Left Atrial Appendage Isolation in Patients With Longstanding Persistent AF Undergoing Catheter Ablation

BELIEF Trial

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ABSTRACT

BACKGROUND Longstanding persistent (LSP) atrial fibrillation (AF) is the most challenging type of AF. In addition to pulmonary vein isolation, substrate modification and triggers ablation have been reported to improve freedom from AF in patients with LSPAF.

OBJECTIVES This study sought to assess whether the empirical electrical isolation of the left atrial appendage (LAA) could improve success at follow-up.

METHODS This was an open-label, randomized study assessing the effectiveness of empirical electrical left atrial appendage isolation for the treatment of LSPAF. Patients were randomly assigned to undergo empirical electrical left atrial appendage isolation along with extensive ablation (group 1; n = 85) or extensive ablation alone (group 2; n = 88). Recurrence of atrial arrhythmias was the primary endpoint. Secondary endpoints included cardiac-related hospitalization, all-cause mortality, and stroke at follow-up.

RESULTS Major clinical characteristics were not different between the 2 groups. At 12-month follow-up, 48 (56%) patients in group 1 and 25 (28%) in group 2 were recurrence free after a single procedure (unadjusted hazard ratio [HR] for recurrence with standard ablation: 1.92; 95% confidence interval [CI]: 1.3 to 2.9; log-rank p = 0.001). After adjusting for age, sex, and left atrial size, standard ablation was predictive of recurrence (HR: 2.22; 95% CI: 1.29 to 3.81; p = 0.004). During repeat procedures, empirical electrical left atrial appendage isolation was performed in all patients. After an average of 1.3 procedures, cumulative success at 24-month follow-up was reported in 65 (76%) in group 1 and in 49 (56%) in group 2 (unadjusted HR: 2.24; 95% CI: 1.3 to 3.8; log-rank p = 0.003).

CONCLUSIONS This randomized study showed that both after a single procedure and after redo procedures in patients with LSPAF, empirical electrical isolation of the LAA improved long-term freedom from atrial arrhythmias without increasing complications. (Effect of Empirical Left Atrial Appendage Isolation on Long-term Procedure Outcome in Patients With Persistent or Longstanding Persistent Atrial Fibrillation Undergoing Catheter Ablation [BELIEF]; NCT01362738) (J Am Coll Cardiol 2016;68:1929–40) © 2016 by the American College of Cardiology Foundation.
Catheter ablation represents a valid therapeutic option for the treatment of paroxysmal atrial fibrillation (AF) (1–4). In contrast, the outcomes of ablation in patients with persistent and longstanding persistent AF (LSPAF) are questioned in the published data (5). Consequently, although broad consensus on ablation endpoints in patients with paroxysmal AF exists, more uncertainty is present in patients with nonparoxysmal AF.

After the initial report by Haissaguerre et al. (6) showing that foci originating from the pulmonary veins (PVs) is an important initiating source of AF, PVs became the standard catheter ablation target. Results of STAR AF II (Substrate and Trigger Ablation for Reduction of Atrial Fibrillation Trial Part II) (7) raised questions regarding the value of lines and complex fractionated atrial electrogram (CFAE) ablation for treating patients with persistent AF. Additionally, controversies remain about the extent of ablation necessary outside the PVs, particularly for nonparoxysmal AF.

Importantly, many non-PV areas may be the source of initiation and maintenance of AF (12–20). The most common sites are the superior vena cava (SVC), the ligament of Marshall, the coronary sinus (CS), the crista terminalis, and the left atrial (LA) posterior wall (21). Furthermore, the LA appendage (LAA) was described as an underreported site of AF initiation in a nonrandomized prospective study (12). Tilz et al. (5) reported a very poor outcome at long-term follow-up in patients undergoing ablation for LSPAF. In their study, the LAA was not a target for ablation (5).

METHODS

BELIEF (Effect of Empirical Left Atrial Appendage Isolation on Long-term Procedure Outcome in Patients With Persistent or Longstanding Persistent Atrial Fibrillation Undergoing Catheter Ablation) was a randomized trial designed to compare the effectiveness of 2 different ablation strategies: an extended PV antrum ablation plus non-PV trigger ablation (standard ablation) versus standard ablation plus non-PV trigger ablation plus empirical electrical left atrial appendage isolation for the treatment of LSPAF. The definition of LSPAF followed the consensus documents by the Heart Rhythm Society, the European Heart Rhythm Association, the American Heart Association, and the American College of Cardiology (1–3).

At the 4 investigational sites, the study enrolled 173 consenting eligible subjects with LSPAF and randomly assigned them (1:1 ratio) to undergo empirical electrical left atrial appendage isolation plus standard ablation (group 1; n = 85) or standard ablation alone (group 2; n = 88) (Figure 1).

Patients 18 to 75 years old with LSPAF refractory to antiarrhythmic drugs (AADs) were included in the study. The exclusion criteria were reversible causes of AF (hyperthyroidism), LA thrombus, moderate to severe valvular heart disease and contraindication for anticoagulation, pregnancy, and life expectancy <12 months. A total of 12 operators at the enrolling institutions performed all procedures.

Freedom from atrial arrhythmia recurrence was the primary endpoint of the study, which was defined as freedom from AF, atrial flutter, or atrial tachycardia (AT) >30 s duration off AADs at follow-up. Any episodes occurring during the first 12 weeks (blanking period) after the procedure were not considered as recurrences. Secondary endpoints included the 12-month post-procedure incidence of stroke, death, and rehospitalization. Rehospitalization was defined as a hospital admission during the post-index procedure follow-up for arrhythmia-related causes or non-arrhythmia-related readmissions resulting from symptoms, signs, or complications of heart failure or ischemic heart disease.

A computer algorithm, written in SAS version 9.2 (SAS Institute, Inc., Cary, North Carolina), was used for generating a central randomization sequence with

Medical Center, San Francisco, California; Cardiac Arrhythmia Research Centre, Centro Cardiologico Monzino IRCCS, Milan, Italy; Section of Electrophysiology, University of Kansas, Kansas City, Missouri; Division of Cardiology, Stanford University, Palo Alto, California; Section of Electrophysiology, Case Western Reserve University, Cleveland, Ohio; Interventional Electrophysiology, Scripps Clinic, San Diego, California; and the Department of Medicine, Dell Medical School, Austin, Texas. Dr. Di Biase is a consultant for Biosense Webster, Boston Scientific Stereotaxis, and St. Jude Medical; and has received speaker honoraria and travel from Medtronic, Attncare, EPiEP, and Biotronik. Dr. Natale has received speaker honoraria from Boston Scientific, Biosense Webster, St. Jude Medical, Biotronik, and Medtronic; and is a consultant for Biosense Webster, St. Jude Medical, and Jansen. Dr. Burkhart is a consultant for Biosense Webster and Stereotaxis. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose. This study was presented at the late-breaking-trial scientific session of the European Society Cardiology Meeting 2015, in London on August 30, 2015.
block size of 4. The study administrator at the enrolling site was provided with blocks of randomization numbers and was required to store them at a restricted-access location. The trial arm allocation was provided to the investigator when the patient was ready for randomization. All patients signed an informed written consent to the procedure. The study was approved by the Institutional Review Boards of the participating institutions.

The study was designed to detect at least a 20% difference in success rates (50% to 70%) at 12-month follow-up (hazard ratio [HR]: 0.515; null hazard: 0.058) at 2-sided type I error of 0.05 and 80% power.

Briefly, 2 right groin femoral accesses (8-F sheath) were used to perform a double transseptal catheterization. A 20-mm decapolar circular mapping catheter was used for mapping the left atrium (Lasso, Biosense Webster, Baldwin Park, California), and a 3.5-mm open irrigated-tip ablation catheter was used for ablation (12,21).

An 11-F left femoral venous access was used to guide a 10-F phased-array ultrasound imaging catheter (Biosense Webster) in the right atrium (12,21). The right internal jugular vein was accessed and was used to place a 20-pole catheter; the distal poles were positioned in the CS, and the proximal poles were placed along the crista terminalis. All procedures were performed with uninterrupted oral anticoagulation strategies with warfarin and/or novel oral anticoagulant agents as described elsewhere by our group (22–29).

Before transseptal access, all patients received a heparin bolus, and extra heparin boluses were administered to maintain the activated clotting time higher than 350 s (29). AADs were discontinued 3 to 5 days before ablation, whereas amiodarone was discontinued 4 to 6 months before the procedure (30).
Briefly, in group 2, PV antrum isolation was performed, guided by a circular mapping catheter and by intracardiac echocardiography (12,21). The procedural endpoint was the local elimination of all the PV potentials along the antrum with demonstration of entry block. The electrical isolation of the PV antrum was extended to the entire posterior wall down to the CS and to the left side of the septum anterior to the right superior PV until electrical silence was achieved (6,16). If the AF organized into an AT, activation and entrainment mapping were performed to attempt termination. In the absence of arrhythmia termination, patients underwent a synchronized direct current shock to restore sinus rhythm (Figure 2).

A challenge test with isoproterenol infusion starting at 20 µg/min and up to 30 µg/min for 10 to 15 min was performed to identify non-PV triggers and/or PV reconnection (12,21). The test also includes 10 to 15 min of recovery time. To avoid hypotension, phentolamine was used at dosages tailored to individual patients in accordance with baseline blood pressure.

Non-PV triggers were disclosed and mapped during the isoproterenol test by positioning the circular mapping catheter in the electrically isolated left superior PV, the ablation catheter in the right superior PV, and the duodecapolar catheter in the right atrium and CS. The circular mapping catheter was positioned in the left superior PV and not in the LAA, to avoid mechanical arrhythmia induction by detecting far-field signals from the LAA. The initiating beat activation sequence was identified and compared with the sinus beat activation sequence. If sustained (>30 s) or nonsustained AF or AT was initiated from non-PV foci, this was mapped and ablated.

During the isoproterenol test, one can observe premature atrial complexes from the right atrium, the left atrium, and in the left atrium from the CS, the perimital region, the LAA, the left side of the septum, and the anterior wall. Once the area of interest was identified, additional mapping was performed either with the ablation catheter or with the circular mapping catheter to determine the earliest activation. The timing of the local electrograms in relation to the P wave is always used to identify the site of earliest activation. Cardioversions were performed to complete the test in case of initiation of a sustained arrhythmia, to look for different non-PV triggers or to finish the mapping. In group 2, the LAA was ablated and isolated only in case of sustained arrhythmia induction according sustained arrhythmia induction according to the protocol. In case of CS triggers, the coronary sinus was electrically isolated and not focally ablated.

When the right atrium low crista was disclosed as non-PV trigger, this was ablated at the site of earliest activation until the local atrial signals were eliminated and/or the trigger source was suppressed. It is important to consider that LA septal ablation is performed routinely as part of antral PV isolation but is limited to the area anterior to the right PVs. More extensive LA septal ablation was performed only in the presence of additional LA triggers in a different part of the septum. In patients demonstrating triggers from the right atrial septum, this was ablated until the local electrograms were eliminated and/or the trigger source was suppressed.

After isoproterenol challenge and non-PV trigger ablation, the SVC was empirically isolated in all

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**FIGURE 2 Ablation Procedure Steps**

- **Patients with LSPF (N=173)**
  - Pulmonary Vein Antrum Isolation
  - Posterior Wall Isolation
  - Ablation of the anterior LA septum
  - Ablation of the Roof

- **Group 1 (N=85)**
  - DCC/Empirical LAA electrical isolation
  - Isoproterenol (ISP) infusion up to 30 mcg/min
  - Ablation of sustained and non-sustained NPV triggers
  - Empirical SVC isolation unless phrenic nerve stimulation

- **Group 2 (N=88)**
  - DCC
  - Isoproterenol (ISP) infusion up to 30 mcg/min
  - Ablation of sustained and non-sustained NPV triggers and sustained arrhythmias from LAA
  - Ablation of sustained and non-sustained NPV triggers

This chart shows the common and divergent ablation procedure steps for each group. DCC = direct current cardioversion; LA = left atrial; LSPF = longstanding persistent atrial fibrillation; NPV = nonpulmonary vein; SVC = superior vena cava; other abbreviation as in Figure 1.
patients with PV-like potentials, provided that high-output pacing at 30 mA did not capture the phrenic nerve (31,32). Radiofrequency (RF) energy was delivered with a 3.5-mm open irrigated ablation catheter with a maximal temperature of 42°C and power up to 45 W with a flow rate of 30 cm²/min. An esophageal probe was used to monitor the temperature in the esophagus. The maximal power over the esophagus and within the CS was limited to 35 W, and energy delivery was discontinued when the esophageal temperature probe reached 39°C (12,21). Each RF lesion lasted no longer than 20 s, with the endpoint of signal elimination.

A 3-dimensional map of the LA was obtained with the CARTO system (Biosense Webster) or the NavX system (St. Jude Medical, St Paul, Minnesota).

As for the ablation, the steps were the same in groups 1 and 2, with the exception of the LAA. In group 1, LAA electrical isolation was performed empirically (EEI-LAA) before the isoproterenol test and after the isolation of the PV antrum extended to the entire posterior wall, down to the CS, and to the left side of the septum. The electrical isolation was performed in AF or immediately after direct current cardioversion in sinus rhythm. EEI-LAA has been extensively described elsewhere (12,21).

Briefly, LAA ablation was guided by intracardiac echocardiography and 3-dimensional mapping systems. The RF generator settings during LAA ablation included power up to 40 W while maintaining a catheter tip temperature of 42°C for a maximum of 20 s per ablation site (12,21). After EEI-LAA, the same isoproterenol test as in group 2 was performed up to 30 μg/min for 10 to 15 min to identify non-PV triggers and/or PV/LAA reconnections (12,21). The test includes 10 to 15 min of recovery time and phenylephrine use to avoid hypotension (Figure 2).

In all patients, after verification and reisolation of previously ablated areas, empirical electrical left atrial appendage isolation as described earlier was performed in all patients.

**POST-ABLATION MANAGEMENT AND FOLLOW-UP.** All patients were discharged on warfarin with a target international normalized ratio (INR) of 2 to 3 or on novel oral anticoagulant agents on the basis of pre-ablation oral anticoagulation management or their previously ineffective AADs, except for amiodarone. Oral anticoagulation was continued for a minimum of 6 months after the blanking period, whereas AADs were administered only during the blanking period. Once AADs were discontinued, any recurrences were reported off AADs. All patients were followed up until the study’s end.

Patients were seen in the outpatient clinic at 1 and 3 months after the procedure and every 3 months thereafter. A 48-h or 7-day Holter monitor recording was obtained at 3, 6, 9, 12, and 15 months post-ablation. Additionally, all patients were given an event recorder for 5 months and were asked to transmit recordings 4 times a week even when asymptomatic and anytime they experienced symptoms. In patients undergoing empirical electrical left atrial appendage isolation, transesophageal echocardiography (TEE) was performed 6 months post-ablation to assess the presence of a consistent A wave, LAA flow velocity, and LAA visual contractility. Patients with poor LAA velocity (<0.4 m/s) and or abnormal LAA function were maintained on oral anticoagulation.

**STATISTICAL ANALYSIS.** Continuous data are described as mean ± SD (median [interquartile range] for non-normal data) and as counts and percent if categorical. Student t test (Mann-Whitney U test if normality not satisfied) and chi-square tests were used to compare groups.

Recurrence-free survival was compared by the log-rank test, and Kaplan-Meier curves were generated. Event-free duration was defined as time from procedure to occurrence of outcome event (arrhythmia recurrence). For patients who were event free at the end of follow-up, time to event was censored. Death from any cause within the study period was considered for mortality analysis.

Univariate and multivariate Cox proportional hazard models were used for identifying significant predictors of AF recurrence. Proportional hazards assumption for the covariates was tested by Schoenfeld residual analysis. Likelihood ratio tests were performed to test nonlinear relation. Age, sex, and LA diameter were fitted in the multivariable model as controlling variables. Hazard ratios and 95% confidence intervals (CIs) from the Cox model are reported in the results.

All enrolled patients who underwent the index procedure constituted the intent-to-treat population and were the subject for safety and efficacy analyses. All tests were 2-sided, and a value of p < 0.05 was considered statistically significant. Analyses were performed using SAS version 9.2 (SAS Institute, Inc.).

**RESULTS**

A total of 173 patients were enrolled in the study. Baseline and major clinical characteristics were not different between the groups (Table 1).

Groups 1 and 2 had comparable procedural and fluoroscopy times. However, the mean RF time was approximately 16 min shorter in group 2 (p < 0.001).
(Table 1). When comparing RF time for standard ablation (excluding the RF time for EEI-LAA), no difference existed between the groups (76.0 ± 24.7 min vs. 74.6 ± 25.9 min in group 1 and 2, respectively; p = 0.73). The non-PV trigger foci mapped and ablated during the isoproterenol challenge are presented in Table 2. The distribution of non-PV trigger ablation was not different between the groups. The maximum esophageal temperature was more than 39°C in 24 patients. The mean maximal esophageal temperature was 38.4°C ± 0.9°C and 38.3°C ± 0.9°C (p = 0.75) in groups 1 and 2, respectively.

During the isoproterenol test in group 2, 32 (36%) patients showed firing from the LAA. A sustained arrhythmia was observed in 8 (9%) group 2 patients; the LAA was isolated in these 8 patients with sustained AF according to protocol, whereas it was not targeted in the remaining 24 patients who showed premature atrial complexes or nonsustained LAA firing. Notably, although all patients in group 1 were scheduled for empirical electrical left atrial appendage isolation, it was prevented in 11 patients because of technical difficulties (the LAA anatomical orientation made it difficult to obtain a stable contact between tissue and the ablation catheter). In these patients, extensive LAA ablation was performed that resulted in LAA activation that was very delayed either within or after the QRS complex. The SVC was empirically ablated in both groups, although the SVC was spared (not isolated) in 13 (15.3%) patients in group 1 and in 15 (17.1%) patients in group 2 because of phrenic nerve stimulation (p = 0.75). Before isoproterenol challenge, organization of AF into LA tachycardia or conversion into sinus rhythm occurred in 41 (48%) patients in group 1 and in 18 (20.5%) in group 2 (p < 0.001). In the remaining patients, electrical cardioversion was used to restore sinus rhythm.

After the isoproterenol test, LA tachycardia was induced in 3 patients in each group and was terminated with ablation. These LA tachycardias were focal tachycardias in 4 cases and macro-re-entry in 2 cases.

**Follow-up.** All enrolled patients were included in the analysis. No patient was lost at follow-up during the study period. At the time of analysis for the index procedure, all recurrence-free patients had completed 12-month follow-up in both groups. Overall compliance with the monitoring protocol was high; minor protocol deviations were reported in 24% of scheduled office visits and 21% of remote transmissions. In group 1, 73 (85.9%) patients were compliant with monitoring, as were 74 (84.1%) patients in group 2 (p = 0.74).

During the blanking period, 13 (15.3%) patients in group 1 and 8 (9.1%) in group 2 underwent electrical cardioversion (p = 0.21). At 12-month follow-up, 48 (56%) patients in group 1 and 25 (28%) in group 2 were recurrence free after a single procedure (unadjusted

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**Table 1** Baseline Characteristics

<table>
<thead>
<tr>
<th></th>
<th>Group 1 (n = 85)</th>
<th>Group 2 (n = 88)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, yrs</td>
<td>64.25 ± 8.25</td>
<td>63.5 ± 8.7</td>
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<tr>
<td>Male</td>
<td>75 (88.2)</td>
<td>73 (83.0)</td>
<td>0.32</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>33.90 ± 8.35</td>
<td>32.5 ± 7.3</td>
<td>0.23</td>
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<tr>
<td>Hypertension</td>
<td>58 (68.2)</td>
<td>60 (68.2)</td>
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<tr>
<td>Diabetes</td>
<td>17 (20.0)</td>
<td>18 (20.5)</td>
<td>0.94</td>
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<tr>
<td>Previous CVA/TIA</td>
<td>9 (10.6)</td>
<td>6 (6.8)</td>
<td>0.38</td>
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<tr>
<td>CHA2DS2-VASc score</td>
<td>2.3 ± 1.6</td>
<td>2.2 ± 1.6</td>
<td>0.44</td>
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<tr>
<td>LVEF, %</td>
<td>53.9 ± 11.3</td>
<td>54.8 ± 10.7</td>
<td>0.63</td>
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<tr>
<td>Dyslipidemia</td>
<td>53 (62.4)</td>
<td>56 (63.6)</td>
<td>0.86</td>
</tr>
<tr>
<td>Congestive heart failure</td>
<td>19 (22.4)</td>
<td>16 (18.2)</td>
<td>0.50</td>
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<tr>
<td>Obstructive sleep apnea</td>
<td>18 (21.2)</td>
<td>20 (22.7)</td>
<td>0.81</td>
</tr>
<tr>
<td>Coronary artery disease</td>
<td>20 (23.5)</td>
<td>19 (21.6)</td>
<td>0.76</td>
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<td>AADs</td>
<td></td>
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<tr>
<td>Beta-blockers</td>
<td>67 (79)</td>
<td>62 (70)</td>
<td>0.21</td>
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<td>ACEI/ARB</td>
<td>37 (44)</td>
<td>46 (52)</td>
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<tr>
<td>Flecainide</td>
<td>12 (14)</td>
<td>16 (18)</td>
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<tr>
<td>Dronedarone</td>
<td>11 (13)</td>
<td>15 (17)</td>
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<td>Propafenone</td>
<td>13 (15)</td>
<td>18 (20)</td>
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<tr>
<td>Dofetilide</td>
<td>14 (16)</td>
<td>17 (19)</td>
<td>0.62</td>
</tr>
<tr>
<td>Sotalol</td>
<td>11 (13)</td>
<td>15 (17)</td>
<td>0.45</td>
</tr>
<tr>
<td>Number of failed AADs</td>
<td>1.8 ± 0.9</td>
<td>2.0 ± 0.8</td>
<td>0.13</td>
</tr>
<tr>
<td>Procedure time, min</td>
<td>182 ± 62</td>
<td>170 ± 56</td>
<td>0.25</td>
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<tr>
<td>Radiofrequency time, min</td>
<td>93 ± 26.2</td>
<td>77.4 ± 29.9</td>
<td>&lt;0.001</td>
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<tr>
<td>Fluoroscopy time, min</td>
<td>72 ± 66</td>
<td>66 ± 29</td>
<td>0.15</td>
</tr>
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</table>

**Table 2** Non-PV Trigger Distribution During Isoproterenol Challenge

<table>
<thead>
<tr>
<th></th>
<th>Group 1 (n = 85)</th>
<th>Group 2 (n = 88)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Coronary sinus</td>
<td>71 (83.5)</td>
<td>75 (85.2)</td>
<td>0.76</td>
</tr>
<tr>
<td>Superior vena cava*</td>
<td>25 (29.4)</td>
<td>25 (28.4)</td>
<td>0.89</td>
</tr>
<tr>
<td>Left atrial appendage</td>
<td>NA</td>
<td>32 (36.4)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Right atrium/septum</td>
<td>26 (30.6)</td>
<td>24 (27.3)</td>
<td>0.63</td>
</tr>
<tr>
<td>Left atrial septum</td>
<td>43 (50.6)</td>
<td>42 (47.7)</td>
<td>0.71</td>
</tr>
<tr>
<td>Mitral valve annulus</td>
<td>3 (3.5)</td>
<td>4 (4.5)</td>
<td>1.00</td>
</tr>
<tr>
<td>Right atrial crista</td>
<td>3 (3.5)</td>
<td>4 (4.5)</td>
<td>1.00</td>
</tr>
</tbody>
</table>

Values are n (%) or %. *This was the documented firing from the superior vena cava including premature atrial complexes, but the superior vena cava was empirically isolated in both groups unless phrenic nerve capture at the ablation site was detected. The 36% reflects sustained and nonsustained arrhythmia firing including premature atrial complexes. By study design, the left atrial appendage was ablated in this group only in case of firing leading to sustained atrial fibrillation or tachycardia, which happened in 8 (9%) patients.

NA = not applicable; PV = pulmonary vein.
HR for recurrence with standard ablation: 1.92; 95% CI: 1.3 to 2.9; log-rank p = 0.001. Cumulative freedom from recurrence of AADs after the first procedure is presented in Figure 3. Seven of the 8 patients in group 2 who underwent empirical electrical left atrial appendage isolation and 7 of 11 patients in group 1 whose LAA could not be isolated were recurrence free during follow-up. After adjusting for age, sex, and LA size (Cox multivariable model), the standard ablation approach was predictive of recurrence (HR: 2.22; 95% CI: 1.29 to 3.81; log-rank p = 0.004).

Of the patients with a failed first procedure, 27 of 37 (73%) in group 1 and 35 of 63 (56%) in group 2 underwent repeat ablation. During this procedure, PV reconnection was detected in 3 (11.1%) patients in group 1 and in 4 (11.4%) in group 2 (p = 1.0). LAA reconnection was detected in 10 of 27 (37%) group 1 patients. EEI-LAA was performed in patients from both groups during redo procedures, and the LAA was reisolated in cases of reconnection.

At 24-month follow-up and an average of 1.3 procedures, the cumulative success rate was 65 (76%) in group 1 and 49 (56%) in group 2 (unadjusted HR: 2.24; 95% CI: 1.3 to 3.8; log-rank p = 0.003) (Figure 4).

Patients undergoing empirical electrical left atrial appendage isolation with sinus rhythm at 6-month follow-up (n = 62; 55 from group 1 and 7 from group 2) underwent TEE. Irrespective of their underlying rhythm, LAA function was assessed in all; 1 LAA thrombus (patient was receiving oral anticoagulation with subtherapeutic INR) and 1 case of LAA spontaneous echocardiographic contrast (INR 2.24 on warfarin) were detected in the empirical electrical left atrial appendage isolation group. Among the 62 patients who had TEE, preserved LAA function was reported in 27 (43.5%) patients. Conversely, an impaired contractile pattern was observed in 35 (56.5%) patients; 28 (80%) had low peak filling and emptying velocities (<0.4 m/s), 4 (11.4%) had an inconsistent A wave, and 3 (8.6%) patients showed both low flow velocity and an inconsistent A wave (Figure 5).

No stroke or transient ischemic attack was reported with empirical electrical left atrial appendage isolation (group 1), whereas 4 (4.5%) patients had stroke after standard ablation (group 2) (p = 0.12). No deaths occurred during the study period. Hospitalization rates were similar: a total of 21 (25%) patients in the empirical electrical left atrial appendage isolation group and 19 (22%) patients in the standard ablation group required rehospitalization for arrhythmia-related causes (p = 0.72). There were 2 (2.4%) heart failure-related hospitalizations in the empirical electrical left atrial appendage isolation group and none in the other group (p = 0.24).

One pericardial effusion occurred in each group (p = 1.00). One case of gastrointestinal bleeding was reported in group 2 (p = 0.49).

**DISCUSSION**

This randomized study showed that empirical isolation of the LAA improved freedom from AF/AT in patients with LSPAF (Central Illustration).
Importantly, evidence of LAA firing was present in only 8% of patients undergoing the standard approach, a finding suggesting the relevance of empirical isolation of the LAA to achieve long-term freedom from atrial arrhythmias.

A major drawback could be represented by the need for long-term anticoagulation, given that the lack of proper mechanical function in the LAA may contribute to stroke. However, it is important to consider that most patients included in this trial would have been receiving long-term oral anticoagulation irrespective of their ablation because of their CHA2DS2-VASC (congestive heart failure, hypertension, age ≥75 years, diabetes mellitus, stroke/transient ischemic attack, vascular disease, age 65 to 74 years, female sex category) score. Furthermore, considering the high success rate after 2 procedures, the risk of long-term anticoagulation is a worthwhile price to pay to stay in sinus rhythm. Besides, several LAA closure devices are available that could be an alternative to long-term anticoagulation for these patients.

This study reinforced the concepts that in patients with LSPAF, PV isolation alone is insufficient to achieve satisfactory results (5). In group 2, in which in addition to PV isolation, only non-PV triggers disclosed by isoproterenol challenge were ablated, the success rate was 28% at 12-month follow up, and that rate increased to 56% after an average of 1.3 procedures once EEI-LAA was added. In the group that had, in addition to PV isolation and non-PV trigger ablation, empirical isolation of the LAA, the success rate was 56% after a single procedure, and it increased to 76% following an average of 1.3 procedures.

The relevance of EEI-LAA in treating these patients is of utmost importance. In contrast to the paper by Tiltz et al. (5) suggesting a mediocre outcome after multiple ablation procedures in patients with LSPAF, we showed that freedom from AF or AT at follow-up off AADs is of clinical relevance if the LAA is electrically isolated.

In the field of catheter ablation for AF, the need to isolate the PVs is established (1-4). However, despite the recognized role of non-PV triggers, opinions about their relevance and the best way to approach these additional sites are not standardized. This trial clearly indicated that in patients with LSPAF, EEI-LAA increased freedom from AF at follow-up without increasing the procedural complication rate.

Isolation of all PVs without a documented trigger for each PV is considered the standard of care. Therefore, we designed the BELIEF trial, in which we empirically isolated the LAA. The greater freedom from AF at follow-up is an important finding because it establishes the inadequacy of any provoking test, such as isoproterenol, in patients with LSPAF. The value of EEI-LAA as a relevant part of the procedure is shown by the high rates of freedom from AF or AT at 2 years with only a mean of 1.3 procedures.

ANATOMY. The LAA derives from the embryonic left atrium. It acquires a trabecular appearance because of the presence of the pectinate muscles, and it progresses from an outgrowth of the PVs. The LAA is a dynamic structure with distinct patterns of contraction and relaxation (33).

Different imaging modalities (TEE, computed tomography, and cardiac magnetic resonance) have...
shown wide variability in assessing configuration, shape, and dimension (34,35). In approximately 50% of the population, the LAA is composed of 2 lobes, and in one-third of the population, it has 3 lobes (36–38). Because the LAA has a very thin wall and may be prone to perforation, the operator should be cautious when trying to achieve EEI-LAA.

Although it is fair to say that expert operators were involved in this trial, no major complications were reported. Empirical electrical left atrial appendage isolation did not increase procedural complication rates or alter the fluid balance of patients (39–45). Several studies revealed that atrial and B-type natriuretic peptides are produced and secreted in the left
atrial appendage and right atrial appendage; thus, its role in volume homeostasis is not well established (46–48).

Another important factor is LAA autonomic innervation. Ganglia are usually present along the groove between the left superior PV and the LAA and may have clinical relevance (39–45). Moreover, in the region between the LAA and the left superior PV is the ligament of Marshall (an epicardial structure containing sympathetic and parasympathetic nerves). This structure appears to be directly connected to the CS. It is conceivable that ablation of the LAA also affects the ligament of Marshall, or vice versa (49,50).

However, in a series of 18 patients with persistent AF and LSPAF, with firing from the LAA, these patients experienced recurrence despite PV antrum isolation plus ethanol ablation of the vein of Marshall. During redo procedures, the PV remained isolated in all but 4 patients, and in each of these patients, firing from the LAA continued despite ethanol ablation of the vein of Marshall. This finding reinforced the concepts that the vein of Marshall does not have any impact on LAA electrical activity and does not suppress its firing (51).

**ROLE OF LAA AS ARRHYTHMIA TRIGGER.** The role of the LAA in initiating and maintaining AF and atrial arrhythmias has not been widely reported. More recently, many studies have focused attention on non-PV triggers as the source of AF; within these, the LAA represents one of the most common sites.

In the LAALA-AF (Left Atrial Appendage Ligation and Ablation for Persistent Atrial Fibrillation) registry (52), 69 patients with persistent AF who were referred for AF ablation underwent LAA ligation with the Lariat endocardi- "

The BELIEF results showed that in patients with LSPAF, both after a single procedure and after redo procedures, EEI-LAA improved long-term freedom from atrial arrhythmias without increasing complications. Future studies examining the pathophysiology of these findings are necessary.

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**PERSPECTIVES**

**COMPETENCY IN PATIENT CARE AND PROCEDURAL SKILLS:** In patients with LSPAF who are undergoing PV antrum isolation and ablation of triggers outside the PVs, additional electrical isolation of the LAA is associated with greater freedom from recurrent AF without increased complication rates.

**TRANSLATIONAL OUTLOOK:** Further studies are needed to evaluate LAA mechanical function following electrical isolation in patients with AF who are undergoing catheter ablation procedures.


KEY WORDS arrhythmia, atrial fibrillation, non-PV trigger, pulmonary vein, radiofrequency