Effects of Cholesterol and Inflammation-Sensitive Plasma Proteins on Incidence of Myocardial Infarction and Stroke in Men

G. Engström, MD, PhD; P. Lind, MD; B. Hedblad, MD, PhD; L. Stavenow, MD, PhD; L. Janzon, MD, PhD; F. Lindgärde, MD, PhD

Background—Although cholesterol is a major cardiovascular risk factor, its association with stroke remains controversial. This study explored whether the cholesterol-related incidence of stroke and myocardial infarction is modified by plasma markers of inflammation in a large, population-based cohort with a long follow-up.

Methods and Results—Plasma cholesterol and 5 inflammation-sensitive plasma proteins (ISP) (fibrinogen, $\alpha_1$-antitrypsin, haptoglobin, ceruloplasmin, and orosomucoid) were determined in 6063 healthy men, 28 to 61 years of age. The incidence of stroke, cardiac events (fatal and nonfatal), and cardiovascular deaths was compared between groups defined by levels of cholesterol and ISP. Mean follow-up was 18.7 years. High ISP level was defined as 2 to 5 ISP in the top quartile. High cholesterol was associated with higher levels of ISP. Hypercholesterolemia ($\geq$6.5 mmol/L, 251 mg/dL) was associated with an increased incidence of ischemic stroke and cardiac events and with a reduced incidence of intracerebral hemorrhage. The ISP levels modified these associations. After risk factor adjustment, men with hypercholesterolemia and high ISP levels had a significantly higher risk of cardiovascular death (relative risk [RR] = 2.4; CI, 1.8 to 3.3), cardiac events (RR = 2.3; CI, 1.8 to 3.0), and ischemic stroke (RR = 2.1; CI, 1.4 to 3.3) than men with normal cholesterol and low ISP levels. In the absence of high ISP levels, hypercholesterolemia was associated with a moderately higher risk of cardiovascular death (RR = 1.4; CI, 1.0 to 2.0) and cardiac events (RR = 1.5; CI, 1.2 to 1.9) but not significantly with ischemic stroke (RR = 1.25; CI, 0.8 to 2.0).

Conclusions—Hypercholesterolemia is associated with high plasma levels of ISP. These proteins increase the cholesterol-related incidence of cardiovascular diseases. In the absence of elevated ISP levels, no statistically confirmed association was found between hypercholesterolemia and ischemic stroke. (Circulation. 2002;105:2632-2637.)

Key Words: stroke ■ myocardial infarction ■ cholesterol ■ inflammation ■ epidemiology

Even though hypercholesterolemia is a major cardiovascular risk factor, epidemiological studies have not found any consistent relation between cholesterol and incidence of stroke.1–5 Yet in clinical trials of patients with cardiovascular diseases, incidence of both stroke and myocardial infarction has been reduced by treatment with statins.6,7 To what extent the reduced incidence of stroke is related to the lipid-lowering or the anti-inflammatory effects of statins is controversial.4–6

It has been demonstrated that plasma levels of fibrinogen and other inflammation-sensitive plasma proteins (ISP), that is, components of the acute and chronic inflammatory response, are associated with incidence of myocardial infarction8–14 and stroke.9,15,16 Furthermore, the probability of myocardial infarction among men with high total cholesterol is significantly increased by, in relative terms, raised levels of C-reactive protein13,14 or fibrinogen.17 However, few population-based studies have studied whether ISP modify the relation between plasma cholesterol and incidence of myocardial infarction. To our knowledge, there are no published studies with regard to incidence of stroke. The objective in this study has been to compare the incidence of myocardial infarction, stroke, and death between groups defined in terms of plasma levels of total cholesterol, fibrinogen, haptoglobin, orosomucoid, $\alpha_1$-antitrypsin, and ceruloplasmin.

Methods

Between 1974 and 1983, 22 444 men participated in a screening program for detection of individuals with high risk for cardiovascular diseases.18 Participation rate was 71%. The 5 plasma proteins were consecutively determined for 6193 men, 28 to 61 years of age, selected at random and corresponding to 30% of the cohort. Men with a history of myocardial infarction, stroke, or cancer (according to questionnaire) were excluded. Of the remaining 6075 men, information on plasma cholesterol was available in 6063.
The health service authority of Malmö approved 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 $\geq$20 cigarettes.

Blood pressure (mm Hg) was measured twice in the right arm after a 10-minute rest. The average of two measurements was used. A sphygmomanometer and a rubber cuff of appropriate size were used. The use of antihypertensive medication was assessed in a questionnaire.

Blood samples were taken after an overnight fast and analyzed at the Department of Clinical Chemistry at Malmö University Hospital. Plasma cholesterol concentrations were analyzed with standard methods at the laboratory. Hypercholesterolemia was defined as cholesterol $\geq$6.5 mmol/L ($\geq$251 mg/dL) according to the national guidelines for treatment of hyperlipidemia.

Blood glucose was analyzed with a hexokinase method. Men with a fasting whole blood glucose $\geq$6.7 mmol/L and men who reported treatment for diabetes were considered diabetic.

Body mass index (BMI) was calculated as weight/height$^2$ (kg/m$^2$).

Inflammation-Sensitive Plasma Proteins

Electroimmunoassay was used to assess the plasma levels of 5 ISP. We have previously shown that the proteins are highly correlated and that the cardiovascular risk increases with the number of ISP in the top quartile. The sample was therefore categorized into those who had 2 to 5 ISP in the top quartile (high ISP levels) and those with 0 to 1 ISP in the top quartile (low ISP levels). High ISP levels were thus defined as at least two of the following criteria: fibrinogen $\geq$4.0 g/L, haptoglobin $\geq$1.76 g/L, ceruloplasmin $\geq$0.36 g/L, orosomucoid ($\alpha_1$-glucoprotein) $\geq$0.94 g/L, and $\alpha_1$-antitrypsin $\geq$1.43 g/L.

Follow-Up

All cases were followed from the baseline examination until death or December 31, 1997. Information on cause of death was retrieved from the Swedish Causes of Deaths register. Cause of death was based on autopsy in $\approx$40%. A cardiac event was defined as fatal or nonfatal myocardial infarction (code 410) according to the International Classification of Diseases, 9th revision, ICD-9) or death caused by chronic ischemic heart disease (ICD-9 codes 412 to 414). In men with more than one cardiac event, only the first event was counted. New cases of nonfatal myocardial infarction were retrieved from the Malmö Myocardial Infarction Register. Stroke was defined as cases coded 430 (subarachnoid hemorrhage), 431 (intra-cerebral hemorrhage), 434 (ischemic stroke), or 436 (unspecified stroke) according the ICD-9. The Malmö Stroke Register, which since 1989 continuously has searched for and validated patients with stroke, was used for case retrieval. Cases of stroke that occurred before 1989 were retrieved from the administrative register of the university hospital and validated by review of medical records with the use of the same procedure as the Malmö Stroke Register. CT scans were available for 172 (of 204) of the strokes that occurred in the city of Malmö. The National Hospital Discharge Register was used for retrieval of cases ($n=34$) that moved out from the city of Malmö. These diagnoses are based on the doctor’s diagnosis at the time of hospital discharge. The unspecified and ischemic strokes were analyzed together, since the number of unspecified strokes was small and it could be assumed that few of them were hemorrhagic.

Statistics

ANOVA and logistic regression was used to study the relations between plasma cholesterol and ISP levels. ANCOVA was used to compare cholesterol levels in categories of ISP and to calculate adjusted mean values. Cox proportional hazards model was used to analyze the event rates in categories of cholesterol and ISP with adjustment for potential confounders. Survival plots of the different risk factor categories confirmed the fit of the proportional hazards model.

Results

Cholesterol in Relation to ISP

The baseline characteristics of the study cohort are presented in Table 1. High plasma cholesterol was associated with

<table>
<thead>
<tr>
<th>Table 1: Baseline Characteristics of the Study Cohort</th>
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</thead>
<tbody>
<tr>
<td>Mean age, y</td>
</tr>
<tr>
<td>Smokers, %</td>
</tr>
<tr>
<td>$&gt;$20 Cigarettes/d, %</td>
</tr>
<tr>
<td>BMI, kg/m$^2$</td>
</tr>
<tr>
<td>Systolic BP, mm Hg</td>
</tr>
<tr>
<td>Diastolic BP, mm Hg</td>
</tr>
<tr>
<td>Cholesterol, mmol/L</td>
</tr>
<tr>
<td>Triglycerides, mmol/L</td>
</tr>
<tr>
<td>Diabetes, %</td>
</tr>
<tr>
<td>Physical inactivity, %</td>
</tr>
<tr>
<td>Fibrinogen, g/L</td>
</tr>
<tr>
<td>$\alpha_1$-Antitrypsin, g/L</td>
</tr>
<tr>
<td>Haptoglobin, g/L</td>
</tr>
<tr>
<td>Orosomucoid, g/L</td>
</tr>
<tr>
<td>Ceruloplasmin, g/L</td>
</tr>
</tbody>
</table>

Values are mean±SD or %.

<table>
<thead>
<tr>
<th>Table 2: Levels of Inflammation-Sensitive Plasma Proteins in Relation to Cholesterol</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cholesterol, mmol/L</td>
</tr>
<tr>
<td>---------------------</td>
</tr>
<tr>
<td>Fibrinogen, g/L</td>
</tr>
<tr>
<td>Haptoglobin, g/L</td>
</tr>
<tr>
<td>Ceruloplasmin, g/L</td>
</tr>
<tr>
<td>Orosomucoid, g/L</td>
</tr>
<tr>
<td>$\alpha_1$-Antitrypsin, g/L</td>
</tr>
<tr>
<td>Two or more proteins</td>
</tr>
</tbody>
</table>

4.5 mmol/L=173 mg/dL, 5.5 mmol/L=212 mg/dL, and 6.5 mmol/L=251 mg/dL.
higher concentrations of ISP (Table 2). Furthermore, the cholesterol levels increased with increasing number of ISP in the top quartile (Figure 1). After adjustment for age, BMI, systolic blood pressure, blood pressure medication, diabetes, smoking, and tobacco consumption, the mean (±SEM) cholesterol levels increased from 5.62±0.02 mmol/L (≈217 mg/dL) among men without any protein in the top quartile to 5.82±0.04 mmol/L (≈225 mg/dL) among men who had 4 or 5 proteins in the top quartile (P for trend=0.002).

Mortality, Stroke, and Cardiac Events
A total of 915 men (15%) died during the follow-up, 375 (41%) of them of cardiovascular diseases (ICD-9 codes 390 to 448). Of the 611 (10%) men who had cardiac events, 274 died within 28 days. Two hundred thirty-eight (3.9%) men had a stroke, 9 a subarachnoid hemorrhage, 29 an intracerebral hemorrhage, 170 an ischemic stroke, and 30 cases were unspecified.

High cholesterol levels were associated with increased incidences of myocardial infarction and cardiovascular deaths. Ischemic stroke showed a positive nonlinear relation with cholesterol. An inverse relation was found for intracerebral hemorrhage (Table 3). Hypercholesterolemia (≥6.5 mmol/L) was significantly associated with incidence of ischemic stroke (relative risk [RR]=1.50; CI, 1.10 to 2.05), cardiac events (RR=1.51; CI, 1.27 to 1.80), and cardiovascular death (RR=1.48; CI, 1.18 to 1.85) after adjustments for smoking, systolic blood pressure, triglycerides, age, BMI, blood pressure medication, physical inactivity, diabetes, and tobacco consumption. Hypercholesterolemia was not associated with incidence of stroke of all subtypes (RR=1.26; CI, 0.94 to 1.70) or all-cause death (RR=1.08; CI, 0.92 to 1.26) in this model.

For all ISP, a concentration in the top quartile was associated with an increased risk (Table 4). The risk increased with number of elevated ISP.

Event Rates in Relation to Categories of Cholesterol and ISP Levels
The men were categorized into groups with normal cholesterol and hypercholesterolemia (≥6.5 mmol/L, 251 mg/dL) and groups with 0 to 1 or 2 to 5 ISP in the top quartile (low versus high ISP levels) (Table 5). The highest incidence of stroke, cardiac events, and cardiovascular deaths was found among those who had hypercholesterolemia and high ISP levels. The increased risk in that group remained statistically significant after adjustments for several potential confounders (Table 5, Figure 2). There was a nonsignificant tendency for higher rates of intracerebral hemorrhage in men with normal cholesterol and high ISP levels.

Separate Analysis of Men With Low ISP Levels
To study whether hypercholesterolemia is a risk factor in the absence of high ISP levels, a separate analysis was performed for men with 0 to 1 ISP in the top quartile. Because the proportion with one ISP in the top quartile was somewhat lower in the group with normal cholesterol (38% versus...
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combination with two or more ISP in the top quartile had a hypercholesterolemia. Men with hypercholesterolemia in proteins aggravated the cardiovascular risk associated with was also associated with increasing ISP levels, and these increased incidence of cardiac events. However, cholesterol expected, hypercholesterolemia was associated with an in-

Cholesterol was positively associated with ischemic stroke and cardiac events, and cardiovascular death. The risk was only moderately increased if hypercholesterolemia occurred in the absence of high ISP levels. Hence, the ISP levels should be taken into account when assessing the prognostic significance of hypercholesterolemia.

The absence of a strong relation between plasma cholesterol and incidence of stroke has been a paradox in cardiovascular epidemiology. Several explanations have been proposed, for example, the heterogeneity of the stroke disease, differences between study populations with regard to cholesterol levels, competing cardiovascular deaths, too-short follow-up periods, and small numbers in the studies.1 According to our results, the stroke risk associated with hypercholesterolemia depends on whether or not ISP levels are elevated. We can only speculate about the reasons for this. It has been suggested that inflammation may reduce plaque stability and increase thrombogenesis.23–26 It is possible that embolism from rupturing atherosclerotic plaques occur more

TABLE 4. Age-Adjusted Relative Risks (95% CI) for Cardiac Events, Stroke, and Cardiovascular Death in Relation to Quartiles of Inflammation-Sensitive Proteins

<table>
<thead>
<tr>
<th>Protein</th>
<th>Cardiac Events</th>
<th>Stroke</th>
<th>CVD Mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fibrinogen</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Q1 (&lt;3.0 g/L)</td>
<td>1.0</td>
<td>1.0</td>
<td>1.0</td>
</tr>
<tr>
<td>Q2 (3.0–3.46 g/L)</td>
<td>1.3 (0.98–1.6)</td>
<td>1.1 (0.76–1.7)</td>
<td>1.4 (1.0–2.0)</td>
</tr>
<tr>
<td>Q3 (3.47–3.99 g/L)</td>
<td>1.3 (1.0–1.7)</td>
<td>1.4 (0.95–2.1)</td>
<td>1.2 (0.85–1.7)</td>
</tr>
<tr>
<td>Q4 (&gt;3.99 g/L)</td>
<td>2.3 (1.8–2.9)</td>
<td>1.9 (1.3–2.7)</td>
<td>2.5 (1.8–3.4)</td>
</tr>
<tr>
<td>Haptoglobin</td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Q1 (&lt;0.89 g/L)</td>
<td>1.0</td>
<td>1.0</td>
<td>1.0</td>
</tr>
<tr>
<td>Q2 (0.90–1.29 g/L)</td>
<td>1.2 (0.95–1.5)</td>
<td>1.1 (0.76–1.6)</td>
<td>1.2 (0.87–1.7)</td>
</tr>
<tr>
<td>Q3 (1.30–1.75 g/L)</td>
<td>1.4 (1.1–1.7)</td>
<td>1.4 (0.98–2.1)</td>
<td>1.5 (1.1–2.1)</td>
</tr>
<tr>
<td>Q4 (&gt;1.75 g/L)</td>
<td>2.0 (1.6–2.5)</td>
<td>1.9 (1.3–2.7)</td>
<td>2.0 (1.5–2.7)</td>
</tr>
<tr>
<td>Ceruloplasmin</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Q1 (&lt;0.26 g/L)</td>
<td>1.0</td>
<td>1.0</td>
<td>1.0</td>
</tr>
<tr>
<td>Q2 (0.27–0.30 g/L)</td>
<td>1.4 (1.1–1.7)</td>
<td>1.3 (0.90–1.9)</td>
<td>1.4 (0.98–1.9)</td>
</tr>
<tr>
<td>Q3 (0.31–0.35 g/L)</td>
<td>1.4 (1.1–1.8)</td>
<td>1.4 (0.94–2.0)</td>
<td>1.5 (1.1–2.1)</td>
</tr>
<tr>
<td>Q4 (&gt;0.35 g/L)</td>
<td>2.1 (1.6–2.6)</td>
<td>2.0 (1.4–3.0)</td>
<td>2.2 (1.6–3.1)</td>
</tr>
<tr>
<td>Orosomucoid</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Q1 (&lt;0.67 g/L)</td>
<td>1.0</td>
<td>1.0</td>
<td>1.0</td>
</tr>
<tr>
<td>Q2 (0.67–0.79 g/L)</td>
<td>1.5 (1.2–2.0)</td>
<td>1.0 (0.71–1.5)</td>
<td>1.5 (1.0–2.0)</td>
</tr>
<tr>
<td>Q3 (0.80–0.93 g/L)</td>
<td>2.0 (1.5–2.6)</td>
<td>1.3 (0.90–2.0)</td>
<td>1.7 (1.2–2.4)</td>
</tr>
<tr>
<td>Q4 (&gt;0.93 g/L)</td>
<td>2.7 (2.1–3.4)</td>
<td>1.8 (1.3–2.6)</td>
<td>3.0 (2.2–4.0)</td>
</tr>
<tr>
<td>α1-Antitrypsin</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Q1 (&lt;1.09 g/L)</td>
<td>1.0</td>
<td>1.0</td>
<td>1.0</td>
</tr>
<tr>
<td>Q2 (1.0–1.27 g/L)</td>
<td>1.3 (0.99–1.7)</td>
<td>1.1 (0.76–1.6)</td>
<td>1.1 (0.78–1.5)</td>
</tr>
<tr>
<td>Q3 (1.28–1.42 g/L)</td>
<td>1.7 (1.3–2.1)</td>
<td>0.99 (0.67–1.5)</td>
<td>1.4 (1.0–2.0)</td>
</tr>
<tr>
<td>Q4 (&gt;1.42 g/L)</td>
<td>2.3 (1.8–2.9)</td>
<td>1.3 (0.89–1.8)</td>
<td>2.2 (1.7–3.0)</td>
</tr>
<tr>
<td>No protein in top Q (n=2443)</td>
<td>1.0</td>
<td>1.0</td>
<td>1.0</td>
</tr>
<tr>
<td>One protein in top Q (n=1563)</td>
<td>1.5 (1.2–1.8)</td>
<td>1.2 (0.87–1.7)</td>
<td>1.6 (1.2–2.1)</td>
</tr>
<tr>
<td>Two proteins in top Q (n=904)</td>
<td>2.2 (1.8–2.8)</td>
<td>1.8 (1.2–2.6)</td>
<td>2.2 (1.6–3.1)</td>
</tr>
<tr>
<td>Three proteins in top Q (n=588)</td>
<td>2.5 (1.9–3.3)</td>
<td>2.1 (1.4–3.2)</td>
<td>2.9 (2.1–4.0)</td>
</tr>
<tr>
<td>Four or five proteins in top Q (n=565)</td>
<td>3.1 (2.4–4.0)</td>
<td>2.1 (1.3–3.1)</td>
<td>3.6 (2.7–5.0)</td>
</tr>
</tbody>
</table>

Q indicates quartile.

45%), further adjustment was made for this difference. Men with hypercholesterolemia had higher rates of cardiovascular death (RR=1.42; CI, 1.00 to 2.0) and cardiac events (RR=1.51; CI, 1.16 to 1.96) than men with normal cholesterol levels, adjusted for potential confounders. No significant relation between hypercholesterolemia and all-cause death (RR=1.09; CI, 0.87 to 1.36), stroke (all subtypes: RR=1.06; CI, 0.69 to 1.64), or ischemic stroke (RR=1.25; CI, 0.79 to 1.97) was observed in the absence of high ISP levels.

Discussion
Cholesterol was positively associated with ischemic stroke and inversely associated with intracerebral hemorrhage. As expected, hypercholesterolemia was associated with an increased incidence of cardiac events. However, cholesterol was also associated with increasing ISP levels, and these proteins aggravated the cardiovascular risk associated with hypercholesterolemia. Men with hypercholesterolemia in combination with two or more ISP in the top quartile had a substantially increased risk of ischemic stroke, cardiac events, and cardiovascular death. The risk was only moderately increased if hypercholesterolemia occurred in the absence of high ISP levels. Hence, the ISP levels should be taken into account when assessing the prognostic significance of hypercholesterolemia.

The absence of a strong relation between plasma cholesterol and incidence of stroke has been a paradox in cardiovascular epidemiology. Several explanations have been proposed, for example, the heterogeneity of the stroke disease, differences between study populations with regard to cholesterol levels, competing cardiovascular deaths, too-short follow-up periods, and small numbers in the studies.1 According to our results, the stroke risk associated with hypercholesterolemia depends on whether or not ISP levels are elevated. We can only speculate about the reasons for this. It has been suggested that inflammation may reduce plaque stability and increase thrombogenesis.23–26 It is possible that embolism from rupturing atherosclerotic plaques occur more
tumor necrosis factor-α has been reported that proinflammatory cytokines, such as interleukin-1, increase the binding of LDL to the endothelium. It is, however, noteworthy that the incidence of intracerebral hemorrhage tended to be higher among those with high ISP levels. The small number of cases with intracerebral hemorrhage, further studies are needed to establish the relations with ISP levels. It is, however, noteworthy that the incidence of intracerebral hemorrhage tended to be higher among those with high ISP levels.

The additive or synergistic effects of cholesterol and ISP could hence reflect factors that accelerate the progression of atherosclerosis in individuals with hypercholesterolemia. The incidence of intracerebral hemorrhage was inversely associated with cholesterol. This adds further evidence to the hypothesis that ischemic stroke and intracerebral hemorrhage are differently related to cholesterol. Hence, the additive or synergistic effect on incidence of stroke has, to our knowledge, not been reported previously. Clinical trials among patients treated with statins after a myocardial infarction have reported a reduced incidence of stroke. Besides the reduction of plasma lipids, statins have been associated with anti-inflammatory effects. It was recently reported that treatment with statins might prevent coronary events among individuals with relatively low lipid levels and high levels of C-reactive protein. Whether the anti-inflammatory effects explain the reduced incidence of stroke and whether statins reduce the stroke incidence among patients with high ISP levels and relatively low cholesterol remain to be evaluated.

The large number of end points, the long follow-up time, and the possibility of studying ischemic strokes separately are strengths of the study. A limitation is that no information was available on the period of time from diagnosis of atherosclerosis to the start of statin treatment or the number of statins prescribed. The number of deaths was corrected for age and sex, which could influence the results. The number of deaths and the number of events could not be corrected for smoking or physical inactivity. The large number of end points, the long follow-up time, and the possibility of studying ischemic strokes separately are strengths of the study. A limitation is that no information was available on the period of time from diagnosis of atherosclerosis to the start of statin treatment or the number of statins prescribed.
available about the subfractions of cholesterol. HDL-cholesterol has been associated with reduced risk of ischemic stroke, and we do not know whether the HDL levels differed between the groups. However, the LDL-to-HDL ratio is strongly related to the triglyceride levels, and the associations persisted after adjustments for triglycerides.

The assessment of the ISP concentrations with electroimmunoassay is an established and reliable method. However, the concentrations of ISP and cholesterol were based on a single blood test, and the intraindividual variation is a possible source of misclassification. A random intraindividual variation would, if anything, bias the result toward negative findings.

Change of exposure is another cause of bias in longitudinal studies. Men with high blood pressure and high lipid levels were referred for further evaluation and treatment. Smokers were advised to quit but were not offered any help to do so. Because these risk factors were more common among men with high ISP levels, they would benefit most from the interventions.

It is concluded that hypercholesterolemia is associated with high plasma levels of ISP. These proteins increase the cholesterol-related incidence of ischemic stroke and myocardial infarction.

Acknowledgments
This study was supported by grants from the Swedish Council for Social Research, the Stohne Foundation, the Segerfalk Foundation, and the Åke Wiberg Foundation.

References
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