Prospective Study of Major and Minor ST-T Abnormalities and Risk of Stroke Among Japanese

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Background and Purpose—The association between minor ST-T abnormalities and stroke incidence has not been well elucidated. We sought to examine the relationship between nonspecific minor or major ST-T abnormalities and the incidence of stroke among Japanese men and women.

Methods—A 15.4-year prospective study was conducted with 10,741 men and women aged 40 to 69 years in 4 Japanese communities. Electrocardiograms were taken at baseline and were read according to the Minnesota Code. The incidence of stroke was ascertained using systematic surveillance.

Results—During the 15.4-year follow-up, 602 strokes (339 ischemic strokes, 129 intracerebral hemorrhages, 80 subarachnoid hemorrhages, and 54 unclassified strokes) occurred. Both men and women with major ST-T abnormalities had approximately 3-fold higher age-adjusted relative risk and 2-fold higher multivariate-adjusted relative risk of total stroke than did those without such abnormalities. Men with minor ST-T abnormalities had a 2.3-fold higher age-adjusted relative risk of total stroke, both ischemic and hemorrhagic, than did those without such abnormalities. After we adjusted further for hypertension category, the relative risk for minor ST-T abnormalities was reduced substantially but remained statistically significant: 1.8 (95% CI, 1.0 to 3.0) for hemorrhagic stroke. For women, however, there was no relation between minor ST-T abnormalities and stroke incidence.

Conclusions—Minor ST-T abnormalities have predictive value for the risk of total stroke, both ischemic and hemorrhagic, among middle-aged Japanese men, as do major ST-T abnormalities for both sexes. (Stroke. 2003;34:e250-e253.)

Key Words: cohort study ■ electrocardiography ■ risk factors ■ stroke, hemorrhagic ■ stroke, ischemic

Non-specific ECG abnormalities are frequently observed in surveys, and the most common non-specific finding is ST segment or T-wave abnormalities, or both (ST-T abnormalities).1,2 ST-T abnormalities, particularly major abnormalities, are associated with increased risk of stroke incidence and mortality.3-7 However, association between minor ST-T abnormalities and stroke incidence has not been well elucidated because most previous studies did not distinguish between major and minor ST-T abnormalities.5,6,7

Since the frequency of minor ST-T abnormalities is >2-fold higher than that of major ST-T abnormalities,8 it is important for stroke risk assessment to determine the association of minor ST-T abnormalities with stroke incidence. No prospective study, however, has examined the relationship between non-specific minor ST-T abnormalities and the incidence of stroke. To examine the relationship between minor and major ST-T abnormalities with the incidence of stroke, we used the data from a 15.4-year follow-up study of men and women in 4 Japanese communities.

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Baseline Examination
Standard 12-lead ECG was obtained in supine position. Each record was coded independently using the Minnesota Code (MC) by 2 trained physicians. The codes in agreement were accepted, and disagreements were discussed between the 2 physicians and if necessary, arbitrated by a third experienced physician. The criteria for minor ST-segment depression were either of the following: (1) MC, 4-1 to 4-2 or 5-1 to 5-2; or (2) left ventricular hypertrophy (MC, 3-1 and 4-1 to 4-3 or 5-1 to 5-3). Cardiovascular disease risk factors were also measured at baseline. Detailed methods of risk factor surveys were described elsewhere. Hypertension was defined as systolic blood pressure (SBP) of 140 mm Hg and diastolic blood pressure (DBP) of 90 mm Hg. All others were classified as having borderline hypertension.

End Point Determination
Stroke incidence was ascertained by 6 overlapping methods: (1) national insurance claims, (2) reports by local physicians, (3) ambulance records, (4) death certificates, (5) reports by public health nurses and health volunteers, and (6) cardiovascular risk surveys. Determination of type of stroke (ie, intracerebral hemorrhage, subarachnoid hemorrhage, and ischemic stroke) was done primarily by CT/MRI in a standardized way. CT/MRI films were available for 74% of the stroke cases. Stroke cases that were diagnosed clinically but showed no lesion on CT/MRI were regarded as unclassified stroke. Stroke cases without CT/MRI films were classified according to the clinical criteria based on Millikan.

Statistical Analysis
The relative risk of stroke incidence was calculated with reference to the risk of persons without ST-T abnormalities, using the Cox proportional hazards model. Covariates included age (years), body mass index (BMI, kg/m²), hypertension category (normotension, borderline hypertension, and hypertension), quartiles of serum total cholesterol (mmol/L), smoking category, alcohol intake, and glycemia status. Because the relations of minor ST-T abnormalities with the incidence of stroke were similar among the 4 populations sampled, we presented results for the combined cohort.

Results
Among 4205 men (mean age, 52.9 years) and 6536 women (mean age, 52.9 years) followed for 15.4 years, 602 incident strokes occurred. These included 339 ischemic strokes, 209 hemorrhagic strokes (129 intracerebral and 80 subarachnoid hemorrhages), and 54 unclassified strokes.

Table 1 shows age-adjusted mean values or proportions of risk characteristics at baseline for incident cases of stroke and for those who remained free of stroke. For men and women, mean values of blood pressure (BP) and BMI, and the prevalence of hypertension and major ST-T abnormalities were higher among subjects with stroke than among subjects without stroke.

The prevalence of major ST-T abnormalities in men and women was 4.2% and 6.4%, respectively. The prevalence of minor ST-T abnormalities in women was 2-fold higher than in men (17.3% versus 8.9%, P<0.001). For men and women, mean values of BP, BMI, and serum cholesterol and the prevalence of hypertension were higher among subjects with major or minor ST-T abnormalities than among subjects without such abnormalities (Table 2).

As shown in Table 3, both men and women with major ST-T abnormalities had an approximately 3-fold higher age-adjusted relative risk of total stroke than did those without such abnormalities. Minor ST-T abnormalities were significantly associated with stroke incidence for men, but not for women. The age-adjusted relative risks of total stroke for minor ST-T abnormalities were 2.3 for men and 1.0 for women. Further adjustment for hypertension category reduced the relative risk to 1.8 but it remained statistically significant. Adjustment for other cardiovascular risk factors did not alter the associations materially.
The present prospective study showed a positive relationship between minor ST-T abnormalities and the risk of stroke among Japanese men, but not women. A previous prospective study of 1673 employed middle-aged US men showed that minor ST-T abnormalities were independently associated with increased risk of death due to myocardial infarction, coronary heart disease, cardiovascular diseases, and all causes. Our study provides further evidence that nonspecific minor ST-T abnormalities are an independent risk factor for stroke incidence among men.

There was no relationship between minor ST-T abnormalities and the incidence of stroke among women. The prevalence of minor ST-T abnormalities in women was higher than in men, as reported by some previous studies, while the incidence of stroke was higher in men than in women.

**TABLE 2. Age-Adjusted Mean (SE) Values or Proportions of Risk Characteristics at Baseline Among Persons With Minor ST-T Abnormalities, Those With Major ST-T Abnormalities, and Those Without ST-T Abnormalities**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Men</th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Normal ECG</td>
<td>Minor ST-T Abnormality</td>
<td>Major ST-T Abnormality</td>
<td><em>P</em></td>
<td>Normal ECG</td>
<td>Minor ST-T Abnormality</td>
<td>Major ST-T Abnormality</td>
<td><em>P</em></td>
</tr>
<tr>
<td>n</td>
<td>3655</td>
<td>373</td>
<td>177</td>
<td></td>
<td>4989</td>
<td>1129</td>
<td>418</td>
<td></td>
</tr>
<tr>
<td>Age, y</td>
<td>52 (0.1)</td>
<td>55 (0.5)</td>
<td>58 (0.7)</td>
<td>&lt;0.001</td>
<td>52 (0.1)</td>
<td>55 (0.3)</td>
<td>56 (0.4)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Systolic blood pressure, mm Hg</td>
<td>135 (0.3)</td>
<td>147 (1.0)</td>
<td>157 (1.5)</td>
<td>&lt;0.001</td>
<td>132 (0.3)</td>
<td>139 (0.6)</td>
<td>145 (0.9)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Diastolic blood pressure, mm Hg</td>
<td>82 (0.2)</td>
<td>88 (0.6)</td>
<td>90 (0.9)</td>
<td>&lt;0.001</td>
<td>79 (0.2)</td>
<td>82 (0.3)</td>
<td>84 (0.6)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Hypertensive subjects, %</td>
<td>23</td>
<td>45</td>
<td>65</td>
<td>&lt;0.001</td>
<td>18</td>
<td>32</td>
<td>42</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
<td>22.7 (0.1)</td>
<td>23.7 (0.1)</td>
<td>24.0 (0.2)</td>
<td>&lt;0.001</td>
<td>23.4 (0.1)</td>
<td>23.9 (0.1)</td>
<td>23.9 (0.2)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Serum total cholesterol, mmol/L</td>
<td>4.72 (0.01)</td>
<td>4.87 (0.05)</td>
<td>4.81 (0.07)</td>
<td>&lt;0.01</td>
<td>5.01 (0.01)</td>
<td>5.09 (0.03)</td>
<td>5.13 (0.04)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Alcohol intake, g/day</td>
<td>27.2 (0.5)</td>
<td>31.8 (1.4)</td>
<td>33.0 (2.1)</td>
<td>&lt;0.001</td>
<td>1.7 (0.2)</td>
<td>1.5 (0.4)</td>
<td>1.9 (0.6)</td>
<td>0.80</td>
</tr>
<tr>
<td>Heavy drinker (≥69 g/day), %</td>
<td>10</td>
<td>16</td>
<td>17</td>
<td>&lt;0.001</td>
<td>0.2</td>
<td>0.1</td>
<td>0.4</td>
<td>0.66</td>
</tr>
<tr>
<td>Current smoker, %</td>
<td>64</td>
<td>68</td>
<td>65</td>
<td>0.37</td>
<td>8</td>
<td>5</td>
<td>7</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Diabetes mellitus, %</td>
<td>9</td>
<td>11</td>
<td>14</td>
<td>0.12</td>
<td>5</td>
<td>7</td>
<td>7</td>
<td>&lt;0.05</td>
</tr>
</tbody>
</table>

* Differences in mean age were tested by ANOVA and differences in other variables were tested by ANCOVA or χ² test.

**TABLE 3. Relative Risks and 95% CIs of Stroke and Stroke Subtypes for Major and Minor ST-T Abnormalities**

<table>
<thead>
<tr>
<th></th>
<th>Men</th>
<th></th>
<th></th>
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<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Normal ECG</td>
<td>Minor ST-T Abnormality</td>
<td>Major ST-T Abnormality</td>
<td></td>
<td>Normal ECG</td>
<td>Minor ST-T Abnormality</td>
<td>Major ST-T Abnormality</td>
<td></td>
</tr>
<tr>
<td>No. at risk</td>
<td>3655</td>
<td>373</td>
<td>177</td>
<td></td>
<td>4989</td>
<td>1129</td>
<td>418</td>
<td></td>
</tr>
<tr>
<td>Person-years of follow-up</td>
<td>55 001</td>
<td>4935</td>
<td>2155</td>
<td></td>
<td>79 706</td>
<td>17 330</td>
<td>5860</td>
<td></td>
</tr>
<tr>
<td>Total stroke</td>
<td>No. of cases</td>
<td>206</td>
<td>51</td>
<td>33</td>
<td>207</td>
<td>55</td>
<td>50</td>
<td></td>
</tr>
<tr>
<td>Age-adjusted RR (95% CI)</td>
<td>1.0</td>
<td>2.3 (1.7–3.2)</td>
<td>3.2 (2.2–4.6)</td>
<td>1.0</td>
<td>1.0 (0.7–1.3)</td>
<td>2.6 (1.9–3.5)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Multivariate-adjusted† RR (95% CI)</td>
<td>1.0</td>
<td>1.8 (1.3–2.4)</td>
<td>2.0 (1.4–3.0)</td>
<td>1.0</td>
<td>0.8 (0.6–1.1)</td>
<td>1.9 (1.4–2.7)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Multivariate-adjusted‡ RR (95% CI)</td>
<td>1.0</td>
<td>1.8 (1.3–2.5)</td>
<td>2.1 (1.4–3.1)</td>
<td>1.0</td>
<td>0.9 (0.6–1.2)</td>
<td>2.1 (1.5–2.8)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ischemic stroke</td>
<td>No. of cases</td>
<td>120</td>
<td>32</td>
<td>26</td>
<td>114</td>
<td>27</td>
<td>20</td>
<td></td>
</tr>
<tr>
<td>Age-adjusted RR (95% CI)</td>
<td>1.0</td>
<td>2.4 (1.6–3.5)</td>
<td>4.1 (2.6–6.2)</td>
<td>1.0</td>
<td>0.8 (0.6–1.3)</td>
<td>1.7 (1.1–2.8)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Multivariate-adjusted† RR (95% CI)</td>
<td>1.0</td>
<td>1.9 (1.3–2.8)</td>
<td>2.7 (1.7–4.2)</td>
<td>1.0</td>
<td>0.7 (0.5–1.1)</td>
<td>1.3 (0.8–2.2)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Multivariate-adjusted‡ RR (95% CI)</td>
<td>1.0</td>
<td>1.8 (1.2–2.7)</td>
<td>2.6 (1.7–4.1)</td>
<td>1.0</td>
<td>0.7 (0.4–1.1)</td>
<td>1.4 (0.8–2.2)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hemorrhagic stroke</td>
<td>No. of cases</td>
<td>66</td>
<td>15</td>
<td>6</td>
<td>74</td>
<td>22</td>
<td>26</td>
<td></td>
</tr>
<tr>
<td>Age-adjusted RR (95% CI)</td>
<td>1.0</td>
<td>2.5 (1.4–4.3)</td>
<td>2.2 (1.0–5.1)</td>
<td>1.0</td>
<td>1.2 (0.8–2.0)</td>
<td>4.3 (2.7–6.7)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Multivariate-adjusted† RR (95% CI)</td>
<td>1.0</td>
<td>1.7 (1.0–3.0)</td>
<td>1.2 (0.5–2.9)</td>
<td>1.0</td>
<td>1.0 (0.6–1.6)</td>
<td>3.1 (1.9–4.9)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Multivariate-adjusted‡ RR (95% CI)</td>
<td>1.0</td>
<td>2.0 (1.1–3.5)</td>
<td>1.4 (0.6–3.2)</td>
<td>1.0</td>
<td>1.1 (0.7–1.8)</td>
<td>3.3 (2.1–5.3)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

RR indicates relative risk; CI, confidence interval.

*Adjusted further for hypertension category.
†Adjusted further for hypertension category, body mass index, smoking category (never, former, and current smokers), alcohol intake, serum total cholesterol levels, and glycemia status (normal, impaired glucose tolerance, and diabetes).
incident rates of stroke for 1000 person-years among men and women were 4.3 and 2.7, respectively ($P<0.01$). Therefore, women may be more likely to have minor ST-T abnormalities as a normal physiological variant.

In this study, the relative risk of total stroke associated with minor ST-T abnormalities was substantially reduced when hypertension category was taken into account. When we further analyzed using continuous value of SBP and current treatment with antihypertensive medication instead of hypertension category, the adjusted relative risk of total stroke was similarly reduced to 1.7 (95% CI, 1.3 to 2.4). Furthermore, hypertensive men with minor ST-T abnormalities tended to have longer durations of hypertension than did those with normal ST-T; the age-adjusted mean duration of hypertension was 3.7 years among men with minor ST-T abnormalities and 2.1 years among those without ST-T abnormalities (difference: $P<0.001$). Thus, minor ST-T abnormalities may reflect an end organ effect of long-term hypertension, a strong risk factor for stroke.

Limitations of the present study warrant discussion. We analyzed the relationship between minor ST-T abnormalities and stroke incidence using a single ECG at baseline. This approach may underestimate the association because the presence of minor ST-T abnormalities has been reported to vary over time. In our study, ECGs were obtained for 74% of the subjects again at follow-up examination (range, 2.1 to 7.3 years; mean 5.2 years after the baseline). At the follow-up examination, 46% of minor ST-T abnormalities at baseline had become into normal ST-T, 45% remained, and 9% changed to major ST-T abnormalities. Age-adjusted relative risks of total stroke tended to be higher for men with 2 recorded occurrences of minor ST-T abnormalities than for men with 1 recorded occurrence: 2.3 (95% CI, 1.5 to 3.7) versus 1.9 (95% CI, 1.3 to 2.7), respectively, consistent with the results of the Chicago Western Electric Study.

In conclusion, minor ST-T abnormalities predict increased risk of total stroke, including both ischemic and hemorrhagic stroke, among middle-aged Japanese men. Men with minor ST-T abnormalities as well as major abnormalities may need intensive medical care, especially blood pressure control, for the prevention of stroke.

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References

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