

EXPEDITED PUBLICATIONS

Treatment of Atrial Fibrillation by the Ablation of Localized Sources

CONFIRM (Conventional Ablation for Atrial Fibrillation With or Without Focal Impulse and Rotor Modulation) Trial

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- Objectives** We hypothesized that human atrial fibrillation (AF) may be sustained by localized sources (electrical rotors and focal impulses), whose elimination (focal impulse and rotor modulation [FIRM]) may improve outcome from AF ablation.
- Background** Catheter ablation for AF is a promising therapy, whose success is limited in part by uncertainty in the mechanisms that sustain AF. We developed a computational approach to map whether AF is sustained by several meandering waves (the prevailing hypothesis) or localized sources, then prospectively tested whether targeting patient-specific mechanisms revealed by mapping would improve AF ablation outcome.
- Methods** We recruited 92 subjects during 107 consecutive ablation procedures for paroxysmal or persistent (72%) AF. Cases were prospectively treated, in a 2-arm 1:2 design, by ablation at sources (FIRM-guided) followed by conventional ablation (n = 36), or conventional ablation alone (n = 71; FIRM-blinded).
- Results** Localized rotors or focal impulses were detected in 98 (97%) of 101 cases with sustained AF, each exhibiting 2.1 ± 1.0 sources. The acute endpoint (AF termination or consistent slowing) was achieved in 86% of FIRM-guided cases versus 20% of FIRM-blinded cases ($p < 0.001$). FIRM ablation alone at the primary source terminated AF in a median 2.5 min (interquartile range: 1.0 to 3.1 min). Total ablation time did not differ between groups (57.8 ± 22.8 min vs. 52.1 ± 17.8 min, $p = 0.16$). During a median 273 days (interquartile range: 132 to 681 days) after a single procedure, FIRM-guided cases had higher freedom from AF (82.4% vs. 44.9%; $p < 0.001$) after a single procedure than FIRM-blinded cases with rigorous, often implanted, electrocardiography monitoring. Adverse events did not differ between groups.
- Conclusions** Localized electrical rotors and focal impulse sources are prevalent sustaining mechanisms for human AF. FIRM ablation at patient-specific sources acutely terminated or slowed AF, and improved outcome. These results offer a novel mechanistic framework and treatment paradigm for AF. (Conventional Ablation for Atrial Fibrillation With or Without Focal Impulse and Rotor Modulation [CONFIRM]; NCT01008722) (J Am Coll Cardiol 2012;60:628–36) © 2012 by the American College of Cardiology Foundation

Atrial fibrillation (AF) is the most common heart rhythm disturbance in the world and a leading cause of hospitalization and death (1). Unfortunately, its therapy remains suboptimal. Catheter ablation is a nonpharmacological therapy that aims to restore sinus rhythm by eliminating tissue causing AF (2,3), and is more effective than medications (4–6). Neverthe-

less, rigorous monitoring reveals that many patients experience “silent” AF after ablation (7). Accordingly, the 1-year success for AF ablation off medications is 40% to 60% for 1 procedure (3,8,9) with a “70% ceiling” for 3 or more procedures

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(3,5,6,10). Thus, many patients require multiple, lengthy, and costly procedures that confer at least modest risk (3).

Contemporary AF ablation is likely limited by 2 main factors. First, current tools may not create durable lesions, evidenced by pulmonary vein reconnection (11,12) and gaps in linear lesions (10,13) in patients with recurrent AF after ablation. However, an important second major limitation of AF ablation is that the mechanisms that sustain AF are not identified (3,14,15), in contrast to all other arrhythmias in which the perpetuating mechanism is the primary target for ablation.

Seminal observations by Haïssaguerre et al. (2) revealed that ectopic beats from the pulmonary veins may trigger AF, establishing the field of AF ablation with pulmonary vein isolation as its cornerstone (3). However, the mechanisms that sustain paroxysmal or persistent AF, once triggered, are not defined (14,16). There are 2 prevailing hypotheses. The multiwavelet hypothesis proposes that continuously meandering electrical waves cause AF (15). However, this hypothesis does not readily explain spatial nonuniformities in AF (17,18), the fact that AF may terminate early in a procedure often before meandering wavelets are substantially constrained (3,10), yet the fact that ablation based on this hypothesis often has little acute periprocedural impact (3,19). Alternatively, the localized source hypothesis is based on experimental models in which organized reentrant circuits (rotors) (16,20) or focal impulses (18) disorganize into AF. However, there has been little (21,22) or no (15) evidence to support localized sources in human AF.

We hypothesized that human AF, even with a wide range of presentations, is sustained by localized sources whose targeted elimination may improve outcome after AF ablation. We tested this hypothesis by developing a novel computational mapping approach to detect localized sources, then tested whether ablation of patient-specific AF sources, namely, focal impulse and rotor modulation (FIRM), acutely modulates AF (by terminating or consistently slowing AF), and improves the long-term success of conventional ablation in the CONFIRM (Conventional Ablation With or Without FIRM) trial.

Methods

Study design and enrollment. We enrolled 92 subjects with symptomatic AF undergoing 107 consecutive ablation procedures for standard indications (3) under specific institutional review board-approved informed consent. Subjects were ≥ 21 years of age, with AF despite 1 or more class I or III antiarrhythmic drugs, and diverse phenotypes including paroxysmal AF (self-limiting episodes), persistent AF (requiring drugs or electrical shock to terminate), long-standing persistent AF (continuous AF for >1 year) (3), and AF despite prior conventional ablation. The only exclusion was an inability or refusal to provide written informed consent for this study. Table 1 summarizes the patient characteristics.

All patients were recruited prospectively under specific institutional review board approval. We performed detailed AF recordings and used computational mapping to reveal localized sources (23), as detailed in the Supplementary Methods (Online Appendix). Processing initially took days and could not be used to guide ablation. However, once computational efficiency made it possible to map sources intraprocedurally, we registered the CONFIRM trial. Consecutive cases were thus prospectively enrolled in a 2-arm 1:2 case cohort design into the FIRM-guided group whenever intraprocedural mapping was available, or the FIRM-blinded group, blinded to any clinical factors. The FIRM-guided group received targeted ablation of sources followed by conventional ablation (by S.M.N. or D.E.K. at 2 centers), whereas the FIRM-blinded group received conventional ablation alone (by S.M.N., D.E.K., or K.S.) at 3 centers.

Electrophysiology study. Electrophysiology study was performed after discontinuing antiarrhythmic medications for 5 half-lives, or >60 days for amiodarone (median 230 days) (Table 1). Catheters were advanced from the femoral veins to the right atrium, coronary sinus and transseptally to the left atrium. A 64-pole basket catheter (Constellation, Boston Scientific, Natick, Massachusetts) was advanced through an 8.5F SL1 sheath (Daig Medical, Minnetonka, Minnesota) to map the left atrium with a wide field of view in all patients. In 73 patients (including all FIRM-guided cases), basket mapping was also performed in the right atrium. Basket insertion (<1 min) was then followed by careful positioning (<5 min). Digital electroanatomic atrial shells were created for clinical guidance of conventional ablation (not FIRM) using NavX (St. Jude Medical, Minneapolis, Minnesota) or Carto (Biosense-Webster, Diamond Bar, California) systems. Intravenous heparin was infused to achieve an activated clotting time >350 s in all cases. Figure 1 shows AF (Fig. 1A) mapped with 1 basket in the left atrium across a transseptal puncture and another in the right atrium (Fig. 1B). Unipolar and bipolar electrograms were filtered at 0.05 Hz to 500 Hz and recorded at 1 kHz sampling frequency for export from our physiological recorder (Bard, Lowell, Massachusetts).

In any patient presenting in sinus rhythm ($n = 28$), AF was induced by pacing at cycle length 500 ms (120 beats/min), reducing in 50 ms steps to 300 ms (200 beats/min), then in 10 ms steps to AF. In 2 cases, isoproterenol was required to initiate AF, and was maintained throughout the procedure. Induced AF was mapped after >15 min, and typically after 1 h to 2 h since induction was performed early in the case, based on preliminary data that spatial maps of induced and spontaneous AF converge within this time.

Abbreviations and Acronyms

AF	= atrial fibrillation
ECG	= electrocardiography
FIRM	= focal impulse and rotor modulation
IQR	= interquartile range

Table 1 Characteristics of Clinical Cases

Characteristics	Conventional Ablation (n = 71)	FIRM-Guided Ablation (n = 36)	p Value
AF presentation			0.12
Paroxysmal	24 (34%)	7 (19%)	
Persistent	47 (66%)	29 (81%)	
Age, yrs	61 ± 8	63 ± 9	0.34
Male/female	68/3	34/2	1.00
Nonwhite race	9 (13%)	6 (17%)	0.57
History of AF, months	45 (18–79)	52 (38–110)	0.04
Left atrial diameter, mm	43 ± 6	48 ± 7	0.001
LVEF, %	55 ± 12	53 ± 15	0.59
CHADS ₂ score			0.09
0 or 1	38 (54%)	13 (36%)	
2 or more	33 (46%)	23 (64%)	
NYHA functional class			0.47
0 to I	61 (86%)	29 (81%)	
II to III	10 (14%)	7 (19%)	
Comorbid conditions			
Hypertension	50 (70%)	31 (86%)	0.07
Diabetes mellitus	22 (31%)	12 (33%)	0.81
Prior stroke/TIA	12 (17%)	6 (17%)	0.95
Coronary disease	20 (28%)	18 (50%)	0.03
Hypercholesterolemia	48 (68%)	30 (86%)	0.05
Prior conventional ablation	18 (25%)	15 (42%)	0.08
Previously failed >1 antiarrhythmic drug	16 (23%)	16 (44%)	<0.05
Class I	16 (23%)	9 (25%)	0.78
Sotalol	30 (42%)	17 (47%)	0.63
Dofetilide	9 (13%)	8 (22%)	0.20
Amiodarone	27 (38%)	22 (61%)	0.02
Days since amiodarone discontinued	150 (60–365)	365 (69–730)	0.08
Concomitant drug therapy			
ACEI/ARB	45 (63%)	21 (58%)	0.61
Beta-adrenoceptor antagonists	48 (68%)	24 (67%)	0.92
Calcium-channel blockers	21 (30%)	11 (31%)	0.92
Statins	42 (59%)	19 (53%)	0.53

Values are n (%), mean ± SD, or median (interquartile range).

ACEI = angiotensin-converting enzyme inhibitor; AF = atrial fibrillation; ARB = angiotensin-receptor blocker; CHADS₂ = defined in Calkins et al. (3); FIRM = focal impulse and rotor modulation; LVEF = left ventricular ejection fraction; NYHA = New York Heart Association; TIA = transient ischemic attack.

Sustained AF was seen, and FIRM maps created, in 101 cases (including all FIRM-guided cases). The remaining 6 FIRM-blinded cases underwent conventional ablation in sinus rhythm.

Computational mapping of patient-specific AF mechanisms.

The physiological rationale, algorithms, and approach we have developed for AF mapping have recently been described (23) and are detailed in the Supplemental Methods (see Online Appendix). Briefly, AF electrograms are analyzed in the context of rate-dependent repolarization (24,25), that indicate the shortest physiological time between successive activations during AF, and rate-dependent conduction slowing (26), used to identify mapped propagation paths that were physiologically possible. The resulting computational maps depict the propagation of electrical activity, color coded from early (in red) to late (in blue), in each atrium (Fig. 1C).

Computational AF maps were generated intraprocedurally in the FIRM-guided group, and post-procedure in the FIRM-blinded group using a novel system (RhythmView, Topera Medical, Lexington, Massachusetts). The FIRM maps of AF revealed electrical rotors (Figs. 1C and 2A) defined as sequential clockwise or counterclockwise activation contours (isochrones) around a center of rotation emanating outward to control local AF activation, or focal impulses (Fig. 2C) defined by centrifugal activation contours (isochrones) from an origin. Rotors and focal impulses showed limited spatial precession (see following text) and were considered AF sources only if consistent in multiple recordings over >10 min (equating to thousands of cycles) to eliminate transient AF patterns of unclear functional significance.

Ablation procedure. In FIRM-guided subjects, ablation commenced with FIRM to eliminate sources. Radiofrequency energy was delivered using a 3.5-mm tip irrigated catheter (Thermocool, Biosense-Webster) at 25 W to 35 W or, in heart failure subjects, an 8-mm tip nonirrigated catheter (Blazer, Boston Scientific, Natick, Massachusetts) at 40 W to 50 W, target 52°C. The catheter was maneuvered to the basket electrode overlying each source, using fluoroscopy (or digital atrial mapping), and radiofrequency energy was applied for 15 s to 30 s. The catheter was moved within the area indicated by FIRM maps to represent the center of rotation or focal impulse origin until AF terminated or ablation time at that source reached ≤10 min, whichever came first (typically <5 min per source). If AF terminated, attempts were made to reinitiate AF using the protocol described for AF initiation. If AF was successfully reinitiated, FIRM ablation was repeated for ≤3 sources (≤30 min permitted by protocol). Conventional ablation was then performed.

Conventional ablation (3), performed after FIRM ablation in the FIRM-guided group, and as sole therapy in the FIRM-blinded group, comprised wide area circumferential ablation to isolate the left and right pulmonary veins in pairs, with verification of pulmonary vein isolation using a circular mapping catheter (Lasso, Biosense-Webster). Ablation power, temperatures, and duration were as noted for the FIRM-guided group. In cases of persistent AF, we also used a left atrial roof line; atrial tachycardia or flutter (n = 7 cases) were ablated appropriately. No other ablation was performed. If AF persisted after completion of the ablation protocol in each group, cardioversion was performed. An esophageal temperature probe was maintained in proximity to the catheter during ablation, and energy was discontinued if a 1°C rise in temperature was noted.

Post-procedure clinical management. Follow-up for recurrent arrhythmias met or exceeded guidelines (3). Within a 3-month blanking period post-ablation, antiarrhythmic medications were continued, and arrhythmias were managed with cardioversion if indicated. However, repeat ablation was not permitted. Subjects were then evaluated at 3, 6, 9, 12, 18, and 24 months. We detected recurrent arrhyth-

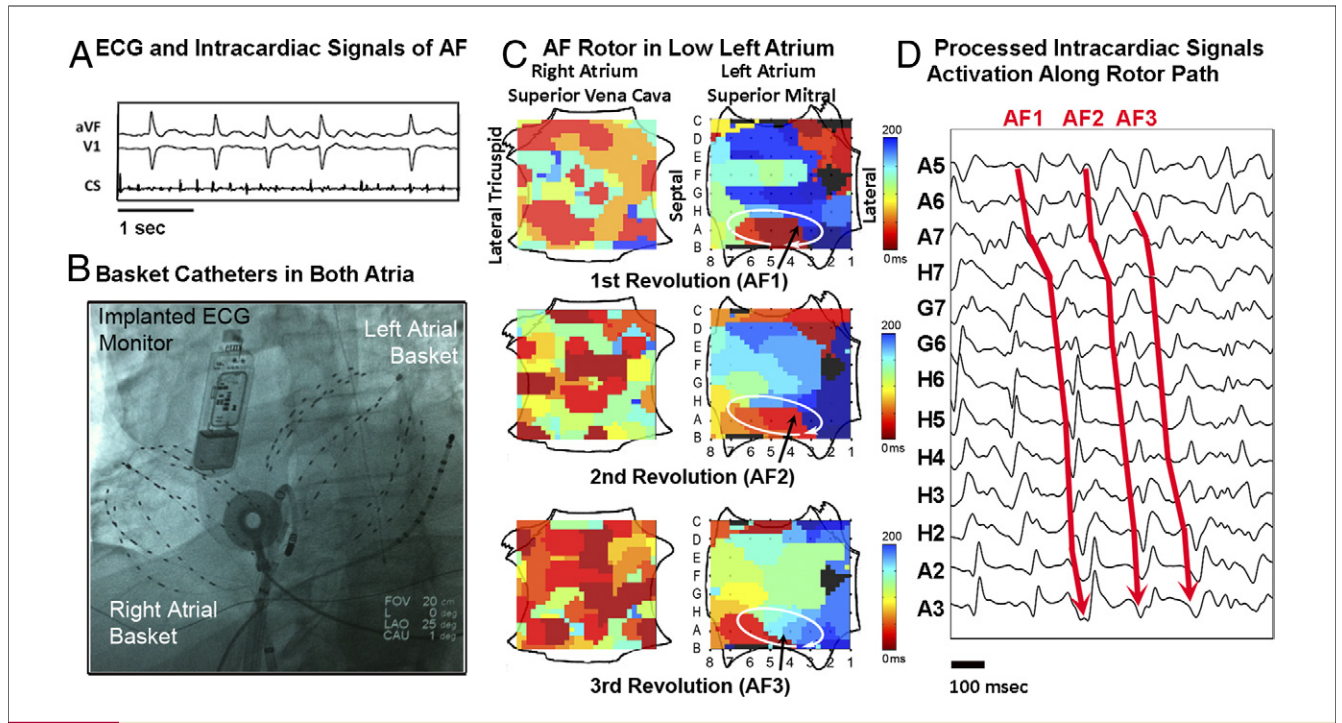


Figure 1 Computational Mapping of "Electrical Rotor" During Atrial Fibrillation

(A) Electrocardiogram (ECG) and intracardiac signals in an 85-year-old man during paroxysmal atrial fibrillation (AF). (B) Fluoroscopy shows a 64-pole catheter in each atrium, an implanted continuous electrocardiography (ECG) monitor, diagnostic catheters in the coronary sinus and left atrium, and an esophageal temperature probe at the inferior left atrium. (C) Left atrial rotor during AF, showing clockwise revolution (coded red to blue based on activation time scale) around a precessing center for 3 cycles (AF1 to AF3; Online Video 1). The right atrium depicts the superior and inferior vena cavae above and below, and lateral and medial tricuspid annuli at left and right. The left atrium depicts superior and inferior mitral annuli above and below, and pulmonary vein pairs. Electrodes are labeled A to H (Online Video 1). The right atrium depicts the superior and inferior vena cavae above and below, and lateral and medial tricuspid annuli at left and right. The left atrium depicts superior and inferior mitral annuli above and below, and pulmonary vein pairs. Electrodes are labeled A to H to 8, respectively. (D) Computationally processed and filtered intracardiac signals show sequential activation over the rotor path for cycles AF1 to AF3 (arrowed). The focal impulse and rotor modulation (FIRM) ablation at this rotor terminated AF to sinus rhythm in <1 min (Online Videos 2 and 3).

mias using implanted continuous electrocardiography (ECG) monitors whenever possible, using Reveal XT (Medtronic, Minneapolis, Minnesota) after its U.S. ap-

proval in 2009 (Fig. 1B), or clinically indicated pacemaker/defibrillators with AF detection algorithms. Continuous monitors were interrogated at scheduled visits and at in-

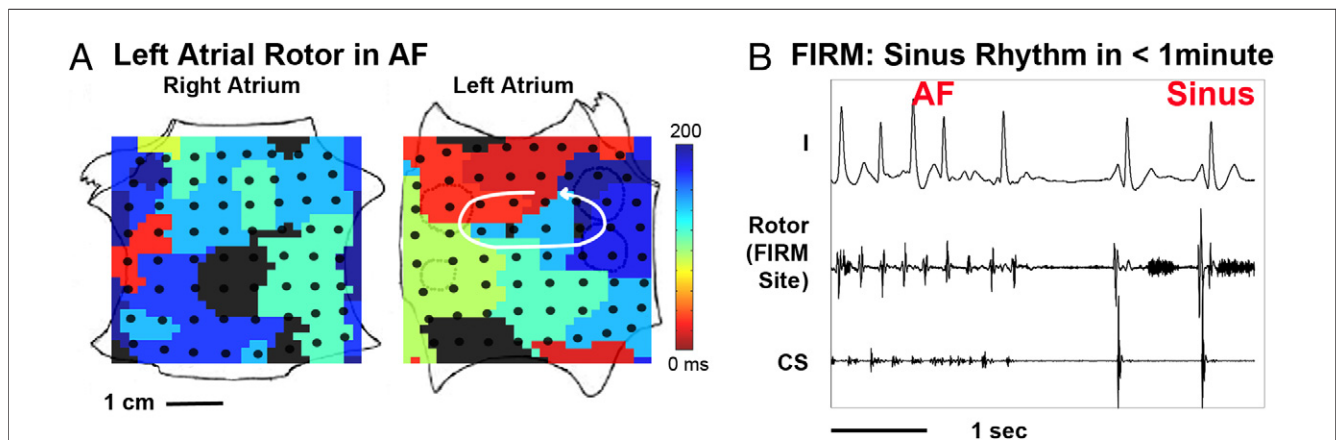


Figure 2 Acute Termination of AF to Sinus Rhythm By FIRM Ablation

(A) Left atrial rotor with counterclockwise activation (red to blue) and disorganized right atrium during atrial fibrillation (AF) in a 60-year-old man. (B) Focal impulse and rotor modulation (FIRM) ablation at left atrial rotor terminated AF to sinus rhythm in <1 min, with ablation artifact recorded at rotor center. The patient is AF-free on implanted cardiac monitor at >1 year. Scale bars 1 cm, 1 s. Atrial orientations as in Figure 1. CS = coronary sinus electrogram.

terim visits for symptoms by nurses, then over-read by a physician, both blinded to the ablation approach. Implanted ECG monitors provide more rigorous monitoring (7,27) than in most prior AF treatment trials. Remaining subjects received 7-day patient-activated event recorders or 24-h ambulatory ECG at each visit.

Study endpoints. The pre-specified acute efficacy endpoint was AF termination or $\geq 10\%$ AF slowing (≈ 15 ms to 20 ms prolongation of AF cycle length), selected as a rigorous marker of AF modulation (prior studies used AF slowing by ablation of 6 ms $\approx 3\%$ to 4%) (28). The AF cycle length was measured as the average in multiple samples over ≈ 5 min. The pre-specified primary long-term efficacy endpoint was defined as freedom from AF for up to 2 years after a single procedure (median 273 days, interquartile range [IQR]: 132 to 681 days), defined as $< 1\%$ burden using continuous implanted ECG monitors, or AF < 30 s on intermittent monitors (3). Secondary efficacy measures included freedom from AF in patients undergoing their first ablation, and freedom from all atrial arrhythmias. The safety endpoint was a comparison of adverse events between groups.

Statistical analysis. Continuous data are represented as mean \pm SD or median and IQR as appropriate. Normality was evaluated using the Kolmogorov-Smirnov test. Comparisons between 2 groups were made with Student's *t* tests and summarized with means and standard deviations for independent samples if normally distributed or, if not normally distributed, evaluated with the Mann-Whitney *U* test and summarized with medians and quartiles. Nominal values are expressed as n (%) and compared with chi-square tests or the Fisher exact test for comparisons when expected cell frequency was < 5 . Associations between continuous variables were evaluated with Spearman's correlation. Raw event rates were compared with chi-square tests, and event-

free survival plots were made by the Kaplan-Meier method and compared with log-rank tests. A probability of < 0.05 was considered statistically significant throughout. Analysis was by intention to treat, and crossovers were not permitted.

Results

Table 1 summarizes the characteristics of our study population. Persistent AF was present in 81% of the FIRM-guided group, and in 66% of the FIRM-blinded group.

Prevalence and characteristics of localized sources for human AF. Electrical rotors and focal impulses were present in 98 of 101 cases with sustained AF (97%), each subject demonstrating 2.1 ± 1.0 sources (median 2, IQR: 1 to 3) of which 70% were rotors and 30% focal impulses. For the AF rotor in Figure 1C, Figure 1D shows the corresponding electrical circuit (arrows) in noise-reduced AF signals, that precessed within an area of 1 to 2 cm² in the low left atrium (Online Videos 1, 2, and 3).

The AF sources, conserved for at least tens of minutes during mapping (FIRM-guided cases), and lay in widespread locations in the left atrium (76%) including sites outside the pulmonary veins, posterior, inferior, roof and anterior regions, and in the right atrium (24%) including the inferolateral, posterior, and septal regions. When sources were present, their number was higher for persistent than for paroxysmal AF (2.2 ± 1.0 vs. 1.7 ± 0.9 ; median 2.0 vs. 1.0; $p = 0.03$) and for spontaneous versus induced (typically paroxysmal) AF (2.1 ± 1.1 vs. 1.6 ± 0.9 ; median 2.0 vs. 1.0; $p = 0.01$), but was unrelated to age ($r = 0.13$, $p = 0.20$), historical duration of AF ($r = 0.14$, $p = 0.17$), or whether subjects were undergoing first ablation or had had prior conventional ablation (2.1 ± 1.1 vs. 2.0 ± 0.8 ; median 2.0 vs. 2.0; $p = 0.71$).

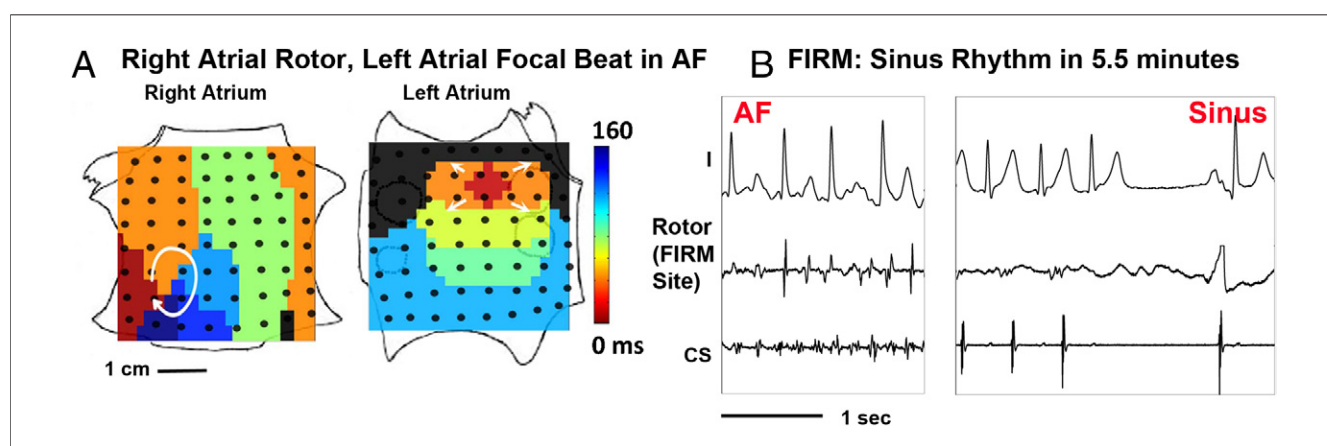


Figure 3 Acute Termination of AF, 2 Sources, to Sinus Rhythm by FIRM Ablation

(A) Right atrial rotor (clockwise) and simultaneous left atrial focal impulse (arrowed) during persistent atrial fibrillation (AF) in a 47-year-old man. (B) Focal impulse and rotor modulation (FIRM) ablation at right atrial rotor terminated AF to sinus rhythm in 5.5 min (Online Videos 4 and 5). Note the slowing of AF rate during ablation. The left atrial focal impulse source was also treated by FIRM ablation. The patient is AF-free on implanted cardiac monitor at > 1 year. Scale bars 1 cm, 1 s. Atrial orientations as in Figure 1. CS = coronary sinus electrogram.

Acute results of FIRM ablation. In Figures 2 and 3, FIRM ablation alone before conventional ablation terminated AF to sinus rhythm with <1 min FIRM ablation at a left atrial rotor (Fig. 2), and with 5.5 min FIRM ablation at a right atrial rotor (Fig. 3).

By intention-to-treat analysis, FIRM ablation alone achieved the acute endpoint in 31 of 36 (86%) patients. The AF terminated in 20 of 36 cases (56%) with 4.3 ± 6.3 min of FIRM ablation at the primary source (median 2.5 min, IQR: 1.0 to 3.1 min) (Table 2). In the 11 of 36 cases in whom AF did not terminate, AF slowed by 33 ± 12 ms (19 ± 8%). Cases in whom FIRM ablation slowed rather than terminated AF had larger LA diameters (53 ± 8 mm vs. 46 ± 6 mm; $p < 0.01$) and more patients with LA diameter >55 mm (poor coverage because the LA was too large for the largest basket; 8 of 11 vs. 1 of 20; $p < 0.001$, Fisher exact test). FIRM ablation could not be completed in 4 of 36 cases in whom sources lay near the phrenic nerve, an atrial pacing lead, the compact AV node, and esophagus; and FIRM ablation was not performed in 1 case without identified sources. Total FIRM ablation time (at all targeted sources) was 16.1 ± 9.8 min (median 18.5 min, IQR: 7.9 to 24.5 min) (Table 2).

By comparison, in the FIRM-blinded group, the acute endpoint was achieved in 13 of 65 cases with sustained AF (20%) after 43.4 ± 28.0 min (median 31.8 min, IQR: 22.1 to 71.5 min) ablation ($p < 0.001$ for both comparisons against FIRM-guided limb).

Long-term efficacy. Two subjects in each group were lost to follow-up. By intention-to-treat analysis, single-procedure freedom from AF was higher for FIRM-guided than for FIRM-blinded cases (82.4% [28 of 34] vs. 44.9%

[31 of 69]; $p < 0.001$) after median 273 days (IQR: 132 to 681 days). FIRM-guided therapy maintained its treatment benefit over FIRM-blinded therapy for first-time ablation cases ($p < 0.001$). No FIRM-guided case recurred after ≈7 months as determined using mostly implanted ECG monitoring. Results were similar excluding subjects without AF who remained on antiarrhythmic medications because of referring physician preference (79.3% [23 of 29] FIRM-guided vs. 35.6% [21 of 59] FIRM-blinded; $p < 0.001$). Freedom from any atrial tachyarrhythmia after a single procedure was also higher in FIRM-guided than in FIRM-blinded cases (70.6% [24 of 34] vs. 39.1% [27 of 69]; $p = 0.003$).

Kaplan-Meier survival plots are illustrated in Figure 4. Follow-up was more rigorous in the FIRM-guided group than in the FIRM-blinded group (implantable ECG monitors in 30 of 34 [88.2%] vs. 18 of 69 [26.1%]; $p < 0.001$). Online Figures 1 and 2 present examples of continuous and intermittent ECG monitoring for recurrent AF. Patients defined as ‘without AF’ (<1% burden) actually had $0.1 \pm 0.2\%$ burden. Neither the total duration of ablation, the aggregate number, nor the type of adverse events differed between groups (Table 2).

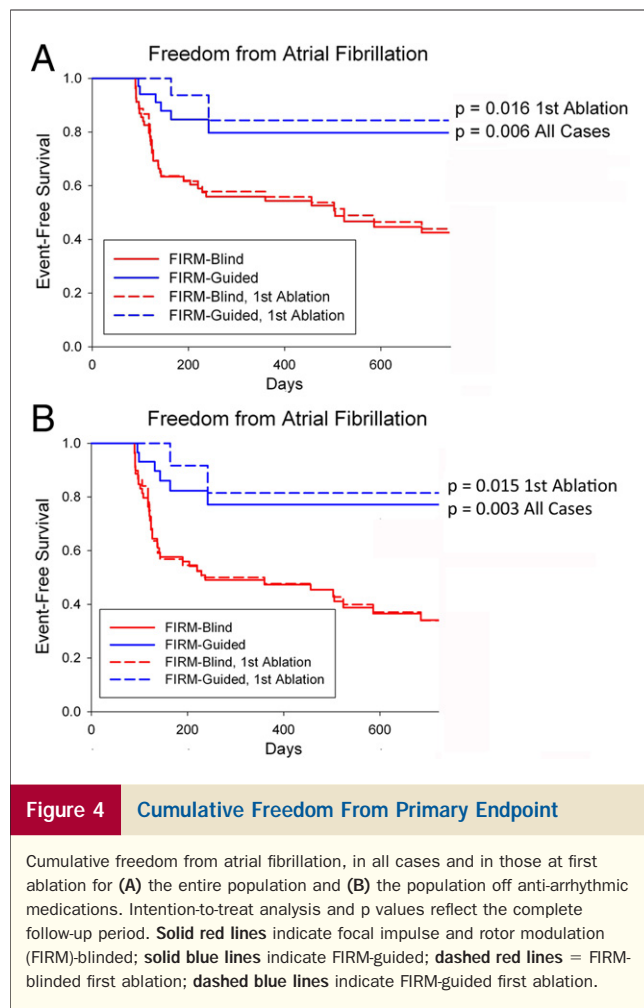
Discussion

The CONFIRM trial demonstrates for the first time that human AF may be sustained by localized sources in the form of electrical rotors and focal impulses. Brief ablation (FIRM) at patient-specific AF-sustaining sources was able to terminate or consistently slow persistent or paroxysmal AF before any conventional ablation in 86% of patients, and

Table 2 Acute Results in All Cases or Those With Sustained AF During Their Procedure

Characteristic	Conventional Ablation	FIRM-Guided Ablation	p Value
Cases with intra-procedural sustained AF	65/71 (92%)	36/36 (100%)	0.10
Subjects with AF sources	63/65 (97%)	35/36 (97%)	1.00
Acute endpoint achieved	13/65 (20%)	31/36 (86%)	<0.001
AF termination endpoint	6/65 (9%)	20/36 (56%)	<0.001
Ablation time, min, at primary source	—	2.5 (1.0–3.1)	
To sinus rhythm/atrial tachycardia	3/3	16/4	0.29
AF slowing (CL prolongation) endpoint	7/65 (11%)	11/36 (31%)	0.01
Extent of AF CL prolongation, ms	28 ± 8 (18 ± 6%)	33 ± 12 (19 ± 8%)	0.38
Ablation time for acute endpoint, min	31.8 (22.1–71.5)	18.5 (7.9–24.5)	<0.001
Total procedural ablation (all cases), min	52.1 ± 17.8	57.8 ± 22.8	0.16
Complications, all cases	6 (8%)	2 (6%)	0.72
Cardiac tamponade	2	1	
Groin bleed requiring transfusion	3	1	
Vascular injury requiring surgical repair	0	0	
Permanent diaphragmatic paralysis	0	0	
Symptomatic pulmonary vein stenosis	1*	0	
Stroke/TIA	0	0	
Atrioesophageal fistula	0	0	
Death	0	0	

Values are n/N (%), mean ± SD, median (interquartile range), n (%), or n. *Required stent. CL = cycle length; other abbreviations as in Table 1.



substantially increase long-term AF elimination using very rigorous monitoring compared to conventional AF ablation alone.

Localized sources for human AF. Electrical rotors in human AF were revealed using a novel computational mapping approach that analyzes electrograms in a wide atrial field of view in the context of physiologically plausible activation rates and conduction dynamics (23–26). No prior trial has identified or successfully targeted localized human AF sources for acute AF termination and elimination on follow-up. However, a number of elegant reports have characterized organized reentry before AF (29), transient rotors in AF (21,22), and sites of rapid (17,18,30,31) or disorganized (32) AF.

The mechanistic role of rotors and focal sources in perpetuating AF is demonstrated by acute AF termination by brief FIRM ablation alone, as we recently illustrated in a video case report (33). Patients in whom FIRM ablation slowed rather than terminated AF had sources that could not be eliminated, for safety considerations or protocol-imposed time limits, or had atria larger than current baskets (illustrated in Narayan [23]) and may have had residual sources in unmapped regions. In fact, intracardiac atrial

dimensions were substantially larger than reported preprocedural estimates. Rotors and focal sources were clinically relevant long-term AF perpetuators based on improved AF elimination using FIRM-guided versus conventional ablation.

Human AF rotors and focal impulses were fewer in number, longer lived, and more conserved in this study than suggested (20,21). That alters our conceptual framework for human AF, and enabled FIRM ablation to be practical and effective. Future work should study whether structural (34) or electrical (14) remodeling, altered innervation (35), or other processes explain these differences in AF. The similar number of sources for patients with and without prior ablation suggests, on the one hand, that prior ablation did not create sources and, on the other hand, that prior ablation may have been unsuccessful because it did not eliminate these AF sources. Both hypotheses require further testing.

Efficacy of FIRM-guided ablation. The FIRM-guided ablation was more effective than conventional ablation for patients undergoing their first procedure (Fig. 4) as well as for patients with prior conventional ablation, who were included to compare the mechanisms of AF across a wide range of presentations. Moreover, FIRM-guided ablation showed substantial efficacy benefit despite the use of highly sensitive implanted ECG monitors in 88% of cases. This is the highest usage of implanted ECG monitors in any AF treatment trial. The use of symptoms or intermittent ECG monitoring in prior AF therapy trials (7,27) likely underestimated the full burden of AF recurrence. Because only 26% of FIRM-blinded cases received implanted monitors, studies on the comparative efficacy of AF monitoring strategies (7,27) suggest that the CONFIRM study may actually underestimate the relative benefit of FIRM-guided over conventional ablation by $\approx 10\%$.

FIRM-guided and conventional ablation. The AF sources in this study are consistent with, and may explain, the results of conventional AF ablation. First, most sources lay in the left atrium, supporting current guidelines that primarily advocate left atrial ablation (3). Interestingly, the presence of right atrial sources in one-quarter of patients may explain the 70% to 80% success ceiling of conventional predominantly left atrial ablation for paroxysmal (6) and persistent (9) AF. Notably, prior studies that included right atrial ablation (36) achieved higher success rates. Second, diverse source locations are consistent with reports that widespread ablation may be required in both atria (10). Third, the higher number of sources in persistent than paroxysmal AF is consistent with lower success and more difficult procedures in the former group.

In the CONFIRM study, FIRM-guided ablation was followed by pulmonary vein isolation, yet total ablation time did not differ between groups (Table 2) because the brief duration of FIRM ablation fell within case-to-case variations of conventional ablation time. Accordingly, FIRM-guided therapy presents an opportunity to improve ablation

outcomes while avoiding more extensive strategies that may result in serious sequelae (3).

Study limitations. This study has the limitations of a nonrandomized design. However, subjects were enrolled consecutively and treated prospectively for pre-specified endpoints. First, the FIRM-guided group had more subjects with persistent AF, higher comorbidity, and more intense monitoring than FIRM-blinded subjects, thus potentially underestimating the benefit of FIRM-guided ablation. Second, although the basket may have suboptimal resolution for a small focal origin or rotor core (16), an AF source will “control” a larger ‘organized domain’ of the atrium for which the basket field of view is well suited to map in clinical practice. The size of a single ablation lesion (≈ 5 to 7 mm diameter) also places a practical limit on the necessary resolution. Conversely, the largest available diameter (≈ 55 to 60 mm when fully deployed) limits the largest atrial size that can be mapped. Third, more extensive FIRM ablation at sources beyond the ≤ 3 protocol limit may have yielded higher rates of AF termination and long-term success, but was not performed because of the study design. Future studies will target all detected sources for FIRM ablation. Finally, this first trial of FIRM-guided ablation needs validation in larger populations, with balanced representation of the sexes, by many more investigators, and in randomized fashion. Such validation is already under way.

Conclusions

Human AF is typically caused by very few localized sources that cause disorganization in the remaining atria. Focal impulse and rotor modulation (FIRM) ablation to eliminate these sources was able to abruptly terminate or consistently slow persistent and paroxysmal AF in the vast majority of cases, and substantially improve long-term AF elimination over conventional ablation alone in this prospective case-cohort study. FIRM mapping may open the possibility for several patient-tailored therapies for AF in addition to ablation for this highly prevalent disease with major public health and societal impact.

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Key Words: ablation ■ atrial fibrillation ■ electrical rotors ■ focal beats ■ multiwavelet reentry ■ therapy.

 APPENDIX

For a supplemental Methods section and supplemental figures, videos, and references, please see the online version of this article.