A Unique Warfarin Therapy in Japan
– Is It Appropriate or Eccentric? –

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Warfarin has been the standard therapy for anticoagulation of patients with atrial fibrillation (AF) for many years. Its efficacy in preventing stroke has been well demonstrated. Unfortunately, however, the benefit of warfarin therapy to a patient varies widely, depending not only on the intensity of anticoagulation as reflected by the international normalized ratio of prothrombin time (PT-INR) but also on the temporal quality of anticoagulation as expressed as time in the therapeutic range (TTR). A lower TTR may result from poor patient compliance, a timid doctor’s anxiety about the hemorrhagic risk, or interactions with other drugs or food, all of which can potentially negate the benefit of warfarin.

A wide variation in warfarin control is typically seen in an individual patient, but there are also wide variations between doctors, institutions, and even countries. Comparisons of the TTR among countries have shown a wide variation ranging from 46.3% to 77.8% in the ACTIVE-W study and from 44% to 77% in RE-LY.1,2 It has been shown that data from individual countries closely follow the relationship between relative risk for major cardiovascular events and TTR.3 If such a tendency exists, the benefit of patients seeing such doctors in such institutions in such countries presenting lower TTR could also be at stake.

In this issue of the Journal, Okumura et al show that the average TTR among 501 AF patients taking warfarin in Japan was 64%.4 Does this relatively high TTR mean a good quality of warfarin control in Japan?

This value is actually higher than the TTR of 57.6% reported by RE-LY subanalysis of the 326 Japanese AF patients.4 Notably, although the target PT-INR of 2–3 was consistent between the 2 studies for those aged <70 years, the present study defined the target PT-INR of 1.6–2.6 for those ≥70 years as recommended by the Japanese guidelines for AF management,5 whereas the Japanese RE-LY trial pursued a PT-INR of 2.0–2.6 for the same age group of patients. The fact that the mean ages were 70 and 71, respectively in this and the Japanese RE-LY studies constitutes a problem, because the majority of study patients would have been close to the age 70, at which the definition of the target PT-INR suddenly changes. In Figure 4 of the present study, one will observe that the distribution of the TTR was in fact not age-dependent, but rather criteria-dependent.

The majority of countries use a target PT-INR of 2–3 and no countries other than Japan use dual definitions of the target PT-INR according to age. There is no convincing evidence in Japan, however, to support that the dual targets of PT-INR are really optimal. The basis for the unique Japanese guideline is essentially derived from a single clinical report on the secondary prevention of stroke in AF patients.6 That report actually shows the combined results of 2 independent 2-year follow-up studies, comprising 115 patients from 19 institutions and 88 patients from 1 institution. It has to be mentioned that those subjects were recruited at least 1 month after the event of stroke or TIA, so the event rate of subsequent major stroke or systemic embolism during warfarin treatment for secondary prevention was low. 4 of 203 patients, all aged 69 years or older, and occurred at PT-INR <1.6. Apparently this will not guarantee that PT-INR >1.6 provides safe protection from stroke or systemic embolism in elderly people, including those without prior ischemic events. Therefore, we currently cannot conclude that the high TTR of 77% in the older age group shown in the present study is associated with greater protection from stroke or systemic embolism.

Similarly, there are not sufficient data to conclude that the low TTR of 46% shown in the younger age group is associated with a lesser protection. It is interesting to note that this low TTR was not reflective of the wide variation of PT-INR during follow-up, but rather reflected consistently weak warfarin control for the same age group as shown by the skewed distribution of the out-of-range data, with the time spent below and above therapeutic range being 51% and 2%, respectively. This finding is consistent with a recent report from the J-RHYTHM registry, describing rates of PT-INR <2 during warfarin therapy for AF that were 60.3% in 3,640 patients <70 years of age and 63.1% in 4,297 patients ≥70.7 The message is that in the majority of clinical practice in Japan, the intensity of the PT-INR is not adjusted by age as recommended by the Japanese guideline.

It should be noted that in the present study there were 198 low-risk patients whose CHADS2 scores were 0 or 1. It follows that approximately 40% of the patients who are not absolute candidates for warfarin therapy did receive warfarin based on the decision of the attending physician. It may not be surprising that those patients with lower CHADS2 scores received relatively lower doses of warfarin, thus showing lower TTR values than those with higher CHADS2 scores.
scores, as demonstrated in Figure 5 of the present study. If these lower values of TTR reflect PT-INRs below the target range, this probably will not be harmful if not effective. And if this is the case, TTR can be misleading or even meaningless in this low-risk subgroup.

Another interesting observation from this study is that the warfarin dose was an independent predictor of TTR. The finding is provocative in suggesting that the higher the dose of warfarin you need, the lower the TTR becomes. The dose requirement of warfarin has been reported to be relatively low in Asians, which can be explained by several factors, including frequent VKORC1 polymorphism, small body size, and high vitamin K content in foods in Asian countries. However, according to the data from RE-LY, the mean TTR values were relatively low in Asian countries. That finding is rather explained by an incomplete pursuit of the target PT-INR for patients requiring a larger amount of warfarin, and this most likely reflects timidity on the doctor’s part.

In conclusion, Okumura et al have shown the current status of TTR in Japanese patients with AF. One has to be reminded that this TTR is based on a unique definition of the target PT-INR used in Japan. Whether this definition is appropriate or eccentric has yet to be fully validated. The contrasting results of high and low TTR shown between elderly and young patients and between those with higher and lower CHADS2 scores and between those requiring lower and higher doses of warfarin warrant further research to be more clinically relevant. Once it has been demonstrated by large prospective clinical studies that lower TTR in subgroups of Japanese AF population is associated with relatively high event rates for stroke compared with other countries with similar TTR but using different criteria, the Japanese guideline is the one to be revised.

References