Direct Oral Anticoagulants in the Setting of Catheter Ablation of Atrial Fibrillation: State of art

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Abstract: Atrial fibrillation (AF) represents the arrhythmia of greatest clinical impact and catheter ablation of AF (CAAF) has become the most effective strategy for rhythm control in selected patients. Therefore, appropriate anticoagulation strategies are of paramount importance for patients undergoing CAAF, especially those at high risk, such those with high CHA2DS2VASc scores. Optimal management of anticoagulation before, during, and after CAAF is crucial. Several studies have evaluated the use of different anticoagulation strategies in the periprocedural period. Randomized controlled trial seem to suggest that in patients undergoing CAAF, uninterrupted (or minimally interrupted) direct oral anticoagulants (DOACs) provides an alternative to continuous vitamin K antagonists strategy, with low thromboembolic and bleeding risk. (Curr Probl Cardiol 2021;46:100622.)

Background

Atrial fibrillation (AF) represents the arrhythmia of greatest clinical impact. Its incidence rises steadily with each decade[1-3] becoming a real "epidemic phenomenon" in patients over

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40 years of age with a very high prevalence in elderly patients.[4,5] Catheter ablation of atrial fibrillation (CAAF) has become the main rhythm control strategy for selected AF patients. More than 150,000 AF patients in the United States undergo ablation annually, and, over time, tremendous progress has been made in ablation strategies and technology as well as in periprocedural anticoagulation to increase the success rate and reduce the risk of associated complications, particularly thromboembolism and bleeding. The reported incidence of thromboembolic events associated with CAAF varies from 0.9% to 5% depending on the ablation strategy and the periprocedural anticoagulation regimen.[5] Therefore, appropriate anticoagulation strategies are essential for patients undergoing CAAF, especially those at high risk, such those with high CHA2DS2VASc scores. The aim of this review is to summarize the state-of-the-art regarding this topic, in particular use of direct oral anticoagulants (DOACs).

Anticoagulation in the Setting of CAAF

Several studies have evaluated the use of different anticoagulation regimens in the periprocedural period of CAAF. Oral anticoagulation has evolved dramatically in the last 15 years with the result of a reduction of periprocedural thromboembolic and bleeding complications. These results are mainly due to the use of uninterrupted anticoagulation strategies, initially with warfarin (vitamin K antagonists [VKA]), performing ablation with a periprocedural therapeutic INR and subsequently with DOACs that replaced warfarin in anticoagulation strategies (Fig 1).[6]

The Warfarin Era

In 2007, Venice Arrhythmias Consensus document and HRS expert consensus Statement stated for the first time a periprocedural

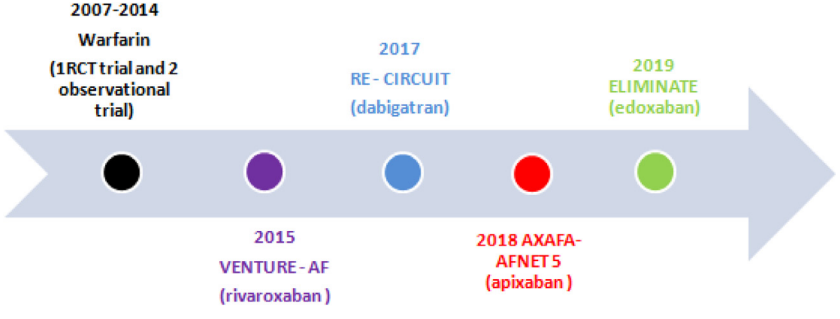

FIG. 1. Chronological route and baseline trials on the use of oral anticoagulant therapy in CAAF.

anticoagulation strategies as "STOP & Interrupted (bridging) Strategy." According to this document, patients with CHADS2 score ≥1 and those with CHADS2 score 0 and persistent AF required oral anticoagulation with warfarin and bridging with intravenous unfractionated heparin (UFH) or subcutaneous low molecular weight heparin before ablation. Warfarin was readministered postablation and UFH or low molecular weight heparin were continued until a therapeutic INR was achieved.[7]

However, CAAF is associated with the potential risk of periprocedural stroke which can range between 1% and 5% during "interrupted (bridging) strategy" and to prevent this dangerous complication Di Biase et al conducted a large, multicenter, nonrandomized study including nearly 6500 patients. This study showed that uninterrupted use of Warfarin with a goal INR of 2, combined with an open irrigation ablation catheter, reduced the risk of periprocedural stroke/transient ischemic attack (TIA) without increasing the risk of haemorrhagic complications.[8] This result was confirmed by a lot of others observational studies underlined how a "continuous warfarin (CW) strategy" during radiofrequency CAAF reduced the risk of thromboembolic complications without increasing the risk of bleeding,[9].

The need for a "standardized protocol" and the role of "ablation modalities" - In 2014 a great randomized study (COMPARE trial) evaluated periprocedural stroke and bleeding complications in patients undergoing CAAF with different anticoagulation management. In this study, 1584 patients were randomized in 2 arms: warfarin discontinuation versus CW. This study stated that "warfarin discontinuation" is at less risk of periprocedural stroke/TIA than "CW" group (0.25% vs 3.7%/1.3%) without increasing the risk of haemorrhagic complications.[10]

However, these results do not consider silent stroke, an undervalued problem that may affect patients undergoing CAAF. According to Anselmino et al this complication varies from 5.6% to 37.5% and it's more frequent during "phased Radiorequency (RF) ablation" rather than "cryoballoon" or "irrigated RF" ablation.[11] Di Biase et al showed that this problem "on warfarin patients" was related to a protocol deviation in terms of maintaining the therapeutic preprocedural international normalized ratio (patients with subtherapeutic INR) and/or failure to receive heparin bolus pretransseptal puncture and/or more than 2 consecutive ACT measurements <300 seconds, demonstrating how a strict adherence to an anticoagulation protocol significantly reduces the prevalence of silent cerebral ischemia after CAAF with RF energy.[12]

According to these findings, the 2012 HRS/EHRA/ECAS consensus on CAAF recommended to perform CAAF "on warfarin" administering

heparin prior to or immediately after transseptal puncture, adjusted to achieve and maintain an activated clotting time (ACT) up to 300 seconds.[13]

The DOAC's Era

The use of DOAC in patients undergoing CAAF has rapidly evolved during the last years, demonstrating efficiency and safety, compared with the traditional VKA.[14] A lot of studies grew up about oral anticoagulation management during CAAF. In particular, 4 RCTs with a similar study design, have highlighted the feasibility as well as efficacy and safety of DOACs in the setting of CAAF (Figs 2 and 3).

The VENTURE-AF study enrolled 248 patients with paroxysmal or persistent nonvalvular atrial fibrillation (mean age 59.6 ± 10.2 years; mean CHA2DS2-VASc score 1.6 ± 1.3) scheduled for pulmonary vein isolation (PVI) and randomised 1:1 to rivaroxaban 20 mg OD (last dose the evening before ablation) or VKA (uninterrupted with INR 2-3). The primary endpoint was major bleeding events after CAAF. Secondary endpoints included thromboembolic events (composite of stroke, systemic

Trial	DOAC	Patients
VENTURE - AF	rivaroxaban	248
RE - CIRCUIT	dabigatran	635
AXAFA - AFNET 5	apixaban	674
ELIMINATE - AF	edoxaban	553

FIG. 2. Main RCTs of DOACs in CAAF and related populations.

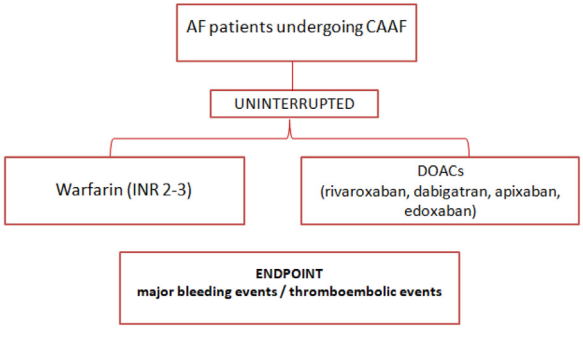

FIG. 3. Common scheme of the main RCTs related to the use of DOACs vs warfarin in patients undergoing CAAF.

embolism, myocardial infarction, and vascular death) and other bleeding or procedure-attributable events. The incidence of major bleeding was low (0.4%; 1 major bleeding event). Similarly, thromboembolic events were low (0.8%; 1 ischemic stroke and 1 vascular death). All events occurred in the VKA arm and all after CAAF. The number of any adjudicated events (26 vs 25), any bleeding events (21 vs 18), and any other procedure-attributable events (5 vs 5) were similar. After 30 ± 5 days of follow-up investigators showed how the use of uninterrupted oral rivaroxaban was feasible and event rates were similar to uninterrupted VKA therapy.[15] This trial was a really "Pilot Study" and results were consistent with "real life data," even if it evaluated a small population (underpowered study) without data regarding imaging evaluations.

The RE-CIRCUIT study considered 678 patients with paroxysmal (68%) or persistent nonvalvular atrial fibrillation (mean age 59 years; mean CHA2DS2-VASc score 2) scheduled for first PVI and randomized 1:1 to dabigatran 150 mg BID (uninterrupted before ablation) or VKA (uninterrupted with INR 2-3). Baseline characteristics were balanced between treatment groups. The incidence of major bleeding events during and up to 8 weeks after ablation was lower with dabigatran than with warfarin (5 patients [1.6%] vs 22 patients [6.9%]; absolute risk difference, −5.3 percentage points; 95% confidence interval, −8.4 to −2.2; $P < 0.001$). The 2 treatment groups had a similar incidence of minor bleeding events. A single thromboembolic event occurred in the warfarin group. According to this study, performing CAAF on uninterrupted dabigatran is a better anticoagulation strategy if compared with uninterrupted warfarin. Like VENTURE-AF, RE-CIRCUIT could be considered a positive study even if statistically underpowered and without imaging data.[16] In an interesting systematic review and meta-analysis, Providência et al described that patients treated with dabigatran had a similar incidence of thromboembolic events and major bleeding compared to warfarin, with low event rates overall. This study, even if not a RCT, represented a favourable support for use of dabigatran as an alternative to warfarin in the setting of CAAF.[17]

In 2018 the AXAFA-AFNET 5 study, an open, blinded endpoint, noninferiority study enrolled 674 patients with AF scheduled for PVI (mean CHA2DS2-VASc score was 2.4, median age 64 years). These patients were randomized 1:1 to apixaban 5 mg BID or 2,5 mg BID, when dose reduction was indicated, (uninterrupted before ablation) or VKA (uninterrupted with INR 2-3). Primary outcome was a composite of death, stroke, or bleeding (Bleeding Academic Research Consortium 2−5). A high-resolution brain magnetic resonance imaging (MRI) sub-study quantified

acute brain lesions in 335 patients. Cognitive function was assessed by Montreal Cognitive Assessment (MoCA) at baseline and at the end of follow-up. The primary outcome was observed in 22/318 patients randomized to apixaban, and in 23/315 randomized to VKA {difference −0.38% [90% confidence interval (CI) −4.0%, 3.3%], non-inferiority; p = 0.0002 at the pre-specified absolute margin of 0.075}, including 2 (0.3%) deaths, 2 (0.3%) strokes, and 24 (3.8%) major bleeding. Acute small brain lesions were found in a similar number of patients in each arm [apixaban 44/162 (27.2%); VKA 40/161 (24.8%); $P = 0.64$]. Cognitive function increased at the end of follow-up (median 1 MoCA unit; p=0.005) without differences between study groups. This underpowered study with imaging data had the advantage to put together all the information learned over time and previously reported, in addition AXAFA-AFNET 5 was the first study to compare cognitive function after CAAF in a controlled trial; however, the assessment was limited to global cognitive function.[18]

In 2019 the ELIMINATE-AF trial, a multicentre, randomized, open-label, parallel-group study, was conducted to assess the safety and efficacy of once-daily edoxaban 60 mg (30 mg as in label) versus VKAs in AF patients undergoing catheter ablation. The primary endpoint (per-protocol population) was time to first occurrence of all-cause death, stroke, or International Society of Thrombosis and Haemostasis – defined major bleeding during the period from the end of the ablation procedure to end of treatment (90 days). 177 subjects underwent brain magnetic resonance imaging to assess silent cerebral infarcts. The primary endpoint (only major bleeding occurred) was observed in 0.3% (1 patient) on edoxaban and 2.0% (2 patients) on VKA (hazard ratio [95% CI]: 0.16 (0.02-1.73)]. Uninterrupted edoxaban represented an alternative to uninterrupted VKA treatment in patients undergoing CAAF.[19] After these RCTs, in the latest European and American guidelines, uninterrupted dabigatran and rivaroxaban are a class I recommendation for patients undergoing CAAF while apixaban and edoxaban are a Class IIa.[20,21]

A practical guide for patients on DOACs undergoing CAAF has been published by Steffel et al[1] and we propose a brief summary considering evidence of the recent literature (see Table 1 below).

Discussion – Unsolved Issues

DOAC's looks like an attractive alternative to VKA because they offer important advantages beyond their easiness of administration, like less interactions and no need of laboratory monitoring.[17]

TABLE 1. "Brief summary for patients on DOAC undergoing CAAF"

Brief summary for patients on DOACs
Uninterrupted DOAC (last dose shortly before ablation) or minimally interrupted (last dose on the day before the procedure) dosing depends on many factors including renal function, CHA2DS2-VASc score, experience of the operator, and routine practice of heparin administration prior to transseptal puncture.
Reasonable to administer a last doe of DOAC 12 hours before the start of the intervention, especially if transseptal puncture is performed without periprocedural imaging
LAA thrombus should be ruled out prior to ablation, especially when adherence is uncertain over prior weeks or if the last DOAC dose is taken $\geq$36 hours before the intervention, or in patients at high risk of TE
During the ablation, IV heparin should be administered to achieve an ACT of 300-350 sec
It seems reasonable to use the same target ACT levels for heparin titration in DOAC-treated patients as in patients on (uninterrupted) VKA
DOAC intake can be resumed 3-5 hours after sheath removal if adequate hemostasis is established and pericardial effusion has been ruled out

Should We Sometimes Shortly Interrupt DOAC's ?

In the last years, some studies also compared continuous-VKA strategy versus interrupted DOAC's strategy. In 2016 a paper of Rillig et al, showed how major complications (groin hematomas requiring transfusion or surgical intervention as well as pericardial effusions requiring drainage) and all clinical thromboembolism (TE) events (such as stroke, TIA, or arterial embolism) using interrupted apixaban, dabigatran, rivaroxaban and C-VKA during CAAF seem to be comparable. Furthermore,complication rates were similar in all patients treated with DOACs.[22]

In 2018, De Heide et al compared a "minimally interrupted" DOAC's strategy versus "uninterrupted VKA strategy." In patients using VKA the target INR level at the day of the procedure was 2.0-2.5, while in patients using DOAC's, anticoagulation was withheld for 24 hours before the procedure (1 or 2 doses withheld). A preprocedural transesophageal echocardiogram was routinely performed on the same day or 1 day prior to ablation. The results show very interesting data considering that in this study anticoagulation with minimally interrupted DOAC was associated with fewer clinically relevant nonmajor bleeding events in comparison with uninterrupted VKA without compromising thromboembolic safety.[23]

According to these studies both "uninterrupted" and "interrupted" DOACs strategy seems to be feasible and safe in the setting of CAAF, but which is better? Nakamura et al try to give us an answer about this issue. In their study published in 2018, patients enrolled were randomly

assigned to noninterruption of DOACs throughout the periprocedural period (uninterrupted DOAC group), or interruption on the day of the procedure and reinitiation of DOACs the morning after the procedure (interrupted DOAC group). In the interrupted DOAC group, the last dose before interruption of the twice-daily DOACs (dabigatran and apixaban) was given in the evening on the day before the procedure while in case of the once-daily DOACs (rivaroxaban and edoxaban) the interruption took place the morning of the day before the procedure. Thirty days after the ablation both groups showed not only a low risk of symptomatic thromboembolisms and major bleeding events, but also similar incidence of silent cerebral ischemic lesions and minor bleeding events.[24]

On another hand, interrupted DOAC's strategy seems to be better in patients with high bleeding risk, such as elderly patients (age $\geq$75 year), as results from the randomized study published by Yanagisawa et al.[25]

Overall, according to these findings, there are no significant differences between uninterrupted/interrupted DOACs and uninterrupted VKA in the setting of CAAF and considering drug interactions, the absence of need for INR monitoring and a trend for fewer major bleeding events favouring DOACs in terms of safety, DOACs should be considered as first line therapy in patients undergoing CAAF.[26] This choice is also supported by a similar incidence of adverse events with the periprocedural administration of DOACs compared to VKA treatment.[27] Regarding the problem of which DOAC to choose, since there is no head-to-head comparison trial between the various drugs, a comparison between the various molecules cannot be made.[26]

Periprocedural Anticoagulation in DOAC's Era

Briceno et al[28] showed that appropriate ACT during CAAF is essential to minimize periprocedural complications. In particular this study analysed the major databases and identified 19 studies in which 7150 patients were enrolled. Heparin dose (U/kg) and time (minutes) to achieve the target ACT was compared among patients receiving VKA versus DOACs. Patients with ACT >300 had less TE (odds ratio 0.51; 95% CI 0.35-0.74) and bleeding (odds ratio 0.70; 95% CI 0.60-0.83) compared to ACT <300, when using any type of oral anticoagulation. The use of VKA was associated with reduced heparin requirements (mean dose: 157 U/kg vs 209 U/kg, $P < 0.03$; SDM −0.86 [95% CI −1.39 to −0.33]), and with lower time to achieve the target ACT (mean time: 24 minutes vs 49 minutes, $P < 0.03$; SDM −11.02 [95% CI −13.29 to −8.75]) compared to DOACs. Based on these data, according to "2017 HRS/EHRA/ECAS/

APHRS/SOLAECE consensus statement on catheter and surgical ablation of atrial fibrillation," during the ablation, regardless of the type of strategy, it is recommended to do heparin bolus to achieve ACT >300 seconds, dose of bolus and time to goal ACT may be variable.[29]

In fact, like prothrombin time and activated partial thromboplastin time, the ACT is not sensitive to DOACs and thus poorly reflects their concentration when the procedure begins. A concentration-dependent increase in the ACT follows a nonlinear flattened curve, with differences in ACT sensitivity according to the various DOAC. Hence, high DOACs concentrations, in particular anti-Xa, may be associated with a normal ACT, and ACT can be different between DOACs despite comparable therapeutic level.[30] Finally, it has been shown that the impact of UFH on the ACT may significantly vary according to the type of uninterrupted DOAC. This data cannot be fully explained by differences in baseline ACT or ACT insensitivity. Molecular interactions have been hypothesized: dabigatran-induced down-regulation of antithrombin expression, thus altering antithrombin-dependent UFH activity; competition between dabigatran or anti-Xa and UFH/antithrombin complex for binding to thrombin or factor Xa, respectively; and finally a compensatory upregulation of expression of prothrombin, which may diminish the effect of UFH. Overall, the foregoing data strongly suggest that we may be administering too much UFH during AF catheter ablation by pursuing a theoretical target (ACT) that has, in fact, limited value in the presence of DOACs.[31] However, in the meantime, ACT monitoring during CAAF in patients with DOACs should probably not be abandoned yet. Although not optimal, this strategy has been used by all published trials, with no reports of unfavorable clinical outcomes in terms of bleeding or thrombosis.[30]

Conclusion

Appropriate anticoagulation strategies are of paramount importance for patients undergoing an AF ablation procedure, especially those at high risk. Optimal management of anticoagulation before, during, and after CAAF is crucial. In this setting, randomized control trials and current European and American Guidelines suggest that uninterrupted (or minimally interrupted) DOACs provide a solid alternative to continuous-VKA strategy, with a low thromboembolic and bleeding risk.

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