1. Frequency

Cerebrovascular disease is classified into three types: cerebral hemorrhage, cerebral infarction and subarachnoid hemorrhage. According to the Japanese Stroke Data Bank, the frequency of cerebrovascular disease according to type in Japan is reported to be approximately 18% for cerebral hemorrhage and approximately 7% for subarachnoid hemorrhage, with the remainder for cerebral infarction\(^1\). Compared with the frequency of cerebrovascular disease according to type observed in Western countries, the frequency of cerebral hemorrhage is higher in Japan, while the frequency of cerebral infarction is lower\(^2\).

Cerebral infarction is further classified into three clinical types: lacunar infarction, atherothrombotic cerebral infarction and cardiogenic cerebral embolism. According to the Hisayama study, lacunar infarction accounts for approximately 50% of cases of cerebral infarction, whereas the incidence of atherothrombotic cerebral infarction and cardiogenic cerebral embolism is slightly less than 30% and slightly more than 20%, respectively\(^3\). The frequency of cerebral infarction (with obvious causes) in Western countries (Caucasians) has been reported to be approximately 30% for both lacunar and atherothrombotic cerebral infarction and approximately 40% for cardiogenic cerebral embolism\(^4\); lacunar infarction occurs more frequently in Japan\(^5\).

2. Risk Factors for the Development of Cerebrovascular Disease

The results of the NIPPON DATA80 indicate that the factors affecting mortality from stroke in Japan include age, systolic blood pressure, smoking and hyperglycemia and that the lipid levels, such as that of total cholesterol (TC), are not considered to be risk factors\(^6\). Similarly, the results of 61 observational studies conducted in Western countries (approximately 0.9 million subjects) indicated no relationships between the TC level and mortality from stroke\(^7\). The results of a meta-analysis of 18 cohort studies in Japan and China showed that blood pressure is the most important risk factor for stroke and that the TC level is much less frequently involved than the blood pressure\(^8\).

In terms of individual cerebrovascular diseases, hypertension is clearly a risk factor for cerebral hemorrhage, and the presence of a cerebral aneurysm is a risk factor for subarachnoid hemorrhage. With respect to cerebral infarction, the major risk factors for cardiogenic cerebral embolism are hypertension and intra-cardiac thrombi\(^9\)\(^,\)\(^10\).

The results of epidemiological studies conducted in Japan have indicated no significant relationships between the serum cholesterol levels (TC, LDL-cholesterol (LDL-C) and non HDL-cholesterol) and the incidence of noncardiogenic cerebral infarction\(^1\)\(^-\)\(^17\). In Western countries, however, epidemiological studies, such as the MRFIT, have reported that an increased TC level is associated with an increased risk of cerebral infarction\(^18\)\(^-\)\(^20\). The results of seven cohort studies (approximately 0.69 million subjects) reported that the incidence of cerebral infarction is significantly decreased by 15% in patients with a decrease in the TC level of 1 mmol/L (38.6 mg/dL)\(^21\), although, other reports have found that the TC level either is not a risk factor for cerebral infarction or is less involved\(^22\)\(^,\)\(^23\).

The results of the Hisayama study, which investi-
gated the risk of cerebral infarction according to type, demonstrated that the LDL-C level is a risk factor for the development of atherothrombotic cerebral infarction; however, it is not associated with the development of other types of cerebral infarction\(^\text{24}\). Furthermore, the Hisayama study reported that blood pressure is strongly associated with lacunar infarction, atherothrombotic cerebral infarction and, in women, cardiogenic cerebral embolism\(^\text{24}\). Reports published in foreign countries indicate that the major risk factor for cerebral infarction, including cardiogenic cerebral embolism, is hypertension\(^\text{22, 23}\). In other words, the cholesterol level is recognized to be a risk factor only for atherothrombotic cerebral infarction, and the major risk factor for all types of cerebral infarction, including atherothrombotic cerebral infarction, is hypertension\(^\text{9}\).

Many reports in various countries, including Japan, have stated that hypocholesterolemia is a risk factor for cerebral hemorrhage\(^\text{16, 25}\). A meta-analysis of cohort studies found that a decrease in the cholesterol level by 1 mmol/L (38.6 mg/dL) is associated with an increase in the frequency of cerebral hemorrhage of 19\%\(^\text{21}\). In Japan, an LDL-C level of ≤80 mg/dL has been reported to increase the frequency of cerebral hemorrhage\(^\text{16}\). However, as described later, the results of a meta-analysis of prevention studies of coronary artery disease (CAD) do not indicate that cholesterol-lowering therapy leads to an increased frequency of cerebral hemorrhage\(^\text{26}\).

There have been many reports in a number of countries, including Japan, stating that a lower HDL-cholesterol level is associated with an increased incidence of cerebral infarction\(^\text{27-30}\).

There are also many reports indicating no certain relationships between the triglyceride (TG) level and stroke\(^\text{23, 31, 32}\). However, the results of a meta-analysis of epidemiological studies conducted in the Asia-Pacific region, in which the fasting TG level was divided into four groups, reported that the patients with the highest TG levels had an increased risk of ischemic stroke of 50\% compared with that observed in the patients with the lowest TG levels\(^\text{33}\). The results of cohort studies of approximately 14,000 subjects indicate that the frequency of ischemic stroke is increased in both men and women when postprandial hypertriglyceridemia is present\(^\text{34}\). These results show that an increase in the postprandial TG level of 1 mmol/L (88.5 mg/dL) is associated with an increase in the frequency of ischemic stroke of 15\%.

### 3. Lipid-Lowering Therapy and Cerebrovascular Disease

Although many prevention studies of CAD using statins have been conducted to date, only the SPARCL study employed the development of stroke as the primary end point, with most studies using stroke as the secondary end point. The results of a meta-analysis of prevention studies conducted in Western countries showed that cholesterol-lowering therapy with statins significantly decreases the incidence of cerebral infarction by 19\%. Additionally, in that study, the incidence of cerebral hemorrhage did not vary significantly (Table 1)\(^\text{26}\). It is unclear why statin treatment decreases the incidence of stroke because the cholesterol level has not been considered to be a risk factor for stroke in observational studies.

As mentioned above, the SPARCL study employed the recurrence of stroke as the primary end point\(^\text{35}\). In that study, high-dose statins were administered in patients with a history of stroke, and the recurrence rate of stroke in these patients was compared with that observed in patients who received placebo treatment. Consequently, the recurrence of stroke significantly decreased (−16\%, \(p=0.03\)), while the incidence of CAD was markedly lower (−35\%, \(p=0.003\)). Therefore, statin treatment is also effective in the secondary prevention of stroke. A post hoc analysis of the breakdown of stroke as an end point found that the incidence of cerebral infarction was significantly decreased (hazard ratio = 0.78), whereas that of cerebral hemorrhage was significantly increased (hazard ratio = 1.66). These results are inconsistent with the findings of the meta-analysis mentioned above, in which statin treatment did not increase the incidence of cerebral hemorrhage\(^\text{26}\). To determine the risk of cerebral hemorrhage associated with cholesterol-lowering therapy, performing further prevention studies is warranted.

Among the various studies conducted in Japan, the MEGA study showed that statin treatment tends to decrease the incidence of stroke, with hazard ratios of 0.66 and 0.63 for men and women, respectively\(^\text{36}\). In particular, in that study, the incidence of ischemic stroke in men and stroke in women ≥55 years of age was significantly decreased\(^\text{36, 37}\). The results of a sub-analysis of the JELIS showed that treatment with statins and ethyl icosapentate (EPA) in patients with a history of stroke significantly inhibits the recurrence of stroke by approximately 20\% compared with statin monotherapy\(^\text{38}\).

### 4. Measures to Prevent Cerebrovascular Disease

Because the greatest risk of cerebrovascular dis-
ease is hypertension, it is important to first control blood pressure. Atrial fibrillation is a major risk factor for cardiogenic embolism, and cerebral aneurysm is a significant risk factor for subarachnoid hemorrhage. Therefore, it is necessary to appropriately manage these risk factors. The management of these risk factors should be performed with reference to the relevant guidelines.)

In Western countries, according to the results of a meta-analysis of prevention studies, lipid-lowering therapy is recommended to prevent noncardiogenic cerebral infarction. In Japan, based on the fact that (1) the incidence of atherothrombotic cerebral infarction is increasing and (2) the MEGA study showed that statins are effective in preventing cerebral infarction, the lipid levels should be managed in order to prevent cerebral infarction. However, it should be emphasized again that managing other risk factors, such as hypertension and smoking, is more important than managing lipids for preventing cerebrovascular disease. It is also desirable to establish management criteria for the prevention of noncardiogenic cerebral infarction in patients with underlying atherosclerosis according to the management criteria for the prevention of ischemic heart disease.

**Footnotes**

This is an English version of the guidelines of the Japan Atherosclerosis Society (Chapter 14) published in Japanese in June 2012.

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**Table 1. Inhibitory Effects of Decreased LDL-C Levels by Statins on Vascular Events (per mmol/L reduction)**

<table>
<thead>
<tr>
<th>End points</th>
<th>Statins on Vascular Events (per mmol/L reduction)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any major coronary events</td>
<td>0.77 (0.74-0.80)</td>
</tr>
<tr>
<td>Hemorrhagic stroke</td>
<td>1.05 (0.78-1.41)</td>
</tr>
<tr>
<td>Presumed ischemic stroke</td>
<td>0.81 (0.74-0.89)</td>
</tr>
</tbody>
</table>

[Modified from Cholesterol Treatment Trialists’ Collaborators. Lancet, 2005; 366: 1267-1278]
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