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EDITORIAL

Safety and efficacy of uninterrupted vs. minimally interrupted periprocedural direct oral anticoagulants for catheter ablation of atrial fibrillation: two sides of the same coin?

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This editorial refers to 'Uninterrupted vs. interrupted periprocedural direct oral anticoagulants for catheter ablation of atrial fibrillation: a prospective randomized single-center study on post-ablation thrombo-embolic and haemorrhagic events' by K. Nakamura *et al.*, on pages 259–267.

Catheter ablation (CA) is an effective rhythm control treatment in patients with atrial fibrillation (AF).[1] Catheter ablation has recently been associated with a 30% relative reduction in ischaemic stroke particularly in patients with CHA_2DS_2-VASc scores ≥ 2.[2]

Yet, though this procedure is considered to be relatively safe and it is widely performed, due to catheter manipulation and the creation of lesions in the left atrium, patients undergoing CA of AF have a considerable risk of peri-procedural clinical stroke, transient ischaemic attack (TIA), or systemic embolism. The periprocedural stroke risk associated with AF ablation is 1%.[3] In addition, several studies and the COMPARE trial have shown that the incidence of this periprocedural complication is higher in patients with non-paroxysmal AF.[4,5]

Continuous anticoagulation with vitamin K antagonists (VKA) prevents periprocedural stroke better than interrupted anticoagulation.[4] In the COMPARE study, patients were randomly assigned in a 1:1 ratio to be off-VKA or on-VKA. In the off-VKA group, 5% of patients experienced thrombo-embolic events compared with 0.25% of patients in the uninterrupted VKA group ($P < 0.001$). Importantly, these results were mostly driven by patients with long-standing persistent AF (LSPAF).[4]

With the advent of direct oral anticoagulants (DOACs), data on the safety of AF ablation on continuous DOAC therapy were needed. The VENTURE-AF trial was the first randomized controlled trial of uninterrupted rivaroxaban vs. warfarin in patients undergoing AF ablation. The number of any adjudicated events, any bleeding events, and any other procedure-attributable events were similar between both groups.[6] This trial demonstrated that in patients undergoing ablation for AF, the use of uninterrupted oral rivaroxaban was feasible, and the event rates were similar to those for uninterrupted warfarin therapy. Likewise, the RE-CIRCUIT trial assigned patients scheduled for CA of AF to receive either dabigatran or warfarin. Uninterrupted dabigatran was associated with fewer bleeding and thrombo-embolic complications than uninterrupted warfarin.[7] The efficacy and safety of periprocedural anticoagulation with apixaban was evaluated in the recently published AXAFA—AFNET 5 trial.[8] The primary outcome was similar in patients randomized to apixaban compared to those randomized to warfarin (non-inferiority $P = 0.0002$).[8]

In this issue of *EP-Europace*, Nakamura *et al.*[9] report a prospective, randomized, single-centre study that aimed to directly compare the safety and efficacy of uninterrupted and minimally interrupted periprocedural anticoagulation protocols with DOACs in patients undergoing AF ablation. A total of 846 AF patients were enrolled. The primary endpoint was a composite of symptomatic thromboembolism and major bleeding events within 30 days following CA. Secondary endpoints included symptomatic and silent thromboembolism and major and minor bleeding events. The primary endpoint occurred in 0.7% of the uninterrupted DOAC group (one TIA and two major bleeding events) and 1.2% of the interrupted DOAC group (one TIA and four major bleeding events); $P = 0.365$. The incidence of major and minor bleeding was comparable between the two groups (0.5% vs. 0.9%, $P = 0.345$; 5.9% vs. 5.4%, $P = 0.753$). Silent cerebral ischaemic lesions (SCI) occurred with a similar frequency in both study groups (19.8% vs. 22.0%, $P = 0.484$), and the percentage of SCIs that were resolved and disappeared on magnetic resonance

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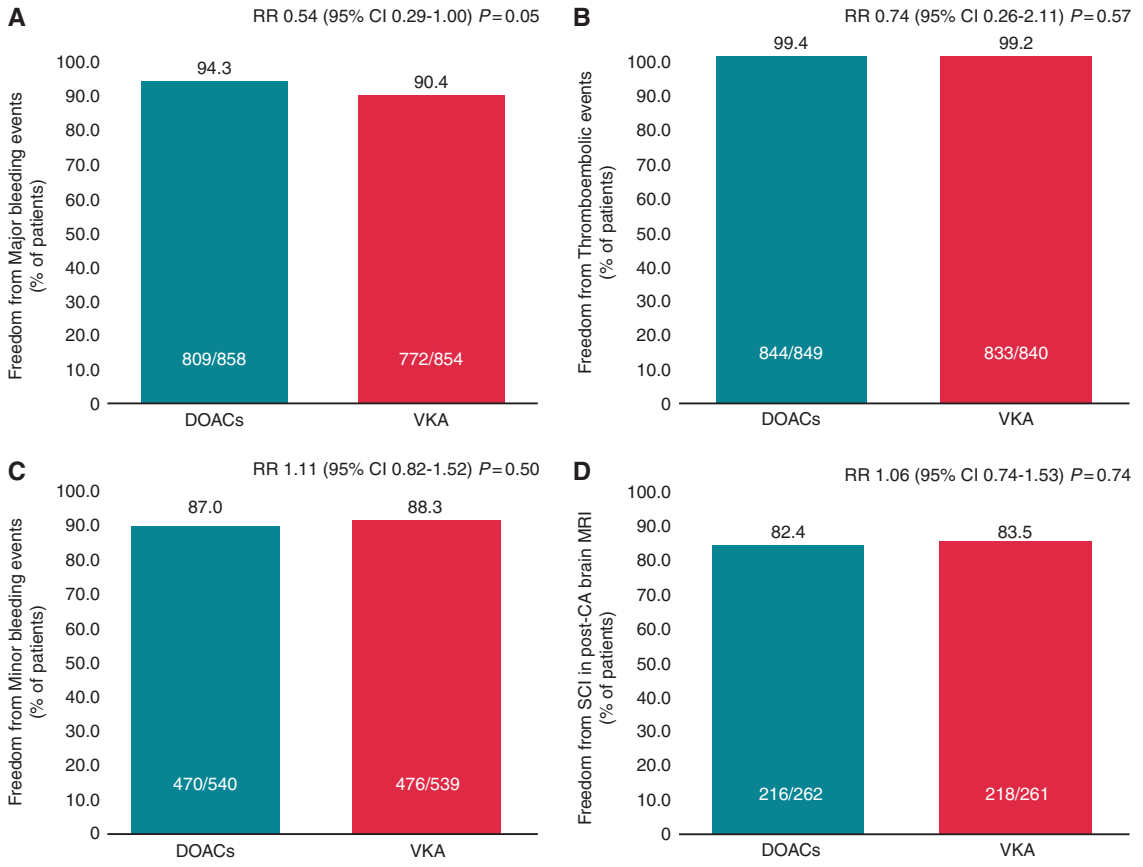

Figure 1 Outcomes of meta-analysis of randomized controlled trials comparing uninterrupted DOAC vs. uninterrupted VKA. (*A*) Freedom from major bleeding events (*B*) Freedom from thrombo-embolic events. (*C*) Freedom from minor bleeding events (*D*) Freedom from silent cerebral infarction lesions in post-catheter ablation brain MRI. Reproduced from Romero *et al.*[10] CA, catheter ablation; CI, confidence interval; DOAC, direct oral anticoagulants; MRI, magnetic resonance imaging; RR, risk ratio; SCI, silent cerebral infarction; VKA, vitamin K antagonist.

imaging (MRI) follow up magnetic resonance imaging (MRI) was also not different between groups (77.8% vs. 82.1%, $P = 0.428$).[9]

Silent cerebral ischaemic lesion associated with AF ablation is still an unresolved problem in the field of electrophysiology, with studies incidence rates as high as 40%. The cause of these SCIs has not yet been fully elucidated. Nakamura *et al.*[9] provide important insight into SCI and their resolution.[9] Follow-up MRI was available in 132 (95.7%) out of the 138 patients with SCIs and was preformed 1 month after the procedure. Among 213 SCIs in the 132 patients undergoing follow-up MRI, 43 (20.2%) of the lesions developed remained detectable upon repeat MRI, while 170 (79.8%) lesions were no longer observed. While the number of SCIs is still too high, their possible resolution provides a certain degree of reassurance, in line with the slight improvement of cognitive function found after AF ablation in patients receiving continuous VKA or apixaban therapy.[8]

How does this study alter clinical management? We have recently conducted a systematic review and meta-analysis of randomized controlled trials comparing uninterrupted DOACs vs. uninterrupted VKA during AF ablation.[10] Our meta-analysis included four trials that enrolled a total of 1716 patients with AF. No significant benefit was seen in major bleeding events [relative risk (RR) 0.54, 95% confidence interval (CI) 0.29–1.00; $P = 0.05$]. No significant differences were found in minor bleeding events (RR 1.11, 95% CI 0.82–1.52;0 $P = 0.50$), thrombo-embolic events (RR 0.74, 95% CI 0.26–2.11; $P = 0.57$), or post-procedural SCI (RR 1.06, 95% CI 0.74–1.53; $P = 0.74$). Interestingly, there was a non-significant trend towards fewer major bleeding events (as defined by a BARC score >2) in patients assigned to uninterrupted DOAC therapy (5.7%) compared with uninterrupted VKA (9.6%, RR 0.54, 95% CI 0.29–1.00; $P = 0.05$) (*Figure 1*).[10] In the study by Nakamura *et al.*,[9] major bleedings occurred more often in the interrupted DOAC therapy group (0.9% vs. 0.5%). Likewise, the percentage of patients who had significant SCI was higher in the minimally interrupted DOAC group when compared to the uninterrupted DOAC group (22% vs. 19.8%). Consequently, there are small, although not statistically significant, safety signals suggesting that uninterrupted DOAC therapy at the time of AF ablation could be preferable to short interruptions. While there is only a small—if any—risk of omitting a single DOAC dose, in our view, there is no apparent reason to interrupt DOAC therapy in patients undergoing AF ablation. Although these differences did not reach statistical significance, we agree with the authors that the study was actually underpowered. The lack of statistical difference may reflect simply a type II error rendering these analyses more speculative than definitive. This occurred probably because there was a lower

than expected rate of a primary endpoint in both study groups. We instead believe that since uninterrupted strategy does not increase the risk of any kind of bleeding, there is no reason to stop any dose of DOAC and take a higher risk of stroke especially in patients with non-paroxysmal AF.

Another point worth discussing regarding the article by the Nakamura *et al.*,[9] is that patients who received rivaroxaban (who comprised almost 40% of the study population), a lower than the standard dose of the drug (10–15 mg) was administered in the morning of the day prior to the procedure. It has been recently shown that the absorption of this medication under fasting conditions is significantly decreased (i.e. ~50%). High bioavailability (≥80%) of 15 mg and 20 mg rivaroxaban is achieved when rivaroxaban is taken with food.[11] Furthermore, some patients had cryoballoon ablation, and radiofrequency hot balloon ablation, which might have a different risk of stroke than radiofrequency CA since the former two technologies do not cause endothelial denudation. These two factors in our opinion might have included some biases to the author's analyses.

It is also worth pointing out that the patients included in this study had a relatively low mean CHA_2DS_2-VASc scores of 2 points, and that 55% of these patients had paroxysmal AF who only required pulmonary vein isolation. As mentioned above, in the COMPARE trial, it was clearly demonstrated that patients with LSPAF had the highest incidence of periprocedural thrombo-embolic events.[4] This is probably due to the fact that patients with LSPAF often require a more extensive ablation, which increases the risk of char and coagulum formation.

Catheter ablation for AF in older patients (age > 80) is associated with a higher total complication rate (9.37%) in comparison with younger patients ($P < 0.001$).[3] VENTURE, RE-CIRCUIT, and AXAFA trials enrolled a relatively young population of patients with AF (mean age 62 years).[6–8] There are currently no data regarding the safety and efficacy of uninterrupted DOAC use in elderly patients during ablation for AF. Yanagisawa *et al.*[12] recently evaluated the efficacy and safety of uninterrupted DOAC and uninterrupted warfarin administration in elderly patients (age >75) undergoing ablation for AF. In the elderly group, there were no significant statistical differences in major bleeding events (2.2% vs. 4.3%, $P = 0.34$) and minor bleeding events (9.7% vs. 8.6%, $P = 0.748$) in the DOAC and warfarin groups, respectively.[12] Interestingly, the elderly group (>75 years) had three times the rate of major bleeding events (3.1% vs. 1.3%, $P = 0.023$) and almost two times the rate of minor bleeding events (9.2% vs. 5.0%, $P = 0.002$) when compared to the younger group. However, there was no significant statistical difference between the patients taking DOAC or VKA in both the groups. These findings are not unexpected since it is well-known that age is a very important risk factor for bleeding. More importantly, it would be interesting to compare in a randomized fashion whether minimally interrupted anticoagulation in the elderly population may mitigate the high bleeding rate when compared to complete uninterrupted anticoagulation regimens.

The 2017 HRS/EHRA/ECAS/APHRS/SOLAECE Expert Consensus Statement on Catheter and Surgical Ablation of AF are ambiguous for the periprocedural management of oral anticoagulation in patients undergoing CA of AF. This consensus recommends either withholding 1 or 2 doses of DOAC prior to the procedure or not withholding any doses at all.[13] To date, there is substantial data proving that uninterrupted DOAC or VKA strategy for ablation of AF is the most efficacious approach without a significantly increased risk of minor or major bleeding events. There is a clear trend favouring DOAC use in terms of major bleeding.[10] Based on the controlled data evaluating uninterrupted DOAC therapy and in view of the study reported here, interrupted and uninterrupted DOACs therapy in patients undergoing AF ablation appear as 'two sides of the same coin', but our preference supported by numerous randomized controlled trials would be uninterrupted DOAC therapy.

The authors must be congratulated for designing and conducting this trial. This is an important study given the fact that there is limited data available in the literature directly comparing clinical outcomes between uninterrupted vs. minimally interrupted DOAC therapy in patients undergoing AF ablation.

Conflict of interest: Dr Di Biase is a consultant for Biosense Webster, Stereotaxis, Boston Scientific and Abbott. Dr Di Biase received speaker honoraria/travel from Medtronic, Pfizer and Biotronik. From the Division of Cardiology at Montefiore-Einstein Center for Heart and Vascular Care, Montefiore Medical Center, Albert Einstein College of Medicine, Bronx, NY, USA.

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