Plasma Fibrinogen Concentrations and Risk of Stroke and Its Subtypes Among Japanese Men and Women

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Background and Purpose—We aimed to examine the impact of fibrinogen concentrations on the incidence of stroke.

Methods—We examined the association between fibrinogen and risk of total stroke and stroke subtypes in an 11-year prospective study of 4608 men and 7589 women aged 40 to 79 years with no history of stroke and/or coronary heart disease. The analysis was repeated, stratified by smoking status, to examine whether the association between fibrinogen and stroke was modified by smoking.

Results—There were 317 incident total strokes comprising 103 hemorrhagic strokes (70 intraparenchymal hemorrhages [22.1% of strokes], 33 subarachnoid hemorrhages [10.4%]), 206 ischemic strokes (65.0%), and 8 strokes of undetermined type (2.5%). The multivariable hazard ratio (95% CI) for the highest versus lowest fibrinogen quartiles after adjustment for age, sex, area, and known cardiovascular risk factors was 2.5 (1.3 to 5.0), P<0.01, for hemorrhagic stroke and 3.2 (1.4 to 7.4), P<0.01, for intraparenchymal hemorrhage. There was no positive association of fibrinogen with risk of ischemic stroke or subarachnoid hemorrhage. Among never-smokers, the multivariable hazard ratio (95% CI) for the highest versus lowest fibrinogen quartiles was 3.5 (1.3 to 9.3), P=0.01, for hemorrhagic stroke and 4.4 (1.3 to 15.2), P=0.02, for intraparenchymal hemorrhage.

Conclusions—High plasma fibrinogen concentration can be a predictor for risk of intraparenchymal hemorrhage. (Stroke. 2006;37:2488-2492.)

Key Words: Japanese ■ plasma fibrinogen ■ prospective study ■ stroke ■ stroke subtypes

Although the association between plasma fibrinogen concentrations and risk of coronary heart disease is well described,1-3 data on the association of plasma fibrinogen with risk of total stroke and stroke subtypes are limited and inconsistent. Fibrinogen, a clotting factor, may accelerate the thrombotic process and could also act as a marker of inflammation.4 Three prospective studies of whites showed that high plasma fibrinogen concentrations were associated with increased risk of total stroke.5-7 The Atherosclerosis Risk in Communities (ARIC) Study, another major prospective study, showed no association between fibrinogen levels and risk of ischemic stroke.8 A recent large meta-analysis has indicated that high plasma fibrinogen concentrations were associated with increased risk of both ischemic and total hemorrhagic stroke.9 The hazard ratio (95% CI) associated with a 1-g/L increase in fibrinogen levels after adjustment for age, sex, and cohort was 2.08 (1.74 to 2.48) for ischemic stroke and 1.44 (1.05 to 1.76) for hemorrhagic stroke. However, those authors did not report hazard ratios after further adjustment for potential confounding factors or hazard ratios for specific types of hemorrhagic stroke, ie, subarachnoid hemorrhage and intraparenchymal hemorrhage. Given the different underlying pathological mechanisms for stroke subtypes,10 accurate subtyping is important to determine whether risk factors differ among stroke subtypes. Smoking raises fibrinogen concentrations11 and also raises the risk of subarachnoid hemorrhage, ischemic stroke, and possibly intraparenchymal hemorrhage.12 Thus, it is uncertain whether the association between fibrinogen and the risk of stroke is mediated through smoking or independent of smoking.

To examine these research questions, we conducted a prospective study to examine the relation between plasma fibrinogen concentrations and the risk of stroke and stroke subtypes, as confirmed by imaging studies, and further
stratified the sample by smoking status among middle-aged Japanese men and women.

Subjects and Methods

Study Cohort
The participants were population-based samples of 12,806 individuals (4,923 men and 7,883 women aged 40 to 79 years) living in 4 areas of Japan. They included residents of Ikawa town, Akita prefecture (participants were 917 men and 1,773 women); Kyowa town, Ibaraki prefecture (1,584 men and 2,144 women); Noichi town, Kochi prefecture (932 men and 1,501 women); and the Minami-Takayasu area of Yao City, Osaka prefecture (1,490 men and 3,065 women). They participated in cardiovascular risk surveys between 1989 and 1996 (mostly between 1989 and 1991), where we obtained data on fibrinogen and confounding variables. The participation rate in the present study was 47% of the total census population. Individual informed consent was not sought at baseline survey, but the participants were informed of the prospective study, based on guidelines of the Council for International Organizations of Medical Science. Also, the community representatives expressed agreement for conducting an epidemiological study for the evaluation of community health status. We excluded 609 individuals with a history of coronary heart disease and/or stroke at the time of baseline inquiry, because our purpose was to examine the association between fibrinogen and the primary incidence of cardiovascular disease; our early report showed a positive association with risk of coronary heart disease. Therefore, a total of 12,197 individuals (4,608 men and 7,589 women) were enrolled in the present study.

For each of the participants, the person-years of follow-up were calculated from the date of completion of the baseline survey to the date of stroke incidence, moving away from the community, or the end of 2003, whichever occurred first. The average follow-up period for the participants was 11.2 years. The participants who moved away from the community (3.3%) or who died (7.2%) were treated as censored data. The Ethics Committee of the University of Tsukuba approved this study.

Determination of Plasma Fibrinogen Concentrations
Blood was drawn as nonfasting samples from seated participants into citrated and siliconized glass tubes. Fibrinogen was measured by the clotting assay of Clauss with reagents obtained from General Diagnostics (Organon-Technika Co) in the laboratory of the Osaka Medical Center for Health Science and Promotion. The fibrinogen values in our laboratory were compatible with those measured in the ARIC laboratory at the University of Texas Health Center at Houston. Mean values of fibrinogen were 276 mg/dL in our laboratory and 275 mg/dL in the ARIC laboratory, and the Pearson correlation coefficient between fibrinogen values obtained by the 2 laboratories was 0.69 (n = 100, P < 0.001).

Determination of Confounding Variables
Serum total cholesterol and HDL cholesterol were measured by enzymatic methods with an automatic analyzer (Hitachi 7250, Hitachi Medical Corp) at the Osaka Medical Center, an international member of the US National Cholesterol Reference Method Laboratory Network. Serum glucose was measured by enzymatic methods. Serum albumin was measured by the bromcresol green method. Systolic and diastolic blood pressures were measured with a standard mercury sphygmomanometer on the right arm of seated participants after a 5-minute rest. Height in stocking feet and weight in light clothing were measured, and body mass index was calculated as weight (kg) divided by height squared (m²). An interview was conducted to ascertain smoking status, the number of cigarettes smoked per day, and usual alcohol intake per week.

Survveillance and Classification of Stroke
The participants were followed up to determine incident strokes occurring by the end of 2003 by passive recruitment and notification of incidence cases. The follow-up was conducted by annual cardiovascular risk surveys to obtain histories of incident stroke; for nonparticipants, notification of stroke was obtained by mailing a questionnaire or examining death certificates. For deaths, cases with stroke (ICD9 classification 430 to 438) as the underlying cause of death were selected from the death certificates. We also used national insurance claims, ambulance records, reports by local physicians, and reports by public health nurses and health volunteers for identification of possible stroke. To confirm the diagnosis, all living patients were visited or invited to take part in risk factor surveys to obtain medical history, and/or, if cases were still alive, neurological examinations by study physicians, and their medical records were reviewed. For deaths, histories were obtained from families, and medical records were reviewed.

Stroke was defined as a focal neurological disorder with rapid onset, which persisted at least 24 hours or until death, and was confirmed by CT and/or MRI. Classification of stroke subtypes, ie, subarachnoid hemorrhage, intraparenchymal hemorrhage, and ischemic stroke, was primarily based on imaging studies. Stroke cases without CT/MRI films were classified according to the clinical criteria based on the work of Millikan. CT/MRI films were available for 99% of stroke cases. The final diagnosis of stroke was made by a panel of 3 or 4 physicians, blinded to the baseline data.

Statistical Analysis
We divided the participants into quartiles to examine the association between plasma fibrinogen and risk of cardiovascular disease. Differences in age- and sex-adjusted mean values and proportions of baseline characteristics were compared with those in the quartiles of fibrinogen with the use of a t test or χ² test when the overall difference was significant. The hazard ratio of cardiovascular incidence was estimated as the incidence rate for participants within the 4 categories of fibrinogen divided by the corresponding rate among the lowest category, according to Cox proportional-hazards models. Adjustments for sex, age (years), area (Ikawa town, Kyowa town, Noichi town, and the Minami-Takayasu area of Yao City), systolic blood pressure (mm Hg), antihypertension medication use (yes or no), serum total cholesterol (mmol/L), serum albumin (g/L), serum HDL cholesterol (quartiles), glucose category (normal, impaired glucose tolerance, and diabetes), body mass index (kg/m²), smoking status (never-, ex-, and current smokers), usual ethanol intake (never-, ex-, and current drinker of ethanol at 1 to 22, 23 to 45, 46 to 68, and ≥69 g/d) were also conducted. The analysis was repeated, stratified by smoking status, to examine whether the association between fibrinogen and stroke was modified through smoking. All probability values for statistical significance were 2-tailed, and all CIs were estimated at the 95% level. All statistical analyses were conducted with SAS, version 8.02 (SAS Institute, Inc).

Results
The mean values (SD) of plasma fibrinogen concentration were 284.1 (61.1) mg/dL in all subjects, 277.3 (60.0) mg/dL in Ikawa town, 289.1 (62.7) mg/dL in Kyowa town, 294.2 (63.6) mg/dL in Noichi town, and 277.9 (57.6) in the Minami-Takayasu area of Yao city. During the 11.2 years of follow-up, we identified 103 hemorrhagic strokes (70 intraparenchymal hemorrhages [22.1% of stroke], 33 subarachnoid hemorrhages [10.4%]), 206 ischemic strokes (65.0%), and 8 strokes of undetermined type (2.5%).

Table 1 shows mean values of risk characteristics at baseline. Persons in the highest fibrinogen quartiles were 7 years older, smoked more, and were more overweight than those in the lowest fibrinogen quartile. The prevalence of smoking was strongly and linearly associated with plasma fibrinogen. There were positive associations of plasma fibrinogen concentrations with systolic and diastolic blood pressures and serum total cholesterol and negative associations...
with serum HDL cholesterol. No significant difference was found in antihypertension drug use, history of diabetes, or usual ethanol intake according to fibrinogen levels.

Table 2 shows age-, sex-, and area-adjusted and multivariable hazard ratios of stroke and its subtypes according to quartiles of plasma fibrinogen concentrations. Compared with persons in the lowest fibrinogen category, those in the highest quartile had a 2-fold higher age-adjusted risk of hemorrhagic stroke and a 3-fold higher risk of intraparenchymal hemorrhage. There was no association of fibrinogen with risk of ischemic stroke or subarachnoid hemorrhage. The adjustment for known cardiovascular risk factors did not materially alter these positive associations. When the fibrinogen values were grouped into tertiles, the multivariable hazard ratio for the highest versus lowest fibrinogen tertiles was 3.3 (1.1 to 10.6), \( P = 0.05 \), † for hemorrhagic stroke and 3.9 (1.4 to 10.0), \( P = 0.01 \), † for intraparenchymal hemorrhage (12 cases in the lowest and 36 cases in the highest tertiles; not shown in the table).

There was no significant interaction with sex and age (\( P \)s for interaction were >0.40 for each stroke subtype). The multivariable hazard ratios (95% CI) for the highest versus lowest quartiles of fibrinogen were 3.3 (1.1 to 10.6), \( P = 0.04 \), for hemorrhagic stroke and 2.3 (0.7 to 7.7), \( P = 0.17 \), for intraparenchymal hemorrhage among men and 2.1 (0.9 to 5.0), \( P = 0.09 \), and 4.2 (1.2 to 14.6), \( P = 0.02 \), respectively, among women. The respective hazard ratios were 3.5 (1.1 to 11.3), \( P = 0.04 \), and 5.0 (1.0 to 24.9), \( P = 0.05 \), among persons aged <60 years and 1.9 (0.8 to 4.5), \( P = 0.13 \), and 2.4 (0.9 to 6.3), \( P = 0.09 \), among those aged ≥60 years (not shown in the table).

We repeated the analysis, stratified by smoking status, to examine whether the fibrinogen-disease association was modified by smoking (not shown in the table). The associations of fibrinogen with risk of stroke subtypes were not altered substantially when stratified by smoking status (\( P \)s for interaction were >0.10 for each stroke subtype). The multivariable hazard ratios (95% CI) for the highest versus lowest quartiles of fibrinogen were 3.5 (1.3 to 9.2), \( P = 0.01 \), for hemorrhagic stroke and 4.4 (1.2 to 15.2), \( P = 0.02 \), for intraparenchymal hemorrhage among never-smokers. The respective hazard ratios among ever-smokers were 1.7 (0.6 to 4.7), \( P = 0.30 \), and 2.2 (0.7 to 7.0), \( P = 0.20 \).

### Discussion

We found a positive association between plasma fibrinogen concentration and risk of hemorrhagic stroke, especially intraparenchymal hemorrhage, among Japanese. This association did not vary between ever-smokers and never-smokers. To our knowledge, this is the first cohort study to show that plasma fibrinogen is associated with risk of intraparenchymal hemorrhage. A recent meta-analysis showed a similar association between fibrinogen and age- and sex-adjusted risk of hemorrhagic stroke. However, they did not report the association after adjustment for other confounding factors or the association with risk of intraparenchymal hemorrhage and subarachnoid hemorrhage separately. We also observed a positive association between fibrinogen and the incidence of intraparenchymal hemorrhage even among never-smokers. Our data suggest that the positive association between fibrinogen and risk of intraparenchymal hemorrhage was not modified by smoking status.

The basic pathology of intraparenchymal hemorrhage is arteriolosclerosis, characterized by necrosis of smooth mus-

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### TABLE 1. Age- and Sex-Adjusted Mean Values or Prevalence of Cardiovascular Risk Factors at Baseline According to Quartiles of Plasma Fibrinogen Concentrations

<table>
<thead>
<tr>
<th>Quartiles of Plasma Fibrinogen Concentration</th>
<th>1 (Low)</th>
<th>2</th>
<th>3</th>
<th>4 (High)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fibrinogen range, mg/dL</td>
<td>102–242</td>
<td>243–274</td>
<td>275–313</td>
<td>314–824</td>
</tr>
<tr>
<td>No. at risk</td>
<td>3019</td>
<td>3101</td>
<td>3019</td>
<td>3058</td>
</tr>
<tr>
<td>Age, y</td>
<td>54.6</td>
<td>56.8†</td>
<td>59.4†</td>
<td>61.4†</td>
</tr>
<tr>
<td>Men, ‰</td>
<td>44</td>
<td>37†</td>
<td>34†</td>
<td>37†</td>
</tr>
<tr>
<td>Systolic blood pressure, mm Hg</td>
<td>130</td>
<td>130</td>
<td>131</td>
<td>131†</td>
</tr>
<tr>
<td>Diastolic blood pressure, mm Hg</td>
<td>78</td>
<td>79*</td>
<td>79†</td>
<td>80†</td>
</tr>
<tr>
<td>Antihypertension medication use, %</td>
<td>17</td>
<td>16</td>
<td>18</td>
<td>17</td>
</tr>
<tr>
<td>Hypertension, %</td>
<td>24</td>
<td>24</td>
<td>26*</td>
<td>26</td>
</tr>
<tr>
<td>Diabetes, ‰</td>
<td>4</td>
<td>4</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>Serum total cholesterol, mmol/L</td>
<td>4.96</td>
<td>5.13†</td>
<td>5.22†</td>
<td>5.23†</td>
</tr>
<tr>
<td>Serum HDL cholesterol, mmol/L</td>
<td>1.56</td>
<td>1.51†</td>
<td>1.46†</td>
<td>1.43†</td>
</tr>
<tr>
<td>Serum total albumin, g/L</td>
<td>43</td>
<td>44†</td>
<td>44†</td>
<td>43</td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
<td>23.1</td>
<td>23.1</td>
<td>23.3†</td>
<td>23.4†</td>
</tr>
<tr>
<td>Current smoker, ‰</td>
<td>24</td>
<td>27†</td>
<td>30†</td>
<td>34†</td>
</tr>
<tr>
<td>Usual ethanol intake, g/d</td>
<td>15</td>
<td>14</td>
<td>14</td>
<td>15</td>
</tr>
</tbody>
</table>

Hypertension was defined as systolic blood pressure ≥160, diastolic blood pressure ≥95, antihypertension medication use, or some combination thereof. Diabetes was defined as fasting glucose ≥126, nonfasting glucose ≥200, antidiabetes medication use, or some combination thereof. Test for difference from the lowest fibrinogen category: † \( P < 0.05 \), † \( P < 0.01 \).
cles cells and increased basement membrane–like substance in intracerebral arteries.20 Extensive pathology investigation by electron microscopy has demonstrated the accumulation of macrophages in the outer layer of smooth muscle cells.21 These histopathological changes enhance the vulnerability of small, intracerebral penetrating arterioles of the basal ganglia, thalamus, and brain stem, leading to intraparenchymal hemorrhage.22 These pathological findings are in line with a destructive inflammatory process.10

The positive association between fibrinogen and other small-vessel disease supports our hypothesis. In previous studies, plasma fibrinogen levels were positively associated with microangiopathy-related cerebral damage,23 the amount of leukoaraiosis in patients with lacunar infarction or Binswanger disease,24 dementia,25 and silent cerebral infarction.26 We did not find a positive association between fibrinogen and risk of ischemic stroke in the present study, whereas we previously reported a strong, positive association between fibrinogen and risk of coronary heart disease.3 Our finding was consistent with the result of the ARIC study showing a positive association of fibrinogen with risk of coronary heart disease but not of ischemic stroke.2,8 In that study, however, other clotting factors, such as factor VIII and von Willebrand factor, were associated with risk of ischemic stroke. Moreover, high levels of C-reactive protein were associated with increased risk of both ischemic stroke and coronary heart disease.27,28 These findings suggest that the role of fibrinogen as a clotting factor or a marker of inflammation may be less important in the pathogenesis of ischemic stroke. Other factors such as hypertension may be strong determinants. The recent meta-analysis has shown a weaker but significant association between fibrinogen levels and ischemic stroke, compared with that of coronary heart disease,8 although no single study has reported a significant association with ischemic stroke.

One limitation of the current study is the small number of incident intraparenchymal hemorrhage in the lowest quartile of fibrinogen (n=11005 in men and n=3 in women). However, we found positive associations between fibrinogen and risk of intraparenchymal hemorrhage. The consistent positive association for both sexes suggests that this association less likely to be observed by chance. For subarachnoid hemorrhage (n=33), the statistical power to detect a significant hazard ratio (1.5 per 1-g/L increase of fibrinogen) was only 11%. Second, the participation rate in the present study was 50% for a total census population, and the low participation rate may have led to selection bias. However, the finding among ages 60 in which the response rate was 59% were similar to those among all of the subjects. Thus, the selection bias was unlikely to be large. Third, we did not measure other markers of inflammation, such as C-reactive protein, which may increase with fibrinogen as predictors of arteriosclerosis. Fourth, we did not measure plasma fibrinogen concentrations repeatedly after baseline. The single baseline measurement

<table>
<thead>
<tr>
<th>TABLE 2. Hazard Ratio (95% CI) for Incidence of Total Stroke and Stroke Subtypes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Quartiles of Plasma Fibrinogen Concentration</td>
</tr>
<tr>
<td>Persons</td>
</tr>
<tr>
<td>---------</td>
</tr>
<tr>
<td>Total stroke</td>
</tr>
<tr>
<td>No.</td>
</tr>
<tr>
<td>Sex-age-area-adjusted HR</td>
</tr>
<tr>
<td>Multivariable-adjusted HR</td>
</tr>
<tr>
<td>Intracerebrovascular hemorrhage</td>
</tr>
<tr>
<td>No.</td>
</tr>
<tr>
<td>Sex-age-area-adjusted HR</td>
</tr>
<tr>
<td>Multivariable-adjusted HR</td>
</tr>
<tr>
<td>Intraparenchymal hemorrhage</td>
</tr>
<tr>
<td>No.</td>
</tr>
<tr>
<td>Sex-age-area-adjusted HR</td>
</tr>
<tr>
<td>Multivariable-adjusted HR</td>
</tr>
</tbody>
</table>

HR indicates hazard ratio. Multivariable adjustment included sex, age (years), area, and known cardiovascular risk factors.
may lead to regression dilution bias and underestimate the strength of associations.\textsuperscript{29}

The strength of the current study is the use of a population-based sample from 4 Japanese communities, and our finding could probably be generalized to other Japanese populations, who have lower fibrinogen levels than whites.\textsuperscript{30}

In conclusion, we showed an association between high plasma fibrinogen concentrations and increased risk of intraparenchymal hemorrhage, but not of subarachnoid hemorrhage or ischemic stroke, among Japanese.

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Disclosures
None.

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