

Comparing Safety and Efficacy of Irrigated Radiofrequency Catheter Ablation Versus Combined Cryoballoon and Catheter Ablation for Persistent Atrial Fibrillation

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Abstract

Background : Catheter and cryoballoon ablation are established treatments for atrial fibrillation. Frequently, substrate modification of the left atrium is performed in patients with persistent AF or evidence of left atrial adverse remodeling. We compared one year outcomes of AF ablation with substrate modification utilizing radiofrequency catheter ablation (RFA) compared to a combination of cryoballoon ablation with radiofrequency catheter ablation (HAFA).

Methods: Ablation for persistent AF was performed using stand-alone catheter ablation (RFA group, n=31) or cryoballoon for pulmonary vein isolation with RFA catheter ablation for substrate modification (HAFA group, n=21) and procedural and clinical outcomes were analyzed. Pulmonary vein isolation and LA substrate modification including creation of left atrial ablation lines and/or CFAEs was performed in all patients. Patients were followed for up to one year. A three- month blinding window was applied for analysis.

Results: Clinical characteristics were similar between groups. Total procedure (244.15±64.7 vs 235.5±54.6, p=0.6) and fluoroscopy time (37±15.4 vs 29.5±15.7, p=0.96) were not different between the HAFA and RFA groups, respectively. Periprocedural complications were similar among groups. AF free survival was not significantly different between groups (p=0.631). Actuarial arrhythmia recurrence in one year was similar among groups (58.1% vs 66.7% for the RFA and HAFA group respectively, p=0.53) Symptomatic improvement was similar at 1 year between groups (81% vs 77.4% for HAFA vs RFA respectively, p=0.76).

Conclusions: Combined cryoballoon and catheter ablation for LA substrate modification (HAFA) has similar safety and efficacy compared to stand-alone catheter ablation for persistent AF. Recurrent atrial flutter is more frequently observed after cryoballoon ablation for persistent AF.

Introduction

Radiofrequency catheter ablation is an established treatment modality for symptomatic drug-refractory atrial fibrillation (AF).¹ Given the frequency of pulmonary vein triggers identified in patients with paroxysmal atrial fibrillation,¹ pulmonary vein isolation (PVI) is commonly utilized as a sole primary ablation approach in this population.² However, achieving permanent PVI with focal RF

catheters is a lengthy and technically challenging process requiring significant technical skills. Recent studies have indicated that PVI using cryoenergy compares favorably to radiofrequency ablation³⁻⁵ and is associated with low risk for both thromboembolic events and pulmonary vein stenosis.⁶

PVI alone has a low success rate in eliminating AF among patients with a persistent form in whom additional atrial ablation lesions are typically required for improved outcomes.⁷ Accordingly, the clinical success of cryoballoon ablation in patients with paroxysmal AF is not achieved in patients with persistent AF^{8,9} due to the more extensive atrial remodeling, requiring additional substrate modification.¹⁰ Focal cryoablation using cryothermal catheters has been employed in such circumstances but is fraught with difficulty due to the inability to apply “dragging lesions” resulting in prolonged procedure time.

Mansour and colleagues¹¹ demonstrated that when left atrial modification is performed following cryoballoon pulmonary vein isolation in patients with significant left atrial substrate abnormalities, short term clinical outcomes are favorable. However, a direct comparison of a combined ablative strategy versus sole radiofrequency

Key Words:

Cryoballoon Ablation, Catheter Ablation, Persistent Atrial Fibrillation, Clinical Outcomes, Substrate Modification

Disclosures:

Drs Dan and Wickliffe are on the speaker's bureau for Medtronic Inc. All other authors have no conflict of interest to declare.

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catheter ablation has not been performed. In the present study, we aimed to assess peri-procedural and clinical outcomes in patients undergoing cryoballoon and catheter ablation when compared to patients undergoing standard radiofrequency catheter ablation for PVI and left atrial substrate modification in patients with persistent AF.

Methods

Study Subjects

52 patients with a history of antiarrhythmic drug (AAD)-refractory persistent AF, who underwent initial AF ablation including pulmonary vein isolation and atrial substrate modification, were analyzed retrospectively. Persistent AF was defined according to the current American College of Cardiology guidelines.¹² The study was approved by the Institutional Review Board at the Piedmont Heart Institute. Cryoballoon PVI ablation with radiofrequency catheter left atrial ablation (HAFA group) was performed in 21 patients whereas only radiofrequency catheter ablation with an open irrigated catheter was performed in 31 patients (RFA group).

Electrophysiologic Study

Each patient gave written informed consent. Studies and data collection were performed according to protocols approved by the Human Research Committee of Piedmont Heart Institute. All patients were anticoagulated for at least one month prior to the procedure with warfarin or dabigatran. For patients presenting with a subtherapeutic INR on the day of procedure, low molecular weight heparin was used as bridging therapy. Transesophageal echocardiography (TEE) was performed in 8/21 patients in the HAFA group (38%) and 14/31 patients in the RFA group (45.2%) ($p=0.78$) based on results of anticoagulation therapy leading to procedure. Preprocedure cardiac computed tomographic (CT) scanning or cardiac magnetic resonance imaging (CMR) was performed in all patients.

Conscious sedation was usually achieved with fentanyl and midazolam. Electroanatomic mapping was performed with either the CARTO mapping system (Biosense Webster, Diamond Bar, CA, USA) or the NavX mapping system (St Jude Medical, St. Paul, MN, USA) according to physician preference. Bipolar intracardiac electrograms were band pass filtered from 30 to 500Hz and digitally recorded along with a 12 lead surface ECG EP med system (EP Med Systems, West Berlin, USA). During electrophysiology study, a multipolar catheter was placed in the right atrium and coronary sinus (CS). An intracardiac echocardiography probe (Acuson, Siemens, Malvern, PA, USA) was placed in the right atrium in 8/21 patients in the HAFA group (38%) and 14/31 patients in the RFA group (45.2%) ($p=0.77$) based on the operator's preference. Two transeptal punctures were performed in 21/21 patients in the HAFA group (100%) and 28/31 patients in the RFA group (90.6%) ($p=0.37$) whereas a single transeptal puncture was performed in the remaining patients. A circular mapping Lasso catheter (Biosense Webster, Diamond Bar, CA, USA) was utilized for mapping in the pulmonary veins. Before transeptal puncture, a bolus of heparin was given based on patient weight followed by intravenous infusion to maintain an activated clotting time of at least 300 seconds.

Mapping and Ablation

The procedure was performed in a stepwise manner. Initially, pulmonary vein isolation (PVI) was performed using either a

cryoballoon catheter (28 or 23mm, ArcticFront, Medtronic, MN, USA) or an externally irrigated catheter (ThermoCool Celsius, 3.5mm, Biosense Webster, Diamond Bar, CA, USA) in the HAFA and RFA group, respectively. In the HAFA group, the size of the cryoballoon was determined based on measurements of the pulmonary vein (PV) diameters on the previously acquired CT or MRI scan. After PV occlusion by the cryoballoon was confirmed with contrast venography, cryoapplication was performed for four minutes. Additional applications were performed until PV electrical isolation was demonstrated. Prior to cryoballoon ablation in the right PVs, a quadripolar catheter was positioned in the superior vena cava for phrenic nerve stimulation during cryoablation. Cryoapplication was immediately terminated upon demonstration of loss of phrenic nerve capture or reduction in amplitude of diaphragmatic contractions. In the RFA group, PVI was performed with an open-irrigated catheter, generally starting at 30 Watts. Ablation at the posterior wall or in close proximity to the esophagus was limited to 30 seconds per target site at 20 Watts. Following PVI with either method, electrical isolation of the pulmonary veins was confirmed with a circular multielectrode mapping catheter positioned sequentially in each vein.

Following PVI, linear lesions were placed on the LA roof, mitral isthmus, LA floor and septum. Ablation continued until block was documented for the lines performed. If AF persisted or was induced after Isoproterenol infusion or pacing, complex fractionated electrograms (CFAEs) were targeted with an externally irrigated catheter. CFAEs were targeted in the left atrium (LA), coronary sinus (CS) and right atrium (RA) based on identification of low amplitude highly fractionated potentials. For ongoing AF or atrial flutter not terminated with ablation, electrical or chemical (ibutilide 1mg over 10 minutes, intravenously) cardioversion was performed.

Follow-Up

After ablation, all patients were observed with continuous ECG monitoring until hospital discharge. All patients were discharged with the same antiarrhythmic therapy as prior to their index admission. Anticoagulation was continued for at least three months; in patients with subtherapeutic INR on presentation, subcutaneous heparin was continued after discharge until the INR reached a value of 2. Antiarrhythmic and anticoagulant medications were typically discontinued at 3 months post ablation unless AF recurrence was observed or major risk factors were present based on CHADS2 score. After discharge, patients had follow up at an electrophysiology outpatient clinic at 1 and 3 months and every 3 months thereafter. Recurrent atrial arrhythmia was assessed based on ECG recordings, event monitoring and/or device interrogation and was defined as AF, atrial flutter or atrial tachycardia over 30 second duration. A 3-month blanking window was applied as early arrhythmia recurrence is typically a transient phenomenon.

Major complications were defined as those resulting in a permanent adverse effect, surgical intervention or prolonged hospitalization beyond 24 hours whereas minor complications were observed complications managed expectantly without significant clinical sequelae.

Statistical Analysis

Continuous variables are expressed as mean or median \pm SD. Categorical and binary variables are presented as frequencies (percentages). Comparison between groups was performed using Student's t test (unpaired). Proportions were compared using Chi-

square analysis and the Fisher exact test. Differences with $p < 0.05$ were considered significant. Arrhythmia free survival curves were created and compared using the Kaplan-Meier method. Potential relationships between procedural and clinical variables and the occurrence of arrhythmia were explored in a time-to-event framework using Cox proportional hazard models. Clinical and procedural variables were assessed in single predictor models and subsequently, variables that were shown to be predictive of arrhythmia recurrence were evaluated in a stepwise multivariable model. Statistical analysis was performed using the Statistical Package for the Social Sciences (version 19.0, SPSS, Inc, Chicago, IL, USA).

Results

Patient Characteristics

Twenty one consecutive patients (17 male; mean age 61.7 ± 7.97 years) were included in the HAFA group. Thirty one consecutive patients (24 male, mean age 64.32 ± 7.6 years) were included in the RFA group. Demographic and clinical characteristics were similar between the HAFA group and RFA group (table 1). All patients had a clinical history of persistent AF and prior failed antiarrhythmic therapy. Mean LA diameter assessed by transthoracic echocardiography was similar between groups (42.53 ± 5.63 mm vs 44.17 ± 5.4 mm for the RFA and HAFA group, respectively, $p = 0.33$). Prior to the index procedure, amiodarone was used in 38.1% in the HAFA group vs 22.6% of patients in the RFA group and class III AAD in 19% in the HAFA group and 29% in the RFA group ($p = 0.23$).

Procedural Characteristics

Procedural characteristics and outcomes are listed in table 2. A total of 205 veins were targeted for electrical isolation. A left common pulmonary vein was observed in 3 patients in the RFA group and a right middle vein was present in one patient in the RFA group.

Atrial flutter or atrial tachycardia was induced during ablation, with atrial pacing or isoproterenol infusion in 11 (35.5%) patients in the RFA and 2 (9.5%) patients in the HAFA group ($p = 0.033$). Effective PVI was completed in all patients for a total of 122 veins in the RFA and 84 veins the HAFA group. In the HAFA group, nine pulmonary veins (10.7%) were not isolated with cryoapplication (three LIPVs, one LSPV, four RIPVs, one RSPV); in those cases, RF

Table 2: Procedural characteristics of patients undergoing HAFA and RFA ablation.

Procedural Data	RFA group (n=31)	HAFA group(n=21)	p value
Left Common Ostium	3 (9.7%)	0	0.200
Rhythm on presentation (n, %)			0.193
a. AF	24 (77.4%)	13 (61.9%)	
b. Atrial flutter	3 (9.7%)	1 (4.8%)	
c. Sinus	4 (12.9%)	7 (33.3%)	
Induced AF or atrial flutter(n, %)	11 (35.5%)	2 (9.5%)	0.033
CFAEs (n, %)	27 (87.1%)	17 (81%)	0.410
Mitral isthmus line (n, %)	6 (19.4%)	6 (28.6%)	0.328
Roof line (n, %)	28 (90.3%)	21 (100%)	0.203
Septal line (n, %)	10 (32.3%)	3 (14.3%)	0.126
CTI line (n, %)	9 (25.8%)	6 (28.6%)	0.535
CS lesions (n, %)	1 (3.2%)	3 (14.3%)	0.174
Procedural endpoints			0.185
AF termination during ablation (n, %)	2 (6.5%)	5 (23.8%)	
Atrial flutter termination during ablation (n, %)	8 (25.8%)	2 (9.5%)	
Ibutilide (n, %)	16 (51.6%)	6 (28.6%)	
Electrical cardioversion (n, %)	9 (30%)	9 (42.9%)	
Ablation times			
Fluoroscopy time (min, mean \pm SD)	29.5 \pm 15.7	37 \pm 15.4	0.96
Procedure time (min, mean \pm SD)	235.5 \pm 54.6	244.15 \pm 64.7	0.6
Contrast (cc, mean \pm SD)	16.8 \pm 20.76	43.2 \pm 34.5	0.001

energy was utilized resulting in effective electrical isolation.

Procedure time and total fluoroscopy time were not different between groups (table 2). Contrast utilization was higher in the HAFA group (43.2 ± 34.5 vs 16.8 ± 20.76 for the HAFA and RFA group respectively, $p = 0.001$).

Left Atrial Ablation

Left atrial ablation including linear lesions and/or CFAEs was performed in all patients (table 2). Ibutilide was utilized in patients who remained in AF after PVI, linear and/or CFAE ablation; organization to atrial flutter or atrial tachycardia was noted in four patients in the RFA group and was terminated with ablation. Intraprocedural cardioversion was performed in 9 (42.9%) patients in the HAFA group and 9 (30%) patients in the RFA group ($p = 0.385$).

Periprocedural Complications

Major periprocedural complications were similar in the two groups (9.5% vs 12.9% for the HAFA and RFA group respectively, $p = 0.7$). One patient in the RFA group had delayed pericardial effusion with tamponade requiring pericardiocentesis one week after the index procedure. Three patients in the RFA group (9.7%) and one patient in the HAFA group (4.2%) developed a pseudoaneurysm treated with thrombin injection. One patient in the HAFA group (4.2%) developed an arteriovenous fistula which was managed conservatively. There were no cerebrovascular events or documented diaphragmatic paralysis.

Follow-Up

Clinical outcomes are presented on table 3. Mean FU was 397 ± 126 (120-620) days for the HAFA group and 520 ± 217 (90-940) days for the RFA group; events up to one year were recorded. During the blanking period, 6 (28.6%) patients in the HAFA group

Table 1: Clinical characteristics of patients undergoing HAFA and RFA ablation.

Clinical Characteristics	RFA group (n=31)	HAFA group (n=21)	p value
Age (years, mean \pm SD)	64.3 \pm 7.6	61.7 \pm 7.9	0.239
Sex (male/female)	25/6	17/4	0.634
BMI (mean \pm SD)	31.0 \pm 4.0	31.0 \pm 5.1	0.941
CHADS2 score ≥ 2 (n, %)	13 (41.9%)	10 (47.6%)	0.451
Hypertension (n, %)	26 (84%)	14 (67%)	0.134
Diabetes mellitus (n, %)	5 (16%)	5 (24%)	0.366
CKD (n, %)	2 (6.5%)	2 (9.5%)	0.535
OSA on CPAP (n, %)	23 (26%)	3 (14%)	0.261
Amiodarone (n, %)	7 (23%)	8 (38%)	0.184
Coumadin (n, %)	29 (93.5%)	19 (90.5%)	0.535
LMWH (n, %)	3 (9.7%)	3 (14.3%)	0.464
Dabigatran (n, %)	1 (3.2%)	2 (9.5%)	0.355
LVEF (% , mean \pm SD)	51.5 \pm 10.3	55.5 \pm 7.6	0.133
LA diameter, long axis (mm, mean \pm SD)	44.17 \pm 5.4	42.53 \pm 5.63	0.332

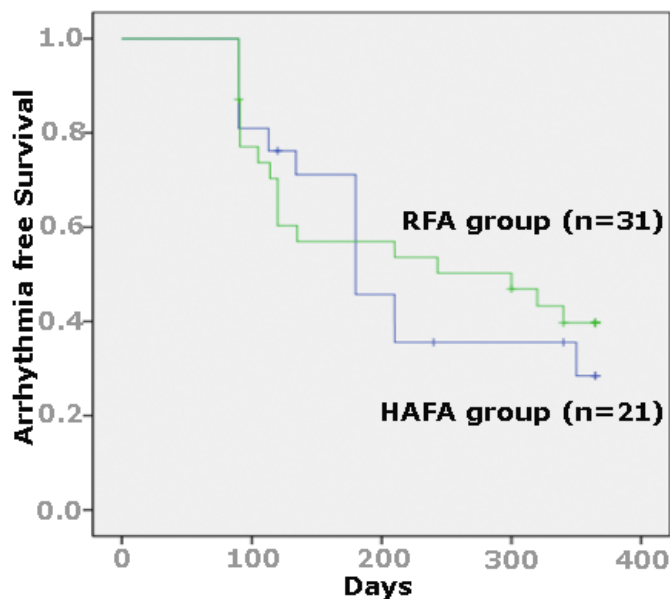


Figure 1: Kaplan Meier curve of arrhythmia free survival after radiofrequency catheter ablation and cryoballoon combined with radiofrequency catheter ablation. There was no statistically significant difference between groups ($p=0.631$).

and 16 (51.6%) patients in the RFA group experienced symptomatic arrhythmia recurrence. At the one year follow up point, excluding the blanking period, 14 (66.7%) patients in the HAFA group and 18 (58.1%) patients in the RFA group experienced recurrent atrial arrhythmias. Arrhythmia-free survival was similar among groups ($p=0.631$) (figure 1).

Recurrent LA flutter was observed more frequently in the HAFA group ($p=0.04$) whereas recurrent AF was the most common arrhythmia observed in the RFA group ($p=0.04$) (table 3 and figure 2). Episodes of paroxysmal AF were infrequent in both groups and responsive to previously ineffective AAD therapy. Two patients in the RFA group developed persistent AF (asymptomatic) and one patient developed permanent symptomatic AAD-refractory AF requiring AV nodal ablation and permanent pacemaker implant.

Repeat RF or cryoballoon ablation within one year was performed in 9 (42.8%) patients in the HAFA group and 7 (22.6%) patients in the RFA group whereas one patient underwent AVN ablation for highly symptomatic permanent AF in the RFA group ($p=0.120$). Repeat PVI due to electrical reconnection of the PVs was required more frequently in the RFA group ($p=0.012$) (table 3).

At one-year follow up, clinically symptomatic improvement (maintenance of sinus rhythm or infrequent episodes of paroxysmal AF successfully managed with previously ineffective AAD therapy) was noted in 17 (81%) patients in the HAFA group and 24 (77.4%) patients in the RFA group ($p=0.76$). Antiarrhythmic drug therapy was utilized in 56% of patients in the RFA group and 49% of patients in the HAFA group at one year ($p=0.157$).

In univariable Cox proportional hazards models, LVEF and AF as presenting rhythm in the EP laboratory were independent predictors of arrhythmia recurrence. On multivariable analysis, mean LVEF remained independently associated with arrhythmia recurrence with a hazard ratio of 0.96 (95% CI 0.92-0.99).

Discussion

To our knowledge, this is the first study assessing one-year clinical

outcomes in patients with persistent atrial fibrillation undergoing cryoballoon ablation combined with radiofrequency catheter ablation for left atrial substrate modification (HAFA). Our main findings were as follows: 1) this approach is feasible and safe, 2) one-year clinical outcomes are comparable to standard radiofrequency catheter ablation and finally 3) recurrent macroreentrant atrial arrhythmias appear to be more frequent with the HAFA approach whereas recurrent disorganized atrial fibrillation is more common with RF alone. The correlation between decrease in LV systolic function (LVEF) and arrhythmia recurrence may be secondary to a global cardiomyopathy with more advanced atrial substrate abnormalities.

Despite significant technologic advances in AF ablation, including sophisticated electroanatomic mapping systems and irrigated catheters, performance of PVI remains technically challenging. Cryoballoon ablation has emerged as an alternative method for PV isolation and preliminary studies have supported a steep learning curve allowing for rapid and safe PV isolation after an initial learning period.¹³ However, AF is recognized to be a disease continuum with localized PV triggers predominantly identified in patients with isolated paroxysmal AF and non-PV triggers emerging as the disease progresses to persistent forms. PVI is the cornerstone of any AF ablative procedure, however it is typically not sufficient in patients with more advanced left atrial disease.¹⁴ Chao and colleagues reported a long-term recurrence-free rate of ablation in non paroxysmal AF of 28.4% after a single RF procedure¹⁵ Staged ablation strategies including addition of CFAE ablation and/or linear ablation have yielded superior results.^{16,17} A systematic review of the existing literature cites a 45% 1-year freedom from recurrent AF in patients treated with cryoballoon based PVI for persistent AF.⁴

In a hypothesis generating study, Mansoor and colleagues described the feasibility of a combined cryoablation and radiofrequency catheter ablation approach in 22 patients with persistent AF.¹¹ Freedom from AF after a single procedure was remarkable (86%), however clinical follow up was limited (up to six months) and there was no direct comparison to standard RF ablation. In the present study, we used a strict definition of arrhythmia recurrence and as such, arrhythmia recurrence was frequently observed at one year. Recurrent atrial arrhythmia was typically paroxysmal as compared to the prior persistent nature of AF and was managed successfully with either prior failed antiarrhythmic therapy or repeat ablative therapy, indicating a significant amelioration of the AF substrate following the initial procedure. Repeat ablation procedures were largely driven by physician and patient preference and were more frequently performed in the HAFA population due to the high prevalence of left atrial flutter, which is highly amenable to elective ablation. Frequent occurrence of left atrial flutter following initial PVI utilizing cryotherapy has been previously reported and is likely due to the extensive atrial ablation achieved with cryo-application resulting in small gaps between anatomic barriers and dense cryo-lesions. The occurrence of organized atrial tachyarrhythmias following initial atrial ablation has been associated with successful immediate procedural outcomes, however long term outcomes are unknown.¹⁸ Further, PV reconnection was more frequently observed in the RFA group, implying more effective and durable PV electrical isolation with the utilization of the cryoballoon.

Given the high prevalence of atrial fibrillation in the general population, frequent failure of antiarrhythmic therapy and improved platforms for left atrial ablation, current guidelines support the

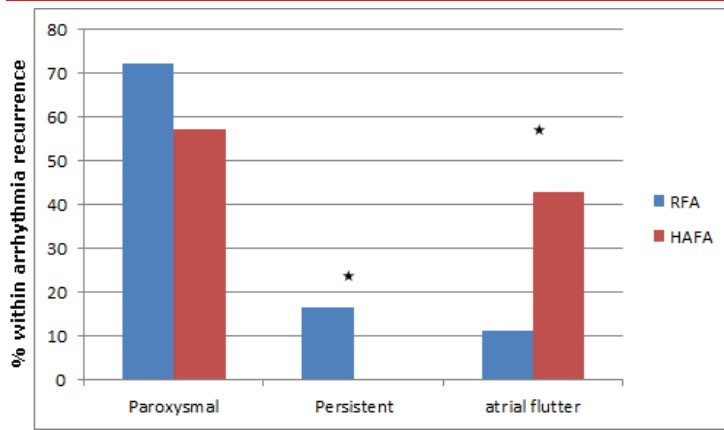


Figure 2: Type of recurrent arrhythmia after RFA or HAFA. Numbers presented are percentage within patients with recurrent arrhythmia. * represents p value <0.005.

utilization of ablation procedures as second line therapy for drug-refractory AF;¹² recent European guidelines suggest that ablation might be offered as first line therapy in selected patients.¹⁹ Considering the widespread utilization of ablative approaches in the management of AF, the association of sinus rhythm maintenance with lower risk of death²⁰ and the rising health care costs associated with the long-term management of AF, data on clinical effectiveness have become increasingly important. Our results are comparable to recent studies demonstrating frequent recurrence of atrial tachyarrhythmias following initial AF ablation for persistent AF.^{15,21} Arrhythmia recurrences tend to cluster in the first year after the initial ablation and repeat ablations are commonly required;¹⁵ results from our study are in accordance with previously published data and demonstrate similar efficacy of a combined (HAFA) approach compared to standard RF ablation.

Study Limitations

The number of patients included in the present analysis is small and as such the number of events is prone to type I statistical errors with multivariable analysis. However, the present study was intended to primarily analyze the comparative effectiveness and safety between the two employed ablative strategies. Long term randomized prospective studies including a larger number of patients may allow for better delineation of predictors of recurrence and definition of patients who may benefit from either approach. Further, cost effectiveness

with either approach was not tested. In addition, different levels of expertise with standard RF catheters versus cryoballoon catheters may have influenced the acute procedural data; the present study was performed during the initial stages of CB utilization in the US and CB-based PVI was lengthier at that time. As such, it is plausible that with improving operator experience with cryotherapy, PVI can be achieved more rapidly.

Conclusions:

A combined approach of cryoballoon and RF ablation for persistent atrial fibrillation is a safe and effective ablative approach to persistent atrial fibrillation. Clinical outcomes with the combined approach are similar to standard RF ablation; recurrent macroreentrant tachyarrhythmias are more commonly observed in the combined approach (HAFA). Randomized studies including a larger number of patients are required to definitively assess the comparative effectiveness between the two ablative strategies.

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Table 3: Clinical outcomes of patients undergoing HAFA and RFA ablation.

Clinical outcomes	RFA group (n=31)	HAFA group (n=21)	p value
Recurrent arrhythmia (n, %)	18 (58.1%)	14 (66.7%)	0.53
Recurrent atrial fibrillation (n, % within recurrence)	16 (88.8%)	8 (57.1%)	0.04
Paroxysmal	13 (72.2%)	8 (57.1%)	
Persistent	3 (16.7%)	0	
Recurrent atrial flutter (n, % within recurrence)	2 (11.1%)	6 (42.8%)	0.04
Repeat ablation (excluding AVN ablation) (n, % within recurrence)	7 (22.6%)	9 (42.8%)	0.198
Repeat PVI on redo ablation (n, % within repeat ablation procedures)	6/7 (85.7%)	2/9 (22.2%)	0.012
Symptomatic improvement at one year (n, %)	24 (77.4%)	17 (81%)	0.76

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