Influence of Plasma Fibrinogen Levels on the Incidence of Myocardial Infarction and Death Is Modified by Other Inflammation-Sensitive Proteins

A Long-Term Cohort Study

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Abstract—Inflammation may play an important role in atherosclerotic disease. Plasma fibrinogen is an established predictor of cardiovascular events. The aim of this study was to evaluate whether other inflammation-sensitive plasma proteins modify this prediction. We studied the incidence of cardiac events and death in men in relation to fibrinogen levels alone and in combination with other proteins. The study was based on 6075 men, who were, on average, 46 years old at the time of the screening examination, which included the quantitative assessment of plasma levels of fibrinogen, orosomucoid, α₁-antitrypsin, haptoglobin, and ceruloplasmin. The concentration of each protein was divided into quartiles for each. This classification made it possible to identify 4 groups, ie, men in the first fibrinogen quartile and at the same time either not belonging to the fourth quartile of any of the other proteins (Q1/No group) or also belonging to the fourth quartile of ≥1 of the additional proteins (Q1/Yes group) and corresponding groups in the fourth fibrinogen quartile (Q4/No and Q4/Yes groups). During the follow-up, which occurred at an average of 16 years, 439 (7.2%) men experienced a cardiac event, and 653 (10.7%) died; 278 of these men died of cardiovascular diseases, with 206 deaths attributed to ischemic heart disease. From the lowest to the highest quartile, there was for each protein a stepwise increase in the incidence of cardiac events and mortality. All-cause mortality and cardiovascular mortality were significantly higher in the Q4/Yes group compared with the Q4/No group, but they were similar in the Q4/No and Q1/Yes groups. The incidence of cardiac events was significantly higher in the Q1/Yes and Q4/Yes groups compared with the Q1/No and Q4/No groups, respectively. The increased cardiovascular mortality and cardiac event rates remained after adjustment for several confounders when the Q4/Yes and Q4/No groups were compared. The results suggest that the incidence of cardiac events and death due to cardiovascular diseases in middle-aged men predicted by plasma levels of fibrinogen is modified by other inflammation-sensitive proteins. (Arterioscler Thromb Vasc Biol. 2001;21:452-458.)

Key Words: atherosclerosis ■ inflammation ■ fibrinogen ■ plasma proteins ■ myocardial infarction

Several studies have confirmed that plasma fibrinogen level is a strong and consistent predictor of cardiovascular disease (CVD).1–3 Fibrinogen also participates more directly in early atherosclerotic plaque formation, and fibrinogen and its split products are contained in these lesions.4–6 However, there is also evidence that plasma fibrinogen and other factors are important not only in atherogenesis but also in arterial thrombosis.7 In these physiological roles, fibrinogen may have a role in the acute and chronic inflammatory process, inasmuch as an increase in plasma levels of fibrinogen and other inflammation-sensitive proteins is a major component of the acute phase as well as in the chronic inflammatory response.8 Because inflammation itself is also assumed to play an important role in the development of atherosclerosis and its complications,9–11 an increasing interest has also been focused on inflammation-sensitive proteins other than fibrinogen. In a study published in 1997, it was found that baseline plasma concentrations of another inflammation-sensitive protein, C-reactive protein, predicted the risk of future myocardial infarction and stroke.12 However, today there are no studies in which it is possible to assess whether the risk predicted by the level of one inflammation-sensitive plasma protein is modified by other plasma proteins.

The aim of the present post hoc study on middle-aged men was to evaluate whether increasing plasma levels of inflammation-sensitive proteins other than fibrinogen, ie, orosomucoid, α₁-antitrypsin, haptoglobin, and ceruloplasmin, further modify the risk of later developing a cardiac event (CE) or death as predicted by the level of fibrinogen in the plasma.
Methods

Study Population
The Department of Preventive Medicine was established in the mid seventies as a part of the Malmö University Hospital, Malmö, Sweden, to facilitate the early detection and treatment of individuals with a higher than normal risk of developing CVD.13,14 Three thousand four hundred women and 22 444 men were screened as part of a baseline examination that was carried out from 1974 to 1983. For clinical purposes, to find possible correlations between plasma protein levels and the individuals’ metabolic and cardiovascular risk factor profiles, the determination of plasma levels of inflammation-sensitive proteins was part of the program for 30% of the male subjects selected at random (in total, 6512 men born between 1921 and 1949 and aged 28 to 61 years at the time of the screening examination).

A self-administered questionnaire was used to record medical history and lifestyle habits. All measurements and analyses were performed under standardized conditions.

One hundred eighteen (1.8%) men with a previous history of either myocardial infarction, stroke, or cancer were excluded, as were another 319 (4.9%) men for whom the computed value of any one of the measured plasma proteins was missing. This led to a study population of 6075 men with a mean age of 46.8±3.7 years.

The screening program of the age cohorts was approved by the health service authority of Malmö, and all participants have given their written consent.

Prevalence of Chronic Bronchitis and Recent Respiratory Infection, Leisure-Time Physical Activity, and Self-Rated Health
Long-term cough associated with enhanced mucous production was, in accordance with the World Health Organization’s criteria, counted as chronic bronchitis.15 Respiratory infection was recorded if it had occurred within 3 weeks before the examination. Two categories were used for the classification of leisure-time physical activity, ie, sedentary or not.

The categorization of self-rated health was limited to depending on whether the participant felt healthy or not.

Cardiovascular Risk Factors
The following smoking categories were used: those who had never smoked, smoker (daily consumption of >1 g tobacco per day), and exsmoker (smokers who had quit smoking at least 1 year before the examination). Body mass index was calculated as weight/height2 (kilograms/meters2). Men with systolic blood pressure ≥160 mm Hg and/or diastolic blood pressure ≥95 mm Hg or with ongoing pharmacological antihypertensive treatment were considered to be hypertensives.16 Blood samples were taken after an overnight fast and analyzed at the Department of Clinical Chemistry at Malmö University Hospital, which is attached to a recurrent standardization system.17 Diabetes mellitus was defined as venous glucose ≥6.7 mmol/L measured in whole blood or a history of antidiabetic medication.18 Hyperlipidemia was defined as being present in patients with serum cholesterol ≥6.5 mmol/L and/or serum triglycerides ≥2.3 mmol/L or in patients under current lipid-lowering drug treatment.19

Inflammation-Sensitive Proteins
An electroimmunosay method20 was used to assess plasma levels of fibrinogen (grams per liter), orosomucoid (α1-acid glucoprotein, grams per liter or percent), α1-antitrypsin (grams per liter or percent), haptoglobin (grams per liter), and ceruloplasmin (grams per liter); these plasma protein analyses are usually used in Swedish routine clinical practice to reflect inflammatory activity. Plasma levels of orosomucoid and α1-antitrypsin were in 2339 of the 6075 individuals expressed in terms of percentage of the concentration in a reference sample mixed from blood donors (Prof Emeritus Carl-Bertil Laurell, Department of Clinical Chemistry, Malmö University Hospital, personal communication, 1997).

Follow-Up
Mortality and cause of death were obtained from the Mortality Register at the Swedish National Bureau of Statistics. The autopsy rate during the follow-up period was ~40%. A CE was defined as an acute myocardial infarction or death due to ischemic heart disease, ie, codes 410 to 414 according to the International Classification of Diseases (ICD), 8th and 9th revisions. Nonfatal cases of myocardial infarction were retrieved via the Malmö Heart Infarction Register.21 Death due to CVD was defined in accordance with ICD codes 390 to 438. In men with >1 CE, only the first event was used for the analyses. Incidence of death and CE has been updated up to December 31, 1994. For all-cause mortality and CE, 97 457 and 96 687 person-years, respectively, were accumulated during a median follow-up time of 16.5 (range 0.14 to 20.3) years and 16.3 (range 0.02 to 20.3) years, respectively.

Statistical Analysis
SPSS was used for the statistical analyses.22 Correlation coefficients were computed between age and logarithmically transformed values of the levels of inflammation-sensitive plasma proteins. Differences regarding the distribution of clinical characteristics between fibrinogen quartiles were compared by ANCOVA after adjustment for age. The Mantel-Haenszel method was used for the evaluation of linear trends.

The Kaplan-Meier method,23 with the generalized Wilcoxon rank sum test, was used for the computation of all-cause mortality, death from CVDs, and CE-free survival rates in relation to levels of fibrinogen and of other inflammation-sensitive proteins, after their division into quartiles.

The Rothman pie model of causation24 was used to assess the interaction between fibrinogen and other inflammation-sensitive proteins. These analyses were limited to men belonging to the first or fourth fibrinogen quartiles. The 75th percentile was used as cutoff point for the definition of belonging to the top quartile of another protein(s).

The interaction effect was calculated as proposed by Rothman24 and Hallqvist et al.25 Interaction was measured with the synergy index (SI), which was defined as follows: SI=(RRQ4/Yes−1)/(RRQ4/No−1)+(RRQ4/ Yes−1), where RR indicates relative risk.26 An SI above unity means positive interaction or synergy; ie, an SI of 1 indicates no interaction, and an SI of 2 indicates an effect among those with combined exposure twice that expected from the additivity of effects.

The Cox proportional hazard model27 was used to estimate the influence of fibrinogen on all-cause mortality and deaths from CVD and CE. The lowest quartile (Q1) was used as reference group.

Adjustments were made for age only in the first model. In the second model, further adjustments were made for hypertension, diabetes mellitus, hyperlipidemia, and smoking. In the third model, adjustments were also made for body mass index, history of chronic bronchitis and recent respiratory infection, physical activity during leisure-time, and self-rated health. Age and body mass index were entered as continuous variables; all other variables were fitted as categorical data (yes or no).

The same Cox models were also used to estimate whether men who belonged to the first and fourth fibrinogen quartiles and at the same time also belonged to the top quartile of at least 1 of the other proteins had an increased all-cause and CVD mortality and CE rate after adjustment for potential confounders.

A similar Cox model was also used to estimate the influence of other inflammation-sensitive proteins on the fibrinogen-related incidence of CEs and deaths in men belonging to the top quartile of fibrinogen after adjustment for potential confounders. The fit of the proportional hazards model was confirmed by plotting the hazards function in the various fibrinogen quartiles and other groups over time. RR’s were computed as the antilogarithm of the coefficient.

Results

Baseline Characteristics
The baseline characteristics for the study population are shown in Table 1. Plasma levels of the other proteins as well as age, body mass index, blood pressure, lipid levels, and
The number of current smokers were increased in a dose-related manner from the lowest to the highest fibrinogen quartile. Self-rated good health was less common in men in the top fibrinogen quartile than in the 3 lower fibrinogen quartiles.

The covariances between proteins are shown in Table 2. There were statistically significant associations between all proteins. The strongest correlation, 0.56, was between orosomucoid and ceruloplasmin. Correlations with age did not exceed 0.12.

One third (n=472) of the men in the first fibrinogen quartile (Q1) had at least 1 of the other proteins in the top quartile. The opposite was found for those in the fourth fibrinogen quartile (Q4), in which almost every fifth man (n=337) did not belong to the highest quartile of any of the other proteins (Table 3).

**Mortality**
Six hundred fifty-three (10.7%) men died; 278 (42.6%) of these men died of CVDs, with 206 (74.6%) of these deaths attributed to ischemic heart disease, and another 211 (32.3%) men died of cancer. From the lowest to the highest quartile, there was for each measured protein (ie, fibrinogen, orosomucoid, α1-antitrypsin, haptoglobin, and ceruloplasmin) a stepwise increase in all-cause mortality, exemplified by fibrinogen with 4.3 (95% CI 3.6 to 5.3), 5.8 (95% CI 4.9 to 6.8), 6.3 (95% CI 5.3 to 7.4), and 10.2 (95% CI 9.0 to 11.5)

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**TABLE 1. Baseline Characteristics in Relation to Plasma Fibrinogen Level**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Quartiles of Fibrinogen Level</th>
<th>Age-Adjusted P</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Q1 (n=1486)</td>
<td>Q2 (n=1560)</td>
</tr>
<tr>
<td>Age, y</td>
<td>46.5±3.7</td>
<td>46.8±3.5</td>
</tr>
<tr>
<td>Inflammation-sensitive plasma proteins</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fibrinogen, g/L</td>
<td>2.56±0.31</td>
<td>3.20±0.15</td>
</tr>
<tr>
<td>Orosomucoid, g/L</td>
<td>0.70±0.16</td>
<td>0.77±0.17</td>
</tr>
<tr>
<td>α1-Antitrypsin, g/L</td>
<td>92.9±21.0</td>
<td>99.6±23.8</td>
</tr>
<tr>
<td>Haptoglobin, g/L</td>
<td>1.14±0.23</td>
<td>1.20±0.24</td>
</tr>
<tr>
<td>Ceruloplasmin, g/L</td>
<td>89.8±19.1</td>
<td>94.4±20.3</td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
<td>24.5±3.0</td>
<td>24.9±3.2</td>
</tr>
<tr>
<td>Blood pressure status</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systolic blood pressure, mm Hg</td>
<td>127.4±14.7</td>
<td>128.9±15.3</td>
</tr>
<tr>
<td>Diastolic blood pressure, mm Hg</td>
<td>86.3±9.8</td>
<td>86.8±9.6</td>
</tr>
<tr>
<td>Hypertension, %</td>
<td>23.1</td>
<td>24.3</td>
</tr>
<tr>
<td>Blood glucose status</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fasting whole blood glucose, mmol/L</td>
<td>4.9±0.9</td>
<td>4.9±0.9</td>
</tr>
<tr>
<td>Diabetes mellitus, %</td>
<td>2.2</td>
<td>2.4</td>
</tr>
<tr>
<td>Blood lipid status</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cholesterol, mmol/L</td>
<td>5.44±0.95</td>
<td>5.66±1.01</td>
</tr>
<tr>
<td>Triglycerides, mmol/L</td>
<td>1.25</td>
<td>1.31</td>
</tr>
<tr>
<td>Hyperlipidaemia, %</td>
<td>20.2</td>
<td>25.3</td>
</tr>
<tr>
<td>Smoking, %</td>
<td>34.8</td>
<td>43.0</td>
</tr>
<tr>
<td>Sedentary life-style during leisure time, %</td>
<td>54.6</td>
<td>54.4</td>
</tr>
<tr>
<td>Self-rated good health, %</td>
<td>75.1</td>
<td>73.7</td>
</tr>
<tr>
<td>History of chronic bronchitis or recent cold, %</td>
<td>7.0</td>
<td>6.9</td>
</tr>
</tbody>
</table>

Values are mean±SD or proportion unless otherwise stated. Triglycerides are median (range).
*See Methods for details.
deaths per 1000 person-years in the quartile in question (P<0.001 for trend). The corresponding mortality rates due to CVD in each fibrinogen quartile were 1.7 (95% CI 1.3 to 4.4), 2.6 (95% CI 2.0 to 3.4), 2.4 (95% CI 1.8 to 3.2), and 4.5 (95% CI 3.7 to 5.4), respectively (P<0.001 for trend).

The mortality rates and survival curves for men in the lowest (Q1) and highest (Q4) fibrinogen quartiles and at the same time either present (Yes) or absent (No) in the top quartile of at least 1 of the other proteins are shown in Table 3 and Figure 1. For the group Q4/Yes, the all-cause mortality rate was significantly higher than for men belonging to the group Q4/No (11.2 [95% CI 9.7 to 12.7] versus 6.8 [95% CI 4.8 to 9.4], respectively, per 1000 person-years; P<0.001; Table 3 and Figure 2). The same pattern was observed for men in the first (Q1) fibrinogen quartile (2.2 [95% CI 1.6 to 3.1] versus 4.0 [95% CI 2.7 to 5.8], respectively, per 1000 person-years; P<0.001).

**Multivariate Analysis**

The increased all-cause mortality and CVD mortality rates for men with fibrinogen levels ranked in the top (Q4) compared with the lowest fibrinogen quartile remained statistically significant in the multivariate analysis after adjustment for several possible confounders (Table 3). The increased CE rate for men in the Q4 fibrinogen quartile similarly remained statistically significant in the multivariate analysis after the introduction of the corresponding covariates.

The increased risk of CVD mortality and the CE rate associated with ≥1 other protein as well as fibrinogen being

### Table 3. Influence of Other Inflammation-Sensitive Proteins on Fibrinogen-Related Incidence of CEs (Myocardial Infarction and CHD Deaths) and Deaths

<table>
<thead>
<tr>
<th>Variable</th>
<th>Fibrinogen Q1</th>
<th>Fibrinogen Q4</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>None* (N=1014)</td>
<td>≥1* (N=472)</td>
</tr>
<tr>
<td>All deaths</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Deaths, n</td>
<td>55</td>
<td>50</td>
</tr>
<tr>
<td>Person-years</td>
<td>16 552</td>
<td>7570</td>
</tr>
<tr>
<td>Crude incidence/1000 person-years (95% CI)</td>
<td>3.30 (2.49–4.30)</td>
<td>6.61 (4.90–8.71)</td>
</tr>
<tr>
<td>RR</td>
<td>1.65 (1.11–2.44)</td>
<td>1.71 (1.12–2.63)</td>
</tr>
<tr>
<td>Adjusted (95% CI)‡</td>
<td>Reference</td>
<td>Reference</td>
</tr>
<tr>
<td>Adjusted (95% CI)†</td>
<td>1.25 (0.87–1.79)</td>
<td>1.50 (0.92–2.45)</td>
</tr>
<tr>
<td>CVD deaths</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Deaths, n</td>
<td>25</td>
<td>17</td>
</tr>
<tr>
<td>Person-years</td>
<td>16 500</td>
<td>7421</td>
</tr>
<tr>
<td>Crude incidence/1000 person-years (95% CI)</td>
<td>1.50 (0.97–2.22)</td>
<td>2.25 (1.31–3.60)</td>
</tr>
<tr>
<td>RR</td>
<td>Reference</td>
<td>Reference</td>
</tr>
<tr>
<td>Adjusted (95% CI)‡</td>
<td>1.25 (0.87–1.79)</td>
<td>1.50 (0.92–2.45)</td>
</tr>
<tr>
<td>Adjusted (95% CI)†</td>
<td>2.00 (1.10–3.93)</td>
<td>2.30 (1.43–3.71)</td>
</tr>
<tr>
<td>Myocardial infarction or CHD deaths</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Events, n</td>
<td>37</td>
<td>30</td>
</tr>
<tr>
<td>Person-years</td>
<td>16 500</td>
<td>7421</td>
</tr>
<tr>
<td>Crude incidence/1000 person-years (95% CI)</td>
<td>2.24 (1.58–3.09)</td>
<td>4.04 (2.73–5.77)</td>
</tr>
<tr>
<td>RR</td>
<td>Reference</td>
<td>Reference</td>
</tr>
<tr>
<td>Adjusted (95% CI)‡</td>
<td>1.25 (0.87–1.79)</td>
<td>1.50 (0.92–2.45)</td>
</tr>
<tr>
<td>Adjusted (95% CI)†</td>
<td>1.88 (1.15–3.06)</td>
<td>2.27 (1.54–3.35)</td>
</tr>
</tbody>
</table>

CHD indicates coronary heart disease.

*Additional inflammation-sensitive proteins, ie, orosomucoid, α₁-antitrypsin, haptoglobin, and/or ceruloplasmin, in upper quartile of distribution.

†Covariates included age, hypertension, diabetes mellitus, hyperlipidemia, smoking, body mass index, history of chronic bronchitis or recent cold, sedentary lifestyle during leisure time, and self-rated good health.

‡Covariates included age, fibrinogen level, hypertension, diabetes mellitus, hyperlipidemia, smoking, body mass index, history of chronic bronchitis or recent cold, sedentary lifestyle during leisure time, and self-rated good health.

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**Incidence of CEs**

There were 439 (7.2%) men with a CE. Of these, 79 (18.0%) suffered a fatal and 288 (65.6%) suffered a nonfatal myocardial infarction. Another 72 (16.4%) men died of chronic ischemic heart disease. The incidence of CE increased in a stepwise manner from the first to the fourth quartile of each protein and is exemplified by fibrinogen, with 2.8 (95% CI 2.2 to 3.6), 4.0 (95% CI 3.3 to 4.9), 4.3 (95% CI 3.5 to 5.3), and 7.2 (95% CI 6.1 to 8.3) CEs per 1000 person-years (P=0.003). The mortality among these 337 men in the group Q4/No was almost the same as for those 472 belonging to the group Q1/Yes (Table 3). The same pattern was observed for CVD mortality.
in the top quartile (Q4/Yes) remained after adjustment for other cardiovascular risk factors, with the fibrinogen level included (RR 2.1, 95% CI 1.1 to 3.9 and RR 1.9, 95% CI 1.2 to 3.1, respectively; Table 3).

Contribution of Other Inflammation-Sensitive Proteins to Predictive Value of Fibrinogen

As demonstrated in Table 3, the exposure from additivity of absolute effects, ie, the incidence rate of CEs and CVD mortality, and the RR excess among those men with combined exposure (Q4/Yes) exceeded the sum of the relative excess risks for men with each of the 2 component causes (Q4/No or Q1/Yes). The SI for CEs and CVD mortality was 1.9 and 4.1, respectively, indicating an effect among those with combined exposure 2-fold and 4-fold, respectively, that expected from additivity effects.

Discussion

Inflammation is part of the process that leads to the progression and rupture of atherosclerotic lesions.9,27 Leukocytes and cytokines30,29 are assumed to play key roles in this course, which may have been initiated by oxidized LDL cholesterol5,30 or by infectious agents, such as Chlamydia pneumoniae (also called TWAR), Helicobacter pylori, and cytomegalovirus.31–33

Various cytokines can induce the synthesis in the liver of proteins, which in the present study have been labeled inflammation-sensitive proteins.9,34–36 Our results are compatible with the view that these proteins may be involved in the development of atherosclerosis and its complications.

Although it has been demonstrated that atherosclerotic plaques may contain fibrinogen and C-reactive protein, it remains unclear whether these proteins are actually involved in the initial inflammatory process preceding the development of plaque.4–6,37 Baseline characteristics within the cohort illustrate the well-known fact that the groups with increased risk of CEs and death are associated with a number of risk modulators.

However, the increased risk of all-cause mortality and mortality from CVDs and CE for men in the top (Q4) fibrinogen quartile remained statistically significant even after adjustment for these possible confounders.

Because fibrinogen covaried with the use of tobacco, blood pressure, and blood lipids, one can assume that it also covaried with the prevalence and extension of atherosclerotic plaques. If this was the case, then differences of the incidence of myocardial infarction and death across fibrinogen quartiles may reflect differences with regard to the degree of atherosclerosis at baseline rather than the influence of fibrinogen on the occurrence of plaques and subsequent formation of thrombi. Although fibrinogen has a key role in this latter process, it seems unlikely that there would be a linear relationship between the probability of thrombotic complications and fibrinogen plasma levels.

If, as it has been claimed, atherosclerosis should be considered an inflammatory disease, associations may hypothetically reflect the inflammatory activity in the vessel wall. It should be stressed, however, that because several conditions and circumstances, ie, chronic inflammatory disorders, infections, trauma, and renal disease may influence the synthesis, release, and excretion of these proteins, it is very difficult to assess, in observational studies, the true nature of the relationship between these proteins and the occurrence of atherosclerosis and its complications. Because 25% of those who were invited to the health examination did not attend, it is not possible to assess whether the study cohort can be claimed to be representative of the corresponding population. However, the death rate for nonparticipants has been studied previously and was found to be more than twice the rate in participants.38 Therefore, it is reasonable to suppose that the RR figures in the present study underestimate the real risk of mortality and CE associated with levels of fibrinogen and the other proteins.

For each of the proteins studied, there was a wide distribution of individual values, and the mortality due to ischemic heart disease during the follow-up was close to the expected
rate. Because these men were, on average, only 47 years old at the time of the examination, one can furthermore conclude that they belong to birth-year cohorts in which very few men at the time of the invitation had died of myocardial infarction. We have in the analyses excluded men with a history of ischemic heart disease, stroke, and cancer.

The possibility of residual confounding is to be discussed. This project did not include the assessment of other chronic conditions (eg, rheumatoid arthritis, collagenosis, and vasculitis) that may influence the synthesis of inflammation-sensitive proteins and the end points used in the present study. However, the significantly increased risk of CE and CVD mortality remained for men in the group Q4/Yes after adjustment for self-rated health, which in this project, as well as in other studies, has been shown to be an independent marker of premature death and CVD.

All residents of the city of Malmö who require hospitalization for somatic disorders are admitted to the University Hospital. Registers have been established to monitor trends and patterns of mortality and the incidence of myocardial infarction and stroke. Vital status at the end of the follow-up period is updated by record linkage for all individuals. Approximately forty percent of the death certificates were based on autopsy. Hence, there is little reason to believe that the incidence of end points has been confounded by biased retrieval and ascertainment of cases. For the estimation of the levels of plasma proteins, a single blood test was taken once. How representative is this single test for correct quartile of the levels of plasma proteins, a single blood test was taken one. How representative is this single test for correct quartile classification? The electroimmunooassay method used for the quantitative estimation of plasma protein levels is a reliable analysis. Nevertheless, a possible source of misclassification is that (with the exception of albumin) most plasma proteins show intraindividual variations in concentration by a coefficient of variation of 15% to 20%. However, a random leveling out in both directions can be expected. Change of exposure is an inherent problem in long-term cohort studies. Screened participants with high blood pressure and high lipid levels were referred for further evaluation and treatment. Those who were smokers were advised to quit but were not offered any help to achieve this goal. Because all the major risk factors for CVD covaried with fibrinogen and the other inflammation-sensitive proteins, the effect of secondary prevention would be to reduce the incidence of disease in a reverse fashion; ie, those in the top quartiles should benefit the most.

Differences in CVD mortality between groups may be related to incidence and survival. The present study shows that fibrinogen and other inflammation-sensitive proteins have an influence on the incidence of ischemic heart disease. It remains to be evaluated to what extent the relationship with cardiovascular mortality can be explained by the influence on the immediate and long-term survival rates. Because there is only one hospital in the city to which patients with myocardial infarction and other acute conditions can be referred, it is unlikely that differences in survival are related to differences in treatment.

The incidence of CVD and death in this population-based cohort study covaried with plasma levels of fibrinogen. The influence was enhanced by exposure to high levels of 1 of the inflammation-sensitive proteins measured. Because the level of fibrinogen covaried with major risk factors for CVD, it is conceivable that there was a similar covariance with the prevalence and severity of atherosclerotic lesions. Further studies are needed to evaluate to what extent this potential confounder may have contributed to differences in the incidence of CVD and death observed across fibrinogen quartiles.

The curves illustrating survivors in each quartile show a similar pattern, with an early and obvious difference in incidences depending on whether men in the lowest (Q1) and the highest (Q4) fibrinogen quartile at the same time belong to the fourth quartile of any of the other proteins (Yes) or not (No). Surprisingly, the corresponding risks were approximately the same for men in the groups Q4/No and Q1/Yes. This phenomenon supports the hypothesis that the risk predicted by fibrinogen is modified by other plasma proteins.

The fairly strong covariance between at least some of these proteins makes it difficult to assess whether one has a stronger modifying effect than the others. It needs to be pointed out that the synthesis of these proteins may be triggered by agents that are not involved in the causation of atherosclerosis.

It is important to take the environmental influence of the fibrinogen level into consideration, and in the multivariate analysis, we have tried to adjust for such possible confounders. Furthermore, studies have found that up to 50% of the variation in plasma level may be hereditary. And in our opinion, levels of different inflammation-sensitive proteins perhaps should be valued together to get a better tool for detecting inflammatory activity. It is thereby possible to evaluate whether there are harmonic changes in the levels of different proteins, inasmuch as levels of separate proteins also vary from different factors other than inflammation, ie, hereditary, lifestyle, and environmental factors, among others.

It is our conclusion that the incidence of myocardial infarction and death predicted by plasma levels of fibrinogen is modified by its covariance with other inflammation-sensitive proteins. This lends support to the hypothesis that inflammation is also involved in the development of atherosclerosis and its complications.

References

Influence of Plasma Fibrinogen Levels on the Incidence of Myocardial Infarction and Death Is Modified by Other Inflammation-Sensitive Proteins: A Long-Term Cohort Study

P. Lind, B. Hedblad, L. Stavenow, L. Janzon, K. F. Eriksson and F. Lindgärde

doi: 10.1161/01.ATV.21.3.452
Arteriosclerosis, Thrombosis, and Vascular Biology is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 1079-5642. Online ISSN: 1524-4636

The online version of this article, along with updated information and services, is located on the World Wide Web at:
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