Risk of Ischemic Stroke and Hemorrhagic Complications in Warfarinized Patients with Non-Valvular Atrial Fibrillation

Key words: international normalized ratio, secondary prevention, hemorrhagic complication, elderly

Strokes associated with non-valvular atrial fibrillation (NVAF) are increasing as the elderly population is rapidly increasing in Japan since atrial fibrillation increases with advancing age among general population. Aging and previous stroke are well-known risk factors for ischemic stroke in patients with NVAF (1-4). In NVAF patients with risk factors for stroke warfarin but not aspirin is indicated (3, 4). Ideal patients for the indication of warfarin might be those with risk factors for ischemic stroke and without risk factors for hemorrhagic complications. Unfortunately, reality is, however, risk factors for ischemic stroke and major hemorrhage, especially intracranial hemorrhage (ICH), overlap in many NVAF patients (5-8). That is, aging, history of stroke and hypertension are risk factors not only for ischemic stroke but also for ICH (5-8).

According to the Stroke Prevention in Atrial Fibrillation (SPAF) II Study (9), among patients older than 75 years, warfarin-assigned patients had a lower rate of ischemic stroke or systemic emboli but a higher rate of ICH than aspirin-assigned patients, and thus the rate of all strokes, ischemic and hemorrhagic, with residual deficit was similar in patients assigned to warfarin and aspirin. However, the upper limit of the target intensity range of international normalized ratio (INR) in the SPAF II Study was 4.5, which was higher than other trials of warfarin therapy for primary stroke prevention in patients with NVAF, and the rate of major bleeding among warfarin-assigned patients exceeded that of the other trials (8).

The SPAF III Study (10) showed that the rate of ischemic stroke and systemic embolism was low (1.9% per year), and ICH (0.9% per year) and major hemorrhage (2.4% per year) were low as well in patients with at least one risk factor (congestive heart failure, previous thrombembolism, systolic hypertension, or women aged over 75 years), who were given warfarin with target INR 2.0-3.0. However, this study was designed essentially for primary prevention of stroke. The risk of major hemorrhage with warfarin even in the same range of INR might be higher in NVAF patients with previous stroke because prior ischemic stroke is a firmly-linked predictor of anticoagulation-related ICH (5-7).

For secondary prevention of stroke in patients with NVAF, efficacy and safety had been evaluated only in a single prospective study of the European Atrial Fibrillation Trial (EAFT) (11). The investigators reported the efficacy of warfarin treatment for secondary prevention with an INR range from 2.5 to 4.0 based on the risk reduction for stroke from 12% to 4% per year, although hemorrhagic complications were observed more frequently in the anticoagulation group than in the control group (hazard ratio 3.4). The INR range used in the EAFT was appropriately high compared with the recommended INR range for primary prevention as well as the usual INR level applied to elderly patients. Therefore, optimal intensity of warfarin to minimize hemorrhagic complications for the secondary prevention of ischemic stroke had still remained to be clarified in elderly patients with NVAF.

Japanese NVAF-Embolism Secondary Prevention Cooperative Study (12) was the first multi-center, prospective, randomized controlled trial to study an optimal intensity of warfarin for the secondary prevention of stroke in Japanese patients with NVAF. The results of this study demonstrated that the low intensity warfarin treatment (INR 1.5-2.1) for prevention of stroke recurrence was safer than the conventional intensity treatment (INR 2.2-3.5) in the elderly. Major hemorrhagic complications occurred at a frequency of 6.6% per year in the conventional-intensity group and the incidence was significantly higher than in the low-intensity group (0% per year), while the annual rate of ischemic stroke did not differ significantly between both groups (1.1% per year in the conventional-intensity group and 1.7% per year in the low-intensity group).

Yasaka et al (13) combined the data of this study with their previously conducted National Cardiovascular Center (NCVC) NVAF Secondary Prevention Study.

See also 1183.

In both studies, all 203 patients with cardiembolic stroke were given warfarin, monitored with INR, and followed up for primary endpoints of stroke and systemic embolism, and for secondary endpoints of major hemorrhagic complications. There were major ischemic stroke and systemic embolism in only 4 patients with INR<1.6 and major hemorrhage in 9 patients with INR 2.30-3.56. In addition, the patients with major ischemic or hemorrhagic events were significantly older than those without any events (75±4 years vs. 67±7 years). Incidence rates of any events at INR ≤1.59, 1.60-1.99, 2.00-2.59, and ≥ 2.60 were 8.6%, 3.8%, 4.9%, and 25.7% per year, respectively. Thus, they concluded that the INR value between 1.6 and 2.6 seems optimal to prevent major ischemic or hemorrhagic events in the elderly NVAF patients.
The SPAF III study (10) demonstrated that the annual event rate of ischemic stroke or systemic embolism was 2.0% for an INR of 1.5–1.9, which was not very different from the rates for INRs of 2.0–2.4 (1.6%) and 2.5 or more (1.5%). The American Academy of Neurology (AAN) Quality Standards Subcommittee recommends a lower target INR of 2.0 (range 1.6 to 2.5) to minimize bleeding, particularly for elderly patients at special risk for bleeding, for those over age 75 years (3). The subanalysis of SPAF III study (10) and the recommendation of AAN (3) support the feasibility of the conclusion drawn from this combined analysis, which provides important information for clinical practice of warfarin treatment for secondary prevention of stroke among elderly NVAF patients.

Shinichiro Uchiyama, MD
The Department of Neurology, Neurological Institute, Tokyo Women’s Medical University, 8-1 Kawada-cho, Shinjuku-ku, Tokyo 162-8666

References