How to Obtain Benefit From Warfarin Therapy for Very Old Japanese Patients

In this issue of the Journal, Kodani et al investigate the effects of warfarin treatment in very old patients with nonvalvular atrial fibrillation (NVAF) using data from the J-Rhythm Registry. They found that the rate of thromboembolism plus major hemorrhage was lower with a prothrombin time-international normalized ratio (PT-INR) between 1.6 and 2.6 in the age groups 70–84 and ≥85 years old (P<0.001, respectively) and concluded that warfarin provided beneficial effects not only in the old NVAF patients (70–84 years old), but also in very old NVAF patients (≥85 years) if the PT-INR is kept between 1.6 and 2.6. Although a significant reduction in the rate of thromboembolism was observed in the youngest group when patients were subdivided at 70 years, it was not significant when the cut-off age was set at 65 years. The authors then considered that it would be difficult to conclude that PT-INR 1.6–2.6 is optimal in patients aged <65 years from their data. Their study clearly supports the Japanese guideline for warfarin management for NVAF patients, in which a PT-INR between 1.6 and 2.6 is recommended in the elderly ≥70 years old.

On the other hand, Western countries recommend a PT-INR...
between 2.0 and 3.0, irrespective of age. There may be racial differences in the appropriate PT-INR for prevention of stroke in NVAF patients. The Japanese Nonvalvular Atrial Fibrillation-Embolism Secondary Prevention Cooperative Study, a prospective, randomized, multicenter trial, issued a bleeding warning for conventional warfarin therapy with a PT-INR from 2.2 to 3.5 in older patients in 2000. My group analyzed the relationship between the occurrence of ischemic and hemorrhagic events with INR and age in 203 patients with NVAF for a mean of 653 days and found that major ischemic or hemorrhagic events occurred often in elderly NVAF patients at a PT-INR below 1.6 and above 2.6. The J-Rhythm Registry, including a large number of patients with AF, was conducted by cardiologists in Japan to elucidate the status of anticoagulant therapy and the appropriate PT-INR in Japanese patients with AF. The result supported the Japanese guideline for warfarin management for NVAF patients, in which a PT-INR between 1.6 and 2.6 is recommended for the elderly ≥70 years old and between 2.0 and 3.0 in the younger <70 years group, and they found paroxysmal AF and permanent AF had the same thromboembolic risk. Yamashita et al compared J-Rhythm Registry data with data from Western countries and found that the PT-INR risk relationship shifted leftward by approximately 0.5 PT-INR for intracranial hemorrhage.

The effect of the high incidence of intracranial bleeding in Japan and East Asia identified by epidemiological studies and the 4-fold higher incidence of brain hemorrhage among Asian compared with Caucasian populations may affect warfarin management in Asia, East Asia, and Japan. Although physicians in Asia have tended to keep the PT-INR in the lower range to avoid hemorrhagic complications, the incidence of intracranial hemorrhage is still higher in East Asian than in Western countries. Considering these racial differences in response to the PT-INR, it is very important to elucidate the appropriate PT-INR in elderly and very elderly Japanese patients, for which the current study by Kodani et al is appreciated. However, because the J-Rhythm Registry study was conducted by cardiologists with good management of warfarin, including a greater time in the therapeutic range, appropriate everyday management of warfarin is required to obtain fruitful results in elderly and very elderly patients with NVAF. Unless warfarin is managed well, we cannot expect any benefit from anticoagulant therapy.

What happens at a PT-INR Below 1.6?

The effect of warfarin treatment with PT-INR ≥1.6 on prevention of ischemic stroke and systemic embolic episode has been shown by previous studies from Japan and the J-Rhythm study in the current issue. So, what happens with warfarin treatment at a PT-INR below 1.6? Of course, there is a risk of ischemic stroke. In fact, the risk may be more than has been considered. It is well known that the plasma level of protein C, a physiological anticoagulant factor dependent on vitamin K, decreases the earliest among the vitamin K-dependent anticoagulant or coagulant factors when the PT-INR is below 1.6 (Figure). Therefore, coagulation activity could be more activated at a PT-INR <1.6 than before introducing warfarin, which is called the “warfarin dilemma” as a warning. Azoulay et al studied whether initiation of warfarin is associated with an increased risk of stroke in patients with AF, using the UK Clinical Practice Research Datalink, and they found that warfarin was associated with a 71% increased risk of stroke in the first 30 days of use when compared with non-use (RR: 1.71, 95% CI: 1.39–2.12), indicating a transient hypercoagulable state associated with earlier reduction of the protein C level than for other coagulant factors at the start of treatment. As such, with warfarin treatment, it is essential to keep the PT-INR at ≥1.6 even for elderly and very elderly patients.

References

10. Hata J, Kiyohara Y. Epidemiology of stroke and coronary artery


