Ablation of Rotor and Focal Sources Reduces Late Recurrence of Atrial Fibrillation Compared With Trigger Ablation Alone

Extended Follow-Up of the CONFIRM Trial (Conventional Ablation for Atrial Fibrillation With or Without Focal Impulse and Rotor Modulation)

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Objectives
The aim of this study was to determine if ablation that targets patient-specific atrial fibrillation (AF)–sustaining substrates (rotors or focal sources) is more durable than trigger ablation alone at preventing late AF recurrence.

Background
Late recurrence substantially limits the efficacy of pulmonary vein isolation for AF and is associated with pulmonary vein reconnection and the emergence of new triggers.

Methods
Three-year follow-up was performed of the CONFIRM (Conventional Ablation for Atrial Fibrillation With or Without Focal Impulse and Rotor Modulation) trial, in which 92 consecutive patients with AF (70.7% persistent) underwent novel computational mapping. Ablation comprised source (focal impulse and rotor modulation [FIRM]) and then conventional ablation in 27 patients (FIRM guided) and conventional ablation alone in 65 patients (FIRM blinded). Patients were followed with implanted electrocardiographic monitors when possible (85.2% of FIRM-guided patients, 23.1% of FIRM-blinded patients).

Results
FIRM mapping revealed a median of 2 (interquartile range: 1 to 2) rotors or focal sources in 97.7% of patients during AF. During a median follow-up period of 890 days (interquartile range: 224 to 1,563 days), compared to FIRM-blinded therapy, patients receiving FIRM-guided ablation maintained higher freedom from AF after 1.2 procedures (median 1; interquartile range: 1 to 1) (77.8% vs. 38.5%, p = 0.001) and higher freedom from all atrial arrhythmias (p = 0.003). Freedom from AF was higher when ablation directly or coincidentally passed through sources than when it missed sources (p < 0.001).

Conclusions
FIRM-guided ablation is more durable than conventional trigger-based ablation in preventing 3-year AF recurrence. Future studies should investigate how ablation of patient-specific AF-sustaining rotors and focal sources alters the natural history of arrhythmia recurrence. (The Dynamics of Human Atrial Fibrillation; NCT01008722) (J Am Coll Cardiol 2014;63:1761–8) © 2014 by the American College of Cardiology Foundation

Atrial fibrillation (AF) is the most common sustained arrhythmia in the world and a leading cause of hospitalization and death (1). Ablation promises to eliminate AF and has enjoyed increased attention (1) as trials question the efficacy of pharmacologic strategies to suppress AF (2) or limit ventricular rate (3). However, although ablation at AF triggers can be effective, its 1-year efficacy is about 40% to 50% for a single procedure (1,4) and 50% to 70%
for multiple procedures (1,5). Moreover, AF often recurs more than 1 year after conventional ablation (1,4) (defined as late AF [1]).

We hypothesized that the elimination of patient-specific AF sources (AF-sustaining substrates) would provide more durable AF elimination than conventional (trigger) ablation, in which unablated substrates can subsequently be engaged by reconnected pulmonary veins (PVs) (6,7) or non-PV triggers (8–10). The CONFIRM (Conventional Ablation for Atrial Fibrillation With or Without Focal Impulse and Rotor Modulation) demonstrated that substrates for persistent and paroxysmal AF include electrical rotors (spiral waves) or focal sources in spatially reproducible locations for each patient that sustain AF. Targeted ablation at AF sources alone in biatrial locations greatly improved the 1-year to 2-year success of conventional ablation in the CONFIRM trial (11), as shown by independent laboratories (12,13).

We studied whether ablation guided by focal impulse and rotor modulation (FIRM) prevented late AF recurrence and thus maintained its relative efficacy over conventional ablation in an extended follow-up of the CONFIRM trial.

**Methods**

**Study design and enrollment.** We studied the 92 unique subjects in CONFIRM undergoing index FIRM-mapping procedures, each referred for ablation of symptomatic AF for standard indications at 3 centers (1). Subjects were ≥21 years of age, with AF despite 1 or more class I or III antiarrhythmic drugs. The only exclusion to enrollment was an inability or a refusal to provide written informed consent. The population included paroxysmal AF (self-limiting episodes), persistent AF (requiring drugs or electrical shock to terminate or continuous AF for >7 days), and longstanding persistent AF (continuous AF for more than 1 year) (1). Table 1 summarizes patient characteristics.

We analyzed AF recorded at multipolar biatrial catheters using described computational methods using phase mapping of electrograms and repolarization and conduction dynamics to map patient-specific sources (14). Consecutive patients were prospectively enrolled under specific institutional review board approval in a 2-arm 1:2 case-cohort design for FIRM-guided ablation, after real-time FIRM mapping had been developed, or the FIRM-blinded group, in which sources were mapped offline. The FIRM-guided group received targeted ablation of sources followed by conventional ablation, while the FIRM-blinded group received conventional ablation alone.

**Electrophysiologic study.** Electrophysiologic studies were performed after discontinuing antiarrhythmic medications for 5 half-lives, or >60 days for amiodarone (median 203 days). Catheters were advanced transvenously to the right atrium and coronary sinus and trans-septally to the left atrium. A 64-pole basket catheter (Constellation, Boston Scientific Corporation, Natick, Massachusetts) was advanced through an 8.5-F SL1 sheath (Daig Medical, Minnetonka, Minnesota) to map AF in left atrium (n = 92) and the right atrium (n = 61). Digital electroanatomic atrial shells were created using NavX (St. Jude Medical, Minneapolis, Minnesota) or Carto (Biosense Webster, Diamond Bar, California) (15). Intravenous heparin was infused to achieve an activated clotting time of >350 s. Unipolar and bipolar atrial electrograms from the basket catheter were filtered at 0.05 to 500 Hz and recorded at 1-kHz sampling frequency for export from our electrophysiologic recording system (Bard, Lowell, Massachusetts).

AF was observed in 88 patients (including all FIRM-guided cases), including AF induced by rapid pacing (n = 26) or isoproterenol (n = 2) when required. Induced and spontaneous AF in a given patient have recently been shown to have similar dominant frequency (16) and spatial (14) patterns. The remaining 4 patients without induced AF underwent conventional ablation in sinus rhythm in routine fashion.

**FIRM mapping of AF sources.** FIRM mapping has been described (11,14). Briefly, AF was recorded using wide-field-of-view basket catheters then analyzed using a mapping system (RhythmView, Topera, Palo Alto, California) using phase-based algorithms to project 3-dimensional maps of AF propagation (an ‘activation trail’) onto grids.

AF (FIRM) maps were analyzed intraoperatively to guide ablation in FIRM-guided patients and post-operatively in FIRM-blinded patients. Electrical rotors (Fig. 1) were defined as phase-mapped rotation, while focal impulses showed centrifugal activation from an origin, both with precession (“wobble”) and complex surrounding breakdown that obscure fibrillatory sources on simple activation maps. Rotors and focal impulses were considered AF sources only if they lay in reproducible regions, with precession (17), on repeated analysis for thousands of cycles.

**Ablation approach.** Radiofrequency energy was delivered with a 3.5-mm-tip irrigated catheter (ThermoCool, Biosense Webster) at 25 to 35 W or, in patients with heart failure, an 8-mm-tip catheter (Blazer, Boston Scientific Corporation) at 40 to 50 W, with a target temperature of 52°C. Ablation commenced with FIRM in FIRM-guided subjects. Each lesion was applied for about 30 s to cover the approximately 2-cm² area of phase-mapped AF source precession (17). Remapping for rotor elimination was not possible in CONFIRM, because early software took hours to process, so that the endpoint was AF termination or 10 min of energy delivery (typically <5 min), whichever came first. FIRM was repeated for ≤3 sources (11) guided by the single FIRM map, followed by conventional ablation. In more recent studies, FIRM maps are generated fast enough to enable remapping to confirm rotor elimination (13).
Conventional ablation (1), performed after FIRM in FIRM-guided patients and as sole therapy in FIRM-blinded patients, was standardized to comprise wide-area circumferential ablation of the left and right PV pairs, with verification of PV isolation (PVI) using a circular mapping catheter (Lasso; Biosense Webster). In patients with persistent AF, a left atrial (LA) roof line was also performed. Clinically relevant atrial tachycardia was ablated. If AF or atrial tachycardia persisted after the completion of ablation, cardioversion was performed.

Postprocedure clinical management. Follow-up for arrhythmia recurrence exceeded guidelines (1). In a 3-month post-ablation “blanking period,” antiarrhythmic medications were continued (except amiodarone), but repeat ablation was not permitted. Subjects were evaluated for recurrence using continuous implanted electrocardiographic monitors (recording 100% of the year) (11) or AF of $<$ 30 s in duration on quarterly monitoring (1) (recording $<$ 28 days or 7.7% of the year). Secondary efficacy measures included freedom from all atrial arrhythmias and arrhythmia freedom after a single procedure. Follow-up was facilitated by the comprehensive electronic medical record system in this largely Veterans Affairs population, and all patients lost to follow-up in the original CONFIRM trial (11) were recaptured. Follow-up continued for $>$ 3 years in all patients, with none lost to follow-up, for a median of 890 days (interquartile range [IQR]: 224 to 1,563 days) when censored at recurrence. Study endpoints. The primary endpoint was freedom from AF, defined as $<$ 1% burden on continuous implanted electrocardiographic monitors (recording 100% of the year) (11) or AF of $<$ 30 s in duration on quarterly monitoring (1) (recording $<$ 28 days or 7.7% of the year). Secondary efficacy measures included freedom from all atrial arrhythmias and arrhythmia freedom after a single procedure. 

### Table 1: Characteristics of Population

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>FIRM-Blind (Conventional)</th>
<th>FIRM-Guided</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type of AF</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Paroxysmal AF</td>
<td>65</td>
<td>27</td>
<td>0.336</td>
</tr>
<tr>
<td>Persistent AF</td>
<td>33.2% (21)</td>
<td>22.2% (6)</td>
<td></td>
</tr>
<tr>
<td>Long-standing persistent AF</td>
<td>52.3% (34)</td>
<td>63.0% (17)</td>
<td></td>
</tr>
<tr>
<td>Age (yrs)</td>
<td>61.2 ± 8.7</td>
<td>63.0 ± 8.3</td>
<td>0.362</td>
</tr>
<tr>
<td>Men/women</td>
<td>63/2</td>
<td>25/2</td>
<td>0.578</td>
</tr>
<tr>
<td>AF history (days)</td>
<td>1.090 (143–2,712)</td>
<td>1.753 (1.127–3.249)</td>
<td>0.056</td>
</tr>
<tr>
<td>LA diameter (mm)</td>
<td>44 ± 7</td>
<td>50 ± 8</td>
<td>$&lt;$ 0.001</td>
</tr>
<tr>
<td>LV ejection fraction (%)</td>
<td>55 ± 12</td>
<td>52 ± 17</td>
<td>0.430</td>
</tr>
<tr>
<td>Prior ablations</td>
<td>20% (13)</td>
<td>22.2% (6)</td>
<td>0.811</td>
</tr>
<tr>
<td>Comorbid conditions</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Hypertension</td>
<td>45/64</td>
<td>25/27</td>
<td>0.049</td>
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<tr>
<td>Diabetes</td>
<td>20/64</td>
<td>11/27</td>
<td>0.383</td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
<td>32.2 ± 5.7</td>
<td>33.5 ± 6.1</td>
<td>0.324</td>
</tr>
<tr>
<td>Obstructive sleep apnea</td>
<td>28/63</td>
<td>21/27</td>
<td>0.007</td>
</tr>
<tr>
<td>Congestive heart failure</td>
<td>26/65</td>
<td>11/27</td>
<td>0.947</td>
</tr>
<tr>
<td>BNP (pg/ml)</td>
<td>199 ± 179</td>
<td>169 ± 131</td>
<td>0.518</td>
</tr>
<tr>
<td>GFR (ml/min)</td>
<td>77.1 ± 19.9</td>
<td>70.0 ± 17.7</td>
<td>0.156</td>
</tr>
<tr>
<td>Magnesium (mg/dl)</td>
<td>2 (1.9–2.2)</td>
<td>2 (1.9–2.2)</td>
<td>0.972</td>
</tr>
</tbody>
</table>

Values are % (n), mean ± SD, or median (interquartile range). Statistical comparisons were performed using chi-square tests (for incidences of AF type, hypertension, diabetes mellitus, and obstructive sleep apnea), the Student t test (for age, LA diameter, LV ejection fraction, body mass index, and laboratory data), and the Fisher exact test (for sex).

AF – atrial fibrillation; BNP – brain natriuretic peptide; FIRM – focal impulse and rotor modulation; GFR – glomerular filtration rate; LA – left atrial; LV – left ventricular.
distributed, as verified using the Kolmogorov–Smirnov test. Otherwise, they are summarized with medians and quartiles or ranges and were compared using Mann-Whitney U tests. Nominal variables were compared using chi-square tests or Fisher exact tests if expected cell frequencies were <5. Long-term outcomes were assessed and reported after a single procedure and after multiple procedures of the same type (i.e., PVI to PVI or FIRM guided ablation to FIRM guided ablation). Survival analyses were conducted using the Cox proportional hazards model. Survival curves were produced using the Kaplan-Meier method and compared using log-rank tests. Covariates were added to this model if there were treatment group differences with p values < 0.10. In multivariate models, AF history was transformed to the common log. A p value < 0.05 was considered statistically significant.

**Results**

Table 1 summarizes the characteristics of the study population.

**Stable localized sources for human AF.** AF was observed intraprocedurally in 88 of 92 patients, in whom FIRM mapping revealed stable AF rotors or focal sources in 86 (97.7%) for 1.9 ± 0.1 concurrent stable sources per patient (median 2; IQR: 1 to 2), of which 67% lay in the left atrium (1.3 ± 0.9 per patient; median 1; IQR: 1 to 2) and 33% lay in the right atrium (0.6 ± 0.7 per patient; median 0; IQR: 0 to 1).

**Long-term efficacy.** Figure 1 illustrates a patient with recurrent arrhythmia after FIRM-guided ablation. At 890 days (IQR: 224 to 1,563 days), freedom from AF was higher for FIRM-guided than conventional therapy (77.8% [21 of 27] vs. 38.5% [25 of 65], p = 0.001) after 1.2 ± 0.4 procedures (median 1; IQR: 1 to 2). After a single procedure alone, freedom from AF was also higher for FIRM-guided than conventional therapy for patients undergoing first ablation (75.0% [15 of 20] vs. 30.2% [16 of 53], p < 0.001) and all patients (66.7% [18 of 27] vs.
27.7% [18 of 65], p < 0.001). Kaplan-Meier survival plots with p values (log-rank test) are illustrated in Figures 2 to 4.

At 890 days (IQR: 224 to 1,563 days), freedom from any atrial tachyarrhythmias was also higher in FIRM-guided than conventional cases after 1.2 ± 0.4 procedures (70.4% [19 of 27] vs. 36.9% [24 of 65], p = 0.003) and after a single procedure including typical cavotricuspid flutter (55.6% [15 of 27] vs. 26.2% [17 of 65], p = 0.001) and excluding typical cavotricuspid flutter (63.0% [17 of 27] vs. 26.2% [17 of 65], p = 0.001). Seven subjects (7.6%) remained on antiarrhythmic medications because of patient or physician preference (3 FIRM guided, 4 conventional).

Repeat procedures were performed in 28 patients (8 FIRM guided, 20 conventional). Of FIRM patients with AF recurrence, 3 had atrial tachycardia (2 cavotricuspid, 1 LA) and were successfully ablated, while 5 AF recurrences were treated by FIRM. Six patients (75.0%) were free of recurrence at 950 days (IQR: 658 to 973 days). Of conventional ablation patients, 12 had repeat PVI (before the availability of real-time FIRM), of whom 6 (50.0%) were recurrence free at 1,435 days (IQR: 836 to 1,767 days) (PVI, then PVI). Eight patients who initially underwent conventional ablation and had AF recurrence crossed over to FIRM ablation (and were excluded from multiprocedure Kaplan-Meier analysis), of whom 6 (75.0%) remained AF free at 1,939 days (IQR: 1,109 to 2,120 days) (PVI, then FIRM-guided ablation).

**On-treatment analysis.** Examining only single-procedure results, ablation in which lesions passed through the sites of ≥1 rotor or focal source (either directly, on FIRM, or coincidentally by anatomically placed lesions) was more successful than ablation that missed all sources (Fig. 5) (p values reflect log-rank tests). Direct ablation through a source did not differ significantly from coincidental ablation of a source in this study (69.2% vs. 57.1%, p = 0.36), which may reflect patient numbers.

**Multivariate predictors of outcomes.** We studied the impact on freedom from AF of FIRM-guided versus conventional ablation and demographic factors that differed between groups with p values <0.10 (from Table 1: presence of hypertension and obstructive sleep apnea; LA diameter and AF history as continuous variables). On multivariate analysis, single-procedure long-term success was associated with FIRM-guided ablation (p < 0.001) and inversely with AF history (p = 0.006), hypertension (p = 0.014), and LA diameter (p = 0.010). Sleep apnea and other clinical factors did not impact outcome when FIRM-guided ablation was considered. Multiple-procedure long-term success was associated with FIRM-guided ablation (p = 0.003) and trended inversely with LA diameter (p = 0.052).

**Discussion**

Elimination of patient-specific electrical rotor and focal sources for AF significantly reduced late recurrence of atrial arrhythmias on rigorous >3-year follow-up compared with trigger ablation alone. On multivariate analysis, FIRM-guided ablation predicted procedural success independently of comorbidities that otherwise favor the progression of AF substrates. These data strengthen the concept that ablation of defined patient-specific AF-sustaining mechanisms prevents recurrent AF even if PVs reconnect or alternative
triggers become active, both of which are major causes of recurrent AF after conventional ablation.

Ablating stable rotors and focal sources substantially improves arrhythmia freedom. These data strengthen the concept that stable localized sources represent important AF-sustaining substrates for human AF after it is triggered, from the CONFIRM trial (11) and independent groups (12,13,18).

These data suggest that the success of FIRM-guided ablation is attributable more to FIRM than to PVI. Over a median follow-up period of >3 years, the single-procedure success of conventional ablation was <40% (Fig. 4), while FIRM-guided ablation produced 70% to 80% arrhythmia freedom. The single-procedure success of conventionally treated patients in this study is in line with results from Weerasooriya et al. (4) (one-third persistent AF) and the <40% to 50% 1-year to 2-year single-procedure success from multicenter trials of paroxysmal AF (5,19,20). The relatively small increment in success with multiple versus 1 procedure (Figs. 2 and 3 vs. Fig. 4) in both limbs reflects fewer patients undergoing repeat procedures in this study (median 1; IQR: 1 to 1; mean 1.2 ± 0.4) than in prior studies (e.g., median 2, mean about 1.8 in Weerasooriya et al.). Finally, ablation was more successful if sources were eliminated, as demonstrated by on-treatment analysis in this report (Fig. 5) and prospectively by the elimination of paroxysmal AF by FIRM-only ablation in the PRECISE-PAF (Precise Rotor Elimination Without Concomitant Pulmonary Vein Isolation for the Successful Elimination of Paroxysmal Atrial Fibrillation) trial (21). Although direct FIRM ablation appeared slightly better than coincidental rotor ablation in this long-term analysis, as may be expected, this was not statistically significant, possibly because of patient numbers.

Stable AF sources explain many observations that are difficult to reconcile by disorganized mechanisms (22), including AF termination by targeted intervention at sites identified a priori hours earlier (11,12,23,24), consistent activation vectors in AF (25,26), stable sites of rapid AF activity (27–31), and organized re-entry before AF (32). While AF rotors are rarely seen simply by activation mapping, due to precession and complex breakdown, they have been reported using methods including phase mapping, wavelet similarity (18), the inverse solution (33), intraoperative mapping (26), and possibly other methods (34). Future work should define how electrical (35), structural (36), or neural (37) remodeling contributes to the formation and localization of AF sources.

Rotor and source ablation prevents late AF recurrence. Recurrence and late recurrence of AF, occurring within 3 to 12 months and >12 months post-ablation, respectively (1), have unclear mechanisms. One hypothesis is that PV reconnection often accounts for recurrence (1,6,7), although, conversely, patients with reconnected PVs often do not have recurrence (38,39). A second mechanism is that non-PV triggers may dominate after PVI (8–10). A third mechanism is that progressive electrical (35), structural (36), or neural (37) remodeling may facilitate the progression of new substrates.

These data support the concept that substrate ablation by FIRM may prevent AF recurrence by rendering reconnected PV or non-PV triggers impotent. It has been shown that patients after FIRM-only ablation may initially show
triggers that no longer initiate sustained AF and may regress (21), a phenomenon also seen after ablation for supraventricular tachycardia. These results open the possibility that elimination of patient-specific AF substrates may attenuate deleterious remodeling, even in patients with clinical comorbidities associated with substrate progression, such as hypertension and sleep apnea.

**Efficacy of FIRM-guided ablation across patient populations.** FIRM-guided ablation retained its efficacy advantage in all patient subgroups. FIRM was more successful if performed as a first rather than a redo procedure (Figs. 4 and 5), which may reflect signal degradation from prior ablation, pro-arrhythmia from prior ablation (Fig. 1), or a biological resistance to therapy in such patients. Nonetheless, despite these issues, patients with previous ablation still achieved excellent long-term outcomes with FIRM-guided therapy. FIRM also retained efficacy in patients with comorbidities that typically confer worse outcomes from PV ablation, such as obesity and sleep apnea, which associate with a larger number of AF rotors that may lie in locations readily targeted by FIRM but missed by PV ablation (40).

**Study limitations.** The major limitation of CONFIRM is that it was nonrandomized, although subjects were enrolled consecutively and treated prospectively for pre-specified endpoints. Differences between groups may have reduced the relative benefit of FIRM therapy. Compared with conventionally treated patients, FIRM-guided patients in this analysis had more persistent AF (77.8% vs. 67.7%), a higher prevalence of implanted loop recorders to detect recurrence (85.2% vs. 23.1%), and more co-morbidities. Although multivariate analysis showed a benefit of FIRM-guided therapy, we accept that such analyses cannot take into account all potential differences. The CONFIRM protocol was not ideal for assessing atrial tachycardia recurrence because, for example, the protocol did not standardize cavotricuspid isthmus ablation (most atrial tachycardia recurrences in FIRM-guided patients). Also, current baskets are suboptimal to ensure contact, that may improve with future designs.

Some of these limitations are balanced by the unique strengths of CONFIRM: implanted devices in >80% of active limb patients and the “captive audience” of the largely Veterans Affairs population in whom the integrated electrical medical record system enabled us to capture events even for noncardiology office visits and hospitalizations. The multi-procedure success of conventional (and FIRM-guided) ablation in this trial would have been higher if more patients had undergone repeat ablation, but because of patient preference, the number of repeat ablations was small (mean 1.2 ± 0.4). Multiprocedure success would also have been higher if crossovers to FIRM-guided ablation had been included (6 of 8 arrhythmia free). Statistically, the sample size imposed limits on the ability to conduct multivariate-adjusted analyses. We limited the number of covariates, but replication in larger samples would be useful. Finally, although CONFIRM predominantly recruited men, studies from other groups have since validated its findings in women (12,13).

**Conclusions**

In this extended follow-up of the CONFIRM trial, FIRM-guided ablation was more effective than conventional ablation alone at preventing early and late arrhythmia recurrences. By removing patient-specific AF substrates, FIRM may prevent recurrent AF from reconnected PVs or non-PV triggers. Future studies should further define how ablation of patient-specific AF-sustaining substrates alters the natural history of long-term arrhythmia recurrence.

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**REFERENCES**


Key Words: ablation • atrial fibrillation • clinical trial • electrical rotors • FIRM.