



Safety of Catheter Ablation for Atrial Fibrillation in Patients With Prior Cerebrovascular Events

Ayman A. Hussein, MD, Abhishek Gadre, MD, Oussama M. Wazni, MD, Walid I. Saliba, MD, Mohammed Bassiouny, MD, Khaldoun Tarakji, MD, Bryan Baranowski, MD, Mina Chung, MD, Mandeep Bhargava, MD, Thomas Callahan, MD, Daniel Cantillon, MD, Thomas Dresing, MD, Patrick Tchou, MD, Mark Niebauer, MD, Mohamed Kanj, MD, Bruce D. Lindsay, MD, Niraj Varma, MA, MD, PhD

ABSTRACT

OBJECTIVES This study sought to report on the safety of catheter ablation for atrial fibrillation (AF) in patients with prior cerebrovascular events (CVEs), at a large-volume tertiary care center over the course of the past 15 years.

BACKGROUND Many patients with drug-refractory AF have a history of a prior CVE. These patients are considered to be at high procedural risk for catheter ablation but data are scant.

METHODS All consecutive patients undergoing AF ablation at the Cleveland Clinic were enrolled in a prospectively maintained data registry, which was used to identify patients with a prior CVE. Strict periprocedural anticoagulation protocols were in place. Extreme care was taken with sheath and catheter manipulation to prevent thrombus formation or air embolism. All thromboembolic and hemorrhagic events occurring periprocedurally and up to 3 months of follow-up were identified.

RESULTS Of 9,413 consecutive patients who underwent AF ablation, 247 patients with a prior CVE were identified (median age, 64 years; 40.1% female; median CHA2DS2-VASC score, 4). Anticoagulants used were warfarin (n = 192), dabigatran (n = 32), rivaroxaban (n = 15), and apixaban (n = 8). All patients received intravenous heparin before transseptal access (activated clotting time target during procedure, 350 to 400 seconds). The energy source was radiofrequency in 242 patients and cryoenergy in 5 patients. Acute procedural complications included 5 groin hematomas (1 requiring transfusion), 5 pericardial effusions with associated tamponade physiology in 2 (1 required pericardiocentesis, 1 required surgery), and 1 arteriovenous fistula (managed conservatively). Importantly, none of the patients had a periprocedural thromboembolic event.

CONCLUSIONS Patients with a prior history of cerebrovascular events do not seem to be predisposed to a significant risk of clinical CVE recurrence when undergoing catheter ablation for AF without interruption of therapeutic anticoagulation. (J Am Coll Cardiol EP 2016;2:162-9) © 2016 by the American College of Cardiology Foundation.

Catheter ablation for atrial fibrillation (AF) is widely practiced and has become an effective treatment for recurrent symptomatic arrhythmia (1). The risk of procedure-related thromboembolism is reported to be between 0% and 7% but is of primary concern because it is potentially devastating (1). Refinements in periprocedural

anticoagulation strategies and close attention to catheter and sheath manipulation in the left atrium (LA) may have reduced this risk.

AF is an independent cause of cardioembolic events (2), a risk that could be potentiated by an ablation procedure (1,3-5), which creates a thrombogenic milieu (1,6). In patients with prior



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cerebrovascular events, the risk of clinical event recurrence, during or following an ablation procedure, remains unclear. Nevertheless, a prior history of stroke or cerebrovascular event in patients with recurrent symptomatic AF is commonly regarded as a risk marker for thromboembolic event recurrence, discouraging catheter ablation as a therapeutic strategy (4). However, existing data regarding this issue are limited by small population size and variable periprocedural anticoagulation, which *per se* affect procedural risk (3,4,7). In contrast, significant bodies of data suggest that ischemic stroke risk increases among patients with prior cerebrovascular events undergoing coronary interventions. However, percutaneous coronary interventions involve aggressive anticoagulation and use a transaortic approach without disruption of left atrial endothelium and therefore generate a different balance of thrombotic potential (8,9).

We hypothesized that patients with a prior history of cerebrovascular events are not predisposed to significant risk of clinical recurrence when undergoing catheter ablation for AF without interruption of therapeutic anticoagulation (10,11), and should not be denied catheter ablation as a treatment option on the basis of their clinical history. We report on our experience with this population, spanning the course of 15 years.

METHODS

STUDY POPULATION. Between January 2000 and August 2014, all consecutive patients undergoing AF ablation at our institution were enrolled in our prospectively maintained AF ablation data registry. Patients with a prior clinical history of a cerebrovascular event, either a stroke or a transient ischemic attack, were selected for the current analysis. Electronic records were abstracted for clinical characteristics and procedural data, including anticoagulation methods, catheter types, mapping techniques, ablation strategies, and procedural complications. All patients had given written informed consent for these ablation procedures undertaken for standard indications. The study was approved by the Cleveland Clinic Institutional Review Board.

ABLATION PROTOCOL. Our AF ablation protocol has been previously published (12). Following left femoral venous access, sheaths were used for placement of an electrode catheter in the coronary sinus and deployment of a phased-array intravascular ultrasound catheter (Siemens AG Inc., Erlangen, Germany, or St. Jude Medical, Sylmar, California) to the right

atrium (RA) to assist with performing transseptal punctures, to guide catheter location and manipulation, and to monitor for complications during the procedure. Two 8-F catheter sheaths were placed in the right femoral vein. For cryoballoon procedures, 8-F and 12-F catheter sheaths were placed in the right femoral vein and 8-F and 9-F catheter sheaths in the left femoral vein. From 2006, ultrasound guidance was frequently used for venous access and by July 2007 became standard of care at our institution (13). The mapping and navigation systems were CARTO (Biosense Webster) or Ensite NavX (St. Jude Medical). Circular mapping catheters were used to guide pulmonary vein isolation and left atrial ablations. Both fluoroscopy and intracardiac echocardiography were used to confirm catheter contact with the atrial surface.

Extreme care is taken to prevent thrombus formation or air embolism. Most operators at our institution perform LA ablations with catheters positioned in the LA and the tip of the sheaths positioned in the RA, unless sheath support is required to reach or maintain a stable position. A constant air-free heparinized flush through long sheaths and irrigated catheters is maintained throughout the procedure, particularly when these sheaths are positioned in the LA. Sheath insertion and catheter exchanges are undertaken cautiously to avoid the introduction of air and air embolism. In general, 5 to 10 ml of blood is aspirated to ensure that no air is still within the sheath and this is generally discarded, which is followed by a wet-to-wet connection with the heparin flush.

Catheters used for ablation transitioned from nonirrigated ablation catheters to irrigated catheters. Cryoballoon was added more recently. For nonirrigated catheters, radiofrequency power was generally set at 30 W with a maximum temperature of 55°C and titrated up in 5-W increments every few seconds, while monitoring for microbubbles, to a maximum of 50 W with 4-mm tip catheters or 70 W with 8-mm tip catheters. The power was titrated down on detection of microbubbles and turned off when a sudden shower of bubbles was seen. The use of nonirrigated catheters for left atrial ablations was superseded at our institution by open-irrigated catheters. Ablation protocol used power set at generally 30 to 35 W with maximum temperature of 42°C for most radiofrequency applications (but decreased to 20 W at the posterior wall). For cryoablations, a 28-mm or 23-mm cryoballoon was used with confirmation of pulmonary vein (PV) occlusion with both Doppler and contrast injection. At least 2 cryoapplications were performed for each of the veins but no other left atrial ablations were performed when cryoenergy was used.

ABBREVIATIONS AND ACRONYMS

AF = atrial fibrillation
INR = international normalized ratio
LA = left atrium
RA = right atrium

In all cases, the primary endpoint of ablation was PV isolation defined as absence or dissociation of PV potentials along the antrum or inside the veins by use of a circular mapping catheter. Additional left atrial ablation lesion sets (e.g., targeting areas of complex rapid and fractionated electrograms, or the posterior wall) were performed at operator discretion. In patients presenting with AF, the decision whether to perform mapping and ablation in sinus rhythm following electrical cardioversion or during AF was left to the operating electrophysiologist. In patients who remained in AF after completion of ablation, electrical cardioversion to sinus rhythm was performed and followed by confirmation of PV isolation. In some cases, after completion of left atrial ablation and withdrawal of catheters to the RA, RA ablation was performed. Cavotricuspid isthmus ablation was performed for all patients with a history of typical atrial flutter.

PERIPROCEDURAL ANTICOAGULATION. Our general approach to periprocedural anticoagulation management has been previously detailed (10,11). Briefly, before 2005, a strategy of interrupted warfarin therapy with bridge with low-molecular-weight heparin periprocedurally was used. This transitioned to performing ablations without interruption of warfarin therapy. For patients who presented with a subtherapeutic international normalized ratio (INR) on the day of ablation, low-molecular-weight heparin was administered (1 mg/kg enoxaparin) before the procedure. Conversely, the procedure was usually cancelled for INR >4 on the day of planned intervention. For patients who presented in AF on the day of the procedure and had a documented subtherapeutic INR within 3 weeks before the ablation procedure, a transesophageal echocardiogram was obtained to rule out left atrial or LA appendage thrombus. More recently, patients prescribed novel anticoagulants (i.e., dabigatran, apixaban, rivaroxaban) omitted only 1 dose of their anticoagulant the day before the procedure and resumed immediately after ablation. For patients who missed 1 or more doses of their novel anticoagulant in the prior 3 weeks, a transesophageal echocardiogram was also obtained. These precautions were taken regardless of the CHA2DS2-VASc scores.

In all patients, transseptal access was preceded by an intravenous bolus of unfractionated heparin (100 to 150 U/kg). During the procedure, heparin infusion rates were adjusted to maintain an activated clotting time in the range of 350 to 400 s. After completion of ablations in the LA, heparin infusion was stopped and catheters and sheaths pulled to the RA. Heparin

anticoagulation was then partially reversed with 10 to 30 mg of protamine, and sheaths were pulled when the activated clotting time was <250 s. All patients received aspirin, 325 mg, before leaving the electrophysiology laboratory or in the recovery room for patients who underwent ablations with general anesthesia. No aspirin was used thereafter unless indicated for other reasons. Novel oral anticoagulants were typically resumed at the end of the procedure. Post-procedurally, close attention was paid to maintaining therapeutic anticoagulation (e.g., patient education, anticoagulation clinics).

COMPLICATIONS AND POST-PROCEDURAL FOLLOW-UP.

Complications were *a priori* categorized into thromboembolic and hemorrhagic. Thromboembolic complications were defined as the occurrence of an ischemic stroke, transient ischemic attack, peripheral embolic event, or venous thromboembolism. Major bleeding complications were defined as the occurrence of cardiac tamponade or hemopericardium that required intervention or caused symptoms, excessive bleeding (>2 g/l decrease in hemoglobin levels or need for transfusion), hematoma causing symptoms or requiring intervention (including extension of hospital stay or rehospitalization), massive hemoptysis, hemothorax, and retroperitoneal bleeding. Minor bleeding complications were defined as the occurrence of hematoma or any bleeding that did not require any intervention and did not cause any symptoms.

All patients were assessed for complications immediately after the procedure, admitted for overnight observation, and reassessed before being discharged on the following day. Patients not residing locally were requested to spend 1 additional night in the local area. All patients were instructed to call our center for AF if any symptoms developed over the course of the first 3 months after ablation. During these telephone encounters, the progress of recovery and symptoms were assessed by a dedicated AF-electrophysiology registered nurse. Patients who had symptoms or suspected complications were asked to seek medical attention at a Cleveland Clinic facility, a local emergency department, or to follow up in our electrophysiology clinic or with their local physician. All documentations related to such encounters were sent to our center for AF and added to our records. All patients who were taking warfarin returned to follow up with their local anticoagulation clinics or local doctors for further dosing adjustment and to maintain a therapeutic INR level. All patients were required to present for a follow-up visit with the electrophysiologist who performed the procedure 3 to

4 months post-ablation. During this follow-up visit, interval progress of recovery and any complications were reviewed and updated.

STATISTICAL ANALYSES. Descriptive statistics were calculated using the statistical software JMP pro version 10.0 (SAS, North Carolina). Numbers are presented as n (%), mean ± SD, or median (interquartile range), as appropriate.

RESULTS

PATIENT POPULATION. Of 9,413 consecutive patients who underwent AF ablation at our institution between January 2000 and August 2014, prior cerebrovascular events were identified in 247 (2.6%) patients. All had been referred for ablation of recurrent symptomatic AF that had failed antiarrhythmic drug therapy (42.2% persistent AF), and 36 (14.6%) had had prior AF ablation procedures at other institutions. Their demographics are summarized in **Table 1**. Patients were predominantly male, age <65 years, with a history of hypertension and no heart failure, with a median CHA2DS2-VASC score of 4.

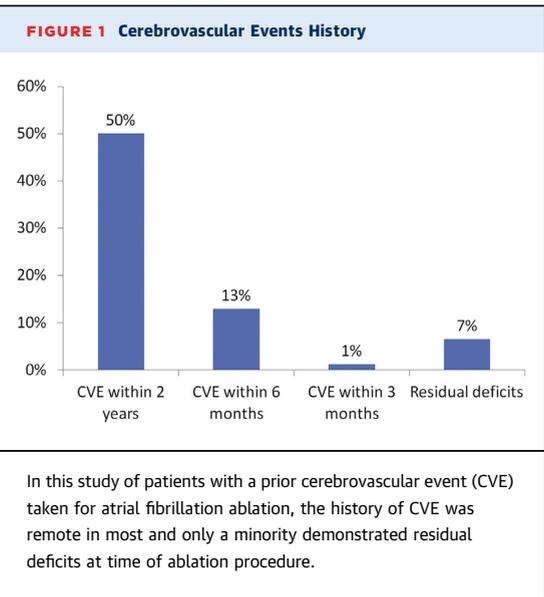
The prior cerebrovascular events were either a prior ischemic stroke (n = 167; 67.6%) or a prior transient ischemic attack (n = 63; 25.5%). These events occurred at a median of 24 months (interquartile range: 10 to 49 months) before the ablation procedures (**Figure 1**). Transient ischemic attacks were reported to have occurred within 3 months before the ablation procedure in 3 patients (1.2%) but no patients had strokes in the preceding 3 months. In the remaining minority (17 of 247; 6.9%), patients had a documented history of a cerebrovascular event but no additional clinical information was available about the initial clinical presentation. On assessment before the ablation procedures, residual neurological abnormalities were present in 16 of 247 (6.5%) patients (residual weakness in 8, speech abnormality in 5, gait abnormality in 2, paresthesias in 2, visual field defect in 1).

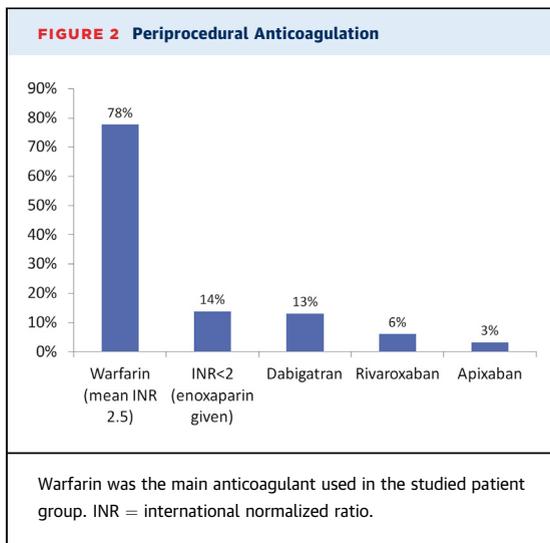
PERIPROCEDURAL ANTICOAGULATION. All patients were on oral anticoagulants before the ablation procedure (**Figure 2**). These anticoagulants were warfarin (n = 192; 77.7%), dabigatran (n = 32; 13.0%), rivaroxaban (n = 15; 6.1%), or apixaban (n = 8; 3.2%). In 1 patient only, warfarin was discontinued and low-molecular-weight heparin was used for bridging periprocedurally. Overall, the mean INR value for patients who were on warfarin was 2.5 ± 0.7. Subcutaneous low-molecular-weight heparin was administered for patients who were on warfarin but had a subtherapeutic INR level on the day of the procedure.

TABLE 1 Baseline Characteristics of the Study Population (N = 247)

Persistent atrial fibrillation	42.2
Stroke	67.6
Transient ischemic attack	25.5
Cerebrovascular event, not specified	6.9
Age, yrs	63.6 ± 9.7
Min-max	32-86
<65	51.0
65-75	37.2
>75	11.7
Women	40.1
Body mass index, kg/m ²	28.6 (24.8-32.5)
Coronary disease	19.4
Prior coronary bypass	10.0
Prior coronary stents	10.9
Heart failure	12.3
Hypertension	63.4
Peripheral arterial disease	6.2
Any vascular disease	20.6
Diabetes mellitus	10.9
Prior venous thromboembolism	4.9
Prior appendage closure	6.1
CHA2DS2Vasc score, median (interquartile range)	4 (3-5)
CHA2DS2Vasc score, %	
2	17.8
3	31.2
4	23.1
5	15.8
6	9.3
7	2.8

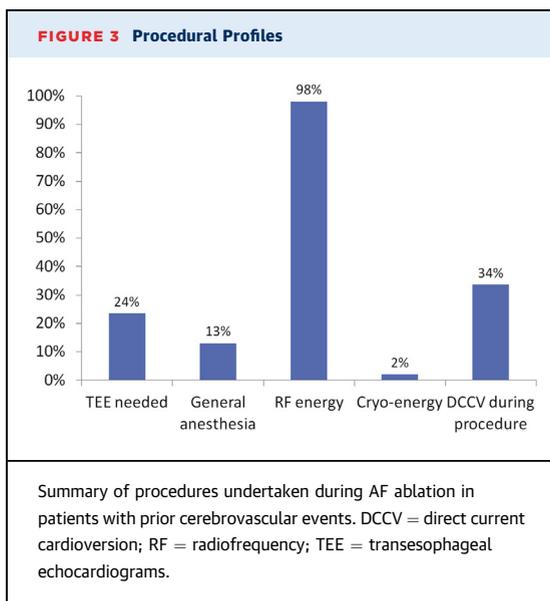
Values are %, mean ± SD, or median (interquartile range).





ABLATION PROCEDURE. On the day of the procedure, presenting atrial rhythms to the electrophysiology laboratory were sinus (59.3%), AF (21.0%), atrial flutter (16.0%), atrial pacing (2.5%), and atrial tachycardia (1.2%). Before the ablation procedures, 58 (23.5%) patients required transesophageal echocardiograms but none showed any left atrial or left atrial appendage thrombi (Figure 3).

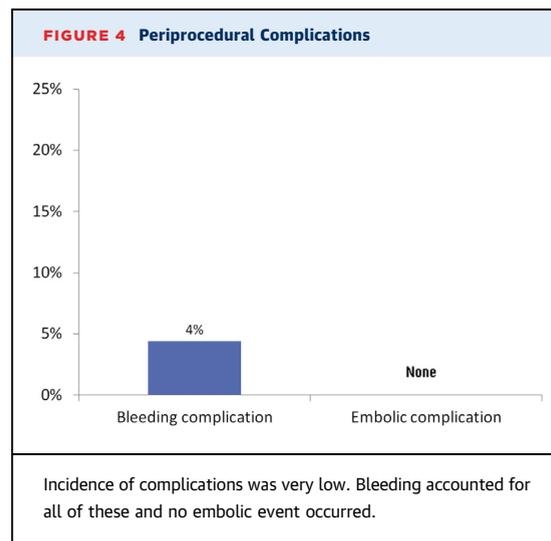
The procedure was performed under general anesthesia in 13.0% of patients and with moderate sedation in the remaining 87.0%. The energy source for left atrial ablations was radiofrequency in 242 (98.0%) patients (56 nonirrigated catheters, 186 irrigated catheters). Cryoablation was performed in a minority (n = 5; 2.0%). All patients had successful isolation of all 4 PVs. The ablations along the PV antra



were extended to the posterior wall and septal to the right veins in 178 patients (72.1%). Most had additional left atrial ablations. These included ablations along the roof or posterior wall to connect the contralateral sets of PV lesions in 140 patients (56.7%), ablations for left atrial tachycardias in 25 patients (10.1%), and left atrial flutter lines in 21 patients (8.5%). Cardioversions to sinus rhythm were performed in 83 patients (33.6%). Only a minority of these (12 of 83) cardioversions were performed before the application of any left atrial ablations.

PERIPROCEDURAL COMPLICATIONS. Information about periprocedural complications was available for all patients (Figure 4). Acute procedural complications included 5 groin hematomas (1 requiring transfusion), 5 pericardial effusions with interventions required in 2 of them because of tamponade physiology (1 pericardiocentesis, 1 surgery), and 1 arteriovenous fistula (managed conservatively). Importantly, none of the patients had a periprocedural thromboembolic event. Moreover, none of those with prior neurological deficits had clinical aggravation of their pre-existing conditions.

All but 1 patient (i.e., 246 of 247; >99%) had at least 4 weeks of follow-up information, and 242 of 247 (98.0%) had clinical information available for at least 3 months following procedure. Of those 242 patients, 232 had in-person clinical visits in the section of cardiac electrophysiology, whereas information for the remaining 10 patients was from clinical visits within the Cleveland Clinic system or via other clinical documentation in electronic records. Importantly, none of the patients had a post-procedural thromboembolic event.



DISCUSSION

The current study with 247 patients is the largest to date to report on the safety of catheter ablation in patients with a prior history of a cerebrovascular event. Most patients were anticoagulated with uninterrupted warfarin and treated with radiofrequency ablation using irrigated catheters. The results are remarkable for showing a zero incidence of new thromboembolic episodes post-procedurally. This indicates that AF ablation undertaken in patients with prior history of cerebrovascular events is not associated with a significant risk of clinical recurrence of such events and may be offered safely in selected cases with the strict anticoagulation protocols used.

Generally, the incidence of thromboembolic events with AF ablation has ranged from 0% to 7% in the published literature (1). Our institutional rates have ranged from 0.1% to 0.5% and has averaged 0.1% in the past 7 years (10,11,14). The current results are compatible with this overall incidence rate indicating that the group of patients with prior cerebrovascular events react no differently to AF ablation. Typically, procedure-related thromboembolic events occur intraprocedurally or within the first 24 hours after the procedure, but the risk period may extend for up to 2 weeks post-ablation (1,3). This time frame was well covered (>99% of patients) in the current study, and any clinical events were unlikely to have been missed.

Prior data regarding AF ablation in these patients are scarce. Two studies (3,7) observed no risk of clinical recurrence but included only a small number of patients with prior thromboembolism. In another, thromboembolic complications during AF ablation were observed in 4 of 43 patients (incidence: 9%; odds ratio: 9.5) and interpreted to indicate that risks were increased by a prior history of stroke or cerebrovascular event (4). However, the anticoagulation protocol differed significantly to ours: warfarin was discontinued and patients bridged periprocedurally with low-molecular-weight heparin. This practice largely has been replaced by continuation of therapeutic anticoagulation at the time of the procedure and stroke incidence with AF ablation procedures has decreased from 5 of 1,000 to 1 to 2 of 1,000 (10,11,14). This was virtually universal practice in our cohort and may have had important bearing on our results. Importantly, the incidence of hemorrhagic complications in this cohort was about 4% and none of these complications was associated with permanent disability. This bleeding event rate is comparable with that of the general population of patients undergoing AF ablation at our institution, which had ranged between 1% and 4% (10,11).

The causes for stroke or thromboembolism related to ablation may be diverse. Hypoxic or anoxic injury secondary to hypoperfusion from anesthetic complications may occur but none were observed in the current report. The overall incidence of cerebrovascular accidents during standard electrophysiology studies and right cardiac ablations is extremely low and ranges from 0.06% to 0.14% (15,16).

Left atrial ablation introduces additional risks. Formation of thrombi within stationary sheaths is possible and therefore it is important to maintain constant air-free heparinized flush through long sheaths and irrigated catheters throughout the procedure, particularly when these sheaths are positioned in the LA. Careful management of sheath insertion and catheter exchanges is critical to avoid air embolism. Generally, sheaths are typically pulled back to the RA after transseptal access unless there is need for sheath support for contact or reach in the LA. In almost one-quarter of patients, transesophageal echocardiograms examination was undertaken because of suboptimal anticoagulation history but did not visualize thrombus. Dislodgement of a pre-existing and undetected atrial thrombus by catheter manipulation or cardioversions may occur, but was not observed in this cohort. Char formation on catheters may occur but is rare with irrigated catheters. A potential mechanism of ablation-related cerebrovascular event from LA ablation is from disruption of the LA endothelial surface, which is potentially prothrombotic (1,6). Of note, ablation protocols vary from one institution to another, especially in persistent AF, and this may affect procedural duration and complications. For example, longer procedures with more extensive left atrial ablations may in theory carry a higher risk of thromboembolic events. Even in our own institution, ablation protocols have evolved considerably during the course of the current study, which spans 15 years, yet the risk of thromboembolic event recurrence remained low, emphasizing the importance of periprocedural anticoagulation protocols and care with sheath and catheter manipulation.

The group of patients studied in the current analysis is important but significantly underrepresented in prior studies. This likely reflects the fact that these patients are not frequently referred or offered ablation procedures because of potential risks. This contention is supported by the observation that about 20% of patients with AF enrolled in medical trials were reported to have had a prior stroke or transient ischemic attack (17-19), yet this group formed only 2.6% of more than 9,000 patients referred for AF ablation procedures at our institution steadily over the course of 15 years. This discrepancy may be

accounted for by perceived concerns about added risk of thromboembolic events and reluctance to proceed with interventional procedures. The current data indicate that this perception is misplaced.

STUDY LIMITATIONS AND STRENGTHS. The study reports the periprocedural complication rates in this population of patients undergoing AF ablation and therefore does not provide information regarding the long-term risk of stroke in these patients. The study has the inherent limitations of observational studies. However, it is well positioned for this safety analysis because it is derived from a large prospectively collected and maintained database, with availability of periprocedural event data in all patients, and follow-up of at least 1 month in >99% patients. This reported experience with 247 patients has significant ramifications for clinical practice, especially because such a patient group is unlikely to be examined prospectively in a randomized clinical trial. Although there was a zero incidence of clinical embolic events following catheter ablation, we cannot comment on subclinical asymptomatic cerebral microembolizations, which are detectable by transcranial Doppler or brain imaging (20,21). Furthermore, the study used clinical documentation to determine the occurrence of stroke or thromboembolic events and no prospective assessment of neurological deficits was performed by a neurologist. As such, subtle nonspecific neurological findings may have been missed in the acute post-procedural period. Another limitation is that only small proportions of the current study population were older than 75 years, had a CHA2DS2Vasc score of >6, heart failure or poor left ventricular ejection fraction, or a recent (<6 months) cerebrovascular event. Furthermore, the study population is heterogeneous from CHA2DS2Vasc risk standpoint. Thus, the findings cannot be generalized to all patients with a prior history of a cerebrovascular event and risk assessment should be performed on a case-by-case basis. Finally, the study findings reflect an experience from a high-volume center and the findings may not be generalizable to lower-volume centers. It provides, however, useful information

for periprocedural and intraprocedural management of these patients.

CONCLUSIONS

In a large population of patients undergoing AF catheter ablation over the course of 15 years at a large tertiary care referral center, only a small minority had prior cerebrovascular events. These had occurred remotely with minimal deficits at time of procedure. Patients typically were younger than 75 years of age with minimal cardiac morbidities, CHA2DS2Vasc scores between 3 and 6, and notably suffered no post-procedural clinical recurrence of cerebrovascular or thromboembolic events. The findings imply that such patients should not be denied catheter ablation of AF as a treatment option simply on the basis of their prior clinical history of cerebrovascular events.

REPRINT REQUESTS AND CORRESPONDENCE: Dr. Niraj Varma, Cardiac Pacing and Electrophysiology, Department of Cardiovascular Medicine/J2-2, 9500 Euclid Avenue, Cleveland, Ohio 44195. E-mail: varman@ccf.org.

PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: Patients with prior cerebrovascular events do not seem to be predisposed to significant risk of clinical cerebrovascular event recurrence when they undergo catheter ablation for atrial fibrillation. Patients with prior cerebrovascular events should not be denied catheter ablation of atrial fibrillation as a treatment option simply on the basis of their prior clinical history of cerebrovascular events.

TRANSLATIONAL OUTLOOK: Catheter ablation significantly reduces AF burden. In patients with prior cerebrovascular events, it remains unclear whether an ablation procedure reduces the long-term risk of cerebrovascular events. This topic deserves further investigation.

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KEY WORDS atrial fibrillation, catheter ablation, stroke