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Original Article

Relationship between lipoprotein subfraction cholesterol and residual risk for cardiovascular outcomes: A *post hoc* analysis of the AIM-HIGH trial

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BACKGROUND: The AIM-HIGH (Atherothrombosis Intervention in Metabolic Syndrome with Low HDL/High Triglycerides and Impact on Global Health Outcomes) trial failed to demonstrate incremental clinical benefit of extended-release niacin (ERN) in 3414 statin-treated patients with established cardiovascular (CV) disease who had low baseline levels of high-density lipoprotein cholesterol (HDL-C) as compared to placebo. A previous secondary analysis suggested that ERN provided outcome benefits in ERN-treated patients with high triglycerides (TGs; >200 mg/dL) and very low HDL-C (<32 mg/dL) at baseline. The current analysis sought to ascertain how changes in TG-enriched lipoproteins and HDL subfractions impact residual risk in the comparator treatment arms.

OBJECTIVES: We evaluated the relationship between niacin treatment, lipoproteins and their subfractions, and CV outcomes in a non-prespecified, post hoc analysis of the AIM-HIGH trial.

METHODS: Lipoprotein subfraction analysis was performed with zonal ultracentrifugation in 2457 AIM-HIGH participants at baseline and 1 year of treatment. Hazard ratios were estimated using Cox proportional hazards models for relationships between lipoproteins and the composite primary endpoint of CV death, myocardial infarction, acute coronary syndrome, ischemic stroke, or symptom-driven revascularization. Analyses were performed for the entire cohort and in participants with TGs > 200 mg/dL and HDL-C < 32 mg/dL.

RESULTS: Apoprotein B–containing lipoproteins and their subfractions decreased significantly in both treatment arms but decreased more with ERN treatment. HDL-C and its subfractions increased significantly in both treatment groups, but more so in patients treated with ERN. For the entire study population, neither apoB- nor apoA1-containing lipoprotein subfractions predicted risk at baseline or at 1 year of follow-up. In the high TG and low HDL-C subgroup treated with placebo, changes at 1 year in HDL_2-C, total cholesterol/HDL_2-C, and non-HDL-C/HDL_2-C may be associated with increased CV

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events, whereas in the ERN treatment arm, changes at 1 year in very low–density lipoprotein cholesterol and very low–density lipoprotein subfractions, total remnant lipoproteins, and various risk ratios may be associated with increased CV events, while HDL_2-C may be associated with reduced risk.

CONCLUSIONS: We provide hypothesis-generating findings that ERN may confer benefit in patients with CHD who have high TGs and low HDL by reducing serum levels of remnant lipoprotein cholesterol and increasing HDL_2-C.

Introduction

The AIM-HIGH (Atherothrombosis Intervention in Metabolic Syndrome with Low HDL/High Triglycerides and Impact on Global Health Outcomes) trial evaluated the incremental impact of extended-release niacin (ERN) adjuvant therapy in patients with stable atherosclerotic cardiovascular (CV) disease.[1] The trial was terminated early (at 36 months) because of a lack of efficacy for ERN therapy in reducing CV events. A *post hoc* analysis of AIM-HIGH suggested that ERN added to simvastatin reduced the composite trial primary CV endpoint by 37% in the high-risk subgroup of subjects with baseline triglyceride (TG) > 200 mg/dL (highest tertile) and high-density lipoprotein cholesterol (HDL-C) < 32 mg/dL (lowest tertile).[2]

The finding of reduced CV risk with ERN in patients with both elevated TG and very low HDL-C levels is similar to a number of *post hoc* analyses from clinical trials testing the efficacy of fibrates[3,4] and omega-3 polyunsaturated fatty acids[5] on risk for acute CV events among patients with elevated TGs and low HDL-C. Elevated levels of TG-enriched remnant lipoproteins (small very low–density lipoproteins [VLDL] and intermediate-density lipoproteins [IDL]) and low serum levels of HDL-C and its subfractions correlate significantly with increased risk for CV events.[6–9] These 2 features of atherogenic dyslipidemia likely reflect some degree of residual CV risk observed even after intensive treatment with high-dose statin therapy, especially among patients with metabolic syndrome, diabetes mellitus, and genetic hypertriglyceridemic states. We hypothesized that elevated serum levels of remnant lipoproteins and reduced levels of HDL are predictive of residual CV risk, and that changes in these lipoproteins and their subfractions account for some of the benefit observed in the previously published AIM-HIGH subgroup analysis characterized by TGs > 200 mg/dL and HDL < 32 mg/dL by Guyton et al.[2]

Materials and methods

AIM-HIGH study population

All persons enrolled in AIM-HIGH had stable CV atherosclerotic disease with low HDL-C, elevated TGs, and well-controlled low-density lipoprotein cholesterol (LDL-C; 40–80 mg/dL).[1] The primary endpoint was a composite of CV mortality, nonfatal myocardial infarction, ischemic stroke, hospitalization for acute coronary syndrome, or symptom-driven coronary or cerebrovascular revascularization. Participants were initially treated with daily simvastatin 40 mg and ERN at doses that increased weekly from 500 to 2000 mg per day during an open-label run-in phase of 4–8 weeks. Participants tolerating a minimum of 1500 mg of ERN daily were then randomized 1:1 to receive ERN or matching placebo. Placebo-ERN tablets each included 50 mg of immediate-release niacin (IRN) to mask the identity of blinded treatment to both patients and study personnel (the daily dose of IRN ranged from 100–200 mg in placebo-treated patients). The dose of simvastatin could be increased and/or ezetimibe 10 mg daily added to maintain on-treatment LDL-C levels in the range of 40–80 mg/dL. The present study included a total of 2457 subjects all of whom were on statin therapy at baseline (1259 placebo-treated participants and 1198 ERN-treated patients [or 72% of the overall study population]). For the high TG (>200 mg/dL)/low HDL-C (<32 mg/dL) subgroup, we identified 129 participants in the placebo group and 169 in the ERN group (n = 298 subjects, or 12% of the present study cohort). Participants not included in these analyses had no serum with which to run analyte determinations.

Vertical auto profile measurements

A full description of vertical auto profile (VAP) methodology and its quality control characteristics may be found in Supplementary Material. The VAP procedure separates lipoproteins into subfractions. Lipoproteins decrease in size as they undergo progressive lipolysis in serum. Using VAP methodology, as lipoproteins become smaller, their numerical assignation increases (LDL_1 is larger than LDL_2, $VLDL_1$ is larger than $VLDL_3$, etc.).

Statistical analyses

Participants were included in the analysis if they were taking a statin at baseline and had VAP measurements at both baseline and 1 year. The high-risk subgroup of this analysis population had HDL-C values < 32 mg/dL and TG values > 200 mg/dL at baseline. Statistical methods were identical for the entire VAP population and for the high-risk subgroup. Baseline lipoprotein levels and their change from