ORIGINAL RESEARCH

# Does Additional Electrogram-Guided Ablation After Linear Ablation Reduce Recurrence After Catheter Ablation for Longstanding Persistent Atrial Fibrillation? A Prospective Randomized Study

Tae-Hoon Kim, MD; Jae-Sun Uhm, MD, PhD; Jong-Youn Kim, MD, PhD; Boyoung Joung, MD, PhD; Moon-Hyoung Lee, MD, PhD; Hui-Nam Pak, MD, PhD

***Background*—**Although circumferential pulmonary vein isolation (CPVI) catheter ablation may not be sufficient for long-standing persistent atrial fibrillation (L-PeAF), it is not clear which ablation strategy is beneficial in addition to CPVI. We sought to investigate whether additional complex fractionated atrial electrogram (CFAE)-guided ablation improves clinical outcomes in L-PeAF patients who exhibit continuous atrial fibrillation (AF) after CPVI and linear ablation (Line).

***Methods and Results*—**This study enrolled 137 L-PeAF patients (71.4% male, 61.6±10.9 years old) who underwent radiofrequency catheter ablation. We conducted CPVI+Line based on the Dallas lesion set (posterior box+anterior line) after baseline CFAE mapping in all patients. If AF was defragmented (terminated or changed to atrial tachycardia), the procedure was stopped (AF-Defrag group, n=29). If AF was maintained after CPVI+Line, we mapped the CFAE again and randomly assigned the patient to the CPVI+Line group (n=54) or the additional CFAE ablation group (CPVI+Line+CFAE group, n=54). L-PeAF was defragmented during CPVI+Line in 21.2% of patients (29/137, AF-Defrag group). The mean CFAE cycle length was prolonged ($P$<0.001), and CFAE area (CFAE cycle length <120 milliseconds) was reduced ($P$<0.001) after CPVI+Line in the remaining patients. Procedure time was longer in the CPVI+Line+CFAE group than the CPVI+Line group ($P$=0.023), but procedure-related complication rates did not vary. During 22.3±13.2 months of follow-up, the clinical recurrence rates were 17.2% in the AF-Defrag group, 18.5% in the CPVI+Line group, and 32.1% in the CPVI+Line+CFAE group (log rank, $P$=0.166).

***Conclusions*—**Although CPVI+Line reduces and localizes CFAE area, additional CFAE ablation after CPVI+Line does not improve the clinical outcomes of catheter ablation in patients with L-PeAF. **(*J Am Heart Assoc*. 2017;6:e004811. DOI: 10.1161/JAHA.116.004811.)**

**Key Words:** ablation • atrial fibrillation • catheter ablation • complex fractionated atrial electrogram ablation • linear ablation • persistent atrial fibrillation

Catheter ablation is an established treatment modality for atrial fibrillation (AF),[1] and circumferential pulmonary vein isolation (CPVI) is the cornerstone technique of AF catheter ablation,[2] particularly for paroxysmal AF. However, the maintenance mechanisms for persistent AF (PeAF) with complex atrial substrates and non–pulmonary vein (PV) triggers are different from their paroxysmal counterpart, and thus CPVI alone does not generally achieve a satisfactory clinical outcome in catheter ablation for PeAF.[3] Many additional substrate modification strategies for PeAF ablation have been proposed, the 2 most widely used of which are additional linear ablation (Line) and complex fractionated atrial electrogram (CFAE) ablation in conjunction with CPVI.[4,5] Many previous studies have demonstrated an incremental benefit of additional linear ablation following CPVI.[4–8] Similarly, some studies and meta-analyses have shown that CFAE performed in addition to CPVI produces better rhythm outcomes than CPVI alone in PeAF.[9,10] However, these efforts have seen only limited clinical success, less than 50% in long-standing PeAF (L-PeAF), raising the question as to whether the current additional strategies beyond CPVI are both appropriate and being performed in appropriate candidates. Moreover, a recent large randomized controlled trial, STAR AF II, failed to show any incremental benefit of additional CFAE ablation or Line following CPVI for PeAF patients with an AF burden of around 80 hours per month.[11] Because of unsatisfactory ablation outcomes in PeAF, several small studies have

*From the Yonsei University Health System, Seoul, Korea.*

An accompanying Table S1 is available at http://jaha.ahajournals.org/content/6/2/e004811/DC1/embed/inline-supplementary-material-1.pdf

**Correspondence to:** Hui-Nam Pak, MD, PhD, 50 Yonseiro, Seodaemun-gu, Seoul 120-752, Korea. E-mail: hnpak@yuhs.ac

Received October 7, 2016; accepted January 5, 2017.

combined the 2 additional strategies, namely, CFAE and linear ablation in addition to CPVI. However, conflicting results have been reported by these studies, raising concerns about the potentially proarrhythmic effects of extensive ablation.[12-14] We hypothesized that additional CFAE ablation might be the most beneficial technique and therefore should be performed only in L-PeAF patients for whom AF was not terminated or defragmented following CPVI and Line. Thus, the aims of this study were (1) to characterize the changes of CFAE area and mean cycle length (CL) before and after CPVI and Line, (2) to explore the prognostic value of additional CFAE ablation after CPVI and Line, and (3) to identify predictors of better clinical outcomes in patients with L-PeAF undergoing catheter ablation.

## Methods

### Study Population

The study protocol adhered to the principles of the Declaration of Helsinki and was approved by the Institutional Review Board at Yonsei University Health System. All patients provided written informed consent for inclusion in the Yonsei AF Ablation Cohort Database, and open-labeled simple randomization with equal allocation into 2 groups was achieved using a table of random numbers (ClinicalTrials.gov Identifier: NCT02175043). We chose the sample size on the basis of statistical analysis to prove the superiority of additional CFAE ablation after CPVI and linear ablation, which was described in a previous study comparing ablation strategies in patients with persistent AF. A 2-sided significance level of 5% was used against an estimated difference between the groups of 25%, and at least 47 patients in each group were required. Considering an AF defragmentation in 25% and a potential dropout rate of 5%, a total study cohort of 136 patients was calculated. The study population included 137 consecutive patients (71.4% male, age 61.6±10.9 years) with L-PeAF, which means AF lasting longer than 1-year (mean AF duration 56.5±53.9 months),[15] who underwent a catheter ablation procedure from June 2014 through December 2015 in Yonsei University Health System, Seoul, South Korea (Figure 1). AF duration was determined using electrocardiographic findings and not based on the presence of symptoms alone. After baseline CFAE mapping, we conducted CPVI and linear ablations using the consistent ablation protocol of the Dallas lesion set: CPVI, cavotricuspid isthmus ablation, posterior wall box lesion (roof line and posterior inferior line), and anterior line.[6] If AF continued after linear ablation, we

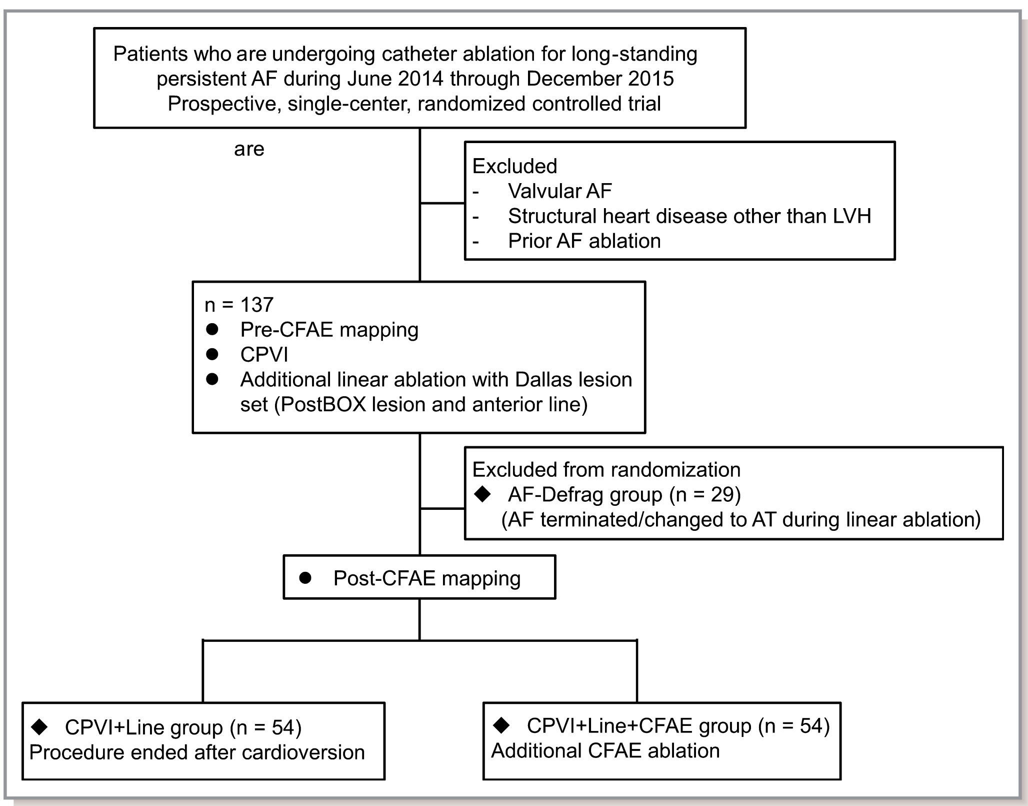


**Figure 1.** Study flowchart of patient distribution. AF indicates atrial fibrillation. CFAE, complex fractionated atrial electrogram; CPVI, circumferential pulmonary vein isolation; Line, linear ablation.

mapped CFAE again, and patients were prospectively and randomly assigned to 1 of 2 groups according to the radiofrequency catheter ablation (RFCA) method. In the CPVI+Line group, patients were cardioverted, and the procedure was finished without additional ablation (n=54), whereas in the CPVI+Line+CFAE group, additional CFAE ablation was performed (n=54). Patients whose AF terminated or changed to atrial tachycardia (AT) were excluded from randomization and classified in the AF-Defrag group (n=29) (Figure 1). We compared pre– and post–linear ablation CFAE maps and clinical outcomes of the CPVI+Line, CPVI+Line+CFAE, and AF-Defrag groups. Exclusion criteria were as follows: (1) permanent AF refractory to electrical cardioversion; (2) AF with valvular disease ≥grade 2; (3) associated structural heart disease other than left ventricular hypertrophy; (4) history of cardiac surgery; and (5) previous ablation procedure. Before all ablation procedures, the anatomy of the LA and PV was visually defined using 3-dimensional (3D)-CT scans (64 Channel, Light Speed Volume CT, Brilliance 63, Philips, Amsterdam, The Netherlands). All antiarrhythmic drugs were discontinued for a period of at least 5 half-lives, and amiodarone was stopped at least 4 weeks before the procedure.

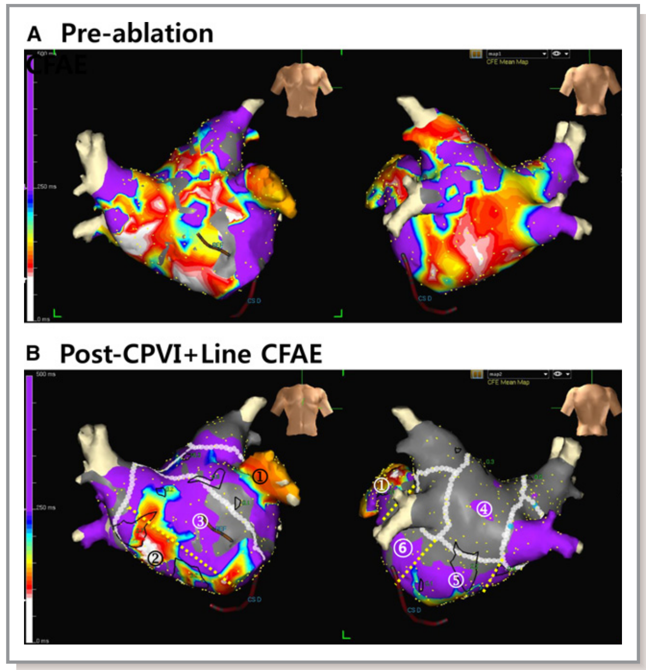


**Figure 2.** CFAE maps before (A) and after CPVI+linear ablation (B). B, LA was divided into 6 regions for CFAE regional analysis as follows: (1) LA appendage, (2) LA septum, (3) LA anterior wall, (4) LA posterior wall, (5) LA posterior inferior wall, and (6) LA isthmus area. Color indicates the mean CFAE cycle length (CFAE-CL) between multiple deflections over a specified period of time, which is represented on the geometric shell as a color-coded display. CFAE areas are defined as sites having a CFAE-CL of <120ms. AF indicates atrial fibrillation; CFAE, complex fractionated atrial electrogram; CPVI, circumferential pulmonary vein isolation; LA, left atrium.

## Electrophysiological Mapping

Intracardiac electrograms were recorded using the Prucka CardioLab™ Electrophysiology system (General Electric Medical Systems, Milwaukee, WI). RFCA was performed in all patients using 3D electroanatomical mapping (NavX, St Jude Medical, Inc, Minnetonka, MN) merged with 3D spiral CT. Double transseptal punctures were made, and multiview pulmonary venograms were obtained. After transseptal access had been secured, a circumferential PV-mapping catheter (Lasso; Biosense-Webster Inc, Diamond Bar, CA) was introduced with a long sheath (Schwartz left 1, St Jude Medical, Inc). Systemic anticoagulation was performed with intravenous heparin to maintain an activated clotting time of 350 to 400 seconds during the procedure. For electroanatomical mapping, the 3D geometries of both the LA and PV were obtained using the NavX system and were then merged with 3D spiral CT images.

## CFAE Mapping

We employed a previously validated CFAE mapping technique with an automated algorithm (NavX, St Jude Medical, Inc).[16] In brief, high-frequency atrial electrograms acquired using a Lasso catheter were analyzed to compute the mean CFAE cycle length (CFAE-CL) between multiple deflections over a specified period of time, which was represented on the geometric shell as a color-coded display. CFAE areas were defined as sites having a CFAE-CL of <120 milliseconds. The recommended CFAE-CL tool settings were peak-to-peak sensitivity of 0.03 to 0.05 mV (to avoid sensing noise), electrogram refractory period of 40 milliseconds, electrogram width of <15 milliseconds, and electrogram segment length of 5 seconds. A dense CFAE map (minimum 500 points) was made for the entire LA (Figure 2A). In all patients whose AF was maintained after linear ablation, post–linear ablation CFAE maps were acquired with the same protocol (Figure 2B). The LA was divided into 6 regions for CFAE regional analysis as follows: LA appendage, LA septum, LA anterior wall, LA posterior wall, LA posterior inferior wall, and left lateral isthmus area (Figure 2B).

## Radiofrequency Catheter Ablation

Details of the RFCA technique and strategy used in our center were described in our previous study.[17] Briefly, we used an open irrigated-tip catheter (Coolflex, St Jude Medical Inc, Minnetonka, MN; 25-35 W; irrigation rate of 10-15 mL/min) to deliver RF energy for ablation. All patients initially underwent CPVI and cavotricuspid isthmus ablation. Roof line, posterior inferior line, and anterior line[6] were added as the standard lesion set, also known as the “Dallas lesion set”

(Figure 2B). Adenosine-guided dormant conduction elimination strategy was not applied in PV isolation. To generate the posterior box lesion, linear ablation of the roof line and posterior inferior line was performed by connecting both sides of the CPVI at the top and bottom levels, respectively. The anterior line was generated by ablation from the mitral annulus at the 12 o'clock position toward the LA roof line.[6] Operators could opt to perform additional ablation in the superior vena cava or non-PV foci at their discretion. In the CPVI+Line+CFAE group, CFAE ablation procedures were guided by CFAE maps. After generating the protocol-directed lesion set, we restored sinus rhythm by internal cardioversion (10- to 20-J biphasic shocks, Physio-Control Corp, Redmond, WA), except for 6 patients whose AF defragmented during additional CFAE ablation. When bidirectional blocks of linear ablation lines were not achieved, additional ablation was performed to generate bidirectional blocks of these lines. However, if bidirectional blocks could not be achieved after 3 attempts of linear ablation, those lines were kept unblocked to avoid collateral damage. If there were mappable AF triggers or atrial premature beats with isoproterenol infusion (5 μg/min), we carefully mapped and ablated the non-PV foci as much as possible. All RFCA procedures were conducted according to the protocol specified above by 2 operators with more than 10 years of experience.

## Postablation Management and Follow-Up

Among 137 patients, 35 (26.2%) maintained antiarrhythmic medication before AF recurrence because of a high chance of recurrence with frequent atrial premature beats or short runs of nonsustained AT. Patients visited the outpatient clinic regularly 1, 3, 6, and 12 months after RFCA and then every 6 months thereafter or whenever they experienced symptoms. All patients underwent electrocardiography during every visit and 24-hour Holter recording at 3 and 6 months and then every 6 months thereafter in accordance with the 2012 HRS/EHRA/ECAS Expert Consensus Statement guidelines.[18] However, patients reporting symptoms of palpitations underwent Holter monitor or event monitor recordings and were evaluated for the possibility of arrhythmia recurrence. The primary endpoint was clinical recurrence of atrial tachyarrhythmia as any episode of AF or AT at least 30 seconds in duration.[18] Any electrocardiographic documentation of AF/AT recurrence after 3 months of the blanking period was diagnosed as clinical recurrence.[18] Secondary endpoints were clinical recurrence of AF/AT off antiarrhythmic drugs, periprocedural complications, total procedure time, and ablation time. However, AF/AT recurrence in the first 3 months after catheter ablation (blanking period) was counted as early recurrence. Early recurrence was neither classified as clinical AF/AT recurrence nor used in all data analyses.

## Statistical Analysis

Statistical analysis was performed using SPSS (Statistical Package for Social Sciences, Chicago, IL) software for Windows (version 20.0). Continuous variables were expressed as the mean±SD and were compared using ANOVA and Student t test. Categorical variables were reported as frequencies (percentage) and were compared using chi-squared test and Fisher exact test. Pre- and post-CFAE mapping data were compared using paired t tests. Kaplan-Meier analyses with log-rank tests were used to calculate AF recurrence-free survival over time and to compare recurrence rates across groups. Multivariate Cox regression analyses were used to assess independent predictors of AF recurrence after catheter ablation. A $P<0.05$ (2-sided) was considered statistically significant.

# Results

## Baseline Characteristics and CFAE Mapping

Baseline characteristics of the overall study population among AF-Defrag, CPVI+Line, and CPVI+Line+CFAE groups are shown in Table 1. There were no significant differences in patient characteristics between the CPVI+Line group and the CPVI+Line+CFAE group, nor among all 3 groups. We acquired baseline CFAE-CL maps in all 137 patients, and baseline CFAE-CLs were not significantly different among the 3 groups (Figure 3A and 3B). AF was terminated (n=20) or changed to AT (n=9) during CPVI and linear ablation in 29 patients (AF Defrag group, 21.2%), and thus, post–linear ablation CFAE-CL maps were available for 108 patients who were subsequently randomized. After linear ablation using the Dallas lesion set, mean CFAE-CL was significantly prolonged ($P<0.001$), and CFAE area (CFAE-CL <120 milliseconds) was significantly reduced regardless of LA region ($P<0.001$, Figure 3C and 3D). The mean 33.9±36.2% of post–linear CFAE area was colocalized with the preablation CFAE area.

## Procedural Characteristics

The CPVI+Line+CFAE group had a longer total procedure time than the CPVI+Line group ($P$=0.023; Table 2). In contrast, there was no difference in procedure-related complication rates between the 2 groups ($P$=0.696). Total procedure time ($P$=0.061), ablation time ($P$=0.539), complication rates ($P$=0.924), and postprocedural antiarrhythmic drug persistence rates ($P$=0.531) were not significantly different among the AF-Defrag, CPVI+Line, and CPVI+Line+CFAE groups (Table 2). LA posterior wall isolation was achieved in 51.8% (71/137) of the total population and in 58.6% (17/29), 42.6% (23/54), and 57.4% (31/54) in the AF-Defrag group,

**Table 1.** Comparison of Baseline Characteristics

| | AF-Defrag (n=29) | CPVI+Line (n=54) | CPVI+Line+CFAE (n=54) | *P* Value* | *P* Value† |
|---|---|---|---|---|---|
| Male (%) | 21 (72.4%) | 35 (64.8%) | 44 (81.5%) | 0.051 | 0.149 |
| Age, y | 63.76±11.76 | 62.59±9.68 | 59.31±11.44 | 0.111 | 0.140 |
| AF duration, months | 45.67±42.20 | 61.82±63.69 | 57.48±50.75 | 0.724 | 0.510 |
| BSA, $m^2$ | 1.79±0.19 | 1.78±0.17 | 1.84±0.19 | 0.085 | 0.222 |
| BMI, $kg/m^2$ | 25.39±2.81 | 25.08±2.74 | 25.22±2.90 | 0.804 | 0.892 |
| $CHA_2DS_2$-VASc score | 2.72±2.10 | 2.72±1.97 | 2.04±1.64 | 0.052 | 0.057 |
| Heart failure (%) | 8 (27.6%) | 12 (22.2%) | 11 (20.4%) | 0.814 | 0.752 |
| Hypertension (%) | 18 (62.1%) | 35 (64.8%) | 29 (53.7%) | 0.240 | 0.481 |
| Diabetes mellitus (%) | 6 (20.7%) | 15 (27.8%) | 12 (22.2%) | 0.505 | 0.709 |
| Stroke/TIA (%) | 7 (24.1%) | 11 (20.4%) | 8 (14.8%) | 0.448 | 0.555 |
| Vascular disease (%) | 5 (17.2%) | 15 (27.8%) | 9 (16.7%) | 0.165 | 0.311 |
| Echocardiographic parameters | | | | | |
| LA diameter, mm | 44.69±5.15 | 45.43±6.14 | 45.24±5.40 | 0.868 | 0.850 |
| LAVI, $mL/m^2$ | 43.13±13.72 | 46.71±15.05 | 43.00±12.47 | 0.174 | 0.334 |
| LVEDD, mm | 50.28±5.82 | 50.19±4.95 | 51.31±6.05 | 0.291 | 0.532 |
| LVEF, % | 61.34±11.30 | 58.94±9.82 | 61.69±8.21 | 0.118 | 0.292 |
| LVMI, $g/m^2$ | 95.76±21.71 | 99.99±24.47 | 97.97±29.98 | 0.716 | 0.807 |
| E/Em | 11.44±3.50 | 11.60±4.71 | 10.33±5.24 | 0.195 | 0.348 |
| LAVI by CT | 97.76±19.31 | 108.91±31.88 | 100.16±21.93 | 0.135 | 0.156 |

Values are expressed as n (%) or mean±SD. BMI indicates body mass index; BSA, body surface area; $CHA_2DS_2$-VASc score, the scoring system that estimates stroke risk of non-valvular AF patients based on the presence of Congestive heart failure, hypertension, Age ≥75 (doubled), Diabetes mellitus, prior Stroke or transient ischemic attack (doubled)-Vascular disease, Age 65–74 years and Sex category (female); E/Em, the ratio of early diastolic mitral inflow velocity (E) to early diastolic mitral annular velocity (Em); LA, left atrium; LAVI, LA volume index; LV, left ventricle; LVEDD, LV end diastolic dimension; LVEF, LV ejection fraction; LVMI, LV mass index; TIA, transient ischemic attack.
**P*-values between the CPVI+Line and CPVI+Line+CFAE groups.
†*P*-values among all 3 groups.

CPVI+Line group, and CPVI+Line+CFAE group, respectively (Table 2).

## Additional CFAE and Clinical Outcomes

During 22.3±13.2 months of follow-up, 32 of 137 patients (23.4%) experienced clinical recurrence of AF. Kaplan-Meier analysis of AF recurrence-free rates showed no significant differences between the AF-Defrag group and AF-sustained groups (*P*=0.339, Figure 4A), nor between the 2 randomized (CPVI+Line vs CPVI+Line+CFAE) groups (log-rank *P*=0.119, Figure 4B). There were also no significant differences among the 3 groups (*P*=0.166, Figure 4C). The proportion of patients taking antiarrhythmic drugs 3 months after ablation was not significantly different among the 3 groups (Table 2), and the clinical rhythm outcomes of the patients without antiarrhythmic drugs were consistent with the overall patient set (Figure 5). According to Cox regression analysis for clinical recurrence of AF among the patients whose AF persisted after linear ablation and were randomized, additional CFAE ablation after linear ablation did not improve clinical outcome of catheter ablation in univariate analysis (HR 1.84, 95% CI 0.84-4.02, *P*=0.128); however, a larger LA volume index measured by heart CT was independently associated with clinical recurrence in multivariate analysis (HR 1.02, 95% CI 1.00-1.03, *P*=0.016; Table 3). Among all patients in the study, both a larger LA volume index (CT; HR 1.02, 95% CI 1.01-1.04, *P*=0.004) and additional CFAE ablation (HR 2.66, 95% CI 1.15-6.17, *P*=0.022) were independently associated with clinical recurrence after catheter ablation for long-standing PeAF in multivariate Cox regression analysis (Table 4).

Among 32 patients with clinical (AF/AT) recurrence, there were no differences in the proportion of patients who required redo ablation procedures (35.7% vs 27.8% *P*=0.712, 7.3% of overall patients). The achievement of bidirectional block of linear lesions also did not affect patterns of recurrence type (AT vs AF recurrence, Table S1). A total of 13.9% (19/137) of patients had non-PV triggers during the ablation procedure; however, their clinical recurrence rate (7/19, 36.8%) was not statistically different from that for negative non-PV trigger patients (25/118, 21.2%, *P*=0.150).

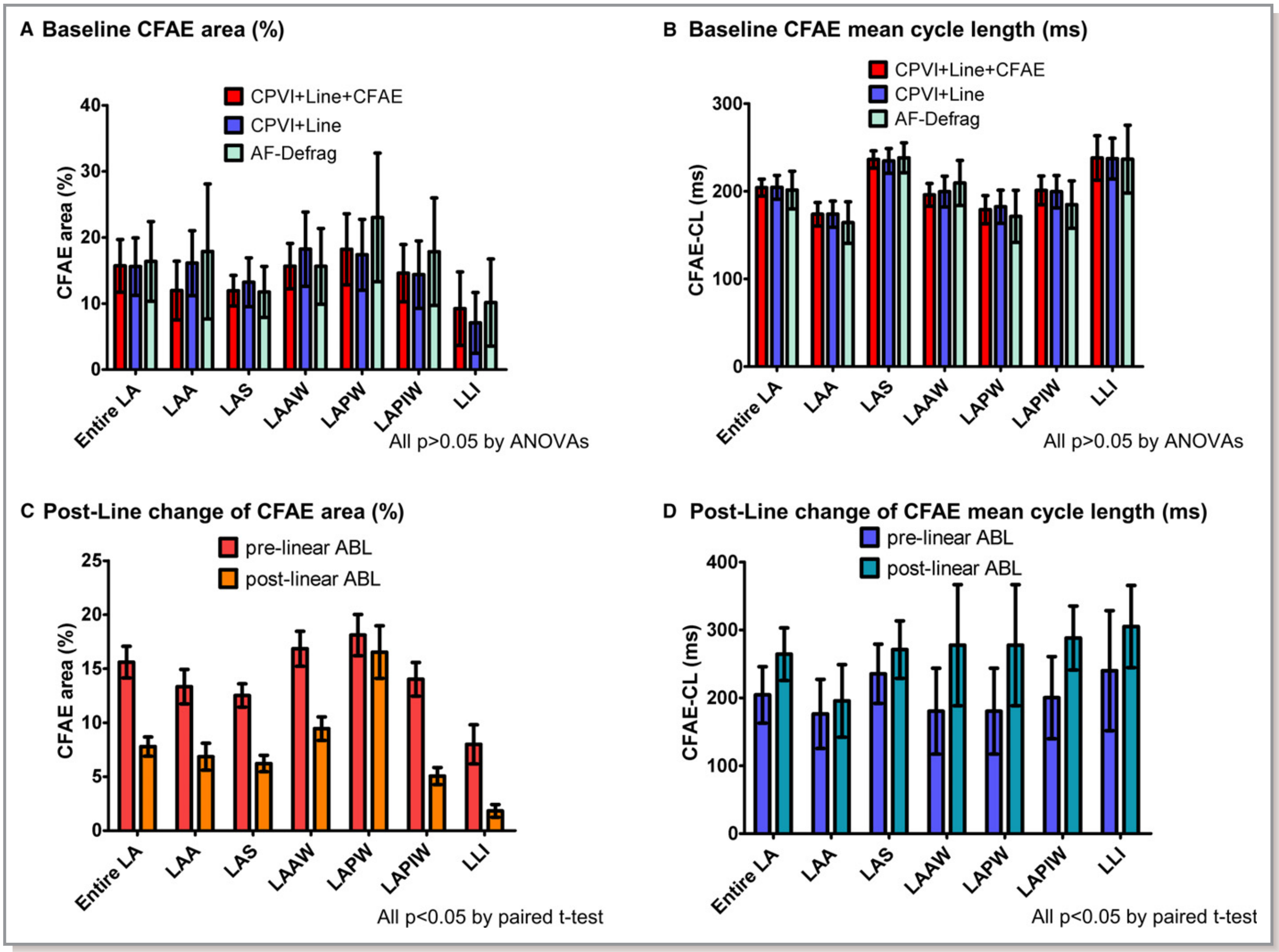


**Figure 3.** Comparisons of CFAE area (%) and CFAE mean cycle length (milliseconds) among the 3 groups (baseline, A, and B), and between pre– and post–linear ablations in the 2 randomized groups (C and D). ABL indicates ablation; AF, atrial fibrillation; AF-Defrag, AF terminated/changed to AT during linear ablation; CFAE, complex fractionated atrial electrogram; CPVI, circumferential pulmonary vein isolation; LA, left atrium; LAA, LA appendage; LAAW, LA anterior wall; LAPIW, LA posterior inferior wall; LAPW, LA posterior wall; LAS, LA septum; Line, linear ablation; LLI, left lateral isthmus area.

## Discussion

The main finding of this prospective randomized study was that additional CFAE ablation did not improve clinical outcome of catheter ablation in patients with L-PeAF who underwent catheter ablation with CPVI and empirical Line with Dallas lesion set (posterior box lesion and anterior line). During CPVI and linear ablation, 21.2% of patients showed AF termination or defragmentation to AT, whereas the remainder demonstrated prolongation of mean CFAE-CL and reduced CFAE area compared to their preablation CFAE map. However, AF defragmentation or termination did not affect clinical outcomes. Compared to CPVI+Line, additional CFAE ablation prolonged procedure time without improving AF-free survival after L-PeAF ablation. Among all of the patients included in this study, a larger LA volume index and additional CFAE were independently associated with clinical recurrence of AF.

## Controversies in CFAE Ablation

CFAE was first reported during intraoperative mapping by Konings et al and is mostly observed in areas of slow conduction and/or at pivot points, where wavelets turn around at the end of the arcs of functional blocks.[19] Nademanee et al demonstrated that CFAEs could be the critical site for AF perpetuation and are an ideal target site for extensive ablation, reporting a 91% success rate of PeAF ablation at 1-year follow-up.[20] However, subsequent randomized studies have revealed conflicting results,[21,22] and the exact mechanisms of CFAE formation by which elimination of CFAE can improve AF-free survival remain unclear. CFAE may

**Table 2.** Comparison of Procedural Results and Clinical Outcomes

| | AF-Defrag (n=29) | CPVI+Line (n=54) | CPVI+Line+CFAE (n=54) | *P* Value* | *P* Value† |
|---|---|---|---|---|---|
| Procedural result | | | | | |
| Procedure time, min | 230.17±48.01 | 219.54±60.70 | 244.91±53.14 | 0.023‡ | 0.061 |
| Ablation time, s | 6842±1223 | 6677±917 | 6956±1631 | 0.276 | 0.539 |
| Complications§ | 2 (6.9%) | 3 (5.6%) | 4 (7.4%) | 0.696 | 0.924 |
| Major complications | 0 (0%) | 0 (0%) | 1‖ (1.9%) | 0.315 | 0.461 |
| BDB achievement | | | | | |
| RL | 25/29 (86.2%) | 49/54 (90.7%) | 45/54 (83.3%) | 0.252 | 0.519 |
| PIL (LAPW isolation) | 17/29 (58.6%) | 23/54 (42.6%) | 31/54 (57.4%) | 0.211 | 0.373 |
| AL | 21/29 (72.4%) | 42/54 (77.8%) | 41/54 (75.9%) | 0.820 | 0.862 |
| Clinical outcomes | | | | | |
| Follow-up, mo | 23 [17-28] | 21 [10-33] | 26 [10-35] | 0.209 | 0.433 |
| Early recurrence | 7/29 (24.1%) | 19/54 (35.2%) | 21/54 (38.9%) | 0.690 | 0.396 |
| AF/AT recurrence | 5/29 (17.2%) | 10/54 (18.5%) | 17/53 (32.1%) | 0.106 | 0.170 |
| AT recurrence | 3/29 (10.3%) | 3/54 (5.6%) | 12/54 (22.2%) | 0.012‡ | 0.035‡ |
| The proportion of recurrence mode | | | | 0.057 | 0.131 |
| AF | 2/5 (40.0%) | 7/10 (70.0%) | 5/54 (29.4%) | | |
| AT | 3/5 (60.0%) | 3/10 (30.0%) | 12/54 (70.6%) | | |
| AAD after blanking period | 6/29 (20.7%) | 11/54 (20.4%) | 15/54 (27.8%) | 0.368 | 0.615 |
| AF/AT recurrence or AAD use as recurrence endpoint | 7/29 (24.1%) | 15/54 (27.8%) | 21/54 (38.9%) | 0.221 | 0.294 |
| AF/AT recurrence in AAD off population | 2/23 (8.7%) | 5/43 (11.6%) | 8/39 (20.5%) | 0.271 | 0.422 |

Values are expressed as n (%), mean±SD or median [interquartile range]. AAD indicates antiarrhythmic drug; AF, atrial fibrillation; AL, anterior line; AT, atrial tachycardia; BDB, bidirectional block; LA, left atrium; LAPW, LA posterior wall; PIL, posterior inferior line; RL, roof line.

**P*-values between the CPVI+Line and CPVI+Line+CFAE groups.

†*P*-values among all 3 groups.

‡$P<0.05$.

§1 case of transient respiratory arrest related to anesthesia, 2 cases of groin puncture site complications that did not require additional surgery or procedures, 5 cases of transient sick sinus node syndrome not requiring pacemaker.

‖1 case of atrioesophageal fistula.

reflect slow conduction with wavelet collision,[19] wavebreaks near high-frequency drivers,[23] locations of epicardial ganglionated plexi,[24] or remote activity at the recording site.[25] Although some of these mechanisms could explain the critical sites for AF perpetuation, others suggest a bystander role. The percentage CFAE area is usually lower in PeAF than

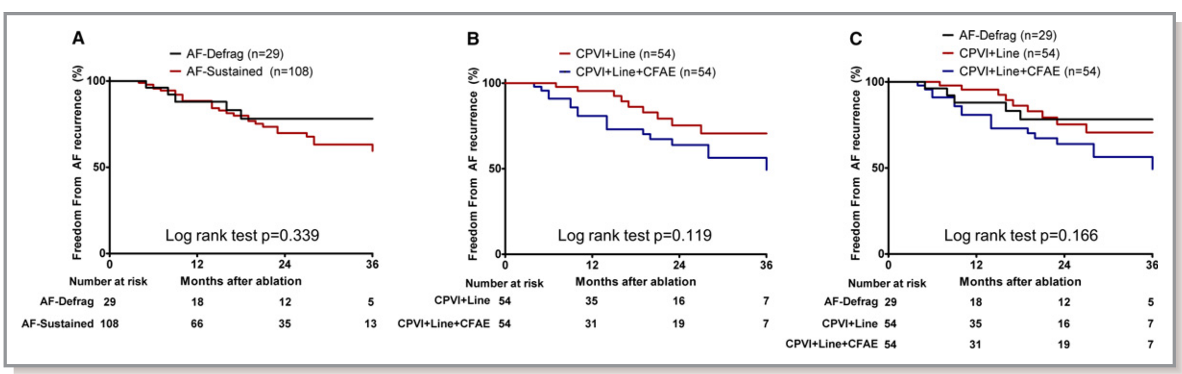


**Figure 4.** Kaplan-Meier analysis of AF recurrence-free rates in AF-Defrag vs AF-sustained group (A), CPVI+Line vs CPVI+Line+CFAE groups (B), and among AF-defrag vs CPVI+Line vs CPVI+Line+CFAE groups (C). AF-Sustained group=Both CPVI+Line group and CPVI+Line+CFAE group. AF indicates atrial fibrillation; AF-Defrag, AF terminated/changed to AT during linear ablation; CFAE, complex fractionated atrial electrogram; CPVI, circumferential pulmonary vein isolation; Line, linear ablation.

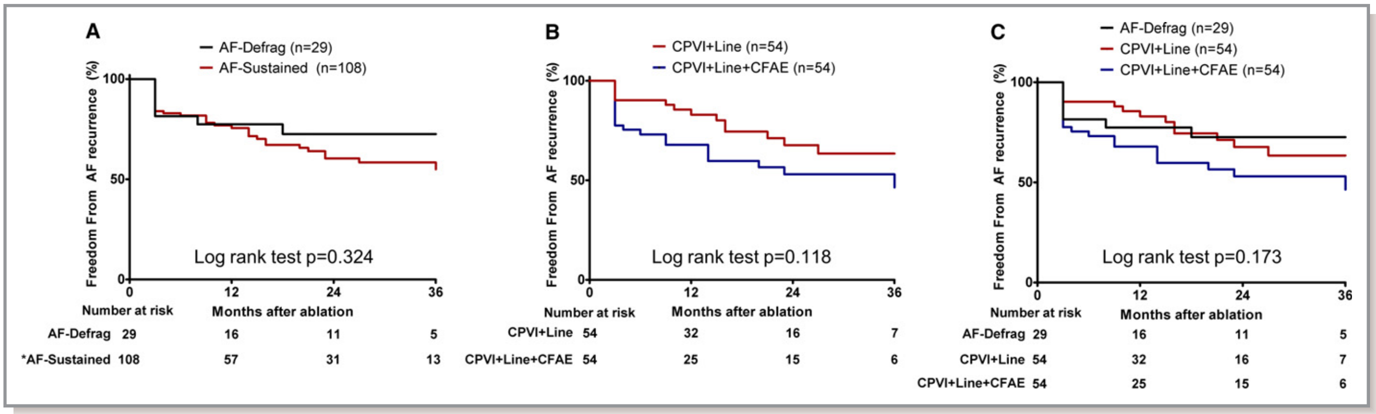


**Figure 5.** Kaplan-Meier analysis of freedom from AF recurrence without antiarrhythmic drugs in AF-Defrag vs AF-sustained groups (A), CPVI+Line vs CPVI+Line+CFAE groups (B), and among AF-defrag vs CPVI+Line vs CPVI+Line+CFAE groups (C). *AF-Sustained group=Both CPVI+Line group and CPVI+Line+CFAE group. AF indicates atrial fibrillation; AF-Defrag, AF terminated/changed to AT during linear ablation; CFAE, complex fractionated atrial electrogram; CPVI, circumferential pulmonary vein isolation; Line, linear ablation.

paroxysmal AF[26] and is more likely to be present in a healthy atrium, particularly in the septum, rather than a dense scar.[27] Extensive CFAE ablation may generate an unnecessary scar that is proarrhythmic after a long-duration of ablation in patients with PeAF.[28,29] Therefore, in this study, we reduced the CFAE area as much as possible using linear ablation and evaluated the effect of additional CFAE ablation. Spatiotemporal reproducibility of an AF driver or high dominant

**Table 3.** Cox Regression Analysis of Clinical Variables Predictive of AF Clinical Recurrence After Catheter Ablation in the AF-Sustained Group

| Clinical Recurrence | Univariate Analysis | | Multivariate Analysis | |
|---|---|---|---|---|
| | HR (95% CI) | *P* Value | HR (95% CI) | *P* Value |
| Additional CFAE | 1.84 (0.84–4.02) | 0.128 | | |
| Male | 1.38 (0.58–3.26) | 0.469 | 1.98 (0.72–5.49) | 0.187 |
| Age | 0.99 (0.95–1.03) | 0.657 | 1.02 (0.97–1.07) | 0.429 |
| AF duration | 1.00 (1.00–1.00) | 0.686 | | |
| BSA | 1.29 (0.18–8.99) | 0.800 | | |
| BMI | 1.01 (0.88–1.15) | 0.944 | | |
| E/Em | 1.02 (0.95–1.10) | 0.548 | | |
| LVEF (%) | 0.99 (0.95–1.04) | 0.701 | | |
| LA diameter | 0.98 (0.92–1.05) | 0.602 | | |
| LA volume index by TTE | 1.02 (0.99–1.05) | 0.251 | | |
| LA volume index by CT | 1.01 (1.00–1.03) | 0.032† | 1.02 (1.00–1.03) | 0.016* |
| Heart failure | 0.99 (0.42–2.34) | 0.975 | | |
| Hypertension | 0.91 (0.42–1.98) | 0.814 | | |
| Diabetes mellitus | 0.93 (0.37–2.30) | 0.869 | | |
| Stroke/TIA | 0.61 (0.30–1.26) | 0.181 | | |
| BDB of RL | 1.23 (0.37–4.11) | 0.736 | | |
| BDB of PIL (LAPW isolation) | 1.19 (0.56–2.56) | 0.649 | | |
| BDB of AL | 1.37 (0.51–3.68) | 0.533 | | |

AF indicates atrial fibrillation; AL, anterior line; AT, atrial tachycardia; BDB, bidirectional block; BMI, body mass index; BSA, body surface area; CFAE, complex fractionated atrial electrogram; CI, confidence interval; E/Em, the ratio of early diastolic mitral inflow velocity (E) to early diastolic mitral annular velocity (Em); HR, hazard ratio; LA, left atrium; LAPW, LA posterior wall; LV, left ventricle; LVEF, LV ejection fraction; PIL, posterior inferior line; RL, roof line; TIA, transient ischemic attack; TTE, transthoracic echocardiography.
AF-Sustained group consists of CPVI+Line group and CPVI+Line+CFAE group.
*$P<0.05$.

**Table 4.** Cox Regression Analysis of Clinical Variables Predictive of AF Clinical Recurrence After Catheter Ablation in the Total Patient Population

| Clinical Recurrence | Univariate Analysis | | Multivariate Analysis | |
|---|---|---|---|---|
| | HR (95% CI) | *P* Value | HR (95% CI) | *P* Value |
| Additional CFAE | 1.92 (0.96–3.86) | 0.066 | 2.66 (1.15–6.17) | 0.022* |
| Male | 1.42 (0.63–3.16) | 0.396 | 2.26 (0.84–6.11) | 0.107 |
| Age | 1.00 (0.96–1.03) | 0.880 | 1.02 (0.98–1.07) | 0.331 |
| AF duration | 1.00 (1.00–1.00) | 0.486 | | |
| BSA | 0.78 (0.13–4.80) | 0.792 | | |
| BMI | 0.98 (0.86–1.11) | 0.705 | | |
| E/Em | 1.01 (0.94–1.08) | 0.846 | | |
| LVEF (%) | 1.00 (0.96–1.04) | 0.969 | | |
| LA diameter | 0.97 (0.91–1.04) | 0.388 | | |
| LA volume index by TTE | 1.01 (0.99–1.04) | 0.393 | | |
| LA volume index by CT | 1.02 (1.00–1.03) | 0.017* | 1.02 (1.01–1.04) | 0.004* |
| Heart failure | 1.18 (0.55–2.56) | 0.667 | | |
| Hypertension | 0.93 (0.46–1.89) | 0.844 | | |
| Diabetes mellitus | 1.01 (0.44–2.35) | 0.979 | | |
| Stroke/TIA | 0.65 (0.36–1.17) | 0.152 | | |
| BDB of RL | 0.86 (0.33–2.24) | 0.759 | | |
| BDB of PIL (LAPW isolation) | 1.17 (0.58–2.35) | 0.670 | | |
| BDB of AL | 1.48 (0.60–3.62) | 0.395 | | |

AF indicates atrial fibrillation; AL, anterior line; AT, atrial tachycardia; BDB, bidirectional block; BMI, body mass index; BSA, body surface area; CFAE, complex fractionated atrial electrogram; CI, confidence interval; E/Em, the ratio of early diastolic mitral inflow velocity (E) to early diastolic mitral annular velocity (Em); HR, hazard ratio; LA, left atrium; LAPW, LA posterior wall; LV, left ventricle; LVEF, LV ejection fraction; PIL, posterior inferior line; RL, roof line; TIA, transient ischemic attack; TTE, transthoracic echocardiography.
*$P<0.05$.

frequency site was reported to be relatively low,[30] and a mean 34% of post–linear ablation CFAE area was colocalized with preablation CFAE in this study. Moreover, identifying optimal target sites for CFAE ablation is usually dependent on a subjective visual approach, and even objective and reproducible automated software has failed to have a significant impact on ablation outcomes.[31]

## Optimal Ablation Strategy for Long-Standing PeAF

The STAR AF-II trial indicated that additional CFAE or linear ablation following CPVI increases procedural time and does not improve ablation outcomes in patients with PeAF.[11] Furthermore, CPVI alone has produced disappointing long-term success for maintenance of sinus rhythm in patients with L-PeAF. On the other hand, highly successful ablation outcomes in PeAF ablation have been reported for the combination of sequential CPVI and elimination of complex atrial electrical activity followed by linear ablation in a "stepwise" approach.[32] Because many previous randomized controlled studies have shown an incremental benefit of linear ablation following CPVI,[4-8] linear ablation seems to reduce critical mass via LA compartmentalization,[33,34] both initiation and perpetuation of AF, and CFAE area[35,36] by changing AF wave dynamics.[36]

Recently, several studies have suggested that CFAE ablation after CPVI and linear ablation may minimize unnecessary collateral damage to the atrium with similar clinical efficacy as the "stepwise" approach.[13,36] However, a randomized study by Wong et al reported no benefit of CFAE ablation after CPVI and linear ablation in PeAF.[14] Therefore, in the present study, we recruited and randomized L-PeAF patients who did not have AF defragmentation after linear ablation, and our results were consistent with the previous study. The proportion of AT recurrence (excluding AF recurrence) seemed to be higher in the CPVI+Line+CFAE group than in the other groups ($P=0.035$), although some of them were taking antiarrhythmic drugs at the timing of clinical recurrence. Furthermore, in overall patients including the AF-Defrag group, CFAE ablation in addition to linear ablation appeared to be an independent predictor for clinical recurrence of AF (Table 4). Additional CFAE ablation seems to generate unnecessary scarring with worsened rhythm outcomes. Although the extent of CFAE ablation in the current study may be controversial, such as right atrial CFAE,[37] it is not clear whether the antifibrillatory effect of extensive CFAE ablation represents true trigger ablation[38] or a reduction in critical mass. Several new strategies for AF ablation have been introduced, such as rotor,[39] dominant frequency,[40] or driver domain.[41] However, optimal mapping and ablation strategies for L-PeAF remain challenging and controversial, and operators need to keep in mind the concept of "more touch, more scar."

## Future Directions

Ablation of L-PeAF is challenging, and the benefit of the 2 most widely used substrate modification strategies, CFAE and linear ablation, remains uncertain. For linear ablation, long-lasting bidirectional block may guarantee favorable outcomes. For CFAE ablation, localization and mapping of true functional CFAE is an important issue. However, both strategies require extensive ablation and carry with them the risk of collateral damage and inadvertent scar generation. Careful mapping and ablation for non-PV triggers could result in better clinical outcomes.[42] Patient-specific substrate modification strategies targeting rotors[39] or low-voltage areas[43] have produced encouraging early results but need to be verified in further studies. Therefore, AF ablation should be considered at the earlier stage of AF progression as much as possible,[44] and careful patient selection according to clinical or genetic factors may improve the outcomes of catheter ablation for L-PeAF.[45]

## Limitations

Our study should be interpreted in the context of the following limitations. First, because the current study included a relatively small number of patients from a single center, the findings cannot be generalized to all patients with L-PeAF. Second, this study could have inherited biases because of the study design with open-labeled simple randomization. Third, because there was no CPVI-alone group, which may achieve similar or even better efficacy, optimal ablation strategy for L-PeAF cannot be clearly suggested in this study. Fourth, CFAE ablation was limited to the LA in this study. Fifth, CFAE detection by a single system (NavX system) could be a limitation because there are significant discordances in CFAE mapping depending on the system and its settings.[46]

## Conclusions

We conducted a prospective randomized study to compare 2 different ablation strategies for L-PeAF and demonstrated that additional CFAE ablation after CPVI and linear ablation does not improve clinical outcomes despite more extensive ablation and longer procedure time.

## Sources of Funding

This work was supported by a grant (A085136) from the Korea Health 21 R&D Project, Ministry of Health and Welfare.

## Disclosures

None.

## References

1. January CT, Wann LS, Alpert JS, Calkins H, Cigarroa JE, Cleveland JC Jr, Conti JB, Ellinor PT, Ezekowitz MD, Field ME, Murray KT, Sacco RL, Stevenson WG, Tchou PJ, Tracy CM, Yancy CW; American College of Cardiology/American Heart Association Task Force on Practice Guidelines. 2014 AHA/ACC/HRS guideline for the management of patients with atrial fibrillation: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and the Heart Rhythm Society. *J Am Coll Cardiol*. 2014;64: e1–e76.
2. Pappone C, Augello G, Sala S, Gugliotta F, Vicedomini G, Gulletta S, Paglino G, Mazzone P, Sora N, Greiss I, Santagostino A, LiVolsi L, Pappone N, Radinovic A, Manguso F, Santinelli V. A randomized trial of circumferential pulmonary vein ablation versus antiarrhythmic drug therapy in paroxysmal atrial fibrillation: the APAF Study. *J Am Coll Cardiol*. 2006;48:2340–2347.
3. Tilz RR, Rillig A, Thum AM, Arya A, Wohlmuth P, Metzner A, Mathew S, Yoshiga Y, Wissner E, Kuck KH, Ouyang F. Catheter ablation of long-standing persistent atrial fibrillation: 5-year outcomes of the Hamburg Sequential Ablation Strategy. *J Am Coll Cardiol*. 2012;60:1921–1929.
4. Willems S, Klemm H, Rostock T, Brandstrup B, Ventura R, Steven D, Risius T, Lutomsky B, Meinertz T. Substrate modification combined with pulmonary vein isolation improves outcome of catheter ablation in patients with persistent atrial fibrillation: a prospective randomized comparison. *Eur Heart J*. 2006;27:2871–2878.
5. Fassini G, Riva S, Chiodelli R, Trevisi N, Berti M, Carbucicchio C, Maccabelli G, Giraldi F, Bella PD. Left mitral isthmus ablation associated with PV isolation: long-term results of a prospective randomized study. *J Cardiovasc Electrophysiol*. 2005;16:1150–1156.
6. Pak HN, Oh YS, Lim HE, Kim YH, Hwang C. Comparison of voltage map-guided left atrial anterior wall ablation versus left lateral mitral isthmus ablation in patients with persistent atrial fibrillation. *Heart Rhythm*. 2011;8:199–206.
7. Pappone C, Manguso F, Vicedomini G, Gugliotta F, Santinelli O, Ferro A, Gulletta S, Sala S, Sora N, Paglino G, Augello G, Agricola E, Zangrillo A, Alfieri O, Santinelli V. Prevention of iatrogenic atrial tachycardia after ablation of atrial fibrillation: a prospective randomized study comparing circumferential pulmonary vein ablation with a modified approach. *Circulation*. 2004;110:3036–3042.
8. Jais P, Hocini M, Hsu LF, Sanders P, Scavee C, Weerasooriya R, Macle L, Raybaud F, Garrigue S, Shah DC, Le Metayer P, Clementy J, Haissaguerre M. Technique and results of linear ablation at the mitral isthmus. *Circulation*. 2004;110:2996–3002.
9. Li WJ, Bai YY, Zhang HY, Tang RB, Miao CL, Sang CH, Yin XD, Dong JZ, Ma CS. Additional ablation of complex fractionated atrial electrograms after pulmonary vein isolation in patients with atrial fibrillation: a meta-analysis. *Circ Arrhythm Electrophysiol*. 2011;4:143–148.
10. Wu SH, Jiang WF, Gu J, Zhao L, Wang YL, Liu YG, Zhou L, Gu JN, Xu K, Liu X. Benefits and risks of additional ablation of complex fractionated atrial electrograms for patients with atrial fibrillation: a systematic review and meta-analysis. *Int J Cardiol*. 2013;169:35–43.
11. Verma A, Jiang CY, Betts TR, Chen J, Deisenhofer I, Mantovan R, Macle L, Morillo CA, Haverkamp W, Weerasooriya R, Albenque JP, Nardi S, Menardi E, Novak P, Sanders P; STAR AF II Investigators. Approaches to catheter ablation for persistent atrial fibrillation. *N Engl J Med*. 2015;372:1812–1822.
12. Brooks AG, Stiles MK, Laborderie J, Lau DH, Kuklik P, Shipp NJ, Hsu LF, Sanders P. Outcomes of long-standing persistent atrial fibrillation ablation: a systematic review. *Heart Rhythm*. 2010;7:835–846.
13. Dong JZ, Sang CH, Yu RH, Long DY, Tang RB, Jiang CX, Ning M, Liu N, Liu XP, Du X, Tse HF, Ma CS. Prospective randomized comparison between a fixed

'2C3L' approach vs. stepwise approach for catheter ablation of persistent atrial fibrillation. *Europace*. 2015;17:1798–1806.

14. Wong KC, Paisey JR, Sopher M, Balasubramaniam R, Jones M, Qureshi N, Hayes CR, Ginks MR, Rajappan K, Bashir Y, Betts TR. No benefit of complex fractionated atrial electrogram ablation in addition to circumferential pulmonary vein ablation and linear ablation: benefit of complex ablation study. *Circ Arrhythm Electrophysiol*. 2015;8:1316–1324.
15. European Heart Rhythm Association; European Association for Cardio-Thoracic Surgery, Camm AJ, Kirchhof P, Lip GY, Schotten U, Savelieva I, Ernst S, Van Gelder IC, Al-Attar N, Hindricks G, Prendergast B, Heidbuchel H, Alfieri O, Angelini A, Atar D, Colonna P, De Caterina R, De Sutter J, Goette A, Gorenek B, Heldal M, Hohloser SH, Kolh P, Le Heuzey JY, Ponikowski P, Rutten FH. Guidelines for the management of atrial fibrillation: the Task Force for the Management of Atrial Fibrillation of the European Society of Cardiology (ESC). *Eur Heart J*. 2010;31:2369–2429.
16. Verma A, Novak P, Macle L, Whaley B, Beardsall M, Wulffhart Z, Khaykin Y. A prospective, multicenter evaluation of ablating complex fractionated electrograms (CFEs) during atrial fibrillation (AF) identified by an automated mapping algorithm: acute effects on AF and efficacy as an adjuvant strategy. *Heart Rhythm*. 2008;5:198–205.
17. Mun HS, Joung B, Shim J, Hwang HJ, Kim JY, Lee MH, Pak HN. Does additional linear ablation after circumferential pulmonary vein isolation improve clinical outcome in patients with paroxysmal atrial fibrillation? Prospective randomised study *Heart*. 2012;98:480–484.
18. Calkins H, Kuck KH, Cappato R, Brugada J, Camm AJ, Chen SA, Crijns HJ, Damiano RJ Jr, Davies DW, DiMarco J, Edgerton J, Ellenbogen K, Ezekowitz MD, Haines DE, Haissaguerre M, Hindricks G, Iesaka Y, Jackman W, Jalife J, Jais P, Kalman J, Keane D, Kim YH, Kirchhof P, Klein G, Kottkamp H, Kumagai K, Lindsay BD, Mansour M, Marchlinski FE, McCarthy PM, Mont JL, Morady F, Nademanee K, Nakagawa H, Natale A, Nattel S, Packer DL, Pappone C, Prystowsky E, Raviele A, Reddy V, Ruskin JN, Shemin RJ, Tsao HM, Wilber D. 2012 HRS/EHRA/ECAS Expert Consensus Statement on Catheter and Surgical Ablation of Atrial Fibrillation: recommendations for patient selection, procedural techniques, patient management and follow-up, definitions, endpoints, and research trial design. *Europace*. 2012;14:528–606.
19. Konings KT, Smeets JL, Penn OC, Wellens HJ, Allessie MA. Configuration of unipolar atrial electrograms during electrically induced atrial fibrillation in humans. *Circulation*. 1997;95:1231–1241.
20. Nademanee K, McKenzie J, Kosar E, Schwab M, Sunsaneewitayakul B, Vasavakul T, Khunnawat C, Ngarmukos T. A new approach for catheter ablation of atrial fibrillation: mapping of the electrophysiologic substrate. *J Am Coll Cardiol*. 2004;43:2044–2053.
21. Elayi CS, Verma A, Di Biase L, Ching CK, Patel D, Barrett C, Martin D, Rong B, Fahmy TS, Khaykin Y, Hongo R, Hao S, Pelargonio G, Dello Russo A, Casella M, Santarelli P, Potenza D, Fanelli R, Massaro R, Arruda M, Schweikert RA, Natale A. Ablation for longstanding permanent atrial fibrillation: results from a randomized study comparing three different strategies. *Heart Rhythm*. 2008;5:1658–1664.
22. Oral H, Chugh A, Yoshida K, Sarrazin JF, Kuhne M, Crawford T, Chalfoun N, Wells D, Boonyapisit W, Veerareddy S, Billakanty S, Wong WS, Good E, Jongnarangsin K, Pelosi F Jr, Bogun F, Morady F. A randomized assessment of the incremental role of ablation of complex fractionated atrial electrograms after antral pulmonary vein isolation for long-lasting persistent atrial fibrillation. *J Am Coll Cardiol*. 2009;53:782–789.
23. Kalifa J, Tanaka K, Zaitsev AV, Warren M, Vaidyanathan R, Auerbach D, Pandit S, Vikstrom KL, Ploutz-Snyder R, Talkachou A, Atienza F, Guiraudon G, Jalife J, Berenfeld O. Mechanisms of wave fractionation at boundaries of high-frequency excitation in the posterior left atrium of the isolated sheep heart during atrial fibrillation. *Circulation*. 2006;113:626–633.
24. Scherlag BJ, Yamanashi W, Patel U, Lazzara R, Jackman WM. Autonomically induced conversion of pulmonary vein focal firing into atrial fibrillation. *J Am Coll Cardiol*. 2005;45:1878–1886.
25. de Bakker JM, Wittkampf FH. The pathophysiologic basis of fractionated and complex electrograms and the impact of recording techniques on their detection and interpretation. *Circ Arrhythm Electrophysiol*. 2010;3:204–213.
26. Park JH, Pak HN, Kim SK, Jang JK, Choi JI, Lim HE, Hwang C, Kim YH. Electrophysiologic characteristics of complex fractionated atrial electrograms in patients with atrial fibrillation. *J Cardiovasc Electrophysiol*. 2009;20:266–272.
27. Park JH, Park SW, Kim JY, Kim SK, Jeoung B, Lee MH, Hwang C, Kim YH, Kim SS, Pak HN. Characteristics of complex fractionated atrial electrogram in the electroanatomically remodeled left atrium of patients with atrial fibrillation. *Circ J*. 2010;74:1557–1563.
28. Chen M, Yang B, Chen H, Ju W, Zhang F, Tse HF, Cao K. Randomized comparison between pulmonary vein antral isolation versus complex fractionated electrogram ablation for paroxysmal atrial fibrillation. *J Cardiovasc Electrophysiol*. 2011;22:973–981.
29. Shim J, Joung B, Park JH, Uhm JS, Lee MH, Pak HN. Long duration of radiofrequency energy delivery is an independent predictor of clinical recurrence after catheter ablation of atrial fibrillation: over 500 cases experience. *Int J Cardiol*. 2013;167:2667–2672.
30. Li C, Lim B, Hwang M, Song JS, Lee YS, Joung B, Pak HN. The spatiotemporal stability of dominant frequency sites in in-silico modeling of 3-dimensional left atrial mapping of atrial fibrillation. *PLoS One*. 2016;11:e0160017.
31. Scott PA, Silberbauer J, Murgatroyd FD. The impact of adjunctive complex fractionated atrial electrogram ablation and linear lesions on outcomes in persistent atrial fibrillation: a meta-analysis. *Europace*. 2016;18:359–367.
32. Haissaguerre M, Hocini M, Sanders P, Sacher F, Rotter M, Takahashi Y, Rostock T, Hsu LF, Bordachar P, Reuter S, Roudaut R, Clementy J, Jais P. Catheter ablation of long-lasting persistent atrial fibrillation: clinical outcome and mechanisms of subsequent arrhythmias. *J Cardiovasc Electrophysiol*. 2005;16:1138–1147.
33. Henry WL, Morganroth J, Pearlman AS, Clark CE, Redwood DR, Itscoitz SB, Epstein SE. Relation between echocardiographically determined left atrial size and atrial fibrillation. *Circulation*. 1976;53:273–279.
34. Hwang ES, Nam GB, Joung B, Park J, Lee JS, Shim J, Uhm JS, Lee MH, Pak HN. Significant reduction of atrial defibrillation threshold and inducibility by catheter ablation of atrial fibrillation. *Pacing Clin Electrophysiol*. 2012;35:1428–1435.
35. Matsuo S, Yamane T, Date T, Tokutake K, Hioki M, Narui R, Ito K, Tanigawa S, Yamashita S, Tokuda M, Inada K, Arase S, Yagi H, Sugimoto K, Yoshimura M. Substrate modification by pulmonary vein isolation and left atrial linear ablation in patients with persistent atrial fibrillation: its impact on complex-fractionated atrial electrograms. *J Cardiovasc Electrophysiol*. 2012;23:962–970.
36. Jones DG, Haldar SK, Jarman JW, Johar S, Hussain W, Markides V, Wong T. Impact of stepwise ablation on the biatrial substrate in patients with persistent atrial fibrillation and heart failure. *Circ Arrhythm Electrophysiol*. 2013;6:761–768.
37. Chen YL, Ban JE, Park YM, Choi JI, Park SW, Kim YH. The spatial distribution of atrial fibrillation termination sites in the right atrium during complex fractionated atrial electrograms—guided ablation in patients with persistent atrial fibrillation. *J Cardiovasc Electrophysiol*. 2013;24:949–957.
38. Verma A, Mantovan R, Macle L, De Martino G, Chen J, Morillo CA, Novak P, Calzolari V, Guerra PG, Nair G, Torrecilla EG, Khaykin Y. Substrate and Trigger Ablation for Reduction of Atrial Fibrillation (STAR AF): a randomized, multicentre, international trial. *Eur Heart J*. 2010;31:1344–1356.
39. Narayan SM, Krummen DE, Shivkumar K, Clopton P, Rappel WJ, Miller JM. 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. *J Am Coll Cardiol*. 2012;60:628–636.
40. Atienza F, Almendral J, Ormaetxe JM, Moya A, Martinez-Alday JD, Hernandez-Madrid A, Castellanos E, Arribas F, Arias MA, Tercedor L, Peinado R, Arcocha MF, Ortiz M, Martinez-Alzamora N, Arenal A, Fernandez-Aviles F, Jalife J; RADAR-AF Investigators. Comparison of radiofrequency catheter ablation of drivers and circumferential pulmonary vein isolation in atrial fibrillation: a noninferiority randomized multicenter RADAR-AF trial. *J Am Coll Cardiol*. 2014;64:2455–2467.
41. Haissaguerre M, Hocini M, Denis A, Shah AJ, Komatsu Y, Yamashita S, Daly M, Amraoui S, Zellerhoff S, Picat MQ, Quotb A, Jesel L, Lim H, Ploux S, Bordachar P, Attuel G, Meillet V, Ritter P, Derval N, Sacher F, Bernus O, Cochet H, Jais P, Dubois R. Driver domains in persistent atrial fibrillation. *Circulation*. 2014;130:530–538.
42. Kim IS, Yang PS, Kim TH, Park J, Park JK, Uhm JS, Joung B, Lee MH, Pak HN. Clinical significance of additional ablation of atrial premature beats after catheter ablation for atrial fibrillation. *Yonsei Med J*. 2016;57:72–80.
43. Rolf S, Kircher S, Arya A, Eitel C, Sommer P, Richter S, Gaspar T, Bollmann A, Altmann D, Piedra C, Hindricks G, Piorkowski C. Tailored atrial substrate modification based on low-voltage areas in catheter ablation of atrial fibrillation. *Circ Arrhythm Electrophysiol*. 2014;7:825–833.
44. Walters TE, Nisbet A, Morris GM, Tan G, Mearns M, Teo E, Lewis N, Ng A, Gould P, Lee G, Joseph S, Morton JB, Zentner D, Sanders P, Kistler PM, Kalman JM. Progression of atrial remodeling in patients with high-burden atrial fibrillation: implications for early ablative intervention. *Heart Rhythm*. 2016;13:331–339.
45. Park JK, Lee JY, Yang PS, Kim TH, Shin E, Park J, Uhm JS, Joung B, Lee MH, Pak HN. Good responders to catheter ablation for long-standing persistent atrial fibrillation: clinical and genetic characteristics. *J Cardiol*. 2016. DOI: 10.1016/j.jjcc.2016.04.017. Available at: http://www.journal-of-cardiology.com/article/S0914-5087(16)30078-8/abstract. Accessed January 20, 2016.
46. Almeida TP, Chu GS, Salinet JL, Vanheusden FJ, Li X, Tuan JH, Stafford PJ, Ng GA, Schlindwein FS. Minimizing discordances in automated classification of fractionated electrograms in human persistent atrial fibrillation. *Med Biol Eng Comput*. 2016;54:1695–1706.

# SUPPLEMENTAL MATERIAL

**Table S1.** Proportion of patients who required repeat ablation procedure and bidirectional block achievement rates of linear ablation lesions according to the mode of recurrence.

| | **AF recurrence (n=14)** | **AT recurrence (n=18)** | **p-value** |
|---|---|---|---|
| Redo procedure | 5 (35.7%) | 5 (27.8%) | 0.712 |
| BDB Achievement | | | |
| Roof line | 78.6% (11/14) | 88.9% (16/18) | 0.631 |
| PI line (LAPW isolation) | 50.0% (7/14) | 61.1% (1/18) | 0.530 |
| Anterior line | 64.3% (9/14) | 88.9% (16/18) | 0.195 |

BDB = bidirectional block, LAPW = Left atrial posterior wall, PI line = posterior inferior line.