<特別講演 II>

Atrial Fibrillation in Stroke Prevention

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About 20% of all ischemic strokes occur as a result of an embolus to a cerebral artery arising from the cardiac chambers or valves. Atrial fibrillation represents the most frequent cardiac source of embolus to the brain accounting for 45% or more of the cardiac causes of ischemic stroke¹⁾. The remaining causes include emboli from left ventricular thrombi in the setting of an acute cardiac infarction or emboli arising from ventricular thrombi located in a ventricular aneurysm or overlying a dyskinetic ventricular wall. Other cardiac sources of emboli include rheumatic valvular disease, prosthetic valve disease and a variety of other less common cardiac abnormalities. Atrial fibrillation is the most common arrhythmia in the general population and is particularly common over the age of 60. The median age of patients with atrial fibrillation in the United States is 75 years²⁾. Atrial fibrillation has been shown to convey a 6-fold increased risk of stroke in the general population compared to similar patients without atrial fibrillation³⁾. This substantial increase has been confirmed by repeated epidemiological studies^{3)~7)}. This increased risk of stroke translates to an annual stroke risk of around 5% per year. About 15% of ischemic stroke patients have atrial fibrillation identified at the time of their stroke and about two-thirds of these will ultimately be concluded to have their ischemic stroke on the basis of an embolus arising from the left atrium. Atrial fibrillation is predominantly a disease of the elderly. Considering the absolute number of patients with atrial fibrillation in the United States it is remarkable that half of all patients with atrial fibrillation are beyond the age of 75²⁾. This predominantly elderly population is less likely to be treated with long-term oral anticoagulation be-

cause of concerns about bleeding risks in this elderly population.

The role of warfarin anticoagulation in patients with atrial fibrillation was investigated by five randomized clinical trials, including the AFASAK Trial⁸⁾, the Stroke Prevention Atrial Fibrillation Trial⁹⁾, the Boston Area Atrial Fibrillation Trial¹⁰⁾, the Canadian Atrial Fibrillation Study (CAFA)¹¹⁾ and the VA Cooperative Trial¹²⁾. The outcomes in these trials were remarkably consistent with a reproducible reduction in stroke risk associated with warfarin therapy over control. In aggregate, the control populations of the randomized clinical trials had an annual stroke rate of 4.5% per year with a 68% risk reduction with the use of warfarin based on an intention to treatment analysis. In fact, most patients suffering an ischemic stroke were not adequately anticoagulated within the target range of the study at the time of their stroke¹³⁾. Patients who were adequately anticoagulated had an 80 % reduction in their stroke risk. Some of the randomized trials also examined aspirin or other antiplatelet agents compared to placebo and found 22-24% risk reduction associated with antiplatelet agents.

One of the important observations arising from the randomized trials was that the risk of stroke in patients with atrial fibrillation is dependent on the presence or absence of certain predictors of increased stroke risk. The factors that have been consistently observed to be predictors of increased stroke risk include advancing age, hypertension, prior stroke or transient ischemic attack and poor left ventricular function. Some, but not all, of the studies have found that additional predictors including diabetes mellitus, systolic hypertension, female gender over the age of

75, hormone replacement therapy, associated coronary artery disease and certain transesophageal echocardiographic (TEE) features¹³⁾. The TEE features that have been associated with increased stroke risk include the detection of left atrial appendage thrombi, spontaneous echo contrast and low flow velocities in the atrial appendage¹⁴⁾. Somewhat unexpectedly left atrial enlargement and intermittency in atrial fibrillation pattern have not been consistently found to be predictors of increased stroke risk. Patients with one or more of the high-risk predictors have an annual stroke rate of around 8% per year. These consistent high-risk predictors include a stroke or TIA history, with an annual stroke rate of 12% untreated in this group, congested heart failure or left ventricular dysfunction, systolic hypertension, age over the age of 75, and diabetes mellitus. Medium risk patients have an annual stroke rate of about 3.5% per year¹³⁾¹⁵⁾. These patients are between the ages of 65-75 years and have a history of hypertension. The risk patients have approximately 1% risk of stroke per year with none of the high-risk features, no history of hypertension and are less than the age of 65 years.

Much attention has been focused on the optimal intensity of anticoagulation to prevent embolic ischemic stroke and minimize the risk for major hemorrhage. In the randomized trials, most patients were inadequately anticoagulated at the time of their ischemic stroke¹⁶⁾. In population and case control studies, examining anticoagulation intensity and stroke risk, there appears to be a dramatic reduction of stroke with INR levels above 2 with the optimal range 2.0-3.0¹⁷⁾¹⁸⁾. There is however a reduction in stroke risk with INR levels below 2, especially those between 1.5 and 2.0¹⁷⁾. The optimal intensity of anticoagulation was examined in the Japanese Nonvalvular Atrial Fibrillation-Embolism Secondary Prevention Cooperative Study¹⁹⁾. In this study patients less than the age of 80 with nonvalvular atrial fibrillation and TIA or stroke of cardiac embolic origin within the past 5 months were randomized to receive either conventional anticoagulation with a target INR range of 2.2-3.5 or to a low intensity group with an INR target range of 1.5-2.1. One hundred and fifteen patients were random-

Table 1 Japanese Secondary Prevention NVAF Study—Baseline Characteristics—

	Conventional (n = 55)	Low-Intensity (n = 60)
Age	65.7 yrs	67.6 yrs
Hypertension	44%	40%
Diabetes	26%	11%
Ischemic Ht. Dis.	4%	11%
Paroxysmal AF	55%	60%
INR	2.3 ± 0.4	1.9 ± 0.3

Table 2 Japanese Secondary Prevention NVAF Study—Results—

	Conventional (n = 55)	Low-Intensity (n = 60)
Ischemic stroke	1 (1.1%)	2 (1.7%)
Major bleed	6*	0
Minor bleed	2	0
Discontinued	12	8
INR	2.3 + / - 0.4	1.9 + / - 0.3

ized into the two groups and followed for a mean of 658 days. Outcome measures included ischemic stroke, systemic embolus, transient ischemic attack and CT or MRI evidence of stroke, along with major hemorrhagic complications. The patients were on an average 66-67 years of age; they had 40% or greater incidence of hypertension and over 50% of the patients having paroxysmal atrial fibrillation (Table 1). The mean INR in the conventionally anticoagulated group was 2.4 ± 0.4 and in the low intensity group was 1.9 ± 0.3 . During follow-up one ischemic stroke occurred in the conventionally anticoagulated group and 2 in the low intensity group for annual stroke rate of 1.1% in the conventional group and 1.7% in the low intensity group. There were significantly more major hemorrhages in the conventionally anticoagulated group where 6 major bleeds occurred compared to none in the low intensity group (Table 2). The major hemorrhages occurred in 3 occasions in the gastrointestinal tract in one case subcutaneous bleeding in another and one cerebellar hemorrhage. Age was an important determinant of major bleeding risk with the mean age in the major hemorrhage patients being

73.7 years compared to a mean age of 66.3 years in the group without major bleeding. The Japanese Secondary Prevention NVAF Study concluded that low intensity anticoagulation (INR = 1.5-2.1) has similar efficacy to conventional levels of anticoagulation following TIA or stroke.

This study also noted that elderly patients with conventional levels of anticoagulation are an increased risk of major bleeding compared to patients anticoagulated at lower target INR ranges.

Intracranial hemorrhage represents one of the most dreaded complications of oral anticoagulant therapy. The risk of intracerebral hemorrhage is increased by 7-10 fold in the presence of oral anticoagulation and carries a mortality of 60%. Two distinct temporal profiles of intracranial hemorrhage have been described, one characterized by the sudden onset of neurological deterioration, stupor and coma with a high mortality due to a rapidly expanding intracerebral hematoma. A second pattern involves a slower progression of hematoma enlargement and accompanying neurological deterioration over a period of 6-24 hours. A number of studies have examined the predictors of increased risk for anticoagulation-related intracerebral hemorrhage^{20,21}. The factors that have been firmly linked with an increased risk for intracerebral hemorrhage include advancing age, the intensity of anticoagulation, prior ischemic stroke, hypertension and leukoaraiosis. Other factors that have been occasionally reported to carry increased risk, but not consistently found by all investigators, include diabetes mellitus, the use of concomitant antiplatelet agents, the implementation of early anticoagulation following ischemic stroke, acute elevations in blood pressure and alcoholic intoxication. Gorter, et al²¹ examined the predictors of intracerebral hemorrhage in two large recent randomized clinical trials of anticoagulation, the Stroke Prevention in Reversible Ischemia Trial (SPIRIT)²² and the European Atrial Fibrillation Trial (EAFT)²³. The SPIRIT Trial included patients with ischemic stroke secondary to atherothrombotic cerebrovascular disease and the European Atrial Fibrillation Trial included patients with presumed cardioembolic stroke secondary to nonvalvular atrial fibrilla-

Table 3 Predictors of Intracerebral Bleed SPIRIT & EAFT

Risk Factor	Hazard Ratio
Age > 65	2.5
Leukoaraiosis	7.5
Severe	15
Diastolic BP > 100	2.1
Medications $\geq$ 3	1.9
INR (per unit)	1.6

Table 4 Predictors of Intracerebral Bleed

Risk Factor	SPIRIT (n = 651)	EAFT (n = 225)
ICH	27	2
Age > 65 y	47%	81%
HTN history	39%	48%
Leukoaraiosis	7%	14%
Mean INR	3.3	2.9

tion. The SPIRIT Study was stopped prematurely because of an excess of intracerebral hemorrhages²². The intracranial bleeding risk in this study was compared to that in the European Atrial Fibrillation Trial, which included patients with cerebral ischemic events associated with atrial fibrillation. Based on an analysis of these two studies, the predictors of intracerebral hemorrhage were assessed. These are summarized in Table 3 and include advancing age, the presence of leukoaraiosis by CT scan, diastolic hypertension, increasing numbers of medications, and the intensity of anticoagulation. The presence of leukoaraiosis on CT scan emerged as an important predictor of intracerebral hemorrhage. There was a dose response relationship of leukoaraiosis to intracerebral hemorrhage risk with moderate degrees of leukoaraiosis carrying a hazard ratio of 5.7 and severe levels of leukoaraiosis hazard ratio of 15. The patients with brain ischemia of arterial origin in the SPIRIT trial had a much higher risk, almost 19-fold, of intracerebral hemorrhage than patients with brain ischemia and atrial fibrillation (Table 4). This observed difference in risk is suggested to possibly be related to increased fragility of small vessels in the brains of patients with ischemia of arterial origin compared with

patients with brain ischemia of cardioembolic origin from atrial fibrillation.

In patients with atrial fibrillation at high risk for ischemic stroke, chronic anticoagulation is a highly effective stroke prevention treatment. A suggested approach to these patients is outlined in the figure. While it is abundantly clear from the randomized clinical trials that warfarin anticoagulation is highly effective in reducing stroke risk, in fact many patients at high risk who appear to be candidates for anticoagulation do not receive anticoagulants. A recent survey by the Healthcare Financing Administration as a part of the National Stroke Project surveyed over 12,000 Medicare inpatients with atrial fibrillation and noted that at hospital discharge only 53.9% were prescribed warfarin²⁴⁾. In addition, warfarin was less likely to be prescribed for elderly patients, for women, and for minority patients including African-Americans and Asians.

Atrial fibrillation represents a major treatable cause of ischemic stroke, particularly in the elderly population. Worldwide, the elderly are increasing in numbers and atrial fibrillation is assuming an increasingly important role as a modifiable risk factor for ischemic stroke. One of the important management principles emerging from the randomized trials is that of risk stratification. It is possible and relatively easy to predict whether a patient has a high, moderate or low risk for stroke and estimate the potential benefits of long term anticoagulant therapy in such individuals. Despite the effectiveness of long-term oral anticoagulation, many high risk patients with atrial fibrillation remain untreated because of concerns about the potential risks of major hemorrhage, including intracerebral hemorrhage along with concerns of the inconvenience of monitoring chronic oral anticoagulation. However, with the proper management of anticoagulation, the risk of stroke can be reduced by over two-thirds and the risk for major bleeding can be minimized. Additional information may emerge with ongoing studies looking at the potential utility of aggressive management of atrial fibrillation by cardioversion and antiarrhythmics to maintain sinus rhythm²⁵⁾. In addition alternative antithrombotic

therapies to warfarin are under study, including thrombin inhibitors and antiplatelet agents. Atrial fibrillation is and will remain an important cause of stroke, particularly in the elderly, with a highly effective treatment.

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