Ununexpectedly High Incidence of Stroke and Left Atrial Appendage Thrombus Formation After Electrical Isolation of the Left Atrial Appendage for the Treatment of Atrial Tachyarrhythmias

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Background—Electric left atrial appendage (LAA) isolation (LAAI) may occur during catheter ablation of atrial tachyarrhythmias. Data regarding the risk of thromboembolic events and stroke after LAAI are sparse. This study evaluated the incidence of LAA thrombus formation and thromboembolic events after LAAI.

Methods and Results—Fifty patients had LAAI (age=71 years; female=56%; CHA2DS2-VASc score before ablation =3 [2;3]). LAAI patients were compared with matched patients with comparable baseline characteristics who underwent atrial fibrillation ablation without LAAI (n=50). Ablation strategies in the LAAI group included pulmonary vein isolation in 50 (100%), left atrial isthmus line in 47 (94%), anterior line in 45 (90%), complex atrial fractionated potentials in 24 (48%), and roofline in 14 (28%) patients. Transesophageal echocardiography was performed during follow-up in 47/50 (94%) patients in the LAAI group and in all patients of the control group. Oral anticoagulation (OAC) independent of CHA2DS2-VASc score was strongly recommended in all patients. During a median follow-up of 6.5 (4–12) months, stroke occurred in 2 patients on OAC and transient ischemic attack in one without OAC in the LAAI group. In the remaining 47 patients, LAA thrombus was identified on transesophageal echocardiography in 10 (21%) patients in the LAAI group and in all patients of the control group. In the control group, no LAA thrombus was detected and no stroke occurred (P<0.001). Stable sinus rhythm was maintained in 32 patients (64%) of the LAAI group after a median follow-up of 6.5 months (4–12), including 17/32 patients on antiarrhythmic drugs.

Conclusions—After LAAI, an unexpectedly high incidence of LAA thrombus formation and stroke was observed despite OAC therapy. (Circ Arrhythm Electrophysiol. 2016;9:e003461. DOI: 10.1161/CIRCEP.115.003461.)

Key Words: appendage isolation ■ atrial fibrillation ■ catheter ablation ■ left atrial appendage ■ stroke ■ thrombus

Pulmonary vein isolation (PVI) has evolved into a widely accepted and effective strategy for the treatment of paroxysmal and short persistent atrial fibrillation (AF). However, stable sinus rhythm (SR) cannot be achieved by PVI alone in some patients with paroxysmal AF and in the majority of patients with persistent or longstanding persistent AF. When adjuvant ablation strategies are performed in addition to PVI, left atrial appendage (LAA) isolation (LAAI) sometimes occurs. Di Biase et al recently demonstrated that ectopsies from the LAA can act as triggers for recurrent AF, and electric LAAI can improve outcomes in recurrent AF during reablation procedures. On the other hand, this ablation strategy may theoretically be associated with an increased risk of thrombus formation within the LAA and thromboembolic events.

Our study aimed to evaluate the incidence of LAA thrombus formation and thromboembolic stroke in patients who had wide-area LAAI after left atrial (LA) linear lesion ablation or extensive complex fractionated atrial electrogram (CFAE) ablation at the anterior and lateral LA wall.

See Editorial by Thompson and Jais

Methods

Patient Characteristics

This prospective, observational study included 50 consecutive patients (28 [56%] female, age 71 [66;74] years, CHA2DS2-VASc score 3 [2;3]) in whom the LAA was isolated during catheter ablation for symptomatic atrial tachyarrhythmia (ATA) between 2011 and 2014. These patients

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WHAT IS KNOWN

- Electric left atrial appendage (LAA)-isolation (LAAI) may occur during catheter ablation of atrial tachyarrhythmias.
- Left atrial appendage isolation might be associated with a beneficial outcome in patients with atrial tachyarrhythmias.

WHAT THE STUDY ADDS

- Wide area isolation of the left atrial appendage is associated with an unexpectedly high incidence of left atrial thrombus formation and stroke despite oral anticoagulation therapy.
- Wide area isolation of the left atrial appendage appears to be associated with a significantly increased risk of left atrial thrombi and stroke when compared to pulmonary vein isolation alone.

were compared with a matched control group of 50 patients who underwent AF ablation without LAAI. The control group was matched for the following variables: age, sex, hypertension, diabetes mellitus, coronary artery disease, CHA2DS2-VASc score, LA diameter, systolic function, and type of anticoagulation therapy.

Ablation Protocol: Initial Procedure

In all patients, transesophageal echocardiography (TEE) was performed within 2 days before the ablation procedure. A longitudinal section of the LAA was imaged by multiplane views (30°–90°), and the LAA flow velocity was assessed. The LA diameter was measured in the anterior–posterior dimension.

This study conforms to the guiding principles of the Declaration of Helsinki 2008 and was approved by the local institutional review board. Written informed consent was obtained from all patients. All authors had full access to the data and have read and agreed to the article as written.

Catheter Ablation

Procedures were performed under deep sedation with midazolam and propofol. A 7F octopolar or decapolar catheter ( Biosense Webster, Diamond Bar, CA or IbI inquiry, St Jude Medical, St. Paul, MN) was placed in the coronary sinus via the left subclavian or femoral veins. After double transseptal punctures, 2 8.5F long sheaths ( SL1, St Jude Medical) were advanced into the LA and continuously flushed with heparinized saline (flow rate 10 mL/h). The activated clotting time was maintained >250 s throughout the procedure. Activated clotting time levels were checked every 30 minutes throughout all procedures. In all patients, a conventional 3.5 mm irrigated-tip ablation catheter (ThermoCool Navi-Star, Biosense Webster) was used for the ablation procedure. During radiofrequency energy delivery, power was limited to 30 to 40 W in the LA and right atrium and 10 to 20 W in the coronary sinus (irradiation rate 17–25 mL/min; temperature limit 43°C).

Ablation Protocol: Initial Procedure

All patients underwent circumferential PVI using irrigated radiofrequency, as previously described. The end point of PVI was defined as the absence of any PV potential for at least 30 minutes after PVI, assessed by a spiral mapping catheter (Lasso, Biosense Webster). After PVI, if AF did not convert to SR or atrial tachycardia (AT), ≤3 biphasic direct current shocks (200 J, 360 J, and 360 J; Medtronic Lifepak 12, Medtronic Inc, MN) were administered to restore SR. If AF was reinduced by a trigger outside the PVs during the waiting period, this trigger was targeted for ablation; however, no CFAE ablation was performed. CFAE ablation was only performed if SR could not be achieved, in an attempt to convert AF to SR or AT, as described previously. AF termination was defined as conversion of AF directly to SR or AT. CFAEs were identified visually and were defined as (1) fractionated electrograms composed of >1 deflection and continuous activation of a prolonged complex and (2) atrial electrograms with a cycle length <120 ms over a 5 second recording period.

If AF was converted to macro-reentrant AT, linear lesions were ablated (Figure 1).8,9 Bidirectional block was validated during SR as described by Jais et al.8 During ablation of CFAEs and LA linear lesions, the spiral catheter was positioned in the LAA to continuously record LAA activity.

Ablation Protocol: Repeat Procedures

Repeat ablation procedures were performed for arrhythmia recurrence, defined as episodes of AF or AT lasting >30 seconds as documented by 12-lead ECG or Holter monitoring. If PVs were electrically reconnected to the LA, conduction gaps were closed with radiofrequency ablation to electrically reisolate the PVs. CFAE ablation was then only performed if (1) after repeat PVI, AF was not converted to SR or AT and cardioversion failed or (2) PVs were not reconnected. For patients in SR at the start of the procedure and without PV reconnection, AF was induced by burst stimulation in the LAA before CFAE ablation.

Electric LAAI was defined as follows: (1) demonstration of entrance block—disappearance of all LAA potentials documented with a spiral catheter placed within the LAA, regardless of the underlying cardiac rhythm and (2) demonstration of exit block—LAA electric activity dissociated from the LA during LAA ectopics or pacing from within the LAA.3,8

Postablation Care and Follow-Up

Anticoagulation After LAAI

After the index LAAI ablation procedure, anticoagulation with low molecular weight heparin was started 6 hours after sheath removal and continued until an international normalized ratio (INR) between 2 and 3 was achieved with phenprocoumon. Lifelong oral anticoagulation (OAC) therapy with a target INR of 2 to 3 and continuation of the previously ineffective antiarrhythmic drug for 3 months postablation were strongly recommended in all patients. For patients on NOAC medications, the first dose was prescribed 6 hours after sheath removal at a reduced dose (ie, Dabigatran 75 mg, Rivaroxaban 10 mg, Apixaban 2.5 mg). The recommended full-dose NOAC was then started the following morning. Surface ECGs, transthoracic echocardiography to rule out pericardial effusion and 24-hour Holter recordings were performed on one-day postprocedure. Routine follow-up consisted of surface ECGs and 24-hour Holter recordings at 1, 3, and 6 months, then 6 monthly thereafter, in our outpatient clinic or by the referring physicians. TEE within 3 to 6 months after ablation was strongly recommended in all patients after LAAI to evaluate LAA flow velocity and assess for LAA smoke or thrombus formation. If a LAA thrombus was detected, OAC therapy was intensified to a target INR of 2.5 to 3.5 when phenprocoumon was used. When NOACs were used, a change to phenprocoumon therapy with a target INR between 2.5 and 3.5 was recommended, with repeat TEEs until thrombus disappearance. Smoke in the LAA was defined as low (1), moderate (2), or severe (3).

LAA Closure

Percutaneous LAA closure within 6 months of the index LAAI procedure was recommended to all patients after LAAI. LAA closure was performed using a WATCHMAN (Boston Scientific, Natick, MA) or Wave crest (Coherex Medical, UT) device. After transseptal puncture, 7500 IU of unfractionated heparin were administered, and whenever possible, a spiral catheter was placed in the LAA to confirm LAAI. The WATCHMAN sheath was then advanced into the LAA using a pigtail catheter for guidance. LAA angiography was performed at different angulations to optimally visualize the LAA morphology. The device was then deployed under TEE guidance. Before device release, device positioning was verified by angiography and TEE, and tug testing was performed.
Statistical Analysis

Continuous data are expressed as mean±standard deviation or median (25th and 75th percentiles) as appropriate; 25th and 75th percentiles are written as ...). Differences of continuous variables between groups were analyzed using the Student t test or Wilcoxon–Mann Whitney test, respectively. Comparisons pre and post ablation were performed with paired t tests.

Categorical variables are summarized with absolute and relative frequencies. Differences between groups were analyzed using Chi-square analysis or Fisher exact test where appropriate.

A P value <0.05 was considered statistically significant. Performing multiple statistical tests, the level of significance was not adjusted. Because of the small sample size and limited number of events, no multivariable analysis was performed.

Risk factors for the combined end point of LAA thrombus formation or embolic event (transient ischemic attack [TIA] or stroke) were analyzed using univariable analysis. Because of the small sample size and limited number of events, no multivariable analysis was performed. The following variables were included in the univariable analysis: all baseline characteristics as displayed in Table 1, LAA morphologies, number of procedures, the isolated LA area and the percentage of isolated LA surface, and the type of anticoagulation, including the subgroups in the NOACs or the use of ASA or Fraxiparin.

All analyses were performed using SAS statistical software (software-version 9.2: Copyright (c) 2002–2008. SAS Institute Inc, Cary, NC).

Results

Patient Characteristics

The baseline characteristics of the overall group (n=100) with comparison between patients with LAAI (n=50) and without LAAI (n=50) are displayed in Table 1

In patients with LAAI, the initial indication for catheter ablation was paroxysmal AF, persistent AF, or longstanding persistent AF in 20 (40%), 23 (46%), and 7 (14%) patients, respectively. The clinical rhythm at the index procedure with
LAAI was SR in 10 (20%), AF in 18 (36%), and LA AT in 22 (44%) patients. CHA2DS2-VASc score was 0 in 5 (10%), 1 in 5 (10%), 2 in 13 (26%), 3 in 15 (30%), 4 in 8 (16%), 5 in 3 (6%), and 6 in 1 (2%) patient.

One patient had a prosthetic mitral valve replacement, 1 had a prosthetic aortic valve replacement, and 2 patients had mitral valve reconstruction before the index ablation procedure.

**Ablation Procedure With LAAI (Index Procedure)**

The index LAAI procedure was performed after a median of 2 (1;3) previous procedures. LAA was isolated in 5 (10%) patients during the first, 8 (16%) patients during the second, 23 (46%) patients during the third, 5 (10%) patients during the fourth, 7 (14%) patients during the fifth, and 2 (4%) patients during the sixth procedure.

Ablation strategies included circumferential PVI in 50 (100%), LA isthmus line in 47 (94%), anterior line in 45 (90%), CFAEs in 24 (48%), and roofline in 14 (28%) patients. LAA was electrically isolated: (1) after ablation of LA linear lesions in 45 (90%) patients and (2) during extensive CFAE ablation in 5 (10%) patients.

LAAI was performed intentionally in 24/50 (48%) patients because of localized reentry AT originating from...
within the LAA. In 21/50 (42%) patients, LAAI was the result of achieving bidirectional block of both an anterior and mitral isthmus line for the treatment of LA macro-reentrant tachycardia. In the remaining 5/50 (10%) patients, LAA was isolated during ablation of CFAEs, as described in the results section.

**Ablation Procedure Without LAAI**
The median number of ablations for the patients in the control group was 1.0 (1.0–2.0), including the index procedure.

Ablation strategies included PVI in 50/50 (100%) patients, LA isthmus line ablation in 6/50 (12%), anterior line ablation in 12/50 (24%), CFAE ablation in 7/50 (14%), and roofline ablation in 3/50 (6%) patients.

**Anticoagulation After the Index Procedure**
Of the patients with LAAI, 24 (48%) patients were treated with phenprocoumon (including one patient with phenprocoumon and clopidogrel 75 mg daily), 21 (42%) patients with NOACs (Apixaban 10 mg/d in 4 patients, Rivaroxaban 20 mg/d in 12 patients, Dabigatran 300 mg/d in 2 patients, 220 mg/d in 3 patients), and 1 patient (2%) with low molecular weight heparin (1.5 mg/d). Four patients (8%) refused OAC therapy and were treated with only acetylic salicylic acid 100 mg/d (3 patients, 6%) or clopidogrel 75 mg/d (1 patient, 2%).

In 17/24 (70.8%) patients using phenprocoumon, bridging was performed with nonfractionated heparin after the ablation procedure until the INR reached the target range of 2 to 3.

In the control group, patients were treated either with phenprocoumon (n=23, 46%) or with NOAC (n=27, 54%). No concomittent therapy with ASA or clopidogrel occurred in this group. The anticoagulation regimen was comparable between the LAAI group and the control group (Table 1).

**Echocardiographic Results and Incidence of LAA Thrombi**
Echocardiographic details of patients with LAA thrombus or cerebral event are displayed in Table 2 and Table I in the Data Supplement.

After LAAI, TEE was repeated in 47/50 (94%) patients after a median follow-up of 3 (2.75–5) months. Three patients refused further TEE investigation. Median LAA flow velocity

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**Table 2. Comparison of Patients With LAA Thrombus (n=10) or Stroke/TIA (n=3) During Follow-Up With Patients Without LAA Thrombus or Cerebral Event (n=37)**

<table>
<thead>
<tr>
<th></th>
<th>Patients With LAA Thrombus (n=10) or Thrombembolic Event (n=3)</th>
<th>Patients Without LAA Thrombus or Stroke/TIA (n=37)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall number of patients</td>
<td>13</td>
<td>37</td>
<td></td>
</tr>
<tr>
<td>Male, n (%)</td>
<td>8 (61.5)</td>
<td>14 (37.8)</td>
<td>0.20</td>
</tr>
<tr>
<td>Age, y</td>
<td>71 (66–74)</td>
<td>71 (67–73)</td>
<td>0.89</td>
</tr>
<tr>
<td>Hypertension, n (%)</td>
<td>8 (61.5)</td>
<td>23 (62.2)</td>
<td>1.0</td>
</tr>
<tr>
<td>Diabetes mellitus, n (%)</td>
<td>2 (15.4)</td>
<td>2 (5.4)</td>
<td>0.27</td>
</tr>
<tr>
<td>CAD, n (%)</td>
<td>2 (15.4)</td>
<td>7 (18.9)</td>
<td>1.0</td>
</tr>
<tr>
<td>LA diameter, mm</td>
<td>48 (46–50)</td>
<td>45 (43–48)</td>
<td>0.16</td>
</tr>
<tr>
<td>TIA before LAA isolation, n (%)</td>
<td>1 (7.7)</td>
<td>5* (13.5)</td>
<td>1.0</td>
</tr>
<tr>
<td>Stroke before LAA isolation (%)</td>
<td>1 (7.7)</td>
<td>1* (2.7)</td>
<td>0.45</td>
</tr>
<tr>
<td>CHA2DS2-VASc score†</td>
<td>3 (2–3)</td>
<td>3 (2–3)</td>
<td>0.63</td>
</tr>
<tr>
<td>Anticoagulation with Phenprocoumon, n (%)</td>
<td>4 (30.8)</td>
<td>20 (54.1)</td>
<td>0.2</td>
</tr>
<tr>
<td>Anticoagulation with NOAC, n (%)</td>
<td>7 (53.8)</td>
<td>14 (37.8)</td>
<td>0.34</td>
</tr>
<tr>
<td>LAA morphology</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cactus, n (%)</td>
<td>2 (15.4%)</td>
<td>6 (16%)</td>
<td>0.94</td>
</tr>
<tr>
<td>Chicken wing, n (%)</td>
<td>9 (69.2%)</td>
<td>19 (51%)</td>
<td>0.26</td>
</tr>
<tr>
<td>Windsock, n (%)</td>
<td>2 (15.4%)</td>
<td>8 (22%)</td>
<td>0.63</td>
</tr>
<tr>
<td>Cauliflower, n (%)</td>
<td>0 (0)</td>
<td>4 (11%)</td>
<td>0.22</td>
</tr>
<tr>
<td>LAA flow velocity after LAA isolation, m/s‡</td>
<td>0.18 (0.17–0.20)</td>
<td>0.2 (0.15–0.4)</td>
<td>0.21</td>
</tr>
<tr>
<td>Isolated LA area, cm²</td>
<td>33±10.5</td>
<td>29.4±6.9</td>
<td>0.16</td>
</tr>
<tr>
<td>Percentage of isolated LA area, %</td>
<td>22.5±5.0</td>
<td>20.8±3.8</td>
<td>0.24</td>
</tr>
</tbody>
</table>

Continuous data: summarized as median (25th and 75th percentiles) or mean (standard deviation), group differences examined with Wilcoxon–Mann Whitney test or 2-sample t test if appropriate. Categorical data: shown with absolute and relative frequencies; group differences examined with χ² test or Fisher exact test in the case of small cell frequencies. CAD indicates coronary artery disease; LA, left atrium; LAA, left atrial appendage; NOAC, novel oral anticoagulation; and TIA, transient ischemic attack.

*including one patient with both TIA and stroke before ablation.
†Median (Q1–Q3).
‡Only patients with TEE postprocedure (n=47).
decreased significantly from 0.40 m/s (0.30–0.50) to 0.20 m/s (0.15–0.35) after the ablation procedure (P<0.001). LAA flow velocity post LAAI and CHA2DS2-VASc scores were similar in patients with LAA thrombus or cerebral event when compared with the remaining patients (LAA flow velocity: 0.18 m/s (0.17–0.2) versus 0.20 m/s (0.15–0.4), P=0.21; CHA2DS2-VASc score: 3 (2–3) versus 3 (2–3), P=0.63).

There was no significant difference between the number of previous ablation procedures in patients with (2; 2–3) and without thromboembolic events (2; 1–2) in the LAAI group (P=0.25). A weak correlation (0.0468) between the number of procedures performed before the index procedure that lead to LAAI and the LAA flow velocity was found in the correlation analysis (Spearman correlation coefficient; P=0.75). That is, a lower number of procedures performed before the index procedure that lead to LAAI correlated with a lower LAA flow velocity.

LAA thrombus formation was detected with TEE in 10/47 (21.3%) patients after the index LAAI procedure (Figure 2). Of the 10 patients with LA thrombus, 9 were anticoagulated with phenprocoumon (n=3) or NOAC (n=6; Dabigatran 220 mg/d n=1, Rivaroxaban 20 mg/d n=4, Apixaban 10 mg/d n=1) at the time of LAA thrombus detection. In the 3 patients on phenprocoumon, INR lowest values were 1.6 (patient No 11), 2.8 (patient No 33), and 1.9 (patient No 34). Patient No 33 had an INR of 2.8 on the day of thrombus detection and a mean INR value of 3.1 in the months before LAA thrombus detection. In the 3 patients on phenprocoumon, INR lowest values were 1.6 (patient No 11), 2.8 (patient No 33), and 1.9 (patient No 34). Patient No 33 had an INR of 2.8 on the day of thrombus detection and a mean INR value of 3.1 in the months before LAA thrombus detection. In the control group, TEE was repeated after a median of 5.0 (3.0, 11.0) months in all patients. No LAA thrombi were identified in the control group. The median LAA flow velocity was 0.48 m/s (0.36–0.57) before and 0.5 m/s (0.44–0.64) after the ablation, and therefore, the difference was not statistically significant (P=0.45).

The incidence and severity of smoke in the LAA between the LAAI group and the control group were similar before ablation but increased after ablation (Table 1).

**Incidence of Thromboembolic Events During Follow-Up**

In the LAAI group, 3/50 (6%) patients, a cerebral thromboembolic event occurred 4 (2–12) months post-LAAI, 2 with stroke (patient Nos 9 and 32) and 1 with TIA (patient No 45).

The patient who developed TIA had discontinued phenprocoumon against strict medical advise and was on acetylic salicylic acid 100 mg/d. Arrhythmia recurrence was detected during 24-hour Holter monitoring in this patient. Furthermore, this patient also refused TEE evaluation post LAAI.

One patient who developed stroke (patient No 9) was treated with phenprocoumon and had an INR of 2.7 on the day of the stroke. In addition, AF recurrence was documented on the day of the cerebral event. This patient had suffered a TIA 2 years before the index procedure and was the clinical event leading to the first diagnosis of AF. At the time of the TIA, this patient was not anticoagulated.

The second stroke patient (patient No 32) was treated with Dabigatran 220 mg/d, and stroke occurred 2 months before the index procedure.
the scheduled LAA closure. No ECG documentation on the day of hospital admission because of stroke was available in patient No 32, but a holter ECG performed 1 month before the stroke event revealed several AF episode lasting for ≤20 minutes.

In the 2 stroke patients, follow-up TEE revealed no LAA thrombus. As stated earlier, the patient with the TIA refused follow-up TEE evaluation. No patients with stroke/TIA during the follow-up period had a patent Foramen ovale or atrial septal defect.

In the control group, no stroke or TIA was reported during a median follow-up of 5.5 (3–12) months.

Using univariable analysis, no parameter was associated with an increased risk for LAA thrombus formation or stroke/TIA. Therefore, a multivariable analysis was not meaningful in this cohort.

Assessment of Isolated LA Area
The isolated LA area in patients with LAAI was measured using the CARTO area measurement function. The mean isolated area was 30.7±8.3 cm², and the mean percentage of the isolated LA surface was 21.4±4.2% in the LAAI group (Table 2). A trend toward a larger isolated area and a higher percentage of the isolated LA surface was seen in patients with LAA thrombus or stroke, not reaching statistical significance (Table 2).

LAA Closure After LAAI
LAA closure was performed in 29/50 (58%) patients after a median period of 3 (3–8) months post LAAI. No peri-procedural complications occurred. In all patients who underwent LAA occlusion device implantation, the device was successfully placed without residual flow. Before LAA closure device implantation, the LAA was assessed for LAAI in 21/29 (72.4%) patients, and LAAI was confirmed in 16/21 (76.2%) patients. In one patient with stroke, LAA reconnection was confirmed during the LAA occlusion device implantation; in one patient who developed LAA thrombus, LAAI was confirmed during the LAA closure procedure.

Maintenance of Sinus Rhythm in Patients With LAAI
During a median follow-up of 6.5 (4–12) months, SR was maintained in 32 patients (64%), including 17/32 (53.1%) patients on antiarrhythmic drug (amiodarone n=8) after LAAI. No significant difference in ATA recurrence was observed between patients with and without LAA thrombus or stroke/TIA (6/13 (46.2%) versus 12/37 (32.4%); P=0.50). Thirteen (26%) patients with arrhythmia recurrence after the index LAAI procedure underwent repeat ablation procedures after a median of 4 (3–8) months. At the reablation procedure, LA-LAA electric reconnection was confirmed in 7/13 (53.8%) patients. In one patient with stroke, a redo procedure was performed and LAAI was confirmed in this patient. In one patient who developed LAA thrombus, the LAA was confirmed to be reconnected during the redo procedure.

In 5 of these patients, LAA reisolation was performed during the reablation procedure. One patient had an intentional atrioventricular-node ablation during the reablation procedure.

Periprocedural Adverse Events
In 3/50 (6%) patients with LAAI, complications occurred during the index procedure as follows: groin hematoma requiring transfusion (n=1), arterio-venous fistula (n=1), and femoral artery aneurysm treated with thrombin injection (n=1).

In 1/50 (2%) patients of the control group, a significant groin hematoma with relevant hemoglobin drop occurred, however, not requiring blood transfusion. Furthermore, 2 minor groin hematomas without relevant hemoglobin drop occurred. All patients recovered without long-term sequelae. No periprocedural stroke or pericardial tamponade occurred.

Uni- and Multivariable Analysis
Using univariable analysis, no parameter was associated with an increased risk for LAA thrombus formation or stroke/TIA. Therefore, a multivariable analysis was not meaningful in this cohort.

Discussion
This study is the first to describe the incidence of LAA thrombus formation and stroke/TIA, as well as the long-term clinical outcomes in patients after wide-area LAAI with LA linear lesion or extensive CFAE ablation for the treatment of ATA. The main findings are the following:

1. Despite OAC, the incidence of LAA thrombus formation and stroke/TIA after wide-area LAAI is substantial.
2. Comparison to a matched control group without LAAI with equal patient size showed a significantly higher incidence of thrombi and stroke in the LAI group.
3. The success rate of maintaining SR after LAAI is reasonable, with an ATA recurrence rate of 36% after multiple procedures.

Risk of Stroke/TIA in AF Patients
The risk of stroke in AF patients is highly dependant on several risk factors, and most of these have been incorporated into the current stroke risk assessment scores, such as the CHA2DS2-VASc risk score.10 Furthermore, the risk of stroke in AF patients treated with OAC has been defined in several recently published large-scale clinical trials11–13 with follow-up durations of ≤2 years. In these trials, the risk of stroke or systemic embolism in AF patients treated with OAC therapy was reported to be between 1.6%11,12 and 2.2% per year.13 Noteably, AF was not treated by catheter ablation in these studies.

Based on data from previous anticoagulation trials for the treatment of AF,11–13 the calculated stroke risk of the patients with LAAI during the median 6.5 month follow-up period in our study should be ≈1.5% using the CHA2DS2-VASc risk score (median CHA2DS2-VASc score = 3). However, the rate of late cerebral embolic events after the LAAI procedure in our study was 6%, which is significantly higher than expected. The incidence of stroke after catheter ablation of AF is to date not well-defined because only limited data currently exists in the literature14 when our patient population is compared with the reported cerebral embolic event rate of 0.45%.

LAAI and Thrombus Formation
The incidence of LAA thrombus detected during TEE in patients therapeutically anticoagulated for >4 weeks varies in
the literature and has been described to be ≤3.6%. In a recently published large randomized trial with TEE performed before electric cardioversion, the incidence of LAA thrombus detected in TEE was <5%. Furthermore, the current literature suggests that ablation of single LA lines, such as an anterior-line only without LAAI is not associated with a significant impairment of LAA flow velocities or LAA thrombi. In a previously published series of >200 patients, no LAA thrombus after distal LAAI was seen on TEE after 3 and 6 months postisolation. Our data are in strong contrast to these findings, with 10/47 (21.3%) patients developing LAA thrombus on TEE evaluation. This is particularly high and clinically important, considering that 90% of these patients were continuously treated with OAC after the index LAAI procedure. One possible explanation for this may be that Di Biase et al used a different ablation strategy with segmental LAAI in or at the LAA base. Our strategy of wide-area LAAI includes LA linear lesions far away from the LAA base. Complete isolation of the LAA with linear lesions in the LA as performed in our study may be different from distal isolation of the LAA, which was described by Di Biase et al. In their study, the base of the LAA was electrically preserved, what may prevent thrombus formation.

Furthermore, in contrast to our patients, >50% of patients had a LAA flow velocity of >0.3 m/s during follow-up in the study by Di Biase et al, which can only be explained by recovered conduction of the LAA. The smaller isolated area in their study, as well as the high LAA flow velocity might explain why Di Biase et al did not find any LAA thrombi after distal LAAI, whereas we found a significant number of LAA thrombi and thromboembolic events. Thus, the benefit of treating a symptomatic arrhythmia with LAAI using linear lesions should be carefully weighed against potential harm because of future thromboembolic complications. The best ablation strategy for LAAI is still unclear. In addition, the findings of both studies need to be confirmed in further trials. Importantly, serial TEEs (median = 3; 2 – 4) before the index LAAI procedure excluded LAA thrombus in our patient cohort. Thus, those patients in our study who developed LAA thrombus had demonstrated a low risk for LAA thrombus formation before LAAI. Therefore, the risk for LAA thrombus formation may be substantially increased after LAAI, and careful evaluation of the indications for LAAI should be performed before proceeding with the procedure.

Reduced LAA flow velocity and LA contractility after maze procedure is associated with a higher risk of thromboembolic events. Although LAAI itself has not been shown to be associated with reduced LA function, similar mechanisms may be the cause for increased thromboembolic risk. Although we demonstrated that LAA flow velocity on TEE was significantly reduced after LAAI, persistent electric LAAI or reduced LAA function could not be proven in all patients in this study. However, it is possible that even delayed LAA activation or partially reduced LAA function/flow velocity could increase the risk of thromboembolic events. In patients with LAA thrombus formation, the LAA flow velocities were not reduced as compared with patients without LAA thrombus formation after LAAI. However, patients with LAAI demonstrated significantly reduced flow velocities as compared with patients without LAAI. This underlines that flow velocity itself is not the only reason for thrombus formation; however, it seems to be an important risk factor for LAA thrombus formation.

To further demonstrate this potential mechanism, we have included a supplementary figure (Figure I in the Data Supplement) and supplementary movie files (Movie I–IV in the Data Supplement) to this article.

Interestingly, the number of females in this study population was high (56%). Because female sex is a risk factor for stroke and therefore implemented in the CHA2DS2-VASc score, the risk of stroke or thrombus formation in this study population could be increased by this phenomenon. However, the patients with stroke or LAA thrombus in the majority were of male sex (Table 2). Thus, larger studies are needed to assess the impact of sex on LAA thrombus formation after LAAI.

A trend toward a higher incidence of thrombus formation and cerebral events was found in the patients treated with NOACs as compared with the phenprocoumon group. Whether this is coincidental or an effect of the NOAC treatment has to be evaluated in larger studies.

Considerations for LAA Closure Device After LAAI

We recommend lifelong OAC after LAAI in all patients. In addition, LAA occlusion has been shown to be a reasonable alternative to warfarin for the reduction of thromboembolic risk in several trials, particularly with the WATCHMAN device. Secondary to the high incidence of LAA thrombus after LAAI, it is our institutional practice to consent all patients for the risk of LAA thrombus formation even with therapeutic OAC and recommend the option of percutaneous LAA occlusion.

Outcome After LAAI

The success rate following AF ablation in patients with persistent or longstanding AF are disappointing during long-term follow-up. Recently published data from Di Biase et al suggests that in patients who presented with ATa recurrence after PVI and when the trigger originates from the LAA, there is a significant benefit in freedom from ATAs when LAAI is performed. This recently published data described a significantly higher success rate after a 12-month follow-up period when the LAA was isolated. In our study, follow-up was shorter and showed a long-term success rate of only 64% after multiple procedures. The limited success rate after several procedures must be considered in addition to the potential increased risk of LAA thrombus formation and stroke before proceeding with LAAI. Finally, LAAI was confirmed only in 53.8% of the patients where LAA activation was assessed during the reablation procedure.

Study Limitations

This analysis has some limitations. First, clinical follow-up was performed using only Holter monitoring; therefore, asymptomatic episodes of paroxysmal AF or AT may remain undetected. Second, TEE was performed during follow-up in only 47/50 (94%) patients after LAAI at different time intervals (median 3 [2.75–5] months). Thus, the optimal timing for follow-up TEEs after LAAI remains unclear, although our data suggests that LAA thrombus formation most often occurs within the first 6 months after the ablation procedure. Echocardiographic assessment of LA or LAA volumes, as well as
measurements of LA mechanical function were not performed but may provide further information in future studies. Finally, this is a single-center, prospective observational study with a matched control group with comparable risk profiles. Although there was a significant and clinically relevant difference in the incidence of LA thrombi and cerebral events, the study was not randomized.

Conclusions Wide-area LAAI is associated with a significantly increased risk of LA thrombus formation despite OAC therapy. LAA closure device implantation should be considered after LAAI.

Disclosures Dr Rillig received travel grants from Biosense, Hansen Medical, and St Jude Medical (SJM), lecture fees from both SJM and Böhringer Ingelheim, and took part at the Boston scientificEPI fellowship. Dr Tilt received research grants from Hansen Medical and SJM, travel grants from SJM, Topera, Biosense Webster, Daiichi Sankyo, speakers bureau honoraria from Biosense Webster, Biotronik, Hansen Medical, Pfizer, Bristol-Myers Squibb; Bayer, Sanofi Aventis. Dr Kuck has received research grants from Biosense Webster, Stereotaxis, Prorhythm, Medtronic, Edwards, and Cryocath and is a consultant to SJM, Biosense Webster, Prorhythm, and Stereotaxis. The other authors report no conflicts.

Unexpectedly High Incidence of Stroke and Left Atrial Appendage Thrombus Formation After Electrical Isolation of the Left Atrial Appendage for the Treatment of Atrial Tachyarrhythmias


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SUPPLEMENTAL MATERIAL

Supplemental Figure (Figure 1s) and video files
LAAI (with automaticity in the LAA) was confirmed using a circular mapping catheter placed within the LAA (Supplemental Figure 1a). During LAA pacing (no conduction to LA, Supplemental Figure 1b) with the lasso catheter, normalization of LAA flow velocity was demonstrated (Supplemental Figure 1c, Supplemental Video File 1). Flow velocity was again reduced when pacing was ceased (Supplemental Figure 1d, Supplemental Video File 2). LAA contraction was passive during SR and normalized during LAA pacing as confirmed via LAA angiography (Supplemental Video File 3 and 4).

Supplemental Video Legends

Supplemental Video 1
Normalization of LAA flow velocity during LAA pacing with the lasso catheter.

Supplemental Video 2
Reduction of Flow velocity after cessation of pacing.

Supplemental Video 3
Passive LAA contraction during SR after LAAI as confirmed via LAA angiography.

Supplemental Video 4
Normalized LAA contraction during LAA pacing as confirmed via LAA angiography.
Supplemental Figure 1

Electrocardiographic and Echocardiographic phenomena after Left atrial appendage isolation.
## Supplemental Table 1

### Characteristics of Patients with LAA thrombus or cerebral event after LAAI

<table>
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<tr>
<th>Patient No</th>
<th>LAA flow velocity prior to LAAI (m/sec)</th>
<th>LAA flow velocity after LAAI (m/sec)</th>
<th>Isolated LA Area* (cm²)</th>
<th>Isolated LA area as compared to overall LA surface (%)</th>
<th>LAA morphology</th>
<th>Patient in SR at time of LAAI thrombus detection or stroke</th>
<th>Smoke in LAA prior to LAAI</th>
<th>Grade of smoke in LAAI prior to LAAI (1=slight, 2=moderate, 3=severe)</th>
<th>Smoke in LAA after LAAI</th>
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*Isolated LA area as assessed by CARTO software
† No flow due to large thrombus in LAA
‡ n.a. = not available (patient refused further TEE control)
§ n.a. = No ECG documentation on the day of hospital admission due to stroke was available in patient 32, but a holter ECG performed one month before the stroke event revealed AF recurrence.