Fibrinogen Independently Predicts the Development of Ischemic Stroke in a Taiwanese Population

CVDFACTS Study

Shao-Yuan Chuang, PhD; Chyi-Huey Bai, PhD; Wei-Hung Chen, MD; Li-Ming Lien, MD; Wen-Harn Pan, PhD

Background and Purpose—Of few prospective studies that have focused on the relationship between fibrinogen and ischemic stroke (IS) in Asian populations, the findings were inconsistent with those conducted in Western countries. Therefore, we aimed to investigate the temporal relationship between fibrinogen levels (plus several related parameters) and IS in a community-based study in Taiwan.

Methods—Baseline data from 3281 adults (≥20 years of age) in the Cardiovascular Diseases Risk Factor Two-Township Study were linked to incidental IS status derived from insurance claims and death certificate records. Hazard ratios and 95% CIs of clotting factors (fibrinogen, factor VII, factor VIII, and antithrombin-III) for IS events were estimated using Cox proportional hazard models.

Results—With 10.4 years (average) follow-up, 128 persons developed IS (3.75 per 1000 person-years). As expected, elevated blood pressure and diabetes were independent predictors of IS events. A dose–response relationship was found in univariate analysis between IS risk and tertiles of fibrinogen (hazard ratio, 3.73; 2.19 to 1.00), factor VII (hazard ratio, 1.86; 1.35 to 1.00), and factor VIII (2.97; 1.70 to 1.00), respectively, but not for antithrombin-III. After adjusting for confounding and known risk factors, fibrinogen independently predicted IS events. A 72% increase (hazard ratio, 1.72; 1.02 to 2.90) in IS risk was observed for individuals with fibrinogen ≥8.79 μmol/L compared with those <7.03 μmol/L.

Conclusions—In addition to hypertension and diabetes, fibrinogen independently predicted future IS risk. We suggest that fibrinogen may be considered in the risk assessment model for IS in the Taiwanese population. (Stroke. 2009;40:1578-1584.)

Key Words: fibrinogen ■ ischemic stroke ■ prospective study ■ risk equation ■ Taiwanese

Recently, the Fibrinogen Studies Collaboration revealed in an individual participant meta-analysis that plasma fibrinogen level was significantly associated with coronary heart disease (CHD), stroke, and other causes of vascular and nonvascular mortality. This meta-analysis study with 2775 nonvascular mortality.1 This meta-analysis study with 2775 patients was linked to the Cardiovascular Health Study. Therefore, it remains controversial as to whether elevated fibrinogen is a risk factor for future IS in Asians.

We conducted a community-based prospective study among Taiwanese subjects to examine the relationship between clotting factors at baseline, including fibrinogen, factor VII, factor VIII, and antithrombin-III and future IS events.

Methods

Study Population

The CardioVascular Disease risk FACtors Two-township Study (CVDFACTS) is a community-based follow-up study focusing on cardiovascular diseases and their risk factors in Taiwan. During 1991 to 1993, all residents ≥3 years of age in 5 villages in Chu-Dung and 5 villages in Pu-Tzu were invited to participate in the baseline examination. A total of 6312 people participated (2902 males and 3410 females), corresponding to 20% of the population, and 5040 participants were 20 years of age. Three follow-up examinations have been performed in 1994 to 1997, 1997 to 1999, and 1999 to 2001. Although the information collected in the follow-up examinations varied, measurements of anthropometric, biochemical, and hemodynamic variables as well as subjects’ self-reported disease status were included in all cycles. Subjects were excluded if they reported a history of stroke at baseline (n=103), had fasted for <8 hours before enrollment, or were unable to be followed in the future.

Received October 20, 2008; accepted November 3, 2008.

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Stroke is available at http://stroke.ahajournals.org

DOI: 10.1161/STROKEAHA.108.540492

1578
hours (n=344), were not covered by National Health Insurance (n=30), or had missing or extreme values for any of the following variables: body mass index, parameters pertaining to the definition of metabolic syndrome (n=1110), and coagulation and hemostatic factors such as fibrinogen, factor VII, factor VIII, and antithrombin-III (n=177). There were 3281 adult subjects eligible for analysis in this study. All participants gave informed consent at baseline and follow-up. Further details about sampling and data collection have been described previously.5,7

Variable Definitions
Criteria to define central obesity and dyslipidemia in The Third Report of the National Cholesterol Education Program Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III) definition were followed in this study to define central obesity (waist circumference ≥90 cm in men and ≥80 cm in women), reduced high-density lipoprotein cholesterol (<40 mg/dL in men and <50 mg/dL in women), high triglyceride (>200 mg/dL), and high total cholesterol (>240 mg/dL). Hypertension9 was defined as systolic blood pressure ≥140 mm Hg, diastolic blood pressure ≥90 mm Hg, or using antihypertension medications. Prehypertension9 was defined as systolic blood pressure 120-139 mm Hg or diastolic blood pressure between 80 and 89 mm Hg. Subjects with systolic/diastolic blood pressure <120/80 mm Hg were used as the reference group.9 Diabetes mellitus was defined as fasting glucose ≥126 mg/dL (7.0 mmol/L) or using antidiabetic medication.10

Examinations were performed in the study clinic in each of the 2 townships. The weight, height, and waist circumference were measured while participants were dressed in light street clothes without shoes.11 Blood pressure was measured 3 times after the subject had been seated for ≥5 minutes, and the mean of the last 2 readings was used for analysis. All subjects were asked to fast overnight for ≥8 hours before blood specimen collection; samples were immediately stored at −70°C and analyzed within 1 month of blood collection. Fasting glucose and triglycerides were measured on stored specimens after thawing at room temperature. The homogeneous method12 was used to measure high-density lipoprotein cholesterol (HDLC). We measured the levels of fibrinogen, factor VII, factor VIII, and antithrombin-III with a commercial kit (STAGO Company). The coefficient of variance was 2.80% in fibrinogen, 6.50% in factor VII, 8.20% in factor VIII, and 7.59% in antithrombin-III. The coefficients of variance in split sample for reproducibility were 4.02% in fibrinogen, 5.32% in factor VII, 6.47% in factor VIII, and 6.54% in antithrombin-III. Individuals attending the baseline and follow-up examinations also completed a questionnaire-based interview. The questionnaire contained items on demographic data, lifestyle, self-reported health history, and family history of diseases. If the participants answered “yes” to the question “Did Doctor ever tell your father/mother/brother/sister had stroke?,” he or she was considered to have a family history of stroke.

IS Ascertainment
Three sources of information were used to determine the first-ever IS status and the time of onset, including death certificate data, insurance claim records of the National Health Insurance database (available after 1996), and subjects’ self-reported disease history.13 During the period before 1996, stroke events were self-reported and crossexamined by medical records and/or death certificate. A total of 99.5% of our studied subjects were covered by National Health Insurance since 1996 (The loss-to-follow-up rate was 0.5%). A time-sequenced record was first generated for each patient with stroke with any codes between 430 to 438 from the International Classification of Diseases. 9th Revision, Clinical Modification, which included all the dates and the names of the hospitals patient ever visited, the procedures the patient went through, the kinds of medication and rehabilitation prescribed after the visits or the examinations as well as the International Classification of Diseases codes given by the physician for each claim. Excluding those claims made by Chinese herbal doctors, dentists, or nonneurologists practicing in public health stations or private clinics, the first-ever stroke was defined when patients met any one of the following 2 conditions: (1) hospitalization claim with International Classification of Diseases codes of 433, 434, or 436 for 1 day followed either by claims for various neurological imaging technology (CT, MRI, transcranial or carotid Doppler sonography) and long-term medications used for IS, or by claims for rehabilitation and long-term IS medications; or (2) ≥3 consecutive outpatient visits to hospitals with these codes followed by the same technology, rehabilitation, and long-term IS medications as described for condition (1). If claim data with codes 433, 434, or 436 did not match any of these rules, or contained codes of other stroke subtypes, the patient’s stroke status was evaluated independently by 3 neurologists blind to the patient’s personal profile. In case of disagreement, consensus was reached after discussion. The initial time point for the appearing of a string of IS International Classification of Diseases codes was designated as the onset time. Using neurologists’ diagnosis recorded in a stroke registry as the gold standard, an unpublished validation study (Bai et al, unpublished data) showed that the sensitivity and specificity for these procedures were 100% and 95%, respectively, in 508 hospital-based stroke cases and age- and sex-matched control subjects from a previous study.14

Statistical Methods
We examined the means and SD of subjects who were stroke-free and who developed IS during follow-up (data not shown) and those who were classified into fibrinogen tertiles. We compared means or proportions among these groups of people by one-way analysis of variance, trend test, or χ² test. The Cox proportional hazard model was used to obtain the hazard ratio and 95% CI associating risk factors with IS. The multivariate Cox regression was used to evaluate the independent effect of clotting factor levels on IS controlling for other confounding factors. We estimated IS incidence for the first, second, and third tertiles of fibrinogen, factor VII, and factor VIII. The trend test for effect on IS was implemented by designating the tertile classes of clotting factors as continuous in the Cox model. All statistic analyses were performed by SAS 9.1.

Results
From 1992 to 2002, the average follow-up time was 10.4 years. During the follow-up period, 128 patients developed IS. The incident rate of IS was 4.83 per 1000 person-years (n=69) in men and 2.97 per 1000 person-years in women (n=59; P=0.0054).

Patients who developed IS were older, more obese, smoked more, and had higher levels of blood pressure, triglycerides, total cholesterol, and glucose, but lower levels of HDL-C (data not shown). The levels of fibrinogen, factor VII, and factor VIII, but not antithrombin-III, were significantly higher at baseline in patients with future IS than in subjects who did not develop IS (data not shown). An increasing trend of ischemic stroke incidence was also observed with higher tertiles of fibrinogen, factor VII, and factor VIII (P<0.05 for all 3 trend tests; Figure). The characteristics of studied population were presented in fibrinogen tertiles (Table 1).

Table 1 shows that mean age, body mass index, waist circumference, systolic/diastolic blood pressure, fasting glucose, triglyceride, and total cholesterol levels were significantly different among fibrinogen tertiles.

Table 2 shows the correlation coefficients of clotting factors to known risk factors of cardiovascular disease. Fibrinogen, factor VII, and factor VIII were associated with body mass index, waist circumference, triglycerides, systolic/diastolic blood pressure, fasting glucose, and total cholesterol. HDL-C was negatively associated with fibrinogen and factor VIII, but not with factor VII. In addition, fibrinogen, factor VII, and factor VIII correlated among one another.
Table 3 shows the results of univariate and multivariate analyses of the Cox proportional hazard model. Those who had increased waist circumference, elevated triglycerides, lower HDL-C, and elevated total cholesterol had a significantly higher risk of developing IS than those in the normal ranges. The highest (12-fold) relative risk of IS was observed for hypertensive patients compared with those having normal blood pressure at baseline. Diabetes increased IS risk by 5-fold with fasting glucose level <126 mg/dL (7.0 mmol/L) as the reference group. The habit of smoking, positive family history of stroke, and other clinically defined disorders had hazard ratios increasing the risk of IS by a factor of 2 to 3. In terms of the effect of clotting factors, the highest hazard ratio was observed for fibrinogen followed by factor VIII and then factor VII.

Table 3 contains 3 multivariate models examining the independent effect of one clotting factor after adjusting all other known cardiovascular risk factors. Model 1 shows that fibrinogen is positively associated with the incidence of IS in addition to age (per 10 years), hypertension (compared with normal blood pressure), diabetes (versus absence), and presence of family history of stroke (versus absence). On the other hand, factor VII (Model 2) and factor VIII (Model 3) were not independently associated with the incidence of IS.

Smoking may affect the association between clotting factors and IS. We found that current smokers (292 mg/dL) had higher age- and sex-adjusted levels of fibrinogen than those who never smoked (279 mg/dL), exsmokers (281 mg/dL), or occasional smokers (284 mg/dL). Factor VIII levels (132%; age- and sex-adjusted) in the never smokers was higher than

Table 1. Characteristics of Subjects at Study Entry by Fibrinogen Tertiles

<table>
<thead>
<tr>
<th>Variables</th>
<th>Low (&lt;7.03, n=1063)</th>
<th>Middle (7.03–8.79, n=1109)</th>
<th>High (≥8.79, n=1109)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ischemic stroke, %</td>
<td>1.79%</td>
<td>3.79%‡</td>
<td>6.04%‡</td>
<td>&lt;0.0001†</td>
</tr>
<tr>
<td>Age, years</td>
<td>41.7±14.0</td>
<td>46.3±14.6‡</td>
<td>51.2±14.8‡</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Male, %</td>
<td>48.3%</td>
<td>40.7%‡</td>
<td>40.5%‡</td>
<td>0.0002†</td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
<td>23.2±3.4</td>
<td>23.5±3.3‡</td>
<td>24.2±3.6‡</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Waist circumference, cm</td>
<td>77.4±9.8</td>
<td>78.1±9.7</td>
<td>80.9±10.2‡</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Systolic blood pressure, mm Hg</td>
<td>113.1±16.2</td>
<td>115.7±18.8‡</td>
<td>118.5±19.3‡</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Diastolic blood pressure, mm Hg</td>
<td>72.5±10.3</td>
<td>73.1±11.0‡</td>
<td>74.2±10.8‡</td>
<td>0.0014</td>
</tr>
<tr>
<td>Glucose, mmol/L</td>
<td>5.41±1.27</td>
<td>5.54±1.37‡</td>
<td>5.83±1.75‡</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Triglycerides, mmol/L</td>
<td>1.06±0.70</td>
<td>1.13±0.76‡</td>
<td>1.25±0.77‡</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Total cholesterol, mmol/L</td>
<td>4.82±1.03</td>
<td>5.00±1.08‡</td>
<td>5.22±1.11‡</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>HDL-C, mmol/L</td>
<td>1.14±0.31</td>
<td>1.12±0.32</td>
<td>1.09±0.31‡</td>
<td>0.0002</td>
</tr>
<tr>
<td>Fibrinogen, μmol/L</td>
<td>5.94±0.82</td>
<td>7.86±0.52‡</td>
<td>10.94±2.02‡</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Factor VII, %</td>
<td>120.2±35.7</td>
<td>127.7±39.5‡</td>
<td>134.1±36.1‡</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Factor VIII, %</td>
<td>119.2±49.0</td>
<td>129.9±59.4‡</td>
<td>143.4±61.5‡</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Antithrombin-III, %</td>
<td>101.7±21.5</td>
<td>105.3±21.5‡</td>
<td>111.0±20.6‡</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Hypertension, %</td>
<td>13.5%</td>
<td>17.3%‡</td>
<td>23.7%‡</td>
<td>&lt;0.0001†</td>
</tr>
<tr>
<td>Diabetes, %</td>
<td>4.6%</td>
<td>6.4%</td>
<td>11.1%‡</td>
<td>&lt;0.0001†</td>
</tr>
<tr>
<td>Family history of stroke, %</td>
<td>7.6%</td>
<td>6.9%</td>
<td>7.9%</td>
<td>0.6635†</td>
</tr>
<tr>
<td>Current smoking, %</td>
<td>25.3%</td>
<td>22.8%</td>
<td>25.2%</td>
<td>0.3184†</td>
</tr>
</tbody>
</table>

*P for mean difference of one-way analysis of variance test.
†P for Pearson CHISQ test.
‡P<0.05 for comparing with the group with low tertile of fibrinogen.
that in the current smokers (126%; \( P=0.0381 \)). Factor VII and antithrombin-III levels did not differ significantly among various smoking status groups. However, the effect of smoking was not independently associated with IS risk.

In summary, the multivariate models revealed that older age, hypertension, diabetes, presence of family history of stroke, and elevated fibrinogen levels were major independent predictors of future IS events.

### Discussion

Among the clotting factors we studied, fibrinogen, factor VII, and factor VIII, but not antithrombin-III, were positively associated with IS in univariate analysis. However, only fibrinogen level independently predicted future IS events in this Taiwanese population. This is the first prospective study in Asia to demonstrate that fibrinogen level independently predicts future IS. Therefore, we provide here a risk assessment equation for predicting IS events as follows for Taiwanese community dwellers aged ≥20 years. Hazard ratio is \( e^R \) for a stroke-free individual, where \( R=0.68 \times \text{age}+0.30 \times \text{gender} (\text{male}=1, \text{female}=0)+0.95 \times \text{family history (yes}=1, \text{no}=0)+1.02 \times \text{HBP1 (prehypertension}=1, \text{otherwise}=0)+1.33 \times \text{HBP2 (hypertension}=1, \text{otherwise}=0)+0.89 \times \text{DM (diabetes}=1, \text{otherwise}=0)+0.47 \times \text{Fib1 (7.03 to 8.79 } \mu \text{mol/L}=1, \text{otherwise}=0)+0.61 \times \text{Fib2 (≥8.79 } \mu \text{mol/L}=1, \text{otherwise}=0) \).

Risk assessment equations tend to differ across ethnic groups. For example, the Framingham CHD risk equation overestimates the risk in Chinese,\(^{15}\) and thus a modified equation has been established and validated for the Chinese\(^{16}\) and Korean\(^{17}\) population. Both of these 2 risk models\(^{16,17}\) concluded that elevated blood pressure, diabetes, total cholesterol, obesity, and smoking are predictive variables. In the model established in the current study, total cholesterol and obesity were not significant. The contribution of obesity may have been masked by hypertension and diabetes. As we elaborate subsequently, blood cholesterol was not an independent risk factor in most Taiwanese studies. In the current study, family history was an independent predictor, possibly indicating that either a shared genetic or environmental component may have contributed to the IS risk. In addition, fibrinogen concentration in the blood adds to the predictive power.

Fibrinogen was prospectively associated with stroke in middle-aged UK subjects\(^{1}\) and in elderly US men.\(^{5}\) In addition, the Copenhagen City Heart Study\(^{3}\) found that patients with IS had significantly higher levels of fibrinogen than control subjects. However, the Atherosclerosis Risk in Communities (ARIC),\(^{18}\) Caerphilly,\(^{19}\) and FINRISK '92 Hemostasis\(^{20}\) studies concluded that fibrinogen was not related to future IS events. Due to this inconsistency, an individual participant meta-analysis was carried out, which showed that plasma fibrinogen levels were indeed significantly associated with CHD and stroke.\(^{1}\) Our present study also revealed that the baseline fibrinogen level independently predicted IS after adjusting for hypertension, diabetes, and smoking, suggesting that fibrinogen may play a pathogenic role in IS in the Chinese.

Very few studies on fibrinogen and stroke/IS have been conducted in Asian populations. The recent prospective Japanese study made the surprising observation that fibrinogen level was associated with hemorrhagic stroke, especially intraparenchymal hemorrhage,\(^{2}\) but had a nonsignificant negative association with IS.\(^{2}\) These findings\(^{2}\) differ not only from those of Western studies,\(^{3-5}\) but also from the present study.

Factor VII is the initial factor in the extrinsic clotting pathway. The epidemiological studies examining the association between factor VII and CHD remain ambiguous. For example, the ARIC study\(^{18}\) did not find factor VII associated with CHD events. In contrast, the Northwick Park Heart Study\(^{21}\) and Prospective Cardiovascular Munster (PROCAM) study\(^{22}\) reported a strong positive association between factor VII and CHD events. Nonetheless, most studies have shown that factor VII is not associated with all events of stroke\(^{4,23}\) and IS.\(^{18-20}\) More prospective studies are needed to clarify the association between factor VII and CHD.

### Table 2. Correlation Coefficients of Clotting Factors and Other Potential Risk Factors for IS

<table>
<thead>
<tr>
<th></th>
<th>Fibrinogen, ( \mu \text{mol/L} )</th>
<th>Factor VII, %</th>
<th>Factor VIII, %</th>
<th>Antithrombin-III, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td>0.26†</td>
<td>0.19†</td>
<td>0.32†</td>
<td>-0.02</td>
</tr>
<tr>
<td>Body mass index, kg/m(^2)</td>
<td>0.11†</td>
<td>0.20†</td>
<td>0.14†</td>
<td>0.03</td>
</tr>
<tr>
<td>Waist circumference, cm</td>
<td>0.14†</td>
<td>0.19†</td>
<td>0.17†</td>
<td>0.07</td>
</tr>
<tr>
<td>Triglycerides, ( \mu \text{mol/L} )</td>
<td>0.13†</td>
<td>0.27†</td>
<td>0.11†</td>
<td>0.15†</td>
</tr>
<tr>
<td>HDL-C, mmol/L</td>
<td>-0.06*</td>
<td>-0.02</td>
<td>-0.07*</td>
<td>-0.02</td>
</tr>
<tr>
<td>Systolic blood pressure, mm Hg</td>
<td>0.12†</td>
<td>0.15†</td>
<td>0.20†</td>
<td>0.02</td>
</tr>
<tr>
<td>Diastolic blood pressure, mm Hg</td>
<td>0.06*</td>
<td>0.14†</td>
<td>0.11†</td>
<td>0.07†</td>
</tr>
<tr>
<td>Glucose, ( \mu \text{mol/L} )</td>
<td>0.14†</td>
<td>0.16†</td>
<td>0.19†</td>
<td>0.10†</td>
</tr>
<tr>
<td>Total cholesterol, ( \mu \text{mol/L} )</td>
<td>0.15†</td>
<td>0.25†</td>
<td>0.16†</td>
<td>0.13†</td>
</tr>
<tr>
<td>Fibrinogen, ( \mu \text{mol/L} )</td>
<td>0.17†</td>
<td>0.16†</td>
<td>0.16†</td>
<td>0.20†</td>
</tr>
<tr>
<td>Factor VII, %</td>
<td>0.17†</td>
<td>0.25†</td>
<td>0.25†</td>
<td>0.19†</td>
</tr>
<tr>
<td>Factor VIII, %</td>
<td>0.16†</td>
<td>0.25†</td>
<td>0.25†</td>
<td>0.01</td>
</tr>
<tr>
<td>Antithrombin-III, %</td>
<td>0.20†</td>
<td>0.19†</td>
<td>0.19†</td>
<td>0.01</td>
</tr>
</tbody>
</table>

\(^{†} P<0.0001.\)

\(^{‡} \text{Log transformation.} \)

\(^{‡} P<0.0001. \)

\(^{‡} \text{Log transformation.} \)
Although the factor VIII level was positively associated with increased risk of IS, and correlated with cardiovascular risk factors in the current study, the relationship lost significance in the multivariate model. Other studies also showed inconsistent observations.\textsuperscript{18,19} The ARIC study\textsuperscript{18} first reported an association between factor VIII level and IS. However, a later prospective analysis\textsuperscript{19} suggested no increase in risk in people in the top tertile of factor VII level. It has been suggested that the association between factor VIII and IS risk might be indirectly due to traditional cardiovascular risk factors, especially cholesterol.\textsuperscript{23} In addition, our present study found no apparent association between antithrombin-III level and IS. Similar observations were also presented by the Caerphilly\textsuperscript{19} and ARIC\textsuperscript{24,25} studies.

Smoking is well established as an important risk factor in cardiovascular disease by increasing the risk of carotid atherosclerosis, in turn decreasing cerebral blood flow and predisposing to stroke events.\textsuperscript{26} A dose–response relationship has been documented between cigarette smoking and stroke risk.\textsuperscript{27} Moreover, stroke risk decreased significantly after cessation of cigarette smoking.\textsuperscript{28} In the current study, smoking was univariately associated with IS (hazard ratio, 1.7). The stroke risk associated with smoking may be partly due to an aggravated clotting profile. This present study revealed that the male smokers had significantly higher levels of fibrinogen (283 mg/dL) compared with men who never smoked (270 mg/dL, $P = 0.0027$). This may be why, in the multivariate models, smoking was no longer independently associated with IS.

Hyperlipidemia, including elevated triglycerides, decreased HDL-C, and elevated low-density lipoprotein cholesterol, were significantly associated with IS univariately, but not in the multivariate model in our study. Whether cholesterol is a risk factor for IS remains controversial.\textsuperscript{29,30} Elevated total cholesterol, triglycerides, and low-density lipoprotein cholesterol did not independently predict cerebral infarction

Table 3. Univariate and Multivariate Analyses Associating Baseline Cardiovascular Risk Factors With Incidence of IS

<table>
<thead>
<tr>
<th>Variables</th>
<th>N</th>
<th>Univariate Analysis</th>
<th>Model 1</th>
<th>Model 2</th>
<th>Model 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (10 years)</td>
<td>3281</td>
<td>2.38 (2.07–2.73)</td>
<td>1.97 (1.67–2.33)</td>
<td>2.03 (1.72–2.39)</td>
<td>2.00 (1.70–2.37)</td>
</tr>
<tr>
<td>Sex, male versus female</td>
<td>1413/1868</td>
<td>1.64 (1.16–2.32)</td>
<td>1.21 (0.75–1.94)</td>
<td>1.18 (0.73–1.90)</td>
<td>1.20 (0.75–1.93)</td>
</tr>
<tr>
<td>Waist circumference, cm</td>
<td>894/2387</td>
<td>2.79 (1.97–3.94)</td>
<td>1.10 (0.75–1.61)</td>
<td>1.12 (0.76–1.63)</td>
<td>1.12 (0.77–1.64)</td>
</tr>
<tr>
<td>Triglycerides, mmol/L</td>
<td>≥2.26 versus &lt;2.26 (200 mg/dL)</td>
<td>1.99 (1.19–3.31)</td>
<td>1.08 (0.63–1.84)</td>
<td>1.12 (0.66–1.93)</td>
<td>1.10 (0.65–1.89)</td>
</tr>
<tr>
<td>HDL-C, mmol/L</td>
<td>&lt;1.04/1.30 versus ≥1.04/1.30 (40/50 mg/dL)</td>
<td>1.63 (1.11–2.39)</td>
<td>1.31 (0.86–1.99)</td>
<td>1.33 (0.87–2.03)</td>
<td>1.33 (0.87–2.03)</td>
</tr>
<tr>
<td>Total cholesterol, mmol/L</td>
<td>≥6.22 versus &lt;6.22 (240 mg/dL)</td>
<td>1.96 (1.30–2.97)</td>
<td>1.08 (0.71–1.65)</td>
<td>1.14 (0.74–1.74)</td>
<td>1.11 (0.73–1.69)</td>
</tr>
<tr>
<td>Blood pressure status* versus normal</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prehypertension</td>
<td>724/1959</td>
<td>6.37 (3.75–10.8)</td>
<td>2.67 (1.54–4.63)</td>
<td>2.70 (1.56–4.68)</td>
<td>2.70 (1.56–3.62)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>598/1959</td>
<td>12.1 (7.31–20.0)</td>
<td>3.60 (2.09–6.20)</td>
<td>3.60 (2.08–6.22)</td>
<td>3.54 (2.05–6.10)</td>
</tr>
<tr>
<td>Diabetes†</td>
<td>Yes versus no</td>
<td>4.96 (3.32–7.41)</td>
<td>2.36 (1.55–3.58)</td>
<td>2.46 (1.62–3.74)</td>
<td>2.38 (1.56–3.62)</td>
</tr>
<tr>
<td>Current smoking status</td>
<td>Yes versus no</td>
<td>1.66 (1.15–2.40)</td>
<td>1.38 (0.85–2.24)</td>
<td>1.43 (0.88–2.33)</td>
<td>1.43 (0.88–2.32)</td>
</tr>
<tr>
<td>Family history of stroke</td>
<td>Yes versus no</td>
<td>2.80 (1.78–4.39)</td>
<td>2.56 (1.62–4.05)</td>
<td>2.53 (1.60–4.00)</td>
<td>2.58 (1.63–4.09)</td>
</tr>
<tr>
<td>Fibrinogen, μmol/L</td>
<td>7.03–8.79 versus &lt;7.03</td>
<td>2.19 (1.27–3.77)</td>
<td>1.51 (0.88–2.61)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Factor VII, %</td>
<td>112–136 versus &lt;112</td>
<td>1.35 (0.84–2.15)</td>
<td>0.94 (0.59–1.52)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Factor VIII, %</td>
<td>102–139 versus &lt;102</td>
<td>1.86 (1.19–2.90)</td>
<td>0.88 (0.55–1.40)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Normal blood pressure: systolic blood pressure (SBP) <120 mm Hg and diastolic blood pressure (DBP) <80 mm Hg; prehypertension: SBP between 120 and 139 mm Hg or DBP between 80 and 89 mm Hg; hypertension: SBP ≥140 mm Hg or DBP ≥90 mm Hg or using antihypertensive medication.
†Diabetes: fasting glucose ≥126 mg/dL (7.0 mmol/L) or using antidiabetic medications. In instances where 2 reference values are indicated for a single measurement, the first indicates the value for men and the second the value for women.
in several other population-based cohort studies. The Chin-Shan Community Cardiovascular Cohort study in Taiwan also showed that cholesterol, triglycerides, HDL-C, and low-density lipoprotein cholesterol at baseline were not independently associated with future stroke events, and cholesterol level was more strongly correlated with CHD than with stroke. Therefore, cholesterol may have a more modest impact on IS compared with CHD in the Taiwanese population. Triglycerides and HDL-C may be associated with IS by virtue of their association with hypertension and diabetes as a part of metabolic syndrome.

Hypertension and diabetes were independent risk factors for IS in this Taiwanese population-based study and other prospective studies. A further observation in our current study revealed a dose–response association between increments of blood pressure values and risk of IS. Moreover, those who were prehypertensive had a significantly higher risk for IS compared with normotensive individuals. This observation implies that prehypertension is clinically predictive.

Conclusion
In addition to hypertension and diabetes, fibrinogen independently predicts future IS risk. We suggest that fibrinogen may be considered in the risk assessment model for IS in the Taiwanese population.

Acknowledgments
We thank neurologists at Shin Kong WHS Memorial Hospital who helped review medical charts of stroke patients and consulted on the development of decision rules to identify new stroke cases from National Health Insurance data.

Sources of Funding
The present study was funded by the National Health Research Institutes in Taiwan (NHRI-EX93-9225PP, NHRI-EX94-9225PP) and National Science Council (NSC 95-2314-B-001-012-MY3). Data collection was supported by the Department of Health in Taiwan (projects: DOH80-27, DOH81-021, DOH8202-1027, DOH83-TD-015, and DOH84-TD-006).

Disclosures
None.

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Stroke. 2009;40:1578-1584; originally published online March 12, 2009;
doi: 10.1161/STROKEAHA.108.540492
Stroke is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0039-2499. Online ISSN: 1524-4628

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