Title

Lp(a) (Lipoprotein(a)) Levels Predict Progression of Carotid Atherosclerosis in Subjects With Atherosclerotic Cardiovascular Disease on Intensive Lipid Therapy

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Authors

Hippe, Daniel S
Phan, Binh An P
Sun, Jie
et al.

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Lipoprotein (a) levels predict progression of carotid atherosclerosis in subjects with atherosclerotic cardiovascular disease on intensive lipid therapy: an analysis of the AIM-HIGH Carotid MRI Sub-study

Daniel S. Hippe[1], **Binh An P. Phan**[2], **Jie Sun**[1], **Daniel A. Isquith**[3], **Kevin O'Brien**[3], **John R. Crouse**[4], **Todd Anderson**[5], **John Huston**[6], **Santica M. Marcovina**[7], **Thomas S. Hatsukami**[1], **Chun Yuan**[1], and **Xue-Qiao Zhao**[3]

[1]Department of Radiology, University of Washington School of Medicine

[2]Division of Cardiology, San Francisco General Hospital, University of California, San Francisco

[3]Division of Cardiology, University of Washington School of Medicine

[4]Department of Medicine, Wake Forest University

[5]Libin Cardiovascular Institute of Alberta and the University of Calgary, Calgary, AB

[6]Department of Radiology, Mayo Clinic

[7]Northwest Lipid Metabolism and Diabetes Research Laboratories, University of Washington

Abstract

Objective—To assess whether lipoprotein (a) [Lp(a)] levels and other lipid levels were predictive of progression of atherosclerosis burden as assessed by carotid MRI in subjects who have been treated with low density lipoprotein cholesterol (LDL-C) lowering therapy and participated in the AIM-HIGH (Atherothrombosis Intervention in Metabolic Syndrome with Low HDL/High Triglycerides: Impact on Global Health Outcomes) Trial.

Approach—AIM-HIGH was a randomized, double-blind study of subjects with established vascular disease, elevated triglycerides, and low high-density lipoprotein cholesterol. One hundred fifty-two AIM-HIGH subjects underwent both baseline and 2-year follow-up carotid artery MRI. Plaque burden was measured by the percent wall volume (%WV) of the carotid artery. Associations between annualized change in %WV with baseline and on-study (1 year) lipid variables were evaluated using multivariate linear regression. P-values were adjusted for multiple comparisons.

Results—Average %WV at baseline was 41.6 ± 6.8% and annualized change in %WV over 2 years ranged from −3.2% to 3.7%/year (mean: 0.2 ± 1.1%/year, p=0.032). Increases in %WV was significantly associated with higher baseline Lp(a) [β = 0.34 per 1-SD increase of Lp(a), 95% CI:

Address for correspondence: Xue-Qiao Zhao, MD, FACC, University of Washington. Box 359720, 325 9th Ave. GEC-37, Seattle, WA 98104, Phone: 206-744-8305 Fax: 206-744-9983, xueqiao@uw.edu.

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0.15 to 0.52, p<0.001] after adjusting for clinical risk factors and other lipid levels. On-study Lp(a) had a similar positive association with %WV progression (β = 0.33, 95% CI: 0.15 to 0.52, p<0.001).

Conclusions—Despite intensive lipid therapy, aimed at aggressively lowering LDL-C to <70 mg/dL, carotid atherosclerosis continued to progress as assessed by carotid MRI and that elevated Lp(a) levels were independent predictors of increases in atherosclerosis burden.

Keywords

lipoprotein; lipids; atherosclerosis; MRI

Subject codes

Lipids and Cholesterol; MRI; Atherosclerosis

Introduction

Lipoprotein (a) [Lp(a)] has been identified to have a continuous and independent association with overall cardiovascular disease (CVD) risk [1,2]. Higher levels of Lp(a) are associated with risk of myocardial infarction [3,4]. In ischemic stroke patients, elevated Lp(a) levels are associated with the presence of carotid atherosclerosis [5]. Inaddition, the AIM-HIGH (Atherothrombosis Intervention in Metabolic Syndrome with Low HDL/High Triglycerides: Impact on Global Health Outcomes) study found that Lp(a) levels at baseline and on-study were predictive of residual CVD risk [6]. Furthermore, Lp(a) was positively associated with high-risk plaque features including intraplaque hemorrhage, mural thrombus, or surface defects [7] and with plaque vascularity [8] in AIM-HIGH. The aim of our study was to assess whether Lp(a) and other lipid levels were predictive of progression of atherosclerosis burden as assessed by carotid MRI in subjects who have been treated with low density lipoprotein cholesterol (LDL-C) lowering therapy and participated in the AIM-HIGH Trial [9].

Material and Methods

Materials and Methods are available in the online-only Data Supplement.

Results

A total of 152 subjects from the AIM-HIGH MRI substudy were included in the analysis after excluding subjects with insufficient image quality or missing clinical measurements as shown by the flowchart of subject inclusion/exclusion in Figure 1. Subjects were 45 to 79 years old (median: 62), with 81% male, 12% non-white, 26% current smokers, 27% with a history of diabetes and 82% with a history of hypertension (Table 1). Median total-C, LDL-C, HDL-C, triglycerides, and Lp(a) at baseline were 145, 72, 35, 162, and 32 nmol/L, respectively. Baseline %WV ranged from 28% to 60% (median: 40%, SD: 7.1%). Most baseline variables were distributed similarly in the monotherapy and combination therapy

arms (Table 1), though the monotherapy group had more white subjects (p=0.025) and lower Lp(a) (p=0.020) than the combination therapy group.

Supplemental Table S1 shows a comparison between subjects included in the present analysis and the remainder of the AIM-HIGH cohort (n=3262). Subjects in the MRI substudy were younger (median: 62 vs. 64 years, p=0.003), were less likely to be white (88% vs. 92%, p=0.042), had lower body mass index (median: 29 vs 30, p=0.002), less likely to be diabetic (27% vs. 34%, p=0.066) and more likely to have a history of hypertension (82% vs. 71%, p=0.002). There were no significant differences in baseline lipids or on-study lipids between the two cohorts. The MRI substudy cohort had a significantly lower rate of cardiovascular events at year 2 than the remainder of the AIM-HIGH cohort (6% vs. 11%, p=0.009).

Over one year, all lipid values except total-C significantly improved on average across both treatment groups (Table 2). However, HDL-C (p<0.001), triglycerides (p=0.033), ApoB (p=0.004), ApoA1 (p=0.001) and Lp(a) (p<0.001) improved more in the combination therapy arm than the monotherapy arm. On average, annualized change in %WV ranged from −3.2 to 3.7% per year (mean: 0.2 ± 1.1% per year, p=0.032) with no significant difference in the amount of change between treatment groups (p=0.67).

Age (p=0.043) and history of hypertension (p=0.061) had marginal associations with annualized change in %WV (Supplemental Table S2). None of the other non-lipid risk factors or treatment assignment were significantly associated with plaque progression. Associations between plaque progression and lipid variables with adjustments for treatment assignment, baseline %WV, and clinical risk factors are summarized in Table 3. Only Lp(a) at baseline (β = 0.33 per 1-SD increase, 95% CI: 0.15 to 0.51, p=0.001) and on-study (β = 0.31, 95% CI: 0.13 to 0.49, p=0.001) were significantly associated with plaque progression at the Bonferroni corrected level α = 0.0036. Baseline (β = 0.34 per 1-SD increase, 95% CI: 0.15 to 0.52, p<0.001) and on-study Lp(a) (β = 0.33, 95% CI: 0.15 to 0.52, p<0.001) remained independently associated with plaque progression after further adjustment for LDL-C, HDL-C, and triglycerides. The difference between baseline and on-study Lp(a) was not significantly associated with plaque progression (p=0.75).

Figure 2 presents an MRI example of carotid plaque progression with elevated Lp(a) at both baseline (263.6 nmol/L) and on-study (159.4 nmol/L), other on-study lipids were well controlled, particularly, on-study LDL-C was 45 mg/dL.

Clinical risk factors and other lipid values between subjects with higher baseline Lp(a) (≥ median of 32 nmol/L) and lower baseline Lp(a) (<32 nmol/L) were compared (Supplemental Table S3). Non-white subjects were more likely to have elevated Lp(a) (p=0.048). Those with higher Lp(a) at baseline tended to have lower total-C (p=0.030), LDL-C (p=0.043), and triglycerides (p=0.048) at 1 year. Baseline %WV was similar between the two groups (median: 40 vs. 41%, p=0.52) and there was no significant correlation between %WV and baseline Lp(a) (Spearman's rho = −0.04, p=0.60).

Discussion

Our study showed that despite intensive lipid therapy, aimed at aggressively lowering LDL-C to <70 mg/dL, carotid atherosclerosis continued to progress as assessed by carotid MRI. Previous studies [10,11] have demonstrated that progression of carotid plaque volume as assessed by 3D ultrasound significantly predicted cardiovascular events including stroke, TIA, MI and death. Engelen and colleagues showed that subjects with >10% of carotid plaque progression over 1 year were considered to have an increased risk for future events [11]. However, the clinical implication of the observed carotid atherosclerosis progression at mean 0.2% and up to 3.7% per year as assessed by MRI would require further investigations.

Unlike earlier imaging studies that have demonstrated combinations of lipid therapies with statin, niacin and or bile acid sequestrants lead to regression or slow progression of atherosclerosis either in coronary arteries [12–15] or in carotid [16,17], there was no significant difference in carotid atherosclerosis progression between the 2 treatment groups in AIM-HIGH. This inconsistency may be potentially attributed to several important differences between the earlier studies and AIM-HIGH. First, patients in AIM-HIGH have been treated with statins and had a mean LDL-C of 74 mg/dL at baseline while subjects in earlier studies were lipid treatment naïve or with higher LDL-C levels. Second, AIM-HIGH compared the combination therapy to statin, not to placebo as in most earlier studies. By the AIM-HIGH study design, the difference in achieved LDL-C between treatment arms on-study was small, 62 mg/dL in the simvastatin plus ERN group and 67 mg/dL in the simvastatin plus placebo group. Finally, maximimum CV benefits from niacin are associated with a significant decrease of triglyceride-rich VLDL, their remnants and dense LDL particles [18]; however, the AIM-HIGH subjects did not have high TG at baseline (a mean of 161 mg/dL). More importantly, the current study results indicate that carotid atherosclerosis continue to progress despite LDL-C lowering to 62 mg/dL and lower LDL-C target is needed in order to stop or reverse atherosclerosis progression as demonstrated in GLAGOV [19] showing that adding evolocumab to statin therapy further lowers LDL-C to a mean of 36.6 mg/dL and reduces coronary atheroscleroma burden.

Importantly, we found that elevated Lp(a) levels were independent predictors of increases in carotid atherosclerosis burden. This fiding is consistent with observations from other AIM-HIGH [6] and epidemiological and genetic association studies showing a continuous and independent association between Lp(a) and cardiovascular disease [3,4,20, 21]. In AIM-HIGH, Lp(a) levels were predictive of residual CV risk with baseline and on-study Lp(a) levels being significantly associated with CV events both in the statin group (baseline HR 1.24, p=0.002 and on-study HR 1.21, p=0.017) and in the statin+ERN group (baseline HR 1.25, p=0.001 and on-study HR 1.18, p=0.028), suggesting that elevated Lp(a) levels continue to impact CVD risk in patients on intensive lipid therapy with well treated LDL-C levels [6]. In a meta-analysis of 18 population studies, Danesh et al. demonstrated that compared to the group with the bottom third of Lp(a) levels, the group with the top third had a hazard ratio of 1.6 (95% CI 1.41–1.8) for CHD death or nonfatal MI [1]. A number of hypothesized mechanisms have been proposed for the contributions of Lp(a) to atherothrombotic vascular diseases, including impairing fibrinolysis, promoting cell

recruitment to vessel wall, acceleration of macrophage form cell formation and contributing to increased levels of pro-inflammatory oxidized phospholipids [22–25]. There have been mixed reports on the association of Lp(a) levels with atherosclerosis burden and progression. In a cohort of young stroke patients, Nasr et al. showed that for each standard deviation increase in Lp(a), the risk of carotid atherosclerosis increased significantly in the second and third tertiles of Lp(a) compared with the first (OR 1.89 and 2.96, respectively) [5]. We previousely reported that Lp(a) was positively associated with high-risk plaque features including intraplaque hemorrhage, mural thrombus, or surface defects [7] and with plaque vascularity [8] in AIM-HIGH. On the other hand, SATURN investigators recently reported that Lp(a) levels were not associated with coronary atheroma progression as measured by IVUS in CAD patients on long-term maximal intensity statin therapy with a mean LDL-C of 60 mg/dL [26].

Treatment with ERN significantly lowered Lp(a) levels by 21% in the AIM-HIGH main trial [9] and 25% in the Carotid MRI substudy cohort, this reduction did not translate into reduction in CV events [9] or atherosclerosis progression. A similar Lp(a) reduction can be achieved with PCSK9 inhibition using evolocumab and alirocumab, with 25.5% achieved in OSLER [27] and 29.3% in ODYSSEY [28], in addition to substantial LDL-C lowering. Although FOURIER [29] showed significant CV event reduction in patients with CV disease and receiving statin therapy, Lp(a) reduction by evolocumb did not add apparent benefit to LDL-C lowering in a population with low Lp(a) at baseline [29]. Whether Lp(a) lowering with PCSK9 inhibition independently contributes to the reductions of coronary atherosclerosis and CV events in patients with elevated Lp(a) remains unknown. On the other hand, aggressive lowering Lp(a) levels by 73% with apheresis in addition to statin therapy has been shown to provide incremental CV event reduction in subjects with established vascular disease [30]. Promising result from the recent development in antisense therapy by inhibiting apo(a) mRNA translation showed that Lp(a) can be decreased by >80% [31]. Future studies are needed to determine the potential of aggressively lowering Lp(a), in addition to LDL-C reduction, on atherosclerosis burden and CV event risk.

Finally, in this hypothesis-generating analysis, while we found a significiant association between Lp(a) and plaque growth, we did not find significant association between baseline Lp(a) levels and baseline carotid atherosclerosis burden. This could be due to AIM-HIGH participants begin enrolled based established CV disease, reducing the range of plaque burden of subjects at baseline.

This study has a number of limitations. The MRI substudy cohort had several diffences compared to the entire AIM-HIGH cohort, potentially limiting the generalizability of these results to the broader population. However, while statistically significant, the actual differences in median age (2 years), race (4%), and body mass index (1 kg/m^2) were relatively small in absolute terms. More notable is that those in the MRI substudy were less likely than the remainder of the AIM-HIGH cohort to be diabetic (27% vs. 34%), potentially because eGFR > 60 $mL/min/1.73m^2$ was required due to the injection of a gadolinium-based contrast agent. The MRI substudy was also much more likely to be hypertensive (82% vs. 71%), though the reason for this is unclear. Within the MRI substudy cohort, there was an imbalance in Lp(a) levels at baseline between the mono- and combination therapy groups,

which was mitigated by adjusting for treatment group throughout the analysis. Lastly, of the lipid variables, Lp(a) was the only one found to be significantly associated with %WV change. It is possible that the sample size of 152 subjects afforded insufficient statistical power to detect associations with other lipid variables, so they should be further evaluated in larger studies.

In conclusion, in patients under intensive LDL-C lowering to <70 mg/dL, carotid atherosclerosis continued to progress as assessed by carotid MRI. Elevated Lp(a) levels independently predicte carotid atherosclerosis progression.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations

Lp(a)	Lipoprotein (a)
CVD	cardiovascular disease
MRI	magnetic resonance imaging
LDL-C	low density lipoprotein cholesterol
HDL-C	high density lipoprotein cholesterol
TC	total cholesterol
TG	triglycerides
ApoB	apolipoprotein B
apoA1	apolipoprotein A1
AIM-HIGH	Atherothrombosis Intervention in Metabolic Syndrome with Low HDL/High Triglycerides: Impact on Global Health Outcomes
HDL-C	high-density lipoprotein cholesterol
ERN	extended release niacin
%WV	percent wall volume

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Highlights

- Carotid atherosclerosis continued to progress during lipid therapy with targeted LDL-C<70 mg/dl.
- This progression was not effected by adding extended-release niacin to simvastatin.
- Lp(a) levels independently predicted carotid atherosclerosis progression.

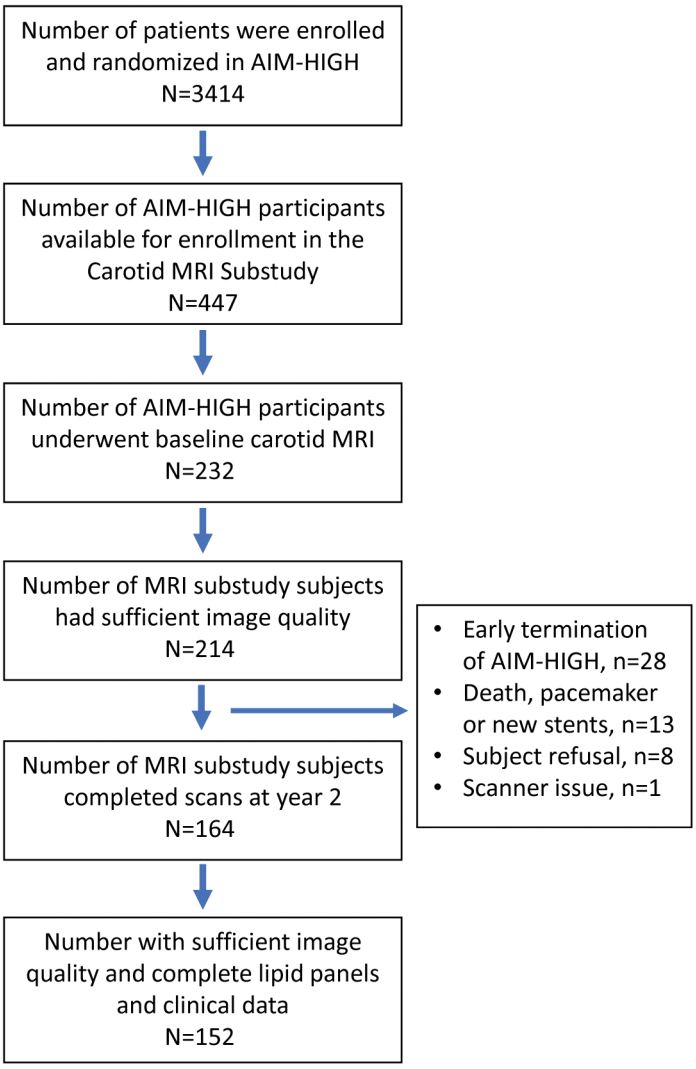

Figure 1.
Flowchart of the study population.

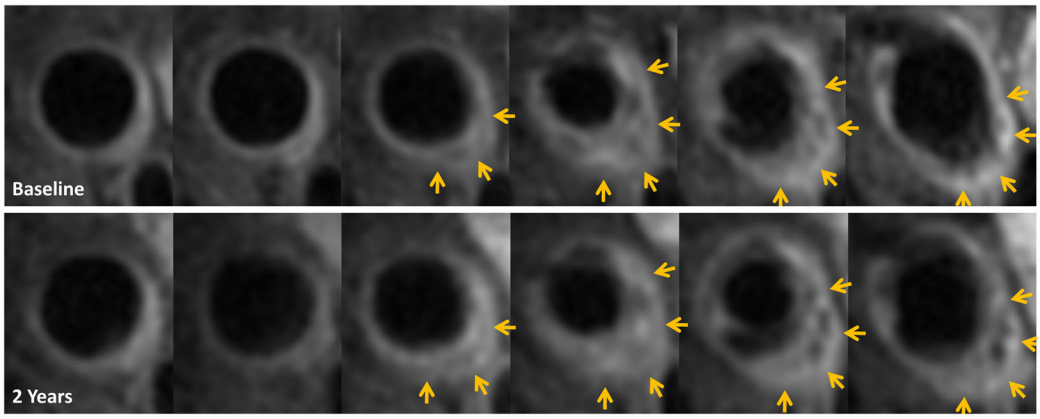

Figure 2.

Example of carotid plaque progression in a subject with elevated Lp(a).

The top panel shows 6 consecutive post-contrast T1-weighted images (2 mm thickness) of the left common carotid artery up to the bifurcation. The lower panel presents the matching locations 2 years later and a noticeable plaque volume progression as indicated by the yellow arrows compared to baseline. This example is from an AIM-HIGH participant who was a current smoker, had a history of coronary artery disease with a prior coronary bypass surgery and on standard of care for secondary prevention, including statin therapy >5 years prior to enrollment in the study. At baseline, body mass index (BMI) = 30, BP = 112/70 mmHg, total cholesterol (TC) = 140 mg/dl, triglycerides (TG) = 203 mg/dl, low density lipoprotein cholesterol (LDL-C) = 64 mg/dl, high density lipoprotein cholesterol (HDL-C) = 35 mg/dl, apolipoprotein B (ApoB) = 92 mg/dl, apolipoprotein A1 (apoA1) = 120 mg/dl, Lp(a) = 263.6 nmol/L [>95 percentile of Lp(a) distribution]. The subject was randomized to simvastatin and placebo for extend-release niacin in AIM-HIGH. On-study lipids showed that TC = 115 mg/dl, TG = 148 mg/dl, LDL-C = 45 mg/dl, HDL-C = 40 mg/dl, ApoB = 64 mg/dl, ApoA1 = 130 mg/dl, Lp(a) = 159.4 nmol/L [>90 percentile of Lp(a) distribution].

Table 1

Clinical, lipid, and carotid plaque characteristics by treatment assignment.

Variable	Treatment Assignment* Monotherapy (N=86)	Combination Therapy (N=66)	P-value†
Baseline Clinical Characteristics			
Male sex	67 (77.9)	56 (84.8)	0.31
Age, years	62 (46 – 78)	60 (45 – 79)	0.55
White race	80 (93.0)	53 (80.3)	0.025
Body mass index, kg/m^2	29 (17 – 44)	30 (21 – 41)	0.46
Current smoker	16 (18.6)	10 (15.2)	0.67
History of diabetes	25 (29.1)	16 (24.2)	0.58
History of hypertension	71 (82.6)	54 (81.8)	>0.99
Baseline Lipid Values			
Total-C, mg/dl	145 (88 – 257)	144 (100 – 245)	0.71
LDL-C, mg/dl	74 (29 – 178)	72 (32 – 167)	0.92
HDL-C, mg/dl	35 (20 – 51)	34 (18 – 52)	0.42
Triglycerides, mg/dl	166 (100 – 333)	154 (101 – 388)	0.34
ApoB, mg/dl	82 (41 – 159)	86 (53 – 175)	0.11
ApoA1, mg/dl	124 (85 – 167)	119 (59 – 168)	0.18
Lp(a), nmol/L	29 (0.5 – 324)	47 (0.3 – 339)	0.020
On-study Lipid Values			
Total-C, mg/dl	140 (97 – 289)	134 (87 – 223)	0.63
LDL-C, mg/dl	69 (28 – 203)	67 (26 – 126)	0.48
HDL-C, mg/dl	39 (21 – 67)	43 (21 – 73)	0.007
Triglycerides, mg/dl	154 (74 – 477)	131 (44 – 464)	0.012
ApoB, mg/dl	77 (51 – 153)	74 (30 – 144)	0.10
ApoA1, mg/dl	128 (88 – 171)	136 (72 – 210)	0.041
Lp(a), nmol/L	24 (0.4 – 321)	33 (0.4 – 353)	0.15

*Values are no. (%) or median (range);

†Fisher's exact test or Wilcoxon rank-sum test comparing treatment groups.

Table 2

Changes in lipids from baseline to 1-year of the study.

		Treatment Assignment*		
Variable	**All (N=152)**	**Monotherapy (N=86)**	**Combination Therapy (N=66)**	**P-value†**
Change in total-C, mg/dl	−2.2 ± 38.0	−2.0 ± 39.6	−2.5 ± 36.0	0.55
Change in LDL-C, mg/dl	−5.3 ± 31.3‡	−4.4 ± 34.1	−6.6 ± 27.4‡	0.38
Change in HDL-C, mg/dl	6.4 ± 7.2‡	4.1 ± 6.2‡	9.5 ± 7.4‡	<0.001
Change in triglycerides, mg/dl	−12.5 ± 80.2‡	−6.8 ± 69.7	−19.9 ± 92.2‡	0.033
Change in ApoB, mg/dl	−8.7 ± 25.7‡	−3.8 ± 24.1	−15.0 ± 26.6‡	0.004
Change in ApoA1, mg/dl	9.9 ± 16.9‡	5.2 ± 13.3‡	16.0 ± 19.1‡	0.001
Change in Lp(a), nmol/L	−9.3 ± 35.6‡	−0.5 ± 27.6	−20.8 ± 41.5‡	<0.001

*Values are mean ± SD;

†Wilcoxon rank-sum test comparing change in lipids between treatment groups;

‡Significant change in lipid values between baseline and on-study by Wilcoxon signed-rank test ($p<0.05$).

Table 3

Associations between individual baseline and on-study lipid variables and carotid plaque progression.

	Model 1		
Variable	**β***	**(95% CI)**	**P-value**
Baseline Lipid Values			
Total-C	0.09	(−0.10, 0.28)	0.34
LDL-C	0.05	(−0.13, 0.24)	0.59
HDL-C	0.06	(−0.15, 0.26)	0.58
Triglycerides†	0.08	(−0.11, 0.27)	0.39
ApoB	0.15	(−0.04, 0.33)	0.12
ApoA1	0.07	(−0.13, 0.27)	0.47
Lp(a)†	0.33	(0.15, 0.51)	0.001
On-study Lipid Values			
Total-C	0.04	(−0.15, 0.23)	0.66
LDL-C	−0.01	(−0.20, 0.18)	0.94
HDL-C	0.01	(−0.19, 0.22)	0.88
Triglycerides†	0.07	(−0.12, 0.26)	0.47
ApoB	0.16	(−0.04, 0.35)	0.11
ApoA1	−0.03	(−0.23, 0.17)	0.76
Lp(a)†	0.31	(0.13, 0.49)	0.001

Model 1 = one lipid variable + adjustments for random assignment, baseline %WV, adjustment for sex, age, race, BMI, current smoker, diabetes, hypertension;

*Mean difference in the annualized change in %WV in units of %/year per 1-SD increase in the lipid variable;

†Variable was log-transformed prior to inclusion in the model to reduce right-skewness.