Prospective STAR Guided Ablation in Persistent AF using Sequential Mapping with Multipolar Catheters

Running title: *Honarbakhsh et al.; Sequential mapping using STAR in persistent AF*

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Abstract:

Background- A novel 'STAR' mapping approach to guide AF ablation using basket catheters recently showed high rates of AF termination and subsequent freedom from AF.

Methods- This study aimed to determine whether STAR mapping using sequential recordings from conventional pulmonary vein mapping catheters could achieve similar results. Patients with persistent AF <2 years were included. Following pulmonary vein isolation (PVI) AF drivers (AFDs) were identified on sequential STAR maps created with PentaRay, IntellaMap Orion, or Advisor HD Grid catheters. Patients had a minimum of 10 multipolar recordings of 30-seconds each. These were processed in real-time and AFDs were targeted with ablation. An ablation response was defined as AF termination or CL slowing ≥30ms.

Results- Thirty patients were included (62.4±7.8 years old, AF duration 14.1±4.3 months) of which 3 had AF terminated on PVI, leaving 27 patients that underwent STAR-guided AFD ablation. Eighty-three potential AFDs were identified (3.1±1.0 per patient) of which 70 were targeted with ablation (2.6±1.0 per patient). An ablation response was seen at 54 AFD (77.1% of AFD; 21 AF termination and 33 CL slowing) and occurred in all 27 patients. No complications occurred. At 17.3±10.1 months, 22/27 (81.5%) patients undergoing STAR guided ablation were free from AF/AT off anti-arrhythmic drugs.

Conclusions- STAR-guided AFD ablation through sequential mapping with a multipolar catheter effectively achieved an ablation response in all patients. AF terminated in a majority of patients, with a high freedom from AF/AT off anti-arrhythmic drugs at long-term follow-up.

Key words: atrial fibrillation; atrial tachycardia; catheter ablation; mapping; mapping technology

Nonstandard Abbreviations and Acronyms

AF- Atrial fibrillation

CL- Cycle length

AFD- AF driver

PV- Pulmonary vein

AT- Atrial tachycardia

RA- Right atrium

LA- Left atrium

PVI- Pulmonary vein isolation

CS- Coronary sinus

WCT- Wilson Central Terminal WCT

Introduction

Several studies have demonstrated the presence of intermittent focal and rotational activations in atrial fibrillation (AF). Ablation at the sites of these phenomena have resulted in cycle length (CL) slowing or AF termination, supporting the notion that they may be localized AF drivers (AFD) [1-5]. These have mostly been identified with panoramic mapping of the atria, but recently sequential mapping using conventional multipolar mapping catheters has shown potential for mapping sites identified using simultaneous mapping with basket catheters [6, 7]. However, sequential mapping of AFD has not been used prospectively to guide ablation. Sequential mapping has several advantages, most notably that it allows the use of a catheter that can also be used to create the geometry and guide isolation of the pulmonary veins (PVs) (avoiding the need for basket catheters) which reduces the cost and complexity of the procedure. Sequential mapping may also allow higher density acquisition of data to identify AFD where limited contact, and electrode coverage are achieved with the basket catheter [7, 8].

A novel 'STAR' mapping approach to guide AF ablation using basket catheters recently showed high rates of AF termination and subsequent freedom from AF [9]. The aim of this study was to determine whether ablation prospectively guided by the STAR mapping method utilizing sequential recordings from a PV mapping catheter could achieve similar results. Different mapping catheters and mapping systems were used to investigate the feasibility of using different datasets. The rates of AF termination and CL slowing were examined using this sequential approach. To investigate long-term success in terms of freedom from AF/atrial tachycardia (AT) with STAR guided ablation generally, outcomes were examined in a larger cohort including those guided by basket mapping and those guided by sequential mapping.

Methods

Patients with persistent AF (<24 months and no previous AF ablation) undergoing catheter ablation were included. Procedures were performed under either general anaesthetic or local anaesthetic and sedation with diamorphine and midazolam. Anticoagulation therapy was uninterrupted, and heparin intravenous boluses were administered to maintain an ACT>300s. Patients that were on anti-arrhythmic therapy pre-ablation had this continued pre-and post-ablation. Patients provided informed consent for their study involvement. The study was approved by the UK National Research Ethics Service (16/LO/1379) and prospectively registered on clinicaltrials.gov (NCT02950844). This was a single-center study and all recruitment occurred at Barts Heart Centre between the periods of 2018-2020. The data, methods used in the analysis and materials used to conduct the research will not be made available to any research for the purposes of reproducing the results or replication the procedure. This is on the grounds that the mapping method is currently undergoing a patent and CE marking application process.

STAR mapping method

The STAR mapping method has been described in detail previously. In brief, the method uses data obtained from multiple individual wavefront trajectories and creates a statistical picture from which it determines the predominant direction of wavefront propagation which allows it to identify atrial regions that most often precede activation of neighboring sites [9, 10]. For these regions to be classified as an AFD it was required to lead for ≥75% of wavefronts during a recording period.

Unipolar recordings were obtained with the multipolar catheters. The export data obtained from each mapping system which consisted of electrogram data, geometry data and electrode coordinates were processed by the STAR mapping method in a custom written Matlab script. STAR maps were displayed on a replica geometry created in Matlab. The same electrodes identifying an AFD on the STAR maps were manually tagged on the identical geometry on the 3D mapping system which was used to guide ablation.

Activation times were compared across all the electrodes of the multipolar catheter used at each position. Importantly, the activation times were compared within each recording taken rather than across all the recordings due to the sequential nature of the recordings. Each sequential catheter recording was then superimposed on the same geometry to produce an 'amalgamation map' of separate recordings.

The STAR mapping method has been effectively validated in AT using both basket catheter mapping and sequential mapping when comparing to conventional local activation mapping [7]. The same previously validated geodesic distances to pair electrodes [10] were used across both mapping methods without the need for any modification. The STAR mapping algorithm used for this study is consistent to that used with the basket catheter. Besides the modifications made to the algorithm to take into account the differences in format of the export data obtained from each mapping system no other changes were made when applied to the different mapping systems. No changes were made to the algorithm to take into account the differences in electrode spacing.

Electrophysiology procedure

The procedures were performed using either CARTO (Biosense Webster, CA, USA), Rhythmia (Boston Scientific, MA, USA), or EnSite Precision system (Abbott, CA, USA). Right (RA) and left atrial (LA) geometries were created in all patients. All patients underwent a minimum of 10 separate 30-second sequential recordings using a multipolar catheter (PentaRay with CARTO, IntellaMap Orion with Rhythmia and Advisor HD Grid with EnSite Precision System) to achieve optimal LA coverage. Sequential multipolar catheter recordings were performed pre- and post-PV isolation (PVI) in all patients. The aim of the study was to map the LA. However, if activation was thought suggestive of an RA AFD as indicated by coronary sinus (CS) activation being predominantly proximal to distal and LA AF CL being fastest around the septum, then the RA was also mapped.

When using the CARTO mapping system the unipolar electrograms were recorded through Bard (Labsystem pro Electrophysiology system). A decapolar catheter (Biosense Webster, CA) positioned in the IVC was used as the indifferent catheter and electrograms were filtered between 0.5-500Hz. With the Rhythmia and EnSite Precision mapping system raw unfiltered unipolar electrograms were obtained from the mapping system using Wilson Central

Terminal (WCT) as the indifferent electrode. Electrode coordinates and anatomical data was obtained from each mapping system. The unipolar electrograms, electrode coordinates and anatomical data were imported into Matlab (Matlab 2017b, MathWorks MA, USA) and using a custom written script, the sequential STAR maps were created.

Ablation strategy

All patients underwent PVI. Following this, a 20-minute waiting period was observed so that no delayed effect of ablation could affect rhythm or CL during AFD ablation. During this waiting period, the sequential mapping data was obtained, and the data exported to create the STAR maps. The post-PVI 'amalgamation' sequential map was used to guide ablation of AFD. The ablation strategy has previously been described in detail [9]. Ablation was performed at the identified AFD with further consolidating lesions surrounding this site intentionally avoiding line formation. All AFD on a STAR map were targeted in order of ranked priority whereby sites that were leading 100% of the time being targeted first followed by 90%, etc.

Ablation at an AFD site was stopped if: (1) 5 minutes of ablation had been performed, (2) no signal remained at the ablation site, or (3) a study-defined ablation response had been achieved. Ablation responses were defined as termination of AF (into AT or sinus rhythm), or CL slowing of ≥30ms. Our group has previously applied this definition [5, 9]. AF CL was measured over 30 beats from the multipolar catheter positioned in the LA appendage. AF CL pre- and post-AFD ablation was used to assess the ablation response. If AF terminated before some AFD had been ablated, these sites were not empirically targeted. No ablation beyond targeting AFD was allowed in AF. If AF organized into an AT this was mapped and ablated. DC cardioversion was performed at the end of the procedure if AF did not terminate following ablation of all identified AFD.

Follow-up

Patients were followed-up at 3, 6, 9 and 12 months, and 6 monthly thereafter. 48-hour Holter monitoring was performed at 6 and 12 months. Documented AF or AT lasting for >30 seconds or the use of antiarrhythmic drugs after the 3-month blanking period was defined as recurrence of AF/AT after a single procedure as per current guidelines [11]. Follow up to date is reported for the sequential STAR guided ablation cohort. To assess long term outcomes in a larger cohort undergoing STAR guided ablation, including those guided by basket catheters and sequential recordings, 1 year outcomes are reported to allow comparison between groups (since the procedures utilizing basket guided ablation were performed prior to the sequential cohort and follow up to date is therefore longer).

Statistical analysis

Statistical analyses were performed using SPSS (IBM SPSS Statistics, Version 24 IBM Corp, NY, USA). Continuous variables are displayed as mean ± standard deviation (SD) or median (interquartile range). Categorical variables are presented as a number and percentage. Fisher exact test was used for the comparison of nominal variables. The student t-test, or its non-parametric equivalent, Mann-Whitney U test when appropriate was used for comparison of continuous variables. P-value of <0.05 was deemed significant.

Results

Procedural data

A total of 30 patients were included in the study. Baseline characteristics are shown in Table 1. The results are summarised in Figure 1. A majority of the patients underwent ablation under local anaesthetic and sedation (26/30, 86.7%). Out of the 30 patients, 2 patients terminated to sinus rhythm and one terminated to cavo-tricuspid isthmus (CTI) dependent flutter on PVI leaving 27 patients who underwent ablation guided by STAR mapping. The mean procedure duration was 259.4 ± 62.1 minutes and the total ablation duration post PVI was 10.3 ± 3.5 minutes (including ablation for AFD and AT if AF terminated to AT during the ablation of AFD). The average ablation duration at an AFD identified using the STAR mapping method was 2.7 ± 0.5 minutes. No complications were encountered in any of the patients.

AFD ablated

After PVI, a mean of 14.4 ± 3.5 sequential acquisitions were made per patient, of the LA which were exported to generate the STAR map in AF. In the 27 patients remaining in AF post-PVI, 83 potential AFD were identified (3.1±1.1 per patient) of which 70 (84.3%) (2.4 ± 1.2 per patient) were targeted with ablation. An ablation response was achieved with 54/70 AFD (77.1%) which included AF termination with 21 AFD and CL slowing ≥30ms in 33 AFD (Supplemental Table 1). This meant that 13 AFD were not targeted because the patient cardioverted before all of their AFD were ablated.

An ablation response was achieved in all 27 patients (Figure 2A-C, Figure 3A-C, Figure 4A-F, Figure 5A-C and Figure 6A-D). On a per patient basis AF termination was achieved with 21 patients (7 sinus rhythm and 14 AT) and CL slowing ≥ 30ms in the 6 remaining patients (Table 2). Out of the 14 patients in whom AF organized into an AT this was mapped and successfully ablated to sinus rhythm in 12 patients whilst the remaining 2 patients underwent DC cardioversion. In one of the patients mitral isthmus block was not achieved whilst the other patient had 3ATs mapped with alternating AT cycle length. The 6 patients that had CL slowing achieved at the end of their procedure underwent DC cardioversion to achieve sinus rhythm. Sequential RA mapping was performed post-PVI in one of the 27 patients. However, no AFD was identified in the RA and therefore no ablation was performed in the RA in any of the patients.

AFD and pre-PVI recordings

For comparison, STAR maps were made of the LA pre-PVI using a mean of 13.2 ± 2.5 sequential recordings and analysed off-line. Out of the 83 AFD identified post-PVI, 42 (50.6%) of these AFD were also identified on the pre-PVI maps. All patients had at least one consistent AFD identified on both the pre- and post-PVI maps (1.6 ± 0.7 AFD per patient).

Out of the 42 AFDs identified on the pre-PVI maps, 40 were targeted on the post-PVI maps. An ablation response was seen with 33/40 (82.5%) of these drivers. Out of the 54 AFD targeted post-PVI that were associated with an ablation response, 34/54 (63.0%) were also identified on the pre-PVI maps. All of the 21 AFD that were associated with AF termination on ablation were identified pre-PVI.

On the pre-PVI maps, 2 additional AFD were identified that were not seen on the post-PVI maps. This was in the 2 patients in whom AF termination occurred during PVI whereby AFD were identified at the PV ostia in both patients on the pre-PVI maps.

Drivers targeted with ablation and identified pre- and post-PVI were more likely to be associated with AF termination than drivers only identified post-PVI (21/40 vs. 0/30; p<0.001).

Mapping system

A majority of the procedures were performed using CARTO (n=24, 80.0%). Out of the 24 patients that had mapping performed with CARTO, 2 terminated to sinus rhythm and one to CTI dependent flutter with PVI. In the remaining 21 patients that had ablation guided by STAR mapping, AF termination was achieved in 16/21 patients (76.2%). Using the Rhythmia and

EnSite Precision mapping system, AF termination was achieved in 3 out of the 4 patients (75.0%; p=1.00) and 1 out of 2 (50%) patients respectively.

Clinical outcomes in sequential STAR mapping cohort

During an average follow-up of 17.3 ± 10.1 months, 25 out of the 30 patients (83.3%) remained free from AF/AT off anti-arrhythmic drugs after a single procedure. When only assessing the 27 patients that underwent STAR mapping guided ablation (so excluding the patients in whom AF terminated with PVI) 22/27 patients (81.5%) remained free from AF/AF during follow-up off anti-arrhythmic therapy after a single procedure. Of the 5 patients with recurrent arrhythmia, 3 had recurrent AF and 2 had AT. Both patients with recurrent AT underwent repeat ablation and were found to have mitral isthmus dependent flutter in one patient and roof dependent flutter in the other.

Electrophysiological and clinical outcomes in larger cohort guided by STAR mapping: comparison of sequential and basket mapping

Electrophysiological outcomes were examined in the 35 patients who underwent STAR guided ablation utilizing basket catheters (reported previously[7]) and the 30 patients comprising the sequential cohort (reported here). The proportion of AFD ablated that resulted in a study-defined ablation response was 127/153 (83.0%). This was comparable between these two groups (54/70, 77.1% sequential vs. 73/83, 88.0% basket; p=0.09). The proportion of AFD whereby ablation resulted in AF termination was 45/127 (35.4%). This was again comparable between groups (21/54, 38.9% sequential vs. 24/73, 32.9% basket; p=0.57). The proportion of patients that had AF termination on ablation was 45/64 (70.3%) and was again similar between groups (21/29, 72.4% sequential vs. 24/35, 68.6% basket; p=0.79).

For examination of clinical outcomes follow-up has been truncated at 1 year (since follow-up in the basket group was longer). In the sequential group 23 patients had reached 1-year follow-up. Therefore, the 1-year freedom from AF/AT after a single procedure off antiarrhythmic drugs was 46/58 (79.3%). The outcome was similar in the 2 cohorts with 18/23 (78.3%) remaining free from arrhythmia in the sequential group compared to 28/35 (80.0%) in the basket group (p=1.00).

Discussion

This study has demonstrated that ablation of persistent AF guided by STAR mapping utilizing sequential recordings is associated with an acute response in all patients, with AF termination in the majority (78%). Rates of freedom from AF/AT during follow-up were high (83%). The acute response to ablation and one-year clinical outcomes with STAR guided ablation were confirmed across a larger cohort including patients mapped with basket catheters and those mapped sequentially, with no apparent difference between modalities. These data also demonstrate that the principles underlying STAR mapping can be consistently applied regardless of the technology used to implement them, and hence this approach was feasible with a range of different catheters and mapping systems.

STAR mapping

The STAR mapping method is a novel mapping method that utilises multiple wavefront trajectories to determine the directionality and patterns of wavefront propagation and thereby identifying originating sites that were defined as AFD. This mapping method has been validated both *in vitro* and *in vivo* [9, 10]. Our group has previously demonstrated that AFD identified on STAR mapping with basket catheters are frequently identified on sequential mapping with a high sensitivity and specificity [7, 12]. This is the first study that has evaluated AF ablation prospectively guided by sequential STAR mapping.

Our group has previously demonstrated that global mapping with basket catheters using the STAR mapping method is associated with high rates of electrophysiological endpoints (AF termination or CL slowing, as in the current study) and freedom from AF/AT during follow-up [9]. In those patients, a high proportion of the AFD (84%) identified on global STAR maps using basket catheters were also identified on sequential STAR maps recorded during the same procedures using a PentaRay catheter but created offline [7]. The AFD that were identified on both global and sequential STAR maps were more likely to be associated with AF termination on ablation rather than CL slowing compared to those drivers that were identified by global mapping with a basket catheter alone [7]. In the current study AF termination was achieved in the majority of patients with ablation prospectively guided by sequential STAR mapping (78%), and again all patients reached the study defined ablation response. Ablation guided by sequential STAR mapping was associated with a high rate of freedom from AF/AT, off antiarrhythmic drugs, at long-term follow up (82% at 17 months). A direct comparison between ablation guided by STAR mapping utilizing sequential and basket catheter mapping showed that the outcomes are comparable in terms of electrophysiological endpoints and freedom from AF/AT during follow-up.

The chaotic nature of AF and variable CL has meant that mapping AF using multipolar catheters has not been widely attempted. Mapping rotors or re-entrant activity using sequential mapping is dependent on mapping the whole circuit to allow distinction with passive activations, and may be further hindered by rotors meandering over small areas. Because the STAR mapping method does not attempt to distinguish AFD mechanism and simply aims to identify organized activity through mapping wavefront propagation away from a source, this does not appear to be a limitation for STAR mapping and the whole circuit does not necessarily need to be mapped. A driver moving over a small area would still demonstrate wavefronts emanating from that area, possibly with more than one electrode leading intermittently (depending on resolution). Theoretically STAR mapping could be performed using any catheter with more than 1 electrode with any resolution, although it is unclear at present how many electrodes over what area is required to apply this technique. These data show that the multipolar catheters used with different numbers of electrodes and resolutions yielded similarly useful information regarding the mapped area.

It has been shown that even though AFD demonstrate temporal periodicity they are recurrent and spatially relatively conserved [1, 5, 13 14 15]. During a 30-second recording an AFD recurs approximately 8 times [5, 13] and therefore would be expected to be identifiable using sequential mapping during this time period. Even though AFD have been shown to be intermittent the STAR mapping method takes this driver characteristic into account. As the STAR mapping method compares data from many wavefront trajectories that occur during the recording duration and then uses the data to generate a statistical picture of the proportion of time an electrode is leading its neighbouring electrodes it is not dependent on the driver being stable but only repetitive. This is a significant advantage of this mapping method.

In contrast to Topera and ECGI mapping systems used to map AFD, the STAR mapping method allows both global and sequential mapping. There are several advantages to using sequential mapping over global mapping with basket catheters. Sequential mapping is less expensive, since the same catheter used to assess for PVI is also used for the unipolar electrogram recordings and therefore there is no need for additional equipment. Sequential mapping also avoids the need for additional operator experience with catheters they may not use routinely for PVI or AT ablation.

Even though the proportion of patients that underwent mapping using the Rhythmia and EnSite Precision mapping systems was small the aim of the study was to demonstrate feasibility in applying the STAR mapping method using a sequential mapping approach. The multipolar catheters used with these mapping systems are very different both in the number of electrodes (20 with CARTO, 16 with EnSite Precision and 64 with Rhythmia) and shape. Therefore, the STAR mapping method can be implemented effectively using different multipolar catheters. Further to this, the geometry created with both of the mapping systems could effectively be used to generate the STAR AF maps. The patient numbers are too small to infer anything meaningful about long-term clinical outcomes between the different mapping systems but there was no significant difference in the AF termination rates on ablation between the mapping systems, and a study defined ablation response was achieved in all patients. In theory the STAR mapping method can be applied to any mapping system that allows export data to be obtained that includes unipolar electrograms, electrode location and geometry data.

This study has shown that AFD identified pre- and post-PVI are more likely to be associated with an ablation response particularly AF termination. This is consistent with the findings from our previous studies [5, 7, 9, 13]. This suggests that these AFD are mechanistically more important. On a practical level this raises the question as to whether STAR mapping should be performed pre- or post-PVI. AFD identified pre-PVI may be more important, but more AFD will be identified on mapping post PVI. Mapping could be performed at both time points to prioritize targets and apply a hierarchical approach to AFD ablation, but this would be time consuming. Further testing of different ablation protocols are necessary. We would still advocate that patients undergo PVI as a baseline procedure because to-date this has been shown to be the most effective strategy for treatment of both persistent and paroxysmal AF.

More recent studies have shown promising results with other novel mapping technologies used to guide AF ablation [16] [17]. However, the success rates reported in the de-novo persistent ablation patients in regards to freedom from AF/AT off anti-arrhythmic drugs following a single procedure were much lower than that seen with the STAR mapping method (58% in RADAR vs. 86% in STAR). UNCOVER trial [14] evaluates the use of non-contact charge density mapping which uses CT reconstruction of the cardiac chamber whilst the STAR mapping method utilizes a replica of the geometry created in the 3D mapping system making it more accurate when tagging AFD for ablation.

Limitations

One of the study limitations is the small patient numbers. Outcome data for a cohort of this size, whilst very encouraging should be viewed as pilot/feasibility data. The patient numbers are compatible to that of other proof of concept studies evaluating novel methods and technologies [9, 18-20].

To determine the mechanistic significance of potential AFD we necessarily focused on electrophysiological end points; since there is arguably no other way to verify that a driver has been mapped. Although termination of AF is clear, the importance of CL prolongation is less certain. Others have used termination of AF or CL prolongation as a surrogate for the interruption of mechanisms important for the maintenance of AF [9, 13 21 22 23 24]. In a patient who may have multiple potential drivers it would seem important to note any marked response to ablation. In defining a significant change in AF CL as ≥30ms we have used the most stringent criteria of any published study reporting AF CL. Nevertheless, even if we only confirmed as drivers those phenomena where AF terminated altogether, the results of this study would be very similar albeit with fewer confirmed drivers.

In this study, the inability to induce AF was not used as an endpoint due to the lack of clinical evidence of its importance in regard to clinical outcomes. However, this is something that would be interesting to evaluate in future studies.

Conclusions

Ablation guided by sequential STAR mapping was associated with AF termination in a majority of patients and produced an ablation response in all patients with short radiofrequency ablation times. This study lends further weight to the driver hypothesis for maintenance of AF and details a novel consecutive mapping approach to identification of AFD. The STAR mapping method can be applied using either global mapping with basket catheters or consecutive mapping with conventional multipolar mapping catheters; each may have advantages, but the results appear similar. The principles underlying STAR mapping consistently identified AFD when different mapping systems and catheters were utilized, and the most effective technique remains to be defined. Prospective randomized studies powered to assess long-term outcomes are needed to evaluate the clinical impact.

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Table 1. Baseline characteristics

Baseline characteristics	Cohort n=30
Age years mean ± SD	62.4±7.8
Male n (%)	23 (76.7)
Diabetes mellitus n (%)	0
Hypertension n (%)	5 (16.7)
TIA/CVA* n (%)	1 (3.3)
Ischemic heart disease n (%)	1 (3.3)
Cardiac surgery n (%)	0
Left ventricular EF† ≥ 50% n (%)	23 (76.7)
LA size cm^2 mean ± SD	25.8±5.2
LA volume ml mean ± SD	55.9±8.2
AF duration months mean ± SD	14.1±4.3
Current medical strategy n (%)	
Beta-blockers including Sotalol	13 (43.3)
Amiodarone	20 (66.7)
Flecainide	2 (6.7)
Anticoagulation therapy n (%)	
Warfarin	5 (16.7)
DOACs‡	25 (83.3)

*TIA/CVA- Transient ischemic event/Cerebrovascular accident
†EF- Ejection fraction
‡DOACs- Direct oral anticoagulants

Table 2. Summarizes the ablation response seen in the cohort of patients that underwent ablation guided by STAR mapping and the mechanism of the ATs mapped.

Ablation response n %	27
Termination to Sinus rhythm	7 (25.9)
Organization to AT	14 (51.9)
CL slowing ≥30ms	6 (22.2)
AT mapped n %	18*
Self-terminated	1 (5.6)
Mitral isthmus-dependent flutter	6 (33.3)
Roof-dependent flutter	2 (11.1)
Cavo-tricuspid isthmus-dependent flutter	3 (16.7)
LA Focal/micro reentrant	6 (33.3)
Mid anterior	4 (66.7)
Posterior-inferior	1 (16.7)
Mid roof	1 (16.7)

*1 AT mapped in 9 patients, 2 ATs mapped in 3 patients and 3 ATs mapped in 1 patient

Figure Legends:

Figure 1. Flow diagram summarizing the study findings.

Figure 2A-C.- Ai. Patient ID 16: STAR map in an AP view and **Aii.** Tilted roof view demonstrating an AFD mapped to the high anterior/roof. On this STAR map the recording segment that demonstrated the AFD that was targeted is only displayed. **Bi.** Rhythmia map in an

AP view and **Bii.** Tilted roof view demonstrating ablation at the AFD. **C-** Bard signals including surface ECG, CS, ablation and selected IntellaMap Orion catheter electrograms demonstrating **i)** AF termination to AT on ablation at the AFD and **ii)** with further consolidating lesions at AFD resulting in AT termination to sinus rhythm.

LUPV- Left upper pulmonary vein; RUPV- Right upper pulmonary vein; MVA- Mitral valve annulus

Figure 3A-C. Ai-ii. Patient ID 18: STAR map in a tilted roof view demonstrating **Ai.** an AFD mapped to the mid roof/RUPV and **Aii.** Roof/LAA. On this STAR map the recording segments that demonstrated the AFD with ablation response are only displayed. **B.** Rhythmia map in a roof view demonstrating ablation at both AFD (the blue tag highlights the site of intermittent organisation and yellow tag highlights site of termination to sinus rhythm). Ablation at an AFD mapped to the high anterior wall did not result in a study-defined ablation response. **Ci-ii.** Bard signals including surface ECG, CS, ablation and selected IntellaMap Orion catheter electrograms demonstrating **Ci-ii-** intermittent AF organization into AT during ablation at the AFD mapped to the mid roof/RUPV and CL slowing and **Cii.** Termination to sinus rhythm on ablation at the AFD mapped to the roof/LAA.

LUPV- Left upper pulmonary vein; RUPV- Right upper pulmonary vein

Figure 4A-F. A. Patient ID 20: STAR map in a tilted lateral view demonstrating an AFD mapped to the mid lateral wall. **Bi.** Rhythmia map in a titled lateral view demonstrating ablation at the AFD. **C.** Bard signals including surface ECG, CS, ablation and selected IntellaMap Orion catheter electrograms demonstrating AF termination to AT on ablation at the AFD. **Di-ii.**

Rhythmia LAT map in a **Di**. lateral valve view and **Dii**. PA view demonstrating a mitral isthmus tachycardia. **E.** Bard signals including surface ECG, CS, ablation and selected IntellaMap Orion catheter electrograms demonstrating AT with a CL of 240ms. **Fi-ii-** Bard electrograms demonstrating entraiment at Fi- CS with a PPI of 14ms and Fii- posterior wall with a PPI of 134ms; LUPV- Left upper pulmonary vein; LAA- Left atrial appendage; MVA- Mitral valve annulus

Figure 5A-C. A. Patient ID 23: Demonstrates a STAR LA map in an anterior-posterior view with an AFD identified mid anterior wall of the LA**. B.** This AFD was targeted with ablation as shown on the CARTO LA map in an anterior-posterior view. On this STAR map the recording segment that demonstrated this AFD is only displayed. **Ci-ii.** Ablation here resulted in AF termination from an AF to AT as shown on the Bard electrograms. The AT was mapped to a focal/micro-reentry AT in the close vicinity to the ablation lesions that organized the AF into AT. Further cluster ablation lesions at this site terminated the AT to sinus rhythm. The Bard electrograms include surface ECG, PV, Map and CS.

LAA- Left atrial appendage; MVA- Mitral valve annulus; RUPV- Right upper pulmonary vein

Figure 6A-D. A. Patient ID 21: Demonstrates a STAR LA map in a posterior-anterior view that highlights two AFD at the posterior wall in close vicinity to each other with the arrows demonstrating that the wavefront is spreading to away from each AFD in the opposite direction suggesting that a potential AF driver is present from which radial spread of activation occurs. This site was targeted with ablation that slowed the AF from ≥30ms and intermittently organized it. On this STAR map the two recording segments that demonstrated this wavefront activation pattern is only displayed. **B.** Demonstrates a STAR LA map in an anterior-posterior view that highlights an ESA at the mid anterior wall. On this STAR map the recording segment that demonstrated this AFD is only displayed. **C.** Ablation was performed at this site as shown on the EnSite Precision system LA map in an anterior-posterior view. **Di-ii.** Ablation here resulted in AF termination to an AT as shown on the Bard electrograms. **Diii.** The AT was mapped to roof dependent flutter and a roof line was ablated with a 10ms slowing in AT cycle length. Remap was suggestive of mitral isthmus dependent AT which was successfully ablated with a mitral line resulting in sinus rhythm as shown on the Bard electrograms. The Bard electrograms include surface ECG, PV, Map and CS.

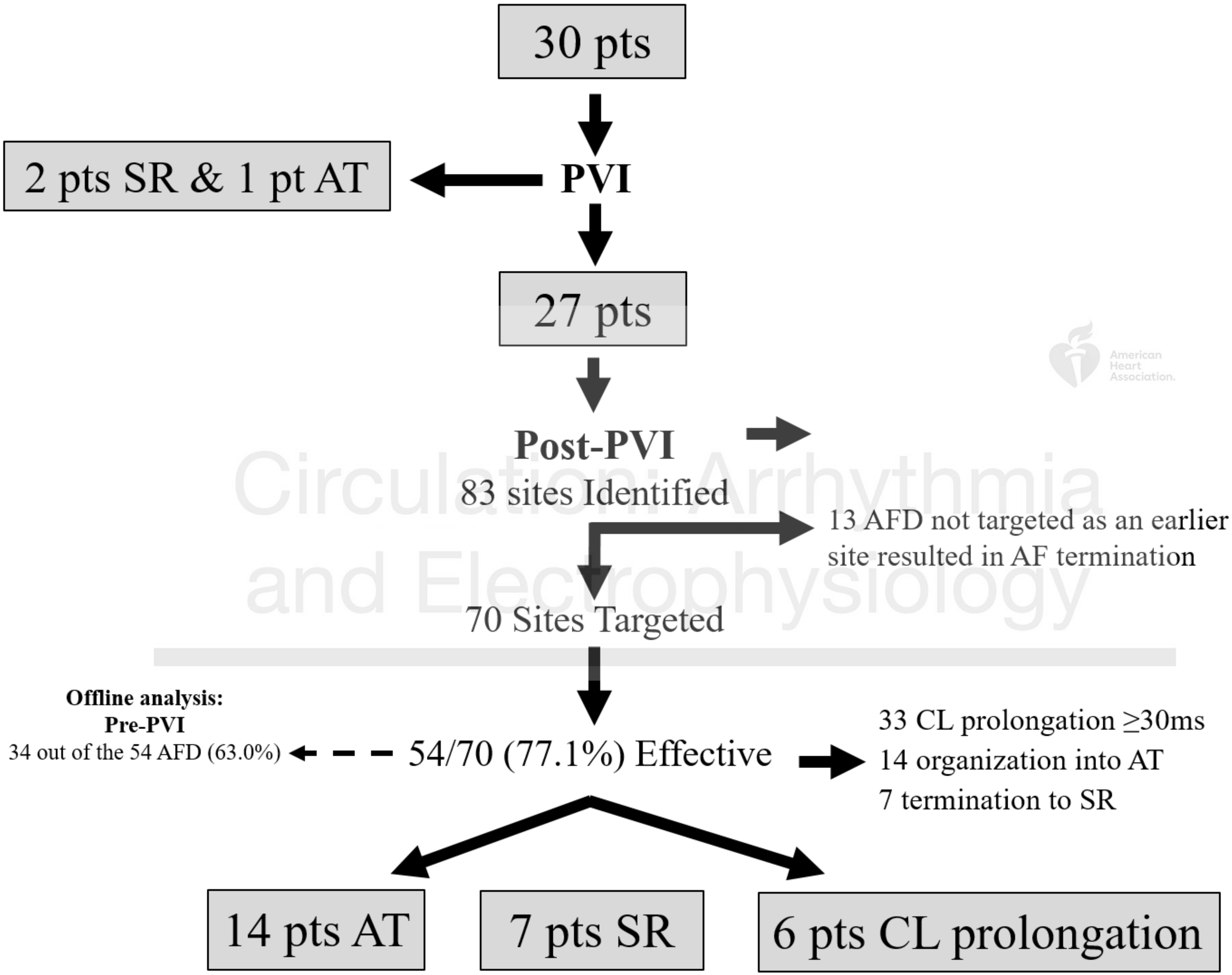
LUPV- Left upper pulmonary vein; MVA- Mitral valve annulus; RUPV- Right upper pulmonary vein

What Is Known:

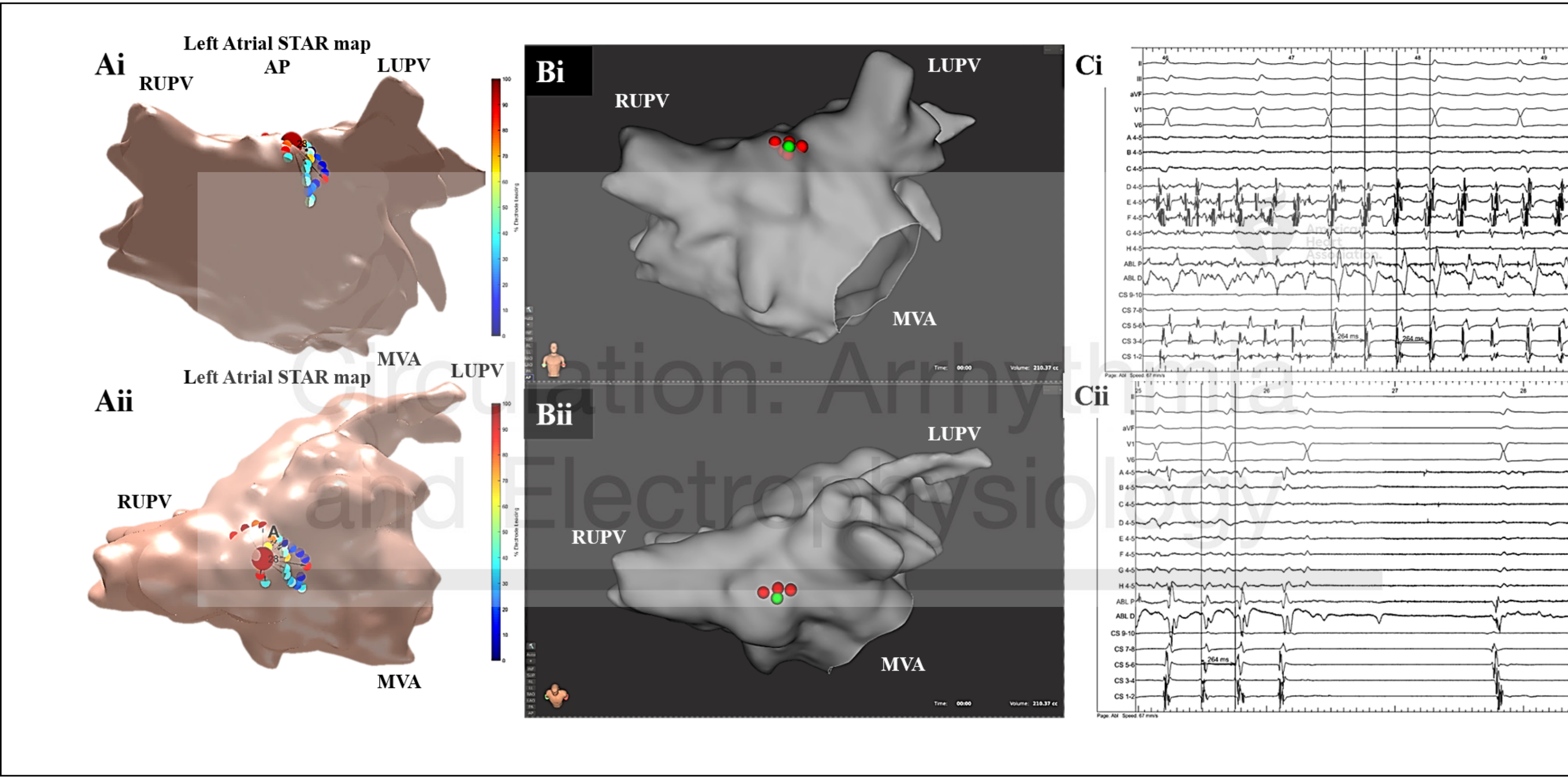
- Success rates of catheter ablation in persistent AF remains limited.
- A novel 'STAR' mapping approach to guide AF ablation using basket catheters recently showed high rates of AF termination and subsequent freedom from AF.
- However, sequential mapping of AF drivers has not been used prospectively to guide ablation.

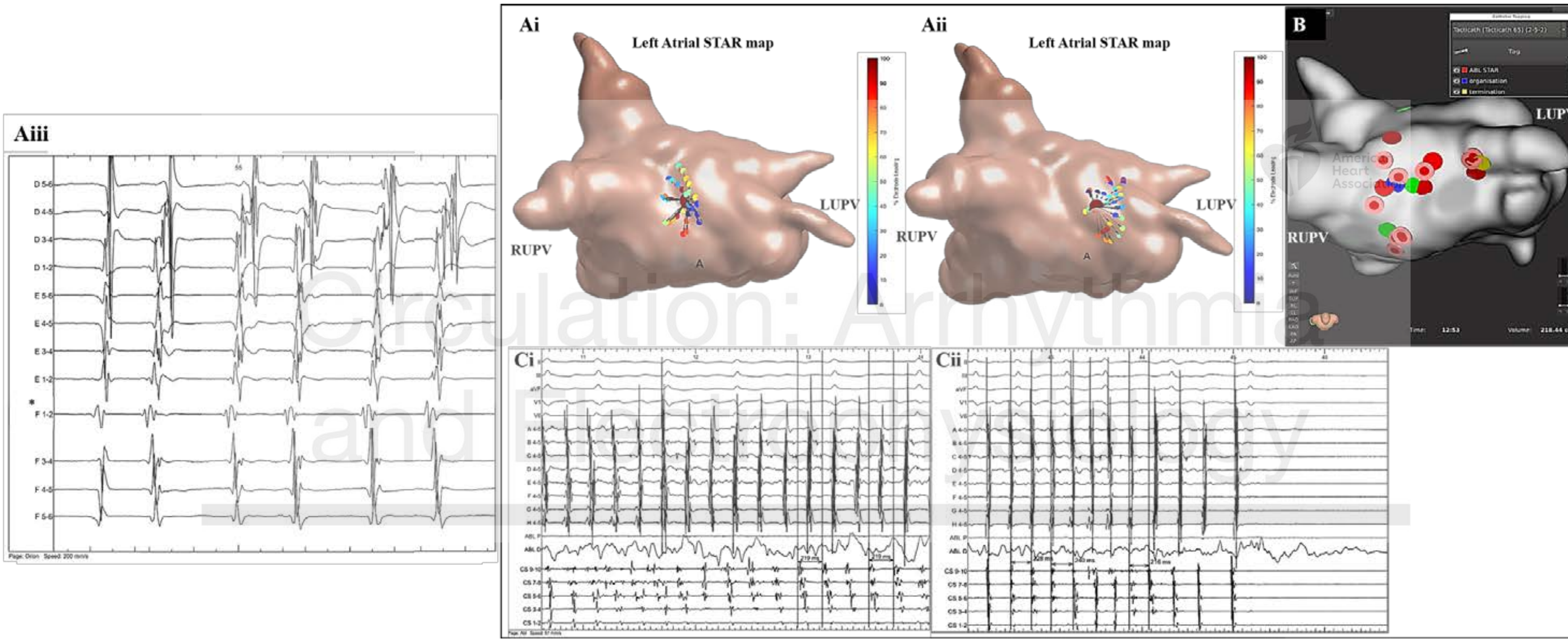
What the Study Adds:

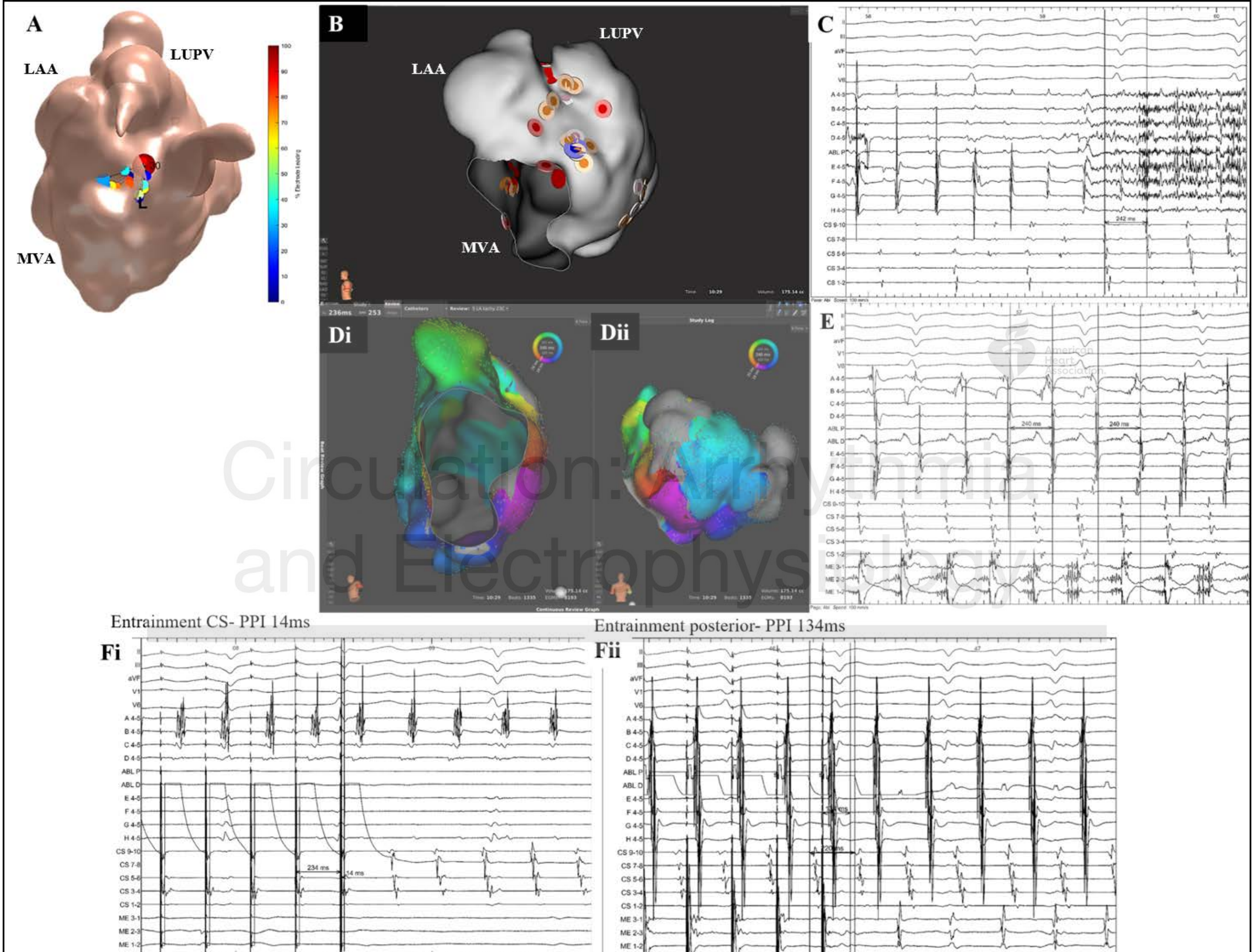
- This study has shown that AF drivers can effectively be identified using sequential mapping with the STAR mapping method.
- STAR mapping guided ablation was associated with a high freedom from AF/AT off anti-arrhythmic drugs at long-term follow-up.
- This study has demonstrated the clinical utility of the novel STAR mapping method in targeting AF drivers.



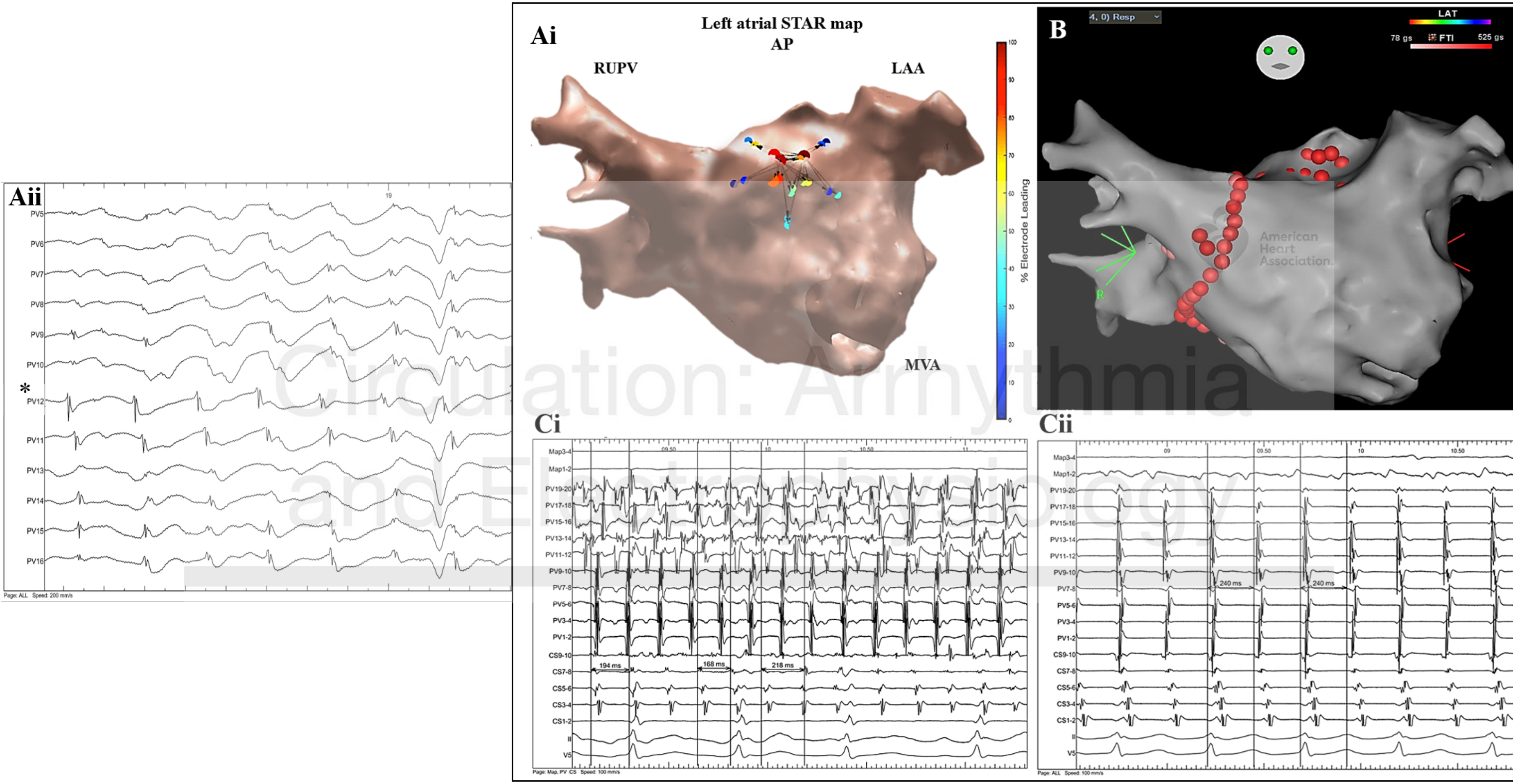
30 pts
PVI
2 pts SR & 1 pt AT
27 pts
Post-PVI
83 sites Identified
13 AFD not targeted as an earlier site resulted in AF termination
70 Sites Targeted
Offline analysis:
Pre-PVI
34 out of the 54 AFD (63.0%)
54/70 (77.1%) Effective
33 CL prolongation ≥30ms
14 organization into AT
7 termination to SR
14 pts AT
7 pts SR
6 pts CL prolongation

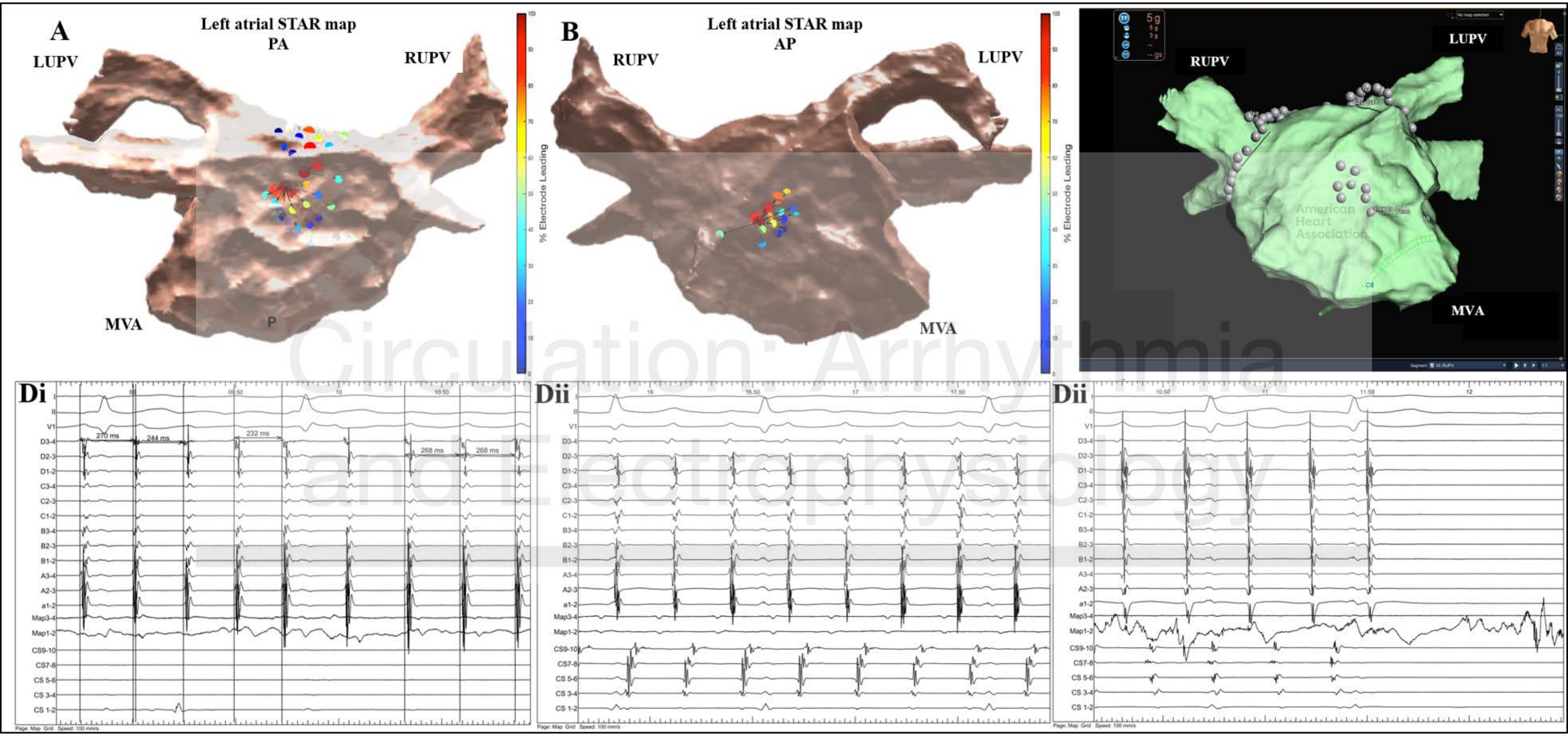

Left Atrial STAR map
Ai
RUPV
AP
LUPV
MVA
Left Atrial STAR map
Aii
LUPV
RUPV
MVA
Bi
LUPV
RUPV
MVA
Bii
LUPV
RUPV
MVA
Ci
Cii
264 ms


Ai
Left Atrial STAR map
LUPV
RUPV
Aii
Left Atrial STAR map
LUPV
RUPV
B
LUPV
RUPV
ABL STAR
organisation
termination
Aiii
Ci
Cii



A
LAA
LUPV
MVA
B
LAA
LUPV
MVA
C
242 ms
Di
Dii
E
240 ms
240 ms
Entrainment CS- PPI 14ms
Fi
234 ms
14 ms
Entrainment posterior- PPI 134ms
Fii

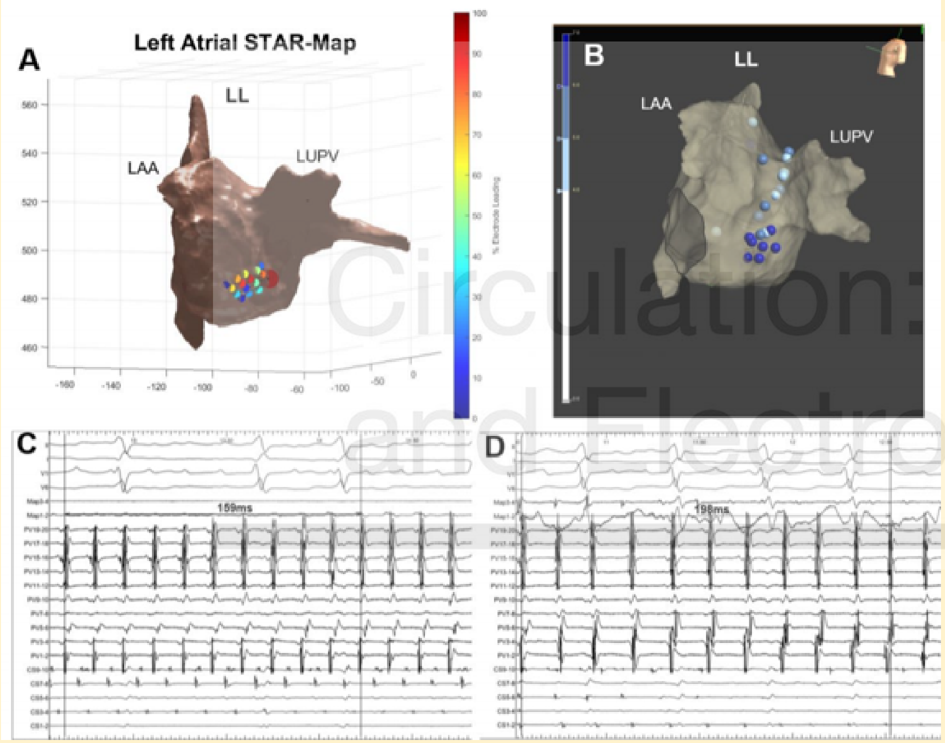

Ai
Left atrial STAR map
AP
RUPV
LAA
MVA
% Electrode Leading
B
LAT
78 gs
FTI
525 gs
Aii
PV5
PV6
PV7
PV8
PV9
PV10
*
PV12
PV11
PV13
PV14
PV15
PV16
Page: ALL Speed: 200 mm/s
Ci
194 ms
168 ms
218 ms
Page: Map, PV CS Speed: 100 mm/s
Cii
240 ms
240 ms
Page: ALL Speed: 100 mm/s



A
Left atrial STAR map
PA
LUPV
RUPV
MVA
B
Left atrial STAR map
AP
RUPV
LUPV
MVA
% Electrode Leading
RUPV
LUPV
MVA
Di
Dii
Dii
270 ms
244 ms
232 ms
268 ms
268 ms

Graphic Abstract

STAR MAPPING



PentaRay, IntellaMap Orion, or Advisor HD Grid catheters

- 27 persistent AF patients
- 83 potential AF Drivers (3.1±1.0 per patient) -70 targeted with ablation (2.6±1.0 per patient).
- Ablation response at 54 AF Drivers: 21 AF terminated and 33 CL slowed in all 27 patients.
- At 17.3±10.1 months, 22/27 (81.5%) free from AF/AT off anti-arrhythmic drugs