Nonvalvular Atrial Fibrillation and Stroke

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Abstract
Cardioembolism, responsible for approximately one-third of cerebral infarctions in Japan, causes serious cerebral infarction with poor prognosis. Nonvalvular atrial fibrillation (NVAF) is the most important cause of cardioembolism. Both the occurrence of NVAF and the frequency of its progression to cerebral infarction increase with age. Timely introduction of warfarin depending on the presence or absence of risk factors for cerebral infarction, including age, is essential for the prevention of cardioembolism. At present, monitoring based on PT-INR is indispensable for warfarin therapy. Oral direct thrombin inhibitors seem promising as a future therapy achieving a stable anticoagulation effect by the use of a fixed dose. Angiotensin II receptor blockers (ARBs) are expected to be effective in preventing new atrial fibrillation and maintaining sinus rhythm, offering a promise of clinical usefulness in reducing cerebral infarction, including the prevention of relapse.

Key words Cardioembolism, Aspirin, Warfarin, PT-INR, Ximelagatran, Angiotensin II receptor blocker (ARB)

Introduction
Japan is a country with an exceptionally long life expectancy. A leading cause of death in the Japanese population is cerebrovascular accident. The mortality rate from this condition has remained largely unchanged for several years, and it is still ranked third among the causes of death. More importantly, cerebrovascular accident is the commonest condition requiring nursing care and is the second-ranked disease in terms of health care cost. This means that the prevention of cerebrovascular accident is a key to the long and healthy life of the Japanese people. Among the types of cerebrovascular accidents, cerebral hemorrhage has been decreasing since its peak around 1960. Cerebral infarction, on the other hand, has been increasing gradually. Cardioembolism, a type of cerebral infarction resulting from atrial fibrillation and other cardiac disorders, often develops suddenly in a person who is leading an apparently healthy life, because atrial fibrillation rarely presents obvious subjective symptoms. This condition involves occlusion of the main trunk arteries of the brain, frequently resulting in massive cerebral infarction, and is apt to progress into hemorrhagic conversion. Both life prognosis and functional prognosis are poor because of these reasons.1-3 An important fact is that appropriate prophylactic treatment may prevent this condition in a considerable percentage of potential patients. This report focuses on nonvalvular atrial fibrillation (NVAF), which is the most frequent cause of cardioembolism, and considers its relevance to the prevention of cerebral infarction.

Stroke and NVAF in the Japanese Population
According to the newest available statistical data on strokes in Japan published in the Acute-phase Stroke Patient Database (Stroke Data Bank 2005),3 the 12,178 registered cases of cerebral infarction in Japan are comprised mostly of patient groups with the 3 major types of cerebral infarction: 32.0% with lacunar infarction, 33.1%
with atherothrombotic infarction, and 27.0% with cardioembolic infarction, each representing approximately one-third of all patients (Fig. 1). Combined with the figures from the J-MUSIC study in 2000 covering 16,922 patients in Japan, these data suggest that complete prevention of cardioembolism would result in the reduction of cerebral infarction to two-thirds of the present level.

Atrial fibrillation is the heart disorder causing cardioembolism in more than a half of cases. Diseases underlying the development of atrial fibrillation include valvular heart disease, hypertensive heart disease, cardiomyopathy, and hyperthyroidism (Fig. 2). In addition, there are cases of atrial fibrillation lacking an identifiable cause, called lone atrial fibrillation. In the context of cerebral infarction, atrial fibrillation is usually categorized into valvular atrial fibrillation and the other types of atrial fibrillation, collectively NVAF.

There are two important points regarding the relation between atrial fibrillation and cerebral embolism. One is the age-related increase in the prevalence of atrial fibrillation, and the other is the age-related increase in the occurrence of cerebral infarction among the patients with atrial fibrillation. This is a fact observed commonly in international studies. According to the statistical data from the Framingham study, the occurrence rate of NVAF is 0.5% at ages 50–59, 1.8% at ages 60–69, about 4.8% at ages 70–79, and 8.8% at ages 80–89. The development of cerebral infarction from NVAF takes place at the rate of 1% at ages below 65 and 3.3% at the age of 75 or more. This rate is reported to be as high as 8.1% in patients with the risk factors discussed below. Many aged persons may have NVAF without subjective symptoms, silently building up the risk for developing cerebral infarction.

While age is an important risk factor for developing cerebral infarction from NVAF, a past history of cerebrovascular accident such as cerebral infarction or transient ischemic attack (TIA) is associated with a dramatically elevated risk of recurrence. Other known risk factors include congestive heart failure, hypertension, diabetes mellitus, and coronary artery disease. Based on the weighted evaluation of these risk factors, the CHADS2 score (C for congestive heart failure, H for hypertension, A for age, D for diabetes mellitus, and S for stroke and TIA) has been devised as a predictor of stroke in patients with atrial fibrillation.

Strategies for Drug Treatment of NVAF

The treatment strategy for a patient with NVAF depends on the presence or absence of each of these risk factors. Following the treatment guidelines in Western countries, the Japanese Circulation Society also formulated the treatment guidelines for NVAF in 2001. Firstly, these guidelines do not discriminate between persistent or permanent atrial fibrillation and paroxysmal atrial fibrillation in NVAF, because these do not differ from each other in the risk of cerebral infarction. The annual risk of cerebral infarction in these patients on the whole is reported to be approximately 5%. In contrast,
a past history of cerebral infarction or TIA increases the annual risk to 12%.\(^\text{12}\) Therefore, the past history of cerebral infarction or TIA by itself is considered a risk factor in patients with NVAF. In addition, patients with NVAF accompanied by any of the risk factors such as hypertension, diabetes mellitus, coronary artery disease, and congestive heart failure are also considered to be a high risk. Oral warfarin is indicated for these high-risk patients. The treatment strategy for patients with NVAF lacking these risk factors varies depending on age. According to the Japanese Circulation Society guidelines,\(^\text{15}\) warfarin is indicated for patients at ages above 75, warfarin or antiplatelet drug (aspirin or ticlopidine) for patients at ages from 60 to 75, and no treatment for patients younger than 60 years old. These treatment strategies are summarized in Fig. 3.

The results of a meta-analysis\(^\text{13}\) of the 6 randomized clinical trials providing a basis for these guidelines indicate that aspirin reduces the risk of cardioembolism in patients with NVAF by 22% as compared with placebo, while warfarin reduces it by 62%. In a direct comparison, warfarin is 36% more effective in reducing the risk than aspirin.

In daily practice, clinicians tend to use aspirin more frequently than warfarin in aged patients, but this choice is not recommendable. Although the meta-analysis certainly showed that aspirin reduced the occurrence of cerebral infarction in patients with NVAF, it is likely that aspirin did not prevent cardioembolism but prevented other types of cerebral infarction (i.e. lacunar infarction) in patients with NVAF. In the Japan Atrial Fibrillation and Stroke Trial (JAST) study conducted by a study team of the Japanese Circulation Society, aspirin and placebo were administered to patients with NVAF and followup was continued for 770 days on average. The results indicated that aspirin did not prevent the development of cerebral, while it increased the occurrence of hemorrhagic complications.\(^\text{14}\) At present, there is no evidence that positively supports the use of aspirin, except for the use in patients with contraindication to warfarin.

**Practical Issues of Warfarin Dose Control**

With respect to the practice of warfarin therapy, international guidelines specify that treatment
should be controlled based on the PT-INR value, which is determined as the prothrombin (PT) time of the patient divided by the PT time of the standard specimen and raised to the exponential power of the international sensitivity index (ISI) of the reagent used in the test (Fig. 4). A PT-INR value of 1.5 or less indicates that the effect of warfarin is almost absent, while a value of 2.6 or more indicates the excessive effect of warfarin. These two values are important, as the risk of cerebral infarction increases when PT-INR is lower than 1.5 and the risk of hemorrhagic complications increases when it is above 2.6. The dose of oral warfarin should be controlled between these levels. Thrombotest was used widely in Japan and some facilities are still using it for the purpose of this control. Although the optimal dose range of warfarin corresponds to the 8–15% range in Thrombotest, this method is not sufficiently accurate. The use of PT-INR is strongly recommended (Fig. 5).

The afore-mentioned guidelines of the Japanese Circulation Society define the target range of warfarin control as PT-INR levels from 2.0 to 3.0 for ages less than 70 and from 1.6 to 2.6 for ages of 70 or more. This reflects the results of studies on the optimal dose of warfarin, which proved that less stringent control is appropriate for patients aged 70 years or more. Oral warfarin may be indicated for patients older than 80 years and occasionally for patients older than 85 years, unless there is contraindication. In such cases, further less stringent control of PT-INR in the range from 1.8 to 1.9 may be a practical goal.

Because warfarin suppresses the production of vitamin K-dependent coagulation factor and exerts an anticoagulation effect, patients should be advised to limit the intake of food containing abundant vitamin K. Medication usually begins with the oral administration at the dose of 2–3 mg once daily, which is the normal maintenance dose. Initial loading (a high dose at the beginning) is avoided because of the risk for transient hypercoagulability called the “warfarin dilemma”, which may result from the effect of warfarin suppressing the activities of protein C and protein S in addition to vitamin K-dependent coagulation factor. Warfarin interacts with various drugs, and therefore should be used with caution. While some patients with poor responsiveness to warfarin may require as much as 10 mg warfarin to achieve the therapeutic level of PT-INR, certain drug interactions may be utilized in such cases. A common method to reduce the dose of warfarin required for achieving a therapeutic effect is the combination of bucolome, an anti-hyperuricemic agent.

**Appropriateness of the Combined Use of Warfarin and Aspirin**

If controlled appropriately, oral warfarin can lower the occurrence of cerebral infarction by half in selected patients. However, this effect is limited to the prevention of cardioembolism, and warfarin may not be effective in preventing lacunar infarction and atherothrombotic infarction. Aspirin is the established first-choice drug for the prevention of these types of infarction, but the benefit of the combined use of warfarin and aspirin is controversial. The consensus from the mega-trials conducted so far has been that the addition of aspirin to low-dose warfarin does not improve the prevention of cerebral infarction but increases the risk of hemorrhagic complica-
However, the data from the National Study for Prevention of Embolism in Atrial Fibrillation (NASPEAF) in Spain, published in the Journal of the American College of Cardiology recently, showed that the combination of warfarin and triflusal, an antiplatelet agent, was better than warfarin alone in the prevention of cerebral infarction and reduced the occurrence of hemorrhagic complications. This result may have an effect on the direction of future treatment. Whatever the case may be, it is essential to minimize the risk of hemorrhagic complications through maintenance of appropriate PT-INR and adequate control of blood pressure during warfarin therapy.

**Tooth Extraction during Warfarin Therapy**

We occasionally encounter a problematic situation where a patient on warfarin therapy requires tooth extraction and the dentist requests discontinuation of warfarin. Recent Western guidelines generally recommend not discontinuing oral warfarin when the patient receives tooth extraction. A majority of the hemorrhagic complications from tooth extraction are considered to be the results of inadequate curettage of exuberant granulation or failure of the sutures after extraction. Because tooth extraction basically stimulates coagulation activity, discontinuation of warfarin may result in the elevated risk of cerebral infarction. It has been confirmed that the risk of hemorrhagic complications remains low if the condition is controlled within the range of 2.6 or less PT-INR. In view of these facts, physicians should cooperate with dentists and develop a system to ensure safe tooth extraction without discontinuing warfarin. Other surgical operations and invasive examinations would require discontinuation of warfarin. No consensus has been reached on whether or not we should switch to intravenous heparin. Decisions in this respect must be made on a case-by-case basis.

**Development of Oral Direct Thrombin Inhibitors**

At present, several oral anticoagulants to replace warfarin are in the process of development. A particularly promising class of these drugs includes oral antithrombins, which directly bind to thrombin and reduce its activity independently of vitamin K metabolism. A typical example is ximelagatran, which once was expected to be useful as an oral drug that, unlike warfarin, would not require frequent blood monitoring and would achieve a stable anticoagulation effect by the use of a fixed dose in all patients. In fact, the results of Stroke Prevention Using Oral Thrombin Inhibitor in Atrial Fibrillation (SPORTIF) III and those of SPORTIF V published last year collectively demonstrated that the prophylactic effect of ximelagatran against systemic embolic events was equivalent to that of warfarin. However, because oral ximelagatran unfortunately induced liver dysfunction, the FDA in the U.S. did not approve this agent. There are no prospects for the approval in Japan, either.

**Atrial Fibrillation and ARB**

Finally, let us consider NVAF and cerebral infarction from a different perspective. While the prevalence of atrial fibrillation increases with age, the development of new atrial fibrillation from sinus rhythm involves various factors. Of the processes leading to fibrillation, electrical remodeling due to alteration of ion channels and anatomical remodeling such as myocardial fibrosis are recognized as particularly important. The involvement of angiotensin II type 1 receptors is well-known, and a growing body of recent evidence indicates that the occurrence of new atrial fibrillation is reduced by angiotensin II receptor blocker (ARB), which is also recognized as a hypotensor. The Valsartan Heart Failure Trial (Val-HeFT) study and the Candesartan in Heart Failure — Assessment of Reduction in Mortality and Morbidity (CHARM) study, respectively, demonstrate that valsartan and candesartan lowered the occurrence of new atrial fibrillation, and the sub-analysis concerning atrial fibrillation in the Losartan Intervention for Endpoint Reduction in Hypertension (LIFE) study also derived similar results regarding the treatment with losartan. The use of these ARBs is considered to be a useful treatment strategy, as it is expected to achieve the prevention of cerebral infarction based on blood pressure management and also to inhibit the onset of NVAF leading to cardioembolism.

In summary, NVAF is extremely important as...
a cause of cerebral embolism. Appropriate therapeutic agents should be selected considering stratification of various risk factors including age.

When warfarin is used, dose monitoring based on PT-INR is essential.

References