Effect of Empirical Left Atrial Appendage Isolation on long-term procedure outcome in patients with Long-Standing Persistent AF undergoing Catheter Ablation: Results from the BELIEF Randomized Trial

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DECLARATION OF INTEREST

- I am a consultant for Biosense Webster, Stereotaxis and St Jude Medical. I received speaker honoraria/travel from Biotronik, Medtronic, Boston Scientific and Epi EP
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ClinicalTrials.gov Identifier: NCT01362738

DISCLOSURES

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Long standing persistent (LSP) atrial fibrillation (AF) is the most challenging type of AF to treat with catheter ablation.
Several studies have shown that in addition to pulmonary vein (PVs) isolation other non PVs areas may be the source of initiation and maintenance of atrial fibrillation in patients. The most common sites are: the superior vena cava, the ligament of Marshall, the coronary sinus, the crista terminalis, the left atrial posterior wall and the left atrial appendage.
Left Atrial Appendage: An Underrecognized Trigger Site of Atrial Fibrillation


Figure 1. Flow chart showing the study design. PAF indicates paroxysmal AF; PER, persistent AF; and LSP, long-standing persistent AF.
Total Population (n=3,966)
PAF 36%, Persistent 20%, LS Persistent 44%

Referred for Redo (n=987)
PAF 29%, Persistent 20%, LS Persistent 51%

No LAA Firing
721 (73%)

LAA Firing 266 (27%)
PAF 18%, PER 23%, LSP 58%

Group 1-LAA Not Ablated (n=43)

Group 2-Focal Ablation (n=56)

Group 3-LAA Isolation (n=167)

LAA Isolation
2nd Redo (n=88)

EVIDENCE of the LAA as a TRIGGER for AF/AT

Localized reentry within the left atrial appendage: arrhythmogenic role in patients undergoing ablation of persistent atrial fibrillation

Mélèze Hocini, MD, Ashok J. Shah, MD, Isabelle Nault, MD, Prashanthan Sanders, MBBS, PhD, Matthew Wright, MBBS, PhD, Sanjiv M. Narayan, MD, FACC, Yoshihide Takahashi, MD, Pierre Jaïs, MD, Seiichiro Matsuo, MD, Sébastien Knecht, MD, Frédéric Sacher, MD, Kang-Teng Lim, MD, Jacques Clémenty, MD, Michel Haïssaguerre, MD

Management of focal atrial tachycardias originating from the atrial appendage with the combination of radiofrequency catheter ablation and minimally invasive atrial appendectomy

Xiao-gang Guo, MD, Jin-lin Zhang, MD, Jian Ma, MD, Yu-he Jia, MD, Zhe Zheng, MD, Hong-yue Wang, MD, Xi Su, MD, Shu Zhang, MD, FHRS

Left Atrial Appendage Ligation and Ablation for Persistent Atrial Fibrillation

The LAALA-AF Registry

Dhanunjaya Lakkireddy, MD, Arun Sridhar Mahankali, MD, Arun Kanmanthareddy, MD, Randall Lee, MD, Nitish Badhwar, MD, Krzysztof Bartus, MD, PhD, Donita Atkins, BSN, Sudharani Bommana, MPH, Jie Cheng, MD, Abd Rasekh, MD, Luigi Di Biase, MD, PhD, Andrea Natale, MD, Jayant Nath, MD, Ryan Ferrrell, MD, Matthew Earnest, MD, Yeruva Madhu Reddy, MD
AIM

We sought to assess whether in patients with Long Standing Persistent AF the EMPRICAL ELECTRICAL ISOLATION of the left atrial appendage (LAA) in addition to extensive PV antrum and triggers ablation could improve freedom from AF/AT at follow up in a multicenter randomized trial.
Methods

• This was a randomized, parallel-group study assessing whether empirical isolation of the LAA in addition to an extensive standard ablation, could improve the freedom from atrial arrhythmia in LSP AF patients.

• Power Calculation: The study had 80% power to detect at least 20% difference in success rate (50% to 70%) at 12 month follow-up (using log-rank test), with two-sided Type I error of 0.05.

• 173 patients were enrolled and randomly assigned (1:1 ratio) to:
  - Extensive ablation plus Empirical LAA isolation (group 1, n=85)
  - Extended PV antrum and non PV triggers ablation (group 2, n=88)

• Patients e18 years of age, with LSP AF refractory to antiarrhythmic drugs were included in the study.
Study Design

173 Patients Enrolled
(e18 years, long-standing persistent AF refractory to antiarrhythmic drugs)

Randomized 1:1

Standard Ablation + Empirical LAA isolation (Group 1): n= 85

Standard Ablation alone (group 2): n= 88

Follow-up After Index Procedure

Ablation Success Assessed at 12 month

62 Patients underwent a second procedure (27 group 1 and 35 group 2). LAA isolation was performed in all patients during repeat ablation

Follow-up after Redo

Outcome Assessed at 24 month
Methods

• **Primary Endpoint:**
  – Recurrence of AF/AT lasting longer than 30 seconds was the primary end point of the study

• **Secondary endpoints included:**
  – Post-ablation hospitalizations due to heart failure and AF related causes
  – Mortality
  – Incidence of stroke
Results

• Baseline and major clinical characteristics were not different between the groups

• The mean radiofrequency time was 93.1 ± 26.2 and 77.4 ± 29.9 minutes (p < 0.001) for group 1 and 2 respectively.

• In group 1, LAA could not be isolated in 11 patients due to technical difficulties
  – Extensive ablation was performed in LAA area with partial isolation of the appendage

• In Group 2, 32 (36%) patients showed firing from LAA during isoproterenol test
  – A sustained arrhythmia was observed in 8 (9%) of these patients and LAA was isolated
  – Consistent PACs or non-sustained arrhythmia were observed in the remaining 24 patients and LAA was not isolated
<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>
<td>0.54</td>
</tr>
<tr>
<td>Male</td>
<td>75 (88.2%)</td>
<td>73 (83.0%)</td>
<td>0.32</td>
</tr>
<tr>
<td>BMI</td>
<td>33.90±8.35</td>
<td>32.5±7.3</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>
</tr>
<tr>
<td>Prior CVA/TIA</td>
<td>9 (10.6%)</td>
<td>6 (6.8%)</td>
<td>0.38</td>
</tr>
<tr>
<td>CHADS 2 Score</td>
<td>1.44±1.1</td>
<td>1.30±1.1</td>
<td>0.4</td>
</tr>
<tr>
<td>0</td>
<td>18 (21.2%)</td>
<td>22 (25.0%)</td>
<td>0.7</td>
</tr>
<tr>
<td>1</td>
<td>29 (34.1%)</td>
<td>32 (36.4%)</td>
<td></td>
</tr>
<tr>
<td>e2</td>
<td>38 (44.7%)</td>
<td>34 (38.6%)</td>
<td></td>
</tr>
<tr>
<td>LA Diameter, mm</td>
<td>45.8±6.4</td>
<td>46.3±7.0</td>
<td>0.6</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>
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<tr>
<td>CHF</td>
<td>19 (22.4%)</td>
<td>16 (18.2%)</td>
<td>0.5</td>
</tr>
<tr>
<td>OSA</td>
<td>18 (21.2%)</td>
<td>20 (22.7%)</td>
<td>0.81</td>
</tr>
<tr>
<td>CAD</td>
<td>20 (23.5%)</td>
<td>19 (21.6%)</td>
<td>0.76</td>
</tr>
<tr>
<td>No. of AADs</td>
<td>1.8±0.9</td>
<td>2.0±0.8</td>
<td>0.13</td>
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<tr>
<td>Procedure Time (min)</td>
<td>182±62</td>
<td>170±56</td>
<td>0.25</td>
</tr>
<tr>
<td>RF Time (min)</td>
<td>93.1±26.2</td>
<td>77.4±29.9</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Fluoroscopy Time (min)</td>
<td>72±26</td>
<td>66±29</td>
<td>0.15</td>
</tr>
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</table>
Results: Arrhythmia Recurrence

• No patients were lost to follow-up

• At the 12 month follow-up, freedom from recurrence after single procedure was reported in
  – 48(56%) in group 1 and 25(28%) in group 2
  – Log-rank p=0.001, unadjusted HR 1.92 (1.3 to 2.9)

• Sixty-two patients (27 group 1 and 35 group 2) underwent a second procedure.
  **LAA isolation was performed in all patients of either groups during repeat ablation**

• After average of 1.3 procedures, success at 24 months follow-up was:
  – 65 (76%) in group 1 and 49 (56%) in group 2
  – Log-rank p= 0.003, unadjusted HR 2.24 (1.3-3.8)
Kaplan–Meier curves: single procedure success rate

At the 12 month follow-up, 48 (56%) in group 1 and 25 (28%) in group 2 were recurrence-free off-AAD after a single procedure. (Log-rank p=0.001, unadjusted HR 1.92 [1.3 to 2.9]).
The cumulative success after multiple procedures was 65 (76%) in group 1 and 49 (56%) in group 2.

ALL THE PATIENTS UNDERWENT LAA ISOLATION

(Log-rank p = 0.003, unadjusted HR 2.24 [95% CI 1.3-3.8])
Results: Predictor of Recurrence

• After adjusting for age, gender, LA diameter in Cox multivariate model
  - Isolation of LAA in addition to standard ablation, was associated with 55% reduction in overall recurrence (HR 0.45 [0.26-0.77], p=0.004)
Results: Trans-esophageal echocardiogram (TEE) after a single procedure in patients undergoing LAA isolation

- Patients undergoing LAA isolation received TEE at 6 month follow up, irrespective of their underlying rhythm.
- Low peak flow velocity (<0.4 m/s) in the LA appendage was observed in 48 patients.
- One LAA thrombus (in patient on OAT with subtherapeutic INR) and one LAA smoke (oral anticoagulant warfarin, INR: 2.24) were detected in the LAA isolation group.
Results:
Trans-esophageal echocardiogram (TEE) after a single procedure in patients undergoing LAA isolation

LAA Isolation: n=93 (Group 1: 85, Group 2: 8)

- Preserved Function: 45 (48%)
- Impaired Function: 48 (52%)

- Inconsistent A wave: 6 (12.5%)
- LAA Peak flow velocity <0.4 m/s: 42 (87.5%)
- Inconsistent A wave and LAA low peak flow velocity: 4 (8.3%)
Hospitalization

**AF Related Hospitalizations**
- Empirical LAA isolation: 22 (25%)
- Standard ablation group: 19 (22%)

**HF Related Hospitalizations**
- P = 0.72
- P = 0.24

Incidence Rate

P = 0.72

P = 0.24
Results: Stroke/TIA and Mortality

• Stroke/TIA:
  - No stroke or TIA was reported in the empirical LAA isolation group,
  - Four (4.5%) patients had stroke in the standard ablation group (p=0.12). None of them in patients with LAA isolation

• No deaths occurred during the study period
Results: Peri-Procedural Complications

- Complications:
  - One pericardial effusion occurred in each group \( (p=1.0) \)
  - One gastrointestinal bleeding was reported in Standard Ablation group \( (p=0.49) \)
Relative contribution of different ablation targets in the AF disease continuum

- Non-PV Triggers
  - PV Triggers
  - Substrate?
  - LAA
  - Other Non-PV Triggers

Paroxysmal Persistent Long-standing persistent
CONCLUSIONS

- The results of this randomized study show that both after a single and redo procedures in patients with long standing persistent AF, the **EMPIRICAL ISOLATION** of the **LAA** improve the long-term freedom from atrial arrhythmias without increasing complications.

- Future studies examining the physiopathology of these findings are necessary.
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Texas Cardiac Arrhythmia Institute at St. David’s Medical Center, Austin, Texas, USA;
California Pacific Medical Center, San Francisco, California, USA;
University of Kansas, Kansas City, USA;
Cardiac Arrhythmia Research Centre, Centro Cardiologico Monzino IRCCS, Milan, Italy;
Effect of Empirical Left Atrial Appendage Isolation on Long-term Procedure Outcome in Patients With Persistent or Long-standing Persistent Atrial Fibrillation Undergoing Catheter Ablation (BELIEF)

This study is currently recruiting participants.
Verified May 2011 by Texas Cardiac Arrhythmia Research Foundation

Sponsor:
Texas Cardiac Arrhythmia Research Foundation

ClinicalTrials.gov Identifier:
NCT01362738

First received: May 26, 2011
Last updated: May 31, 2011
Last verified: May 2011
Optimal Method and Outcomes of Catheter Ablation of Persistent AF: The STAR AF 2 Trial

ClinicalTrials.gov NCT01203748

ESC 2014 HOTLINE Presentation
Results - Primary Outcome

Documented AF > 30 seconds after one procedure with or without AAD

\[ p = 0.15 \]

<table>
<thead>
<tr>
<th>Survival function</th>
<th>Number of months since first ablation</th>
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<tbody>
<tr>
<td>Pulmonary vein isolation</td>
<td>61 60 50 41 36</td>
</tr>
<tr>
<td>Isolation + Electrograms</td>
<td>244 242 161 137 124</td>
</tr>
<tr>
<td>Isolation + Lines</td>
<td>244 240 152 133 115</td>
</tr>
</tbody>
</table>

59% 48% 44%