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Persistent Atrial Fibrillation Ablation With Contact Force–Sensing Catheter

The Prospective Multicenter PRECEPT Trial

Moussa Mansour, MD,[a] Hugh Calkins, MD,[b] Jose Osorio, MD,[c] Scott J. Pollak, MD,[d] Daniel Melby, MD,[e] Francis E. Marchlinski, MD,[f] Charles A. Athill, MD,[g] Craig Delaughter, MD,[h] Anshul M. Patel, MD,[i] Philip J. Gentlesk, MD,[j] Brian DeVille, MD,[k] Laurent Macle, MD,[l] Kenneth A. Ellenbogen, MD,[m] Srinivas R. Dukkipati, MD,[n] Vivek Y. Reddy, MD,[n] Andrea Natale, MD[o]

ABSTRACT

OBJECTIVES This study sought to evaluate the safety and effectiveness of catheter ablation of persistent atrial fibrillation (PsAF) using a porous tip contact force–sensing catheter.

BACKGROUND Although the safety and effectiveness of catheter ablation of paroxysmal atrial fibrillation are established, there are limited data on outcomes in patients with PsAF. As such, no ablation catheter is currently approved by the Food and Drug Administration for PsAF ablation.

METHODS The prospective, multicenter, nonrandomized PRECEPT (Prospective Review of the Safety and Effectiveness of the THERMOCOOL SMARTTOUCH SF Catheter Evaluated for Treating Symptomatic PersistenT AF) study was conducted at 27 sites in the United States and Canada. Enrollment criteria included documented symptomatic PsAF and nonresponse or intolerance to ≥1 antiarrhythmic drug (Class I or III). An individualized treatment approach was used including pulmonary vein isolation with ablation of additional targets permitted at the investigators' discretion. To optimize treatment outcomes, a 3-month post-ablation medication adjustment period followed by a 3-month therapy consolidation period were included. Arrhythmia recurrences were stringently monitored by monthly and symptomatic transtelephonic monitoring, electrocardiography, and Holter monitoring for up to 15 months after ablation.

RESULTS Of 381 enrolled participants, 348 had the investigational catheter inserted and underwent ablation. The primary adverse event rate was 4.1% (15 events in 14 participants). Kaplan-Meier analyses estimated a primary effectiveness success rate of 61.7% and a clinical success rate of 80.4% at 15 months.

CONCLUSIONS The results demonstrate the clinical safety and effectiveness of PsAF ablation using contact force–sensing technologies. The primary adverse event was within the expected range and similar to those reported in historical studies of paroxysmal AF ablation. (Prospective Review of the Safety and Effectiveness of the THERMOCOOL SMARTTOUCH SF Catheter Evaluated for Treating Symptomatic PersistenT AF; NCT02817776)
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From the [a]Massachusetts General Hospital, Boston, Massachusetts; [b]Johns Hopkins University, Baltimore, Maryland; [c]Arrhythmia Institute at Grandview, Birmingham, Alabama; [d]Florida Hospital Cardiovascular Institute, Orlando, Florida; [e]Minneapolis Heart Institute, Minneapolis, Minnesota; [f]Hospital of the University of Pennsylvania, Philadelphia, Pennsylvania; [g]San Diego Cardiac Center, San Diego, California; [h]Baylor Scott & White Heart and Vascular Hospital, Fort Worth, Texas; [i]Emory Saint Joseph's Hospital, Atlanta, Georgia; [j]Sentara Norfolk General Hospital, Norfolk, Virginia; [k]The Heart Hospital Baylor Plano, Plano, Texas; [l]Montreal Heart Institute, Montreal, Quebec, Canada; [m]Virginia Commonwealth University, Richmond, Virginia; [n]Icahn School of Medicine at Mount Sinai, New York, New York; and the [o]Texas Cardiac Arrhythmia Research Foundation, Austin, Texas. The PRECEPT study was funded and sponsored by Biosense Webster, Inc. Dr. Natale serves as a consultant for Abbott, Biosense Webster, Inc., Biotronik, Boston Scientific, Baylis, and Medtronic. Dr. Mansour has served as a consultant for Biosense Webster, Inc., Abbott, Medtronic, Boston Scientific, Janssen, Philips, Novartis, and Sentre Heart; has received research grants from Biosense Webster, Inc., Abbott, Boston Scientific, Medtronic, Pfizer, and Boehringer Ingelheim; and has an equity interest in EPD Solutions, NewPace Ltd, and Affera. Dr. Calkins has received honoraria and consulting fees from Biosense Webster, Inc., Medtronic, Abbott, Atricure, and Boston Scientific. Dr. Osorio serves as a consultant for Biosense Webster, Inc. and Boston Scientific; and has received

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Radiofrequency (RF) catheter ablation therapy, with the aim of achieving electrical isolation of the pulmonary veins (PVs), is the cornerstone of treatment for atrial fibrillation (AF) (1). The superiority of catheter ablation of drug-resistant paroxysmal AF in comparison to antiarrhythmic drug (AAD) therapy has been well established, with continued improvements in success rates demonstrated over the past decade with advancement in ablation technologies, especially after the introduction of contact force (CF)-sensing catheters (1–4). In a significant portion of patients, paroxysmal AF progresses to more chronic forms of arrhythmia, including persistent atrial fibrillation (PsAF), defined as AF that continues beyond 7 days (5).

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The increased AF burden resulting from PsAF is associated with a higher risk of stroke, heart failure, and mortality compared with paroxysmal AF (6). Although approximately one-third of AF catheter ablation procedures worldwide are currently performed for persistent or long-standing persistent AF, there are currently limited data on the outcomes of AF ablation in patients with nonparoxysmal AF (1,5). To date, there is no ablation catheter approved by the Food and Drug Administration for PsAF.

The PRECEPT (Prospective Review of the Safety and Effectiveness of the THERMOCOOL SMARTTOUCH SF Catheter Evaluated for Treating Symptomatic PersistenT AF) study (NCT02817776) is the first prospective, multicenter U.S. investigational device exemption (IDE) clinical study designed to evaluate the safety and effectiveness of catheter ablation in patients with PsAF using the THERMOCOOL SMARTTOUCH SF (STSF) catheter (Biosense Webster, Inc., Irvine, California) porous tip CF catheter (**Central Illustration**).

ABBREVIATIONS AND ACRONYMS

AAD = antiarrhythmic drug
AFL = atrial flutter
AT = atrial tachycardia
CF = contact force
CI = confidence interval
ECG = electrocardiography
LA = left atrium/left atrial
PsAF = persistent atrial fibrillation
PV = pulmonary vein
PVI = pulmonary vein isolation
RF = radiofrequency

METHODS

The Institutional Review Board or Ethics Committee at each of the 27 participating centers approved the study protocol (see the Supplemental Appendix for a list of the clinical sites and participating investigators). All patients enrolled in the study provided written informed consent.

STUDY DESIGN. This prospective, multicenter, nonrandomized clinical study was designed to evaluate the safety and effectiveness of the STSF catheter in the treatment of drug-refractory symptomatic PsAF compared with predetermined performance goals. The ablation catheter has been described in detail elsewhere (7,8).

The study design is summarized in **Figure 1**. As accepted in the most recent consensus statement (1), a 3-month medication adjustment period and a 3-month therapy consolidation period (i.e., blanking period) were included after ablation. Dose modification of the currently used AAD, the addition of a new

honorarium and research grants from Biosense Webster, Inc. and Boston Scientific. Dr. Pollak has received personal fees from Biosense Webster, Inc. Dr. Melby has received honoraria for physician education from Biosense Webster, Inc. Dr. Marchlinski serves as a consultant for Abbott, Medtronic, Biosense Webster, Inc.; and has received honorarium from Biotronik and Boston Scientific. Dr. Athill has received a research grant from Biosense Webster, Inc.; has received honoraria from Janssen; and is a consultant for Abbott and Boston Scientific. Dr. Delaughter serves as a consultant for Biosense Webster, Inc. Dr. Patel has received research grant and personal fees from Biosense Webster, Inc. Dr. DeVille has served as a consultant for Biosense Webster, Inc., Medtronic, and Boston Scientific; and has received honorarium from Biosense Webster, Inc., Medtronic, and Boston Scientific. Dr. Macle has received research grants from Biosense Webster, Inc. and Abbott; and has received honorarium from Biosense Webster, Inc. Dr. Dukkipati has received a research grant from Biosense Webster, Inc. Dr. Reddy has received research grants from Biosense Webster, Inc.; serves as an unpaid consultant to Biosense Webster, Inc; is a consultant to Abbott, Ablacon, Acutus Medical, Affera, Apama Medical, Aquaheart, Autonomix, Axon, Backbeat, BioSig, Biotronik, Boston Scientific, Cardiofocus, Cardionomic, CardioNXT/AFTx, Circa Scientific, Corvia Medical, East End Medical, EBR, EPD, Epix Therapeutics, EpiEP, Eximo, Farapulse, Fire1, Impulse Dynamics, Javelin, Keystone Heart, LuxCath, Manual Surgical Sciences, Medlumics, Medtronic, Middlepeak, Newpace, Nuvera, Philips, Stimda, Surecor, Thermedical, Valcare, and Vizara; and has equity in Ablacon, Acutus Medical, Affera, Apama Medical, Aquaheart, Autonomix, Baclbeat, BioSig, Circa Scientific, Corvia Medical, East End Medical, EPD, Epix Therapeutics, EpiEP, Eximo Farapulse, Fire 1, Javelin, Keystone Heart, LuxCath, Manual Surgical Sciences, Medlumics, Middlepeak, Newpace, Nuvera, Surecor, Valcare, and Vizara. Dr. Ellenbogen serves as a consultant for Biosense Webster, Inc., Medtronic, Boston Scientific, and Abbott; and has received honorarium from Biosense Webster, Medtronic, Boston Scientific, and Abbott. Dr. Natale has served as a consultant for Abbott, Biosense Webster, Inc., Biotronik, Boston Scientific, Baylis, and Medtronic. Dr. Gentlesk has reported that he has no relationships relevant to the contents of this paper to disclose.

The 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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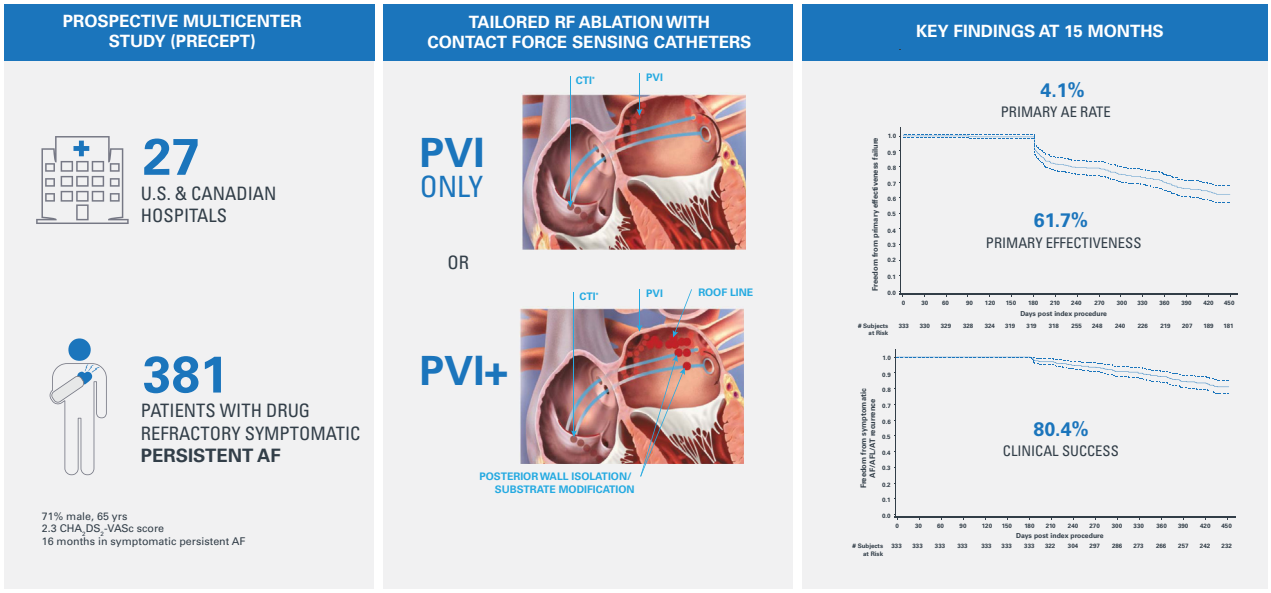
CENTRAL ILLUSTRATION **Drug-Refractory Symptomatic Persistent Atrial Fibrillation Can Be Successfully and Safely Treated by Radiofrequency Catheter Ablation**



Mansour, M. et al. J Am Coll Cardiol EP. 2020;6(8):958-69.

*CTI ablation with documented atrial flutter. AF = atrial fibrillation; AFL = atrial flutter; AT = atrial tachycardia; CTI = cavotricuspid isthmus; PVI = pulmonary vein isolation; PVI+ = additional left atrial ablation per operator's discretion.

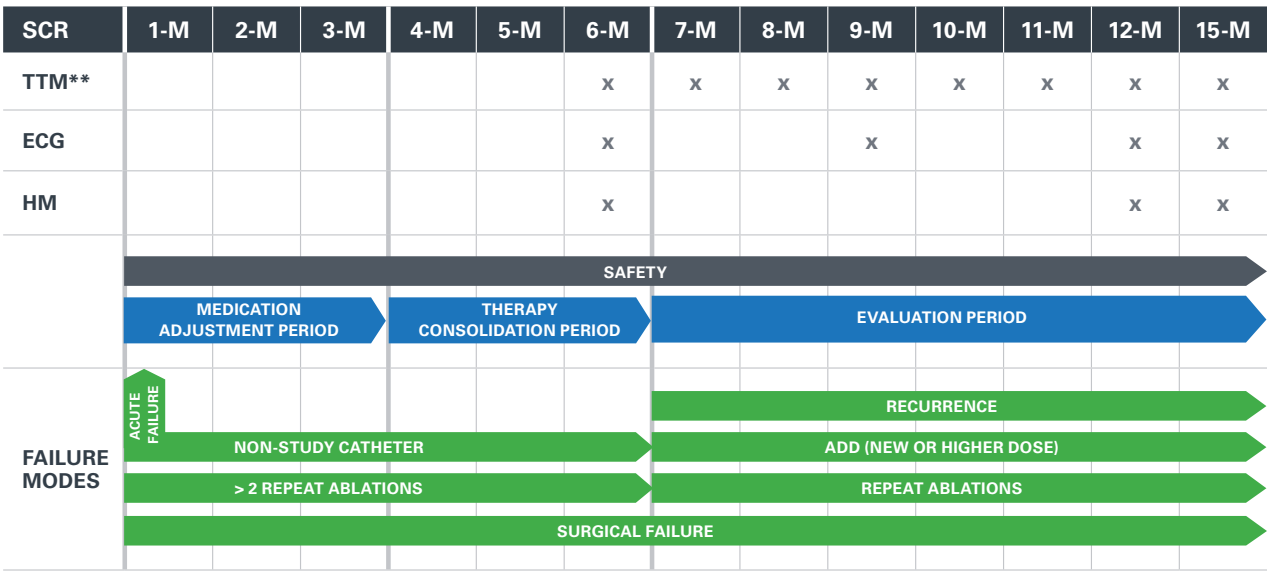
AAD, and substrate remodeling might occur during the medication adjustment period. During the subsequent therapy consolidation period, the status of the medication adjustment was assessed, and repeat ablation was performed as necessary. Cardioversion was allowed if the arrhythmia recurrence persisted during the therapy consolidation period. Participants were followed up at 1, 3, 6, 9, 12, and 15 months after ablation. Arrhythmia recurrences were stringently monitored. Electrocardiograms were obtained at baseline, discharge, and the 6-, 9-, 12-, and 15-month visits. Twenty-four-hour Holter monitoring was performed at baseline and the 6-, 12-, and 15-month visits, and transtelephonic monitoring (TTM) transmissions were performed monthly or when symptoms occurred during the 9-month evaluation period. All recordings were independently adjudicated by a core laboratory for consistency in interpretation. An independent safety monitoring committee reviewed and adjudicated all adverse events.

STUDY POPULATION. Eligible participants had documented symptomatic PsAF, defined as continuous AF sustained beyond 7 days but <1 year, and nonresponse or intolerance to at least 1 AAD (class I or III).

The study exclusion criteria included age younger than 18 years, continuous AF for more than 12 months' duration, ejection fraction <40%, left atrial (LA) diameter ≥50 mm, documented LA thrombus, previous AF ablation, a coronary artery bypass graft procedure in the last 6 months, any cardiac surgery within the past 2 months, carotid stenting or endarterectomy, a prior valvular cardiac surgical procedure, the presence of an implantable cardioverter-defibrillator, New York Heart Association functional Class III or IV, myocardial infarction within the previous 2 months, a thromboembolic event in the previous 12 months, a history of clotting or bleeding disorders, significant pulmonary disease, contraindication to anticoagulation medications, and life expectancy under 12 months.

ABLATION PROCEDURE. After transseptal puncture, electroanatomic mapping was performed using the CARTO 3 System with either the LASSO Catheter or the PENTARAY NAV Catheter (Biosense Webster, Inc.). Ablation was performed with the STSF catheter guided by the VISITAG module using the following recommended settings: location stability of 3 mm, a minimum time of 3 s, and a force-over-time filter ≤50%. The isolation of all PVs was

FIGURE 1 Schedule of Follow-Up, Arrhythmia Monitoring, and Definition of Primary Effectiveness Failure Modes*



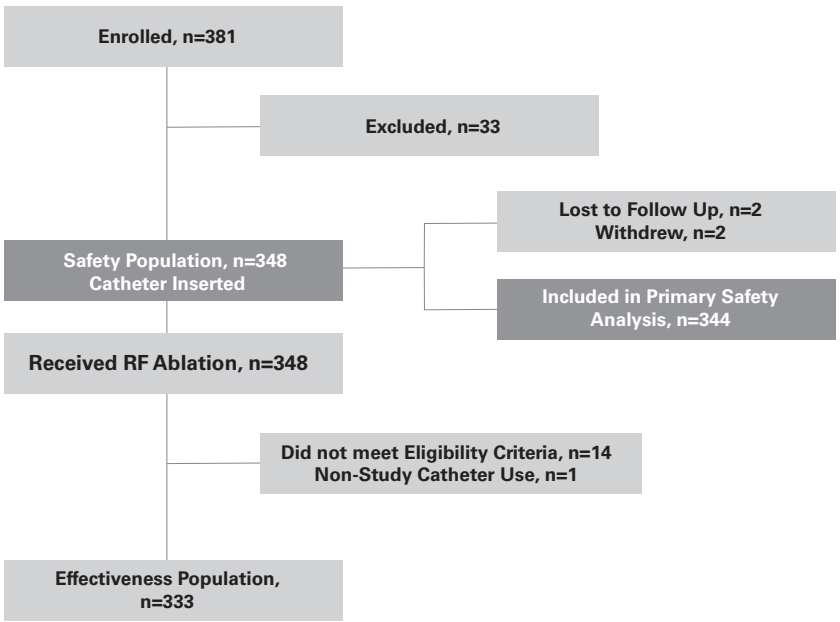
PRIMARY EFFECTIVENESS: FREEDOM FROM THE FOLLOWING FAILURE MODES

FAILURE MODE	DESCRIPTION	EVALUATION PERIOD
1. Recurrence	Documented AF/AFL/AT (≥30 sec) identified by TTM (monthly), HM (at 6, 12, 15M), ECG (at 6, 9, 12,15M), and other acknowledged devices (at 6, 9, 12, 15M)	Day 181-450
2. Acute Procedural Failure	1. Failure to confirm entrance block in all PVs 2. Use of non-study catheter in the index procedure	Day 0
3. Non-study Catheter Failure	Use of non-study catheter for repeat procedure for the treatment of study arrhythmia	Day 1-180
4. Repeat Ablation Failure	1. >2 repeat procedure during blanking period 2. Any repeat procedure post blanking	1. Day 1-180 2. Day 181-450
5. AAD Failure	Taking new class I/III AAD for AF Taking previously failed AAD at a higher dose for AF	Day 181-450
6. Surgical Failure	Undergoing surgical AF ablation or AF surgery	Day 0-450

*Patients had a phone follow-up visit at 7 days. The clinic follow-up visits occurred at 1, 3, 6, 9, 12, and 15 months. **All symptomatic cardiac episodes should be recorded and transmitted via TTM at the time of event(s). AAD = antiarrhythmic drug; AF = atrial fibrillation; AFL = atrial flutter; AT = atrial tachycardia; ECG = electrocardiogram; HM = Holter monitoring; PV = pulmonary vein; SCR = scheduled clinical review; TTM = transtelephonic monitoring.

required. Linear ablation lines were only required to treat documented macro-re-entry atrial tachycardias (ATs) and limited to the LA roof line, mitral valve isthmus line, LA floor line, and cavotricuspid isthmus. A right atrial cavotricuspid isthmus linear ablation was required in cases with documented typical atrial flutter either before or during the procedure. Ablation of spontaneous non-PV triggers or those induced by adenosine or isoproterenol were at the operator's discretion. Complex fractionated atrial electrogram ablation (LA, right atrial, and coronary sinus) was performed only if normal sinus rhythm was not spontaneously restored after ablation of PV and non-PV triggers and substrate modification with linear ablation. PVI was confirmed via entrance block with the LASSO or PENTARAY catheter. After PVI confirmation, a 30-min waiting period from the last RF application

FIGURE 2 Participant Accountability and Disposition



was required, with the adenosine/isoproterenol challenge to rule out dormant reconduction.

SAFETY OUTCOMES. The primary safety endpoint was the incidence of primary adverse events (PAEs) occurring within 7 days of the initial and repeat ablation procedures using the study catheter. PAEs included death, atrioesophageal fistula, cardiac tamponade/perforation, myocardial infarction, stroke/cerebrovascular accident, thromboembolism, transient ischemic attack, diaphragmatic paralysis, pneumothorax, heart block, PV stenosis, pulmonary edema, pericarditis, and major vascular access complication or bleeding. PV stenosis and atrioesophageal fistulas occurring more than 7 days after the index procedure were also considered PAEs.

EFFECTIVENESS OUTCOMES. The primary effectiveness endpoint was freedom from documented recurrence of AF/atrial flutter (AFL)/AT episodes of 30 s or longer duration and freedom from the following additional 5 failure modes at 15 months: acute procedural failure, use of a nonstudy catheter, repeat procedures, use of a new/higher dose of AAD, and surgical ablation (Figure 1). The secondary effectiveness outcomes included acute procedural success (defined as confirmation of entrance block in all PVs) and single procedure success (defined as freedom from documented AF/AT/AFL recurrence during the evaluation period after a single ablation procedure; any repeat ablation procedures after the index procedure were deemed effectiveness failure for this analysis). Because most PsAF studies reported atrial arrhythmia recurrences by standard of care electrocardiography (ECG)/Holter monitoring only, an exploratory analysis using only atrial arrhythmia recurrences as detected by ECG/Holter monitoring up to 12 months of follow-up was also performed for comparison with published data. Freedom from repeat ablation was analyzed at 12 and 15 months. Clinical success was defined as freedom from documented symptomatic AF/AFL/AT recurrence (episodes of 30 s or longer) evaluated after all ablation procedures at 15 months.

STATISTICAL METHODS. Patient demographic, cardiovascular medical history, AAD history, baseline CHA_2DS_2-VASc score, AF history, and procedure data were summarized descriptively. Categoric variables were presented using frequencies and percentages. Continuous variables were presented using mean and standard deviation.

The primary safety endpoint was evaluated using the exact test for a binomial proportion at a 2-sided significance level of 5%. The upper bound of the 1-sided exact 97.5% confidence interval of the primary safety endpoint rate was compared with the performance goal of 16%.

Kaplan-Meier analyses were conducted separately on the primary effectiveness endpoint, single procedure success, clinical success, and repeat procedure

during the evaluation period in the effectiveness population. To identify factors associated with the primary effectiveness outcomes, univariable and multivariable logistic regression models were fit to the data. In the first steps, univariate logistic regression models were used to evaluate the association between demographics, baseline medical history, and procedural data with the primary effectiveness endpoint. Continuous variables were divided into categories such as age (<60, 60 to 70, or ≥70 years), CHA_2DS_2-VASc score at baseline (≥2 or <2), number of Class I/III AADs failed at baseline (≥1 or 0), CF high range (g) (>40, 30 to 40, or ≤30), total RF application duration (min) (>60, 30 to 60, or ≤30), and baseline Atrial Fibrillation Effect on Quality of Life score (≥50 vs. <50). In the second step, if any statistically significant associations were observed at a 0.10 level in the univariate logistic regression, the variables were considered for the multivariable model.

Based on a primary effectiveness performance goal of 40% and an anticipated freedom from AF recurrence rate of 50%, 330 subjects were required to obtain at least 90% power at a 2-sided significance level of 0.05 using the exact binomial method. The safety population consisted of all enrolled participants who had undergone insertion of the study catheter and was used as the analysis population for the primary safety endpoint. The effectiveness population included participants who were enrolled, met all eligibility criteria, and underwent RF ablation with the study catheter for study-related arrhythmia. All statistically analyses were performed using SAS Studio 3.4 or SAS 9.4 (SAS Institute Inc., Cary, North Carolina).

TABLE 1 Participant Characteristics and Medical History at Study Baseline

	Effectiveness Population (n = 333)	Safety Population (n = 348)
Male	237 (71.2)	246 (70.7)
Age, yrs	65.4±8.8	65.4±8.7
Medical history		
Coronary disease	74 (22.2)	77 (22.1)
Myocardial infarction	19 (5.7)	19 (5.5)
Hypertension	227 (68.2)	238 (68.4)
Cardiomyopathy	39 (11.7)	42 (12.1)
TIA/stroke	15 (4.5)	16 (4.6)
Atrial flutter	65 (19.5)	68 (19.5)
Diabetes	61 (18.3)	62 (17.8)
Obstructive sleep apnea	132 (39.6)	134 (38.5)
CHA_2DS_2-VASc score	2.3 ± 1.5	2.3 ± 1.5
NYHA functional class		
I	16 (4.8)	17 (4.9)
II	27 (8.1)	28 (8.0)
III	0 (0.0)	1 (0.3)
Unknown	9 (2.7)	9 (2.6)
Number of failed AADs at baseline	1.3 ± 0.6	1.3 ± 0.6
Baseline AAD history		
Class I	119 (35.7)	121 (34.8)
Class II	189 (56.8)	199 (57.2)
Class III	252 (75.7)	259 (74.4)
Class IV	60 (18.0)	62 (17.8)
Class V	13 (3.9)	14 (4.0)
LVEF	56.2 ± 7.2	56.2 ± 7.2
LA dimension, mm	42.6 ± 5.1	42.4 ± 5.1
Symptomatic PsAF duration, months	15.9 ± 30.8	15.5 ± 30.2

Values are n (%) or mean ± SD. Values for NYHA are only for patients with heart failure.
AAD = antiarrhythmic drug; LA = left atrial; LVEF = left ventricular ejection fraction; NYHA = New York Heart Association; PsAF = persistent atrial fibrillation; SD = standard deviation; TIA = transient ischemic attack.

RESULTS

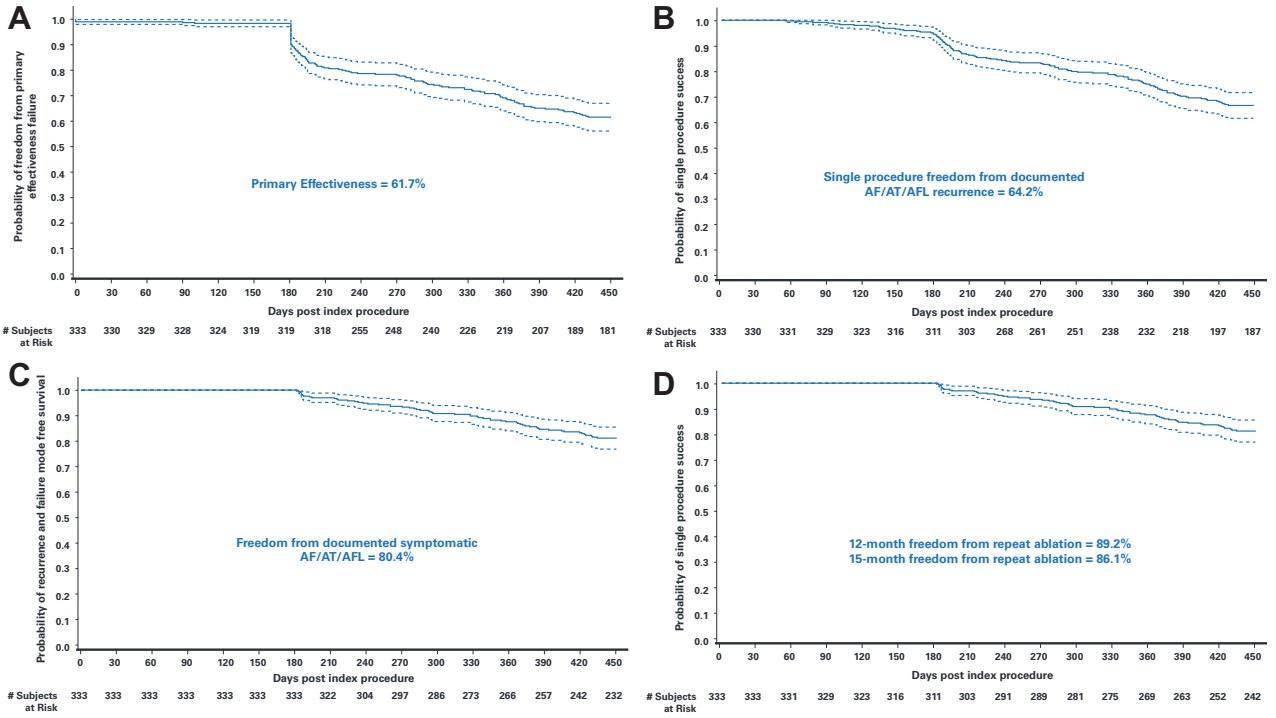
PATIENTS. Between July 27, 2016, and February 6, 2018, 381 participants were enrolled in the study. Participant disposition and accountability are detailed in Figure 2. Of the 381 enrolled participants, 348 had the investigational catheter inserted and comprised the safety population. All participants in the safety population underwent RF ablation. Four participants had missing 3-month data for safety assessment and thus were removed from the primary safety endpoint analysis. The effectiveness population was composed of 333 participants after the exclusion of 14 participants who did not meet the inclusion criteria and 1 participant who was ablated with a nonstudy catheter. The overall follow-up visit compliance rate was 96%. At each follow-up visit (7 days and 1 to 15 months), the compliance rates were 90% or higher (91% to 99%). The compliance rate for the 15-month follow-up visit was 94%. Participant

TABLE 2 Primary Adverse Events (Safety Analysis Population, n = 344)

Death	0 (0.0)
Atrioesophageal fistula	0 (0.0)
Cardiac tamponade	5 (1.5)
Myocardial infarction	0 (0.0)
Cerebrovascular accident/stroke	1 (0.3)
Thromboembolism	0 (0.0)
Transient ischemic attack	0 (0.0)
Diaphragmatic paralysis	1 (0.3)
Pneumothorax	0 (0.0)
Heart block	0 (0.0)
Pulmonary vein stenosis	0 (0.0)
Pulmonary edema (respiratory insufficiency)	3 (0.9)
Pericarditis	2 (0.6)
Major vascular access complication/bleeding	3 (0.9)

Values are n (%).

FIGURE 3 Kaplan-Meier Analyses (Effectiveness Population, n = 333)



Kaplan-Meier analyses of **(A)** time to primary effectiveness failure, **(B)** single procedure failure, **(C)** documented symptomatic AF/AFL/AT recurrence, and **(D)** repeat ablation through 15 months after the procedure. Abbreviations as in Figure 1.

characteristics at study baseline are described in Table 1 and Supplemental Table 1.

All participants underwent PVI, with 193 procedures (55.5%) completed with only PVI. The remaining 44.5% included additional non-PV targets (complex fractionated atrial electrograms, non-PV triggers, and substrate modification).

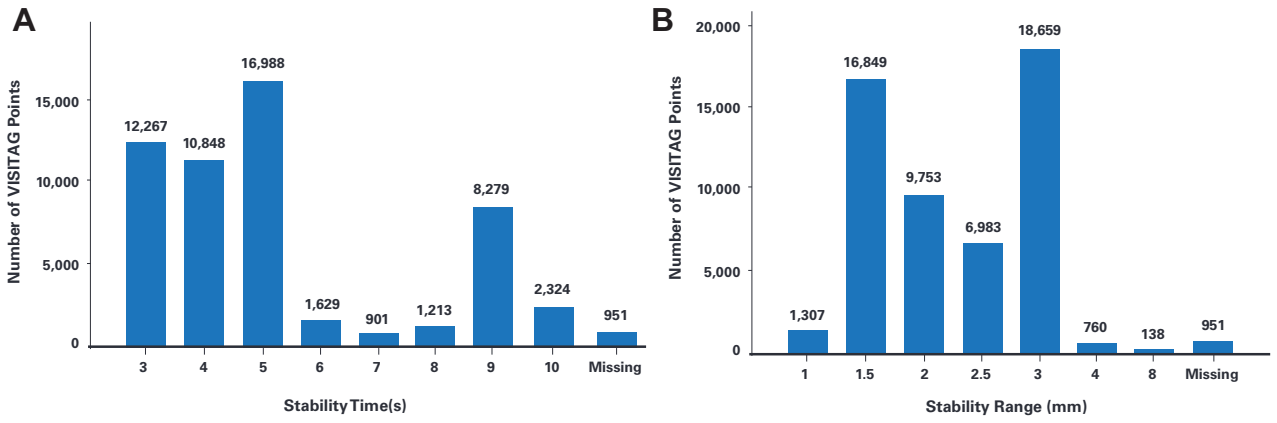
SAFETY OUTCOMES. Overall, 15 PAEs were reported for 14 participants (Table 2). The PAE rate was 4.1% (14 of 344), and the 1-sided exact 97.5% upper confidence bound was 6.7%, significantly less than the specified performance goal of 16.0%. Therefore, the results met the protocol-established performance criteria for primary safety. Thirteen events were resolved without sequelae. One patient with cardiac tamponade underwent a surgical repair procedure, during which an ablation and LA appendage closure were also performed. One case of phrenic nerve

TABLE 3 Univariable and Multivariable Logistic Regression Analysis of the Primary Effectiveness Endpoint (n = 333)

	Univariable Analysis			Multivariable Analysis		
	Odds Ratio	95% CI	p Value	Odds Ratio	95% CI	p Value
Sex (male vs. female)	0.54	0.33-0.90	0.018	0.56	0.32-0.97	0.040
Number of DCCV in the past 180 days	1.26	0.96-1.65	0.098	1.23	0.92-1.64	0.168
Pulmonary hypertension (yes vs. no)	7.76	0.90-67.30	0.063	6.84	0.71-65.66	0.096
Left ventricular systolic dysfunction (yes vs. no)	4.20	1.09-16.18	0.037	5.77	1.44-23.20	0.014
Stroke (yes vs. no)	3.14	0.92-10.66	0.067	3.00	0.81-11.14	0.101
Number of Class III AADs failed (≥1 vs. 0)	1.76	0.99-3.14	0.053	1.70	0.93-3.13	0.086
Contact force high range (g) (>30 and ≤40 vs. ≤30)	1.37	0.77-2.45	0.289	1.27	0.68-2.36	0.446
Contact force high range (g) (>40 vs. ≤30)	2.95	1.10-7.96	0.032	2.31	0.77-6.98	0.136
AFEQT score (≥50 vs. <50)	0.56	0.34-0.91	0.020	0.56	0.32-0.96	0.034

AAD = antiarrhythmic drug; AFEQT = Atrial Fibrillation Effect on Quality of Life; CI = confidence interval; DCCV = direct current cardioversion; RF = radiofrequency.

FIGURE 4 Operator-Configured VISITAG Stability Time and Stability Range per VISITAG Point (Safety Population, n = 348)



(A) VISITAG stability time. **(B)** VISITAG stability range.

paralysis occurred, and the injury persisted at the final follow-up.

EFFECTIVENESS OUTCOMES. Acute procedural success (confirmation of entrance block on all PVs) was achieved in 330 of 333 participants (99.1%). Kaplan-Meier analysis estimated a 15-month primary effectiveness success rate of 61.7% (Figure 3A). The 1-sided exact 97.5% lower confidence bound of 54.1% was significantly higher than the predetermined performance criteria of 40.0%, and the primary effectiveness performance criteria were met. Twenty patients failed the primary effectiveness endpoint because of the use of new or higher doses of AADs. Among the patients who reached the primary effectiveness endpoint, 18% (32 of 178 patients) were on class I/III AADs that were previously ineffective. Among those, 1.7% (3 of 178 patients) patients were on amiodarone. In contrast, of the 381 enrolled patients, 34.4% (131 of 381 patients) had used amiodarone at baseline.

Kaplan-Meier estimates of the single procedure success rate was 64.2% by all 3 study arrhythmia monitoring methods (Figure 3B). Clinical success of freedom from documented symptomatic atrial arrhythmia was 80.4% at 15 months after the procedure (Figure 3C). Kaplan-Meier estimates of freedom from all documented and documented symptomatic atrial arrhythmia off Class I/III AAD was 57.7% and 64.7%, respectively.

To facilitate indirect comparison of the study results with the published data, exploratory analysis of single procedure success by Holter/ECG monitoring only at the 12-month follow-up with the 3-month blanking was performed with a success rate of 73.2%.

REPEAT ABLATION. Overall, 378 procedures (index and repeat) were performed for 333 participants in the effectiveness population, including 19 repeat ablations during the blanking period (5.7%) and 26 repeat ablations after the blanking period (7.8%). The mean number of procedures performed per participant was 1.14. At 12 and 15 months, the Kaplan-Meier estimated freedom from repeat ablation was 89.2% and 86.1%, respectively (Figure 3D).

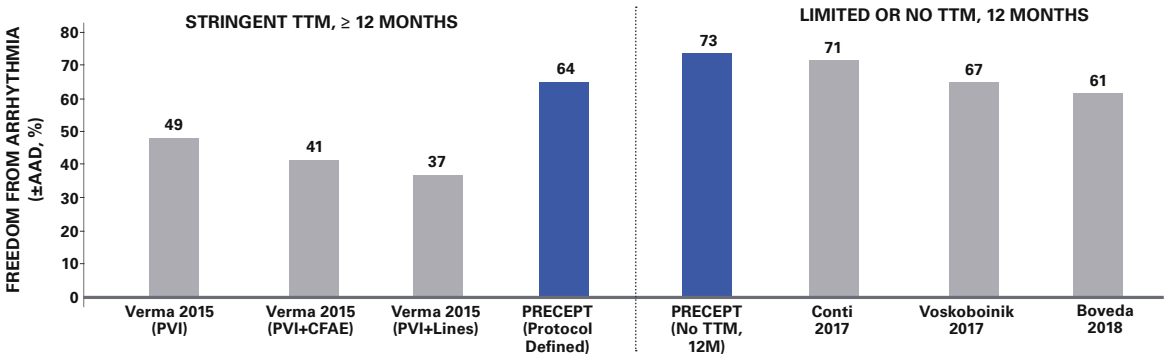
RISK FACTORS ASSOCIATED WITH PRIMARY SAFETY AND EFFECTIVENESS OUTCOMES. Logistic regression modeling was performed to identify potential risk factors associated with primary effectiveness (Table 3). Multivariable modeling indicated that female sex, the presence of left ventricular systolic dysfunction, and a low Atrial Fibrillation Effect on Quality of Life score at baseline (≤50) were associated with a higher risk of primary effectiveness failure.

TABLE 4 Procedural Data (Safety Population, n = 348)

Anesthesia type	
Conscious sedation	16/348 (4.6)
General anesthesia	332/348 (95.4)
Total procedure time, min (n = 348)	178.0 ± 71.0
Total ablation time, min (n = 348)	107.7 ± 48.6
Total fluoroscopy time, min (n = 348)	15.3 ± 16.6
Total RF application duration, min (n = 348)	55.56 ± 23.0
Total mapping time, min (n = 348)	15.3 ± 17.5
Fluid delivered via study catheters, ml (n = 339)	886.3 ± 391.2

Values are n/N (%) or mean ± SD.
Abbreviations as in Tables 1 and 3.

FIGURE 5 Single Procedure Freedom From AF/AT/AFL Recurrence in Studies of PsAF Ablation



REFERENCE		VERMA 2015 (PVI)	VERMA 2015 (PVI+CFAE)	VERMA 2015 (PVI+LINES)	PRECEPT (PROTOCOL DEFINED)	PRECEPT (NO TTM, 12M)	CONTI 2017	VOSKOBOINIK 2017	BOVEDA 2018
Ablation Technology		Non-CF RF			CF RF	CF RF	CF RF	CB, Non-CF or CF RF	CB2
Arrhythmia Monitoring	12-lead ECG	Yes			Yes	Yes	Yes	Yes	Yes
	Holter Monitor	24-hr			24-hr	24-hr	48-hr	Mostly 24-hr	48-hr
	TTM	Stringent			Stringent	None	Limited	Mostly none	None
Follow-up Visit		3 to 18 months			6 to 15 months	3 to 12 months	3 to 12 months	Mostly 3 to 12 months	3 to 12 months
Repeat Ablation after blanking period		14 (22%)	67 (26%)	83 (33%)	26/333 (7.8%)	31/333 (9.3%)	21 (17%)	N/A	17 (17%)

CB = cryoballoon; CB2 = second-generation cryoballoon; CF = contact force; PsAF = persistent atrial fibrillation; PVI = pulmonary vein isolation; RF = radiofrequency; other abbreviations as in Table 1.

STABILITY TAG SETTINGS. CARTO data were available for 298 procedures, 294 of which had stability time/location range captured. A total of 55,400 VISITAG points with stability time were identified in 294 procedures. The most frequently selected settings were a stability time of 3 to 5 s (72.4%) and location stability of ±3 mm (33.7%) or ±1.5 mm (30.4%) (Figure 4). Most operators did not use the force-over-time (88.5% VISITAG points with force over time = 0) feature of the VISITAG module.

PROCEDURE DETAILS. Table 4 summarizes the ablation procedure parameters. The average total procedure time was 178.0 min. Of this time, fluoroscopy was used for an average of 15.3 min per procedure. The mean ablation time, from the time of the first RF application to the time of the last application, was 107.7 min.

DISCUSSION

PRECEPT is the first IDE clinical study with stringent atrial arrhythmia monitoring that demonstrated the long-term safety and effectiveness of RF catheter ablation in drug-refractory symptomatic PsAF using the STSF catheter guided by the VISITAG module. The rate of PAEs was low (4.1%) with a long-term overall protocol-defined success rate of 62% and a clinical success rate of 80%.

Despite the higher risk factors and comorbidities inherent to the PsAF population, the low rate of PAEs in the current study is similar to that reported in paroxysmal AF ablation studies (3,4,7). Notably, there were no unexpected adverse events, deaths, strokes, atrioesophageal fistulas, or cases of PV stenosis. Cardiac tamponade was the most frequently reported PAE in the PRECEPT study with a rate of 1.5%, which is within the acceptable 0.2% to 5% range reported in the current international consensus statement (1) and similar to the rates of 1.2% to 1.3% reported in 2 worldwide surveys of AF procedure safety (9,10).

Comparison of the current results with the published data on ablation of PsAF is challenging. Patients with PsAF are highly heterogeneous across different studies, and few studies have used stringent arrhythmia monitoring (such as regular TTM transmissions) with contemporary ablation technologies. To put the PRECEPT study findings into perspective, we performed an indirect comparison of our results with previously published studies using 2 approaches:

first, comparison with studies that used stringent arrhythmia monitoring and, second, comparison with studies that used standard of care monitoring.

Few studies used stringent arrhythmia monitoring with regular TTM. First, the STAR AF II (Substrate and Trigger Ablation for Reduction of Atrial Fibrillation Trial Part II) study compared ablation of PsAF with PVI alone versus PVI plus ablation of electrograms showing complex fractionated activity or PVI plus additional linear ablation across the LA roof and mitral valve isthmus (11). The study used arrhythmia monitoring using Holter and TTM transmission but was conducted before the availability of CF catheters. The single procedure success rate reported in the STAR AF II study was 37% to 49% at 18 months, lower than the rate of 64% reported in the PRECEPT study. Consistent with this finding is the lower repeat ablation rate in the PRECEPT study (7.8%) compared with the STAR AF II study (21% to 33%, **Figure 5**). In the latest STOP Persistent AF trial (12), a Food and Drug Administration–regulated IDE study similar to PRECEPT, PsAF patients (with <6 months of PsAF history) were treated with cryoballoon catheters using a PVI-only approach, yielding a 12-month success rate of 55% and freedom from repeat ablation of 87%. In contrast, PRECEPT included a broader group of PsAF patients (PsAF up to 1-year duration) with higher baseline comorbidities and resulted in a better outcome. The difference in outcome may be partially explained by the fact that some patients in the PRECEPT study received additional ablation beyond PVI, which is likely to be needed in some patients with PsAF.

The majority of the PsAF ablation studies used standard of care monitoring to assess arrhythmia recurrence, with 12-lead ECG and limited Holter monitoring and only limited or no TTM. In order to compare the current study with these study findings, we performed an exploratory analysis of the PRECEPT results using only data on atrial arrhythmia as detected by ECG and/or Holter monitoring (**Figure 5**). Exploratory analysis of the single procedure success rate at 12 months with ECG/Holter monitoring was estimated at 73% in the PRECEPT study. This rate is similar to the 71% rate at the 12-month follow-up reported in the recent TOUCH AF (Therapeutic Outcomes Using Contact Force Handling During Atrial Fibrillation Ablation) study, which used 48-h Holter and 12-lead ECG arrhythmia monitoring at each clinic visit but limited loop recording or TTM only when the patient reported symptoms (13). Two recent publications that included older RF or non-RF ablation technologies reported 12-month single procedure success rates for PsAF ablation between 61% and 67%, slightly lower than that observed in the PRECEPT study (14,15). In both publications, the enrolled patients had a low prevalence of structural heart disease. Specifically, in the Cryo4Persistent AF (Cryoballoon Ablation for Early Persistent Atrial Fibrillation) study, patients enrolled were on average slightly younger, had a lower prevalence of comorbidities (e.g., hypertension, diabetes, or coronary artery disease), and had a lower stroke risk compared with the participants enrolled in the PRECEPT study, and the study only allowed for PVI ablation (14), likely because of the aforementioned patient characteristics. These prior results, when put in perspective with PRECEPT (higher single procedure success rate in patients with a greater comorbidity burden but with an individualized and optimized treatment approach), makes the findings of the study especially encouraging in comparison.

It is possible that a higher success rate may have been observed if the PRECEPT study had included only "early persistent" patients with lower underlying comorbidities (1). In the recent PRAISE (Pulmonary Vein Reconnection Following Ablation Index-guided Ablation: a Success Evaluation) study, which used a novel CF-sensing catheter and an automated CF stability module and enrolled relatively lower-risk patients (mean CHA_2DS_2VASc score of 1, majority of patients without structural heart disease), 95% of patients were in sinus rhythm and a recurrence of arrhythmia was documented in only 20% of patients at the 12-month follow-up, similar to outcomes observed in paroxysmal AF patients (16).

It is worth noting that both the Cryo4Persistent AF and PRAISE studies, which included largely PsAF patients with fewer comorbidities, used a PVI-only ablation strategy, likely based on AF disease presentation. This is in contrary to the PRECEPT study in which ablation strategies were at the discretion of the investigators, representing more closely standard of care practice with a broader range of patient population. The 2017 consensus statement recognized the range of disease presentation and ablation outcome of PsAF patients. Specifically, responses of "early" and "late" PsAF patients may be different in that those with more advanced disease presentation may have a worse outcome similar to long-standing PsAF patients (1). There is currently no consensus on appropriate patient segmentation (i.e., "early" vs. "late" PsAF) and an associated optimal ablation strategy for PsAF. These questions need to be evaluated in future trials.

The primary effectiveness endpoint of the PRECEPT study was based on the conventional outcome of freedom from recurrence of any documented atrial arrhythmia episodes lasting 30 s or longer, an

outcome that may not be clinically relevant to individual patients with PsAF. A clinically meaningful definition of success in this population is freedom from documented symptomatic AF/AFL/AT recurrence because AF symptoms represent the main burden on patients' quality of life, and the goal of AF ablation treatment is symptomatic relief. The PRECEPT results showed a clinical success rate of 80% at 15 months. Many individuals with AF experience symptoms such as palpitations and dyspnea with exertion. Data from the ORBIT-AF (Outcomes Registry for Better Informed Treatment of Atrial Fibrillation) study have shown that a higher AF symptom burden is associated with lower quality of life and higher rates of hospitalization (17). An analysis of data from the STAR AF (Substrate and Trigger Ablation for Reduction of Atrial Fibrillation) study demonstrated that quality of life after AF ablation was improved regardless of procedural outcomes as defined by the study protocol and that quality of life scores were negatively affected only in patients with a high symptomatic burden of arrhythmia recurrence. The results suggested that a significant reduction in symptom burden improves quality of life even in the absence of total elimination of AF episodes (18).

STUDY LIMITATIONS AND FUTURE RESEARCH NEEDS. The PRECEPT study was not designed to compare outcomes with different ablation strategies. Although PVI remains the cornerstone of AF ablation even in the PsAF population (1), in the current study, approximately half of the patients received additional ablation beyond PVI at the investigators' discretion. The underlying assumption of a one-size-fit-all concept for most PsAF ablation studies deserves reevaluation and consideration. It is important to understand underlying patient characteristics for clinical decision making toward different ablation strategies that may be tailored to individual patient's needs.

The gold standard for defining success in catheter ablation studies is arrhythmia-free survival over a 12-month follow-up, as measured by a 30-s episode of AF. There is increasing consensus that a more clinically relevant outcome is needed for defining treatment success. For PsAF treatment, a more clinically meaningful treatment goal for patients is the reduction of symptoms and associated AF burden. The CLOSE to CURE (CLOSE-Guided Pulmonary Vein Isolation as Cure for Paroxysmal Atrial Fibrillation?) study recently showed a near 100% reduction in atrial tachyarrhythmia burden, as measured by an implantable loop recorder, during 2 years of follow-up after paroxysmal AF ablation (19). The results from the PRECEPT study showed an 80% symptomatic arrhythmia-free survival at the 15-month follow-up. Future studies are needed to evaluate the associated reduction in atrial arrhythmia burden from continuous monitoring after catheter ablation treatment.

CONCLUSIONS

The PRECEPT study demonstrated the clinical safety and effectiveness of PsAF ablation using CF-sensing technologies with a protocol-defined effectiveness of 62% and a clinical success rate of 80%. The PAE rate was within the acceptable and expected range and similar to that for paroxysmal AF ablation. Comparison with other multicenter studies suggests an individualized ablation approach based on the patient's clinical presentation may optimize treatment outcome.

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ADDRESS FOR CORRESPONDENCE: Dr. Moussa Mansour, Cardiac Arrhythmia Service, Heart Center, Massachusetts General Hospital, 55 Fruit Street, GRB 109, Boston, Massachusetts 02114. E-mail: mmansour@mgh.harvard.edu.

PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: Drug-refractory symptomatic PsAF can be successfully and safely treated by RF catheter ablation using CF–sensing technologies.

TRANSLATIONAL OUTLOOK 1: Although PRECEPT showed a high rate of freedom from symptomatic atrial arrhythmia, future studies should evaluate reductions in AF burden and associated quality of life in more detail.

TRANSLATIONAL OUTLOOK 2: There is currently no consensus on appropriate patient segmentation and an associated optimal ablation strategy for PsAF, so the findings of PRECEPT need to be expanded on in future studies comparing different ablation strategies in this patient population.

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KEY WORDS atrial arrhythmia, porous tip catheter, pulmonary vein isolation, symptomatic atrial fibrillation, transtelephonic monitoring

APPENDIX For a supplemental table and a list of the participating sites, please see the online version of this paper.