

Anticoagulation during the atrial fibrillation ablation periprocedural period – an update

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Abstract

Atrial fibrillation (AF) is the most common arrhythmia diagnosed in clinical practice and is often treated with pulmonary vein isolation (PVI). This procedure has both high bleeding and thromboembolic risk; therefore well evidenced anticoagulation protocols are important. The anticoagulation strategy in patients undergoing PVI is described in the Expert Consensus. We analyzed studies released after 2018 pertaining to anticoagulation during PVI. Different anticoagulation approaches for AF ablation were studied. New evidence on edoxaban and apixaban for PVI emerged. Direct oral anticoagulants (DOACs) seemed to be safer in terms of bleeding risk and equally effective in stroke prevention compared to vitamin K antagonists (VKAs) according to one metanalysis. Uninterrupted and interrupted anticoagulation strategies with novel oral anticoagulants (NOACs) were studied and brought conflicting results. The “dabigatran bridge” strategy

for PVI was tested. New knowledge on the occurrence and clinical significance of silent brain ischemic lesions after PVI is described. An alternative heparin dosing strategy during PVI in patients on NOACs was proposed.

Introduction

Catheter ablation for atrial fibrillation (AF) is widely used as an alternative treatment to the administration of antiarrhythmic drugs. The state of knowledge pertaining to anticoagulation strategies in patients undergoing atrial fibrillation ablation was characterized in two documents: the 2017 HRS/EHRA/ECAS/APHRS/SOLAECE expert consensus statement on catheter and surgical ablation of atrial fibrillation^[1] and the 2018 European Heart Rhythm Association Practical Guide on the use of non-vitamin K antagonist oral anticoagulants in patients with atrial fibrillation^[2]. Since the release of these documents, there has been a constant shift from vitamin K

antagonist (VKAs) to direct oral anticoagulants (DOACs) both as long-term anticoagulation and ablation periprocedural anticoagulation for ischemic stroke prevention. Uninterrupted anticoagulation with oral anticoagulants through pulmonary vein isolation (PVI) is commonly used in clinical practice in accordance with recommendations from the aforementioned documents that assigned a class I recommendation for uninterrupted warfarin, dabigatran and rivaroxaban periprocedural usage. Nevertheless, the use of different anticoagulation protocols is still being researched and various interruptive and non-interruptive anticoagulation approaches for PVI are being tested.

This literature review will focus on new available research concerning different anticoagulation management strategies of patients undergoing catheter ablation for atrial fibrillation that were published after the release of the mentioned documents.

The PubMed database from January 2018 to December 2019 was searched for studies pertaining to anticoagulation in the PVI periprocedural period. The keywords "periprocedural", "catheter ablation", "atrial fibrillation", and "anticoagulation" were used. Ten studies were selected. The papers can be divided into 5 distinct topics, according to which they will be discussed in the article: (1) the uninterrupted use of apixaban and edoxaban during AF ablation – results from ELIMINATE-AF and AXAFA – AFNET 5 trials; (2) safety and efficacy of uninterrupted and minimally interrupted use of oral anticoagulants during ablation of atrial fibrillation; (3) the "dabigatran bridge" approach during AF ablation; (4) NOACs vs VKAs in AF ablation – meta-analysis; (5) effective heparin dosing during AF ablation in patients on NOACs.

Long awaited results of ELIMINATE-AF and AXAFA – AFNET 5 trials – new evidence for edoxaban and apixaban in AF ablation

The RE-CIRCUIT^[3] and VENTURE-AF^[4] trials compared uninterrupted periprocedural anticoagulation with dabigatran and rivaroxaban to warfarin and were discussed and considered in the available Consensus.

ELIMINATE-AF^[5] was a multinational, multicenter, randomized study that investigated the safety and efficacy of once-daily edoxaban vs. vitamin K antagonists (VKAs) in AF patients undergoing catheter ablation. During the study period, including on the day before the procedure, patients randomized to once-daily edoxaban took their scheduled dose in the evening. For patients treated with VKAs, the international normalized ratio (INR) within the range 2.0-3.0 at the last measurement before the ablation procedure was required. Patients were randomized 2:1 to either edoxaban or VKA. The primary endpoint was a composite of death, stroke, and major bleeding, that occurred in 0.3% of patients in the edoxaban arm versus 2.0% in the warfarin arm (hazard ratio 0.16; 0.02–1.73; $p =$ non-significant). There was no statistically significant difference in the incidence of major bleeding between edoxaban and VKA arms. In both groups the magnetic resonance imaging (MRI) sub-study revealed similar rates of

acute cerebral microemboli (13.8% for edoxaban vs. 9.6% for warfarin $p=NS$) after catheter ablation.

The trial provided evidence supporting the safety and efficacy of uninterrupted anticoagulation with edoxaban for catheter ablation of AF.

A similar study on apixaban, AXAFA – AFNET 5^[6], was reported. Patients were randomized in a ratio of 1:1 to apixaban or VKA therapy. Apixaban was continued during the ablation procedure without interruption, including the morning dose before the ablation. The last INR prior to ablation needed to be 1.8 or higher. Also a high-resolution MRI sub-study for detection of silent brain ischemic lesions (silent stroke) was performed. Cognitive decline after the atrial fibrillation ablation was previously suggested in the literature^[7]. An interesting novelty of this trial was a cognitive function assessment at baseline and after the procedure in order to test for cognitive decline 90 days after the procedure. Apixaban was non-inferior to VKA based on the non-inferiority margin of 7.5% (a difference of -0.38%, 90% CI (-4.0%)–3.3%, non-inferiority $P = 0.0002$). Acute small brain lesions were found in a similar number of patients in each arm (27.2% – apixaban, 24.8% – VKA; $P = 0.64$). Quality of life and cognitive function improved equally in both study groups after ablation. Interestingly, cognitive function at the end of follow-up was not different in patients with or without acute brain lesions in MRI after ablation.

The final conclusions of these two studies were that both continuous edoxaban and apixaban therapy are safe and effective alternatives to VKA in patients undergoing atrial fibrillation ablation with respect to stroke, major bleeding and MRI-detected acute brain ischemic lesions. AXAFA – AFNET 5 also presented reassuring data regarding cognitive function after ablation which was not negatively affected by the PVI under either VKA or apixaban anticoagulation. It is noteworthy that cognitive dysfunction was not more prevalent in patients in whom acute brain ischemic lesions in MRI after AF ablation were diagnosed in comparison to those where these lesions did not occur- this observation adds new knowledge about in this the matter and clinical significance of "silent stroke" detected in MRI after the procedure

Safety and efficacy of interrupted vs uninterrupted direct oral anticoagulant protocols during catheter ablation AF

The objective of the recently published large single-center, randomized prospective study performed by Nakamura, K., et al.^[8] was to compare the incidence of embolisms and bleeding events between uninterrupted and interrupted anticoagulation protocols using DOACs during PVI. The total of 846 patients with atrial fibrillation receiving DOACs were randomized prior to ablation to uninterrupted ($n = 422$) or interruption (DOACs interrupted by one dose) ($n = 424$) of the DOACs on the day of the procedure. Neurological assessments of patients were performed before and after the procedure. Furthermore, post-ablation magnetic resonance (MR) imaging one day after the procedure was performed in order to identify silent brain ischemic lesions followed by another magnetic resonance examination one month thereafter in cases where ischemic

lesions after ablation were identified. The primary endpoint was a composite of symptomatic thromboembolisms and major bleeding events within 30 days after ablation and occurred in 0.7% of the uninterrupted DOAC group 1.2% of the interrupted DOAC group ($P=0.480$). Within secondary endpoints, major bleeding (0.5% vs. 0.9%, $P=0.345$) and minor bleeding (5.9% vs. 5.4%, $P=0.753$) were comparable between the groups. Silent cerebral ischemic lesions were observed in 138 (20.9%) of the 661 patients who underwent post-ablation magnetic resonance (MR) imaging. The uninterrupted and interrupted DOAC groups showed a similar incidence of silent stroke (19.8% vs. 22.0%, $P=0.484$). There was also a similar disappearance rate of silent brain ischemic lesions on follow-up MR imaging (77.8% for uninterrupted; 82.1% for interrupted, $P=0.428$) in both strategies, resulting in 22.2% (uninterrupted) and 18.4% (interrupted) of the lesions developing into chronic infarcts. The authors concluded that both the uninterrupted and interrupted DOAC strategies revealed a similarly low risk of symptomatic thromboembolisms and major and minor bleeding events and also similar incidence of silent brain ischemia and may both be feasible for periprocedural anticoagulation in AF patients undergoing PVI.

The single-center, randomized study^[9] performed by Nagao, T., et al. investigated the uninterrupted and minimally interrupted (one dose omitted) rivaroxaban, apixaban, and edoxaban but not dabigatran in the AF ablation periprocedural period in terms of the risk of occurrence of silent stroke (silent brain ischemic lesions) and trends in coagulation markers. The researchers randomly and evenly assigned 200 consecutive patients receiving DOACs into an uninterrupted group and a minimally interrupted group. Post-operative magnetic resonance imaging revealed significantly higher prevalence of silent stroke in the interrupted (17%) vs uninterrupted (4%) group ($p<0.005$) even though there were no differences in occurrence of symptomatic thromboembolic events or the rate of bleeding complications between the two groups. Analysis of coagulation markers revealed a significant increase in prothrombin fragment 1 + 2 (PF1 + 2) values in the interrupted compared with the uninterrupted group on the operative and first postoperative days. Intraoperative cardioversion and prolonged procedure time independently predicted the occurrence of silent brain ischemic lesions in the interrupted anticoagulation approach. The researchers concluded that uninterrupted anticoagulation through the AF ablation approach might decrease the risk of occurrence of silent brain ischemic lesions and decrease hypercoagulability periprocedurally while not increasing the risk of bleeding complications.

Further evidence regarding different anticoagulation strategies and their relation to the asymptomatic cerebral infarction (silent brain ischemic lesions in magnetic resonance imaging) rate comes from the ASCERTAIN trial^[10] conducted by Kimura, T et al. This was a randomized, two-center, assessor-blind study that compared uninterrupted rivaroxaban vs uninterrupted warfarin strategies using an enhanced methodology different from other studies previously described in this section of the article: MRI was performed twice during the periprocedural period – within 2 weeks before (pre-AF

ablation MRI) and the day after (post-AF ablation MRI) – to exclude the possibility of attributing older, pre-ablative lesions to those associated with the procedure. A total of 127 patients were enrolled in the study. Sixty-four patients received rivaroxaban, and 63 patients received warfarin. The rate of silent stroke in the rivaroxaban group (15.6%) was similar to that in the warfarin group (15.9%) ($p=1.000$). No evident thromboembolic events occurred in either group and no differences in major (3.1% – rivaroxaban vs. 1.6% – warfarin; $p=NS$) or non major bleeding (18.8% – rivaroxaban; 19.0% – warfarin; $p=NS$) rates were observed. The analysis of MRI patterns before ablation (pre-AF ablation MRI) was performed and included in multiple regression analysis for the risk of occurrence of new silent brain ischemic lesions after ablation. The analysis revealed that the presence of severe deep and subcortical white matter hyperintensities (odds ratio OR: 5.323, $p=0.002$) before ablation and the frequency of cardioversions during ablation (OR: 1.250, $p=0.016$) were independently associated with the incidence of new silent brain ischemic lesions after PVI. The authors concluded that uninterrupted rivaroxaban was equal to uninterrupted warfarin in stroke prevention, silent brain ischemic lesions occurrence and major and non-major bleeding events. The researchers pointed out that silent stroke may be a multifactorial complication after AF ablation that may involve both patient-related risk factors and procedural factors.

Another study for apixaban – the AEIOU trial^[11], a prospective, multi-center study – sought to compare outcomes with uninterrupted and minimally interrupted strategies at the time of atrial fibrillation ablation. Three hundred patients were randomized 1:1 to uninterrupted or minimally interrupted periprocedural apixaban. There were no stroke or systemic embolism events in either group. Clinically significant bleeding occurred in 11.3% in uninterrupted apixaban and in 9.7% in interrupted apixaban ($p=NS$). The researchers also compared outcomes of patients treated with both apixaban periprocedural strategies combined to that of historical patients treated with uninterrupted warfarin, revealing no difference in clinically significant bleeding (10.5% apixaban vs 9.8% warfarin, $p=NS$). The researchers concluded that apixaban was equally safe in both dosing strategies in terms of bleeding risk and comparable to uninterrupted warfarin.

“Dabigatran bridge” – temporary switching to dabigatran for catheter ablation of atrial fibrillation – a safe approach?

The major concern of performing AF ablation with uninterrupted factor Xa inhibitors (edoxaban, apixaban, rivaroxaban) was the risk of bleeding, particularly life-threatening ones such as pericardial tamponade, with the lack of an antidote. To overcome this problem, DOACs were often withheld on the day before the procedure (minimally interrupted strategy). Dabigatran offered an available solution antidote – idarucizumab, whose efficacy is well evidenced and therefore can be safely used by the physician in the event of dangerous bleeding complications during AF ablation. Taking into account this unique attribute of dabigatran and also the well proven safety profile in the periprocedural period reflected by the

highest, IA, recommendation in the Consensus^[1], attempts are being made to use it periprocedurally in order to increase the safety of PVI.

Daisetsu Aoyama et al. recently published a study whose aim was to investigate the efficacy and feasibility of “dabigatran bridge” – temporary switching to dabigatran periprocedurally and continuing through AF ablation to the “minimally interrupted DOAC” protocol. This was a non-randomized, single-center, prospective study. In the minimally interrupted DOAC group, the DOACs were interrupted only on the day of the procedure (for 1 day) with heparin infusion after ablation and resumption of DOACs the morning of the next day. In the dabigatran bridge group all DOACs were temporarily switched to dabigatran 110 mg that was administered uninterruptedly during the periprocedural period with no heparin bridging. Anticoagulation was subsequently switched back to the original DOAC three days after the ablation. The study recruited 272 patients managed with NOAC. In total the dabigatran bridge strategy was used in 135 patients and the minimally interrupted DOAC protocol in 137. In baseline characteristics the dabigatran bridge group was significantly older (67.3 ± 9.8 – dabigatran bridge; 64.4 ± 10.9 – minimally interrupted DOAC, $p=0.02$). The follow-up of adverse events during and up to 8 weeks after the procedure was collected according to the definition of the International Society on Thrombosis and Haemostasis. The incidence rates of all adverse events were comparable between the two groups (8/137 versus 8/135, $p=0.96$). In detail, one patient experienced stroke in the minimally interrupted DOAC group, and one experienced cardiac tamponade in the “dabigatran bridge” group that was safely managed with idarucizumab. As mentioned before, the dabigatran bridge group was slightly but significantly older and therefore potentially more vulnerable to both bleeding and thromboembolic events. In conclusion, the study did not show a statistically significant difference in the incidence of all adverse events that could favor the dabigatran bridge against the minimally interrupted DOAC approach in the ablation periprocedural period. Nevertheless, the authors underline some clinical implications of the study: dabigatran bridge is much simpler than a heparin bridging protocol in patients taking factor Xa inhibitors at the time of AF ablation, and therefore dabigatran bridge might be a feasible approach in everyday clinical practice.

In another study, a non-randomized prospective study^[12] conducted by Nakamura R et al., the researchers investigated the prevalence of cerebral embolisms after cryoablation of atrial fibrillation in two patient groups: DOACs interrupted on the day of the CA (minimally interrupted strategy) (228 patients) or dabigatran bridge (105 patients). The study revealed no significant differences in symptomatic cerebral infarctions. However, brain magnetic resonance imaging (MRI) performed on the day following the cryoablation revealed that the strategy with minimally interrupted DOAC resulted in a statistically significantly higher rate of cerebral infarction than the non-interrupted dabigatran bridge approach (29% vs 13%, $p < 0.01$). Additionally, the two approaches showed no difference in terms of adverse bleeding events ($p = 0.62$)

including groin hematomas, epicardial effusions, and hemorrhagic gastric ulcers. The authors concluded that uninterrupted dabigatran periprocedurally might decrease the risk of silent brain ischemic lesions in comparison to minimally interrupted NOACs.

There are however data suggesting decreased effectiveness of dabigatran in the periprocedural period in comparison to other NOACs. The single-center, non-randomized prospective study^[13] by Nagao, T., et al. aimed to determine the incidence of silent stroke (silent brain ischemic lesions in MRI-DW performed after ablation) and periprocedural trends in coagulation markers among patients undergoing AF ablation under uninterrupted periprocedural anticoagulation with different oral anticoagulants. In total, 280 consecutive patients with atrial fibrillation treated with warfarin or DOACs (dabigatran, rivaroxaban, apixaban, and edoxaban) were prospectively enrolled in the study. In all patients, anticoagulation was continued through the PVI. The levels of coagulation markers fibrin monomer complexes (FMC) and prothrombin fragment 112 (PF112) were measured before, directly after and the next day after ablation. The FMC and PF112 levels were significantly higher in the dabigatran group in the perioperative period. The incidence of silent stroke detected via MRI-DW after the procedure in dabigatran was significantly higher than in the other groups (dabigatran 17%, rivaroxaban 6%, apixaban 3%, edoxaban 7%, warfarin 4%; $p < 0.05$). Moreover, no significant difference in the incidence of silent stroke was found among the warfarin and the factor Xa inhibitor (rivaroxaban, apixaban, edoxaban) groups ($p = 0.84$). In multivariate logistic regression analysis dabigatran use independently predicted the occurrence of silent stroke (odds ratio [OR] 4.12; 95% confidence interval [CI] 1.37–12.7; $p = 0.05$). The rate of bleeding complications or symptomatic ischemic stroke/TIA was equivalent among all groups. The researchers speculated that the observed results can be explained by dabigatran’s mode of action that is distinct from other NOACs. Dabigatran mainly affects the intrinsic clotting system by direct inhibition of thrombin, which is activated when blood contacts with external materials (e.g. an ablation electrode), whereas rivaroxaban, apixaban, and edoxaban inhibit FXa, which affects both the extrinsic and intrinsic clotting systems. FXa inhibitors might suppress the entire anticoagulation systems more effectively than dabigatran, especially as the procedure of AF ablation is considered to lead to activation of the coagulation cascade and thrombus formation primarily through the extrinsic clotting pathway due to extensive damage of atrial tissues during application of RF energy.

New meta analysis – safety and efficacy NOACs vs VKAs during catheter ablation of AF

Ge Z. et al. published a meta-analysis^[14] covering studies published until the end of 2017 with the aim of determining the safety and efficacy of periprocedural anticoagulation with NOACs compared with VKAs in AF patients undergoing catheter ablation. The primary safety endpoint was major bleeding events, and the primary efficacy endpoint was throm-

boembolic events (a composite of systemic thromboembolism, transient ischemic attack, and stroke). A total of 29 studies with 12 644 patients were included in the meta-analysis. Overall, patients on NOACs had a significantly lower risk of major bleeding compared to VKAs either in observational studies (OR 0.68; 95% CI: 0.48-0.95; $p = 0.022$; $I^2 = 20\%$) or in RCTs (OR 0.30; 95% CI: 0.14-0.62; $p = 0.001$; $I^2 = 28\%$). Uninterrupted NOACs reduced the risk of major bleeding when compared to uninterrupted VKAs (OR 0.66; 95% CI: 0.45-0.96; $p = 0.028$; $I^2 = 1\%$). Similarly, interrupted NOACs lowered the risk of major bleeding compared to interrupted VKAs (OR 0.29; 95% CI: 0.13-0.66; $p = 0.003$; $I^2 = 0\%$; $p_{\text{interaction}} = 0.076$). The rate of thromboembolic complications was very low and did not significantly differ between the study groups either in observational studies (OR 0.91; 95% CI: 0.49-1.67; $p = 0.755$; $I^2 = 0\%$) or in RCTs (OR 0.14; 95% CI: 0.01-1.30; $p = 0.083$; $I^2 = 0\%$). The authors concluded that NOACs' use periprocedurally seems to decrease the risk of bleeding while maintaining stroke protection similar to that of VKAs.

Initial heparin bolus during atrial fibrillation ablation in patients treated with NOACs- what is the appropriate dose?

The Consensus^[1] recommends that heparin should be administered for AF catheter ablation procedures and the dose should be adjusted to achieve and maintain an ACT of at least 300 seconds for protection against thromboembolic events. Patients receiving VKAs require less heparin and reach the target ACT faster compared with NOACs^[1, 15]; therefore in the case of NOAC anticoagulated patients higher heparin doses are advised. The Consensus proposes initially 50 units of heparin per kg in patients who are treated with warfarin and 120 units per kg for NOAC anticoagulated patients who have had one to two doses before the procedure withheld.

Payne JE et al. performed a retrospective, observational single-center study^[16] with a small prospective validation cohort that consisted of manual chart review of atrial fibrillation ablation in order to determine an appropriate baseline weight-based heparin dosage to achieve therapeutic ACT during AF ablation for patients on DOACs. Eighty-nine patients treated with DOACs (minimally interrupted – NOACs interrupted by one dose) and 43 with warfarin (uninterrupted) were analyzed. Intraprocedural anticoagulation was performed in step with the Consensus. The DOAC group was subject to further analysis where two subgroups were created: (1) a high-dose cohort based on heparin dosage percentile ≥ 150 units/kg ($n = 28$ patients), and (2) a low-dose cohort of patients who received a dose < 150 units/kg ($n = 61$). The high-dose group had a significantly higher percentage of therapeutic ACT during the procedure. Subsequently a prospective validation study of patients treated with rivaroxaban or apixaban (interrupted by one dose) was performed using a higher initial heparin dose – mean 160.1 ± 12.5 units/kg. The mean procedural ACT appeared to be similar to that of the high-dose retrospective subgroup, suggesting a predictable response to the higher initial heparin dosage regimen. The authors concluded the study by suggesting that a higher initial bolus of heparin of

at least 150 units/kg heparin appears to be appropriate in patients treated with NOACs interrupted by one dose before the procedure and that patients above 89.65 kg may require an even higher initial heparin bolus.

Conclusions

Since 2017 and 2018, when the Consensus statements^[1, 2] regarding anticoagulation during atrial fibrillation period were published, results of some important new studies have been released.

Uninterrupted apixaban and edoxaban proved to be a safe and effective alternative to warfarin for AF ablations in large, randomized multi-center trials.

Uninterrupted and interrupted anticoagulation strategies with NOACs through ablation have been tested. Most studies showed equally low bleeding and stroke risks in both approaches. However, there were conflicting results regarding the prevalence of silent brain ischemic lesions in MRI after ablation – some of the studies noted a higher rate of silent stroke in interrupted than in uninterrupted NOACs through PVI, while others showed an equivalent rate.

With regard to silent brain ischemic lesions after PVI, some new knowledge concerning their significance and patient-related risk factors for occurrence was gained; the majority of the lesions tend to disappear over time and were not associated with decreased cognitive function.

The dabigatran bridge strategy as a potentially safer uninterrupted anticoagulation approach through AF ablation was tested but the data are non-confirmatory and further research is required.

Meta-analysis revealed lower risk of bleeding and similar protection from thromboembolism in NOACs versus VKAs during AF ablation.

The need of higher doses of heparin bolus for adequate anticoagulation during AF ablation of patients managed with NOACs was proposed.

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