See related article, p 1739.

Atrial fibrillation (AF) is a global problem, contributing to a significant burden of mortality and morbidity, particularly from stroke and systemic thromboembolism. Effective stroke prevention requires oral anticoagulation (OAC), and until recently our options were limited to the vitamin K antagonist (VKA; eg, warfarin) class of drugs. VKAs were an inconvenient drug that required regular monitoring to keep within a relatively narrow therapeutic range, and the efficacy and safety were dependent on treatment adherence and good quality anticoagulation control (as reflected by a time in therapeutic range [TTR]).

In Asian patients, the VKAs have additional issues, when compared with non-Asians, they have a higher risk for intracranial bleeding, major hemorrhage, and stroke, as well as difficulties in maintaining a high TTR. There was also uncertainty over what was the optimal target international normalized ratio (INR) range in Asians, which was perceived to be lower than the range recommended in non-Asians (ie, INR, 2.0–3.0).

The availability of the non-VKA OACs (NOACs; previously referred to as new or novel OACs) has resulted in a major change in the landscape for stroke prevention, given that these drugs offer relative efficacy, safety, and convenience when compared with the VKAs. Trials in Asian patients and ancillary publications from the large Phase 3 clinical trials comparing Asian versus non-Asian patients all consistently show that NOACs offer effective and safe options for stroke prevention when compared with VKAs. Expectations are, therefore, high.

In this issue of Stroke, Wong et al investigated the efficacy and safety of rivaroxaban for stroke prevention in East Asian subgroup of patients from the ROCKET-AF trial and demonstrated that the observed relative efficacy and safety of rivaroxaban versus warfarin were similar among patients within and outside East Asia, thus concluding that rivaroxaban 20 mg once daily was an alternative to warfarin for prevention in East Asians with nonvalvular AF.

Pharmacological Considerations

The NOACs have peaks and troughs in their concentration curves when given once or twice a day. In the peak phases, coagulation is suppressed directly and strongly by the inhibition of thrombin or factor Xa. In the trough phases, especially for the drugs given once a daily use, it may not inhibit the coagulation cascade because the activity of rivaroxaban, for example, is low at trough phase according to its concentration curve because of its short half-life time of half a day. However, the Japanese Rivaroxaban Once Daily Oral Direct Factor Xa Inhibition Compared With Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation (J ROCKET) and Rivaroxaban Once Daily Oral Direct Factor Xa Inhibition Compared With Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation (ROCKET AF) trials and the ROCKET-AF East Asian subgroup clearly demonstrated similar efficacy and safety of rivaroxaban versus warfarin among patients within and outside East Asia. 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, that suppress thrombus formation if activity of thrombin increases during the trough phase. 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 or twice a daily, intermittent anticoagulation with other NOACs, as well as continuous anticoagulation with VKAs, is also thought to suppress the continuous activation of thrombin, thus preventing thrombus formation in the cardiovascular system even at the trough phase. During warfarin treatment, the anticoagulation is mediated by the inhibition of vitamin K–dependent clotting factors and not by physiological coagulation inhibitors because protein C and protein S (the main substance of physiological coagulation inhibitors) are suppressed strongly by warfarin. With NOAC treatment, both mechanisms of anticoagulation by NOAC and physiological coagulation inhibitors may play roles in preventing thrombus formation. At the peak phase, NOAC strongly suppresses thrombin activity, and physiological coagulation inhibitors are not exhausted and recover, although at the trough phase, the anticoagulation effect of NOAC per se would be weak but physiological coagulation inhibitors still work in preventing thrombus formation, perhaps conferring hybrid anticoagulation.

Characteristics of Asian Patients in Anticoagulation Trials

On the basis of ROCKET AF and Randomized Evaluation of Long-Term Anticoagulation Therapy (RE-LY) trials, we found that East Asian or Asian people with AF have lower body weight, creatinine clearance, and previous myocardial infarction but a higher rate of previous stroke when compared with patients from outside East Asia. The average TTR was generally lower in Asians when compared with that in non-Asians; furthermore, more Asian people had INRs <2.0 and less had INRs >3.0.
It seems that trial investigators in Asia tended to keep INRs in the lower range, with a perception of avoiding hemorrhagic complications. The tendency of lower TTRs, higher prevalence of previous stroke, and lower creatinine clearance may increase stroke risk in Asians. Although on VKA treatment, previous stroke and Asian race are major risks of intracranial hemorrhage.\textsuperscript{15,16} In the RE-LY trial, predisposing factors for intracranial bleeding were assignment to warfarin (relative risk, 2.9; \textit{P}<0.001), aspirin use (relative risk, 1.6; \textit{P}=0.01), age (relative risk, 1.1 per year; \textit{P}=0.001), and previous stroke/transient ischemic attack (relative risk, 1.8; \textit{P}=0.001), and among the patients actually assigned to warfarin treatment, race other than white was an independent risk factor for intracranial bleeding. The higher rate of intracranial bleeding in Asians may be because of their race and higher rate of previous stroke among Asians.

**Expectations for NOACs in Asia**

On the basis of randomized trials, we found that all the NOACs show a lower incidence of stroke and systemic embolism in both Asia and outside Asia, except for edoxaban 30mg. However, it would be important to use these drugs because they were studied in their respective clinical trials. For example, patients with AF and severe renal impairment were excluded from all the randomized trials, as were patients with significant valvular disease or prosthetic mechanical valves.

Particularly, impressive is the incidence of intracranial bleeding with each NOAC was substantially lower than with warfarin in both Asians and non-Asians (Table 1).\textsuperscript{9,10,12,17,18} This may be because of the characteristics of NOACs, which do not affect plasma concentrations of factor VII and complexes of tissue factor and factor VIIa that are essential for the first reaction in the coagulation cascade, whereas warfarin suppresses factor VII production even within the therapeutic range of INR, resulting in higher rate of intracranial hemorrhage.\textsuperscript{19}

In summary, Asians seem to do poorly on VKAs, with lower efficacy, poorer safety, and more intracranial bleeding when compared with non-Asians. Asians also seem to have poorer quality of anticoagulation control, as reflected by low TTRs, when compared with non-Asians. Aspirin is not the answer, given its lack of efficacy and poor safety. Therefore, NOACs, whether dabigatran, rivaroxaban, apixaban, or (when licensed) edoxaban would seem the best option for stroke prevention in treating Asian patients with nonvalvular AF.

**Disclosures**

Dr Lip has served as a consultant for Bayer, Astellas, Merck, Sanofi, Bristol-Myers Squibb/Pfizer, Daiichi-Sankyo, Biotronik, Medtronic, Portola, and Boehringer Ingelheim and has been on the speaker bureau for Bayer, BMS/Pfizer, Boehringer Ingelheim, Daiichi-Sankyo, Medtronic, and Sanofi Aventis. Dr Yasaka has received Lecture fees from Nippon Boehringer Ingelheim, Bayer Yakuhin, and Bristol-Myers Squibb.

**References**


**Key Words:** anticoagulants ▪ atrial fibrillation ▪ stroke