Published in final edited form as:
Arterioscler Thromb Vasc Biol. 2002 January ; 22(1): 141.

Relation of Apo(a) Size to Carotid Atherosclerosis in an Elderly Multiethnic Population

Furcy Paultre[1], **Catherine H. Tuck**[1], **Bernadette Boden-Albala**[2,4,5], **Douglas E. Kargman**[2,4], **Elizabeth Todd**[1], **Jeffrey Jones**[1], **Myunghee C. Paik**[3], **Ralph L. Sacco**[2,4], and **Lars Berglund**[1]

[1] Department of Medicine, Columbia University, New York, NY

[2] Department of Neurology, Columbia University, New York, NY

[3] Department of Biostatistics, Columbia University, New York, NY

[4] Department of Epidemiology, Columbia University, New York, NY

[5] Department of Socio-Medical Sciences, Columbia University, New York, NY

Abstract

Lipoprotein(a) [Lp(a)] is a novel risk factor for atherosclerosis, whose role in multiracial populations has been debated. We recently demonstrated a significant association of elevated levels of Lp(a) carried in particles containing small apolipoprotein(a) [apo(a)] isoforms with coronary artery disease in African American and white men. To extend these findings, we investigated the associations between Lp(a) levels, apo(a) size, and maximum internal carotid artery plaque thickness (MPT) in a randomly selected elderly multiethnic population (173 men and 253 women, consisting of 135 African Americans, 146 Hispanics, and 145 whites; mean age 70.5±11.4 years). Lp(a) levels were not associated with MPT. Among white men, MPT was associated with a small apo(a) isoform size (P=0.03) as well as with the amount of Lp(a) carrying the small apo(a) size (P=0.04), and the latter showed a borderline association in African American men (P=0.07). Among white women, but not in Hispanic or African American women, MPT was associated with the amount of Lp(a) carrying a small apo(a) isoform size (P<0.01). For all patients, the amount of Lp(a) carrying the small apo(a) size was associated with carotid atherosclerosis when there was control for age, sex, ethnicity, high density lipoprotein cholesterol, low density lipoprotein cholesterol, triglycerides, diabetes mellitus, hypertension, waist-to-hip ratio, and current smoking status (P=0.03). This association was significant for all men (P=0.03) and for white women (P=0.007). The results suggest that molecular properties of apo(a) are important in determining the atherogenicity of Lp(a).

Keywords

lipoprotein(a); carotid arteries; risk factors; African American; Hispanic

Lipoprotein(a) levels have been associated with coronary artery disease (CAD) as well as cerebrovascular disease in case-control studies1–7 and in most prospective studies.8–13 No significant associations between Lp(a) levels and CAD have been found in African Americans, although Lp(a) levels are higher than the levels in whites.14,15 This lack of association has

Correspondence to Lars Berglund, MD, PhD, Department of Medicine, Columbia University, PH 10-305, 630 West 168th St, New York, NY 10032. E-mail lfb9@columbia.edu.

†Dr Catherine H. Tuck passed away on May 24, 2001.

Drs Paultre and Tuck contributed equally to the present study.

resulted in uncertainty regarding the role of Lp(a) as a risk factor for atherosclerosis. Furthermore, there is a paucity of data on associations between Lp(a) and CAD in Hispanics.

The apo(a) locus determines ≈90% of the variation in plasma Lp(a) levels.16 The apo(a) gene contains a variable number of copies of the kringle 4 (K4) domain, resulting in an apo(a) protein size polymorphism.17 There is a general inverse relationship between apo(a) size and Lp(a) levels.18 Whether the higher Lp(a) levels in African Americans can be attributed to genetic differences in apo(a) has not been clarified.19 The complexity of this issue is illustrated by a recent study concluding that Lp(a) levels, primarily those in the intermediate apo(a) isoform size range (20 to 25 K4 repeats), were greater among African Americans than whites.20

The size polymorphism of apo(a) has been suggested to be of importance in conveying risk for cardiovascular disease, inasmuch as several studies (largely carried out in white populations) have shown an association between small apo(a) isoform sizes and CAD or cerebrovascular disease.21–26 Indeed, in some of these studies, high plasma Lp(a) levels were associated with CAD only among carriers of small apo(a) isoform sizes.23,25,26 In a recent case-control study, we demonstrated that elevated levels of Lp(a) associated with small apo(a) size was a risk factor for CAD in African American and white men.27 We concluded that the difference in distribution of Lp(a) levels over specific apo(a) sizes between African Americans and whites likely had confounded previous results. Interestingly, no significant association was found in women, irrespective of ethnicity. To confirm these findings on a population level and to extend them to cardiovascular disease beyond CAD, we evaluated the relationship between Lp(a) levels, apo(a) isoform size, and carotid atherosclerosis in a random sample from an elderly multiethnic population.

Methods

Subjects

Subjects were randomly selected according to ethnic group from the stroke-free group enrolled in the Northern Manhattan Stroke Study (NOMASS), a prospective community-based study for determining stroke incidence and risk factors among different racial/ethnic groups.[28] The enrollment procedure has been described in detail previously. Briefly, subjects were initially identified by random-digit dialing. Inclusion criteria included completion of a telephone interview, no prior history of stroke, age >39 years, residence in 1 of the 5 zip codes of northern Manhattan for at least 3 months, and access to a telephone in the home. Race/ethnicity was based on self-identification. The study protocol was approved by the Columbia-Presbyterian Institutional Review Board. Subjects underwent a standardized interview and physical examination, fasting blood specimens were obtained, and an ECG was performed. Approximately two thirds of the subjects were randomly selected to undergo carotid duplex Doppler sonography. The 426 subjects in the present study (173 men and 253 women) represent the subjects for whom carotid sonography, Lp(a) levels, and apo(a) isoform size were available.

Definition of Baseline Variables

Standardized questions were asked regarding sociodemographic characteristics, risk factors (such as hypertension, diabetes mellitus, cardiac disease, and peripheral vascular disease), and other medical conditions. Cigarette smoking was characterized as current or not. Hypertension was defined as a systolic blood pressure ≥160 mm Hg or a diastolic blood pressure ≥95 mm Hg (assessed as the mean of 2 blood pressure measurements) or a patient's self-report of a history of hypertension or use of antihypertensive medication. Diabetes mellitus was defined by patient's self-report, by use of insulin or oral antidiabetics, or by a fasting blood sugar >126 mg/dL. CAD was defined as a patient's self-report of a history of exercise-induced chest pain,

myocardial infarction, angioplasty, or coronary artery bypass graft surgery. Obesity was defined as body mass index ≥27.8 for men and ≥27.3 for women.

Carotid Plaque Determination

Carotid atherosclerosis was assessed by duplex ultrasound as previously described in detail.[28] Briefly, both internal carotid arteries were examined for the presence of atherosclerotic plaque, defined as an area of focal hyperechoic wall thickening. If no atherosclerosis was identified, maximum internal carotid artery plaque thickness (MPT) was recorded as zero. If a plaque was imaged, the view showing the thickest plaque was frozen, and by use of an electronic cursor, the intimal-medial wall thickness, including the thickness of the atherosclerotic plaque, was calculated and recorded as MPT.[29] For the analysis, the greater of the right and left MPT was used.

Laboratory Measurements

Plasma total cholesterol and triglyceride levels were determined by using standard enzymatic techniques. HDL cholesterol was determined after precipitation of apoB-containing lipoproteins with phosphotungstic acid (Boehringer-Mannheim). LDL cholesterol levels were calculated and, where appropriate, corrected for the cholesterol carried in Lp(a).30 Serum levels of apoA-I and apoB were determined by using commercially available reagents (Beckman), and non-Lp(a) apoB levels were estimated.31 Lp(a) levels were analyzed by using an immunonephelometric procedure.32 The interassay coefficients of variation were 2% for cholesterol, 3% for HDL cholesterol, 4% for triglycerides, 3.9% for apoA-I, and 3.4% for apoB. For Lp(a), our assay had interassay coefficients of variation of 4% and 8% at Lp(a) levels of 48 and 8 mg/dL, respectively. Quality control measurements were performed by using commercially available standards. Apo(a) phenotyping was performed by using Western blotting.27,32 In subjects carrying 2 different apo(a) isoforms, the relative contribution of each isoform to plasma Lp(a) levels was based on the relative intensity of staining of the 2 bands by Western blot as estimated by 3 independent observers. This approach was verified by computerized scanning of the blots. The relative intensity of each apo(a) isoform was multiplied by the total plasma Lp(a) level to compute the Lp(a) level associated with each apo(a) isoform.

Statistical Analysis

The mean±SD values were calculated for continuous measurements such as MPT, lipid, and apolipoprotein values, whereas proportions were used to describe categorical clinical characteristics such as hypertension, smoking, and categories of apo(a) isoform size. Because the distribution for triglycerides was skewed, logarithmic transformations of these data were performed before statistical analysis. Medians were used to describe Lp(a) levels. Comparisons between groups were made by using the Wilcoxon rank sum test. Linear regression was used for analysis in assessing the relationship between MPT and Lp(a) carrying differently sized apo(a) isoforms. As described previously, the model used assumes that the natural logarithm of MPT is a linear function of covariates.[28] In these calculations, MPT was logarithmically transformed as appropriate to adjust for nonnormal distribution of error terms, as tested by the Shapiro-Wilk statistics. SAS was used for all calculations.

Results

Regarding demographic and clinical characteristics of the subjects, women were older than men (72±12 versus 68±11 years, $P<0.001$), had a higher degree of obesity (49% versus 31%, $P<0.001$) and hypertension (60% versus 47%, $P<0.05$), but had a less frequent history of CAD (16% versus 27%, $P<0.01$). African Americans, Hispanics, and whites were different from each other in several aspects. For both men and women, whites were the oldest and Hispanics were the youngest, reflecting the age spectrum of stroke onset in our community. The African

American and Hispanic groups were more obese and had more hypertension and diabetes than did the white group. However, more of the white subjects reported a previous history of CAD. For details, please see online data supplement at atvb.ahajournals.org

Total cholesterol, LDL cholesterol, "corrected LDL cholesterol," and HDL cholesterol levels as well as apoA-I levels were higher among women than men, and these findings were generally observed within the different ethnic groups (Table 1). In agreement with previous studies,[33] we also found differences between the 3 ethnic groups. Thus, Hispanics had the highest triglyceride and lowest HDL cholesterol levels. African Americans had higher apoA-I levels and the highest HDL cholesterol levels.

The distribution of MPT and Lp(a) levels for each ethnic/sex group is given in Table 2. The distributions of MPT values were skewed toward zero in all 3 ethnic groups, but mean and median MPT values were greater among African Americans and whites compared with Hispanics. There was no significant difference in mean or median MPT levels between men and women in any of the ethnic groups. As expected, African Americans had mean and median Lp(a) levels that were approximately twice the levels of whites ($P<0.001$). Hispanics had mean and median Lp(a) levels that were intermediate between the levels of African Americans and whites. The distributions were highly skewed toward lower levels in whites and Hispanics but more uniformly distributed in African Americans. There was no significant association between Lp(a) levels and MPT among all men or women or in any of the sex/ethnicity subgroups (data not shown).

We next evaluated the association between apo(a) isoform size and MPT. As seen in Table 3, the presence of at least 1 small apo(a) isoform (<22 K4 repeats) was associated with MPT among all men; this association was due to the presence of a strong association among white men. There was an association of borderline significance ($P=0.05$) between MPT and small apo(a) isoform size among white women.

We next considered the association between the amount of Lp(a) associated with specific sizes of apo(a) isoforms and MPT. To determine the extent of confounding by other risk factors of the association between MPT and small isoform Lp(a) levels, we performed multiple linear regression with a model controlling for age, sex, race/ethnicity, diabetes, hypertension, smoking, waist-to-hip ratio, and plasma concentrations of small isoform Lp(a), HDL cholesterol, LDL cholesterol corrected for cholesterol content of Lp(a), and logarithmically transformed triglycerides. When controlling for these factors, we found that small isoform Lp (a) remained significantly associated with MPT for all patients ($P=0.03$). Neither total cholesterol, HDL cholesterol, nor triglyceride level was significantly associated with MPT, whereas an association was seen for hypertension ($P=0.02$) and smoking ($P=0.04$). Diabetes mellitus showed a borderline association ($P=0.07$). For the various subgroups, a similar significant association between small isoform Lp(a) and MPT was found for men ($P=0.03$) but not women. Among men, the association between small isoform Lp(a) and MPT showed a significant association for whites ($P=0.04$) and a borderline association for African Americans ($P=0.07$). In women, MPT was significantly associated with small isoform Lp(a) among whites ($P=0.007$) but not among the other ethnic groups.

Discussion

The main finding in the present study was the association between small isoform Lp(a) [ie, Lp (a) particles containing a small-sized apo(a)] levels, but not Lp(a) levels, and carotid atherosclerosis among men and white women from an elderly multiethnic population. This relationship remained significant after adjustment for age, ethnicity, hypertension, diabetes, lipoprotein levels, waist-to-hip ratio, and current cigarette smoking.

In previous studies, the role of Lp(a) as a risk factor for cardiovascular disease, particularly among multiracial populations, has been debated. Recently, we reported that the risk conferred by Lp(a) was due to the amount of Lp(a) associated with small-sized apo(a) and that the different distribution of Lp(a) levels over the apo(a) isoform size spectrum in African Americans and whites could be a confounder for the association of plasma Lp(a) levels with CAD.[27] However, because these results were obtained in a case-control study and, furthermore, because the association was observed in men but not in women, it was important to extend these findings to a random population-based sample. Our present study was conducted in elderly subjects representing 3 different ethnic groups. We noted several differences between these groups. As expected, compared with whites, African Americans had higher mean Lp(a) levels, and the distribution was less skewed. The Hispanic group had Lp(a) levels intermediate between the 2 other groups, with a distribution skewed toward lower levels. There are few studies performed among Hispanics, and data available so far show that Mexican Americans have Lp(a) levels even lower than those of the white population.34

In the present study population, the distribution of plaque thickness was skewed, with ≈25% of subjects having no visible plaque. Compared with African Americans and whites, Hispanics also had less plaque. These findings are consistent with recently published data from the entire NO-MASS control subject cohort.28 Plaque thickness was related to age, hypertension, and current smoking but not Lp(a) plasma levels. This finding is not consistent with other reports that have found associations between Lp(a) levels and carotid atherosclerosis in predominantly white populations.3,7,13 The Atherosclerosis Risk in Communities (ARIC) study, in which a biracial population was recruited, found an association between Lp(a) and carotid score among white and African American men but only among women who were smokers and diabetic. 35 The reason for our inability to identify an association between Lp(a) levels and MPT is unclear. Other studies have identified an association only at certain carotid sites or for subjects with high LDL levels.35,36 A study of subjects with end-stage renal disease on dialysis found an association between apo(a) size but not Lp(a) and carotid atherosclerosis.26

In contrast to the lack of association between Lp(a) levels and MPT, we found a significant association between small apo(a) isoform size (<22 K4 units) and MPT among all men. This finding was clearly driven by the strong association between MPT and presence of small apo (a) isoform size in white men. A borderline association was also found in white women but not among Hispanic or African American women despite similar numbers of subjects. Associations between small apo(a) isoform size and atherosclerosis have been reported in several studies of white populations.7,22,25,26 A prospective case-control study of a mostly white population showed an association between small apo(a) size (≤22 K4 units) and myocardial infarction or coronary death in men but not women.12 Only a few studies have examined the relationship between apo(a) isoform size and atherosclerosis in nonwhite subjects to date. In agreement with our previous results, which demonstrated that elevated levels of small isoform Lp(a), but not plasma Lp(a) levels or apo(a) isoform size, were associated with CAD in African American men,27 an association of either apo(a) isoform size or Lp(a) levels with CAD was not found in middle-aged black subjects.14 No previous study has examined apo(a) isoform size in relation to carotid atherosclerosis in African American or Hispanic subjects. The present findings demonstrates that elevated levels of Lp(a) particles carrying small apo(a) isoforms were associated with risk for carotid atherosclerosis in men from a random sample of an elderly population.

In the present study, we examined a stratified sample of stroke-free subjects from NOMASS, which included comparable numbers from all 3 represented racial/ethnic groups. The possibility to directly compare multiple racial/ethnic groups represents a particular strength of the study. All subjects resided in the same community and were recruited by random-digit dialing. Limitations of this design are that the different racial/ethnic groups were not matched

for several key variables, such as age, obesity, diabetes, previous CAD, and lipid variables. Also, a potential bias could be whether individuals with certain Lp(a) levels or apo(a) isoforms died at an earlier age. On the other hand, there was a high prevalence of carotid atherosclerosis, resulting in a larger range of MPT values than would have been possible if the population were younger.

For all subjects, levels of Lp(a) carrying small apo(a) isoform sizes were significantly associated with MPT when adjustment was made for other stroke risk factors. Interestingly, no significant associations were seen for other lipoproteins. Overall, as expected from previous studies, age was strongly associated with carotid atherosclerosis.28,34 In addition, well-established risk factors such as hypertension and smoking were significantly associated with MPT, whereas a borderline association was found for diabetes mellitus. It is notable that in addition to our findings in men, there was a strong association between MPT and elevated small isoform Lp(a) among white women, arguing against the possibility of a consistent sex difference across ethnicities. Rather than interpret our results as an indication that apo(a) molecular properties have different atherogenic effects in different sex/ethnicity groups, we hypothesize that differences in these groups with regard to age, lipid levels, and degree of carotid atherosclerosis may account for our observations.37 In summary, our results in this elderly population underline the emerging concept that the amount of Lp(a) carrying small apo (a) size rather than plasma Lp(a) levels is important for the development of atherosclerosis. The apparent sex/ethnic differences suggest that the atherogenic effect of apo(a) size could be balanced by other factors, such as age, lipid levels, or other cardiac risk factors. Further studies are necessary, particularly in multiethnic groups, to examine this effect in more detail.

Acknowledgments

This work was supported by grants from the National Institute of Neurological Disorders and Stroke (R01 NS-27517, R01 NS-29993, and T32 NS-07153), the General Clinical Research Center (RR-00645), and the National Heart, Lung, and Blood Institute (HL-62705).

References

1. Danesh J, Collins R, Peto R. Lipoprotein(a) and coronary heart disease: meta-analysis of prospective studies. Circulation 2000;102:1082–1085. [PubMed: 10973834]
2. Milionis HJ, Winder AF, Mikhailidis D. Lipoprotein (a) and stroke. J Clin Pathol 2000;53:487–496. [PubMed: 10961170]
3. Zenker G, Koltringer P, Bone G, Niederkorn K, Pfeiffer K, Jürgens G. Lipoprotein(a) as a strong indicator for cerebrovascular disease. Stroke 1986;17:942–945. [PubMed: 2945294]
4. Pedro-Botet J, Senti M, Nogues X, Rubies-Prat J, Roquer J, D'Olhaberriague L, Olive J. Lipoprotein and apolipoprotein profile in men with ischemic stroke: role of lipoprotein(a), triglyceride-rich lipoproteins, and apolipoprotein E polymorphism. Stroke 1992;23:1556–1562. [PubMed: 1440702]
5. Shintani S, Kikuchi S, Hamaguchi H, Shiigai T. High serum lipoprotein(a) levels are an independent risk factor for cerebral infarction. Stroke 1993;24:965–969. [PubMed: 8322396]
6. Schreiner PJ, Chambless LE, Brown SA, Watson RL, Toole J, Heiss G. Lipoprotein(a) as a correlate of stroke and transient ischemic attack prevalence in a biracial cohort: the ARIC study. Ann Epidemiol 1994;4:351–359. [PubMed: 7981841]
7. Jurgens G, Taddei-Peters WC, Koltringer P, Petek W, Chen Q, Greilberger J, Macomber PF, Butman BT, Stead AG, Ransom JH. Lipoprotein(a) serum concentration and apolipoprotein(a) phenotype correlate with severity and presence of ischemic cerebrovascular disease. Stroke 1995;26:1841–1848. [PubMed: 7570736]
8. Stein JH, Rosenson RS. Lipoprotein Lp(a) excess and coronary heart disease. Arch Intern Med 1997;157:1170–1176. [PubMed: 9183227]

9. Schaefer EJ, Lamon-Fava S, Jenner JL, McNamara JR, Ordovas JM, Davis CE, Abolafia JM, Lippel K, Levy RI. Lipoprotein(a) levels and risk of coronary heart disease in men: the lipid research clinics coronary primary prevention trial. JAMA 1994;271:999–1003. [PubMed: 8139085]
10. Ridker PM, Stampfer MJ, Hennekens CH. Plasma concentration of lipoprotein(a) and the risk of future stroke. JAMA 1995;273:1269–1273. [PubMed: 7715039]
11. Bostom AG, Cupples LA, Jenner JL, Ordovas JM, Seman LJ, Wilson PWF, Schaefer EJ, Castelli WP. Elevated plasma lipoprotein(a) and coronary heart disease in men aged 55 years and younger: a prospective study. JAMA 1996;276:544–548. [PubMed: 8709403]
12. Wild SH, Fortmann SP, Marcovina SM. A prospective case-control study of lipoprotein(a) levels and apo(a) size and risk of coronary heart disease in Stanford Five-City Project participants. Arterioscler Thromb Vasc Biol 1997;17:239–245. [PubMed: 9081676]
13. Koltringer P, Jürgens G. A dominant role of lipoprotein(a) in the investigation and evaluation of parameters indicating the development of cervical atherosclerosis. Atherosclerosis 1985;58:187–198. [PubMed: 2936355]
14. Moliterno DJ, Jokinen EV, Miserez AR, Lange RA, Willard JE, Boerwinkle E, Hillis LD, Hobbs HH. No association between plasma lipoprotein(a) concentrations and the presence or absence of coronary atherosclerosis in African-Americans. Arterioscler Thromb Vasc Biol 1995;15:850–855. [PubMed: 7600116]
15. Sorrentino MJ, Vielhauer C, Eisenbart JD, Fless GM, Scanu AM, Feldman T. Plasma lipoprotein(a) protein concentration and coronary artery disease in black patients compared with white patients. Am J Med 1992;93:658–662. [PubMed: 1466362]
16. Boerwinkle E, Leffert CC, Lin J, Lackner C, Chiesa G, Hobbs HH. Apolipoprotein (a) gene accounts for greater than 90% of the variation in plasma lipoprotein (a) concentrations in plasma. J Clin Invest 1992;90:52–60. [PubMed: 1386087]
17. McLean JW, Tomlinson JE, Kuang WJ, Eaton DL, Chen EY, Fless GM, Scanu AM, Lawn RM. cDNA sequence of human apolipoprotein(a) is homologous to plasminogen. Nature 1987;330:132–137. [PubMed: 3670400]
18. Lackner C, Boerwinkle E, Leffert CC, Rahmig T, Hobbs HH. Molecular basis of apolipoprotein (a) isoform size heterogeneity as revealed by pulsed-field gel electrophoresis. J Clin Invest 1991;87:2153–2161. [PubMed: 1645755]
19. Mooser V, Scheer D, Marcovina SM, Wang J, Guerra R, Cohen J, Hobbs HH. The apo(a) gene is the major determinant of variation in plasma Lp(a) levels in African Americans. Am J Hum Genet 1997;61:402–417. [PubMed: 9311746]
20. Marcovina SM, Albers JJ, Wijsman E, Zhang ZH, Chapman NH, Kennedy H. Differences in Lp(a) concentrations and apo(a) polymorphs between black and white Americans. J Lipid Res 1996;37:2569–2585. [PubMed: 9017509]
21. Sandholzer C, Saha N, Kark JD, Rees A, Jaross W, Dieplinger H, Hoppichler F, Boerwinkle E, Utermann G. Apo(a) isoforms predict risk for coronary heart disease: a study in six populations. Arterioscler Thromb 1992;12:1214–1226. [PubMed: 1390593]
22. Kraft HG, Lingenhel A, Kochl S, Hoppichler F, Kronenberg F, Abe A, Muhlberger V, Schonitzer D, Utermann G. Apolipoprotein(a) kringle IV repeat number predicts risk for coronary artery disease. Arterioscler Thromb Vasc Biol 1996;16:713–719. [PubMed: 8640397]
23. Gazzaruso C, Garzaniti A, Buscaglia P, Bonetti G, Falcone C, Fratino P, Finardi G, Geroldi D. Association between apolipoprotein(a) phenotypes and coronary heart disease at a young age. J Am Coll Cardiol 1999;33:157–163. [PubMed: 9935023]
24. Bowden J-F, Pritchard PH, Hill JS, Frohlich JJ. Lp(a) concentration and apo(a) isoform size: relation to the presence of coronary artery disease in familial hypercholesterolemia. Arterioscler Thromb 1994;14:1561–1568. [PubMed: 7918305]
25. Kronenberg F, Kronenberg MF, Kiechl S, Trenkwalder E, Santer P, Oberhollenzer F, Egger G, Utermann G, Willeit J. Role of lipoprotein(a) and apolipoprotein(a) phenotype in atherogenesis: prospective results from the Bruneck Study. Circulation 1999;100:1154–1160. [PubMed: 10484534]
26. Kronenberg F, Kathrein H, Konig P, Neyer U, Sturm W, Lhotta K, Grochenig E, Utermann G, Dieplinger H. Apolipoprotein(a) phenotypes predict the risk for carotid atherosclerosis in patients with end-stage renal disease. Arterioscler Thromb 1994;14:1405–1411. [PubMed: 8068600]

27. Paultre F, Pearson TA, Weil HFC, Tuck CH, Myerson M, Rubin J, Francis CK, Marx H, Philbin E, Reed RG, et al. High levels of lipoprotein(a) carrying a small apolipoprotein(a) isoform is associated with coronary artery disease in both African American and Caucasian men. Arterioscler Thromb Vasc Biol 2000;20:2619–2624. [PubMed: 11116062]
28. Sacco RL, Roberts JK, Boden-Albala B, Gu Q, Lin IF, Kargman DE, Berglund L, Hauser WA, Shea S, Paik MC. Race-ethnicity and determinants of carotid atherosclerosis in a multi-ethnic population: the Northern Manhattan Stroke Study. Stroke 1997;28:929–935. [PubMed: 9158627]
29. Pignoli P, Tremoli E, Poli A, Oreste P, Paoletti R. Intimal plus medial thickness of the arterial wall: a direct measurement with ultrasound imaging. Circulation 1986;74:1399–1406. [PubMed: 3536154]
30. Nauck M, Winkler K, Marz W, Wieland H. Quantitative determination of high-, low-, and very-low-density lipoproteins and lipoprotein(a) by agarose gel electrophoresis and enzymatic cholesterol staining. Clin Chem 1995;41:1761–1767. [PubMed: 7497617]
31. Maher VMG, Brown BG, Marcovina SM, Hillger LA, Zhao XQ, Albers JJ. Effects of lowering elevated LDL cholesterol on the cardiovascular risk of lipoprotein(a). JAMA 1995;274:1771–1774. [PubMed: 7500507]
32. Tuck CH, Holleran S, Berglund L. Hormonal regulation of lipoprotein(a) levels: effect of estrogen replacement therapy on lipoprotein(a) and acute phase reactants in postmenopausal women. Arterioscler Thromb Vasc Biol 1997;17:1822–1829. [PubMed: 9327783]
33. Brown SA, Hutchinson R, Morrisett J, Boerwinkle E, Davis CE, Gotto AM Jr, Patsch W. the ARIC Study Group. Plasma lipid, lipoprotein cholesterol, and apoprotein distributions in selected US communities: the Atherosclerosis Risk in Communities (ARIC) Study. Arterioscler Thromb 1993;13:1139–1158. [PubMed: 8343489]
34. Haffner SM, Gruber KK, Morales PA, Hazuda HP, Valdez RA, Mitchell BD, Stern MP. Lipoprotein (a) concentrations in Mexican Americans and non-Hispanic Caucasians: the San Antonio Heart Study. Am J Epidemiol 1992;136:1060–1068. [PubMed: 1462966]
35. Schreiner PJ, Heiss G, Tyroler HA, Morrisett JD, Davis CE, Smith R. Race and gender differences in the association of Lp(a) with carotid artery wall thickness: the Atherosclerosis Risk in Communities (ARIC) Study. Arterioscler Thromb Vasc Biol 1996;16:471–478. [PubMed: 8630675]
36. Rankinen T, Vaisanen S, Mercuri M, Rauramaa R. Apolipoprotein(a), fibrinopeptide A, and carotid atherosclerosis in middle-aged men. Thromb Haemost 1994;72:563–566. [PubMed: 7878633]
37. Baldassarre D, Tremoli E, Franceschini G, Michelagnoli S, Sirtori CR. Plasma lipoprotein(a) is an independent factor associated with carotid wall thickening in severely but not moderately hypercholesterolemic patients. Stroke 1996;27:1044–1049. [PubMed: 8650712]

TABLE 1

Lipid and Lipoprotein Levels of Study Subjects

	Men				Women			
	All (n=173)	**African Americans (n=45)**	**Whites (n=66)**	**Hispanics (n=62)**	**All (n=253)**	**African Americans (n=90)**	**Whites (n=79)**	**Hispanics (n=84)**
Chol, mg/dL	193±37	183±36	197±34	194±39	215±39*	218±37*	215±38†	212±42‡
Triglycerides, mg/dL	136±62	126±53	134±57	147±72	141±64	125±56	143±56	155±74
LDL Chol, mg/dL	123±34	112±33	125±32	127±35	134±36†	135±35*	134±36	131±37
Corr LDL Chol, mg/dL	110±33	97±32	115±31	115±34	121±35†	117±32†	127±36‡	119±37
HDL Chol, mg/dL	43±12	46±12	45±12	38±11	53±16*	58±19*	52±12*	50±15*
ApoB, mg/dL	112±29	104±26	112±27	118±32	117±30	117±31‡	116±28	117±31
Corr apoB, mg/dL	106±29	95±25	106±27	113±32	109±30	106±30§	111±29	110±30
ApoA-I, mg/dL	136±23	142±22	140±25	128±19	156±28*	163±31*	150±25‡	153±27*

Chol indicates cholesterol; Corr, corrected. Values are mean±SD. For LDL Chol and Corr LDL Chol, there were 252 women (89 African Americans), and for apoA-I, apoB, and Corr apoB, there were 148 men (36 African Americans, 61 whites, and 51 Hispanics) and 229 women (81 African Americans, 75 whites, and 73 Hispanics).

*$P<0.001$,

†$P<0.01$, and

‡$P<0.05$ for men vs women of the same ethnic group;

§$P=0.058$ for men vs women of the same ethnic group.

TABLE 2

Distribution of MPT and Lp(a) in Study Subjects

	Men				Women			
	All (n=173)	**African Americans (n=45)**	**Whites (n=66)**	**Hispanics (n=62)**	**All (n=253)**	**African Americans (n=90)**	**Whites (n=79)**	**Hispanics (n=84)**
Mean MPT, mm	1.4±1.4	1.6±1.4	1.6±1.4	1.2±1.3	1.5±1.4	1.8±1.4	1.7±1.4	1.0±1.3
Maximum MPT, mm	6.1	5.2	6.1	4.8	7.3	5.4	7.3	4.6
75% (Q3), mm	2.5	2.8	2.5	2.0	2.3	2.5	2.5	1.6
Median MPT, mm	1.4	1.6	1.6	0.8	1.5	1.6	1.7	0.0
25% (Q1), mm	0.0	0.0	0.0	0.0	0.0	0.0	0.8	0.0
Minimum MPT, mm	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
Mean Lp(a), mg/dL	41±40	49±35	35±34	42±48	43±41	61±43	24±28	41±40
Mean ln Lp(a)	3.2±1.2	3.6±0.8	3.0±1.2	3.1±1.3	3.2±1.3	3.8±0.9	2.4±1.4	3.2±1.2
Median Lp(a), mg/dL	28.4	41.0	26.9	24.1	31.6	53.6	14.4	28.5

Q3 indicates quartile 3; Q1, quartile 1. Values are mean±SD or as indicated.

TABLE 3

MPT in Various Apo(a) Isoform Size Groups

	Men				Women			
	All	**African Americans**	**Whites**	**Hispanics**	**All**	**African Americans**	**Whites**	**Hispanics**
N	173	45	66	62	253	90	79	84
Any isoform <22 K4								
n	37	7	14	16	53	20	16	17
MPT (mean±SD), mm	1.9±1.6	1.7±1.7	2.4±1.7	1.5±1.4	1.6±1.7	1.3±1.4	2.4±1.8	1.3±1.7
MPT (median), mm	2.1	2.1	2.4	1.7	1.5	1.1	2.5	0.7
MPT (Q3–Q1), mm	2.9	3.4	2.8	2.8	2.8	2.2	1.9	1.6
No isoform <22 K4								
n	136	38	52	46	200	70	63	67
MPT (mean±SD), mm	1.3±1.3	1.6±1.4	1.4±1.3	1.0±1.3	1.5±1.3	1.9±1.4	1.5±1.2	0.9±1.2
MPT (median), mm	1.3	1.5	1.6	0.3	1.5	1.8	1.6	0
MPT (Q3–Q1), mm	2.1	2.8	2.1	1.8	2.3	1.4	2.3	1.6
P	0.03	NS	0.03	NS	NS	NS	0.05	NS

Q3–Q1 represents MPT for interquartile range (75th to 25th percentiles). Values of *P* are by Wilcoxon rank test.