Lipoprotein[a] as a Risk Factor for Preclinical Atherosclerosis

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Elevated mean levels of lipoprotein[a] (Lp[a]) have been associated with symptomatic cardiovascular diseases such as clinically manifest myocardial infarction (MI), coronary artery disease, restenosis of coronary artery vein grafts after bypass, and a family history of MI. Associations of Lp[a] with arterial wall thickening in asymptomatic individuals previously have not been addressed and are evaluated in this report among participants of the Atherosclerosis Risk in Communities (ARIC) Study. Intima–media wall thickening in the extracranial carotid arteries was assessed noninvasively with B-mode ultrasonography; Lp[a] was measured as its total protein component. Individuals with wall thickening ≥90th percentile of the population maximum far-wall thickness were pair matched to participants <75th percentile of wall thickness by race, gender, center, 10-year age group, and time of examination. These selection criteria yielded 492 matched pairs, with 395 white pairs and 97 black pairs. The mean Lp[a] protein level for all black participants was 174.6 μg/mL compared with 77.8 μg/mL for whites. Conditional logistic regression analysis for the association of Lp[a] with case–control status yielded a statistically significant prevalence odds ratio (OR) estimate of 1.49, based on a 1-SD difference in Lp[a] protein, after adjusting for age, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, fibrinogen, hypertension, and cigarette smoking. None of these risk factors significantly altered the OR, in agreement with reports that Lp[a] is unaffected by environmental influences. In addition, no differential effect of Lp[a] protein on case–control status (effect modification) was observed by race, gender, low-density lipoprotein cholesterol, or fibrinogen in this population. We conclude that Lp[a] is an independent risk factor for intima–media carotid thickening in individuals free of prevalent cardiovascular disease. Further investigation of racial effects may benefit from a population-based analysis that includes additional black participants as well as from elucidation of apolipoprotein[a] polymorph differences between races and degree of wall thickening. (Arteriosclerosis and Thrombosis 1993;13:826–833)

Key Words • lipoprotein[a] • atherosclerosis • B-mode ultrasonography • race

Lipoprotein[a] (Lp[a]) is a lipoprotein whose plasma concentration contributes to the risk of both cardiovascular (CVD) and cerebrovascular (CBD) disease. Lp[a] has been shown to be a risk factor for these conditions in adults, independent of age, diet, physical activity, smoking status, ethanol consumption, and gender.1,2 The two major apoproteins present in Lp[a], apolipoprotein B (apoB) and apolipoprotein[a] (apo[a]), can each be implicated with a specific component of these disease processes. The apoB moiety is similar in molecular weight and amino acid composition to apoB in low-density lipoprotein (LDL), the major carrier of cholesterol in the blood.

Apo[a] is highly homologous to plasminogen and may compete with it in the fibrinolytic pathway.

Elevated levels of Lp[a] have been associated with a family history of myocardial infarction (MI) in asymptomatic individuals,2 as well as with clinical MI,3 coronary artery disease,4,5 and restenosis of coronary artery vein grafts.6 These associations have been observed in both white and Asian populations, primarily in middle-aged or older men. The subjects in these studies have generally presented with evidence of specific cardiac or cerebrovascular conditions. In most studies examining the association of Lp[a] with atherosclerotic disease, coronary atherosclerosis4,7 or atherosclerosis in the extracranial carotid arteries8 has generally been detected during examinations of individuals who have had either an MI, angina, or ischemic stroke. Few studies have focused on Lp[a] as a risk factor for preclinical CVD or CBD.

The investigation reported here examines the putative association between Lp[a] apolipoprotein and atherosclerosis of the extracranial carotid arteries in asymptomatic individuals. A population-based sample of individuals with evidence of atherosclerotic wall thickening, based on carotid intima–media wall thickness measurements made using B-mode ultrasound, and without symptomatic CVD was selected from the Ath-
erosclerosis Risk in Communities (ARIC) Study and compared with control subjects free of arterial wall thickening.

Methods

The ARIC Study, a prospective, multicenter investigation of atherosclerotic clinical events and noninvasively measured atherosclerosis, examined 15,800 individuals aged 45–64 years between 1987 and 1989 in four field centers. Three of these centers—Forsyth County, N.C.; Minneapolis, Minn.; and Washington County, Md.—examined a general population sample from the appropriate age range; the fourth center, Jackson, Miss., derived its population entirely from the black residents of Jackson.

Carotid artery wall thickness was measured in the ARIC Study by B-mode ultrasonography (Reference 10, manual 6; and References 11 and 12) by the technique of Pignoli et al.

Cases were selected as those subjects having a maximum carotid artery far-wall thickness >2.5 mm or bilateral thickening greater than the approximate 90th percentile of the ARIC cohort distribution (corresponding to 1.7 mm in the internal carotid artery, 1.8 mm in the carotid bifurcation, and 1.6 mm in the common carotid artery). Control subjects were chosen from those participants having a maximum far-wall thickness <75th percentile at the far and near walls of each of the carotid segments and of the popliteal artery. Cases and control subjects were required to meet minimum visualization criteria of arterial wall boundaries on ultrasound. Each case was then matched to one control by race, gender, 10-year age group, study center, and a 6-month “window” of examination date. Cases and control subjects were excluded if they had any evidence of symptomatic CVD or CBD, as defined by a history of symptomatic CVD or CBD.

Case-Control Attributes

The 492 matched pairs examined in this study were a predominantly white sample: 395 of the pairs were white versus 97 pairs who were black, consisting of 62% males (303 pairs) and 38% females (189 pairs). Mean Lp[a] protein values were significantly higher in cases than control subjects (110.8 versus 79.3 μg/mL, respectively). In general, cases were older (despite matching by 10-year age group), heavier, and had higher blood pressures than their respective control subjects (Table 1).

Results

Case-Control Attributes

The 492 matched pairs examined in this study were a predominantly white sample: 395 of the pairs were white versus 97 pairs who were black, consisting of 62% males (303 pairs) and 38% females (189 pairs). Mean Lp[a] protein values were significantly higher in cases than control subjects (110.8 versus 79.3 μg/mL, respectively). In general, cases were older (despite matching by 10-year age group), heavier, and had higher blood pressures than their respective control subjects (Table 1). Cases also had higher mean LDL and total cholesterol values, with lower HDL cholesterol and higher triglyceride values. A higher percentage of cases (40.7%) than control subjects (19.1%) were current smokers, and more control subjects than cases had never smoked; the frequency of former cigarette smokers was equal in cases and their control subjects. Cases were also more likely to be diabetic and had higher mean values of fibrinogen. All of the aforementioned differences reached statistical significance at the p ≤ 0.008 level. Because Lp[a] protein has a strongly right-skewed frequency distribution in whites, case-control differences were also tested by t testing of logarithmically transformed Lp[a] protein values and by the nonparametric Mann-Whitney U test; both procedures replicated the statistics generated by t testing Lp[a] protein differences (p < 0.0001). Therefore, normal statistics are supplied here for ease of presentation and convention.

Although this study was not designed to test racial effects in a multivariable model (because of the matching criteria employed), mean Lp[a] protein values were higher among black examinees, thus corroborating previous findings. Mean Lp[a] protein values (±SD) for cases and control subjects combined were 174.6 ± 132.2 in blacks compared with 77.8 ± 88.8 μg/mL in whites; a smaller standard deviation relative to the mean for blacks is reflective of the more normal Lp[a] protein distribution curve characteristic of black populations.

Lp[a] protein distributional differences between racial groups are presented in Table 2. Blacks, whether cases or control subjects, had higher Lp[a] protein levels than did whites (208.4 and 139.4 μg/mL in black cases and control subjects, respectively, compared with 89.5 and 66.2 μg/mL, respectively, in white cases and control subjects). In addition, cases had higher Lp[a] protein values than control subjects in both racial groups. Although neither black nor white participants exhibited a completely normal Lp[a] protein distribution, the median value in blacks was closer to the mean than in whites.

Table 3 shows the Spearman correlation coefficients of selected continuous variables presented in Table 1 for cases and control subjects; Spearman correlations are given to account for any deviation from normal distributions. Among control subjects, only LDL cholesterol and fibrinogen values were statistically significantly correlated with Lp[a] protein; at the lower Lp[a] protein levels found among control subjects, LDL was only
TABLE 1. Mean Values of Cardiovascular Risk Factors in Cases of Atherosclerosis and Their Matched Controls (n=492 Pairs) and Mean Case-Control Differences: The Atherosclerosis Risk in Communities Study Baseline Survey, 1987-1989

<table>
<thead>
<tr>
<th>Risk factor</th>
<th>No. of paired values</th>
<th>Mean of cases</th>
<th>Mean of controls</th>
<th>Mean differences*</th>
<th>p†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lp[a] protein (μg/mL)</td>
<td>469</td>
<td>110.8</td>
<td>79.3</td>
<td>31.5</td>
<td>0.0001</td>
</tr>
<tr>
<td>Total cholesterol (mg/dL)</td>
<td>483</td>
<td>223.5</td>
<td>206.4</td>
<td>17.1</td>
<td>0.0001</td>
</tr>
<tr>
<td>Triglycerides (mg/dL)</td>
<td>437</td>
<td>142.2</td>
<td>116.0</td>
<td>26.2</td>
<td>0.0001</td>
</tr>
<tr>
<td>HDL cholesterol (mg/dL)</td>
<td>483</td>
<td>48.2</td>
<td>52.9</td>
<td>-4.7</td>
<td>0.0001</td>
</tr>
<tr>
<td>LDL cholesterol (mg/dL)</td>
<td>470</td>
<td>147.4</td>
<td>130.4</td>
<td>17.0</td>
<td>0.0001</td>
</tr>
<tr>
<td>Age (years)</td>
<td>492</td>
<td>57.0</td>
<td>55.8</td>
<td>1.2</td>
<td>0.0001</td>
</tr>
<tr>
<td>Systolic blood pressure (mm Hg)</td>
<td>491</td>
<td>127.8</td>
<td>118.2</td>
<td>9.6</td>
<td>0.0001</td>
</tr>
<tr>
<td>Diastolic blood pressure (mm Hg)</td>
<td>491</td>
<td>74.1</td>
<td>72.3</td>
<td>1.8</td>
<td>0.0053</td>
</tr>
<tr>
<td>Fibrinogen (mg/dL)</td>
<td>487</td>
<td>317.2</td>
<td>288.7</td>
<td>28.5</td>
<td>0.0001</td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
<td>492</td>
<td>27.0</td>
<td>26.2</td>
<td>0.8</td>
<td>0.0079</td>
</tr>
<tr>
<td>Diabetics (%)‡</td>
<td>362</td>
<td>11.5</td>
<td>5.8</td>
<td>5.7</td>
<td>0.002</td>
</tr>
<tr>
<td>Current smokers (%)</td>
<td>492</td>
<td>40.7</td>
<td>19.1</td>
<td>21.6</td>
<td>0.0001§</td>
</tr>
<tr>
<td>Former smokers (%)</td>
<td>492</td>
<td>37.2</td>
<td>37.4</td>
<td>-0.2</td>
<td>0.947§</td>
</tr>
<tr>
<td>Never smoked (%)</td>
<td>492</td>
<td>22.1</td>
<td>43.5</td>
<td>-21.4</td>
<td>0.0001§</td>
</tr>
</tbody>
</table>

Lp[a], lipoprotein[a]; HDL, high-density lipoprotein; LDL, low-density lipoprotein.

*Mean difference is the mean of cases minus the mean of controls.
†p values were calculated by paired t testing for continuous variables and Mantel-Haenszel χ² testing for categorical variables.
‡Diabetics defined as 1) having a fasting glucose value ≥140 mg/dL, 2) reporting a positive history of diabetes, or 3) reporting the use of medication for diabetes mellitus.
§p value trend for overall smoking status between cases and controls.

Weakly (r=0.121) associated with Lp[a] protein while fibrinogen shows a stronger correlation (r=0.240). Conversely, among cases, Lp[a] protein was correlated with all of the lipid covariates (triglycerides, HDL cholesterol, and LDL cholesterol) as well as with fibrinogen; the strongest association in cases was that of Lp[a] protein with LDL (r=0.207), with a weaker association between Lp[a] protein and fibrinogen (r=0.160).

Nonmissing mean-mean and mean-maximum carotid artery far-wall thickness measurements for case-control pairs are presented in Table 4. These data indicate the effectiveness of the case-control selection criteria in identifying individuals with atherosclerosis as defined by B-mode ultrasound and control subjects free of carotid artery wall thickening. At all sites, cases had greater mean-mean and mean-maximum carotid intima-media far-wall thicknesses than their matched counterparts. Mean wall thicknesses were close to maximum values in control subjects, consistent with the absence of marked intima-media thickening in the control group. Conversely, mean far-wall thicknesses were considerably smaller than maxima among cases. Of all sites, the largest percent difference between cases and control subjects occurred at the carotid bifurcation and the internal carotid artery, sites with a predilection to atherosclerotic plaque formation.

Odds Ratio Estimates and Assessment of Confounding

Table 5 shows the results of a series of statistical models predicting risk of atherosclerosis from known cardiovascular risk factors by using conditional logistic regression. The first model shows that the odds of being a case increased by approximately 50% with each 1-SD increase in the mean population value of Lp[a] protein; this relation was statistically independent of other lipoproteins, body mass index (not shown owing to a lack of association), ethanol consumption (not shown), fibrinogen, smoking status, and hypertension. Substitution of the apolipoproteins apoA-I and apoB for HDL and LDL, respectively, in this model yielded essentially the same results (odds ratio [OR] of 1.53, 95% confidence interval [CI] 1.23, 1.90). The next two models show the effects on the OR estimates of removing smoking and hypertension, respectively, from the multivariable model. These were the only two covariates that had any effect on the OR estimate of the Lp[a]-atherosclerosis association, but the ORs were not sufficiently changed by these covariates to be considered as important confounding factors; OR estimates for a larger sample may reveal significant changes between models. Since this was a largely white population that exhibited a right-skewed Lp[a]-protein frequency distribution, a logarithmic transformation of Lp[a] protein was performed; this transformation did not affect the OR estimate (not shown). Testing the above associations with data from the white subgroup only yielded analogous results and are, therefore, not presented here; a small sample size among black case-control pairs with complete labora-

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Cases</th>
<th>Controls</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lp[a] protein (Lp[a])</td>
<td>1.000</td>
<td>1.000</td>
</tr>
<tr>
<td>Triglycerides (TG)</td>
<td>-0.091*</td>
<td>-0.054*</td>
</tr>
<tr>
<td>HDL cholesterol (HDL)</td>
<td>0.128*</td>
<td>0.033</td>
</tr>
<tr>
<td>LDL cholesterol (LDL)</td>
<td>0.207*</td>
<td>0.196*</td>
</tr>
<tr>
<td>Age</td>
<td>0.022</td>
<td>0.034</td>
</tr>
<tr>
<td>Systolic blood pressure (SBP)</td>
<td>0.017</td>
<td>0.062</td>
</tr>
<tr>
<td>Fibrinogen (Fib)</td>
<td>0.033</td>
<td>0.062</td>
</tr>
<tr>
<td>Body mass index (BMI)</td>
<td>0.076</td>
<td>0.076</td>
</tr>
</tbody>
</table>

### TABLE 4. Mean and Maximum Extracranial Carotid Far-Wall Thickness Values (as Measured by B-Mode Ultrasound) for Atherosclerosis Cases and Their Matched Control Subjects: The Atherosclerosis Risk in Communities Study Baseline Survey, 1987-1989

<table>
<thead>
<tr>
<th>Carotid site</th>
<th>Mean of cases (mm)</th>
<th>Mean of controls (mm)</th>
<th>Differences (%)</th>
<th>p†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean values (mm)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Left common, optimal angle</td>
<td>0.836</td>
<td>0.596</td>
<td>28.7</td>
<td>0.0001</td>
</tr>
<tr>
<td>Right common, optimal angle</td>
<td>0.804</td>
<td>0.603</td>
<td>25.0</td>
<td>0.0001</td>
</tr>
<tr>
<td>Left bifurcation</td>
<td>1.456</td>
<td>0.665</td>
<td>54.3</td>
<td>0.0001</td>
</tr>
<tr>
<td>Right bifurcation</td>
<td>1.624</td>
<td>0.679</td>
<td>58.2</td>
<td>0.0001</td>
</tr>
<tr>
<td>Left internal</td>
<td>1.313</td>
<td>0.536</td>
<td>59.2</td>
<td>0.0001</td>
</tr>
<tr>
<td>Right internal</td>
<td>1.517</td>
<td>0.566</td>
<td>62.7</td>
<td>0.0001</td>
</tr>
<tr>
<td>Maximum values (mm)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Left common, optimal angle</td>
<td>1.042</td>
<td>0.697</td>
<td>33.1</td>
<td>0.0001</td>
</tr>
<tr>
<td>Right common, optimal angle</td>
<td>1.011</td>
<td>0.707</td>
<td>30.1</td>
<td>0.0001</td>
</tr>
<tr>
<td>Left bifurcation</td>
<td>2.066</td>
<td>0.793</td>
<td>61.6</td>
<td>0.0001</td>
</tr>
<tr>
<td>Right bifurcation</td>
<td>2.363</td>
<td>0.806</td>
<td>65.9</td>
<td>0.0001</td>
</tr>
<tr>
<td>Left internal</td>
<td>1.664</td>
<td>0.632</td>
<td>62.0</td>
<td>0.0001</td>
</tr>
<tr>
<td>Right internal</td>
<td>1.946</td>
<td>0.670</td>
<td>65.6</td>
<td>0.0001</td>
</tr>
</tbody>
</table>

*p values calculated by paired t testing.

Lp[a], lipoprotein[a]; HDL, high-density lipoprotein; LDL, low-density lipoprotein.

*p<0.05.
have the potential to alter the apparent effect of \( \text{Lp[a]} \) protein on case-control risk status at different levels of exposure. Statistical interaction of \( \text{Lp[a]} \) with race, gender, LDL cholesterol as a continuous variable, LDL cholesterol dichotomized at the NCEP cutpoint of 160 mg/dL, and fibrinogen was assessed by the likelihood-ratio test obtained through conditional maximum likelihood estimation. For these data, all interaction terms were nonsignificant at the 95% confidence level. Of the potential interactions, only race and fibrinogen approached statistical significance \((p=0.228\) and \(p=0.052\), respectively). The magnitude of the association between \( \text{Lp[a]} \) protein and atherosclerosis was greater for blacks than for whites; because of the small number of blacks represented in this study, the 95% CIs for race-specific tests were extremely wide (blacks: OR of 1.87, CI 1.20, 2.91; whites: OR of 1.38, CI 1.07, 1.78). Analysis of a larger black population would clarify this association. Finally, although Armstrong et al.® reported that coronary heart disease risk associated with \( \text{Lp[a]} \) increased markedly with increasing LDL cholesterol concentrations (suggestive of a statistical interaction between \( \text{Lp[a]} \) and LDL), LDL levels did not significantly affect the association of \( \text{Lp[a]} \) protein with case-control status in the study presented here \((p=0.83)\).

**Discussion**

In this cross-sectional study to determine the association of \( \text{Lp[a]} \) with extracranial carotid atherosclerosis, we have found that \( \text{Lp[a]} \) protein is a statistically independent risk factor for intima-media carotid thickening in individuals free of prevalent CVD or CBD. Our results are consistent with the literature on \( \text{Lp[a]} \) as a risk factor for symptomatic clinical disease but are unique in relating elevated levels of \( \text{Lp[a]} \) protein with atherosclerotic vascular disease in asymptomatic individuals.

Previous studies of \( \text{Lp[a]} \) as a risk factor for CVD have focused on MI and coronary artery disease. The association between MI, or a family history of MI, and \( \text{Lp[a]} \) is historically the oldest and has generally been reported for males. These studies revealed similar relations in selected white populations²-⁷ and in Asians,²⁴ but did not examine blacks, females, or distributions of \( \text{Lp[a]} \) in healthy populations. The association between \( \text{Lp[a]} \) and coronary artery disease was also confirmed via angiography⁶,⁷ in whites and among hypercholesterolemics. When \( \text{Lp[a]} \) became known as a risk factor for thrombotic stroke in white and Asian populations,²⁶-²⁸ the extracranial carotid territory was also examined with Doppler ultrasonic imaging for prevalence of plaque.⁸ \( \text{Lp[a]} \) was found to be an equally strong risk factor for cardiovascular and cerebrovascular outcomes²⁸ and a risk factor for plaque detected in the extracranial carotid arteries of patients with CBD. These studies, for the most part, dealt with individuals who presented with a chronic disease outcome. If \( \text{Lp[a]} \) is indeed a genetic risk factor that is present at comparable levels throughout adulthood, detection of preclinical CVD and CBD manifestations would allow for modification of more easily altered risk factors and behaviors. B-mode ultrasonography provides such information in a noninvasive, reliable manner.

B-mode ultrasound was used to assess atherosclerosis in this study. A noninvasive, low-risk procedure such as B-mode ultrasound is suitable for use in asymptomatic
volunteers, thus reducing the potential for bias that is common in the selection of symptomatic study populations. Perceived symptoms and/or medical intervention in such populations can lead to a modification of the disease process or its antecedent risk factors. As documented on ARIC Study participants, B-mode ultrasound can be standardized for population-based, multicenter applications, achieving a high degree of reproducibility in scanning and reading. In addition, ultrasonography is more appropriate than angiography for measurement of early, subclinical atherosclerosis that may have little or no lumen involvement. Ricotta et al compared the ability of B-mode ultrasonography and angiography to identify atherosclerosis and found B-mode superior in quantifying the extent of plaque formation. Quantitative imaging of the early stages of wall thickening permits observation of developing atherosclerosis rather than its outcome: advanced, and often complicated, lesions. Furthermore, B-mode ultrasound reduces the potential for misclassification that is inherent in identifying the absence of clinically manifest atherosclerotic disease in individuals who may or may not exhibit preclinical atherosclerosis. Because Lp[a] has both atherogenic and thrombogenic potential, investigation of preclinical atherosclerosis can address the impact of Lp[a] as an atherogenic agent before the occurrence of a CVD or CBD event.

The presence of apoB as one of the apolipoprotein components of Lp[a] raises the question as to whether Lp[a] measurements include LDL cholesterol and conversely, whether LDL cholesterol values include Lp[a] cholesterol. In the ARIC Study, Lp[a] protein is detected by a double-antibody enzyme-linked immunosorbent assay for apo[a], thereby eliminating the possibility of LDL cholesterol contamination of Lp[a]. However, because LDL cholesterol is estimated by the Friedewald formula and total cholesterol contains (in addition to cholesterol from other lipoproteins) Lp[a] cholesterol, LDL cholesterol estimated in this manner does contain a small percentage of cholesterol attributable to Lp[a]. Kurschinski et al. examining whether Lp[a] can be derived from the Friedewald equation, found that when Lp[a] is linearly regressed separately against total cholesterol, triglycerides, HDL cholesterol, or estimated LDL cholesterol, no linear correlation existed between any of the pairs.

Lp[a] protein and LDL cholesterol are weakly correlated (r=0.12) among control subjects in this study and slightly more strongly correlated in cases (r=0.21), consistent with correlations found in the healthy population described by Guyton et al. Although elevated Lp[a] concentrations are associated with increased CVD prevalence in hypercholesterolemic and/or bilateral arterial wall thickening as an index of atherosclerosis. Choosing cases from the highest decile of the population of wall-thickness distribution greatly reduces the possibility of wall thickening due to other nonatherosclerotic causes of wall thickening, such as medial hyperplasia, being misclassified as atherosclerosis.

The atherosclerosis cases in this study had significantly higher levels of several well-established cardiovascular risk factors, including total cholesterol, LDL cholesterol, triglycerides, blood pressure, age, and body mass; mean HDL cholesterol values were lower in cases. Cases were more likely than control subjects to be current smokers and were composed of a higher proportion of diabetics. Despite the highly significant differences in cardiovascular risk factor levels between cases and control subjects, Lp[a] protein remained a statistically independent predictor of atherosclerotic risk after multivariable adjustment for the other variables.

Although Lp[a] levels appear to be unaffected by lifestyle attributes such as diet and physical activity, some classes of antihypercholesterolemic agents may have an effect on Lp[a] concentrations. Reports that these medications can produce reduction of atherosclerotic plaque in hypercholesterolemic populations suggest the possibility that medication usage can alter the effect of Lp[a] on plaque development. Of these medications, niacin and neomycin alone or in combination appear to be the only commonly used antihypercholesterolemic agents that do lower Lp[a] levels. Since only 27 individuals in our study were taking any kind of antihypercholesterolemic medication and only two of the cases were taking niacin, we did not test for these effects. The impact of antihypercholesterolemic therapy on the Lp[a] protein-atherosclerosis association remains to be tested in a larger population.

Significant differences in the mean Lp[a] protein concentrations exist between the black and white subjects in this study: 174.6 versus 77.8 μg/mL, respectively, with the black population exhibiting a more normal distribution than their white counterparts. These results are in agreement with those previously reported by Guyton et al and Utermann in both American and African black populations. Because the participants in the case-control study were matched by race in the design phase, we were unable to test for race as a confounding factor in the association between Lp[a] protein and atherosclerosis in multivariable modeling; however, race was not a significant effect modifier of this association.

Early reports of the properties of Lp[a] indicated no gender difference in the effect of Lp[a] on disease outcome, although most of these studies dealt with middle-aged or older white men with hypercholesterolemia or heart disease. In the current study, the Lp[a]-atherosclerosis association did not differ by gender. Recent reports on noncontraceptive hormone replacement therapy in postmenopausal women indicate that estrogen users have lower mean Lp[a] values than nonusers; furthermore, women using progestin and estrogen in combination have lower Lp[a] values than either nonusers or estrogen users. Again, these relations could not be tested here because of sample size, but future work in the full ARIC Study population will address the issue of menopause.

The case-control approach presented here has several advantages. Because our assessment of atherosclerosis by B-mode ultrasonography is based solely on the thickness of the carotid wall (without consideration of morphology), case selection criteria encompassed only extreme and/or bilateral arterial wall thickening as an index of atherosclerosis. Choosing cases from the highest decile of the population of wall-thickness distribution greatly reduces the possibility of wall thickening due to other nonatherosclerotic causes of wall thickening, such as medial hyperplasia, being misclassified as atherosclerosis.
therosclerosis were selected as cases, their inclusion would only tend to underestimate the observed association between LP[a] and intima-media wall thickening. Analogously, although control subjects were selected from <75th percentile of the maximum carotid artery wall thickness distribution, these individuals may have atherosclerosis in other arterial territories. This occurrence is unlikely but is of unknown frequency and must be considered in interpreting our results. This misclassification among controls, if present, would also tend to bias the reported OR toward unity.

Our study design excluded from analysis those individuals with prevalent CVD or CBD. Because of the association of CVD risk factors with these outcomes, this exclusion criterion eliminated three times more cases than control subjects from the study. Again, while this could tend to underestimate the effect of LP[a] on case-control status by excluding some individuals who are more likely to have advanced atherosclerotic disease, this design was felt to be preferable to the alternative of incorporating the effect of medical intervention among cases with clinical manifestations. Conversely, choosing cases and control subjects based on measurements of carotid artery wall thickness offers no guarantee that atherosclerosis is systemic in the cases nor that carotid atherosclerosis will ultimately precipitate a stroke or be associated with an MI. A cross-sectional study such as ours, examining the early phases of plaque formation, cannot establish that elevated levels of LP[a] protein (or any risk factor, for that matter) will lead to progression of the disease process or will eventually lead to a CVD or CVD event. Follow-up of the ARIC cohort for changes in carotid wall thickness and clinical events will help to elucidate the role of LP[a] protein in these processes.

Taking this limitation into account, we conclude that plasma LP[a] concentration is statistically significantly associated with ultrasound-derived evidence of carotid atherosclerosis in a middle-aged, biracial population who have no clinical manifestations of CVD or CBD. This association persisted with univariate and multivariate adjustment for other risk factors. In addition, no differential effect of LP[a] protein on case-control risk status was observed by race, gender, total cholesterol, apoB, or fibrinogen in this population. Because of recently reported relations between apo[a] polymorphs and LP[a] levels as well as between polymorphs and CVD,47 48 we believe that subject classification based on apo[a] phenotype or genotype49 may reveal even stronger associations.

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References

10. National Heart, Lung, and Blood Institute: ARIC Manuals of Operation: No. 1, General Description and Study Management; No. 2, Cohort Component; No. 3, Surveillance Component Procedures; No. 4, Pulmonary Function Assessment; No. 5, Electrocardiography; No. 6, Ultrasound Assessment; No. 7, Blood Collection and Processing; No. 8, Lipid and Lipoprotein Determinations; No. 9, Hemostasis Determinations; No. 10, Clinical Chemistry; No. 11, Sitting Blood Pressure; No. 12, Quality Assurance. Chapel Hill, NC, ARIC Coordinating Center, School of Public Health, University of North Carolina
41. Cashin-Hemphill L, Sanmarco ME, Blankenhorn DH and the CLAS coronary film panelists and staff: Augmented beneficial effects of colestipol-niacin therapy at four years in the CLAS trial. (abstract) *Circulation* 1989;90(suppl I):I-381