Journal of the American College of Cardiology
© 2013 by the American College of Cardiology Foundation
Published by Elsevier Inc.

Vol. 61, No. 4, 2013
ISSN 0735-1097/$36.00
http://dx.doi.org/10.1016/j.jacc.2012.10.030

The Current State of Niacin in Cardiovascular Disease Prevention

A Systematic Review and Meta-Regression

Paul M. Lavigne, MD, Richard H. Karas, MD, PhD

Boston, Massachusetts

Objectives This study sought to assess the efficacy of niacin for reducing cardiovascular disease (CVD) events, as indicated by the aggregate body of clinical trial evidence including data from the recently published AIM-HIGH (Atherothrombosis Intervention in Metabolic Syndrome with Low HDL/High Triglycerides: Impact on Global Health Outcomes) trial.

Background Previously available randomized clinical trial data assessing the clinical efficacy of niacin has been challenged by results from AIM-HIGH, which failed to demonstrate a reduction in CVD event incidence in patients with established CVD treated with niacin as an adjunct to intensive simvastatin therapy.

Methods Clinical trials of niacin, alone or combined with other lipid-altering therapy, were identified via MEDLINE. Odds ratios (ORs) for CVD endpoints were calculated with a random-effects meta-analyses. Meta-regression modeled the relationship of differences in on-treatment high-density lipoprotein cholesterol with the magnitude of effect of niacin on CVD events.

Results Eleven eligible trials including 9,959 subjects were identified. Niacin use was associated with a significant reduction in the composite endpoints of any CVD event (OR: 0.66; 95% confidence interval [CI]: 0.49 to 0.89; $p = 0.007$) and major coronary heart disease event (OR: 0.75; 95% CI: 0.59 to 0.96; $p = 0.02$). No significant association was observed between niacin therapy and stroke incidence (OR: 0.88; 95% CI: 0.5 to 1.54; $p = 0.65$). The magnitude of on-treatment high-density lipoprotein cholesterol difference between treatment arms was not significantly associated with the magnitude of the effect of niacin on outcomes.

Conclusions The consensus perspective derived from available clinical data supports that niacin reduces CVD events and, further, that this may occur through a mechanism not reflected by changes in high-density lipoprotein cholesterol concentration. (J Am Coll Cardiol 2013;61:440–6) © 2013 by the American College of Cardiology Foundation

Extensive epidemiological data have established elevated low-density lipoprotein cholesterol (LDL-C) as a major predictor of cardiovascular disease (CVD) risk. Current national CVD prevention guidelines strongly reflect this observation, focusing on lipid intervention strategies primarily targeting LDL-C (1–3). This approach is supported by considerable evidence derived from randomized controlled trials (RCTs) of 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitor (statin) therapy demonstrating a reduction in CVD event rate proportional to the achieved absolute reduction in LDL-C (4). Recent analyses indicate that this quantitative relationship between LDL-C and CVD risk persists throughout even very low LDL-C concentrations, suggesting that as many as 40% of CVD events may be prevented by intensive statin therapy (5,6). While validating the incremental benefit of aggressive statin use, however, a review of recent RCTs revealed a substantial CVD event rate in those treated to achieve even the most stringent LDL-C targets (7–11). Recognition of this sizable residual risk has intensified efforts to identify novel therapeutic interventions.

Current understanding of the pathophysiology underlying atherosclerosis suggests a complex, multifactorial mechanism, only partially modulated by the most prominent target of statins, LDL-C. Niacin, a broad-spectrum lipid-regulating agent, has been shown to exert multiple favorable effects on cholesterol metabolism, including reduction of total cholesterol, triglycerides, very low-density lipoprotein, LDL-C, lipoprotein (a), and augmentation of high-density lipoprotein cholesterol (HDL-C) (12,13). It has also been

From the Molecular Cardiology Research Institute, Division of Cardiology, Department of Medicine, Tufts Medical Center, Boston, Massachusetts. Dr. Karas has received consulting fees from Abbott Laboratories and Merck. Dr. Lavigne has reported that he has no relationships relevant to the contents of this paper to disclose.

Manuscript received June 27, 2012; revised manuscript received October 15, 2012, accepted October 28, 2012.

recently suggested that niacin may exert nonlipid-mediated atheroprotective effects (13,14). As such, niacin has been in clinical use for many decades for the prevention of CVD. Previous clinical trials evaluating the efficacy of niacin treatment in cardiovascular outcomes yielded promising results. The Coronary Drug Project, a randomized, placebo-controlled secondary prevention trial, demonstrated a significant reduction in CVD events in the niacin intervention arm compared with that in placebo-treated subjects (15). Subsequent trials examining the combined effect of niacin added to statin therapy reported similar benefit with respect to various surrogate endpoints (16–21).

These somewhat limited empirical data supporting niacin's clinical efficacy have been challenged by the recently published results of the AIM-HIGH (Atherothrombosis Intervention in Metabolic Syndrome with Low HDL/High Triglycerides: Impact on Global Health Outcomes trial) (22). Cosponsored by the National Heart, Lung, and Blood Institute, AIM-HIGH was designed to evaluate the addition of extended-release niacin to intensive statin therapy in patients with established CVD and atherogenic dyslipidemia (characterized by low HDL-C, elevated triglycerides, and small, dense LDL-C), compared with statin use alone. The study was stopped prematurely after an interim analysis revealed futility with respect to the primary clinical endpoint and a trend toward increased stroke incidence in niacin-treated subjects.

We sought to assess the impact of these results on the collective body of evidence evaluating the clinical efficacy of niacin. Described here is a systematic analysis of niacin RCTs that report CVD outcome data.

Methods

Trial inclusion. A MEDLINE search identified trials of niacin therapy, alone or in conjunction with additional lipid-altering interventions, published in the English language literature between January 1966 and December 2011. Eligible studies were of randomized, controlled design reporting clinical CVD event data with a minimum of 6 months of follow-up. The electronic search strategy included the terms *niacin*, *niaspan*, *nicotinic acid*, *acipamox, vitamin B3*, and *vitamin pp*. Citations were limited using the terms *human*, *English language*, and *randomized controlled trial*. To ensure a comprehensive identification of appropriate trials, we conducted a supplemental manual review of citations from all eligible studies and relevant systematic analyses (23,24).

Data extraction and quality assessment. All citations were screened at the abstract level, and full articles of eligible trials were independently reviewed. The following variables were collected from the published article of each eligible study as available: baseline demographic characteristics of study participants (sample size, age, sex, diabetes, smoking status, and body mass index); baseline and on-treatment serum HDL-C, LDL-C, total cholesterol, and triglyceride levels; and the occurrence of clinical CVD events (cardiac death, nonfatal myocardial infarction, hospitalization for acute coronary syndrome, stroke, or revascularization). In the event of multiple active treatment arms, analysis was limited to the 2 groups from each trial least confounded with respect to niacin use. This was achieved by exclusion of subjects receiving non-niacin therapy in the intervention arms of 2 trials (15,25), those assigned to treatment with antioxidant vitamins in another (16), and the niacin monotherapy arm of a fourth study in which control subjects received combination therapy with ezetimibe and simvastatin (26).

Abbreviations and Acronyms

CHD = coronary heart disease

CI = confidence interval

CVD = cardiovascular disease

HDL-C = high-density lipoprotein cholesterol

LDL-C = low-density lipoprotein cholesterol

OR = odds ratio

RCT = randomized controlled trial

The quality of individual trial design and execution was assessed via evaluation of randomization methods, concealment of treatment allocation, and description of withdrawals and dropouts, which was quantified using Jadad's scale (27).

Analysis. Our pre-specified primary analysis estimated the summary effect of niacin, as either monotherapy or an adjunctive lipid-modifying intervention, on the composite endpoint of any CVD event (defined as cardiac death, nonfatal myocardial infarction, hospitalization for acute coronary syndrome, stroke, or revascularization procedure). Two secondary endpoints were also analyzed: major coronary heart disease (CHD) event, (defined as nonfatal myocardial infarction or cardiac death), and stroke (ischemic or hemorrhagic). A pre-specified subgroup analysis evaluated the effect of niacin as an adjunct to statin therapy on each of the primary and secondary clinical outcome measures (16,17,19,22,26). An additional analysis was performed limited to trials in which the lipid-modifying intervention differed only with respect to the presence of niacin therapy between treatment and control arms (15,17,22,26).

An exploratory meta-regression analysis was performed examining a potential association between the difference in HDL-C concentration between trial arms with the calculated effect size of each respective trial for the primary endpoint of any CVD event.

Statistical methods. Measures of effect size with respect to the prespecified clinical endpoints for each included study are presented as odds ratios (ORs). The I^2 statistic was calculated to quantify the proportion of inconsistency observed across trials. Given the variation in baseline population characteristics and lipid-modifying regimens used within the included studies, a random-effects model (DerSimonian and Laird) was chosen to estimate the pooled effect of all trials for each prespecified clinical endpoint. To determine the extent to which inclusion of the 2 largest trials influenced the overall findings, sensitivity analyses