Prevention of strokes using anticoagulants is the main target of the management of atrial fibrillation (AF). To achieve this, warfarin and other oral anticoagulants have been prescribed and are now mainstream therapy for AF. However, it has been reported that there are regional differences in the safety profile of warfarin, namely, Asians or East Asians have a higher risk of bleeding events, including intracranial hemorrhage, than non-Asians despite a lower PT-INR control.\(^1\)–\(^3\) Therefore, clinicians in Asia are always concerned about the risk of bleeding side-effects, and warfarin is often under-prescribed or under-dosed in the real world.\(^1\)–\(^6\) Non-vitamin K antagonist oral anticoagulants (NOACs) have been recently introduced and have demonstrated many clinical advantages compared with warfarin in patients with nonvalvular AF (NVAF). However, it has also been reported that the efficacy and safety profile of each NOAC differs regionally and with individual characteristics (ie, age, body weight (BW), renal function, etc). Therefore, it is important to analyze the efficacy and safety of anticoagulants according to region and individual characteristics.

**Regional Differences in Renal Function Between Asian and Non-Asian Patients**

In general, BW in Asians is lower than in non-Asians. In fact, the mean (median) BW of patients in (East) Asia was significantly lower than that of those from non-(East) Asia in recent global clinical trials of NOACs, and the difference was not negligible: 20 kg in RELY, 16 kg in ROCKET AF, and 17 kg in ARISTOTLE (Figure 1A).\(^1\)–\(^3\) BW is an important factor in estimating renal function, and the creatinine clearance (CCr) is estimated using Cockcroft-Gault equations that are calculated by the serum creatinine level, age, BW, and sex of the patient. Renal function is crucial in patients with NVAF receiving anticoagulation therapy. Impaired renal function increases the risk of strokes and bleeding in patients with AF compared with those with a preserved renal function, irrespective of whether the patients are treated with warfarin or NOACs.\(^7\)–\(^10\)

Figure 1B shows the percentage of patients in each renal function level (CCr ≥ 80, 50–80, and < 50 ml/min) in the clinical trials (RELY, ROCKET-AF, and ARISTOTLE).\(^1\)–\(^3\) The mean CCr was lower, and a mild or moderate renal impairment (CCr < 80 ml/min) was more frequently observed in (East) Asians than in non-(East) Asians because of the substantially lower BW in (East) Asians, but the (East) Asian patients were younger than the non-(East) Asian patients in these trials.\(^1\)–\(^3\)

The efficacy and safety of anticoagulation are influenced by renal function, and it is lower in Asian patients than in non-Asian patients. Therefore, it is important to assess efficacy and safety according to renal function in Asian AF patients.

In this issue of the Journal, Hori et al analyze the Asian patients in the RE-LY trial to evaluate the relationship between the baseline renal function or CHADS2 score category and the prevention of strokes using anticoagulants is the main target of the management of atrial fibrillation (AF). To achieve this, warfarin and other oral anticoagulants have been prescribed and are now mainstream therapy for AF. However, it has been reported that there are regional differences in the safety profile of warfarin, namely, Asians or East Asians have a higher risk of bleeding events, including intracranial hemorrhage, than non-Asians despite a lower PT-INR control.\(^1\)–\(^3\) Therefore, clinicians in Asia are always concerned about the risk of bleeding side-effects, and warfarin is often under-prescribed or under-dosed in the real world.\(^1\)–\(^6\) Non-vitamin K antagonist oral anticoagulants (NOACs) have been recently introduced and have demonstrated many clinical advantages compared with warfarin in patients with nonvalvular AF (NVAF). However, it has also been reported that the efficacy and safety profile of each NOAC differs regionally and with individual characteristics (ie, age, body weight (BW), renal function, etc). Therefore, it is important to analyze the efficacy and safety of anticoagulants according to region and individual characteristics.

**Regional Differences in Renal Function Between Asian and Non-Asian Patients**

In general, BW in Asians is lower than in non-Asians. In fact, the mean (median) BW of patients in (East) Asia was significantly lower than that of those from non-(East) Asia in recent global clinical trials of NOACs, and the difference was not negligible: 20 kg in RELY, 16 kg in ROCKET AF, and 17 kg in ARISTOTLE (Figure 1A).\(^1\)–\(^3\) BW is an important factor in estimating renal function, and the creatinine clearance (CCr) is estimated using Cockcroft-Gault equations that are calculated by the serum creatinine level, age, BW, and sex of the patient. Renal function is crucial in patients with NVAF receiving anticoagulation therapy. Impaired renal function increases the risk of strokes and bleeding in patients with AF compared with those with a preserved renal function, irrespective of whether the patients are treated with warfarin or NOACs.\(^7\)–\(^10\)

Figure 1B shows the percentage of patients in each renal function level (CCr ≥ 80, 50–80, and < 50 ml/min) in the clinical trials (RELY, ROCKET-AF, and ARISTOTLE).\(^1\)–\(^3\) The mean CCr was lower, and a mild or moderate renal impairment (CCr < 80 ml/min) was more frequently observed in (East) Asians than in non-(East) Asians because of the substantially lower BW in (East) Asians, but the (East) Asian patients were younger than the non-(East) Asian patients in these trials.\(^1\)–\(^3\)

The efficacy and safety of anticoagulation are influenced by renal function, and it is lower in Asian patients than in non-Asian patients. Therefore, it is important to assess efficacy and safety according to renal function in Asian AF patients.

In this issue of the Journal, Hori et al analyze the Asian patients in the RE-LY trial to evaluate the relationship between the baseline renal function or CHADS2 score category and the prevention of strokes using anticoagulants is the main target of the management of atrial fibrillation (AF). To achieve this, warfarin and other oral anticoagulants have been prescribed and are now mainstream therapy for AF. However, it has been reported that there are regional differences in the safety profile of warfarin, namely, Asians or East Asians have a higher risk of bleeding events, including intracranial hemorrhage, than non-Asians despite a lower PT-INR control.\(^1\)–\(^3\) Therefore, clinicians in Asia are always concerned about the risk of bleeding side-effects, and warfarin is often under-prescribed or under-dosed in the real world.\(^1\)–\(^6\) Non-vitamin K antagonist oral anticoagulants (NOACs) have been recently introduced and have demonstrated many clinical advantages compared with warfarin in patients with nonvalvular AF (NVAF). However, it has also been reported that the efficacy and safety profile of each NOAC differs regionally and with individual characteristics (ie, age, body weight (BW), renal function, etc). Therefore, it is important to analyze the efficacy and safety of anticoagulants according to region and individual characteristics.
efficacy and safety outcomes. In their study, 2,782 Asian patients from 10 Asian countries were evaluated, with a mean age of 68 years, mean BW of 66.3 kg, and mean CCr of 65.3 ml/min. They conclude that the bleeding and stroke rates in Asian patients varied according to renal function and CHADS2 score, but the relative efficacy and safety of dabigatran over warfarin were preserved when analyzed by subcategories.

Renal Function Deterioration in AF Patients Receiving Anticoagulation Therapy

There is another important topic concerning the relationship between renal function and anticoagulation: the change in renal function during anticoagulation. Roldán et al12 evaluated the changes in glomerular filtration rate (GFR) during long-term follow-up of patients receiving anticoagulation with acenocoumarol. After excluding patients with a baseline GFR <30 ml/min/1.73m2, a mean GFR decrease >10 ml/min/1.73 m2 was observed in 181 of 863 patients (21%) during a median follow-up of 875 days. Böhmm et al evaluated the changes in GFR for up to 30 months in patients enrolled in the RELY trial, and reported that the GFR declined in all treatment groups (dabigatran 220 mg/day, 300 mg/day, and warfarin). Interestingly, they also found that the decline in the GFR was significantly greater with warfarin than with either dose of dabigatran. We recently evaluated the time course of renal function in 807 consecutive NVAF patients treated with NOACs and with a CCr ≥50 ml/min. During a mean follow-up of 382±288 days, 751 (93%) patients maintained a CCr ≥50 ml/min (group A), whereas the CCr declined to <50 ml/min in the remaining 56 (7%) patients (group B). We showed that renal function deterioration was not uncommon in patients receiving anticoagulation and that patients with a higher CHADS2 score were more prone to develop impaired renal function. In addition, renal function deterioration during anticoagulation was associated with more frequent adverse events, including major bleeding events in NVAF patients.

Figure 2 shows the CHADS2 score and risk factors for chronic kidney disease. Some of those (age, hypertension, and diabetes mellitus) are identical to the risk factors used to calculate the CHADS2 score. Therefore, we should keep in mind that many AF patients with a CHADS2 score ≥1 have risks not only for stroke, but also for renal function deterioration, which may lead to an increasing concentration of anticoagulation drugs and bleeding events.

Anticoagulation using NOACs could confer a greater benefit to Asian NVAF patients than non-Asian patients, including a substantially reduced incidence of intracranial hemorrhages compared with warfarin. To put the NOAC treatment to safer, practical use, we need to monitor the laboratory data, including the renal function, carefully during anticoagulation therapy.

Disclosures

K.K. received lecture fees from Bayer, Boehringer Ingelheim, Bristol-Myers, Pfizer, Daiichi-Sankyo, and Eisai. K.M. received lecture fees from Bristol-Myers.

References

1. Goto S, Zhu J, Liu L, Oh BH, Wijdya DM, Aylward P, et al. Efficacy and safety of apixaban compared with warfarin for stroke prevention in patients with atrial fibrillation from East Asia: A subanalysis of the Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation (ARISTOTLE) Trial. Am Heart J 2014; 168: 290 – 309.

2. Hori M, Connolly SJ, Zhu J, Liu LS, Lau CP, Pais P, et al. Dabigatran versus warfarin: Effects on ischemic and hemorrhagic strokes and bleeding in Asians and non-Asians with atrial fibrillation. Stroke 2013; 44: 1891 – 1896.

3. Wong KS, Hu DY, Oomman A, Tan RS, Patel MR, Singer DE, et al. Rivaroxaban for stroke prevention in East Asian patients from the ROCKET AF trial. Stroke 2014; 45: 1739 – 1747.

4. Iroha H, Atarashi H, Okumura K, Yamashita T, Kumagai N, Origasa H. Thromboembolic events in paroxysmal vs. permanent non-valvular atrial fibrillation: Subanalysis of the J-RHYTHM Registry. Circ J 2014; 78: 2388 – 2393.

5. Kakkar AK, Mueller I, Bassand JP, Fitzmaurice DA, Goldhaber SZ, Goto S, et al. Risk profiles and antithrombotic treatment of patients newly diagnosed with atrial fibrillation at risk of atrial fibrillation at risk of stroke: Perspectives from the international, observational, prospective GARFIELD registry. PLoS One 2013; 8: e63479, doi:10.1371/journal.pone.0063479.

6. Tada H. Thromboembolic risks that require consideration for anti-thrombotic therapy in Japanese patients with atrial fibrillation. Circ J 2014; 78: 2373 – 2375.

7. Connolly SJ, Ezekowitz MD, Yusuf S, Eikelboom J, Oldgren J, Parekh A, et al. Dabigatran versus warfarin in patients with atrial fibrillation. N Engl J Med 2009; 361: 1139 – 1151.

8. Giugliano RP, Ruff CT, Braunwald E, Murphy SA, Wiviott SD, Halperin JL, et al. Edoxaban versus warfarin in patients with atrial fibrillation. N Engl J Med 2013; 369: 2093 – 2104.

9. Granger CB, Alexander JH, McMurray JJ, Lopes RD, Hylek EM, Hanna M, et al. Apixaban versus warfarin in patients with atrial fibrillation. N Engl J Med 2011; 365: 981 – 992.

10. Patel MR, Mahaffey KW, Garg J, Pan G, Singer DE, Hacke W, et al. Rivaroxaban versus warfarin in nonvalvular atrial fibrillation. N Engl J Med 2011; 365: 883 – 891.

11. Hori M, Fukaya T, Kleine E, Reilly PA, Ezekowitz MD, Connolly SJ, et al. Efficacy and safety of dabigatran etexilate vs. warfarin in Asian RE-LY patients according to baseline renal function or CHADS2 Score. Circ J 2015; 79: 2138 – 2147.

12. Roldán V, Marin F, Fernandez H, Manzano-Fernandez S, Gallego P, Valdes M, et al. Renal impairment in a “real-life” cohort of anticoagulated patients with atrial fibrillation (implications for thromboembolism and bleeding). Am J Cardiol 2013; 111: 1159 – 1164.

13. Bohn M, Ezekowitz MD, Connolly SJ, Eikelboom JW, Hohnloser SH, Reilly PA, et al. Changes in renal function in patients with atrial fibrillation: An analysis from the RE-LY Trial. Am Coll Cardiol 2015; 65: 2481 – 2493.

14. Miyamoto K, Aiba T, Aihiro S, Watanabe M, Kokubo Y, Ishibashi K, et al. Impact of renal function deterioration on adverse events during anticoagulation therapy using non-vitamin K antagonist oral anticoagulants in patients with atrial fibrillation. Heart Vessels 2015 August 15, doi:10.1007/s00380-015-0725-6.

15. Japanese Society of Nephrology. Clinical practice guidebook for diagnosis and treatment of chronic kidney disease. Tokyo: Igakusha, 2012 (in Japanese).