Atrial fibrillation (AF) is the most common sustained cardiac arrhythmia,\textsuperscript{1} and carries a 4- to 5-fold increased risk of stroke. Oral vitamin K antagonists, such as warfarin, has been extensively used for the prevention of AF-associated stroke, and effectively reduce the risk by approximately 65%. The problem with using warfarin is its narrow therapeutic range. Most of the international guidelines suggest keeping the international normalized ratio (INR) in the range of 2.0–3.0.\textsuperscript{2} The optimal INR of 2.0–3.0 was validated in Westerners,\textsuperscript{3} but has never been confirmed in Asians. Though most of the studies done in Asia suggest a lower range of INR (1.6–2.6), they have been either retrospective or small-scale. It is generally believed that Asians are prone to bleeding, so a lower INR should be advocated.\textsuperscript{4,5}

Are Asians Prone to Bleeding?

The most catastrophic side effect of warfarin is intracranial hemorrhage. In a retrospective cohort study of warfarin-treated AF patients with the same target INR of 2.0–3.0 across all races, the hazard ratio for intracranial hemorrhage in Asians was 4.06 compared with white people.\textsuperscript{6} Similarly, most of the Asian studies suggest an increased risk of major bleeding at much lower INR (≥2.3) for the use of warfarin in Asians.\textsuperscript{4} As already mentioned, most of the Asian studies were retrospective or small-scale, and major bleeding was ill-defined. Furthermore, the time in therapeutic range (TTR) was not provided. The best way to see whether warfarin therapy carries a high bleeding risk in Asians, including Japanese, is to examine the data from multinational randomized controlled trials (RCTs) comparing new oral anticoagulants with warfarin.\textsuperscript{7-9} In these RCTs, the risk of major bleeding from warfarin use in Asians can be compared with that in non-Asians with a similar target INR range and known TTR, under similar background risks of bleeding and stroke.

There were 2,782, 1,781, and 2,916 Asian patients in the RE-LY trial,\textsuperscript{7} ROCKET AF trial,\textsuperscript{8} and ARISTOTLE trial,\textsuperscript{9} respectively. All these trials used a target INR of 2.0–3.0 in all participating countries, except a minor modification in RE-LY A.
for Japanese, in which an INR of 2.0–2.6 was used for age ≥70 years. There were 326 Japanese patients in the RE-LY trial, and 336 in the ARISTOTLE trial. Japanese patients were not enrolled in the ROCKET AF trial because of a disagreement over the target INR. The Asian data in these trials were either published or included in the original paper or supplementary appendix. The Japanese data in ARISTOTLE were not published, but can be found in the FDA reviews (202155Orig1s000MedR.pdf; http://www.accessdata.fda.gov/drugsatfda_docs/nda/2012/202155Orig1s000TOC.cfm). The mean or median TTR was generally lower in Asians, with less time above 3.0 and more time below 2.0. For instance, Asian patients in the RE-LY trial had a mean TTR (INR 2.0–3.0) of 54.5% (non-Asians: 66.2%), with 35.4% of INR <2.0 (non-Asians: 19.8%) and 10.1% of INR >3.0 (non-Asians: 14.0%). These data suggest that physicians in Asia tended to keep the INR in the lower range (more than one-third had INR <2.0 in the RE-LY trial) on the presumption that a lower INR might protect Asian patients from bleeding.

The incidence of major bleeding in warfarin users in these 3 RCTs is shown in Figure 1. Asians had higher risk of bleeding than non-Asians across all 3 RCTs, despite a lower INR. The risk of major bleeding was highest in Japanese, as shown in the ARISTOTLE trial. The slightly lower risk of major bleeding in Japanese in the RE-LY trial might be related to the adjusted INR (2.0–2.6) for age ≥70 years. These data strongly suggest that warfarin-users in Asians are prone to bleeding. Keeping the INR in the lower range might not be effective to prevent bleeding in Asian patients.

Is Lower INR Protective Against Stroke for Asians? Figure 2 shows the risk of stroke plus systemic embolism in warfarin-users in the 3 RCTs. Apparently, the risk was higher in Asians and Japanese than in non-Asians. The baseline risk of stroke before treatment (ie, mean CHADS2 score) was similar for Asians and non-Asians. For instance, the mean CHADS2 score was 2.1 in non-Asians, and 2.2 for Asians in the RE-LY trial. It is possible that insufficient anticoagulation (lower INR) accounts for the higher risk in Asians. This finding is similarly to a recent meta-analysis of warfarin use, in which the risk of stroke plus systemic embolism in Asians was 70% higher than in non-Asians.

What Did J-RHYTHM Tell Us? In this issue of the Journal, Inoue et al report their findings from J-RHYTHM, an observational cohort of 7,527 patients with non-valvular AF in Japan for a mean follow-up of 2 years. They conclude that an INR of 1.6–2.6 was the best target for the prevention of thromboembolism, particularly for patients aged ≥70 years, and that an INR of 2.6–2.99 was associated with an increased risk of major bleeding. The authors should be congratulated for this important finding in Japanese. It is generally agreed that the an INR in the upper range (2.6–3.0) is associated with increased risk of bleeding in Asians. But an INR of 1.6–1.99 might not be protective against stroke, a finding drawn from the 3 RCTs. A major limitation in the present report, which is also mentioned by the authors, is that only the baseline INR was used in their analysis. The use of antithrombotics was not controlled, nor was TTR provided. Until an RCT comparing target INRs of 1.6–1.99, 2.0–2.59, and 2.6–3.0 is available, we will never know the optimal range of INR in Asians and Japanese. Fortunately, the new oral anticoagulants are equal or even superior to warfarin in Asians, so the use of warfarin will become obsolete in the future.

In conclusion, the optimal range of INR for Asians and Japanese might be narrower than for non-Asians. We will never know the correct answer unless RCTs are available.

References