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ORIGINAL ARTICLE

Targeting Nonpulmonary Vein Sources in Persistent Atrial Fibrillation Identified by Noncontact Charge Density Mapping

UNCOVER AF Trial

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BACKGROUND: Identification and elimination of nonpulmonary vein targets may improve clinical outcomes in patients with persistent atrial fibrillation (AF). We report on the use of a novel, noncontact imaging and mapping system that uses ultrasound to reconstruct atrial chamber anatomy and measures timing and density of dipolar, ionic activation (ie, charge density) across the myocardium to guide ablation of atrial arrhythmias.

METHODS: The prospective, nonrandomized UNCOVER AF trial (Utilizing Novel Dipole Density Capabilities to Objectively Visualize the Etiology of Rhythms in Atrial Fibrillation) was conducted at 13 centers across Europe and Canada. Patients with persistent AF (>7 days, <1 year) aged 18 to 80 years, scheduled for de novo catheter ablation, were eligible. Before pulmonary vein isolation, AF was mapped and then iteratively remapped to guide each subsequent ablation of charge density–identified targets. AF recurrence was evaluated at 3, 6, 9, and 12 months using continuous 24-hour ECG monitors. The primary effectiveness outcome was freedom from AF >30 seconds at 12 months for a single procedure with a secondary outcome being acute procedural efficacy. The primary safety outcome was freedom from device/procedure-related major adverse events.

RESULTS: Between October 2016 and April 2017, 129 patients were enrolled, and 127 underwent mapping and catheter ablation. Acute procedural efficacy was demonstrated in 125 patients (98%). At 12 months, single procedure freedom from AF on or off antiarrhythmic drugs was 72.5% (95% CI, 63.9%–80.3%). After 1 or 2 procedures, freedom from AF was 93.2% (95% CI, 87.1%–97.0%). A total of 29 (23%) retreatments because of arrhythmia recurrence were performed with average time from index procedure to first retreatment being 7 months. The primary safety outcome was 98% with no device-related major adverse events reported.

CONCLUSIONS: This novel ultrasound imaging and charge density mapping system safely guided ablation of nonpulmonary vein targets in persistent AF patients with 73% single procedure and 93% second procedure freedom from AF at 12 months.

CLINICAL TRIAL REGISTRATION: URL: https://www.clinicaltrials.gov. Unique identifier: NCT02825992 EU/NCT02462980 CN.

VISUAL OVERVIEW: A visual overview is available for this article.

Key Words: atrial fibrillation ■ Canada ■ Europe ■ heart atria ■ humans

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WHAT IS KNOWN?

- Catheter ablation outcomes in the persistent atrial fibrillation patient population are suboptimal when compared with the reported 1-y postindex procedure arrhythmia-free outcomes of 70% to 80% seen in paroxysmal atrial fibrillation (including atrial tachycardia/atrial flutter).
- Clinical studies in the persistent atrial fibrillation patient population have failed to show a difference in outcomes when more extensive ablation beyond pulmonary vein isolation is added.

WHAT THE STUDY ADDS?

- Noncontact charge density imaging and mapping to guide ablation therapy of nonpulmonary vein triggers in addition to pulmonary vein isolation, offers the potential to provide targeted treatment for persistent atrial fibrillation on a patient-specific basis with improved prognostic benefit.
- Elimination and even lowering of arrhythmia burden was associated with improvement in overall patient health and quality of life.

Atrial fibrillation (AF) is the most common clinically diagnosed arrhythmia with considerable impacts on the public health.[1–3] For symptomatic patients who fail antiarrhythmic drugs (AADs), pulmonary vein isolation (PVI) is the interventional approach of choice for paroxysmal AF and is commonly applied in de novo cases of persistent AF (PersAF).[3–7] The clinical outcomes of PVI for PersAF even with added empirical or anatomically targeted ablation have been disappointing.[8,9] The effectiveness estimate of 1-year freedom from AF following a single catheter ablation (CA) procedure for PersAF is 43% increasing to 69% with multiple procedures on or off AADs.[10] Accordingly, questions regarding appropriate ablation strategies for PersAF remain the subject of intense debate.[11]

One widely held view is that improvement in CA outcomes in PersAF would follow precise identification and eradication of functional drivers located at sites distant to the pulmonary veins.[2,11] Because of the need to serially collect contact points over time, conventional 3-dimensional voltage-based mapping systems are ill suited to display the continuous chaotic activation that is characteristic of PersAF and identify such targets.[3] Here we report on a novel, full-chamber, noncontact imaging and mapping system that uses ultrasound to reconstruct atrial chamber anatomy and an inverse algorithm to derive charge density (CD).[12,13] Animated, global activation maps, referred to as CD maps, and having a 4-fold increment in resolution compared with voltage maps, are created to guide ablation therapy.[12,13] Ablation strategies are individualized per patient to address dynamic activation patterns identified in addition to PVI. The aim of UNCOVER AF (Utilizing Novel Dipole Density Capabilities to Objectively Visualize the Etiology of Rhythms in Atrial Fibrillation) was to examine both clinical effectiveness and safety of ultrasound chamber reconstruction and CD mapping to guide an ablation therapy strategy in PersAF.

METHODS

This study is based on proprietary technology; thus the data, analytic methods, and study materials will not be made available to investigators or researchers not involved in this study.

Study Design and Participants

UNCOVER AF was a prospective, single-arm, nonrandomized, multicenter, premarket trial in Canada and a postmarket trial in Europe. Patients aged 18 to 80 years scheduled for de novo ablation of PersAF, defined as sustained AF lasting >7 days and <1 year without electrical cardioversion, were recruited from 13 clinical sites in Europe and Canada. A full listing of sites and number of patients enrolled at each is provided in Appendix in the Data Supplement. Patients were excluded for prior history of ablation or surgical intervention for any atrial arrhythmia, AF episode lasting longer than 12 months, left ventricular ejection fraction < 40% or left atrial (LA) size > 50 mm, and any history of documented cerebrovascular event or systemic embolism. The study was registered at www.clinicaltrials.gov (NCT02825992 EU/NCT02462980 CN), complied with the Declaration of Helsinki, was approved by local ethics committees, with all participants signing informed consent before study participation. Monitoring of data were provided by an independent clinical research organization (ICON plc, Dublin, Ireland).

Procedures

Comprehensive clinical history and procedural data were collected for each subject. Use of AADs leading up to the procedure followed institutional standard of care. Discontinuation of amiodarone for 60 days before the ablation was recommended. Transthoracic echocardiography was performed within the preceding 6 months to determine left ventricular function and atrial dimension. Transesophageal echocardiography was completed within 72 hours before the procedure to rule out atrial thrombus.

CA procedures were conducted under either conscious sedation or general anesthesia per institutional standard of care with central venous access gained and then fluoroscopic guidance used for trans-septal access to the LA. Following LA access, intravenous heparin was administered to maintain ACT > 350 seconds. The ultrasound and CD imaging and mapping catheter (AcQMap; Acutus Medical, Inc, Carlsbad, CA) was positioned in the LA, via a steerable sheath, to generate 3D surface reconstructions and maps of atrial activation.

The AcQMap High-Resolution Imaging and Mapping System (Acutus Medical, Inc) reconstructs the endocardial anatomic surface and then overlays high-resolution CD maps of electrical activation. The chamber surface is sampled from 48 ultrasound transducers distributed across

the AcQMap catheter (Figure 1) at a rate of up to 115,000 surface points per minute. An anatomic image representing end-diastolic volume and shape is obtained from the points in <5 minutes and with limited rotation of the catheter (Movie I in the Data Supplement).

Following reconstruction of the anatomic shell, a CD map was generated during AF. If the patient did not present in AF at the time of procedure, arrhythmia was induced by rapid atrial pacing down to the atrial effective refractory period with or without isoproterenol. During mapping, the system samples the intracardiac potential field (ie, cavitary voltage) at 150 000 acquisitions per second from 48 noncontact electrodes distributed across the AcQMap catheter splines. An inverse algorithm, based on Poisson equation, is then applied to the measured cavitary potentials to derive the distribution of positive and negative ionic charges located across the chamber surface.[12,13] Activation maps (≈5 seconds of AF) are created within 2 minutes and displayed as a spatiotemporal window of activation history across the ultrasound-acquired image. The color red is used to delineate the leading edge of the wave front associated with the present instant of time, as indicated by the waveform time cursor (ie, the key wave front in the window of history). The trailing color bands display the earlier locations of the wave front within the window of history, which enables comprehension of complex conduction patterns. Wave front velocity can be discerned at any location from the width of the color bands. The result is a full-chamber view of high-resolution CD maps of cardiac activation that capture the instantaneous pattern of conduction for each activation cycle and enables mapping of both stable and unstable arrhythmias. Far-field artifacts dominant in voltage-based mapping are reduced in CD-based maps, enhancing discernment of complex and irregular arrhythmias including AF. Figure 1 shows the design of the AcQMap catheter along with examples of an ultrasound-reconstructed anatomy and a CD map. Right atrial ablation was not mandated by the protocol but was allowed at physician discretion. Ablation to the point of noninducibility was left to the discretion of the physician. Procedure flow is depicted in Figure 2.

The system supports an open platform allowing the use of irrigated radiofrequency, force sensing radiofrequency, or cryothermy ablation catheters to perform PVI and target ablation sets. Physicians performed wide antral PVI, defined as delivery of encircling ablation lesions outside of the pulmonary vein (PV) ostia to achieve complete isolation of all PVs with confirmation of entrance block into each vein. During PVI, the protocol encouraged the incorporation of any AcQMap-identified targets near the PVs into the wide antral lesion set. A minimum power of 25 to 30 W was suggested with a flow rate of 15 to 30 ml/min as determined by the catheter manufacturer for open-irrigated radiofrequency. Balloon-based cryothermy was also allowed as an alternative for PVI. A minimum of 2 lesions with a 28-mm balloon for 3 minutes each were required for each vein ablated.

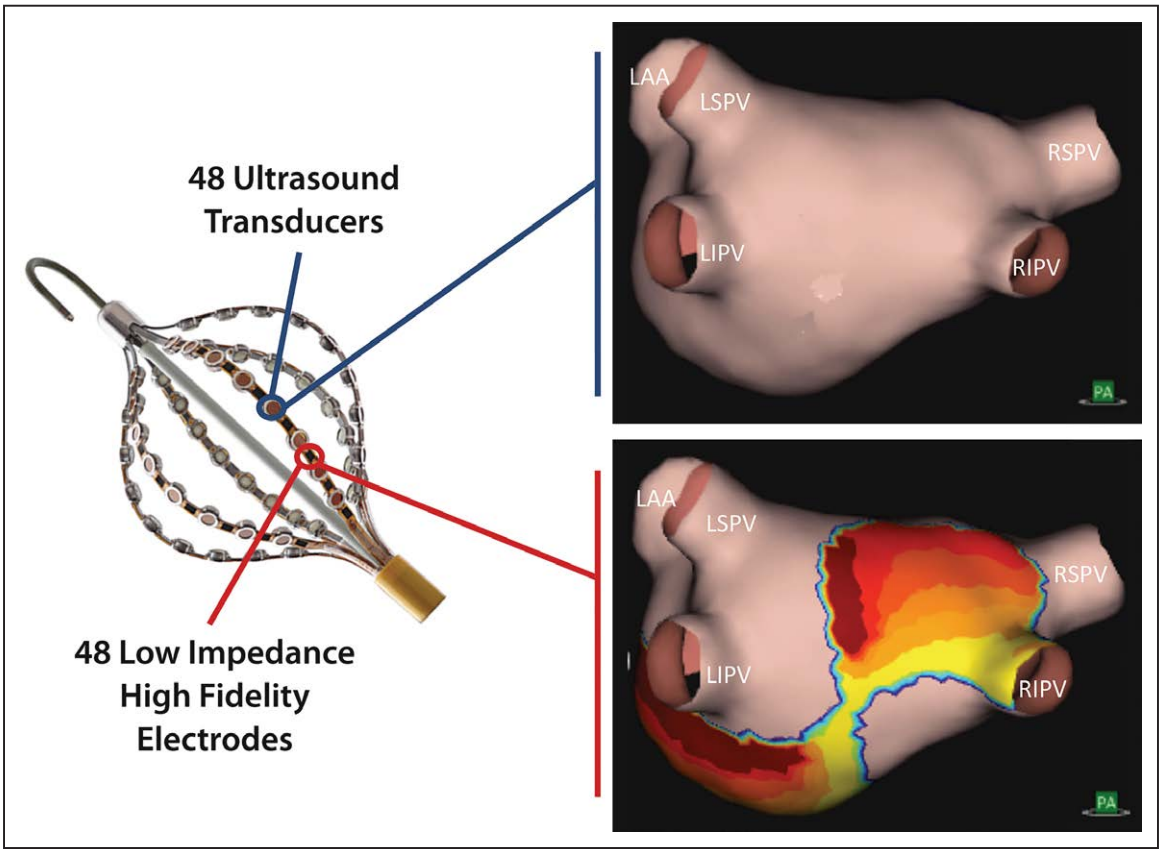

Figure 1. The AcQMap catheter has 6 splines, each of which is populated with 8 ultrasound transducers for anatomic reconstruction (upper right) interspersed with 8 low-impedance, high-fidelity electrodes for recording biopotential signals to create propagation history maps (lower right). Dark red represents the leading edge of the activation wave front, with the trailing color bands showing earlier wave front locations. Propagation velocity can be discerned at any location from the width of the color bands. LAA indicates left atrial appendage; LIPV, left inferior pulmonary vein; LSPV, left superior pulmonary vein; RIPV, right inferior pulmonary vein; and RSPV, right superior pulmonary vein.

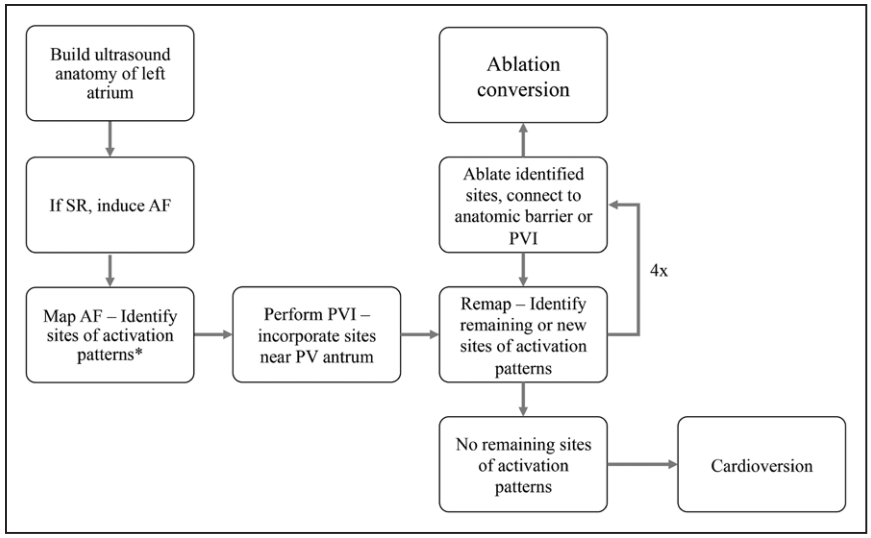

Figure 2. Procedural flow.
The procedural end point was the electrical isolation of the pulmonary veins and elimination or modification of the sites with activation patterns. Cardioversion was performed if the final procedural rhythm was not converted to sinus rhythm (SR). AF indicates atrial fibrillation; PV, pulmonary vein; and PVI, pulmonary vein isolation. *Focal, rotational, and irregular activation.

After PVI, another CD map was acquired to confirm consistency of abnormal conduction patterns to target for ablation. The protocol defined 3 discrete patterns of abnormal activation to be targeted based on early feasibility studies[12,13] (see Results). Physicians were trained to identify these activation patterns before inclusion of patients in the protocol. The protocol also required that all identified targets of abnormal conduction patterns were ablated. If the target was located within 2 cm of a fixed anatomic boundary, its core was anchored to minimize the possibility of subsequent pivoting or rotation. Discrete ablation was performed to eliminate focal activations. The efficiency with which maps are created encouraged iterative mapping to assess resultant changes in activation following each energy delivery.

Follow-Up

Clinical follow-up data were collected at predischarge, 7 days, and 1, 3, 6, 9, and 12 months. Safety was evaluated at each visit, and analysis of patient rhythm was completed at the 3-, 6-, 9-, and 12-month follow-up visits. Standard 12-lead ECG and a 24-hour continuous ECG recording at each visit documented recurrence of atrial arrhythmias. The continuous 24-hour ECG monitor was a P-wave centric patch monitor, designed to discriminate between atrial and ventricular activity. A core laboratory (Ingress Global, Grantham, United Kingdom) analyzed and reported all 24-hour ECG monitor recordings. Per protocol, recurrence of AF, atrial flutter (AFL), or atrial tachycardia (AT) outside of required visits was documented by ECG, 24-hour continuous ECG monitor, or Holter and recorded as an unscheduled visit. A 3-month blanking period was used during which recurrences of AF/AFL/AT were not counted as failures as per standard guidelines.[3,5] In contrast to previous studies,[6,14,15] repeat ablation was not allowed during the blanking period. Retreatment reset the 3- and 6-month follow-up schedule; the 12-month follow-up visit was timed from the index procedure. Continuation of AAD therapy and the use of cardioversion were used to maintain sinus rhythm (SR) throughout the 3-month blanking period in accordance with standards of care, but discontinuation of AAD was encouraged thereafter. A repeat transthoracic echocardiography was performed at the 12-month visit.

Outcomes

The primary safety outcome of the study was freedom from device/procedural complications within 24 hours of the start of the CA procedure. Prespecified major adverse events (MAEs) were death, cardiac perforation/tamponade, cerebral infarction, transient ischemic attack or systemic embolism, major bleeding, mitral or tricuspid valve damage, and serious adverse events adjudicated as probably related to the AcQMap System. Sites were required to report all clinical adverse events throughout the follow-up period. An independent clinical events committee reviewed all adverse events for seriousness and procedure or device relatedness.

The primary effectiveness outcome was freedom from AF >30 seconds (symptomatic or asymptomatic) at 12 months after the index procedure with or without AADs. Secondary outcomes included freedom from atrial arrhythmia >30 seconds (symptomatic or asymptomatic) off AADs; freedom from atrial arrhythmias >30 seconds (symptomatic or asymptomatic) after 2 procedures; acute efficacy outcome, defined as procedural conversion to SR within 12 hours of the index procedure; AF burden as determined from the combined Holter recordings from each patient through 12 months.

Patient quality of life was assessed at each follow-up visit using Atrial Fibrillation Effect on Quality of Life (AFEQT) disease-specific questionnaire. This outcome measure evaluates daily activities, treatment concerns, and satisfaction with treatment from patients' perspectives providing a discrete overall score. Treatment satisfaction is presented as a separate subscore. Scores range from 0 to 100. A score of 0 corresponds to complete disability; a score of 100 corresponds to no disability.

Statistical Analysis

The study required a sample size of 125 patients to achieve the safety objective within a margin of error of 3.89% (ie, a 95% CI half-width), assuming the observed proportion

of patients who are free from device/procedure-related MAEs that occur within the first 24 hours post-procedure is 96.0%. Descriptive statistics were used for all additional outcomes. Baseline and demographic characteristics, including a detailed arrhythmia history, were summarized for all patients in the safety population and effectiveness outcomes for all patients in the treatment population. Continuous variables are presented as mean, SD, median, and interquartile range if applicable, and categorical variables are summarized via counts and percentages. Freedom from AF or atrial arrhythmia is represented by Kaplan-Meier curve analysis. Multivariate logistic regression was used to identify outcome predictors at 12 months. Change scores from baseline to 12 months were calculated for the AFEQT symptom severity, daily activity, treatment concerns, satisfaction with treatment, and total burden score domains. Kendall Tau rank correlation was used to measure the relationship between AFEQT domain scores and total atrial Burden. Analyses were performed with SAS, version 9.4 (SAS, Inc, Cary, NC). Statistical significance was established at $P<0.05$.

RESULTS

Patient Flow and Characteristics

Between October 2016 and April 2017, 141 patients scheduled for de novo CA of PersAF were screened, and 129 patients were enrolled at 13 centers (Table I in the Data Supplement). The procedure was terminated for clinical reasons in 2 patients. As such, data for 129 patients were evaluated for the safety outcome, while data for 127 patients were analyzed for procedural effectiveness outcomes. The study flow is outlined in Figure 3. Clinical follow-up data through the 12-month visit window were available for 121 (95.3%) patients. No deaths were reported during the 12-month follow-up period.

Baseline characteristics of the 129 enrolled patients are shown in Table 1. The time from onset of first diagnosed PersAF, defined as continuous AF for at least 7 days and ≤1 year, to the point of patient screening was

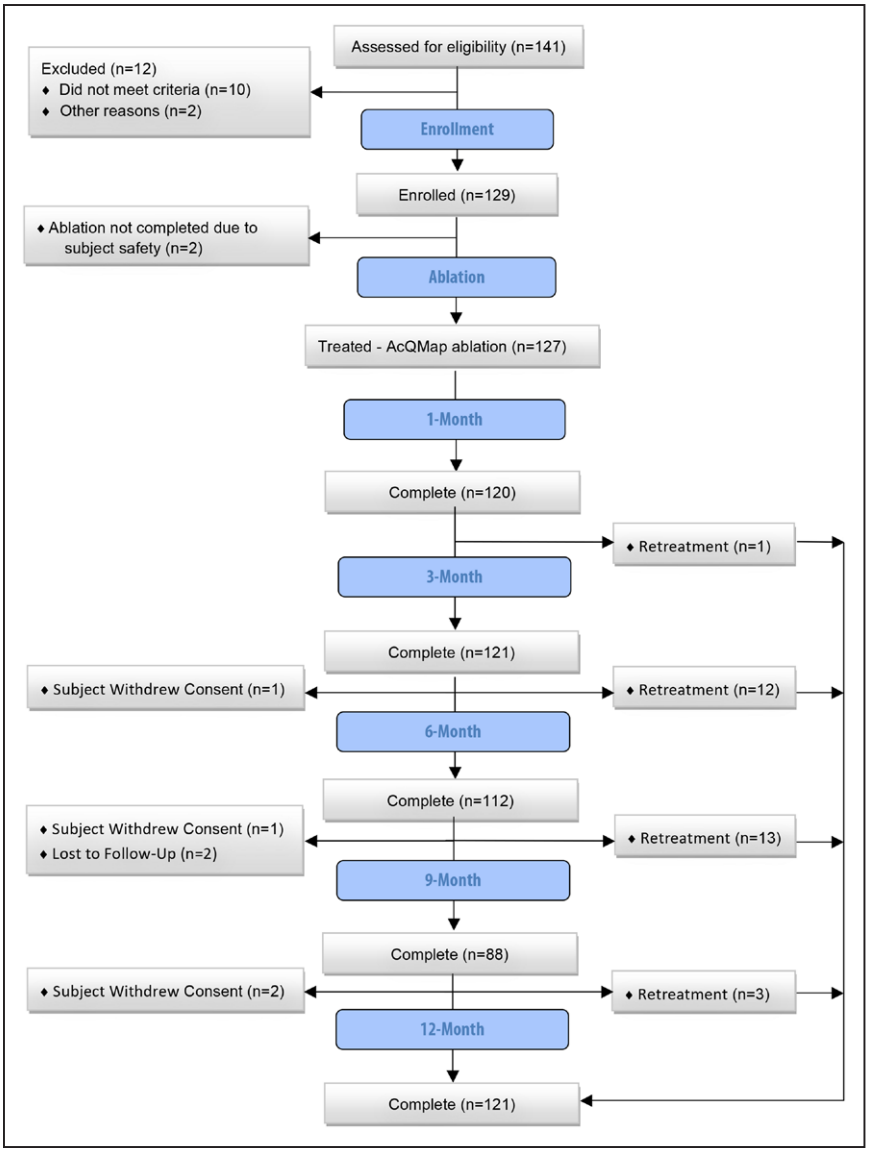

Figure 3. Study consort diagram.

Table 1. Description of Baseline Clinical Characteristics of Patients

Clinical Characteristics	Safety Cohort (n=129)
Mean age±SD, y	62.4±8.6
Sex	
Men, n (%)	97 (75.2)
Women, n (%)	32 (24.8)
BMI, kg/m^2	29.2±4.7
Onset of first diagnosed AF, y	3.21±3.93
Onset of first diagnosed PersAF, y	1.94±3.13
Average number of failed AADs	0.9±0.8
Cardioversions in the past 2 y per patient	1.3±1.0
Comorbidities	
Hypertension, n (%)	74 (57)
Coronary artery disease, n (%)	16 (12)
Diabetes mellitus, n (%)	14 (11)
Valvular disease, n (%)	13 (10)
Cardiomyopathy, n (%)	6 (5)
Heart failure, n (%)	5 (4)
LA diameter, mm	43.0±4.1
LVEF, %	57.6±7.2
Antiarrhythmic medications	
Class Ic	16 (12.4)
Class III	32 (24.8)
CHA2DS2-VASc score, n (%)	
0	30 (23)
1	40 (31)
2	36 (28)
3	15 (12)
4	8 (6)

Data are mean (±SD), n (%). AAD indicates antiarrhythmic drug; AF, atrial fibrillation; BMI, body mass index; LA, left atrium; LVEF, left ventricular ejection fraction; and PersAF, persistent atrial fibrillation.

1.94±3.1 years. The average number of failed AAD before CA was 0.9. At screening, the average number of days since the most recent cardioversion was 277 (±393.1), and the average number of days since AF recurred post-cardioversion was 138 (±139.6). At study start, all 129 patients were confirmed to have PersAF. Transthoracic echocardiography performed ≤6 months before the index procedure demonstrated a mean LA diameter of 43.0±4.1 mm at baseline and 42.1±6.2 mm at the 12-month follow-up visit.

Procedural Characteristics

Procedural data are shown in Table 2. Of the 127 patients who underwent CA, 63% were in AF at the start of the procedure. In the other 37% of patients, AF was induced, before PVI, by rapid atrial pacing. Cardioversion was performed at procedure end on 85 of 125 (68%) patients, while 40 of 125 (32%) either spontaneously converted to SR or converted during ablation energy delivery. In 28 patients, other SVT rhythms (AFL/AT) were recorded during the procedure (spontaneous or induced during ablation; Table 3). Six subjects

Table 2. Description of Mapping and Ablation Procedure

Procedural Data		
	Procedural Cohort (n=127)*	Percentage
Procedure time, h (first stick to catheter removal)	4.1±1.1	
Total fluoroscopy time, min	31.1±12.9	
Time to create atrial anatomy, min	4.3±2.0	
Ablation time PVI, min	30.5±11.8	
Ablation time non-PVI targets, min	23.8±17.7	
Acute conversion to SR	125	98%
With cardioversion	85/125	68%
Without cardioversion	40/125	32%
Anesthesia, %	General	Conscious sedation
	54%	46%

PVI indicates pulmonary vein isolation; and SR, sinus rhythm.
*All values are mean±SD, n (%).

Table 3. Description of Non-AF Rhythm per Patient Incidence and Patient Pattern Distribution

Non-AF Rhythm per Patient Distribution		
	Procedural Cohort (n=127)*	Percentage
CTI-dependent AFL	7/127	5.5%
Non-CTI AFL	16/127	12.6%
AT	9/127	7.1%
CTI ablation	8/127	6.3%
Mitral isthmus line	12/127	9.4%
Additional linear lines	19/127	15%
Pattern location		
AP1	4/127	3.1%
AP2	4/127	3.1%
AP3	7/127	5.5%
AP4	3/127	2.4%
AP7	1/127	0.8%
PA3	2/127	1.6%
PA4	1/127	0.8%
PA7	1/127	0.8%
PA8	1/127	0.8%
PA9	2/127	1.6%
PA10	3/127	2.4%
PA11	3/127	2.4%
PA12	4/127	3.1%

AF indicates atrial fibrillation; AFL, atrial flutter; AT, atrial tachycardia; and CTI, cavotricuspid isthmus.
*All values are mean±SD, n (%).

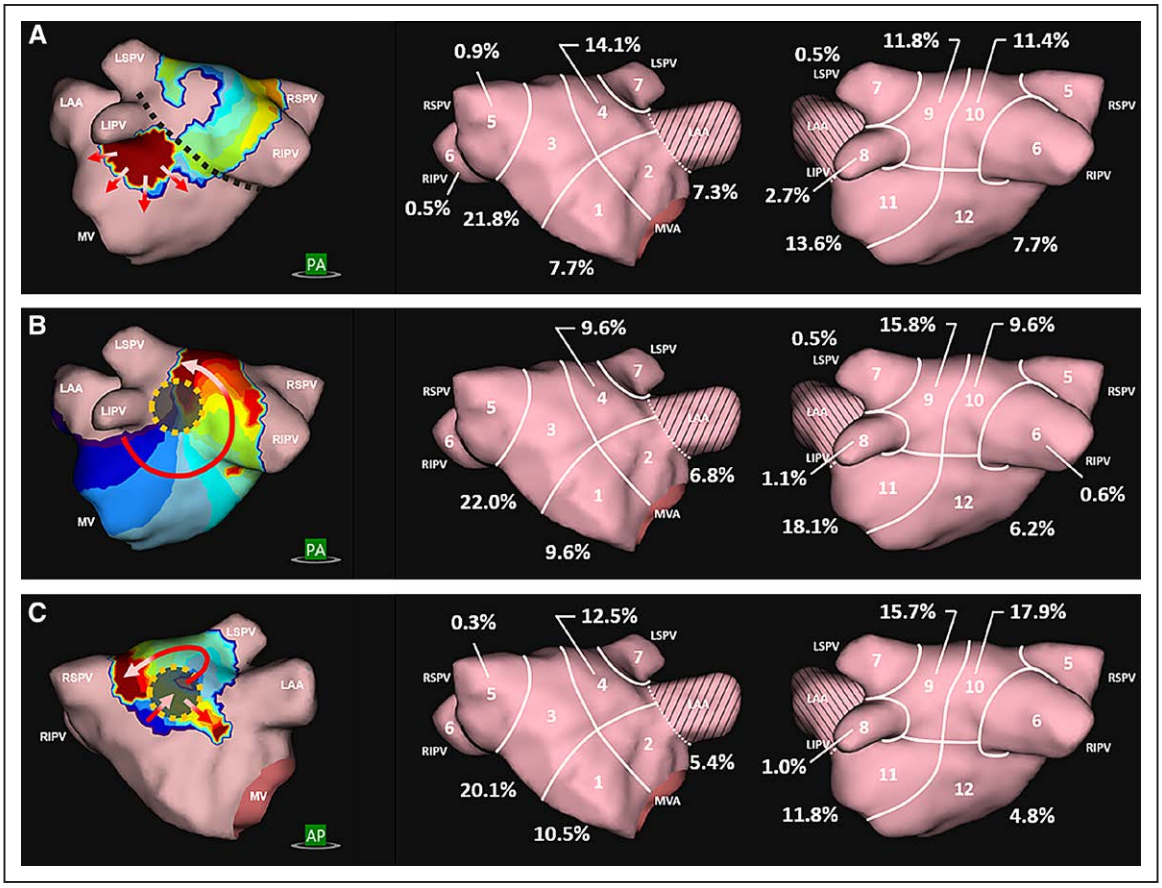

Figure 4. Cardiac image and mapping.
The cardiac anatomy is partitioned into 12 quadrants. The quadrant and number of activation patterns of interest identified per location are displayed. **A** represents focal activity characterized by radial conduction from a single location; **B** shows localized rotational activation characterized by ≥270 degrees of conduction around a fixed, confined zone, whereas **C** shows localized irregular activation characterized by repetitive, multidirectional entry, exit, and pivoting conduction through and around a fixed, confined zone. AP indicates anteroposterior; LAA, left atrial appendage; LIPV, left inferior pulmonary vein; LSPV, left superior pulmonary vein; MV, mitral valve; MVA, mitral valve annulus; PA, posteroanterior; RIPV, right inferior pulmonary vein; and RSPV, right superior pulmonary vein.

remained in AFL/AT at procedure end and were cardioverted to SR. The remaining 22 patients were either ablated to SR or reverted to AF requiring cardioversion. Within 12 hours of the procedure, 125 patients (98%) had successfully converted to SR. Two patients remained in AF post-procedure, with 1 spontaneously converting to SR at 8 days and then remaining in SR through the 12-month follow-up; 1 patient remained in AF and was retreated 5 months later. PVI and substrate modification were performed in 125 patients. Two patients had PVI alone because of the absence of non-PV targets and the noninducibility of AF by atrial burst pacing despite isoproterenol. For the 38 patients who did not require cardioversion, on average, 2.4±1.5 additional ablation cycles (map/ablate) were delivered before conversion. The remaining 85 patients who were cardioverted, an additional 3.4±1.4 ablation cycles (map/ablate) were delivered before conversion. Cavotricuspid isthmus ablation was performed in 8 patients. Other linear ablation is detailed in Table 3.

Throughout the procedure, 3 distinct subcategories of abnormal conduction patterns with atrial origins were observed: (1) localized irregular activation (LIA) where the activation displayed repetitive, multidirectional entry, exit, and pivoting conduction through and around a confined (isthmus like) zone; (2) focal requiring at least 3 firings from the same location; and (3) localized rotational activation spiraling >270 degrees around a confined central zone. There were 710 unique atrial activation patterns identified during the 127 index procedures. Details of the patterns are shown in Figure 4. Of the patterns identified, 313 (44.1%) were LIA, 220 (31.0%) were focal, and 177 (24.4%) were localized rotational activation. The average number of patterns identified per patient was 5.0±3.4. Locations of patterns are shown in Figure 4 with the number and percentages of patterns per location shown in Table 3. AP3—the area anterior to the right superior PV—demonstrated the greatest number of activation patterns, 63 (20.1%) LIA, 48 (21.8%) focal, and 39 (22%) localized rotational activation. Mapping and targeting abnormal right atrial conduction patterns was not mandated by the protocol. Details of abnormal AF pattern distributions are shown in Table 4.

Table 4. Description of the Location and Incidence of Identified Patterns for All Study Patients

Anatomic Location	LIA (n=313)	Focal (n=177)	LRA (n=220)	Total API/Site (n=710)	Patients With Pattern (n=127)
AP1	33 (10.5)	17 (7.7)	17 (9.6)	67 (9.4)	51 (40.2)
AP2	17 (5.4)	16 (7.3)	12 (6.8)	45 (6.3)	37 (29.2)
AP3	63 (20.1)	48 (21.8)	39 (22)	150 (21.1)	89 (70.1)
AP4	39 (12.5)	31 (14.1)	17 (9.6)	87 (12.3)	50 (39.4)
AP5	1 (0.3)	2 (0.9)		3 (0.4)	3 (2.4)
PA6			1 (0.6)	1 (0.1)	1 (0.8)
PA7		1 (0.5)	1 (0.6)	2 (0.1)	1 (0.8)
PA8	3 (1.0)	6 (2.7)	3 (1.1)	12 (1.7)	10 (7.9)
PA9	49 (15.7)	26 (11.8)	28 (15.8)	103 (14.5)	68 (53.5)
PA10	56 (17.9)	25 (11.4)	17 (9.6)	98 (13.8)	73 (57.5)
PA11	37 (11.8)	30 (13.6)	32 (18.1)	99 (13.9)	63 (49.6)
PA12	15 (4.8)	17 (7.7)	11 (6.2)	43 (6.1)	34 (26.8)

All values are n (%) per region by pattern type. LIA indicates localized irregular activation; and LRA, localized rotational activation.

Outcomes

For the primary safety outcome, 3 MAEs were adjudicated by the clinical events committee to be probably related to the procedure; 126 of 129 (98%) study subjects were MAE free (95% CI, 94%–100%). Cardiac tamponade developed in 2 patients, and 1 patient had a stroke, which resolved after 5 days. There were no reported MAEs related to the use of the system. However, 3 additional serious adverse events were reported in 3 subjects and adjudicated to be related to procedure. One was related to air embolism introduced via the steerable sheath positioned in the LA that led to ventricular fibrillation. The patient was immediately defibrillated and recovered fully without further intervention. The other 2 were a femoral arteriovenous fistula and a femoral lymphocele. Total procedural complication rate was 6/129 (4.6%). Major complications are listed in Table 5.

Table 5. Description of the Safety Data

Major Complications	
Study-defined MAEs	n
Death	0
Cardiac tamponade	2
Stroke/TIA	1
Procedural serious adverse events	
Phrenic nerve injury	0
Esophageal dysfunction	0
Atrial esophageal fistula	0
Symptomatic pulmonary vein stenosis	0
Air embolism causing ventricular fibrillation	1
Femoral arteriovenous fistula	1
Lymphocele right groin	1

MAE indicates major adverse event; and TIA, transient ischemic attack.

Table 6. Description of the Chronic Efficacy Outcomes at 12 mo

Efficacy Variable	12 mo, %
Freedom from >30 s AF after 1 procedure, with or without AAD	(72.5)
Freedom from >30 s AF after 1 procedure without AAD	(59.2)
Freedom from >30 s atrial arrhythmias after 1 procedure, with or without AAD	(69.2)
Freedom from >30 s atrial arrhythmias after 1 procedure, without AAD	(55.8)
Freedom from >30 s AF after multiple procedures, with or without AAD	(93.2)
Freedom from >30 s AF after multiple procedures without AAD	(71.2)
Freedom from >30 s atrial arrhythmias after multiple procedures, with or without AAD	(86.4)
Freedom from >30 s atrial arrhythmias after multiple procedures, without AAD	(66.1)

AAD indicates antiarrhythmic drug; and AF, atrial fibrillation.

For the effectiveness outcomes, Table 6 reports freedom from AF and atrial arrhythmias at 12 months. The primary effectiveness outcome for a single procedure indicated 72.5% (95% CI, 63.9–80.3) of patients were free from AF, on or off AADs, and 59.2% (95% CI, 50.4–68.0) were free from AF off AADs at 12 months. After 2 procedures, 93.2% (95% CI, 87.1–97.0) were AF-free on or off AADs, and 71.2% (95% CI, 63.0–79.4) off AADs at 12 months post-index procedure (Figure 5).

Retreatment procedures were performed on 29 (23%) patients, 20 with the AcQMap system and 9 using a conventional approach. On the day of retreatment, (6/29) 21% of total population of patients were in AF, (6/29) 21% in AFL, (4/29) 14% in AT, and (13/29) 45% were in SR. The average time from index procedure to first retreatment was 7 months. Although not permitted by the protocol, 1 patient did receive a retreatment procedure during the blanking period. This patient remained in SR through 12 months and was considered a first procedure failure and first and second procedure success. Between 3 and 6 months, 12 patients were retreated, 13 retreatments occurred between 6 and 9 months, and 3 retreatments after the 9-month cutoff date (Figure 3). Retreatment after the 9-month follow-up was considered a protocol deviation; therefore, the 3 patients were censored from the results.

Demographic and procedural predictors of 12 months of the effectiveness outcome following a single procedure are presented in Table 7. Procedural predictors included the ablation of 3 to 4 activation patterns (focal, localized rotational activation or LIA), presen-

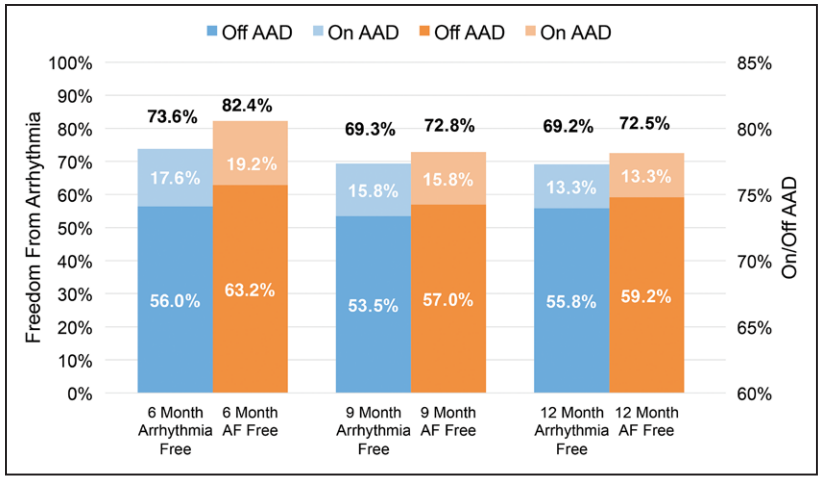

Figure 5. Chronic efficacy outcome following a single procedure, on and off antiarrhythmic drug (AAD).
Values based on 24-h continuous ECG monitoring. Retreatments were not allowed during the initial 3-mo blanking period. AF, atrial fibrillation

tation at the index procedure in SR, and the ablation of at least 2 or 3 pattern types. Demographic predictors included fewer days since AF diagnosis and lower $CHADS_2$ score.

AF burden, defined as total time spent in AF/AFL/AT >30 seconds, captured on 24-hour continuous ECG monitor, was low following single and multiple procedures. Following a single procedure, 81% of patients had 0 episodes of AF/AFL/AT lasting >30 seconds, and 98% of patients spent <30% of time in an atrial arrhythmia. After 1 and 2 procedures, 68% of the patients had 0 episodes of AF/AFL/AT >30 seconds, with 87% having ≤30% burden. Burden data are shown in Figure 6. Kaplan-Meier curves were constructed for single and multiple procedures illustrating the time to first recurrence of AF or atrial arrhythmia, retreatment, or cardioversion after the 3-month visit (Figures 7 and 8).

AFEQT change scores from baseline to 12 months showed meaningful improvement (exceeding the minimal important difference of 19 points in AFEQT scores),[16] in the total burden score for patients in SR compared with those who were in an atrial arrhythmia (*P*=0.02; Figure I in the Data Supplement). The symptom severity, daily activity, treatment concern, and treatment satisfaction domain scores similarly demonstrated meaningful improvement for patients in SR at 12 months (*P*=0.02, *P*=0.04, *P*=0.03, and *P*=0.002, respectively). Patients not in SR at 12 months also

Table 7. Description of the Demographic and Procedural Predictors at 12-mo Arrhythmia-Free Success Based on 24-h Continuous Holter Monitoring

Predictor	Odds Ratio (95% CI)	*P* Value
Presenting to index procedure in SR	5.12 (1.87–14.05)	0.002
CHADS2 score of 3	3.03 (1.24–7.43)	0.015
At least 2 of 3 pattern types ablated (focal, LRA, LIA)	2.84 (1.16–6.94)	0.02
<534 d since AF diagnosis	2.50 (1.0–6.21)	0.05
3–4 focal, LRA or LIA patterns ablated	9.39 (2.0–44.09)	0.004

AF indicates atrial fibrillation; LIA, localized irregular activation; LRA, localized rotational activation; and SR, sinus rhythm.

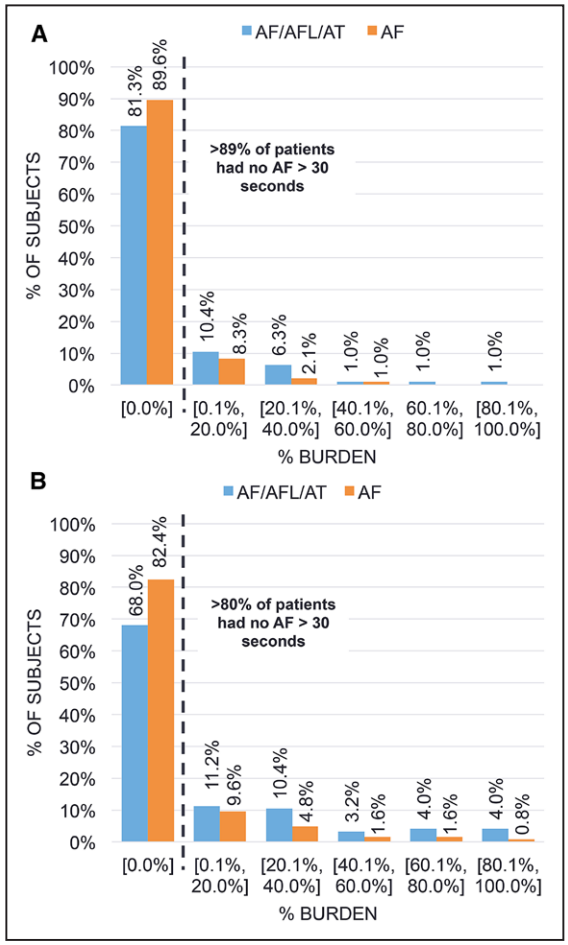

Figure 6. Atrial fibrillation burden before and after catheter ablation.
A, Atrial burden. Following a single catheter ablation (CA), 89% of patients had 0 episodes of atrial fibrillation (AF) lasting >30 s across the sum of available continuous 24-h ECG monitor data collected at 3, 6, 9, and 12 mo. No patient experienced >50% AF on all continuous ECG monitoring combined over all follow-ups, indicating patients transitioned from persistent AF to paroxysmal atrial fibrillation (PAF). **B**, After 1 or 2 procedures, >80% of the patients in this study had no episodes of AF >30 s. Average total recording duration was 85 h for single procedure and 83 h for 1 or 2 procedures. AF indicates atrial fibrillation; AFL, atrial flutter; and AT, atrial tachycardia.

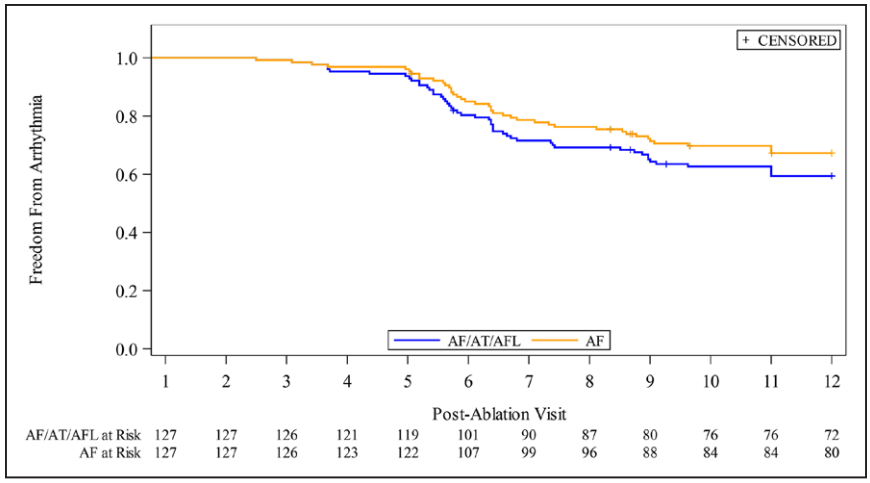

Figure 7. Freedom from atrial arrhythmias. Kaplan-Meier estimate of freedom from all documented arrhythmias (on or off antiarrhythmic drug) for a single procedure. A 3-mo blanking period was implemented. Data were censored at 12 mo. AF indicates atrial fibrillation; AFL, atrial flutter; and AT, atrial tachycardia.

showed improvement in the symptom severity and treatment satisfaction domains. When correlated with the AF burden score, the AFEQT measures of total burden, symptom severity, daily activity, and treatment satisfaction improved as burden was reduced (P=0.004, P=0.02, P=0.006, and P=0.03, respectively).

DISCUSSION

CA outcomes in the PersAF patient population are suboptimal when compared with the reported 1-year postindex procedure arrhythmia-free outcomes of 70% to 80% seen in paroxysmal AF (including AT/AFL). PersAF represents an advanced patient population in which atrial structural remodeling and fibrosis promotes maintenance of AF,[17,18] The most recent guidelines for AF ablation identify the minimal chronic acceptable 12-month AF-free off AAD outcome for PersAF at 40%.[3] The 12-month off AAD, single procedure, AF-free outcomes observed in UNCOVER AF were 59.2% and 71.2% after 2 procedures, which exceeded the standard and provided results consistent with prior publications for paroxysmal AF.[14,15,19] STAR AF II (Substrate and Trigger Ablation for Atrial Fibrillation Reduction Trial II)[20] and CHASE AF (Catheter Ablation of Persistent Atrial Fibrillation)[9] established PersAF single procedure, on or off AAD, arrhythmia-free outcomes at 18 and 12 months, respectively, of 37% to 50% regardless of ablation strategy (PVI or empirical PVI Plus). In recent CA studies in the PersAF population, when contact force technologies or cryoballoon applications were used, single procedure off AAD AF-free outcomes ranged between 60% and 64%.[21,22] In contrast to the trials cited, which had the benefit of mature technologies and extensive device experience, the majority of investigators in UNCOVER AF had no prior experience with CD mapping. CD mapping revealed conduction patterns outside the pulmonary veins in all but 2 patients. Application of the map, ablate, remap strategy used in the study demonstrated a progression in reduction of pattern complexity through the ablation cycles. As more widespread experience and understanding of iterative CD mapping and adaptive ablation accrues, the potential exists to advance the AF-free outcomes beyond 60%.

The results of the DISCERN AF trial motivate consideration of a broader definition in patient outcomes in the PersAF population.[23] Specifically, DISCERN AF demonstrated that, after ablation, a daily arrhythmia burden

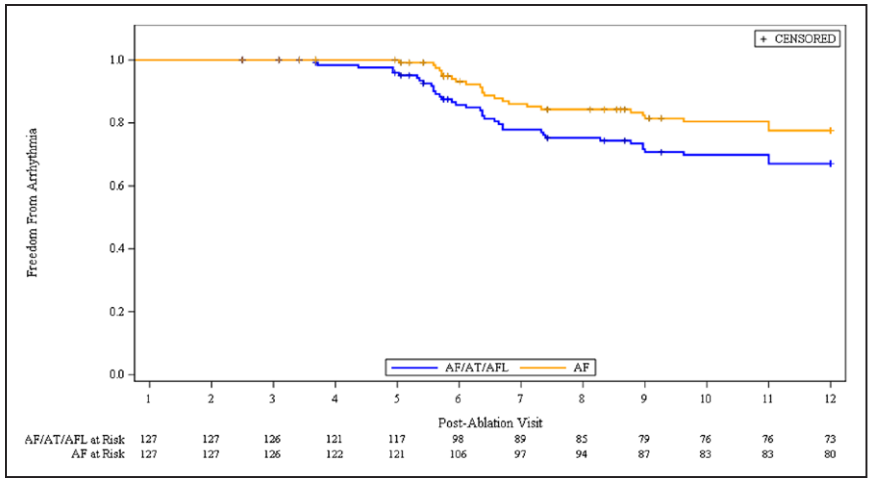

Figure 8. Freedom from atrial arrhythmias. Kaplan-Meier estimate of freedom from all documented arrhythmias (on or off antiarrhythmic drug) for multiple procedures. A 3-mo blanking period was observed. Data were censored at 12 mo. AF indicates atrial fibrillation; AFL, atrial flutter; and AT, atrial tachycardia.

of >35% led to a progressive decrease in daily activity. The authors concluded that hours, not minutes, of daily arrhythmia burden impacted daily activity. In UNCOVER AF, after a single procedure, 90% of patients had no recorded episodes of AF/AFL/AT and 98% had <30% arrhythmia burden. The reduced levels of arrhythmia burden after CA were significantly associated with a clinically meaningful improvement in overall health status and quality of life as measured by the AFEQT. These studies suggest that both eliminating and lowering arrhythmia burden post-ablation provides clinical benefit in a PersAF population—a hypothesis that warrants further research.

The unique differentiator in this study was the use of noncontact CD mapping with iterative mapping capability to identify patient-specific areas of interest outside the pulmonary veins. Focal and rotational activation patterns have been previously described using conventional, contact, voltage-based mapping systems.[11,22,24,25] The key advantage of CD mapping is the ability to globally discern both focal and rotational patterns, as well as other more complex patterns characterized by localized changes in conduction velocity, direction, and wave front pivoting (LIA).[12,13] Earlier work has shown the consistency of targets in occurring within the atria when remapping is performed.[12,13,26] CD-guided ablation resulted in prolongation of the fibrillatory cycle length in 99% of subjects, with 55% of subjects having a >50-ms change in cycle length. Predictors of SR at 12 months included a 2.8× higher likelihood when at least 2 of 3 pattern types were ablated during the procedure and a 9.4× higher likelihood when 3 to 4 focal, rotational, or irregular patterns were ablated. In the future, iterative mapping and adaptive ablation may lead patient-specific stratification of patterns according to clinical relevance.

Limitations include a nonrandomized design limiting the generalizability of the results. Second, verification of rhythm status was 24 hours in duration at each scheduled follow-up and by ECG, 24-hour continuous ECG monitor, or Holter at unscheduled follow-ups as compared with an implantable loop recorder, which measures AF burden continuously; therefore, this study may reflect an overinflation of outcome rates. Third, no assessment of AF burden was made at baseline; therefore, delineation of AF persistence was based on patient medical history. Fourth, the need for retreatment was attributed to AF, which, because lack of documentation, may have been AFL or AT. Finally, these data represent outcomes obtained with a first-generation system design and specification that has since undergone upgrades enhancing stability of ablation catheter localization and broadening the range and type of ablation catheters operable with the system.

In conclusion, we report for the first time, rapid global iterative mapping to guide adaptive ablation therapy in a PersAF population. Procedural outcomes were based on durably ablating neither too little nor too much, suggesting that PVI plus ablation of individualized, patient-specific non-PV targets provides benefit to conventional approaches. Elimination and even lowering of arrhythmia burden was associated with improvement in overall health and quality of life. Identification and characterization of such targets provides a platform for a greater understanding of disease pathophysiology[27] and the possibility of positive impacts on the natural history of the disease.[28,29]

ARTICLE INFORMATION

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REFERENCES

1. Chugh SS, Havmoeller R, Narayanan K, Singh D, Rienstra M, Benjamin EJ, Gillum RF, Kim YH, McAnulty JH Jr, Zheng ZJ, Forouzanfar MH, Naghavi M, Mensah GA, Ezzati M, Murray CJ. Worldwide epidemiology of atrial fibrillation: a global burden of disease 2010 Study. *Circulation.* 2014;129:837–847. doi: 10.1161/CIRCULATIONAHA.113.005119
2. Kirchhof P. The future of atrial fibrillation management: integrated care and stratified therapy. *Lancet.* 2017;390:1873–1887. doi: 10.1016/S0140-6736(17)31072-3
3. Calkins H, Hindricks G, Cappato R, Kim YH, Saad EB, Aguinaga L, Akar JG, Badhwar V, Brugada J, Camm J, Chen PS, Chen SA, Chung MK, Nielsen JC, Curtis AB, Davies DW, Day JD, d'Avila A, de Groot NMSN, Di Biase L, Duytschaever M, Edgerton JR, Ellenbogen KA, Ellinor PT, Ernst S, Fenelon G, Gerstenfeld EP, Haines DE, Haissaguerre M, Helm RH, Hylek E, Jackman WM, Jalife J, Kalman JM, Kautzner J, Kottkamp H, Kuck KH, Kumagai K, Lee R, Lewalter T, Lindsay BD, Macle L, Mansour M,

Marchlinski FE, Michaud GF, Nakagawa H, Natale A, Nattel S, Okumura K, Packer D, Pokushalov E, Reynolds MR, Sanders P, Scanavacca M, Schilling R, Tondo C, Tsao HM, Verma A, Wilber DJ, Yamane T. 2017 HRS/EHRA/ECAS/APHRS/SOLAECE expert consensus statement on catheter and surgical ablation of atrial fibrillation. *Heart Rhythm.* 2017;14:e275–e444. doi: 10.1016/j.hrthm.2017.05.012

4. Kirchhof P, Benussi S, Kotecha D, Ahlsson A, Atar D, Casadei B, Castella M, Diener HC, Heidbuchel H, Hendriks J, Hindricks G, Manolis AS, Oldgren J, Popescu BA, Schotten U, Van Putte B, Vardas P; ESC Scientific Document Group. 2016 ESC Guidelines for the management of atrial fibrillation developed in collaboration with EACTS. *Eur Heart J.* 2016;37:2893–2962. doi: 10.1093/eurheartj/ehw210
5. January CT, Wann LS, Alpert JS, Calkins H, Cigarroa JE, Cleveland JC Jr, Conti JB, Ellinor PT, Ezekowitz MD, Field ME, Murray KT, Sacco RL, Stevenson WG, Tchou PJ, Tracy CM, Yancy CW; ACC/AHA Task Force Members. 2014 AHA/ACC/HRS guideline for the management of patients with atrial fibrillation: executive summary: a report of the American College of Cardiology/American Heart Association Task Force on practice guidelines and the Heart Rhythm Society. *Circulation.* 2014;130:2071–2104. doi: 10.1161/CIR.0000000000000040
6. Packer DL, Kowal RC, Wheelan KR, Irwin JM, Champagne J, Guerra PG, Dubuc M, Reddy V, Nelson L, Holcomb RG, Lehmann JW, Ruskin JN; STOP AF Cryoablation Investigators. Cryoballoon ablation of pulmonary veins for paroxysmal atrial fibrillation: first results of the North American Arctic Front (STOP AF) pivotal trial. *J Am Coll Cardiol.* 2013;61:1713–1723. doi: 10.1016/j.jacc.2012.11.064
7. Latchamsetty R, Morady F. Atrial fibrillation ablation. *Annu Rev Med.* 2018;69:53–63. doi: 10.1146/annurev-med-041316-090015
8. Verma A, Kalman JM, Callans DJ. Treatment of patients with atrial fibrillation and heart failure with reduced ejection fraction. *Circulation.* 2017;135:1547–1563. doi: 10.1161/CIRCULATIONAHA.116.026054
9. Vogler J, Willems S, Sultan A, Schreiber D, Lüker J, Servatius H, Schäffer B, Moser J, Hoffmann BA, Steven D. Pulmonary Vein isolation versus defragmentation: the CHASE-AF clinical trial. *J Am Coll Cardiol.* 2015;66:2743–2752. doi: 10.1016/j.jacc.2015.09.088
10. Clarnette JA, Brooks AG, Mahajan R, Elliott AD, Twomey DJ, Pathak RK, Kumar S, Munawar DA, Young GD, Kalman JM, Lau DH, Sanders P. Outcomes of persistent and long-standing persistent atrial fibrillation ablation: a systematic review and meta-analysis. *Europace.* 2018;20(FI_3):f366–f376. doi: 10.1093/europace/eux297
11. Nattel S, Dobrev D. Controversies about atrial fibrillation mechanisms: aiming for order in chaos and whether it matters. *Circ Res.* 2017;120:1396–1398. doi: 10.1161/CIRCRESAHA.116.310489
12. Grace A, Willems S, Meyer C, Verma A, Heck P, Zhu M, Shi X, Chou D, Dang L, Scharf C, Scharf G, Beatty G. High-resolution noncontact charge-density mapping of endocardial activation. *JCI Insight*. 2019;4:e126422.
13. Conti S, Giewercer D, Whaley B, Verma A. Novel multipolar mapping system identifying coexistence of multiple conduction patterns in persistent AF: a case report. *Pacing Clin Electrophysiol.* 2018;41:210–213. doi: 10.1111/pace.13132
14. Kuck KH, Brugada J, Fürnkranz A, Metzner A, Ouyang F, Chun KR, Elvan A, Arentz T, Bestehorn K, Pocock SJ, Albenque JP, Tondo C; FIRE AND ICE Investigators. Cryoballoon or radiofrequency ablation for paroxysmal atrial fibrillation. *N Engl J Med.* 2016;374:2235–2245. doi: 10.1056/NEJMoa1602014
15. Wilber DJ, Pappone C, Neuzil P, De Paola A, Marchlinski F, Natale A, Macle L, Daoud EG, Calkins H, Hall B, Reddy V, Augello G, Reynolds MR, Vinekar C, Liu CY, Berry SM, Berry DA; ThermoCool AF Trial Investigators. Comparison of antiarrhythmic drug therapy and radiofrequency catheter ablation in patients with paroxysmal atrial fibrillation: a randomized controlled trial. *JAMA.* 2010;303:333–340. doi: 10.1001/jama.2009.2029
16. Dorian P, Burk C, Mullin CM, Bubien R, Godejohn D, Reynolds MR, Lakkireddy DR, Wimmer AP, Bhandari A, Spertus J. Interpreting changes in quality of life in atrial fibrillation: how much change is meaningful? *Am Heart J.* 2013;166:381.e8–387.e8. doi: 10.1016/j.ahj.2013.04.015
17. Proietti R, Hadjis A, AlTurki A, Thanassoulis G, Roux JF, Verma A, Healey JS, Bernier ML, Birnie D, Nattel S, Essebag V. A Systematic review on the progression of paroxysmal to persistent atrial fibrillation: shedding new light on the effects of catheter ablation. *JACC Clin Electrophysiol.* 2015;1:105–115. doi: 10.1016/j.jacep.2015.04.010
18. Prabhu S, Voskoboinik A, McLellan AJA, Peck KY, Pathik B, Nalliah CJ, Wong GR, Azzopardi SM, Lee G, Mariani J, Ling LH, Taylor AJ, Kalman JM, Kistler PM. Biatrial electrical and structural atrial changes in heart failure: electroanatomic mapping in persistent atrial fibrillation in humans. *JACC Clin Electrophysiol.* 2018;4:87–96. doi: 10.1016/j.jacep.2017.08.012
19. Heeger CH, Wissner E, Knöll M, Knoop B, Reissmann B, Mathew S, Sohns C, Lemes C, Maurer T, Santoro F, Riedl J, Inaba O, Fink T, Rottner L, Wohlmuth P, Goldmann B, Ouyang F, Kuck KH, Metzner A. Three-year clinical outcome after 2nd-generation cryoballoon-based pulmonary vein isolation for the treatment of paroxysmal and persistent atrial fibrillation- a 2-center experience. *Circ J.* 2017;81:974–980. doi: 10.1253/circj.CJ-16-1334
20. Verma A, Jiang CY, Betts TR, Chen J, Deisenhofer I, Mantovan R, Macle L, Morillo CA, Haverkamp W, Weerasooriya R, Albenque JP, Nardi S, Menardi E, Novak P, Sanders P; STAR AF II Investigators. Approaches to catheter ablation for persistent atrial fibrillation. *N Engl J Med.* 2015;372:1812–1822. doi: 10.1056/NEJMoa1408288
21. Conti S, Weerasooriya R, Novak P, Champagne J, Lim HE, Macle L, Khaykin Y, Pantano A, Verma A. Contact force sensing for ablation of persistent atrial fibrillation: a randomized, multicenter trial. *Heart Rhythm.* 2018;15:201–208. doi: 10.1016/j.hrthm.2017.10.010
22. Tondo C, Iacopino S, Pieragnoli P, Molon G, Verlato R, Curnis A, Landolina M, Allocca G, Arena G, Fassini G, Sciarra L, Luzi M, Manfrin M, Padeletti L; ClinicalService 1STOP Project Investigators. Pulmonary vein isolation cryoablation for patients with persistent and long-standing persistent atrial fibrillation: clinical outcomes from the real-world multicenter observational project. *Heart Rhythm.* 2018;15:363–368. doi: 10.1016/j.hrthm.2017.10.038
23. Proietti R, Birnie D, Ziegler PD, Wells GA, Verma A. Postablation atrial fibrillation burden and patient activity level: insights from the DISCERN AF Study. *J Am Heart Assoc.* 2018;7:e010256. doi: 10.1161/JAHA.118.010256
24. Narayan SM, Krummen DE, Shivkumar K, Clopton P, Rappel WJ, Miller JM. Treatment of atrial fibrillation by the ablation of localized sources: CONFIRM (Conventional Ablation for Atrial Fibrillation With or Without Focal Impulse and Rotor Modulation) trial. *J Am Coll Cardiol.* 2012;60:628–636. doi: 10.1016/j.jacc.2012.05.022
25. Zaman JAB, Rogers AJ, Narayan SM. Rotational drivers in atrial fibrillation: are multiple techniques circling similar mechanisms? *Circ Arrhythm Electrophysiol.* 2017;10:e006022.
26. Nuhrich J, Moser J, Schaffer B, Akbulak RO, Eickholt C, Kuklik P, Meyer C, Willems S. Mapping stability with ultrasound-based imaging and dipole density mapping in patients with persistent atrial fibrillation [abstract]. *Heart Rhythm*. 2017;14:S531.
27. Grace AA, Roden DM. Systems biology and cardiac arrhythmias. *Lancet.* 2012;380:1498–1508. doi: 10.1016/S0140-6736(12)61462-7
28. Healey JS, Oldgren J, Ezekowitz M, Zhu J, Pais P, Wang J, Commerford P, Jansky P, Avezum A, Sigamani A, Damasceno A, Reilly P, Grinvalds A, Nakamya J, Aje A, Almahmeed W, Moriarty A, Wallentin L, Yusuf S, Connolly SJ; RE-LY Atrial Fibrillation Registry and Cohort Study Investigators. Occurrence of death and stroke in patients in 47 countries 1 year after presenting with atrial fibrillation: a cohort study. *Lancet.* 2016;388:1161–1169. doi: 10.1016/S0140-6736(16)30968-0
29. Marrouche NF, Brachmann J, Andresen D, Siebels J, Boersma L, Jordaens L, Merkely B, Pokushalov E, Sanders P, Proff J, Schunkert H, Christ H, Vogt J, Bänsch D; CASTLE-AF Investigators. Catheter ablation for atrial fibrillation with heart failure. *N Engl J Med.* 2018;378:417–427. doi: 10.1056/NEJMoa1707855