"Niacin Doesn't Work and Is Harmful!" Proclaim the Headlines. Yet Another Highly Publicized Questionable Study to Discredit Integrative Medicine

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The impact of conventional medicine's use of the news and social media to widely promulgate misleading anti-integrative medicine research was recently highlighted for me. In July, several media stories, blogs, etc, loudly proclaimed, "Niacin Does Not Work!" or "Niacin Fails Again!" Worse, they asserted its use was associated with increased adverse events. (A Google search of "niacin does not work HPS2-Thrive July 2014" yielded a remarkable 139 000 hits.) Within a few days, one of my basketball buddies chastised me for referring him to a colleague who had prescribed niacin and red rice yeast for his elevated cholesterol levels. He asked why I would refer him to a doctor who would recommend something that did not work. Although I had not yet read the study, I assured him that there were a large number of studies proving niacin does work and is safe, and that he should not be misled by a single, highly publicized study. Nonetheless, the damage was done—showing that news stories that we may easily discount because of our knowledge of the research can have a damaging impact on our patients and our relationship with them. So when Mark Houston, MD, asked me to join him in coauthoring a rebuttal, I was quite honored and receptive. After reading his excellent draft, I realized a clinically oriented rebuttal would be of interest to our readers. Following is my modification of Mark's excellent article.

– Joseph Pizzorno, ND, Editor in Chief

HPS2-THRIVE

HPS2-THRIVE[1] was a study of an investigational drug, Tredaptive (Merck) containing both extended release niacin (ERN) (2 g) and the drug laropiprant (40 mg) to decrease the flushing effect of niacin. Laropiprant is a selective antagonist of the prostaglandin D_2 receptor subtype 1(DP1R), which appears to be the mechanism for niacin's flushing.[2] This study included 25 673 high-risk, niacin-tolerant patients who were randomized to either placebo or ERN plus laropiprant (ERNL). The primary endpoint was the time to first major vascular event, defined as the composite of nonfatal MI or coronary death, any stroke, or any arterial revascularization. So far, sounds like a good study that could help make niacin more acceptable for our patients.

The primary composite endpoint of major vascular events (MVE) was not significantly reduced (relative risk [RR] = 0.96; 95% CI, 0.90-1.03; P = .3). "Serious adverse events" were found in 3% of subjects in the active arm, although most were "minor hyperglycemic problems." Myopathy generally was uncommon (0.34%/y) but was 4-fold higher overall in the active arm and 10-fold higher among Chinese subjects.

Now the problems.

Niacin Not Indicated

The study subjects were aggressively pretreated with statin therapy (simvastatin 40 mg/d) achieving an average low-density lipoprotein (LDL) cholesterol of 63 mg/dL (optimal = <70 mg/dL), high-density lipoprotein (HDL) cholesterol of 44 mg/dL (good = >40 mg/dL), and triglycerides of 125 mg/dL (optimal = <150 mg/dL). The National Lipid Association (NLA) in the March 2013 position paper stated that in HPS2-THRIVE "… niacin was clinically irrelevant in the average study subject. The investigators 'tested a drug in patients who, on average, had no indication to take it.'"[3] There was no reason to expect improvement from niacin in these optimally treated statin patients.

Nonetheless, there were several positive effects of treated patients on ERNL. These included reductions in weight, blood pressure, lipoprotein(a), a significant reduction in arterial vascularization procedures (P = .03), and significant reduction in cardiovascular (CV) risk in the subgroup with the higher baseline LDL cholesterol level (P = .02).

Table 1. Clinical Trails Demonstrating Efficacy of Niacin

Study	Result
Coronary Drug Project	Reduced CHD and reduced total morality at 15 y
HATS	Reduced CV events and coronary atheroma
ARBITOR 2	NS trend to reduce carotid IMT and increased HDL 7 mg/dL on 1000 mg/d with statin
ARBITOR 3	Regression of carotid IMT and increased HDL 9 mg/dL (23%) at 12-24 mo on 1000 mg/d with statin
Oxford Niaspan Study	MRI showed regression of carotid plaque and increased HDL 23% in 12 mo on 2000 mg/d with statin
FATS, CLAS I, CLAS II, AFRS	Reduced progression of coronary atherosclerosis with colestipol

Abbreviations: CHD = coronary heart disease; CV = cardiovascular; IMT = intima-media thickness; HDL = high-density lipoproteins; MRI = magnetic resonance imaging.

Discussed later in this article, there has been decades of research showing efficacy of niacin monotherapy in reducing CV events as well as total mortality.[4] There is also research showing that niacin is effective in conjunction with statins when LDL cholesterol or triglyceride remain elevated and HDL cholesterol remains low after treatment with statins. In other words, niacin is effective when indicated as shown in the subgroup earlier in this article and other clinical research.

Adverse Events Inconsistent With Other Studies of Niacin With Statins

HPS2-THRIVE, unlike other studies using statins and niacin in combination, showed increases in serious adverse events: 3.7% absolute excess adverse events including myalgia (0.7%; $P < .001$), new onset diabetes (NOD) (1.3%; $P < .001$), gastrointestinal problems (1.0%; $P < .001$), skin problems (0.3%; $P < .003$), infections (1.4%; $P < .001$), and bleeding (0.7%; $P < .001$). This fixed, high-dose niacin treatment may have contributed to dose-related adverse effects.

Complicating the study, approximately 43% of the study population was Chinese. This influenced many of the adverse effects, especially the myopathy and skin eruptions.[5] As noted in the paper,

> The absolute risk of myopathy in the placebo group was higher in China than in Europe and the relative risk with ERNL versus placebo was 5.2 in China, as compared to 1.5 in Europe. China participants had 50 cases of myopathy per 10 000 versus 3 cases per 10 000 in Europe.

My clinical takeaway from these numbers is that we need to be more careful prescribing both niacin and statins in patients of Chinese descent.

The Adverse Events Likely Due to Laropiprant

Laropiprant has several mechanisms of action that could either increase or decrease thrombotic risk and potentially cause adverse effects.[6] Laropiprant with aspirin or clopidogrel induces a prolongation of bleeding time and an inhibitory effect on platelet aggregation ex vivo in healthily subjects and in patients with dyslipidemia and may suppress immune function. This may explain some of the findings in increased infections and lack of CV efficacy in HPS2-THRIVE.

Niacin Is Effective When Indicated

Niacin has been shown to provide numerous clinical and physiologic benefits. (25-34). The clinical trials that showed CV benefits from niacin alone or with other agents are shown in Table 1.

In a recent meta-analysis of niacin and coronary heart disease (CHD), definitive benefit was demonstrated for CVD and CHD.[7] These 11 trials of 9959 patients found a reduction in composite endpoints in CVD of 34% and a decrease major CHD event by 25%. There was no change in cerebrovascular accident (CVA). Interestingly, the magnitude of improvement did not totally correlate with improvements in lipid parameters. This suggests that some of niacin's reduction in CVD events may occur through other, nonlipid mechanisms. Note that niacin use for 3 years increased glucose levels by only 5 mg compared with placebo and did not increase diabetes mellitus risk.[8] Based on the analysis of Guyton et al of the AIM HIGH trial reported at the AHA meeting in November 2012, niacin is most effective for CVD reduction when the baseline HDL is less than 32 mg/dL and triglyceride is greater than 200 mg/dL.

Table 2 lists the many beneficial physiological effects of niacin. These mechanisms include favorable lipid effects and nonlipid effects as well as improvement on endothelial and vascular function and structure.

Table 2. Beneficial Physiological Effects of Niacin[9,10,11,12,13,14]

- Reduces Lp(a).
- Lowers TC, ApoB, LDL, small dense LDL, shifts small LDL-B to big LDL-A (more cholesterol).
- Reduces LDL-P (linear dose response) more than LDL is lowered.
- Inhibits LDL oxidation.
- Increases total HDL and reduces HDL-*ApoA1* uptake.
- Alters HDL composition. Increases HDL, especially large HDL type 2B by 16% at 1 g/d (logarithmic dose response) and decreases small HDL-3.
- Increases HDL-P by 16% at 1 g.
- Improves HDL functionality.
- Increased CETP and LCAT.
- Significant reductions in VLDL and TGs.
- Modulates TG lipolysis in adipose tissue.
- Increases ApoB degradation.
- Reduces fractional catabolic rate of HDL-*ApoA1*.
- Fibrinolysis, inhibits platelet function.
- Inhibits cytokines, CAMs.
- Potent antioxidant.
- Increases adiponectin and reduces FFA.
- Improves reverse cholesterol transport and CEC. Improved CEC with all efflux pathways (improved function) measured.
- Decrease MPO release from neutrophils.
- Improved endothelial function.
- Inhibits hepatocyte surface expression of B-chain ATP synthase, inhibits removal of HDL-*ApoA1* and increases ApoA1 containing HDL particles.
- Increase hepatic ABCA-1 transporter, which increases A1–mediated *ApoA1* lipidationand increases HDL biogenesis.
- Decreased inflammation/GPR 109A mediated.

Abbreviations: Lp(a) = lipoprotein(a); TC = total cholesterol; ApoB = apolipoprotein; LDL = low-density lipoproteins; LDL-P = LDL particle number; HDL = high-density lipoproteins; HDL-P = high-density lipoprotein particles; CETP = cholesterylester transfer protein; LCAT = lesterol acyltransferase; VLDL = very low-density lipoprotein; TG = triglyceride; CAM = cell adhesion module; FFA = free fatty acid; CEC = cholesterol efflux capacity; MPO = myeloperoxidase; ATP = adenosine triphosphate; ABCA-1 = ATP-binding cassette; GPR = G protein-coupled receptor.

Conclusions

(1) Niacin is an efficacious agent for the treatment of dyslipidemia and prevention of CVD as monotherapy, as well as with statins and other lipid-lowering agents.
(2) The vast majority of clinical trials with niacin or niacin with other drug therapies for dyslipidemia show significant reductions in CVD, CHD, and carotid atherosclerosis.
(3) Therapeutic dosages of ERN has a relatively low side effect profile.
(4) The addition of laropiprant may have induced many of the adverse effects. The data do not support the conclusion that niacin alone caused the adverse effects on clinical or metabolic parameters.
(5) Niacin monotherapy has many positive effects on lipids such as LDL reduction and LDL particle number reduction. It also increases LDL size, increases HDL, HDL-2B, HDL particle number, and HDL function. It reverses cholesterol transport, cholesterol efflux capacity, and triglyceride. Patients not at LDL goal or patients with CVD and dyslipidemia with HDL < 32 mg/dL and triglyceride > 200 mg/dL may benefit from ERN added to intensive statin-based LDL cholesterol–lowering therapy.
(6) Niacin has many nonlipid actions that are clinically important to prevent and treat CVD and CHD.

In This Issue

Few have had as big an impact on this medicine as my friend Jeff Bland, PhD. He is—with Susan Bland—the cofounder of the Institute for Functional Medicine (IFM), an inspirational speaker, the first member of the founding Board of Trustees of Bastyr University, a prolific author, an expert spokesman to Congress—he has communicated and led in many venues. *IMCJ* is pleased to provide in this issue a review by Lara Pizzorno, MDiv, MA, LMT, of his excellent new book, *The Disease Delusion*.

While Jeff and Susan are widely appreciated for founding IFM, its remarkable success would not have been possible without the great leadership, inspiration and wisdom of founding president David Jones, MD, and my dear friend. Innovision publisher Dick Benson provides us remarkable insight into this physician whose insight and clinical expertise has fundamentally changed not only what we practice, but how we practice. I especially appreciate how David came to recognize the importance of personalization and the patient's story. Equally important is his understanding that clinicians need to be science using rather than to be used by the recommendations of generic science. I think we should start a groundswell movement to nominate David for Surgeon General of the USA. Think of how this would transform medicine and solve the healthcare crisis.

IMCJ welcomes case studies because they provide important insight to real patient experiences. Mary J. Warpenburg, BS, CMT, BCTMB, AAS, a professional massage therapist, courageously writes about her experience being treated with deep friction massage for radiation-induced fibrosis. This is an important story for our suffering patients recovering from cancer treatment.

We continue our interviews of keynote speakers at upcoming conferences. Managing editor Craig Gustafson interviewed Howard Hindin, DDS, who will speak on sleep and immune system function at the American College for the Advancement of Medicine conference. I have been wondering how much of the dementia epidemic we are suffering is due to the dramatic reduction in sleep the past century. Hmm, looks like a good topic for a future editorial.

I am delighted with the guest commentary on sodium by David L. Katz, MD, MPH. As I have looked into the research on diet-induced acidosis (yet another topic for a future editorial), the problem with excessive sodium has become quite apparent.

I think a key reason low sodium diets have not been shown to be as beneficial as expected is that decreasing table salt also results in decreased iodine consumption. As discussed in my editorial in the June 2012 *IMCJ*,[15] iodine deficiency is becoming more common (50% reduction in intake the past 20 years), so salt restriction likely aggravates the problem.

Great critique of the shamelessness of leadership in the medical industrial complex by John Weeks! Reminded me of a meeting hosted by Microsoft, seeking advice from the health care community on ways to decrease their huge health care costs. Hospital presidents, medical directors of insurance companies, and directors of regulatory agencies were profound in their recommendations—most of which were some version of rationing and using their latest and greatest program to decrease costs. And then there was the lone nonconventional invitee … though 15 years ago now, I still vividly remember the response when I suggested that the only real solution of the problem was for Microsoft to improve the health of their employees. You could have heard a pin drop in the carpeted room—they all looked at me in fear as their institutions were dependent on ever-worse disease needing ever-more expensive and exotic interventions. Yes, we need the hospitals, insurance, high tech interventions, etc. They truly save lives. But the only real solution to the health care crisis, as we all know, is to decrease the need for the huge medical industrial complex that now consumes one-sixth of the GDP.

For the past several years, we have written a review of the annual IFM symposium. Held in May in San Francisco, "Functional Perspectives on Food and Nutrition: The Ultimate Upstream Medicine" focused on the role of diet in health and disease. I thought the conference excellent, especially the "playoff" debate between proponents of the Paleo (Loren Cordain, PhD), Mediterranean (Mimi Guarneri, MD), and plant-based diets (Joel Fuhrman, MD). Considering all the controversy surrounding the "best" diet debate we decided to make this review more rigorous than those in the past. As the presenters provide numerous citations for their positions, our reviewer, Lara Pizzorno, MDiv, MA, LMT, read their references and reported what was actually found in the research. You may be surprised by what she found …

Back Talk by Bill Benda, MD: There is nothing I can add.

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