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AUTHOR'S REPLY

JCS/JHRS Guideline: Rivaroxaban Not Recommended for Patients With Nonvalvular Atrial Fibrillation and High Bleeding Risk — Reply —

We greatly appreciate the interest and comments by Hirayama et al on our JCS/JHRS 2020 Guideline on Pharmacotherapy of Cardiac Arrhythmias.[1] The selection of direct oral anticoagulants (DOACs) in Table 35 of the Guideline provides recommendations for the proposition "Which DOACs should be chosen in patients with bleeding concerns?". Guidelines should often provide recommended treatment options in clinical practice, even if specific evidence has not been well established. Indeed, it should be noted that patients with a history of bleeding or those with dual-antiplatelet treatment were excluded from phase III clinical trials of the 4 DOACs, and the level of evidence at the time of the proofreading the guideline was not sufficient to make a strong recommendation. Therefore, the guideline direction is not to refrain from the use of drugs with high bleeding risk, but rather to select DOACs with low bleeding risk and deductively assume that these are suitable for prescription for patients with high bleeding risk.

Although the lack of clinical evidence from large-scale trials directly comparing among DOACs requires careful interpretation, a meta-analysis of randomized clinical trials (RCTs) found a Heterogeneity in the hazard ratios (HR) for major bleeding events for DOACs vs. warfarin.[2] There were significant HR reductions of major bleeding events in ARISTOTLE 0.71 [0.61–0.81], ENGAGE-AF 0.80 [071–0.90] for apixaban and edoxaban, respectively. On the other hand, HRs in RE-LY and ROCKET-AF for dabigatran (150 mg BID) and rivaroxaban were comparable to that of warfarin, respectively. In RE-LY, the HR for major bleeding in the low-dose group of dabigatran (110mg BID) vs. warfarin was 0.80 [0.69–0.93], showing a significant risk reduction.[3]

A meta-analysis based on pharmacological analysis of prothrombin time data measured by RCTs showed that prothrombin time ratios varied among the trials and there was correlation between the prothrombin time ratio and incidence of major bleeding.[4] In that analysis, the ARISTOTLE, AVERROES, and ENGAGE-AF trials (high-dose and low-dose groups) with lower prothrombin time ratios had a lower incidence of bleeding events, whereas the ROCKET-AF and J-ROCKET AF trials with more prolonged prothrombin time ratios revealed higher bleeding event rates. In addition, EHRA guidance issued in 2018 discussed that apixaban and edoxaban might be preferable in patients with severe renal dysfunction (creatinine clearance 15–29 mL/min), because their dosages have to be reduced by 50% according to the dose reduction criteria, whereas the dosage of rivaroxaban has to be reduced by 25% under similar conditions.[5]

The concept is not to avoid DOAC use with a high risk of bleeding, but rather to consider DOACs that can be selected safely with evidence of lower bleeding risk. Therefore, the present guideline recommends selecting a DOAC that can be prescribed more safely in patients with higher risk of bleeding, not because of failing to show a significant reduction in the risk of major bleeding by rivaroxaban. Thus, it is stated, "For patients with high risk of bleeding, consider agent/dose of DOAC that was significantly lower than warfarin in the large-scale clinical trials (apixaban, dabigatran 110 mg bid, edoxaban)".

Currently, the only RCT that clearly defines "high bleeding risk" is ELDERCARE-AF.[6] With the accumulation of further evidence focused on bleeding risk, recommendations for DOACs in patients at high bleeding risk will be updated in the next Focus-Update version of the JCS/JHRS 2020 Guideline on Pharmacotherapy of Cardiac Arrhythmias.

Disclosures

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