Fatality of Future Coronary Events Is Related to Inflammation-Sensitive Plasma Proteins

A Population-Based Prospective Plasma Proteins

Gunnar Engström, MD; Bo Hedblad, MD; Lars Stavenow, MD; Patrik Tydén, MD; Peter Lind, MD; Lars Janzon, MD; Folke Lindgärde, MD

Background—Approximately 40% of men suffering a first acute coronary event die the first day; most of them never reach hospital. It is largely unknown whether a low-grade inflammation in healthy men predicts the fatality of future coronary events.

Methods and Results—Five inflammation-sensitive plasma proteins (ISPs; fibrinogen, orosomucoid, α1-antitrypsin, haptoglobin, and ceruloplasmin) were measured in 6075 apparently healthy men, 680 of whom had a first coronary event [nonfatal myocardial infarction (MI) or death from coronary heart disease (CHD)] over a mean follow-up of 19 years. Of the 680 men who had a coronary event, 197 died the first day and 228 died within 28 days. Elevated ISPs were significantly associated with both nonfatal MI and CHD death, but the relative risks for CHD death were higher than for nonfatal MI. Among men who subsequently had a coronary event, the proportion of fatal events was related to the number of elevated ISPs at the baseline examination. The proportions who died the first day were 26%, 25%, 29%, and 35%, respectively, among men with 0, 1, 2, and ≥3 elevated ISPs (trend: P=0.01, adjusted for risk factors). The corresponding proportions who died within 28 days were 30%, 31%, 34%, and 38%, respectively (trend: P=0.03).

Conclusions—Men who have been exposed to a low-grade inflammation many years earlier have higher fatality in future coronary events, with a higher proportion of CHD deaths and less nonfatal MI. This relation should be regarded when inflammatory markers are considered for risk assessment in primary prevention. (Circulation. 2004;110:27-31.)

Key Words: inflammation ■ coronary disease ■ risk factors

Approximately 40% of men who suffer a first acute coronary event die within the first days, and most of them never reach hospital.1 Many prospective studies have reported an increased incidence of myocardial infarction (MI) or cardiovascular deaths in apparently healthy individuals with elevated levels of inflammation-sensitive plasma proteins (ISPs).2–6 Whether the severity of the events is worse among patients who previously have been exposed to a low-grade inflammation is unclear. A nested case-control study from the Multiple Risk Factor Intervention Trial (MRFIT) cohort suggested that raised levels of C-reactive protein (CRP) were associated with deaths from coronary heart disease (CHD) and not with nonfatal MI. However, the hypothesis of different relationships with fatal and nonfatal events was not tested, and events from the first years of follow-up were unavailable for the analysis. It is largely unknown whether markers of inflammation, measured in apparently healthy subjects, are associated with the prognosis of subsequent acute coronary events.

Studies of clinical samples, eg, patients hospitalized for MI or unstable heart disease, have reported associations between elevated plasma levels of various inflammatory markers and an adverse outcome.7–10 However, as many CHD deaths occur outside hospital, the inclusion of out-of-hospital deaths is an important prerequisite for a representative study of survival after acute coronary events.1

Previous studies from the population-based cohort “Malmö Preventive Study” have shown that the incidence of MI and stroke is increased in men with elevated plasma levels of fibrinogen, orosomucoid (α1-acid glucoprotein), α1-antitrypsin, haptoglobin, or ceruloplasmin, ie, 5 ISPs. Furthermore, the risk is gradually increased with cumulative number of elevated ISPs.2,11,12 The present study explored whether elevated ISPs at baseline were associated with fatal outcome in those who experienced a first coronary event over a mean follow-up of 19 years.

Methods

Complete birth cohorts from the city of Malmö, Sweden, were invited to a screening examination at the Department of Preventive Medicine in Malmö.2,13 A total of 24,444 men participated (attendance rate, 71%). Determination of 5 plasma proteins was part of the
program for 6193 men randomly selected from birth cohorts examined between 1974 and 1982. After exclusion of men with a history of MI, stroke, or cancer, 6075 men remained, with a mean age of 46.8 ± 3.7 years (range, 28 to 61 years). The health service authority of Malmö approved and funded the screening program. All participants gave informed consent.

Baseline Examinations
Subjects were categorized into smokers and nonsmokers. Smokers were categorized into consumers of <10 cigarettes per day, 10 to 19 cigarettes, and daily consumption of 20 cigarettes or more. Blood pressure (mm Hg) was measured twice in the right arm after a 10-minute rest. The average of 2 measurements was used. A sphygmomanometer and a rubber cuff of appropriate size were used. Use of antihypertensive medication was assessed in a questionnaire.

Blood samples were taken after an overnight fast. Serum cholesterol and triglyceride concentrations were analyzed with standard methods at the laboratory of the hospital.

Physical activity was assessed in a questionnaire. Men who reported that they were mostly sedentary in their spare time were considered to be physically inactive.

Inflammation-Sensitive Plasma Proteins
Electroimmunoassay was used to analyze the plasma levels of 5 sensitive plasma proteins (ISPs). The samples were analyzed consecutively at the time of screening. The precision of the analysis had a variation of <5%. The detection limits were 20 mg/L for ceruloplasmin, 50 mg/L for α1-antitrypsin, and 350 mg/L for orosomucoid, haptoglobin, and fibrinogen.

We have previously shown that all ISPs are associated with incidence of cardiovascular diseases, with largely the same relative risks for all individual ISPs. Moreover, the cardiovascular risk increases with the number of ISPs in the top quartile. In accordance with the previous studies, the sample was categorized according to the number of ISPs in the fourth quartile. The fourth quartiles were as follows: fibrinogen >4.0 g/L, orosomucoid >0.93 g/L, α1-antitrypsin >1.42 g/L, haptoglobin >1.76 g/L, and ceruloplasmin >0.36 g/L. The reliability in terms of internal consistency was fully adequate for this composite score, both in the entire cohort (Cronbach’s α = 0.65) and in the subgroup who subsequently had a coronary event (α = 0.64).

Follow-Up and Definition of End Points
At the baseline examination, none of the men had a history of MI according to self-report, the Malmö Myocardial Infarction Register, or the Swedish Hospital Discharge register. All men were followed up from the baseline examination until the first coronary event, death, or December 31, 1998.

A coronary event was defined as nonfatal MI (ICD-9 code 410) or death from CHD (ICD 410 to 414) in subjects with no previous clinical history of MI. The CHD deaths during the first day include those who died outside hospital or during the first day in hospital. CHD deaths within 28 days include out-of-hospital deaths and deaths within 28 days after hospitalization.

Of the 228 CHD deaths that occurred within 28 days, cause of death was based on autopsy in 157 patients (69%). Of the remaining 71, cause of death was based on examinations in-hospital before death for 56 patients, on findings from examinations outside hospital before death for 8 patients, and on other sources for 7 patients.

Of the 680 coronary events, 452 were nonfatal MI (ie, survived 28 days).

Statistics
ANOVA and Pearson’s χ² were used to study differences in risk factors between nonfatal MI and CHD deaths. A general linear model adjusted the blood pressure levels for the difference in age. Cox proportional-hazards regressions calculated adjusted relative risks of nonfatal MI and CHD deaths, respectively. The Kaplan-Meier test with the log-rank statistics tested the crude survival rates during the first days after a first acute coronary event. Logistic regression, with nonfatal MI versus CHD deaths as dependent variable, was used to adjust the relation between ISPs and fatal outcome for potential confounders. The probability values for trends were obtained by modeling the number of elevated ISPs as an ordinal variable. Blood pressure medication, diabetes, smoking, angina, and physical inactivity were modeled as categorical variables. All other covariates were modeled as continuous variables.

Results
Incidence of CHD Deaths and Nonfatal MI in Relation to ISPs
A total of 680 men experienced a first acute coronary event. The mean time between the examination and the coronary event was 12.9 ± 5.8 years. Of the 680 patients with coronary events, 197 (29%) died the first day and 228 (33.5%) died within 28 days. Incidence of CHD deaths (28 days) was 2.0 per 1000 person-years and for nonfatal MI, 3.9 per 1000 person-years.

The incidences of both CHD deaths and nonfatal MI showed highly significant relationships with the number of

### Table 1: Incidence of Nonfatal Myocardial Infarction and CHD Deaths in Relation to Number of Elevated ISPs in 6075 Apparently Healthy Men

<table>
<thead>
<tr>
<th>ISPs in the Top Quartile</th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>≥3</th>
<th>P for Trend</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of men</td>
<td>2449</td>
<td>1563</td>
<td>908</td>
<td>1155</td>
<td></td>
</tr>
<tr>
<td>CHD deaths at 28 days, n (%)</td>
<td>56 (2.3)</td>
<td>50 (3.2)</td>
<td>44 (4.8)</td>
<td>78 (6.8)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Per 1000 person-years</td>
<td>1.16</td>
<td>1.67</td>
<td>2.63</td>
<td>3.79</td>
<td></td>
</tr>
<tr>
<td>Age-adjusted RR</td>
<td>1.00</td>
<td>1.4 (0.99–2.1)</td>
<td>2.3 (1.5–3.4)</td>
<td>3.3 (2.4–4.7)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Risk factor–adjusted RR</td>
<td>1.00</td>
<td>1.2 (0.8–1.8)</td>
<td>1.7 (1.1–2.5)</td>
<td>2.3 (1.6–3.3)</td>
<td>&lt;0.00005</td>
</tr>
<tr>
<td>Nonfatal myocardial infarction, n (%)</td>
<td>128 (5.2)</td>
<td>110 (7.0)</td>
<td>87 (9.6)</td>
<td>127 (11.0)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Per 1000 person-years</td>
<td>2.64</td>
<td>3.68</td>
<td>5.20</td>
<td>6.17</td>
<td></td>
</tr>
<tr>
<td>Age-adjusted RR</td>
<td>1.00</td>
<td>1.4 (1.1–1.8)</td>
<td>2.0 (1.5–2.6)</td>
<td>2.4 (1.8–3.0)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Risk factor–adjusted RR</td>
<td>1.00</td>
<td>1.1 (0.8–1.4)</td>
<td>1.4 (1.05–1.8)</td>
<td>1.5 (1.1–1.9)</td>
<td>0.001</td>
</tr>
</tbody>
</table>

RR indicates relative risks from a Cox proportional-hazards model adjusted for age at baseline or risk factors (age, smoking, tobacco consumption, systolic blood pressure, blood pressure medication, body mass index, cholesterol, triglycerides, diabetes, physical inactivity, angina).
Fatality in Future Coronary Events in Relation to ISPs at Baseline

The Figure presents the mortality rates during the first days after the acute coronary event in relation to the number of elevated ISPs at the baseline examination. Among the 680 men who had an acute coronary event, the mortality was higher in those who previously had had 2 or ≥3 elevated ISPs.

After adjustments for potential confounders, the proportions of CHD deaths (first day or within 28 days) increased significantly with cumulative number of elevated ISPs at baseline (P = 0.01 and P = 0.03, respectively) (Table 3). The relation with CHD deaths within 28 days, however, was explained by increased mortality during day 1. Age at the coronary event (OR, 1.06 per year, P = 0.007) and diastolic blood pressure (OR, 1.03 per mm Hg, P = 0.03) were also significantly associated with CHD deaths (28 days) in the multiple logistic regression.

For all individual ISPs, the proportions of fatal outcomes tended to be higher for men in the top quartile than those in the first, second, or third quartile. After adjustment for risk factors, none of the individual ISPs showed a significant relationship with the proportion of CHD deaths (28 days) (not shown).

The relationships between number of elevated ISPs and the proportions of CHD deaths were analyzed separately in men who had an acute coronary event during the first 10 years after the screening examination (n = 214) and after >10 years (n = 466). For events during the first 10 years, there was no relation between the ISPs and the proportion of CHD deaths. For coronary events that occurred after >10 years of follow-up, the number of elevated ISPs was associated with an increased proportion of fatal outcomes that remained significant in the multivariate model (CHD deaths, first day: P for trend = 0.008; CHD deaths, 28 days: P = 0.03).

Discussion

The relation between elevated ISPs and an increased incidence of acute coronary events is now well established. Whether the fatality of the events is related to the previous exposure to a low-grade inflammation has been unclear. In the entire cohort, the relative risks were higher for CHD deaths than for nonfatal MI. Among men who subsequently had acute coronary events, the number of elevated ISPs at baseline showed significant associations with the proportions of fatal outcomes (first day or within 28 days). The individual ISPs showed nonsignificant differences between CHD deaths and nonfatal MI. However, in accordance with many previous studies, the prognostic information increased substantially if all 5 ISPs were used.2,11,12,15 The results show that men who have been exposed to a low-grade inflammation many years earlier have higher fatality in future acute coronary events, with a higher proportion of CHD deaths and less nonfatal MI. If this finding can be replicated in other population-based studies, this is another argument for using markers of inflam-
tivity, 21 diabetes, 23 and smoking 20 are factors that have been cardiovascular risk factors. Hypertension, 20 the prognosis after MI in relation to the previous exposure to inflammation in unstable coronary plaque and the effects of the myocardial ischemia on the degree of inflammation could contribute to these relationships. Elevated ISPs, measured many years before the coronary events, were associated with a higher proportion of CHD deaths in the present study. If inflammation in unstable coronary plaque was the main cause for the relationships between elevated ISPs and fatal outcome, it could be assumed that the relationships would be strongest during the first years of follow-up. However, the relationship persisted after the exclusion of events that occurred during the first 10 years after the screening examination. The results show that the relation between elevated ISPs and an adverse outcome is not limited to the time at which clinical disease has been established.

Treatment and care of patients with acute MI has been improved during the past few decades, which has increased the short- and long-term survival among patients who reach hospital. 19 Few population-based studies have investigated the prognosis after MI in relation to the previous exposure to cardiovascular risk factors. Hypertension, 20–22 physical inactivity, 21 diabetes, 23 and smoking 20 are factors that have been associated with increased case-fatality. However, the results from previous studies are not fully consistent.

Size and location of the infarction and ventricular electrical instability are well-known prognostic markers among those who survive the acute phase. Whether the relation between previous exposure to a low-grade inflammation and the increased proportion of fatal outcomes is mediated through these factors is, for obvious reasons, almost impossible to study in population-based settings that include out-of-hospital deaths. We can only speculate about the causal relationships. Men with high ISPs could have a predisposition for developing unstable coronary plaque with infiltrates of inflammatory cells, which could cause coronary events of a greater severity. It is also possible that elevated ISPs are associated with an increased incidence of other risk factors, eg, hypertension and diabetes, 15,24 that could increase the risk of fatal outcome. Yet another possibility is that elevated ISPs are associated with deaths caused by ventricular arrhythmia. Elevated ISPs have been associated with an increased incidence of hypertension, 15 which could cause left ventricular hypertrophy and ventricular arrhythmia. Raised CRP levels have been associated with atrial fibrillation. 25 Inflammation could facilitate electrical remodeling in men with arrhythmia. 26,27 The increased mortality in men who had had elevated ISPs was apparent even during the first day, which suggests that elevated ISPs are associated with an increased proportion of sudden cardiac deaths. Unfortunately, we do not know whether the increased mortality already occurred during the first hour after onset of symptoms.

All men in this study were without a history of MI at the screening examination, according to self-report and local and national registers of hospitalized MIs. All the acute coronary events in this study were thus first clinically apparent events. However, it has been shown that many MIs are unrecognized. 28 As no ECG recordings were performed at the baseline examination, we do not know whether some men had had a silent MI.

A validation study from the National Hospital Discharge Register has shown that the diagnosis “myocardial infarction” is false in only 5% of the patients. 17 The autopsy rates are very high, particularly for those who died outside hospital. There is no reason to suspect any bias with respect to case-retrieval in the different categories of ISPs.

The laboratory tests were performed at the time of screening, and the measurements are limited to those available in clinical practice at that time. No data on fractions of cholesterol were available. However, in accordance with previous studies, 20,21 neither cholesterol nor triglycerides were associated with the proportion of CHD deaths in this study. CRP is another analysis that was unavailable at that time. Many previous studies have shown that CRP and the ISPs in this
study show similar associations with development of cardiovascular disease and cardiovascular risk factors. Although the relation between inflammation and the proportions of fatal outcomes has not been shown for CRP, a nested case-control study from the MRFIT cohort suggests that this could be true for CRP as well.

In the entire cohort, the relative risks among men with high ISPs were higher for CHD deaths than for nonfatal MI. Although this relation needs to be replicated in other population-based studies, it should be regarded when inflammatory markers are considered for risk assessment in primary prevention.

Acknowledgments

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References

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