Brief Report

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

An Analysis of the AIM-HIGH (Atherothrombosis Intervention in Metabolic Syndrome With Low HDL/High Triglycerides: Impact on Global Health Outcomes) Carotid Magnetic Resonance Imaging Substudy

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

Approach and Results—AIM-HIGH was a randomized, double-blind study of subjects with established vascular disease, elevated triglycerides, and low HDL-C (high-density lipoprotein cholesterol). One hundred fifty-two AIM-HIGH subjects underwent both baseline and 2-year follow-up carotid artery magnetic resonance imaging. 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. Average %WV at baseline was 41.6±6.8% and annualized change in %WV over 2 years ranged from −3.2% to 3.7% per year (mean: 0.2±1.1% per year; $P=0.032$). Increases in %WV were significantly associated with higher baseline Lp(a) (β=0.34 per 1-SD increase of Lp(a); 95% CI, 0.15–0.52; $P<0.001$) 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, 0.15–0.52; $P<0.001$).

Conclusions—Despite intensive lipid therapy, aimed at aggressively lowering LDL-C to <70 mg/dL, carotid atherosclerosis continued to progress as assessed by carotid magnetic resonance imaging and that elevated Lp(a) levels were independent predictors of increases in atherosclerosis burden. (***Arterioscler Thromb Vasc Biol*****. 2018;38:00-00. DOI: 10.1161/ATVBAHA.117.310368.)**

Key Words: atherosclerosis ■ lipids ■ lipoprotein ■ risk factors ■ triglycerides

Lp(a) (lipoprotein(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] In addition, the AIM-HIGH study (Atherothrombosis Intervention in Metabolic Syndrome With Low HDL/High Triglycerides: Impact on Global Health Outcomes) 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 magnetic resonance

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Nonstandard Abbreviations and Acronyms

%WV	percent wall volume
AIM-HIGH	Atherothrombosis Intervention in Metabolic Syndrome With Low HDL/High Triglycerides: Impact on Global Health Outcomes
apo A1	apolipoprotein A1
ApoB	apolipoprotein B
CVD	cardiovascular disease
HDL-C	high-density lipoprotein cholesterol
LDL-C	low-density lipoprotein cholesterol
Lp(a)	lipoprotein(a)
MRI	magnetic resonance imaging
VLDL	very-low-density lipoprotein

imaging (MRI) in subjects who have been treated with LDL-C (low-density lipoprotein cholesterol)–lowering therapy and participated in the AIM-HIGH trial.[9]

Materials 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% nonwhite, 26% current smokers, 27% with a history of diabetes mellitus, and 82% with a history of hypertension (Table 1). Median total cholesterol, LDL-C, HDL-C (high-density lipoprotein cholesterol, triglycerides, and Lp(a) at baseline were 145, 72, 35, 162, and 32 nmol/L, respectively. Baseline percent wall volume (%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.

Table I in the online-only Data Supplement 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 versus 64

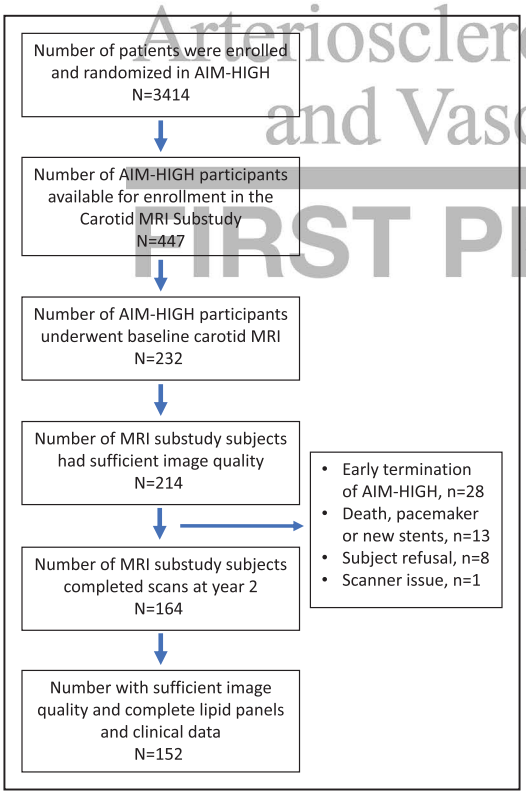

Figure 1. Flowchart of the study population. AIM-HIGH indicates Atherothrombosis Intervention in Metabolic Syndrome With Low HDL/High Triglycerides: Impact on Global Health Outcomes; and MRI, magnetic resonance imaging.

Table 1. Clinical, Lipid, and Carotid Plaque Characteristics by Treatment Assignment

Variable	Treatment Assignment*		*P* Value†
	Monotherapy (n=86)	Combination Therapy (n=66)	
Baseline clinical characteristics			
Male sex	67 (77.9)	56 (84.8)	0.31
Age, y	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 mellitus	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
Apo A1, 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
Apo A1, mg/dL	128 (88–171)	136 (72–210)	0.041
Lp(a), nmol/L	24 (0.4–321)	33 (0.4–353)	0.15

Apo indicates apolipoprotein; C, cholesterol; HDL, high-density lipoprotein; LDL, low-density lipoprotein; and Lp(a), lipoprotein(a).

*Values are n (%) or median (range).

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

years; *P*=0.003), were less likely to be white (88% versus 92%; *P*=0.042), had lower body mass index (median, 29 versus 30; *P*=0.002), less likely to be diabetic (27% versus 34%; *P*=0.066), and more likely to have a history of hypertension (82% versus 71%; *P*=0.002). There were no significant differences in baseline lipids or on-study lipids between the 2 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% versus 11%; *P*=0.009).

Over 1 year, all lipid values except total cholesterol significantly improved on average across both treatment groups (Table 2). However, HDL-C (*P*<0.001), triglycerides (*P*=0.033), ApoB (apolipoprotein B; *P*=0.004), Apo A1 (apolipoprotein A1; *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 (Table II in the online-only Data Supplement). None of the other nonlipid 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, 0.15–0.51; *P*=0.001) and on study (β=0.31; 95% CI, 0.13–0.49; *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, 0.15–0.52; *P*<0.001) and on-study Lp(a) (β=0.33; 95% CI, 0.15–0.52; *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, and 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 (Table III in the online-only Data Supplement). Nonwhite subjects were more likely to have elevated Lp(a) (*P*=0.048). Those with higher Lp(a) at baseline tended to have lower total cholesterol (*P*=0.030), LDL-C (*P*=0.043), and triglycerides (*P*=0.048) at 1 year. Baseline %WV was similar between the 2 groups (median, 40% versus 41%; *P*=0.52), and there was no significant correlation between %WV and baseline Lp(a) (Spearman ρ=−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 3-dimensional ultrasound significantly predicted cardiovascular events including stroke, TIA, MI, and death. van Engelen et al[11] showed that subjects with >10% of carotid plaque progression over 1 year were considered to have an increased risk for future events. 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 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, whereas subjects in earlier studies were lipid treatment naive 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

Table 2. Changes in Lipids From Baseline to 1 Year of the Study

Variable	All (n=152)	Treatment Assignment*		*P* Value†
		Monotherapy (n=86)	Combination Therapy (n=66)	
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 Apo A1, 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

Apo indicates apolipoprotein; C, cholesterol; HDL, high-density lipoprotein; LDL, low-density lipoprotein; and Lp(a), lipoprotein(a).
*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

Variable	Model 1	
	β* (95% CI)	*P* Value
Baseline lipid values		
Total C	0.09 (–0.10 to 0.28)	0.34
LDL-C	0.05 (–0.13 to 0.24)	0.59
HDL-C	0.06 (–0.15 to 0.26)	0.58
Triglycerides†	0.08 (–0.11 to 0.27)	0.39
ApoB	0.15 (–0.04 to 0.33)	0.12
Apo A1	0.07 (–0.13 to 0.27)	0.47
Lp(a)†	0.33 (0.15 to 0.51)	0.001
On-study lipid values		
Total C	0.04 (–0.15 to 0.23)	0.66
LDL-C	–0.01 (–0.20 to 0.18)	0.94
HDL-C	0.01 (–0.19 to 0.22)	0.88
Triglycerides†	0.07 (–0.12 to 0.26)	0.47
ApoB	0.16 (–0.04 to 0.35)	0.11
Apo A1	–0.03 (–0.23 to 0.17)	0.76
Lp(a)†	0.31 (0.13 to 0.49)	0.001

Model 1=one lipid variable+adjustments for random assignment, baseline percent wall volume (%WV), adjustment for sex, age, race, body mass index, current smoker, diabetes mellitus, and hypertension. Apo indicates apolipoprotein; C, cholesterol; HDL, high-density lipoprotein; LDL, low-density lipoprotein; and Lp(a), lipoprotein(a).

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

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

was small, 62 mg/dL in the simvastatin plus extended-release niacin group and 67 mg/dL in the simvastatin plus placebo group. Finally, maximum CV benefits from niacin are associated with a significant decrease of triglyceride-rich very LDL (VLDL), their remnants, and dense LDL particles[18]; however, the AIM-HIGH subjects did not have high triglycerides at baseline (a mean of 161 mg/dL). More importantly, the current study results indicate that carotid atherosclerosis continues to progress despite LDL-C lowering to 62 mg/dL and lower LDL-C target is needed 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 finding 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 CVD.[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+extended-release niacin 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[1] demonstrated that compared with 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. Many 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 proinflammatory 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[5] showed that for each SD 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). We previously 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 extended-release niacin 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 CVD and receiving statin therapy, Lp(a) reduction by evolocumab 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, although we found a significant 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 because of AIM-HIGH participants begin enrolled based established CVD, reducing the range of plaque burden of subjects at baseline.

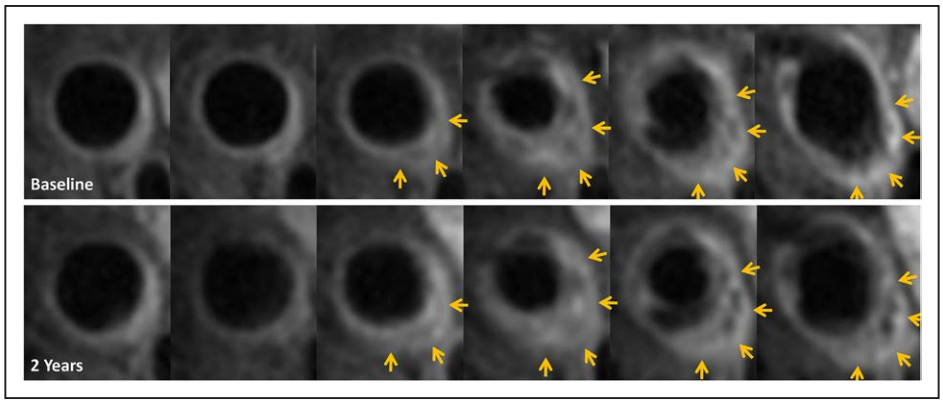

Figure 2. Example of carotid plaque progression in a subject with elevated Lp(a) (lipoprotein(a)). **Top**, Six consecutive postcontrast T1-weighted images (2 mm thickness) of the left common carotid artery up to the bifurcation. **Lower**, Matching locations 2 y later and a noticeable plaque volume progression as indicated by the yellow arrows compared with baseline. This example is from an AIM-HIGH (Atherothrombosis Intervention in Metabolic Syndrome With Low HDL/High Triglycerides: Impact on Global Health Outcomes) 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 y before enrollment in the study. At baseline, body mass index (BMI)=30, BP=112/70 mm Hg, total cholesterol (TC)=140 mg/dL, triglycerides (TG)=203 mg/dL, LDL-C (low-density lipoprotein cholesterol)=64 mg/dL, HDL-C (high-density lipoprotein cholesterol)=35 mg/dL, ApoB (apolipoprotein B)=92 mg/dL, apo A1 (apolipoprotein A1)=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, Apo A1=130 mg/dL, Lp(a)=159.4 nmol/L (>90 percentile of Lp(a) distribution).

This study has several limitations. The MRI substudy cohort had several differences compared with 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% versus 34%), potentially because eGFR >60 mL min^{-1} 1.73 m^{-2} was required because of the injection of a gadolinium-based contrast agent. The MRI substudy was also much more likely to be hypertensive (82% versus 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. Last, 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 predicted carotid atherosclerosis progression.

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Disclosures

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Highlights

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

Arteriosclerosis, Thrombosis, and Vascular Biology

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Lp(a) (Lipoprotein(a)) Levels Predict Progression of Carotid Atherosclerosis in Subjects With Atherosclerotic Cardiovascular Disease on Intensive Lipid Therapy: An Analysis of the AIM-HIGH (Atherothrombosis Intervention in Metabolic Syndrome With Low HDL/High Triglycerides: Impact on Global Health Outcomes) Carotid Magnetic Resonance Imaging Substudy

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Material and Methods

AIM-HIGH Trial

AIM-HIGH was a randomized, double-blind study of subjects with established vascular disease, elevated triglycerides between 150-400 mg/dL, and low high-density lipoprotein cholesterol (HDL-C) ≤40 mg/dL for a man or ≤ 50 mg/dL for a woman. Subjects were randomized to treatment with therapy with simvastatin plus placebo (monotherapy group) or simvastatin plus extended release niacin (ERN) (combination therapy group), 1.5-2 gm/day, with ezetimibe added on as needed to maintain on-treatment LDL-C between 40-80 mg/dL. The overall trial was stopped early due to lack of efficacy of the addition of ERN to reduce CV events; although in-study LDL-C levels achieved <70 mg/dL in both treatment groups (median of 62 mg/dL in the simvastatin plus ERN group and 67 mg/dL in the simvastatin plus placebo group) and HDL-C was increased from a median of 35 mg/dL to 42mg/dL in the simvastatin plus ERN group.

Lp(a) was measured at baseline and 1 year post-randomization using a monoclonal antibody-based enzyme-linked immunoadsorbent assay (ELISA) method, which was considered the gold standard method for measuring Lp(a), developed in the Northwest Lipid Research Laboratory [1].

AIM-HIGH Carotid MRI Substudy

Of the 3414 AIM-HIGH subjects, 232 underwent baseline carotid MRI, of which 214 had qualified image quality [2]. Imaging was performed using General Electric or Philips 3T whole body scanners with two separate phased-array carotid coils and standardized carotid MRI scan protocol as previously published [2]. Of the 214 subjects with interpretable baselime MRI, 164 had a 2-year follow-up MRI scan (**Figure 1**). The

early termination of the main trial prohibited 28 subjects to receive 2-year follow-up scan. Using a custom-designed image analysis tool, boundaries of the carotid lumen and outer wall were identified and contoured. Volumes were derived from summing the contoured areas across slices from the same vessel and multiplying the sum by the slice thickness (2 mm). All readers went through standardized training and throughout the study measurements were reviewed by a separate reader to achieve consensus and maintain high reliability in measurements. The primary measure of plaque burden was based on the percent wall volume (%WV) calculated using the formula: (wall volume/total vessel volume) x 100. As previously published, in an AIM-HIGH MRI sub-study of 68 subjects scanned at 16 imaging centers using the AIM-HIGH protocol, the scan-rescan coefficient of variation (CV) and an intraclass correlation coefficient (ICC) of lumen volume, wall volume, and total vessel volume ranged from 2.5-4.9% and 0.98-0.99, respectively. The measurement variability was evaluated for one reader reading two different scans of the same subjects acquired within 2 weeks [3].

Statistical Methods

Categorical variables were summarized as count (percentage) and continuous variables as mean ± standard deviation (SD) or median (range). The Kaplan-Meier estimator was used to estimate cardiovascular event rates at year 1 and year 2 of follow up. Groups of subjects were compared using Fisher's exact test (categorical variables), the Wilcoxon rank-sum test (continuous variables) and the log-rank test (cardiovascular events). The Wilcoxon signed-rank test was used to test for changes in lipid variables and %WV over follow up.

The primary analysis was to test whether any baseline or on-study lipid variables were predictive of changes in %WV using linear regression models. A total of 14 lipid variables were included in the analysis (7 baseline measurements and 7 on-study measurements). Each lipid variable was first tested individually in separate models. Multivariate models which included baseline or on-study LDL-C, HDL-C, triglycerides, and lp(a) together were then tested. All of these models were adjusted for random treatment assignment, baseline %WV, sex, age, race, BMI, current smoker, diabetes, and hypertension. Triglycerides and Lp(a) were log-transformed prior to inclusion in the models to reduce right-skewness. To account for testing 14 lipid variables, a Bonferroni corrected significance level of $\alpha = 0.0036$ (0.05/14) was used to assess statistical significance in the primary analysis. A significance level of $\alpha = 0.05$ was used for the other analyses. All statistical calculations were conducted with the statistical computing language R (version 3.1.1; R Foundation for Statistical Computing, Vienna, Austria).

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Supplemental Table I. Clinical, lipid, and carotid plaque characteristics of the MRI substudy subjects and AIM-HIGH cohort.

	AIM-HIGH Participant included in the MRI Substudy*		
Variable	**Yes (N=152)**	**No (N=3262)**	**P-value†**
Treatment Assignment			
Monotherapy	86 (56.6)	1610 (49.4)	0.097
Combination therapy	66 (43.4)	1652 (50.6)	
Baseline Clinical Characteristics			
Male sex	123 (80.9)	2787 (85.4)	0.13
Age, years	62 (45 - 79)	64 (44 - 89)	0.003
White race‡	133 (87.5)	3015 (92.5)	0.042
Body mass index‡, kg/m^2	29 (17 - 44)	30 (14 - 64)	0.002
Current smoker‡	26 (17.1)	596 (18.4)	0.75
History of diabetes	41 (27.0)	1117 (34.2)	0.066
History of hypertension	125 (82.2)	2314 (70.9)	0.002
Baseline Lipid Values			
Total-C, mg/dl	145 (88 - 257)	143 (70 - 290)	0.63
LDL-C, mg/dl	72 (29 - 178)	72 (19 - 180)	0.52
HDL-C, mg/dl	35 (18 - 52)	35 (16 - 53)	0.91
Triglycerides, mg/dl	162 (100 - 388)	165 (93 - 400)	0.11
ApoB‡, mg/dl	84 (41 - 175)	81 (30 - 329)	0.16
ApoA1‡, mg/dl	122 (59 - 168)	123 (61 - 194)	0.49
Lp(a)‡, nmol/L	32 (0.3 - 339)	34 (0.1 - 620)	0.86
On-study Lipid Values			
Total-C‡, mg/dl	139 (87 - 289)	138 (67 - 359)	0.50
LDL-C‡, mg/dl	69 (26 - 203)	67 (20 - 208)	0.24
HDL-C‡, mg/dl	40 (21 - 73)	40 (15 - 101)	0.61
Triglycerides‡, mg/dl	148 (44 - 477)	139 (26 - 1240)	0.68
ApoB‡, mg/dl	75 (30 - 153)	74 (23 - 199)	0.18
ApoA1‡, mg/dl	131 (72 - 210)	129 (67 - 219)	0.31

Lp(a)‡, nmol/L	27 (0.4 - 353)	29 (0.1 - 630)	0.71
Incidence of Cardiovascular Events			0.009
By 1 year	3.9%	6.0%	
By 2 years	5.9%	11.3%	

*Values are no. (%), median (range), or Kaplan-Meier estimates of the cumulative event rate;
†Comparison of the two cohorts using Fisher's exact test, the Wilcoxon rank-sum test, or the log-rank test as appropriate;
‡Subjects with missing values were excluded from the corresponding summary statistic: race (n=1), body mass index (n=5), current smoker (n=26), baseline apolipoproteins (n=61), lp(a) (n=55), and on-study lipids (n=299-311).

Supplemental Table II. Associations between individual baseline clinical characteristics and carotid plaque progression.

Variable	β*	(95% CI)	P-value*
Combination therapy group	0.00	(-0.37, 0.37)	0.99
Male sex	-0.29	(-0.75, 0.18)	0.23
Age, per 5-year increase	0.11	(0.00, 0.22)	0.043
White race	0.19	(-0.38, 0.76)	0.52
Body mass index, per 5-kg/m^2 increase	0.03	(-0.19, 0.25)	0.79
Current smoker	0.00	(-0.48, 0.49)	0.99
History of diabetes	-0.16	(-0.57, 0.25)	0.44
History of hypertension	0.46	(-0.02, 0.93)	0.061

*Mean difference in the annualized change in %WV in units of % / year, with adjustment for treatment assignment and baseline %WV.

Supplemental Table III. Comparison of clinical, lipid, and carotid plaque characteristics by high and low Lp(a) at baseline.

	Lipoprotein(a) Group*		
Variable	**≥32 nmol/L (N=77)**	**<32 nmol/L (N=75)**	**P-value†**
Baseline Clinical Characteristics			
Male sex	66 (85.7)	57 (76.0)	0.15
Age, years	62 (46 - 79)	61 (45 - 78)	0.70
White race	63 (81.8)	70 (93.3)	0.048
Body mass index, kg/m^2	29 (21 - 44)	29 (17 - 40)	0.42
History of tobacco use	12 (15.6)	14 (18.7)	0.67
History of diabetes	17 (22.1)	24 (32.0)	0.20
History of hypertension	61 (79.2)	64 (85.3)	0.40
Baseline Lipid Values			
Total-C, mg/dl	142 (89 - 245)	146 (88 - 257)	0.28
LDL-C, mg/dl	71 (33 - 167)	74 (29 - 178)	0.60
HDL-C, mg/dl	34 (18 - 51)	35 (20 - 52)	0.97
Triglycerides, mg/dl	145 (100 - 388)	166 (101 - 370)	0.094
ApoB, mg/dl	85 (41 - 156)	81 (47 - 175)	0.32
ApoA1, mg/dl	122 (59 - 151)	122 (85 - 168)	0.88
On-study Lipid Values			
Total-C, mg/dl	133 (95 - 223)	142 (87 - 289)	0.030
LDL-C, mg/dl	64 (41 - 126)	71 (26 - 203)	0.043
HDL-C, mg/dl	39 (21 - 73)	41 (23 - 67)	0.65
Triglycerides, mg/dl	135 (44 - 477)	154 (54 - 464)	0.048
ApoB, mg/dl	76 (36 - 144)	75 (30 - 153)	0.67
ApoA1, mg/dl	129 (72 - 210)	132 (99 - 186)	0.38
Baseline %WV	40 (27 - 62)	41 (30 - 60)	0.52

*Values are no. (%) or median (range); higher and lower Lp(a) groups were defined by the median Lp(a) value of 32 nmol/L;

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