Lower-Dose Rivaroxaban Made for Japan

According to their comparisons between Caucasians and Japanese of the pharmacokinetics of rivaroxaban, the J-ROCKET AF investigators selected once-daily main dose of the oral direct factor Xa inhibitor, rivaroxaban, that is 15 mg lower than the 20 mg in the global ROCKET AF. In this issue of the Journal, Hori et al report the results of the J-ROCKET AF in which rivaroxaban 15 mg once daily was compared with warfarin with a target INR 2.0–3.0 in patients aged <70 years and 1.6–2.6 in those aged ≥70 years, based on a guideline for warfarin control in patients with non-valvular atrial fibrillation (NVAF) by the Japanese Circulation Society. The study demonstrated that rivaroxaban was not inferior to warfarin for the principal safety outcome and that there was a trend for a reduction in stroke and non-central nervous system embolism observed in patients treated with rivaroxaban. These favorable outcomes are consistent with the results from the 14,264 patients global ROCKET AF trial presented in 2011.

Intracranial Bleeding

Novel anticoagulants such as dabigatran, rivaroxaban, and apixaban have demonstrated in global phase III trials that they have a much lower risk of inducing intracranial hemorrhage than warfarin. Because intracranial bleeding during anticoagulation is often devastating and results in a poor outcome for the patient, the lower risk associated with these novel anticoagulants is good news for patients requiring anticoagulation and may affect the assessment of an individual patient’s risk of stroke balanced with their likelihood of intracranial bleeding on treatment. The J-ROCKET AF study also showed that fewer intracranial hemorrhages were observed with rivaroxaban therapy compared with warfarin therapy. This lower risk of intracranial bleeding with the novel anticoagulants may be explained by tissue factor and VIIa complex formation, the first reaction in the coagulation cascade. The concentration of tissue factor in the brain is as high as in the lung and placenta, and higher than in other parts of the body. However, warfarin suppresses vitamin K-dependent carboxylation of coagulation factor VII, resulting in low concentrations of VIIa and low production of tissue factor and VIIa complex. Thus, it is difficult for the coagulation cascade to start and for bleeding to stop. Another possibility is the effect on a single target in the hemostatic system by the novel anticoagulants vs. the multiple targets affected by warfarin. The therapeutic range of concentration for the novel anticoagulants is wider than that for warfarin, and a trough phase in the concentration of the novel agents may contribute to the lower incidence of intracranial bleeding.

Major Gastrointestinal Bleeding

J-ROCKET AF demonstrated that the rate of major GI bleeding in the rivaroxaban group tended to be lower than that in the warfarin group, whereas the global ROCKET AF showed major GI bleeding more frequently in the rivaroxaban group than in the warfarin group. The investigators explain this discrepancy in the rate of GI bleeding between J-ROCKET AF and global ROCKET AF as ethnic differences in GI bleeding, healthcare divergence by country in the endoscopic diagnosis/treatment of GI tract diseases, different patient awareness of GI bleeding and a lack of robustness of the outcome analysis because of the limited number of patients. The main dose of once-daily 15 mg rivaroxaban selected in the J-ROCKET AF, lower than that of the once-daily 20 mg administered in the global ROCKET AF, is an alternative explanation.

Miracle of Once-Daily Administration Irrespective of Short Half-Life

The novel anticoagulants have peaks and troughs in their concentration curves once or twice daily. In the peak phases, coagulation is suppressed by inhibition of thrombin or factor Xa directly. On the other hand, in the trough phases, especially of rivaroxaban with once-daily use, the novel agent may not inhibit the coagulation cascade at all because it seems that rivaroxaban activity disappears completely in the trough phase, according to its concentration curve. However, the J-ROCKET AF trial demonstrated a trend for reduction in stroke and non-central nervous system embolism in patients treated with once-daily 15 mg rivaroxaban. One potential explanation for the lack of thrombus formation during the trough phase is the presence of physiological coagulation inhibitors, such as tissue factor pathway inhibitor, antithrombin, protein C, protein S and the fibrinolytic system, which suppress thrombus formation if they are active during the trough phase (Figure). Continuous activation of thrombin may reduce the activity of physiological coagulation inhibitors, and of the fibrinolytic system, by exhausting them in a strongly activated reaction of the coagulation pathway. Once-daily or twice-daily intermittent anticoagulation by the novel anticoagulants is thought to suppress the continuous activation of thrombin, thus preserving activity.
of coagulatim inhibitors and preventing thrombus formation in the cardiovascular system even in the trough phase.

Further Studies to Refine Rivaroxaban Treatment
Although the J-ROCKET AF demonstrates favorable results, there are several issues to address in further studies. First of all, data regarding the procedure for dealing with a major hemorrhagic complication, including immediate reversal of rivaroxaban with prothrombin complex concentrate, should be collected and analyzed for establishing the most appropriate way of managing major bleeding. Secondly, we need to understand the relationship between hemorrhagic complications and the prothrombin time, which is well known to correlate with the concentration of the rivaroxaban. We also need more data concerning safety when 10 mg of rivaroxaban is administered once daily to patients with creatinine clearance between 15 and 30 ml/min, for whom administration of this dosage is permitted in Japan despite the lack of data. It is a big concern to know whether t-PA thrombolytic therapy for acute stroke during rivaroxaban treatment is indicated or not. Decision making for t-PA administration would need the data of the time from the last administration of rivaroxaban and the prothrombin time, at least, in addition to routine management and examination. A study of the effectiveness and safety of rivaroxaban for patients with CHADS\(^2\) score of 0 or 1 seems needed because neither the ROCKET AF nor the J-ROCKET AF trial included patients with a low risk for stroke. Although there are several issues to be taken into account in clinical decision making, the characteristics of rivaroxaban and the results of J-ROCKET AF trial increase the expectations for lower-dose rivaroxaban made for Japan.

References