RADAR
A Multicenter Food and Drug Administration Investigational Device Exemption Clinical Trial of Persistent Atrial Fibrillation

Subbarao Choudry, MD; Moussa Mansour, MD; Sri Sundaram, MD; Duy T. Nguyen, MD; Srinivas R. Dukkipati, MD; William Whang, MD; Paul Kessman, MS; Vivek Y. Reddy, MD

BACKGROUND: Pulmonary vein isolation is insufficient to treat all patients with persistent atrial fibrillation (AF), and effective adjunctive ablation strategies are needed. Ablation of AF drivers holds promise, but current technologies to identify drivers are limited by spatial resolution. In a single-arm, first-in-human, investigator-initiated Food and Drug Administration Investigational Device Exemption study, we used a novel system for real-time, high-resolution identification of AF drivers in persistent AF.

METHODS: Patients with persistent or long-standing persistent AF underwent ablation using the RADAR (Real-Time Electrogram Analysis for Drivers of Atrial Fibrillation) system in conjunction with a standard electroanatomical mapping system. After pulmonary vein isolation, electrogram and spatial information was streamed to the RADAR system and analyzed to identify driver domains to target for ablation.

RESULTS: Across 4 centers, 64 subjects were enrolled: 73% male, age, 64.7±9.5 years; body mass index, 31.7±6.0 kg/m²; left atrium size, 54±10 mm, with persistent/long-standing persistent AF in 53 (83%)/11 (17%), prior AF ablation (re-do group) in 26 (41%). After 12.6±0.8 months follow-up, 68% remained AF-free off all antiarrhythmics; 74% remained AF-free and 66% remained AF/atrial tachycardia/atrial flutter-free on or off AADs (antiarrhythmic drugs). AF terminated with ablation in 35 patients (55%) overall and in 23/38 (61%) of de novo ablation patients. For patients with AF termination during ablation, 82% remained AF-free and 74% AF/atrial tachycardia/atrial flutter-free during follow-up on or off AADs. Patients undergoing first-time ablation generally had higher rates of freedom from AF than the re-do group.

CONCLUSIONS: This novel technology for panoramic mapping of AF drivers showed promising results in a persistent/long-standing persistent AF population. These data provide the scientific basis for a randomized trial.

CLINICAL TRIAL REGISTRATION: URL: https://www.clinicaltrials.gov. Unique identifier: NCT03263702; IDE#G170049.

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

Key Words: ablation • atrial fibrillation • follow-up • human • pulmonary vein

Atrial fibrillation (AF) is the most common sustained arrhythmia encountered in clinical practice. Pulmonary vein isolation (PVI) is the cornerstone of ablative treatment for paroxysmal AF. However, when AF is persistent, PVI alone is not sufficient for many patients. The optimal ablation strategy beyond PVI for persistent AF remains unclear. A variety of adjunctive ablation strategies have been explored: linear ablation, posterior wall ablation, ablation of complex fractionated electrograms, ganglionic plexus ablation, isolation of the left atrial
We studied a novel system designed to identify AF drivers at high resolution in real time using conventional signal acquisition and processing techniques. The system involves the sequential collection of AF electrograms using a standard high-density regional mapping catheter; the system then stitches these together to form a coherent panoramic AF map of the full atrial chamber. This system has previously been used to characterize AF drivers in a retrospective fashion.\(^{18,19}\) In a prospective, multicenter, Food and Drug Administration investigator-initiated Investigational Device Exemption, single-arm clinical trial, RADAR (Real-Time Electrogram Analysis for Drivers of Atrial Fibrillation), we report the first-in-human results of this system for real-time identification of drivers for ablation of persistent AF.

**WHAT IS KNOWN?**
- Pulmonary vein isolation alone is not sufficient for catheter ablation of persistent atrial fibrillation. The optimal ablation strategy beyond pulmonary vein isolation is unknown.
- High resolution contact mapping of atrial fibrillation has previously not been possible due to the disorganized nature of the arrhythmia.

**WHAT THE STUDY ADDS?**
- A novel technology allows for high-resolution panoramic contact mapping of atrial fibrillation using traditional mapping techniques.
- Ablation of atrial fibrillation drivers identified with this technology in addition to pulmonary vein isolation resulted in favorable 1-year success rates in a persistent and long-standing persistent atrial fibrillation population.

| Nonstandard Abbreviations and Acronyms |
|--------------------------------------|
| **AAD** | antiarrhythmic drug |
| **AF** | atrial fibrillation |
| **AT** | atrial tachycardia |
| **AFL** | atrial flutter |
| **CS** | coronary sinus |
| **PVI** | pulmonary vein isolation |
| **VOM** | Vein of Marshall |

appendage, and stepwise methods incorporating multiple strategies.\(^{1–9}\) While incremental benefit has been reported with some of these approaches, other studies have failed to show a benefit. Additionally, intraatrial ablation often increases the frequency of macro-reentrant atrial arrhythmias—atrial tachycardia (AT) or atrial flutter (AFL)—and can cause other complications, such as thrombus formation and increased risk for stroke with left atrial appendage isolation.\(^{10}\)

More recent efforts have attempted to identify drivers that perpetuate AF. Previous work has implicated both focal impulses and rotational activity (rotors) as important drivers for AF.\(^{11,12}\) Sites of high-frequency activity are more commonly seen outside the pulmonary vein region in persistent AF; which may help to explain the lower success rates of PVI in this group.\(^{13}\) Real-time identification of AF drivers to help guide ablation is challenging due to the transient nature of these drivers and the disorganization of the atria during AF. This confounds traditional sequential approaches to chamber mapping. Alternatively, panoramic mapping techniques have been studied.\(^{14,15}\) But the current methods of panoramic mapping are limited by spatial resolution, which can cause rotors to be missed, improperly localized, or artefactually created.\(^{16,17}\)

**METHODS**

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

**Trial Design**

The RADAR trial is a multicenter, single-arm trial conducted under an Food and Drug Administration investigator-initiated Investigational Device Exemption (NCT03263702; IDE#G170049). The trial was funded by AFTx, Inc, the manufacturer of the RADAR system. The study was conducted by AFTx. However, the authors had full access to the primary data, take full responsibility for the accuracy and integrity of the data, made the decision to publish, wrote the initial draft, and had final authority over the content of the manuscript. The trial was approved by the ethics committee at each center before enrollment of any patients.

**Study Population**

Patients were eligible for enrollment if they had persistent or long-standing persistent AF refractory to a Class 1 to 4 AAD (antiarrhythmic drug) and were planned to undergo catheter ablation for AF. Previous AF ablation was allowed. Subjects were excluded if they had rheumatic heart disease, NYHA class IV congestive heart failure, MI, or CABG within 6 weeks, CVA or TIA within 3 months, contraindications to anticoagulation, estimated life expectancy <1 year, or current intracardiac thrombus.

**The RADAR System**

The RADAR system (AFTx, Inc, Westminster, CO) uses high-density electroanatomic maps created with standard mapping equipment and unipolar signal processing methods to identify AF driver domains at high resolution. Repetitive morphological patterns of atrial activation are seen during AF. These distinct patterns are identified using electrograms from a stationary coronary sinus (CS) catheter, which is used as a reference (Figure 1). A standard multielectrode regional mapping catheter is used to collect data at a number of locations throughout the atrium. Local unipolar atrial electrograms and electrode positions are extracted from the mapping system, and these electrograms are matched to the corresponding CS pattern, or phase, occurring at the same

---

**Circ Arrhythm Electrophysiol.** 2020;13:e007825. DOI: 10.1161/CIRCEP.119.007825
time. This approach enables high-density contact mapping of the full atrial chamber, which has not otherwise been possible in AF.

The unipolar electrograms are processed by first subtracting the ventricular components of the signals. Band pass filtering (with cutoffs at 0.5 and 300 Hz) is applied to remove DC bias and high-frequency noise. The signals are then smoothed through a Savitzky-Golay filter to remove far-field noise while preserving signal morphology. Representative signals calculated and used by the system are shown in Figure 2.

Electrograms from the various anatomic locations are then sorted and stitched together to create a panoramic 3-dimensional conduction vector map for each CS phase. Conduction vectors are then calculated. Distance between electrodes is calculated using the positions obtained from the mapping system. Using these distances and the depolarization timings at each electrode, conduction vector velocities are calculated between electrode pairs. An average of 587 electrode locations are used to map the chamber. Conduction vectors are computed using combinations of all of these electrode positions and depolarization timings.

Sites of rotational activity and focal impulses are identified in the individual conduction vector maps, which are then combined to create a driver density map. Border zones suggestive of scar borders where low voltage (<0.5 mV) during AF abuts higher voltage tissue are identified. When rotational or focal activity is detected in these voltage border zones, the region is highlighted. The conduction vector maps and voltage data are fused to create a single Probabilistic Atrial Driver Assessment map. The Probabilistic Atrial Driver Assessment map thus incorporates spatiotemporal repetition of drivers and areas of voltage transition to highlight putative AF driver domains, which can then be targeted for ablation (Figure 3).
At the start of the trial, sites of rotational activity and focal impulses were identified by visual inspection and manual annotation of each conduction vector map. After the sixth case, a software update allowed for automatic annotation of these sites; the remainder of the cases were performed with automatic driver detection.

**Procedure Flow**

All patients underwent PVI if not previously performed, or if incomplete from prior procedures. Cavotricuspid isthmus ablation was allowed but not required. The RADAR system was used to identify AF driver domains. For patients presenting in sinus rhythm, AF was induced by rapid atrial pacing. Catheter location and electrogram data were streamed from the mapping system (Ensite Precision; Abbott, Inc, Minneapolis, MN) to a computer running the RADAR system (Figure 4). The CS catheter was situated in a stable position in the CS and used as a reference to define phases in AF. Atrial electrograms were recorded using a standard 20-pole mapping catheter (AFocus II, Abbott, Inc). Electrogram and location data were recorded for 20 seconds at each site in the atrium from the mapping catheter and CS until adequate coverage of the atrium was achieved.

The domains highlighted on the Probabilistic Atrial Driver Assessment map were targeted for ablation. If the patient remained in AF after ablation of the highlighted driver domains, additional RADAR maps could be created in the left or right atrium at the discretion of the operator. No other empirical ablation was permitted.

Antiarrhythmic medications were to be stopped by 8 weeks after ablation. As per the guidelines, the 3 months after ablation were considered a blanking period, and arrhythmias during this time were not counted toward the efficacy end points. Patients with symptoms or documentation of recurrent AF or AT/AFL after the blanking period were permitted to start or resume the use of antiarrhythmic medications. After this time, any documented episode of AF lasting 30 seconds or longer was counted as an arrhythmia recurrence. A second ablation procedure using the RADAR software was allowed for AF recurrences during the 1-year follow-up period. Ambulatory cardiac monitoring was performed for 7 to 14 days at the 3-, 6-, and 12-month timepoints.

**END POINTS**

Primary end points were acute procedural outcome analysis and freedom from recurrent AF after 1 procedure at 12 months and after 2 procedures at 12 months. Secondary end points included freedom from AF, other ATs, or AFL at 12 months, radiofrequency ablation time, fluoroscopy time, procedure time, and procedure-related adverse events.

**Statistical Analysis**

Data collection and statistical analysis was performed by AFTx, Inc. Outcome analyses were performed on patients who underwent an ablation procedure and were followed for longer than the initial 3-month blanking period. Survival analyses were performed for the primary outcome and for time-to-event secondary outcomes. Kaplan-Meier curves were generated. Categorical variables are expressed as number of patients and percentages, where appropriate. Continuous variables are expressed as mean±SD, with ranges given when appropriate for

---

**Figure 2. Processed unipolar signals.**

Three separate processed recordings are shown from the coronary sinus (A–C) and circular mapping (D–F) catheters in red, green, and blue. These signals are overlaid and shown in different coronary sinus (CS) phases (green, yellow) and for different mapping catheter positions (triangle, square). The preservation of remote atrial activation during specific CS activation patterns is illustrated by the overlapping signals on the mapping catheter at different time points and locations.
additional understanding. Data were managed with Microsoft Excel software and analyzed with Minitab software, version 19.

RESULTS

Study Population

A total of 64 subjects were enrolled at 4 centers in the United States between June 2017 and June 2018. As summarized in Table 1, the study population was: 73% male; age, 64.7±9.5 years; BMI, 31.7±6.0 kg/m²; CHA2DS2-VASc, 2.6±1.6; left atrium size, 54±10 mm. The longest duration of AF averaged 13.4±35.5 months (range 1–240 months). The cohort consisted of 53 patients (83%) with persistent AF, and 11 patients (17%) with long-standing persistent AF. Previous AF ablation (the re-do group) had been performed in 26 patients (41%), with 1.6±0.9 prior ablation procedures (range, 1–5) in this group. The remaining 38 patients (59%) were undergoing their first AF ablation procedure (de novo group).

Acute Procedural Outcomes

Acute procedural outcomes are summarized in Table 2. RADAR mapping and ablation times were 22.5±5.7 and 28.3±20.4 minutes. In total, 88 left atrial conduction vector maps were created, with an average of 1.3±0.6 maps per patient (range, 1–3). An average of 3.9±1.3 left atrium drivers were identified per patient. Right atrial mapping was performed in only 8 patients (13%), with 2.5±1.4 right atrium drivers identified per patient.

A total of 252 left atrial drivers were detected, with 184 sites of rotational drivers and 68 sites of focal impulses observed. The types and locations of left atrial drivers identified are summarized in Figure 5. Drivers were seen throughout the left atrium: anterior wall (24%), posterior wall (35%), roof (11%), septum (11%), and lateral left atrium including the left atrial appendage (19%).

Acute termination of AF during the procedure was achieved in 35/64 patients (55%). Termination was seen in a higher proportion of patients undergoing first-time ablation (23/38, 61%) than those who had previous ablation (12/26, 46%).
Clinical Outcomes

Over a mean follow-up of 12.6±0.8 months, 38 patients (68% [95% CI, 60.0%–82.9%]) remained free of AF off all AADs; 42 patients (74% [95% CI, 69.4%–89.9%]) remained free of AF with the addition of antiarrhythmics (on or off drugs; Figure 6). Three patients were withdrawn from the study with no follow-up, and 4 patients were lost with partial follow-up. Statistical analysis with censoring was performed accordingly. Of the 19 patients who developed AF during follow-up, 4 were noted to have posterior wall drivers that were not ablated during the index procedure due to proximity to the esophagus. There were 10 patients (16%) who developed AT or AFL during follow-up: 5 patients (14%) in the de novo group and 5 patients (21%) in the re-do group.

The Kaplan-Meier estimates for freedom from AF off AADs was higher in patients undergoing first-time AF ablation (72%) than those patients undergoing re-do ablation (60%). There were 9 patients (15%) who underwent repeat ablation for recurrent arrhythmia, 6 patients from the de novo group and 3 from the re-do group. Kaplan-Meier estimates of single procedure success rates after addition of AADs for initial recurrence were 74% for freedom from AF (72% de novo, 78% re-do), and 66% for freedom from AF/AT/AFL (69% de novo, 60% re-do). After 2 procedures, on or off AADs, 84% of patients remained AF free (86% de novo, 83% re-do), and 76% were AF/AT/AFL free (83% de novo, 64% re-do). These data are summarized in Table 3.

There were no adverse events associated with RADAR mapping or related to AF ablation, including no instances of pericardial tamponade, stroke, atrioesophageal fistula, pulmonary vein stenosis, or phrenic nerve injury.

Table 1. Study Population

|                          | De Novo | Re-Do  | All   |
|--------------------------|---------|--------|-------|
| Number of patients       | 38      | 26     | 64    |
| Prior ablations          | 1.6±0.9 |        |       |
| Age, y                   | 64.2±9.4| 65.4±9.9| 64.7±9.5 |
| Male sex, %              | 26 (8%) | 21 (81%)| 47 (73%) |
| AF duration, longest, mo | 11.6±24.6| 16.1±47| 13.4±35.5 |
| BMI, kg/m²               | 32.3±6.5| 30.8±5.0| 31.7±6.0 |
| LA size, cm              | 5.2±0.9 | 5.6±1.1| 5.4±1.0 |
| CHA2DS2-VASc score       | 2.3±1.6 | 2.7±1.6| 2.5±1.6 |
| Diabetes mellitus        | 4 (11%) | 4 (15%)| 8 (13%) |
| Hypertension             | 26 (68%)| 22 (85%)| 48 (75%) |
| Obstructive sleep apnea  | 17 (45%)| 10 (38%)| 27 (42%) |
| Coronary artery disease  | 10 (26%)| 9 (35%) | 19 (30%) |
| Congestive heart failure | 6 (16%) | 6 (23%) | 12 (19%) |
| Ejection fraction, %     | 55±9    | 54±13  | 55±11  |
| Baseline AAD, class I or III | 17 (45%)| 14 (54%)| 31 (48%) |
| Class I AAD              | 5 (13%) | 3 (12%)| 8 (13%) |
| Class III AAD            | 12 (32%)| 11 (42%)| 23 (36%) |

AAD indicates antiarrhythmic drug; AF, atrial fibrillation; BMI, body mass index; and LA, left atrium.
DISCUSSION

Ablation of AF driver domains guided by the novel RADAR mapping system revealed promising 1-year outcomes in this persistent AF cohort. The freedom from recurrent AF with and without the use of AADs after one procedure was 74% and 68%, respectively.

The patients included in this trial have more advanced disease than has traditionally been included in studies of persistent AF. Persistent AF of any duration was allowed, with 17% of the overall cohort having long-standing persistent AF; 41% of patients had at least 1, and up to 5, prior failed ablation procedures for AF. This cohort was generally older, had a higher BMI, and had a larger left atrial size than those included in previous large ablation trials for persistent AF. The overall results of this trial should be viewed in this context.

Ten patients (16%) remained free of recurrent AF but developed AT or AFL during follow-up. These arrhythmias are presumably related to circuits related to scarring from either intraatrial ablation or from the AF itself. This has also been seen in other trials of persistent AF, with seemingly higher rates when anatomic lines of block are attempted. In those cases, incomplete block across the attempted lines can be proarrhythmic.2 Many operators

Table 2. Acute Procedural Data

|                  | De Novo | Re-Do | All  |
|------------------|---------|-------|------|
| Number of patients | 38      | 26    | 64   |
| Presenting in sinus rhythm, % | 9 (24%) | 6 (23%) | 15 (23%) |
| RADAR mapping time, min | 22.3±6.0 | 22.6±5.6 | 22.5±5.7 |
| Number of maps acquired, per pt | 1.2±0.4 | 1.6±0.6 | 1.3±0.6 |
| LA drivers, per pt | 3.9±1.1 | 4±1.5 | 3.9±1.3 |
| RA driver maps, number of pts, % | 2 (5%) | 6 (23%) | 8 (13%) |
| RA drivers, per pt that was mapped | 2.5±0.7 | 2.5±1.6 | 2.5±1.4 |
| RADAR ablation time, min | 23.6±20.3 | 34.5±19.3 | 28.3±20.4 |
| Fluoroscopy time, min | 25.5±13.1 | 24.1±9.0 | 24.9±11.6 |
| Fluoroscopy exposure, mGy | 245±201 | 241±197 | 244±198 |
| Acute termination of AF, % | 23 (61%) | 12 (46%) | 35 (55%) |

AF indicates atrial fibrillation; LA, left atrium; RA, right atrium; and RADAR, Real-Time Electrogram Analysis for Drivers of Atrial Fibrillation.

Figure 5. Driver characteristics.
The study population had an average of 3.9 left atrial drivers identified. The distribution of left atrial drivers is shown: rotational sources are shown as red circles, while focal impulses are shown as blue stars. LA indicates left atrium; and RA, right atrium.
view recurrence of organized arrhythmias such as AT or AFL as more favorable than AF recurrence, as they are often more amenable to repeat catheter ablation.

In the subgroup of 34/61 patients with acute termination of AF with ablation who completed follow-up, 28 patients (82%) remained AF-free and 25 (74%) remained AF/AT/AFL free. In the subgroup for whom acute termination was not achieved and cardioversion was required, 63% remained AF-free and 52% remained AF/AT/AFL-free on or off AADs. A subgroup of 33/61 patients (54%) underwent CTI ablation, which was optional in the protocol. After a single procedure including CTI ablation, 27 (82%) remained AF-free; and 24 patients (73%) remained AF/AT/AFL-free on or off

*Figure 6. Kaplan-Meier estimates of single-procedure freedom from atrial fibrillation (AF).* Shown are the curves for the full cohort (blue line), the de novo-alone group (red line), and the re-do group (green line) without the use of antiarrhythmic drugs (top), and with the addition of antiarrhythmic drugs (bottom). Three patients were withdrawn with no follow-up and 4 patients were lost with partial follow-up. Statistical analysis with censoring was performed accordingly, using Minitab 19 software. AAD indicates antiarrhythmic drug.
AADs. Further analysis in larger populations is necessary to validate these subgroup results.

**Driver Ablation for Persistent AF**

A number of prior studies have examined other technologies for identification of AF drivers to improve success rates of ablation. The CONFIRM trial (Conventional Ablation for Atrial Fibrillation With or Without Focal Impulse and Rotor Modulation)\(^\text{20}\) studied ablation guided by focal impulse and rotor modulation, using a 64-pole basket catheter in the atrium to collect electrogram data for analysis. In patients with paroxysmal or persistent AF, acute termination of AF occurred in 56% with Focal Impulse and Rotor Modulation-guided ablation, 82.4% of patients remained free of AF, and 70.6% remained free of any atrial tachyarrhythmia at 1 year. Other single-center experiences have also reported success with this technology. But these results have notably not been replicated by other groups,\(^\text{21,22}\) And most importantly, the results of the REAFFIRM trial (Randomized Evaluation of Atrial Fibrillation Treatment With Focal Impulse and Rotor Modulation Guided Procedures) were recently presented.\(^\text{23}\) In this 350-patient multicenter clinical trial, patients with persistent AF were randomized to either conventional PVI or focal impulse and rotor modulation–guided ablation followed by PVI. The single procedure 1-year freedom from AF/AT was 69.3% in the focal impulse and rotor modulation group and 67.5% in the PVI alone group (\(P=0.96\)).\(^\text{23}\)

The 252-electrode surface ECG mapping vest has also been studied for guiding ablation of persistent AF sources. This technology uses reconstructed unipolar electrograms from potentials recorded on the torso for phase mapping to identify AF drivers. In the initial experience in over 100 patients with persistent atrial fibrillation, termination of AF was achieved in 80% of patients—63% with ablation of driver regions alone, whereas the remainder terminated during ablation of additional lines.\(^\text{24}\) After 12 months of follow-up, 80% of patients remained free of AF, and 64% remained AF/AT/AFL free. However, when this approach was studied in a multicenter prospective fashion, a significant proportion of patients had recurrent atrial arrhythmia.\(^\text{25}\) Of the 77% of patients who remained AF free at 1 year, 49% of them had at least one episode of AT requiring either AAD therapy, cardioversion, or repeat ablation.

These approaches rely on calculation of phase singularities to identify potential AF drivers rather than traditional mapping and electrogram processing techniques. They are also impeded by the lower spatial resolution of these technologies, which can cause drivers to be missed, incorrectly located, or artefactually created where they do not actually exist.\(^\text{16,17}\) In contrast, the RADAR system uses high-density contact mapping and standard electrogram processing techniques to circumvent these limitations.

High-resolution characterization of AF drivers may also help to discern driver characteristics that are important for maintenance of AF. This could, in turn, decrease the amount of ablation required. Development of more focused ablation methods is an important goal to (1) help reduce procedure time, (2) decrease the substrate for subsequent development of macroreentrant atrial arrhythmias, and perhaps most important, (3) minimize the extent of atrial ablation so as to preserve atrial mechanical/contractile function. Panoramic high-resolution contact mapping of AF may provide a way to develop consistent treatment strategies for patients with refractory persistent AF.

The use of the RADAR system for driver identification does add time to the procedure, both for mapping and for the additional ablation that is required. But since it is used in conjunction with a standard mapping system and interpretation of the Probabilistic Atrial Driver Assessment map is simple, the system is easily incorporated into standard AF ablation workflow. Furthermore, since additional mapping equipment is unnecessary beyond a standard multielectrode mapping catheter, there is no additional cost incurred by its use. Our multicenter data

---

**Table 3. Clinical Outcomes**

| Procedure                  | All Patients (n=61*) | De Novo (n=37) | Re-Do (n=24) |
|----------------------------|----------------------|----------------|--------------|
| Single Procedure Off AAD   |                      |                |              |
| Single Procedure On or Off AAD | 19 (31%)           | 15 (25%)       | 5 (16%)      |
| Two Procedures Off AAD     | 10 (27%)             | 10 (27%)       | 5 (14%)      |
| Two Procedures On or Off AAD | 6 (16%)             | 5 (14%)        | 2 (5%)       |
| On AAD                    | n/a                  | n/a            | n/a          |
| Repeat ablation           | n/a                  | n/a            | n/a          |
| Freedom from AF/AT/AFL†   | 28 (52%)             | 36 (66%)       | 43 (76%)     |
| Freedom from A†           | 38 (68%)             | 42 (74%)       | 48 (84%)     |

*Three patients did not have follow-up and were withdrawn from the study.
†Percentages for freedom from arrhythmia are taken from Kaplan-Meier estimates at the end of follow-up for each cohort.
show comparable results to the initial favorable studies of other driver mapping technologies in a relatively small number of patients with more advanced disease. Driver ablation for persistent AF can be a useful strategy if these results can be replicated in a larger trial.

In contrast to driver ablation, Pamburt et al.\(^\text{26}\) recently described a purely anatomic approach to persistent AF ablation. In this pilot series, 10 patients underwent ablation at multiple anatomic sites (CS musculature, cavotricuspid isthmus, mitral isthmus, and roof line). Before ablation, Vein of Marshall ethanol injection was performed to target epicardial Vein of Marshall potentials and assist with achieving mitral isthmus block. This approach is likely to also incidentally disrupt some AF drivers located near the ablation sites, though it should not affect drivers on the anterior wall, posterior wall, and septum. It will be important to observe AF recurrence rates with this anatomic method.

**Limitations**

There are several limitations to this study. It is a heterogeneous persistent AF population with a relatively small number of patients. There is no control group for comparison. Generalization of these results to specific populations should be undertaken with caution. Although multiple centers participated in this trial, all operators had significant prior experience with AF ablation. Techniques for ablation of the identified drivers were not standardized. Despite these apparent limitations, the initial outcomes are favorable in this refractory population of patients with AF.

**Conclusions**

Mapping of AF drivers is limited by spatial resolution. In this first-in-human multicenter RADAR clinical trial, we observed promising results with the real-time use of this high-resolution mapping system to define targets for ablation in persistent AF. This sets the stage for a randomized trial to investigate this strategy in a more definitive fashion.

**References**

1. Verma A, Mantovani R, Macle L, De Martino G, Novak P, Calzolari V, Guerra PG, Nair G, et al. Substrate and Trigger Ablation for Reduction of Atrial Fibrillation (STAR AF): a randomized, multicentre, international trial. *Circ. Heart Fail.* 2016;9:28–36. doi: 10.1161/CIRCHEARTFAILURE.115.003461

2. Verma A, Mantovani R, Macle L, De Martino G, Novak P, Calzolari V, Guerra PG, Nair G, et al. Substrate and Trigger Ablation for Reduction of Atrial Fibrillation (STAR AF): a randomized, multicentre, international trial. *Circ. Heart Fail.* 2016;9:28–36. doi: 10.1161/CIRCHEARTFAILURE.115.003461

3. Sanders P, Hocini M, Jais P, Sacher F, Hsu LF, Takahashi Y, Rotter M, Rosotch T, Nalliah CJ, Clémenty J, et al. Complete isolation of the pulmonary veins and posterior left atrium in chronic atrial fibrillation. *Nat. Rev. Cardiovasc. Med.* 2007;3:336–346. doi: 10.1038/nrctm.2007.157

4. Di Biase L, Burkhart DO, Mohanty P, Mohanty S, Sanchez JE, Trivedi C, Gómez M, Gókoğlan Y, Giannì C, Horton RP, et al. Left atrial appendage isolation in patients with longstanding persistent AF undergoing catheter ablation: BELIEF Trial. *J Am Coll Cardiol.* 2011;58:1929–1940. doi: 10.1016/j.jacc.2011.07.070

5. Atienza F, Almeida J, Oramboe JM, Moya A, Martínez-Alaya JD, Hernández-Madrid A, Castellanos E, Arribas F, Arias MÁ, Tercedor L, et al. RADAR-AF Investigators. Comparison of radiofrequency catheter ablation of drivers and circumferential pulmonary vein isolation in atrial fibrillation: a noninferiority randomized multicenter RADAR-AF trial. *J Am Coll Cardiol.* 2010;56:2743–2752. doi: 10.1016/j.jacc.2010.09.088

6. Driessen AHG, Berger WR, Krul SRL, van den Berg NWE, Neefs J, Pieraerts RF, Chen Pin Yin DRPP, de Jong JSSG, van Boven WP, de Groot Jr. Ganglion plexus ablation in advanced atrial fibrillation: the AFACT Study. *J Am Coll Cardiol.* 2016;68:1155–1165. doi: 10.1016/j.jacc.2016.05.036

7. Di Biase L, Burkhart DO, Mohanty P, Mohanty S, Sanchez JE, Trivedi C, Gómez M, Gókoğlan Y, Giannì C, Horton RP, et al. Left atrial appendage isolation in patients with longstanding persistent AF undergoing catheter ablation: BELIEF Trial. *J Am Coll Cardiol.* 2011;58:1929–1940. doi: 10.1016/j.jacc.2011.07.070

8. Atienza F, Almeida J, Oramboe JM, Moya A, Martínez-Alaya JD, Hernández-Madrid A, Castellanos E, Arribas F, Arias MÁ, Tercedor L, et al. RADAR-AF Investigators. Comparison of radiofrequency catheter ablation of drivers and circumferential pulmonary vein isolation in atrial fibrillation: a noninferiority randomized multicenter RADAR-AF trial. *J Am Coll Cardiol.* 2010;56:2743–2752. doi: 10.1016/j.jacc.2010.09.088

9. Verma A, Jiang CY, Betts TR, Chen J, Deisenhofer I, Mantovan R, Macle L, Morillo CA, Haverkamp W, Weerasooriya R, et al; STAR AF II Investigators. Approaches to catheter ablation for persistent atrial fibrillation. *N Engl J Med.* 2015;372:1812–1822. doi: 10.1056/NEJMoa1408288

10. Rüegg A, Tilz RR, Lin T, Fink T, Heeger CH, Araya A, Metzner A, Mathew S, Wissner E, Makimoto H, Wohlmuth P, et al. Unexpectedly high incidence of stroke and left atrial appendage thrombus formation after electrical isolation of the left atrial appendage for the treatment of atrial tachyarrhythmias. *Circ Arrhythm Electrophysiol.* 2016;9:e003461. doi: 10.1161/CIRCEP.115.003461

11. Haissaguerre M, Jais P, Shah DC, Takahashi A, Hocini M, Quiniou G, Haïssaguerre M, Jaïs P, Takahashi Y, Hocini M, et al. Spontaneous initiation of atrial fibrillation by ectopic beats originating in the pulmonary veins. *N Engl J Med.* 1998;339:659–666. doi: 10.1056/NEJM199809033391003

12. Mandapati R, Skanes A, Chen J, Berenfeld O, Jalife J. Stable microreentrant circuits in atrial fibrillation. *J Am Coll Cardiol.* 2000;36:194–199. doi: 10.1016/S0735-1097(00)00224-4

13. Sanders P, Berenfeld O, Hocini M, Jais P, Vassylyanathan R, Hsu LF, Garrigue S, Takahashi Y, Rotter M, Sacher F, et al. Experimental strategies identify sites of high-frequency activity maintaining atrial fibrillation in humans. *Circulation.* 2005;112:789–797. doi: 10.1161/01.CIR.0000195101.19011.7b

14. Narayan SM, Krummen DE, Eneyart MW, Rappel WJ. Computational mapping identifies localized mechanisms for ablation of atrial fibrillation. *PloS One.* 2012;7:e49034. doi: 10.1371/journal.pone.0049034

15. Haissaguerre M, Hocini M, Shah AJ, Derval N, Sacher F, Jais P, Dubois R. Noninvasive panoramic mapping of human atrial fibrillation mechanisms: a feasibility report. *J Cardiovasc Electrophysiol.* 2013;24:711–717. doi: 10.1111/jce.12075

16. King B, Porta-Sánchez A, Massé S, Zani M, Balasundaram K, Kusha M, Jackson N, Haldar S, Umapathy K, Nanthakumar K. Effect of
spatial resolution and filtering on mapping cardiac fibrillation. Heart Rhythm. 2017;14:608–615. doi: 10.1016/j.hrthm.2017.01.023

17. Roney CH, Cantwell CD, Bayer JD, Qureshi NA, Lim PB, Tweedy JH, Kanagaratnam P, Peters NS, Vign mond EJ, Ng FS. Spatial resolution requirements for accurate identification of drivers of atrial fibrillation. Circ Arrhythm Electrophysiol. 2017;10:e004899. doi: 10.1161/CIRCEP.116.004899

18. Kurian T, Janardhan AH, Doshi A, Kessman P, Nguyen B, Atkinson J, Edwards JR, Efimov I, Sanchez JM. Characterization of drivers in patients with persistent atrial fibrillation to identify substrate based rotor ablation targets. JCRM. 2015;6:2153–2161.

19. Kurian T, Doshi A, Kessman P, Nguyen B, Edwards J, Pieper S, Efimov I, Janardhan AH, Sanchez M. Rotors in patients with persistent atrial fibrillation: case report of a left atrial appendage rotor identified by a novel computational mapping algorithm integrated into 3-dimensional mapping and termination of atrial fibrillation with ablation. Card Electrophysiol Clin. 2015;7:157–163. doi: 10.1016/j.jcep.2014.11.009

20. Narayan SM, Krummen DE, Shivkumar K, Clopton P, Rappel WJ, Miller JM. Treatment of atrial fibrillation by the ablation of localized sources: CON-FIRM (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

21. Buch E, Share M, Tung R, Benharash P, Sharma P, Koneru J, Mandapati R, Ellenbogen KA, Shivkumar K. Long-term clinical outcomes of focal impulse and rotor modulation for treatment of atrial fibrillation: a multicenter experience. Heart Rhythm. 2016;13:636–641. doi: 10.1016/j.hrthm.2015.10.031

22. Mohanty S, Gianni C, Trivedi C, Metz T, Bai R, Al-Ahmad A, Bailey S, Burkhardt JD, Gallinghouse GJ, Horton R, et al. Impact of rotor ablation in non-paroxysmal AF patients: findings from the per-protocol population of the OASIS trial at long-term follow-up. Am Heart J. 2018;205:145–148. doi: 10.1016/j.ahj.2018.05.021

23. Brachmann J, Hummel JD, Wilber DJ, Sarver AE, Rapkin J, Shpun S, Szili-Torok T. Prospective randomized comparison of rotor ablation vs conventional ablation for treatment of persistent atrial fibrillation - the REAF- FIRM Trial [abstract S-LBCT01-02]. Heart Rhythm. 2019:16:963–964.

24. Haissaguerre M, Hocini M, Denis A, Shah AJ, Komatsu Y, Yamashita S, Daly M, Amraoui S, Zellerhoff S, Picat MQ, et al. Driver domains in persistent atrial fibrillation. Circulation. 2014;130:530–538. doi: 10.1161/CIRCULATIONAHA.113.005421

25. Knecht S, Sohal M, Deisenhofer I, Albenque JP, Arentz T, Neumann T, Cauchemez B, Duyschsaever M, Ramoul K, Verbeet T, et al. Multicentre evaluation of non-invasive biatrial mapping for persistent atrial fibrillation ablation: the AFACART study. Europace. 2017;19:1302–1309. doi: 10.1093/europace/euw168

26. Pambrun T, Denis A, Duchateau J, Sacher F, Hocini M, Jais P, Haissaguerre M, Denel N. MARSHALL bundles elimination, Pulmonary veins isolation and Lines completion for ANotomical ablation of persistent atrial fibrillation: MARSHALL-PLAN case series. J Cardiovasc Electrophysiol 2019;30:7–15. doi: 10.1111/jce.13797