Lipoprotein(a) and Apolipoprotein(a) Isoforms
No Association With Coronary Artery Calcification in
The Dallas Heart Study

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Background—Elevated plasma levels of lipoprotein(a) [Lp(a)] are an independent risk factor for cardiovascular disease in whites. Blacks have 2- to 3-fold higher plasma levels of Lp(a) than whites and yet do not have a correspondingly higher rate of coronary events. It remains unclear whether elevated plasma levels of Lp(a) are an independent risk factor for coronary atherosclerosis in individuals of African descent.

Methods and Results—The relationship between plasma levels of Lp(a), apolipoprotein(a) isoform sizes, and the presence of coronary calcium was examined in 761 blacks and 527 whites (men aged ≥40 years, women aged ≥45 years) from a population-based sample. No relationship was found between plasma levels of Lp(a), apolipoprotein(a) isoform size, or a combination of these 2 variables and coronary artery calcium (CAC) in whites or blacks. No correlation was observed between plasma levels of Lp(a) and coronary calcium scores in any group, although all black men with very high plasma levels of Lp(a) (>300 μmol/L; n=7) were CAC-positive. Whites with high plasma levels of Lp(a) plus elevated plasma levels of LDL cholesterol (men) or reduced levels of HDL cholesterol (men and women) or who smoked (women) had a higher prevalence of CAC. In contrast, no joint effects between plasma levels of Lp(a) and other cardiovascular risk factors on coronary calcium were found in blacks.

Conclusions—No consistent independent relationship between plasma levels of Lp(a) or apolipoprotein(a) isoform size and coronary calcium was found in whites or blacks. (Circulation. 2005;111:1471-1479.)

Key Words: lipoproteins ■ apolipoproteins ■ arteriosclerosis ■ coronary disease ■ risk factors

Lipoprotein(a) [Lp(a)] is a cholesteryl ester–rich lipoprotein distinguished from other lipoproteins by the presence of a unique apolipoprotein (apo), apo(a). Plasma concentrations of Lp(a) vary over a 1000-fold range, and the distribution of levels is highly skewed, with most whites and Asians having low levels. Until recently, controversy persisted about the status of elevated plasma levels of Lp(a) as an independent risk factor for the development of coronary atherosclerosis; however, a meta-analysis of 27 prospective studies, which included 5436 coronary heart disease cases, demonstrated a consistent, positive association between high plasma levels of Lp(a) and coronary atherosclerotic events in whites. The distribution of plasma levels of Lp(a) in blacks is less skewed, and the median level is 2 to 4 times greater than in whites. Paradoxically, the higher levels of Lp(a) in blacks are not associated with a corresponding increase in the prevalence of coronary atherosclerosis.

A possible explanation for the apparent dissociation between plasma Lp(a) levels and coronary atherosclerotic risk in blacks is that only a subset of individuals with high plasma levels of Lp(a), those with apo(a) isoforms of small size, are at increased risk. The apo(a) gene (APOA) is highly polymorphic in size owing to allelic differences in the number of a kringle-encoding sequence resembling kringle 4 of plasminogen. In vitro studies suggest that apo(a) interferes with plasminogen, a centralzymogen in thrombosis, and that smaller apo(a) isoforms are more effective at inhibiting thrombolysis. In some studies, whites with apo(a) isoforms of small size have an increased incidence of coronary atherosclerosis. Because plasma levels of Lp(a) are inversely related to the size of the apo(a) gene and isoforms in whites, most whites with high plasma levels of Lp(a) have a small isoform. Therefore, it has been difficult to distinguish the relative atherogenic effects of apo(a) isoform size and plasma levels of Lp(a) in whites. In contrast, many blacks with high plasma levels of Lp(a) have apo(a) isoforms of intermediate size. Thus, examination of the relationship between plasma levels of Lp(a), apo(a) isoforms, and coronary atherosclerosis in blacks provides an opportunity to
assess the relative contributions of isofrom size and plasma levels of Lp(a) to coronary atherosclerotic risk.

In the present study, we examined the relationship between plasma levels of Lp(a), apo(a) isofrom size, and coronary atherosclerotic burden in 1288 blacks and whites from the Dallas Heart Study (DHS), using electron-beam computed tomography (EBCT), a sensitive and noninvasive method to assess coronary atherosclerotic burden. Because Lp(a) has been demonstrated in vitro to adhere to multiple components of the extracellular matrix in the arterial wall, it has been proposed that the accumulation of Lp(a) within the lesion wall promotes accumulation of LDL. As the atherosclerotic lesion develops, calcium is deposited in the arterial wall. If the major effect of Lp(a) were to promote atherosclerosis, it would be expected that individuals with high plasma levels of Lp(a) would have a greater prevalence and/or amount of coronary calcium.

**Methods**

**Study Population**

The study subjects were obtained from the DHS, a multiethnic population-based probability sample of Dallas County, Texas, in which ethnicity was self-reported. The Institutional Review Board of the University of Texas Southwestern Medical Center approved the study, and all participants provided informed consent in accordance with institutional guidelines. Fasting blood samples were obtained from 3398 subjects (1760 blacks, 1068 whites, and 570 Hispanics). Blood was maintained at 4°C until the plasma was separated, placed in aliquots, and stored at −80°C. Plasma levels of Lp(a) and apo(a) isofrom sizes were determined with well-validated assays. Of the participants who underwent phlebotomy, 2971 (50% black) completed a clinic visit at which coronary artery calcification (CAC) was evaluated by EBCT. A total of 970 blacks and 593 whites (men aged ≥40 years and women aged ≥45 years) underwent duplicate EBCT scans. A complete data set of the variables for this analysis in men aged ≥40 years and women aged ≥45 years included 1288 subjects (380 black women, 241 white women, 381 black men, and 286 white men).

**Risk Factor Profiling of Subjects**

The assessment of cardiovascular risk factor status in the DHS is as described previously. The mean of the middle 3 (of 5) blood pressure measurements from the clinic visit was used in the present study. Subjects with blood pressure >140/90 mm Hg or taking antihypertensive medications were classified as hypertensive. The age-adjusted ORs were used to analyze the joint effect of Lp(a) with other cardiovascular risk factors on CAC status. To consider the possible loss of information associated with the use of a binary scale for EBCT scores, we also used ordinal regression analysis and classified the amount of CAC based on the atherosclerotic burden using the Rumberger scale: 0 to 10 (minimal), 10 to 100 (mild), 100 to 400 (moderate), and >400 (extensive) Agatston units.

Continuous variables were summarized with means or medians and SDs. Two-sample t tests and ANOVA F tests were used to assess differences in means. To compare 2 skewed distributions, we assessed differences in medians. For large sample sizes, the sample median is normally distributed, and therefore, the difference in sample medians is normally distributed. The reported probability values for median differences are thus derived from the normal based Wald test: $Z = (\bar{W} - \mu)/\sigma(W)$, where $\bar{W}$ is a test statistic, $\sigma(W)$ is the standard error for $W$, and $\mu$ is the hypothesized value for $W$. In this case, $W$ is the difference in sample medians and $\mu$ is zero. The analytic expression for $\sigma(W)$ is based on the asymptotic variance formula for a sample median. $\chi^2$ tests were used for contingency table analysis of categorical variables. Lp(a) levels were summarized on their original scale and log-transformed before logistic and ordinal regression analysis because of the skewness of the distribution.

The joint effect of Lp(a) with other cardiovascular risk factors on the presence of CAC can be analyzed with logistic and ordinal regression models that include both main and interaction effects; however, because of the large sample size in the present study, we were able to conduct a more straightforward analysis within each race-gender subgroup without imposing model assumptions. To assess the joint effect of plasma levels of Lp(a) and a binary risk factor on CAC status, we compared the odds of being CAC+ in subjects with the risk factor and high Lp(a) to the odds of being CAC+ in subjects without the risk factor and low Lp(a). To analyze the joint effect of Lp(a) and continuous risk factors, we defined the top 30% tail of the risk factor as a positive risk factor effect and the bottom 30% as a negative risk factor effect and proceeded as above. The ORs for the risk factors were age-adjusted with logistic regression as follows. Let $P$ denote the probability of disease. With 2 predictor variables, $x_1$ and $x_2$, the logistic model associates a person’s log-odds of disease with the 2 predictors: $\log[P/(1-P)] = \beta_0 + \beta_1 x_1 + \beta_2 x_2$. To obtain age-adjusted ORs, we defined $P$ as the probability of being CAC+, $x_1$ as age, and $x_2$ as an indicator variable for risk group membership (high, low) defined by a given risk factor. The estimated value of $\beta_1$ represents the change in log-odds of CAC+ associated with a 1-year increase in age, adjusted for $x_2$. According to the model, this change is assumed to be constant for persons of all ages. Of particular interest is the estimated value of $\beta_2$, which is interpreted as the age-adjusted log-OR for $x_2$. Therefore, if $x_2$ represents an indicator (yes/no) for hypertension, then $\beta_2$ is the log-OR of CAC+ for a person with hypertension relative to a person without hypertension. The age-adjusted ORs were used to analyze the joint effects of Lp(a) and other cardiovascular factors on CAC status.

The DHS is a probability-based survey with oversampling for blacks. Sample weights were used to extrapolate statistical inferences to the population, as described previously. Statistical analyses were performed with and without sample weights. Because the 2
sets of results were almost always in agreement, we reported unweighted data and results. Analyses were completed with the statistical packages S-Plus (Insightful) and Stata (Stata Corporation).

Results

Demographic and selected clinical characteristics of the 1288 black and white subjects (men aged >40 years, women aged ≥45 years) in the DHS who obtained an EBCT are provided in Table 1. No significant differences were found between black and white women in mean age; plasma levels of LDL-C, HDL-C, or triglycerides; or the prevalence of smoking and postmenopausal status. Mean body mass index and the prevalence of hypertension and diabetes were significantly higher (P <0.0001) in black women than in white women. Black men had significantly lower plasma levels of HDL-C (P <0.0001) than their white counterparts. A significantly greater proportion of black men were smokers and hypertensive (P <0.0001), as well as diabetic (P <0.0003).

Plasma levels of Lp(a) were significantly higher in blacks than in whites (Table 1). Levels of plasma Lp(a) were significantly higher (P <0.0001) in black women than in black men, but no gender difference was apparent in whites. Distributions of plasma Lp(a) by ethnicity and gender were similar to those of prior studies19 and did not differ between subjects who did and did not obtain an EBCT scan (data not shown).

To determine whether plasma levels of Lp(a) were associated with the presence of coronary calcium, the prevalence of positive CAC scores was determined for individuals within each Lp(a) quintile (Figure 1). No significant differences were found in the proportion of individuals who were CAC+ among the quintiles. Similarly, median plasma levels of Lp(a) were not significantly different in black men, black women, white men, or white women who were CAC+ and CAC− (Table 2), nor was any significant association between log-transformed plasma levels of Lp(a) and CAC status found in either logistic or ordinal regressions (data not shown). The relationship between plasma levels of Lp(a) and coronary calcium after the amount of CAC was classified for each individual with the Rumberger scale31 was also examined; no significant relationship was found between the 2 variables for any of the ethnic and gender-specific groups (data not shown). Accounting for age and smoking did not change the negative results of the logistic and ordinal regressions.

Mean plasma levels of Lp(a) were also not significantly different in the CAC+ and CAC− subjects, with 1 exception. Black men who were CAC+ had a significantly higher mean plasma level of Lp(a) (95 nmol/L) than black men without CAC (79 nmol/L; P =0.03; Table 2). To probe why the mean (but not median) plasma level of Lp(a) was significantly higher in the CAC+ black men, we examined and compared the distribution of plasma Lp(a) levels in CAC+ and CAC− black men (Figure 2). Although no overall correlation be-
TABLE 2. Plasma Levels of Lp(a) and Homocysteine and CAC+ Prevalence in the DHS Stratified by Ethnicity and Gender

<table>
<thead>
<tr>
<th>Age, y</th>
<th>Median Lp(a), nmol/L</th>
<th>Mean Lp(a), nmol/L</th>
<th>Mean HCY, μmol/L</th>
<th>Median HCY, μmol/L</th>
<th>P</th>
<th>CAC+ (n=126)</th>
<th>CAC− (n=254)</th>
<th>CAC+ (n=162)</th>
<th>CAC− (n=219)</th>
<th>CAC+ (n=118)</th>
<th>CAC− (n=168)</th>
<th>P</th>
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<tr>
<td>Black Women</td>
<td>56±5</td>
<td>110±87</td>
<td>10±4</td>
<td>9</td>
<td>0.07</td>
<td>8</td>
<td>1</td>
<td>11±5</td>
<td>14</td>
<td>&lt;0.01</td>
<td>65±7</td>
<td>49±6</td>
</tr>
<tr>
<td>White Women</td>
<td>53±5</td>
<td>113±82</td>
<td>9±3</td>
<td>8</td>
<td>0.04</td>
<td>8</td>
<td>0</td>
<td>11±6</td>
<td>10</td>
<td>&lt;0.01</td>
<td>65±6</td>
<td>49±5</td>
</tr>
</tbody>
</table>

HCY indicates homocysteine.

Values are mean±SD, except where indicated.

*Mean values were compared with t tests, and the bootstrap test was used to compare medians.
size of the major apo(a) isoform and plasma levels of Lp(a) in black and white subjects classified by their CAC status (Figure 5). A joint effect would be evident if a predominance of CAC+ individuals had smaller apo(a) isoforms and higher plasma levels of Lp(a). No such relationship was observed in any of the 4 ethnic-gender groups, which indicates the absence of a joint effect. The slopes of the regression line of log-Lp(a) on apo(a) isoform size in each CAC/H1001 and CAC/H1002 subgroup were not significantly different (P>0.05).

Finally, we investigated the possibility that high plasma levels of Lp(a) are atherogenic in the presence of other risk factors. CAC/H1001 scores were adjusted for age in these analyses, because age was significantly associated with CAC/H1001 status in all groups (P<0.01; Table 2). The odds of being CAC+ in subjects with high plasma levels of Lp(a) and high risk factors were compared with the odds in subjects with low plasma levels of Lp(a) and low risk factors. The OR of high LDL to low LDL was 1.5 (P=0.24) and increased to 4.2
(P=0.03) when high-LDL/high-Lp(a) was compared with low-LDL/low-Lp(a) groups in white men (Table 3). White men also showed a strong joint effect between high plasma levels of Lp(a) and a low plasma level of HDL-C (OR=8.3, P=0.01) and high levels of plasma triglyceride (OR=5.2, P=0.03); a similar joint effect between high plasma levels of Lp(a) and low plasma levels of HDL-C was seen in white women (OR increasing from 2.5 to 4.6). No interactive effects were seen between high plasma levels of Lp(a) and high plasma levels of homocysteine in either white women or men, in contrast to what was observed previously. Of the discrete variables examined (diabetes, hypertension, and smoking), only smoking showed a joint effect with plasma levels of Lp(a) in white women. To assess the validity of the significant joint effects, we evaluated possible confounding factors between the high-Lp(a)/high-risk-factor subjects and the low-Lp(a)/low-risk-factor subjects; no evidence for confounding was found for diabetes, smoking, hypertension, or body mass index. No joint effects between plasma levels of Lp(a) and any of the continuous variables (plasma levels of LDL-C, HDL-C, triglycerides, body mass index, homocysteine) or the discrete variables (diabetes, hypertension and body mass index) were observed in any of the groups studied.

Figure 4. Relationship between size of major apo(a) isoform and prevalence of CAC+ status. Apo(a) isoforms were binned into 4 groups of similar sample size (shown above bars), and percentage of individuals who were CAC+ in each group was determined (y-axis).

Figure 5. Relationship between size of major apo(a) isoform (x-axis), plasma level of Lp(a) (y-axis), and presence (blue) or absence (red) of CAC, as assessed by EBCT. Vertical axis is in natural log-scale.
smoking) were found in black men or women (data not shown).

**Discussion**

The major finding of this study was that the presence of CAC is not significantly related to plasma levels of Lp(a), apo(a) isoform size, or the combination of apo(a) isoform size and plasma level of Lp(a) in whites or in black women. These data constitute the most representative sample of blacks in which this relationship has been studied. Extremely high plasma levels of Lp(a) (≥300 nmol/L), but not apo(a) isoform size, were associated with a higher prevalence of coronary calcium in black men. Further analysis revealed that elevated plasma levels of Lp(a) significantly increased the odds of having detectable coronary calcium in whites with selected cardiovascular risk factors, including high plasma levels of LDL-C, elevated plasma levels of triglycerides, or low plasma levels of HDL-C in men. In white women, elevated plasma levels of Lp(a) acted synergistically with a smoking history and with low plasma levels of HDL-C to increase the odds of being CAC+.

Because the median level of Lp(a) in blacks is 2- to 3-fold higher than in whites, and the prevalence of established cardiovascular risk factors is equivalent or greater in blacks than in whites (Table 1), the burden of coronary atheroscle-

<table>
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<tr>
<th>Risk Factor</th>
<th>Percentiles</th>
<th>Low Risk Factors, % CAC</th>
<th>High Risk Factors, % CAC</th>
<th>OR† (P) (95% CI)</th>
<th>Low Risk Factors/Low Lp(a), % CAC</th>
<th>High RF/High Lp(a), % CAC</th>
<th>OR† (P) (95% CI)</th>
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<td>Women</td>
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<td>LDL-C</td>
<td>88, 121</td>
<td>21</td>
<td>29</td>
<td>1.6 (0.26)</td>
<td>13</td>
<td>31</td>
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<td>2.5 (0.04)</td>
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<td>17</td>
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<td>28</td>
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<td>22</td>
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<td>53</td>
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<td>34</td>
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TG indicates triglycerides; BMI, body mass index; HCY, homocysteine; and HTN, hypertension.

*High and low levels of risk factors defined by top and bottom 30% tails, respectively.
†ORs have the high (low) risk factor tail in the numerator (denominator) and are age-adjusted. OR for HDL-C has the low (high) HDL-C tail in the numerator (denominator). Average sample sizes are n=75 per tail for univariate OR and n=32 per tail for bivariate OR.
rosis would be expected to be greater in the black population. Yet, most studies find the rate of preclinical atherosclerosis and ischemic events is similar in blacks and whites, although black women may have increased odds of disease compared with white women. A major limitation of most studies examining the relationship between plasma levels of Lp(a) and coronary atherosclerosis in blacks is that they have been small and not representative. The largest study assessing the effect of plasma levels of Lp(a) on cardiovascular events in blacks was the Atherosclerosis Risk in Communities Study, in which only a marginally significant relationship was found. The DHS is the most representative study to date that has examined the relationship between plasma levels of Lp(a) and coronary atherosclerotic burden. The present results support previous findings that plasma levels of Lp(a) are not associated with the presence of coronary atherosclerotic lesions in blacks.

An appealing possible explanation for the finding that blacks have significantly higher plasma levels of Lp(a) and yet do not have a correspondingly higher incidence of coronary atherosclerosis is that only a subset of apo(a) isoforms, those of smaller size (<22 kringle) are atherogenic. No evidence to support a relationship between the presence of coronary calcium and either apo(a) isoform size or plasma levels of Lp(a) in blacks or whites was found in the present study (Figures 1 and 4). Thus, if apo(a) isoforms have an independent effect on the atherogenicity of Lp(a), it does not manifest as increased calcium deposition in the coronary arteries.

The present study also represents one of the largest population-based samples in which plasma levels of Lp(a) and apo(a) isoforms have been measured in both blacks and whites with an Lp(a) assay that accurately measures the number of circulating Lp(a) particles, irrespective of the number of kringle 4 repeats. Black women had a significantly higher plasma level of Lp(a) than black men, as has been noted previously, whereas no such gender difference was present in whites. In the future, gender differences in plasma levels of Lp(a) may provide clues as to the nongenetic factors that contribute to plasma levels of Lp(a).

If the major effect of Lp(a) were to promote atherosclerosis, as has been proposed, individuals with high plasma levels of Lp(a) would have been expected to have a greater prevalence of coronary calcium in the present study. Yet, with the exception of black men with very high plasma levels of Lp(a), no evidence for an independent relationship between plasma levels of Lp(a) and coronary calcium, assessed either as a quantitative or qualitative trait, was seen in either blacks of whites; however, the odds of being CAC+ were greatly increased in whites who had other cardiovascular risk factors, which suggests Lp(a) may only increase the risk of coronary atherosclerosis in those already at higher risk. The finding that high plasma levels of Lp(a) significantly increased the odds for having significant coronary atherosclerosis in white men with high plasma levels of LDL-C has been observed in other studies. Synergistic effects of high plasma levels of Lp(a) and LDL-C on lesion development were also apparent when recombinant apo(a) was expressed in the Watanabe Heritable Hyperlipidemic rabbit.

The present study does not conflict with the meta-analysis that found that plasma levels of Lp(a) are an independent risk factor for coronary events or the study that found a relationship with angina, because we did not measure these variables. The results of this study instead suggest that the major adverse cardiovascular effect of Lp(a) may not be due to its effects on the development of the atherosclerotic lesion but rather to its effects on lesion stability or susceptibility to thrombosis later in the transition of atherosclerosis to cardiovascular events. Additional large-scale studies need to be performed in blacks to determine whether Lp(a) levels confer risk for cardiac events.

Apo(a) isoform size cannot be used to explain the apparent paradox of blacks having higher plasma levels of Lp(a) and yet similar amounts of coronary atherosclerosis. Because coronary calcium was used as a marker for atherosclerosis in the present study, we cannot exclude the possibility that plasma levels of Lp(a) are associated with cardiovascular event rates in blacks, although there is not strong evidence to support this possibility.

The mechanisms responsible for ethnic- and gender-specific differences in the relative concentrations of Lp(a) and its association with coronary atherosclerosis remain unclear. Future studies focusing on these differences may provide much needed insights into the mysteries surrounding the physiological role and pathological effects of this enigmatic lipoprotein. It is possible that the absence of a relationship between elevated plasma levels of Lp(a) and coronary atherosclerosis in blacks (except those black men with very high levels) may reflect the action of a protective factor in this population. Identification of this factor could have therapeutic implications for other populations.

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