

Does Niacin Provide Incremental Benefits in CVD Patients Already on Aggressive Lipid-Lowering Therapy?

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Study Overview

Objective. To determine whether the addition of high-dose niacin to existing therapy improves cardiovascular outcomes in patients with cardiovascular disease (CVD) and well-controlled LDL levels but low HDL levels at baseline.

Design. Double-blind randomized controlled trial.

Setting and participants. The study took place across 92 centers in the United States and Canada. Patients were eligible for participation if they were ≥ 45 years of age and had known CVD (including coronary artery disease, cerebrovascular or carotid disease, or peripheral arterial disease). Additionally, patients needed to have low HDL levels (≤ 40 mg/dL for men and ≤ 50 mg/dL for women), elevated triglyceride levels (150–400 mg/dL), and, for those not on a statin at baseline, LDL levels ≤ 180 mg/dL. Eligible patients first discontinued lipid-modifying drugs other than statins and ezetimibe for 4 weeks (during which time a baseline level of fasting lipids was obtained). They then underwent a 4- to

8-week open-label phase of simvastatin plus niacin treatment. Patients who tolerated at least 1500 mg/day of niacin without major side effects were randomized to the treatment or control arm of the study. Patients were excluded if they had suffered a stroke within 8 weeks before enrollment or had been hospitalized for acute coronary syndrome (ACS) or undergone a planned revascularization within 4 weeks.

Patients in the intervention group received 1500 to 2000 mg of extended-release niacin per day plus simvastatin (dose adjusted with the goal of maintaining LDL 40–80 mg/dL) and ezetimibe 10 mg daily if needed for further LDL lowering. Those in the control group received simvastatin, ezetimibe if needed, and placebo tablets containing 50 mg of immediate-release niacin per 500- or 1000-mg tablet. Both groups also remained on any drug used for their chronic disease management (eg, beta blockers, ACE inhibitors, diabetes medications) prior to enrolling in the trial. Patients were followed for up to 36 months after enrollment and seen at 6-month intervals (at which time pills were counted) with alternate quarterly phone call-ins between visits.

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Main outcome measures. The primary endpoint was a composite outcome of death from coronary heart disease, nonfatal myocardial infarction, ischemic stroke, hospitalization for ACS, or symptom-driven revascularization. Two secondary composite outcome measures included subgroups of the above conditions and were modified to include only those with “high-risk” ACS hospitalizations (“accelerating” symptoms, EKG changes, increase in cardiac biomarkers). Tertiary endpoints included all-cause mortality as well as individual components of the primary endpoint and several subgroup analyses. Endpoint determination was conducted by a blinded, remote clinical committee. It is worth noting that the investigators initially designed the study with a primary endpoint that did not include hospitalization for any ACS or symptom-driven revascularization. These components were added after the investigators observed an unusually low event rate in the study population.

Results. Of 8162 eligible and consented patients, 3414 were randomized to niacin ($n = 1718$) or placebo ($n = 1696$). The mean (SD) age was 64 (9) years. The vast majority of patients were white (92.2%) men (85.2%) and many had comorbid illness (33.9% with diabetes, 71.4% with hypertension, and 81% with metabolic syndrome). The niacin and placebo groups were very similar with respect to baseline characteristics. 93.6% of patients were already on a statin at trial entry and had LDL levels that were quite well controlled at baseline (median, 71 mg/dL) but low HDL (median, 35 mg/dL) and elevated triglyceride levels (161 mg/dL).

Changes in lipid levels at 2 years of follow-up differed significantly between the niacin and placebo groups and persisted at the end of 3 years. Specifically, HDL levels increased more (25% vs 9.8% increase) and triglyceride levels had a greater decrease (28.6% vs 8.1%) in niacin patients versus placebo patients. Additionally, there was a significantly greater decrease in LDL levels among niacin patients (12% vs 5.5%).

Despite these differences in serum lipid levels, clinical outcomes were similar between the 2 groups. Using a Cox proportional hazards model to compare niacin patients to placebo, the hazard ratio (95% confidence interval) for the primary composite outcome was 1.02 (0.87–1.21), with an overall event rate of 16.4% (niacin) and 16.2% (placebo). The secondary composite outcomes also showed no significant improvement with niacin.

Overall, the event rate for components of the primary outcome was lower than expected. Despite the low overall rates, however, there was a striking imbalance between the 2 groups with respect to ischemic stroke as first event, with a higher number in the niacin arm (27 patients versus 15 patients in placebo group). This fact, combined with interim data that showed the trial crossing the pre-specified boundary for lack of efficacy, led the data and safety monitoring board to terminate the trial early in April 2011 (instead of December 2012).

During the follow-up period, more patients discontinued niacin (25.4%) than placebo (20.1%) ($P < 0.001$). Also, significantly more patients in the placebo group were on the maximum dose of simvastatin (80 mg per day) (24.7% vs 17.5%; $P = 0.02$) and they were more likely to be on ezetimibe (21.5% vs 9.5%; $P < 0.001$) than those in the niacin group. The investigators were unable to determine endpoints for just 52 patients out of 3414 randomized. Analyses were conducted as intention-to-treat.

Conclusion. Despite a significant improvement in lipid profiles over placebo, niacin did not show any incremental benefit in clinical cardiovascular outcomes when added to a statin-containing regimen in high-risk patients with well-controlled LDL levels.

Commentary

There are many trials from the 1960s onward demonstrating niacin’s favorable effects on lipid profiles, raising HDL and lowering LDL and triglyceride levels [1,2]. Furthermore, niacin is believed to affect intermediate outcomes such as degree of coronary artery stenosis [3] and carotid intima media thickness [4]. The landmark Coronary Drug Project showed that in patients not on statin therapy, niacin reduced the risk of myocardial infarction [4]. However, treatment advances have been significant over the past few decades, correlating with a decline in mortality among patients with chronic CVD [5]. In part this is due to the advent of interventions for acute coronary events and stroke, but it is also because of new drugs, such as statins, that help patients achieve long-term control of serum cholesterol levels, cardiovascular workload and blood pressure. Now that we live in a world where many CVD patients can achieve excellent LDL lowering with statin therapy, it is important to address the question of whether or not niacin further improves

the risk profile in this group. An editorial focusing on the AIM-HIGH trial points out that we spend nearly \$800 million per year in the United States on niacin therapy, and that discontinuing it in patients where there is unlikely to be incremental benefit may result in substantial cost savings [6].

This randomized trial aimed to quantify the incremental benefit of niacin in CVD patients already on aggressive drug regimens and in whom, despite good control of LDL, HDL remained low. The investigators hypothesized that niacin would raise HDL and lower triglycerides, resulting in further decreased risk of CVD events in this group relative to the placebo arm. They in fact found no difference in the overall hazard of cardiovascular events between the groups and noted a higher rate of stroke in the niacin group compared with placebo.

The design of this trial was robust; it was a large randomized controlled trial with double blinding. Because of characteristic side effects of niacin, the investigators recognized that maintaining blinding of patients would be difficult. In light of this, they introduced a small amount of immediate-release niacin into the placebo. They assert that this dose would not affect lipids (or by association, cardiovascular outcomes). The investigators also achieved very high rates of follow-up, and rigorously collected and reviewed data on clinical outcomes. In addition to a strong study design and impressive follow-up, the study question itself is important, as it addresses how best to further reduce the cardiovascular event rate in a high-risk population.

The trial was to some degree limited by the fact that it was stopped early. Perhaps with a longer follow-up period, or more power to look for a smaller incremental effect, there would have been a difference in primary outcome rates between the 2 groups. Additionally, the generalizability of the findings is limited by the fact that the vast majority of the trial participants were white men. Many minorities and postmenopausal women suffer from CVD and it is unclear whether the lack of effect of niacin in this trial would be applicable to them. Furthermore, there are many patients who do not fit the profile of those in the study because of statin intolerance. Those patients are likely to benefit from adding niacin to their regimen. As the authors mention, there are several other large prospective trials ongoing which should shed light on these questions in the coming years.

One perplexing finding was the higher rate of stroke in the niacin group compared with placebo. The authors state that there is no clear physiologic reason for niacin to increase stroke risk, and that this could have been related to statistical chance in the setting of multiple tests being performed. It is worth noting, however, that the placebo patients were on significantly higher doses of statins than the niacin patients. Statins are known to reduce stroke risk in patients via mechanisms independent of lipid-lowering [7], and perhaps it is this pathway that led to lower rates of stroke in the placebo patients, rather than the lack of niacin.

Applications for Clinical Practice

This randomized controlled trial of niacin therapy in CVD patients with well-controlled LDL did not show any incremental clinical benefit of niacin. Many patients have difficulty adhering to complex drug regimens, particularly those containing drugs with unpleasant side effects. Therefore, the ability of providers to simplify regimens in high-risk patients by eliminating ineffective drugs would likely improve population-level outcomes. The results of this trial should be interpreted with caution, however, as they apply to a very specific group of patients.

—Review by Kristina Lewis, MD, MPH

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