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Cryoballoon ablation of pulmonary veins for persistent atrial fibrillation: Results from the multicenter STOP Persistent AF trial

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Cryoballoon ablation of pulmonary veins for persistent atrial fibrillation: Results from the multicenter STOP Persistent AF trial

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BACKGROUND Pulmonary vein isolation (PVI) is the cornerstone of catheter ablation to treat patients with symptomatic drug-refractory atrial fibrillation (AF).

OBJECTIVE The purpose of this study was to assess the safety and efficacy of PVI using the cryoballoon catheter to treat patients with persistent AF.

METHODS *STOP Persistent AF* (ClinicalTrials.gov Identifier: NCT03012841) was a prospective, multicenter, single-arm, Food and Drug Administration–regulated trial designed to evaluate the safety and efficacy of PVI-only cryoballoon ablation for drug-refractory persistent AF (continuous episodes <6 months). The primary efficacy endpoint was 12-month freedom from ≥30 seconds of AF, atrial flutter (AFL), or atrial tachycardia (AT) after a 90-day blanking period. The prespecified performance goals were set at >40% and <13% for the primary efficacy and safety endpoints, respectively. Secondary endpoints assessed quality of life using the AFEQT (Atrial Fibrillation Effect on Quality of Life) and SF (Short Form)-12 questionnaires.

RESULTS Of 186 total enrollments, 165 subjects (70% male; age 65 ± 9 years; left atrial diameter 4.2 ± 0.6 cm; body mass index 31 ± 6) were treated at 25 sites in the United States, Canada, and Japan. Total procedural, left atrial dwell, and fluoroscopy times were 121 ± 46 minutes, 102 ± 41 minutes, and 19 ± 16 minutes, respectively. At 12 months, the primary efficacy endpoint was 54.8% (95% confidence [CI] 46.7%–62.1%) freedom from AF, AFL, or AT. There was 1 primary safety event, translating to a rate of 0.6% (95% CI 0.1%–4.4%). AFEQT and SF-12 assessments demonstrated significant improvements from baseline to 12 months postablation (P <.001).

CONCLUSION The STOP Persistent AF trial demonstrated cryoballoon ablation to be safe and effective in treating patients with drug-refractory persistent AF characterized by continuous AF episodes <6 months.

KEYWORDS Cryoballoon ablation; Persistent atrial fibrillation; Pulmonary vein isolation; Quality of life; Repeat ablation

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Introduction

Atrial fibrillation (AF) manifests on a continuum from brief, infrequent episodes to many prolonged episodes, and can progress from paroxysmal to persistent atrial fibrillation (PsAF).[1] No ablation lesion set has been demonstrated to improve outcomes for patients with PsAF beyond that of pulmonary vein isolation (PVI) alone in randomized clinical trials.[2–6] Therefore, despite the heterogeneous clinical

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presentation of AF, PVI is the cornerstone of catheter ablation for both drug-refractory paroxysmal AF and PsAF.[1] Cryoballoon catheter ablation is an established, Food and Drug Administration (FDA)–approved method for PVI to treat recurrent, symptomatic, drug-refractory paroxysmal AF.[1,7–9] It also has been used effectively for treatment of PsAF.[10–12] There is a critical need for an FDA-approved ablation catheter for the treatment of patients with PsAF. Accordingly, the STOP Persistent AF trial was designed to evaluate the safety and efficacy of cryoballoon ablation for the treatment of patients with recurrent, symptomatic, drug-refractory PsAF using a "PVI-only" ablation strategy for FDA approval of this expanded indication.

Methods

Study design

STOP Persistent AF was a prospective, multicenter, single-arm study with prespecified primary safety and efficacy performance goals. Patients with drug-refractory PsAF were evaluated during a 12-month follow-up period at 25 sites across the United States, Canada, and Japan (Table S1). Each patient provided informed consent before enrollment. The study was approved by each site's ethics and/or institutional review board, conducted in accordance with the Declaration of Helsinki, and registered on ClinicalTrials.gov (Identifier: NCT03012841).

Inclusion and exclusion criteria

Patients older than 18 years with symptomatic PsAF and documented failure or intolerance to at least one class I or III antiarrhythmic drug (AAD) were eligible for inclusion. Patients were required to have continuous PsAF episodes $>$7 days but $<$6 months documented by consecutive electrocardiographic (ECG) recordings or an ECG recording and a physician assessment. All exclusion criteria are detailed in the Supplemental Material, including left atrial (LA) diameter $>$5.0 cm, left ventricular ejection fraction $\leq$35%, and any previous cardiac surgery.

Cryoballoon ablation procedure

The cryoballoon ablation procedure has been described in detail previously.[7–14] In brief, subjects were sedated, and LA access was obtained via femoral venous access and a transseptal approach. Targeted activated clotting time was $\geq$300 seconds. A dedicated 15F delivery sheath (FlexCath; Medtronic, Inc, Minneapolis, MN) was introduced into the LA over-the-wire along with the cryoballoon catheter (Arctic Front Advance; Medtronic). A dedicated inner-lumen mapping catheter (Achieve; Medtronic) was commonly used for delivery of the cryoballoon and sheath.

The Achieve mapping catheter/guidewire was maneuvered into a pulmonary vein (PV). The inflated cryoballoon was advanced toward the antral surface of the PV, and a cryoapplication was initiated. Recommended cryoballoon application time was 3 minutes per ablation; however, the number and duration of cryoapplications were left to physician discretion. Phrenic nerve pacing was conducted using a diagnostic catheter at the level of the right subclavian vein during right-sided ablation, and diaphragmatic movement was monitored. Catheter ablation was immediately terminated upon weakened diaphragmatic response.

A focal 8-mm-tip cryoablation catheter (Freezor MAX; Medtronic) was allowed as an adjunctive tool to complete PVI, but any adjunctive LA ablation was not allowed. Investigators were permitted to test acute PVI with isoproterenol and/or adenosine. Electrical or pharmacologic cardioversion to sinus rhythm was attempted after PVI if sinus rhythm was not achieved. If medically necessary (eg, history of typical right atrial flutter), a focal ablation catheter could be used to create a cavotricuspid isthmus (CTI) line. Postablation care and patient discharge followed individual hospital policies and procedures. Discontinuation of class I and III AADs by the end of the 90-day blanking period was recommended. Systemic anticoagulation was recommended for at least 2 months after the procedure.

Patient follow-up

Follow-up was conducted over 12 months and included a phone call at 6 weeks; in-office visits at 3, 6, and 12 months; and transtelephonic monitoring weekly and additionally upon symptoms beginning 3 months postprocedure throughout follow-up. A 12-lead ECG was recorded at each in-office visit, and a 24-hour Holter monitor recording was also performed at 6 and 12 months. Recordings were sent to an independent core laboratory for review. Quality-of-life surveys (SF [Short Form]-12 and AFEQT [Atrial Fibrillation Effect on Quality of Life] questionnaires) were administered before the ablation procedure and at the 6- and 12-month office visits.

Endpoints

Freedom from the primary efficacy endpoint at 12 months was measured against a predefined performance goal of 40% and defined by 4 criteria: (1) acute procedural success defined as PVI achieved by cryoablation (non-PVI cryoablation/LA radiofrequency catheter ablation was not permitted); (2) freedom from recurrent atrial arrhythmia (ie, AF/atrial flutter [AFL]/atrial tachycardia [AT] $\geq$30 seconds or $\geq$10 seconds on a 12-lead ECG) after a 90-day blanking period; (3) freedom from repeat ablation after the blanking period (1 repeat PVI-only cryoablation or CTI ablation was allowed during blanking); and (4) no class I or III AAD initiation or dose increase after the blanking period.

The primary safety event rate was measured against a predefined performance goal of 13% and included the following serious system- or procedure-related adverse events: (1) death, transient ischemic attack, cerebrovascular accident, major bleeding that requires transfusion, myocardial infarction, cardiac perforation, tamponade, or pericardial effusion within 7 days of the ablation procedure; (2) PV stenosis ($>$75% reduction in cross-sectional area) or atrioesophageal fistula within 12 months of the ablation procedure; or (3)

unresolved phrenic nerve injury (PNI) at 12 months after the ablation procedure. All adverse events were reported, reviewed, and adjudicated by an independent physician committee. Secondary endpoints included assessment of quality of life at baseline, 6 months, and 12 months after the index ablation procedure as measured by AFEQT and SF-12. Ancillary endpoints were recorded to give further details on procedural characteristics and ongoing clinical care.

Statistical analysis

The Kaplan–Meier method was used to estimate the primary efficacy endpoint and the primary safety rate through 12 months. Standard error was approximated using the Greenwood formula. Primary safety and efficacy hypotheses were tested using a 1-sided test at a significance level of 0.025. Predefined performance criteria were a primary safety event rate at 12 months <13% and a primary efficacy rate at 12 months >40%. A primary efficacy success rate of 54% at 12 months, a primary safety event rate of 5% at 12 months, and an estimated early study exit up to 10% were assumed in the study protocol. Therefore, a total of 165 treated subjects afforded 92% power to test the efficacy endpoint and 93% power to test the safety endpoint.

A separate paired Student *t* test for each quality-of-life endpoint (AFEQT, SF-12 mental, SF-12 physical) was used to test a change from baseline to 12 months. Change in total number of arrhythmia-related symptoms from baseline to 12 months was assessed with a paired Student *t* test. The McNemar test was used to assess change for each specific arrhythmia-related symptom from baseline to month 12. Statistical analyses were performed using SAS software Version 9.4 (SAS Institute, Cary, NC) and R statistical software version 3.2.5 (Foundation for Statistical Computing, Vienna, Austria).

Results

Patients and procedural characteristics

Between March 2017 and July 2018, 186 patients with drug-refractory symptomatic PsAF were enrolled into the STOP Persistent AF trial. Of those patients, 165 were treated by cryoballoon PVI, and 145 completed the required 12-month follow-up schedule (Figure 1). Scheduled follow-up visits were completed for 96.3% of subjects, and weekly transtelephonic monitoring sessions were transmitted for 73.2% of the weeks in which patients were followed. Baseline patient characteristics are summarized in Table 1. Overall, 70% of the cohort was male, mean age was 65 ± 9 years, LA diameter 4.2 ± 0.6 cm, body mass index 31 ± 6 kg/m^2, and 73.3% of subjects had a previous cardioversion. Procedural characteristics are listed in Table 2.

Primary efficacy endpoint

The trial met the predefined performance goal of >40% freedom from primary efficacy failure, with a 12-month Kaplan–Meier estimate of 54.8% (95% confidence interval [CI] 46.7%–62.1%; $P < .001$) (Figure 2A). In total, 72 subjects

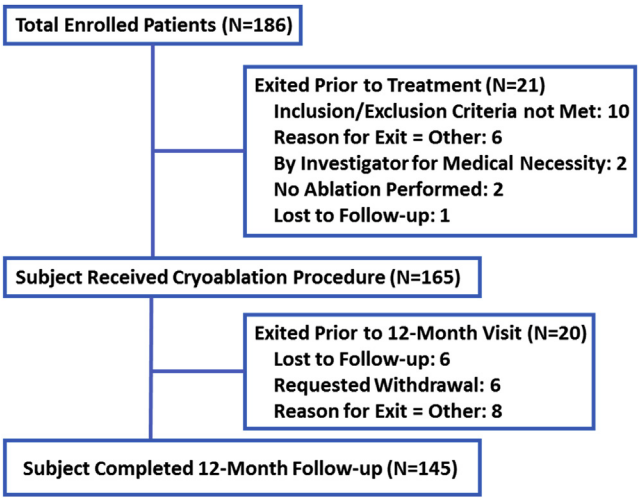

Figure 1 Patient enrollment and subject disposition. Patient flow and disposition from time of enrollment to study completion.

reached a primary efficacy failure endpoint event (Table 3). One subject had an acute efficacy failure due to PVI touchup via radiofrequency ablation. Two subjects had efficacy failures during repeat procedures in the blanking period for radiofrequency ablation or non-PV ablation. Ten subjects had a change/increase in AAD dosage beyond the 90-day blanking

Table 1 Baseline patient characteristics (N = 165)

Male sex	116 (70.3%)
Age (y)	65 ± 9
Left atrial diameter (cm)	4.2 ± 0.6
Left ventricular ejection fraction (%)	57 ± 7
AF at baseline visit	134 (81.2%)
Years since paroxysmal AF onset	5.1 ± 6.5
Years since persistent AF onset	0.6 ± 1.3
Duration of most recent AF episode (d)	60.5 ± 46.5
Duration of longest AF episode (d)	71.6 ± 48.9
No. of failed antiarrhythmic drugs	1.2 ± 0.5
Cardioversion before enrollment	121 (73.3%)
Cardioversions/patient before enrollment	1.9 ± 2.3
History of atrial flutter	28 (17.0%)
Body mass index (kg/m^2)	31 ± 6
Systolic blood pressure (mm Hg)	129 ± 18
Diastolic blood pressure (mm Hg)	79 ± 12
Race or ethnicity origin	
White or Caucasian	142 (86.1%)
Black	2 (1.2%)
Japanese	15 (9.1%)
Filipino	1 (0.6%)
Other Asian	1 (0.6%)
Subject chose not to provide	4 (2.7%)
Coronary artery disease	18 (10.9%)
Previous myocardial infarction	8 (4.8%)
Hypertension	98 (59.4%)
Previous stroke/transient ischemic attack	6 (3.6%)
Diabetes	20 (12.1%)
Sleep apnea	50 (30.3%)
Chronic obstructive pulmonary disease	10 (6.1%)
Renal impairment	9 (5.5%)
History of congestive heart failure	32 (19.4%)
CHA_2DS_2-VASc score	2.2 ± 1.4

Values are given as n (%) or mean ± SD.
AF = atrial fibrillation.

Table 2 Index procedural characteristics (N = 165)

Total procedure time (min)	121±46
Left atrial dwell (min)	102±41
Study device left atrial dwell (min)	66±25
Total fluoroscopy time (min)	19±16
Cryoapplication duration (min)	24±8
Cavotricuspid isthmus line	50 (30.3%)
Acute success*	164 (99.4%)
PVI success by cryoballoon only	156
PVI touchup with focal cryocatheter	8
Cryoballoon applications	
No. of applications per vein	2.3±1.4
PVs treated with single cryoapplication	141/648 (21.8%)
Duration of cryoapplication (sec)	154±47
Median (interquartile range)	180 (120, 180)
Isoproterenol and/or adenosine used to assess PVI	24 (14.5%)

Values are given as mean ± SD, n (%), or n unless otherwise indicated.
PV = pulmonary vein; PVI = pulmonary vein isolation.
*Acute procedural failure in 1 subject resulted from radiofrequency ablation to complete PVI.

period. The remaining 59 subjects had atrial arrhythmia recurrence outside the 90-day blanking period.

Primary safety endpoint

The predefined primary safety performance goal of <13% was met with a 12-month Kaplan-Meier estimate of 0.6% (95% CI 0.1%–4.4%; $P = .002$) (Figure 2B). The single primary safety event observed in this trial was an aortic root perforation during transseptal puncture that occurred during a planned radiofrequency repeat ablation 163 days after the index procedure. The patient recovered from this event within 1 month of the procedure and underwent a successful reablation upon recovery. No reports of death, stroke, transient ischemic attack, major bleeding that required transfusion, myocardial infarction, tamponade, pericardial effusion, atrioesophageal fistula, PV stenosis, or PNI unresolved at study exit met the endpoint criteria.

Additional procedure-related events

A total of 10 serious adverse events were reported in 9 subjects (5.5%) in the study:1 primary safety event and 9 additional events related to the procedure. Of those events, 5 were classified as related to the cryoablation system in 5 subjects (3.0%) (Table 4). The most common serious adverse event was vascular pseudoaneurysm, which occurred in 2 subjects (1.2%). Two subjects experienced transient PNI that resolved before discharge from the index procedure, and 1 subject experienced PNI that resolved before completing study follow-up. Because all PNI events resolved, none were adjudicated as serious adverse events.

Quality of life, AAD usage, and repeat ablations

Quality of life was measured at baseline, 6 months, and 12 months using 2 separate questionnaires: AFEQT and SF-12 (Figures 3A and 3B, and Table 5). AFEQT score improved by 25.8 (95% CI 22.1–29.5) from baseline (63.7 ± 20.6) to 12 months (89.5 ± 13.7; $P < .001$). SF-12 mental score

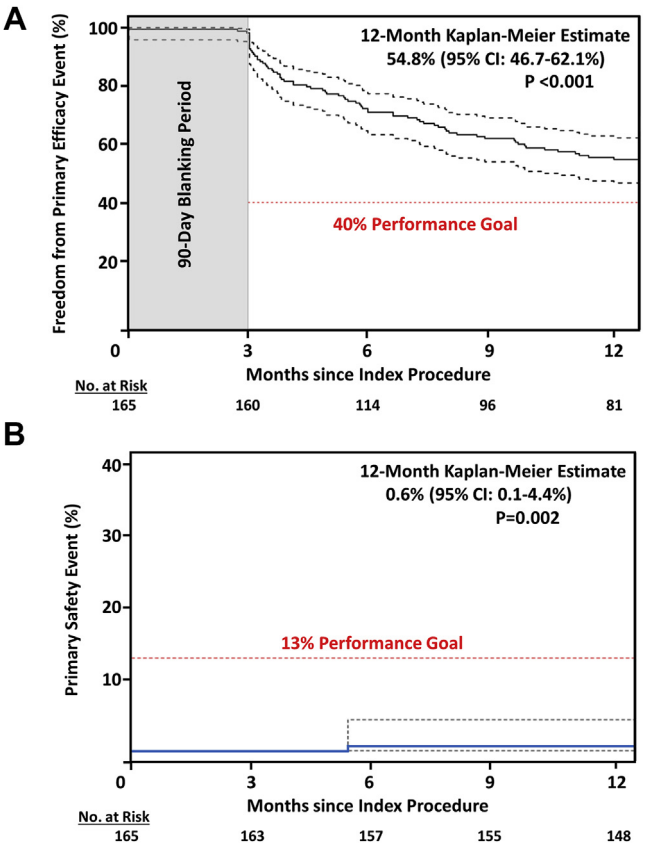

Figure 2 Primary endpoints. **A:** Kaplan–Meier 12-month estimate of freedom from primary efficacy failure (acute procedural failure, initiation/dose increase of class I or III antiarrhythmic drugs, ≥30-second recurrence of atrial fibrillation/atrial flutter/atrial tachycardia, or repeat ablation after a 90-day blanking period). The prespecified performance goal of >40% (*dashed red line*), Kaplan–Meier estimate (*solid black line*), and 95% confidence intervals (CIs) (*dashed black lines*) are depicted. The 12-month estimate of 54.8% (95% CI 46.7%–62.1%) freedom from the primary efficacy endpoint exceeded the 40% performance goal, so the primary objective was met ($P < .001$). **B:** The 12-month estimate of 0.6% (95% CI 0.1%–4.4%) is below the prespecified performance goal of 13% (*red dashed line*); the safety objective was met ($P = .002$).

increased by 4.9 (95% CI 3.2–6.6) from baseline (49.3 ± 9.8) to 12 months (54.2 ± 7.7; $P < .001$), and SF-12 physical score improved by 5.0 (95% CI 3.5–6.5) from baseline (44.2 ± 9.7) to 12 months (49.2 ± 8.3; $P < .001$). All patients reported AF-related symptoms at baseline; 82% of patients without a recurrence and 49% of patients with a recurrence over the study period reported no AF-related symptoms at the 12-month visit. Patient-reported AF arrhythmia-related symptoms were significantly reduced from baseline to 12 months for all symptoms but syncope (3% to 1%; $P = .18$), including dizziness (29% to 6%), palpitations (65% to 18%), rapid heartbeat (19% to 9%), dyspnea (57% to 16%), and fatigue (58% to 16%) (all other symptoms $P < .01$) (Figure 3C). An increase in quality of life (as measured by AFEQT and SF-12) and a reduction in AF-related symptoms was observed in patients with and without recurrence ($P < .05$ for all).

Discontinuation of AADs after the blanking period was recommended but not required by protocol. The proportion of subjects on AADs reduced from 42% at the end of the

Table 3 Description of failure events within the primary efficacy endpoint

Efficacy failure event	No. of subjects
Acute procedural failure	1
Ablation beyond PVI within 90-day blanking	1
Radiofrequency repeat PVI within 90-day blanking	1
Change in antiarrhythmic drugs*	10
Atrial arrhythmia recurrence during follow-up	59
Atrial fibrillation	46
Atrial flutter	9
Atrial fibrillation and atrial flutter	1
Atrial tachycardia	3
Total	72

PVI = pulmonary vein isolation.
*Antiarrhythmic drug dose greater than the preablation maximum dose after the 90-day blanking period.

blanking period to 21% at 12 months after cryoballoon PVI. In total, 24 reablations were performed in 21 subjects from the time of the index procedure through the 12-month follow-up, which included 5 (3 CTI, 2 cryoballoon PVI) protocol-permitted redo procedures conducted during the 90-day blanking period. The resultant 12-month Kaplan–Meier estimate showed that 86.8% (95% CI 80.5%–91.2%) of subjects were free of a repeat catheter ablation during the trial follow-up period (Figure 3D).

Discussion

The STOP Persistent AF trial was a multicenter, prospective, single-arm study that evaluated the safety and efficacy of a PVI-only approach using cryoballoon ablation in patients with drug-refractory PsAF with continuous AF episode duration(s) <6 months. This study was FDA-regulated in support of cryoballoon catheter approval for ablation of patients with PsAF. The 12-month primary safety and primary efficacy endpoints met the prespecified performance goals: 0.6% of patients had a primary safety event, and 54.8% of patients maintained freedom from AF/AFL/AT during the 12-month follow-up period. Significant improvements in patient quality of life were documented by both the AFEQT score and SF-12 surveys, and patient-reported AF symptoms declined from baseline to the 12-month trial endpoint. These data indicate that cryoballoon PVI for the treatment of these patients with PsAF is safe and effective.

Table 4 Serious device- and procedure-related adverse events through 12 months*

Adverse event	Cryoablation system-related events [n (%) of subjects]	Ablation procedure-related events [n (%) of subjects]
Aortic perforation†	0 (0, 0%)	1 (1, 0.6%)
Atrial tachycardia‡	1 (1, 0.6%)	1 (1, 0.6%)
Pericarditis	1 (1, 0.6%)	1 (1, 0.6%)
Vascular pseudoaneurysm	2 (2, 1.2%)	2 (2, 1.2%)
Acute cardiac failure	0 (0, 0%)	1 (1, 0.6%)
Postoperative ileus	0 (0, 0%)	1 (1, 0.6%)
Puncture site hematoma	1 (1, 0.6%)	1 (1, 0.6%)
Respiratory failure	0 (0, 0%)	1 (1, 0.6%)
Urinary tract infection‡	0 (0, 0%)	1 (1, 0.6%)
Total	5 (5, 3.0%)	10 (9, 5.5%)

*A total of 189 ablation procedures were performed through 12 months: 165 index cryoballoon PVI and 24 repeat ablations.
†The single primary safety event observed was an aortic root perforation during transseptal puncture that occurred during a planned radiofrequency repeat ablation 163 days after the index procedure. The event met the primary safety event component of cardiac perforation.
‡Events reported after repeat cryoballoon procedures.

Efficacy and efficiency of cryoballoon PVI in PsAF

The observed results were in line with previously reported studies that reported 1-year freedom from atrial arrhythmia of 60.7%–76.2% in patients with PsAF treated with cryoballoon PVI.[10–12] The major difference in our trial was that patients were monitored weekly for arrhythmia recurrence vs every 3–6 months. These results corroborate that PVI is essential to treating patients with PsAF. Indeed, adjunctive ablation sets designed to target the heterogeneous physiology of PsAF with radiofrequency ablation have failed to demonstrate improved efficacy at the cost of prolonged procedural durations in large, randomized cohorts of pateints.[2–6] Total procedural time and cryoballoon LA dwell time in this trial are consistent with procedural times previously reported for cryoballoon ablation of patients with either paroxysmal AF or PsAF.[7–12,15]

Similar to findings from previous cryoballoon PVI trials in patients with either paroxysmal AF or PsAF,[11,16] significant and clinically meaningful improvements in mental and physical health after cryoballoon ablation were observed.[17,18] Despite failing the primary endpoint, subjects with recurrence reported significant improvements in quality of life and a significant reduction in AF-related symptoms. Furthermore, prescription of AADs was reduced between the blanking period and 12-month follow-up, and 86.8% of patients were free from repeat ablation inclusive of reablations during blanking. These data suggest that irrespective of a ≥30-second arrhythmia recurrence, cryoballoon ablation improved patient quality of life, reduced AF-related symptoms, and limited the need for subsequent intervention in the management of PsAF.

Safety outcomes of cryoballoon PVI in PsAF

No transient ischemic attack, cerebrovascular accident, major bleeding, cardiac tamponade, myocardial infarction, PV stenosis, atrioesophageal fistula, or death related to the procedure occurred during the STOP Persistent AF trial. Furthermore, no patient experienced unresolved PNI at the time of study exit, which is consistent with the CRYO4PERSISTENT study.[11] In our trial, 1 patient suffered from an aortic puncture during a repeat procedure. Although this event was not related to the cryoballoon system, it did meet the primary safety event endpoint criteria, resulting in a primary safety event rate of 0.6%. Overall, the 5.5% rate of serious procedural related events in STOP Persistent AF

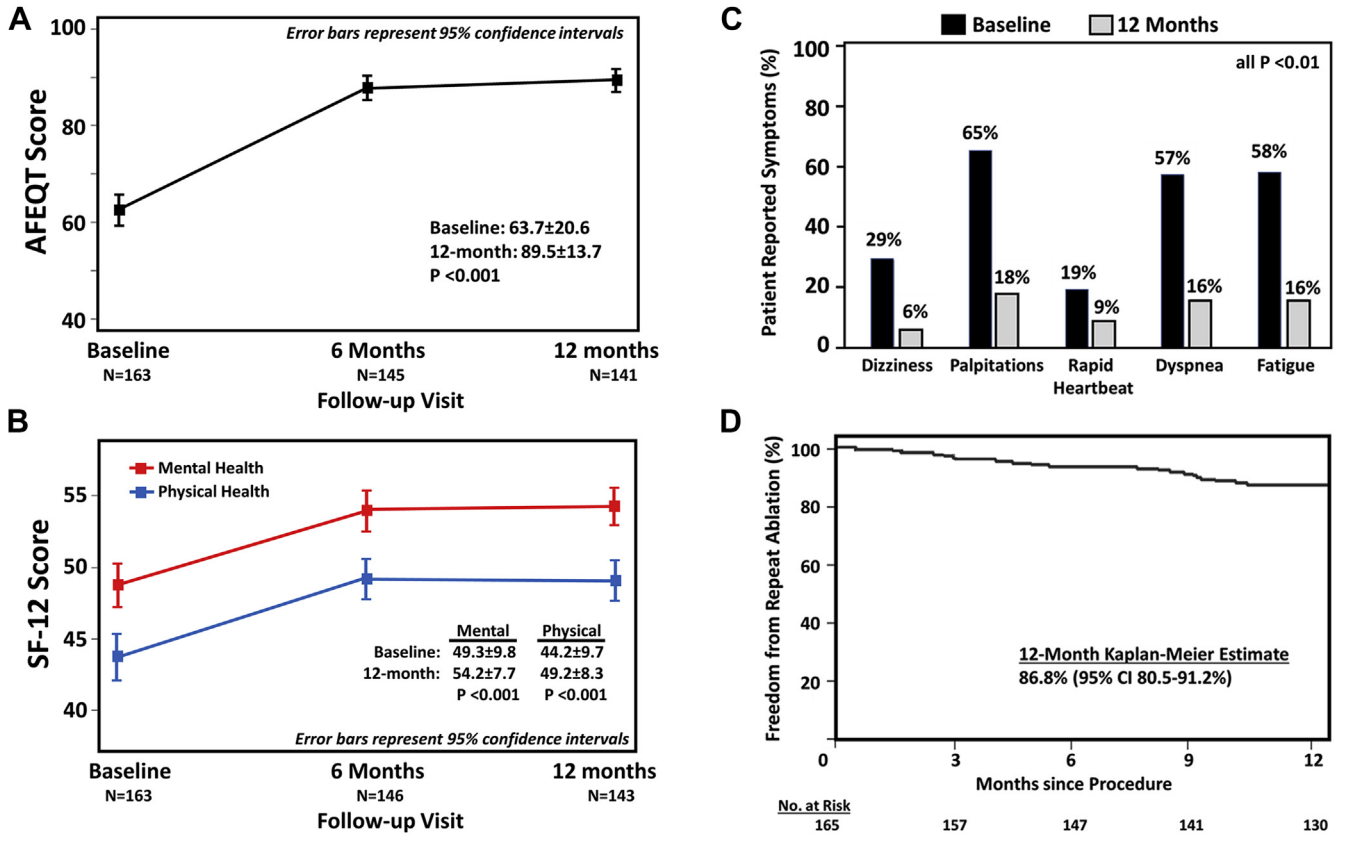

Figure 3 Quality of life, symptoms, and repeat ablation. Mean Atrial Fibrillation Effect on Quality of Life (AFEQT) score (**A**) and mean physical and mental health Short Form (SF)-12 measurements (**B**) of the total cohort at baseline, 6 months, and 12 months after cryoballoon ablation are shown. AFEQT score significantly improved from baseline to the 12-month endpoint ($P < .001$). Both the SF-12 physical and mental health scores significantly improved from baseline to the 12-month endpoint ($P < .001$). **C:** There was a significant reduction in the presented atrial fibrillation–related symptoms measured between baseline and 12 months ($P < .01$). **D:** Kaplan–Meier 12-month estimate of the freedom from repeat ablation during the 12-month trial period inclusive of reablations during the blanking period was 86.8% (95% confidence interval [CI] 80.5%–91.2%).

(3.0% for serious cryoballoon-related events) is similar to the recently reported major adverse event rate of 4.0% in the CRYO4PERSISTENT trial and the 5.8% serious adverse event rate published in a contemporary report of cryoballoon PVI in patients with paroxysmal AF.[9,11] Together, these observations suggest the safety risk of cryoballoon PVI is similar for patients with paroxysmal AF and PsAF.

PsAF patient population

In line with the Heart Rhythm Society (HRS) 2017 consensus definition of PsAF, the studied patients were characterized by PsAF lasting >7 days.[1] However, continuous AF episodes were limited to <6 months in this cohort. The average maximum-episode duration was 71.6 days, with 73.3% of patients cardioverted before enrollment. There were no inclusion criteria specific to the time diagnosed with PsAF. On average patients were diagnosed with PsAF 7 months before treatment; 1 patient had PsAF for 9.9 years before enrollment. Thus, the STOP Persistent AF inclusion criteria and resultant cohort are different from the CRYO4PERSISTENT trial, which only allowed patients diagnosed with symptomatic PsAF for <12 months.[11] Other recent multicenter studies included patients with sustained episodes of AF >7 days but <12 months.[10,12] Although these study cohorts have varied baseline characteristics, cryoballoon PVI has consistently resulted in >50% freedom from arrhythmia recurrence.[10–12]

Table 5 Quality of life measured at baseline and 12 months

Survey	Baseline	12 months	Change (95% CI)	*P* value
AFEQT	63.7±20.6	89.5±13.7	25.8 (22.1–29.5)	<.001
SF-12 mental	49.3±9.8	54.2±7.7	4.9 (3.2–6.6)	<.001
SF-12 physical	44.2±9.7	49.2±8.3	5.0 (3.5–6.5)	<.001

Values are given as mean ± SD unless otherwise indicated.
AFEQT = Atrial Fibrillation Effect on Quality of Life; SF = Short Form.

Study limitations

Although this trial was single-armed and nonrandomized, it was performed with the rigor required for an FDA evaluation process. Ablation success required freedom from recurrent AF/AT/AFL lasting ≥30 seconds evaluated via a rigorous monitoring schedule. Predefined performance criteria and robust inclusion/exclusion criteria were used to reduce the risk of bias in interpretation of the results and patient selection, respectively. The trial was designed to evaluate patients with PsAF episodes <6 months in continuous duration;

therefore, results may not apply to patients with PsAF episodes of longer duration. Measurements of symptoms and quality of life can be impacted by variables not controlled for in the trial. In addition, 20 of 165 patients who underwent cryoballoon ablation dropped out of the study before the 12-month follow-up: 6 lost to follow-up (3.6% lost to follow-up rate) and 14 exited the study early. Early-exit patients were monitored for a mean of 10.5 months before study exit, and reasons for exit were not due to an adverse event or worsening AF. Continuous monitoring was not used to measure patient outcomes in terms of AF burden.

Conclusion

Cryoballoon ablation used exclusively for isolation of the PVs for treatment of patients with PsAF is both safe and effective. Independent of arrhythmia recurrence $\geq$30 seconds, this treatment strategy resulted in significant improvements in quality of life and a reduction in AF-related symptoms for treated patients.

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Appendix

Supplementary data

Supplementary data associated with this article can be found in the online version at https://doi.org/10.1016/j.hrthm.2020.06.020.

References

1. Calkins H, Hindricks G, Cappato R, et al. 2017 HRS/EHRA/ECAS/APHRS/SOLAECE expert consensus statement on catheter and surgical ablation of atrial fibrillation. Heart Rhythm 2017;14:e275–e444.
2. Verma A, Jiang CY, Betts TR, et al; STAR AF II Investigators. Approaches to catheter ablation for persistent atrial fibrillation. N Engl J Med 2015;372:1812–1822.
3. Dixit S, Marchlinski FE, Lin D, et al. Randomized ablation strategies for the treatment of persistent atrial fibrillation: RASTA study. Circ Arrhythm Electrophysiol 2012;5:287–294.
4. Verma A, Sanders P, Champagne J, et al. Selective complex fractionated atrial electrograms targeting for atrial fibrillation study (SELECT AF): a multicenter, randomized trial. Circ Arrhythm Electrophysiol 2014;7:55–62.
5. Wong KC, Paisey JR, Sopher M, et al. No benefit of complex fractionated atrial electrogram ablation in addition to circumferential pulmonary vein ablation and linear ablation: Benefit of Complex Ablation Study. Circ Arrhythm Electrophysiol 2015;8:1316–1324.
6. Fink T, Schlüter M, Heeger CH, et al. Stand-alone pulmonary vein isolation versus pulmonary vein isolation with additional substrate modification as index ablation procedures in patients with persistent and long-standing persistent atrial fibrillation: the Randomized Alster-Lost-AF Trial (Ablation at St. Georg Hospital for Long-Standing Persistent Atrial Fibrillation). Circ Arrhythm Electrophysiol 2017;10:e005114.
7. Packer DL, Kowal RC, Wheelan KR, et al; STOP AF Cryoablation Investigators. Cryoballoon ablation of pulmonary veins for paroxysmal atrial fibrillation: first results of the North American Arctic Front (STOP AF) pivotal trial. J Am Coll Cardiol 2013;61:1713–1723.
8. Kuck KH, Brugada J, Fürnkranz A, et al; FIRE AND ICE Investigators. Cryoballoon or radiofrequency ablation for paroxysmal atrial fibrillation. N Engl J Med 2016;374:2235–2245.
9. Knight BP, Novak PG, Sangrigoli R, et al; STOP AF PAS Investigators. Long-term outcomes after ablation for paroxysmal atrial fibrillation using the second-generation cryoballoon: final results from STOP AF Post-Approval Study. JACC Clin Electrophysiol 2019;5:306–314.
10. Akkaya E, Berkowitsch A, Zaltsberg S, et al. Five-year experience with pulmonary vein isolation using the second-generation cryoballoon for treatment of persistent atrial fibrillation. J Cardiovasc Electrophysiol 2018;29:1500–1507.
11. Boveda S, Metzner A, Nguyen DQ, et al. Single-procedure outcomes and quality-of-life improvement 12 months post-cryoballoon ablation in persistent atrial fibrillation: results from the Multicenter CRYO4PERSISTENT AF Trial. JACC Clin Electrophysiol 2018;4:1440–1447.
12. Tondo C, Iacopino S, Pieragnoli P, et al; ClinicalService 1STOP Project Investigators. Pulmonary vein isolation cryoablation for patients with persistent and long-standing persistent atrial fibrillation: clinical outcomes from the real-world multicenter observational project. Heart Rhythm 2018;15:363–368.
13. Su W, Kowal R, Kowalski M, et al. Best practice guide for cryoballoon ablation in atrial fibrillation: the compilation experience of more than 3000 procedures. Heart Rhythm 2015;12:1658–1666.
14. Su W, Aryana A, Passman R, et al. Cryoballoon best practices II: practical guide to procedural monitoring and dosing during atrial fibrillation ablation from the perspective of experienced users. Heart Rhythm 2018;15:1348–1355.
15. Andrade JG, Champagne J, Dubuc M, et al. Cryoballoon or radiofrequency ablation for atrial fibrillation assessed by continuous monitoring: a randomized clinical trial. Circulation 2019;140:1779–1788.
16. Jain SK, Novak PG, Sangrigoli R, et al. Sustained quality-of-life improvement post-cryoballoon ablation in patients with paroxysmal atrial fibrillation: results from the STOP-AF Post-Approval Study. Heart Rhythm 2020;17:485–491.
17. Dorian P, Burk C, Mullin CM, et al. Interpreting changes in quality of life in atrial fibrillation: how much change is meaningful? Am Heart J 2013;166:381–387.
18. Stewart AL, Greenfield S, Hays RD, et al. Functional status and well-being of patients with chronic conditions. Results from the Medical Outcomes Study. JAMA 1989;262:907–913.