High-Sensitivity C-Reactive Protein and Coronary Heart Disease in a General Population of Japanese
The Hisayama Study
Hisatomi Arima, Michiaki Kubo, Koji Yonemoto, Yasufumi Doi, Toshiharu Ninomiya, Yumihiro Tanizaki, Jun Hata, Kiyoshi Matsumura, Mitsuo Iida, Yutaka Kiyohara

Objective — The purpose of this study was to investigate the effects of high-sensitivity C-reactive protein (hs-CRP) on the risks of coronary heart disease (CHD) in a general population of Japanese.

Methods and Results — The Hisayama study is a population-based prospective cohort study. A total of 2589 participants aged 40 years or older were followed up for 14 years. Outcomes are incident CHD (myocardial infarction, coronary revascularization, and sudden cardiac death). The median hs-CRP level was 0.43 mg/L at baseline. During the follow-up period, 129 coronary events were observed. Age- and sex-adjusted annual incidence rates of CHD rose progressively with higher hs-CRP levels: 1.6, 3.3, 4.5, and 7.4 per 1000 person-years for quartile groups defined by hs-CRP levels of <0.21, 0.21 to 0.43, 0.44 to 1.02, and >1.02 mg/L, respectively (P < 0.0001 for trend). The risk of CHD in the highest quartile group was 2.98-fold (95% CI, 1.53 to 5.82) higher than that in the lowest group even after controlling for other cardiovascular risk factors.

Conclusions — hs-CRP levels were clearly associated with future CHD events in a general population of Japanese. In Japanese populations, the hs-CRP cut-off point for high-risk of future development of CHD is likely to be >1.0 mg/L, which is much lower than that for Western populations. (Arterioscler Thromb Vasc Biol. 2008;28:1385-1391)

Key Words: inflammation ■ C-reactive protein ■ coronary heart disease ■ prospective cohort study ■ general population

Coronary heart disease (CHD) is estimated to be one of the leading causes of death in Japan as well as other countries around the world, placing a burden on the community.1 Although the burden of CHD has been reduced in several developed countries in the past few decades,2 its incidence rates have not declined in Japan.3 Effective prevention will require a strategy based on knowledge of the importance of novel and traditional risk factors for CHD in Japan.

See accompanying article on page 1222

Recently, inflammation has emerged as an important factor in atherosclerosis,4 and high-sensitivity C-reactive protein (hs-CRP) has attracted clinical attention as a novel risk factor for CHD. However, current knowledge of the importance of hs-CRP as a risk factor for CHD is derived mainly from studies done in Western populations,5–12 and it is unclear to what extent these findings apply to Japanese populations. The Hisayama Study is a prospective cohort study of a general Japanese population. A previous report from the Hisayama Study showed a positive association between hs-CRP levels and the risks of ischemic stroke among Japanese men.13 The objective of the present analysis is to examine the relationship between serum hs-CRP levels and future development of coronary heat disease in a general population of Japanese.

Methods

Study Design and Participants
Since 1961, we have been conducting a long-term prospective cohort study of cardiovascular disease in the town of Hisayama, a suburb of Fukuoka City in Southern Japan.1,14 In 1988, a screening survey for the present study was performed in the town. A total of 2736 residents aged 40 years or older (80.9% of the total population of this age group) consented to participate in the examination.13,15 After the exclusion of 102 subjects with a history of stroke or CHD and 45 subjects whose frozen blood samples were of insufficient quantity for the measurement of serum hs-CRP, the remaining 2589 individuals were enrolled in this study.

The ethics committee of Kyushu University approved this study, participants provided written informed consent, and the procedures followed were in accordance with national guidelines.

Follow-Up Survey
The subjects were followed up prospectively from December 1988 to November 2002 by repeated health examinations. A detailed description of the study methods has been published previously.13,15

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1385
brief, the health status of any subject who had not undergone a regular examination or who had moved out of town was checked yearly by mail or telephone. We also established a daily monitoring system among the study team and local physicians or members of the town’s Health and Welfare Office. When a subject died, an autopsy was performed at the Departments of Pathology of Kyushu University. During the follow-up period, 545 subjects died, of whom 412 (75.6%) underwent autopsy. Only one participant was lost to follow-up.

Outcomes
The primary outcome of the present analysis was CHD. The criteria for a diagnosis of CHD included first-ever acute myocardial infarction (MI), silent MI, sudden cardiac death within 1 hour after the onset of acute illness, or coronary artery disease followed by coronary artery bypass surgery or angioplasty. Acute MI was diagnosed when a subject met at least 2 of the following criteria: (1) typical symptoms, including prolonged severe anterior chest pain; (2) abnormal cardiac enzymes more than twice the upper limit of the normal range; (3) evolving diagnostic electrocardiographic (ECG) changes; (4) morphological changes including local asynergy of cardiac wall motion on echocardiography, a persistent perfusion defect on cardiac scintigraphy, or myocardial necrosis or scars >1 cm long accompanied by coronary atherosclerosis at autopsy. Silent MI was defined as myocardial scarring without any historical indication of clinical symptoms or abnormal cardiac enzyme changes. The secondary outcomes of the present investigation were deaths attributable to any cardiovascular disease (ICD-10 codes I00-I99), deaths attributable to noncardiovascular disease, and total deaths.

Risk Factors
Plasma glucose levels were determined by the glucose-oxidase method, and diabetes was defined by a 75-g oral glucose tolerance test and by fasting (≥7.0 mmol/L) or postprandial (≥11.1 mmol/L) blood glucose levels or by the use of hypoglycemic agents. Total cholesterol, high-density lipoprotein (HDL) cholesterol, and triglyceride levels were determined enzymatically. Low-density lipoprotein (LDL) cholesterol level was estimated using the Friedewald formula.

Hypercholesterolemia was defined as a serum cholesterol level of 5.69 mmol/L or higher. Serum specimens collected at the time of death were divided into cardiovascular and noncardiovascular diseases, the relationship of hs-CRP to cardiovascular deaths was examined using a logistic regression model, with an estimated odds ratio (OR) and 95% confidence interval (95% CI). The cumulative incidence of CHD was estimated using Cox’s proportional hazards model. The incidence rates were calculated by the person-year method and standardized for age and sex distribution of the world standard population by the direct method using 10-year age groupings. The age- and sex-adjusted or multivariate-adjusted hazard ratio (HR) and 95% CI were estimated using Cox’s proportional hazard model. Comparison of the effects hs-CRP between participants with and without other cardiovascular risk factors was done, and the probability value for homogeneity was estimated by adding an interaction term to the statistical model. All analyses were performed using the SAS software package (SAS Institute).

Results
Among the 2589 participants, the median hs-CRP level was 0.43 mg/L. The baseline characteristics of the subjects by hs-CRP quartile groups are shown in Table 1. Subjects with higher hs-CRP levels were older and less frequently women. The age- and sex-adjusted logistic regression analysis revealed that hypertension (OR, 1.40; 95% CI, 1.16 to 1.69), diabetes (OR, 1.67; 95% CI, 1.29 to 2.16), obesity (OR, 1.80; 95% CI, 1.47 to 2.22), hypercholesterolemia (OR, 1.32; 95% CI, 1.09 to 1.60), metabolic syndrome (OR, 2.04; 95% CI, 1.67 to 2.50), and smoking habits (OR, 1.96; 95% CI 1.56 to 2.47) were significantly associated with elevated hs-CRP levels, which were defined as the highest quartile (>1.02 mg/L).

During the 14 years of follow up, 129 coronary events were observed. The Figure shows the age- and sex-adjusted cumulative incidence of CHD according to hs-CRP quartiles. The cumulative incidence of CHD clearly increased with rising hs-CRP levels. The age- and sex-adjusted incidence rates of CHD according to hs-CRP quartiles are shown in Table 2. The incidence rates rose progressively with higher hs-CRP levels: 1.6, 3.3, 4.5, and 7.4 per 1000 person-years from the first to the fourth quartile groups, respectively (P<0.0001 for trend). Table 2 also shows age- and sex-adjusted and multivariate-adjusted HRs and 95% CIs for the development of CHD according to the hs-CRP quartiles. The risks of CHD significantly increased with rising hs-CRP levels even after controlling for age, sex, systolic BP, ECG abnormalities, diabetes, BMI, total and HDL cholesterol, smoking habits, alcohol intake, and regular exercise (P=0.0002 for trend). The risk of CHD in the highest quartile group was significantly higher than that in the lowest group (multivariate-adjusted HR, 2.98; 95% CI, 1.53 to 5.82).

During the follow-up period, 545 participants died (158 died of cardiovascular disease and 387 died of noncardiovascular disease). The age- and sex-adjusted total and cause-specific mortality rates are shown in Table 3. The age-and sex-adjusted all-cause mortality rates rose progressively with higher hs-CRP levels (P<0.0001 for trend). The age- and sex-adjusted and multivariate-adjusted HRs also increased with rising hs-CRP levels even after controlling for other risk factors (Table 3; P<0.0001 for trend). When causes of death were divided into cardiovascular and noncardiovascular diseases, the relationship of hs-CRP to cardiovascular deaths was stronger than that to noncardiovascular deaths.

Age- and sex-adjusted hazard ratios of hs-CRP (highest versus lowest quartiles) for the development of CHD among
major clinical subgroups defined by the absence or presence of other cardiovascular risk factors are shown in Table 4. There were comparable effects of hs-CRP on the risk of CHD for participants who were and those who were not hypertensive ($P_{\text{homogeneity}}/H_1<0.7$). Likewise, there were no clear differences in the effects of hs-CRP for participants with and without other cardiovascular risk factors such as diabetes, obesity, hypercholesterolemia, metabolic syndrome, or smoking habits (all $P_{\text{homogeneity}}/H_1<0.4$).

**Discussion**

The present analysis demonstrated that serum hs-CRP levels were clearly associated with future coronary events in a general population of Japanese. The association between hs-CRP and CHD was strong and continuous down to very low hs-CRP levels of less than 0.21 mg/L. These associations remained strong even after controlling for age, sex, systolic BP, ECG abnormalities, diabetes, BMI, total and HDL cholesterol, smoking habits, alcohol intake, and regular exercise. Furthermore, the effects of hs-CRP were comparable for subjects with and without other cardiovascular risk factors such as hypertension, diabetes, obesity, hypercholesterolemia, metabolic syndrome, and smoking habits.

Large-scale nested case-control studies have reported that participants with incident CHD had higher levels of hs-CRP $5,6,8-11$. Likewise, large-scale cohort studies have clearly demonstrated that hs-CRP levels predicted future coronary events. $7,12$ However, these studies were mainly conducted in Western populations, and it is unclear to what extent these associations apply to Japanese populations. The Honolulu Heart Program has reported a clear association between hs-CRP levels and the future development of CHD in a population of Japanese Americans. $20$ The present analysis from the Hisayama Study confirmed the results from these previous observational studies in a general population of Japanese, finding that the relative risks of increasing hs-CRP levels for the development of CHD were similar to those
obtained from other observational studies conducted in Western populations or in a population of Japanese Americans. These findings suggest that hs-CRP is an important risk factor for CHD among Japanese as well as among Westerners.

In the present analysis, hs-CRP levels in Japanese (median 0.43 mg/L) were much lower than those in Western populations (median approximately 1.5 to 2.0 mg/L). This is consistent with the findings of other cross-sectional studies in which Asian subjects had lower hs-CRP levels compared to Western subjects. The reason for this ethnic difference is not clearly resolved, but genetic diversity has been reported to influence hs-CRP levels. The relatively low BMI in Japanese and differences in diet and lifestyle may also have modulated hs-CRP levels. The Honolulu Heart Program reported a median hs-CRP level of 0.54 mg/L among Japa-

Table 2. Incidence Rates and Adjusted Hazard Ratios for Development of Coronary Heart Disease According to Quartiles of High-Sensitivity C-Reactive Protein

<table>
<thead>
<tr>
<th>hs-CRP Levels, mg/L</th>
<th>No. of events/person-years</th>
<th>Crude incidence rate (per 1000 person-years)</th>
<th>Age- and sex-adjusted incidence rate (per 1000 person-years)</th>
<th>Age- and sex-adjusted hazard ratio (95% CI)</th>
<th>Multivariate-adjusted hazard ratio* (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;0.21 (n=648)</td>
<td>11/8589</td>
<td>1.3</td>
<td>1.6</td>
<td>1 (reference)</td>
<td>1 (reference)</td>
</tr>
<tr>
<td>0.21 to 0.43 (n=647)</td>
<td>22/8297</td>
<td>2.7</td>
<td>3.3</td>
<td>1.75 (0.85 to 3.61)</td>
<td>1.60 (0.77 to 3.31)</td>
</tr>
<tr>
<td>0.44 to 1.02 (n=645)</td>
<td>36/8073</td>
<td>4.5</td>
<td>4.5</td>
<td>2.55 (1.30 to 5.02)</td>
<td>1.97 (0.98 to 3.95)</td>
</tr>
<tr>
<td>&gt;1.02 (n=649)</td>
<td>60/7485</td>
<td>8.0</td>
<td>7.4</td>
<td>3.96 (2.07 to 7.57)</td>
<td>2.98 (1.53 to 5.82)</td>
</tr>
</tbody>
</table>

P Trend

Table 3. Mortality Rates and Adjusted Hazard Ratios for Total and Cause-Specific Deaths According to Quartiles of High-Sensitivity C-Reactive Protein

<table>
<thead>
<tr>
<th>hs-CRP Levels, mg/L</th>
<th>No. of events/person-years</th>
<th>Age- and sex-adjusted mortality rate (per 1000 person-years)</th>
<th>Age- and sex-adjusted hazard ratio (95% CI)</th>
<th>Multivariate-adjusted hazard ratio* (95% CI)</th>
</tr>
</thead>
</table>
| Total deaths
| <0.21 (n=648)       | 79/8624                    | 12.7                                           | 1 (reference)                           | 1 (reference)                          |
| 0.21 to 0.43 (n=647)| 106/8365                   | 15.2                                           | 1.08 (0.81 to 1.45)                     | 1.13 (0.84 to 1.51)                    |
| 0.44 to 1.02 (n=645)| 143/8181                   | 18.9                                           | 1.30 (0.99 to 1.72)                     | 1.41 (1.06 to 1.87)                    |
| >1.02 (n=649)       | 217/7626                   | 23.5                                           | 1.80 (1.39 to 2.34)                     | 1.85 (1.41 to 2.43)                    |

Cardiovascular deaths
| <0.21 (n=648)       | 16/8624                    | 2.2                                           | 1 (reference)                           | 1 (reference)                          |
| 0.21 to 0.43 (n=647)| 28/8365                    | 3.7                                           | 1.38 (0.75 to 2.55)                     | 1.40 (0.75 to 2.60)                    |
| 0.44 to 1.02 (n=645)| 47/8181                    | 6.0                                           | 2.15 (1.22 to 3.80)                     | 2.28 (1.27 to 4.09)                    |
| >1.02 (n=649)       | 67/7626                    | 7.2                                           | 2.77 (1.60 to 4.80)                     | 3.00 (1.70 to 5.28)                    |

Noncardiovascular deaths
| <0.21 (n=648)       | 63/8624                    | 10.5                                          | 1 (reference)                           | 1 (reference)                          |
| 0.21 to 0.43 (n=647)| 78/8365                    | 11.5                                          | 1.00 (0.72 to 1.40)                     | 1.06 (0.76 to 1.48)                    |
| 0.44 to 1.02 (n=645)| 96/8181                    | 12.9                                          | 1.09 (0.79 to 1.50)                     | 1.18 (0.85 to 1.64)                    |
| >1.02 (n=649)       | 150/7626                   | 16.4                                          | 1.55 (1.15 to 2.08)                     | 1.56 (1.14 to 2.13)                    |

P Trend

hs-CRP indicates high-sensitivity C-reactive protein; 95% CI, 95% confidence interval.

*Hazard ratios controlling for age, sex, systolic blood pressure, ECG abnormalities, diabetes, body mass index, total and HDL cholesterol, smoking habits, alcohol intake, and regular exercise.
nese Americans without CHD, which was lower than that of Western populations but higher than that obtained from the present analysis. These findings suggest that lower hs-CRP levels among Asian populations are derived from differences in genetic factors as well as differences in BMI, diet, and lifestyle.

Another important finding obtained from the present analysis is that the association between hs-CRP levels and CHD was continuous from very low hs-CRP levels and that a slightly elevated hs-CRP level of more than 1 mg/L was clearly associated with increased risk of future coronary events in Japanese. Similar findings were obtained from the Honolulu Heart Program, whose subjects were Japanese American. A low cut-off point of hs-CRP (<1 mg/L) has also been suggested as the target of lipid lowering therapy with statin for maximum reduction of recurrent coronary events or deaths among Western patients with acute coronary syndrome. These findings imply that the association between hs-CRP and CHD are likely to be continuous down to very low hs-CRP levels among Asian as well as Western subjects. The American Heart Association and the Centers for Disease Control have recommended categorizing subjects using hs-CRP cut-off points of <1, 1 to 3, and >3 mg/L into low-, average-, and high-risk categories, respectively, based mainly on the findings obtained from studies done in Western populations. Among Asian subjects whose hs-CRP levels are much lower than those of Western subjects, however, an hs-CRP level of >1 mg/L is likely to be the cut-off point for the high-risk category.

In the present analysis, the effects of hs-CRP on the risks of future coronary events were independent of other cardiovascular risk factors and did not differ between participants with and those without traditional risk factors such as hypertension, diabetes, obesity, hypercholesterolemia, metabolic syndrome, or smoking habits. These results suggest that measurement of hs-CRP is likely to provide additional information for the detection of high-risk individuals among subjects without traditional risk factors as well as for the detection of extremely high-risk individuals among those with traditional risk factors. This finding is consistent with other observational studies suggesting that inclusion of hs-CRP into risk prediction models improves the accuracy of cardiovascular risk classification.

Several limitations of our study should be discussed. The primary limitation is that we estimated the cut-off point of hs-CRP for detection of high-risk subjects based on analysis using quartile groupings despite continuous relationships between hs-CRP and the risks of CHD. The cut-off point

| Table 4. Age- and Sex-Adjusted Hazard Ratios of High-Sensitivity C-Reactive Protein (Highest vs Lowest Quartiles) for Development of Coronary Heart Disease Among Major Clinical Subgroups Defined by the Absence or Presence of Other Cardiovascular Risk Factors |
|---------------------------------|------------------|------------------|------------------|------------------|
|                                | No. of Events/Person-Years | Hazard Ratio* (95% CI) | P Homogeneity |
|                                | Highest Quartile (hs-CRP >1.02 mg/L) | Lowest Quartile (hs-CRP <0.21 mg/L) |                  |
| Hypertension†                  | Absent 18/3843 | 6/6224 | 3.18 (1.25 to 8.08) | 0.7              |
|                                | Present 42/3643 | 5/2365 | 4.27 (1.68 to 10.82) |                  |
| Diabetes‡                      | Absent 45/6276 | 9/8122 | 3.73 (1.81 to 7.68) | 0.7              |
|                                | Present 15/1210 | 2/467 | 2.84 (0.65 to 12.43) |                  |
| Obesity§                       | Absent 45/5113 | 10/7412 | 3.63 (1.81 to 7.28) | 0.7              |
|                                | Present 15/2373 | 1/1177 | 5.42 (0.71 to 41.35) |                  |
| Hypercholesterolemia| Absent 32/4448 | 5/5975 | 4.74 (1.83 to 12.26) | 0.4              |
|                                | Present 28/3037 | 6/2614 | 2.83 (1.16 to 6.88) |                  |
| Metabolic syndrome¶           | Absent 27/4340 | 7/7068 | 3.34 (1.44 to 7.75) | 1.0              |
|                                | Present 29/2631 | 3/1122 | 3.31 (1.00 to 10.92) |                  |
| Current smoking                | Absent 34/4910 | 9/7030 | 3.39 (1.61 to 7.15) | 0.5              |
|                                | Present 26/2576 | 2/1559 | 5.94 (1.40 to 25.12) |                  |

hs-CRP indicates high-sensitivity C-reactive protein; 95% CI, 95% confidence interval.

*Hazard ratios for the highest vs the lowest quartile of high-sensitivity C-reactive protein.
†Blood pressure ≥140/90 mm Hg or current use of antihypertensive agents.
‡Fasting glucose ≥7.0 mmol/L, postprandial blood glucose ≥11.1 mmol/L, or current use of hypoglycemic agents.
§Body mass index ≥25 kg/m².
¶Defined by the modified National Cholesterol Education Program Adult Treatment Panel III criteria.
could change depending on the way of grouping the subjects or on the way of selecting the reference group. Given that this limitation might have overestimated the cut-off point, the true cut-off point for detection of high-risk subjects may be lower than 1 mg/L. A second limitation is that our findings are based on a 1-time measurement of serum hs-CRP, which may not accurately reflect the status of a study participant. However, this source of variability could not account for the relationship observed in the present study, because a random misclassification of such nature would tend to underestimate study findings and bias the results toward the null hypothesis. Thus, the true association may be stronger than that observed in our study. A third limitation is that the serum samples were measured after being stored at −20°C for a long period. However, the Reykjavik Study confirmed the stability of CRP concentrations in serum preserved at this temperature for an average of 12 years.10 The last limitation is that our study lacked information on drug use at baseline and during the follow-up period. It is known that several medications, including statin, angiotensin-converting enzyme inhibitors, fibrate, niacin, thiazolidinedione, and estrogen/progestogen hormone can alter CRP levels.33 However, these medications were rarely used in Japan in 1988, when the serum samples for our study were collected. This suggests that such a bias did not invalidate the present findings. It is also known that some medications have been shown to be beneficial for the prevention of CHD, and high-risk individuals with higher hs-CRP levels were likely to receive these medications. Given that this limitation might have underestimated the association between hs-CRP and CHD, the true association may be stronger than that obtained from the present analysis.

In conclusion, the present analysis has clearly demonstrated that hs-CRP levels were associated with future coronary events in a general population of Japanese. In Japanese populations, the hs-CRP cut-off point for high-risk of future development of CHD is likely to be >1 mg/L, which is much lower than that for Western populations. High-risk approaches for the prevention of CHD using hs-CRP measurement are likely to provide additional protection against the burden of CHD in Japan.

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Disclosures

None.

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