ORIGINAL ARTICLE

Approaches to Catheter Ablation for Persistent Atrial Fibrillation

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ABSTRACT

BACKGROUND

Catheter ablation is less successful for persistent atrial fibrillation than for paroxysmal atrial fibrillation. Guidelines suggest that adjuvant substrate modification in addition to pulmonary-vein isolation is required in persistent atrial fibrillation.

METHODS

We randomly assigned 589 patients with persistent atrial fibrillation in a 1:4:4 ratio to ablation with pulmonary-vein isolation alone (67 patients), pulmonary-vein isolation plus ablation of electrograms showing complex fractionated activity (263 patients), or pulmonary-vein isolation plus additional linear ablation across the left atrial roof and mitral valve isthmus (259 patients). The duration of follow-up was 18 months. The primary end point was freedom from any documented recurrence of atrial fibrillation lasting longer than 30 seconds after a single ablation procedure.

RESULTS

Procedure time was significantly shorter for pulmonary-vein isolation alone than for the other two procedures (P<0.001). After 18 months, 59% of patients assigned to pulmonary-vein isolation alone were free from recurrent atrial fibrillation, as compared with 49% of patients assigned to pulmonary-vein isolation plus complex electrogram ablation and 46% of patients assigned to pulmonary-vein isolation plus linear ablation (P=0.15). There were also no significant differences among the three groups for the secondary end points, including freedom from atrial fibrillation after two ablation procedures and freedom from any atrial arrhythmia. Complications included tamponade (three patients), stroke or transient ischemic attack (three patients), and atrioesophageal fistula (one patient).

CONCLUSIONS

Among patients with persistent atrial fibrillation, we found no reduction in the rate of recurrent atrial fibrillation when either linear ablation or ablation of complex fractionated electrograms was performed in addition to pulmonary-vein isolation. (Funded by St. Jude Medical; ClinicalTrials.gov number, NCT01203748.)

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Percutaneous catheter ablation is an effective treatment for paroxysmal atrial fibrillation,[1-3] particularly in cases that are refractory to antiarrhythmic medications.[4-6] Most triggers for paroxysmal atrial fibrillation come from the pulmonary veins, so ablation involves creating circumferential lesions around the veins to electrically isolate them from the rest of the left atrium.[7]

Catheter ablation for persistent atrial fibrillation is more challenging and is associated with less favorable outcomes.[8,9] To improve outcomes, ablation targeting the substrate that maintains fibrillation (i.e., substrate modification) is often added to pulmonary-vein isolation.[10,11] The two most common techniques for substrate modification are the creation of linear lesions in the left atrium[12,13] and focal ablation to eliminate atrial signals that show complex activity (sometimes called "complex fractionated electrograms").[7,14]

Data from randomized trials comparing methods of ablation for persistent atrial fibrillation are limited.[15-19] Despite the paucity of data, guidelines suggest that "operators should consider more extensive ablation based on linear lesions or complex fractionated electrograms" for ablation of persistent atrial fibrillation.[7] Whether more extensive ablation improves outcomes is unclear. Therefore, this trial compared three approaches to ablation for persistent atrial fibrillation: ablation with pulmonary-vein isolation alone, pulmonary-vein isolation plus ablation of complex fractionated electrograms, and pulmonary-vein isolation plus linear ablation.

Methods

Trial Design

The Substrate and Trigger Ablation for Reduction of Atrial Fibrillation Trial Part II (STAR AF II) was a randomized trial comparing three strategies of ablation for persistent atrial fibrillation. The trial design has been published previously.[20]

The trial was sponsored by St. Jude Medical and approved by the appropriate national authorities and the ethics committee at each center. An international steering committee (see the Supplementary Appendix, available with the full text of this article at NEJM.org) was responsible for the study design, conduct, and reporting. Data monitoring, collection, and primary data analysis were performed by the sponsor in partnership with the steering committee. The authors vouch for the accuracy and completeness of the data and for the fidelity of this report to the trial protocol, available at NEJM.org. The sponsor reviewed the manuscript before submission but was not involved in the study design, in the writing of the manuscript, or in the decision to submit the manuscript for publication.

Study Participants

Patients were recruited from 48 experienced centers in 12 countries. Patients were eligible if they were 18 years of age or older, had symptomatic persistent atrial fibrillation (i.e., a sustained episode lasting more than 7 days) refractory to at least one antiarrhythmic agent, and were undergoing ablation for the first time.[7] Exclusion criteria included paroxysmal atrial fibrillation, sustained atrial fibrillation lasting more than 3 years, and a left atrial diameter of 60 mm or greater. Detailed inclusion and exclusion criteria are provided in Table S1 in the Supplementary Appendix. All participating patients provided written informed consent.

Study Procedures

Patients were randomly assigned in a 1:4:4 ratio to one of the following three strategies: pulmonary-vein isolation alone (hereafter referred to as isolation alone), pulmonary-vein isolation plus ablation of complex fractionated electrograms (isolation plus electrograms), or pulmonary-vein isolation plus linear ablation across the roof of the left atrium and in the mitral valve isthmus (isolation plus lines) (Fig. 1, and Fig. S1 in the Supplementary Appendix). Randomization was performed with the use of an automated telephone system and stratified according to study site. Patients were unaware of the ablation strategy. Before ablation, treatment with antiarrhythmic medications was stopped and patients received oral anticoagulation for at least 4 weeks.

Ablation was performed with the use of radiofrequency energy delivered by a catheter with an open, irrigated tip. A three-dimensional mapping system (EnSite Velocity, St. Jude Medical) was used to guide the procedures. Details are provided in the Supplementary Appendix.

The use of antiarrhythmic medications was allowed during the first 3 months after the initial

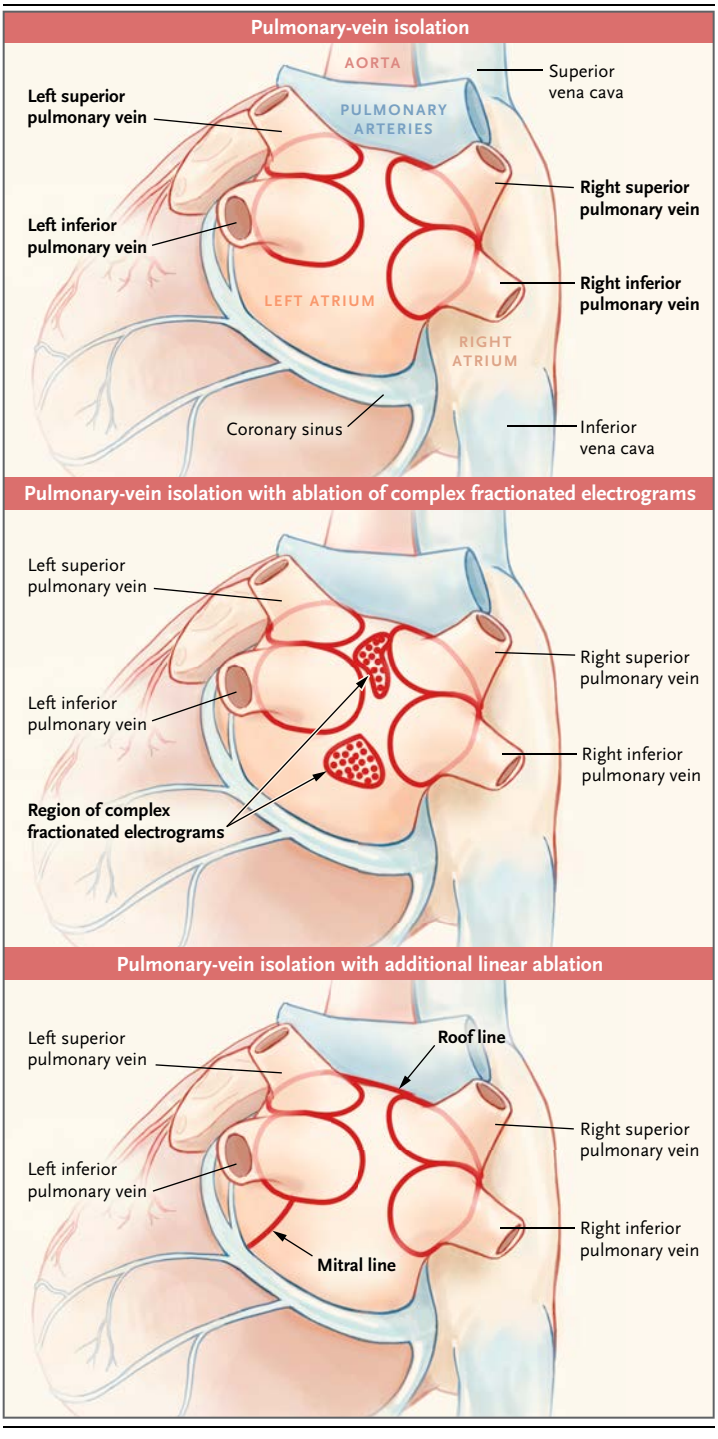


Figure 1. Three Strategies of Ablation for Persistent Atrial Fibrillation.

Patients randomly assigned to pulmonary-vein isolation had ablation lesions (red circles) encircling each pulmonary vein until all signals within each vein were abolished (entrance block), as confirmed by a circular catheter, and pacing inside each vein failed to conduct into the left atrium (exit block). For the strategy involving pulmonary-vein isolation plus complex fractionated electrograms, pulmonary-vein isolation (red circles) was followed by mapping and ablation of electrograms that showed either rapid or continuous electrical activity during atrial fibrillation; these were identified by validated, automated software in the mapping system. Electrograms were ablated until atrial fibrillation terminated to sinus rhythm or until all complex fractionated regions were completely eliminated. For the strategy involving pulmonary-vein isolation plus linear ablation, pulmonary-vein isolation (red circles) was followed by ablation of linear lesions along the left atrial roof and the mitral valve isthmus. Conduction block was confirmed by prespecified pacing maneuvers. The view is from the posterior.

ablation (the postablation "blanking period"[7]), after which their use was discouraged. Patients with recurrent atrial fibrillation after the blanking period were allowed to start or resume the use of antiarrhythmic medications; they were also allowed to undergo a repeat ablation by means of the strategy to which they were initially randomly assigned. If such a repeat ablation was deemed appropriate, we recommended that it be performed 3 to 6 months after the initial procedure. Anticoagulation was continued after ablation for a minimum of 3 months; after 3 months, anticoagulation treatment was administered at the discretion of the treating clinician.

Clinical assessments, 12-lead electrocardiograms, and 24-hour Holter-monitor recordings were obtained at baseline and at 3, 6, 9, 12, and 18 months after the initial ablation. Patients were given a transtelephonic monitor (Tele-ECG-Card, Vitaphone) for the 18-month follow-up period and were asked to transmit rhythm recordings weekly and any time they had symptoms such as palpitations, dizziness, or shortness of breath. Electrocardiograms and Holter-monitor recordings were read by clinicians who were unaware of the treatment assignments. Transmissions from the transtelephonic monitor were read independently by core laboratory personnel who were unaware of the treatment assignments.

STUDY OUTCOMES

The primary study outcome was freedom from any documented episode of atrial fibrillation last-

ing longer than 30 seconds and occurring after the performance of a single ablation procedure, with or without the use of antiarrhythmic medications. A clarification of the primary end point, as defined in the original trial protocol and in subsequent revisions, is included in the Supplementary Appendix.

For the primary outcome, no episode of atrial fibrillation occurring within the initial 3-month blanking period after ablation was counted, in accordance with the guidelines.[7] An episode of atrial fibrillation was considered part of the primary outcome analyses if it lasted longer than 30 seconds and was documented by any form of monitoring, regardless of symptoms. A repeat left atrial ablation procedure at any time was also considered to constitute a recurrence for the purpose of the outcome analyses. Patients who completed fewer than 3 months of follow-up and thus did not complete the blanking period were excluded from end-point analysis. There was no blanking period after a second procedure.

Main secondary outcomes included freedom from documented atrial fibrillation after two ablation procedures, freedom from any documented atrial arrhythmia (including atrial fibrillation, flutter, or tachycardia) after one ablation procedure and after two ablation procedures, use of antiarrhythmic medication, procedure time, incidence of repeat procedures, and incidence of periprocedural complications. Detailed definitions of the secondary outcomes are provided in the Supplementary Appendix.

An independent events committee, whose members were unaware of the study assignments, adjudicated all adverse events and their relation to ablation. Adverse events were also scrutinized for unreported outcomes.

STATISTICAL ANALYSIS

Sample-size calculations were based on a pilot study.[10] The expected freedom from atrial fibrillation after one ablation procedure was 75% for isolation plus electrograms and 45% for isolation alone. The pilot study did not include a group assigned to isolation plus lines, so freedom from atrial fibrillation for this procedure was estimated from the literature at 60%.[8,9,11] A one-sided log-rank test was used for sample-size calculation. To test whether the isolation-plus-electrograms strategy was superior to isolation plus lines and to isolation alone, we determined that 468 patients were needed, with a randomization ratio of 1:4:4 (a ratio of isolation alone to isolation plus electrograms to isolation plus lines), for the study to have a power of 90% at a one-sided alpha level of 0.025. The rationale for unequal randomization was that the expected success rate with isolation alone would be lower than that with the other procedures; the rationale was also based on guidelines suggesting that pulmonary-vein isolation alone was insufficient for these patients.[21] Assuming a dropout rate of 15%, we needed 549 patients (61 for isolation alone and 244 each for the other groups).

All outcome analyses were performed on patients who underwent an ablation procedure and were followed for longer than the initial 3-month blanking period. We performed survival analyses to compare study groups for the primary outcome and for time-to-event secondary outcomes. Kaplan–Meier curves were generated, and comparisons among the three groups were performed with the use of the log-rank test with two degrees of freedom. In addition, post hoc pairwise analysis was performed with the use of the Holm method. Subgroup analyses were performed with the use of Cox proportional-hazards regression; the interaction of each subgroup factor and treatment was tested. If the proportionality assumption was violated for a covariate, the interaction of time was added to the analysis.

Categorical variables, including percentages of patients who were not taking antiarrhythmic medications, were compared with the use of the Pearson's chi-square test or Fisher's exact test. Ordinal data were compared with the use of the Cochran–Mantel–Haenszel test. Continuous variables were compared with one-way analysis of variance (type III) or the Kruskal–Wallis test. No imputation was used. A two-sided P value of less than 0.05 was considered to indicate statistical significance. Data were managed with the use of Oracle Clinical software, version 4.5, and analyzed with the use of SAS software, version 9.2 (SAS Institute), and NCSS 2007 software.

RESULTS

PATIENTS

A total of 589 patients were enrolled between November 2010 and July 2012 and were randomly

Table 1. Characteristics of the Patients at Baseline.*

Characteristic	Isolation Alone (N=67)	Isolation plus Electrograms (N=263)	Isolation plus Lines (N=259)
Age — yr	58±10	60±9	61±9
Male sex — no. (%)	52 (78)	213 (81)	196 (76)
Ejection fraction — %	55±11	57±10	57±10
Left atrial diameter — mm	44±6	44±6	46±6
Time from first diagnosis of atrial fibrillation — yr	4.3±6.3	4.2±5.0	3.6±4.2
Burden of atrial fibrillation at baseline — hr/mo†	83±36	85±33	80±37
Constant atrial fibrillation for >6 mo — no. (%)	52 (78)	207 (79)	186 (72)
Medical history — no. (%)			
Hypertension	32 (48)	143 (54)	158 (61)
Diabetes	6 (9)	31 (12)	26 (10)
Coronary disease	2 (3)	21 (8)	29 (11)
Stroke or transient ischemic attack	6 (9)	14 (5)	19 (7)
Heart failure	3 (4)	10 (4)	15 (6)
$CHADS_2$ score — no. (%)			
0	31 (46)	93 (35)	81 (31)
1	25 (37)	126 (48)	127 (49)
2	6 (9)	31 (12)	29 (11)
>2	5 (7)	10 (4)	19 (7)
Baseline CCS SAF score — no./total no. (%)			
0	2/63 (3)	12/248 (5)	14/243 (6)
1	14/63 (22)	55/248 (22)	53/243 (22)
2	19/63 (30)	79/248 (32)	70/243 (29)
3	24/63 (38)	86/248 (35)	89/243 (37)
4	4/63 (6)	16/248 (6)	17/243 (7)
Baseline medications — no. (%)			
Beta-blocker	43 (64)	148 (56)	160 (62)
Calcium-channel blocker	9 (13)	42 (16)	46 (18)
Cardiac glycoside	8 (12)	39 (15)	39 (15)
Propafenone	2 (3)	2 (1)	7 (3)
Flecainide	8 (12)	32 (12)	28 (11)
Sotalol	3 (4)	13 (5)	15 (6)
Amiodarone	16 (24)	50 (19)	62 (24)
Dronedarone	3 (4)	19 (7)	15 (6)
Dofetilide	0	3 (1)	1 (<1)
Vitamin K antagonist	55 (82)	189 (72)	190 (73)
Oral direct thrombin inhibitor	5 (7)	27 (10)	23 (9)
Acetylsalicylic acid	5 (7)	29 (11)	29 (11)

* Plus–minus values are means ±SD. There were no significant differences between groups ($P<0.05$ was considered to indicate statistical significance). Isolation alone denotes ablation involving pulmonary-vein isolation, isolation plus electrograms denotes pulmonary-vein isolation plus additional ablation of complex fractionated electrograms, and isolation plus lines denotes pulmonary-vein isolation plus additional linear ablation. CCS SAF denotes the Canadian Cardiovascular Society Severity in Atrial Fibrillation scale, which grades a patient's symptoms of atrial fibrillation on a scale of 0 to 4, with 0 indicating asymptomatic and 4 indicating symptoms that have a severe effect on quality of life[22]; the $CHADS_2$ score is a measure of the risk of stroke in which congestive heart failure, hypertension, an age of 75 years or older, and diabetes mellitus are each assigned 1 point and previous stroke or transient ischemic attack is assigned 2 points; the score is calculated by summing all the points for a given patient, and a higher score corresponds to a higher risk of stroke.[23]

† The burden of atrial fibrillation at baseline applies only to patients who did not have constant atrial fibrillation for more than 6 months.

Table 2. Major Efficacy Outcomes.

Variable	Isolation Alone (N=61)	Isolation plus Electrograms (N=244)	Isolation plus Lines (N=244)	P Value
		number (percent)		
Freedom from documented atrial fibrillation after one procedure, with or without antiarrhythmic drugs	36 (59)	119 (49)	112 (46)	0.15
Freedom from documented atrial fibrillation after one procedure, without antiarrhythmic drugs*	29 (48)	90 (37)	81 (33)	0.11
Freedom from documented atrial arrhythmia after one procedure, with or without antiarrhythmic drugs	30 (49)	100 (41)	90 (37)	0.15
Freedom from documented atrial arrhythmia after one procedure, without antiarrhythmic drugs*	25 (41)	81 (33)	71 (29)	0.08
Freedom from documented atrial fibrillation after two procedures, with or without antiarrhythmic drugs	44 (72)	146 (60)	142 (58)	0.18
Freedom from documented atrial arrhythmia after two procedures, with or without antiarrhythmic drugs	37 (61)	122 (50)	117 (48)	0.24
Documented atrial flutter or tachycardia after one procedure, with or without antiarrhythmic drugs	7 (11)	27 (11)	34 (14)	0.57
Documented atrial flutter or tachycardia after two procedures, with or without antiarrhythmic drugs	7 (11)	32 (13)	29 (12)	0.98
Patients undergoing a second ablation procedure	13 (21)	63 (26)	81 (33)	0.10

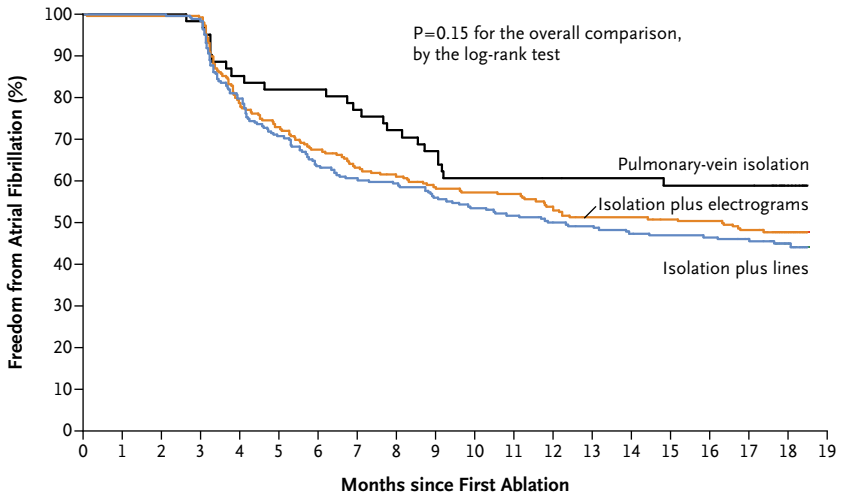
* P values are for the overall comparisons among the three groups. An unplanned post hoc, pairwise multiple comparison (performed with the use of the Holm method) showed that there was significantly less freedom from atrial fibrillation and from atrial arrhythmia, without antiarrhythmic medications, in the group assigned to isolation plus lines than in the group assigned to isolation alone (P=0.04 for both comparisons).

assigned to isolation alone (67 patients), isolation plus electrograms (263 patients), or isolation plus lines (259 patients) (see Fig. S2 in the Supplementary Appendix). Baseline characteristics were balanced between groups (Table 1).

A total of 21 patients did not receive any ablation after randomization, and 19 more dropped out before the end of the 3-month blanking period; these patients were not included in the outcome analyses. A total of 90% of patients receiving ablation completed the 18-month follow-up. Adherence to Holter monitoring at each visit was 85%, and adherence to a minimum of weekly transtelephonic transmission during the 18 months was 75% for all patients, with no significant differences between groups.

PROCEDURAL CHARACTERISTICS

At the time of ablation, 79% of patients were in spontaneous atrial fibrillation. Successful pulmonary-vein isolation was achieved in 97% of all patients, with no significant differences between groups. For the group assigned to isolation plus electrograms, complex fractionated electrograms were successfully eliminated in 80% of patients; in 11%, complex fractionated electrograms were not mapped according to the protocol because atrial fibrillation was noninducible after pulmonary-vein isolation; in 9%, all complex fractionated electrograms could not be eliminated. For the group assigned to isolation plus lines, all patients had the required lines performed, with 74% showing complete conduction block across both lines. Procedure time and exposure to fluoroscopy were significantly less for isolation alone as compared with isolation plus electrograms and as compared with isolation plus lines (P<0.001 for both comparisons). Repeat ablation was performed in 21% of patients in the group receiving isolation alone, 26% in the group receiving isolation plus electrograms, and 33% in the group receiving isolation plus lines (P=0.10 for between-group comparisons). See Table S2 in the Supplementary Appendix for further procedural details.



No. at Risk

Pulmonary-vein isolation	61	60	50	41	36	23
Isolation plus electrograms	244	242	161	137	124	72
Isolation plus lines	244	240	152	133	115	57

Figure 2. Freedom from Atrial Fibrillation.

The graph shows Kaplan–Meier estimates of freedom from documented atrial fibrillation more than 30 seconds after a single procedure, with or without the use of antiarrhythmic medications. There were no significant differences between groups (P=0.15). Isolation plus electrograms denotes ablation with pulmonary-vein isolation plus additional ablation of complex fractionated electrograms; isolation plus lines refers to ablation with pulmonary-vein isolation plus additional linear ablation.

PRIMARY OUTCOME

At 18 months, a documented recurrence of atrial fibrillation lasting longer than 30 seconds after one ablation procedure, with or without the use of antiarrhythmic medications, had occurred in 25 of 61 patients (41%) randomly assigned to isolation alone, 125 of 244 patients (51%) assigned to isolation plus electrograms, and 132 of 244 patients (54%) assigned to isolation plus lines. Rates of the primary outcome were not significantly different among the three groups (59% for the group receiving isolation alone, 49% for the group receiving isolation plus electrograms, and 46% for the group receiving isolation plus lines; P=0.15 for between-group differences) (Table 2 and Fig. 2).

Overall, 12% of patients who were free from recurrence of atrial fibrillation at 18 months were taking antiarrhythmic medications (7 patients in the group receiving isolation alone, 28 in the group receiving isolation plus electrograms, and 29 in the group receiving isolation plus lines). The rate of freedom from recurrence of atrial fibrillation after one procedure, without antiarrhythmic medication, was not significantly different among the three groups (Table 2).

SECONDARY OUTCOMES

Rates of freedom from atrial fibrillation after two ablation procedures, with or without antiarrhythmic medication, were not significantly different among groups (Table 2, and Fig. S3 in the Supplementary Appendix). Rates of freedom from any atrial arrhythmia, including atrial flutter and atrial tachycardia, after a single ablation procedure and after two ablation procedures were not significantly different among groups (Table 2, and Fig. S4 and S5 in the Supplementary Appendix).

The total burden of atrial fibrillation was significantly reduced after ablation and was not significantly different among the three groups (Fig. S6 in the Supplementary Appendix). Post hoc analyses showed that the group assigned to isolation plus lines had a significantly higher incidence of arrhythmia recurrence without an-

Table 3. Procedural Adverse Events.*

Adverse Event	Isolation Alone (N=64)	Isolation plus Electrograms (N=254)	Isolation plus Lines (N=250)	Total (N=568)
		number of events		
Hematoma at access site	2	0	3	5
Arteriovenous fistula or pseudoaneurysm at access site	0	3	3	6
Pericarditis	0	1	2	3
Fluid overload	0	1	3	4
Sedation-related complication	0	3	5	8
Skin burn	1	0	0	1
Cardiac tamponade	1	0	2	3
Transient ischemic attack or stroke	0	2	1	3
Death due to atrioesophageal fistula	0	1	0	1

* Adverse events are reported for patients who underwent an ablation procedure, regardless of whether they completed at least 3 months of follow-up. There were no significant differences between groups.

tiarrhythmic medication than did the group assigned to isolation alone (Table 2).

ADVERSE EVENTS

Periprocedural adverse events occurring in patients who underwent any ablation procedure are shown in Table 3. The most common adverse events were sedation-related complications (8 events), arteriovenous fistula or pseudoaneurysm at the access site (6 events), hematoma at the access site (5 events), and fluid overload (4 events). Of these 23 most frequently occurring adverse events, only 2 hematomas at the access site occurred in the group assigned to isolation alone; the remainder occurred in the groups assigned to isolation plus electrograms or isolation plus lines. Serious adverse events included 3 instances of cardiac tamponade and 3 instances of stroke or transient ischemic attack. In one patient in the group assigned to isolation plus electrograms, a procedure-related atrioesophageal fistula developed that was complicated by stroke; this was successfully treated by esophageal stenting, but the patient died 3 months later of aspiration pneumonia. Nonprocedural adverse events are shown in Table S3 in the Supplementary Appendix.

SUBGROUP ANALYSES

Pairwise subgroup analyses were performed for eight prespecified subgroups for each pair of assigned treatments (Fig. S7 in the Supplementary Appendix). No significant treatment-according-to-subgroup interactions were identified.

DISCUSSION

In this randomized trial, we evaluated three approaches to radiofrequency ablation for patients with persistent atrial fibrillation. We found no reduction in the rate of recurrent atrial fibrillation when either linear ablation or ablation of complex fractionated electrograms was performed in addition to ablation with pulmonary-vein isolation. These results, which were observed during 18 months of follow-up with rigorous monitoring, held across the primary outcome and all secondary outcomes. Our findings are not in accordance with the current guideline recommendation that patients with persistent atrial fibrillation who undergo pulmonary-vein isolation should have additional substrate ablation to improve outcome.[2,7]

Most published studies of catheter ablation have involved patients with paroxysmal atrial fibrillation.[7] Although we are aware of no large trials on the outcomes of ablation for persistent atrial fibrillation, small studies report lower success rates than those achieved in studies of paroxysmal atrial fibrillation.[9,24,25] Our data suggest that pulmonary-vein isolation alone can achieve a successful outcome in about half of patients,

with success rates close to 60% after two procedures, similar to the findings of a smaller trial.[19] Our data are also similar to results reported in larger studies involving patients with paroxysmal atrial fibrillation,[4,5,24] especially given our rigorous monitoring and follow-up for more than 12 months.

The reason for the lack of benefit associated with additional ablation in our trial is unclear. More extensive ablation may cause new, iatrogenic areas of arrhythmogenesis where tissue is incompletely ablated or linear block is not achieved.[26,27] However, in this study, the rates of successful complex electrogram ablation and achievement of linear block were high and consistent with those obtained by experienced operators.[10,18,27] Furthermore, the results did not change after two procedures. Perhaps neither complex electrograms nor lines are the correct supplemental targets for ablation.[17,28,29] More selective targets may be needed to better characterize an individual patient's specific arrhythmic substrate.

Performing additional, and perhaps unnecessary, ablation could increase risk. Procedure time in this study was longer by almost an hour in the additional-ablation groups and was associated with increased exposure to fluoroscopy for the patient and the operator. Although the overall rate of serious adverse events, such as tamponade or stroke, was very low in this trial, it is noteworthy that an atrioesophageal fistula led to the death of one patient who had received additional electrogram ablation after pulmonary-vein isolation.

Some important limitations of this trial should be considered. We did not include a group assigned to the combination of pulmonary-vein isolation, ablation of complex electrograms, and linear ablation. Single-center data have suggested that a combination of all three methods of ablation is superior to either one or two alone.[30] Such procedures are potentially effective, but they are also very long and not widely performed; risk is increased if operators only rarely perform such complex procedures.[31] After our study was designed, other supplemental targets, including identification of non–pulmonary-vein triggers[17] and rotational activity within the atria,[32] have been reported to be effective adjuvant ablation strategies. Although these targets may be important, our results suggest that any new strategy must be subjected to larger-scale study before wide implementation. Maneuvers to improve durability of pulmonary-vein isolation (e.g., adenosine provocation) may have influenced outcome, but we did not use such maneuvers, and data supporting the utility of this approach were not available at the time of this study. Finally, the 1:4:4 randomization ratio of pulmonary-vein isolation to other strategies means that the trial was underpowered to show whether pulmonary-vein isolation alone was superior to the combined strategies. At the time, guidelines and pilot data suggested that an additional strategy would be superior clinically. Although post hoc analysis suggested that pulmonary-vein isolation alone was superior to pulmonary-vein isolation plus linear ablation for selected outcomes, further investigation would be necessary.

In summary, we conducted a randomized trial to evaluate three approaches to radiofrequency ablation for patients with persistent atrial fibrillation. We found no reduction in the rate of recurrent atrial fibrillation when either linear ablation or ablation of complex fractionated electrograms was performed in addition to pulmonary-vein isolation.

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Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

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