Radiofrequency catheter ablation (RFCA) is an effective treatment for atrial fibrillation (AF), especially for paroxysmal AF (PAF). Elimination of the triggers of AF through circumferential pulmonary vein isolation (CPVI) has been the basis of most AF ablation techniques. Although RFCA for persistent AF (PeAF) is more challenging, CPVI alone was generally accepted as an insufficient modality for long-term maintenance of sinus rhythm in these populations until recently. This discrepancy might be because of changes in mechanism over the course of AF; that is, triggers predominate early in the course of AF, and then changes in the underlying substrate promote AF persistence as the arrhythmia becomes more established. Thus, additional substrate modification strategies for improving clinical outcome have been developed for patients with PeAF. The Data Supplement is available at http://circep.ahajournals.org/lookup/suppl/doi:10.1161/CIRCEP.116.004915/-/DC1. Correspondence to Hui-Nam Pak, MD, PhD, Yonsei University Health System, 50–1 Yonsei-ro, Seodaemun-gu, Seoul 120–752, Republic of Korea. E-mail hnpak@yuhs.ac © 2017 American Heart Association, Inc.

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WHAT IS KNOWN
- In addition to circumferential pulmonary vein isolation, substrate modification strategies have been developed to improve clinical outcomes after catheter ablation for persistent atrial fibrillation (AF).
- A recent prospective randomized trial showed that linear ablation or electrogram-guided ablation did not have any incremental benefit of rhythm outcome in addition to pulmonary vein isolation in patients with persistent AF.
- However, category of persistent AF includes broad spectrum of AF with variable degree of AF progression or structural remodeling.

WHAT THE STUDY ADDS
- Circumferential pulmonary vein isolation alone is an effective rhythm control strategy with a shorter procedure time compared with additional linear ablation in persistent AF patients who converted to paroxysmal type with antiarrhythmic drug therapy.
- Achievement of a complete bidirectional block of linear lesions was associated with a favorable rhythm outcome within the additional linear ablation group.

Recently, the AF classification system was revised. AF that terminates with intervention within 7 days is now classified as PAF; previously, this type of AF was classified as PeAF. However, the current definition of AF still does not reflect its pathophysiology in depth. The type of AF may change depending on condition and timing, and some patients who initially present with PeAF can be changed to PAF after use of antiarrhythmic drugs (AAD) and electric cardioversion. Currently, there is no clear definition for AF that is changed into PAF from PeAF after electric or pharmacological cardioversion and, therefore, no consensus for an appropriate ablation strategy for this population. Thus, this trial compared the efficacy of CPVI alone versus CPVI with an added linear ablation, including anterior line, for PeAF to PAF. We evaluated whether the addition of linear lesions and achievement of a complete bidirectional block of linear lesions improves clinical outcome in patients with PeAF to PAF.

Methods

Study Cohort
The study protocol (Table I in the Data Supplement) adhered to the Declaration of Helsinki and was approved by the institutional review board. Proper written informed consent was obtained from all patients. The study cohort included 113 patients with PeAF to PAF (male 75%, 60.4±10.1 years old) who underwent RFCA for symptomatic and drug-refractory nonvalvular AF at 3 tertiary hospitals in Korea. Exclusion criteria were as follows: (1) AF with rheumatic valvular disease; (2) significant structural heart disease other than left ventricular hypertrophy; (3) LA diameter of ≥60 mm; and (4) a history of AF ablation or cardiac surgery. Before all ablation procedures, the absence of LA thrombus was confirmed by transesophageal echocardiography, and the anatomy of the LA and pulmonary veins (PVs) was visually defined by 3-dimensional (3D) computed tomography scans (64 Channel, Light Speed Volume CT, Philips, Brilliance 63, Amsterdam, The Netherlands). All AADs were discontinued for a period of at least 5 half-lives. Patients were prospectively and randomly assigned to 2 groups according to the method of RFCA: the CPVI alone group (n=59) or the CPVI plus linear ablation (CPVI+Line) group (posterior box+anterior line; n=54).

Electrophysiological Mapping
Intracardiac electrograms were recorded using the Prucka CardioLab Electrophysiology system (General Electric Medical Systems, Inc., Milwaukee, WI), and RFCA was performed in all patients using 3D electroanatomical mapping (NavX, St Jude Medical, Inc., Minnetonka, MN) merged with 3D spatial computed tomography. Double transseptal punctures were made, and multiview pulmonary venograms were obtained. Systemic anticoagulation was performed with intravenous heparin to maintain an activated clotting time of 350 to 400 s during the procedure. For electroanatomical mapping, 3D geometry of both the LA and PV was generated using the NavX system and then merged with 3D spatial computed tomography images. LA electrogram voltage maps were generated during high right atrial pacing at 500 ms after CPVI to maintain sinus rhythm. We obtained the peak-to-peak amplitude of contact bipolar electrograms from 350 to 500 points on the LA endocardium, and the mean LA electrogram voltage was calculated. If frequently recurring AF persisted after 3 attempts at cardioversion, no further efforts were made to generate an LA voltage map.

Echocardiographic Evaluation
All patients underwent transthoracic echocardiography (Sonos 5500, Philips Medical System, Andover, MA, or Vivid 7, GE Vingmed Ultrasound, Horten, Norway) prior to RFCA. Chamber size, transmural Doppler flow velocity, and ratio of the early diastolic peak mitral inflow velocity and early diastolic mitral annular velocity (E/Em) were acquired following the American Society of Echocardiography guidelines. Transesophageal echocardiography was performed to exclude any intracardiac thrombi. The emptying velocity of the LA appendage was measured in all patients.

Radiofrequency Catheter Ablation
Details of the RFCA technique and strategy were described in our previous studies. Briefly, for CPVI ablation, circumferential lesions were created at the level of the LA antrum encircling the right and left PV (Figure 1A) guided by the NavX system using an open-irrigated, 3.5-mm tip deflectable catheter (Celsius; Johnson & Johnson, Inc., Diamond Bar, CA; Coolflex; St Jude Medical, Inc., Minnetonka, MN; 25–35 W; 45°C). RFCA was performed by maintaining the ablation catheter at each target point for 30 s, but in a continuous manner (≤3 W for the anterior aspects of LA and PVs, but 25–30 W for posterior LA). We moved the catheter if voltage abatement was seen on the electrogram or the patient complained pain at the LA posterior wall. We conducted CPVI and cavotricuspid isthmus ablation in all patients. The end point of CPVI was electric isolation of PV potentials and bidirectional block of PVs. PV and non-PV trigger mappings were obtained immediately after cardioversion under isoproterenol infusion (5–10 μg/min). The end points of cavotricuspid isthmus block were defined by bidirectional pacing. For the CPVI+Line group, additional linear ablation of posterior box lesions and anterior linear ablation was performed. To generate the posterior box lesion, linear ablations on the roof and posterior inferior wall were made by connecting both sides of the CPVI at the top and bottom levels, respectively (Figure 1B). Anterior linear ablation was generated by ablation from the mitral annulus at the 12 o’clock direction toward the LA roof line. Bidirectional block of roof lines was confirmed by differential pacing from LA appendage versus LA posterior wall, and successful generation of posterior box lesions was defined as no endocardial electrogram in the LA posterior wall with a roof line block (Figure 1B).
block of anterior lines was confirmed by differential pacing from the LA appendage versus LA septum. The procedure ended when there was no immediate recurrence of AF within 10 minutes after cardioversion with an isoproterenol infusion (5–10 μg/min). Anticoagulation therapy was maintained for at least 4 weeks before catheter ablation in all participants.

**Postablation Management and Follow-Up**

Patients visited the outpatient clinic regularly at 1, 3, 6, and 12 months and then every 6 months thereafter or whenever symptoms occurred after RFCA. All patients underwent ECG during every visit and 24-hour Holter recording at 3 and 6 months and every 6 months, according to the 2012 Heart Rhythm Society/European Heart Rhythm Association/European Cardiac Arrhythmia Society Expert Consensus Statement guidelines.23 Holter monitoring or event monitor recordings were obtained when patients reported symptoms of palpitation suggestive of arrhythmia recurrence. The Holter analysis and adjudication were performed by an individual blinded to the study group assignment. AF recurrence was defined as any episode of AF or atrial tachycardia (AT) of at least 30 s in duration. Any ECG documentation of AF recurrence within a 3-month blanking period was diagnosed as an early recurrence, and AF recurrence >3 months after the procedure was diagnosed as a clinical recurrence. The primary study end point was freedom from documented episodes of AF or AT lasting longer than 30 s and occurring after a 3-month blanking period after a single ablation procedure, with or without the use of AADs. The secondary end points included achievement of a complete bidirectional block of additional linear lesions, utilization of AADs, procedure time, and incidence of periprocedural complications.

**Data Analysis**

Sample-size calculations were based on our previous study outcome.22 The expected freedom from AF recurrence after one ablation procedure was ≈70%. For a true difference in favor of CPVI alone of 10%, 116 patients (58 in each group) were required to be 80% sure that the upper limit of a one-sided 95% confidence interval would exclude a difference in favor of CPVI plus linear ablation of >10%. Continuous variables were summarized as mean±standard deviation and were compared by Student's t tests and analysis of variance. Categorical variables were summarized as a percentage of the group total and were compared by χ² tests or Fisher’s exact tests. All outcome analyses were performed on patients who underwent RFCA and were followed for longer than the initial 3-month blanking period. Kaplan–Meier analysis with log-rank test was used to calculate AF recurrence-free survival over time and to compare recurrence rates across groups. A 2-sided P value of <0.05 was considered to indicate statistical significance. Statistical analysis was performed using SPSS (version 20.0, Statistical Package for Social Sciences, Chicago, IL, USA) software for Windows.

**Results**

**Patient Characteristics**

The patients were prospectively and randomly assigned to the CPVI alone group (n=59) or CPVI+Line group (n=54). Baseline clinical characteristics of the study population are summarized in Table 1. The mean age was 60.4±10.1 years, and a total of 85 patients (75%) were male. The mean CHA 2DS2-VASc score was 2.2±1.8. Among a total of 113 study participants, 35 (31%) patients had prior history of electric cardioversion, and there was no difference in the rate of preablational cardioversion between groups (P=0.354).

Table 2 shows the utilization of AAD before and after RFCA. Before RFCA, flecainide (42%) and amiodarone (35%) were the most frequently prescribed AADs. AAD utility rates at discharge (17% versus 11%; P=0.374) or during overall follow-up periods after blanking (22% versus 30%; P=0.356) were not significantly different between the 2 groups.

**Shorter Procedure Time in the CPVI Alone Group**

The procedural results and clinical outcomes are summarized in Table 3. The total procedure time (187.2±58.0 vs 211.2±63.9 min; P=0.043) and radiofrequency energy
the CPVI+Line group. Among a total of 27 patients with clinical recurrence, 17 patients showed AF and 10 patients showed AT at the time of the recurrence. Patients in the CPVI alone group tended to recur with AF rather than AT, as compared with those in CPVI+Line group (82% versus 50%); however, this result was not statistically significant (P=0.124). The Kaplan–Meier analysis showed no significant difference in overall AF recurrence (Log-rank; P=0.206; Figure 2A) and AAD-free AF recurrence (Log-rank; P=0.321; Figure 2B) between the 2 groups. In addition, among 27 patients with AF recurrence, 6 (22%; 1 in CPVI alone group and 5 in CPVI+Line group) underwent repeat procedures at 23.3±8.4 months after the de novo procedure. The bidirectional block maintenance rates for the roof line, posterior inferior line, and anterior line were 60% (3 of 5), 100% (2 of 2), and 100% (2 of 2), respectively. Among 5 patients, 3 recurred with AT from focal origin, 1 with AF triggered from left superior PV, and 1 with perimital macroreentrant atrial flutter.

In the 1-year postablation echocardiogram, the LA dimension was significantly reduced in both the CPVI alone group (from 42.5±4.8 to 38.2±4.5 mm; P<0.001) and the CPVI+Line group (from 43.7±5.2 to 39.8±6.2 mm; P<0.001) compared with preablation echocardiogram (Figure 3A). However, there were no significant differences in LA dimension changes and LV ejection fraction changes on 1-year postablation echocardiogram between the 2 groups (Figure 3B).

Effects of Complete Bidirectional Block of Linear Ablation
We achieved both CPVI and bidirectional block of the cavitricuspid isthmus in 100% of patients in both groups. In the CPVI+Line group (n=54), bidirectional block of the roof line, posterior inferior line, and anterior line was achieved in 91% (n=49), 46% (n=25), and 72% (n=39) of patients, respectively. Overall, 35% (n=19) of the CPVI+Line group achieved a complete bidirectional block with the linear lesion set. Although there was no difference in the early recurrence rates among groups (CPVI alone, CPVI+Line with complete bidirectional blocks, and CPVI+Line with incomplete bidirectional blocks), the clinical recurrence rate was significantly lower among patients with CPVI and complete bidirectional blocks of the linear lesion set (Figure IA in the Data Supplement). However, the Kaplan–Meier analysis showed no significant difference in AAD-free AF recurrence among the 3 groups (Figure IB in the Data Supplement).
Main Findings
In this prospective randomized study comparing 2 ablation strategies in patients with PeAF to PAF, additional linear ablations to CPVI did not improve clinical outcome in spite of longer procedure or ablation time compared with CPVI. However, in a subgroup analysis of the CPVI+Line group, achievement of a complete bidirectional block with the linear lesion was associated with a favorable rhythm outcome. The procedure-related major complication rate was also not significantly different between the 2 groups.

AF Progression and Types of AF
AF is a progressive disease that evolves from PAF to PeAF and permanent AF. Recent American Heart Association/American College of Cardiology/Heart Rhythm Society guidelines for the management of patients with AF revised the definition of AF types. Episodes of AF that are terminated with electrical or pharmacological cardioversion within 7 days are now classified as PAF episodes; previously, these were classified as PeAF. However, current AF-type definitions do not reflect pathophysiology and the degree of atrial remodeling. Moreover, when sinus rhythm is restored by electric or pharmacological cardioversion, the precise duration of AF episodes is difficult to determine. Consequently, there is currently no consensus on a clear definition of AF that is changed into PAF from PeAF after AAD use or electric cardioversion.

Recent studies have shed light on the effect of catheter ablation on AF progression. Pappone et al showed that catheter ablation rather than AAD therapy is beneficial in eliminating recurrences and delaying AF progression. Catheter ablation of AF is associated with significantly reduced progression to persistent forms compared with studies in the general population. However, catheter ablation of PeAF is associated with lower success rates compared with that of PAF. Therefore, it seems reasonable to perform ablation while AF is still of the paroxysmal type. In addition, results from several trials suggest that early restoration and long-term maintenance of sinus rhythm provides considerable benefits, including improvement in cardiac function and quality of life and a lower risk of death in select populations. Furthermore, a recent study in patients with long-standing PeAF suggested that transformation from nonparoxysmal to PAF after catheter ablation may...
represent a step toward long-term freedom from recurrent arrhythmia.\textsuperscript{31}

**Antiarrhythmic Mechanisms of CPVI in AF Ablation**

The paradigm of catheter ablation for AF has shifted from a segmental PV ostial isolation toward more extensive circumferential PV antral ablation.\textsuperscript{32} This approach results not only in the elimination of peri-PV ostial triggers or drivers, but also in targeting ganglionic plexi or cardiac autonomic nerves\textsuperscript{33,34} and wide atrial debulking with reduction of the effective atrial surface.\textsuperscript{35} However, CPVI alone may be insufficient to control AF because of the presence of non-PV foci or atrial substrate remodeling, especially in patients with PeAF.\textsuperscript{36} We previously demonstrated better clinical outcome with ablation using a strategy of targeting immediate postcardioversion recurrence of atrial premature beats as non-PV foci.\textsuperscript{21} Also, favorable outcomes in catheter ablation of long-standing PeAF has been reported for the combination of sequential CPVI and complex fractionated atrial electrogram–guided ablation followed by linear ablation of the LA roof and mitral isthmus in a stepwise approach.\textsuperscript{7} On the other hand, controversy remains regarding whether linear ablation or complex fractionated atrial electrogram –guided ablation in addition to CPVI improves clinical outcome of PeAF. Recently, the STAR AF II trial reported no reduction in the rate of AF recurrence when either linear ablation or ablation of complex fractionated atrial electrogram was performed in addition to conventional CPVI in patients with PeAF.\textsuperscript{13} Another randomized study indicated that complex fractionated atrial electrogram ablation did not confer incremental benefit when performed in addition to CPVI and linear ablation in patients with PeAF.\textsuperscript{37} In the present study, we sought to compare 2 ablation strategies in patients with PeAF to PAF, and our findings were generally consistent with the previous studies.

**Meaning of Linear Ablation in Rhythm Control of PeAF**

Previous studies have provided evidence for the benefits of linear ablation in addition to CPVI in PeAF.\textsuperscript{9,38,39} However, performing additional ablation may increase time, cost, and risk of adverse events. Total procedure time and ablation time were longer in the additional linear ablation group and might be associated with increased exposure to radiation for patients and operators. Although the overall rate of major complications was low in this study, it is noteworthy that an atrioesophageal fistula led to the death of 1 patient in the CPVI+Line group. In addition, the benefits of additional linear ablation have not been consistently demonstrated,\textsuperscript{4} and clear evidence regarding which linear lesion set may contribute to better clinical outcomes after catheter ablation of AF is lacking. RFCA success rate depends on the operator’s ablation technique, and incomplete bidirectional block of linear lesion is common and an important cause of macroreentrant AT or atrial flutter.\textsuperscript{40-42} Furthermore, in a previous study, we found that a long duration of RF energy delivery in AF ablation was an independent risk factor of clinical recurrence.\textsuperscript{43} LA anterior linear ablation results in remarkable conduction delay to the LA appendage and may induce intraatrial or atrioventricular dyssynchrony. However, magnetic resonance imaging or echocardiographic follow-up studies did not show any significant hemodynamic derangement in spite of intra-LA conduction delay after LA anterior linear ablation in our previous report\textsuperscript{12} and others.\textsuperscript{44}

In the present study, we demonstrated the favorable outcomes of complete bidirectional block with the linear lesion set in patients with PeAF to PAF. In addition, single-center data have suggested that a combination of CPVI, linear ablation, and ablation of complex electrograms is superior to either 1 or 2 alone.\textsuperscript{11} Although achievement of complete linear lesions can be technically difficult, they may improve long-term freedom from recurrence of atrial arrhythmia.\textsuperscript{9} In addition to preventing macroreentrant tachyarrhythmia, compartmentalization and reduction of critical mass may decrease both initiation and maintenance of AF. A recent study showed the impact of linear ablation on the atrial substrate based on the change in spectral components, which may indicate AT that coexist with AF and that are uncovered after elimination of higher frequency drivers by ablation.\textsuperscript{45} These components were more prevalent in AF with longer duration, and a complete linear lesion set led to their reduction and elimination. Alteration of AF wavelet propagation and elimination of spectral components may explain our observed favorable clinical outcome from complete bidirectional block of linear lesions.

**Limitations**

Some potential limitations of this study should be considered. First, the current study included a relatively small number of patients, so findings from this study cannot be generalized to all patients with PeAF to PAF. Second, complete bidirectional block with the linear lesion set was achieved in only 35% of
patients in the CPVI-Line group. The low achievement of bidirectional block, because of efforts to avoid esophageal injury during posterior inferior linear ablation, may have affected the statistical power of current findings. Also, although we confirmed the bidirectional block of each linear lesion at the time of the procedure, some may have been reconnected during the follow-up period, which may confound the clinical outcome. A future study with a larger number of patients and achievement of a higher level of complete bidirectional block is warranted.

Conclusion
CPVI alone is an effective rhythm control strategy with a shorter procedure time for patients with PeAF converted to PAF with AADs, compared with CPVI with additional linear

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Disclosures
None.

References
CIRCEP.113.000922.


Pulmonary Vein Isolation Alone Versus Additional Linear Ablation in Patients With Persistent Atrial Fibrillation Converted to Paroxysmal Type With Antiarrhythmic Drug Therapy: A Multicenter, Prospective, Randomized Study

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SUPPLEMENTAL MATERIAL

Supplemental Table 1. Study protocol

Supplemental Figure 1. Kaplan–Meier analysis of AF recurrence-free survival rate (A) and AF and AAD-free survival rate (B) according to the ablation strategies and the bidirectional block status of linear ablations
**Supplemental Table 1. Study protocol**

<table>
<thead>
<tr>
<th>Purpose of the study</th>
<th>To compare clinical outcomes, procedure times, complication rates of patients who were changed to paroxysmal atrial fibrillation (PAF) from persistent atrial fibrillation (PeAF) between ablation with circumferential pulmonary vein isolation (CPVI) and ablation with CPVI with additional linear lesions.</th>
</tr>
</thead>
</table>
| Scientific evidence of the study | 1. In atrial fibrillation (AF) patients, maintenance of normal sinus rhythm facilitates a significant reduction in mortality.  
2. Drug therapy with anti-arrhythmic drugs involves many complications and side effects, thus non-drug therapy, such as radiofrequency catheter ablation (RFCA), has been developed.  
3. RFCA has been performed for 10 years worldwide and has shown superior treatment outcomes, compared with drug therapy.  
4. However, there is no consensus on proper ablation strategies for patients changed to PAF from PeAF.  
5. While additional ablation would increase the extent of myocardial injury, this paradoxically has been found to increase recurrence rates and, thus, is controversial.  
6. We sought to compare the efficacy of CPVI alone vs. CPVI with an added linear ablation. |
| Methods | 1. Treatment of all patients with AF was performed according to standard treatment guidelines for AF.  
2. There was no additional blood sampling, imaging study, or any other |
invasive procedure.

| Study contents | 1. To evaluate effective ablation strategies in patients changed to PAF from PeAF.  
|                | 2. We compared CPVI and CPVI with additional liner ablation, both of which are conventional ablation strategies performed worldwide. |
| Study type     | Interventional |
| Study design   | Allocation: Randomized  
|                | Intervention Model: Parallel Assignment  
|                | Masking: Single Blind (Investigator)  
|                | Primary Purpose: Treatment |
| Study arms     | 1. Active Comparator: CPVI plus Line  
|                | - A group of positive controls underwent operation with additional liner ablation to CPVI among patients who were changed to PAF from PeAF.  
|                | 2. Experimental: CPVI alone  
|                | - A group of negative controls underwent operation with CPVI alone among patients who were changed to PAF from PeAF. |
| Institution    | 1. Yonsei University Severance Hospital  
|                | 2. Korea University Anam Hospital  
<p>|                | 3. Ewha Womans University Hospital |
| Estimated enrollment | 116 |
| Inclusion criteria | Patients undergoing RFCA for symptomatic and drug refractory AF |</p>
<table>
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<tr>
<th>Exclusion criteria</th>
<th>1. AF with rheumatic valvular disease</th>
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<td>2. Significant structural heart disease other than left ventricular hypertrophy</td>
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<td>3. Left atrial (LA) diameter of 60 mm or greater</td>
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<td>4. A history of AF ablation or cardiac surgery</td>
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<td></td>
<td>5. Patients with age less than 19</td>
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<td>Sexes eligible for study</td>
<td>All</td>
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<tr>
<td>Primary endpoint</td>
<td>Freedom from documented episodes of AF or AT lasting longer than 30 seconds and occurring after a 3-month blanking period after a single ablation procedure, with or without the use of AADs.</td>
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<tr>
<td>Secondary endpoint</td>
<td>Achievement of a complete bidirectional block of additional linear lesions, utilization of AADs, procedure time, and incidence of peri-procedural complications.</td>
</tr>
<tr>
<td>Statistical analysis</td>
<td>1. Baseline characteristics, utilization of AADs, procedure time, and incidence of peri-procedural complications will be compared by Student's t-tests or Chi-square tests.</td>
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<tr>
<td></td>
<td>2. Kaplan–Meier analysis with log-rank test will be used to calculate AF recurrence-free survival over time and to compare recurrence rates across groups.</td>
</tr>
</tbody>
</table>
Supplemental Figure 1. Kaplan–Meier analysis of AF recurrence-free survival rate (A) and AF and AAD-free survival rate (B) according to the ablation strategies and the bidirectional block status of linear ablations. AF, atrial fibrillation; AAD, anti-arrhythmic drug; CPVI, circumferential pulmonary vein isolation; BDB, bidirectional block.