The Apolipoprotein B/AI Ratio and the Metabolic Syndrome Independently Predict Risk for Myocardial Infarction in Middle-Aged Men

Lars Lind, Bengt Vessby, Johan Sundström

Background—Both the metabolic syndrome and an increased apolipoprotein B/AI (apoB/AI) ratio are powerful risk factors for cardiovascular events. We hypothesized that the apoB/AI ratio well-characterizes the dyslipidemia associated with insulin resistance and the metabolic syndrome and investigated those relations and if the apoB/AI ratio and the metabolic syndrome independently predicted subsequent myocardial infarction (MI).

Methods and Results—A community-based sample of 1826 men aged 50 was investigated at baseline and again at age 70. ApoB/AI ratio and the metabolic syndrome (National Cholesterol Education Program definition) were evaluated, and the incidence of fatal and nonfatal MI was followed for a median of 26.8 years from the age 50 baseline. ApoB/AI ratio was significantly higher in men with versus without the metabolic syndrome (P<0.0001), and increased with the number of components defining the syndrome (P<0.0001). ApoB/AI ratio was inversely related to euglycemic insulin clamp glucose disposal rate at age 70 (r=-0.34, P<0.0001). During follow-up from age 50, 462 subjects developed an MI. An apoB/AI ratio≥0.9 (hazard ratio [HR], 1.48; 95% confidence interval [CI], 1.15 to 1.91) and presence of the metabolic syndrome (HR, 1.69; 95% CI, 1.30 to 2.21) at baseline were independent predictors for MI, adjusting for low-density lipoprotein cholesterol and smoking.

Conclusion—The apoB/AI ratio was related to the metabolic syndrome, as well as to a direct measurement of insulin resistance. Despite this, the apoB/AI ratio and the metabolic syndrome were both independent long-term predictors of MI in a community-based sample of middle-aged men. (Arterioscler Thromb Vasc Biol. 2006;26:406-410.)

Key Words: apolipoprotein ■ insulin resistance ■ metabolic syndrome ■ myocardial infarction

The metabolic syndrome (MetS) is a cluster of cardiovascular disease risk factors for which insulin resistance is believed to be of pathogenetic importance.1 The MetS defined according to a recently proposed clinically feasible definition2 predicts cardiovascular mortality independently of some established risk factors, including total or low-density lipoprotein (LDL) cholesterol.3-6

Insulin resistance and the MetS are related to certain lipid disturbances, including low levels of high-density lipoprotein (HDL) particles, high fasting and postprandial levels of triglyceride-rich lipoproteins (mainly very-low-density lipoprotein [VLDL]), and increased levels of small, dense LDL particles.7 The former 2 aberrations are included in the current definitions of the MetS,5,8 but no assessment of the LDL disturbance is included in the MetS definitions, although it is believed to be of importance as small dense LDLs are more easily oxidized and atherogenic.9

Circulating levels of apolipoproteins reflect the number of, rather than the cholesterol concentration of, lipoprotein particles. Specifically, the level of apolipoprotein B-100 (apoB) reflects the number of triglyceride-rich VLDL particles and the number of LDL particles. It thus gives more weight to the number of small dense LDL particles than the more regular measurement of LDL cholesterol does. The level of apolipoprotein AI (apoAI) reflects the number of HDL particles. The ratio of apolipoproteins B and AI (apoB/AI) would therefore theoretically be an ideal marker for the lipid disturbances associated with insulin resistance and the MetS. The apoB/AI ratio has previously been related to the MetS in a medium-sized sample10 and to the homeostasis model assessment of insulin resistance in a large sample,11 and has been demonstrated to predict coronary events in large population-based samples.12-15 Its relation to insulin resistance, measured directly, and prognostic independence of the MetS is not known.

We investigated the relations of the apoB/AI ratio to the MetS and insulin resistance (using the gold standard measurement of insulin resistance, the euglycemic insulin clamp), and the prognostic independence of the apoB/AI ratio and the MetS for subsequent fatal and nonfatal myocardial infarction in a large sample of middle-aged men with long follow-up.
Methods

Study Samples
In 1970 to 1973, all men born in 1920 to 1924 and residing in the county of Uppsala were invited to a health survey (at age 50) aimed at identifying risk factors for cardiovascular disease; 82% of the invited men participated (n=2322). The design and selection criteria for the cohort have been described previously.16 At a re-examination of the cohort in 1991 to 1995 (at age 70), 73% participated (n=1221).17 The present study used both of these examinations for the cross-sectional analyses, but only the examination at age 50 for the longitudinal analyses. For the present study, we included 1826 men at age 50 and 548 men at age 70 who had complete data on apoB and apoAI and covariates. Informed consent was obtained and the Uppsala University Ethics Committee approved the study.

Baseline Examinations and MetS Definition
The examination at age 50 has been described in detail previously.16 Blood samples for fasting concentrations were drawn in the morning after an overnight fast. Cholesterol and triglyceride concentrations in serum and HDLs were assayed by enzymatic techniques. Coding of smoking was based on interview reports. Supine systolic and diastolic blood pressures were measured twice in the right arm after 10 minutes rest, and means were calculated. ApoB was determined by a 2-site immunoradiometric assay and apoAI by a competitive radioimmunoassay, using commercial kits from Pharmacia (Uppsala, Sweden), in samples that had been stored in liquid nitrogen (LN2) since the phlebotomy. The intra-individual coefficients of variation were 2.5% for apoB and 2.4% for apoAI.

At the examination at age 70, in addition to the mentioned analyses, insulin sensitivity was determined with the hyperinsulinemic euglycemic clamp technique, performed according to DeFronzo et al18 with a slight modification [insulin was infused at a constant rate of 56 μU/(min·m²)]. Insulin sensitivity was measured as the glucose disposal rate [mg glucose infused/(minute* kg body weight)] during the last 60 minutes of the 2-hour clamp.

We used the National Cholesterol Education Program (NCEP) definition of the MetS in the present study.2 Because waist circumference was only measured in a subsample of 480 persons at the age 50 examination (in 377 of the participants who also had apoB and apoAI measurements), the NCEP definition was modified using a body mass index (BMI) cut-point instead of the waist circumference definition. This is the most relevant risk population, and that the age 50 sample was >3-fold larger than the sample at age 70. Cross-sectional analyses at age 50 included t tests comparing means of the apoB/AI ratio and other lipid variables between men with versus without the MetS, men with versus without the individual MetS components, and men with apoB/AI ratio at or above versus below 0.9; ANOVAs investigating differences in mean apoB/AI ratio according to number of MetS components; and unadjusted logistic regression models investigating the relations of the continuous variables apoAI and apoB (both per standard deviation), and dichotomized apoB/AI ratio (at or above versus below 0.9) to the MetS. At age 70, Pearson’s correlation coefficients were used to examine relations of the apoB/AI ratio to clamp glucose disposal rate. For the longitudinal analyses from age 50, we investigated the incidence rate of myocardial infarction by baseline decentiles of apoB/AI ratio, and chose a cut-off value based on this for subsequent dichotomized analyses of apoB/AI ratio, as the relation of apoB/AI ratio to myocardial infarction incidence appeared slightly nonlinear. Nelson-Aalen curves were used to confirm proportionality of hazards and to graphically describe incidence of myocardial infarction after age 50. Cox proportional hazards regression models were then used to examine the relations of baseline variables to the incidence of myocardial infarction. All analyses were defined a priori. Stata 8.2 (StataCorp, College Station, Tex) was used for all analyses.

Follow-Up
Follow-up was from the examination at age 50 (in 1970 to 1973) to December 31, 1999, with a maximum of 29.7 years of follow-up (median 26.8 years, 53 333 person-years at risk).

Outcome Measure
The end point was defined a priori using the Swedish national cause-of-death and hospital discharge registers, as fatal or nonfatal myocardial infarction (International Classification of Diseases-9 code 410, International Classification of Diseases-10 code I21). The cause-of-death and hospital discharge registers, as fatal or nonfatal myocardial infarction. All analyses were defined a priori. Stata 8.2 (StataCorp, College Station, Tex) was used for all analyses.

Statistical Analyses
Initially, univariate analyses were conducted to assess the distributional properties of the baseline variables. All analyses used the age 50 baseline except the analysis of relations of apoB/AI ratio to insulin sensitivity, because the clamp investigation was only performed at age 70. The reason for focusing on the cohort at age 50 was that this is the most relevant risk population, and that the age 50

Results

Cross-sectional Analyses
Clinical characteristics of the cohort at ages 50 and 70 are presented in Table 1. The prevalence of the MetS at age 50 was 12.7%. ApoB levels and the apoB/AI ratio were significantly higher, and ApoAI levels lower, in men with the MetS, when compared with those without the syndrome (Table 2). The apoB/AI ratio increased with the number of MetS components (P<0.0001) (Figure I, available online at http://atvb.ahajournals.org). Less than 10 subjects had all 5 components of the syndrome and were therefore not included in these analyses. Investigating the relations of the apoB/AI ratio to the individual components of the MetS, the apoB/AI ratio was increased in those who fulfilled the obesity, hypertension, triglyceride or HDL cholesterol criteria, but not in those with impaired glucose regulation (Table 1). The highest

| TABLE 1. Clinical Characteristics at Ages 50 and 70 |
|---------------------------------|---------|---------|
| Variables | Age 50 | Age 70 |
| No. of individuals | 1826 | 548 |
| ApoB, g/L | 1.24±0.28 | 1.04±0.23 |
| ApoAI, g/L | 1.43±0.25 | 1.29±0.23 |
| ApoB/AI ratio | 0.89±0.26 | 0.83±0.22 |
| BMI, kg/m² | 25.0±3.2 | 26.3±3.4 |
| Waist circumference, cm | 87.8±8.8 | 94.0±9.7 |
| SBP supine, mm Hg | 133.1±18.1 | 146.8±18.5 |
| DBP supine, mm Hg | 83.7±11.2 | 83.8±9.5 |
| Fasting glucose, mmol/L | 5.0±0.9 | 5.8±1.5 |
| Serum cholesterol, mmol/L | 6.9±1.3 | 5.8±1.0 |
| LDL cholesterol, mmol/L | 5.3±1.3 | 3.9±0.9 |
| HDL cholesterol, mmol/L | 1.4±0.4 | 1.3±0.3 |
| Serum triglycerides, mmol/L | 1.9±1.2 | 1.4±0.8 |

Data are means±SD. ApoB/AI indicates ratio of apolipoproteins B and AI; BMI, body mass index; DBP, diastolic blood pressure; HDL, high-density lipoprotein; LDL, low-density lipoprotein; SBP, systolic blood pressure; TG, triglycerides.

Waist circumference was measured in 377 men at age 50.
apoB/AI ratio was observed in those who fulfilled the low HDL cholesterol criterion, followed by those with hypertriglyceridemia (Table 1).

In unadjusted logistic regression models, continuous apoAI was somewhat stronger than apoB related to the MetS (odds ratio [OR], 0.32; 95% confidence interval [CI], 0.27 to 0.39; z value -11.5; P<0.0001; and OR, 1.72; 95% CI, 1.51 to 1.96; z-value 8.00; P<0.0001; per standard deviation, respectively). An apoB/AI ratio ≥0.9 was also highly predictive of presence of the MetS (OR, 6.17; 95% CI, 4.45 to 8.55; z-value 10.9; P<0.0001).

At age 70, insulin sensitivity measured as the clamp glucose disposal rate was significantly inversely related to the apoB/AI ratio (r = -0.34; P<0.0001) (Figure 1). ApoB and apoAI were related to clamp glucose disposal rate separately, but less close relationships were observed (r = -0.27 and r = 0.19, respectively) compared with when the apoB/AI ratio was used. Serum triglycerides, HDL cholesterol, and their ratio were more closely related to clamp glucose disposal rate (r = -0.39, r = 0.37, and r = -0.40, respectively). Despite this, the apoB/AI ratio was significantly related to the glucose disposal rate at clamp then the effect of serum triglycerides or HDL cholesterol was taken into account in multiple regression analysis.

Longitudinal Analyses

During follow-up after the age 50 baseline, 462 subjects experienced a fatal or nonfatal myocardial infarction. Figure II (available online at http://atvb.ahajournals.org) shows a display of the incidence rate of myocardial infarction by deciles of apoB/AI ratio. Because the incidence appeared not truly linearly related to apoB/AI ratio, we chose the 7th decile as our cut-off value for further dichotomized analyses (corresponding to 0.9, a previously suggested cut-off level2). In unadjusted Cox proportional hazard analysis, both the metabolic syndrome (hazard ratio [HR], 2.0; 95% CI, 1.6 to 2.6; P<0.0001) and an apoB/AI ratio ≥0.9 (HR, 2.1; 95% CI, 1.7 to 2.6; P<0.0001) at age 50 were significant predictors for development of myocardial infarction during the follow-up period. When both of these variables were entered in the same model, they were both significant independent predictors of myocardial infarction. This was also the case when LDL cholesterol and current smoking were added to the model (Table 3). Replacing apoB/AI ratio with the 2 variables apoB and apoAI in that model, both were independent predictors of myocardial infarction, with apoB having the highest z-value, whereas LDL cholesterol was not a significant predictor (Table 3).
We hypothesized that the apoB/AI ratio would be an ideal marker for the lipid disturbances associated with insulin resistance and the MetS, because it captures the major aspects of the dyslipidemia associated with insulin resistance and the MetS (low HDL levels and high VLDL and small, dense LDL levels). The observations in the present study of a close relation of the apoB/AI ratio to insulin resistance and the MetS supports our hypothesis. A relation between apoB concentration and the MetS has previously been described in type 2 diabetic subjects. This apoB dysregulation, involving increased apoB secretion and impaired apoB catabolism, may be caused by increased nonesterified fatty acid flux to the liver or by an altered cholesterol homeostasis (low cholesterol absorption and high cholesterol synthesis). Previous studies of relations of apoAI to insulin resistance or glucose dysregulation have given inconsistent results. In the present study, the apoB/AI ratio was consistently related to the triglyceride and HDL criteria of the MetS. Notably, this was not the sole explanation for the association between the apoB/AI ratio and the MetS, because the apoB/AI ratio was also related to the number of components defining the MetS and to a direct measurement of insulin resistance. An apoB/AI ratio ≥0.9 was a fair predictor of presence of the MetS, comparable to apoB or apoAI on a continuous scale.

Insulin resistance has been proposed to be the common denominator of the MetS, but insulin resistance per se is not a compulsory element of the NECP MetS definition used in the present study. Nonetheless, in the present analysis the apoB/AI ratio was closely inversely related to insulin sensitivity as measured directly by the gold standard, the euglycemic insulin clamp method, suggesting that the apoB/AI ratio could be added to the list of risk factors that are related to insulin resistance. It should be noted that the causal relations between insulin resistance and dysapolipoproteinemia cannot be determined using the present study design, and that other lipid measurements which do not reflect LDL metabolism, such as serum triglycerides and HDL-cholesterol, also were related to insulin resistance and that the apoB/AI ratio was not superior to those variables in terms of the strength of the relation with insulin resistance in the present study.

The MetS has previously been demonstrated to predict cardiovascular mortality independently of total and LDL cholesterol, and the apoB/AI ratio is a stronger risk factor for coronary heart disease than LDL cholesterol. Because of the hypothetical link between the apoB/AI ratio and the MetS, we investigated for the first time to our knowledge the prognostic independence of the apoB/AI ratio and the MetS. As demonstrated in Figure 2, an apoB/AI ratio ≥0.9 or the MetS alone appeared to be equally important as risk factors, whereas the combination of the 2 was associated with a substantially increased risk. The use of a cut-off value of 0.9 for the apoB/AI ratio was based on previous suggestions, as well as on analysis of the present data (Figure II).

In the present study with a long follow-up, both a high apoB/AI ratio and presence of the MetS at age 50 were independent risk factors for myocardial infarction also after adjustment for LDL cholesterol and smoking. Thus, even though the apoB/AI ratio was closely related to the MetS, these 2 powerful risk factors carry important information regarding the risk for myocardial infarction independently of each other. The reasons for this observation remain speculative. In addition to the anthropometric and blood pressure alterations in men with the MetS, the lipid disturbance in men

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**TABLE 3. Multivariable Cox Proportional Hazards Models for Development of Myocardial Infarction After Age 50**

<table>
<thead>
<tr>
<th>Independent Variable</th>
<th>Hazard Ratio</th>
<th>z-Value</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Model with apoB/AI ratio (≥ vs &lt;0.9)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ApoB/AI ratio (≥ vs &lt;0.9)</td>
<td>1.48 (1.15–1.91)</td>
<td>3.1</td>
<td>0.002</td>
</tr>
<tr>
<td>Metabolic syndrome (vs not)</td>
<td>1.69 (1.30–2.21)</td>
<td>3.9</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Smoking (vs not)</td>
<td>1.42 (1.14–1.77)</td>
<td>3.2</td>
<td>0.002</td>
</tr>
<tr>
<td>LDL cholesterol (per 1 mmol/L)</td>
<td>1.16 (1.07–1.27)</td>
<td>3.6</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Model with continuous apoB and apoAI</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ApoB (per SD)</td>
<td>1.42 (1.17–1.73)</td>
<td>3.52</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>ApoAI (per SD)</td>
<td>0.88 (0.78–0.99)</td>
<td>−2.09</td>
<td>0.036</td>
</tr>
<tr>
<td>Metabolic syndrome (vs not)</td>
<td>1.55 (1.18–2.05)</td>
<td>3.12</td>
<td>0.002</td>
</tr>
<tr>
<td>Smoking (vs not)</td>
<td>1.39 (1.12–1.73)</td>
<td>2.98</td>
<td>0.003</td>
</tr>
<tr>
<td>LDL cholesterol (per 1 mmol/l)</td>
<td>1.00 (0.86–1.15)</td>
<td>−0.04</td>
<td>0.97</td>
</tr>
</tbody>
</table>

Cox proportional hazards ratios (95% confidence intervals) of 2 multivariable models, with 4 and 5 independent variables, respectively.

The cumulative incidence of myocardial infarction during follow-up by presence versus absence of the metabolic syndrome and apoB/AI ratio at or above versus below 0.9 is displayed in Figure 2.

**Figure 2.** Cumulative incidence of fatal and nonfatal myocardial infarction by four groups: apoB/AI ratio ≥0.9 only (“apo only”), metabolic syndrome only (“MetS only”), both of these risk factors, and none of them, determined at age 50. P < 0.0001 for differences between groups.
with the MetS was characterized mainly by low apoAI levels and high serum triglyceride levels, as evident in Table 2. The lipid disturbance in men with apoB/AI ratio ≥0.9 was characterized relatively by high apoB levels and high serum and LDL cholesterol levels. Men with apoB/AI ratio ≥0.9 thus had most features of the MetS and they also had high LDL cholesterol levels, but an apoB/AI ratio ≥0.9 beyond these 2 features may involve the high apoB levels or low apoAI levels per se, or may involve other factors associated with a high apoB/AI ratio that were not measured in the present study.

The strengths of this study include the large population, the long follow-up and nonexistent loss to follow-up in the longitudinal analysis (because of the Swedish national registers, which include all in-hospital and mortal events for all inhabitants), the reliable end point definition, and the detailed metabolic characterization of the cohort including the euglycemic insulin clamp, which is the gold standard method for assessment of insulin sensitivity. Furthermore, the availability of 2 investigations 20 years apart strengthens this study and corroborates the observed relation of apoB/AI ratio to the MetS. Limitations of the study include the homogenic sample (only 1 in-habitant), the reliable end point definition, and the detailed longitudinal analysis (because of the Swedish national registers).

In conclusion, the apoB/AI ratio was related to the MetS, as well as to a direct measurement of insulin resistance. Despite this, the apoB/AI ratio and the metabolic syndrome were both independent long-term predictors of myocardial infarction in middle-aged men.

Acknowledgments
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**Table I. ApoB/AI Ratio at Age 50 by Presence vs. Absence of Metabolic Syndrome Components**

<table>
<thead>
<tr>
<th></th>
<th>Present</th>
<th>Absent</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Obesity</td>
<td>0.97±0.25 (151)</td>
<td>0.88±0.26 (1 675)</td>
<td>0.0001</td>
</tr>
<tr>
<td>Hypertension</td>
<td>0.90±0.26 (1 189)</td>
<td>0.86±0.25 (637)</td>
<td>0.002</td>
</tr>
<tr>
<td>Triglycerides</td>
<td>1.01±0.25 (870)</td>
<td>0.87±0.20 (956)</td>
<td>0.0001</td>
</tr>
<tr>
<td>HDL-cholesterol</td>
<td>1.14±0.26 (325)</td>
<td>0.84±0.23 (1 501)</td>
<td>0.0001</td>
</tr>
<tr>
<td>Glucose</td>
<td>0.87±0.21 (55)</td>
<td>0.89±0.26 (1 771)</td>
<td>0.47</td>
</tr>
</tbody>
</table>

Data are means±standard deviations, and number of individuals in parentheses.
Online Figure Legends

Figure I.
Means and standard errors of the mean for the apoB/AI ratio by number of metabolic syndrome components at age 50.

Figure II.
Incidence rate of myocardial infarction by decentiles of apoB/AI ratio at age 50. The lower cut-off value for the 7th decentile corresponds to a value of 0.9.
ApoB/AI ratio

None
n=331

1
n=679

2
n=550

3
n=203

4
n=41

Number of MetS components

ApoB/AI ratio
Incidencerate of myocardial infarction (per 1000)

Decentiles of ApoB/Al ratio