Risk Factors in Patients with Occlusive Cerebrovascular Disease: Implications for Cerebral Embolism Treatment

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ABSTRACT

The cases of all of the 359 inpatients seen at our hospital in one year were reviewed for cause of admission and risk factors that may have contributed to the visit. One hundred twenty-one patients were admitted due to current occlusive cerebrovascular disease (CVD). Among these 121 patients, the prevalence of hypertension in lacuna, embolism, and atherothrombosis cases were significantly higher than that of the control. There were 34 cerebral embolism cases (representing 20% of the occlusive CVD) of which the mean age (77.5 years-old) was significantly higher than those of the other subgroups of CVD. The cause of embolism was determined as cardiogenic (arrhythmia in 33 cases and post-valve replacement in one case). Arrhythmia could be broken down as follows: 19 cases were classified as continuous atrial fibrillation; 8 cases expressed paroxysmal atrial fibrillation; and 9 cases displayed sick sinus syndrome (3 cases overlap). Twenty-four of the 34 patients had had a history of treatment or realization for arrhythmia or valve replacement, however, 16 of these 24 patients had never been treated with warfarin, which resulted in current CVD. Eight patients had been treated with warfarin, however, only 2 of these 8 patients were thought to be well managed with warfarin treatment. It is now more than a decade since the effectiveness of warfarin has been proven to prevent occurrence of cerebral embolism. Every physician seems to be aware of this fact; even so, practical neglect still exists. We would like to propose and emphasize that atrial fibrillation patients should be properly managed with warfarin administration, especially elderly patients.

INTRODUCTION

The prevalence of cerebrovascular disease (CVD) has not changed much over the last decade, in spite of the growing understanding of the precise mechanism concerning its pathogenesis. Nowadays, it is widely accepted that, in order to

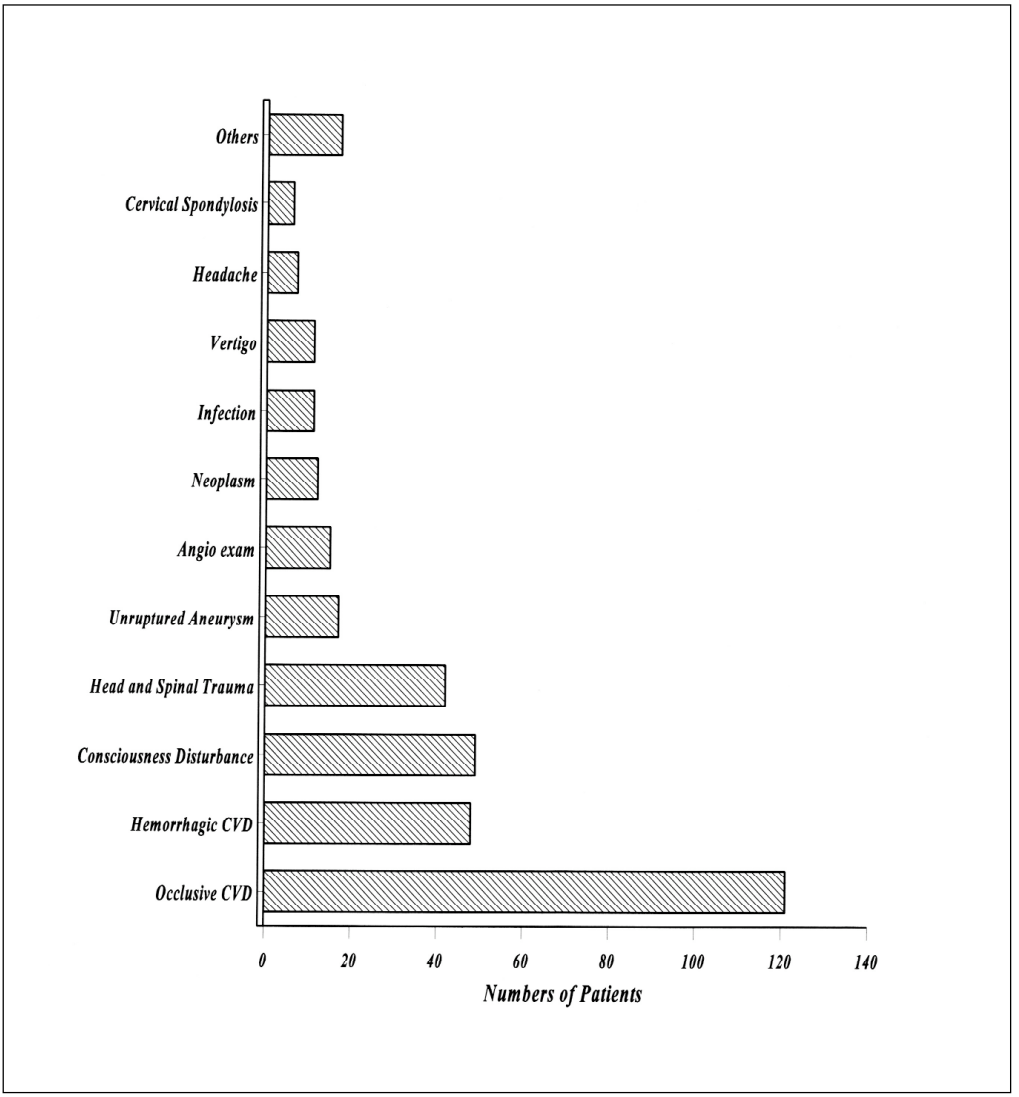

Figure 1. Distribution of 359 patients according to causes. CVD indicates cerebrovascular disease; and Angio exam, examination by cerebral angiography.

prevent CVD, the management of risk factors is most important. In spite of this enlightenment, there still exists a certain amount of ignorance regarding the elimination of these risk factors by patients themselves and even by physicians.

We have examined the annual number of patients admitted to our hospital in order to clarify what type of risk factor is responsible for current occlusive CVD, in the era of magnetic resonance (MR) imaging.

MATERIALS AND METHODS

Our hospital has 120 beds and is oriented to treat neurological patients, such as CVD, brain tumor, head trauma, and consciousness disturbance in association with other causes. The outpatient department is available for patients who require a variety of examinations. An emergency department for stroke patients operates around the clock.

We have examined the records of patients admitted from January 1, 2002

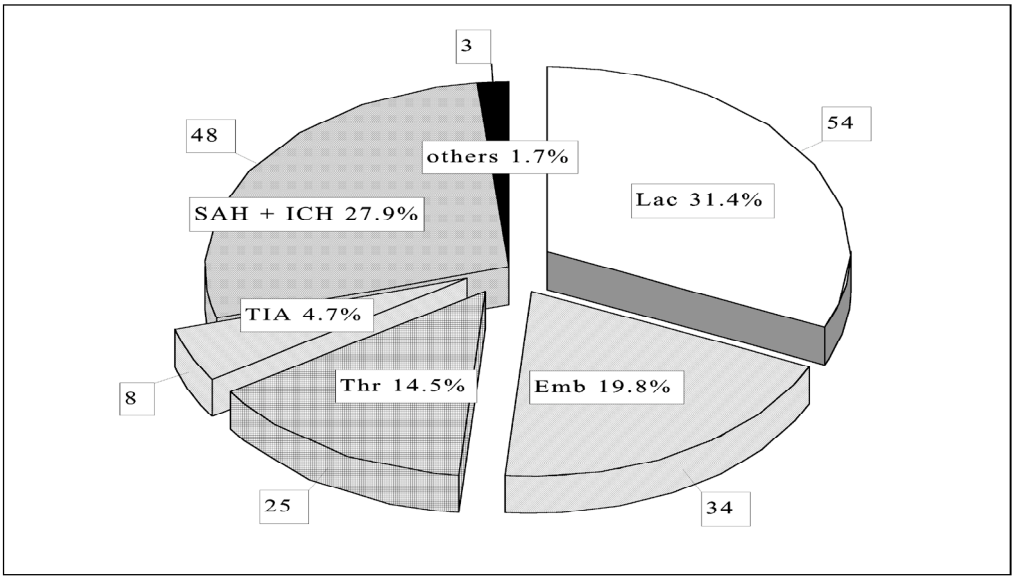

Figure 2. Distribution of the patients in each cerebrovascular disease group. Boxed numbers represent numbers of patients. Lac indicates lacunar stroke; Emb, cerebral embolism; Thr, atherothrombosis; TIA, transient ischemic attack; SAH, subarachnoid hemorrhage; and ICH, intracerebral hematoma.

to December 31, 2002; the total case number was 372. Among them, 11 patients were admitted more than once. Therefore, the exact number of admitted patients included 359 individuals.

Among these 359 patients, risk factors such as hypertension, diabetes mellitus, hyperlipidemia, hyperuricemia, and habituation of smoking and alcohol intake were all examined. Arrhythmia was judged by routine 12-lead ECG, continuous ECG monitoring during ICU admission, and/or the use of holter ECG monitoring. The ratio of patients having these risk factors is discussed in terms of occlusive CVD.

Statistical analysis was performed by the χ^2 square test and/or Student *t* test according to the items. A probability of less than 0.05 was regarded as significant. We had 42 patients with head or spinal trauma, which included 4 children. Therefore, we excluded the 4 children and used the 38 adult trauma patients for the control group for statistical reference.

RESULTS

The primary cause of admission is classified and summarized in Figure 1. One hundred-seventy-two patients (48%) out of 359 were admitted due to current CVD. Of these 172 CVD cases, 121 cases represented occlusive CVD. Among these 121 occlusive CVD cases, the breakdown of pathogenesis can be categorized as 45% of lacunar stroke, 28% of cerebral embolism, 21% of atherothrombosis, and 7% of transient ischemic attack (Figure 2). On the other hand, 48 cases were classified into the hemorrhagic CVD group, mostly consisting of intracerebral hematoma (77%) and subarachnoid hemorrhage (SAH; 23%).

Forty-nine cases represented consciousness disturbance with causes other than CVD. As previously described, 42 cases were admitted with head or spinal trauma.

Age of Each Group

Among the occlusive CVD groups the

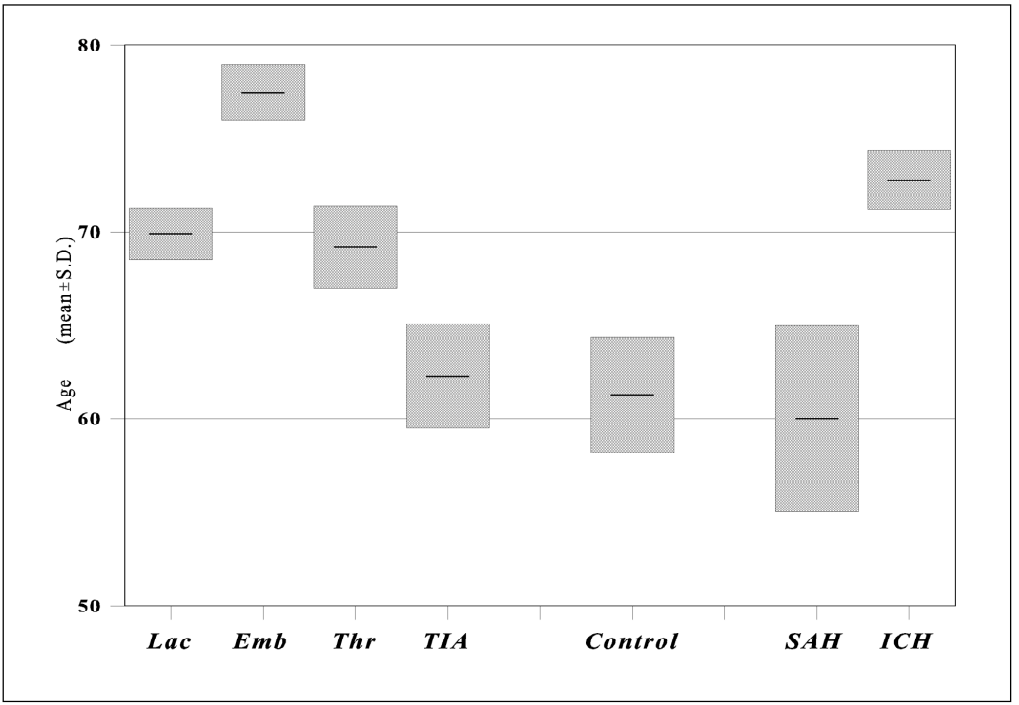

Figure 3. Comparison of mean age between each cerebrovascular disease group. The mean age of lacunar stroke, cerebral embolism, atherothrombosis and intracerebral hematoma groups is significantly higher than that of control group. The mean age of cerebral embolism is also significantly higher than those of other occlusive cerebrovascular disease groups. Lac indicates lacunar stroke; CVD, cerebrovascular disease; Emb, cerebral embolism; Thr, atherothrombosis; TIA, transient ischemic attack; SAH, subarachnoid hemorrhage; and ICH, intracerebral hematoma.

average age of each group was as follows: lacunar stroke, 69.9 years; cerebral embolism, 77.5 years; and atherothrombosis, 69.2 years. These groups showed a significantly higher age than that of the control group (61.4 years), while the age of transient ischemic attack (62.3 years) did not demonstrate a significant difference (Figure 3).

The mean age of the cerebral embolism group (77.5 years) was significantly higher age than any other CVD group.

The mean age of the intracerebral hematoma group (72.8 years) was significantly higher than that of the SAH group (60.0 years) and the control group (61.4 years).

Prevalence of Risk Factors

The prevalence of hypertension in lacunar stroke (70.4%), cerebral embolism (70.6%), atherothrombosis (80.0%), and intracerebral hematoma (89.2%) groups is significantly higher than that of the control group (43.2%) (Figure 4, Table 1).

The prevalence of diabetes mellitus is significantly higher only in the lacunar stroke group (46.3%), when compared to the control group (21.6%).

The prevalence of hyperlipidemia and hyperuricemia, and the frequency of the smoking and alcohol intake habituation are not significantly higher in any of the subdivided groups.

Holter ECG Monitoring

Of the total 359 patients, holter ECG monitoring was performed on 280 patients, 78% of the total. Among those, 121 cases (43%) showed certain abnor-

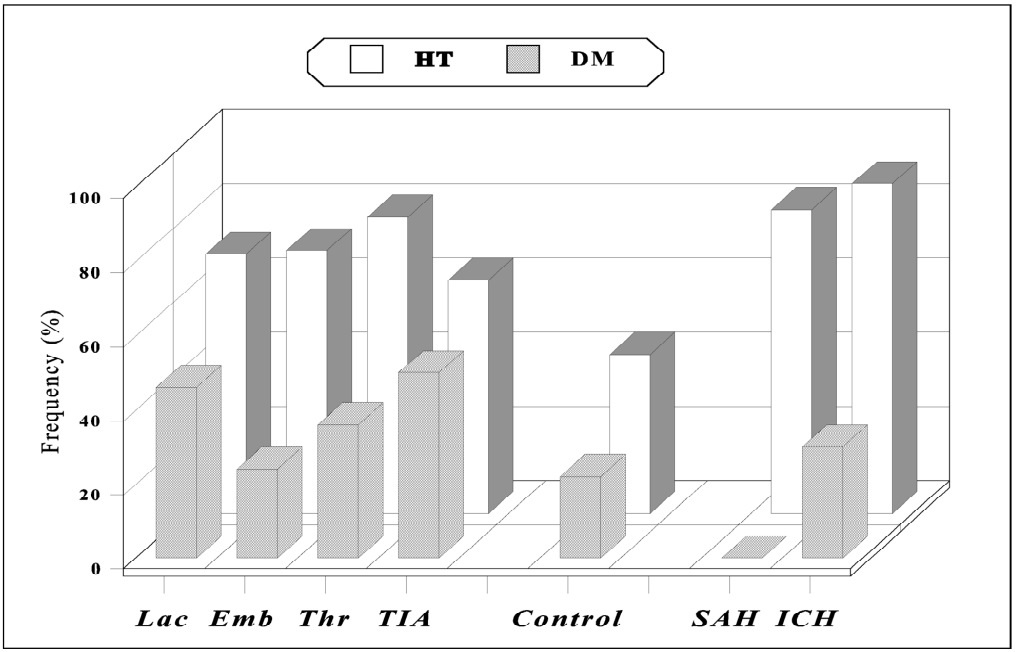

Figure 4. Prevalence of hypertension and diabetes mellitus in each cerebrovascular disease group. The prevalence of diabetes mellitus is significantly high only in lacunar stroke group. Prevalence of hypertension in lacunar stroke, cerebral embolism, atherothrombosis, and intracerebral hematoma groups is significantly higher than that of control group. Lac indicates lacunar stroke; Emb, cerebral embolism; Thr, atherothrombosis; TIA, transient ischemic attack; SAH, subarachnoid hemorrhage; HT, prevalence of hypertension; DM, diabetes mellitus; and ICH, intracerebral hematoma.

malities. In 34 cases (12.1%), the abnormality itself, revealed by holter ECG monitoring, was responsible for the current admission, such as Adam-Stokes' attack by sick sinus syndrome (SSS).

The frequency of the abnormality in holter ECG monitoring (90.3%) is significantly higher only in the cerebral embolism group (Figure 5).

Analysis of Cerebral Embolism Group

In all 34 cases, cardiogenic factors were considered the cause of embolism, which included one postvalve replacement case and 33 arrhythmia cases. The responsible arrhythmia was as follows: 19 cases of continuous atrial fibrillation, 8 cases of paroxysmal atrial fibrillation, and 9 of SSS (3 cases overlap because they harbor SSS caused by bradycardiac atrial fibrillation) (Figure 6).

Out of the 34 cases, 24 patients had a past history of treatment or realization for arrhythmia or valve replacement. However, 16 of these 24 patients had never been treated with warfarin (Figure 7). The remaining 8 patients had been treated with warfarin, however, warfarin was not effective in 4 cases. Furthermore, warfarin was arbitrarily stopped in one case and in another it was purposely ceased due to complicated intestinal bleeding. Only 2 patients were thought to be well managed by warfarin administration, even so they each had a current ischemic attack (one of them was the postvalve replacement patient).

DISCUSSION

In spite of a recent decline in the mortality rate due to CVD, the actual preva-

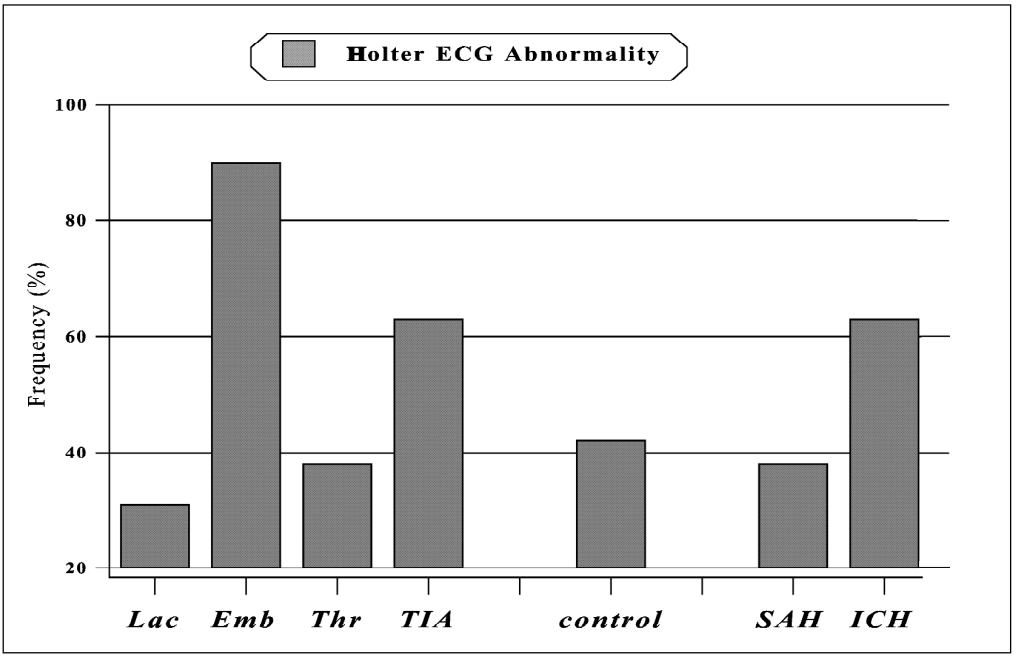

Figure 5. Abnormality ratio of holter ECG monitoring in each cerebrovascular disease group. The frequency is markedly high only in the cerebral embolism group. Lac indicates lacunar stroke; Emb, cerebral embolism; Thr, atherothrombosis; TIA, transient ischemic attack; SAH, subarachnoid hemorrhage; and ICH, intracerebral hematoma.

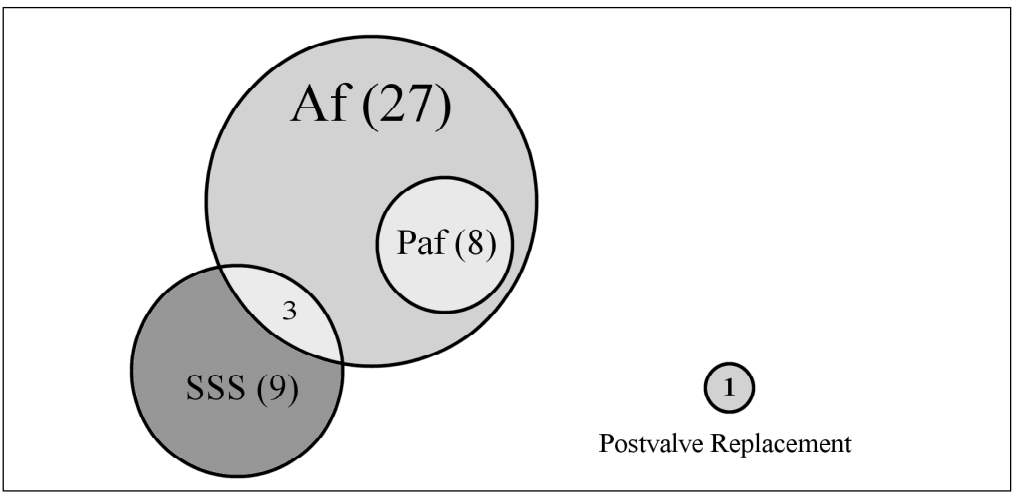

Figure 6. Distribution of causes of 34 embolism cases. Continuous atrial fibrillation is most common. Af indicates atrial fibrillation; Paf, paroxysmal Af; and SSS, sick sinus syndrome.

lence seems to be increasing.[1,2] In our series of yearly admitted cases, patients with CVD were the most prevalent and occupied about half of the total number of admitted patients. Furthermore, 70% of CVD cases were due to occlusive CVD, more specifically, cerebral ischemia was the most common reason for admission. In our risk factor analysis, among occlusive CVD, hypertension

Table 1. Statistical Analysis of Risk Factors in Each Cerebrovascular Disease Group*

	Age	HT	DM	HL
Occlusive CVD				
Lacunar S	69.9	38/54 (70.4%)	25/54 (46.3%)	26/54 (48.1%)
significance	0.0141	0.0097	0.0162	ns
Embolism	77.5	24/34 (70.6%)	8/34 (23.5%)	19/34 (55.9%)
significance	<0.0001	0.0203	ns	ns
Thrombosis	69.2	20/25 (80.0%)	9/25 (36.0%)	19/25 (76.0%)
significance	0.0422	0.0040	ns	ns
TIA	62.3	5/8 (62.5%)	4/8 (50.0%)	4/8 (50.0%)
significance	ns	ns	ns	ns
Hemorrhagic CVD				
ICH	72.8	33/37 (89.2%)	11/37 (29.7%)	18/37 (48.6%)
significance	0.0015	<0.0001	ns	ns
SAH	60.0	9/11 (81.8%)	0/11 (0%)	7/11 (63.6%)
significance	ns	ns	ns	ns
Control	61.4	16/37 (43.2%)	8/37 (21.6%)	20/37 (54.1%)

*CVD indicates cerebrovascular disease; DM, diabetes mellitus; HL, hyperlipidemia; Holter Ab, abnormality in Holter ECG monitoring; HT, hypertension; HU, hyperuricemia;
ICH, intracerebral hematoma; Lacunar S, lacunar stroke; significance, *P* value; ns, not significant; SAH, subarachnoid hemorrhage; and TIA, transient ischemic attack.

seems to be the cause most often. Furthermore, among occlusive CVD cases, lacunar stroke was most common (45%) and diabetes mellitus is thought the main contributing factor to causing lacunar formation.

The second major pathogenesis of occlusive CVD was embolism. Although the average age of cerebral embolism group was significantly older, they usually showed less severe sclerotic changes of arteries on magnetic resonance angiography. In other words, this type of cerebral artery occlusion is not a matter directly related to the cerebral artery itself, even in the case of aging. Therefore, cerebral embolism could be prevented by the treatment of anticoagulation therapy with warfarin.[3,4] However, to treat or prevent cerebral embolism, patients still face 2 major problem areas. One important thing to keep in mind is the *realization* that the patient is suffering or will suffer from cerebral embolism. This realization is the beginning of treatment, that is, prophylaxis. As a practical matter, some physicians still do not realize the high risk of atrial fibrillation, which will cause cerebral embolism, facing asymptomatic patients. Then in order to confirm that the pathogenesis of the current cerebral ischemia is an embolism, continuous monitoring of ECG or the holter monitoring of ECG are the best methods and should be performed.[5] The type of onset of cerebral ischemia or the MR images can indicate that the patients suffer from cerebral infarction but may not always indicate whether or not they suffer from cerebral embolism. In our series, continuous atrial fibrillation represented 56% of the cerebral embolism group. More importantly, paroxysmal atrial fibrillation or SSS cannot always be properly judged by a simple 12-lead ECG. This means holter ECG monitoring is much more helpful. Nevertheless, in one case, paroxysmal atrial fibrillation was not detected by 12-lead or holter monitor-

HU	Smoking	Alcohol Intake	Holter Ab	Total
7/53 (13.2%)	28/54 (51.9%)	19/54 (35.2%)	16/51 (31.4%)	54
ns	ns	ns	ns	
5/34 (14.7%)	15/33 (45.5%)	17/33 (51.5%)	28/31 (90.3%)	34
ns	ns	ns	0.0003	
3/25 (12.0%)	17/25 (68.0%)	11/25 (44.0%)	9/24 (37.5%)	25
ns	ns	ns	ns	
2/8 (25.0%)	5/8 (62.5%)	4/8 (50.0%)	5/8 (62.5%)	8
ns	ns	ns	ns	
5/37 (13.5%)	16/37 (43.2%)	10/37 (27.3%)	12/32 (37.5%)	37
ns	ns	ns	ns	
0/11 (0%)	7/11 (63.6%)	3/11 (27.3%)	5/8 (62.5%)	11
ns	ns	ns	ns	
2/37 (5.9%)	19/37 (51.4%)	13/37 (35.1%)	10/24 (41.7%)	38

ing, instead it was revealed by the continuous monitoring of ECG during the ICU admission. Therefore, various kinds of ECG monitoring should be combined to prove arrythmia as the cause of embolism, rather than single 12-lead ECG.[6] Additionally, the prevalence of atrial fibrillation is reportedly underestimated, because quite a number of atrial fibrillation patients are asymptomatic and, in most reports, the diagnosis of arrhythmia was confirmed only by a single ECG examination.[2] In our series, holter ECG monitoring was performed in 78% of the cases of admitted patients, where abnormality was pointed out in 43% of the cases and also the cause of the current admission was revealed in 12% of the cases. Thus, the holter ECG monitoring proved as important as investigating risk factors by laboratory blood examinations.

The second problem is that even if we know the pathogenesis to be embolic, obtaining an optimum value of warfarin effectiveness is sometimes troublesome for both patients and physicians.[7] This is the major reason, in spite of the evidence of the effectiveness of warfarin administration, why most physicians fail or hesitate to give warfarin in an aggressive manner.

It may be possible to prevent the occurrence of cerebral embolism simply by warfarin administration.[3,4] The management of the patient, in order to obtain the optimum effectiveness of warfarin, was again sometimes troublesome. In fact, the effectiveness of warfarin heavily depends on the individual patient and their condition, and the effectiveness also increases with age. Furthermore, a racial difference in warfarin's effectiveness is noted.[8] However, since the concept of international normarized ratio (INR) was introduced for the coagulofibrinolytic examination, management has become easier. That is, by utilizing a prothrombin time frame with the index of INR, we can treat

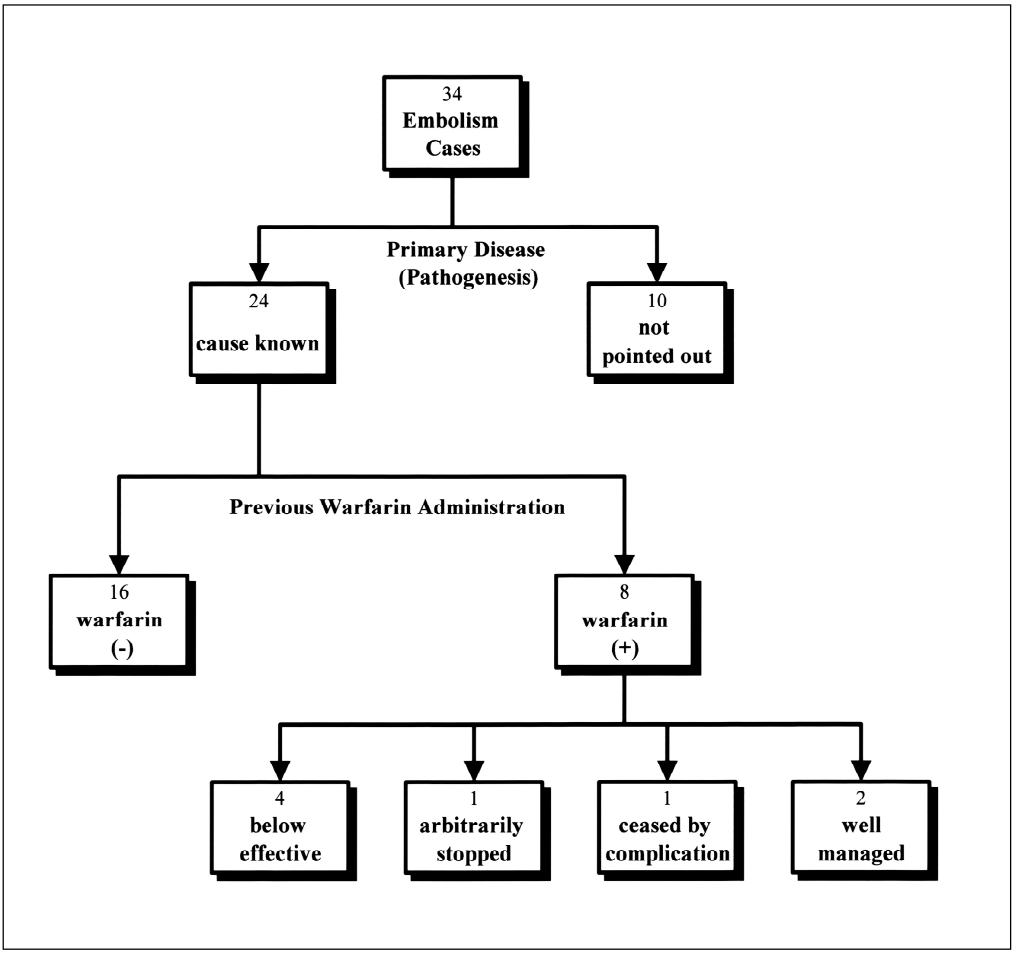

Figure 7. Summary of 34 embolism cases according to suspected cause of cerebral embolism. Although 24 cases were recognized as suspected cerebral embolism, only 8 cases were treated with anticoagulation therapy with warfarin.

patients more effectively and easily without causing a severe hemorrhagic complication. This means that most cerebral embolism cases can be prophylactic to a significant rate, by the simple administration of warfarin.

We would like to propose again that atrial fibrillation patients should be managed with warfarin administration, especially older patients, since atrial fibrillation represents a major treatable cause of ischemic stroke. More than a decade has passed since the effectiveness of warfarin was proven to prevent cerebral embolism.[9] Every physician seems to be aware of this; even so, practical neglect still exists. Antiplatelet agents can not significantly reduce the risk of the occurrence of cerebral embolism; warfarin has a far better profile for reducing this risk.[10]

REFERENCES

1. Feinberg WM, Blackshear JL, Laupacis A, et al. Prevalence, age distribution, and gender of patients with atrial fibrillation. Analysis and implications. *Arch Intern Med.* 1995;155:469-473.
2. Ryder KM, Benjamin EJ. Epidemiology and significance of atrial fibrillation. *Am J Cardiol.* 1999;84:131R-138R.

3. Hart RG, Benavente O, McBride R, Pearce LA. Antithrombotic therapy to prevent stroke in patients with atrial fibrillation: A meta-analysis. *Ann Intern Med.* 1999;131:492-501.

4. ACA/AHA/ESC guidelines for the management of patients with atrial fibrillation: Executive summary. A report of the American college of cardiology/ American heart association task force on practice guidelines and the European society of cardiology committee for practice guidelines and policy conferences (Committee to develop guidelines for the management of patients with atrial fibrillation). *Circulation.* 2001;104:2118-2150.

5. Sherman DG. Atrial fibrillation in stroke prevention. *No Socchu (Jpn J Stroke).* 2001;23:275-279.

6. Bansil S, Karim H. Detection of atrial fibrillation in patients with acute stroke. *J Stroke Cerebrovascu Dis*. 2004;13:12-15.

7. Nilasena DS, Kresowik TF, Piskac AF, et al. National rates of warfarin use in medicare patients with atrial fibrillation: Results from the national stroke project. *Stroke.* 2001;32:328-a.

8. Yasaka M, Minematsu K, Yamaguchi T. Optimal intensity of international normalized ratio in warfarin therapy for secondary prevention of stroke in patients with non-valvular atrial fibrillation. *Intern Med.* 2001;40:1183-1188.

9. Albers GW. Atrial fibrillation and stroke. Three new studies, three remaining questions. *Arch Intern Med.* 1994;154:1443-1448.

10. Stroke Prevention in atrial Fibrillation Investigators. Adjusted-dose warfarin versus low-intensity, fixed-dose warfarin plus aspirin for high-risk patients with atrial fibrillation: Stroke Prevention in Atrial fibrillation III randomised clinical trial. *Lancet.* 1996;348:633-638.