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INVITED EDITORIAL

Is It Safe (and When) to Stop Oral Anticoagulation After Ablation for Atrial fibrillation? (Do We Have Enough Evidence to Solve the Dilemma?)

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Atrial fibrillation (AF), the most common sustained cardiac arrhythmia, is associated with significant impairment in functional capacity and quality of life and increased morbidity and mortality [1–3]. Indeed, AF is independently associated with an overall 3.5-fold risk increase of mortality, which is predominantly due to increased risk of stroke and systemic embolic events (S/SE) and ventricular dysfunction [4]. Non-anticoagulated patients with AF have a 3- to 5 fold increased risk of ischemic strokes, and it is estimated that up to 30% of all ischemic strokes and 10% of cryptogenic strokes are related to this arrhythmia [1–3]. Furthermore, ischemic strokes associated with AF are nearly twice as likely to be fatal and generally more severe and more recurrent than strokes unrelated to AF [5, 6].

Catheter ablation of AF (CAAF) is an effective therapeutic strategy recommended in clinical practice guidelines (CPGs) as a first-line rhythm control therapy in selected patients with symptomatic paroxysmal and persistent AF with and without risk factors for AF recurrence or as a second-line rhythm control therapy, being an alternative to class I or III antiarrhythmic drugs when these drugs failed or are contraindicated [1–3, 7].

When performed by well-trained operators, CAAF is a safe and superior alternative to antiarrhythmic drug therapy for reducing arrhythmia burden and improving quality of life in patients with symptomatic AF [7–9]. However, randomized clinical trials (RCTs) have not clearly demonstrated a significant reduction in all-cause mortality, stroke, or major bleeding event (MBEs) following CAAF, and, therefore, the indications for this procedure have not been broadened beyond symptom relief, except to reverse left ventricular dysfunction when tachycardiomyopathy is highly probably [7–11]. Nevertheless, the CASTLE-AF trial found that CAAF reduced the risk of death and heart failure hospitalization compared with medical therapy in selected patients with heart failure with reduced ejection fraction (HFrEF) [12], a result confirmed in other studies [13, 14]. Restoration of sinus rhythm also improved left ventricular ejection fraction, functional capacity, and ventricular remodeling [15]. However, the benefit associated with CAAF appeared to be more modest in routine practice than that reported in the CASTLE-AF trial [16], and, in addition, some authors have raised criticism about the selected population enrolled in the trial. Two recent systematic reviews and meta-analysis found that CAAF was associated with a mortality benefit as compared with medical treatment, and this benefit was restricted to patients with AF and HFrEF [17, 18].

Although CAAF is considered a relatively safe invasive procedure, it can be occasionally complicated by periprocedural thromboembolic (S/SE, transient ischemic attacks-TIA) and bleeding events [1–3], even when some complications can also occur weeks or months following ablation. CAAF is a complex interventional procedure that involves catheter manipulation and ablation in the delicate thin-walled atria, trans-septal punctures, left atrial (LA) endothelial damage, char formation on ablation catheters, air bubble ingress, a prothrombotic state associated with the arrhythmia, activation of the clotting cascade, and blood flow alteration after sinus rhythm is established [19]. These changes increase the risk of S/SE during and for several weeks after ablation even in patients considered to have a low-risk of stroke according to the tools for risk assessment ($CHADS_2$, CHA_2DS_2-VASc, and ABC scores) [7–9, 20].

Prospective, registry-based data show that up to 14% of patients undergoing CAAF experience complications, 2–3%

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of which are potentially life-threatening [7, 11, 21, 22]. Several surveys enrolling mainly paroxysmal AF patients undergoing CAAF showed an incidence of thromboembolic events < 1.0%, but asymptomatic cerebral embolism can appear in 5–15% and bleeding complications in 1–4% of patients [7, 11, 20]. Thus, adequate oral anticoagulation therapy (OAT) is recommended before (for at least 3 weeks in case of stroke risk factors), during, and for at least 2 months post-CAAF to prevent these thromboembolic complications even at the risk of increasing bleeding events [1–3].

Oral Anticoagulant Therapy

To date, OAT is the only therapeutic intervention that has shown to improve survival in patients with AF. For almost 50 years, adjusted doses of vitamin K antagonists (VKAs, mainly warfarin) were the mainstay OAT prescribed for the prevention of S/SE in AF patients. Today, VKAs are still used in many patients and are the only OAT recommended in those with moderate-to-severe mitral stenosis and/or prosthetic mechanical valves [1–3]. In a meta-analysis of 9 studies (27,402 patients), CAAF performed under therapeutic warfarin (international normalized ratio-INR 2.0–3.5) was associated with a striking decrease of S/SE (OR, 0.10; 95% CI, 0.05–0.23; $P < 0.001$) and minor bleeding complications (OR, 0.38; 95% CI, 0.21–0.71; $P = 0.002$) compared with warfarin discontinuation and did not increase the risk of MBEs, including cardiac tamponade [23]. In the COMPARE study, which recruited patients at high-risk of stroke (24% had persistent AF and 51% long-standing persistent AF; ≈70% with a $CHADS_2$ score ≥ 2), uninterrupted warfarin therapy reduced periprocedural stroke/TIA and minor bleeding complications, as long as the INR remained within the therapeutic range (TTR) ≥ 70% of the time, while warfarin temporary discontinuation with enoxaparine bridging emerged as a strong predictor of periprocedural S/SE [24]. However, the use of VKAs is limited by their multiple mechanisms of action, slow onset/offset of action, narrow therapeutic range, wide inter-individual variability in anticoagulant response, need for regular INR monitoring and dose adjustments to optimize the TTR, and multiple drug interactions [25].

New direct oral anticoagulants (DOACs: apixaban, dabigatran, edoxaban and rivaroxaban) present a more targeted mechanism of action, rapid onset-offset of action, predictable anticoagulation effects so that they can be used at fixed doses without regular monitoring and fewer drug interactions. Thus, in patients on VKAs with a low TTR (< 70%) at follow-up, switching to a DOAC is recommended [1–3]. In four pivotal phase 3 RCTs in patients with NVAF, compared with warfarin, DOACs significantly reduced S/SE (19%) mainly driven by a reduction in hemorrhagic stroke (51%), intracranial hemorrhage (52%), and all-cause mortality (10%) but increased gastrointestinal bleedings (25%) at long term follow-up [26]. Thus, DOACs are more convenient for both patients and physicians and are replacing VKAs in general practice, including patients undergoing CAAF. Several clinical trials [27–32] and meta-analysis (Table 1) [33–42] comparing the use of uninterrupted DOAC vs. warfarin therapy for CAAF reported no differences in the incidence of stroke/SE/TIA or minor bleeding events, but DOAC therapy was associated with reduced risk of MBEs, which translated into a significant net clinical benefit. Thus, unless they are contraindicated (i.e., patients with moderate-to-severe mitral stenosis and/or mechanical heart valves), uninterrupted OAT with DOACs is preferred to VKAs for S/SE prevention in patients undergoing CAAF [1–3]. However, and because of their short half-lives (10–14 h), it is critical to educate the patient about the importance of strict adherence to the prescribed regimen.

The selection of OAT before CAAF should be based on the risk of thromboembolic complications, irrespective of the pattern of AF (paroxysmal, persistent, permanent), and individualized after discussion of the efficacy and risks of thromboembolic and bleeding events as compared with antiarrhythmic drug therapy, taking into consideration the patient's values and preferences [1–3].

Recommendations in Current Practical Clinical Guidelines

CPGs recommended that AF patients with stroke risk factors should receive uninterrupted preprocedural OAT with VKAs (INR 2.0–3.0) or DOACs for at least 3 weeks before CAAF and to perform the procedure without OAT interruption [1–3]. However, some authors consider that it is reasonable to hold one to two doses of the DOACs prior to ablation with reinitiation of OAT postablation [55,56,57]. After CAAF, CPGs recommend continuing OAT for S/SE prevention for at least 2 months in all patients regardless of stroke risk factors [1–3]. Beyond this time, the decision to continue or stop OAT should not be based on the apparent success or failure of CAAF or pattern of AF, but on the stroke (CHA_2DS_2-VASc score) and bleeding risks (HAS-BLED score) and comorbidities of the patient [1,2,3,58]. However, the estimated bleeding risk, in the absence of absolute contraindications to OAT, is not recommended to guide the decision to use OAT for stroke prevention (3).

The recommendation of long-term OAT therapy for S/SE prevention is maintained in patients at high risk of stroke (i.e., CHA_2DS_2-VASc score ≥ 2 for men or ≥ 3 for women, prior history of stroke), in whom the reduction in the risk of a disabling stroke may outweigh the risk of bleeding [1–3]. For patients with intermediate stroke risk (CHA_2DS_2-VASc

Table 1 Clinical trials and meta-analysis that analyzed whether it is safe to stop oral anticoagulant therapy after successful catheter ablation of atrial fibrillation

Study	Design	Patients, type of AF, OAT discontinuation	Primary endpoint	Results/conclusions
Di Biase et al. [24]	P, OL, R, PG, M Patients with CHADS2 score ≥ 1	1584 27% with pAF 73% with PAF and LSP 790 discontinued warfarin	S/SE/TIA 48 h after ablation	Performing CAAF without warfarin discontinuation in patients at high risk for stroke significantly reduced the occurrence of periprocedural stroke/TIA and NMBEs. Warfarin discontinuation was a strong predictor of periprocedural TE (OR 13; $P < 0.001$)
Oral et al. [44]	Observational 54% had ≥ 1 risk factor for stroke Mean FU: 25 months	755 490 with pAF, 265 with CAF In 522 patients, warfarin was discontinued 3–6 months post-CAAF: 79% of patients without risk factors, 68% of patients with ≥ 1 risk factor	TEs	Rate of TEs: 0.9% within 30 days and 0.2% beyond 30 days post-CAAF. None of the patients in whom OAT was discontinued had a TE during follow-up. Discontinuation of warfarin 3–6 months after CAAF appears to be safe in patients without baseline risk factors for stroke and in patients with risk factors (other than age > 65 years and history of stroke) with a successful CAAF
Themistoclakis et al. [45]	Observational CHADS2 scores 0 (53%), 1 (29%) and ≥ 2 (18%) Mean FU: 28 months	3355 (60% with pAF, 18% PAF) 2692 discontinued OAT 3–6 months after CAAF (Off-OAT group); 663 remained On-OAT after this period	Ischemic strokes, MBEs	Low rates of ischemic stroke (0.07% and 0.45%) in Off-OAT and On-OAT patients. No Off-OAT patients with a CHADS2 score ≥ 2 had an ischemic stroke. MBEs were observed in 0.04% and 2% of the Off-OAT and On-OAT patients ($P < 0.001$). The risk–benefit ratio favored the suspension of OAT after successful CAAF in patients at moderate-high risk of TE

Table 1 (continued)

Study	Design	Patients, type of AF, OAT discontinuation	Primary endpoint	Results/conclusions
Yagishita et al. [46]	Observational Drug-refractory symptomatic AF CHADS2 score ≥ 2: 16% Mean FU: 44 months	524 362 with PAF, 162 with PAF Warfarin was discontinued in 400 patients without AF recurrence	TEs	None of the patients without AF recurrence suffered TEs, but 3% of patients with AF recurrence did ($P < 0.001$). 2 non-fatal MBEs in patients with AF recurrence on warfarin; no events in patients free from AF. Maintenance of SR after CAAF was associated with a low incidence of TEs
Wikle et al. [47]	Mean $CHADS_2$ score = 3.0 Mean CHA_2DS_2-VASc score = 4.1 Mean FU: 2.2 years	108 with prior stroke/TIA OAT was discontinued in 71 patients in SR 7.3 months following the final CAAF	Stroke/TIA	One patient with a mechanical valve had a stroke despite OAT. Bleeding occurred in 8.3% of patients On-OAT (0% in patients Off-OAT; $P = 0.027$). Patients with prior CVA/TIAs, who undergo successful CAAF, have a low incidence of subsequent TEs
Karasoy et al. [48]	Danish Administrative Registries CHA_2DS_2-VASc scores 1 (31%) and 2 (37%) Median FU: 3.4 years	4050 Half of the population and 70% of high-risk patients remained on OAT beyond the first year post-CAAF	TEs and MBEs	TE risk beyond 3 months after CAAF was relatively low compared with a matched non-ablated cohort but was counterbalanced by serious bleeding risk (HR 2.5)
Nührich et al. [63]	Group 1 (mean $CHADS_2$ score 4.2). Group 2 (mean $CHADS_2$ score 1.6) Mean FU: 489 days	Group 1: 83 patients Group 2: 377 patients OAT was discontinued in 38.6% (group 1) and 66.3% (group 2) of patients	TEs (stroke or TIA)	TE occurred more often in group 1 than in group 2 (4.3 vs. 0.3%, $P < 0.05$) These data argue against OAT discontinuation after CAAF in patients with previous stroke
Noseworthy et al. [49]	Retrospective CHA_2DS_2-VASc scores 0–1: (31.3%), 2 (23.6%), 3 (19.8%), and ≥ 4 (25.4%)	6886 Only 60.5% and 31.3% of patients remained on OAT at 3 and 12 months after CAAF	S/SE	Stroke occurred in 1.4% of patients with CHA_2DS_2-VASc score ≥ 2 and 0.3% of those with CHA_2DS_2-VASc 0 or 1 The risk of S/SE in the first 3 months after CAAF increased among patients with any time Off-OAT (HR 8.06; $P < 0.05$); beyond 3 months, the risk increased among high-risk (HR 2.48), but not low-risk patients

Table 1 (continued)

Study	Design	Patients, type of AF, OAT discontinuation	Primary endpoint	Results/conclusions
Gallo et al. [50]	Mean FU: 60 months	1500 Group A: maintain VKA. Group B: discontinued VKAs. Group C: rate control strategy and VKA therapy	TEs, bleeding events	TEs did not differ among groups, but hemorrhagic events were observed in groups A (1.8%) and C (2.4%), not in group B ($P=0.003$). Among patients with CHA_2DS_2-VASc score ≤ 2, TE did not differ in groups A and B, but hemorrhagic events were more common in groups A and C. All TEs occurred in patients from groups A and B who experienced AF relapses. In patients with high TE risk routine rhythm monitoring is essential after AVK discontinuation
Själander et al. [51]	Swedish retrospective cohort study Mean CHA_2DS_2-VASc score 1.5. Mean FU 2.6 years	1585 360 discontinued warfarin treatment during the first year	Ischemic stroke, ICH, and death	Discontinuation of warfarin increases the risk of ischemic stroke in patients with a CHA_2DS_2-VASc score ≥ 2 ($P=0.046$) or with previous ischemic stroke (HR 4.6; $P=0.046$). Discontinuation of warfarin is not safe in high-risk patients
Liang et al. [53]	Retrospective cohort Mean FU: 3.6 years	200 PAF, 200 LSP 207 selected patients discontinued OAT post-CAAF per physician discretion	Stroke/TIA, MBEs	Patients without AF recurrence, with persistent (vs LSP) AF and with a CHA_2DS_2-VASc score <2 was less likely to continue OAT. There was a low incidence of TEs (0.49/100 patient years) and MBEs (0.98/100 patient years) during the follow-up. OAT discontinuation in well selected, closely monitored patients, was associated with a low rate of stroke/TIA

Table 1 (continued)

Study	Design	Patients, type of AF, OAT discontinuation	Primary endpoint	Results/conclusions
Yang et al. [54]	CHA_2DS_2-VASc score ≥ 2 (mean score 2.3) FU: 24.2 months	4512 3149 discontinued OAT 3 months post-CAAF; 1363 continued on OAT beyond this period	TEs and MBEs beyond 3 months after CAAF	Among patients who discontinued OAT, the long-term incidence of TE and MBE was very low (0.54 and 0.19%/years): No difference in TEs between those who discontinued vs those who continued OAT. It may be safe to discontinue OAT under diligent monitoring and in the absence of AF recurrence, history of S/TIA/SE, and diabetes mellitus
Meta-analysis of clinical trials				
Zhao et al. [33]	19 studies Periprocedural DOACs vs warfarin	7996	MBEs, NMBEs, and TEs	DOACs produced fewer bleeding events than continuous (RR = 0.78; $P = 0.01$) or interrupted warfarin (RR = 0.58; $P = 0.0002$). NOACs did not increase the risk of TEs compared with warfarin treatment. Periprocedural therapy was as effective as continuous warfarin therapy for preventing TE but produced fewer bleedings
Atti et al. [34]	9 observational studies CHA2DS2-VASc ≥ 2 or CHADS2 score ≥ 2	3436 1815 on-OAT 1621 off-OAT	S/SE and MBEs	No significant difference in the risk of S/SE. Continuation of OAT increased the risk of major bleeding (RR: 6.50, $P = 0.0001$). Discontinuation of OAT 3 months after CAAF appears to be safe in highly selected closely monitored patients
Brunetti et al. [35]	Meta-analysis of 4 studies comparing VKAs and DOACs	2118	MBEs, NMBEs, and TEs (stroke or TIA)	Compared with patients receiving VKAs, patients receiving DOACs had fewer MBEs (RR, 0.61; $P = 0.02$) and TEs. No differences in NMBEs. Thus, uninterrupted DOAC strategy appears to be superior to uninterrupted VKA in terms of safety

Table 1 (continued)

Study	Design	Patients, type of AF, OAT discontinuation	Primary endpoint	Results/conclusions
Zhao et al. [36]	6 RCTs Uninterrupted VKAs vs uninterrupted DOACs	1903	MBEs, NMBEs, and TEs	No differences between DOACs and VKAs in the incidence of stroke/TIA, SCEs, TEs or NMBEs, but DOACs produce fewer MBEs (OR = 0.45; $P < 0.01$). Thus, uninterrupted NOACs is as effective but safer than uninterrupted VKAs treatment
Cardoso et al. [37]	12 studies, Uninterrupted periprocedural DOACs vs uninterrupted VKAs	4962	Stroke/TIA, MBEs	No differences in the incidence of stroke, TIA or SCEs. There were fewer MBEs in the NOAC group (0.9%) than in VKA-treated patients (2%; $P < 0.01$). Uninterrupted NOACs are associated with a low incidence of stroke/TIA and significantly fewer MBEs as compared with uninterrupted VKAs
Proietti et al. [38]	16 studies, 10 prospective cohorts and 6 retrospective cohorts Stratified by $CHADS_2$and CHA_2DS_2-VASc scores	25,177 13,166 Off-OAT 12,011 On-OAT	TEs and MBEs	No significant differences in CVEs between On-/Off-OAT even after stratification by CHA_2DS_2VASC score. Off-OAT patients presented significantly less bleeding than those On-OAT (RR 0.17). The risk–benefit ratio favoured the suspension of OAT after successful CAAF even in patients at moderate-high risk
Romero et al. [39]	6 randomized studies Uninterrupted DOACs vs uninterrupted VKAs	2256	MBEs, NMBEs, and TEs	Uninterrupted DOACs produces fewer MBEs compared with uninterrupted VKAs (RR, 0.45; $P = 0.05$). No differences between groups in NMBEs, TEs or SCEs. Thus, uninterrupted DOACs appears to be safer than uninterrupted VKAs

Table 1 (continued)

Study	Design	Patients, type of AF, OAT discontinuation	Primary endpoint	Results/conclusions
Romero et al. [40]	5 studies CHA_2DS_2-VASc scores ≤ 1: (50.1%) and ≥ 2 (49.9%) On-OAT vs Off-OAT	3956	TEs, ICH	On-OAT reduced the risk of TE in patients with CHA_2DS_2-VASc ≥ 2 (RR 0.41, $P = 0.01$). ICH was significantly higher in the ON-OAT (RR 5.78; $P = 0.02$). Continued OAT offers no benefit with $CHA_2DS_2VASC \leq 1$. Continuation of OAT with $CHA_2\ DS_2\ VASc \geq 2$ significantly decreased TEs and produced a favorable net clinical benefit despite an increase in ICH
Ottóffy et al. [41]	42 studies. Uninterrupted and minimally interrupted periprocedural DOAC vs uninterrupted VKA therapy	22,715 patients	Stroke or TIA, MBEs, net clinical benefit	There were no differences in TEs between these strategies, but DOAC therapy was associated with significantly fewer MBEs, which translated into a significant net clinical benefit of DOACs compared to VKAs
Yang et al. [42]	12 RCTs Uninterrupted, minimally interrupted (1 dose skipped) or completely interrupted DOACs vs continuous or interrupted warfarin	5597	TE, MBEs, NMBEs	The three DOAC strategies have similar safety and efficacy in terms of TEs and MBEs. Total bleeding risk of completely interrupted OAT was higher than that of uninterrupted and minimally interrupted DOACs. For TEs, minimally interrupted or uninterrupted NOACs and continuous VKAs were better than interrupted warfarin. Minimally interrupted DOAC therapy without heparin bridging may be the optimal treatment for reducing the risk of TE and bleeding in patients undergoing CAAF

Abbreviations: *AF* atrial fibrillation, *AVK* antivitamin K antagonists, *CAAF* catheter ablation of atrial fibrillation, *CVEs* cardiovascular events, *DOACs* direct oral anticoagulants, *FU* follow-up, *HR* hazard ratio, *IA* interrupted anticoagulation, *ICH* intracranial hemorrhage, *LSP* long-standing PAF, *M* multiceter, *MBEs* major bleeding events, *MRI* magnetic resonance imaging, *NMBEs* non-major bleeding events, *OAT* anticoagulant therapy, *OL* open label, *OR* odds ratio, *P* prospective, *PA* parallel assignment, *pAF* paroxysmal AF, *PAF* persistent atrial fibrillation, *PG* parallel group, *R* randomized, *RR* risk ratio, *SCEs* silent cerebral events, *SR* sinus rhythm, *S/SE* stroke/systemic embolism, *TEs* thromboembolic events, *TIA* transient ischemic attack, *VKA* vitamin K antagonists

score 1 in men or 2 in women), long-term OAT therapy is also recommended. However, because of lack of RCTs to guide OAT therapy, some physicians consider that in selected patients without AF in whom a diligent follow-up of AF recurrences is performed, OAT therapy can be discontinued based on net clinical benefit (risk of S/SE weighed against the risk of bleeding) and taken into consideration patient's values and preferences [59,52]. Finally, in patients at low risk of stroke [CHA_2DS_2-VASc score = 0 (men), or 1 (women)], the risk of S/SE in observational studies is very low (0–0.2%), and the risk of bleeding associated with long-term OAT outweighs the benefits of stroke prevention; thus, discontinuation of OAT should be considered 2 months post-CAAF regardless of AF recurrence [40,60,61,62].

Do We Follow the Clinical Guideline Recommendations?

An important question to answer is whether the recommendations of the CPGs are regularly followed. Despite the recommendation for continued OAT in patients at moderate-high risk of stroke, real-world patterns of OAT therapy in these patients are heterogeneous. In some studies, ≈1 in 4 patients with a CHA_2DS_2-VASc score ≥ 2 had their OAT discontinued sometime after ablation with no safety strategy in place [63,64]]. Thus, discontinuation of OAT after ablation is common and physicians (including some members of the writing committee of CPGs) are not following the recommendations on post-ablation OAT, and the clinical consequences of this conduct remain uncertain. This finding confirms that recommendations are commonly not being followed in clinical practice, reflecting the lack of randomized trial data to guide practice. Thus, there is a critical need to further evaluate the association between discontinuation of OAT post-CAAF and subsequent outcomes.

Do We Have Enough Data to Recommend that It Is Safe to Discontinue OAT After Catheter Ablation of Atrial Fibrillation?

To answer this question, a systematic review in PubMed, EMBASE, SCOPUS, and Google Scholar up to December 31, 2020, was performed to identify studies comparing continuation vs discontinuation of OAT after an apparent successful CAAF using the following heading terms and key words: atrial fibrillation, ablation, catheter ablation, warfarin, vitamin K antagonist, direct oral anticoagulants, apixaban, dabigatran, edoxaban, rivaroxaban, factor Xa inhibitors, direct thrombin inhibitors, stroke, thromboembolism, major and minor bleeding, and combinations of these keywords. Clinical outcomes included cerebrovascular events, systemic thromboembolism, major/minor bleeding, and net clinical benefit.

Several retrospective non-randomized studies [24, 43–53] and meta-analysis [33–42] examined whether it was safe to discontinue OAT after successful CAAF using the CHA_2DS_2-VASc score for risk stratification and S/SE as the primary outcomes (Table 1). Some studies reported a low risk of S/SE (0.8–1.1%) and a lower risk of serious bleedings in patients who discontinue OAT several months after CAAF [43–47, 50, 52, 53]. Conversely, other studies confirmed that OAT discontinuation after CAAF is not safe in high-risk patients [23, 47–49, 51, 53]. However, these studies presented important limitations which are summarized in Table 2, and, therefore, their conclusions should be interpreted carefully and need to be confirmed in properly designed prospective RCTs that assess the efficacy and safety of discontinuing OAT after CAAF. Thus, at the present time, there is no information from prospective RCTs to recommend whether it is safe or not to discontinue OAT after CAAF in patients with intermediate-to-high stroke risk.

Proietti et al. permorfed systematic review of 10 prospective cohort and 6 retrospective cohort studies (25,177 patients) that reported cerebrovascular events (CVE) after CAAF and compared patients on- vs off-OAT [38]. No significant differences in the incidence of CVE emerged between on- and off-OAT patients after CAAF, and this result persisted after stratification by $CHADS_2$ and CHA_2DS_2-VASc score. Off-OAT patients suffered significantly less bleeding than those on-OAT (RR, 0.17; CI, 0.09, 0.34), but they have lower $CHADS_2$ scores than on-OAT, probably reflecting the reluctance of clinicians to discontinue OAT in high thromboembolic risk patients and the influence of current guidelines. However, it should be mentioned that there was a high degree of heterogeneity among the studies, all the studies but two used warfarin as OAT (so, it is uncertain whether these results can be extrapolated also to DOACs), and they did not provide sufficient data to predict the risk of bleeding (e.g., HAS-BLED scores) or assess the impact of AF recurrence on the incidence of CVE in the studied population.

Is It Possible to Stop OAC Therapy Post-Successful Ablation?

In this sea of doubts, it seems reasonable to recommend caution against discontinuation of OAT after an apparently successful CAAF in patients with a CHA_2DS_2-VASc score ≥ 2 []. Of note, many recently diagnosed healthy AF patients develop cardiovascular diseases with a consequent change in thromboembolic risk profile within a short time frame. A close follow-up of these patients is needed to avoid over- and under-treatment with OAT.

Table 2 Main limitations of present evidence

- Most clinical studies were retrospective and/or non-randomized, which can introduce potential performance bias
  - In the absence of a randomized comparison of chronic OAT versus discontinuation of OAT after CAAF definite conclusions are not possible
- There are significant differences among trials design, stroke risk of participants, pattern (paroxysmal vs persistent) of AF, dosing regimens of DOACs, ablation techniques, and follow-up duration
  - The time frame of discontinuation of OAT ranged from 3 to 8 months at the discretion of the physician
  - Episodes of silent AF can be underestimated due to lack of continuous ECG monitoring during follow-up
  - The definition of bleeding was not consistent throughout the studies
  - No pre-ablation magnetic resonance imaging was performed to evaluate the presence of any pre-existing cerebral ischemic lesions
- Only a small subset of patients had a CHA_2DS_2-VASc score ≥ 2, and a reduced number of patients were at extreme increased stroke risk due to a prior stroke or TIA
- The short overall follow-up duration does not allow to evaluate the effect of AF recurrences on thromboembolic events (S/SE) and bleeding complications
- Meta-analysis are biased and underpowered due to the relatively small sample sizes and the low event rates of the studies
- There are no head-to-head comparative studies among DOACs, even when they present important pharmacodynamic/pharmacokinetic differences
- DOACs were studied in a relatively young population of AF patients (mean age 62 years), but there is little information in older patients (> 75 years) or in patients with chronic kidney disease, at higher risk of bleeding complications
- Relevant studies were conducted at high-volume centres with low adverse event rates, but procedural risks for both bleeding and stroke might be higher at low-volume centres with less procedural experience
- The temporal dissociation between AF episodes and stroke suggests that some strokes may not be caused by AF directly, but AF simply represents a marker for other other stroke risk factors and vascular mechanisms with which AF is frequently associated

Abbreviations: *AF* atrial fibrillation, *CAAF* catheter ablation of atrial fibrillation, *DOACs* direct oral anticoagulants, *OAT* oral anticoagulant therapy, *S/SE* stroke/systemic embolism, *TIA* transient ischemic attack

The question is how to determine the cut-off amount of AF to be considered an AF recurrence for which OAT should be continued or reinitiated. A recent retrospective study evaluated the rates of stroke/SE as a function of both CHA_2DS_2-VASc score and AF duration in 21,768 patients with implantable cardiovascular devices who were not anticoagulated [70]. Both the increase in AF duration and CHA_2DS_2-VASc score were significantly associated with an annualized risk of S/SE. Although the S/SE rates were low in patients with a CHA_2DS_2-VASc score of 0 to 1 regardless of device-detected AF duration, the stroke risk crossed an actionable threshold (defined as > 1%/year) in patients with a CHA2DS2-VASc of 2 with > 23.5 h of AF, with a CHA_2DS_2-VASc score of 3–4 with > 6 min of AF, and with a CHA_2DS_2-VASc score ≥ 5 even with no AF. In patients with a daily AF duration between 6 min and 23.5 h, a CHA_2DS_2-VASc score > 3 is required to justify OAT, while an AF burden > 23.5 h would justify OAC at a CHA2DS2-VASc score of 2. Thus, AF duration, as detected on implantable cardiac devices, and CHA_2DS_2-VASc risk score can be used to define the threshold required for the initiation and/or maintenance of OAT in patients with underlying stroke risk factors. Furthermore, this study showed that in patients with elevated CHA_2DS_2-VASc score, some strokes may not be caused by AF directly, but may represent a marker for other stroke risk factors and vascular mechanisms with which AF is frequently associated.

After all these considerations, it is generally accepted that OAT should not be discontinued after CAAF in the following patients:

(1) At very high risk of stroke, such as those with valvular AF (mitral stenosis or valvular disease requiring surgery), hypertrophic cardiomyopathy, cardiac amyloidosis, large LA (> 5 cm) which remains dilated after ablation, thrombus in the LA appendage, or LA spontaneous echocardiographic contrast post-ablation [53,71], even after apparently successful AF ablation, because in these patients recurrences of AF are more frequent than in the general population.

(2) At high risk of stroke (CHA_2DS_2-VASc2 ≥ 2 in men or ≥ 3 in women), specially if they are elderly (> 75 years) or have prior stroke and/or TIA [54,72].

(3) At high risk of AF recurrences after CAAF, because many patients develop asymptomatic episodes of AF, AF recurrences can occur months after CAAF, and there is a lack of clear temporal association between AF recurrence and S/SE [73–75]. Among patients with a CHADS2 score of ≥ 3, 26.9% of the recurrences occurred 2 years post-CAAF and the recurrence rates increased in later years [76]. Thus, we can not be sure that in patients with a CHA_2DS_2-VASc ≥ 2 it is safe to stop OAT. A similar comment is valid for patients with asymptomatic AF episodes post-CAAF because they are exposed to an increased risk of S/SE if OAT is restarted too late. In the ASSERT study, subclinical atrial tachyarrhythmias (defined as episodes of atrial rate $\geq$ 190 bpm) lasting > 6 min, as compared with no episodes, were associated with an increased risk of ischemic stroke or SE (HR 2.49;

1.28–4.85; $P=0.007$) [77]. Similarly, in the TRENDS study, an atrial tachycardia/AF burden of ≥ 5.5 h on any given day during the antecedent 30 days appeared to double the thromboembolic event risk [78].

(4) Who are unable or unwilling to assess their heart rhythm regularly and reliably to screen for asymptomatic AF episodes [79].

Mobile health technologies are rapidly developing, including smart and wearable devices, external loop recorders, wearable patch monitors, and implantable electronic devices, to increase the likelihood of detecting asymptomatic AF, assess ventricular rate control, and correlate patient symptoms with heart rate [80, 81]. In a retrospective cohort study of 1,965 adults with paroxysmal AF (median ATRIA stroke risk score 4, CHA_2DS_2-VASc score 3), a greater cumulative burden of AF (≥ 11%) identified using up to 14-day continuous, noninvasive electrocardiographic monitoring was independently associated with a higher risk of subsequent ischemic stroke or arterial thromboembolism, while patients were not taking OAT, even after adjusting for known stroke risk factors [82]. Thus, AF burden following CAAF rather than just mere AF recurrence is a new parameter which could assist patients and physicians in having a more informed, shared decision-making discussion about stroke prevention strategies. Current limitations preventing the widespread adoption of wearable devices include the limited accuracy and insufficient outcome-based evidence to support clinical decision-making [80].

Conclusions

OAT (with VKAs or DOACs) decreases the risk of S/SE in patients with AF and stroke-risk factors, but long-term OAT can also result in severe bleeding complications. Unfortunately, at the present time there is no information from prospective RCTs to recommend whether it is safe or not to discontinue OAT therapy after successful CAAF in patients with intermediate-to-high stroke risk. Therefore, the decision of whether OAT can be safely discontinued post-CAAF remains controversial, but it can be considered in patients at intermediate clinical risk of S/SE on an individual-case basis considering the risk/benefit ratio and patients' preferences. Thus, there is an unmet need of solid evidence coming from large, long-term, prospective RCTs designed to properly answer this question. Furthermore, the existing differences between the pharmacological characteristics of DOACs and between the different procedures currently used to perform CAAF emphasize the need for more information about the optimal DOAC therapy in different patient populations and for each catheter ablation device. We hope that ongoing trials can shed some light and provide more definitive guidance on which is the best OAT regimen and in which populations it is safe or not to discontinue OAT after successful CAAF.

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Declarations

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