Total Atherosclerotic Cardiovascular Disease Residual Risk Associated with Increased Lipoprotein(a) Levels among Statin-Treated Adults with Cardiovascular Disease

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Background and Objectives

- The relation between elevated **lipoprotein(a) [Lp(a)]** with **atherosclerotic cardiovascular disease (ASCVD) residual risk** in patients with known cardiovascular disease (CVD) on statin therapy is not well-established.
- Guidelines (e.g., NLA, Multisociety) consider lp(a) levels ≥50 mg/dL to be a risk enhancer favoring initiation or intensification of therapy especially when LDL-C ≥70 mg/dL .
- Lp(a) cutpoints associated with increased ASCVD risk despite statin use with controlled LDL-C levels are not established, however. Such information would be helpful to understand the remaining residual risk in such persons due to elevated Lp(a) and where to best target emerging therapies aimed to lower Lp(a) levels.
- We examined the first and total recurrent ASCVD risk among such patients using the AIM-HIGH cohort.

Methods

Study population

- 3,359 patients from the Metabolic Syndrome with Low HDL / High Triglycerides: Impact on Global Health Outcomes (AIM-HIGH) clinical trial cohort [1].
- multi-centered clinical trial on the effect of niacin added to statin therapy on reducing the risk of CV events
- 45 years of age or older with established ASCVD, low baseline levels of HDL-C and elevated triglyceride levels.

Study Outcomes

- AIM-HIGH-defined the primary composite ASCVD endpoint as death from coronary heart disease, nonfatal myocardial infarction, ischemic stroke, hospitalization (for >23 hours) for an acute coronary syndrome, or symptom-driven coronary or cerebral revascularization.
- Both the first recurrent ASCVD event and total recurrent ASCVD events during follow-up of 3.3 years were obtained.

Statistical Analysis

- First and total ASCVD event rates (per 1000 person-years) were calculated stratified by Lp(a) categories.
- Hazard ratios (HRs) adjusted for age, sex, white race, DM, LDL-C, SBP, DBP, HbA1c, HDL-C, trig, BMI, current smoker. alcohol, family history of CVD, trial treatment and education were calculated examining the relation of Lp(a) with first and total ASCVD events using the Prentice, Williams and Peterson (PWP) model [2]

Results

Table 1. Baseline Characteristic by the Occurrence of Subsequent ASCVD During Follow-Up

	No subsequent ASCVD during follow-up (N=2,815)	Subsequent ASCVD during follow-up (N=544)
Age, year	63.5±8.7	64.3±8.6
Male	2380 (84.6%)	480 (88.2%)*
White race	2600 (92.4%)	500 (91.9%)
Current smoker	516 (18.3%)	100 (18.4%)
Alcohol consumption	1460 (52.3%)	238 (44.2%) †
Family history of CVD	1105 (39.3%)	245 (45.0%)*
Diabetes	1100 (39.1%)	254 (46.7%) †
SBP, mmHg	128.2±16.1	128.6±17.4
BMI, kg/m2	31.2±5.3	31.5±5.5
HbA1c,%	6.0±0.8	6.1±0.9*
LDL-C, mg/dL	74.0±23.4	74.6±21.7
HDL-C, mg/dL	34.8±5.6	34.2±5.5*
Triglycerides, mg/dL	182.0±66.4	185.9±68.8
Lp(a), mg/dL	73.3±87.4	92.2±93.8‡
Lp(a) categories		
<15mg/dL	1497 (53.2%)	236 (43.4%)
15 - <30mg/dL	367 (13.0%)	68 (12.5%)
30 - <50mg/dL	273 (9.7%)	59 (10.9%)
50 - <70mg/dL	263 (9.3%)	60 (11.0%)
≥70mg/dL	415 (14.7%)	121 (22.2%)

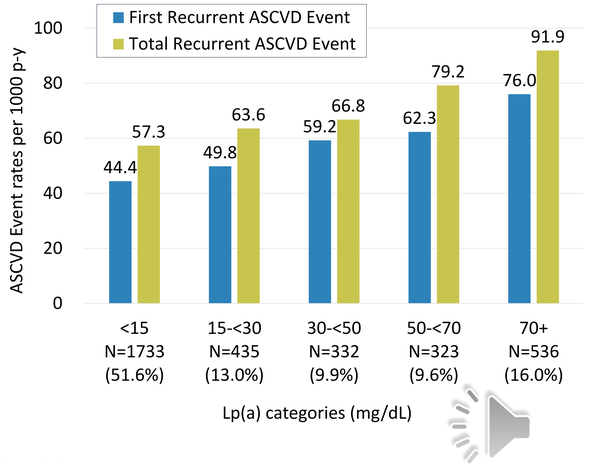
* P<0.05, †P<0.001, ‡P<0.0001

Table 2. Hazard ratio of 1st and total recurrent ASCVD events during follow-up

	1st event	Total Events
Lp(a) per 20 mg/dL	1.10 (1.06-1.14) †	1.08 (1.04-1.12) §
Lp(a) categories		
<15mg/dL	Ref	Ref
15 - <30mg/dL	1.11 (0.85-1.47)	1.04 (0.82-1.32)
30 - <50mg/dL	1.30 (0.97-1.73)	1.15 (0.88-1.49)
50 - <70mg/dL	1.38 (1.04-1.85)*	1.27 (1.00-1.63)
≥70mg/dL	1.77 (1.42-2.21) †	1.51 (1.25-1.84) †

* P<0.05, † P<0.0001. PWP models were adjusted for DM, LDL-C, age, SBP, DBP, HbA1c, HDL-C, trig, BMI, Sex, White race, current smoker. Alcohol, family history of CVD, trial treatment and education.

Figure. First and Total Recurrent ASCVD Event Rates by Lp(a) categories



RESULTS SUMMARY

- 747 total events occurred during follow-up, among which 544 were first recurrent events.
- Lp(a) was significantly higher among those with at least one ASCVD event compared to those with no ASCVD during follow-up (Table 1)
- There was a stepwise increase of first and total recurrent ASCVD event rates by Lp(a) categories, with levels of 50 mg/dL or higher associated with an increased risk of first recurrent events (Figure).
- Lp(a) showed strong independent associations with first and total ASCVD event risks. The association of Lp(a) and recurrent ASCVD was similar in the two trial arms, indicating no effect of niacin (Table 2).
- While Lp(a) category relationships with ASCVD events stratified by baseline LDL-C <70 mg/dL vs. >70 mg/dl were similar (p-interactions=ns), risks tended to be especially increased in those with Lp(a) ≥70 mg/dL who had LDL-C ≥70 mg/dl (Table 3).

Table 3. Lp(a) Categories and CVD Event Risk According to Baseline LDL-C Status

	1st event		Total Events	
	LDL<70mg/dL N=1764	LDL>=70 mg/dL N=2189	LDL<70mg/dL N=1764	LDL>=70 mg/dL N=2189
<15mg/dL	Ref	Ref	Ref	Ref
15-<30mg/dL	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-<50mg/dL	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-<70mg/dL	1.43 (0.93-2.21)	1.32 (0.89-1.96)	1.26 (0.88-1.82)	1.27 (0.90-1.79)
≥ 70mg/dL	1.45(1.01-2.09)*	1.98(1.48-2.66)‡	1.27 (0.93-1.74)	1.77(1.37-2.30)‡
Interaction test	0.58		0.66	

* P<0.05, ** P<0.01, † p<0.001, ‡ p<0.0001
PWP models were adjusted for DM, LDL-C, age, SBP, DBP, HbA1c, HDL-C, trig, BMI, Sex, White race, current smoker. Alcohol, family history of CVD, trial treatment and education level.

Strengths and Limitations

- Besides examining first recurrent ASCVD events with Lp(a) categories, we examined total ASCVD events which provides a better description of total ASCVD burden and residual risk despite statin therapy.
- AIM-HIGH had standardized assessment of risk factors and adjudication of events.
- The residual risks are specific to the participants in AIM-HIGH who were generally well-controlled for LDL-C and thus may not be generalized to the US population on statin therapy.
- Follow-up time was relatively short to estimate the long-term associations which could be different with longer follow-up.

Conclusions

First and total recurrent ASCVD events are greater with higher Lp(a) levels, especially when ≥70 mg/dL among adults with known CVD on statin therapy after controlling for LDL-C and other cardiovascular risk factors. Future therapies may consider targeting elevated Lp(a) levels to reduce ASCVD residual risk.

References

1. Aim-High Investigators. NEJM. 2011;365:2255-67.
2. Prentice RL, et al. Biometrika 1981;68:373–9.

Disclosure:
Drs. Sung and Browne are employees in Novartis Inc. Dr. Wong receives research support through UC Irvine from Novartis, Amgen, Boehringer-Ingelheim, Amarin, and Novo Nordisk and advisory board/consultant /speaking fees from Sanofi, Amarin, and Astra-Zeneca. This analysis and study was funded by Novartis.

Abbreviations:
ASCVD = atherosclerotic cardiovascular disease; BMI = body mass index; HbA1c= Hemoglobin A1c; HDL-C = high density lipoprotein-cholesterol; HTN = hypertension; LDL-C = low density lipoprotein-cholesterol; Lp(a) =lipoprotein (a); SBP = systolic blood pressure.