CLINICAL RESEARCH STUDY

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# Effects of Extended-Release Niacin Added to Simvastatin/Ezetimibe on Glucose and Insulin Values in AIM-HIGH

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## ABSTRACT

**BACKGROUND:** Niacin is an antidyslipidemic agent that may cause blood sugar elevation in patients with diabetes, but its effects on glucose and insulin values in nondiabetic statin-treated subjects with cardiovascular disease and at high risk for diabetes are less well known.

**METHODS:** This was a prespecified, intent-to-treat analysis of the Atherothrombosis Intervention in Metabolic syndrome with low high-density lipoprotein/high triglycerides: Impact on Global Health outcomes trial which randomized 3,414 participants at 92 centers in the US and Canada to extended-release niacin (ERN) plus simvastatin/ezetimibe (ERN) or simvastatin/ezetimibe plus placebo (Placebo). Baseline and annual fasting glucose and insulin values were measured. Those experiencing an adverse event indicative of diabetes or starting medications for diabetes were considered to have confirmed diabetes. In addition, nondiabetic subjects with 2 annual follow-up glucose measurements were categorized into normal, impaired fasting glucose or newly diagnosed diabetes (presumed or confirmed) states.

**RESULTS:** Compared with placebo, ERN increased annual fasting glucose from baseline to 1 year in both those with normal ($7.9 \pm 15.8$ vs $4.3 \pm 10.3$ mg/dL; $P < .001$) and impaired fasting glucose ($4.1 \pm 18.7$ vs $1.4 \pm 14.9$; $P < .02$) and increased insulin levels. Both effects waned over the next 2 years. There were less consistent effects in those with baseline diabetes. There was an increased risk of progressing from normal to presumed or confirmed impaired fasting glucose (ERN 197/336) cases (58.6%) vs placebo 135/325 cases (41.5%; $P < .001$) over time, but no difference in diabetes development in the 2 treatment groups except in those with normal fasting glucose at baseline.

**CONCLUSIONS:** The addition of ERN to simvastatin/ezetimibe had marginal effects on glycemia in those with diabetes at baseline, and there was a trend toward increased development of new-onset diabetes. In addition, ERN increased the risk of developing impaired fasting glucose, which may have deleterious consequences over time and warrants further study.

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**KEYWORDS:** Clinical trial; Diabetes; Extended release niacin; Glucose and insulin; Heart disease; Impaired fasting glucoses

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Trial Registration: Niacin Plus Statin to Prevent Vascular Events (AIM-HIGH); https://clinicaltrials.gov/ct2/show/NCT00120289 (Clinicaltrials.gov Identifier NCT00120289.

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Niacin has been widely used to treat dyslipidemia. One of its well-known side effects is the tendency to increase blood glucose levels,[1] which is thought to be related to an increase in insulin resistance.[2] This has been well studied in subjects with preexisting diabetes, although the effect has been demonstrated to be modest in most reports,[3] except in those with poorly controlled diabetes.[4] Thus, in those with known diabetes, it is appropriate that physicians monitor glucose levels carefully when niacin is being used, in the event that modification of glycemic control is required. Because it is generally recommended that patients with diabetes perform home glucose self-monitoring, potential worsening of glycemic control due to niacin therapy may thereby be corrected.

**CLINICAL SIGNIFICANCE**

- Addition of extended-release niacin to simvastatin/ezetimibe therapy (ERN) in subjects with cardiovascular disease increases fasting glucose and insulin levels compared with simvastatin/ezetimibe alone.
- There was a trend toward an increase in new-onset diabetes in the ERN group.
- There was a significantly greater increase in the development of impaired fasting glucose among those with baseline normal fasting glucose in the ERN group.

By contrast, the effect of niacin treatment in nondiabetic subjects, particularly those at high risk for diabetes, has been less well known. Because such patients are likely not monitoring their glucose levels, niacin treatment in this group may lead to undetected diabetes. A recent meta-analysis of controlled clinical trials of niacin treatment reporting the development of new-onset diabetes concluded that niacin therapy was associated with a moderate increased risk of incident diabetes.[5] However, this study did not examine whether trial participants were normoglycemic or dysglycemic at baseline, and not all of the trials were performed in high-risk subjects with atherosclerotic cardiovascular diseases, which would influence the incidence of new-onset diabetes. Furthermore, none of these trials evaluated the effect of niacin on the development of dysglycemia in previously euglycemic individuals. Because even mild elevations in glucose levels may be associated with increased morbidity,[6] it would be of value to assess the impact of niacin therapy on glucose levels in the prediabetic range, particularly among those with atherosclerotic cardiovascular disease because of their high risk for dysglycemia and diabetes.[7] Furthermore, because the majority of these individuals are receiving statins, which also increase the risk of diabetes development,[8] addition of niacin to statin therapy may further aggravate the risk for diabetes in some subjects. Recent, well-conducted randomized trials have failed to demonstrate a reduction in long-term clinical events with extended-release niacin (ERN) when added to statin therapy,[9,10] making the future place of ERN therapy in the management of dyslipidemia unclear.[11] We felt it important to report the effects of ERN on glucose and insulin levels in a prespecified secondary analysis in the Atherothrombosis Intervention in Metabolic syndrome with low high-density lipoprotein/high triglycerides: Impact on Global Health (AIM-HIGH) trial. This study compared the effects of ERN with simvastatin and ezetimibe (ERN) therapy vs placebo with simvastatin and ezetimibe (Placebo) therapy in subjects with atherosclerotic cardiovascular disease.[9]

## METHODS

### Study Design

AIM-HIGH was a randomized, placebo-controlled clinical trial designed to test the hypothesis that in patients with atherosclerotic cardiovascular disease and atherogenic dyslipidemia, treatment with ERN (Niaspan, AbbVie, Inc, North Chicago, IL) to raise baseline levels of high-density lipoprotein cholesterol (HDL-C) would decrease the rate of cardiovascular endpoints (coronary artery disease death, nonfatal myocardial infarction, ischemic stroke, hospitalization for acute coronary syndrome or symptom-driven coronary or cerebral revascularization).[9] Entry criteria for AIM-HIGH have been described in detail.[12] Briefly, patients were included if they were at least 45 years old and had established stable atherosclerotic cardiovascular disease with HDL-C $< 40$ mg/dL for men, $< 50$ mg/dL for women, high triglycerides (100-400 mg/dL) and low-density lipoprotein cholesterol (LDL-C) $< 180$ mg/dL (conversion factor to SI units for cholesterol $\times$ 0.0259 and for triglyceride $\times$ 0.0113). Lipoprotein inclusion criteria were adjusted according to baseline treatment to account for estimated effects of ongoing treatment. Established atherosclerotic cardiovascular disease was defined as stable coronary heart disease with prior documented myocardial infarction or acute coronary syndrome or documented multivessel coronary artery disease; cerebrovascular or carotid disease with ischemic sequelae, carotid revascularization, or asymptomatic carotid stenosis $> 70\%$; or peripheral arterial disease with ankle-brachial index $< 0.85$ or prior revascularization. Subjects with significant comorbidities (eg, left ventricular ejection fraction $< 30\%$) or increased risk for medication adverse effects were excluded.

### Procedures

The study was conducted at 92 centers in the US and Canada. After providing written informed consent, subjects entered a 4- to 8-week open-label phase during which they received simvastatin 40 mg daily, plus ERN at doses increasing weekly from 500 mg to 2000 mg per day. Subjects tolerating at least 1500 mg ERN daily were randomly assigned, in a 1:1 ratio, to ERN or matching placebo tablets. To mask treatment assignment to ERN, placebo tablets included 50 mg