Periprocedural Anticoagulation Interruption Strategies for Ablation of Atrial Fibrillation: What Is the Best Current Practice?

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Proper periprocedural anticoagulation is essential to reduce the risk of thromboembolic events and bleeding complications in patients undergoing catheter ablation for the treatment of atrial fibrillation (AF).

The results of the COMPARE trial (Role of Coumadin in Preventing Thromboembolism in AF Patients Undergoing Catheter Ablation) [1] showed that performing catheter ablation of AF with uninterrupted vitamin K antagonist (VKA) reduces the occurrence of periprocedural stroke and minor bleeding complications compared with VKA discontinuation and bridging with low-molecular-weight heparin. These findings have led to the recommendation of performing AF ablation without interruption of warfarin [2]. In comparison to warfarin, the non-VKA oral anticoagulants (NOACs) have an improved efficacy-to-safety ratio, a predictable anticoagulant effect without need for routine coagulation monitoring, and fewer food and drug interactions. This has led to increased utilization of NOACs among patients with AF, including in the post-ablation period. The elimination half-time of NOACs is much shorter than that of warfarin, practically eliminating the need for bridging with heparin/low-molecular-weight heparin before procedures. Full interruption of NOAC therapy peri-procedural is associated with an increased risk of thromboembolic events and thus it is not a recommended regimen [3].

There are several studies that compared uninterrupted warfarin to uninterrupted NOACs in patients undergoing AF ablation. It should be noted that these studies were underpowered for assessment of superiority. The RE-CIRCUIT trial (randomized evaluation of dabigatran etexilate compared to warfarin in pulmonary vein ablation: assessment of an uninterrupted periprocedural anticoagulation strategy) [4] investigated the clinical outcome of uninterrupted dabigatran (150 mg twice daily) compared with uninterrupted warfarin in 704 patients undergoing AF ablation. In the dabigatran group, 41% of the patients received the final dose of dabigatran <4 h before the transseptal puncture, 37% received it between 4 and 8 h, and 20% received it ≥8 h before the puncture. At 8 weeks after ablation, patients in the dabigatran group had a significantly lower incidence of major bleeding events than in the warfarin group (1.6 vs. 6.9%; $p < 0.001$). There were no thromboembolic events in either arm. The VENTURE-AF trial (active-controlled multi-center study with blind-adjudication designed to evaluate the safety of uninterrupted rivaroxaban and uninterrupted vitamin K antagonists in subjects undergoing catheter ablation for non-valvular atrial fibrillation) [5] randomized 248 patients to uninterrupted rivaroxaban (20 mg once daily), preferentially with the evening meal the day before ablation or uninterrupted warfarin. There were no sig-

nificant differences in the risk of embolism or major bleeding events between the two groups. In the AXAFA–AFNET 5 trial (anticoagulation using the direct factor Xa inhibitor apixaban during atrial fibrillation catheter ablation: comparison to VKA therapy) [6], 674 patients were randomized to either apixaban or warfarin. In this study, the primary outcome was the composite of stroke, major bleeding, and death. It showed that uninterrupted apixaban is non-inferior to uninterrupted warfarin at 90 days of follow-up. In the ELIMINATE-AF trial (a prospective, randomized, open-label, blinded endpoint evaluation parallel group study comparing edoxaban versus VKA in subjects undergoing catheter ablation of non-valvular atrial fibrillation) [7]. A total of 614 patients randomized to uninterrupted once-daily evening dose of edoxaban and uninterrupted warfarin. The results of this trial were comparable between the two groups.

Current consensus documents for periprocedural anticoagulation management of patients treated with NOAC suggest two possible regimens for patients undergoing AF ablation [2, 8]. The first is a truly uninterrupted regimen (administer the last NOAC dose shortly before the procedure), and the second is a minimally interrupted regimen (last NOAC dose on the day before the procedure or to hold one or two doses before ablation). In this regard, current consensus documents do not differentiate between NOACs given twice daily and those given once daily.

There is lack of evidence to recommend minimally interrupted NOAC or truly uninterrupted NOAC for patients undergoing AF ablation. In the AEIUO trial (apixaban evaluation of interrupted or uninterrupted anticoagulation for ablation of atrial fibrillation) [9], 300 patients undergoing catheter ablation for AF were randomized to a fully uninterrupted versus minimally interrupted apixaban (holding 1 dose). In the AEIUO study, there were no thromboembolic events in both arms, and there were no significant differences in bleeding rates (risk difference: 1.7% [95% confidence interval: –5.5 to 8.8%], $p = ns$). Due to the low incidence of both thromboembolic and major bleeding events after ablation, most studies aiming to evaluate different periprocedural anticoagulation strategies may be underpowered to detect differences in clinical events unless enrolling thousands of patients.

In this issue of *Cardiology*, Bejinariu et al.[10] report the results of a survey on periprocedural oral anticoagulation strategies for AF ablation in 35 EP centers in Germany including more than 10,000 procedures performed between September 2018 and September 2019. The inves-

tigators found that in patients taking VKA, all centers used the uninterrupted VKA approach. In patients taking NOACs, most centers (54%) used a minimally interrupted NOAC approach, 37% an interrupted approach, and only 9% used a truly uninterrupted approach. After 12 months, 3 centers (9%) changed from the minimally interrupted to the truly uninterrupted approach. Most centers (86%) performed transseptal puncture by fluoroscopy and without additional imaging.

Notably, in the current study the truly uninterrupted strategy was defined if the patient received the standard NOAC dose before or after AF ablation on the procedure day for once-daily NOACs, or if the patient received the standard NOAC dose before and after AF ablation on the procedure day for twice-daily NOACs. The minimally interrupted strategy was defined if the NOAC dose was reduced or skipped on the procedure day for once-daily NOACs, or if the NOAC was only skipped before the procedure on the day of ablation for twice-daily NOACs.

The truly uninterrupted NOAC approach was adopted more often in patients treated with once-daily NOACs (43% for rivaroxaban, and 40% for edoxaban) than for patients treated with twice-daily NOACs (9% for both apixaban and dabigatran). The authors show that for most patients taking once-daily NOACs, the drug was given in the morning of the day before the procedure and in the evening of the procedure day. This may suggest that many centers make changes in timing of once-daily NOAC administration and still apply to the definition of truly uninterrupted approach.

There are several factors to consider before adopting a truly uninterrupted regimen. Among those factors are patient-related risks for bleeding and thromboembolic events, risks related to the specific agent used, such as renal excretion and availability of an antidote, once-daily versus twice-daily use, and risks related to the procedure including operator experience, volume of procedures performed per center, ruling out thrombus before the procedure, and additional imaging to guide trans-septal puncture. The current study did not address all of these complex issues and reported the results as per-institution decision.

In summary, this important survey presents the current practice of periprocedural NOAC management for patients undergoing AF ablation in certified EP centers in Germany, demonstrating that most centers employ the minimally interrupted NOAC approach. Further research is needed to compare the clinical outcome of truly uninterrupted and minimally interrupted approaches and investigate the possible effects of different periproce-

dural NOAC interruption definitions on clinical outcome among patients receiving once-daily or twice-daily NOAC doses.

Disclosure Statement

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References

- 1 Di Biase L, Burkhardt JD, Santangeli P, Mohanty P, Sanchez JE, Horton R, et al. Periprocedural stroke and bleeding complications in patients undergoing catheter ablation of atrial fibrillation with different anticoagulation management: results from the Role of Coumadin in Preventing Thromboembolism in Atrial Fibrillation (AF) Patients Undergoing Catheter Ablation (COMPARE) randomized trial. *Circulation*. 2014 Jun;129(25):2638–44.
- 2 Calkins H, Hindricks G, Cappato R, Kim YH, Saad EB, Aguinaga L, et al.; Document Reviewers. 2017 HRS/EHRA/ECAS/APHRS/SOLAECE expert consensus statement on catheter and surgical ablation of atrial fibrillation. *Europace*. 2018 Jan;20(1):e1–160.
- 3 Winkle RA, Mead RH, Engel G, Kong MH, Patrawala RA. Peri-procedural interrupted oral anticoagulation for atrial fibrillation ablation: comparison of aspirin, warfarin, dabigatran, and rivaroxaban. *Europace*. 2014 Oct;16(10):1443–9.
- 4 Calkins H, Gerstenfeld EP, Schilling R, Verma A, Willems S; RE-CIRCUIT Study Steering Committee. RE-CIRCUIT study-randomized evaluation of Dabigatran etexilate compared to warfarin in pulmonary vein ablation: assessment of an uninterrupted periprocedural anticoagulation strategy. *Am J Cardiol*. 2015 Jan;115(1):154–5.
- 5 Cappato R, Marchlinski FE, Hohnloser SH, Naccarelli GV, Xiang J, Wilber DJ, et al.; VENTURE-AF Investigators. Uninterrupted rivaroxaban vs. uninterrupted vitamin K antagonists for catheter ablation in non-valvular atrial fibrillation. *Eur Heart J*. 2015 Jul;36(28):1805–11.
- 6 Kirchhof P, Haessler KG, Blank B, De Bono J, Callans D, Elvan A, et al. Apixaban in patients at risk of stroke undergoing atrial fibrillation ablation. *Eur Heart J*. 2018 Aug;39(32):2942–55.
- 7 Hohnloser SH, Camm J, Cappato R, Diener HC, Heidbüchel H, Mont L, et al. Uninterrupted edoxaban vs. vitamin K antagonists for ablation of atrial fibrillation: the ELIMINATE-AF trial. *Eur Heart J*. 2019 Sep;40(36):3013–21.
- 8 Steffel J, Verhamme P, Potpara TS, Albaladejo P, Antz M, Desteghe L, et al.; ESC Scientific Document Group. The 2018 European Heart Rhythm Association Practical Guide on the use of non-vitamin K antagonist oral anticoagulants in patients with atrial fibrillation. *Eur Heart J*. 2018 Apr;39(16):1330–93.
- 9 Reynolds MR, Allison JS, Natale A, Weisberg IL, Ellenbogen KA, Richards M, et al. A Prospective Randomized Trial of Apixaban Dosing During Atrial Fibrillation Ablation: the AEIOU Trial. *JACC Clin Electrophysiol*. 2018 May;4(5):580–8.
- 10 Bejinariu AG, Makimoto S, Wakili R, Mathew S, Kosiuk J, Linz D, et al. One-year course of periprocedural anticoagulation in atrial fibrillation ablation: results of a German nationwide survey. *Cardiology*. DOI: 10.1159/000509399.