Abstract—Left atrial catheter ablation (LACA) has become an established therapy to abolish drug-refractory symptomatic paroxysmal and persistent atrial fibrillation. Restoring sinus rhythm by LACA may help to prevent atrial fibrillation-related strokes, but presently there is no evidence from randomized clinical trials to support this notion. This review summarizes the current knowledge and uncertainties regarding LACA and procedure-related ischemic stroke. In fact, most patients who undergo LACA have a rather low annual stroke risk even when left untreated, whereas LACA imposes a risk of procedure-related stroke of $\approx0.5\%$ to $1\%$. In addition, LACA may cause cerebral microemboli, resulting in ischemic lesions. These cerebral lesions, detectable by high-resolution MRI, could contribute to neuropsychological deficits and cognitive dysfunction. Furthermore, recurrent atrial fibrillation episodes can be detected up to years after LACA and might cause ischemic strokes, especially in those patients in whom therapeutic anticoagulation was discontinued. Further prospective multicenter trials are needed to identify procedure-dependent risk factors for stroke and to optimize postprocedural anticoagulation management. (Stroke. 2012;43:265-270.)

Key Words: anticoagulation ■ atrial fibrillation ■ ischemic stroke ■ left atrial catheter ablation ■ silent stroke

See related article, page 11.

Atrial fibrillation (AF) is the most frequent arrhythmia worldwide, and its prevalence and costs will continue to increase in the next years. Paroxysmal, persistent, or permanent AF markedly increases the risk of ischemic stroke, and $\approx$1 in 5 ischemic strokes is caused by AF. Furthermore, AF is independently associated with cognitive decline, dementia, and higher all-cause mortality. In addition, AF-related symptoms such as palpitations, fatigue, and dizziness can reduce quality of life. Effective rhythm control therapy might alleviate arrhythmia-related symptoms and may have the potential to prevent AF-related cerebrovascular events.

Within the past few years, left atrial catheter ablation (LACA) of the pulmonary veins has become an established therapeutic approach for restoring sinus rhythm in patients with symptomatic AF who are refractory to antiarrhythmic medication. According to recent guidelines, LACA is a class IIa (level A) recommendation for treatment of symptomatic paroxysmal or persistent AF in Europe, and a class I (level A) indication for selected patients treated at specialized centers in the United States, whereas there is no proven benefit for LACA in patients with asymptomatic AF. The rate of sinus rhythm after pulmonary vein isolation in patients with paroxysmal AF varies between 70% and 90%, at least after repeated ablation procedures. AF recurrence is more likely in patients with advanced atrial disease, even when additional ablations are performed. Success rates for LACA are highest in younger AF patients and in those without structural heart disease, rendering LACA as a method that is often used in patients at low risk for stroke at the time of intervention. However, individual stroke risk accrues over time if AF persists, because patients get older and concomitant cardiovascular conditions develop.

Randomized controlled trials demonstrated the superiority of LACA over antiarrhythmic drug AF treatment with regard to restoration of sinus rhythm and quality of life. Moreover, a retrospective matched-pair analysis suggested similar rates of death, stroke, and dementia in AF patients after successful LACA compared to patients without AF. Irrespective of the post hoc analysis of the ATHENA trial, there is no evidence from prospective trials that rhythm control therapy reduces vascular events in AF patients. This prevailing assumption is currently being tested in the prospective multicenter Catheter Ablation versus Antiarrhythmic Drug Therapy for AF (CABANA; clinicaltrials.gov: NCT00911508) trial as a secondary outcome and the Early Treatment of AF for Stroke Prevention trial (EAST; clinicaltrials.gov: NCT01288352) as part of the primary outcome.

Major complications of LACA (including pericardial tamponade, phrenic nerve injury, cerebral embolic events, pulmonary vein stenosis and, very rarely, atrio-esophageal fistula) were reported in 3.9% to 5% in total, with an increased risk in elderly patients and those with structural heart disease. LACA-related deaths were reported to occur in $\approx0.1\%$. 

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LACA-Associated Stroke

The periprocedural stroke risk amounts to 0.1% to 0.8% (Table 1), and there is a similar risk for transient ischemic attacks (0.1%–0.7%). Notably, many patients undergo several LACA interventions, which further adds to the total stroke risk.13 The majority of these LACA-associated strokes occur within 48 hours after the intervention but typically do not lead to persisting disability when adequately managed.19,20

In addition to these clinically apparent ischemic strokes, brain imaging can identify further cerebral damage in patients after LACA, similar to those reported after invasive cardiovascular procedures like diagnostic coronary angiography, carotid endarterectomy, or cardiac surgery.21–26 Lickfett et al were the first to demonstrate the utility of diffusion-weighted MRI to detect clinically “silent” strokes after LACA. A recent update of their observational cohort study indicated ischemic lesions in 11.3% patients, whereas physical examination revealed a transient reflex abnormality in 1 patient.22 The presently largest prospective MRI study reported 1 (0.4%) periprocedural TIA and new brain lesions in 33 (14.2%) out of 232 LACA patients without apparent neurological deficits.23 Smaller nonrandomized MRI studies reported acute brain lesions in 7.9% to 9.5% of all patients after LACA using radiofrequency or cryoenergy.24,25 A nonrandomized multicenter study revealed a significantly higher rate of diffusion-weighted MRI lesions after LACA using a multi-electrode nonirrigated pulmonary vein ablation catheter compared to an irrigated-tip radiofrequency catheter or a cryoballoon, respectively (33.3%, 7.4%, or 4.3%).26 These findings were confirmed by a nonrandomized single-center study demonstrating more diffusion-weighted MRI-detected brain lesions after LACA using a multi-electrode nonirrigated pulmonary vein ablation catheter (new lesions in 38.9% of these patients) compared to an irrigated-tip radiofrequency catheter (8.3%) or a cryoballoon (5.6%).27 Overall, the majority of patients had small (diameter <10 mm) and predominantly single lesions, distributed throughout the brain, often involving the cortex.23,26,27

So-called silent strokes may not result in focal neurological deficits known to indicate clinical stroke, but they might contribute to neuropsychological deficits and memory impairment,28 even when occurring during LACA only. A small

Table 1. Left Atrial Catheter Ablation-Associated Periprocedural Stroke Risk According to Recent Registries and Cohort Studies Using Almost Exclusively Radiofrequency Ablation

<table>
<thead>
<tr>
<th>Reference, Year</th>
<th>Stroke Rate</th>
<th>TIA Rate</th>
<th>Sum Stroke Rate</th>
<th>N</th>
<th>Follow-Up</th>
<th>Anticoagulation†</th>
</tr>
</thead>
<tbody>
<tr>
<td>46, 2009</td>
<td>0.10%</td>
<td>0%</td>
<td>0.10%</td>
<td>3052</td>
<td>1 d</td>
<td>ACT 350–450 s + INR ≥1.8</td>
</tr>
<tr>
<td>38, 2010</td>
<td>††</td>
<td>††</td>
<td>0.60%</td>
<td>6454</td>
<td>2 d</td>
<td>ACT ≥350 s + INR ≥2</td>
</tr>
<tr>
<td>19, 2010</td>
<td>0.82%</td>
<td>0.03%</td>
<td>0.85%</td>
<td>3060</td>
<td>2 d</td>
<td>ACT 250–450 s*</td>
</tr>
<tr>
<td>17, 2008</td>
<td>††</td>
<td>††</td>
<td>1.09%</td>
<td>641</td>
<td>1 d</td>
<td>ACT 300–400 s*</td>
</tr>
<tr>
<td>18, 2007</td>
<td>0.40%</td>
<td>0.10%</td>
<td>0.50%</td>
<td>1011</td>
<td>1–2 d</td>
<td>ACT 300–400 s*</td>
</tr>
<tr>
<td>20, 2009</td>
<td>††</td>
<td>††</td>
<td>1.39%</td>
<td>721</td>
<td>6 d</td>
<td>ACT 300–400 s*</td>
</tr>
<tr>
<td>16, 2009</td>
<td>0.30%</td>
<td>0.10%</td>
<td>0.40%</td>
<td>1000</td>
<td>8 d</td>
<td>ACT target of 300 s*</td>
</tr>
<tr>
<td>13, 2010</td>
<td>0.23%</td>
<td>0.71%</td>
<td>0.94%</td>
<td>20 825</td>
<td>†</td>
<td>ACT 200–350 s</td>
</tr>
</tbody>
</table>

ACT indicates activated clotting time; INR, international normalized ratio; TIA, transient ischemic attack.
*Oral anticoagulants were withdrawn before ablation.
†Not reported in detail.
‡During LACA catheter ablation.

Table 2. Silent Stroke Rate Detected by 1.5-T Magnetic Resonance Imaging Within Days After Left Atrial Catheter Ablation According to Cohort Studies

<table>
<thead>
<tr>
<th>Reference, Year</th>
<th>Silent Stroke Rate</th>
<th>N</th>
<th>Follow-Up (d)</th>
<th>Age (y)</th>
<th>Male</th>
<th>AF Type</th>
<th>Heart Disease</th>
<th>LACA</th>
<th>ACT† (s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>22, 2010</td>
<td>11.3%</td>
<td>53</td>
<td>1</td>
<td>53 ± 12 mean ± SD</td>
<td>85%</td>
<td>89% paroxysmal; 11% persistent</td>
<td>6%</td>
<td>RF</td>
<td>&gt;250</td>
</tr>
<tr>
<td>23, 2010</td>
<td>14.2%</td>
<td>232</td>
<td>1</td>
<td>58 ± 10 mean ± SD</td>
<td>78%</td>
<td>59% paroxysmal; 41% persistent</td>
<td>13%</td>
<td>RF</td>
<td>250–300</td>
</tr>
<tr>
<td>24, 2011</td>
<td>7.9%</td>
<td>89</td>
<td>1</td>
<td>46–63 range</td>
<td>63%</td>
<td>81% paroxysmal; 19% persistent</td>
<td>16%</td>
<td>49% RF, 51% cryoenergy</td>
<td>&gt;300</td>
</tr>
<tr>
<td>25, 2011</td>
<td>9.5%</td>
<td>21</td>
<td>2–4</td>
<td>54 ± 9 mean ± SD</td>
<td>57%</td>
<td><em>Recurrent</em>; 4.3%</td>
<td>RF,* cryoenergy*</td>
<td>≥300</td>
<td></td>
</tr>
<tr>
<td>26, 2011</td>
<td>14.9%</td>
<td>74</td>
<td>*</td>
<td>61 ± 9 mean ± SD</td>
<td>68%</td>
<td>62% paroxysmal</td>
<td>36% RF, 31% cryoenergy, 32% PVAC</td>
<td>&gt;300</td>
<td></td>
</tr>
<tr>
<td>27, 2011</td>
<td>17.8%</td>
<td>108</td>
<td>1</td>
<td>56 ± 9 mean ± SD</td>
<td>67%</td>
<td>Paroxysmal</td>
<td>. . .</td>
<td>33% RF, 33% PVAC, 33% cryoenergy</td>
<td>&gt;300</td>
</tr>
</tbody>
</table>

ACT indicates activated clotting time; LACA, left atrium catheter ablation; PVAC, pulmonary vein ablation catheter; RF, radiofrequency; SD, standard deviation.
*Not reported in detail.
†During LACA.
cohort study reported lower verbal memory scores 3 months after pulmonary vein isolation even in patients without “silent” strokes, as similarly observed in stroke-free AF patients without LACA. It remains to be clarified whether maintaining sinus rhythm after LACA might prevent AF-related cognitive impairment, and whether the elimination of AF-related spontaneous thromboembolism to the brain can “offset” the procedure-associated cerebral lesions reported (Table 2). Future trials using brain MRI and serial neuropsychological tests have to compare LACA patients to patients with a similar burden of AF who do not undergo LACA.

Another surrogate marker to quantify LACA-associated cerebral thromboembolism is the detection of microembolic signals by transcranial ultrasound. A single-center observational study revealed microembolic signals during LACA in all 202 patients, underlining the profound risk of periprocedural cerebral thromboembolism.

Potential Mechanisms of LACA-Associated Stroke
LACA requires the insertion of an ablation catheter into the left atrium via a femoral vein and a trans-septal puncture. The ablation catheter needs to make contact with the left atrial endocardium to deliver the ablation energy. The initial target of catheter ablation is isolation of the pulmonary veins, usually performed by generating circular lesions around their antra. This procedure generates several potential risks for thrombus formation. First, catheters and sheaths used during the intervention are thrombogenic, and left atrial thrombus formation on the mapping catheter or the trans-septal sheath was observed in an early case series using intracardiac echocardiography.

Second, LACA causes endothelial lesions, which are prone to thrombus formation at the wound surface. Local heating during energy delivery can increase the risk of thrombus formation at the catheter tip or at the ablated sites. Third, LACA induces an immediate systemic activation of platelets and of the coagulation system. Fourth, despite a high spontaneous closure rate, the trans-septal puncture may leave a persisting atrial septal defect even after 6 months, opening the door for paradoxical embolism. Fifth, periprocedural cardioversion may increase the risk of thrombus formation, but available data are inconsistent. Sixth, a LACA-related impaired left atrial diastolic dysfunction (stiff left atrial syndrome) is present in ~1% of all patients. Seventh, air emboli might occur, admitted very rarely, during trans-septal catheter exchange even with continuous flushing of the left atrial sheaths.

What Can Be Performed to Limit LACA-Associated Stroke Risk?
Current strategies include patient selection, technical advances, and periprocedural antithrombotic medication. Moreover, performing LACA requires experienced medical staff. This can be concluded by the fact that stroke rates in high-volume centers today are much lower compared to that of former case series.

Patient Selection
A prospective multicenter registry reported a significantly higher rate of stroke or transient ischemic attack in LACA patients with congestive heart failure, diabetes, or nonparoxysmal AF. According to a post hoc analysis of registry data, a CHADS 2 score ≥2 and a history of stroke as well as male gender, nonparoxysmal AF, coexisting diabetes, or coronary artery disease were risk factors for periprocedural stroke. However, available information is limited because of the restricted number of reported strokes. In larger MRI case series, there was no significant correlation of LACA-associated clinically silent cerebral lesions with age, AF-type, structural heart disease, previous stroke, or CHADS 2 score.

Ablation Strategy, Catheter System, and Further Technical Details
No prospective randomized trial data are available regarding the optimal technical approach to reduce thromboembolic risk of LACA. Despite limited statistical reliability, it seems reasonable to assume that continuous catheter tip irrigation, low power settings, and high-flow flushing of heparinized saline through the sheaths may help to prevent LACA-associated thrombus formation. Recent MRI data did not confirm that LACA using cryoenergy might cause a lower rate of thromboembolism compared to LACA using radiofrequency. However, both ablation techniques caused fewer MRI-detected brain lesions than a multi-electrode unirrigated radiofrequency pulmonary vein ablation catheter.

Gaita et al found no impact of procedure duration, additional linear lesions or atrial fragmentation, existence of a patent foramen ovale, or a trans-septal approach on MRI-detected cerebral lesions, but the incidence of cerebral embolism significantly correlated to electric cardioversion during LACA. However, a recent multicenter study did not confirm this association. Whether sequential point-by-point ablation, single shot devices, or circumferential mapping are beneficial remains an open question. In addition, the relevance of periprocedural intracardiac ultrasound, vascular protection devices, and biological markers (ie, von Willebrand factor, β-thromboglobulin, platelet factor 4, D-dimer) needs to be clarified.

Periprocedural and Postprocedural Anticoagulation Management
The management of anticoagulation is not standardized, although some consensus has been published. At present, discontinuing oral anticoagulation several days before LACA and bridging with heparin is a practice widely used during the ablation procedure. However, the safety of this strategy has not been documented in a prospective randomized trial. Current guidelines recommend monitoring the activated clotting time every 20 to 30 minutes during LACA because sufficient anticoagulation during the procedure appears to protect against left atrial thrombus formation, embolic events, and MRI-detected silent strokes. These data indicate that an activated clotting time of 300 to 400 seconds may be optimal for minimizing thromboembolic events, whereas there was no benefit from heparin and a glycoprotein IIb/IIIa inhibitor application compared to heparin alone. The time point of heparin application also seems to be important because hemostatic activation and thrombus formation were significantly
increased in patients receiving heparin only after trans-septal puncture. Interestingly, recent cohort studies and case-control series (Table 1) provide evidence for safety and efficacy of continuous oral anticoagulation during the ablation procedure and do not report a significantly higher incidence of major bleeding complications or pericardial tamponade. According to a prospective multicenter registry, an international normalized ratio of ≥2 significantly reduced the odds of periprocedural stroke or transient ischemic attack compared to LACA patients with periprocedural heparin bridging only. Similarly, a large case series revealed a procedure-related ischemic stroke rate of 0.1% in patients in whom anticoagulation with warfarin was continued and additional heparin was administered, whereas bleeding complications occurred in 1.1% of all patients. Whereas therapeutic international normalized ratio in combination with a strictly regulated heparin administration seems to be a safe approach to prevent periprocedural strokes, novel thrombin, or factor Xa inhibitors may offer therapeutic options for the periprocedural management of LACA in the near future.

The probability of “late” cerebrovascular events after LACA requires attention. Recent guidelines recommend that oral anticoagulation should be routinely applied to all patients after LACA for ≥2 to 3 months. Furthermore, indefinite anticoagulation is urgently recommended in patients with concomitant risk factors for stroke to avoid postprocedural strokes. Interestingly, a nonrandomized study stated a risk–benefit ratio in favor of discontinuing anticoagulation 3 to 6 months after LACA in AF patients. However, no prospective data from randomized studies are available so far.

Future Perspectives

Large prospective LACA trials are needed to better understand LACA-associated harms and benefits. Using stroke as a predefined end point, the reported rate of (clinically evident) strokes affords a considerable number of study patients to ensure a sufficient power to compare different catheter techniques or regimes of anticoagulation. The ongoing CABANA is designed to randomize ≥3000 AF patients worldwide to LACA or antiarrhythmic drug therapy. This trial may generate data on periprocedural strokes because cardiovascular death and disabling strokes are defined as secondary outcome measures. Moreover, EAST will randomize 2810 patients to usual care or an early rhythm control therapy using antiarrhythmic drugs and LACA. The primary outcome of EAST is a composite of cardiovascular death, stroke, and hospitalization attributable to myocardial infarction or heart failure. Stroke is one of the centrally adjudicated secondary outcomes of the EAST trial. The results of either trial, however, will become available in a few years, but the length of scheduled follow-ups will presumably clarify whether the LACA-related stroke risk is outweighed by long-term benefits in stroke prevention. In addition, the precise detection of LACA-related cerebral infarction by diffusion-weighted imaging can provide important information from much smaller LACA cohorts. Moreover, detection of the real burden of AF is vital because AF episodes accrue over years after LACA and contribute to cerebral thromboembolism. Current consensus suggests ECG follow-up with 6-month intervals for at least 2 years. Because the length of ECG recording directly correlates with AF detection rate, these recommendations seem to be a minimum approach for AF detection and insertable cardiac monitors may play a role in the near future. The likelihood of recurrent AF after LACA might require continuous antithrombotic therapy in the majority of patients who are at risk for ischemic stroke.

Conclusions

LACA has emerged as a standard therapeutic approach to limit drug-refractory symptomatic paroxysmal or persistent AF. Whereas large prospective trials are underway to assess whether LACA is able to prevent strokes over the long-term, the invasive procedure is associated with a total stroke risk of ~0.5% to 1% and has an additional risk of clinically silent cerebral embolism. Technical improvements such as continuous periprocedural anticoagulation with high activated clotting time levels during the procedure, irrigated-tip radiofrequency catheters, low power settings, and continuous flushing of all left atrial materials are reasonable measures to reduce cerebral damage induced by LACA. Prospective multicenter trials are needed to identify LACA-associated risk factors for stroke and to optimize postprocedural anticoagulation management.

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