Incidence and Risk Factors for Subtypes of Cerebral Infarction in a General Population
The Hisayama Study

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Background and Purpose—We estimated the incidence of first-ever cerebral infarction in regard to its subtypes and analyzed their risk factors separately in a community-based prospective cohort study in Japan.

Methods—Stroke-free subjects (n=1621) aged ≥40 years were followed up for 32 years from 1961. During this period, 298 cerebral infarctions occurred and were divided into 167 lacunar, 62 atherothrombotic, 56 cardioembolic, and 13 undetermined subtypes of infarction on the basis of clinical information including brain imaging and autopsy findings.

Results—The age-adjusted incidence of lacunar infarction (3.8 per 1000 person-years for men and 2.0 for women) was higher than that of atherothrombotic infarction (1.2, 0.7) and cardioembolic infarction (1.3, 0.5) in both sexes. Time-dependent Cox’s proportional hazard analysis revealed systolic blood pressure as well as age to be independent risk factors for all subtypes of cerebral infarction except for cardioembolic infarction in men. Additionally, ST depression on ECG, glucose intolerance, and smoking in men and left ventricular hypertrophy on ECG and body mass index in women remained significant risk factors for lacunar infarction. ST depression was also significantly related to events of atherothrombotic infarction in women. The risk of atrial fibrillation for cardioembolic infarction was outstandingly high in both sexes, and left ventricular hypertrophy and lower total cholesterol were additional risk factors for cardioembolic infarction in women.

Conclusions—In this Japanese population, lacunar infarction was the most common subtype of cerebral infarction and had a greater variety of risk factors, including not only hypertension but also ECG abnormalities, diabetes, obesity, and smoking, than did atherothrombotic infarction or cardioembolic infarction. (Stroke. 2000;31:2616-2622.)

Key Words: cerebral embolism ▪ lacunar infarction ▪ prospective studies ▪ risk factors ▪ thrombosis

Cerebral infarction is the most common type of stroke in Japan as well as in other developed countries. Cerebral infarction is clinically categorized into several subtypes on the basis of the size and location of the affected cerebral arteries and on their pathogenesis: lacunar, atherothrombotic, and cardioembolic infarction. Because of differences in pathogenesis, prognosis, and treatment among cerebral infarction subtypes, risk factor assessment for each cerebral infarction subtype should be performed separately. However, since the correct classification of cerebral infarction subtypes requires detailed clinical information, including that from morphological examination, most of the previous reports concerning frequency and risk factors of cerebral infarction subtypes have been based on hospital-based registration studies, and those utilizing prospective cohort studies have been very few.

Since 1961, we have been performing a long-term prospective cohort study of cardiovascular disease in the community of Hisayama on Kyushu Island, in Japan. In this study, study-team physicians performed physical and neurological examinations on a majority of the subjects who developed stroke and collected clinical information, including information on the course of the disease. Furthermore, morphological examinations by autopsy and/or brain imaging were performed on 93% of the cerebral infarction subjects. This characteristic study design provided us an opportunity to classify cerebral infarction cases into subtypes with a high degree of accuracy. In the present article we estimated incidence of cerebral infarction by subtypes and analyzed their risk factors, taking into account the dynamic transition of risk factors, by means of follow-up examinations and by using the time-dependent Cox’s proportional hazards model.

Subjects and Methods

Study Protocol
In 1961 we performed a screening examination among residents of the town of Hisayama and established a cohort consisting of 1621...
stroke-free subjects aged ≥40 years (88% of the total population in that age group).9 This population was followed up for 32 years between November 1, 1961, and October 30, 1993, by repeated health examinations every 2 years until 1974 and then every 5 years after that. For subjects who did not undergo regular examination or who moved out of town, health status was checked by mail or telephone. In addition, we collected information regarding new cardiovascular events, including stroke, through a daily monitoring system established by the study-team physicians, local practitioners, and staff of the division of Health and Welfare of the town. When new neurological symptoms were suspected, study-team physicians evaluated the subject, and an effort was made to obtain further diagnostic information. In deceased cases, the cause of death and types of stroke were determined clinically and verified pathologically. During the follow-up period, 1063 subjects died, and of these, 861 (81%) underwent autopsy. Autopsies were performed at the Department of Pathology of Kyushu University. Only 2 subjects were lost to follow-up.

**Definition of Subtype of Cerebral Infarction**

The diagnosis of stroke was made according to the following classification system on the basis of the clinical information and autopsy findings. Stroke was defined as a sudden onset of noncon- vulsive and focal neurological deficit persisting for >24 hours and was classified as either cerebral infarction, cerebral hemorrhage, subarachnoid hemorrhage, or undetermined type of stroke.10 Cases of cerebrovascular disease due to rare causes such as collagen disease, hematologic disorders, trauma, cerebral arterial spasm after subarachnoid hemorrhage, chronic subdural hematoma, and moyamoya disease were not included in stroke cases. Cerebral infarction was further divided into 4 clinical categories—lacunar infarction, atherothrombotic infarction, cardioembolic infarction, and undetermined subtype of cerebral infarction—on the basis of the Classification of Cerebrovascular Disease III proposed by the National Institute of Neurological Disorders and Stroke,2 as well as on the basis of the diagnostic criteria of the Trial of Org 10172 in Acute Stroke Treatment (TOAST) study11 and Cerebral Embolism Task Force12 for cerebral infarction subtypes. The diagnoses of cerebral infarction and its subtypes were made by reference to detailed clinical features and ancillary laboratory examinations, such as an analysis of cerebrospinal fluid, cerebral angiography, recent brain imaging including CT and MRI, echocardiography, carotid duplex imaging, and autopsy. We considered the morphological findings significant and used clinical features as reference information. During the follow-up period, a total of 298 cases developed first-ever cerebral infarction, and of these, 277 (93%) underwent morphological examinations. Autopsies were performed on 222 cerebral infarction cases (74%). Two neurologists (Y.T. and Y.K.) made the diagnoses of cerebral infarction subtypes separately, using collected clinical and pathological information. Their diagnoses agreed in 279 cerebral infarction cases (94%), and in the remaining 19 cases, the diagnoses were determined by a detailed panel discussion. When sufficient clinical and morphological information was obtained, a diagnosis of cerebral infarction subtype was defined as “definite.” When the amount of either type of information was insufficient, the diagnostic level was defined as “probable.”

**Lacunar Infarction**

These cerebral infarction cases lack evidence of cerebral cortical impairment, cerebellar dysfunction, and disturbance of consciousness. Classification into this subtype also requires the presence of a relevant brain stem or subcortical hemispheric lesion with a diameter of <1.5 cm as demonstrated on CT, MRI, or autopsy. The absence of a potential cardiac source for embolism and of a significant stenosis (>50%) in an ipsilateral large artery further support the clinical diagnosis.

**Atherothrombotic Infarction**

Atherothrombotic infarction patients have clinical and morphological findings of either significant stenosis (>50%) or occlusion of a major cerebral artery or a cortical branch artery. Clinical findings include those of cerebral cortical impairment (eg, aphasia, agnosia) or cerebellar dysfunction. History of transient ischemic attacks in the same vascular territory, a carotid bruit, and the absence of cardiac sources for embolism support the clinical diagnosis. Infarcts >1.5 cm in diameter on brain imaging or autopsy are considered to be of potential large-artery atherosclerotic origin. Cases of artery-to-artery embolism, diagnosed by abrupt onset of the maximal neurological deficit without cardiac sources for embolism and with either significant stenosis or occlusion in an ipsilateral large artery, are included in this category.

**Cardioembolic Infarction**

The diagnosis of this category is determined on the basis of modified clinical features suggestive of cardioembolic infarction reported by the Cerebral Embolism Task Force.12 They consist of 3 primary and 4 secondary features. The primary features are as follows: (1) abrupt onset of the maximal neurological deficit; (2) presence of cardiac sources for embolism, as described in the TOAST classification of risk sources of cardioembolism11; and (3) multiple brain infarcts involving multiple arterial territories. The secondary features are as follows: (1) absence of hemorrhagic infarct; (2) cortical infarct area corresponding exactly to a major cerebral arterial territory but not to a branch territory; (3) absence of either significant stenosis or occlusion in the ipsilateral artery; and (4) evidence of embolism to other organs. This subtype of cerebral infarction is diagnosed by the presence of ≥2 primary features or by the presence of 1 primary feature and ≥2 secondary features.

**Undetermined Subtype**

This category includes all cerebral infarction cases for which the subtype cannot be determined because of insufficient clinical or morphological information.

On the basis of the above criteria, we subdivided the 298 cases of cerebral infarction into 167 cases of lacunar infarction (81 men and 86 women), 62 of atherothrombotic infarction (29 men and 33 women), 56 of cardioembolic infarction (31 men and 25 women), and 13 of undetermined subtype (3 men and 10 women). Among these diagnoses, 272 were defined as definite and 26 as probable. In this study we present the data regarding definite and probable cerebral infarction cases together, since these combined data were almost identical to that for definite cases only.

**Risk Factors**

We assessed risk factors for cerebral infarction using data from the baseline and 5 major follow-up examinations performed in 1967, 1974, 1978, 1983, and 1988. More than 80% of the total number of surviving subjects participated in each follow-up examination.

Blood pressures were measured 3 times at each examination, and the average values were used for the analysis. Left ventricular hypertrophy (LVH) (Minnesota code 3-1), ST depression (4-1,2,3 except for 3-1), and atrial fibrillation (AF) (8-3) on ECG were separately evaluated. Glucose intolerance was determined by an oral glucose tolerance test in subjects with glycosuria in 1961 and 1967, by fasting and postprandial glucose concentrations in 1974, 1978, and 1983, and by a 75-g oral glucose tolerance test in 1988, in addition to medical history of diabetes.13,14 Body weight and height were measured in light clothing without shoes, and body mass index (BMI) was calculated. Serum cholesterol level was determined by the Zak-Henly method with a modification by Yoshikawa in 1961 and 1967, by the Zurkowski method in 1974, and by the enzymatic method in 1978, 1983, and 1988.15-18 Information on antihypertensive treatment, smoking habits, and alcohol intake was obtained with the use of a standard questionnaire, and these factors were classified as being either habitually used or not used.

**Statistical Analysis**

The incidence of cerebral infarction and its subtypes was calculated by the person-year method. Relative risk (RR) was estimated by the time-dependent Cox’s proportional hazards model, in which all risk factors except for age and sex were allowed to change on the basis of data from the 5 follow-up examinations.17 If subjects had missing
TABLE 1. Means (± 1 SD) or Frequencies of Risk Factors for Stroke in Men and Women at Baseline Examination in 1961, the Hisayama Study

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Men</th>
<th>Women</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>56±9</td>
<td>57±12</td>
</tr>
<tr>
<td>Systolic blood pressure, mm Hg</td>
<td>135±26</td>
<td>135±26</td>
</tr>
<tr>
<td>Diastolic blood pressure, mm Hg</td>
<td>79±14</td>
<td>77±13</td>
</tr>
<tr>
<td>Antihypertensive agents, %</td>
<td>2.1</td>
<td>2.2</td>
</tr>
<tr>
<td>LVH, %*</td>
<td>22.0</td>
<td>10.3</td>
</tr>
<tr>
<td>ST depression, %†</td>
<td>2.1</td>
<td>3.8</td>
</tr>
<tr>
<td>AF, %‡</td>
<td>0.7</td>
<td>0.7</td>
</tr>
<tr>
<td>Glucose intolerance, %</td>
<td>12.2</td>
<td>4.8</td>
</tr>
<tr>
<td>Total cholesterol, mmol/L</td>
<td>3.9±0.9</td>
<td>4.2±1.0</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>21.5±2.4</td>
<td>21.7±3.0</td>
</tr>
<tr>
<td>Smoking habits, %</td>
<td>76.2</td>
<td>66.8</td>
</tr>
<tr>
<td>Alcohol intake, %</td>
<td>69.3</td>
<td>8.3</td>
</tr>
</tbody>
</table>

*R Minnesota code 3-1.
†Minnesota code 4-1,2,3 except for 3-1.
‡Minnesota code 8-3.

Results

The characteristics of study subjects at baseline examination are described by sex in Table 1. The mean age was 56 years for men and 57 years for women. The mean systolic and diastolic blood pressures as well as the frequency of antihypertensive medication were the almost same for both sexes. The frequency of LVH on ECG was twice as high in men than in women, while the opposite sex-related difference was observed for ST depression. The frequency of AF was low in both sexes (0.7%). Glucose intolerance was more prevalent in men than in women, while the mean total cholesterol and BMI were higher in women. Men consumed alcohol and cigarettes more than did women.

As shown in Table 2, the age-adjusted incidence of lacunar infarction was higher than that of atherothrombotic infarction and cardioembolic infarction in both sexes, and the incidence of cerebral infarction as well as that of 3 major subtypes was approximately twice as high in men as in women.

The age-adjusted RRs and 95% CIs of each risk factor for cerebral infarction and its subtypes are given by sex in Tables 3 and 4. The RRs for undetermined subtypes were not estimated because of the small number. Systolic and diastolic blood pressures, LVH, ST depression, AF, and glucose intolerance were all significant risk factors for cerebral infarction in both sexes. When analyzed by cerebral infarction subtypes, systolic and diastolic blood pressures appeared to be significant risk factors for all cerebral infarction subtypes in both sexes except for cardioembolic infarction in men (P<0.05). With regard to other risk factors, LVH and glucose intolerance were additional risk factors for lacunar infarction in both sexes (P<0.05). Smoking and ST depression were also significantly associated with the occurrence of lacunar infarction in men (P<0.05), while BMI was a significant risk factor for lacunar infarction in women (P<0.05). Only ST depression was an additional risk factor for atherothrombotic infarction for women (P<0.01). All ECG abnormalities except for ST depression in women were significant risk factors for cardioembolic infarction in both sexes (P<0.05), while total cholesterol showed an inverse correlation to the risk of cardioembolic infarction in women (P<0.05).

Multivariate analysis revealed age, systolic blood pressure, LVH, and AF as independent risk factors for cerebral infarction in both sexes, and ST depression and glucose intolerance were additional risk factors in men (Tables 5 and 6). With regard to subtypes of cerebral infarction, systolic blood pressure (P<0.01) as well as age was an independent risk factor of the same magnitude for all subtypes of cerebral infarction except for cardioembolic infarction in men; RRs for a 10-mm Hg increase ranged between 1.2 and 1.3. Additionally, ST depression (P<0.01), glucose intolerance (P<0.01), and smoking habits (P<0.01) remained significant risk factors for lacunar infarction in men, while LVH (P<0.05) and BMI (P<0.05) were significant risk factors for lacunar infarction in women. ST depression was also significantly related to events of atherothrombotic infarction in women (P<0.05). AF was an exceptionally significant risk factor for cardioembolic infarction in both sexes (RR=17.8 for men and RR=5.9 for women; P<0.01), and LVH (P<0.05) and lower total cholesterol (P<0.05) were additional risk factors for cardioembolic infarction in women.

Discussion

Subtype of Cerebral Infarction

To our knowledge, this is the first community-based prospective cohort study that estimates incidence of cerebral infarction in terms of subtypes and analyzes the risk factors. Among our subjects, lacunar infarction was the most common subtype of cerebral infarction and accounted for 56% of the total number of cerebral infarction cases, followed by atherothrombotic infarction and cardioembolic infarction. A previous autopsy study of Hisayama residents similarly found that 76% of cerebral infarction cases featured infarcts <1 cm in diameter (lacunes).18 In contrast, stroke registries in Western
countries\(^3\)-\(^6\) have reported lower frequencies of lacunar infarction than of atherothrombotic infarction and cardioembolic infarction. Japanese are at higher risk for arteriosclerosis of the cerebral parenchymatous small arteries than they are for arteriosclerosis of the cervical or intracranial large arteries, while the latter condition is dominant in white persons.\(^19\)

**Risk Factors for Subtypes of Cerebral Infarction**

**Hypertension**

Hypertension is the most powerful risk factor for all types of stroke, including cerebral infarction, irrespective of sex, race, or nationality. The present study showed that elevated blood pressure as well as age was a risk factor for all subtypes of cerebral infarction in both sexes except for cardioembolic infarction in men. Time-dependent multivariate RRs of systolic blood pressure were constant for all subtypes, ranging between 1.2 and 1.3 for a 10-mm Hg increase, suggesting that the risk of blood pressure was the same for all cerebral infarction subtypes. Since most prospective epidemiological studies have assessed the risk of hypertension using only a single blood pressure measurement at baseline, the increase in the frequency of hypertension with advancing age during a follow-up period has not been considered. In our study, however, this bias was minimized by the incorporation of follow-up blood pressure measurements into the analysis.

### TABLE 3. Age-Adjusted RRs and 95% CIs of Each Risk Factor for Cerebral Infarction and its Subtypes for Men in the Hisayama Study, 1961–1993

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Cerebral Infarction (n=144)</th>
<th>Lacunar (n=81)</th>
<th>Atherothrombotic (n=29)</th>
<th>Cardioembolic (n=31)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Systolic blood pressure*</td>
<td>1.2 (1.1–1.3)</td>
<td>1.2 (1.1–1.3)</td>
<td>1.3 (1.2–1.5)</td>
<td>1.1 (1.0–1.3)</td>
</tr>
<tr>
<td>Diastolic blood pressure*</td>
<td>1.4 (1.3–1.6)</td>
<td>1.4 (1.2–1.6)</td>
<td>1.9 (1.5–2.5)</td>
<td>1.2 (0.9–1.6)</td>
</tr>
<tr>
<td>LVH</td>
<td>2.0 (1.4–2.8)</td>
<td>1.8 (1.1–2.9)§</td>
<td>1.9 (0.8–4.4)</td>
<td>2.5 (1.1–5.3)§</td>
</tr>
<tr>
<td>ST depression</td>
<td>3.4 (1.8–6.4)</td>
<td>3.7 (1.6–8.9)</td>
<td>2.4 (0.6–10.8)</td>
<td>3.8 (1.1–13.2)§</td>
</tr>
<tr>
<td>AF</td>
<td>4.7 (2.5–9.0)</td>
<td>1.6 (0.4–6.6)</td>
<td>1.7 (0.2–12.8)</td>
<td>17.5 (7.2–42.4)</td>
</tr>
<tr>
<td>Glucose intolerance</td>
<td>1.8 (1.2–2.6)</td>
<td>2.3 (1.4–3.8)</td>
<td>1.4 (0.6–3.3)</td>
<td>1.2 (0.5–2.8)</td>
</tr>
<tr>
<td>BMI†</td>
<td>1.1 (1.0–1.1)</td>
<td>1.1 (1.0–1.2)</td>
<td>1.0 (0.9–1.2)</td>
<td>1.1 (1.0–1.2)</td>
</tr>
<tr>
<td>Total cholesterol‡</td>
<td>1.1 (0.9–1.4)</td>
<td>1.2 (1.0–1.5)</td>
<td>1.1 (0.7–1.6)</td>
<td>1.0 (0.7–1.5)</td>
</tr>
<tr>
<td>Smoking habits</td>
<td>1.3 (0.9–1.9)</td>
<td>2.0 (1.1–3.4)§</td>
<td>0.9 (0.4–2.0)</td>
<td>0.7 (0.3–1.4)</td>
</tr>
<tr>
<td>Alcohol intake</td>
<td>1.2 (0.8–1.7)</td>
<td>1.1 (0.7–1.7)</td>
<td>0.9 (0.4–2.0)</td>
<td>2.0 (0.9–4.5)</td>
</tr>
</tbody>
</table>

All risk factors are time-dependent covariates. Values are RRs (95% CIs).

*Risk for an increase of 10 mm Hg.
†Risk for an increase of 1 kg/m\(^2\).
‡Risk for an increase of 1 mmol/L.
§P<0.05.
||P<0.01.

### TABLE 4. Age-Adjusted RRs and 95% CIs of Each Risk Factor for Cerebral Infarction and its Subtypes for Women in the Hisayama Study, 1961–1993

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Cerebral Infarction (n=154)</th>
<th>Lacunar (n=86)</th>
<th>Atherothrombotic (n=33)</th>
<th>Cardioembolic (n=25)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Systolic blood pressure*</td>
<td>1.2 (1.2–1.3)</td>
<td>1.2 (1.1–1.3)</td>
<td>1.3 (1.1–1.4)</td>
<td>1.3 (1.2–1.5)</td>
</tr>
<tr>
<td>Diastolic blood pressure*</td>
<td>1.5 (1.3–1.7)</td>
<td>1.5 (1.2–1.7)</td>
<td>1.6 (1.2–2.0)</td>
<td>1.4 (1.0–2.0)§</td>
</tr>
<tr>
<td>LVH</td>
<td>2.0 (1.4–2.9)</td>
<td>1.9 (1.2–3.2)§</td>
<td>0.8 (0.3–2.4)</td>
<td>4.2 (1.9–9.7)§</td>
</tr>
<tr>
<td>ST depression</td>
<td>1.7 (1.0–2.9)§</td>
<td>1.1 (0.5–2.6)</td>
<td>3.6 (1.5–8.5)</td>
<td>1.2 (0.3–5.0)</td>
</tr>
<tr>
<td>AF</td>
<td>2.9 (1.4–6.3)</td>
<td>2.4 (0.7–7.6)</td>
<td>NA</td>
<td>12.0 (3.9–37.0)</td>
</tr>
<tr>
<td>Glucose intolerance</td>
<td>1.9 (1.2–3.0)</td>
<td>2.0 (1.1–3.6)§</td>
<td>1.7 (0.7–4.6)</td>
<td>1.2 (0.3–4.1)</td>
</tr>
<tr>
<td>BMI†</td>
<td>1.0 (1.0–1.1)</td>
<td>1.1 (1.0–1.2)§</td>
<td>1.0 (0.9–1.1)</td>
<td>0.9 (0.8–1.0)</td>
</tr>
<tr>
<td>Total cholesterol‡</td>
<td>1.1 (1.0–1.3)</td>
<td>1.2 (1.0–1.5)</td>
<td>1.4 (1.0–1.9)</td>
<td>0.6 (0.4–0.9)§</td>
</tr>
<tr>
<td>Smoking habits</td>
<td>0.9 (0.6–1.6)</td>
<td>0.6 (0.3–1.4)</td>
<td>1.0 (0.3–2.8)</td>
<td>2.0 (0.7–5.4)</td>
</tr>
<tr>
<td>Alcohol intake</td>
<td>0.6 (0.3–1.4)</td>
<td>0.5 (0.2–1.6)</td>
<td>1.3 (0.4–4.2)</td>
<td>0.5 (0.1–3.7)</td>
</tr>
</tbody>
</table>

All risk factors are time-dependent covariates. Values are RRs (95% CIs). NA indicates not applicable because there were no cases among subjects with AF.

*Risk for an increase of 10 mm Hg.
†Risk for an increase of 1 kg/m\(^2\).
‡Risk for an increase of 1 mmol/L.
§P<0.05.
||P<0.01.
Thus, the risk assessment in this study more closely reflects the actual relationship between blood pressure and each subtype of cerebral infarction.

**ECG Abnormalities**

Our data showed that LVH and ST depression on ECG were independent risk factors for each cerebral infarction subtype, though not in all sex-subtype categories. The prevalence of these ECG abnormalities in our subjects increased with elevating age and blood pressure (data not shown), suggesting that they reflect a longer duration of hypertension.

It is evident that AF is the most frequent source of cardiac embolism and is associated with a 4- to 5-fold increase in the risk of stroke in white populations.\(^{12,20}\) In our study AF presented a relatively low risk for total cerebral infarction (RR = 3.7 for men and RR = 2.8 for women). This discrepancy was probably due to the relatively low frequency of cardioembolic infarction, for which the risk of AF was outstandingly high (RR = 17.8 for men and RR = 5.9 for women), among our cerebral infarction cases.

**Smoking**

Smoking is widely accepted as one of the risk factors for cerebral infarction in Western populations,\(^{21,22}\) but this relationship has not been observed in most Japanese epidemiological studies,\(^{23,24}\) and was not observed here. However, in our further investigation of cerebral infarction by subtypes, smoking surfaced as a risk factor for lacunar infarction in men, a larger percentage of whom were current smokers than were the women. This finding is consistent with those of previous case-control studies on lacunar syndrome.\(^{25,26}\) Although several explanations of the relation of smoking to cerebral infarction are plausible, smoking is thought to affect lacunar infarction mainly through reversible factors, such as increased platelet aggregation and arterial vasoconstriction induced by augmented sympathetic activity, rather than through atherogenic factors.\(^{27}\) This hypothesis is supported by reports that stroke risk in smokers decreases to the level of that in nonsmokers relatively quickly (several years) after cessation of smoking.\(^{21,22}\)

**TABLE 5. Multivariate RRs and 95% CIs of Risk Factors for Cerebral Infarction and its Subtypes for Men in the Hisayama Study, 1961–1993**

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Cerebral Infarction (n=144)</th>
<th>Lacunar (n=81)</th>
<th>Atherothrombotic (n=29)</th>
<th>Cardioembolic (n=31)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age*</td>
<td>2.2 (1.8–2.6)§</td>
<td>2.2 (1.7–2.9)§</td>
<td>2.7 (1.7–4.3)§</td>
<td>2.2 (1.4–3.5)§</td>
</tr>
<tr>
<td>Systolic blood pressure†</td>
<td>1.2 (1.1–1.2)§</td>
<td>1.2 (1.1–1.3)§</td>
<td>1.3 (1.2–1.5)§</td>
<td>...</td>
</tr>
<tr>
<td>LVH</td>
<td>1.6 (1.1–2.4)‡</td>
<td>...</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>ST depression</td>
<td>2.6 (1.3–5.2)§</td>
<td>3.7 (1.5–9.0)§</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>AF</td>
<td>3.7 (1.8–7.3)§</td>
<td>17.8 (7.3–43.2)§</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>Glucose intolerance</td>
<td>1.5 (1.0–2.2)‡</td>
<td>2.0 (1.2–3.3)§</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>Smoking</td>
<td>...</td>
<td>2.2 (1.3–3.9)§</td>
<td>...</td>
<td>...</td>
</tr>
</tbody>
</table>

All risk factors except for age are the time-dependent covariates. Values are RRs (95% CIs).

*Risk for an increase of 10 years.
†Risk for an increase of 10 mm Hg.
‡P<0.05.
§P<0.01.

**TABLE 6. Multivariate RRs and 95% CIs of Risk Factors for Cerebral Infarction and its Subtypes for Women in the Hisayama Study, 1961–1993**

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Cerebral Infarction (n=154)</th>
<th>Lacunar (n=86)</th>
<th>Atherothrombotic (n=33)</th>
<th>Cardioembolic (n=25)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age*</td>
<td>2.2 (1.9–2.7)¶</td>
<td>2.3 (1.8–2.9)¶</td>
<td>2.3 (1.6–3.4)¶</td>
<td>2.1 (1.3–3.4)¶</td>
</tr>
<tr>
<td>Systolic blood pressure†</td>
<td>1.2 (1.1–1.3)¶</td>
<td>1.2 (1.1–1.3)¶</td>
<td>1.3 (1.1–1.5)¶</td>
<td>1.3 (1.2–1.6)¶</td>
</tr>
<tr>
<td>LVH</td>
<td>1.5 (1.0–2.2)¶</td>
<td>1.8 (1.0–3.0)¶</td>
<td>...</td>
<td>3.0 (1.2–7.2)¶</td>
</tr>
<tr>
<td>ST depression</td>
<td>...</td>
<td>...</td>
<td>2.9 (1.2–6.8)¶</td>
<td>...</td>
</tr>
<tr>
<td>AF</td>
<td>2.8 (1.3–6.1)¶</td>
<td>...</td>
<td>...</td>
<td>5.9 (1.9–18.7)¶</td>
</tr>
<tr>
<td>BMI‡</td>
<td>...</td>
<td>1.1 (1.0–1.2)¶</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>Total cholesterol§</td>
<td>...</td>
<td>...</td>
<td>...</td>
<td>0.8 (0.7–0.9)¶</td>
</tr>
</tbody>
</table>

All risk factors except for age are the time-dependent covariates. Values are RRs (95% CIs).

*Risk for an increase of 10 years.
†Risk for an increase of 10 mm Hg.
‡Risk for an increase of 1 kg/m².
§Risk for an increase of 1 mmol/L.
¶P<0.05.
§P<0.01.
Glucose Intolerance

In our male subjects, glucose intolerance was an especially high risk for lacunar infarction, and this relationship remained significant even after controlling for other risk factors (RR = 2.0). These results are consistent with previously reported case-control studies of lacunar syndrome (odds ratio = 2.0 to 2.3)\textsuperscript{25,26} and with a recent 4.5-year follow-up study of elderly subjects with isolated systolic hypertension (RR = 3.0).\textsuperscript{8} Diabetes is associated with elevated coagulation factors and hyperinsulinemia, which may play a crucial role in the development of lacunar infarction.\textsuperscript{28,29}

Glucose intolerance is also thought to accelerate the atherosclerotic process of large cerebral arteries, resulting in atherothrombotic infarction. However, we did not find a significant relationship between glucose intolerance and atherothrombotic infarction in our subjects. This is in accord with the findings of the aforementioned short-term follow-up study of isolated systolic hypertension in the elderly.\textsuperscript{8} Atherosclerotic disease, including atherothrombotic infarction, is generally a slow pathoanatomic process that may take a long time to reach a clinical end stage in healthy populations. Thus, long-term observation may be necessary for evaluation of the relationship between glucose intolerance and atherothrombotic infarction. On the other hand, the time-dependent Cox’s proportional hazards model used in this study is considered to reflect mainly the short-term effect of risk factors by taking into account those measured in the nearest examinations before the events of cerebral infarction.\textsuperscript{30} This characteristic of the statistical method used here may be one of the reasons why glucose intolerance was not a risk factor for atherothrombotic infarction in our subjects.

Body Mass Index

Recently, 2 large cohort studies,\textsuperscript{31,32} 1 on Japanese-American men and 1 on American nurses, have reported a direct relationship between elevated BMI and stroke. In our subjects, BMI was not an apparent risk factor for cerebral infarction but was independently correlated with the occurrence of lacunar infarction in women. Obesity is closely related to other cardiovascular risk factors, such as hypertension, dyslipidemia, and glucose intolerance, and is thought to affect cardiovascular disease through these atherogenic factors. Among Hisayama residents, the associations between BMI and other risk factors, especially diabetes, were stronger in women than men. Thus, elevated BMI might affect lacunar infarction through glucose intolerance and other correlated risk factors as well, such as elevated sympathetic activity.\textsuperscript{33}

Serum Cholesterol

Some epidemiological studies from Western countries have shown a significant relationship between hypercholesterolemia and the risk of stroke.\textsuperscript{34,35} However, our female subjects showed an inverse relationship between total cholesterol level and the risk of cardioembolic infarction. Although the reason for this is unknown, the possibility exists that the cholesterol level in our subjects was generally low, and a lowered cholesterol level might increase the risk of AF,\textsuperscript{36} which is known to be a prominent risk factor for cardioembolic infarction.

Limitations of the Study

We used information derived from the initial and 5 follow-up examinations for estimating RRs for cerebral infarction subtypes. There is a possibility that the results of this study were biased because some subjects did not return for the follow-up examinations. However, >80% of the total number of surviving stroke-free subjects participated in each examination. In addition, when we analyzed the relationship between baseline risk factors and cerebral infarction events in the total cohort and then in the subgroup consisting of the total cohort minus the subjects who did not return, the results were similar (data not shown). These facts make it unlikely that this bias invalidates the findings of the present study.

Another potential problem in our study was that the methods for measuring serum cholesterol and the criteria for glucose intolerance changed during the follow-up period. This limitation of the risk factor measurement was likely to have contributed to a bias toward finding no effect. Therefore, our estimates of the effect of risk factors are probably conservative. Nonetheless, we believe that our findings contribute to a better understanding of risk factors for each cerebral infarction subtype and its prevention.

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