Abstract—Background: There is scant information on secular trends in the incidence and survival of ischemic stroke subtypes. Methods: The authors established three cohorts of Hisayama residents age ≥40 years in 1961 (1,618 subjects), 1974 (2,038 subjects), and 1988 (2,637 subjects). They followed up with each cohort for 12 years, comparing the incidence and survival rate of ischemic stroke subtypes. Morphologic examinations by autopsy or brain imaging was performed on most of the ischemic stroke cases in all cohorts. Results: The age-standardized incidence of lacunar infarction significantly declined by 59% for men and by 28% for women from the first to the second cohort. It continued to decline by 41% for men, but the decline decelerated for women between the second and third cohort. The age-standardized incidence of atherothrombotic infarction tended to decline from the first to the second cohort, whereas it was sustained between the second and third cohort for both sexes. The age-standardized incidence of cardioembolic infarction was unchanged throughout the cohorts. In these cohorts, mean blood pressure levels among hypertensive subjects and the prevalence of current smoker decreased with time, though the prevalence of hypertension remained stable. The 5-year survival rate after lacunar infarction significantly improved among the cohorts, but those of atherothrombotic and cardioembolic infarction did not.

Conclusions: These data suggest that, in the Japanese population, the incidence of lacunar infarction steadily declined for the last 40 years. The improvement of hypertension control and decreasing prevalence of smoking might be responsible for this trend.

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Stroke is the major cause of mortality and the third leading cause of death in Japan and in Western countries. Ischemic stroke is the most common type of stroke in developed countries, and it can be further divided into several subtypes based on the size and location of the affected cerebral arteries and their pathogenesis: that is, lacunar (LI), atherothrombotic (ATI), and cardioembolic (CEI) infarction. A few cohort studies in Japan, including ours, have shown that the incidence of ischemic stroke significantly declined in the 1970s, but that in recent years, the rate of decline has decreased. As risk factors, prognosis, and treatment among subtypes of ischemic stroke are different, it would be informative to examine trends in the incidence and long-term survival of ischemic stroke by subtypes to improve our understanding of its pathogenesis and assist in establishing preventive measures. However, there has been very little information on this issue, as the definitive classification of ischemic stroke into subtypes requires detailed clinical data, including information on the disease course, neurologic symptoms, and morphologic features.

The Hisayama study is a population-based study that has established three cohorts at times corresponding to periods of remarkable lifestyle changes in Japan. In this study, study-team physicians performed physical and neurologic examinations on the subjects who developed stroke and collected detailed clinical information. Furthermore, morphologic examinations by autopsy or brain imaging were performed in most of the stroke cases in each cohort. These characteristics of the study design enabled us to examine secular trends in the incidence and survival rate of ischemic stroke subtypes.

Methods. Study population. Hisayama Town is a suburban community adjacent to Fukuoka City, a metropolitan area on Kyushu Island in southern Japan. The population of the town has been stable for many years (annual variation rate <5%) and has been shown to be representative of Japan as a whole on the basis of data from the national census. The study design and characteristics of the subject population have been described in detail elsewhere. In brief, we established three study cohorts from Hisayama residents age ≥40 years in 1961, 1974, and 1988 after screening examinations. In 1961, a total of 1,658 subjects in that age group consented to participate in the screening examination (participation rate 90.1%). After the exclusion of 28 subjects with...
a history of stroke or myocardial infarction and 12 subjects who
died or moved out of town during the examination, 1,618 subjects
were enrolled as the first cohort. In the same manner, we estab-
lished the second cohort consisting of 2,038 subjects from 2,135
participants (participation rate, 81.2%) in 1974 and the third co-
hort of 2,637 subjects from 2,742 participants (participation rate,
80.9%) in 1988.

Follow-up. We followed up with each cohort for 12 years by
repeat health examinations. Health status was checked every
year by mail or telephone for any subjects who did not undergo a
regular examination or who moved out of town. We also estab-
lished a daily monitoring system organized by the study team,
local physicians, and members of the local health and welfare
office. When the subjects died, autopsy examinations were per-
formed at the Department of Pathology of Kyushu University.
During the follow-up period of each cohort, to the best of our
knowledge, morphologic examinations by autopsy or brain imaging
were performed on 372 subjects (81.6% of the deceased subjects) in
the first cohort, 342 subjects (86.2%) in the second cohort, and 366
subjects (75.5%) in the third cohort. Only two subjects in the first
cohort, two in the second cohort, and one in the third cohort were
lost follow-up.

Definition of ischemic stroke subtype. The diagnosis of stroke
was determined on the basis of clinical information and autopsy
findings. Stroke was defined as a sudden onset of nonconvulsive
and focal neurologic deficit persisting for >24 hours and
was classified as ischemic stroke, cerebral hemorrhage, sub-
arachnoid hemorrhage, or undetermined type. Two stroke neuro-
logists reviewed all gathered information about stroke cases and
made the diagnoses of ischemic stroke subtypes separately on the
basis of the Classification of Cerebrovascular Disease III proposed
by the National Institute of Neurological Disorders and Stroke12
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 Force. Their diagnoses agreed in 94% of cases,
and in the remaining cases, the diagnoses were determined by a
detailed panel discussion. When sufficient clinical and morpho-
logic information was obtained, a diagnosis of ischemic stroke
subtype was defined as "definite." When the amount of either type
of information was insufficient, the diagnostic level was defined
"probable."

Details of the diagnostic criteria of ischemic stroke subtypes
have been described previously.4 In brief, LI was diagnosed as the
presence of a relevant brainstem or subcortical hemispheric lesion
with a diameter of <1.5 cm demonstrated on brain imaging or
autopsy and no evidence of cerebral cortical or cerebellar impair-
ment. ATI was diagnosed when the subjects had significant steno-
sis (>50%) or occlusion of a major cerebral artery with infarct size
≥1.5 cm on brain imaging or autopsy. The diagnosis of CEI was
made on the basis of primary and secondary clinical features sus-
teguous of CEI as reported by the Cerebral Embolism Task
Force.12 Their diagnoses agreed in 94% of cases, and in the remaining
cases, the diagnoses were determined by a detailed panel discussion. When sufficient clinical and morpho-
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of information was insufficient, the diagnostic level was defined
"probable."

During the follow-up period of each cohort, first-ever ischemic
stroke developed in 122 subjects (78 cases of LI, 26 of ATI, 13 of
CEI, and 5 of UND) in the first cohort, 124 in the second cohort
(67 of LI, 26 of ATI, 28 of CEI, and 3 of UND), and 137 in the third
cohort (77 of LI, 33 of ATI, 30 of CEI, and 0 of UND). Among
these, morphologic examinations by autopsy or brain imaging
were performed on 110 patients (90.2%) in the first cohort, 118
(95.2%) in the second cohort, and 137 (100%) in the third cohort.
In this study, we present the data regarding definite and probable
ischemic stroke subtype cases together, as these combined data
were almost identical to those for definite cases only.

Recumbent blood pressures were measured three times at every examination, and hypertension was defined as
a mean systolic blood pressure of ≥140 mm Hg or a mean
diastolic blood pressure of ≥90 mm Hg or a current use of anti-
hypertensive agents. Glucose intolerance was defined by an oral
glucose tolerance test in the subjects with glycosuria in 1961, by
fasting and postprandial glucose concentrations in 1974, and by a
75-g oral glucose tolerance test in the subjects with a history of diabetes. Serum cholesterol levels were measured by the
Zak-Henly method with a modification by Yoshikawa in 1961, by
the Zuckowski method in 1974, and by the enzymatic method in
1988.5 Hypercholesterolemia was defined as total cholesterol level
of ≥6.2 mmol/L (240 mg/dL). Body height and weight were mea-
sured in light clothing without shoes, and obesity was defined as
body mass index of ≥25.0 kg/m². Information on antihypertensive
treatment, alcohol intake, and smoking habits was obtained with
the use of a standard questionnaire and was categorized as cur-
rent habitual use or not.

Statistical analysis. The incidence rates of ischemic stroke
and its subtypes were calculated by the person-year method and
adjusted for the age distribution of the World Standard Popula-
tion by the direct method. The differences in the incidence among
the three cohorts were tested by sex with the use of the Cox
proportional hazards model after adjustment for age. Subjects
who developed ischemic stroke were also followed up for the
subsequent 5 years or to the end of the follow-up in every cohort, and
surviving subjects were each estimated with the Cox proportional
hazards model. All statistical analyses were performed with the SAS pro-
gram package. Values of p < 0.05 were considered significant in
all analyses.

Results. Trends in risk factors. We compared the prev-
ance of cardiovascular risk factors at the baseline exami-
nation among the three cohorts by sex (table 1). In both sexes,
the prevalence of hypertension was not different
among the cohorts, but the proportion of individuals using
antihypertensive agents consistently increased with time.
As a result, among hypertensive subjects, mean blood press-
sures significantly decreased from the first to the third
cohort in both sexes. The prevalence of glucose intolerance,
hypercholesterolemia, and obesity increased progressively
with time. The proportion of current smokers in both sexes
and that of male drinkers declined linearly over the
cohorts.

Trends in incidence of ischemic stroke subtype. The age-standardized incidence of ischemic stroke for men
declined throughout the cohorts (table 2; p < 0.05). For
women, the incidence also declined from the first to the
second cohort (p < 0.05), but this declining trend was
slowed between the second and third cohort. The age-
standardized incidence of LI for men declined by 59% from
the first to the second cohort (p < 0.01), and it continued to
decline by 41% from the second to the third cohort (p <
0.05). The age-standardized incidence of LI for women also
decreased by 28% from the first to the second cohort, but the
decine decelerated between the second and third cohort
(15%). The age-standardized incidence of ATI declined by
41% from the first to the second cohort for both sexes, but
the difference was not significant probably owing to the
small number of events. The age-standardized incidence
of ATI for women was slightly decreased in the third cohort
(11%), but that for men was not. The age-standardized
incidence of CEI did not change significantly among the
cohorts for either sex.

The proportions of ischemic stroke subtypes among the
cohorts by sex are shown in table 3. For men, the propor-
tion of the subjects with LI steadily decreased from the
first to the third cohort, whereas those of ATI and CEI
increased. For women, the proportion of the subjects with
CEI increased slightly from the first to the third cohort,
but the proportions of the other subtypes were constant
among the cohorts.

Trend in age-specific incidence of ischemic stroke subtype. The age-specific incidence rates of ischemic stroke
subtypes for men and women combined among the three
cohorts are shown in figure 1. The incidence of each subtype
of ischemic stroke increased with advancing age in every
cohort. The incidence of LI consistently decreased from the
first to the third cohort mainly in the aged subjects. The incidence of ATI in the subjects age <80 decreased from the first to the second cohort but was unchanged in the third cohort. In contrast, the incidence of ATI remained high and showed no significant trend in the subjects age ≥80. The incidence of CEI showed no significant change in any age group.

**Trends in survival of ischemic stroke subtype.** Age- and sex-adjusted 5-year survival curves after ischemic stroke by its subtypes are shown in figure 2. The 5-year survival after LI was better than those after other subtypes and improved from the first (54%) to the third cohort (86%; \( p < 0.05 \)). The 5-year survival after ATI tended to improve from the first (17%) to the second cohort (40%; \( p = 0.08 \)) but showed no further improvement in the third cohort (40%). The 5-year survival after CEI was lowest among ischemic stroke subtypes and remained low throughout the study period (16% in the first, 24% in the second, and 26% in the third cohort).

**Discussion.** To our knowledge, this is the first report to examine secular trends in the incidence and survival rates of ischemic stroke by its subtype. Among three cohorts established at different times in a Japanese community, the incidence of LI declined significantly from the first to the third cohort, especially for men. The incidence of ATI tended to decline from the first to the second cohort, but it was sustained in the third cohort for both sexes. The incidence of CEI was unchanged throughout the study period. As a result, for men, the proportion of individuals with LI decreased from the first to the third cohort, and an opposite trend was observed for ATI and CEI. The 5-year survival rate after LI improved significantly among the cohorts, but those of ATI and CEI did not.

In our three cohorts, blood pressure levels were significantly decreased with time as a result of the

**Table 1 Prevalence of cardiovascular risk factors at baseline among three cohorts in 1961, 1974, and 1988 of the Hisayama study by sex**

<table>
<thead>
<tr>
<th>Variables</th>
<th>First cohort, n = 705</th>
<th>Second cohort, n = 855</th>
<th>Third cohort, n = 1,110</th>
<th>p for trend</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>55 ± 11</td>
<td>56 ± 11</td>
<td>57 ± 12</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Hypertension, %</td>
<td>38.6</td>
<td>40.4</td>
<td>41.5</td>
<td>0.22</td>
</tr>
<tr>
<td>Antihypertensive agents, %</td>
<td>2.1</td>
<td>8.5</td>
<td>14.3</td>
<td>0.001</td>
</tr>
<tr>
<td>Systolic blood pressure, mm Hg</td>
<td>161</td>
<td>158</td>
<td>152</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Diastolic blood pressure, mm Hg</td>
<td>91</td>
<td>87</td>
<td>84</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Glucose intolerance, %</td>
<td>12.1</td>
<td>13.8</td>
<td>31.9</td>
<td>0.001</td>
</tr>
<tr>
<td>Hypercholesterolemia, %</td>
<td>1.7</td>
<td>5.3</td>
<td>14.9</td>
<td>0.001</td>
</tr>
<tr>
<td>Obesity, %</td>
<td>7.4</td>
<td>11.6</td>
<td>23.2</td>
<td>0.001</td>
</tr>
<tr>
<td>Current smoker, %</td>
<td>76.3</td>
<td>73.0</td>
<td>49.9</td>
<td>0.001</td>
</tr>
<tr>
<td>Current drinker, %</td>
<td>69.4</td>
<td>64.0</td>
<td>60.2</td>
<td>0.001</td>
</tr>
</tbody>
</table>

Hypertension was defined as systolic blood pressure ≥140 mm Hg or diastolic blood pressure ≥90 mm Hg or a current use of antihypertensive agents. Hypercholesterolemia was defined as total cholesterol level ≥6.2 mmol/L (240 mg/dL). Obesity was defined as body mass index ≥25.0 kg/m².

* Mean systolic and diastolic blood pressures among hypertensive subjects in each cohort.

**Table 2 Age-standardized incidence rate (per 100,000 person-years) of ischemic stroke and its subtypes among three cohorts of the Hisayama study by sex, with a 12-year follow-up in each cohort**

<table>
<thead>
<tr>
<th></th>
<th>Men</th>
<th>Women</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n Rate</td>
<td>n Rate</td>
</tr>
<tr>
<td>Ischemic stroke</td>
<td>63 801</td>
<td>59 506*</td>
</tr>
<tr>
<td>Lacunar</td>
<td>44 559</td>
<td>28 229*</td>
</tr>
<tr>
<td>Atherothrombotic</td>
<td>12 165</td>
<td>12 98</td>
</tr>
<tr>
<td>Cardioembolic</td>
<td>6 67</td>
<td>18 169</td>
</tr>
<tr>
<td>Undetermined</td>
<td>1 10</td>
<td>1 10</td>
</tr>
</tbody>
</table>

\* p < 0.05 vs first cohort; † p < 0.05 vs second cohort.
sevenfold increment in the use of antihypertensive medication, though the prevalence of hypertension remained stable. The prevalence of smoking habits for men was 4.5-fold higher than that for women in the first cohort, and it decreased significantly for both sexes in the third cohort. Contrary to these declining trends of the risk factors, the prevalences of glucose intolerance, hypercholesterolemia, and obesity were greatly increased over the study period for both sexes. These changes in risk factors might have affected trends in the incidence of ischemic stroke subtype.

In our Japanese population, LI was the most common subtype of ischemic stroke, contrary to the previous reports of Western populations. An autopsy study comparing small intracerebral arteriosclerosis between Japanese and Japanese American men demonstrated that small intracerebral artery lesions

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### Table 3 Proportion of subjects with subtypes of ischemic stroke among three cohorts of the Hisayama study by sex

<table>
<thead>
<tr>
<th></th>
<th>Men</th>
<th>Women</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n (%)</td>
<td>n (%)</td>
</tr>
<tr>
<td>Lacunar</td>
<td>44 (69.9)</td>
<td>28 (47.5)</td>
</tr>
<tr>
<td>Atherothrombotic</td>
<td>12 (19.0)</td>
<td>12 (20.3)</td>
</tr>
<tr>
<td>Cardioembolic</td>
<td>6 (9.5)</td>
<td>18 (30.5)</td>
</tr>
<tr>
<td>Undetermined</td>
<td>1 (1.6)</td>
<td>1 (1.7)</td>
</tr>
<tr>
<td></td>
<td>n (%)</td>
<td>n (%)</td>
</tr>
<tr>
<td>Lacunar</td>
<td>34 (57.6)</td>
<td>39 (60.0)</td>
</tr>
<tr>
<td>Atherothrombotic</td>
<td>14 (23.7)</td>
<td>14 (21.5)</td>
</tr>
<tr>
<td>Cardioembolic</td>
<td>7 (11.9)</td>
<td>10 (15.4)</td>
</tr>
<tr>
<td>Undetermined</td>
<td>4 (6.8)</td>
<td>2 (3.1)</td>
</tr>
</tbody>
</table>
were more common in Japanese at every age.\textsuperscript{15} Moreover, high blood pressure and a typical Asian diet were significantly associated with small intracerebral artery lesions.\textsuperscript{15} The differences in race and lifestyle-related factors might contribute to the difference in the proportion of ischemic stroke subtypes between Japan and Western countries.

During the study period, the incidence of LI declined steeply, especially in men. The improvement of hypertension control and the decreasing prevalence of smoking may have been responsible for this finding. In contrast to the dynamic changes in the incidence of LI, the incidence of ATI has remained stable in recent years. One of the reasons for this finding may have been that the steep increase in metabolic disorders, such as glucose intolerance, dyslipidemia, and obesity, hindered the beneficial effects of the secular improvement of hypertension control and the cessation of smoking. Another possible reason is that hypertension control might be less effective for prevention of ATI.\textsuperscript{16}

Despite the marked changes in cardiovascular risk factors among the cohorts, the incidence of CEI showed no significant change in this study. The effect of cardiovascular risk factors on the incidence of CEI was weaker than the effect on other subtypes.\textsuperscript{6} In addition, the prevalence of atrial fibrillation, the most common risk factor for CEI, increased from 0.7\% in the first cohort to 1.4\% in the third cohort. These factors may have contributed to the sustained incidence of CEI. As a result of dynamic changes in risk factors, the proportion of ischemic stroke subtypes in our subjects has become closer to that of Western populations in recent years. However, it is important to note that this trend was caused not by the increase in the incidence of ATI and CEI, but by the steep decrease in the incidence of LI.

Consistent with previous studies,\textsuperscript{17-19} we found that the 5-year survival rate was higher for LI, and lower for CEI in each cohort. Moreover, the survival rate improved significantly with time in the subjects with LI, but not in the subjects with ATI or CEI. Stroke is more severe in subjects with ATI and CEI than in those with LI. In addition, the incidence of coronary heart disease, a more common comorbidity in ATI and CEI,\textsuperscript{19} is increasing among elderly individuals in Japan.\textsuperscript{3} These factors may have contributed to the sustained low survival rate in ATI and CEI.

Our study had several possible limitations. First, the method for diagnosing stroke has been remarkably changed by the improvement of diagnostic techniques, and this may have affected the incidence rate.\textsuperscript{20,21} It is possible that the decrease in the LI incidence could be artificial, that is, correspond to inclusion of the same patients into another category, for example, small deep infarction due to cardioembolism. In this study, however, methods for case ascertainment and the criteria for ischemic stroke subtypes were consistent among the cohorts, and the classification of ischemic stroke subtype was confirmed by detailed clinical and morphologic examination, the latter of which was performed in most of the ischemic stroke cases (90 to 100\%). These facts make it unlikely that this bias invalidates the findings of the current study. Second, we established three cohorts independently in the same manner, but the subjects in later cohorts included many survivors of the former cohorts. This may have affected the development of stroke; however, we enrolled most of the unselected residents in every cohort, and the prevalence rate of cardiovascular risk factors in the third cohort was similar to that of the National Nutritional Survey of Japan.\textsuperscript{3} Third, there were a small number of cases in each cohort, indicating a larger chance of bias in the results of this study. Nonetheless, we believe that the findings of our study represent precise secular trends, as we performed this study using a highly accurate method for determining all cardiovascular events.

Our findings indicate that correction of increasing metabolic disorders such as obesity, dyslipidemia, and glucose intolerance as well as strict management of hypertension have become more important to prevent ischemic stroke in contemporary Japanese individuals.

Acknowledgment
The authors thank the residents of Hisayama Town for their participation in the survey and the staff of the Division of Health and Welfare of Hisayama for their cooperation in this study.

References
Intraplaque dissection of the basilar artery

Michelle L. Mauermann, MD; C. Douglas Phillips, MD; and Bradford B. Worrall, MD, MSc, Charlottesville, VA

A 61-year-old right-handed man with hypertension, hyperlipidemia, and tobacco abuse presented with sudden dysarthria, left hemiparesis, and hemianesthesia. Examination also revealed left hemiataxia and hemianopsia. MRI revealed multiple acute infarctions in the right posterior cerebral artery territory. Magnetic resonance angiography revealed a narrowed and irregular basilar artery. Computed tomographic angiography demonstrated extensive calcific atherosclerotic changes with an intraluminal filling defect in the mid-basilar artery (figure). Fat-suppressed axial T1-weighted images confirmed intraplaque dissection (figure); T2 images showed low signal consistent with subacute intraplaque clot. MRI can characterize complicated atheroma and distinguish intraplaque from juxtaluminal thrombosis in the anterior circulation.1,2 In this case, CT and MRI were complementary for the characterization of the symptomatic lesion and helped guide choice of antithrombotic therapy.

Disclosure: The authors report no conflicts of interest.

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