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Cardiometabolic Risk

Relationship of Apolipoproteins A-1 and B, and Lipoprotein(a) to Cardiovascular Outcomes

The AIM-HIGH Trial (Atherothrombosis Intervention in Metabolic Syndrome With Low HDL/High Triglyceride and Impact on Global Health Outcomes)

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Objectives This study sought to examine the relationship between baseline and on-study apolipoproteins (apo) A-1 and B and lipoprotein(a) [Lp(a)] levels and the development of subsequent cardiovascular (CV) events in the AIM-HIGH (Atherothrombosis Intervention in Metabolic Syndrome with Low HDL/High Triglyceride and Impact on Global Health Outcomes) trial.

Background Niacin has been reported to lower apoB and Lp(a) and to raise apoA-1.

Methods Individuals with CV disease and low baseline levels of high-density lipoprotein cholesterol were randomized to simvastatin plus placebo or simvastatin, plus extended-release niacin ([ERN], 1,500 to 2,000 mg/day), with ezetimibe added as needed, in both groups, to maintain an on-treatment low-density lipoprotein cholesterol in the range of 40 to 80 mg/dl. Hazard ratios (HRs) were used to evaluate the relationship between levels of apoA-1, apoB, and Lp(a), and CV events in each treatment group.

Results Baseline apoB and the apoB/apoA-I ratio were significantly predictive of CV events only for the placebo group (HR: 1.17 [p = 0.018] and HR: 1.19 [p = 0.016]). Baseline and on-study Lp(a) were predictive of CV events in both simvastatin plus placebo (baseline HR: 1.24 [p = 0.002] and on-study HR: 1.21 [p = 0.017]) and the simvastatin plus ERN group (baseline HR: 1.25 [p = 0.001] and on-study HR: 1.18 [p = 0.028]). The ERN modestly increased 1-year apoA-1 (7%), decreased apoB (13%), decreased the ApoB/ApoA-1 ratio (19%), and decreased Lp(a) 21%, but did not reduce CV events.

Conclusions Lp(a) was associated with increased CV risk in both treatment groups indicating that it contributes to residual CV risk. However, there was no evidence that ERN reduced CV risk, despite favorable lipoprotein changes. (J Am Coll Cardiol 2013;62:1575–9) © 2013 by the American College of Cardiology Foundation

The AIM-HIGH (Atherothrombosis Intervention in Metabolic Syndrome with Low HDL/High Triglycerides: Impact on Global Health Outcomes) trial was a prospective, randomized, double-blind clinical trial of participants with established atherothrombotic cardiovascular (CV) disease, low levels of high-density lipoprotein cholesterol (HDL-C) and elevated triglycerides at baseline (1). The AIM-HIGH trial investigators previously reported that among patients with CV disease treated with low-density lipoprotein (LDL)-lowering therapy (mean low-density lipoprotein

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Abbreviations and Acronyms

Apo = apolipoprotein
CV = cardiovascular
ELISA = enzyme-linked immunoadsorbent assay
ERN = extended-release niacin
HDL-C = high-density lipoprotein cholesterol
HR = hazard ratio
LDL = low-density lipoprotein
LDL-C = low-density lipoprotein cholesterol
Lp(a) = lipoprotein(a)

cholesterol [LDL-C] at baseline, 71 mg/dl/1.81 mmol/l), with the addition of ERN to simvastatin therapy during a 3-year mean follow-up period was associated with a 25% increase in HDL-C, a further 12% reduction in LDL-C, and a 30% additional reduction in triglyceride levels (1). However, the trial was stopped 18 months earlier than planned because a pre-defined lack of efficacy boundary had been crossed, so the addition of ERN failed to further reduce the incidence of CV events. This report focuses on the effect of LDL-lowering therapy (simvastatin with or without ezetimibe), plus ERN versus LDL-lowering therapy alone on Lp(a), apoA-1, and apoB, and the relationships of their levels (at baseline and on-treatment) to CV outcomes.

First, our aim was to evaluate the impact of intensive LDL-lowering therapy alone or in combination with ERN on apoA-1, apoB, and Lp(a). Second, our aim was to assess whether apoA-1, apoB, or Lp(a) levels are predictive of CV events in either group at baseline or in-trial. Third, our aim was to assess whether a subgroup of participants, defined by baseline apolipoprotein values, who demonstrated clinical benefits from niacin therapy could be identified.

Methods

Study population. The AIM-HIGH trial population and baseline characteristics were previously described (1). The primary composite outcome was death from coronary disease, nonfatal myocardial infarction, ischemic stroke, hospitalization for acute coronary syndrome, or symptom-driven coronary or cerebrovascular revascularization. In this paper, we evaluated only participants who were prescribed statin therapy prior to the trial (n = 3,196; 94% of randomized subjects). Per protocol, samples for apolipoprotein analyses were collected at baseline and 1-year post-baseline.

Analytical measurements. Analyses of apoA-1 and apoB were performed using Siemens reagent on a Seimens BNII nephelometer (Seimens Healthcare Diagnostics, Newark, Delaware). Analysis of Lp(a) was performed by a monoclonal antibody-based enzyme-linked immunoadsorbent assay (ELISA) method developed in the laboratory, as previously reported (2), which was considered the gold standard method for measuring Lp(a).

Statistical analyses. Baseline Lp(a) values were compared with the Framingham study using the Wilcoxon rank sum test. Treatment differences for change from baseline are presented as least-square means from generalized linear models, including treatment, sex, diabetes, baseline imbalances, and baseline apolipoprotein as covariates. Percent change is calculated from these results. Relationships between apolipoproteins and cardiovascular events were examined using the primary study endpoint.

Hazard ratios (HRs) examining the relationship between baseline values and events were calculated from Cox proportional hazards survival models, adjusted for sex, diabetes, and baseline ApoA-1. Heterogeneity of the relationship between baseline values and events across randomization assignment was assessed by adding value-by-treatment interaction terms. Subgroups were examined using quartiles for Lp(a) and tertiles otherwise. Differences in the effect of treatment across baseline levels of Lp(a) and apoB/apoA-1 were tested by adding a level-by-treatment interaction term to the models.

The relationships between on-study standardized apolipoprotein levels and events were evaluated using Cox proportional hazards survival models with time-dependent covariates, adjusted for sex, diabetes, baseline ApoA-1, and HDL2-C. Subjects who reached the primary endpoint prior to 1 year (scheduled collection) were excluded from this analysis.

Two-sided p values <0.05 were considered significant. No adjustments were made for multiple testing. The SAS Version 9.2 (SAS Institute, Inc., Cary, North Carolina) was used for all statistical analyses.

Results

Participants and baseline characteristics. The mean age of study participants was 63.7 years (85.2% were men and 92.2% were Caucasian). Baseline demographic and clinical characteristics were similar in the 2 groups randomized to either control LDL-lowering therapy or LDL-lowering therapy plus ERN, except mean body mass index (BMI),

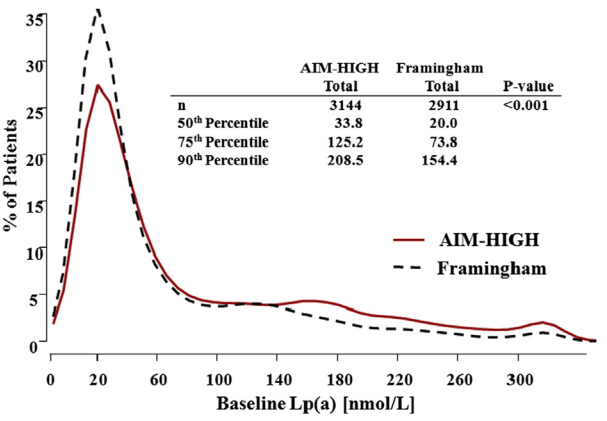

Figure 1 Comparison of the AIM-HIGH Trial and Framingham Baseline Lp(a) Distribution

Histogram of baseline lipoprotein(a) [Lp(a)] [nmol/l] for each study. Lp(a) distributions are compared using the Wilcoxon rank sum test.

Table 1 Least-Square Mean Values at Baseline, Year 1, and Percent Change in Apo and Lp(a)*

	Statin Plus Placebo				Statin Plus ERN				
Test	N	Base	Year 1	Percent Change†	N	Base	Year 1	Percent Change†	Diff. in Percent Change‡ vs. Placebo
ApoB (mg/dl)	1,443	82.0	79.6	−2.9	1,424	81.8	71.3	−12.8	-10.7§
ApoA-1 (mg/dl)	1,443	126.2	128.6	1.9	1,424	125.6	134.5	7.1	4.7§
ApoB/ApoA-1 ratio	1,459	0.7	0.6	−6.6	1,440	0.7	0.5	−19.4	−13.6
Lp(a) (nmol/l)	1,440	78.3	73.7	−5.9	1,427	80.2	63.4	−21.0	-19.4¶
Log Lp(a) (nmol/l)	1,440	3.5	3.4	−3.4	1,427	3.5	3.2	−9.9	−9.7¶

*Participants with measurements at baseline and 1-year post-baseline are included. Baseline analysis of covariance (ANCOVA) models adjusted for sex and diabetes; year 1 ANCOVA models adjusted for sex, diabetes, ApoA-I, and high-density lipoprotein 2 cholesterol (HDL2-C) (imbalanced at baseline). †Percent change from baseline to year 1 post-baseline. ‡Based on ANCOVA. §$p < 0.001$. ¶$p < 0.05$ for comparison of percent change by treatment.

Apo = apolipoprotein; Base = baseline value; Diff = difference; ERN = extended-release niacin; N = number of patients with data; Percent Change = change from baseline to year 1.

which was slightly lower in the control group (30.9 vs. 31.5; $p = 0.003$).

Baseline apolipoprotein and Lp(a) levels. Consistent with participant selection criteria, mean apoB and apoA-1 levels were low. However, the median level of Lp(a) (33.8 nmol/l) was elevated as compared with the median Lp(a) level (20 nmol/l) of healthy, predominantly Caucasian adults from Framingham (3). Comparison of the Lp(a) distribution of the AIM-HIGH trial with the Framingham cohort, determined by the same ELISA method, indicates that the Lp(a) distribution at baseline of the AIM-HIGH trial participants was shifted to higher levels (Fig. 1). Nearly 30% of the AIM-HIGH trial cohort at baseline had Lp(a) levels >100 nmol/l compared with 20% of Framingham.

Apolipoprotein and Lp(a) levels after 1 year of treatment. In the ERN group and the placebo group, apoB decreased by 13% and 3%, apoA-1 increased by 7% and 2%, and the apoB/apoA-1 ratio decreased by 19% and 7%, respectively (Table 1). For the ERN group, Lp(a) decreased by 21% overall with 20%, 39%, and 64% decreases in the 50th, 75th, and 90th Lp(a) percentiles, respectively. An overall decrease of 6% for Lp(a) was also observed in the placebo group; thus, the overall least-square mean decrease in Lp(a) due to ERN was 19%.

Baseline apolipoprotein and Lp(a) levels and subsequent CV events. Baseline levels of apoB and apoB/apoA-1 were only associated with CV events in the placebo and not in the ERN group, but the treatment interactions were not significant. Lp(a) was significantly associated with CV events and exhibited the highest hazard ratios in both treatment groups (Table 2). As shown in Figures 2 and 3, similar hazard ratios for the second, third, and fourth Lp(a) quartiles were observed in the placebo and ERN groups (1.19, 1.37, and 1.87 vs. 1.19, 1.37, and 1.90, respectively). Kaplan-Meier estimates of the percentages of participants free from a primary event by baseline Lp(a) quartile for both treatment groups are shown in Figures 2 and 3.

1-year apolipoprotein and Lp(a) levels and CV events within treatment groups. A 1 SD (0.16) higher apoB/apoA-1 ratio in the placebo group was associated with a 21% higher risk of a primary event ($p = 0.031$), and a 1 SD (1.55) higher log Lp(a) was associated with a 21% increase in CV event risk (HR: 1.21; $p = 0.017$). For the ERN group, apoB/apoA-1 at 1 year was not associated with CV event risk (HR: 1.06; $p = 0.50$), whereas the log Lp(a) level did remain related to CV event risk (HR: 1.18; $p = 0.028$) (Table 3).

Comparison of on-treatment apolipoprotein and Lp(a) levels and CV events between treatment groups. Overall, and within each quartile of baseline Lp(a), a similar numbers of events occurred in the placebo and ERN groups; for the highest Lp(a) quartile, there were 78 events in the placebo group versus 83 in the ERN group. There was no significant difference in primary event rate between the placebo and ERN group for any quartile of baseline Lp(a) ($p = 0.994$ for treatment effect by Lp(a) quartile) despite greater decreases in Lp(a) for those taking ERN as compared to placebo. Comparing baseline quartiles of Lp(a)

Table 2 Association Between 1 SD Increase in Baseline* Apo, Lp(a), and CV Events

		Statin Plus Placebo				Statin Plus ERN				
Test	SD	HR†	95% CI		p Value	HR†	95% CI		p Value	Int. p Value‡
ApoB (mg/dl)	18.3	1.17	1.03	1.33	0.018	1.11	0.97	1.27	0.124	0.905
ApoA-1 (mg/dl)	16.2	0.94	0.83	1.07	0.373	0.93	0.81	1.07	0.337	0.82
ApoB/apoA-1 ratio	0.16	1.19	1.03	1.36	0.016	1.13	0.99	1.30	0.078	0.87
Lp(a) (nmol/l)	88.7	1.22	1.10	1.35	<0.001	1.16	1.04	1.28	0.006	0.646
Log Lp(a) (nmol/l)	1.55	1.24	1.08	1.43	0.002	1.25	1.10	1.42	0.001	0.987

*Proportional hazards models adjusted for stratification factors and ApoA-1. †HR is the increase in risk of an increase of 1 SD. ‡Test for heterogeneity of treatment effect across values.

CI = confidence interval; CV = cardiovascular; HR = hazard ratio; Int. = interaction between randomization assignment and value; SD = standard deviation; other abbreviations as in Table 1.

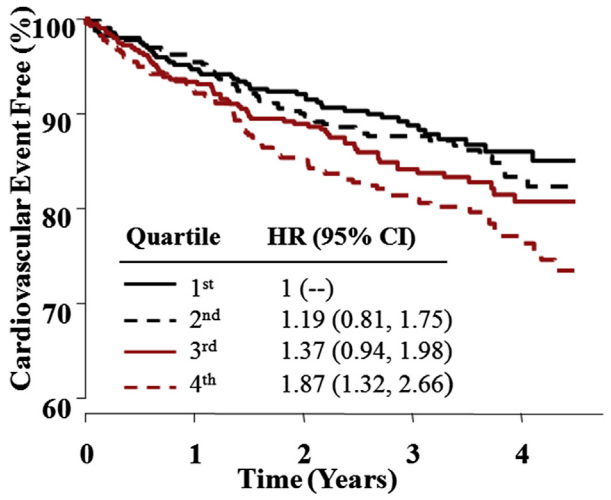

Figure 2 Time to First Cardiovascular Event for Statin Plus Placebo Arm by Baseline Lp(a) Quartile

Kaplan-Meier curves show time to first cardiovascular event for quartiles of baseline Lp(a) (nmol/L) in patients randomized to low-density lipoprotein (LDL)-lowering therapy plus placebo. Hazard ratio (HR) and 95% confidence interval (CI) are based on Cox proportional hazards survival regression, including terms for sex and diabetes. Abbreviations as in Figure 1.

between treatment groups, the hazard ratio for the highest quartile was 0.98 (95% confidence interval [CI]: 0.73 to 1.32); similarly, there was no effect of ERN treatment in any of the lower quartiles. From this analysis, it is clear that even

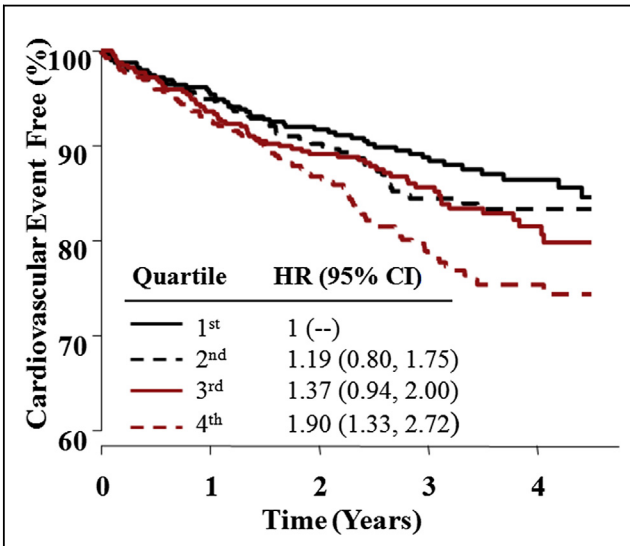

Figure 3 Time to First Cardiovascular Event for Statin Plus Niacin Arm by Baseline Lp(a) Quartiles

Kaplan-Meier curves show time to first cardiovascular event for quartiles of baseline Lp(a) (nmol/L) in patients randomized to LDL-lowering therapy plus niacin. The HR and 95% CI are based on Cox proportional hazards survival model of regression, including terms for sex and diabetes. Abbreviations as in Figures 1 and 2.

the on-study ERN group in the highest Lp(a) quartile, which was >125 nmol/l, did not benefit from the addition of niacin to the statin-based therapy.

Because niacin increases apoA-1, lowers apoB, and consequently lowers apoB/apoA-1, we also evaluated the HR for apoB/apoA-1 tertiles at baseline. Within the highest tertile of apoB/apoA-1, there was no detectable reduction in CV event risk with ERN.

Discussion

The principal findings of our study were at 1 year, compared to the placebo group, those randomized to ERN had significantly higher apoA-I levels, a lower apoB/apoA-I ratio, and lower levels of Lp(a). Despite these favorable changes with ERN, apoA-1, apoB, and Lp(a) variables did not identify any subgroup of participants who benefited from ERN therapy. Baseline and on-study Lp(a) predicted CV events in both treatment groups.

Lp(a) levels and the prediction of CV events. A particularly interesting result of the AIM-HIGH trial is that baseline and on-study Lp(a) predicted CV events in both the control LDL-lowering therapy plus placebo and LDL-lowering therapy plus ERN arms, suggesting that Lp(a) still contributes to residual CV risk in patients achieving target LDL-C levels with statin therapy. These results contradict our earlier post-hoc analysis of the Familial Atherosclerosis Treatment Study, in which men with coronary artery disease and elevated LDL-C, Lp(a) correlated strongly with both baseline CV disease severity and progression in the placebo group (4). However, in those receiving statins, in whom LDL-C was reduced substantially, but Lp(a) levels were unaffected, Lp(a) levels were no longer associated with risk of CV events or progression. Meta-analysis has demonstrated a consistent, continuous, and independent association between Lp(a) level and CV risk, without indicating a specific threshold (5). Despite the desire for a specific clinical risk threshold (6) based on meta-analyses and consistent with our analysis of Lp(a) quartiles in the AIM-HIGH trial, CV disease risk continues to increase at high levels of Lp(a). Our study also indicates that ERN is not associated with clinical benefit, even for those with the highest baseline Lp(a) levels.

Causality of Lp(a) for CV disease. Several studies have provided strong support for the causality of elevated Lp(a) for premature coronary artery disease (7,8). Further support for this causality depends on demonstrating that reduction of elevated Lp(a) reduces CV events. Jaeger et al. (9) treated patients with CV disease and elevated Lp(a) >95th percentile with lipid-lowering drugs to lower LDL-C. Subsequently, these patients underwent LDL apheresis, which dramatically lowered Lp(a) by 73%. The rate of major adverse CV events was reduced in patients with either further substantial or minimal LDL reduction, suggesting that lowering Lp(a) was beneficial. Participants in the AIM-HIGH trial treated with ERN had only

Table 3 Association Between a 1 SD Increase in Apo and Lp(a) Levels After 1 Year of Treatment* and CV Events

		Statin Plus Placebo				Statin Plus ERN				
Test	SD	HR†	95% CI		p Value	HR†	95% CI		p Value	Int. p Value‡
ApoB (mg/dl)	18.3	1.15	0.98	1.35	0.092	1.04	0.88	1.23	0.648	0.457
ApoA-1 (mg/dl)	16.2	0.89	0.75	1.06	0.185	1.03	0.86	1.23	0.734	0.717
ApoB/apoA-1 ratio	0.16	1.21	1.02	1.43	0.031	1.06	0.90	1.25	0.499	0.452
Lp(a) (nmol/L)	88.7	1.23	1.07	1.42	0.004	1.18	1.00	1.39	0.048	0.624
Log Lp(a) (nmol/L)	1.55	1.21	1.03	1.42	0.017	1.18	1.02	1.36	0.028	0.647

*Proportional hazards models adjusted for stratification factors ApoA-1 and HDL2-C. †HR is the increase in risk of an increase of 1 SD. ‡Test for heterogeneity of treatment effect across values. Abbreviations as in Tables 1 and 2.

a modest lowering of Lp(a) of 19% compared to placebo, and no reduction in CV events Although it is possible that the between-group difference in Lp(a) levels was too small to detect a benefit, a therapeutic intervention that lowers Lp(a) more effectively and selectively would be a stronger test of the hypothesis that Lp(a) reduction decreases CV events.

Conclusions

The AIM-HIGH trial demonstrated that Lp(a) contributes to residual CV risk in patients who achieved target LDL-C levels with statin therapy. We have further observed that favorable changes in apoliproteins and Lp(a) from ERN did not result in CV event reduction. It is possible that the relatively modest differences between the treatment groups may have been insufficient to cause a reduction in CV risk over the 3-year treatment study. The much larger HPS-2–THRIVE (Heart Protection Study-2–Treatment of HDL to Reduce the Incidence of Vascular Events) clinical trial, performed in more than 25,000 subjects, appears to confirm the lack of clinical benefit of niacin added to LDL-lowering therapy on CV outcomes observed in the AIM-HIGH trial (10).

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Key Words: apolipoproteins ■ cardiovascular risk ■ lipoprotein(a) ■ niacin ■ simvastatin.