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Long-Term Outcomes After Ablation for Paroxysmal Atrial Fibrillation Using the Second-Generation Cryoballoon

Final Results From STOP AF Post-Approval Study

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ABSTRACT

OBJECTIVES STOP AF PAS is the first prospective, multicenter, 3-year study in North America to assess long-term safety and effectiveness of the cryoballoon for treatment of patients with drug-refractory symptomatic pAF.

BACKGROUND The STOP AF PAS (Sustained Treatment of Paroxysmal Atrial Fibrillation Post-Approval Study) was required by the US Food and Drug Administration at the time of approval of the first-generation cryoballoon for the treatment of paroxysmal atrial fibrillation (pAF). The second-generation cryoballoon (CB2) was commercially released shortly after this trial was initiated.

METHODS The study was nonrandomized. Enrollment was completed with 344 eligible patients undergoing pulmonary vein isolation (PVI) using the CB2. Procedure-related safety and freedom from AF and symptomatic atrial flutter/atrial tachycardia through 3 years were determined. Documented atrial arrhythmias ≥30 s were considered treatment failures.

RESULTS Acute PVI was achieved in 99.3% (1,341 of 1,350) of veins. Mean follow-up was 34 ± 7 months. The rate of major complications was 5.8%, including a 3.2% rate of phrenic nerve injury, which resolved in all but 1 patient by 36 months. At 36 months, 11.7% of patients were prescribed antiarrhythmic agents, inclusive of "pill-in-the-pocket" administration. Freedom from AF was 81.6% at 12 months, 73.8% at 24 months, and 68.1% at 36 months. Freedom from AF and symptomatic atrial flutter/atrial tachycardia was 79.0% at 12 months, 70.8% at 24 months, and 64.1% at 36 months. Freedom from a repeat ablation procedure was 80.9% at 36 months.

CONCLUSIONS PVI using the CB2 was an effective treatment for patients with pAF, with freedom from all atrial arrhythmias of 64% at 36 months. (Sustained Treatment of Paroxysmal Atrial Fibrillation Post-Approval Study [STOP AF PAS]; NCT01456949.) (J Am Coll Cardiol EP 2018;■:■-■) © 2018 by the American College of Cardiology Foundation.

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ABBREVIATIONS AND ACRONYMS

AF = atrial fibrillation

AFL = atrial flutter

AT = atrial tachycardia

CB2 = second-generation cryoballoon

CMAP = compound motor action potential

CBA = cryoballoon ablation

CT = computed tomography

FDA = US Food and Drug Administration

LCPV = left common pulmonary vein

LIPV = left inferior pulmonary vein

LSPV = left superior pulmonary vein

MRI = magnetic resonance imaging

pAF = paroxysmal atrial fibrillation

PNI = phrenic nerve injury

PV = pulmonary vein

PVI = pulmonary vein isolation

RIPV = right inferior pulmonary vein

RMPV = right middle pulmonary vein

RSPV = right superior pulmonary vein

Pulmonary vein isolation (PVI) using cryoballoon ablation (CBA) has been shown to be an effective therapy for patients with drug-refractory, recurrent, symptomatic paroxysmal atrial fibrillation (pAF) (1). The US Food and Drug Administration (FDA) approved the first-generation cryoballoon system, the Arctic Front Cardiac CryoAblation System (Medtronic, Minneapolis, Minnesota), in December 2010 after completion of the STOP AF (A Clinical Study of the Arctic Front Cryoablation Balloon for the Treatment of Paroxysmal Atrial Fibrillation) investigational device exemption trial. STOP AF PAS (Sustained Treatment of Paroxysmal Atrial Fibrillation Post-Approval Study) was a FDA-required condition of approval study to provide prospective long-term safety and effectiveness data for the Arctic Front system.

Shortly after STOP AF PAS enrollment started in 2012, a second-generation cryoballoon (CB2) became commercially available. In brief, the addition of 4 injection ports in CB2 allowed for more even distribution of nitrous oxide refrigerant across the distal hemisphere of the cryoballoon. Single-center studies typically with 1-year follow-up have evaluated clinical outcomes using CB2 with freedom from recurrence ≥80% (2–11). The randomized FIRE AND ICE Trial, conducted at 16 centers and 4 countries in Europe with an average of 1.5 years of follow-up per patient, resulted in a noninferiority of CBA for the treatment of patients with drug-refractory pAF compared with radiofrequency ablation (12). There are limited long-term data, however, regarding the multicenter experience of CB2 regarding the efficacy and procedural safety in the United States and Canada, particularly at 36 months of follow-up (13). The present analysis reports the STOP AF PAS long-term data in the predominant subgroup of patients treated with CB2. These data include: 1) adverse events; 2) procedural outcomes; and 3) long-term efficacy outcomes for patients at 36 months' post-ablation.

METHODS

STUDY DESIGN. STOP AF PAS was the largest, prospective, FDA-regulated, multicenter, single-arm, unblinded clinical study to provide long-term safety and effectiveness data on the cryoballoon system in North America. A total of 39 sites from the United States and Canada participated in the study, including 30 sites that were recent adopters of CBA at the time of study initiation (Online Table S1). The study was approved by each site's ethics/institutional review board and was registered on ClinicalTrials.gov (NCT01456949). All patients provided written informed consent before study participation, and the follow-up period was ≥3 years.

Patients were seen at 3, 6, and 12 months and annually thereafter for at least 3 years. During scheduled and unscheduled visits, all patients were assessed for their clinical history, and underwent a physical examination and a 12-lead electrocardiogram. Serial ambulatory electrocardiogram monitoring was performed using a 24-h Holter monitor at the 6-month visit and a 48-h Holter monitor at each annual visit for all patients. Patients who presented with symptoms believed to be due to an atrial arrhythmia not captured on an electrocardiogram or Holter monitor were provided with an event recorder for 30 days. Recurrence of AF was reported when there was a documented episode of AF lasting >30 s (both symptomatic and asymptomatic) and/or symptomatic atrial flutter (AFL)/atrial tachycardia (AT) was reported as an adverse event outside of the 90-day blanking period. Use of antiarrhythmic drugs post-ablation was not pre-specified in the study protocol.

In June 2012, the first patient was consented. A total of 402 patients were enrolled in the study, with 344 patients meeting inclusion/exclusion criteria and being treated with CB2 (mean follow-up, 34.3 ± 7.4 months). Fifty-eight patients were not included, including 24 patients who exited the study before the procedure (Online Table S2), 10 who were treated with the first-generation cryoballoon, 12 who did not meet the entrance criteria, 6 enrolled previously under a continued access protocol, and 6 who did not have complete data reported due to site noncompliance. All patients who remained in the study were followed up for a minimum of 3 years, and study

All authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the *JACC: Clinical Electrophysiology* author instructions page.

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follow-up was completed in November 2017. An independent committee adjudicated all adverse events, including arrhythmia recurrences.

INCLUSION AND EXCLUSION CRITERIA. Patients were required to have at least 2 episodes of symptomatic drug-refractory pAF within 3 months before enrollment and 1 episode of documented AF in the 12 months before enrollment. They were required to have failed to respond to at least 1 membrane-active antiarrhythmic drug. Major exclusion criteria included previous left atrial ablation, pre-existing hemidiaphragmatic paralysis, left atrial diameter >5.5 cm, a stroke within the previous 6 months, and the presence of a pacemaker or implantable cardioverter-defibrillator.

ABLATION PROCEDURE. The procedural techniques have been previously described (1), and the goal for CBA was acute isolation of all pulmonary veins (PVs). In brief, a pre-procedural transesophageal echocardiogram was performed to assess for the presence of intracardiac thrombus, and magnetic resonance imaging (MRI) or computed tomography (CT) imaging was performed to review the anatomy of the left atrium and PVs before the procedure. The management of peri-procedural oral anticoagulation was left to the discretion of the physician.

Transseptal catheterization was performed via the femoral vein. The transseptal sheath was exchanged for a 15-F OD steerable sheath (FlexCath Steerable Sheath; Medtronic). A 23- or 28-mm diameter CB2 was advanced through the FlexCath sheath into the left atrium and positioned into the antrum of each PV. Intravenous heparin was administered before and during left atrium ablation. Left-sided PVs were typically ablated first. Selection between the 2 balloon sizes was determined according to pre-procedural imaging (MRI/CT), pulmonary venography, and/or intracardiac echocardiography. Use of general anesthesia, CT/MRI, intracardiac echocardiography, esophageal temperature monitoring, three-dimensional mapping, compound motor action potential (CMAP) recordings, and/or multielectrode diagnostic catheters was left to the discretion of the physician.

During CBA, the balloon catheter was delivered by using an over-the-wire technique. This delivery was performed by using either a traditional J-tip guidewire or a dedicated cryoballoon inner-lumen octapolar circular mapping catheter (Achieve Mapping Catheter; Medtronic). Adequate PV occlusion with the balloon was determined by injection of radiopaque contrast agent through the distal end of the catheter. When the inner lumen circular mapping catheter was used, the electrodes were positioned as closely as possible to the PV antrum to monitor for PVI. Typically, a minimum of 2 cryoballoon freezes (each with a duration of 180 to 240 s) was performed at the ostium of each PV. Cryoapplications lasting <60 s were classified as aborted ablation attempts and excluded from the analysis. The endpoint was electrical isolation of each PV with verification of entrance block using the circular mapping catheter. Demonstration of exit block was not required.

The physician determined the total cryoapplication number, the duration of each freeze, the choice of focal ablation catheter when CBA was insufficient alone to achieve PV isolation, additional ablation (e.g., right/left AFL line or AF trigger ablation), and adjunctive tools/methods used to monitor the ablation (e.g., intracardiac echocardiography, three-dimensional mapping). Use (including discontinuation) of antiarrhythmic drugs post-ablation was not pre-specified in the study protocol.

PHRENIC NERVE MONITORING. To minimize the risk of phrenic nerve injury (PNI), right phrenic nerve stimulation was performed by pacing from an electrode catheter in the superior vena cava or right subclavian vein, and capture was confirmed by manual detection of abdominal contractions per the instructions for use. Application of cryoenergy was terminated immediately upon attenuation or loss of phrenic nerve capture. Some investigators used adjunctive methods such as recording and displaying the CMAP of diaphragmatic contractions during phrenic nerve pacing, but the use of CMAP was not mandated in the protocol.

Cinefluoroscopy was performed in all patients to document the movement of the right diaphragm at the beginning and at the end of the procedure. Patients with PNI were required to have a follow-up chest radiograph with inspiratory and expiratory views at the 3-month follow up visit and annually until resolution or study completion. Symptomatic and asymptomatic PNI was reported when any abnormal diaphragmatic excursion was observed or reported.

PV STENOSIS MONITORING. The presence or absence of PV stenosis was determined by using a follow-up MRI or CT scan performed for all patients at the 6-month visit. For any patient having a >50% reduction from baseline PV area, an additional review was performed by an independent core laboratory to determine whether PV stenosis, defined by the protocol as >75% reduction from baseline PV area, was present. For any patient with PV stenosis confirmed by the core laboratory, an additional MRI or CT scan was performed at 12 months and annually thereafter.

TABLE 1 Characteristics of 344 Patients Enrolled in STOP AF PAS Treated With the Second-Generation Cryoballoon

	Value
Age, yrs	60.2 ± 10.4
Height, in	68.8 ± 4.2
Weight, lb	201.4 ± 45.3
Body mass index, kg/m^2	29.9 ± 6.1
Male	228 (66.3)
Ethnicity (white or Caucasian)	319 (92.7)
Cardiovascular history	
Hypertension	168 (48.8)
Dyslipidemia	143 (41.6)
Diabetes	35 (10.2)
Myocardial infarction	9 (2.6)
Coronary artery disease	33 (9.6)
Left atrial diameter, mm	39.8 ± 5.6
AF (paroxysmal)	344 (100)
AF onset (years before consent)	4.5 ± 5.4
Failed to respond to antiarrhythmic agent at baseline	1.3 ± 0.5
NYHA functional class	
I	52 (15.1)
II	20 (5.8)
No heart failure	272 (79.1)
$CHADS_2$ score	
0	134 (39.0)
1	138 (40.1)
2	63 (18.3)
3	8 (2.32)
4	1 (0.3)

Values are mean ± SD for continuous data, and n (%) of patients for categorical data.

AF = atrial fibrillation; $CHADS_2$ = congestive heart failure, hypertension, age ≥75 years, diabetes mellitus, and stroke/transient ischemic attack; NYHA = New York Heart Association; STOP AF PAS = Sustained Treatment of Paroxysmal Atrial Fibrillation Post-Approval Study.

TABLE 2 STOP AF PAS Index Procedure Characteristics of 344 Patients

	Value
Total laboratory occupancy time, min	231.6 ± 73.1
Left atrial dwell time, min	80.4 ± 31.4
PV cryoablation time, min	31.2 ± 10.5
Total fluoroscopy time, min	20.1 ± 12.1
No. of cryoballoon cryoapplications	9.0 ± 2.6
23-mm Cryoballoon nadir ablation temperature (n = 38), °C	-53.1 ± 6.9
28-mm Cryoballoon nadir ablation temperature (n = 315), °C	-47.5 ± 5.0
28-mm Cryoballoon use	306 (89.0)
23-mm Cryoballoon use	29 (8.4)
Use of both 23- and 28-mm cryoballoons	9 (2.6)

Values are mean ± SD for continuous data, and n (%) of patients for categorical data.

PV = pulmonary vein; STOP AF PAS = Sustained Treatment of Paroxysmal Atrial Fibrillation Post-Approval Study.

STATISTICAL ANALYSIS. Continuous data are reported as mean and SD; categorical data are expressed as percentages. Logistic regression was used to examine the relationship between PNI, clinical measurements, and procedural variables. The Kaplan-Meier method was used to determine efficacy (freedom from AF, symptomatic AFL/AT; and repeat ablation). Major device and/or procedure-related events with onset up to 30 days' post-procedure were included in this analysis. All PV stenosis reports were included in the analysis, regardless of onset date. Values of $p < 0.05$ were considered significant.

RESULTS

PATIENT AND PROCEDURAL CHARACTERISTICS. Three hundred forty-four patients (228 male subjects [66%]; mean age 60 ± 10 years; mean left atrial diameter 40 ± 6 mm) with a history of drug-refractory pAF underwent ablation with CB2. Patient characteristics are summarized in Table 1. A total of 1,350 PVs in the 344 patients were targeted for ablation (311 left superior PVs [LSPVs], 310 left inferior PVs [LIPVs], 2 left middle PVs, 36 left common PVs [LCPVs], 337 right superior PVs [RSPVs], 335 right inferior PVs [RIPVs], 18 right middle PVs [RMPVs], and 1 right common PV). Cryoapplications <60 s in duration occurred in 159 (4.9%) of 3,272 freezes and were considered aborted attempts. The number of aborted attempts per PV was as follows: RIPV, 48; RSPV, 40; RMPV, 0; LIPV, 17; LSPV, 51; and LCPV, 3. The average ablation durations were as follows: RIPV, 23.4 s; RSPV, 27.6 s; LIPV, 27.9 s; LSPV, 22.6 s; and LCPV, 28.3 s. The mean number of CB2 applications per vein was as follows: LSPV, 2.4 ± 1.1; LIPV, 2.3 ± 1.0; RSPV, 2.2 ± 1.1; and RIPV, 2.3 ± 1.0.

All procedural characteristics associated with use of the CB2 are summarized in Tables 2 and 3. Acute PVI was achieved in 99.3% (1,341 of 1,350) of the PVs. The 28-mm CB2 was used most frequently and was used exclusively in 306 (89.0%) patients. The 23-mm balloon was used in 29 (8.4%) patients, and both the 23- and 28-mm balloons were used in 9 (2.6%) patients. The mean nadir temperature with the 23-mm CB2 was -53.1 ± 6.9°C, and the mean nadir temperature with the 28-mm CB2 was -47.5 ± 5.0°C. To achieve acute PVI, adjunctive focal ablation using cryoenergy was used in 0.4% (5 of 1,350) of veins and 1.2% (4 of 344) of patients; focal radiofrequency was used in 1.9% (25/1,350) of veins and 6.1% (21 of 344) of patients. The mean total laboratory occupancy time was 231.6 ± 73.1 min, left atrial dwell time was 80.4 ±

31.4 min, and fluoroscopy exposure time was 20.1 ± 12.1 min.

FOLLOW-UP COMPLIANCE. Of the 344 patients enrolled in the study, 317 (95.2%) of 333 completed the 12-month follow-up, 301 (94.7%) of 318 completed a 24-month follow-up visit, and 290 (96.7%) of 300 completed the 36-month follow-up (all denominators are patients at risk at each follow-up). Holter monitor compliance was 96.1% at the 6-month visit, 94.0% at the 12-month visit, 90.0% at the 24-month visit, and 87.2% at the 36-month visit. In total, Holter monitor compliance was 92.0%, and electrocardiogram compliance was 99.1% at scheduled follow-up visits. Early exit rates were low, with 12.8% (44 of 344) exiting before 36 months; 11 patients were lost to follow-up, 9 patients relocated their home, 4 patients were withdrawn by the investigator, and 20 patients withdrew.

FREEDOM FROM AF, ANTIARRHYTHMIC DRUG USE, AND REPEAT ABLATIONS. As shown in Figure 1, freedom from AF was 81.6% (95% CI, 77.1 to 85.4) at 12 months, 73.8% (95% CI, 68.6 to 78.2) at 24 months, and 68.1% (95% CI, 62.7 to 72.9) at 36 months. Freedom from AF and symptomatic AFL/AT was 79.0% (95% CI, 74.2 to 82.9) at 12 months, 70.8% (95% CI, 65.5 to 75.4) at 24 months, and 64.1% (95% CI, 58.6 to 69.1) at 36 months. Of the 117 patients who were not free from arrhythmia over 36 months, the initial recurrence was AFL or AT for 13 (11.1%) of 117 patients; the remaining 104 first recurrences (88.9%) were AF. Freedom from repeat ablations (independent of arrhythmia recurrence) was 88.2% (95% CI, 84.3 to 91.2) at 12 months, 83.5% (95% CI, 79.1 to 87.1) at 24 months, and 80.9% (95% CI, 76.2 to 84.8) at 36 months.

At 36 months of follow-up, 63 patients had a total of 70 repeat ablation procedures (57 patients had one repeat procedure, 5 patients had two repeat procedures, and 1 patient had three repeat ablation procedures). During the 90-day blanking period, 15 patients had a repeat ablation procedure. Of the 51 patients with a repeat ablation post-blanking, 49 repeat ablations occurred after arrhythmia recurrence, 1 repeat ablation was performed before documented arrhythmia recurrence at day 141 for AFL with recurrence documented on day 198, and 1 patient had a repeat ablation associated with supraventricular tachycardia on day 408. Three of the 63 patients had repeat ablations both within the blanking period and the post-blanking period. Among the 70 repeat ablations, the cryoballoon was used exclusively in 20 procedures, radiofrequency energy was used exclusively in 49 procedures, and both cryoballoon and radiofrequency energy were used in 1 procedure.

TABLE 3 Cryoablation Application Duration and Dosing According to PV

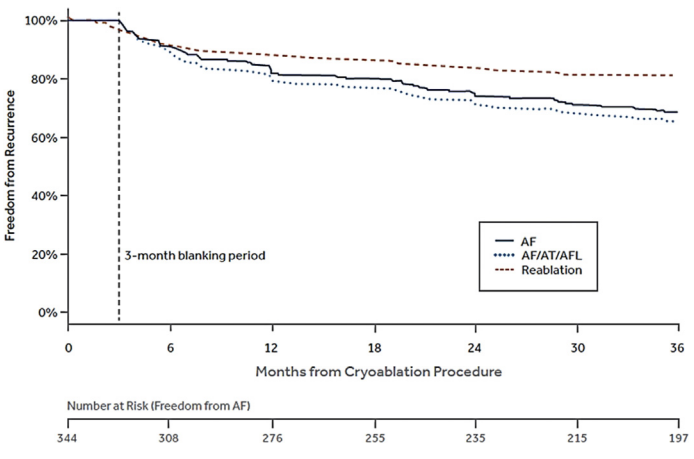
	Applications per Vein (Mean ± SD, No. of Patients)	Dosing per Application, s (Mean ± SD, No. of Applications)	Nadir Temperature per Vein, °C (Mean ± SD, No. of Patients)
Right superior PV	2.2 ± 1.1 (337)	200.3 ± 52.9 (740)	−50.5 ± 6.8 (337)
Right inferior PV	2.3 ± 1.0 (335)	205.0 ± 52.3 (760)	−47.0 ± 7.8 (335)
Right middle PV	1.7 ± 0.8 (18)	197.0 ± 58.9 (30)	−41.2 ± 8.1 (18)
Right common PV	2.0 ± NA (1)	193.0 ± 11.3 (2)	−66.0 ± 0.0 (1)
Left superior PV	2.4 ± 1.1 (311)	210.8 ± 47.0 (738)	−50.1 ± 7.0 (311)
Left inferior PV	2.3 ± 1.0 (310)	214.3 ± 47.9 (703)	−46.4 ± 6.5 (310)
Left middle PV	1.5 ± 0.7 (2)	240.0 ± 0.0 (3)	−54.0 ± 2.8 (2)
Left common PV	3.8 ± 2.0 (36)	200.3 ± 42.3 (137)	−48.4 ± 8.5 (36)

NA = not applicable; PV = pulmonary vein.

Although there were no protocol requirements for antiarrhythmic drug management, medication data were collected for class I and III antiarrhythmic prescriptions during the study. Patients could continue taking antiarrhythmic medications in the absence of recurrent atrial arrhythmias. At 12, 24, and 36 months, 12.2%, 9.8%, and 11.7% of patients, respectively, were being prescribed antiarrhythmic drug therapy, which included as-needed "pill-in-the-pocket" administration.

COMPLICATIONS. Major device and/or procedure-related adverse events occurred in 20 patients (5.8%) (Table 4). The most frequent complication was PNI present post-ablation in 11 (3.2%) of 344 patients. As shown in Figure 2, PNI was symptomatic in 3

FIGURE 1 Freedom From AF Recurrence



Kaplan-Meier curve of time to first recurrence of atrial fibrillation (AF), time to first AF/atrial flutter (AFL)/atrial tachycardia (AT) recurrence, and time to first repeat ablation through 36 months.

TABLE 4 Major Procedure-Related Adverse Events

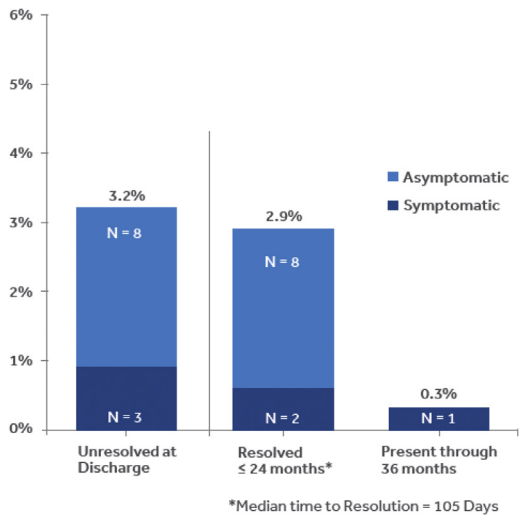
	No. (%) of Patients (N = 344)
PNI present post-ablation	11 (3.2)
Cerebrovascular accident	1 (0.3)
Pericardial effusion	3 (0.9)
Hemoptysis	3 (0.9)
PV stenosis	2 (0.6)
Atrioesophageal fistula	0 (0.0)
Death	0 (0.0)
Total	20 (5.8)

PNI = phrenic nerve injury; PV = pulmonary vein.

(0.9%) of 344 patients and resolved before 36 months in 10 of 11 patients (median resolution, 105 days). PNI persisted beyond 36 months in 1 (0.3%) of 344 patients. Procedural characteristics for the single patient with PNI ongoing at 36 months include: utilization of CMAP, administration of a total of 5 cryoablations, nadir cryoballoon temperatures between -51°C and -56°C, and application durations ≤180 s.

One patient (0.3%) experienced a cerebrovascular accident. Three patients (0.9%) had a pericardial effusion. One of the patients with a pericardial effusion required pericardiocentesis. Asymptomatic stenosis of the left superior PV >75% was noted in 2 (0.6%) patients. There were no procedure- or device-related atrioesophageal fistulas or deaths.

FIGURE 2 PNI Frequency and Resolution



Rate of symptomatic and symptomatic phrenic nerve injury (PNI) occurrence in the STOP AF PAS (Sustained Treatment of Paroxysmal Atrial Fibrillation Post-Approval Study) and time to resolution in safety cohort of 344 patients.

PREDICTORS OF PNI. Table 5 presents the patient and procedural characteristics among patients who experienced PNI with resolution pre-discharge (3 of 344) or PNI that was present post-ablation (11 of 344) versus those who did not experience PNI. Variables predictive of PNI based on logistic regression analysis were a shorter mean application duration to right PVs (179.6 ± 34.4 s vs. 203.9 ± 36.8 s; p = 0.02) and fewer right-sided applications (3.5 ± 1.6 vs. 4.5 ± 1.8; p = 0.01). However, the shorter application duration and lower number of right-sided applications in the cases complicated by PNI are likely a result of operators terminating the cryoablation at the earliest signs of phrenic injury and avoiding additional applications. The use of focal cryoenergy, nadir temperature, and patient body size were not predictors of PNI.

Although CMAP monitoring was adopted over time by several operators during enrollment in this clinical study, monitoring of the diaphragmatic CMAP was performed in only 32.8% of patients. The use of CMAP monitoring was not associated with a lower risk of PNI (p = 0.73).

DISCUSSION

MAIN FINDINGS. The major findings from this STOP AF PAS study are that PVI using the CB2 in patients with medically refractory pAF was effective, with freedom from AF of 68.1% and freedom from all atrial arrhythmias of 64.1% at 36 months. In addition, freedom from repeat ablation procedures at 36 months' post-ablation, for any arrhythmia recurrence, was 80.9%. The rate of major complications was 5.8%, with only 1 patient having ongoing PNI at 36 months.

COMPARISON WITH PREVIOUS STUDIES. The results of the present North American study at 1 year are consistent with the results of the European randomized FIRE AND ICE Trial, which included use of both the first-generation cryoballoon and CB2s. In the STOP AF PAS, 79% of patients were free of arrhythmia recurrence at 12 months, compared with 69% of patients treated with the CB2 in the FIRE AND ICE Trial who were free of a primary efficacy event at 12 months (12). Unlike the STOP AF PAS, resumption of an antiarrhythmic agent was considered a failure in the FIRE AND ICE Trial. Three-year follow up was not reported in the FIRE AND ICE Trial. In the STOP AF PAS trial, only 13.5% of patients experienced a recurrence between 12 and 36 months of follow-up.

Although procedure times are not reported consistently across all studies, procedure time and fluoroscopy times were dramatically reduced from the initial STOP AF trial versus the durations reported in STOP AF PAS (371 vs. 232 min, and 63 vs. 20 min, respectively) (1). In the FIRE AND ICE Trial (which did not report laboratory occupancy time), reported procedure, left atrial dwell, and fluoroscopy times were 124, 92, and 22 minutes, respectively (12). These data are consistent with the STOP AF PAS procedure times.

Nevertheless, the procedure times in this study, which first enrolled patients in 2012, seem to be relatively long compared with current experiences. These procedure times partly reflect the fact that several investigators in this post-approval study were new users of the cryoballoon technology. In addition, this study started at the same time as approval of the CB2. Since these procedures were performed, much has been learned about cryoenergy dosing with the CB2. These lessons have led to a reduction in the time per freeze from 4 to 3 min in most laboratories and use of the time to PVI to limit the number of freezes per vein in many cases.

PNI AND PV STENOSIS. The most common complication associated with the CBA procedure in both the STOP AF PAS and the FIRE AND ICE Trial was PNI, which occurred in 3.2% and 2.7% of patients, respectively (12). In the STOP AF PAS, during which both symptomatic and asymptomatic PNI were evaluated, the incidence of PNI among the 344 patients treated with CB2 was 3.2% (n = 11), with 0.3% (n = 1) of patients having ongoing PNI at 36 months. The low rate of PNI is not surprising with the increased adoption and utilization of the 28-mm cryoballoon, phrenic nerve pacing, adjunctive monitoring such as CMAP (14–16), fewer balloon applications to the right-sided PVs, applying the minimal amount of force required to achieve occlusion, active balloon deflation (double-stop technique) at the moment of PNI (17), and ensuring balloon positioning outside the PV. In a study of 200 procedures using both phrenic pacing and diaphragmatic electromyographic monitoring, Mondésert et al. (18) reported only 1.5% of patients with PNI that was persistent at the time of hospital discharge, and all PNI resolved within 6 months. Similarly, a large, multicenter report from Germany reported that the occurrence of PNI in their last 420 patients was only 0.7% (19).

The reported incidence of PV stenosis with the cryoballoon has steadily decreased over time since the pivotal STOP AF study, which used the first-generation cryoballoon, reported a PV stenosis rate of 3.1% (1). No PV stenosis was reported in the FIRE AND ICE Trial (12). This trend is supported by the present analysis, which identified <1% of patients with asymptomatic PV stenosis. This reduction in PV stenosis over time is most likely due to increased operator experience resulting in more antral positioning of the cryoablation, use of intracardiac echocardiography to confirm an antral location, and a reduction in the number and duration of freezes. Nonetheless, additional efforts are needed to completely eliminate this complication.

TABLE 5 Comparison of Patient and Procedural Characteristics Among Patients Who Experienced PNI (Resolved and Unresolved at Discharge) and Those Who Did Not

Variable	PNI (n = 14*)	No PNI (n = 330)	p Value
Use of 23-mm balloon	2 (14.3%)	36 (10.9%)†	0.69
Use of 28-mm balloon	12 (85.7%)	303 (91.8%)†	0.43
Use of focal cryocatheter	0 (0.0%)	4 (1.2%)	0.99‡
Body mass index, kg/m^2	30.3 ± 5.6	29.9 ± 6.2	0.82
No. of applications to right PVs	3.5 ± 1.6	4.5 ± 1.8	0.007
Maximum application duration to right PVs >240 s	1 (7.1%)	31 (9.4%)	0.77
Mean application duration to right PVs, s	179.6 ± 34.4	203.9 ± 36.8	0.02
Minimum temperature to right PVs, °C	-55.8 ± 7.2	-54.6 ± 6.7	0.53
Mean temperature to right PVs, °C	-51.1 ± 7.0	-48.4 ± 6.3	0.13
Utilization of CMAP	4 (28.6%)	109 (33.0%)	0.73

Values are mean ± SD unless otherwise indicated. *Analysis includes 11 patients with PNI present post-ablation and 3 patients with PNI resolved before discharge. †Nine patients were treated with both the 23- and 28-mm cryoballoon. ‡From the Fisher exact test.

CMAP = compound motor action potential; other abbreviations as in Table 4.

REPEAT ABLATION PROCEDURES. Certain aspects of the study design of the STOP AF PAS, such as not requiring routine long-term continuous electrocardiographic monitoring after the ablation, may have resulted in significant overestimation of the efficacy of the CB2 for ablation of pAF. These are included in the study limitations discussed later. However, it is also likely that the atrial arrhythmia-free rate of 64.1% found in this study at 3 years underestimates the actual clinical benefit to patients. Although AF burden reduction was not evaluated in the STOP AF PAS, it is likely that some patients considered a clinical trial failure because of recurrent atrial arrhythmias after their ablation procedure still experienced a clinically meaningful reduction in their AF burden and AF-related symptoms. Evidence to support this theory is the observation that <20% of patients in the present study underwent a repeat ablation procedure within 3 years of their initial procedure, including repeat ablations performed during the blanking period. The low 3-year redo rate of 20% in the present study is consistent with the secondary analyses from the FIRE AND ICE Trial, which showed that only 11.8%

of patients treated with the cryoballoon had a repeat ablation procedure after a mean follow-up of 1.5 years (20).

STUDY LIMITATIONS. The major limitations of the present study are that there was no control group and there was limited electrocardiographic monitoring. The absence of routine continuous monitoring post-ablation may have resulted in significant over-estimation of freedom from recurrence. In addition, because the study was originally designed to evaluate AF recurrence only, and not asymptomatic AFL and AT, there is potential for overestimating freedom from AFL/AT because these arrhythmias were only required to be reported as an adverse event if they were symptomatic. Another limitation was that there were no protocol requirements for discontinuation of antiarrhythmic agents post-ablation. Finally, repeat ablation procedures during the blanking period may have contributed to overestimation of freedom from arrhythmia recurrence post-blanking.

CONCLUSIONS

The STOP AF PAS is the largest North American multicenter study to report the safety and efficacy of PVI using CB2 at 36 months' follow-up in patients with drug-resistant, symptomatic pAF. Freedom from AF was 81.6% at 12 months, 73.8% at 24 months, and 68.1% at 36 months. At 36 months, freedom from all atrial arrhythmias was 64.1%, freedom from repeat ablation procedures (for any arrhythmia recurrence) was 80.9%, only 12% of patients were taking an antiarrhythmic drug, and PNI was persistent in only 1 patient. Future studies are needed to determine the effect of CBA on AF burden and quality of life.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: Use of the cryoballoon to perform PVI in patients with drug-refractory pAF is effective but is associated with some risks such as right-sided PNI that are more common with the cryoballoon compared with point-by-point radiofrequency ablation.

TRANSLATIONAL OUTLOOK: Prospective, randomized controlled trials are needed to compare the safety and efficacy of the CBA catheter to achieve electrical isolation of the PVs versus other point-by-point and balloon-based tools that are under development for the treatment of patients with AF.

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APPENDIX For a supplemental table, please see the online version of this paper.