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Relation of First and Total Recurrent Atherosclerotic Cardiovascular Disease Events to Increased Lipoprotein(a) Levels among Statin Treated Adults with Cardiovascular Disease

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Abstract

The relation between elevated lipoprotein(a) and total atherosclerotic cardiovascular disease (ASCVD) residual risk in persons with known cardiovascular disease on statin therapy is not well-established. We examined first and total recurrent ASCVD event risk in statin-treated adults with prior ASCVD. We studied 3,359 adults (mean age 63.6 years, 85.1% male) with prior ASCVD on statin therapy from the AIM-HIGH clinical trial cohort. The first and total ASCVD event rates were calculated by lipoprotein(a) [Lp(a)] categories. Cox regression and Prentice, Williams and Peterson (PWP) models provided hazard ratios (HRs) for ASCVD events over a mean follow-up of 3.3 years, adjusted for age, sex, trial treatment, LDL-C, and other risk factors. A total of 747 events occurred during follow-up, among which 544 were first events. First and total ASCVD event rates were greater with higher Lp(a) levels. Compared to Lp(a)<15 mg/dL, HRs (95% CIs) for subsequent total ASCVD events among Lp(a) levels of 15-<30, 30-<50, 50-<70 and ≥70 mg/dL were 1.04 (0.82-1.32), 1.15 (0.88-1.49), 1.27 (1.00-1.63) and 1.51 (1.25-1.84). Moreover, a continuous relation for total events was observed (HR=1.08 [1.04-1.12] per 20 mg/dL greater Lp(a). Findings for first ASCVD events and in those with LDL-C ≥70 mg/dL versus <70 mg/dL and without diabetes were similar. The risk of first and total ASCVD events is increased with Lp(a) levels of ≥70 mg/dL and ≥50 mg/dL, respectively, among adults with known CVD on statin therapy.

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Author Credit Statement

Dr. Nathan Wong designed the study and wrote the manuscript.

Dr. Yanglu Zhao conducted the analysis and provided critical review and revision.

Drs. Sung and Browne provided critical review and revision.

Keywords

lipoprotein(a); statins; cardiovascular disease

Introduction

Lipoprotein (a) [Lp(a)] is a lipoprotein in which the apolipoprotein B component of a low density lipoprotein-like particle is linked by a disulfide bond to an apo(a), the distinct protein component of Lp(a) responsible for its signature, structural and functional properties. Observational and genetic studies support a causal relation of Lp(a) with atherosclerotic cardiovascular disease (ASCVD) (1-4). Lp(a) has a linear relationship with ASCVD event risk (5) and mediates CVD risk through the atherogenicity of its LDL-like moiety, anti-fibrinolytic effects of its apo(a) moiety, and the pro-inflammatory effects of its oxidized phospolipids (4). Lp(a) frequently remains elevated despite moderate or high intensity statin therapy. The question of residual risk due to elevated Lp(a) specifically in those with ASCVD on statin therapy has not been adequately addressed (6,7). We evaluated in the Atherothrombosis Intervention in Metabolic Syndrome with Low HDL/High Triglycerides: Impact on Global Health Outcomes (AIM-HIGH) trial (8) the association of Lp(a) levels on first as well as total ASCVD events in statin-treated patients with ASCVD. We also examined these relationships stratified by LDL-C levels and diabetes status.

Methods

We utilized data from the AIM-HIGH trial, a multi-center clinical trial evaluating the effect of niacin added to intensive statin therapy on reducing the risk of ASCVD in patients with established ASCVD and high density lipoprotein-cholesterol (HDL-C) and(or) triglycerides dyslipidemia. The study design of the trial has been previously published (9). In brief, patients were recruited at 92 clinical centers in the United States and Canada. Eligible patients were 45 years of age or older and had established ASCVD with normal baseline LDL-C, low HDL-C and elevated triglyceride levels. 3,414 patients who tolerated at least 1500 mg of niacin per day were randomly assigned, in a 1:1 ratio, to niacin or matching placebo in addition to 40 to 80 mg of simvastatin per day. The trial was stopped due to lack of efficacy to reduce ASCVD events. In this analysis, we included 3,359 participants with Lp(a) measurement data and follow-up information for subsequent ASCVD events. Our study was determined to be exempt from institutional review board approval and used de-identified data provided by the NIH Biologic Specimen and Data Repository.

Lp(a) was measured at baseline using a monoclonal antibody-based enzyme-linked immune adsorbent assay (ELISA) method, developed in the Northwest Lipid Research Laboratory. Lp(a) per mg/dL were calculated by Lp(a) per nmol/L divided by an average conversion unit of 2.4 as previously recommended (9). Patients were categorized into 5 groups based on their baseline Lp(a) levels: <15 mg/dL, 15-<30 mg/dL, 30-<50 mg/dL, 50-<70 mg/dL and ≥70 mg/dL groups. Baseline age, sex, race, smoking status, education level, alcohol consumption, systolic (SBP) and diastolic blood pressure (DBP), LDL-C, HDL-C,

triglycerides, hemoglobin A1c (HbA1c), body mass index (BMI), family history of premature ASCVD were utilized as covariates.

After the first year, participants were seen every six months in the clinic. ECGs were obtained annually to assess for potential silent myocardial infarction (MI). A clinical events committee reviewed suspected endpoints with supporting documentation. The composite ASCVD outcome for this study was the AIM-HIGH primary endpoint, which included death from coronary heart disease, non-fatal myocardial infarction (MI), ischemic stroke, hospitalization (for >23 hours) for an acute coronary syndrome, or symptom-driven coronary or cerebral revascularization. Both first and total ASCVD events were obtained during follow-up. For total ASCVD events, revascularization or death due to the same vascular events and within the same hospitalization was only counted as one event.

Baseline characteristics were compared between those with vs. without ASCVD events during follow-up, using t-tests for continuous variables or Chi^2 tests of proportions for categorical variables. First and total ASCVD event rates were calculated per 1000 person-years stratified by Lp(a) categories. Hazard ratios (HRs) examining the relationship between Lp(a) categories and total ASCVD events during follow-up were calculated from the Prentice, Williams and Peterson (PWP) models by assuming the beta coefficients for the *Nth* events were equal (10). Both Cox regression or the PWP models were used to calculate the HRs for the first ASCVD event during follow-up. The above models were adjusted for age, sex, race, smoking status, education level, alcohol consumption, SBP and DBP, LDL-C, HDL-C, triglycerides, HbA1c, BMI, family history of premature CVD and trial treatment (niacin vs. placebo). Lp(a) were additionally examined as a continuous variable in PWP models. We also examined the relation of Lp(a) with individual endpoints of myocardial infarction and revascularization (there were an insufficient number of events to do so for other component outcomes). In subgroup analysis, associations of Lp(a) and total/first ASCVD were re-examined by LDL-C levels (≥70 mg/dL vs. < 70 mg/dL), diabetes mellitus (DM) status (yes vs. no) at baseline as well as by trial arm (niacin vs. placebo, both on background of simvastatin). Two-sided p-value < 0.05 was considered statistically significant. SAS 9.4 was used for all analyses.

Results

In total, 3359 subjects (85.1% male, mean age 63.7 years, 92.3% white) from original AIM-HIGH cohort were included in the analysis. 554 (16.2%) had at least one ASCVD event during the follow-up. Compared to those without ASCVD events during follow-up, those with ASCVD events were older, more likely were men, and had greater proportions with family history of CVD and diabetes, but a lower proportion of alcohol consumers. They also tended to have lower HDL-C, higher serum creatinine, higher homocysteine levels (Table 1). Lp(a) was also significantly higher among those with at least one ASCVD event compared to those with no ASCVD event.

During a mean follow-up of 3.3 years, 554 (16.2%) first and 747 (22.2%) total ASCVD events occurred. Figure 1 shows the first and total ASCVD event rates by Lp(a) categories. There was a stepwise increase in the rate of first and total ASCVD events by Lp(a)

categories. First and total ASCVD event rates among those with Lp(a) ≥ 70 mg/dL were 76.0 and 91.9 per 1000 person-years, respectively (Figure 1).

We also examined the independent association of Lp(a) with first and total ASCVD events in the PWP models (Figure 2). Compared to those with Lp(a) <15 mg/dL, the adjusted HRs of total ASCVD events were 1.04 (95% CI: 0.82-1.32), 1.15 (95% CI: 0.88-1.49), 1.27 (95% CI: 1.00-1.63) and 1.51 (95% CI: 1.25-1.84) for those with Lp(a) 15-<30 mg/dL, 30-<50 mg/dL, 50-<70 mg/dL and ≥70 mg/dL, respectively. For first ASCVD events these HRs were 1.11 (95% CI: 0.85-1.47), 1.30 (95% CI: 0.97-1.73), 1.38 (95% CI: 1.04-1.85), and 1.77 (95% CI: 1.42-2.21), respectively. There were 117 2nd, 41 3rd and 35 4thASCVD events during follow-up, however, insufficient power to examine Lp(a) levels in relation to these interim events. Lp(a) increase per 20 mg/dL was associated with a 10% higher first ASCVD event risk and an 8% higher total ASCVD event risk (both p <0.0001). The adjusted HRs for first events from the Cox regression models were nearly identical to those from the PWP models (results not shown). Additional analyses examined relationships of Lp(a) with individual components of our primary endpoint showed those with an Lp(a) of ≥70 mg/dL (compared to <15 mg/dL) had a HR=1.54 (1.05-2.27) for myocardial infarction, and a HR=1.69 (1.17-2.45) for first and HR=1.60 (1.13-2.28) for total coronary or cerebral revascularization. In addition, the relation of Lp(a) with ASCVD in PWP models were similar in each of the AIM-HIGH treatment arms (niacin vs. placebo), indicating no differential effect of niacin treatment (interaction terms not significant for either first or total ASCVD events between treatment arms), justifying our pooling of subjects in both study arms (results not shown).

The association of Lp(a) with ASCVD events stratified by baseline LDL-C <70 mg/dL vs. ≥ 70 mg/dL was similar: in those with LDL-C ≥ 70 mg/dL, HRs comparing Lp(a) ≥ 70 mg/dL vs. < 15 mg/dL were 1.98 (95% CI: 1.48-2.66) and 1.77 (95%CI: 1.37-2.30) for first and total ASCVD events, respectively; while when LDL-C < 70 mg/dL, corresponding HRs were 1.45 (95% CI: 1.01-2.09) and 1.27 (95% CI: 0.93-1.74). Although p-values for interaction tests were not significant for either continuous or categorical Lp(a) in relation with ASCVD events (p=0.42-0.66), both total and first ASCVD risks were especially increased in those with Lp(a) ≥70 mg/dL (Table 2).

We additionally compared Lp(a) in relation to first and total ASCVD events in those with (n=1354) and without (n=2005) DM (Table 3). For Lp(a) measured continuously, HRs did not differ significantly in those with vs. without DM for either first events or total events (interaction terms not significant). Analyses by Lp(a) categories also showed little difference between those with and without DM, although for those with Lp(a) levels of 70 mg/dL or greater, those with DM tended to have slightly lower HR's for first and total events (1.54 and 1.38, respectively, both p<0.05) than those without DM (1.90 and 1.70, respectively, both p<0.0001).

The added predictive ability of Lp(a) for first ASCVD events was assessed by improvement in the Harrell's C-statistics, over a model of age, sex, race, and standard risk factors, including LDL-C. Clinical utility was further assessed by the category-free net reclassification index (NRI) to examine the proportion of persons whose risk was

reclassified from the addition of Lp(a) over standard risk factors. The addition of Lp(a) to the base model increased C-statistics from 0.58 to 0.60 for ASCVD events although increases were not significant for either the continuous or the categorical Lp(a) measures. Category-free NRI for ASCVD was 5.7% comparing models with vs. without categorical Lp(a) and 7.8% comparing models with vs. without continuous Lp(a) (both p values >0.05).

Discussion

Our study is the first to document total ASCVD event burden associated with increased levels of Lp(a) and shows initial and total ASCVD events to be greater in persons with Lp(a) levels of ≥50 mg/dL and ≥70 mg/dL, respectively. A continuous gradient of greater ASCVD event rates is seen for both first and total events beyond Lp(a) levels of 15 mg/dL. We also show in our cohort of ASCVD patients that Lp(a) levels are predictive of future ASCVD events both in those with and without LDL-C levels controlled to <70 mg/dL; however, relationships appeared strongest for those with LDL-C ≥70 mg/dL. We additionally show Lp(a) to remain a predictor of subsequent events among statin treated persons with ASCVD with and without DM.

Lp(a) levels have been recently documented to have a linear relationship with cardiovascular event risk in a large meta-analysis with mean follow-up of 3.0 years (5); however, no separate analysis was reported in persons specifically with known ASCVD. The question of remaining residual risk due to elevated Lp(a) levels is an important one, and a recent analysis of 13,167 statin-treated patients (although mixed primary and secondary prevention) showed a hazard ratio of 1.61 in the setting of an LDL-C of 89.1 mg/dl and Lp(a) of 54.9 mg/dl (4^{th} quartile) (3). The risk of CVD events associated with Lp(a) has been reported to be curvilinear with an inflection point for accelerated risk above 24 mg/dl (6). A previous analysis in the AIM-HIGH cohort showed Lp(a) both at baseline and after 1 year of treatment to predict future ASCVD events similarly in both the niacin and placebo groups (11); however, specific cutpoints or risk of total events were not examined in this prior study as we have done. Analysis of another clinical trial cohort with high use of statins (97%), dal-Outcomes, however, showed no relation of Lp(a) levels to future CVD outcomes (7), and in a large analysis of 6,762 patients with coronary artery disease from three major studies, there was also no relation of Lp(a) levels with subsequent CVD events (12). Recent National Lipid Association (NLA) guidelines (13) suggest measurement of Lp(a) to be reasonable in those with premature ASCVD or progressive ASCVD despite optimal lipid-lowering. Those guidelines also noted that there is insufficient evidence that lowering Lp(a) independently of LDL-C, reduces ASCVD events in individuals with established ASCVD. Moreover, the most recent ACC/AHA multisociety guideline on cholesterol management (14) indicates Lp(a) levels of >50 mg/dL to be a risk enhancing factor that can be used to better inform the treatment decision in persons at borderline or intermediate risk of ASCVD. Of note, a recent pre-specified analysis of Odyssey Outcomes data involving alirocumab did show reduction of Lp(a) lead to decreased ASCVD events independently of LDL-C lowering, suggesting Lp(a) to be an appropriate target of treatment (15). Newer therapies in development that reduce Lp(a) plasma levels up to 80% are currently being investigated for CVD event reduction (16).

We also report that Lp(a) predicts future ASCVD events similarly among statin treated patients with ASCVD both with and without known DM, although with increased risk seen most clearly at 70 mg/dL or greater. Recently, Lp(a) levels above 10 mg/dL were shown to be predictive of future CVD events among persons with DM and known ASCVD in a large longitudinal Chinese cohort, most who were on statins (17). The Atherosclerosis Risk in Communities Study also recently showed Lp(a) as a predictor of CVD events in persons with DM and pre-DM (18).

Our study has strengths and limitations. The AIM-HIGH study was conducted with standardized assessment of Lp(a) levels and ascertainment of incident CVD events among the many study sites included. While most subjects were on a stable dose of simvastatin that maintained an LDL-C between 40-80 mg/dL, this limited the range of LDL-C available in the study and thus the ability of LDL-C to predict subsequent events. Also, our findings could differ had all patients been on a high intensity statin (as is the recommended standard of care today) or had lower baseline LDL-C levels. However, recent real-world claims data show current practice to be far from this recommended standard where mean LDL-C averaged 95 mg/dL, far higher than our 74 mg/dL, and with only 44% on a statin (11% on a high intensity statin) (19). Thus, our showing the value of Lp(a) to predict future ASCVD events at least as well in those with LDL-C ≥70 as compared to <70 mg/dL is actually quite relevant. Moreover, inclusion of persons with low HDL-C makes the AIM-HIGH cohort somewhat selective and may not be fully representative of all ASCVD patients. In addition, there was limited follow-up available (3.3 years on average) and relationships of Lp(a) and CVD events (including total events) may differ with longer follow-up; we also did not have a sufficient power to clearly examine relationships with components of the primary endpoint, especially for acute coronary syndrome or stroke. Importantly, while this was a clinical trial with half of patients taking niacin, our inclusion of niacin treatment as an interaction factor in sensitivity analysis showed this to be non-significant, therefore not impacting on our results. Further, the predominantly male, white composition of the AIM-HIGH cohort limits its representativeness to the greater US population.

In conclusion, our study uniquely shows total ASCVD event burden associated with increased Lp(a) levels despite statin therapy among persons with known ASCVD with Lp(a) levels of 70 mg/dL or greater. Ongoing clinical trials of newer therapies targeting Lp(a) will define whether lowering Lp(a) levels in persons at or above these levels will have a beneficial impact of further reducing residual ASCVD event risk.

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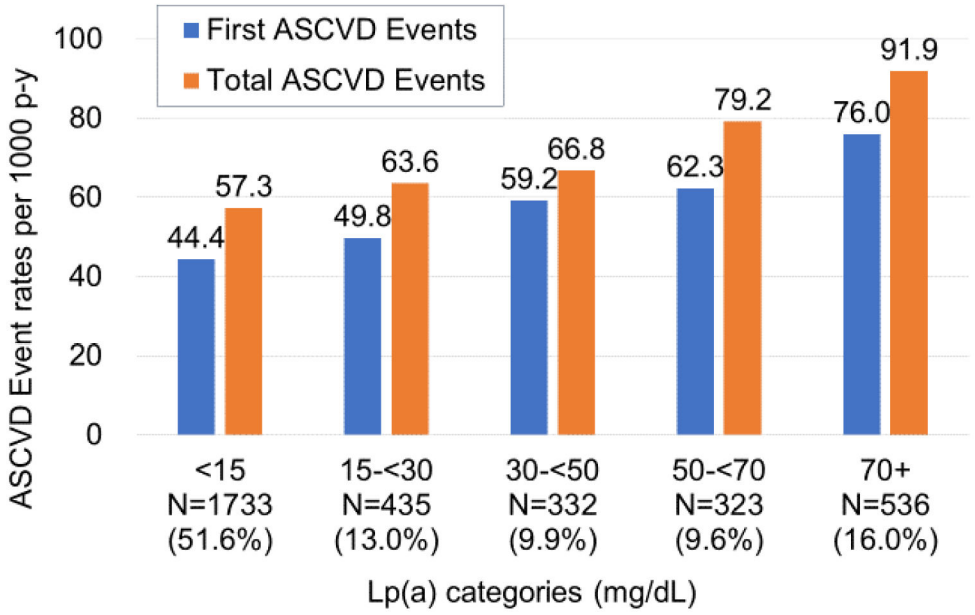

Figure 1.
First and Total ASCVD Event Rates by Lp(a) Categories.

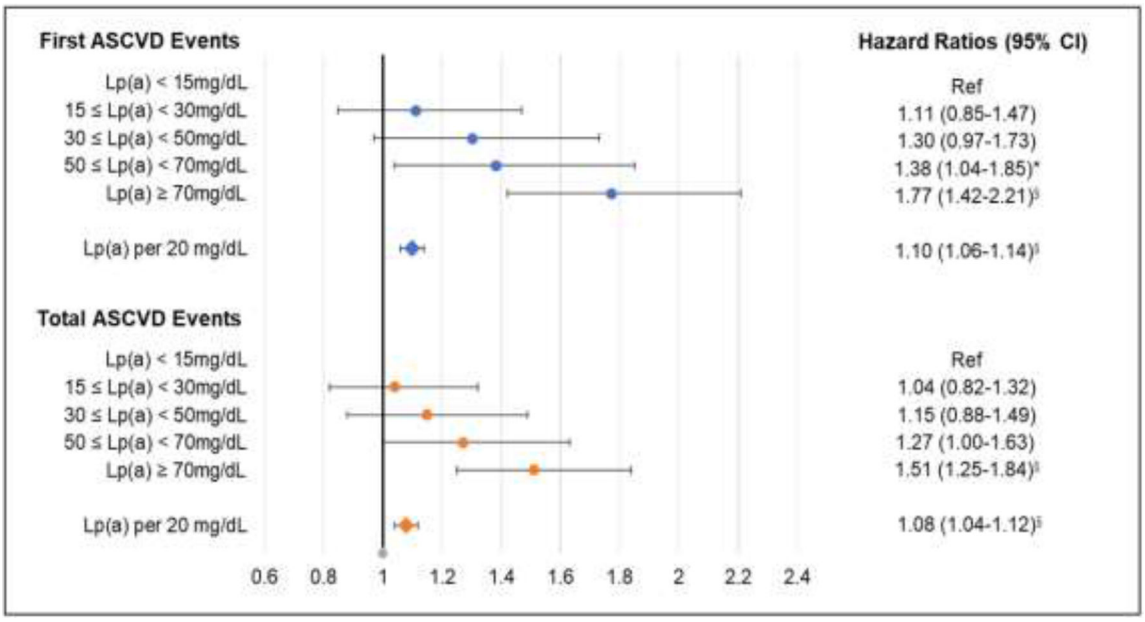

Figure 2. Hazard Ratios of First and Total ASCVD Events During Follow-Up.

PWP models were adjusted for DM, LDL-C, age, SBP, DBP, HbA1c, HDL-C, trig, BMI, Sex, White race, current smoker, alcohol use, family history of CVD, trial treatment and education level. ASCVD= atherosclerotic cardiovascular disease, SBP=systolic blood pressure, DBP=diastolic blood pressure, BMI=body mass index, LDL-C=low density lipoprotein-cholesterol, HDL-C=high density lipoprotein-cholesterol, HbA1c=glycated hemoglobin. * P<0.05, † P<0.01,‡ p<0.001, § p<0.0001.

Table 1.

Baseline Characteristics by Incident ASCVD

Variable	Total (N=3,359)	Subsequent ASCVD in Follow-up		p value
		No (N=2,815)	Yes (N=544)	
Age (years)	63.66 ± 8.73	63.53 ± 8.74	64.31 ± 8.63	0.058
Men	2860 (85.14%)	2380 (84.55%)	480 (88.24%)	0.027
White	3100 (92.29%)	2600 (92.36%)	500 (91.91%)	0.718
Current smoker	616 (18.34%)	516 (18.33%)	100 (18.38%)	0.977
Alcohol consumption (yes vs. no)	1698 (50.95%)	1460 (52.25%)	238 (44.16%)	0.0006
Family history of CVD	1350 (40.21%)	1105 (39.28%)	245 (45.04%)	0.012
Diabetes mellitus	1354 (40.31%)	1100 (39.08%)	254 (46.69%)	0.0009
Systolic blood pressure (mmHg)	128.26 ± 16.35	128.19 ± 16.14	128.63± 17.38	0.583
Diastolic blood pressure (mmHg)	74.35 ± 9.81	74.45 ± 9.82	73.82 ± 9.73	0.167
Body mass index (kg/m^2)	31.24 ± 5.34	31.19 ± 5.30	31.50 ± 5.50	0.213
Glycated hemoglobin (%)	5.98 ± 0.81	5.97 ± 0.79	6.07 ± 0.87	0.017
Glucose (mg/dL)	110.54 ± 22.53	110.46 ± 22.39	110.95 ± 23.27	0.642
Low density lipoprotein-cholesterol(mg/dL)	74.08 ± 23.11	73.97 ± 23.37	74.58 ± 21.72	0.558
High density lipoprotein-cholesterol (mg/dL)	34.72 ± 5.61	34.83 ± 5.64	34.18 ± 5.47	0.013
Triglycerides (mg/dL)	182.64 ±66.84	182.02 ±66.44	185.88± 68.83	0.218
Serum creatinine (mg/dL)	0.99 ± 0.24	0.98 ± 0.23	1.02 ± 0.26	0.001
Homocysteine (μmol/L)	11.44 ± 5.16	11.31 ± 4.74	12.1 ± 8.4	0.024
Lp(a) (mg/dL)	31.83 ± 36.97	30.56 ± 36.41	38.40 ± 39.10	<0.0001
<15	1733 (51.59%)	1497 (53.18%)	236 (43.38%)	
15-<30	435 (12.95%)	367 (13.04%)	68 (12.50%)	
30-<50	332 (9.88%)	273 (9.70%)	59 (10.85%)	
50-<70	323 (9.62%)	263 (9.34%)	60 (11.03%)	
≥ 70	536 (15.96%)	415 (14.74%)	121 (22.24%)	

Continuous variables are expressed as mean ± SD; categorical variables are expressed as frequency (percentage).

ASCVD= atherosclerotic cardiovascular disease

Table 2.

Hazard Ratios of First and Total ASCVD Events for Lp(a) (in mg/dL) During Follow-Up in Those with LDL-C < 70 mg/dL and ≥70 mg/dL

	1st Events		Total Events	
	LDL-C < 70 (N=1,481)	**LDL-C ≥ 70 (N=1,878)**	**LDL-C < 70 (N=1,481)**	**LDL-C ≥ 70 (N=1,878)**
Number of events	240	291	338	386
Lp(a) per 20 mg/dL	1.08 (1.01-1.16) *	1.11 (1.06-1.17) §	1.05 (0.99-1.12)	1.10 (1.05-1.15) §
p-interaction	0.42		0.48	
Lp(a) (mg/dL)				
<15	Ref	Ref	Ref	Ref
15-<30	1.15 (0.77-1.74)	1.13 (0.77-1.65)	0.98 (0.68-1.39)	1.15 (0.83-1.60)
30-<50	1.23 (0.80-1.90)	1.41 (0.95-2.09)	1.02 (0.69-1.50)	1.30 (0.91-1.86)
50-<70	1.43 (0.93-2.21)	1.32 (0.89-1.96)	1.26 (0.88-1.82)	1.27 (0.90-1.79)
≥70	1.45 (1.01-2.09) *	1.98 (1.48-2.66) §	1.27 (0.93-1.74)	1.77 (1.37-2.30) §
p-interaction	0.58		0.66	

* P<0.05

† P<0.01

‡ p<0.001

§ p<0.0001

PWP models were adjusted for age, sex, diabetes mellitus, low density lipoprotein-cholesterol, high density lipoprotein-cholesterol, triglycerides, systolic and diastolic blood pressure, glycated hemoglobin, White race, current smoker. alcohol, family history of cardiovascular disease, trial treatment and education level.

Table 3.

Hazard Ratios of First and Total ASCVD Events for Lp(a) During Follow-Up in Those With and Without Diabetes Mellitus (DM)

	1st Events		Total Events	
	DM (N=1,354)	**Non-DM (N=2,005)**	**DM (N=1,354)**	**Non-DM (N=2,005)**
Number of events	246	285	360	387
Lp(a) per 20 mg/dL	1.07 (1.00-1.14) *	1.11 (1.06-1.17) §	1.06 (1.00-1.12) *	1.10 (1.05-1.16) §
p-interaction	0.34		0.32	
Lp(a) (mg/dL)				
<15	Ref	Ref	Ref	Ref
15 - <30	1.20 (0.81-1.79)	1.02 (0.69-1.50)	1.00 (0.71-1.41)	1.09 (0.78-1.53)
30 - <50	1.68 (1.12-2.53) *	1.04 (0.68-1.58)	1.26 (0.87-1.84)	1.06 (0.73-1.52)
50 - <70	1.34 (0.88-2.03)	1.44 (0.96-2.16)	1.37 (0.97-1.93)	1.21 (0.84-1.75)
≥70	1.54 (1.08-2.19) *	1.90 (1.42-2.55) §	1.38 (1.02-1.87) *	1.70 (1.31-2.21) §
p-interaction	0.42		0.72	

* p<0.05

† p<0.01

‡ p<0.001

§ p<0.0001

PWP models were adjusted for age, sex, diabetes mellitus, low density lipoprotein-cholesterol, high density lipoprotein-cholesterol, triglycerides, systolic and diastolic blood pressure, glycated hemoglobin, White race, current smoker. alcohol, family history of cardiovascular disease, trial treatment and education level.