichung Veterans General Hospital	8
Thailand	Ramathibodi Hospital	4
	Siriraj Hospital	3
United Kingdom	Liverpool Heart and Chest Hospital	56
	St Bartholomew's Hospital	3

Country	Center	Number of Patients
	St George's University Hospitals - NHS Trust	2
	The Newcastle upon Tyne Hospitals - Freeman Hospital	5

In the Cryo AF Global Registry, patients were classified at enrollment as either a heart failure patient or no heart failure by their clinician. For those with heart failure, a NYHA assessment was performed during baseline testing. Table 1 summarizes the baseline characteristics by NYHA classification. A progression and greater incidence of comorbidities are observed from no heart failure to NYHA I supporting the investigator classification of heart failure for the NYHA I patients.

Table S2. Patient Baseline Characteristics.

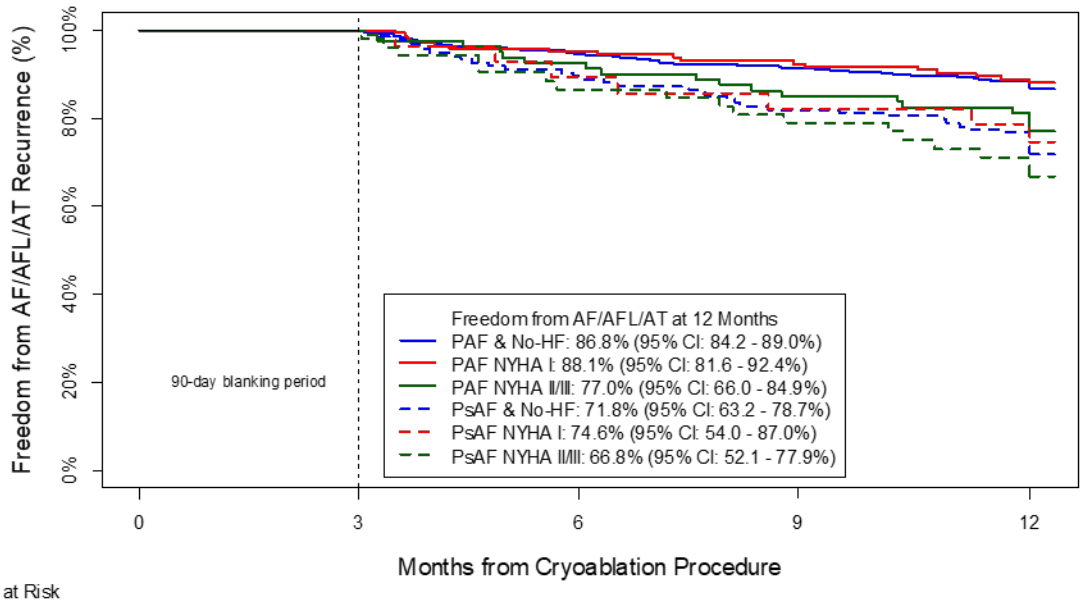
Subject Characteristics	No Heart Failure (N = 985)	Heart Failure NYHA I (N = 179)	Heart Failure NYHA II/III (N = 139)	p-value (No HF vs NYHA I)
Female sex (N (%))	331 (33.6%)	81 (45.3%)	64 (46.0%)	< 0.01
Age in years (mean ± STD)	60 ± 12	63 ± 11	64 ± 11	< 0.01
Body mass index in kg/m^2 (mean ± STD)	27 ± 5	27 ± 5	29 ± 6	0.86
CHA_2DS_2-VASc Score (mean ± SD)	1.6 ± 1.4	3.2 ± 1.5	3.6 ± 1.7	< 0.01
Paroxysmal AF (N (%))	844 (85.7%)	150 (83.8%)	86 (61.9%)	0.49
Years diagnosed with AF (mean ± STD)	3.3 ± 5.1	3.5 ± 4.9	2.9 ± 3.7	0.54
History of Atrial Flutter	50 (5.1%)	7 (3.9%)	1 (0.7%)	0.71
History of Atrial Tachycardia	12 (1.2%)	2 (1.1%)	1 (0.7%)	1.00
Left atrial diameter in cm (mean ± STD)	40 ± 7	43 ± 10	45 ± 8	< 0.01
Left ventricular ejection fraction in % (mean ± STD)	62 ± 7	62 ± 10	53 ± 14	0.89
LVEF <= 40%	6 (0.6%)	6 (3.4%)	28 (20.1%)	
LVEF 40-50%	15 (1.5%)	5 (2.8%)	12 (8.6%)	
LVEF >= 50%	816 (82.8%)	138 (77.1%)	88 (63.3%)	
Not reported (N,%)	148 (15.0%)	30 (16.8%)	11 (7.9%)	
Number of failed AADs (mean ± STD)	0.8 ± 0.7	0.8 ± 0.8	0.8 ± 0.7	0.82
First-line cryoablation (N (%))	306 (31.1%)	51 (28.5%)	38 (27.3%)	0.48
Hypertension (N (%))	484 (49.1%)	111 (62.0%)	105 (75.5%)	< 0.01
Prior cardiac device implant (N (%))	33 (3.4%)	9 (5.0%)	20 (14.4%)	0.28
Prior myocardial infarction (N (%))	17 (1.7%)	4 (2.2%)	8 (5.8%)	0.55
Prior stroke/transient ischemic attack (N (%))	56 (5.7%)	14 (7.8%)	10 (7.2%)	0.30
Coronary artery disease (N (%))	60 (6.1%)	22 (12.3%)	24 (17.3%)	< 0.01
Diabetes (N (%))	100 (10.2%)	19 (10.6%)	35 (25.2%)	0.89
Sleep apnea (N (%))	31 (3.1%)	8 (4.5%)	6 (4.3%)	0.37

AF: atrial fibrillation; HF: heart failure; NYHA Class: New York Heart Association functional classification; CHA_2DS_2-VASc Score: congestive heart failure, hypertension, age (2 points), diabetes, previous stroke/transient ischemic attack (2 points), vascular disease; LVEF: left ventricular ejection fraction; AAD: anti-arrhythmic drug.

Figure S1 displays the Kaplan-Meier estimate of 12-month freedom from AF/AT/AFL recurrence in subgroups based on NYHA classification. In a Cox regression sub-analysis of the HF cohort and NYHA classification, 12-month freedom from atrial arrhythmia recurrence was not statistically different between patients with No-HF vs HF NYHA Class I vs HF NYHA Class II/III (P=0.08).

AF: atrial fibrillation; AFL: atrial flutter; AT: atrial tachycardia; PAF: paroxysmal atrial fibrillation; PsAF: persistent atrial fibrillation; HF: heart failure; No-HF: no heart failure; NYHA Class: New York Heart Association functional classification.

Figure S1. Freedom from atrial arrhythmia recurrence over 12-months by NYHA subgroup

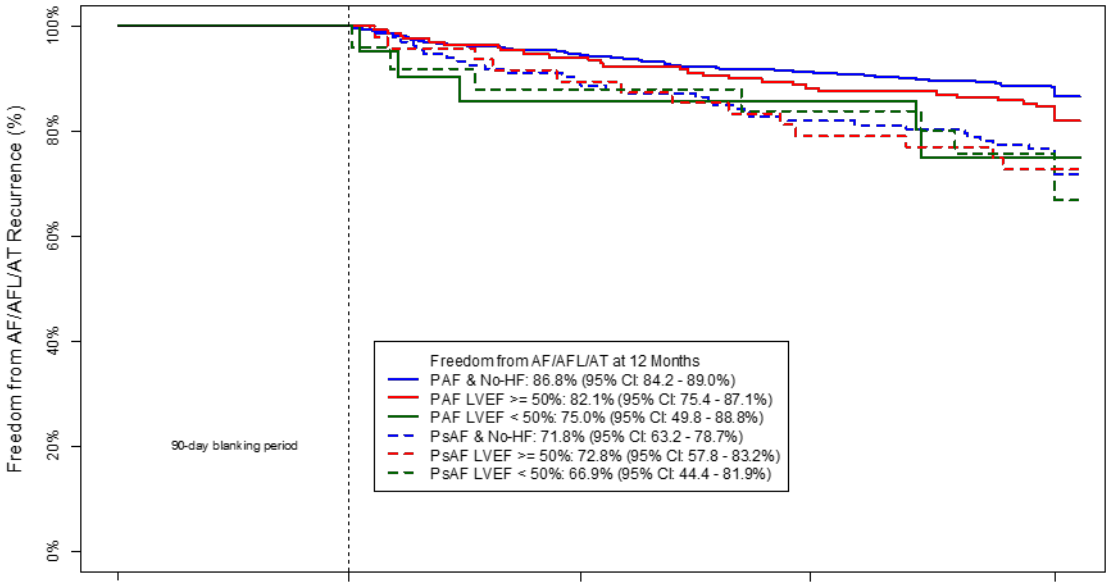


Number at Risk					
PAF & No-HF	844	809	755	716	659
PAF NYHA I	150	145	138	132	118
PAF NYHA II / III	86	81	74	67	60
PsAF & No-HF	141	136	118	108	95
PsAF NYHA I	29	28	25	23	20
PsAF NYHA II / III	53	52	45	41	34

Figure S2 displays the Kaplan-Meier estimate of 12-month freedom from AF/AT/AFL recurrence in subgroups based on LVEF (no-HF, HF & preserved LVEF, HF & reduced LVEF). In a Cox regression sub-analysis of the cohorts, 12-month freedom from atrial arrhythmia recurrence was not statistically different between patients with No-HF vs HF-pEF vs HF-rEF (P=0.23).

AF: atrial fibrillation; AFL: atrial flutter; AT: atrial tachycardia; PAF: paroxysmal atrial fibrillation; PsAF: persistent atrial fibrillation; No-HF: no heart failure; LVEF: left ventricular ejection fraction

Figure S2. Freedom from atrial arrhythmia recurrence over 12-months by LVEF subgroup



Number at Risk

PAF & No-HF	844	809	755	716	659
PAF LVEF >= 50%	177	172	161	149	132
PAF LVEF < 50%	25	21	18	17	13
PsAF & No-HF	141	136	118	108	95
PsAF LVEF >= 50%	49	48	43	38	33
PsAF LVEF < 50%	26	25	22	21	17