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Relationship of Lipoproteins to Cardiovascular Events

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

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Objectives This study sought to examine the relationship between niacin treatment, lipoproteins, and cardiovascular (CV) outcomes in this secondary analysis of the AIM-HIGH (Atherothrombosis Intervention in Metabolic Syndrome With Low HDL/High Triglycerides and Impact on Global Health Outcomes) trial.

Background During a 3-year follow-up in 3,414 patients with established CV disease and low high-density lipoprotein cholesterol (HDL-C) levels, combined niacin + low-density lipoprotein cholesterol (LDL-C)–lowering therapy did not reduce CV events compared with LDL-C–lowering therapy alone.

Methods Subjects taking simvastatin and/or ezetimibe were randomized to receive extended-release (ER) niacin 1,500 to 2,000 mg or minimal immediate-release niacin (≤150 mg) as placebo at bedtime. LDL-C levels in both groups were maintained from 40 to 80 mg/dl. Hazard ratios were estimated by using Cox proportional hazards models for relationships between lipoproteins and the composite endpoint of CV death, myocardial infarction, acute coronary syndrome, ischemic stroke, or symptom-driven revascularization.

Results CV outcomes were not associated with ER niacin in any baseline lipoprotein tertile. In a subset of patients in both the highest triglyceride (≥198 mg/dl) and lowest HDL-C (<33 mg/dl) tertiles, ER niacin showed a trend toward benefit (hazard ratio: 0.74, p = 0.073). In-trial LDL-C levels, non–HDL-C levels, and the total cholesterol/HDL-C ratio were positively associated with CV events in the control group, but these relationships were absent in the ER niacin group.

Conclusions Baseline lipoprotein tertiles did not predict differential benefit or harm with ER niacin added to LDL-C–lowering therapy, but a small dyslipidemic subgroup may benefit. ER niacin attenuated expected relationships of lipoprotein risk factors with CV events, raising the possibility that nonlipoprotein actions of niacin could affect risk. (Niacin Plus Statin to Prevent Vascular Events [AIM-HIGH]; NCT00120289) (J Am Coll Cardiol 2013;62:1580–4) © 2013 by the American College of Cardiology Foundation

In the AIM-HIGH (Atherothrombosis Intervention in Metabolic Syndrome With Low HDL/High Triglycerides and Impact on Global Health Outcomes) trial, extended-release (ER) niacin added to intensive low-density lipoprotein cholesterol (LDL-C)–lowering therapy did not reduce atherothrombotic events compared with intensive

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LDL-C–lowering therapy alone (1). Recently, HPS2-THRIVE (Heart Protection Study 2–Treatment of HDL to Reduce the Incidence of Vascular Events) likewise showed no benefit for combination ER niacin/laropiprant therapy (2,3). However, niacin added to ongoing statin therapy has been associated with atherosclerotic lesion regression (4,5). In an early randomized trial, a niacin monotherapy group experienced fewer events than subjects receiving placebo (6). Combination drug regimens including niacin were associated with event reductions in 3 smaller trials (7–9).

Pharmacological effects of niacin can be separated into lipoprotein effects thought to be mediated by actions in the liver (10,11) and nonlipoprotein effects mediated by the G-protein–coupled receptor 109A (GPR109A) on adipocytes, macrophages, and dermal dendritic cells or by a direct action on endothelial cells (10,12–15). These varying effects of niacin lend importance to the present analysis of the interaction between plasma lipoproteins, niacin treatment, and atherothrombotic events in the AIM-HIGH trial.

Methods

Study design. As described previously, AIM-HIGH trial participants had established stable atherosclerotic disease with high-density lipoprotein cholesterol (HDL-C) levels <40 mg/dl for men and <50 mg/dl for women, high triglyceride (TG; 150 to 400 mg/dl) level, and LDL-C levels <180 mg/dl (adjusted for LDL-C–lowering treatment) (1). All subjects initially received simvastatin 40 mg daily, plus ER niacin at doses increasing weekly from 500 to 2,000 mg per day. Subjects tolerating at least 1,500 mg of ER niacin daily were randomized 1:1 to receive ER niacin or matching placebo tablets. To disguise treatment assignment, placebo tablets included 50 mg of immediate-release niacin in each 500- or 1,000-mg tablet. In both treatment groups, simvastatin doses were adjusted and/or ezetimibe 10 mg daily was added to maintain LDL-C levels within 40 to 80 mg/dl.

Statistical analysis. Lipoprotein values were measured according to protocol at baseline and at 1, 3, and 6 months and each year after randomization. Baseline lipoprotein tertiles were constructed across all randomized subjects. Baseline was defined as the last measurement before randomization.

Abbreviations and Acronyms

CV = cardiovascular
ER = extended-release
HDL-C = high-density lipoprotein cholesterol
HR = hazard ratio
GPR109A = G-protein–coupled receptor 109A
LDL-C = low-density lipoprotein cholesterol
TG = triglyceride

Relationships between lipoproteins and cardiovascular (CV) events were examined by using the primary study endpoint, which was the first occurrence of death from coronary heart disease, nonfatal myocardial infarction, ischemic stroke, hospitalization for acute coronary syndrome, or symptom-driven coronary or cerebral revascularization. Time-to-event analyses examined the period from randomization to a primary endpoint event, withdrawal of consent, loss to follow-up, administrative censoring, or the end of the double-blind period. Each lipoprotein was standardized according to the overall baseline SD.

Hazard ratios (HRs) examining the relationship between standardized baseline lipoprotein tertiles and events were calculated from Cox proportional hazards models, adjusted for sex and diabetes. Heterogeneity between baseline lipoprotein tertiles and events across randomization assignment was assessed by including lipoprotein-by-treatment interaction terms. A subgroup analysis of subjects simultaneously in the highest tertile of baseline TG and the lowest tertile of baseline HDL-C was specified a priori.

The relationship between in-trial standardized lipoprotein values and events was assessed by averaging values from scheduled visits after randomization and before the first confirmed primary event, study termination, or the date of last contact. For each lipoprotein separately, within-subject averages were included in the Cox proportional hazards models, adjusted for sex and diabetes. Sensitivity analyses were performed as described in Online Tables 2 and 3. Heterogeneity of joint effects of HDL-C, LDL-C, and log(TG) across treatments was assessed by using the likelihood ratio test to compare the reduced model, including terms for randomized treatment assignment, HDL-C, LDL-C, log(TG), sex, and diabetes, with the full model, including these terms plus the 3 lipoprotein-by-treatment interactions (16,17).

Two-sided p values <0.05 were considered significant, without adjustment for multiple testing. SAS version 9.2 (SAS Institute, Inc., Cary, North Carolina) was used for all analyses.

Results

Study population and lipoprotein changes. All randomized subjects were evaluated (N = 3,414). Baseline lipoprotein levels were assessed in patients receiving statin therapy (n = 3,196 [93.6%]) and those without statin therapy (n = 218 [6.4%]). These groups were combined for the present analysis. Lipoprotein changes according to baseline lipoprotein tertiles are shown in Online Table 1.

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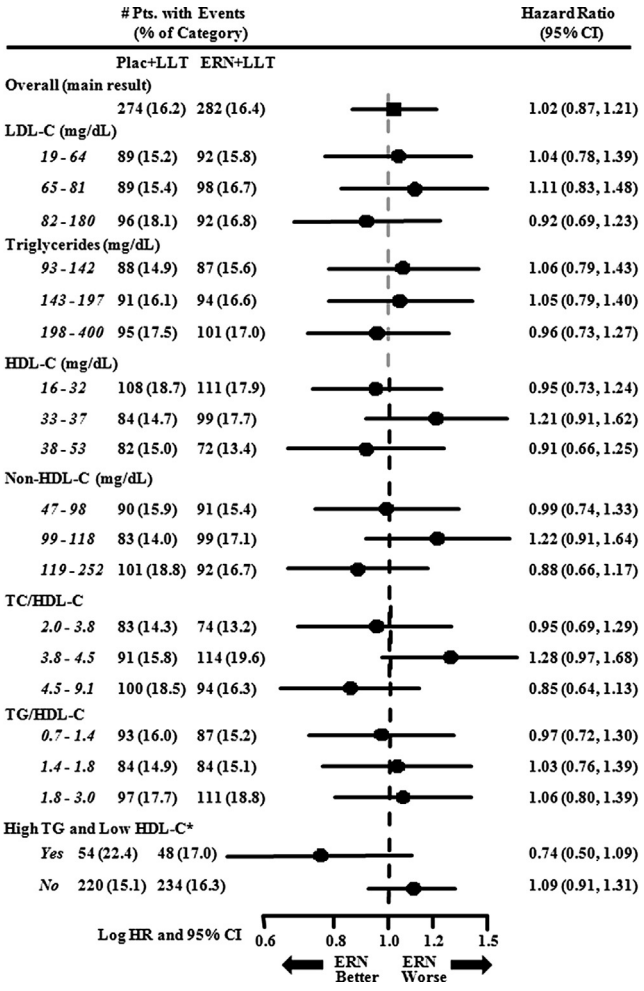

Figure 1 Effect of Treatment on CV Events by Baseline Lipoprotein/Lipid Tertiles

Hazard ratios (HR) for the effect of treatment assignment were calculated by using Cox proportional hazards models, including terms for sex and diabetes. *High triglycerides (TG) and low high-density lipoprotein cholesterol (HDL-C) designates subjects with highest-tertile TG and lowest-tertile HDL-C levels. Placebo (Plac) tablets included 100- to 150-mg immediate-release niacin. CI = confidence interval; CV = cardiovascular; ERN = extended-release niacin; LLT = low-density lipoprotein cholesterol–lowering therapy; Pts = Patients; TC = total cholesterol.

Effect of treatment on CV events by baseline lipid/lipoprotein tertiles. Figure 1 shows that treatment assignment did not significantly affect the primary endpoint of the first major CV event in any baseline tertile of lipoprotein or lipoprotein ratio. For the 522 subjects (15.3%) who simultaneously had baseline TG levels in the highest tertile (≥198 mg/dl) and HDL-C levels in the lowest tertile (<33 mg/dl), a nonsignificant trend toward reduction of CV risk was evident in the ER niacin group (HR: 0.74, $p = 0.073$). In a smaller group (n = 439 [12.9%]) that met somewhat stricter criteria of TG levels ≥200 mg/dl and HDL-C levels <32 mg/dl, the trend toward reduced events in the niacin group was stronger (HR: 0.64, $p = 0.032$).

Relation of CV events to lipoprotein variables. Baseline and in-trial HDL-C levels were not significantly associated with CV events in either treatment group (Table 1). In-trial LDL-C levels, non–HDL-C levels, and the total cholesterol/HDL-C ratio significantly predicted events only in the control group ($p < 0.001$ to $p = 0.003$).

HRs for lipoprotein effects on CV events were closer to 1.00 in ER niacin–treated subjects compared with control subjects for every baseline and in-trial variable (Table 1). In particular, in-trial LDL-C and non–HDL-C levels were associated with CV events in the control group (HR: 1.39 and 1.31, respectively) but not in the ER niacin group (HR: 1.01 and 0.98, respectively), and tests for heterogeneity were significant. Sensitivity analyses either confirmed or did not contradict this conclusion (Online Tables 2 and 3). Multivariable analysis was performed to determine whether the overall predictive impact of in-trial lipoprotein variables (including LDL-C, HDL-C, and log[TG]) differed according to treatment assignment. This analysis showed that the treatment groups

Table 1 Relationship of Cardiovascular Events to Baseline and In-Trial Lipoprotein Variables

	LLT + Placebo*				LLT + ERN			
	SD	Hazard Ratio	(95% CI)	p Value	Hazard Ratio	(95% CI)	p Value	Interaction p Value†
Baseline								
LDL-C, mg/dl	23.0	1.05	0.94–1.18	0.37	1.02	0.92–1.14	0.66	0.60
Log(TG), mg/dl	0.34	1.06	0.93–1.19	0.38	0.98	0.87–1.10	0.70	0.44
HDL-C, mg/dl	5.6	0.91	0.80–1.05	0.19	0.96	0.85–1.08	0.47	0.78
Non–HDL-C, mg/dl	27.0	1.09	0.97–1.22	0.16	1.01	0.90–1.13	0.89	0.31
TC/HDL-C ratio	0.97	1.13	1.01–1.27	0.035	1.02	0.92–1.14	0.68	0.22
TG/HDL-C ratio	0.41	1.08	0.95–1.23	0.22	1.00	0.89–1.12	0.94	0.44
In-trial								
LDL-C, mg/dl	23.0	1.39	1.16–1.67	<0.001	1.01	0.83–1.22	0.96	0.01
Log(TG), mg/dl	0.34	1.06	0.95–1.19	0.28	0.97	0.87–1.08	0.56	0.31
HDL-C, mg/dl	5.6	0.95	0.84–1.07	0.37	0.99	0.91–1.08	0.79	0.85
Non–HDL-C, mg/dl	27.0	1.31	1.13–1.52	<0.001	0.98	0.83–1.15	0.78	0.008
TC/HDL-C ratio	0.97	1.20	1.06–1.35	0.003	1.04	0.89–1.20	0.64	0.19
TG/HDL-C ratio	0.41	1.08	0.96–1.21	0.20	0.99	0.89–1.09	0.77	0.38

*Placebo tablets included 100 to 150 mg of immediate-release niacin. †Interaction p value assesses the heterogeneity of the effect of lipoprotein across treatment groups.
CI = confidence interval; ERN = extended-release niacin; HDL-C = high-density lipoprotein cholesterol; LDL-C = low-density lipoprotein cholesterol; LLT = LDL-C–lowering therapy; TC = total cholesterol; TG = triglyceride.

differed significantly ($p = 0.025$), suggesting that the use of ER niacin in patients treated with intensive LDL-C–lowering therapy reduced the overall impact of lipoproteins on CV events.

Discussion

The primary result of AIM-HIGH was the lack of an effect on CV events despite a 15% higher HDL-C level in the group receiving ER niacin compared with the control group receiving intensive LDL-C–lowering therapy alone. The present analysis extends the concept of lack of relationship with HDL-C because HDL-C levels showed no correlation with events.

We found no baseline group defined by lipoprotein tertiles in which combined therapy was significantly better than control LDL-C–lowering therapy alone. However, a nonsignificant trend toward better outcomes with ER niacin combined therapy appeared in a small group who had baseline TG levels in the highest tertile with simultaneous HDL-C levels in the lowest tertile. This trend toward benefit in a dyslipidemic subgroup has been noted in randomized trials of fibrates, which (as with niacin) lower TG and raise HDL-C levels (18).

In the AIM-HIGH control group, in-trial LDL-C, non–HDL-C, and the total cholesterol/HDL-C ratio significantly predicted atherothrombotic events. In contrast, none of these atherogenic lipoprotein variables predicted atherothrombotic events in the group receiving ER niacin. We also examined the joint impact of in-trial LDL-C, HDL-C, and TGs on events, finding a significant difference between the control group and the ER niacin combined therapy group.

The loss of the relation of in-trial atherogenic lipoproteins to CV events in ER niacin–treated patients suggests that niacin may affect the relationship between lipoproteins and events. This altered relationship implies: 1) niacin-induced compositional changes in lipoproteins that make them neutral with regard to atherothrombosis; 2) an influence of niacin on CV events independent of lipoproteins; or 3) both. We consider the first option to be unlikely as a sole explanation and favor the idea that nonlipoprotein effects of niacin may influence atherothrombotic events, obscuring the effects of lipoproteins and leading to HRs close to unity in the ER niacin combined therapy group.

Recent results from HPS2-THRIVE highlighted the potential for clinical harm from niacin related to a variety of off-target (nonlipoprotein) adverse events (2,3). The present analysis fits with the hypothesis of clinically important nonlipoprotein effects and extends their potential impact to the primary outcome variable of CV events.

A well-recognized nonlipoprotein action of niacin is GPR109A-dependent inhibition of adipocyte TG lipolysis. Plasma nonesterified fatty acid levels rapidly fall >60%, then rebound and overshoot after 1 to 2 h (10,12). This metabolic perturbation repeated every night could promote CV events via impaired myocardial fuel supply, subsequent excess in fatty acid anion concentrations, and/or a counter-regulatory hormone response, including catecholamines (19,20). Myocardial energetics are known to shift from fatty acid to glucose oxidation after niacin administration to fasting humans (12).

Niacin was administered at mealtimes before the introduction of ER niacin in the late 1990s. Mealtime dosing may avert the metabolic perturbation just described, because food absorption supports myocardial fuel supply, and epinephrine is specifically suppressed (21). The AIM-HIGH trial was designed largely on the basis of previous niacin trials with mealtime dosing (6–9). However, in both the AIM-HIGH and the HPS2-THRIVE trials, niacin administration shifted to bedtime, potentially magnifying the consequences of adipocyte lipolysis inhibition. This nonlipoprotein action of niacin needs further study in the fasting and post-prandial states.

Cellular effects of niacin include suppression of inflammatory responses in endothelial cells and macrophages, and increased cholesterol efflux in macrophages (13–15). Niacin inhibited atherogenesis in wild-type, but not GPR109A-negative, mice, and the effect was transferable with GPR109A-competent bone marrow cells (13). In contrast to adipocyte lipolysis inhibition, these cellular effects seem generally beneficial. The net effect of multiple nonlipoprotein actions of niacin, together with the relatively small 15% HDL-C increase seen in the AIM-HIGH trial, could bring about a balance of harm and benefit leading to no overall change in CV events. This hypothesis brings together diverse clinical and basic results regarding niacin and is testable at multiple levels.

Study limitations. The present study has limitations as a secondary analysis, and results should be considered hypothesis-raising rather than conclusive. The identification of an apparent benefit in a small dyslipidemic subgroup is subject to error due to multiplicity. Further insights may be gained by considering apolipoproteins, lipoprotein(a), and HDL and LDL particle concentrations, which are being analyzed and presented separately (22).

Conclusions

This analysis reinforces a diminished role for niacin-induced HDL-C increases in the prevention of atherothrombotic events. Baseline lipoprotein tertiles did not predict differential benefit or harm with ER niacin added to aggressive LDL-C–lowering therapy, but a small subgroup of subjects with baseline dyslipidemia showed possible benefit. Atherogenic lipoproteins correlated positively with CV events in the control group but not in the ER niacin–treated group. This observation raises the possibility that nonlipoprotein effects of niacin might have influenced CV events in AIM-HIGH.

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Key Words: cardiovascular events ■ clinical trial ■ GPR109A ■ lipoproteins ■ niacin.

APPENDIX

For supplemental tables, please see the online version of this article.