Risk of Stroke in Relation to Level of Blood Pressure and Other Risk Factors in Treated Hypertensive Patients

Yuriko Makino, MD; Yuhei Kawano, MD; Junichi Minami, MD; Takenori Yamaguchi, MD; Shuichi Takishita, MD

Background and Purpose—Treatment of hypertension effectively reduces the risk of stroke. However, many treated patients still have high blood pressure (BP), other cardiovascular risk factors, and complications. The risk of stroke in treated hypertensive patients is not well understood.

Methods—We analyzed the level of BP over 1 year before the onset of stroke and other cardiovascular risk factors in treated hypertensive patients in a case-control study. The study population included 126 hypertensive patients (74 men; mean age, 70.9 years) with first strokes during 1988–1993 who had been treated for >1 year before stroke onset (stroke group). As a control group, we selected 126 sex- and age-matched hypertensive patients who were treated during the same period and were free from stroke.

Results—Mean 12-month BP was not significantly different between stroke and control groups, although systolic BP was 2.5 mm Hg higher in the stroke group (148.7 [95% CI, 146.1 to 151.3]/82.1 [95% CI, 80.5 to 83.7] versus 146.2 [95% CI, 143.8 to 148.6]/82.4 [95% CI, 81.0 to 83.8] mm Hg). In patients aged <70 years, mean systolic BP was significantly higher in the stroke group than the control group (150.5 [95% CI, 146.3 to 154.7] versus 144.0 [95% CI, 140.6 to 147.4] mm Hg). Mean pulse pressure was also significantly higher in the stroke group than the control group in patients aged <70 years but not in older patients. In the stroke group, the level of BP within 1 month before stroke onset did not differ from the mean value over the 12-month period. Patients with brain hemorrhage had higher diastolic BP than those with other subtypes. The stroke group had higher plasma glucose, lower HDL cholesterol, and higher frequencies of diabetes mellitus, proteinuria, atrial fibrillation (29.4% versus 4.0%), and use of antiplatelet (31.0% versus 11.1%) and anticoagulant (10.3% versus 1.6%) agents than the control group.

Conclusions—The onset of stroke in treated hypertensive patients was related to a higher level of BP in subjects <70 years old, although this relationship was not obvious in older patients. The risk of stroke in these patients was associated with the presence of metabolic risk factors and cardiovascular complications. Office BP did not change significantly 1 month before the onset of stroke. (Stroke. 2000;31:48-52.)

Key Words: blood pressure ■ elderly ■ hypertension ■ risk factors ■ stroke

Mortality due to stroke has been declining in Japan, as in most countries, but stroke is still the second leading cause of death in Japan.2,3 Hypertension is the most powerful risk factor of stroke, and higher levels of systolic and diastolic blood pressure (BP) have been associated with an increased incidence of ischemic and hemorrhagic stroke in people of all ages and both sexes.1–5 Many intervention studies have demonstrated that antihypertensive therapy effectively reduces morbidity and mortality of stroke in hypertensive subjects, including elderly patients with isolated systolic hypertension.5–9 Therefore, there is no doubt that control of hypertension is particularly important for the prevention of stroke.

However, there is persistent excess cardiovascular morbidity in treated hypertensive patients.10 The level of BP before the onset of stroke is less well characterized, and the risk of stroke in treated patients has not been clarified well. A number of treated patients still have high BP and often have other cardiovascular risk factors and complications.11,12 The incomplete control of hypertension may be related to the risk of stroke.13 On the other hand, an excessive decrease in BP may increase cardiovascular complications. We observed previously that low diastolic BP is associated with increased recurrence of stroke or myocardial infarction.14,15 It has also been suggested that the level of optimal BP may be age dependent.16

A large number of hypertensive patients have been treated at our outpatient clinic, and >90% of those patients who suffered from stroke were admitted to the Stroke Care Unit of our hospital. In the present case-control study, we analyzed...
the relation between the level of BP and the risk of first stroke using multiple BP readings over 1 year before the onset of stroke, with particular attention to BP at 1 month before onset. We also analyzed other cardiovascular risk factors and complications in relation to the risk of stroke.

Subjects and Methods

The study population consisted of 126 consecutive hypertensive patients (74 men and 52 women; mean age, 70.9 years [95% CI, 69.3 to 72.5 years] with first strokes during 1988–1993, who had visited the outpatient clinic of our institute monthly for at least 1 year before the onset of stroke (stroke group). All of these patients were admitted to our Stroke Care Unit, and the diagnosis of stroke was confirmed by specialists on the basis of the results of several examinations, including brain CT and MRI. We compared each patient with an age- and sex-matched hypertensive patient without stroke (control group), who visited the same clinic during the same period. Patients were diagnosed as having hypertension if they had systolic BP $>140$ mm Hg or diastolic BP $>90$ mm Hg or if they had received antihypertensive medication.

In the stroke group, 17 patients (13.5%) were on nonpharmacological treatment alone, while 77 (61.1%), 31 (24.6%), 32 (25.4%), 14 (11.1%), and 4 (3.2%) were given calcium channel blockers, angiotensin-converting enzyme inhibitors, diuretics, β-blockers, α-blockers, and others, respectively, before the onset of stroke. In the control group, the number of patients on nonpharmacological treatment alone was 13 (10.3%), and numbers of patients given the aforementioned treatments were 93 (73.8%), 25 (19.8%), 29 (23.0%), 33 (26.2%), 10 (7.9%), and 1 (0.8%), respectively. Multiple antihypertensive agents were given to 55 patients (43.7%) in the stroke group and 56 (44.4%) in the control group.

Before the onset of stroke, office BP was measured twice at each visit by physicians using a standard sphygmomanometer, with patients in the sitting position. The patients remained seated for at least 5 minutes before BP was measured. Korotkoff phase V was taken as diastolic BP. In the control group, BP was measured in the same manner during the corresponding period. The mean office BP values were calculated during the 12 months before the onset of stroke in the stroke group and during the same period in the control group. The mean BP values were also divided into 5 categories, with cutoffs of 160, 150, 140, and 130 mm Hg for systolic BP and 95, 90, 85, and 80 mm Hg for diastolic BP.

The stroke group was classified into the following stroke subtypes: atherothrombotic brain infarction, lacunar brain infarction, cardioemolic brain infarction, brain hemorrhage, and brain infarction of undetermined type. Classification for these stroke subtypes was performed by stroke specialists, as described previously. Of 126 stroke group patients, 43 (34.1%) were classified as atherothrombotic brain infarction, 18 (14.3%) as lacunar brain infarction, 26 (20.6%) as cardioemolic brain infarction, 17 (13.5%) as brain hemorrhage, and 22 (17.5%) as brain infarction of undetermined type.

Several metabolic variables were examined during the 1-year period before the onset of stroke in the stroke group and during the same period in the control group. Fasting blood glucose, serum creatinine, total cholesterol, HDL cholesterol, and triglyceride were measured with an autoanalyzer. The 12-lead ECGs of each patient recorded during the 1-year period before the onset of stroke were coded according to the revised Minnesota code. The presence of high QRS voltage (code 3.1 or 3.3) was considered evidence of left ventricular hypertrophy. Duration of hypertension, smoking habit, body mass index, presence or absence of diabetes, dyslipidemia, proteinuria, and use of antplatelet or anticoagulant agents were examined from the medical record of each patient.

Values are expressed as means and 95% CIs. Statistical analyses were performed with χ² test, Student’s t test, or ANOVA when appropriate. When a significant overall effect was detected by ANOVA, Scheffé’s F test was used for comparison of 2 variables. Analyses were performed with StatView software (Abacus Concepts Inc). A value of $P < 0.05$ was considered statistically significant.

### TABLE 1. Clinical Characteristics of the Subjects

<table>
<thead>
<tr>
<th></th>
<th>Stroke Group (n=126)</th>
<th>Control Group (n=126)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>70.9 (69.3–72.5)</td>
<td>70.9 (69.1–72.7)</td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
<td>22.4* (21.8–23.0)</td>
<td>24.2 (23.6–24.8)</td>
</tr>
<tr>
<td>Duration of hypertension, y</td>
<td>18.6 (16.2–21.0)</td>
<td>17.2 (15.4–19.0)</td>
</tr>
</tbody>
</table>

| Smoking habit, %     | 47.6                  | 38.9                  |
| Drinking habit, %    | 39.5                  | 47.6                  |
| Diabetes, %          | 34.2*                 | 16.8                  |
| Dyslipidemia, %      | 54.2                  | 49.2                  |
| Proteinuria, %       | 23.8*                 | 11.1                  |
| ECG high voltage, %  | 33.3                  | 31.0                  |
| Atrial fibrillation, % | 29.4*             | 4.0                   |
| Use of antplatelet agents, % | 31.0*                | 11.1                  |
| Use of anticoagulant agents, % | 10.3*         | 1.6                   |

Values are mean (95% CI). *$P<0.05$ between the 2 groups.

### TABLE 2. Office BP Within 1 Month and Mean 12-Month BP Before the Onset of Stroke in the Stroke Group and That During Corresponding 12-Month Period in the Control Group

<table>
<thead>
<tr>
<th></th>
<th>Stroke Group</th>
<th>Control Group</th>
</tr>
</thead>
<tbody>
<tr>
<td>Within 1 month</td>
<td>Mean 12-month</td>
<td>Mean 12-month</td>
</tr>
<tr>
<td>Systolic BP</td>
<td>147.7 (143.3–152.1)</td>
<td>148.7 (146.1–151.3)</td>
</tr>
<tr>
<td>Diastolic BP</td>
<td>82.3 (79.5–85.1)</td>
<td>82.1 (80.5–83.7)</td>
</tr>
<tr>
<td>&lt;70 years (n=55)</td>
<td>Systolic BP</td>
<td>148.5 (141.1–155.9)</td>
</tr>
<tr>
<td></td>
<td>Diastolic BP</td>
<td>84.9 (81.1–88.7)</td>
</tr>
<tr>
<td>≥70 years (n=71)</td>
<td>Systolic BP</td>
<td>147.2 (141.8–152.6)</td>
</tr>
<tr>
<td></td>
<td>Diastolic BP</td>
<td>80.4 (76.6–84.2)</td>
</tr>
</tbody>
</table>

Values are mean (95% CI), expressed in millimeters of mercury. *$P<0.05$ vs control group.
Clinical characteristics of the stroke and control groups are shown in Table 1. There were no significant differences in age, duration of hypertension, proportional frequencies of smoking history, drinking habit, high voltage on ECG, or dyslipidemia between the groups. The stroke group had a significantly lower body mass index and higher frequencies of diabetes mellitus, proteinuria, atrial fibrillation, and use of antiplatelet and anticoagulant agents than the control group.

The mean office BP value during the 12 months before the onset of stroke in the stroke group was not significantly different from that during the same period in the control group (Table 2). Patients aged <70 years, however, had significantly higher systolic BP than those in the control group. The mean systolic and diastolic BP values were comparable between both groups in patients aged ≥70 years. The younger patients in the stroke group also had significantly higher pulse pressure than those in the control group (65.8 [95% CI, 62.2 to 69.4] mm Hg versus 59.6 [95% CI, 56.0 to 63.2] mm Hg). The pulse pressure was not significantly different between the 2 groups for the older patients or for all patients.

In the stroke group, office BP within 1 month before the onset of stroke was not significantly different from the mean value for the 12-month observation period (Table 2). The lack of changes in BP before the onset of stroke was observed in both younger and older patients.

The distribution of systolic and diastolic BP was not significantly different between the 2 groups (Figure). In patients aged <70 years, however, the distribution of systolic BP was significantly different between the stroke and control groups, and the proportion of subjects with systolic BP ≥160 mm Hg was higher in the stroke group than in the control group (25.5% versus 7.4%). In older patients, the proportion of subjects in each category of systolic and diastolic BP was similar between the 2 groups.

The mean systolic BP during the 12-month observation period was not significantly different among patients with different subtypes of stroke (Table 3). Patients with lacunar brain infarction had higher systolic BP than those in the control group (P<0.05). The mean diastolic BP was significantly higher in patients with brain hemorrhage than in those with lacunar brain infarction, those with brain infarction of undetermined type, or the control group.

Fasting plasma glucose level was significantly higher in the stroke group than in the control group (Table 4). Serum creatinine tended to be higher and plasma HDL cholesterol tended to be lower in the stroke group than in the control group (P<0.05). Other metabolic factors, such as total cholesterol and triglycerides, were comparable between the 2 groups.

### Discussion
In the present study mean BP for the 12 months before the onset of stroke in treated hypertensive patients was not significantly different from that in treated hypertensive patients without stroke. In subjects aged <70 years, however, the mean systolic BP was significantly higher in patients with than in those without stroke. The stroke group had a higher incidence of diabetes mellitus, proteinuria, and atrial fibrilla-
tion than the control group. These results suggested that higher BP (particularly for patients aged <70 years) and the presence of cardiovascular risk factors other than hypertension and target organ damage increase the risk of first stroke in treated hypertensive patients.

Hypertension is the most powerful risk factor for stroke, and antihypertensive treatment effectively reduces the risk of stroke in hypertensive patients. Detection and treatment of hypertension are routinely performed, and the age-adjusted mortality risk for stroke has decreased markedly in many countries, including Japan. However, the efficiency of hypertension treatment still seems insufficient. According to the 1991–1994 US National Health and Nutrition Examination Survey, the percentages for treatment and control (<140/90 mm Hg) of hypertension were 54% and 27%, respectively. In the 1992 Japanese National Nutrition Survey, in which normotensive subjects were included, mean BP in the group aged 60 to 69 years was 146/85 mm Hg for men and 144/83 mm Hg for women. A cooperative study including our institute showed that mean BP was 143/81 mm Hg in treated hypertensive patients aged ≥50 years.

Mean BP before the onset of stroke was higher and the proportion of subjects with systolic BP >160 mm Hg was greater in the stroke group than in the control group in our patients aged <70 years old. Du et al also showed that the risk of stroke increases with the level of BP in treated hypertensive patients. They suggested that control of BP to <150/90 mm Hg is required for optimal stroke prevention. In the Hypertension Optimal Treatment (HOT) study, the lowest incidence of stroke occurred at a mean achieved systolic BP of 142 mm Hg, while the level of diastolic BP did not predict the onset of stroke. The lowest incidence of major cardiovascular events occurred at 139/83 mm Hg in this trial. Taken together, more strict control of BP may be beneficial to prevent the first stroke in hypertensive subjects, especially in relatively young patients.

In our study, however, the level of mean BP before the onset of stroke was not significantly different from the mean BP in the control group in all subjects or in subjects aged ≥70 years. The relative risk of stroke in hypertensive subjects decreases with age, although the absolute risk for stroke is high in elderly hypertensive subjects. In the Hisayama Study, the relative risk for stroke mortality was 10-fold higher in hypertensive subjects aged <60 years than normotensive subjects of similar age, but it was 3-fold higher in hypertensive subjects aged ≥60 years. The mean age of our patients was 71 years, which was higher than that in other studies investigating the risk of higher BP for stroke. In addition, all patients in our study were treated at a single hospital by specialists. Few patients had very high BP under treatment, and the mean systolic BP in the stroke group was <150 mm Hg. These factors may account for the lack of significant differences in treated BP between the stroke and control groups in all subjects.

Our results do not mean that hypertension control is not important for patients aged ≥70 years. Several intervention studies have shown that treatment of hypertension effectively reduces stroke mortality and morbidity in the elderly. The cutoff point of age 70 years in our study was arbitrary, although it was close to the mean age of study subjects. The sample size of stroke cases and controls may not be large enough to draw definite conclusions. However, we observed similar results when the size of the control group was increased by the addition of 94 patients with similar distribution of age from our previous study.

A J-shaped relationship was reported between the level of BP (especially diastolic BP) and incidence of myocardial infarction, suggesting that low diastolic BP may be a risk for subsequent cardiovascular disease. We also observed that low diastolic BP was associated with increased recurrence of stroke or myocardial infarction. However, the proportion of patients whose BP values were in the lowest range (<130/80 mm Hg) was not different between the stroke and control groups in the present study. Several intervention trials have failed to observe the J-curve phenomenon between the level of treated BP and the incidence of stroke or myocardial infarction in hypertensive subjects, including patients with isolated systolic hypertension. These results indicated that low BP does not increase the risk of first stroke in treated hypertensive patients, although rapid and exaggerated reduction of BP may be harmful.

In the present study BP was measured monthly, and we used mean BP over a period of 12 months for analysis. It has been shown that mean BP from repeated measurements is more predictive than casual BP for stroke occurrence. On the other hand, acute changes in BP may trigger the onset of stroke. It was reported that the variability of BP was associated with subsequent incidence of coronary heart disease. If the nearest BP obtained before the onset of stroke is different from previous values, it would be helpful to identify high-risk patients. However, the level of BP within 1 month before stroke was not significantly different from the 12-month mean in our study. The onset of stroke does not appear to be predictable from recent changes in monthly measured BP.

With regarding to stroke subtype, patients with brain hemorrhage had higher diastolic BP before the onset of stroke than those with other subtypes. Mean systolic BP was relatively high in patients with lacunar brain infarction, and this group had significantly higher systolic BP than the control group. Since brain hemorrhage and lacunar infarction are more closely related to hypertension than other subtypes, strict control of BP would be required for their prevention.

Various antihypertensive agents may have different effects on brain vasculature and circulation. Although antihypertensive treatment has been shown to reduce the risk of stroke, the relative efficacy of these drugs in the prevention of stroke has not been clarified. In the present study, calcium channel blockers were most frequently used in both stroke and control groups, as in other institutes in Japan. There were no significant differences in the use of each class of antihypertensive agent or in the proportion of patients on multiple drug regimens between the 2 groups.

In the present study the stroke group had a higher prevalence of cardiovascular risk factors and organ damage such as diabetes, proteinuria, and atrial fibrillation than the control group. The level of HDL cholesterol tended to be lower in the stroke group. Since these factors have been shown to be
predictive of stroke,27–29 their presence may increase the risk of stroke in treated hypertensive patients even though BP is controlled. Early detection and treatment of risk factors are important for the effective prevention of stroke. In particular, strict control of BP appears to be beneficial for hypertensive patients with diabetes.11,30

The use of anticoagulant and antiplatelet agents was more frequent in the stroke group than in the control group. This may have been reflected by the high prevalence of atrial fibrillation and other cardiovascular complications in the stroke group. Similar results were observed regarding the use of aspirin in the Cardiovascular Health Study.31 It has been shown that warfarin prevents stroke in patients with atrial fibrillation.5,27,32 However, there is no evidence of primary prevention of stroke in treated hypertensive patients. Early detection and treatment of these risk factors before the development of target organ damage are strongly recommended.

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