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Lipoprotein(a)-cholesterol levels estimated by vertical auto profile correlate poorly with Lp(a) mass in hyperlipidemic subjects: Implications for clinical practice interpretation of Lp(a)-mediated risk

Calvin Yeang, MD, PhD, Paul C. Clopton, MS, Sotirios Tsimikas, MD*

Division of Cardiovascular Diseases, Department of Medicine, Sulpizio Cardiovascular Center, University of California, La Jolla, CA, USA (Drs Yeang and Tsimikas); and San Diego Veteran's Administration Medical Center, La Jolla, CA, USA (Dr Clopton)

Abstract

BACKGROUND: Lipoprotein(a) [Lp(a)] is generally measured as total mass of the entire particle or as apolipoprotein(a) particle number.

OBJECTIVE: The cholesterol content of Lp(a) [Lp(a)-C] can be estimated by the vertical auto profile (VAP) method. We assessed whether this is an accurate surrogate measurement of Lp(a) mass.

METHODS: VAP-Lp(a)-C and VAP-high density lipoprotein cholesterol (HDL-C) estimated by the VAP technique, Lp(a) mass, oxidized phospholipids on apolipoprotein B-100 (OxPL-apoB) that primarily reflect OxPL on Lp(a), and HDL-C measured by enzymatic methods were measured in 552 hypercholesterolemic patients at baseline and 24 weeks after therapy with niacin monotherapy (N = 118), ezetimibe/simvastatin monotherapy (n = 155), or ezetimibe/simvastatin (10/20 mg) + niacin (to 2 g) (N = 279) in a randomized, double-blind trial.

RESULTS: VAP-Lp(a)-C correlated only modestly with Lp(a) mass at baseline ($r = 0.56$, $P < .001$) and 24 weeks ($r = 0.56$, $P < .001$), explaining only 31% of the association. VAP-Lp(a)-C correlated with HDL-C at baseline ($r = 0.34$, $P < .001$) and 24 weeks ($r = 0.30$, $P < .001$) and with VAP-HDL-C at baseline ($r = .39$, $P < .001$) and 24 weeks ($r = 0.33$, $P < .001$). In contrast, Lp(a) mass did not correlate with HDL-C at baseline ($r = 0.06$, $P = .12$) and 24 weeks ($r = -0.01$, $P = .91$). Lp(a) mass correlated strongly with oxidized phospholipids on apolipoprotein B-100 at baseline ($r = 0.81$, $P < .001$) and 24 weeks ($r = 0.79$, $P < .001$). VAP-Lp(a)-C levels increased linearly with HDL-C and VAP-HDL-C quartiles ($P < .001$ for both) but Lp(a) mass did not. Quantitating the percent of cholesterol present on Lp(a) by dividing VAP-Lp(a)-C by Lp(a) mass revealed that 25% of patients had a percentage >100 , which is not possible.

CONCLUSIONS: VAP-Lp(a)-C is a poor estimate for Lp(a) mass and likely reflects the content of HDL-C in the overlapping density spectrum of Lp(a) and HDL. These data suggest that patients with prior VAP-Lp(a)-C measurements may have misclassification of Lp(a)-related risk.

*Corresponding author. Vascular Medicine Program, University of California San Diego, 9500 Gilman Dr., BSB 1080, La Jolla CA 92093-0682, USA. stsimikas@ucsd.edu.

Keywords

Lipoprotein(a); Lipoprotein(a)-cholesterol; VAP; Oxidized phospholipids; Niacin; HDL-Cholesterol

Introduction

Lp(a) consists of apolipoprotein(a) [apo(a)] covalently bound to apoB on low-density lipoprotein (LDL) and is the major lipoprotein carrier of oxidized phospholipids (OxPL).^{1,2} Lp(a) measurements as either total particle mass at levels >30 mg/dL³ or particle number >75 nmol/L⁴ predict incident myocardial infarction, coronary artery disease,⁵ peripheral artery disease,⁶ stroke, calcific aortic valve disease,⁷ and faster progression of pre-existing aortic stenosis.⁸

Lp(a), by virtue of containing apolipoprotein B-100 (apoB-100) also contains free and esterified cholesterol in a similar proportion to LDL (~50% of mass). However, because apolipoprotein(a) is a very large glycoprotein, and often larger than apoB-100 (which is approximately 550 kDa), the relative proportion of cholesterol on Lp(a) is lower and estimated to be approximately 30% to 45% of total Lp(a) mass.^{9–12} The cholesterol content of Lp(a) contributes to the laboratory measurement of “LDL-C,” as all clinical assays, including direct LDL assays, cannot differentiate LDL-C vs Lp(a)-C.¹³ Therefore, as Lp(a) mass increases, so does the relative contribution of Lp(a)-C to the laboratory measurement of “LDL-C.” For example, when Lp(a) mass is 100 mg/dL and LDL-C is 100 mg/dL, the contribution of Lp(a)-C to “LDL-C” is 30% to 45% of Lp(a) mass, or ~33 to 45 mg/dL, and estimated true LDL-C is 55 to 66 mg/dL.

Lp(a)-C, determined by the vertical auto profile (VAP) method (VAP-Lp(a)-C) has been a widely used clinical method for estimating Lp(a)-related risk.¹² However, whether it is a precise, accurate, and reliable surrogate for Lp(a) mass or in predicting cardiovascular disease is not known. Appropriate Lp(a) measurements are needed for population cutoffs, clinical risk prediction, and classification of patients into proper risk categories.¹⁴

VAP-Lp(a)-C is determined by measuring the cholesterol content of the Lp(a) fraction of plasma separated by ultracentrifugation.¹⁵ The VAP technology uses nonequilibrium density ultracentrifugation to resolve plasma lipoproteins in a single tube and spin, followed by continuous analysis of cholesterol concentrations, and hence separates by flotation rate, which is a function of both lipoprotein density and size. The different classes of lipoproteins are continuously but sequentially flowed out of the spin tube and mixed with reagents for enzymatic colorimetric cholesterol determination. The raw data are represented as absorbance over time, and software algorithms are used to decompose the absorbance profile into discrete lipoprotein-associated cholesterol levels. VAP-Lp(a)-C has been compared with more traditional forms of Lp(a) measurements infrequently, and anecdotal experiences from lipidology clinics have raised concerns regarding its accuracy. Here, we examine how VAP-Lp(a)-C compares with Lp(a) mass in a hyperlipidemic population undergoing lipid-lowering therapy.

Material and methods

Patients and study design

Plasma samples were obtained from the previously completed study by Guyton et al.¹⁶ This was a randomized, double-blind study in which patients of ages 18 to 79 years with LDL-C levels 130 to 190 mg/dL and triglyceride levels <500 mg/dL were initially randomized to 3 arms: extended release niacin titrated up to 2 g (N), ezetimibe 10 mg/simvastatin 20 mg (E/S), or triple combination therapy of E/S/N after an initial 4-week washout period. The samples included in this study reflect trial completers (75%) that included 552 patients with complete baseline and 24-week on-treatment plasma samples for VAP-Lp(a)-C, VAP-high density lipoprotein cholesterol (HDL-C), HDL-C, Lp(a) mass, and oxidized phospholipids on apolipoprotein B-100 (OxPL-apoB), and full characteristics of these study subjects were described by Yeang et al.¹⁷

Measurement of Lp(a) mass

Lp(a) mass quantification was performed by the University of California San Diego (UCSD) assay with a double-antibody enzyme-linked immunosorbent assay as previously described.¹⁸ Plasma from each sample was diluted 1:400 and added to microtiter wells coated with the monoclonal antibody MB47 (5 µg/mL). Biotinylated LPA4 (1 µg/mL), a monoclonal antibody, was added to determine the amount bound detected by a chemiluminescent technique. The coefficient of variation of the assay is 6.0% to 7.4%. This assay has been validated previously and the methodology and standardization were recently described in detail.¹⁹

A second, commercially available, Food and Drug Administration-approved Lp(a) mass assay (Polymedco, Inc, Cortlandt Manor, NY) was also used in a subset of 75 patients on niacin monotherapy, 88 patients on E/S monotherapy, and 175 patients on E/S/N (approximately 62% of total group) with complete data on HDL-C by VAP, Lp(a)-C by VAP, and Lp(a) mass.

Measurement of OxPL-apoB levels

OxPL-apoB levels were measured in a chemiluminescent immunoassay using the murine monoclonal antibody E06 that recognizes the phosphocholine (PC) group on oxidized but not on native phospholipids (Taleb et al²⁰ and references therein). A 1:50 dilution of plasma was added to microtiter wells coated with the apoB100-specific monoclonal antibody MB47, and biotinylated E06 was then used to determine the content of OxPL-apoB. These values were recorded as relative light units and then converted to nanomolar (nM) PC-OxPL using a standard curve of nM PC equivalents, as recently described.^{6,21} Because each well contains equal numbers of apoB100 particles, the OxPL-apoB value reflects the content of OxPL per apoB100-containing lipoprotein.

Lipid measurements

Plasma lipid and lipoprotein cholesterol measurements are previously described.¹⁶ Briefly, LDL-C was determined using the Friedewald equation as follows: $\text{LDL-C} = \text{plasma-C} - \text{HDL-C} - \text{TG}/5$. Plasma cholesterol and triglycerides were determined using commercial

enzymatic methods. VAP-Lp(a)-C and VAP-HDL-C were determined by the VAP method at LabCorp, Inc.

Statistical analyses

Analysis of the changes in lipid and lipoprotein parameters on treatment with N, E/S, or E/S/N was performed comparing 24-week treatment levels to baseline levels. Data are presented as mean (standard deviation) except for Lp(a) mass and OxPL-apoB data were distributed in a non-Gaussian fashion and presented as median (interquartile range [IQR]). The significance of the treatment change in each group from baseline to 24 weeks was determined by paired sample *t*-test. Statistical significance of comparisons of the percent changes in lipid parameters across treatment regimens were evaluated using analysis of variance. Correlations between Lp(a) mass, VAP-Lp(a)-C, VAP-HDL-C, OxPL-apoB, and HDL-C and statistical significance of these correlations were determined by Spearman's rho. Statistical significance for a linear relationship between median Lp(a) mass or VAP-Lp(a)-C levels across HDL-C quartiles was determined using analysis of variance. All statistics were performed using SPSS version 23.

Results

Baseline parameters

Full baseline lipid parameters of this population were described by Yeang et al.¹⁷ Baseline Lp(a) mass, VAP-Lp(a)-C, HDL-C by enzymatic methods, VAP-HDL-C, and OxPL-apoB are summarized in Table 1. Individuals who received niacin monotherapy had a median (IQR) percent decrease in UCSD Lp(a) mass by 12.1 (−49.9 to 8.7) but in contrast had an increase in VAP-Lp(a)-C by $34.1 \pm 47.1\%$ ($P < .001$) at 24 weeks. Both HDL-C and VAP-HDL-C showed a mean percent increase of 27.8 ± 18.4 and 19.9 ± 18.9 . Median (IQR) OxPL-apoB decreased by 14.1 (−35.2 to 6.8) at 24 weeks. Individuals who received E/S had a median (IQR) percent increase in Lp(a) mass by 11.9 (−29.9 to 30.5) and mean increase in VAP-Lp(a)-C by $7.7 \pm 42.3\%$ at 24 weeks. HDL-C and VAP-HDL-C had mean percent increases of 7.9 ± 13.0 and 3.2 ± 11.6 . Median OxPL-apoB was increased by 38.1 (7.2–91.7) at 24 weeks. Individuals who received E/S/N had a median (IQR) percent increase in Lp(a) mass by 1.9 (−33.9 to 21.6), and mean increase in VAP-Lp(a)-C of $20.6 \pm 44.8\%$ at 24 weeks. Both HDL-C and VAP-HDL-C had mean percent increases of 30.2 ± 22.9 and 21.3 ± 21.3 . Median OxPL-apoB was increased by 24.9 (−6.6 to 76.1) at 24 weeks.

Correlations among variables

Table 2 presents the Spearman correlation coefficients between variables at baseline and 24 weeks. At baseline, using the UCSD Lp(a) mass assay, Lp(a) mass did not correlate with HDL-C, but correlated weakly ($r = 0.11$, $P = .080$) with VAP-HDL-C, modestly ($r = 0.56$, $P < .001$) with VAP-Lp(a)-C and strongly ($r = 0.81$, $P < .001$) with OxPL-apoB. VAP-Lp(a)-C correlated moderately with both HDL-C ($r = 0.34$, $P < .001$) and VAP-HDL-C ($r = 0.39$, $P < .001$). Similar results were noted at 24 weeks (Table 2).

Using the commercial Lp(a) mass assay, Lp(a) mass and VAP-Lp(a)-C correlated weakly at baseline ($r = 0.10$, $P = .028$) but not at 24 weeks ($r = 0.02$, $P = .74$). In contrast, Lp(a) mass

did not correlate with HDL-C at baseline ($r = 0.07$, $P = .25$) nor at 24 weeks ($r = -0.002$, $P = .96$).

Lp(a) mass and VAP-Lp(a)-C by HDL-C and VAP-HDL-C quartiles

When data were analyzed by quartiles of HDL-C, there was a significant linear trend for higher baseline VAP-Lp(a)-C levels ($P < .001$), whereas there was no statistical significance for a linear trend of baseline Lp(a) mass grouped by quartiles of HDL-C ($P = .502$; Table 3). Similar findings were present for quartiles of VAP-HDL-C.

Mathematical derivation of Lp(a)-C

The percent cholesterol content of Lp(a) can be estimated by the formula $\text{Lp(a) mass} \times 0.3$ or $\text{Lp(a) mass} \times 0.45$.¹³ Lp(a)-C estimated as either 30% or 45% of Lp(a) mass only modestly correlates with VAP-Lp(a)-C (Spearman $r = 0.56$, $P < .001$ for both). Furthermore, the percent cholesterol content of Lp(a) can also be directly derived by estimated as $\text{VAP-Lp(a)-C} / \text{Lp(a) mass} \times 100\%$. Using this calculation, 25% of the subjects in this study had an Lp(a)-C content of 102.9%, 20% of subjects had 122.9%, and 10% of subjects had 209.9% (Table 4). Since it is not feasible for >100% of Lp(a) mass to be cholesterol, these VAP-Lp(a)-C values are likely erroneous.

Discussion

This study demonstrates that VAP-Lp(a)-C correlates only modestly with Lp(a) mass, which is the gold standard for determining cardiovascular disease risk. Furthermore, VAP-Lp(a)-C correlates with and also rises with increasing HDL-C while Lp(a) mass does not, suggesting methodologic issues in the accurate estimation of Lp(a)-C, possibly due to the wide overlap of the Lp(a) and HDL densities on gradient ultracentrifugation.^{22,23} Since millions of patients have had VAP lipid profile measurements that include Lp(a)-C in clinical practice,¹² these data suggest that a significant proportion of patients may have had their Lp(a)-related risk misclassified. Clinicians should be aware of these data and consider alternative Lp(a) measures or confirmatory measurements with mass or particle number assays to accurately assess Lp(a)-related risk.

Traditionally, Lp(a) has either been measured as total Lp(a) particle mass, which includes apolipoprotein(a), apolipoproteinB-100, OxPL, free cholesterol, cholesteryl esters, triglycerides and carbohydrate, or particle number as measured by molar quantities of apo(a).⁴ Albers et al²⁴ originally defined Lp(a) mass in mg/dl, using an immune-chemical assay that was calibrated against purified Lp(a) with known protein, lipid, and carbohydrate mass. Subsequent assays measuring Lp(a) in mg/dL have been calibrated against pooled plasma standards. Contemporary assays also measure the apo(a) component of Lp(a) immunologically, and these values are calibrated against standard calibrators derived from pooled plasma samples, which are often traced back to the World Health Organization/ International Federation of Clinical Chemistry and Laboratory Medicine reference Lp(a) standard.²⁵ As there is exactly 1 mole of apo(a) on each Lp(a) particle, these assays report Lp(a) levels in nanomoles (nM).

In this study, Lp(a) mass and OxPL-apoB, primarily reflecting OxPL on Lp(a), were decreased with niacin treatment, and HDL-C increased as expected.²⁶ However, VAP-Lp(a)-C levels were increased on niacin rather than decreased as expected. This increase in VAP-Lp(a)-C is unanticipated as a biological consequence of reduction of Lp(a) mass. In addition, the percent of Lp(a) mass that is the cholesterol content, calculated using VAP-Lp(a)-C results, exceeds 100% in one-quarter of all subjects at baseline, which is biologically impossible. These findings suggest that VAP-Lp(a)-C poorly reflects Lp(a) mass, and we propose this is due to overlap of Lp(a) (1.050–1.090 g/mL) with HDL-C densities (1.063–1.210 g/mL) on ultracentrifugation and misidentification of HDL-C as Lp(a)-C.²³

Other reports have demonstrated that VAP-Lp(a)-C correlates with HDL-C. For example, in obese African-American children, VAP-Lp(a)-C correlated with HDL-C ($r = 0.45$, $P < .001$) but poorly with LDL-C ($r = 0.14$, not significant).²⁷ Furthermore, data from a lipidology referral clinic showed that higher VAP-Lp(a)-C levels were associated with higher HDL-C levels, whereas VAP-Lp(a)-C levels were discordant with Lp(a) particle number.²⁸ Finally, a genome-wide association study of an Old Order Amish population showed that VAP-Lp(a)-C was significantly ($b = 0.459$, $P = 8 \times 10^{-8}$) associated with a single nucleotide polymorphism near the APOA5–APOA4–APOC3–APOA1 gene cluster on chromosome 11q23, which was in turn highly associated with HDL-C ($b = 14.6$, $P = 4 \times 10^{-9}$).²⁹ This suggests that a component of HDL-C is recorded as VAP-Lp(a)-C and that the associations of *LPA* single nucleotide polymorphisms with HDL-C are likely erroneous and need to be confirmed with an Lp(a) mass assay. These findings have broad implications in appropriate interpretation of genetic data using Lp(a)-C measurements as opposed to mass or particle number measurements.

Although the association between VAP-Lp(a)-C and HDL-C laboratory measurements is most likely due to the overlap of the cholesterol content of HDL onto Lp(a), it may be possible that there is a physiologic connection between HDL and Lp(a) unrelated to the cholesterol content. In an in vitro study using the human hepatocarcinoma Hep G2 cell line, addition of purified Lp(a) to these cells enhanced cholesterol efflux to apolipoprotein AI.³⁰ The authors demonstrated that OxPL on Lp(a) upregulates the adenosine triphosphate-binding cassette 1 via signaling through the scavenger receptor B1. These findings have implications for a regulatory effect of Lp(a) on upregulation of HDL-C in vivo. However, the correlation between Lp(a) mass and HDL-C in clinical populations is weak at best. For example, in the multiethnic Dallas Heart Study involving 3481 patients³¹ and in the Myocardial Ischemia Reduction With Aggressive Cholesterol Lowering trial of 2342 patients with acute coronary syndromes,³² baseline levels of Lp(a) mass correlated poorly but in a significant manner with HDL-C ($r = 0.15$, $P < .001$). Therefore, the potential contribution of Lp(a) on regulation of HDL-C levels in vivo is likely to be minor.

Accurate Lp(a) measurements are needed for clinical risk assessment. In that regard, in the Framingham Offspring cohort, 2 separate Lp(a) mass assays were associated with cardiovascular risk in the after multivariate analysis, but Lp(a)-C, determined by cholesterol measurement of Lp(a) separated from other plasma lipoproteins via affinity purification with lectin, was not associated with higher risk.³³

Study limitations

The subjects described in this study may not be fully representative of the general population as they were hypercholesterolemic. Further comparisons of Lp(a) mass and VAP-Lp(a)-C in diverse populations are needed. The content of cholesterol on Lp(a) is estimated to be 30% to 45% based on other studies, but this has not been analyzed in broad populations, and therefore these figures are estimates and may vary depending on the Lp(a) levels, particularly after therapeutic interventions that affect Lp(a) levels.^{34–36}

Significance

Accurate Lp(a) measurements are essential for clinical risk assessment and for ongoing clinical trials of Lp(a) lowering.³⁴ This work suggests that VAP-Lp(a)-C may not accurately reflect Lp(a) mass levels. Clinicians who have relied on past measures of VAP Lp(a)-C to ascertain Lp(a)-mediated risk should consider reevaluating risk patients with alternative Lp(a) assays.

Alternative methods to determine the cholesterol content of Lp(a) are needed, particularly as we enter the PCSK9 therapeutic era, where very low LDL-C is achieved and most of the laboratory measure termed “LDL-C” may on fact be Lp(a)-C.¹³ The clinical implications of predominantly circulating Lp(a)-C in the face of very low LDL also need to be determined.

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Authors' contributions:

Dr Yeang performed data analysis, wrote first draft; Dr Clopton performed statistical analysis; Dr Tsimikas obtained funding, organized laboratory measurements, statistical analysis, edited manuscript for intellectual content, overall responsibility for manuscript.

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Table 1
Differences in lipid parameters with 24 weeks of E/S, E/S/N, or niacin treatment compared with baseline

Variable	Niacin (n = 118)				E/S (n = 155)				E/S/N (n = 279)			
	0 wk	24 wk	P value	Baseline	24 wk	P value	Baseline	24 wk	P value	Baseline	24 wk	P value
Lp(a) (mg/dL)	10.7 (4.2–37.7)	9.1 (3.1–32.6)	<.001	11.5 (6.0–36.4)	13.3 (6.1–52.9)	<.001	11.6 (5.5–47.2)	11.7 (4.7–42.4)	<.001	11.6 (5.5–47.2)	11.7 (4.7–42.4)	<.001
VAP-Lp(a)-C, mg/dL	7.2 (3.2)	9.0 (3.7)	<.001	7.3 (3.7)	7.5 (4.1)	<.001	7.8 (3.9)	8.8 (3.8)	<.001	7.8 (3.9)	8.8 (3.8)	<.001
HDL-C, mg/dL	49.6 (13.9)	62.8 (17.0)	<.001	48.7 (12.9)	51.9 (12.4)	<.001	49.6 (12.2)	63.7 (15.9)	<.001	49.6 (12.2)	63.7 (15.9)	<.001
VAP-HDL-C, mg/dl	49.9 (12.2)	59.4 (15.1)	<.001	48.8 (11.5)	49.9 (11.1)	<.001	49.7 (10.8)	59.7 (14.0)	<.001	49.7 (10.8)	59.7 (14.0)	<.001
OxPL-apoB, nM	3.6 (2.2–8.6)	3.0 (1.8–7.0)	<.001	3.5 (2.1–7.8)	4.8 (3.0–11.3)	<.001	3.3 (2.0–9.4)	5.0 (2.6–11.9)	<.001	3.3 (2.0–9.4)	5.0 (2.6–11.9)	<.001

Niacin (n = 118)				E/S (n = 155)				E/S/N (n = 279)			
Mean/median		% change 0–24 wk		Mean/median		% change 0–24 wk		Mean/median		% change 0–24 wk	
Lp(a) (mg/dL)		–12.1 (–49.9 to 8.7)		11.9 (–29.9 to 30.5)		1.9 (–33.9 to 21.6)		1.9 (–33.9 to 21.6)		.013	
VAP-Lp(a)-C, mg/dL		34.1 (47.1)		7.7 (42.3)		20.6 (44.8)		20.6 (44.8)		<.001	
HDL-C, mg/dL		27.8 (18.4)		7.9 (13.0)		30.2 (22.9)		30.2 (22.9)		<.001	
VAP-HDL-C, mg/dl		19.9 (18.9)		3.2 (11.6)		21.3 (21.3)		21.3 (21.3)		<.001	
OxPL-apoB, nM		–14.0 (–35.2 to 6.8)		38.1 (7.2 to 91.7)		24.9 (–6.6 to 76.1)		24.9 (–6.6 to 76.1)		<.001	

ANOVA, analysis of variance.

P ANOVA is for difference for each variable from 0 weeks to 24 weeks between groups. Data are presented as mean (SD) or median (IQR).

Table 2

Spearman correlations among variables at baseline and 24 weeks

	HDL-C	VAP-HDL-C	VAP-Lp(a)-C	OxPL-apoB
Baseline				
UCSD Lp(a)				
Correlation coefficient	0.07	0.11	0.56	0.81
Sig. (2 tailed)	0.12	0.008	<0.001	<0.001
HDL-C				
Correlation coefficient		0.94	0.34	0.02
Sig. (2 tailed)		<0.001	<0.001	0.65
VAP-HDL-C				
Correlation coefficient			0.39	0.05
Sig. (2 tailed)			<0.001	0.21
VAP-Lp(a)-C				
Correlation coefficient				0.50
Sig. (2 tailed)				<0.001
24 wk				
UCSD Lp(a)				
Correlation coefficient	0.01	0.08	0.55	0.82
Sig. (2 tailed)	0.91	0.074	<0.001	<0.001
HDL-C				
Correlation coefficient		0.97	0.45	0.01
Sig. (2 tailed)		<0.001	<0.001	0.90
VAP-HDL-C				
Correlation coefficient			0.50	0.06
Sig. (2 tailed)			<0.001	0.15
VAP-Lp(a)-C				
Correlation coefficient				0.50
Sig. (2 tailed)				<0.001

OxPL-apoB, oxidized phospholipids on apolipoprotein B-100.

Table 3
Baseline Lp(a) mass and VAP-Lp(a)-C levels in relation to quartiles of baseline HDL levels

	HDL-C (mg/dL) levels by quartiles					P for trend
	27.0–40.0 (n = 146)	41.0–47.0 (n = 137)	48.0–54.0 (n = 136)	56.0–114.0 (n = 133)		
Lp(a) mass (mg/dL), median (IQR)	9.9 (5.1–38.6)	12.1 (5.4–49.6)	9.9 (5.1–41.0)	13.6 (6.2–39.9)		.36
VAP-Lp(a)-C (mg/dL), mean (SD)	6.3 (3.1)	7.2 (3.6)	7.5 (3.3)	9.4 (4.2)		<.001
VAP-HDL-C (mg/dL) levels by quartiles						
	29.0–41.0 (n = 137)	42.0–47.0 (n = 140)	48.0–55.0 (n = 135)	56.0–104.0 (n = 140)		
Lp(a) mass (mg/dL), median (IQR)	8.9 (4.6–38.0)	11.4 (5.3–37.7)	11.4 (5.8–44.4)	14.2 (6.2–41.4)		.36
VAP-Lp(a)-C (mg/dL), mean (SD)	6.3 (3.1)	6.7 (3.5)	7.7 (3.3)	9.4 (4.2)		<.001

IQR, interquartile range.

Table 4

Distribution of the percent cholesterol content of Lp(a) as a function of VAP-Lp(a)-C

Percentile	All subjects at baseline (%)
25th percentile	21.1
50th percentile	49.3
75th percentile	102.9
80th percentile	122.9
90th percentile	209.9

Calculated for each subject using the formula: $\text{VAP-Lp(a)-C/Lp(a) mass} \times 100\%$, within all subjects at baseline and in those treated with niacin at 24 wk.