Clinical Lipidology

The appropriate clinical use of niacin in the treatment of dyslipidemia

"The claim that HPS2 THRIVE proved that niacin induced more adverse effects than the statin arm of the study is not supported by the data."

Keywords: cardiovascular disease • coronary heart disease • dyslipidemia • laropiprant • niacin

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Purpose

The purpose of this commentary is to provide an additional evaluation of the results of the HPS 2 THRIVE study within the context of the global evidence of niacin in the treatment of dyslipidemia and cardiovascular disease (CVD).

It is our contention that niacin remains an efficacious treatment for specifically defined types of dyslipidemia, reduces CVD, has a low incidence of adverse effects (dose related) and cannot be singled out as the cause of most of the adverse effects or the relative lack of clinical efficacy in the HPS 2 THRIVE study.

HPS 2 THRIVE

HPS2-THRIVE [1] was a study of an investigational drug (Tredaptive, Merck, NY, USA) containing both extended release niacin (ERN) and the drug laropiprant, a selective antagonist of the prostaglandin D2(PGD2) receptor subtype 1(DP1R), which partially blocks the dermal flushing response to niacin [2,3].

HPS2-THRIVE randomized 25,673 high-risk niacin-tolerant patients to either placebo or ERN plus laropiprant (ERNL). All study subjects received simvastatin 40 mg (alone or in combination with ezetimibe 10 mg) to achieve LDL goal. The primary end point was the time to first major vascular events, defined as the composite of nonfatal myocardial infarction (MI) or coronary death, any stroke or any arterial revascularization [1].

The primary end point was not significantly reduced (risk ratio: 0.96; 95% CI: 0.90–1.03; p = 0.3) in the active arm. 'Serious adverse events' were reported more commonly in the active arm. A large percentage of the study population were Chinese (43%). Myopathy generally was uncommon (0.34%/year), but was fourfold higher overall in the active arm, and 16-fold higher among Chinese subjects [1].

The study subjects had excellent baseline control of serum lipids on statin therapy (simvastatin 40 mg/day +/- ezetimibe 10 mg/day) with an average LDL-cholesterol (LDL-C) of 63 mg/dl, HDL of 44 mg/dl and triglycerides of 125 mg/dl. As stated by the National Lipid Association (NLA) in their March 2013 position paper [4], on HPS2-THRIVE "Niacin was clinically irrelevant in the average study subject, and there was substantial subgroup heterogeneity. The investigators in HPS2 THRIVE tested a drug in patients who, on average, had no indication to take it." Major vascular events reduction with ERN was strongly predicted by baseline LDL-C (heterogeneity p = 0.02). The apparent net benefit of cardiovascular disease (CVD) reduction was seen only in those patients whose LDL-C was above 58 mg/dl at study entry. Therefore, this study population was not likely to have any significant CVD reduction due to the very low baseline treated LDL-C. At this level of LDL-C, increasing HDL or reducing TG may have minimal effects on the reduction of CVD. Early data from the Coronary Drug Project (CDP) [5] showed significant reductions in cardiovascular events when niacin was used alone in individuals with documented heart

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disease. The CDP and many other niacin trials have documented benefits of additive therapy on top of statins when LDL-C or triglycerides remain elevated and HDL remains low [6,7].

The claim that HPS2 THRIVE proved that niacin induced more adverse effects than the statin arm of the study is not supported by the data. Laropriprant could also have increased the adverse effects. HPS 2 THRIVE found a 3.7% absolute excess adverse events including myalgia (0.7%; $p < 0.001$), new onset diabetes (NOD) (1.3%; $p < 0.001$), gastrointestinal problems (1.0%; $p < 0.001$), skin problems (0.3%; $p < 0.003$), infections (1.4%; $p < 0.001$) and bleeding (0.7%; $p < 0.001$). Niacin has known dose-related adverse effects, but smaller doses still provide clinical efficacy [6,7]. About 43% of the study population were Chinese who have been reported to have higher incidences of myopathic and dermatologic reactions to statins and ERNL [1,8]. This may be the reason for the excess adverse event rate in HPS2 THRIVE, especially myopathy and skin eruptions [1,8]. 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 ERN versus placebo was 5.2 among Chinese versus 1.5 among the non-Chinese. "This is significantly greater in China participants with 50 cases per 10,000 versus 3 cases per 10,000 in Europe." Also the risk for NOD on ERNL with statins must be compared with statin monotherapy [9–11]. HPS2 THRIVE treated patients on combined ERNL (2 g ERN and 40 g/l) per day with concomitant statin therapy (simvastastin 40 mg per day + ezetimibe) for a median follow up of 3.9 years, had NOD risk of 9.1 versus 7.3% in placebo group (HR: 1.27; 95% CI: 1.14–1.41; $p = 0.0001$). A meta-analysis of 13 large randomized placebo-controlled statin trials with 91,140 participants and a mean follow up of 4 years [11] reported a 9% increased risk of NOD (OR: 1.09; 95% CI: 1.02–1.17). The SPARCL trial [10] (Stroke Reduction by Aggressive Reduction in Cholesterol Levels) of 4731 patients on atorvastatin 80 mg for 4.9 years showed 34% higher incidence of NOD (OR: 1.34; 95% CI: 1.05–1.71). Adding the SPARCL trial to the statin meta-analysis increased the NOD risk to 12% (OR: 1.12; 95% CI: 1.05–1.18) on statin monotherapy. This percentage is higher than that seen with ERN in the HPS 2 THRIVE study.

The investigational drug laropiprant may induce changes in bleeding risk [12–14]. Laropiprant with aspirin or clopidogrel induces a prolongation of bleeding time and an inhibitory effect on platelet aggregation *ex vivo* both in healthy subjects and in patients with dyslipidemia [13].

The AIM HIGH Trial should also be mentioned [15]. This study was stopped early by DSMB due to lack of efficacy in CVD outcomes in an interim analysis. There was a nonsignificant increase in ischemic CVA in niacin group due to chance, small number of patients or other reasons. This has not been seen in any other niacin clinical trial:

- Niacin 28 CVA 1.6% NS ($p = 0.09$);
- Placebo 12 CVA 0.7% NS.

Nine of the ischemic CVA in niacin group occurred after stopping the niacin 67 to 1467 days later! This was probably not related to niacin treatment. The study stopped early at 3 years to due lack of efficacy in treatment group with only 274 versus 282 events. In the niacin treated group at 2 years there was an increase in HDL from 32–42 mg/dl (25%) with HDL 2 increase 6.1–10.8 mg/dl, HDL 3 increase 28.7–33.3 and apoA1 increase 122.5 to 132.5 mg/dl, decrease TG 164–122 mg/dl (28.6%) and decrease LDL 74–62 mg/dl (12%). ApoB decreased 77.6 to 70.4 mg/dl and Lp(a) decreased 36.1 to 27 mg/dl. In the placebo group at 2 years there was an increase in HDL by 9.8%, with HDL 2 increasing from 6.3 to 7.6, HDL 3 from 29 to 31.4 and apoA1 from 123.7–127.5, a decrease in TG by 8.1%, and a decrease LDL of 5.5%. ApoB decreased 82.8–77.6 mg/dl and Lp(a) decreased 32.7–30.6 mg/dl. This group received more simvastatin and ezetimibe ($p < 0.02$ and 0.001, respectively). The discontinuation rate was 25.4% Niacin group and 20.1% placebo group. There are many potential issues in this AIM HIGH study that complicate its interpretation. These include:

- Small sample size to determine relative CVD risks between groups;
- Lower risk subjects;
- Wrong cohort;
- Inadequate statistical power for an underpowered study;
- Low dose of immediate release niacin in placebo group altered results;
- Titration of simvastatin in placebo group to higher dose and LDL goal resulted in imbalances in lipid modification treatment, plaque progression and regression and plaque stability, and other pleiotrophic effects of statins that reduce CVD and coronary heart disease (CHD);
- Stopped study too soon before end points reached;

- LDL already low at entry <70 mg/dl, thus HDL is a minimal factor for CVD;
- Did not measure LDL-P which drives CHD risk;
- Did not measure HDL-P or HDL function;
- Cannot generalize the study population to the general population re low HDL, low LDL, CHD or more severely ill subjects with recent MI and acute coronary syndrome;
- Most >94% already on statins for years which improves plaque stability, reduces rupture and MI, has other pleiotrophic effects as well as LDL;
- Low percentage of women and minorities;
- Placebo group was not placebo, but actually got extended release niacin 100–200 mg per day;
- Follow up period only 3 years, which may be too short for adequate end point analysis.

The role of prostaglandin D2, its receptors & metabolites

Prostaglandin D2, its metabolites and the PD2 receptors play a role in the efficacy and adverse effects of ERN [12,14,16–19]. Prostaglandin D2 acts through two G protein-coupled receptors (GPCRs), the prostanoid DP receptor (DP1R) and CRTH2 receptor (DPR2). The complex metabolism of PGD2 and derivatives and the balance of the clinical effects of these two receptors reinforces the difficulty inherent with attempting to interrupt pathways that have both beneficial and harmful effects [12,14, 16–19].

There is little information regarding the serum levels of PGD2 or the co-stimulation of the DP2R subtype during blockade of the DP1R subtype by laropiprant. It is known that niacin interferes with cyclic AMP/protein kinase A pathway and will stimulate PGD2 formation by 400- to 800-fold at a dose of 500 mg per day [19]. In addition, the stimulation of DP1R not DP2R induces niacin flushing. It is not known if PGD2 serum levels are increased with laropiprant treatment. PGD2 has an eightfold lower affinity for the DP2R compared with the DP1R.

The metabolites of PGD2 such as dihydroketo PGD2 and PGJ2 (15 deoxy delta 12, 14, PGJ2) may have balanced effects on health, inflammation and antioxidant responses [14,16–19]). For example, PGJ2 is a selective PPAR gamma agonist that is antimitotic and antiproliferative. PGJ2 may inhibit platelet aggregation, lower blood pressure, improve insulin resistance, reduce arterial inflammation and lower iNOS In addition PGJ2 decreases C0X2, MMP (metalloproteinase) 9, ICAM (intracellular adhesion molecule), VCAM (vascular cell adhesion molecule), TNF-α, MCP (monocyte chemotactic protein), hsCRP, PAI-1 (plasminogen activator inhibitor) and fibrinogen. PGJ 2 also reduces NF-KB stimulation, ADMA (asymmetric dimethyl arginine) and lowers Angiotensin–II (A-II) induced fibronectin by HPMC (human peritoneal mesothelial cells). PGJ2 will increase Keap I and Nrf2 ARE with increases in glutathione synthase. In addition, there is a decrease in thrombosis, modulation of Th2 cells, adipogenic effects and improved HDL function with increased reverse cholesterol transport (RCT). Niacin stimulates the CD 36 and ATP binding cassette (A 1 (ABCA-1) via PGJ 2 [18]. The effect on CD 36 but not on ABCA 1 was prevented by cyclooxygenase inhibition [18].

Clinical & biological effects of niacin

There were several positive effects of treated patients on ERNL. These included reductions in weight, blood pressure, Lp(a), a significant reduction in arterial vascularization procedures ($p = 0.03$) and a significant reduction in CV risk in the subgroup with the higher baseline LDL-C level ($p = 0.02$). The adherence rate was poor at one year and at completion of the study, which may have altered hard CV outcomes. The average age was 64.9 years and mostly men. The data cannot be totally extrapolated to a younger population or perhaps to females.

Niacin has numerous clinical and physiologic benefits [20–26]. The clinical trials that showed CV benefits from niacin alone or with other agents are shown below. In all of these clinical trials there is a dose-related reduction in TC and LDL of about 15–20%, decreases in TG of 25% and increases in HDL up to 20%. The effective dose of niacin ranges from about 1000–4000 mg per day depending on individual responses. There does not appear to be gender specific response in these clinical studies.

- Coronary Drug Project with reduced CHD and total mortality;
- HATS reduced CV events and coronary atheroma;
- ARBITOR 2 had a nonsignificant trend to reduce carotid intimal medial thickness (IMT) and HDL increased 7 mg/dl on 1000 mg/day in combination with a statin;
- ARBITOR 3 had regression of carotid IMT and increased HDL 9 mg/dl (23%) at 12–24 months on 1000 mg/day with a statin;
- Oxford Niaspan Study: MRI showed regression of carotid plaque and increased HDL 23% in 12 months on 2000 mg/day with a statin;

- FATS, CLAS I, CLAS II, AFRS: Reduced progression of coronary atherosclerosis with colestipol;
- Niacin with a statin is superior to ezetimibe and a statin to induce regression of Carotid IMT.

In a recent meta-analysis of niacin studies and CHD, definitive benefit was demonstrated for CVD and CHD [7]. This included eleven trials of 9959 patients showing a reduction in composite end points of any CVD by 34% and a reduction of major CHD event by 25%.

There was no change in CVA. The magnitude of on-treatment HDL difference between treatment arms was not significantly associated with the magnitude of the effect of niacin on outcomes. Niacin reduction on CVD events may occur through a mechanism not reflected by changes in HDL or other lipid parameters. Niacin use over 3 years increased glucose levels by 5 mg /dl compared with placebo without any increased DM risk [25]. Niacin significantly reduced CHD progression and stenosis and other major CV events in 407 subjects in FATS, HATS, AFREGS and CPC clinical trials [25]. An analysis of the AIM HIGH trial by Guyton *et al.*, presented during the AHA meeting, November 2012 in Los Angeles, CA, USA indicated CV benefit with baseline HDL <32 mg/dl and triglyceride >200 mg/dl in niacin treatment subjects.

It is important to note the difference in subjects in all of these trials such as the meta-analysis of 9959 participants from eleven clinical trials versus 25,673 in HPS2-THRIVE and 3414 in AIM-HIGH, There are also potential issues with publication bias and some of the older trials that may not have been conducted to the same rigorous standards. The analysis above allows one to have a better perspective of HPS 2 THRIVE and AIM HIGH (related to both older and newer studies) which despite their large size still do not provide definitive data about niacin and CVD. It should be noted that smaller doses of niacin may provide surrogate as well as outcome benefit in lower doses which would obviate some of the recently described adverse effects that are dose related. More studies will need to be done to clarify and verify this hypothesis.

Niacin improves CV outcomes by both lipid and non-lipid mechanisms. The GPR109 niacin receptor mediates flushing and possible lipid lowering effects but also may be involved in nonlipid effects that improve vascular outcomes [20–26]. The GPR 109 effects include reduction in lipolysis in adipocytes, flushing in the dermal Langerhans cells, increased cholesterol efflux capacity (CEC), reduction of inflammation in the macrophages and reduction ROS, VCAM and MCP-1 in the endothelial cells. Most of the lipoprotein effects are mediated by non GPR mechanisms via the liver.

These include:

- Reduces Lp(a). This is dose related with average 15–20% reduction;
- Lowers TC in dose related fashion of about 15–20%, apoB, LDL, small dense LDL, shifts small LDL B to big LDL A;
- Reduces LDL particle number (LDL-P) (linear dose response) more than LDL is lowered. LDL is lowered about 15–20% in a dose related manner;
- Inhibits LDL oxidation;
- Increases total HDL about 5–20% and reduces HDL-apoA1 uptake;
- Alters HDL composition. Increases HDL especially large HDL 2b by 16% at 1 g per day (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 TG;
- Modulates TG lipolysis in adipose tissue and reduces TG about 25%;
- 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 RCT and (CEC). Improved CEC with all efflux pathways measured by:
  - Passive diffusion;
  - ABC G1;
  - SR-B.
- Decreases MPO(myeloperoxidase) 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 ATP-binding cassette (ABCA-1) transporter which increases A-1 mediated apoA1 lipidation and increases HDL biogenesis;
- Decreased inflammation/GPR 109 A mediated.

Future perspective

Niacin will require additional well designed and controlled clinical trials to verify its role for therapy in dyslipidemia as monotherapy or in combination with statins. In addition, the appropriate clinical situation must be identified for which niacin will provide reduction in cardiovascular events. Whether lower doses of niacin will reduce side effects and also will have important biological and clinical effects will require additional studies.

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No writing assistance was utilized in the production of this manuscript.

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