Association of levels of lipoprotein Lp(a), plasma lipids, and other lipoproteins with coronary artery disease documented by angiography

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ABSTRACT In a study of 307 white patients who underwent coronary angiography, the relationship of coronary artery disease (CAD) to plasma levels of lipoprotein Lp(a) and other lipid-lipoprotein variables was examined. Lp(a) resembles low-density lipoprotein (LDL) in several ways, but can be distinguished and quantified by electroimmunoassay. CAD was rated as present or absent and was also represented by a quantitative lesion score derived from estimates of stenosis in four major coronary vessels. Coronary lesion scores significantly correlated with Lp(a), total cholesterol, triglycerides, LDL cholesterol, and high-density lipoprotein (HDL) cholesterol levels by univariate statistical analysis. By multivariate analysis levels of Lp(a) were associated significantly and independently with the presence of CAD (p < .02), and tended to correlate with lesion scores (p = .06). Among subgroups Lp(a) level was associated with CAD in women of all ages and in men 55 years old or younger. An apparent threshold for coronary risk occurred at Lp(a) lipoprotein mass concentrations of 30 to 40 mg/dl, corresponding to Lp(a) cholesterol concentrations of approximately 10 to 13 mg/dl. Plasma Lp(a) in white patients appears to be a major coronary risk factor with an importance approaching that of the level of LDL or HDL cholesterol.


THE ASSOCIATION between coronary artery disease and a plasma lipoprotein migrating on agarose gel or cellulose acetate electrophoresis as a distinct pre-beta, band was reported independently in 1972–1973 from several laboratories.1–3 The activity of the pre-beta, lipoprotein4 was soon discovered to be identical to Lp(a) plasma antigenic activity, discovered by Berg in 1963,5 and results of quantitative assays for Lp(a) likewise were associated with various manifestations of coronary artery disease.6, 6, 7 Studies using quantitative assays of plasma Lp(a) have tended to confirm an association with coronary artery disease, but thus far statistically significant associations have been reported from these studies only in the context of retrospective subgroup analysis8–9 or dichotomization of Lp(a) levels above and below an arbitrary value.10 Furthermore, the relative strength and independence of Lp(a) as an atherosclerotic risk factor have not been tested in direct comparison with other, better known risk factors.

Lipoprotein Lp(a) is a cholesterol-rich lipoprotein that generally makes up less than 15% of the total plasma cholesterol. On ultracentrifugation it is recovered mostly within the high-density lipoprotein (HDL) range.11 Apolipoprotein B and apolipoprotein [a], linked to each other by one or more disulfide bonds, form the protein portion of Lp(a). Antigenic sites on the latter apolipoprotein have provided the basis for several quantitative immunoassays.8, 9, 12, 13 Probably because of the apolipoprotein B on its surface, lipoprotein Lp(a) resembles low-density lipoprotein (LDL) with regard to plasma clearance rate and cellular receptor interaction.14, 15 Like LDL, Lp(a) has been observed by immunofluorescence to be specifically localized in human atherosclerotic lesions.16

Coronary arteriography provides anatomic data on the extent of human coronary atherosclerosis that cannot be obtained by other means. While selection biases in clinical studies based on coronary arteriography must be recognized, the value of this technique in
elucidating coronary risk factors has been demonstrated repeatedly. In one previous coronary arteriographic study, a positive qualitative assay for Lp(a) was associated with significantly greater lesion severity.

We determined plasma levels of Lp(a), cholesterol, triglycerides, HDL cholesterol, and LDL cholesterol in 307 patients undergoing coronary arteriography. We applied a point-score system for quantifying stenoses in four major vessels to provide an assessment of presence or absence of coronary artery disease and a reproducible quantitative index of overall lesion severity. Plasma Lp(a) level proved to be a significant univariate predictor of lesion severity and a significant multivariate predictor of the presence of coronary artery disease.

Methods

Subjects. The initial study population consisted of 415 consecutive patients undergoing coronary arteriography, performed by members of a single cardiology service at The Methodist Hospital, Houston. Patients gave informed consent and were evaluated according to a protocol approved by the Human Research Institutional Review Boards of Baylor College of Medicine and The Methodist Hospital. Excluded from the study were patients undergoing arteriography for reasons other than chest pain or positive exercise stress test, patients with previous coronary artery bypass surgery, and patients with left main coronary lesions that precluded adequate evaluation of distal vessels (see below). Black persons were also excluded, because as a group they have much higher Lp(a) levels than whites, without a corresponding increase in coronary artery disease. The final study group consisted of 307 patients, with 220 men and 87 women. HDL cholesterol levels were not available for five patients, and these were excluded from appropriate analyses. Approximately 40% of study patients had a history of myocardial infarction, and approximately 75% had chest pain suggesting probable angina pectoris.

Cardiac catheterization and coronary angiography. Selective coronary arteriography was performed in patients in the fasting, nonsedated state. The coronary arteries were injected with 3 to 7 ml of meglumine diatrizoate and examined in anteroposterior, hemial, and right and left oblique views. Films were obtained with use of a 9 inch image intensifier and were evaluated for obstructive coronary lesions on a Tagarno projector.

Determination of coronary lesion score. All arteriograms were examined independently by two experienced angiographers. The right coronary artery was considered to be a single entity and the left coronary artery was subdivided into left anterior descending, circumflex, and obtuse marginal branches. Obstructions of diagonal and other lesser branches were not tabulated. The arteries were judged by visual estimation to be normal (0%), 25%, 50%, 75%, 90%, or 100% obstructed, according to the maximum obstruction in any projection. A coronary score was obtained by summation of the maximum obstructions noted in the four vessels. The scores were tabulated independently without knowledge of clinical or laboratory information or the score assessed by the other observer. The mean score from the two observers was used in all analyses. Interobserver variability was minimal, as evidenced by a mean difference of 8 (representing 8% greater or lesser stenosis in one vessel) and a Pearson correlation coefficient of .91.

Plasma lipid and lipoprotein determinations. Blood samples were drawn after a 12 hr fast in the morning before cardiac catheterization. Serum and plasma (anticoagulated with EDTA) were separated within 1 to 2 hr by low-speed centrifugation. Total plasma levels of cholesterol, triglycerides, and HDL cholesterol were determined without delay according to methods of the Lipid Research Clinics Program. Since plasma triglyceride levels exceeded 400 mg/dl in only two instances, with a maximum value of 621 mg/dl, values for LDL cholesterol were estimated according to the formula:

LDL cholesterol = total cholesterol - HDL cholesterol - triglycerides

5

Determination of Lp(a) levels. Electroimmunoassay for Lp(a) was performed as previously described. To prepare antisera, rabbits were immunized with Lp(a) isolated from plasma by ultracentrifugation and gel filtration on a Bio-Gel A-15m column. To obtain an antisera monospecific for Lp(a) antigen, the rabbit anti-Lp(a) serum was adsorbed with isolated LDL, and the visible precipitate was removed by low-speed centrifugation. On Ouchterlony gels, the adsorbed antiserum gave a single precipitin line with plasma, showing complete identity with Lp(a) but not LDL. Electroimmunoassay was used to quantitate Lp(a) in serum samples within 1 or 2 days after blood was drawn. Samples were stored at 4°C until they were analyzed. Lp(a) concentrations were calculated by comparison of peak heights in sample and standard rockets. A serum sample from an individual with a high Lp(a) level was kept frozen at -60°C in small aliquots and used as a standard. This serum was standardized against purified Lp(a) with known protein and lipid contents by electroimmunoassay. The lowest standard dilution always gave a peak height higher than that in the samples, and the standard dilution curve was linear with a correlation coefficient of .99. Double determinations of Lp(a) concentrations in the control serum in each run gave a between-day coefficient of variation of 4.2%.

Electroimmunoassay for Lp(a) has been performed on LDL purified by zonal ultracentrifugation from plasma pooled from 18 individuals and less than 1% of the protein content of this preparation was detected as Lp(a) protein by electroimmunoassay.*

Statistical procedures. Parametric and nonparametric analyses were performed with the Statistical Package for the Social Sciences. Nonparametric correlation by the Kendall rank procedure was preferred for univariate analysis, because the distributions of the two major variables — Lp(a) levels and coronary lesion scores — clearly deviated from normality. Because of the marked association between HDL cholesterol levels and gender, Kendall rank correlation was performed both with and without adjustment of HDL cholesterol levels for gender. Multivariate procedures included linear discriminant analysis and multiple linear regression. Discriminant analysis was by a stepwise forward-backward procedure with the goal of minimizing Wilks’ lambda. The significance of a variable’s unique contribution was computed from the final F-to-remove statistic. The significance level of a variable entering stepwise multiple regression was computed from the change in variance produced.

Results

The distribution of Lp(a) levels among the subject population (figure 1) was, as expected, highly skewed, with a mean Lp(a) level of 19.6 mg/dl and a median of

10.3 mg/dl. Levels of Lp(a) below the limit of detectability (approximately 5 mg/dl), found in 37% of the subjects, were recorded as zero and included in the statistical analyses. The distributions of other lipid and lipoprotein levels in the study were approximately bell shaped. Only 13% of the subjects were hypercholesterolemic as defined by plasma cholesterol levels above 250 mg/dl, and only 2% had plasma cholesterol levels of 300 mg/dl or greater. Triglyceride levels above 250 mg/dl were found in 16% of the subjects.

Lp(a) levels were found to correlate with those of LDL cholesterol (r = .13, p = .03 among men; r = .39, p < .001 among women). Since Lp(a) is precipitated by heparin-manganese during the procedure for measurement of HDL cholesterol,* the value calculated for LDL cholesterol actually represents cholesterol contained in both LDL and Lp(a). If a term representing Lp(a) cholesterol is subtracted from the calculated LDL cholesterol level, then the difference should represent true LDL cholesterol more accurately. After subtracting this term [0.3 × Lp(a) mass concentration] for each subject, there was no longer any correlation between LDL cholesterol and Lp(a) levels among men, but a highly significant correlation (r = .26, p = .01) was still obtained among women. Lp(a) also correlated significantly with total plasma cholesterol.

The frequency distribution for mean angiographic scores is shown in figure 2. The subjects could be divided, according to coronary scores, into three groups with approximately equal numbers in each group, with the use of scores less than 25, those from 25 to 150, and those greater than 150. Table 1 lists lipid and lipoprotein levels in these groups subdivided by sex. Among men, the groups with the positive coronary scores were significantly older than the group with negative angiograms. No lipid or lipoprotein variable differed significantly between these groups of men. Among the women, the group with the highest coronary scores had significantly higher cholesterol, LDL cholesterol, and Lp(a) levels than those with negative angiograms.

Table 2 lists the results of univariate, nonparametric correlation of lipid-lipoprotein variables and coronary lesion scores. Significant effects of plasma levels of cholesterol, triglycerides, LDL cholesterol, HDL cholesterol, and Lp(a) were shown for the entire study group. In subgroup analyses, significant correlations between coronary scores and Lp(a) were found among women and younger men. Coronary scores did not correlate with any lipid-lipoprotein variable among older men.

Figure 3 gives additional information on the univariate relationship between Lp(a) levels and coronary lesion score. Subjects were ranked in order of their Lp(a) levels and then grouped by population deciles. The decile assignments of the overall population were retained, to provide consistency, in all four histograms in figure 3. These groups almost matched deciles of

Lp(a) levels within age-sex subpopulations. Within each Lp(a) decile, the mean coronary lesion score is represented by a histogram bar. The histogram for all subjects shows an apparent threshold for Lp(a) effect at the 70th percentile, corresponding to an Lp(a) level of 30 mg/dl. An important boundary level in the subpopulations appears to be the 80th percentile, corresponding to an Lp(a) level of 39 mg/dl. Women with Lp(a) levels higher than this had an average coronary lesion score 167% higher than women with lower Lp(a) levels. For men under age 56, those with such high Lp(a) levels had an average score 80% higher than those with lower Lp(a) levels. In men over age 55 no effect of Lp(a) on coronary lesion score was noted.

Multivariate statistical analyses were performed to gauge the independence of risk factor effects. LDL cholesterol was not evaluated as a multivariate risk factor, because the LDL cholesterol level is itself a derived linear function of the measured variables. To perform discriminant analysis, the patients were divid-

### TABLE 1
Mean (±SD) plasma lipid and lipoprotein levels in relation to coronary score

<table>
<thead>
<tr>
<th></th>
<th>Group 1 (coronary score &lt;25)</th>
<th>Group 2 (coronary score 25-150)</th>
<th>Group 3 (coronary score &gt;150)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Men</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>n</td>
<td>47</td>
<td>84</td>
<td>89</td>
</tr>
<tr>
<td>Age</td>
<td>52.0 (10.7)</td>
<td>57.0 (9.1)</td>
<td>59.9 (9.2)</td>
</tr>
<tr>
<td>Cholesterol</td>
<td>198 (37)</td>
<td>204 (39)</td>
<td>204 (46)</td>
</tr>
<tr>
<td>Triglycerides</td>
<td>172 (72)</td>
<td>176 (69)</td>
<td>189 (67)</td>
</tr>
<tr>
<td>HDL-C</td>
<td>35.9 (9.3)</td>
<td>32.6 (7.0)</td>
<td>33.0 (10.7)</td>
</tr>
<tr>
<td>LDL-C&lt;sup&gt;b&lt;/sup&gt;</td>
<td>129 (35)</td>
<td>136 (36)</td>
<td>133 (44)</td>
</tr>
<tr>
<td>Lp(a)</td>
<td>13.7 (15.3)</td>
<td>20.5 (22.2)</td>
<td>20.4 (21.2)</td>
</tr>
<tr>
<td><strong>Women</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>n</td>
<td>47</td>
<td>19</td>
<td>21</td>
</tr>
<tr>
<td>Age</td>
<td>55.2 (11.0)</td>
<td>62.1 (10.1)</td>
<td>58.4 (7.2)</td>
</tr>
<tr>
<td>Cholesterol</td>
<td>200 (42)</td>
<td>213 (50)</td>
<td>244 (53)</td>
</tr>
<tr>
<td>Triglycerides</td>
<td>161 (73)</td>
<td>177 (104)</td>
<td>190 (133)</td>
</tr>
<tr>
<td>HDL-C</td>
<td>47.3 (16.4)</td>
<td>41.0 (8.8)</td>
<td>42.4 (14.2)</td>
</tr>
<tr>
<td>LDL-C&lt;sup&gt;b&lt;/sup&gt;</td>
<td>119 (42)</td>
<td>136 (53)</td>
<td>164 (55)</td>
</tr>
<tr>
<td>Lp(a)</td>
<td>12.7 (17.2)</td>
<td>27.9 (26.5)</td>
<td>33.9 (32.0)</td>
</tr>
</tbody>
</table>

HDL-C = HDL cholesterol; LDL-C = LDL cholesterol.
<sup>a</sup>For HDL-C and LDL-C, results were not available for five patients.
<sup>b</sup>LDL-C was calculated from cholesterol – HDL-C – triglycerides/5.

### TABLE 2
Univariate, nonparametric correlation of risk factors with coronary scores

<table>
<thead>
<tr>
<th></th>
<th>Age</th>
<th>Cholesterol</th>
<th>TG</th>
<th>HDL-C</th>
<th>LDL-C</th>
<th>Lp(a)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All subjects (n = 302)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>r value</td>
<td>.15</td>
<td>.08</td>
<td>.08</td>
<td>-.10</td>
<td>.11</td>
<td>.10</td>
</tr>
<tr>
<td>p value</td>
<td>.001</td>
<td>.02</td>
<td>.02</td>
<td>.01</td>
<td>.003</td>
<td>.007</td>
</tr>
<tr>
<td>Women (n = 86)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>r value</td>
<td>NS</td>
<td>.23</td>
<td>NS</td>
<td>NS</td>
<td>.22</td>
<td>.22</td>
</tr>
<tr>
<td>p value</td>
<td>NS</td>
<td>.002</td>
<td>NS</td>
<td>.003</td>
<td>.005</td>
<td></td>
</tr>
<tr>
<td>Men ≤55 yr old (n = 88)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>r value</td>
<td>NS</td>
<td>NS</td>
<td>.15</td>
<td>-.17</td>
<td>NS</td>
<td>.15</td>
</tr>
<tr>
<td>p value</td>
<td>NS</td>
<td>.03</td>
<td>NS</td>
<td>.02</td>
<td>.03</td>
<td></td>
</tr>
<tr>
<td>Men &gt;55 yr old (n = 128)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>r value</td>
<td>.11</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>p value</td>
<td>.03</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

In the analysis for all subjects, HDL cholesterol (HDL-C) was adjusted for gender differences. The analyses using adjusted HDL-C values yielded r = -.18, p ≤ .001. r value is the Kendall rank correlation coefficient.

TG = triglycerides; LDL-C = LDL cholesterol; NS = p > .05.
Discussion

Our results demonstrate a highly significant relationship between quantitatively determined plasma Lp(a) levels and findings at coronary angiography. As a univariate predictor of lesion severity and as an independent multivariate predictor of the presence of coronary artery disease, the plasma Lp(a) level exerted effects comparable in magnitude to those of the more commonly recognized factors of total plasma cholesterol and HDL cholesterol.

Coronary angiography as a mode of epidemiologic investigation has the major advantage of measuring anatomically defined atherosclerotic lesions. The lesion scoring method that we chose had the advantages of ease of application and good reproducibility. While it was more subjective than recently developed quantitative angiographic techniques, the newer techniques are cumbersome and do not have demonstrated superiority for studies relating risk factors to coronary artery disease. Our lesion scoring system represents a reasonable compromise between elaborate quantitation and the simple strategy of categorizing patients by the number of coronary branches involved.

The epidemiologic peculiarities of angiographic data must be considered. The primary difficulty relates to the selection of patients, which, in this study as in others, was done entirely on clinical grounds. Theoretically the patients may be divided into two categories — those having coronary artery disease as the cause for their presentation and subsequent evaluation, and those in whom coronary anatomy is unrelated to the complaints that brought them to the cardiologist’s attention. The frequency distribution of coronary scores that we found clearly deviates from normal and reflects the existence of these two groups of patients. For this reason, many studies using coronary angiography have dichotomized the angiographic results and performed various analyses to determine which risk parameters are able to discriminate between those patients with and without coronary artery disease. In other studies risk factors were related to quantitative indexes of lesion severity or both types of analyses were performed.

We used three complementary approaches to judge the significance of the association between plasma Lp(a) levels and coronary artery disease. First, a high-

![FIGURE 3. Mean coronary lesion scores within deciles of patient population ranked by Lp(a) levels. Since 37% of the subjects had undetectable Lp(a), the first four deciles were grouped together.](http://circ.ahajournals.org/)

### TABLE 3

| Multivariate discriminant analysis of the ability of risk factors to predict presence or absence of substantial coronary narrowing (coronary score ≥70 or <70, respectively) |
|-----------------|-----------------|-----------------|-----------------|-----------------|
|                 | Age             | Gender          | Cholesterol     | HDL cholesterol |
| Standardized coefficient C<sub>i</sub> | .44             | .63             | .40             | −.33            |
| p value         | .002            | <.001           | .004            | .02             |

All subjects (n = 302) were included in the analysis.
ly significant univariate correlation was demonstrated by a nonparametric method, with the correlation coefficient for Lp(a) quite comparable to those for plasma cholesterol and HDL cholesterol. Our second approach, discriminant analysis, has epidemiologic validity as well as practical clinical utility, because of the theoretical dichotomy discussed above among patients undergoing angiography. By this technique Lp(a) level was shown to be an independent predictor of the presence of coronary lesions, whether the criterion for presence of disease was a lesion score greater than zero or a more clinically relevant level of 70 or greater. The statistical method used to calculate significance levels ensured that only the unique contribution of Lp(a) level to discrimination between patient groups was considered, after accounting for the effects of all other significant variables.

Stepwise multiple linear regression failed to show a significant independent correlation between Lp(a) level and overall lesion severity. However, the significance level (p = .06) was borderline and should not be interpreted to indicate no independent effect, but rather simply to be nonconfirmatory. The presence and severity of lesions as determined at angiography obviously relate not only to atherogenic factors, but also to other factors governing the production of ischemia and symptoms, which may hasten or postpone the clinical expression of stenosis. Such confounding factors might include the development of collateral vessels or the patient’s recent level of physical exertion. The complex interplay between atherogenic and other factors might explain the minor discrepancy between results of our analyses for overall lesion severity and those for presence/absence of disease.

Our results are consistent with those of two studies in which plasma Lp(a) levels were quantified in survivors of myocardial infarction. Albers et al. found a shift in the Lp(a) distribution to higher levels in patients with infarction as compared with control subjects. The shift was apparently not statistically significant when the total study group was considered, but it was significant in the subgroup of patients with Lp(a) levels higher than the median. Patients who had their myocardial infarctions at age 50 or below had significantly higher levels than older patients with infarction. We found a similar relationship with respect to age in that younger men showed a marked association between Lp(a) levels and coronary lesion scores, while in men over age 55 there was no trend at all (figure 3). Murai et al. found that a group of patients surviving myocardial infarction or having angina with electrocardiographic evidence of coronary disease included a significantly greater proportion with Lp(a) levels of at least 17 mg/dl than did a control group. Kostner et al. measured serum Lp(a) concentration in male survivors of myocardial infarction between the ages of 40 and 60 years and in a comparable control group. Statistically significant differences were not demonstrated among the total study population. These data do suggest, however, that among normolipidemic subjects, those with Lp(a) levels greater than 30 mg/dl may have a risk for myocardial infarction 1.75 times that of subjects with Lp(a) levels below this level. Among men 55 years old or less in our study, Lp(a) levels above 30 mg/dl were associated with an average 58% increase in coronary lesion score. This is quite consistent with the high level of risk suggested by Kostner et al. The potential impact of Lp(a)-associated coronary risk in a white population is emphasized by the fact that 25% of subjects in the control group of Kostner et al. and 19% of our patients with normal coronary arteries had such high Lp(a) levels. These percentages represent estimates of the fraction of a white population at risk for Lp(a)-associated acceleration of coronary atherogenesis. In the studies of Albers et al. and Kostner et al., statistical independence of the Lp(a) effect was presumed on the basis of lack of correlation between Lp(a) and other variables. The results of discriminant analysis in the present study definitively make this point.

Recently considerable attention has focused on plasma apolipoprotein levels as predictors of coronary artery disease. Since our Lp(a) assay is based on electroimmunoassay for apolipoprotein antigenic determinants, the present study falls within this context. Apolipoprotein B level has been found to be a better positive predictor of coronary artery disease than that of cholesterol or LDL cholesterol in most, but not all studies. In one study the residual effect of apolipoprotein B was examined after accounting for the effects of other variables, including plasma cholesterol, and the apolipoprotein B effect remained highly significant. In a group of healthy subjects in Houston, we found plasma Lp(a) levels to correlate weakly but significantly with apolipoprotein B levels. This was not surprising, since apolipoprotein B and apolipoprotein [a] coexist within the Lp(a) lipoprotein. While apolipoprotein B and apolipoprotein [a] probably act to a large degree independently on coronary risk, the question of interaction must be investigated in the future.

The correlation between Lp(a) and LDL cholesterol levels found in the present study was hardly unexpected, since the common clinical method for estimating levels of LDL cholesterol actually measures Lp(a) cho-
lesterol as well. Among men, the subtraction of estimated Lp(a) cholesterol from LDL cholesterol abolished the correlation. This is consistent with the idea that LDL and Lp(a) lipoprotein levels are not linked metabolically. Certain interventions that altered plasma levels of LDL have had little, no, or opposite effects on levels of Lp(a). Among women in this study, we found a surprising correlation between Lp(a) levels and LDL cholesterol that remained quite significant even after subtraction of Lp(a) cholesterol from the latter. This finding might reflect a metabolic or genetic link between levels of the two lipoproteins in women. However, an alternative possibility is that LDL and Lp(a) may act synergistically to promote atherogenesis in women, so that women who happen to have high levels of both would be particularly prone to develop symptoms resulting in their referral for coronary angiography.

The present study was performed on a population consisting entirely of white persons, and results do not necessarily apply to other racial groups. We have found that black subjects in Houston have average Lp(a) levels twice as high as whites, with a bell-shaped distribution of levels rather than the highly skewed distribution typical for whites. Despite their high levels of Lp(a), black men in particular appear to have a lower death rate from coronary heart disease than do white men. This example indicates that it will be necessary to confirm the coronary risk associated with Lp(a) in racial groups other than the largely white populations studied thus far. Recently coronary and cerebrovascular disease were found to be significantly associated with high plasma Lp(a) levels among Japanese subjects.

In this and other studies lipoprotein Lp(a) apparently exerted atherogenic effects when it carried 10 to 30 mg/dl of plasma cholesterol. The effects were comparable to those attributable to LDL, despite the fact that LDL cholesterol levels were typically five- to tenfold higher. In women and younger men, Lp(a) may be considerably more potent in promoting atherogenesis than LDL on a molar or per milligram cholesterol basis.

Thus far the relationship of lipoprotein Lp(a) to atherosclerotic disease has been demonstrated solely by cross-sectional statistical associations. Prospective studies and eventually studies of prophylactic intervention will be necessary to clarify the atherogenic role of this lipoprotein.

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