Atrial fibrillation (AF) is a cardiovascular disorder that continues to increase in incidence in the 21st century. In patients with AF, stroke is one of the most serious complications, which leads to substantial morbidity and mortality. Thus, stroke prevention is the cornerstone in managing patients with AF and anticoagulation is the most effective treatment to prevent stroke. However, the risk of bleeding is a drawback of this therapy, and it is important to strike a balance between the thromboembolic and bleeding risks.

In this issue of the Journal, Murata et al demonstrate the effectiveness and safety of off-label underdosing of direct oral anticoagulants (DOAC) using data from the SAKURA AF Registry, a prospective multicenter observational registry in Japan. They report that approximately 26% of DOAC users received an inappropriate dose of DOAC (4% over-dose and 22% underdose); net clinical events were higher in the over-dosed DOAC group, whereas they were equivalent (or might be better because of the decrease in major bleeding events) in the underdosed group.

Inappropriate dosing of anticoagulant drugs has been a problem in real-world clinical practice. With regard to warfarin, under- or overdosing was common because of the narrow therapeutic range and interactions with food and other drugs, thereby making it difficult to maintain optimal therapeutic intensity. DOACs were expected to reduce under-/overdosing, because they are prescribed at a fixed dose and do not require routine or frequent laboratory monitoring. Optimal doses of each DOAC are determined according to age, renal function, and body weight, and the efficacy of these doses has been confirmed by the large-scale randomized clinical trials (RCT). However, inappropriate dosing of DOAC-treated patients is commonly seen in current daily clinical practice. ORBIT-AF II, a large-scale observational study of AF patients in the USA, showed that 9.7% of DOAC-treated patients were underdosed, and 3.4% were overdosed.

The Fushimi AF Registry, a cohort study of AF patients in Japan, also showed that nearly half of patients receiving low-dose regimens of DOAC were off-label underdosed. The main problem of prescribing an inappropriate dose of DOAC is that it may be associated with poor outcomes. In ORBIT-AF II, overdosing was associated with increased all-cause death compared with recommended doses (adjusted hazard ratio: 1.91; 95% confidence interval [CI]: 1.02–3.60), and underdosing was...
associated with increased cardiovascular hospitalization (adjusted hazard ratio: 1.26; 95% CI: 1.07–1.50). A study from a large US administrative database also showed a higher risk of major bleeding in patients with overdosed DOACs and a higher risk of stroke in patients with underdosed apixaban, but not in those with dabigatran or rivaroxaban. Similar results were shown in large-scale RCTs of DOACs; both RE-LY and ENGAGE AF TIMI-48 demonstrated that underdosing regimens had a higher incidence of ischemic stroke despite a decrease in major bleeding events. In the Fushimi AF Registry, in which a certain number of underdosed patients were included, the incidence of both thromboembolism and major bleeding was comparable between patients with and without OACs, which suggested that underdosing of OAC was less effective in preventing thromboembolism.

Therefore, it is crucial to avoid under-/over-dose prescription and to be consistent with the labeled dose when treating AF patients with a DOAC. However, the present study from the SAKURA AF Registry had an apparently conflicting result, in which underdosing of DOACs might have a potential benefit in Japanese AF patients. This result will be attractive to many physicians because underdosing is an easy and convenient way to avoid bleeding, but should be carefully interpreted. This was an observational study, and the baseline clinical characteristics of both groups (on-label vs. underdose) were different, which was also the case even after any elaborate and sophisticated statistical adjustment.

One possible reason for the apparent discrepancy was that underdosing might be optimal for some Japanese AF patients. It is well known that AF differs considerably between Asians and Caucasians, in terms of epidemiology, clinical profile, and optimal anticoagulation levels. Because the risks of major bleeding and intracranial hemorrhage (ICH) are higher in Asian patients with AF compared with Caucasians, Japanese AF guidelines recommend an international normalized ratio (INR) range of 1.6–2.6 with warfarin for AF patients older than 70 years, whereas the recommended INR range for Caucasians is 2.0–3.0. Regarding DOACs, the same dose criteria as Caucasians are used for Japanese patients, except for rivaroxaban.

Despite the results from the SAKURA AF Registry regarding underdosing for Japanese AF patients, we should be cautious about applying such treatment. The efficacy of on-label dose DOAC was confirmed in a subanalysis of RCTs of DOACs in Japanese AF patients, and the incidence of ICH in Asian AF patients with on-label doses of DOACs did not differ from that in Caucasians, despite the incidence of ICH in patients on warfarin being significantly higher in Asians than in Caucasians. On-label dosing of DOACs has been demonstrated as effective even in Japanese patients.

DOACs have such predictable pharmacokinetics and pharmacodynamics that routine coagulation monitoring should be unnecessary. However, measurement of anticoagulant intensity might provide more information about the optimal dose of DOACs for patients at high risk such as older age, low body weight, and renal insufficiency. In general, routine coagulation tests [prothrombin time (PT) and activated partial thromboplastin time (aPTT)] do not provide an accurate assessment of DOAC anticoagulant intensity, and more specialized assays (anti-factor Xa chromogenic assays or diluted thrombin time test and the ecarin chromogenic assay) may be useful. Despite this, the assays are not available in daily clinical practice; if they were, we could confidently adjust the dosing of DOACs for Asian patients.

In conclusion, we should currently prescribe on-label doses of DOACs to prevent thromboembolism in patients with AF. However, there might be more optimal doses for Japanese patients (Figure). Further studies are necessary to establish more ideal anticoagulation therapy.

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