Risk of Thromboembolic Events After Percutaneous Left Atrial Radiofrequency Ablation of Atrial Fibrillation

Hakan Oral, MD; Aman Chugh, MD; Mehmet Özyaydın, MD; Eric Good, DO; Jackie Fortino, RN; Sundar Sankaran, MD; Scott Reich, MD; Petar Igic, MD; Darryl Elmouchi, MD; David Tschopp, MD; Alan Wimmer, MD; Sujoya Dey, MD; Thomas Crawford, MD; Frank Pelosi, Jr, MD; Krit Jongnarangsin, MD; Frank Bogun, MD; Fred Morady, MD

Background—In patients with atrial fibrillation (AF), the risk of thromboembolic events (TEs) is variable and is influenced by the presence and number of comorbid conditions. The effect of percutaneous left atrial radiofrequency ablation (LARFA) of AF on the risk of TEs is unclear.

Methods and Results—LARFA was performed in 755 consecutive patients with paroxysmal (n=490) or chronic (n=265) AF. Four hundred eleven patients (56%) had ≥1 risk factor for stroke. All patients were anticoagulated with warfarin for ≥3 months after LARFA. A TE occurred in 7 patients (0.9%) within 2 weeks of LARFA. A late TE occurred 6 to 10 months after ablation in 2 patients (0.2%), 1 of whom still had AF, despite therapeutic anticoagulation in both. Among 522 patients who remained in sinus rhythm after LARFA, warfarin was discontinued in 79% of 256 patients without risk factors and in 68% of 266 patients with ≥1 risk factor. Patients older than 65 years or with a history of stroke were more likely to remain anticoagulated despite a successful outcome from LARFA. None of the patients in whom anticoagulation was discontinued had a TE during 25±8 months of follow-up.

Conclusions—The risk of a TE after LARFA is 1.1%, with most events occurring within 2 weeks after the procedure. Discontinuation of anticoagulant therapy appears to be safe after successful LARFA, both in patients without risk factors for stroke and in patients with risk factors other than age >65 years and history of stroke. Sufficient safety data are as yet unavailable to support discontinuation of anticoagulation in patients older than 65 years or with a history of stroke.

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Key Words: atrial fibrillation $\blacklozenge$ catheter ablation $\blacklozenge$ stroke $\blacklozenge$ embolism

In association with other risk factors such as age, hypertension, and congestive heart failure, atrial fibrillation (AF) increases the risk of thromboembolic events (TEs). Left atrial radiofrequency ablation (LARFA) results in maintenance of sinus rhythm in a majority of patients with paroxysmal and chronic AF$^1-^6$ and thereby may reduce the risk of TEs. However, for the following reasons, it cannot be assumed that ablation of AF eliminates the risk of TEs: (1) Patients with a history of AF and comorbid conditions may be at risk of TEs even when in sinus rhythm.$^7$ (2) LARFA reduces left atrial transport function by up to 30%,$^8$ which may predispose to TEs even in the setting of sinus rhythm. In theory, this could increase the risk of TEs in patients who were at low risk before ablation. (3) Patients with an apparently successful ablation procedure could have asymptomatic episodes of AF during long-term follow-up. For these reasons, it is unclear whether anticoagulation can safely be discontinued after LARFA of AF.

Clinical Perspective p 765

The purpose of the present study was to describe the prevalence and predictors of TEs in patients with and without other risk factors for stroke who underwent LARFA to eliminate paroxysmal or chronic AF.

Study Subjects

The subjects of this study were 755 consecutive patients with AF who underwent LARFA at the University of Michigan Medical Center from January 2003 to July 2005. The AF was paroxysmal in 490 patients and chronic in 265 patients. The mean age of the patients was 55±11 years (range, 17 to 79 years). There were 577 men and 178 women. AF was first diagnosed 6±6 years before ablation. The mean left atrial diameter was 42±7 mm in patients with paroxysmal AF and 46±9 mm in patients with chronic AF ($P<0.001$). The mean left ventricular ejection fraction was 0.56±0.08.

Based on previous studies of thromboembolic risk in patients with nonvalvular AF,$^9-^11$ 5 clinical variables were identified as risk factors...
A successful outcome after LARFA was defined as the absence of recurrent AF or atrial flutter in the absence of antiarrhythmic drug therapy. Because early recurrences of atrial arrhythmias may be transient, a blanking period of 2 months was used.13 Any episode of recurrent AF or atrial flutter in the absence of antiarrhythmic drug therapy was treated as a recurrence. Pacemaker implantation was not considered a recurrence or a failure of treatment. Freedom from recurrent atrial tachyarrhythmias was determined by event monitor recordings. Patients were contacted by telephone by a nurse practitioner every 3 to 6 months for 1 to 2 years. Thereafter, they were contacted by telephone by a nurse practitioner every 3 to 6 months for 1 to 2 years. After the last ablation procedure, the patients were seen in an outpatient clinic at 3 months after the last ablation procedure.

**Statistical Analysis**

Continuous variables are expressed as mean±SD. Results were compared by Student t test. Categorical variables were compared by χ² analysis. Multivariate regression analysis was performed to determine the independent predictors of continuing anticoagulant therapy after LARFA. Kaplan-Meier analysis was performed to determine freedom from recurrent atrial tachyarrhythmias and freedom from TEs. Freedom from TEs in the patients in this study was compared with a control group of individuals with no history of AF. The control group data were derived by applying the results of the Framingham study to a hypothetical cohort of age-matched subjects.14 A 2-tailed P<0.05 indicated statistical significance.

All authors had full access to the data and take full responsibility for its integrity. All authors have read and agree to the manuscript as written.
Results

Embolic Events Before Ablation

Among the 755 patients in this study, 34 (5%) had a history of TEs before ablation, consisting of a transient ischemic episode in 26 patients, a stroke in 7 patients, and a brachial artery embolus in 1 patient.

The prevalence of a preablation TE was 4% among the 490 patients with paroxysmal AF and 5% in the 266 patients with chronic AF ($P=0.8$).

Early Postablation TEs

TEs occurred in 7 of 755 patients (0.9%) within 30 days of LARFA. A total of 929 procedures were performed in 755 patients, and an embolic event occurred after 0.8% of these procedures (Table 2). One of the 7 embolic events (14%) occurred within 6 hours after the procedure, 3 TEs (43%) occurred 1 to 7 days after the procedure, and the other 3 TEs (43%) occurred 1 to 2 weeks after the procedure. The clinical characteristics of these patients are described in Table 2.

Among the 7 patients with an early TE, 6 (71%) had 1 or more risk factors for stroke. In the 748 patients who did not have an early TE, 406 patients (54%) had ≥1 risk factor ($P=0.2$, Table 2). At the time of the TE, an INR ≥2.0 was documented in only 1 of the 7 patients, and the mean INR was 1.6±0.5. Four of the 7 patients (57%) were receiving low-molecular-weight heparin.

Late Embolic Events

Among the 755 patients, 2 (0.3%) had a TE beyond 30 days after the procedure. The clinical characteristics of these 2 patients are described in Table 2 (patients 8 and 9). One patient with 2 risk factors for stroke (hypertension and diabetes) had left hemiparesis 6 months after ablation. He was in AF with a therapeutic INR at the time of the TE. The second patient, who did not have any risk factors, had a renal infarct 10 months after ablation. He was in sinus rhythm but had severely compromised left atrial transport function by echocardiography. During the ablation procedure, large areas of very low voltage were noted in the left atrium before ablation. The patient was being treated with warfarin and had an INR of 2.6 at the time of the TE.

At 24 months of follow-up after the last ablation procedure, 99% of the patients with no baseline risk factors for stroke and 98.5% of patients with ≥1 risk factor for stroke were free from any TE. In comparison, the expected 24-month freedom from stroke in the hypothetical control group was 99% ($P=0.69$, Figure).

Anticoagulation Status

Among the 256 patients who remained in sinus rhythm and did not have any risk factors for stroke, anticoagulation was discontinued in 203 (79%) at a median of 4 months after LARFA. Among the 266 patients who remained in sinus rhythm and had ≥1 risk factor, anticoagulation was discontinued in 180 (68%) at a median of 5 months after LARFA ($P=0.003$ compared with patients without risk factors). A

![Cumulative proportion of patients free from TEs after LARFA. The proportion of patients with no risk factors (blue line) or ≥1 baseline risk factor (red line) who were free from TEs after LARFA was similar to the freedom from stroke in a hypothetical group of age-matched control subjects with no history of AF (green line).](http://circ.ahajournals.org/)

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Age, y</th>
<th>Gender</th>
<th>LA, mm</th>
<th>LV EF</th>
<th>Risk Factors</th>
<th>Time to TE After LARFA</th>
<th>TE</th>
<th>Rhythm During TE</th>
<th>Level of INR During TE</th>
<th>LMWH During TE</th>
<th>Residual Symptoms</th>
<th>Time to Recovery After EE</th>
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</thead>
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<tr>
<td>1 PAF 57 M</td>
<td>57</td>
<td>M</td>
<td>0.55</td>
<td>0</td>
<td>0</td>
<td>Difficulty swallowing and aphasia</td>
<td>AF</td>
<td>1.1</td>
<td>No</td>
<td>None</td>
<td>30 d</td>
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<td>2 PAF 67 F</td>
<td>67</td>
<td>F</td>
<td>0.60</td>
<td>0.64</td>
<td>0</td>
<td>Right arm and hand weakness</td>
<td>AF</td>
<td>...</td>
<td>Yes</td>
<td>Yes</td>
<td>8 mo</td>
<td></td>
</tr>
<tr>
<td>3 PAF 58 M</td>
<td>58</td>
<td>M</td>
<td>0.55</td>
<td>0.60</td>
<td>0</td>
<td>Left arm paresis</td>
<td>SR</td>
<td>...</td>
<td>Yes</td>
<td>None</td>
<td>18 h</td>
<td></td>
</tr>
<tr>
<td>4 PAF 51 M</td>
<td>51</td>
<td>M</td>
<td>0.60</td>
<td>0.55</td>
<td>H</td>
<td>5 d Amaurosis fugax</td>
<td>AF</td>
<td>1.0</td>
<td>Yes</td>
<td>None</td>
<td>1 h</td>
<td></td>
</tr>
<tr>
<td>5 PAF 57 M</td>
<td>57</td>
<td>M</td>
<td>0.60</td>
<td>0.55</td>
<td>H</td>
<td>10 d Transient visual field change</td>
<td>AF</td>
<td>1.7</td>
<td>No</td>
<td>None</td>
<td>2 h</td>
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<tr>
<td>6 PAF 66 M</td>
<td>66</td>
<td>M</td>
<td>0.60</td>
<td>0.55</td>
<td>A</td>
<td>14 d Left hemiparesis</td>
<td>AF</td>
<td>1.4</td>
<td>No</td>
<td>None</td>
<td>1 d</td>
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<tr>
<td>7 CAF 66 M</td>
<td>66</td>
<td>M</td>
<td>0.55</td>
<td>0.60</td>
<td>H/A</td>
<td>14 d Right hemiparesis and dysarthria</td>
<td>SR</td>
<td>2.0</td>
<td>Mild weakness</td>
<td>2 wk</td>
<td></td>
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<tr>
<td>8 CAF 55 M</td>
<td>55</td>
<td>M</td>
<td>0.60</td>
<td>0.60</td>
<td>H/D</td>
<td>180 d Left hemiparesis</td>
<td>AF</td>
<td>3.2</td>
<td>No</td>
<td>Residual weakness</td>
<td>3 mo</td>
<td></td>
</tr>
<tr>
<td>9 CAF 40 M</td>
<td>40</td>
<td>M</td>
<td>0.60</td>
<td>0.60</td>
<td>0</td>
<td>300 d Renal infarct</td>
<td>SR</td>
<td>2.6</td>
<td>No</td>
<td>No</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

PAF indicates paroxysmal AF; CAF, chronic AF; LA, left atrial diameter; LV, left ventricular; EF, ejection fraction; C, congestive heart failure; H, hypertension; A, age; D, diabetes; S, prior stroke or transient ischemic attack; INR, international normalized ratio; LMWH, low-molecular-weight heparin; and SR, sinus rhythm.
similar percentage of patients with a history of paroxysmal (70%) and chronic (66%) AF were taken off of warfarin (P=0.4). Among the 233 patients with recurrent AF or atrial flutter after LARFA, 218 (94%) continued to be anticoagulated with warfarin. The anticoagulation status of patients who remained in sinus rhythm and who had recurrent AF or atrial flutter after LARFA is shown with respect to their risk factors for stroke in Tables 3 and 4.

**Continuation of Anticoagulant Therapy After LARFA**

Among the variables of age >65 years, gender, whether episodes of AF had been paroxysmal or chronic, hypertension, diabetes mellitus, congestive heart failure, and prior stroke or transient ischemic attack, age >65 years (odds ratio, 1.82; confidence interval [±95%], 1.06 to 3.11; P=0.03) and prior stroke/transient ischemic attack (odds ratio, 3.63; confidence interval [±95%], 1.47 to 8.98; P=0.005) were independently associated with continuation of warfarin therapy after a successful LARFA procedure (P<0.001).

**Rhythm After Ablation**

At 12 months after the most recent ablation procedure, 77% of the 490 patients with paroxysmal AF and 66% of the 265 patients with chronic AF were free from recurrent AF and atrial flutter in the absence of antiarrhythmic drug therapy (P=0.001, log-rank test). At 24 months of follow-up, 73% of the patients with paroxysmal AF and 62% of the patients with chronic AF were free from recurrent AF and atrial flutter in the absence of antiarrhythmic drug therapy. Recurrent AF was more common after ablation of chronic AF (32%) than after ablation of paroxysmal AF (23%, P=0.01). Eighteen patients with paroxysmal AF (4%) and 14 patients with chronic AF (5%) had only recurrent atrial flutter (P=0.3).

Among 383 patients who remained in sinus rhythm and were no longer receiving anticoagulant therapy, there were no late TEs regardless of whether they had no risk factors for stroke (0 of 203) or ≥1 risk factor (0 of 180).

No embolic events occurred in 15 of the 233 patients (6%) who had recurrent AF after LARFA and were not anticoagulated. None of these patients had a history of stroke/transient ischemic attack before the ablation.

**Major Bleeding Complications**

A cerebral hemorrhage occurred in 2 patients (0.3%) who were in AF and were being treated with warfarin 1 and 3 months after LARFA. One patient was 70 years old and had an INR of 3.5 and the other patient was 53 years old and had intracranial bleeding after head trauma.

**Discussion**

**Main Findings**

In this series of 755 consecutive patients who underwent LARFA for paroxysmal or chronic AF, the risk of postablation TEs was 1.2%, with the period of highest risk being the first 2 weeks after ablation, usually before attainment of a therapeutic degree of anticoagulation after resumption.
of warfarin. The risk of late TEs was 0.2%, with these events occurring despite therapeutic anticoagulation with warfarin. Pooling patients with early and late TEs, there were no demographic or clinical predictors of TE after LARFA. Overall, ≈75% of patients who were apparently free of recurrent AF were taken off of warfarin 3 to 6 months after ablation, and none of these patients had a TE during a mean of 2 years of follow-up. However, patients who were older than 65 years or had a history of stroke often were maintained on warfarin even when there was no evidence of recurrent AF.

The results of the study clearly indicate that LARFA is associated with early postprocedure TEs, regardless of the postprocedure rhythm and regardless of whether or not the patient has risk factors for stroke. This emphasizes the importance of aggressive anticoagulation during the first few weeks after ablation. The results also suggest that it is safe to discontinue anticoagulation at 3 to 6 months after ablation in many patients who have had an apparently successful outcome, even in patients with risk factors such as hypertension, diabetes, or congestive heart failure. Because the patients in this study who were older than 65 years or who had a history of stroke generally were maintained on warfarin, however, there are inadequate data to confirm the safety of discontinuation of warfarin in patients with these 2 risk factors.

Early TEs

All of the early TEs after LARFA occurred within the first 2 weeks after ablation. Because the early TEs were unrelated to the rhythm or to demographic/clinical variables, their most likely cause was char and/or thrombus formation at sites of left atrial endocardial ablation.

The INR was documented to be subtherapeutic in 4 of 7 patients who had an early TE. Also noteworthy is that 4 of 7 patients were no longer receiving low-molecular-weight heparin, and even in the patients who were still receiving the low-molecular-weight heparin, compliance may have been incomplete. Furthermore, because early in our experience with LARFA we found that full-dose (1 mg/kg twice a day) low-molecular-weight heparin was associated with an increased risk of groin hematomas, a reduced dosage of 0.5 mg/kg twice a day was used in the patients in this study.

Because data on postprocedure INRs and usage of low-molecular-weight heparin were not available in the patients in this study who did not have early TE, the extent to which a subtherapeutic INR was responsible for the TEs in this study is unclear. Nevertheless, the results suggest that aggressive postprocedure anticoagulation is important, especially in the first 2 weeks after ablation. However, early TE may occur even in the face of therapeutic anticoagulation, indicating that there is an inherent procedure-related risk of TEs that cannot be completely eliminated by adequate anticoagulation.

In this study, all patients underwent LARFA with an 8-mm-tip catheter. Now that an irrigated-tip ablation catheter is available, we no longer use the 8-mm-tip catheter for LARFA. It is possible that this catheter less often causes char/thrombus formation at endocardial ablation sites. However, it remains to be determined whether the irrigated-tip ablation catheter is associated with a lower risk of early postablation TE than the 8-mm-tip catheter.

Late Embolic Events

A late TE occurred in only 0.2% of the 755 patients in this study. This risk is similar to the risk of TEs in age-matched, otherwise healthy individuals without AF.16 The risk of TEs in patients with AF is variable and dependent on age and comorbid conditions. Therefore, the risk of late TEs after LARFA should be considered with respect to the baseline risk of TEs. Although there were no late TEs in patients without recurrent AF who did not have risk factors for stroke and who were not anticoagulated long term, it may be argued that the risk of TEs would have been low in these patients even if they were still having AF. However, a potential concern with LARFA is that radiofrequency ablation can impair left atrial transport function, thereby increasing the risk of late TEs in previously low-risk patients. The absence of late TEs during >1000 patient-years of follow-up in this study therefore is reassuring and suggests that impaired left atrial function after LARFA may not be clinically significant.

It is noteworthy that 1 of the 2 patients in this study with a late TE despite anticoagulation and despite the absence of recurrent AF had evidence of an atrial myopathy, with severely impaired left atrial function before ablation.17 Therefore, although the compromise in left atrial function attributable to LARFA may not be clinically significant by itself, a patient may still be at risk of late TE because of inherent left atrial dysfunction.

With regard to patients who do have risk factors for stroke, these patients may be at ongoing risk of late TEs even in the absence of recurrent AF.7 Furthermore, the deleterious effects of anatomic remodeling and/or LARFA on left atrial systolic function and late recurrences of asymptomatic AF in patients considered to have had a successful outcome could predispose to late TEs in patients with baseline risk factors for stroke. These factors may justify continued anticoagulation in patients with baseline risk factors even when there is no evidence of recurrent AF. In this study, however, there were no late TEs in patients with 1 or more risk factors for stroke who had no evidence of recurrent AF in whom anticoagulation was discontinued. This suggests that the risk of late TEs in patients with baseline risk factors for stroke is not augmented by LARFA and possibly may be diminished. The comparison of TEs in the patients in this study with the risk of stroke in a historic control group of individuals with no history of AF also suggests that LARFA does not increase the risk of late TEs.

A point of caution is that anticoagulation was maintained long term in 31% of patients with a successful outcome who had baseline risk factors for stroke and that many of these patients were >65 years old or had a preablation history of stroke. In the absence of long-term surveillance of a large number of patients over the age of 65 years or with a history of stroke who were taken off...
warfarin after LARFA of AF, it may be prudent to continue anticoagulation indefinitely in patients with these 2 risk factors.

The proportion of patients who were free of AF at 2 years after LARFA was ≈5% lower than at 12 months of follow-up. Late recurrences of AF in a small percentage of patients indicate the importance of ongoing clinical follow-up to confirm that sinus rhythm is maintained beyond 1 year after ablation.

Prior Studies
Prior studies have indicated a 0.5% to 7% risk of stroke and transient ischemic episodes after radiofrequency ablation.5,12,18–23 However, no prior studies have examined the time course of TEs or the interactions between TEs, baseline risk factors, outcome of ablation, and anticoagulation status.

Limitations
This was an observational cohort study, not a randomized, clinical trial. In the absence of a randomized comparison of chronic anticoagulation versus discontinuation of anticoagulation after LARFA, definite conclusions regarding the safety of stopping therapy with warfarin are not possible. Another limitation of this study is that the mean duration of follow-up was 2 years. It is possible that late recurrences of AF several years after LARFA will increase the risk of TEs beyond the risk noted in this study, particularly if the late recurrences of AF are not otherwise symptomatic.

Last, detailed data on left atrial systolic function after ablation were not available in most patients in this study. Therefore, the effect of this potential risk factor for late TEs on outcomes after LARFA is uncertain.

Conclusions
Until the results of larger studies with several years of follow-up become available, the true long-term safety of discontinuing long-term anticoagulation after LARFA will remain unclear. However, this study provides some evidence that justifies the discontinuation of warfarin 3 to 6 months after LARFA in patients without baseline risk factors for stroke and in patients with risk factors (other than age >65 years and history of stroke) who have had an apparently successful outcome.

At present, the principal indication for catheter ablation of AF is to improve quality of life. However, our experience has indicated that many patients with AF who are asymptomatic are motivated to undergo LARFA solely to avoid the need for long-term warfarin use. Whether avoidance of long-term anticoagulation will ever be a legitimate indication for catheter ablation of AF remains to be determined.

Disclosures
Drs Oral and Morady are founders of and stockholders in Ablation Frontiers, Inc. Drs Oral and Morady have consulted for Ablation Frontiers and Biosense-Webster. The other authors report no conflicts.

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CLINICAL PERSPECTIVE

Patients with atrial fibrillation (AF) may be at risk for thromboembolic events (TEs). However, this risk is often variable from patient to patient, based on the presence of comorbid conditions such as age ≥65 years, congestive heart failure, hypertension, diabetes, and history of stroke. Left atrial radiofrequency ablation (LARFA) eliminates AF in a majority of patients. However, patients with AF may be at risk for TEs even when they are in sinus rhythm because of the presence of comorbid conditions; LARFA may impair left atrial transport function and may predispose to TEs; and asymptomatic episodes of AF after LARFA may occur and could be associated with TE risk. Therefore, the purpose of this study was to determine the risk of TEs in patients with and without other risk factors for stroke who underwent LARFA to eliminate AF. In this study, LARFA was performed in 755 consecutive patients with AF. There was ≥1 risk factor for stroke in 411 patients (56%). A TE occurred in 9 patients (1.1%) after LARFA. Patients older than 65 years or with a history of stroke were more likely to remain anticoagulated despite a successful outcome from LARFA. None of the patients in whom anticoagulation was discontinued had a TE during 25±8 months of follow-up. Therefore, it appears to be safe to discontinue anticoagulant therapy after successful LARFA in patients who do not have risk factors for stroke and in patients with risk factors other than age ≥65 years and history of stroke.
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