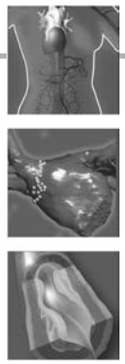

Does catheter ablation of atrial fibrillation eliminate the need for anticoagulation?

The data from observational studies provide evidence that successful ablation may modify the natural progression of atrial fibrillation. The alteration in risk of stroke may have an influence on the decision to start anticoagulation, which, in turn, exposes the patient to an increased risk of bleeding. However, the definition of 'successful ablation' is arbitrary, and success rates are affected by the intensity of monitoring after the ablation. The duration of an atrial fibrillation episode that elevates the risk of thromboembolism has been reported to be <6 min to 24 h. Furthermore, it is not clear whether there is an increased risk of cardioembolic stroke risk in patients with high CHADS2 scores in sinus rhythm. The data from observational studies are persuasive enough to justify a randomized trial to conclusively answer this question.

KEYWORDS: ablation ■ anticoagulation ■ atrial fibrillation ■ cessation ■ sinus rhythm

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Atrial fibrillation (AF) is the most common arrhythmia encountered in clinical practice. Its prevalence has increased over the last few decades and is projected to rise further by 2.5-fold by the middle of the 21st century. This has been associated with an exponential increase in the number of hospitalizations and economic costs [1]. AF is responsible for one-sixth of all strokes and is associated with a fivefold increased stroke risk in the general population [2]. Furthermore, evidence suggests that cardioembolic strokes are more severe and are twice as likely to be fatal [3]. Anticoagulation remains to be the cornerstone in the management of AF.

Although catheter ablation is performed for symptomatic AF, there are emerging data that catheter ablation may modify the natural history of AF [4–6]. However, the long-term results of catheter ablation are sobering, with present guidelines recommending continuation of anticoagulation after catheter ablation based on stroke risk score [7–9]. Despite these guidelines, the practice of anticoagulation following successful catheter ablation for AF differs across centers.

Rationale behind stopping anticoagulation after successful catheter ablation for AF

There are two potential rationales for the cessation of anticoagulation after ablation. First, elimination of AF after successful ablation results in the maintenance of sinus rhythm and, therefore, presumably reverses the heightened stroke risk. Second, there is an established risk of major bleeding with anticoagulation therapy [10,11]. Furthermore, the patients deemed at a higher stroke risk are often at a greater risk of major bleeding [12]. Therefore, the recommendation for the cessation of anticoagulation is based on the alteration of this risk–benefit determination after AF ablation.

Although extremely promising, this approach has certain weaknesses. It is based on the assumption that elimination of clinical AF will eliminate the risk of stroke. However, there are a number of confounding factors that need to be considered. First, there is increasing evidence that argues in favor of the compounding effect of the prothrombogenic conditions that frequently coexist with AF. Second, the definition of successful ablation differs across centers, based on varying degrees of intermittent or continuous monitoring. Indeed, there is evidence that even in the highly symptomatic patients undergoing ablation for AF, approximately 30–40% will subsequently have only asymptomatic recurrence [13,14]. Finally, the jury is still out on how much AF burden is required to significantly elevate stroke risk [15].

Current guidelines for anticoagulation after catheter ablation for AF

The European Society of Cardiology guidelines on follow-up after AF ablation recommends that the guidelines for anticoagulation at the time of cardioversion for AF should apply to patients with AF at the time of ablation (if AF termination is sought at the time of ablation) [8,9,16]. It is also recommended that catheter ablation should be

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performed on oral anticoagulation or heparin. Low molecular weight or unfractionated heparin should be utilized to bridge the resumption of systemic anticoagulation. The anticoagulation should continue for at least 3 months and discontinuation of warfarin is not recommended in patients at high risk of stroke.

Current practice of anticoagulation after catheter ablation for AF

A survey across Canadian centers brings forth the current practice for anticoagulation after ablation for AF [17]. For patients with a CHADS2 score of ≤1, warfarin was continued for at least 3 months by most physicians (89% for paroxysmal and 94% for persistent AF), but rarely beyond a year (6% for paroxysmal and 3% for persistent AF) after a successful ablation. However, in patients with CHADS2 score of ≥2, warfarin was discontinued in only 11% (persistent AF) to 14% (paroxysmal AF), after 1 year of successful ablation. For patients with an unsuccessful procedure, warfarin was continued for at least 3 months, but rarely beyond a year if the CHADS2 score was ≤1. However, warfarin was prescribed to all patients with a CHADS2 score of ≥2 for at least 3 months and 92% (paroxysmal AF) to 94% (persistent AF) of patients beyond 1 year. The reasons for cessation of warfarin were not provided. By contrast, another study reported cessation of anticoagulation in 84% of patients after 3 months of successful ablation for AF [18]. Among the patients without arrhythmic recurrences who discontinued anticoagulation, they reported a low stroke risk of 0.4% over a mean follow-up of 836 days and suggested that this is a safe approach following successful ablation. However, the study did not provide data on the CHADS2 score for stroke risk stratification.

Mechanism of thromboembolism in AF

AF is associated with stasis in the left atrium in conjunction with elevated left atrial volume and reduction in mechanical function. It has been demonstrated that left atrial appendage thrombus formation is associated with reduced contractility and the left atrial appendage emptying velocities in AF, as well as sinus rhythm [19]. Furthermore, termination of AF and restoration of sinus rhythm leads to transient mechanical dysfunction of the atria [20]. This is associated with an increased incidence of thrombus formation in the left atrium and the left atrial appendage leading to a thromboembolic phenomenon. The incidence of atrial stunning after the conversion of AF to sinus rhythm ranges from 38 to 80% [21]. This process is independent of the mode of cardioversion and has been reported with the conversion of AF or atrial flutter by transthoracic electrical cardioversion, low energy internal electrical cardioversion, pharmacological cardioversion, spontaneous conversion, conversion by overdrive pacing of atrial flutter and radiofrequency ablation of atrial flutter [22–35]. Atrial stunning is at maximum immediately after cardioversion and progressively improves with a complete or near complete resolution within a few minutes to 4–6 weeks, depending on the duration of the preceding AF, atrial size and structural heart disease [24–26,34]. This has been, in part, the basis for recommendation of anticoagulation for a minimum of 2–3 months after an AF procedure.

Virchow's triad describes three factors contributing to the development of thrombus: stasis, endothelial injury and a hypercoagulability [36]. There is an increasing body of evidence to support the presence of endothelial dysfunction and hypercoagulability in AF. Endothelial damage in the left atrium due to inflammation has been well described in patients with AF [37]. Hypertension, heart failure and aging are all accompanied by fibrosis and infiltration as components of left atrial remodeling [38–40]. This is associated with disruption of the collagenous extracellular matrix that forms the framework for myocyte attachment and has a potential to perpetuate not only conduction abnormalities promoting AF but also thrombus formation [41]. P-selectin and von Willebrand factor facilitate leukocyte recruitment and macrophage accumulation in inflamed endothelium. They are stored in the Weibel–Palade bodies in the endothelium and are released by inflammatory stimuli. Elevated levels of platelet P-selectin and endothelial von Willebrand factor and diminished nitric oxide production have been documented in cases of AF [42–44]. This heightened thrombotic state in AF is also found to be more severe in the left atrium [45].

Natural history of AF after catheter ablation

Calkins *et al.* reported the outcomes of two meta-analyses analyzing the safety and efficacy of catheter ablation of AF and antiarrhythmic drug therapy [46]. The results of 63 radiofrequency ablation studies were included in these analyses. The single-procedure success rate of ablation with no antiarrhythmic drug therapy was 57%, the multiple-procedure success rate with no antiarrhythmic drugs was

71% and the multiple-procedure success rate with antiarrhythmic drugs or with unknown antiarrhythmic drug usage was 77%. A meta-analysis of four randomized studies has reported a similar success rate of 76% at 1 year after procedure [47]. However, long-term follow-up studies have shown considerable attrition in the success rates [48]. Similarly, the efficacy of catheter ablation after persistent AF is quite humbling at a follow-up of 2 years [7]. Single-procedure, drug-free clinical success associated with case series data suggest that, with the exception of pulmonary vein isolation alone (mean 21%) and complex fractionated atrial electrogram ablation alone (mean 37%), all contemporary substrate ablation techniques for persistent/long-standing AF provide a 47% mean success rate over a period of 2 years. Hence, AF is a progressive disease with the success rate of catheter ablation diminishing over time and influenced by the type of AF.

The success rates for catheter ablation for AF are dependent on several parameters ranging from type of AF, presence of comorbid factors such as hypertension, diabetes, heart failure, obesity and obstructive sleep apnea, the definition of procedural success, and the duration of follow-up. In order to standardize the reporting of results, the Heart Rhythm Society has laid down certain guidelines [8,9,16]. This consensus statement on AF recommends that success should be defined as freedom from symptomatic and asymptomatic AF or atrial flutter lasting longer than 30 s at 12 months after the index procedure. A 3-month blanking period is also recommended as transient atrial arrhythmias in the postablation period are common due to pericardial inflammation. However, the definition of success is arbitrary and does not take into account symptomatic improvement or stroke risk.

Postablation monitoring for recurrence of AF

The ambulatory monitoring for recurrence of AF postablation has been variable in different clinical trials diverging from varying degrees of intermittent to continuous monitoring [49–51]. The studies reporting the safety of cessation of oral anticoagulants after successful catheter ablation have usually employed variable intensities of monitoring, ranging from continuous transtelephonic monitoring during the initial period to annual Holter monitoring as adjuncts to clinical visits and 12 lead ECGs [4,18,52–54].

In paroxysmal AF, prolonged noncontinuous recording may facilitate AF detection. It has been estimated that 7-day Holter ECG recording or daily and symptom-activated event recordings may document the arrhythmia in 70% of AF patients, and that their negative predictive value for the absence of AF is between 30 and 50% [13,50,51]. In stroke survivors, a step-wise addition of five daily short-term ECGs, one 24-h Holter ECG, and another 7-day Holter ECG will each increase the detection rate of AF to a similar extent [8,55]. It has been demonstrated that the sensitivity of 24-h Holter monitoring is dependent on the frequency of monitoring and at quarterly intervals, the sensitivity when compared with implantable loop recorder is unsatisfactory at only 0.60 [56].

Multiple studies have demonstrated that asymptomatic AF commonly occurs in patients following catheter ablation [14,57]. The methods employed for monitoring recurrence have important implications if a decision for stopping oral anticoagulation is based on demonstrating the absence of AF as a measure of success of the catheter ablation. Furthermore, the duration of AF that would provoke thrombus formation is not well established. Evidence from continuous monitoring suggests that episodes as short as 6 min increase the risk of stroke [15]. A study analyzing data from device interrogations suggests that an AF duration of >5.5 h is associated with a twofold risk of stroke compared with those who had shorter episodes of AF (2.4 vs 1.1%) [58]. Another retrospective device-based study has demonstrated significantly increased risk with 24-h AF episodes [59]. The duration of AF episode when combined with stroke risk scores improved risk stratification for stroke [15,59–61]. However, the data at present are inadequate to provide guidelines on the duration under which AF may not significantly increase risk of thrombus formation.

Thromboembolism after cessation of oral anticoagulants following successful catheter ablation for AF

Despite the advances in catheter ablation for AF in the last decade, there is a lack of robust data on the impact of this strategy on the risk of stroke and mortality. However, there are recent registry data to suggest that stroke risk after catheter ablation of AF is favorable and comparable with a population without AF [6]. Similarly, another multicentric registry-based study suggests that restoration of sinus rhythm by catheter ablation of AF is associated with a lower risk of stroke and death compared with patients treated medically [5].

There are large case series that report low thromboembolic risk in patients undergoing

successful catheter ablation for AF (Table 1) [4,18,52–54]. However, the patient cohort in these case series has been a low-to-intermediate risk with a relatively small period of follow-up after cessation of anticoagulation. Oral *et al.* reported no stroke following cessation of warfarin during a 2-year follow-up of low-to-intermediate-risk patients with successful ablation for AF [54]. Anticoagulation was discontinued 3–6 months after ablation. However, the authors acknowledged that the patients who had previous history of stroke or were over 65 years of age often received anticoagulation despite successful outcome of

Table 1. Cessation of anticoagulation after successful catheter ablation for atrial fibrillation.

Study (year)	Subjects in whom OAT increased (n)	CHADS2 score (%)	Method of monitoring for AF	Anticoagulation cessation after ablation	Duration of follow-up	Ischemic stroke risk (%)	Comment	Ref.
Oral *et al.* (2006)	203 (CHADS2:0), 180 (CHADS2:1)	0, 1	Event recorder and/or serial ECG and 24 h Holters	4 months (CHADS2: 0), 5 months (CHADS2: 1) in absence of reoccurrence	25 ± 8 months	0	Patients with history of stroke or older than 65 years were not taken off anticoagulation	[54]
Nademanee *et al.* (2008)	434	–	Clinical symptoms, ECG, event recorders, annual Holters, interrogation of implanted devices	3 months of established sinus rhythm	836 ± 605 days	0.4	Restarted OAT if recurrence of atrial arrhythmia with duration >12 h	[18]
Themistoclakis *et al.* (2010)	2692	0 (60), 1 (27), ≥2 (13)	Quarterly follow-up, Holter and/or TTM TTM was either continuous for 5- or 1-month blocks immediately postablation, at 6–12 weeks and 6 months	3 months of no atrial tachyarrhythmia (>1 min), and absence of PV stenosis and LA mechanical dysfunction	28 ± 13 months	0.07	Multicenter retrospective data OAT restarted if recurrence occurred Data collected up to the time of recurrence Excluded patients with LA dysfunction	[53]
Saad *et al.* (2011)	327	0–1 (31), 2 (45), 3 (23)	Office visit with 24 h Holter at 1, 3, 6, 9 and 12 months 7-day Holter at 6 and 12 months if feasible	3 months if no AF after blanking period	46 ± 17 months	0	46% anticoagulated for 6 months after ablation and 28% for 12 months after ablation These included older patients, or presence of structural heart disease In high-risk patients (investigator discretion) OAT not stopped	[52]
Hussein *et al.* (2011)	587	≤2 (i.e., 0 [46]; 1 [43]; 2 [11])	Event recorder first 3 months 3- and 6-monthly 24-h Holter, and 6-monthly thereafter	12 months of absence of AF	44 months	0.66 per year	Warfarin stopped in 32% of patients with a CHADS2 score of 2 at physician discretion after successful ablation Anticoagulation cessation on a case-to-case basis	[4]

AF: Atrial fibrillation; LA: Left atrial; OAT: Oral anticoagulant therapy; PV: Pulmonary vein; TTM: Transtelephonic monitoring.

catheter ablation. Thermistoclakis *et al.*, in a multicentric retrospective analysis, reported a 0.07% risk of ischemic stroke after cessation of oral anticoagulant therapy after successful ablation [53]. Similarly, other investigators have reported low stroke rates following cessation of oral anticoagulants after successful catheter ablation for AF (Table 1). However, these studies suffer from retrospective design and investigator bias. A select population underwent cessation of anticoagulation and those perceived at higher risk by the treating physician were continued on warfarin. Patients with previous history of stroke, left atrial dysfunction and older age were not considered for anticoagulation cessation. Furthermore, the period of follow-up was not very long, given that a proportion of patients received anticoagulation for several months after the ablation. It is not clear how anticoagulation was managed, whether the patients underwent repeat ablation and how this period was accounted for in the follow-up duration in one study [52]. In addition, anticoagulation was restarted and data were analyzed up to the time of recurrence in another study [53], suggesting that patients who stop anticoagulation should be closely monitored for recurrence of AF. Furthermore, aspirin was continued indefinitely after cessation of oral anticoagulant therapy.

Conclusion & future perspective

AF is a progressive disease. Late recurrences have been described during long-term follow-up of catheter ablation for AF. Furthermore, the stroke risk is dynamic with accretion of additional stroke risk factors over time.

Cessation of anticoagulation is a very attractive concept after successful ablation of AF. However, to approach this, certain questions require clarification, most importantly: what is the minimum duration of AF episodes or cumulative AF that can provoke thrombus formation, and how does it change across different stroke risk categories? What is the risk of stroke in sinus rhythm in the presence of high CHADS2 score and CHA2DS2–VASc scores? Which is the best tool to monitor the recurrence of AF of the above duration with reasonable confidence? These answers could potentially guide us in assessing the stroke risk and, accordingly, the risk–benefit of oral anticoagulants in this scenario. Furthermore, the introduction of novel oral anticoagulants with superior risk–benefit ratios has added another variable to the equation. In addition, left atrial appendage closure may have a role in stroke risk reduction in selected cases.

Given the absence of randomized data, it is prudent to continue anticoagulation after catheter ablation in patients at high risk of stroke. In our opinion, cessation of anticoagulation following catheter ablation should only be considered in the presence of documented durable absence of recurrent atrial arrhythmias in patients at low-to-intermediate stroke risk. The patients should be made aware of the current consensus guidelines and allowed to make an

Executive summary

Background

- The data from observational studies suggests that successful ablation for atrial fibrillation (AF) may modify its natural progression and reduce the risk of stroke.
- The rationale behind stopping anticoagulation after successful catheter ablation for AF is that the maintenance of sinus rhythm after successful ablation may reduce the risk of stroke and alter the risk/benefit ratio for the use of oral anticoagulants in AF.

Mechanism of thromboembolism in AF

- In addition to stasis, there is emerging evidence that endothelial injury and hypercoagulability play a role in thrombus formation in AF.

Natural progression of AF after catheter ablation

- The success rate of ablation for AF after multiple procedures is high at 1 year; however, there is considerable attrition over time.

Postablation monitoring for recurrence of AF

- The postablation monitoring varies from intermittent to continuous monitoring, with sensitivity increasing with intensity of monitoring.

Thromboembolism after cessation of oral anticoagulants following successful catheter ablation for AF

- Several observational single- and multi-center studies have reported reduced risk of stroke, despite cessation of oral anticoagulants, following successful catheter ablation for AF in patients with low-to-intermediate risk of stroke.
- However, these observational studies suffer from bias with cessation of anticoagulation offered to patients deemed at lower risk.

Conclusion & future perspective

- In the absence of randomized data, anticoagulation should be continued for patients with AF and high risk for stroke. In patients with intermediate risk, the decision should be individualized and patients made aware of current guidelines in the event of discontinuation of oral anticoagulants.
- The duration of AF that is thrombogenic, the degree of thrombus risk in sinus rhythm in the presence of stroke risk factors and a sensitive monitoring tool are important issues that require clarification.
- A randomized trial is essential to adequately address this important issue.

informed decision on an individual basis. Upon cessation of oral anticoagulant therapy, these patients should be carefully monitored and anticoagulation re-instituted promptly in the event of recurrence of atrial tachyarrhythmias.

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