Atrial fibrillation (AF) is known to be associated with an increased risk of ischemic stroke, secondary to cerebral embolism, and such strokes are generally attributable to left atrial thromboembolism. The risk of ischemic stroke in patients with AF is dependent on associated stroke risk factors. Clinical stroke risk stratification schemes have been introduced to aid the identification of patients with non-valvular AF who are at risk for ischemic stroke. These schemes include the CHADS2: score, and the CHA2DS2-VASc score with HAS-BLED; the latter comprises a more detailed stroke risk scoring system, and includes an assessment of the 1-year risk of complications resulting from excessive bleeding. Guidelines produced by the Japanese Circulation Society and the European Society of Cardiology recommend the use of an oral vitamin K antagonist (VKA; ie, warfarin) at a well-controlled adjusted dose, or new/non-VKA oral anticoagulants (NOACs; ie, dabigatran, rivaroxaban, apixaban, and edoxaban) for patients with non-valvular AF and one or more stroke risk factor(s). Furthermore, these guidelines state that NOACs are more useful as an alternative to warfarin for the prevention of stroke and systemic thromboembolism in patients with non-valvular AF, on the basis of their relative convenience in clinical practice. A recent meta-analysis of randomized trials supports the recommendations made in these guidelines.

The efficacy and safety of NOACs have been demonstrated...
in 4 global phase III trials (Randomized Evaluation of Long-Term Anticoagulation Therapy [RE-LY], \(^5\) including Japanese patients with dabigatran; Rivaroxaban Once Daily Oral Direct Factor Xa Inhibitor Compared with Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation [ROCKET AF], \(^6\) excluding Japanese patients with rivaroxaban; Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation [ARISTOTLE], \(^7\) including Japanese patients with apixaban; Effective aNiticoaGulation with factor xA nG in Atrial Fibrillation [ENGAGE AF-TIMI 48], \(^8\) including Japanese patients with edoxaban) and a domestic phase III trial in Japan (J-ROCKET AF \(^9\) with rivaroxaban). Based on the results of these studies, the Ministry of Health, Labour and Welfare (MHLW) in Japan approved the following NOACs for insurance coverage between March 2011 and September 2014: dabigatran, in both 150 mg twice daily (b.i.d.) and 100 mg b.i.d. doses; \(^10\) rivaroxaban, 15 mg once daily (o.d.) (10 mg o.d. for patients with estimated creatinine clearance [CCr] 30–50 ml/min); \(^11\) apixaban, 5 mg b.i.d. (2.5 mg b.i.d. for patients with at least 2/3 of the following indices: age ≥80 years, body weight ≤60 kg, serum creatinine ≥1.5 mg/dl; \(^12\) and edoxaban, 60 mg o.d. (30 mg o.d. for patients with body weight ≤60 kg). \(^13\) Therefore, physicians now can choose from 4 NOACs for the management of Japanese patients with non-valvular AF. Recently, attention has been drawn to the proper use of and discrimination between these 4 NOACs.

Data derived from phase III trials can be used to compare the safety outcomes of NOACs with those of warfarin, in a population with moderate renal impairment (Figure 1). Because NOACs are renally excreted, physicians must check renal function and consider dose-adjustment (ie, selection of a lower NOAC dose prior to initiation of antithrombotic therapy). The package insert of each NOAC provides information regarding the use of these drugs in patients with renal impairment. Dabigatran, for example, cannot be used in AF patients with severe renal impairment (CCr <30 ml/min) because of a high renal clearance (85%). \(^14\) Rivaroxaban apixaban, and edoxaban may be used with caution, at an adequately low dose (10 mg o.d., 5 mg b.i.d., and 30 mg o.d., respectively), in AF patients with moderate renal impairment (CCr, 30–50 ml/min); the 3 drugs may be also used at these dosages with “extreme caution” in AF patients with severe renal impairment (CCr, 15–30 ml/min) because of lower renal clearances (33%, \(^14\) 27%, \(^14\) and 50%, \(^14\) respectively). However, in AF patients with severe renal impairment (CCr, 15–30 ml/min), there is no clinical evidence related to the efficacy and safety of rivaroxaban, apixaban, or edoxaban.

In this issue of the Journal, Koretsune et al \(^15\) assess the safety and plasma concentrations of a very low dose edoxaban (15 mg o.d.) in Japanese patients with non-valvular AF and severe renal impairment (CCr, 15–30 ml/min). Their results indicated that edoxaban 15 mg o.d. was similar, in terms of safety, to the 30 mg and 60 mg doses used in AF patients with normal renal function or mild renal impairment; there was no increase in the risk for bleeding, plasma concentration of edoxaban, or biomarkers, such as prothrombin time (PT), PT expressed as an international normalized ratio, and activated partial thromboplastin time. This study was short-term, observation in nature, and the efficacy related to ischemic stroke events with follow-up is not shown; however, the effect is considered to be significant, because the results demonstrated the feasibility of using a very low dose of edoxaban in Japanese AF patients with severe renal impairment.

Recently, Nielsen et al \(^16\) investigated the relative effect of warfarin vs. each of the 4 NOACs, in terms of thrombotic and bleeding outcomes, in subgroups of patients with varying degrees (moderate [CCr 25–50 or 30–50 ml/min] or mild [CCr

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**Figure 2.** Selection of NOACs, according to an index for renal impairment (CCr) based on the package inserts of the relevant NOAC, in Japanese patients with non-valvular AF at risk for thromboembolism and bleeding. Although there are no published clinical data regarding NOACs shown with thin-line squares (CCr 15–30 ml/min), Koretsune et al \(^15\) demonstrated the safety of edoxaban when used at a very low dose. CCr, estimated creatinine clearance; NOAC, new/non-VKA oral anticoagulant; VKA, Vitamin K antagonist.
50–80 ml/min) of renal impairment. Those authors used a meta-analysis of major phase III trials to assess whether the subgroup effect differed across NOACs. They concluded that the efficacy and safety of NOACs are similar to warfarin, across different levels of renal function. In addition, the results indicated that apixaban and edoxaban were associated with a better safety profile in patients with moderate renal impairment. However, as noted by the authors, caution is warranted when interpreting indirect comparisons of drugs investigated in different trials. Physicians should select the most appropriate NOAC for each AF patient, to provide individualized and effective stroke prevention.

Selection of NOACs in Japanese AF patients at risk for thromboembolism and bleeding based on an index of renal impairment (CCr), according to the package insert of each NOAC, is shown in Figure 2. Rivaroxaban, apixaban, and edoxaban may be used with extreme caution, but to date there are no clinical data to support their use. With regard to edoxaban, safety was confirmed by Koretsune et al. The question remains: which NOACs can be selected for use in Japanese AF patients with severe renal impairment (CCr 15–30 ml/min), to prevent ischemic stroke and to avoid major bleeding? This author answers that it is still unknown. Further studies would be needed in a larger population, and with a long follow-up period, to understand which NOAC is safest and most effective in AF patients with severe renal impairment.

Disclosures
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