Plasma Fibrinogen as a Predictor of Total and Cause-Specific Mortality in Elderly Japanese-American Men

Katsuhiko Yano, John S. Grove, Randi Chen, Beatriz L. Rodriguez, J. David Curb, Russell P. Tracy

Abstract—The relation between plasma fibrinogen and total and cause-specific mortality was investigated in a cohort of 3571 Japanese-American men aged 71 to 93 years during a median follow-up of 4.4 years. There were a total of 728 deaths, of which 37% were accounted for by cardiovascular disease and 27% by cancer. The age-adjusted relative risk (RR) for total mortality in the top quintile of fibrinogen (>3.51 g/L) compared with the bottom quintile (<2.57 g/L) was 4.3 ($P<0.0001$) in the first year of follow-up. RR was reduced to 1.7 in the second year but remained significantly and slightly increased in subsequent years. After adjustment for age and confounding risk factors, the RRs (and 95% confidence intervals) associated with a 1-SD increment of fibrinogen (0.64 g/L) for all-cause, cardiovascular disease, cancer, and other-cause mortality were 1.3 (1.2 to 1.4), 1.2 (1.1 to 1.4), 1.3 (1.2 to 1.5), and 1.3 (1.2 to 1.5), respectively. Preexisting diseases did not influence the significant association of fibrinogen with mortality. There was a significant interaction of fibrinogen with white blood cell count but not with cigarette smoking. We conclude that plasma fibrinogen is an independent risk factor for mortality from a broad spectrum of diseases in elderly men and that this universal effect of fibrinogen on mortality may be mediated partly through inflammation. (Arterioscler Thromb Vasc Biol. 2001;21: 1065-1070.)

Key Words: Asian Americans ■ cancer ■ cardiovascular disease ■ fibrinogen ■ mortality

The ability of standard risk factors, including hypertension, elevated blood cholesterol, cigarette smoking, and diabetes mellitus, to predict coronary heart disease (CHD) is limited.1,2 There is growing evidence for the important roles of new risk factors related to hemostasis, blood rheology, inflammation, and infection in the pathogenesis of atherosclerotic vascular diseases.2–6 Plasma fibrinogen is a major factor affecting blood coagulation, viscosity, smooth muscle proliferation, and endothelial function.7 It is also an acute-phase reactant that is a sensitive marker for systemic inflammation.8 Since publication of the reports from the Northwick Park Heart Study in the 1980s,9,10 an elevated level of plasma fibrinogen has been identified as a major independent risk factor for ischemic cardiovascular disease (CVD). In 3 recent review articles,11–13 meta-analyses of 6 to 18 prospective studies have consistently shown predictive values of fibrinogen for CHD and stroke incidence and mortality that are independent of standard risk factors.

However, most of the available data are based on middle-aged men, and there is a relative lack of information on the relation of fibrinogen to both total and CVD mortality in elderly people. In this report, we present results of a prospective investigation of the association between baseline levels of plasma fibrinogen and subsequent total and cause-specific mortality during a median follow-up of 4.4 years among 3571 Japanese-American men aged 71 to 93 years.

Methods

Study Population
The Honolulu Heart Program (HHP) is a long-term prospective study of CVD among Japanese-American men who were living on Oahu island, Hawaii, in 1965. A total of 8006 eligible men aged 45 to 68 years participated in the initial examination between 1965 and 1968. Details of the cohort selection process were previously published.14 This cohort was reexamined 2, 6, and 26 years later. Plasma fibrinogen levels were first determined in the fourth HHP examination (1991 to 1993) on 3571 men aged 71 to 93. These men represented 80% of the surviving members of the original cohort. This analysis was based on the data obtained from the follow-up of these 3571 men through the end of 1996. The Kuakini Medical Center institutional review committee approved the study protocol, and informed consent was obtained from all participants.

Data Collection
The fourth HHP examination included demographic questions, medical history, anthropometry, standard blood pressure measurements, smoking habits, alcohol intake, physical activity assessment, resting 12-lead electrocardiogram, pulmonary function tests, and collection of fasting blood specimens to measure levels of plasma fibrinogen, total cholesterol, HDL cholesterol, triglyceride, glucose, insulin, and hematological values. A standard oral glucose tolerance test was performed in 3090 men 2 years after the examination. Additional details of the examination were previously published.15

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From the Honolulu Heart Program, Kuakini Medical Center (K.Y., R.C., B.L.R., J.D.C.), Honolulu, Hawaii; the Division of Clinical Epidemiology, Department of Medicine (K.Y., R.C., B.L.R., J.D.C.), and the Biostatistics Program, Department of Public Health (J.S.G.), John A. Burns School of Medicine, University of Hawaii at Manoa, Honolulu, Hawaii; and the Department of Pathology (R.P.T.), University of Vermont, Laboratory for Clinical Biochemistry Research, Colchester.
Correspondence to Katsuhiko Yano, MD, Pacific Health Research Institute, 846 S Hotel St, Suite 306, Honolulu, HI 96813. E-mail yano@phri.hawaii-health.com
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test was performed. Diabetes mellitus was defined by a fasting glucose level $>126\, \text{mg/dL}$, a 2-hour glucose level $\geq 200\, \text{mg/dL}$, or active treatment with insulin or oral hypoglycemic agents. Hypertension was defined as a systolic blood pressure $\geq 160\, \text{mm Hg}$, a diastolic blood pressure $\geq 95\, \text{mm Hg}$, or use of antihypertensive drugs. Body mass index was calculated as weight (kg)/square of height (m$^2$). A summary measure of physical activity was estimated by the method used in the Framingham Study. The number of hours spent per 24-hour period in 5 different activity levels was recorded, and the weighted sum of hours spent for each activity was used as the physical activity index.

Plasma fibrinogen levels were determined at the Laboratory for Clinical Biochemistry Research, University of Vermont, Colchester, as the rate of clot formation by a semiautomated modification of the Clauss method, as determined on a BBL fibrinometer (Becton Dickinson). Details of the calibration and quality control data were previously published. Other laboratory measurements were conducted by standardized procedures.

Mortality data were obtained through a comprehensive surveillance system that has been used successfully since the beginning of the HHP. All deaths were ascertained by continuous monitoring of obituaries in local newspapers, mortality notices, hospital discharge records, and death certificates. The underlying cause of death was determined by a panel of study physicians at bimonthly conferences and was based on all available information, including HHP examinations, hospital records, death certificates, autopsy reports, and telephone inquiries to physicians and families. Three major categories were used to classify the underlying cause according to the eighth revision of the International Classification of Disease: CVD (codes 390 to 459), cancer (codes 140 to 208), and all other causes combined.

## Statistical Analysis

Rates of survival through the end of 1996 by quintile of baseline fibrinogen level were calculated by using the Kaplan-Meier method. Significant differences in survival among the quintile groups were evaluated by the log-rank test. Temporal changes in the relation between fibrinogen and mortality were examined by estimating age-adjusted relative risks (RRs) and 95% confidence intervals (CIs) for total mortality in each of the second to the fifth quintiles of fibrinogen, compared with the first quintile, by using Cox proportional-hazards regression models for separate follow-up years.

The independent role of fibrinogen as a predictor of total and cause-specific mortality was evaluated by using Cox regression models, with separate adjustments for age, potentially confounding factors, and preexisting diseases. Confounding factors were selected on the basis of previously reported cross-sectional analyses in this study and other studies. These factors included body mass index, total and HDL cholesterol, triglyceride, hematocrit, white blood cell (WBC) count, smoking (pack-years), alcohol intake (oz/ mo), physical activity index, and the presence or absence of hypertension and diabetes mellitus (as defined above). Preexisting diseases included CHD, stroke, and cancer, which were identified at the baseline examination.

In these analyses, predictive values of fibrinogen for total and cause-specific mortality were evaluated by RRs in each of the second through the fifth quintiles of baseline fibrinogen compared with the first quintile. In a separate analysis, fibrinogen was treated as a continuous variable, and standardized relative risks (SRRs) for total and cause-specific mortality associated with an increment of 1 SD of fibrinogen (0.64 g/L) were estimated.

Possible interactions between fibrinogen and other variables were examined by including fibrinogen (continuous variable), age, each variable one at a time, and the product of fibrinogen $\times$ each variable simultaneously in Cox regression models. For statistical significance, 2-sided probability values $<0.05$ were used throughout the analysis.

## Results

For the 3571 participants, during the follow-up through the end of 1996 (median 4.4 years), a total of 728 men had died. Table 1 shows the number of total and cause-specific deaths by quintile of baseline fibrinogen level. CVD accounted for 37% of all deaths, which included 124 cases of CHD, 102 cases of stroke, and 32 cases of other circulatory diseases. Cancer was the second most frequent cause, accounting for 27% of deaths. Among the 273 remaining deaths, senile dementia, chronic obstructive pulmonary disease, pneumonia, liver cirrhosis, diabetes, and accidents/suicide were relatively common causes. None of the deaths due to these miscellaneous causes exceeded 50.

Figure 1 illustrates survival curves by quintile of fibrinogen. Among the lower 3 quintile groups, survival curves were very similar and showed much better survival rates than those for the upper 2 quintiles. The fifth quintile group showed the worst survival. This result was evident from the first year of follow-up. Overall differences in survival among quintile groups of fibrinogen were highly significant ($P<0.0001$).

Figure 2 shows age-adjusted RRs and 95% CIs of total mortality for each of the second through the top quintiles of fibrinogen compared with the lowest quintile by year of follow-up. Because of the similarity in patterns of RRs, the
follow-up years after the second were combined. There were substantial decreases in RRs for every quintile group between the first and second year of follow-up. The reduction was greatest for the top quintile group, dropping from 4.3 to 1.7. However, the RRs tended to increase consistently in subsequent years, with an average of 1.9 for the top quintile. The RRs for the top quintile group were significantly greater than 1.0 in every year of follow-up, whereas those for the fourth quintile group were significant only after the second year. None of the RRs for the second and third quintile groups were significant in any of the follow-up years. Exclusion of preexisting diseases (1187 men; 349 deaths) altered these temporary patterns of RR over time.

Figure 3 shows age-adjusted RRs and 95% CIs of total and cause-specific mortality during the entire follow-up period for each of the second through the top quintiles of fibrinogen compared with the lowest quintile. There were significant increases in mortality for the top quintile of fibrinogen (>3.51 g/L) compared with the lowest quintile (<2.57 g/L): 2.1 times in all causes, 2.4 times in CVD, 2.8 times in cancer, and 1.6 times in all other causes. Significant increases in mortality (1.5 times in all causes and 2.1 times in cancer) were also noted for the fourth quintile of fibrinogen (3.14 to 3.51 g/L). On the other hand, there was no significant increase in mortality for the second and third quintiles of fibrinogen, except that the second quintile had a 1.6-fold increase in cancer mortality. Thus, there might be a threshold of fibrinogen above which mortality risk is increased. However, when fibrinogen level was treated as a continuous variable in Cox regression models, a test for nonlinearity was not significant. These results suggest that the difference in risk increases exponentially with fibrinogen level, a curve that mimics a threshold effect.

Table 2 shows SRRs and 95% CIs for total and cause-specific mortality associated with an increment of baseline fibrinogen by 1 SD (0.64 g/L). In this analysis, effects of fibrinogen as a continuous variable on mortality were evaluated by Cox regression models. Three models were used, with adjustments for (1) age alone; (2) age and standard risk factors for CVD; and (3) age, risk factors, and preexisting diseases (CHD, stroke, and cancer). When the adjustment was made only for age, the SRR was greatest for CVD mortality (1.40), followed by cancer (1.38), all causes (1.36), and other causes (1.31). All of these SRRs were statistically significant. After adjustment for risk factors, however, there was a substantial reduction in the SRR for CVD (1.21), a relatively small reduction for cancer (1.32) and all-cause mortality (1.28), and a slight increase for other causes (1.32). The reduction in SRR for CVD mortality suggests greater confounding effects of these risk factors on CVD mortality. Further adjustment for preexisting diseases slightly reduced the SRR for CVD mortality but left the other SRRs unchanged.

When these analyses were repeated after excluding deaths that occurred within 1 year of the follow-up, all SRRs remained significant, although their values tended to be smaller. In particular, there was a 10 percentage point decrease (from 1.38 to 1.28) in the age-adjusted SRR for cancer mortality. These findings are consistent with the reduction of RRs for total mortality between the first and second year of follow-up that was shown in Figure 2.

Figure 4 illustrates interactions between fibrinogen and 2 other variables for the association with total mortality. The figure on the left shows age-adjusted mortality rates for 9 subgroups classified by combinations of fibrinogen tertiles (<2.76, 2.76 to 3.22, and >3.22 g/L) and WBC tertiles (<5.4, 5.4 to 6.6, and >6.6×10^9/L). Within the lowest tertile of WBC, there was only a small increase in mortality with fibrinogen, except that the second quintile had a 1.6-fold increase in cancer mortality. Thus, there might be a threshold of fibrinogen above which mortality risk is increased. However, when fibrinogen level was treated as a continuous variable in Cox regression models, a test for nonlinearity was not significant. These results suggest that the difference in risk increases exponentially with fibrinogen level, a curve that mimics a threshold effect.
TABLE 2. Standardized Relative Risks for Total and Cause-Specific Mortality Associated With an Increment of Baseline Fibrinogen Levels by 1 SD (0.64 g/L)

<table>
<thead>
<tr>
<th>Cause of Death</th>
<th>Adjusted for Age</th>
<th>Adjusted for Age and Risk Factors*</th>
<th>Adjusted for Age, Risk Factors, and Preexisting Diseases†</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>SRR (95% CI)</td>
<td>SRR (95% CI)</td>
<td>SRR (95% CI)</td>
</tr>
<tr>
<td>All causes</td>
<td>1.36 (1.27, 1.45)</td>
<td>1.28 (1.18, 1.39)</td>
<td>1.27 (1.18, 1.38)</td>
</tr>
<tr>
<td>CVD</td>
<td>1.40 (1.26, 1.55)</td>
<td>1.21 (1.05, 1.39)</td>
<td>1.18 (1.03, 1.36)</td>
</tr>
<tr>
<td>Cancer</td>
<td>1.38 (1.23, 1.56)</td>
<td>1.32 (1.15, 1.52)</td>
<td>1.32 (1.14, 1.52)</td>
</tr>
<tr>
<td>Other</td>
<td>1.31 (1.17, 1.45)</td>
<td>1.32 (1.15, 1.52)</td>
<td>1.32 (1.15, 1.51)</td>
</tr>
</tbody>
</table>

Other includes non-CVD, noncancer deaths.
*Risk factors included body mass index, total and HDL cholesterol, triglyceride, hematocrit, WBC count, physical activity index, cigarette smoking (pack-years), alcohol intake (oz/mo), presence or absence of hypertension (blood pressure ≥160 mm Hg systolic or ≥95 mm Hg diastolic or taking antihypertensive medicine), presence or absence of diabetes mellitus (fasting glucose ≥126 mg/dL, 2-hour glucose ≥200 mg/dL, or treated with insulin or oral hypoglycemics).
†Preexisting diseases included CHD, stroke, and cancer.

Discussion

In this report, we demonstrated that plasma fibrinogen was a strong predictor of total and cause-specific mortality, independent of standard risk factors, in a large cohort of elderly Japanese-American men who were known to have a low risk for ischemic CVD and a long life expectancy. It is remarkable that an increased level of fibrinogen was universally associated with increasing risk of mortality from diverse causes, including CVD, cancer, and other miscellaneous diseases. The association was strongest with cancer and weakest with CVD after adjustment for confounding risk factors. This result may simply be due to the fact that the risk factors selected are, by and large, CVD risk factors and not necessarily cancer-related risk factors (except for smoking and alcohol intake).

It is interesting to note that the association of fibrinogen with mortality, especially cancer mortality, was greater in the first year of follow-up than in subsequent years. This finding might imply that elevated levels of fibrinogen were consequences of subclinical disease or underlying conditions. However, this hypothesis explains only partly the fibrinogen-mortality association because the higher mortality in men with increased levels of fibrinogen persisted after exclusion of early deaths, not only for total mortality but also for every category of cause-specific death. Tracy observed similar findings in the Cardiovascular Health Study and postulated the concept of "proximate pathophysiology," in which it was hypothesized that individuals with chronic diseases might enter a time of destabilization and rapid worsening and decline 6 months to 2 years before an event (or death).

These findings also suggest that 1 of the main pathophysiological mechanisms of the increased all-cause mortality associated with elevated levels of fibrinogen may be an inflammatory process. Acute or chronic inflammation is a common underlying condition of many diseases leading to death. Older individuals are most vulnerable to inflammatory conditions, and predictive values of fibrinogen for mortality from a variety of causes are particularly important in old age.

C-reactive protein is known to be a sensitive marker for chronic systemic inflammation. Although direct information on C-reactive protein was not available in the present analysis, fibrinogen was found to be highly correlated with C-reactive protein (r=0.59) in a random sample of this study cohort. Furthermore, in a separate report from the HHP, there was a significant correlation (r=0.24) of fibrinogen with WBC count, another marker for inflammation/infection. Nonetheless, both fibrinogen and WBC count were independently associated with total mortality in the present study. Also, there was a significant interaction between fibrinogen and WBC count, which indicates joint effects of...
these 2 markers of inflammation. Simultaneously elevated levels of both variables might simply mean an increased severity of the underlying inflammatory process, or it might reflect multiple causal pathways of the inflammation. It is known from other prospective studies that WBC is an independent predictor of CVD, cancer, and total mortality. There are a few prospective studies showing a significant association of fibrinogen with total mortality, independent of standard risk factors. In the Northwick Park Heart Study, plasma fibrinogen predicted 10-year total and ischemic heart disease mortality among 1511 men aged 40 to 64 years. However, there was no significant association of fibrinogen with cancer mortality. According to the 18-year follow-up data of the Framingham Study cohort (1274 men and women aged 47 to 79 years), an increment of baseline fibrinogen by 1 SD (0.56 g/L) increased the age-adjusted risk for both all-cause mortality and CVD mortality in men by 30%. After adjustment for other risk factors, the increased risks were reduced to 20%. These results are very similar to those in our study. In a 21-year follow-up of CVD and total mortality among Swedish men aged 54 to 75, plasma fibrinogen was a strong predictor of all-cause, CHD, stroke, and non-CVD mortality when smoking was excluded from the analysis. In the 8-year follow-up data of the Scottish Heart Health Study (5095 men and 4860 women aged 40 to 59 years), fibrinogen was a strong predictor of CHD and total mortality, even after adjustment for smoking in both sexes and with or without preexisting CHD. There appeared to be a threshold effect, with individuals in the fifth quintile of fibrinogen having a much increased risk of total and CHD mortality. In the Atherosclerosis Risk in Communities Study, a 5.2-year follow-up of 14,477 men and women aged 45 to 64 years who were free of CHD showed that both fibrinogen and WBC count were significantly associated with total mortality in men, with multivariate-adjusted RRs (per 1-SD increment) of 1.30 and 1.15, respectively. However, there was no interaction between fibrinogen and WBC count. These findings in other studies are generally consistent with those in our study.

Cigarette smoking is the strongest known determinant of fibrinogen levels and is 1 of the most important risk factors for CVD and all-cause mortality. The Framingham Study provided detailed analyses of the interrelation of fibrinogen with smoking and CVD. It was estimated that half of the increased risk of CVD due to smoking was mediated through its effects on increasing fibrinogen. In our study, however, both fibrinogen and smoking were significant predictors of total mortality, independent of each other. These 2 variables were weakly but significantly correlated \((r=0.07, P<0.001)\), yet there was no interaction of fibrinogen with smoking on mortality. Similar findings have been shown in another prospective study.

Although a causal relation between fibrinogen and mortality can be determined only by clinical trials, the clinical importance of plasma fibrinogen as a potent and independent predictor of mortality from a broad spectrum of chronic diseases appears to be clear. In old age, when the association of traditional risk factors with mortality is weakened, this relatively inexpensive test should provide a useful measure to identify high-risk persons. Whether or not lowering fibrinogen levels can reduce mortality risk awaits further studies.

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### References


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