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EDITORIAL COMMENT

Rivaroxaban Monotherapy for Atrial Fibrillation and Coronary Artery Disease in Underweight/Obese Patients

Evidence Is Needed*

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The number of patients with both atrial fibrillation (AF) and coronary artery disease (CAD) has been increasing in the aging society. The medication management for these patients is of great importance because 30% of AF patients have stable CAD and up to 15% of stable CAD patients also have AF.[1] Anticoagulation is essential for AF patients to reduce stroke/systemic embolism risk, whereas antiplatelet therapy is needed in CAD patients to minimize coronary ischemic events. Theoretically, anticoagulant plus antiplatelet therapy is required in patients with coexisting AF and stable CAD. However, the increased bleeding risk is a main concern. Therefore, researchers have tried to explore the effectiveness and safety of anticoagulant monotherapy in this population during the last decade.

The AFIRE (Atrial Fibrillation and Ischemic Events with Rivaroxaban in Patients with Stable Coronary Artery Disease) trial is a multicenter, open-label, randomized controlled study conducted in Japan. AF patients (with $CHADS_2$ score of ≥1) who had stable CAD (have a history of percutaneous coronary intervention or coronary artery bypass graft ≥1 year before enrollment or have angiographic CAD not requiring revascularization) were randomized to receive rivaroxaban monotherapy or combination therapy with rivaroxaban plus a single antiplatelet agent.[2] The study showed that rivaroxaban monotherapy was superior to combination therapy for the primary safety endpoint and was noninferior to combination therapy for the primary efficacy endpoint, providing strong evidence for the current guideline.[2] Nevertheless, as a direct oral anticoagulant (DOAC), rivaroxaban has a "one size fits all" dose strategy regardless of patient weight. No evidence exists on whether DOAC monotherapy is still suitable across body mass index (BMI) categories. In particular, the effectiveness of DOAC monotherapy is worth considering in obese AF patients with CAD.

In this issue of *JACC: Asia*, Ishii et al[3] sought to answer the question by performing a post hoc subgroup analysis of the AFIRE trial.[3] They categorized 2,054 patients who received either rivaroxaban monotherapy or combination therapy for AF and stable CAD into 4 BMI categories: underweight (BMI: <18.5 kg/m^2), normal weight (BMI: 18.5-25 kg/m^2), overweight (BMI: 25-30 kg/m^2), and obesity (BMI: ≥30 kg/m^2). After a median 721 days of follow-up, they found that the clinical outcomes of patients who received rivaroxaban monotherapy were similar to or better than those for patients who received combination therapy across all BMI categories. No significant interaction was found in the association between BMI categories and the effect of monotherapy on clinical outcomes.

There are several strengths of the current study worth highlighting. Although the study excluded 161 patients without BMI values, the patient number was balanced between monotherapy and combination therapy in 4 BMI categories. Furthermore, because it was difficult to conduct a randomized study in this regard, this post hoc analysis of a randomized study is of great clinical value.

Of note, some main limitations of this study should be emphasized. As the authors acknowledge,

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the numbers of underweight patients (n = 72) and obese patients (n = 144) were small. In addition, the absolute numbers of events were low. Only 9.8% of events of the primary efficacy endpoint and 4.2% of the primary safety endpoint occurred during follow-up. Further large-scale studies are needed to verify the safety and effectiveness of DOAC monotherapy in underweight patients and obese patients.

Another limitation of the study is that the rivaroxaban dose was based on the Japanese Rivaroxaban Once Daily Oral Direct Factor Xa Inhibition Compared with Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation trial (15 mg/day for those with a creatinine clearance rate [CCR] of ≥50 mL/min and 10 mg/day for those with a CCR of <50 mL/min). This dosing strategy is recommended only in Japan and Taiwan. In other regions of Asia, the standard dose is 20 mg/day for patients with a CCR of ≥50 mL/min, and the adjusted dose should be 15 mg/day for those with a CCR of <50 mL/min. Thus, the findings may not be generalizable to patients in other regions.

Interestingly, the result of this study suggest that underweight patients needed more attention. Compared with normal-weight patients, a significantly higher risk of primary efficacy endpoints, net adverse clinical events, and major adverse cardiac and cerebral events were found in underweight patients. This finding is similar to a previous meta-analysis, which found a significantly increased thromboembolic and mortality risk in underweight anticoagulated AF patients.[4] On the one hand, the older age and a higher comorbidity burden could contribute to worse clinical outcomes. On the other hand, 62% of underweight patients received a reduced rivaroxaban dose in this study, which might lead to inadequate efficacy. The dose of rivaroxaban was decided at the discretion of the investigators in the AFIRE trial, and another post hoc analysis of the AFIRE trial indicated that a substantial number of patients (356/1,378 patients with a CCR of ≥50 mL/min) received an off-label underdose.[5] Several studies have demonstrated that inappropriate underdosing use of DOACs was associated with worse clinical outcomes, including major adverse clinical events, stroke/systemic embolism, and myocardial infarction in Asian individuals.[6,7] Regrettably, the study did not report the proportion of patients who received off-label underdose rivaroxaban and adjusted the reduced rivaroxaban dose.

Also, it should be noted that the antithrombotic strategy in morbidly obese (BMI >40 kg/m^2) patients are a missing piece of pharmacologic strategies for AF and stable CAD. The study did not report outcomes of rivaroxaban monotherapy in this population. Although some recent studies have suggested the feasibility of DOACs in morbidly obese AF patients,[8] according to guidance by the Scientific and Standardization Committee of the International Society on Thrombosis and Haemostasis, DOACs should not be used in morbidly obese patients.[9] For morbidly obese AF patients who had concomitant stable CAD, the observational retrospective studies of DOACs are worth anticipating.

The type of anticoagulant is another issue needing further exploration in AF patients with CAD. Recently, a study (N = 36,094) reported a reduced risk of ischemic stroke, bleeding, and mortality in AF patients using DOACs vs warfarin across all BMI categories.[10] A meta-analysis of 5 trials and 21 observational studies has also demonstrated that DOACs (irrespective of the DOAC type) were better than warfarin (both in safety and effectiveness) in the Asian AF population.[11] Therefore, the comparison between warfarin and DOACs in obese or underweight AF patients who had concomitant stable CAD is of great importance. Moreover, comparing different types of DOACs in this population is very interesting.

In summary, Ishii et al[3] presented a clinically relevant comparison between rivaroxaban monotherapy vs rivaroxaban plus a single antiplatelet agent for AF and stable CAD across a broad range of BMI categories. They proved the safety and effectiveness of rivaroxaban monotherapy in normal-weight/overweight patients and provided some confidence in monotherapy therapy in obese/underweight patients. Nevertheless, more evidence is needed in obese/underweight patients, and a study of antithrombotic strategy in morbidly obese patients who have AF and CAD is warranted. Further studies evaluating different rivaroxaban dosages across BMI categories are necessary. In addition, the comparison between different types of DOAC and warfarin will contribute to clinical management in this population.

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