Are There Enough Data to Safely Withdraw Anticoagulation After Atrial Fibrillation Catheter Ablation?

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Atrial fibrillation catheter ablation (AFCA) can significantly reduce the symptoms and total burden of the arrhythmia. Whether it can sufficiently reduce the associated thromboembolic risk to warrant discontinuation of anticoagulation in successful cases, is an important issue with impact on the increasing number of patients undergoing the procedure. Observational data suggests that successful AFCA may reduce the risk, but with the increasingly prevalent diagnosis of asymptomatic atrial fibrillation (AF), it needs careful consideration, especially as the value of anticoagulation in this setting is incompletely understood. In the absence of randomised trial data, expert consensus recommends continued risk stratification according to baseline risk factors, independent of procedural outcome. Despite this, a number of electrophysiologists routinely discontinue anticoagulation in moderate- to high-risk patients. Detailed counselling, prolonged intensive monitoring periods and outcome-based decision-making tools have supported these operators to keep their published stroke rates low. Anticoagulation conveys an inherent risk of major bleeding which is also seen with anti-platelet therapies, making this an illogical ‘step-down’ therapy. The risks of both, a continuation or discontinuation strategy, support the randomised study of anticoagulation after AFCA which is ongoing. However, the observational nature of the currently available data is insufficient to support change in practice. Whilst further results are awaited, our duty is to support patient decision-making explaining that, ultimately, best practice is currently unknown. The objective of this review is to critically analyse the existing data regarding discontinuation in this setting and also to consider the additional factors that may influence clinical decision-making on this contended issue.

The global disease burden of atrial fibrillation (AF) is considerable, and a significant proportion is attributable to the associated thromboembolic risk. The pro-thrombotic environment resulting from AF accrues a five-fold increase in stroke risk, with the arrhythmia implicated in 30% of all strokes. Evaluating thromboembolic risk should be a primary concern for any healthcare practitioner responsible for a patient with AF. Fortunately, this vulnerability can largely be mitigated with the timely prescription of oral anticoagulation therapy (OAT). Large-scale randomised controlled trial data has shown that OAT can significantly reduce thromboembolic events in at-risk patients with non-valvar AF. Although warfarin is the traditionally prescribed OAT, direct oral anticoagulants (DOACs) have become an increasing part of contemporary practice with similar, if not superior efficacy. Their desirable anti-thrombotic effect inadvertently predisposes takers to an increased risk of bleeding. Major bleeding events such as intracranial haemorrhage and gastro-intestinal bleeds are associated with greater morbidity in the context of OAT, although potentially less so with DOACs than warfarin. Nevertheless, these risks need to be considered when prescribing these drugs.

Risk stratification scores have been developed for the AF population to aid the counselling process for patients in whom OATs are being considered. The CHADS2 or CHA2DS2-VASc scores, and the HASBLED scores are probably the most commonly used for thromboembolic and bleeding risk assessment. These tools have been validated in AF populations managed using non-invasive rate control and/or rhythm control strategies.

The pro-thrombotic pathophysiology in AF is complex. Observational data suggests an association between AF burden and stroke risk, and it is intuitive to think that the effective restoration of sinus rhythm would reduce this risk. Medication-based rhythm control strategies have not demonstrated significant impact on thromboembolic risk. The question therefore arises whether the restoration and maintenance of sinus rhythm with ablation will impact stroke prevention. The purpose of this review is to critically analyse the observation data regarding discontinuation of OAT in this setting. We will also consider the implications of asymptomatic AF (AAF) and cardiac devices on risk stratification.

Anticoagulation practice after atrial fibrillation catheter ablation
AF catheter ablation (AFCA) has evolved as an effective therapy for treating symptomatic AF in selected patients. It is more effective than anti-arrhythmic medications at achieving sustained
sinus rhythm. 27 It leads to a marked reduction in total AF burden in experienced hands. 28 Regarding anti-coagulation, best practice in the short-term following AFCA is largely agreed upon, with consensus supporting OAT for at least 2–3 months following the procedure. 29 Although there is little evidence justifying this approach, it is generally felt that resolution and endothelialisation of ablation lesions, reduction in post-operative inflammation and recovery of atrial function may be important factors exposing the patient to an increased risk of thrombosis in the early post-ablation period that OAT may protect from. Reverse remodelling occurs although this is not always associated with return of active atrial function. Thus, the implications on longer-term thromboembolic risk are less clear. Whether procedural success can shift the thromboembolic–bleeding risk balance sufficiently to advocate long-term discontinuation of OAT, is the topic of ongoing study and debate.

Current guidelines recommend indefinite continuation of OAT based on thromboembolic risk assessment scores, regardless of the perceived procedural outcome. 30 Discontinuation of OAT after AFCA is a commonly held patient expectation and occasionally is the primary incentive for undergoing the procedure. 31 In a 2012 survey, 16% (11/68) of European operators’ practice. 32

Increasing numbers of centres are performing rising numbers of AFCA procedures. The issue of how to best manage this expanding cohort of successfully ablated patients is significant and was highlighted as an important unanswered question in the most recent International expert consensus statement on AFCA. 33 An overview of the relevant literature is important to inform practice. In the absence of consensus, this review will also consider the factors that can support personalised decision-making.

The impact of atrial fibrillation catheter ablation on thromboembolic risk
Jarman et al. undertook a retrospective observational analysis (n = 4,991) in an attempt to characterise the longitudinal impact of AFCA on stroke risk compared to an extensively propensity-matched cohort managed medically. 34 Repeated measures methodology demonstrated a similar baseline annual incidence of stroke (0.30% versus 0.28%, p=0.829) but with significant divergence over the 5 years following the indexed AFCA, cardioversion or hospital visit (0.64% versus 1.84%, p<0.001). These findings would suggest AFCA can convey an attractive risk reduction that persists over many years. However, the influence of selection bias through unmatched variables on this disparity should be considered. Outcome detection was also dependent on a health-record key-word search which may under-represent the true incidence.

Two large, prospective case series have independently reported a significantly lower stroke risk in populations that underwent AFCA versus age- and gender-matched AF cohorts treated medically. 35,36 Over 3-years follow-up, both series reported the incidence of stroke after AFCA became comparable to matched populations with no known AF. Hunter et al. further found that ‘freedom from AF’ was an independent predictor of stroke-free survival after multi-variate analysis (hazard ratio [HR] 0.33; 95% confidence interval [CI] 0.17–0.67) potentially delineating a dependent relationship with procedural outcome. 37 However, longer-term observational data suggests this ablation outcome-dependent association may not endure over time with a comparable 10-year stroke risk between those who remain in sinus rhythm and those who do not (HR 0.79; 95% CI 0.48–1.29; p=0.34). 38

Although the three aforementioned studies are observational with inherent limitations as a result of their design, the cohorts undergoing AFCA reflect clinical practice. The absolute annual incidence of stroke reported in these cohorts is very low and comparable to cohorts in lifelong sinus rhythm. However, the standard practice in these studies was to manage thromboembolic risk according to their pre-procedural risk score regardless of procedural success. A contemporary retrospective analysis of Canadian administrative data suggests the risk reduction in the post-AFCA period may be attributable to better OAT compliance; an unmatched variable in these studies. 39 The authors reported a significant reduction in event rate (stroke/transient ischaemic attack/retinal infarct) after AFCA compared to a propensity-matched, medically managed AF cohort (HR 0.43; 95% CI 0.37–0.50). However, it became comparable after adjustment for OAT use (HR 0.88; 95% CI 0.63–1.21). This study too, however, was observational and may be subject to its own selection bias. There was a difference in baseline stroke risk between the unadjusted control and AFCA (CHA2DS2-VASc scores 3.2 ± 1.6 versus 1.1 ± 1.2) groups potentially due to selection bias that improved after adjustment for OAT use (2.3 ± 1.4 versus 2.2 ± 1.3).

In attempt to better control for such features, a large, randomised controlled trial compared AFCA to medical management, with the incidence of stroke over 4 years reported as a secondary end-point. 40 The CABANA investigators reported no significant difference in the prevalence of disabling stroke at follow-up (HR 0.42; 95% CI 0.11–1.62; p=0.19). The study was, however, underpowered to detect a difference and this finding should be read with this in consideration. Despite enrolling 2,204 patients over 4 years, this multicentre trial remained underpowered for this endpoint due to the very low event rate in both the intervention and medication arms (0.3% versus 0.6%). OAT prescription was at the physician’s discretion and almost all participants were taking one form at time of follow-up (95% versus 96%). This may have diluted any difference in effect by contributing to the low event rates in both groups.

Discontinuation of oral anticoagulation therapy in the post-atrial fibrillation catheter ablation period
OAT discontinuation after AFCA is routinely practised in a number of centres who have published their experiences. Saad et al. published a series of 327 patients who were switched from OAT to anti-platelet therapy in the absence of any suspicion of recurrence 3 months after AFCA (and resumed if AF was detected). 41 A total of 225 (68.8%) of these patients to continue on OAT. In total, 663 (19.7%) patients were continued therapy in the post-atrial fibrillation catheter ablation period.
thromboembolic events occurred in the ‘off-OAT’ group and 3 (0.45%) in the ‘on-OAT’ group. The incidence was not significantly different (p=0.06), although any inter-cohort comparison is of limited value given the inherent differences between the two groups. However, the study did demonstrate two key points; discontinuation of OAT may be feasible after AFCA as standard protocol without any clear increase in thromboembolic events, and that a simple criteria-based tool may identify patients in whom to continue OAT.

The incidence of stroke in both studies remained low after AFCA despite OAT discontinuation with short-term outcomes comparable to observational case series wherein it was continued. These findings favour discontinuation in patients with medium to high risk and suggests AFCA could be a predominant driver for risk reduction.

A study of OAT discontinuation exclusively in high-risk patients has demonstrated similar short-term outcomes.35 One-hundred-and-eight patients undergoing AFCA with a prior stroke and an average CHA2DS2-Vasc score of 4.1 ± 1.4 were enrolled. The authors chose to implement a prolonged post-procedural surveillance period with repeated rhythm checks to more confidently determine procedural outcome. After a mean period of 7.3 months, 55 patients were subsequently diagnosed as free of recurrence and, after counselling, discontinued OAT. Although the sample size of this single-centre study was small, no strokes were reported over the 2.2 ± 1.3-year follow-up period, supporting the observational body of data. Meta-analysis of nine observational studies (n=3,436) of OAT continuation versus discontinuation after AFCA found no significant difference in thromboembolic events in patients at moderate or greater risk at baseline.35

Bleeding risk of oral anticoagulation therapy continuation

The bleeding risk associated with OAT must be cautiously considered in every patient with AF. The same holds for the re-assessment of short-term and long-term risk in the post-ablation period. The incidence, morbidity and mortality of major bleeding events are significantly increased on OAT, with intracranial haemorrhage and gastro-intestinal bleeding the most significant.34 Large randomised controlled trial data has suggested an annual bleeding risk of 2.1–3.6% with warfarin and 3.1–3.4% with DOACs.4,4,4 A meta-analysis of these DOAC-versus-warfarin trials suggests a lower bleeding risk with DOAC use, although agent reversal and interactions represent different challenges that need consideration.

Secondary prevention with OAT after a stroke is not advocated in patients with sinus rhythm. AF itself is not associated with greater bleeding risk. The prevalence and burden of thromboembolic events due to AF means a high bleeding risk alone should not lead to withholding of OAT.4 However, this recommendation cannot be held if the bleeding risk is unbalanced. Bleeding risk stratification tools in the setting of OAT prescription for AF have been established to aid the physician to identify and address associated risk factors.4 Although periprocedural bleeding is a recognised complication of AFCA, there has not been any data to suggest the procedure increases longer-term risk of major bleeding. The CABAANA trial showed comparable rates of serious bleeding between the ablation and medically managed cohorts who largely continued OAT over the 4-year follow-up period (HR 0.98; 95% CI 0.62–1.56; p=0.93).35

Many of the above experiences reported bleeding event rates as a secondary outcome and found either a significantly greater incidence associated with OAT continuation or no difference.29,30 The greatest disparity in major bleeding was reported by Themistocleakis et al., with 13 events in the on-OAT cohort compared to two (2.0% versus 0.3%; p=0.001).31 A meta-analysis of nine such studies reporting on OAT discontinuation after AFCA found a significantly higher incidence of major bleeding events in those who were continued on OAT. (OR 6.5; 95% CI 1.93–21.86; p=0.002).36 However the lack of randomised data is again the limitation. Risk factors for bleeding and thromboembolism overlap (age, hypertension, previous stroke) and thus by continuing OAT in high thromboembolic risk patients may compound an inherently higher risk of bleeding.

The published series sought to switch OAT for life-long aspirin after the discontinuation of OAT.39,40 However, aspirin is not an anti-coagulant and there is no strong evidence to suggest it is effective preventative therapy against thromboembolic events in patients with AF. A meta-analysis of the relevant randomised trials comparing aspirin to OAT in AF patients demonstrated an inferiority of the anti-platelet in reducing thromboembolic events despite a comparable bleeding risk to novel OAT across all risk groups.35 European guidelines issue a class IIb recommendation for aspirin in this cohort due to the unjustified bleeding risk – even in low-risk patients.3 For patients in sinus rhythm, anti-platelet therapy does have a role in the secondary prevention of vaso-occlusive events associated with acute coronary syndromes and cerebrovascular accidents. As primary prevention in this cohort, its value is limited even amongst the elderly or high-risk. Thus, the routine prescription in place of OAT is not logical – if there is suspicion of arrhythmia recurrence, or if the clinician chooses to manage the patient according their pre-AFCA alternative indication. Whether such a personalised approach would have led to a lower bleeding risk following OAT discontinuation thus further skewing the thromboembolic–bleeding risk is unknown but would be a valuable insight from future studies in this field.

Implications of arrhythmia recurrence on thromboembolic risk

AF can recur after AFCA and the potential unmitigated thromboembolic risk of AAF recurrence is a concern when considering OAT discontinuation. AAF is not unique to the post-AFCA population and has been documented both in patients known, and not known, to have AF.39,40 Identification in the latter often happens after a thromboembolic event or during routine interrogation of an otherwise-indicated cardiac implantable electronic device (CIED).29 The findings have reiterated that AF is a continuous variable rather than existing in two dichotomous states (present or absent). Although CIEDs are able to capture even brief episodes of AAF (<2 minutes), these do not appear to convey significant stroke risk. The minimum duration required to do so varies across the literature with 6-minute and 24-hour episodes of AAF reported as the lower thresholds.35,36 Further uncertainty exists regarding the onward management of AAF. Whether OAT can significantly reduce the thromboembolic risk associated with this phenomenon has not yet been established, questioning the merit of intensive surveillance post-AFCA.

The absolute AF burden is substantially reduced after AFCA as well as the duration of any paroxysmal episodes. The ratio of AAF:symptomatic AF, however, increases; dissociating symptoms from the arrhythmia.14 No predictor of AAF vulnerability has been identified although the duration of AF pre-ablation and number of AFCA procedures are independent predictors.34,41
Conventional symptom-directed follow-up may underestimate the true prevalence of arrhythmia recurrence. However, these undetected episodes of AAF tend to be much shorter than symptomatic AF and usually of duration below that associated with thromboembolic risk. AAF is uncommon in the absence of concurrent symptomatic AF and whether their detection would significantly alter risk and management needs to be determined. However, recurrence after AFCA may be a progressive phenomenon with AAF being the initial phase, evolving into longer, symptomatic episodes. And although early detection of AAF may not alter thromboembolic risk, it may afford an opportunity to intervene to reduce the duration of symptoms or episodes of atrial tachyarrhythmia ≥30 seconds may be considered to be in sustained sinus rhythm. Enrolled patients with CHA2DS2-VASC ≥1 will then be randomised to continue on OAT or switched to low-dose aspirin. The investigators intend to follow-up patients with thromboembolic event rate as primary and bleeding event rate as secondary end-points. The study is not expected to be completed until 2021. As we have discussed already, the use of aspirin as an alternative to OAT may not be a logical choice. Left atrial appendage occlusion is an alternative OAT-free substitute strategy aimed at reducing thromboembolic risk after AFCA and is in undergoing evaluation in a recently registered multi-centre randomised controlled trial against DOAC therapy.

In counselling our patients as to the best approach for their long-term anticoagulation after AFCA the best we can do at present is be honest about the lack of robust data in this area and the dangers of inferring truth from case-cohort studies and observation. In doing so, we can be clear that ongoing AF and a high-risk score would strongly favour continuing OAT when possible. In the absence of recurrent AF particularly in patients who have developed risk factors some years after a successful AFCA it is probably reasonable to not re-institute OAT. For those patients between these two extremes we will have to continue to be honest and tell them that at the moment no-one knows what is correct and to do our best to help them make a decision that they are comfortable with.

CIEDs present a novel paradigm for targeted OAT prescription during paroxysms of AF only facilitated by the advent of direct OAT agents with quick onset. This would avoid the unmitigated increase in bleeding risk during periods of sinus rhythm. Two trials, REACT.COM (n=59) and TACTIC-AF (n=48) have recently demonstrated the feasibility of a device-guided strategy in their small studied cohorts which included patients post-AFCA. Whereas REACT.COM reported a 94% reduction in time on OAT using a 1-hour threshold for episode significance, TACTIC-AF reported a 75% reduction using a 6-hour threshold. Although this presents an attractive, personalised approach to risk stratification in this sub-group, outstanding concerns such as the AF episode duration threshold to initiate OAT commencement, the duration of therapy required per episode, and importantly whether the approach can significantly impact thromboembolic outcomes, limits wider application. The single randomised controlled trial assessing superiority of device-guided OAT versus standard of care for patients with dual chamber and biventricular defibrillators, was terminated early due to futility. It demonstrated no significant difference in thromboembolic or major bleeding outcomes. However, an historic diagnosis of AF was not an inclusion criterion and participants predominantly had concomitant heart failure by virtue of their device indication. A better understanding of the association, including the temporal relationship, between AF episodes and thrombogenesis is required before consideration in carefully selected patients.

**Conclusion**

Observational series have demonstrated a reduced incidence of thromboembolic events in cohorts undergoing AFCA compared to matched counterparts. Centres routinely practising in OAT discontinuation after AFCA have reported the feasibility of adjusted follow-up protocols and no associated increased risk in their cohorts. The association between AAF and stroke is being more precisely defined, and this uncertainty underlying a primary concern of routine discontinuation. Smart-devices offer a potential non-invasive, remote monitoring tool that could enable more reactive decision-making; however, this would require high-sensitivity devices and effective patient autonomy. Importantly, large randomised controlled trials to determine the impact of OAT on AAF-associated stroke risk are already underway and their outcomes are eagerly awaited to help guide practice.

The international expert consensus papers recognise the potential incoherence of OAT in the presence of sustained sinus rhythm and the need for further evidence. However, in the absence of any prospective randomised controlled trial data supporting discontinuation, this recommendation is unlikely to be revised. A prospective multi-centre, randomised controlled trial is underway, recruiting over 1,500 patients in hope to provide clarity on this issue (NCT02168829). Following AFCA for symptomatic AF, enrolled patients will be followed up with two 24-hour Holter over 12 months, and in the absence of any symptoms or episodes of atrial tachyarrhythmia ≥30 seconds will be considered to be in sustained sinus rhythm. Enrolled patients with CHA2DS2-VASC ≥1 will then be randomised to continue on OAT or switched to low-dose aspirin. The investigators intend to follow-up patients with thromboembolic event rate as primary and bleeding event rate as secondary end-points. The study is not expected to be completed until 2021. As we have discussed already, the use of aspirin as an alternative to OAT may not be a logical choice. Left atrial appendage occlusion is an alternative OAT-free substitute strategy aimed at reducing thromboembolic risk after AFCA and is in undergoing evaluation in a recently registered multi-centre randomised controlled trial against DOAC therapy.

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