Serum Lipids and Apolipoprotein Levels in Women with Acute Myocardial Infarction

Saga Johansson, Göran Bondjers, Gunnar Fager, Hans Wedel, Alecka Tsipogianni, Sven-Olof Olofsson, Anders Vedin, Olle Wiklund, and Claes Wilhelmsson

In this study covering more than 150,000 person-years from women younger than 55 years of age, 61 survived a first acute myocardial infarction (AMI). Of these, 59 were compared with a random sample from the same population regarding serum lipids and apolipoproteins (apo) A-I, A-II, B, and E, as well as several other cardiovascular risk factors. Mean values of serum cholesterol, triglycerides, apo B, and apo E were significantly higher and high density lipoprotein cholesterol and apo A-I were significantly lower among patients with infarction than among controls. Those who sustained and survived an AMI more often had a history of hypertension and of tobacco smoking than did the controls. Cigarette smoking, a history of hypertension, age, high serum triglycerides and apo E, as well as low levels of apo A-I, were independently and significantly associated with infarction. Sixty percent of the cases and 11% of the controls were distributed in the highest quartile of risk. A major contribution to the association with AMI was accounted for by the conventional risk factors, cigarette smoking and hypertension, as well as high serum triglycerides. In this group of relatively young women, high serum triglycerides were strongly associated with infarction, while levels of serum cholesterol were not. (Arteriosclerosis 8:742-749, November/December 1988)

In men, as well as in women, smoking, hypertension, high levels of serum cholesterol and triglycerides, and low levels of high density lipoprotein (HDL) cholesterol have been associated with acute myocardial infarction (AMI).

Among women, serum cholesterol independently contributed to the risk of coronary heart disease (CHD), particularly at a young age. Serum triglycerides, mainly investigated in women older than 50 years of age, were positively correlated with CHD by univariate analyses, but not unequivocally by multivariate analyses. HDL cholesterol was negatively associated with risk, even when the levels of serum cholesterol and triglycerides were taken into account.

It has been argued that the protein moieties of lipoproteins (the apolipoproteins) may be more sensitive indicators of CHD risk than the lipid moieties. Among men, apolipoprotein (apo) A-I or apo A-II independently differentiated between infarction survivors and controls, even when lipids were accounted for. In a recent case control study, high levels of apo B in men was the single best discriminator of AMI.

Since there is reason to expect correlations between several apolipoproteins, lipids, and other risk factors in women to be similar to those observed in men, the analyses of the associations with AMI require multivariate statistics.

The aim of this study was to determine simultaneously serum cholesterol and triglyceride levels, HDL cholesterol levels, levels of apolipoproteins A-I, A-II, B, and E, together with other risk factors in a population-based study of AMI in women younger than 55 years and to evaluate the results with multivariate statistical procedures.

Methods

Epidemiological Methods

Selection of Acute Myocardial Infarction Survivors

Cases of AMI occurring in Göteborg are registered in a special AMI register. After discharge from the hospital, the survivors have been followed at a special post-AMI outpatient clinic. For this study, all women (n=61) ages 54 years old or younger, who survived their first AMI between January 1, 1978 and December 31, 1981 were selected (Table 1). The mean annual incidence per 100,000 women increased from 14 at ages 38 to 39 to 63 at ages 50 to 54. One woman never attended the post-AMI clinic, and in one patient, blood sampling failed for technical reasons. The mean age of these 59 participants was 48.7±5.1 years (mean±SD), 61% of whom were postmenopausal (Table 2). The mean time between AMI and the investigation was 11 months (range 3 to 37 months).
participants were treated in a standardized way. At the time of this study, 28 patients were taking beta-blockers; 6, diuretics; 14, a combination of beta-blocker and diuretic; and 13, digitalis. Five women had diabetes (including two who were being treated with insulin). None was being treated with lipid-lowering drugs and none used oral contraceptive or noncontraceptive estrogens.

Selection of a Random Population Sample

This study is part of a more extensive investigation aimed at characterizing female MI patients as to psychological, genetic, and hormonal factors and psychiatric morbidity. A random population sample was therefore, selected to permit estimations of the prevalence rates of these factors. The present sample (n=170) was selected at random from the total female population of Göteborg who were born between 1925 and 1941 (n=40,351). A proportion of each age stratum was selected for the control group (Table 1). Out of the 170 invited women, 142 women were examined; however, two refused to give blood, so the final control group consisted of 140 women (participation rate, 82%). Their mean age was 45.8±4.9 years (mean±SD) of whom 24% were postmenopausal (Table 2). Three women were taking beta-blockers; three, diuretics; two, a combination of beta-blocker and diuretic; one, digitalis; one, insulin; three, oral contraceptives; and seven, noncontraceptive steroids. None took lipid-lowering drugs. All participants gave their informed consent to the study.

Clinical Investigation

Basic characteristics of the women, including disease history, smoking habits, physical activity, and pharmacotherapy were recorded on standardized questionnaires. Smoking habits were scored from 1 to 6 with increasing tobacco consumption. The levels of physical activity at work were scored on an increasing scale: 1 = office, mainly sitting; 2 = easy mobile; 3 = rather heavy; 4 = heavy work; physical activity levels during leisure time were: 1 = mainly sitting, passive, watching TV; 2 = walks, etc; 3 = regular training; 4 = hard training, competition sports. For AMI survivors, their habits of smoking and physical activity were recorded at the time of infarction, as well as at the time of the investigation. Sitting blood pressure was recorded, and diastolic blood pressure was read at phase 5 according to the method of Rose and Blackburn. Relative body weight was calculated as body mass index (BMI = weight [kg]/height [m]²). Nonpregnant women were regarded as postmenopausal if they had been amenorrhoic for 6 months or more.

Biochemical Methods

Blood Sampling and Serum Preservation

Participants from both groups were investigated at randomly scattered times during the year. They were asked to refrain from alcohol for 48 hours and from food and tobacco for 12 hours before blood sampling. Blood was drawn in the morning. In menstruating women in both groups, the times of blood sampling were scattered at

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>AMI survivors (n=59) (%)</th>
<th>Controls (n=140) (%)</th>
<th>P</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>History of hypertension</td>
<td>Nonadjusted</td>
<td>Age-adjusted</td>
<td>Nonadjusted</td>
<td>Age-adjusted</td>
</tr>
<tr>
<td>Diabetes</td>
<td>48</td>
<td>43</td>
<td>13</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Smokers</td>
<td>82</td>
<td>84</td>
<td>37</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Physical activity at work, score 3 to 4*</td>
<td>43</td>
<td>37</td>
<td>29</td>
<td>&gt;0.20</td>
</tr>
<tr>
<td>Physical activity at leisure time, score 3 to 4*</td>
<td>9</td>
<td>5</td>
<td>6</td>
<td>0.093</td>
</tr>
<tr>
<td>Postmenopausal</td>
<td>61</td>
<td>40</td>
<td>24</td>
<td>0.025</td>
</tr>
</tbody>
</table>

*For definition, see Grimby et al. The test is based on all four groups of physical activity.
random over the menstrual cycle. For the determination of HDL cholesterol, menstruating women were called for another blood sample on the third day of the cycle. Serum samples of 0.5 ml were frozen and kept at −85°C for lipoprotein measurements.

Lipid Analyses

Serum cholesterol and triglycerides were determined with fully enzymatic procedures in sera stored at −85°C as previously described.20 HDL cholesterol was determined in unfrozen serum within 24 hours of blood sampling.20

Determination of Apoproteins A-I and A-II

All apolipoprotein concentrations were determined after completion of the study and within a period of 2 weeks in aliquots that had been stored at −85°C. Apo A-I21 and apo A-II22 were determined with electroimmunoassay as earlier described.

Determination of Apoprotein B

Apo B was determined with solid-phase radioimmunoassay.

LDL (d=1.030 to 1.050 g/ml) were prepared by sequential ultracentrifugation23 and a monospecific rabbit antiserum against human apo B (the protein moiety of LDL) was raised as reported elsewhere.11 Controls of purity and specificity were those reported previously. LDL were labeled with 125I by the procedure of McFarlane,24 which was modified according to Shepherd et al.25 The reagents were separated from labeled lipoproteins with two consecutive chromatographs on disposable Sephadex G25 columns (PD 10, Pharmacia Fine Chemicals, Uppsala, Sweden). The lipoproteins eluted in the void volume carried about 25% of added radioactivity. Less than 4% of the lipoprotein-bound radioactivity was extractable in chloroform/methanol/water 5:5:2 (vol/vol/vol) in a two-phase system. More than 85% of the radioactivity was precipitable in 15% trichloroacetic acid, and 90% to 95% was precipitated in the presence of excess antiserum. No preparation of 125I-LDL was more than 2 months old when used. Goat antirabbit immunoglobulin bound to Immunobeads (BioGel Chemicals, Richmond, CA) were suspended in water as recommended.

The antiserum was diluted in a 0.5 M phosphate buffer containing 0.15 M NaCl, 1 mM EDTA, 0.05% (wt/vol) sodium azide, and 0.2% (wt/vol) bovine serum albumin (Buffer A). The dilution (1:25 000 (vol/vol) was selected to precipitate 50% of 125I-LDL in the absence of unlabeled LDL. An aliquot of 1 ml of this antiserum dilution was mixed with 0.1 ml of 125I-LDL (approximately 5000 cpm) and 0.1 ml sample, and this was incubated overnight at room temperature. In the next step of the assay, 0.4 ml of immunoglobulin-coated Immunobead suspension was added, and the samples were reincubated at room temperature under continuous mixing for 4 hours. The amount of Immunobeads chosen was sufficient to precipitate the expected 50% of the radioactivity in the absence of unlabeled LDL. Incubation for more than 4 hours caused no more radioactivity to bind to the solid phase. After the second incubation, the pellet was recovered by centrifugation at 3000 g for 15 minutes; the pellet was counted in a gamma counter (RIA-Gamma, LKB, Stockholm, Sweden).

In routine analyses, dilutions of a reference serum was used to construct a standard curve. When plotted as:

\[ \frac{B}{B_0} = \frac{1}{\left(1 + \frac{B}{B_0}\right)} \]

\(B = \text{counts in sample}, \ B_0 = \text{counts when unlabeled LDL were absent}, \) versus log (concentration of apo B), and the curve was linear between 0.07 and 2.2 mg/l. The reference serum was standardized against three different preparations of LDL (d=1.030 to 1.050 g/ml). Dilutions of the LDL preparations and of the reference serum gave parallel curves from which the apo B concentration of the reference was calculated. The reference serum was stored in aliquots at −85°C. Samples were diluted 1/1600 (vol/vol). Dilutions of sera and of labeled and unlabeled LDL were made in Buffer A.

The variations within and between assays of apo B (SD/mean×100) were 3.9% (n=32) and 6.6% (n=3×19), respectively. The results obtained by radioimmunoassay correlated with those obtained by electroimmunoassay of apo B26 (y=0.97x + 0.29, r=0.87, n=30).

Determination of Apoprotein E

Serum apo E levels were determined with electroimmunoassay by using a monospecific antiserum against human apo E.

Apo E was prepared from the serum fraction of d<1.020 g/ml,23 was dialyzed against doubly distilled water, and then was lyophilized. The protein moiety was dissolved in 2 M acetic acid after delipidization with chloroform/methanol by the methods described earlier.23 The solubilized apolipoproteins were chromatographed on a Sephadex G 100 (Pharmacia Fine Chemicals, Uppsala, Sweden) column (150×5 cm) in 2 M acetic acid. Fractions of 10 ml were collected. A 0.1 ml aliquot from each fraction was lyophilized and analyzed with polyacrylamide gel electrophoresis (PAGE) in the presence of sodium dodecyl sulphate (SDS).27 Fractions containing apo E were pooled, lyophilized, and solubilized in 3 ml 8 M urea containing 2% (vol/vol) Nonidet P40 (Shell International Chemical Trading Company, London, U.K.) and 5% (wt/vol) Ampholine (LKB, Stockholm, Sweden) pH 4 to 6. The solubilized material was further purified by preparative isoelectric focusing in Ultradex (LKB, Stockholm, Sweden) that was equilibrated with 5% Ampholine, 1.5% Nonidet P40 and 5.4 M urea using an LKB Multiphore equipment (LKB, Stockholm, Sweden). The set points were 1280 V, 12 mA, and 8 W, and the focusing was carried out for 16 hours. The granulated bed was divided into 30 fractions. The protein material in each fraction was eluted with 0.1 M Tris-HCl (pH 7.5), containing 8 M urea, 0.1% (wt/vol) Na3 and 1 mM phenyl-methyl-sulphonyl-fluorid (PMSF) (Sigma Chemical Company, St. Louis, Missouri) and was analyzed with PAGE. Fractions containing only apo E were pooled, were dialyzed exhaustively against distilled water, and were lyophilized.

To produce an antiserum to human apo E, a New Zealand White rabbit was immunized with apo E dissolved...
in 0.01 M Tris-HCl with 8 M urea (pH 7.5) and this was
diluted with equal volumes of Freund's adjuvants as pre-
viously described.21 The obtained antiserum reacted with
apo E as judged from immunodiffusion, crossed
immunoelectrophoresis, and immunoblotting,28 but not
with other apolipoproteins.
The electroimmunoassay was carried out with 1% (vol/
vol) antiserum against human apo E in 1.5% (wt/vol)
Indubiose A37 gel (l'Industrie Biologique Francaise, Genne-
villiers, France) containing 5% (wt/vol) dextran T10 (Phar-
macia Fine Chemicals, Uppsala, Sweden) in 0.05 M bar-
bital buffer (pH 8.5) as previously described for apo A-I.21
Electrophoresis was carried out at 7 V/cm for 7.5 hours.
The rocket heights of sampled sera, which were diluted
1/100, were compared with a linear standard curve con-
structed from the heights of rockets of dilutions (1/50 to
1/400) of a reference serum.
The appearances of the rocket precipitates at electroim-
munooassay of purified lipid-free apo E and of apo E in
lipoprotein form in serum were not similar. Such a dissim-
ilarity may well be explained by differences in the anti-
genic reactivity of apo E in different physical-chemical
forms and discloses a direct comparison of absolute
concentration of apo E between such different forms.
Therefore, we prefer to give our results as the percents of
the reference serum. This seems to be justified in within-
study comparisons.
The variations within and between assays for apo E
were 2.6% (n=57) and 4.8% (n=3×15), respectively.

Statistical Methods
Pittman's nonparametric permutation test was used to
test differences in continuous and discrete variables
between cases and controls. For binary variables, this test
is equivalent to Fisher's exact test in a fourfold table.
Correlations between study variables were evaluated with
Spearman's rank correlation coefficient.

Associations between lipid and nonlipid measurements and
AMI were tested by means of a multiple logistic
regression analysis adapted for a case-control study.29
Variables remaining significantly associated with AMI
after controlling for age with conventional methods were
included in the model. The importance of different varia-
tives for the prevalence of AMI were evaluated from the
logistic regression coefficient for the factor. Two-tailed
tests were used, and values of p<0.05 were considered
statistically significant.
The relative risk and the attributable risk were com-
puted as follows:
\[
\frac{P \times (R-1)}{1 + P \times (R-1)} \times 100
\]
where P=prevalence of characteristic and R=relative risk
(See Table 7). High serum triglycerides were defined as
values above quartile 4 in the random population sample.
The attributable risk indicates what percentage of risk
might be spared in the population if the adverse charac-
teristic was converted to a more healthful one.

Results

Basic Characteristics
A history of hypertension and smoking was more com-
mon among AMI survivors before their infarction than
among controls (Table 2). The AMI cases were more often
postmenopausal than the controls. This difference did not
remain after adjustment for age.
At the time of this investigation (mean time after AMI = 11 months), the AMI survivors and the controls were comparable with regard to age-adjusted BMI, systolic and diastolic blood pressure, and smoking habits (Table 3).

**Lipoprotein Data**

Serum cholesterol, triglycerides, apo B, and apo E were higher, and HDL cholesterol and apo A-I were lower among patients with AMI than among controls (Table 4). After adjustment for age, serum cholesterol was not significantly different between the two groups.

To evaluate the possible influence on lipoprotein variables of treatment with beta-blockers and diuretics, the AMI group was stratified according to such treatments (not shown). There were no significant differences between these strata. Subjects on beta-blockers (n = 28) or diuretics (n = 20) did not have higher levels of serum triglycerides or lower levels of HDL cholesterol and apo A-I than those without such treatment (n = 11).

**Correlations between Study Variables in Random Controls**

The serum levels of apo A-I, apo A-II, and HDL cholesterol were strongly intercorrelated (Table 5). Serum apo B and apo E levels were also strongly intercorrelated, as well as correlated with serum cholesterol and triglycerides. A negative correlation was found between HDL cholesterol and serum triglycerides. Serum cholesterol, apo B, apo E, and postmenopausal status were positively correlated with age. Several weaker correlations were also found (Table 5).

**Association between Study Variables and AMI**

After controlling for age, each of the variables (cigarette smoking before infarction, history of hypertension, serum triglycerides, HDL cholesterol, apo A-I, apo B, and apo E) appeared to have more than a chance relation to the prevalence of AMI in the study population. These variables were entered into a multivariate analysis. The results are presented in Table 6. Cigarette smoking, history of hypertension, high serum triglycerides, and age remained associated with infarction, as did low levels of apo A-I and high levels of apo E. HDL cholesterol and apo B did not contribute independently to infarction.

The distribution of cases with infarction and controls in quartiles of risk, obtained by the logistic regression function (Table 6), including all variables significantly associated with AMI (eg., age, cigarette smoking, history of hypertension, serum triglycerides, apo A-I, and apo E) is presented in Figure 1 (Model I). Of the cases with AMI, 84% were distributed in the highest risk quartile. A further model (Table 6), including all variables significantly associated with AMI (eg., age, cigarette smoking, history of hypertension, serum triglycerides, apo A-I, and apo E) is presented in Figure 1 (Model II). The conventional risk factors, age, cigarette smoking, history of hypertension, and serum triglycerides, is also shown in Figure I (Model II). The conven-

---

**Table 5. Correlation Coefficients between Risk Factors and Lipoprotein Variables in Controls**

<table>
<thead>
<tr>
<th>Variable</th>
<th>History of hypertension</th>
<th>Smoking</th>
<th>Menopause</th>
<th>Body mass index</th>
<th>Serum cholesterol</th>
<th>Serum triglycerides</th>
<th>HDL cholesterol</th>
<th>Apo A-I</th>
<th>Apo A-II</th>
<th>Apo B</th>
<th>Apo E</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>0.11</td>
<td>-0.04</td>
<td>0.56†</td>
<td>0.14</td>
<td>0.36‡</td>
<td>0.08</td>
<td>0.07</td>
<td>-0.04</td>
<td>0.08</td>
<td>0.27†</td>
<td>0.22†</td>
</tr>
<tr>
<td>History of hypertension</td>
<td>-0.07</td>
<td>0.11</td>
<td>0.25†</td>
<td>0.09</td>
<td>0.05</td>
<td>-0.10</td>
<td>-0.04</td>
<td>0.02</td>
<td>0.05</td>
<td>0.04</td>
<td></td>
</tr>
<tr>
<td>Smoking</td>
<td>-0.10</td>
<td>-0.05</td>
<td>0.02</td>
<td>0.20*</td>
<td>-0.15</td>
<td>0.04</td>
<td>0.13</td>
<td>0.17*</td>
<td>0.07</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Menopause</td>
<td>0.05</td>
<td>0.22*</td>
<td>-0.01</td>
<td>0.17</td>
<td>-0.06</td>
<td>0.00</td>
<td>0.12</td>
<td>0.06</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Body mass index</td>
<td>0.04</td>
<td>0.29‡</td>
<td>-0.35‡</td>
<td>-0.19*</td>
<td>0.09</td>
<td>0.24*</td>
<td>0.16</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Serum cholesterol</td>
<td>0.33‡</td>
<td>0.15</td>
<td>0.25†</td>
<td>0.25†</td>
<td>0.70‡</td>
<td>0.71‡</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Serum triglycerides</td>
<td>-0.31‡</td>
<td>-0.02</td>
<td>-0.23†</td>
<td>0.52‡</td>
<td>0.51‡</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HDL cholesterol</td>
<td>0.56†</td>
<td>0.10</td>
<td>-0.21*</td>
<td>-0.28†</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Apo A-I</td>
<td>0.46‡</td>
<td>0.02</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Apo A-II</td>
<td>-0.19*</td>
<td></td>
<td>0.17*</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Apo B</td>
<td></td>
<td></td>
<td>0.74‡</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*p < 0.05, †p < 0.01, ‡p < 0.001.

**Table 6. Multiple Logistic Regression Analysis of Relation of Coronary Risk Factors to First Nonfatal Myocardial Infarction in Women**

<table>
<thead>
<tr>
<th>Risk factor</th>
<th>Model I*</th>
<th>Model II†</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Beta</td>
<td>SE</td>
</tr>
<tr>
<td>Smoking score</td>
<td>0.70</td>
<td>0.16</td>
</tr>
<tr>
<td>Serum triglycerides</td>
<td>1.51</td>
<td>0.51</td>
</tr>
<tr>
<td>History of hypertension</td>
<td>1.34</td>
<td>0.53</td>
</tr>
<tr>
<td>Age</td>
<td>0.09</td>
<td>0.03</td>
</tr>
<tr>
<td>Serum apo A-I</td>
<td>-0.04</td>
<td>0.02</td>
</tr>
<tr>
<td>Serum apo E</td>
<td>0.04</td>
<td>0.02</td>
</tr>
<tr>
<td>Serum apo B</td>
<td>-2.22</td>
<td>1.21</td>
</tr>
<tr>
<td>HDL cholesterol</td>
<td>0.66</td>
<td>0.84</td>
</tr>
</tbody>
</table>

*Data on 53 cases and 113 controls. †Data on 57 cases and 135 controls.
was not possible to separate any residual influence of this study must, however, be confined to survivors of AMI. The total observation period was more than 90% of all infarctions occurring in the community. The risk of AMI increases with age in both sexes, and it is obvious that this is also true for women in this study. It was, however, no significant differences in lipoprotein variables by the way in which serum was collected. Beta-blockers and thiazides have been associated with variation and fluctuation during the menstrual cycle. In our study. This suggests that apo E and serum triglycerides may be better representatives of an atherogenic risk factor for coronary heart disease, smoking and hypertension, were strongly associated with infarction in this study, findings that correspond to previous observations in younger women. The importance of smoking as a risk indicator for myocardial infarction in older women is less obvious.

High serum triglycerides have been associated with CHD among older women in univariate analyses as well as in multivariate analyses. Our results in younger women are in accord with these findings, since high serum triglycerides were independently and significantly associated with the prevalence of infarction, whereas serum cholesterol levels were not. Similar results were observed in a previous case-control study among men within the same population. Recent studies have indicated that high levels of serum triglycerides were not only a stronger risk factor for CHD in women but were also a better predictor of the severity of atherosclerosis as scored at arteriography than were high levels of serum cholesterol. The importance of serum triglycerides as a risk indicator of CHD in men seems less obvious than in women. This may indicate a sex difference in the importance of metabolic disturbances for the development of the disease.

Apo A-I and apo A-II are the main apolipoproteins in HDL. This is reflected in the present study by the strong correlation between apo A-I, apo A-II, and HDL cholesterol. In several previous studies, these variables were found to discriminate cases of AMI from controls, but with varying strength and degree of independence. This variation may, of course, be only a matter of statistical chance. Among men, apo A-I was the better discriminator in case-control studies and in prospective studies. In a previous study of men, we found apo A-II to be a more sensitive discriminator of AMI survivors than apo A-I and HDL cholesterol. A large number of studies have found a strong relationship between low HDL cholesterol levels and present or future CHD. The present study confirms the importance of low HDL in separating female survivors of AMI from controls and suggests that apo A-I may be the more sensitive discriminator.

There were strong correlations between serum cholesterol, serum triglycerides, apo B, and apo E. This association may reflect the fact that they primarily reside within the LDL and very low density lipoprotein density region of lipoproteins. Previously, apo B, but not apo E, was measured and found to be positively correlated to CHD in accordance with our univariate analysis. Of the two, only apo E was an independent discriminator of AMI survivors in our study. This suggests that apo E and serum triglycerides may be better representatives of an atherogenic lipoprotein than are apo B and serum cholesterol.

We feel that we have controlled for the influence of infarction itself and for the possibility of seasonal variation and fluctuation during the menstrual cycle on lipoprotein variables by the way in which serum was collected. Beta-blockers and thiazides have been associated with changes in several lipoprotein variables in some studies, but not in others. In this study, there were, however, no significant differences in lipoprotein values.

Table 7. Relative and Attributable Risks of Nonfatal Myocardial Infarction in Women according to Selected Adverse Characteristics

<table>
<thead>
<tr>
<th>Adverse characteristic</th>
<th>Prevalence of abnormality (%)</th>
<th>Relative risk</th>
<th>Community attributable risk (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>History of hypertension</td>
<td>12.8</td>
<td>3.1</td>
<td>21</td>
</tr>
<tr>
<td>Smoking</td>
<td>37</td>
<td>4.5</td>
<td>56</td>
</tr>
<tr>
<td>High serum triglycerides*</td>
<td>76</td>
<td>3.5</td>
<td>65</td>
</tr>
</tbody>
</table>

* >1.18 mmol/l (within quartile 4 in random population sample). Women were younger than 55 years and lived in Gothenburg, Sweden.

Discussion

The Myocardial Infarction Register in Göteborg covers more than 90% of all infarctions occurring in the community. The total observation period was more than 150,000 person-years, and the participation rates of cases and controls in this community-based study were high in comparison with most previous studies. The conclusion of this study must, however, be confined to survivors of AMI. The risk of AMI increases with age in both sexes, and it is obvious that this is also true for women in this study. It was not possible to separate any residual influence of postmenopausal status on the presence of infarction when age was considered. The two well-established risk factors for coronary heart disease, smoking and hypertension, were strongly associated with infarction in this study, findings that correspond to previous observations in younger women. The importance of smoking as a risk indicator for myocardial infarction in older women is less obvious.

High serum triglycerides have been associated with CHD among older women in univariate and multivariate analyses. Our results in younger women are in accord with these findings, since high serum triglycerides were independently and significantly associated with the prevalence of infarction, whereas serum cholesterol levels were not. Similar results were observed in a previous case-control study among men within the same population. Recent studies have indicated that high levels of serum triglycerides were not only a stronger risk factor for CHD in women but were also a better predictor of the severity of atherosclerosis as scored at arteriography than were high levels of serum cholesterol. The importance of serum triglycerides as a risk indicator of CHD in men seems less obvious than in women. This may indicate a sex difference in the importance of metabolic disturbances for the development of the disease.

Apo A-I and apo A-II are the main apolipoproteins in HDL. This is reflected in the present study by the strong correlation between apo A-I, apo A-II, and HDL cholesterol. In several previous studies, these variables were found to discriminate cases of AMI from controls, but with varying strength and degree of independence. This variation may, of course, be only a matter of statistical chance. Among men, apo A-I was the better discriminator in case-control studies and in prospective studies. In a previous study of men, we found apo A-II to be a more sensitive discriminator of AMI survivors than apo A-I and HDL cholesterol. A large number of studies have found a strong relationship between low HDL cholesterol levels and present or future CHD. The present study confirms the importance of low HDL in separating female survivors of AMI from controls and suggests that apo A-I may be the more sensitive discriminator.

There were strong correlations between serum cholesterol, serum triglycerides, apo B, and apo E. This association may reflect the fact that they primarily reside within the LDL and very low density lipoprotein density region of lipoproteins. Previously, apo B, but not apo E, was measured and found to be positively correlated to CHD in accordance with our univariate analysis. Of the two, only apo E was an independent discriminator of AMI survivors in our study. This suggests that apo E and serum triglycerides may be better representatives of an atherogenic lipoprotein than are apo B and serum cholesterol.

We feel that we have controlled for the influence of infarction itself and for the possibility of seasonal variation and fluctuation during the menstrual cycle on lipoprotein variables by the way in which serum was collected. Beta-blockers and thiazides have been associated with changes in several lipoprotein variables in some studies, but not in others. In this study, there were, however, no significant differences in lipoprotein values.
variables between cases with and without such therapy. Indeed, untreated cases differed from controls in the same manner as did all AMI cases. We, therefore, consider the therapy with beta-blockers and diuretics as less likely explanations of our results.

The present study confirms the importance of the major cardiovascular risk factors, cigarette smoking, hypertension, and high serum triglyceride levels, for the prevalence of AMI in relatively young women and emphasizes the importance of further investigations into the role of metabolic disturbances in women with CHD. It also supports the concept that low levels of apo A-I and high levels of apo E characterize young women with AMI. Further studies on the value of apolipoproteins as risk indicators for CHD in women of all ages are warranted.

References


Index Terms: apolipoproteins • myocardial infarction • risk factors • women
Serum lipids and apolipoprotein levels in women with acute myocardial infarction.
S Johansson, G Bondjers, G Fager, H Wedel, A Tsipogianni, S O Olofsson, A Vedin, O Wiklund and C Wilhelmsson

Arterioscler Thromb Vasc Biol. 1988;8:742-749
doi: 10.1161/01.ATV.8.6.742
Arteriosclerosis, Thrombosis, and Vascular Biology is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 1988 American Heart Association, Inc. All rights reserved.
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:
http://atvb.ahajournals.org/content/8/6/742

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Arteriosclerosis, Thrombosis, and Vascular Biology can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Arteriosclerosis, Thrombosis, and Vascular Biology is online at:
http://atvb.ahajournals.org//subscriptions/