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Initial Independent Outcomes from Focal Impulse and Rotor Modulation Ablation for Atrial Fibrillation: Multicenter FIRM Registry

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Abstract

Introduction—The success of pulmonary vein isolation (PVI) for atrial fibrillation (AF) may be improved if stable AF sources identified by Focal Impulse and Rotor Mapping (FIRM) are also eliminated. The long-term results of this approach are unclear outside the centers where FIRM was developed; thus, we assessed outcomes of FIRM-guided AF ablation in the first cases at 10 experienced centers.

Methods—We prospectively enrolled $n = 78$ consecutive patients (61 ± 10 years) undergoing FIRM guided ablation for persistent ($n = 48$), longstanding persistent ($n = 7$), or paroxysmal ($n = 23$) AF. AF recordings from both atria with a 64-pole basket catheter were analyzed using a novel

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mapping system (Rhythm View™; Topera Inc., CA, USA). Identified rotors/focal sources were ablated, followed by PVI.

Results—Each institution recruited a median of 6 patients, each of whom showed 2.3 ± 0.9 AF rotors/focal sources in diverse locations. 25.3% of all sources were right atrial (RA), and 50.0% of patients had 1 RA source. Ablation of all sources required a total of 16.6 ± 11.7 minutes, followed by PVI. On >1 year follow-up with a 3-month blanking period, 1 patient lost to follow-up (median time to 1st recurrence: 245 days, IQR 145–354), single-procedure freedom from AF was 87.5% (patients without prior ablation; 35/40) and 80.5% (all patients; 62/77) and similar for persistent and paroxysmal AF ($P = 0.89$).

Conclusions—Elimination of patient-specific AF rotors/focal sources produced freedom-from-AF of $\approx 80\%$ at 1 year at centers new to FIRM. FIRM-guided ablation has a rapid learning curve, yielding similar results to original FIRM reports in each center's first cases.

Keywords

atrial fibrillation; catheter ablation; FIRM-guided ablation; rotors; focal impulse

Introduction

Atrial fibrillation (AF) is a major public health problem that causes morbidity from palpitations, reduced exercise tolerance, stroke, and even death.¹ However, medical therapy to limit ventricular rate in AF² and to maintain sinus rhythm^{3,4} has been disappointing. Catheter ablation to eliminate arrhythmogenic tissue shows promise, but its success in AF has been limited in part by mechanistic uncertainty due to difficulties in mapping AF.^{5–7} AF ablation thus currently isolates potential triggers in the pulmonary veins (PV) and other regions,⁸ or targets unclearly defined electrical substrates using lines or ablation of complex fragmented atrial electrograms, with a single procedure 1-year success of ≈ 50 – 60% for paroxysmal AF^{9–12} and lower success for persistent AF.⁷

It has recently been shown^{13,14} that human AF, after it has been triggered,^{15,16} is sustained by the electrical substrates of spiral waves (rotors) and focal sources that are sufficiently stable to be eliminated by localized ablation (Focal Impulse and Rotor Modulation, FIRM). In the CONFIRM trial (CONventional ablation for AF with or without FIRM), elimination of sources and conventional ablation improved freedom from AF to 82.4% from 44.9% by conventional ablation alone in patients with persistent and paroxysmal AF¹³ that has recently been confirmed at 3 years.¹⁷ However, the efficacy of FIRM-guided ablation is unclear outside these initial centers.

We performed a prospective registry study of FIRM mapping and ablation at 10 centers new to the technique. We set out to define, acutely, whether AF rotors and focal sources on FIRM-mapping lay near or remote from conventional PV targets and, long-term, to establish the outcome from FIRM-guided ablation in patients with paroxysmal and persistent AF by centers early in their learning experience.

Methods

Patient Enrollment

We report 78 consecutive patients undergoing FIRM-guided AF mapping and ablation in the 1-year period from November 30, 2011 to November 29, 2012. These were the first FIRM cases at 10 experienced U.S. ablation centers: Indiana University School of Medicine; Heart Place, Baylor University Medical Center, Dallas, TX; Arizona Heart Institute, Phoenix, AZ; Duke University Medical Center, Durham, NC; Ohio State University, Columbus, OH; Intermountain Heart Institute, Murray, UT; Medical College of Virginia, Richmond, VA; Mount Sinai Medical Center, NY; UCLA Cardiac Arrhythmia Center, Los Angeles, CA; and Valley Health System, Ridgewood, NJ. Patients from the Veterans' Affairs and University of California Medical Centers, San Diego (where FIRM was developed), were intentionally excluded from this report. The acute response to FIRM-only ablation in the first $n = 14$ patients has been reported.¹⁴

We enrolled patients with paroxysmal, persistent, and longstanding persistent AF referred for standard indications.⁷ Enrollment was performed in consecutive patients studied during the initial learning-phase availability of FIRM mapping and ablation, many of whom had failed conventional ablation ($n = 38$). Left atrial diameter was assessed by intracardiac echocardiography or preprocedural imaging and, although diameter <55 mm was suggested since the largest basket has diameter 55–60 mm when fully deployed, patients' atria were often larger (Table 1). All patients provided written informed consent, with data inclusion approved by the IRB at each center. The registry includes data recorded at each FIRM-procedure, with follow-up data provided by each site to the writing group (JMM, RCK, SMN, KS).

Procedural Details

Procedures were performed >5 half-lives after discontinuing antiarrhythmic medications except amiodarone (Table 1). Via femoral venous access, a multipolar catheter was placed in the coronary sinus and a 64-pole basket catheter (Constellation, Boston Scientific Inc., Natick, MA, USA, 48 or 60 mm diameter) was advanced to right then left atrium via 8.5 F sheaths.¹³ Fluoroscopy, electrography, and intracardiac echocardiography (according to investigator preference) were used to achieve optimal contact.¹⁸ Heparin was administered by infusion routinely to maintain ACT >300 seconds. Mapping could not be performed in 2 patients due to technical issues with cabling, so acute data are reported in 76 patients with intention-to-treat follow-up reported in all 78 patients.

We mapped spontaneous AF, or AF induced by rapid atrial pacing (e.g., cycle lengths [CL]: 500, 450, 400, 350, 300 milliseconds, then in 10 milliseconds steps to AF) with isoproterenol in a minority of cases as described.¹³ Sustained AF was achieved in all $n = 76$ mapped patients, and analyzed after >5 minutes for stabilization of AF. Unipolar electrograms were filtered at 0.05–500 Hz and exported digitally from electrophysiological recorders at each site for analysis on RhythmView™ (Topera, Palo Alto, CA, USA).

AF Mapping and Definition of Stable AF Sources

The FIRM-mapping and ablation workflow was consistent for all sites in the registry, and is shown in Figure 1A. Three-dimensional basket catheters were placed successively in each atrium (Fig. 1B) to record AF electrograms that were exported for analysis. The FDA-approved RhythmView™ console (Topera Inc.) comprises a workstation with analytic software that applies computational approaches^{18,19} to create an activation trail that can identify AF rotors or focal sources within the atria.^{18–20} The system performs an assessment of electrogram quality based primarily upon atrial signal amplitude above noise, and represents lack of signal as black. Basket repositioning was recommended to optimize basket contact in cases with very large atria or if regions of interest had no signals. AF propagation maps from contact recordings were projected onto 2D grids aligned to atrial anatomy (Fig. 1B).

AF maps were used to diagnose *sustained rotors* if observed on multiple epochs (1-minute recording segments) spanning several minutes (typically >10 minutes). The core regions of AF sources are spatially reproducible within precession areas of 1–2 cm² for prolonged periods of time as described^{20,21} (i.e., bounded by ≈2 electrodes in each axis) with spiral arms that emanate and disorganize (fibrillatory conduction). AF focal sources were diagnosed if they showed centrifugal activation from an origin to surrounding atrium, also with peripheral disorganization and also in multiple recordings typically for >10 minutes.¹³ The ablation target was defined by the source precession area. Map interpretation and ablation were performed by the operator at each site.

Focal Impulse and Rotor Modulation (FIRM) Ablation

Ablation commenced with FIRM at sources identified from AF maps at all centers. Ablation was performed per investigator preference using various energy sources: 3.5-mm tip irrigated radiofrequency catheter (ThermoCool™, Biosense-Webster, Diamond Bar, CA, USA; Safire Blu™, St. Jude Medical, Minnetonka, MN, USA) at 25–40 W, a cryoballoon at sources near the PV antra in n = 2 cases (Arctic Front, Medtronic, MN, USA) or by an 8-mm nonirrigated radiofrequency catheter (Blazer, Boston Scientific, Sunnyvale, CA, USA) at 40–50 W, 52 °C target temperature. Ablation was applied to the basket grid coordinates of the center of rotation or focal impulse origin (≈2 cm² areas²⁰), identified either from fluoroscopy or from electrode positions on electroanatomic shells. Ablation continued until the source area was covered and sources were eliminated on repeat FIRM maps.

Conventional ablation for all patients in this registry followed guidelines,⁷ was performed *after* FIRM ablation was completed and comprised wide-area antral PV isolation verified using a circular catheter (Lasso™; Biosense-Webster or Optima™, St. Jude Medical). Additional ablation included a left atrial roof line in persistent AF patients, and ablation of observed clinically relevant atrial tachycardias or flutters. Ablation power, temperatures, and duration were as noted above. If AF persisted after completion of the ablation protocol, cardioversion was used to restore sinus rhythm.

Postprocedure Clinical Management

Follow-up for arrhythmia recurrence followed guidelines²² at each center. In the first 3 months postablation, antiarrhythmic medications were permitted but repeat ablation was not. Subjects were followed for >1 year, with no repeat procedures. The follow-up time censored at first recurrence was 245 days (IQR 145–354). Arrhythmia recurrence in this registry was detected by symptoms and event monitors to coincide with clinic visits, and also event monitoring at interim intervals at the time of symptoms as in other recent studies.

Study Endpoints

The primary long-term efficacy endpoint was freedom from AF, defined as AF >30 seconds on intermittent monitors.²² Secondary efficacy measures included outcomes in patients at first ablation, freedom from all atrial arrhythmias, and freedom from AF in patients with paroxysmal versus persistent AF. Patients were followed for 1 year after the single ablation procedure with a 3-month blanking period and no repeat procedures. Follow-up was censored at the first arrhythmia recurrence or last arrhythmia-free clinic visit, whichever came first (median time 245 days, IQR 145–354), with 1 patient lost to follow-up.

Statistical Analysis

Continuous data are represented as mean \pm standard deviation (SD). The Student's *t*-test was used to compare continuous variables between 2 groups, such as ablation time. Paired continuous variables were compared using linear regression and the paired *t*-test. The chi-square test was applied to contingency tables for categorical variables. Log-rank test was used to compare survival distributions. A *P* value of < 0.05 was considered statistically significant.

Results

Clinical characteristics of our population are summarized in Table 2, representing the first 6 (median) FIRM-guided cases in each institution. There was no significant difference in the characteristics of patients undergoing repeat versus first AF ablation. In Table 2, patients with persistent AF had lower LVEF, a higher remote use of amiodarone prior to ablation and a trend for larger left atria than those with paroxysmal AF. For technical connectivity issues, FIRM mapping was not completed in the first FIRM-guided ablation case at each of 2 institutions (*n* = 2 cases), who were followed on an intention-to-treat basis.

Acute Results from FIRM Mapping and Ablation

AF sources were detected in 100% of patients in whom FIRM mapping was performed (76/76), or 97.4% (76/78) by intention-to-treat (2 patients were not mapped). Sources were spatially stable across multiple FIRM maps (Table 3).

Each patient had an average of 2.3 ± 0.9 concurrent rotors or focal sources (total of 174), with 1.8 ± 0.7 left atrial sources per patient and 1.1 ± 0.3 right atrial sources per patient. Notably, right atrial sources comprised 25.3% of the total, and 39/78 (50%) of patients showed at least 1 right atrial source (Table 3). Sources were predominantly rotors (172/174, 98.9%), with 1.1% focal sources (all of which lay in the left atrium). There was a

nonsignificant trend towards more AF sources in those in whom a prior ablation had been done ($P = 0.08$) but no significant differences in numbers or right/left atrial distribution of sources.

Figure 2 summarizes the distributions of AF sources within the atria in patients with paroxysmal AF ($n = 24$, 51 sources; Fig. 2A) and persistent AF ($n = 54$, 123 sources; Fig. 2B), as proportions of all detected sources. Sources were often remote from conventional PV ablation targets. From these source distributions, the estimated number of AF sources that may have been ablated coincidentally by wide area PVI with posterior wall ablation was $\approx 49\%$ in paroxysmal AF, and $\approx 41\%$ in persistent AF.

Total ablation time required to eliminate these sources was 16.6 ± 11.7 minutes, typically in both atria in each patient. There was no significant difference between the populations at first and repeat procedure in the ablation time required to eliminate right and left atrial sources in each patient.

No procedural complications occurred, and specifically neither thromboemboli nor perforations from use of the basket catheter, in agreement with prior reports.¹³

Long-Term Outcome After FIRM-Guided Ablation

After 1-year follow-up, Figure 3 presents Kaplan–Meier curves showing that the single procedure freedom from AF was 80.5% (62/77) for all patients, and 87.5% in patients with no prior ablation (35/40; $n = 32$ persistent/longstanding persistent). In Figure 4, single procedural freedom from all atrial arrhythmias was 71.4% (55/77) for all cases and 75% (30/40) in patients undergoing their first ablation ($n = 40$; $n = 32$ persistent/longstanding persistent). Antiarrhythmic medications were continued at last follow-up due to physician or patient preference in $n = 13$ patients without arrhythmia recurrence and 7 with arrhythmia recurrence (i.e., counted as failures) for 20 overall. For the entire population, the proportions of patients who remained on antiarrhythmic drugs did not differ between persistent and paroxysmal AF (15/54, 27.8% vs. 5/24, 20.8%, $P = 0.59$, Fisher's exact test) or between first ablation and redo cases (9/40, 22.5% vs. 11/38, 28.9%, $P = 0.51$ chi-square test), respectively.

Figure 5 presents Kaplan–Meier curves showing that single procedural freedom from AF did not differ significantly between patients with persistent AF (44/54, 81.5%) and paroxysmal AF (18/23, 78.3%; $P = 0.89$).

Discussion

The FIRM-registry provides the first prospective multi-center data on long-term outcomes from FIRM-guided ablation for AF. In this learning experience at each center, the single FIRM-guided procedural elimination of AF was 80.5% for all patients and 87.5% in patients at first ablation, in a population mostly of persistent AF. The number of stable concurrent AF sources in each patient and long-term results from FIRM-guided ablation were similar to those reported in the original CONFIRM trial although the proportion of rotors to focal sources was higher in this registry. Notably, unlike almost all prior AF ablation trials,

FIRM-guided ablation had similar success in this registry for patients with persistent or paroxysmal AF. These data further support the predominant mechanistic role of rotors in sustaining AF across a wide range of presentations, and show that successful elimination of patient-specific sources can be achieved after a short learning curve to achieve a high level of arrhythmia freedom on follow-up.

Comparison of FIRM-Guided Outcomes with Previous Published Reports

This first independent validation of FIRM-guided AF ablation yielded similar results to the CONFIRM trial.¹³ Freedom from AF and atrial arrhythmias in patients at first ablation were actually slightly higher than in the CONFIRM trial, despite the fact that these were the first cases performed at each center.

A limitation of this study is the absence of a control group receiving conventional ablation alone, which will be addressed in recently started multicenter randomized controlled trials. However, the 1-year single FIRM-guided procedural AF freedom in this study (80.5%) is higher than the $\approx 50\%$ single-procedure success of conventional ablation in recent reports of paroxysmal AF,^{9–12} $<40\text{--}50\%$ in persistent AF⁷ or $40\text{--}50\%$ in mixed populations in CONFIRM¹³ and other experienced groups.²³ Single FIRM-procedural freedom from all atrial arrhythmias was also higher than prior studies, although many prior trials did not report this endpoint for comparison.^{10,11} The mode of recurrence of AF or tachycardias after FIRM-guided ablation remain unclear at this point, since only a minority of patients have been repeat FIRM mapped (and none in this series), but this is under active investigation.

Comparison of Results with Prior Reports of Rotors

The numbers of AF sources in this study were similar to those reported in the CONFIRM trial,¹³ and were similar between patients at their first ablation and those with AF despite prior conventional ablation (Table 3). The predominance of rotors and lower prevalence of focal sources in this multicenter registry compared to the CONFIRM trial¹³ may reflect improved RhythmView™ software, or differences in interpretive experience or patients between centers, and should be tracked in ongoing studies of FIRM³⁹ at other centers. The diverse locations of AF sources including the right atrium (Fig. 2) may explain why ablation success rises with extensive empirical ablation lesions, which have been shown to coincidentally ablate AF rotors and focal sources in prior studies.²⁴

Several groups have recently investigated sources for human AF using diverse techniques including Shannon entropy²⁵ or wave similarity analysis²⁶ during conventional mapping, suggesting sufficient stability to be detected by detailed point-by-point mapping. Studies of virtual electrograms from the inverse solution initially reported very few and short-lived AF rotations,²⁷ although newer analytic methods reveal rotors with this approach that are described as unstable yet remain in the same atrial area for days and are targeted by localized ablation.²⁸ Studies are needed to define how these reports differ from FIRM, which uses specific physiologically directed algorithms to track spatially precessing rotors with spiral arm disorganization via fibrillatory conduction.^{18–21} To date, this study and the CONFIRM trial are the only reports of long-term outcomes from the FIRM-guided approach to rotor elimination.

Localized Sources as a General Mechanism for AF

FIRM-guided ablation produced highly unusual similar success for patients with paroxysmal and persistent AF, in contrast to nearly all prior studies showing lower success for persistent versus paroxysmal AF.⁷ Patients with paroxysmal and persistent AF differed in anticipated parameters (Table 2), with left atria sizes in both groups measured by intracardiac echocardiography or preprocedural MRI that may produce higher values than transthoracic echocardiography. These results support the concept that rotors and focal sources are a central AF-sustaining mechanism for a range of AF presentations, with the caveat that the study is relatively small. Further studies are required to test if outcomes remain similar between groups over longer follow-up periods.

The localized source model for AF has gained ground in recent years, based on elegant animal models in which spiral waves (rotors)^{29,30} or repetitive focal impulses³¹ cause extremely disordered surrounding activation (so-called “fibrillatory conduction”) that hampers their detection by simple activation or phase mapping. Stable AF sources readily explain clinical observations that AF exhibits conserved nonuniformities in rate and activation vector,^{32–34} and why ablation can in some cases rapidly terminate AF^{13,14,35} before PVs have been isolated.

Limitations

The first major limitation is the absence of a control group undergoing conventional ablation alone, although this information can be estimated by several recent trials of conventional ablation that produce lower success than by FIRM-guided ablation. Second, this study has the typical limitations of a registry design, including variations in guideline-driven conventional ablation between investigators. Follow-up was less rigorous than the CONFIRM trial, yet followed clinical guidelines and was analogous to many recent AF trials. As in any multicenter experience, some groups provided few patients. A resulting strength of these limitations, however, is that the study shows a rapid learning curve with FIRM-guided ablation results in a “real-world” experience similar to those of the CONFIRM trial. This contrasts with some approaches that have been difficult to extend beyond the originating center.^{36–38}

The freedom from AF observed in cases of prior failed ablation in our study may theoretically reflect the impact of those lesions (“cleaning up” prior ablation). However, few series report success rates at this level, and were higher in patients undergoing their first ablation than those undergoing repeat ablation after a prior failed procedure.

FIRM-guided ablation still presents several limitations. Many patients had atria larger than current basket catheters (55–60 mm diameter fully deployed), using accurate intraprocedural imaging, which almost certainly limited efficacy. Two patients were not mapped due to technical issues that were resolved with experience, and one patient was lost to long-term follow-up. Notably, despite the lack of prior experience with the basket catheter at many centers, no complications were reported. By limiting ablation within the atrium, it is reasonable to hope that FIRM mapping (if used as a primary approach) may increase the safety of ablation. This requires further testing.

Conclusions

In this multicenter learning curve experience of FIRM mapping, mapping and elimination of patient-specific rotors and focal sources with trigger isolation provided >80% single procedure AF elimination in patients predominantly with persistent AF. These acute and chronic results were similar to those originally reported from FIRM by the originating group. FIRM-guided ablation for AF thus has a rapid learning curve at experienced ablation centers, and may help to improve outcomes for ablation of this troublesome arrhythmia.

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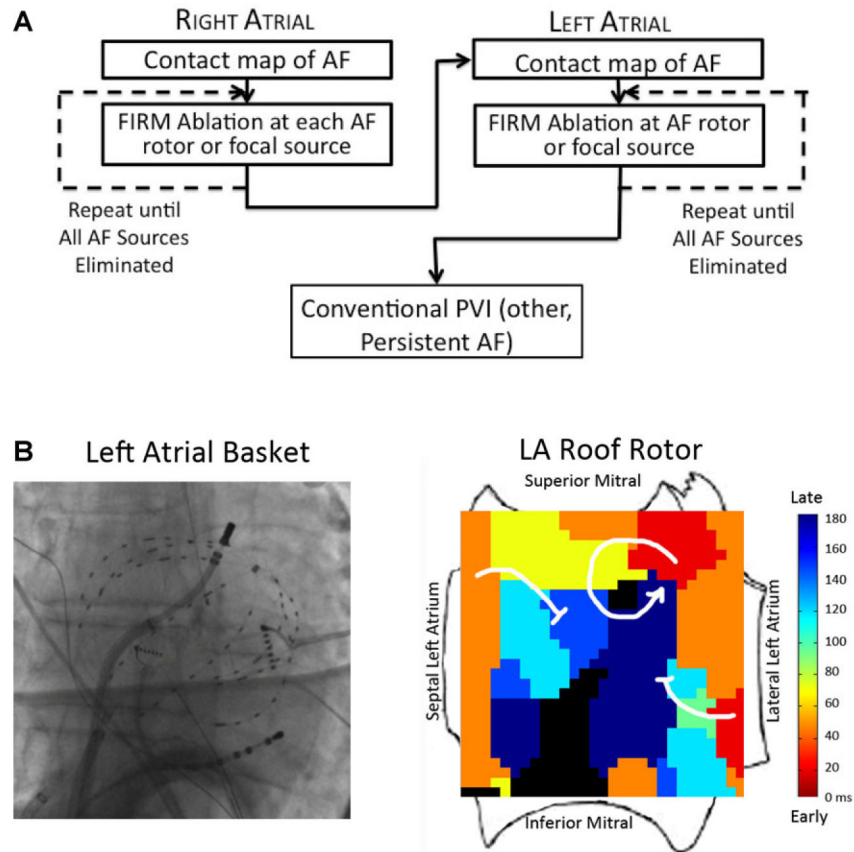


Figure 1.

(A) Workflow for FIRM-guided ablation of AF. (B) Typical basket placement and results from FIRM-guided ablation. Basket placed in left atrium, with resulting FIRM map showing AF rotor at roof with surrounding spiral arms disorganizing and fusing with the fibrillatory milieu (blocked arrows) and rotor precession within a limited area on successive cycles (not shown).

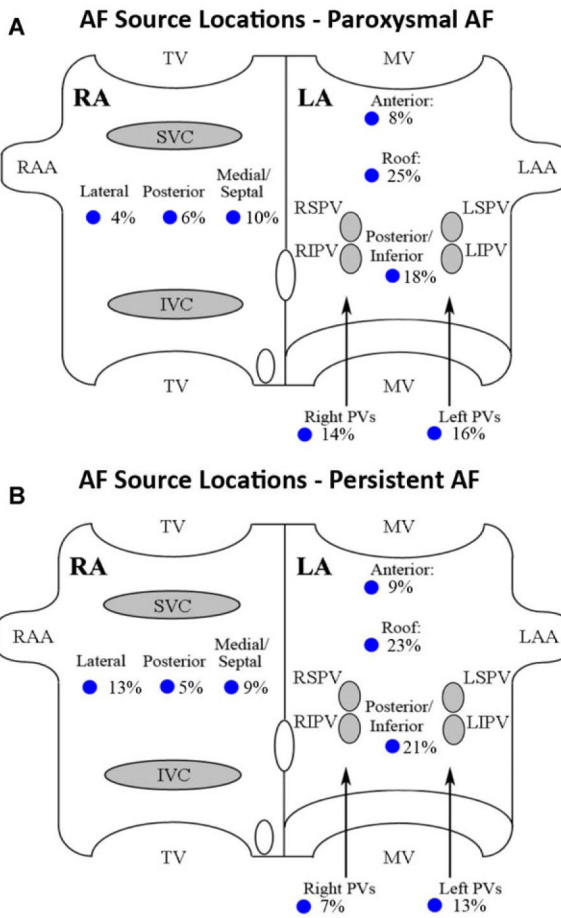


Figure 2.
AF source locations in both atria for patients with (A) paroxysmal and (B) persistent AF.

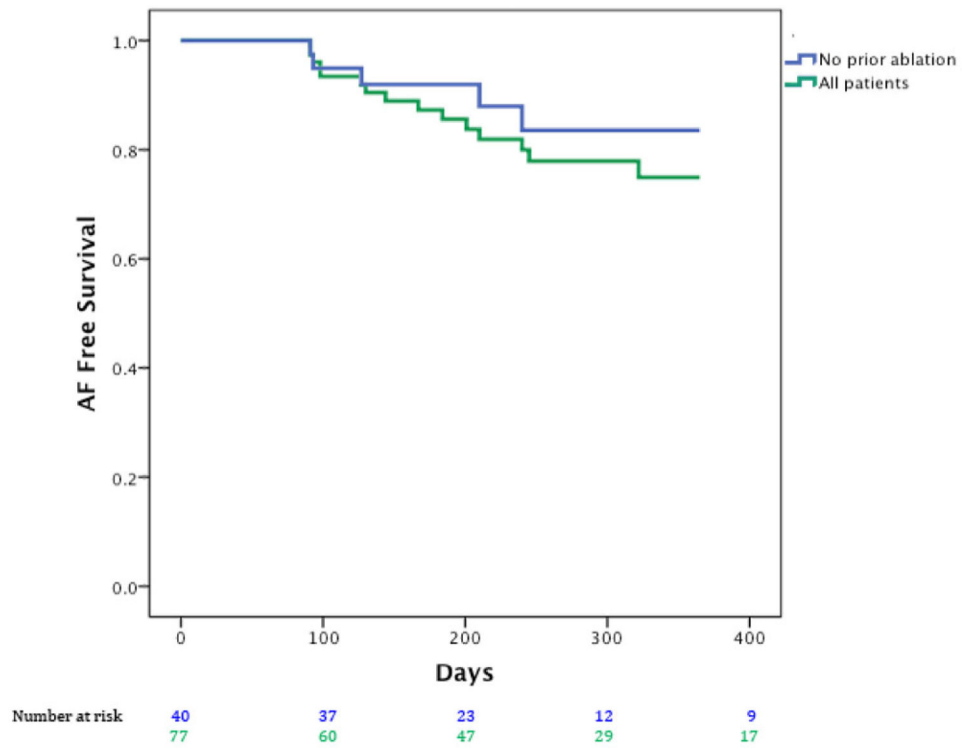


Figure 3. Freedom from atrial fibrillation after single (index) FIRM + PVI procedure for all cases (green) and patients at their first ablation (blue).

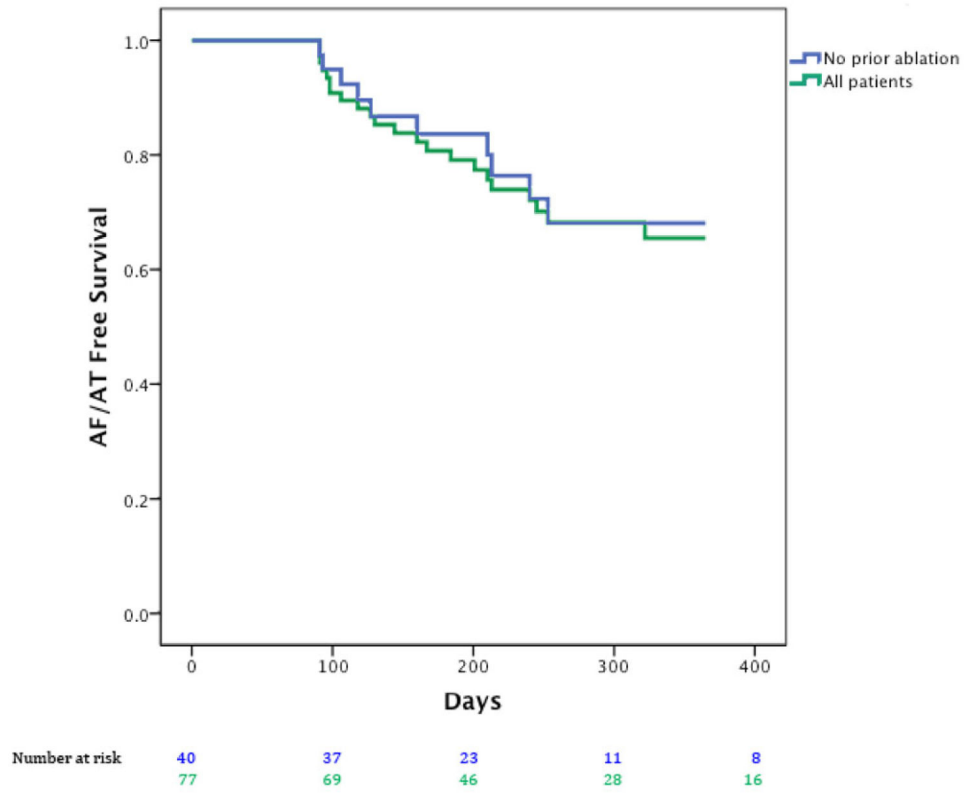


Figure 4. Freedom from all atrial arrhythmias (atrial fibrillation and atrial tachycardia) after a single (index) FIRM + PVI procedure for all cases (green) and patients at their first ablation (blue).

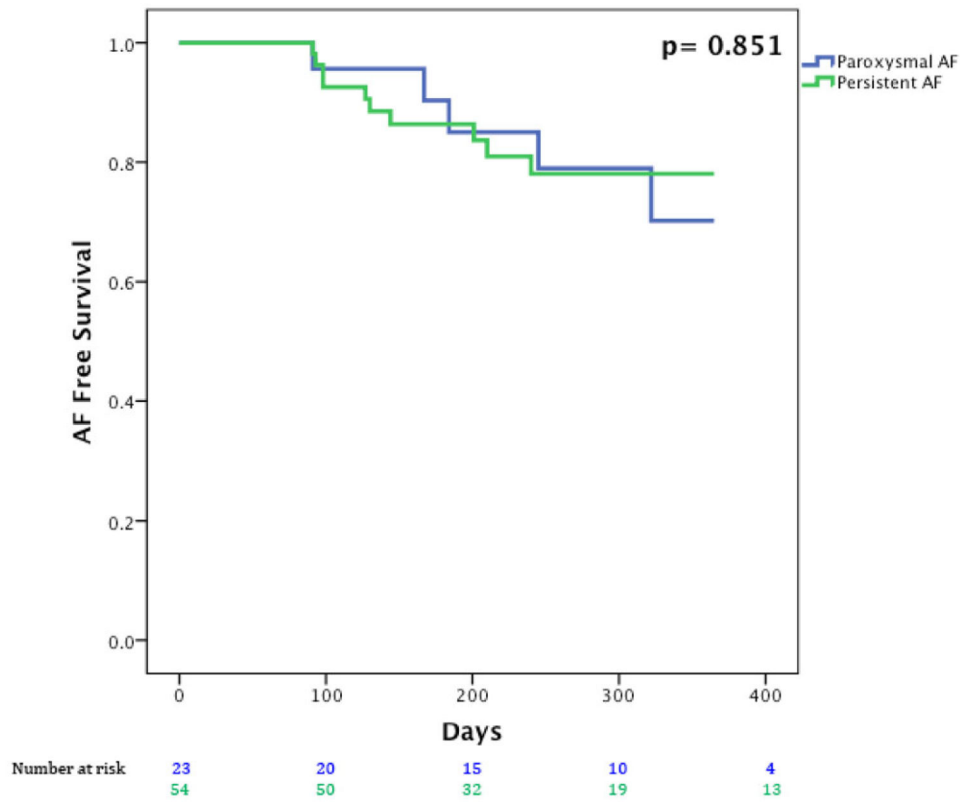


Figure 5. Freedom from atrial fibrillation after a single index FIRM + PVI procedure for patients with paroxysmal AF in blue and persistent AF (including longstanding persistent AF) in green.

TABLE 1

Clinical Characteristics of Population

Characteristic	All Patients	First Ablation	Prior Failed PVI	P value
Number of patients	78	40	38	
AF type (N [%])				0.10
Paroxysmal	24 (29.5%)	8 (20.0%)	16 (39.5%)	
Persistent	47 (61.5%)	28 (70.0%)	19 (52.6%)	
Longstanding persistent	7 (9.0%)	4 (10.0%)	3 (7.9%)	
Age (years)	61.3 ± 10.1	61.6 ± 10.9	60.9 ± 9.4	0.77
Gender (Male/female)	55/23	28/12	27/11	0.55
Left atrial diameter (mm)	56 ± 9	56 ± 9	57 ± 10	0.78
No. with LA >55 mm (%)	38 (50.4%)	18 (45%)	20 (52.6%)	0.43
LVEF (%)	55 ± 8	54 ± 8	56 ± 8	0.28
Remote amiodarone use (N [%])	12 (15.4%)	5 (12.5%)	7 (18.4%)	0.47

AF = atrial fibrillation; PVI = pulmonary vein isolation; LA = left atrium; LVEF = left ventricular ejection fraction; Remote amiodarone = prior treatment with amiodarone. P value for AF type was assessed by Fisher's test with Freeman-Halton extension.

TABLE 2

Clinical Characteristics of Patients with Persistent and Paroxysmal AF

Characteristic	All Patients	Paroxysmal AF	Persistent AF	P value
Number of patients	78	24	54	
Age (years)	61.3 ± 10.1	60.6 ± 10.4	61.6 ± 10.1	0.71
Gender (male/female)	55/23	16/8	39/15	0.79
Left atrial diameter (mm) (intracardiac echocardiogram)	56 ± 9	53 ± 7	58 ± 10	0.06
No. with LA >55 mm (%)	38 (50.4%)	8 (33%)	30 (55.6%)	0.09
LVEF (%)	55 ± 8	58 ± 6	54 ± 8	0.04
Remote amiodarone use (N [%])	12 (15.4%)	0 (0.0%)	12 (22.2%)	0.01

TABLE 3

Acute Characteristics of AF Sources

Characteristic	All Patients N = 78	First Ablation N = 40	Prior Failed PVI N = 38	P value
Patients mapped	76	38	38	
Patients with detected sources	76/76 (100%)	38/38 (100%)	38/38 (100%)	1.0
No. patients with sources in LA vs RA	71/39	35/16	36/23	–
No. concurrent biatrial AF sources/patient	2.3 ± 0.9	2.1 ± 0.8	2.4 ± 0.9	0.08
No. of LA sources/patient	1.8 ± 0.7	1.8 ± 0.6	1.9 ± 0.8	0.49
No. of RA source/patient	1.1 ± 0.3	1.1 ± 0.3	1.1 ± 0.3	0.96
LA/RA sources, as % of total sources	74.7%/25.3%	76.8%/23.2%	73.8%/26.2%	0.63
Total FIRM-ablation time, all sources (min, Mean ± SD)	16.6 ± 11.7	14.7 ± 11.3	18.5 ± 11.8	0.20

AF = atrial fibrillation; LA = left atrium; RA = right atrium.