Reconsideration of Anticoagulant Therapy in Japanese Patients With Atrial Fibrillation and Moderate Renal Impairment

Tsuyoshi Shiga, MD

RENAL IMPAIRMENT is an independent risk factor for stroke and atrial fibrillation (AF). A meta-analysis of 21 prospective studies revealed that renal impairment, defined as an estimated glomerular filtration rate (eGFR) <60 ml/min·1.73 m−2, was independently related to incident stroke. Furthermore, a subgroup analysis of the same study showed that Asian individuals (including Japanese individuals) with a low eGFR had a higher risk of stroke than non-Asian individuals. Furthermore, renal impairment was also identified as an independent risk for developing AF.

AF and renal impairment both increase the risk of stroke, and these factors may be related. Go et al have suggested that low eGFR is associated with an increased risk of stroke in AF patients, based on a large clinical database that included 10,980 patients with non-valvular AF in the United States. Recently, a Danish nationwide cohort study of 132,372 patients with non-valvular AF showed that the risk of stroke/systemic thromboembolism was increased in AF patients with renal impairment. However, few well-designed cohort studies in Japan have examined this issue.

Although the mechanism by which renal impairment leads to stroke is not fully understood, renal impairment is an important marker for risk of stroke in patients with AF.

Clinical Dilemma: Anticoagulant Therapy for AF With Renal Impairment

Warfarin has been shown to provide >60% reduction of stroke risk in AF patients, but also an increased bleeding risk. Major bledding, such as intracranial hemorrhage, is a critical adverse event in patients receiving warfarin. Warfarin-related intracranial hemorrhage was reported to be higher in Asian individuals than in Caucasian individuals.

Renal impairment is a risk factor for bleeding in patients receiving anticoagulant therapy. A Danish cohort study showed that warfarin decreased the risk of stroke/systemic thromboembolism for patients with renal impairment, but the risk of bleeding was increased. It is unclear whether the benefits outweigh the risks of bleeding for these patients and which factor the patients consider to be more serious. However, few reports have investigated the effect of the degree of renal impairment on bleeding risk in Japanese patients receiving warfarin.

Will New Oral Anticoagulants Offer a Benefit to Japanese AF Patients With Moderate Renal Impairment?

The new oral anticoagulants (dabigatran, rivaroxaban and apixaban) have been recently reported as associated with stroke rates that are lower than or comparable to that for warfarin, and all these anticoagulants have shown reduced intracranial hemorrhage compared with warfarin. These 3 new drugs are mainly or partially eliminated by the kidneys (dabigatran 80%, rivaroxaban 33%, apixaban 25%). Patients with a creatinine clearance (CrCl) <30 ml/min (<25 ml/min in the ARISTOTLE trial) were excluded from large prospective phase III clinical trials. In the RE-LY trial, 19% of participants had moderate renal impairment (CrCl 30–49 ml/min). Despite a 2.3-fold increase in the steady-state trough concentration of dabigatran compared with patients with normal renal function, patients with moderate renal function showed a greater stroke reduction when taking dabigatran 150 mg twice daily compared with warfarin (hazard ratio 0.46, 95% confidence interval [CI] 0.29–0.73). Furthermore, the risk for major bleeding was comparable to that of warfarin (hazard ratio 0.97, 95% CI 0.74–1.27). Therefore, the FDA approved dabigatranat with no dose adjustment for patients with a CrCl of 30–49 ml/min. However, there are no appropriate clinical data for Japanese patients.

Subanalyses of the ROCKET AF and ARISTOTLE trials indicated that moderate renal impairment was associated with increased risk of stroke/systemic thromboembolism and bleeding, and that rivaroxaban or apixaban did not increase the risk of major bleeding (including intracranial hemorrhage) in AF patients with moderate renal impairment.

Pharmacokinetic modeling of the steady-state of rivaroxaban indicated that 15 mg once daily for Japanese patients would be a comparable exposure to 20 mg once daily in Caucasian patients. The J-ROCKET AF study was conducted entirely in Japan to evaluate the safety of 15 mg once daily of rivaroxaban indicated that 15 mg once daily for Japanese patients would be a comparable exposure to 20 mg once daily in Caucasian patients. The J-ROCKET AF study was conducted entirely in Japan to evaluate the safety of 15 mg once daily of rivaroxaban and of 10 mg of rivaroxaban once daily in patients with a CrCl of 30–49 ml/min compared with warfarin dosed according to Japanese guidelines. The results of the J-ROCKET AF study were consistent with the global ROCKET-AF trial.

In this issue of the Journal, Hori et al present their evaluation of whether the adjusted dose of rivaroxaban 10 mg once daily in Japanese AF patients with a CrCl of 30–49 ml/min

The opinions expressed in this article are not necessarily those of the editors or of the Japanese Circulation Society.

Received January 15, 2013; accepted January 16, 2013; released online January 30, 2013
Department of Cardiology, Tokyo Women’s Medical University, Tokyo, Japan
Mailing address: Tsuyoshi Shiga, MD, Department of Cardiology, Tokyo Women’s Medical University, 8-1 Kawada-cho, Shinjuku-ku, Tokyo 162-8666, Japan. E-mail: mshiga@hij.twmu.ac.jp
All rights are reserved to the Japanese Circulation Society. For permissions, please e-mail: cj@j-circ.or.jp
would have similar effects and safety compared with warfarin from their subanalysis of the J-ROCKET AF study. This study is the first to address the effect of new anticoagulants or warfarin on stroke and bleeding in Japanese patients with AF and moderate renal impairment. First, the age, prevalence of female sex and mean CHADS2 score were all higher in patients with a ClCr of 30–49 ml/min than in those with ClCr ≥50 ml/min. Incidences of bleeding events and stroke/systemic embolism were higher in patients with a ClCr of 30–49 ml/min than in those with ClCr ≥50 ml/min. Second, the incidence of major bleeding was not significantly different between AF patients with a ClCr of 30–49 ml/min receiving rivaroxaban and those receiving warfarin, and the number of reports of intracranial hemorrhage was low (2 patients with rivaroxaban and 4 with warfarin). Third, rivaroxaban did not increase the incidence of stroke/systemic thromboembolism compared with warfarin in AF patients with a ClCr of 30–49 ml/min. Pharmacokinetic evaluation showed an increased blood concentration of rivaroxaban in patients with a ClCr of 30–49 ml/min compared with subjects with a ClCr ≥80 ml/min, but the prolongation of prothrombin time was less affected. Although the influence of renal impairment on the pharmacokinetics of the anticoagulants has concentration-effect relationships, therapeutic margins do exist. The role of warfarin and the new oral anticoagulants should be evaluated in clinical studies that include Japanese AF patients with moderate renal impairment.

In summary, renal impairment is an important marker for risk of stroke in patients with AF. Anticoagulants that show certain clinical effects with no increase of bleeding risk are necessary for patients who are at increased risk of bleeding. It is time to reconsider anticoagulant therapy in Japanese patients with AF and moderate renal impairment because racial/ethnic differences do exist in the occurrence of stroke and bleeding, as well as in the pharmacokinetic profile.

References