Safety and efficacy of cryoballoon ablation for the treatment of paroxysmal and persistent AF in a real-world global setting: Results from the Cryo AF Global Registry

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Abstract
Background: Cryoballoon ablation is a commonly used approach to treat patients with atrial fibrillation (AF).

Objectives: Report on the safety and efficacy of cryoballoon ablation for the treatment of AF in the largest global cohort of cryoablated patients prospectively studied within a single registry.

Methods: The Cryo AF Global Registry is a prospective, multi-center registry. Patients with paroxysmal AF (PAF) or persistent AF (PsAF) were treated with the cryoballoon catheter according to routine practices at 93 sites across 36 countries. Primary efficacy endpoints included freedom from AF and freedom from AF/atrial flutter (AFL)/atrial tachycardia (AT) ≥30 seconds. The primary safety endpoint was serious device- or procedure-related adverse events over 12 month follow-up.

Results: During this evaluation window, 2922 subjects completed an index cryoballoon procedure, and 1440 completed 12 month follow-up. The cohort was 61 ± 12 years of age, 36.3% female, and 78.7% PAF. Serious device- and procedure-related adverse event rates were 1.5% and 3.4%, respectively. Freedom from AF/AFL/AT after the 90 day blanking period was 86.4% (95% CI: 84.3%-88.3%) in patients with PAF and 70.9% (95% CI: 64.6%-76.4%) in patients with PsAF. Freedom from AF/AFL/AT at the 90 day blanking period was 86.4% (95% CI: 84.3%-88.3%) in patients with PAF and 70.9% (95% CI: 64.6%-76.4%) in patients with PsAF. Freedom from AF/AFL/AT in first-line PAF and PsAF was 90.0% (95% CI: 86.4%-92.7%) and 72.9% (95% CI: 58.6%-83.0%) at 12 months, respectively.

Conclusions: The Cryo Global AF Registry is the largest evaluation to demonstrate cryoablation is an efficient, safe, and effective treatment for patients with AF worldwide. Cryoablation was commonly used to treat patients prior to an AAD failure and may facilitate earlier therapy for patients on the AF disease continuum.

Abbreviations: AAD, antiarrhythmic drug; AEF, atrioesophageal fistula; AF, atrial fibrillation; AFL, atrial flutter; AT, atrial tachycardia; LA, left atrium; PAF, paroxysmal atrial fibrillation; PNI, phrenic nerve injury; PsAF, persistent atrial fibrillation; PV, pulmonary vein; PVI, pulmonary vein isolation.
1 | INTRODUCTION

The Arctic Front™ Cardiac Cryoablation System has been widely adopted for the treatment of patients with atrial fibrillation (AF), and local standards of care with the cryoballoon catheter have been established at hospitals worldwide. Well-controlled clinical trials evaluating cryoballoon ablation have demonstrated the safety and efficacy of pulmonary vein isolation (PVI) when treating patients with either paroxysmal (PAF) or persistent AF (PsAF) who are refractory to antiarrhythmic drugs (AADs). Recent reports from controlled clinical trials have also demonstrated the safety and efficacy of cryoballoon ablation for treatment of patients prior to AAD failure. The characteristics that define patients selected for, and outcomes of, cryoballoon ablation for the treatment of AF in real-world practice globally is unknown. The Cryo AF Global Registry was designed to assess the procedural characteristics, safety, and efficacy of cryoablation for treatment of patients with AF according to real-world practice in a broad spectrum of global care centers.

2 | METHODS

2.1 | Study design

The Cryo AF Global Registry (ClinicalTrials.gov registration: NCT02752737) is a prospective, multi-center, observational, post-market registry with ongoing data collection. In this evaluation window, data were collected on procedures performed by 239 unique operators at 93 sites across 36 countries in Africa, Europe, Asia, North America, and South America (Table S1). The objectives of this analysis were to assess the acute procedural characteristics, safety, and efficacy when using a cryoballoon ablation catheter (Medtronic, Inc) to treat patients with AF. The study was conducted according to Good Clinical Practices, in compliance with local laws, regulations and standards, and in accordance with the principles outlined in the Declaration of Helsinki. Each site received approval by an independent ethics/institutional review board and obtained written informed patient consent for all subjects prior to enrollment. This registry was sponsored by Medtronic, Inc. A seven-member international physician steering committee was utilized to advise and oversee data collection methods, data quality, analyses, and publication cadence based on data collection milestones.

2.2 | Patient population

Subjects were required to be ≥18 years old (or minimum age determined by local regulations) and have a planned procedure using the Medtronic cryoablation system to be included in the registry. Patients were excluded if they were participating in a concurrent, unapproved trial or were unable to participate according to local laws. Additionally, subject data were excluded from this current analysis if patients were diagnosed with long-standing PsAF (continuous AF > 12 months), had a prior cardiac ablation for the treatment of an atrial arrhythmia(s), had incomplete baseline data reported, or had not completed an index ablation procedure at the time of the database freeze. Within the dataset, subjects with zero failed AADs prior to enrollment in the trial were considered non-drug refractory. First-line’ patients were denoted as patients who were: (a) non-drug refractory and (b) not taking an AAD at baseline. Subjects were classified as having PAF if they had an episode(s) of AF that terminated spontaneously or with intervention within 7 days of onset. Patients were classified as having PsAF if they had a sustained episode(s) of AF that lasted longer than 7 days but less than 12 months, including episodes ≥7 days that were terminated by cardioversion.

2.3 | Cryoballoon ablation procedure

The cryoballoon ablation procedure was conducted according to standard of care at each participating site. This procedure has been described in detail and typical utilization has been published. In brief, transseptal puncture provided access to the left atrium (LA). A dedicated, 15-F OD steerable sheath (FlexCath or FlexCath Advance Steerable Sheath; Medtronic, Inc) was used to introduce a 23 or 28 mm cryoballoon ablation catheter (Arctic Front; Arctic Front Advance; Arctic Front Advance – ST; Arctic Front Advance Pro; Medtronic, Inc) into the LA. The cryoballoon catheter and sheath were delivered to the targeted pulmonary vein (PV) with either a J-tip guidewire or a dedicated inner-lumen octopolar/decapolar circular mapping catheter (Achieve or Achieve Advance, Medtronic, Inc). Upon antral occlusion of the targeted PV, the cryoapplication was initiated. The number and duration of cryoapplications per PV were determined by the physician.

Sites were recommended to monitor phrenic nerve function during right-sided PVI by pacing with a diagnostic catheter at the level of the right subclavian vein and adjacent monitoring for diaphragmatic function. All cryoapplications were terminated upon detection of an attenuated diaphragmatic response. Adjunctive imaging (eg, intracardiac echocardiography, three-dimensional electroanatomical mapping), intraprocedural esophageal temperature monitoring, ablation tools (eg, focal cryoablation, radiofrequency catheter ablation), and/or adjunctive lesions applied to each patient were physician determined and documented. PVI was demonstrated by entrance and/or exit block following the ablation. Further, postablation testing (eg, testing acute PVI with adenosine or isoproterenol), periprocedural anticoagulation, and AAD initiation or continuation

**KEYWORDS**

antiarrhythmic drug, atrial fibrillation, catheter ablation, cryoballoon, pulmonary vein isolation
was left to the discretion of the physician. Patients were discharged from the hospital using local standard-of-care policies.

### 2.4 Patient follow-up

This analysis examined patients enrolled and treated in the registry with either complete or ongoing follow-up between May 2016 and January 2020. Patients were followed according to center standard-of-care protocols with a postprocedure visit either in person or by phone required at 12 months post the index procedure. Arrhythmia recurrence was monitored by any of the following methods: electrocardiogram, Holter monitor, trans-telephonic monitor, insertable cardiac monitor, pacemaker, and/or implantable cardioverter defibrillator. Additional information collected included cardiovascular medications, adverse events, and quality of life assessments as measured by the EQ-5D-3L questionnaire.

### 2.5 Endpoints

The primary efficacy objectives were the 12 month freedom from a ≥30 second recurrence of AF and the 12 month freedom from a ≥30 second recurrence of combined AF, atrial flutter (AFL) and/or, atrial tachycardia (AT) following a 90 day blanking period. During the 90 day blanking period patients were managed per standard of care. Thereafter, during the efficacy follow-up assessment, a patient was monitored for atrial arrhythmia recurrence with or without the usage of AADs. Freedom from recurrence of AF/AFL/AT was also analyzed in sub-cohorts of first-line subjects with PAF and PsAF. The primary safety objective was the serious device- or procedure-related adverse event rates. Investigators classified adverse events by seriousness (according to international standards [ISO 14 155:2001]) and relatedness to the cryoablation system and/or ablation procedure. Serious adverse events included all events that led to death, or to a serious deterioration in health that resulted in either (a) a life-threatening illness or injury, (b) a permanent impairment in body structure or function, (c) in-patient or prolonged hospitalization, or (d) medical intervention to prevent life-threatening illness or injury. All adverse events were followed until the event resolved, the event was unresolved with no further actions, or the subject exited the study. Ancillary objectives were examined in this dataset, including: patient baseline demographics, characterization of the cryoablation procedure, and quality-of-life post cryoballoon ablation. Changes in quality of life over the study period were measured by the EQ-5D-3L questionnaire (score of 1 represents maximal quality of life) at baseline and 12 month follow-up.

### 2.6 Statistical analysis

Baseline characteristics and clinical data were summarized using the appropriate summary statistics; continuous variables are summarized as mean and standard deviation, and categorical variables are summarized as counts and percentages. Differences in baseline characteristics between the cohort of subjects enrolling with PAF vs subjects enrolling with PsAF were tested with a two-sample t-test for continuous variables and Fisher’s exact test for categorical variables. Kaplan-Meier methods were used to estimate 12 month freedom from arrhythmia recurrence. Standard error was approximated with Greenwood’s formula. Differences in arrhythmia recurrence rates were compared between PAF and PsAF cohorts with a log-rank test. Differences in recurrence rates were compared between first-line and drug-refractory patients with a Cox regression model after accounting for differences in baseline AF classification (PAF or PsAF). In the regression model, arrhythmia recurrence was the dependent variable while AAD status (first-line or drug-refractory) and baseline AF type were included as covariates. Differences in safety event rates between PsAF and PAF patients were assessed with a Fisher’s exact test. Changes in quality of life from baseline to 12 months were assessed with a t-test. Values of \( P < .05 \) were considered significant. Statistical analyses were conducted using SAS software version 9.4 (SAS Institute).

### 3 RESULTS

#### 3.1 Patient follow-up and characteristics

Of the 3276 subjects enrolled in the Cryo AF Global Registry between May 2016 and January 2020, 2922 eligible subjects completed a cryoballoon ablation index procedure (denoted the Procedure Analysis Cohort). Within this timeframe, 1440 subjects from 26 of 36 countries had been followed for 12 months post ablation (denoted the Efficacy Analysis Cohort; Figure 1). Of the Efficacy Analysis Cohort, 1320 (91.7%) patients had at least one follow-up visit with an average of 3.0 visits per patient over 12 month follow-up. While rhythm monitoring was not protocol required at follow-up visits, 1151 (79.9%) patients underwent arrhythmia monitoring at least once in the 12 months after the cryoablation, and 62.6% of patients were monitored remotely (eg transtelephonic monitoring), and 62 (4.3%) patients had implanted cardiac devices from which rhythm data were reviewed by a clinician. The frequency, timing, and type of arrhythmia monitoring utilized is provided in Figure 2. During follow-up, 81 of the 1440 (5.6%) subjects exited early for the following reasons: 2 (0.1%) withdrawn by the investigator, 55 (3.8%) lost to follow-up, 22 (1.5%) subjects requested withdrawal, and 2 (0.1%) for other reasons.

Baseline patient characteristics are detailed in Table 1. On average, the cohort was 61 ± 12 years of age, 36.3% female, had a CHA2DS2-VASc score of 2.1 ± 1.6, and was diagnosed with AF for
Subjects Enrolled (N=3276)

Exited Prior to Cryoablation Procedure (N=21)
- 9: Inclusion/exclusion criteria not met
- 4: Investigator withdrew subject
- 3: Other
- 3: Subject requested withdrawal from the study
- 2: Investigator deemed as medically necessary

Excluded from Analyses (N=333)
- 36: Long-standing persistent AF
- 4: Incomplete baseline data form
- 31: Enrolled, no procedure reported at time of database freeze
- 262: Prior atrial ablation; pulmonary vein isolation or ablation for atrial flutter

Procedure Analysis Cohort: Subjects with an index Procedure (N=2922)

12 month follow-up not accrued at time of analysis (N=1482)
Subjects followed less than 12 months post ablation at time of analysis; therefore, not included in primary efficacy analyses

Efficacy Analysis Cohort: Subjects 12 months post ablation (N=1440)
- 1359: Completed 12 month follow-up
- 81: Exit Early
  - 2 withdrawn by the investigator
  - 55 lost to follow-up
  - 22 subject requested withdrawal
  - 2 for other reasons

FIGURE 1 Patient Flow. Subject enrollment and criteria for the Procedure Analysis Cohort and Efficacy Analysis Cohort. Efficacy analyses were completed on the subset of subjects who were a minimum of 12 months post cryoablation at the time of the analysis.

FIGURE 2 Monitoring Methods for Atrial Arrhythmia Recurrence. The portion of the Efficacy Analysis Cohort to be monitored for atrial arrhythmia recurrence during the 12 month follow-up period with one (blue), two (yellow), or three or more (green) ECGs, ≥24 hour Holter Monitors, and all combined methods for arrhythmia monitoring is depicted. Patients who were evaluated with continuous monitoring methods (black) are also presented. In total, 79.9% of patients underwent monitoring for atrial arrhythmia recurrence at least once during the follow-up period.

A mean of $3.1 \pm 4.6$ years prior to cryoablation. In total, 41.5% of subjects had not failed an AAD prior to the cryoablation procedure and were deemed non-drug refractory. For 904 (30.9%) subjects, the cryoablation was considered first-line therapy as they were non-drug refractory and were not on an AAD at the time of study enrollment. Subjects with PAF comprised 78.7% of the total cohort. The PsAF sub-group had a significantly larger mean LA diameter, lower left ventricular ejection fraction, higher body mass index, higher CHA$_2$DS$_2$-VASc scores, was older, was more often male, and had a higher rate of co-morbidities ($P < .01$).

3.2 | Procedural characteristics

Procedure-related data are detailed in Table 2. Non-general anesthesia was utilized in 62.6% of procedures. Subjects were predominantly treated with the Arctic Front Advance (second-generation) cryoballoon (92.8%), and a 28 mm cryoballoon was used in 99.3% of procedures. Pre-procedural imaging with MRI or CT was performed in 21.3% of subjects, and intraprocedural 3D electroanatomical mapping was performed in 13.3% of procedures. Phrenic nerve function was monitored during ablation in 99.1% of procedures with a pace and palpate technique employed in 87.9% of cases. The mean total procedure duration (time from first venous access to last catheter removal) was 82 ± 34 minutes, mean LA dwell time was 55 ± 25 minutes, and average fluoroscopy time was 18 ± 18 minutes.

Overall, 95.0% of patients had all targeted PVs acutely isolated during the index procedure. Of those, PVI was completed in 0.1% of subjects with focal cryoablation, and with focal radiofrequency ablation in 1.4% of subjects. Cavo-tricuspid isthmus line ablation was performed in 9.8% of patients, and other non-PV ablation adjunctive to
PVI was performed in 4.9% of subjects during the index procedure. The average number of freezes per PV was $1.5 \pm 0.9$ for a mean duration of $185 \pm 53$ seconds. The mean balloon nadir temperature of the freezes was $-48 \pm 7^\circ$C, and PV potentials were monitored during 82.0% of cryoapplications.

### 3.3 Safety

Of the 2922 subjects in the Procedure Analysis Cohort, 110 serious procedure-related events in 100 (3.4%) subjects occurred. Among
| Procedural characteristics | Total cohort (N = 2922) | Paroxysmal AF (N = 2301) | Persistent AF (N = 621) |
|----------------------------|-------------------------|---------------------------|-------------------------|
| **Ablation tools** | | | |
| 23 mm Cryoballoon (N [%]) | 34 (1.2%) | 26 (1.1%) | 8 (1.3%) |
| 28 mm Cryoballoon (N [%]) | 2903b (99.3%) | 2285 (99.3%) | 618 (99.5%) |
| Arctic Front Advance (N [%]) | 2711 (92.8%) | 2149 (93.4%) | 562 (90.5%) |
| Arctic Front Advance Pro (N [%]) | 202 (6.9%) | 143 (6.2%) | 59 (9.5%) |
| Achieve Mapping Catheter (N [%]) | 2624 (89.8%) | 2075 (90.2%) | 549 (88.4%) |
| **Total lab occupancy time in minutes** (mean ± STD) | 138 ± 53 | 138 ± 54 | 137 ± 48 |
| **Total procedure time in minutes** (mean ± STD) | 82 ± 34 | 81 ± 34 | 85 ± 34 |
| **Left atrial dwell time in minutes** (mean ± STD) | 55 ± 25 | 54 ± 25 | 59 ± 27 |
| **Total fluoroscopy time in minutes** (mean ± STD) | 18 ± 18 | 18 ± 18 | 17 ± 20 |
| **Total cryoapplication duration in minutes** (mean ± STD) | 18.9 ± 6.6 | 18.7 ± 6.4 | 19.8 ± 7.4 |
| **Sedation method (N [%])** | | | |
| General anesthesia | 1093 (37.4%) | 863 (37.5%) | 230 (37.0%) |
| Conscious sedation | 1828 (62.6%) | 1437 (62.5%) | 391 (63.0%) |
| Pre-procedural imaging (CT and/or MRI) | 621 (21.3%) | 464 (20.2%) | 157 (25.3%) |
| Intra-procedural 3D electroanatomical mapping | 389 (13.3%) | 365 (15.9%) | 24 (3.9%) |
| Intracardiac echocardiography | 769 (26.3%) | 594 (25.8%) | 175 (28.2%) |
| Esophageal temperature monitoring (N [%]) | 1090 (37.3%) | 866 (37.6%) | 224 (36.1%) |
| Pulmonary vein venography | 2774 (94.9%) | 2189 (95.1%) | 585 (94.2%) |
| Phrenic nerve monitoring | 2896 (99.1%) | 2282 (99.2%) | 614 (98.9%) |
| Pacing / palpate | 2568 (87.9%) | 2008 (87.3%) | 560 (90.2%) |
| Diaphragm stimulation | 1050 (35.9%) | 772 (33.6%) | 278 (44.8%) |
| Compound motor action potential | 890 (30.5%) | 708 (30.8%) | 182 (29.3%) |
| Other | 277 (9.5%) | 210 (9.1%) | 67 (10.8%) |
| Pulmonary vein ablation acute successb (N [%]) | 2775 (95.0%) | 2174 (94.5%) | 601 (96.8%) |
| PVI touch-up with focal cryo catheter (N [%]) | 4 (0.1%) | 4 (0.2%) | 0 (0.0%) |
| PVI touch-up with focal RF catheter (N [%]) | 40 (1.4%) | 31 (1.3%) | 9 (1.4%) |
| Isoproterenol and/or adenosine to assess PVI (N [%]) | 377 (12.9%) | 280 (12.2%) | 97 (15.6%) |
| **Additional ablation lesions** | | | |
| Cavo-tricuspid isthmus line (N [%]) | 286 (9.8%) | 256 (11.1%) | 30 (4.8%) |
| Other non-PVI ablation (N [%]) | 142 (4.9%) | 129 (5.6%) | 13 (2.1%) |
| **Cryoballoon applications** | | | |
| PV electrical potentials monitored (N [%]) | 2396 (82.0%) | 1886 (82.0%) | 510 (82.1%) |
| Number of applications per vein (mean ± STD) | 1.5 ± 0.9 | 1.5 ± 0.9 | 1.5 ± 1.0 |
| (median [IQR]) | 1 [1, 2] | 1 [1, 2] | 1 [1, 2] |
| Number of veins | 11517 | 9042 | 2475 |
| Duration of cryoapplication in seconds | | | |
| ALL PVs | | | |
| (mean ± STD) | 185 ± 53 | 183 ± 53 | 193 ± 54 |
| (median [IQR]) | 180 [179, 240] | 180 [172, 240] | 180 [180, 240] |
| Number of applications | 17829 | 14011 | 3818 |
| RIPV | 184 ± 54 | 181 ± 53 | 191 ± 56 |
| RSPV | 178 ± 55 | 176 ± 54 | 184 ± 56 |

(Continues)
those events, 47 were physician classified as serious cryoballoon device-related adverse events that occurred in 44 (1.5%) subjects. There were no differences in the rate of serious device-related adverse events (1.3% vs 1.8%; \( P = .57 \)) or serious procedure-related adverse events (3.4% vs 3.5%; \( P = .80 \)) among subjects with PAF or PsAF, respectively (Figure 3). Overall, the most frequent serious adverse events were supraventricular arrhythmia recurrences (25 subjects). These events were deemed serious as they required hospitalization, cardioversion, or repeat ablation. Adverse events related to the puncture site for catheter access were the second most frequent event with 21 (0.7%) serious procedure-related events (nine of which were related to the study device). Phrenic nerve injury (PNI) unresolved at discharge was observed in 15 subjects (0.5%). Of the 15 PNI, nine (0.3%) resolved in a timeframe between 2 days and 6 months after the procedure, three (0.1%) resolved by 12 months (prior to study exit), and three (0.1%) asymptomatic events remained unresolved at 12 months. Procedure-related cardiac tamponade/pericardial effusion occurred in 11 subjects (0.4%), of those nine were treated with pericardiocentesis and the remaining two were treated without surgical intervention. There were five (0.2%) procedure-related stroke or transient ischemic attack events. A full list of serious adverse events is provided in Table 3.

Death occurred in 12 (0.4%) subjects during the data collection period. Three of the deaths occurred within 30 days of the procedure; the remaining deaths occurred between day 104 and 315 after the index procedure and were unrelated to the AF ablation procedure. The cause of death as reported by the investigator for the three subjects who died within 30 days of the procedure were as follows: (a) a cerebrovascular accident 24 days after the index procedure that was related to the AF ablation procedure; (b) pneumonia/chronic obstructive pulmonary disease unrelated to the AF ablation 14 days after the procedure; and (c) a non-ST elevated myocardial infarction with cardiogenic shock unrelated to the AF ablation that occurred 3 days after the procedure.

## 3.4 | Efficacy

Of the 218 patients who reported an atrial arrhythmia recurrence during follow-up, 79.8% recurred with AF, 10.6% with AFL/AT, and 9.6% recurred with both AF and AFL/AT. The 12 month Kaplan-Meier estimate of freedom from a ≥30 second recurrence of AF after the 90 day blanking period was significantly higher for patients with PAF (87.9% [95% CI: 85.8%-89.7%]) compared to the estimate of freedom from AF for patients with PsAF at the 12 month timepoint (73.1% [95% CI: 66.8%-78.3%]; \( P < .01 \)). Likewise, the 12 month Kaplan-Meier estimate of freedom from ≥30 second recurrence of AF/AFL/AT for subjects with PAF was greater than subjects with PsAF at 86.4% (95% CI: 84.3%-88.3%) and 70.9% (95% CI: 64.6%-76.4%), respectively (\( P < .01 \); Figure 4A). Overall, the rate of freedom from AT/AFL/AT recurrence was significantly higher in first-line patients compared to AAD refractory patients (\( P = .02 \); Figure 4B). The 12 month Kaplan-Meier

### Table 2 (Continued)

| Procedural characteristics | Total cohort (N = 2922) | Paroxysmal AF (N = 2301) | Persistent AF (N = 621) |
|----------------------------|------------------------|--------------------------|-------------------------|
| LIPV                       | 190 ± 52               | 187 ± 52                 | 202 ± 52                |
| LSPV                       | 189 ± 51               | 187 ± 51                 | 196 ± 50                |
| LCPV                       | 193 ± 51               | 193 ± 49                 | 192 ± 57                |
| Cryoballoon nadir temperature (°C) |                        |                          |                         |
| ALL PVs                    |                        |                          |                         |
| (mean ± STD)               | -48 ± 7                | -48 ± 7                  | -48 ± 7                 |
| (median [IQR])             | -48 [-53, -43]         | -47 [-53, -43]           | -48 [-54, -43]          |
| Number of veins\(^1\)      | 11498                  | 9026                     | 2472                    |
| RIPV                       | -47 ± 7                | -47 ± 7                  | -48 ± 7                 |
| RSPV                       | -51 ± 6                | -51 ± 6                  | -51 ± 7                 |
| LIPV                       | -45 ± 6                | -45 ± 6                  | -45 ± 6                 |
| LSPV                       | -49 ± 6                | -49 ± 6                  | -50 ± 6                 |
| LCPV                       | -49 ± 7                | -50 ± 7                  | -47 ± 7                 |

Abbreviations: IQR, interquartile range; PV, pulmonary vein; PVI, pulmonary vein isolation; STD, standard deviation.

\(^1\)Of the 2922 procedures, cryoballoon device model was reported in 2913

\(^2\)24 patients were treated with both a 23 mm and 28 mm; 19 PAF and 5 PsAF subjects

\(^3\)2913 subjects reported total lab occupancy time; 2294 PAF and 619 PsAF

\(^4\)2912 subjects reported total procedure time; 2291 PAF and 621 PsAF

\(^5\)2911 subjects reported left atrial dwell time; 2290 PAF and 621 PsAF

\(^6\)2808 subjects reported total fluoroscopy time; 2204 PAF and 604 PsAF

\(^7\)2913 subjects reported total cryoapplication duration; 2292 PAF and 621 PsAF subjects

\(^8\)All targeted pulmonary veins isolated after cryoballoon ablation and focal touch-up

\(^9\)Of the 11517 pulmonary veins treated, nadir temperature was reported in 11498 veins
estimate of freedom from AF/AFL/AT in first-line PAF compared to drug-refractory PAF was 90.0% (95% CI: 86.4%-92.7%) vs 84.4% (95% CI: 81.5%-86.8%; \( P = .01 \)), respectively. First-line PsAF subjects had a 12 month Kaplan-Meier estimate of freedom from AF/AFL/AT of 72.9% (95% CI: 58.6%-83.0%) compared to 70.2% (95% CI: 62.9%-76.4%; \( P = .67 \)) of subjects with drug-refractory PsAF. Irrespective of arrhythmia recurrence, the number of patients on AADs reduced from 49% at index procedure discharge to 23% at the 12 month follow-up.

3.5 | Quality of Life

A significant increase in patient reported quality of life as measured by the EQ-5D-3L questionnaire was observed across the full study cohort at 1 year (Table 4). The average EQ-5D-3L score increased from 0.89 ± 0.14 at baseline to 0.92 ± 0.12 (difference of 0.03 ± 0.14, \( P < .01 \)) at 1 year. This increase in quality of life was observed in both the patients with PAF (increase of 0.03 ± 0.14, \( P < .01 \)) and patients with PsAF (increase of 0.03 ± 0.14, \( P < .01 \)).

4 | DISCUSSION

To our knowledge, the Cryo AF Global Registry is the first and largest assessment of a global patient population who underwent cryoballoon ablation for the treatment of AF examined over a 12 month follow-up period. Cryoablation in this diverse cohort of patients with PAF and PsAF was completed safely with a 3.4% procedure-related serious adverse event rate (1.5% device-related serious adverse event rate) and efficiently with a mean 82 ± 34 minute procedure time. Freedom from AF/AT/AFL at 12 months was 86.4% (95% CI: 84.3%-88.3%) for PAF and 70.9% (95% CI: 64.6%-76.4%) for PsAF cohorts, and both sets of patients reported significant improvements in EQ-5D-3L measures of quality of life (\( P < .01 \)). Overall, freedom from arrhythmia recurrence was higher in first-line subjects compared to AAD-refractory subjects (\( P = .02 \)). These observations demonstrate that cryoballoon ablation is safe and effective for the treatment of patients with AF when delivered according to varying world-wide standard-of-care policies. These data also demonstrate the benefit of earlier catheter ablation on reducing atrial arrhythmia recurrence.

4.1 | Global standard of care for cryoballoon ablation

Similar to controlled clinical trials, patients with PsAF had baseline characteristics indicative of more advanced AF disease progression and a higher rate of comorbidities than enrolled patients with PAF.3,4 Regardless of AF classification, standard-of-care approaches to treat patients with AF resulted in a consistent and efficient procedure with an average total procedure time of 82 minutes. Procedural techniques may have enabled these efficiencies. Specifically, a PVI-only approach was commonly employed (86%) for patients with both PAF and PsAF, corroborating the essential role of PVI for the treatment of all forms of AF.10 The frequent use of conscious sedation (63%) in the registry may also have contributed to the observed procedural efficiency as conscious sedation has been reported to confer shorter procedure times compared to general anesthesia with similar safety, efficacy, and patient reported satisfaction.11-13 Additionally, few procedures were conducted with adjunctive equipment or additional PVI testing methods, including: pre-procedural imaging (21%), electroanatomical mapping (13%), or isoproterenol/adenosine testing to assess acute PVI (13%). The ability to perform an effective cryoballoon ablation procedure with few adjunctive tools worldwide corroborates prior regional reports.14,15 These data support the utility of this cryoablation system to address the growing population of patients with AF in a resource constrained environment.

4.2 | Real-World safety of cryoballoon ablation

World-wide safety of AF ablation has not been published since 2010, in which outcomes after AF ablation performed by radiofrequency ablation catheters were estimated via a voluntary survey.16 Here, the world-wide safety profile of cryoballoon ablation procedures conducted according to standard practice at 93 unique global centers (3.4% serious procedure- and 1.5% serious device-related
adverse event rate) aligns with smaller, controlled cryoballoon ablation trials and region-specific observational registries.\(^4\) Despite larger LA diameters and generally higher rates of comorbidities in the PsAF cohort compared to the PAF cohort, adverse event rates were similar for both groups treated in this registry.

Specifically, the rates of PNI at discharge (0.5%), cardiac tamponade/pericardial effusion (0.4%), and neurological events (0.2%) were low. Phrenic nerve monitoring to aid in early detection of diaphragmatic injury was conducted in 99% of procedures and likely contributed to the low rate of PNI, which is in alignment with contemporary reports.\(^17\) Previous studies have also reported low rates of cardiac tamponade/pericardial effusion following cryoballoon ablation,\(^17\) and the Cryo AF Global Registry confirms the low risk of this event after cryoballoon ablation in typical practice. Finally, one procedure-related death was reported in this registry (0.03%), which indicates the improved safety of AF ablation since the Cappato et al 2010 survey, which reported 0.15% AF procedure-related deaths.\(^16\) This dataset of nearly 3000 patients treated according to standard of care by 239 different operators with varying experience across 36 countries, confirms the safety of cryoballoon ablation for the treatment of patients with AF in a real-world setting.

### 4.3 Clinically relevant efficacy of cryoballoon ablation

Freedom from arrhythmia recurrence in PAF (86%) and PsAF (71%) observed in this world-wide registry is similar to other real-world reports of success after cryoablation ranging between 73% and 87% in PAF and 56%-64% in PsAF populations.\(^17\)\(^-\)\(^22\) Despite relatively similar baseline patient characteristics, the real-world success of cryoballoon ablation in patients with PsAF in this registry was numerically higher than the recently reported STOP Persistent AF clinical trial.\(^4\) The STOP Persistent AF trial included weekly trans-telephonic monitoring and may have influenced this difference, but both studies demonstrated improvement in indicators of AF disease burden including significant improvements in measures of quality of life. As monitoring methods were aligned with standard clinical practice,\(^23\) the success observed in this registry may better reflect the incidence of clinically relevant atrial arrhythmia recurrences following cryoballoon ablation of PAF and PsAF.

Notably, 42% of all treated patients had not failed an AAD prior to cryoballoon ablation in this registry, which often pre-empts enrollment in a clinical trial. This observation indicates that cryoablation is used to treat patients early in the disease process, and it may be employed as an alternative to prescription of an AAD in real-world clinical practice. Early rhythm control was recently reported to reduce the risk of cardiovascular morbidities in patients with AF.\(^24\) Further, ablation for the treatment of AF earlier (after diagnosis of AF) has been demonstrated to improve success of catheter ablation and reduce the risk of AF disease progression.\(^25\)\(^-\)\(^27\) Indeed, in this study first-line cryoballoon ablation resulted in significantly higher rates of success compared to drug refractory patients; 90% of PAF and 73% of PsAF first-line patients maintained freedom from arrhythmia recurrence at 12 months. Initial results from the CRYO FIRST and STOP First trials (presented online at DGK 2020 and EHRA, respectively) demonstrate that first-line cryoballoon catheter ablation improves efficacy compared to AADs
with a similar risk for serious adverse events. The observations in this registry indicate that cryoballoon ablation in non-drug-refractory patients with PAF and PsAF is performed as standard-of-care therapy safely and effectively and may contribute to earlier and improved management of AF in real-world practice.

4.4 | Study limitations

This study was designed to evaluate the real-world use of cryoballoon ablation for the treatment of AF according to standard-of-care policies across the globe; therefore, it was a non-randomized, observational study design. Patients were not excluded from the trial for pre-existing baseline characteristics, and investigators were trained to approach all eligible patients for participation in the registry; however, the results may be influenced by patient selection bias. Comparisons between sub-cohorts (eg, PAF, PsAF, No-AAD, first-line, and drug refractory) may be influenced by baseline characteristics. Patients were monitored for atrial arrhythmia recurrence according to site-specific standard practice, and a uniform approach was not protocol required across centers. As follow-up was physician and patient determined, and 20% of patients did not have atrial arrhythmia monitoring performed during follow-up, it is possible that asymptomatic and other atrial arrhythmias were not detected; however, the results reflect the real-world clinical experience of patients and providers. As the registry is ongoing, 12 month follow-up was not available for all patients who were treated with cryoballoon ablation during the study window, and not all geographies in the study had 12 month follow-up data included in this report. Therefore, procedural outcomes were evaluated among all 2922 eligible patients who underwent an index procedure (Procedure Analysis Cohort) and efficacy was assessed in the subset of 1440 patients with 12 month follow-up available during this study window (Efficacy Analysis Cohort).

5 | CONCLUSIONS

The Arctic Front Cardiac Cryoblation System has been adopted globally, and the results from this Cryo AF Global Registry demonstrate robust safety, efficiency, and efficacy across a broad range of patients with AF when cryoballoon ablation is performed according to local standards of care. Cryoballoon ablation was frequently performed with few adjunctive tools, which may contribute to procedural efficiencies. Additionally, the high rates of freedom from
arrhythmia recurrence that were observed in this real-world experience are congruent with the significant improvements in quality of life measured between baseline and the 12 month timepoint. A large percentage of non-drug-refractory and first-line patients were treated within this registry and suggests that cryoballoon ablation can be used safely and effectively as a first-line therapy.

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DISCLOSURE
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SUPPORTING INFORMATION
Additional supporting information may be found online in the Supporting Information section.

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