Editorial to “Safety and Efficacy of Uninterrupted Treatment with Edoxaban or Warfarin During the Peri-Procedural Period of Catheter Ablation for Atrial Fibrillation”

Catheter ablation (CA) for atrial fibrillation (AF) has merged as a first-line therapy, and the total number of procedures in Japan has been increasing. Anticoagulation therapy is crucial for AF patients to prevent thromboembolic events; however, CA for AF potentially has a high bleeding risk as well as a high thromboembolic risk. After the release of the COMPARE trial, uninterrupted warfarin became the gold standard for peri-procedural anticoagulation for AF. Besides, after the launch of direct oral anticoagulants (DOACs), several randomized control studies to evaluate the safety of uninterrupted DOACs during the procedure were performed: that is, the VENTURE-AF (rivaroxaban), RE-CIRCUIT (dabigatran), AXAF-AFNETS (apixaban), and ELIMINATE-AF² (edoxaban) trials. However, since only the RE-CIRCUIT included Japanese patients, the actual data for Japanese patients has been lacking.

In this issue, Naito et al⁴ evaluated the safety and efficacy of uninterrupted edoxaban and warfarin during the perioperative period of CA for AF. A total of 256 patients (153 and 103 patients in the edoxaban and warfarin groups, respectively) who underwent CA for AF at two Japanese centers were retrospectively enrolled in this study. The incidence of major bleeding complications were 0.7% and 2.9% and that of the total major/minor bleeding complications were 7.8% and 8.7% in the edoxaban and well-controlled warfarin groups (time in therapeutic range was 73.7%), respectively. Additionally, they stated that the patients with an estimated glomerular filtration rate (eGFR) ≤30% or HAS-BLED score ≥3 had a markedly higher incidence of bleeding complications in the warfarin group, whereas the patients in the edoxaban group did not. The important findings of this paper were that the uninterrupted edoxaban and warfarin were relatively safe for AF patients during the peri-procedural period of CA in the real-world clinical practice in Japan.

Regarding the safety of edoxaban in this issue, Takahashi, et al previously performed an excellent, relatively large, prospective edoxaban single-arm study, that is, the KYU-RABLE study.⁵ In this study, only one major bleeding complication (cardiac tamponade during the procedure: 0.2%), clinically relevant non-major bleeding events in 1.4%, and minor bleeding events in 1.9% were observed in the 537 enrolled patients. The incidence of bleeding complications was quite low, when compared to the present study⁴ or ELIMINATE-AF trial.² Although the anticoagulation strategy used in the KYU-RABLE study was a one dose delayed administration of edoxaban, they confirmed that the plasma concentration of edoxaban was still preserved on some level during the procedure. It seems reasonable because there were no thromboembolic events in the study, and therefore, I would address that the one dose delayed edoxaban was thoroughly safe.

The question that will always be raised is the time interval between taking the DOACs and the CA procedure, especially for once daily DOACs. In the present study, edoxaban was administered within 8 hours prior to or after the procedure, that is, this strategy was a so-called uninterrupted strategy. Therefore, it may be associated with the relatively higher bleeding complication rate in the study.

With respect to the safety outcome, it has been reported that asymptomatic stroke still occurred even under a minimally interrupted OAC. Some reports have suggested that the incidence of an asymptomatic stroke was significantly reduced with a strictly uninterrupted OAC. In the present study, although asymptomatic stroke could not be denied, there were no stroke/thromboembolic events. Considering these results, uninterrupted edoxaban is feasible as a peri-procedural anticoagulation for AF ablation, and I would state that we could choose the strategies of the one dose delayed edoxaban for patients with a higher risk of bleeding or the strictly uninterrupted edoxaban for those with a higher thromboembolic risk.

Concerning another safety issue, a specific antidote for edoxaban has not yet become available in Japan. The incidence of cardiac tamponade is recently reported in 1%, and has been decreasing, however, it would be critical if it occurred. We can only use idarucizumab for dabigatran, and prothrombin complex concentrates for warfarin as reversals. Andexanet-alfa, which is a modified recombinant inactive form of anti-Xa OAC, has yet to be launched in Japan, therefore, I have to emphasize that the Japanese guideline shows a different class of recommendations between dabigatran/warfarin (class I) and anti-Xa OACs (Class IIa) as peri-procedural anticoagulation for AF ablation. Nevertheless, there are no enough data from Japan regarding this peri-procedural anticoagulation strategy of CA for AF. Although this study was retrospective and had a limited...
number of cases, these results may well be a major step forward in AF ablation with uninterrupted edoxaban. Further studies with a larger number of patients will still be necessary to clarify not only the safety but also the efficacy of edoxaban during procedures in the Japanese real-world practice.

DISCLOSURE
HF received lecture fees from Boehringer Ingelheim and Daiichi-Sankyo.

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