ISIFMC* Position Paper on the HPS2-THRIVE Study

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Introduction
In this brief paper, we review data from the study known as "HPS2-Thrive"¹ and establish our position in refutation of this work.

Summary of Data
HPS2-THRIVE¹ is a recent study of an investigational drug (Tredaptive, Merck) containing both extended release niacin (Niaspan, ERN) and the drug laropiprant, a selective antagonist of the prostaglandin D2 receptor subtype 1 (DP1R), which partially blocks the dermal flushing response to niacin.²,³ HPS2-THRIVE randomized 25,673 high-risk patients who could tolerate niacin to either placebo or extended-release niacin (ERN) plus laropiprant (ERNL). The study subjects were all on simvastatin 40 mg/day. The primary endpoint was the time to first major vascular event, defined as the composite of non-fatal myocardial infarction (MI) or coronary death, stroke, or any arterial revascularization.¹

The primary composite endpoint of major vascular events (MVE) 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 found in 3% more subjects in the active arm, although most were “minor hyperglycemic problems.” Myopathy generally was uncommon (0.34% per year), but was 4-fold higher overall in the active arm, and 10-fold higher among Chinese subjects.14

The study subjects had excellent baseline control of serum lipids on statin therapy (simvastatin 40 mg/day) with an average LDL-C of 63 mg/dl, HDL of 44 mg/dl, and triglycerides of 125 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” and “there was substantial subgroup heterogeneity” and concluded that the investigators “tested a drug in patients who, on average, had no indication to take it.” MVE reduction with ERNL was strongly predicted by baseline LDL-C (heterogeneity p=0.02), with apparent net benefit if LDL-C was above 58 mg/dl at study entry. Therefore and importantly, this study population was not likely to have any significant CVD reduction. In addition to the early data from the Coronary Drug Project (CDP)56, which showed significant reductions in cardiovascular events when niacin was used alone in individuals with documented heart disease, as well as many other niacin trials, there are documented benefits of additive therapy on top of statins when LDL-C or triglyceride remain elevated and HDL remains low.

Several clinical benefits of ERNL were noted, including reductions in weight, blood pressure, lipoprotein(a), a significant reduction in arterial vascularization procedures (p= 0.03) and significant reduction in CV risk in the subgroup with the higher baseline LDL cholesterol level (p=0.02). The adherence rate was poor at one year and at the completion of the study, and this noncompliance may have altered hard CV outcomes. The average age was 64.9 years, and the study population was mostly male. Thus, the data cannot be confidently extrapolated to a younger population nor perhaps to females.

Position
The claim that HPS2-THRIVE proved that niacin induced more harm than the statin arm of the study is not supported by the data. To evaluate this paper, one must consider 1 the participants’ risk at entry, 2 their demographics (especially the Chinese population), 3 known and measured benefits of ERNL, 4 potential harm of laropiprant, 5 research support for the benefits of niacin, and 6 whether the flushing response to niacin correlates with and/or mediates part of its benefit. Unlike other studies using statins and niacin in combination, this study showed increases in serious adverse events (ADE) (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)
- Bleeding (0.7%, p<0.001)

The dose of niacin was high and fixed resulting in dose-related adverse effects. About 43% of the study population were of Chinese descent; this influenced many of the adverse effects, especially the myopathy and skin eruptions.147 As noted in the original 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. This is 10x greater in China participants with 50 cases per 10,000 versus 3 cases per 10,000 in Europe.” Overall, the absolute risk of ADEs was low.

The investigational drug laropiprant has documented mechanisms of harm similar to the Cox-2 inhibitors and non-steroidal anti-inflammatory drugs to which it is related as well as many other potential adverse effects.8-14 Laropiprant with aspirin or clopidogrel induces a prolongation of bleeding time and an inhibitory effect on platelet aggregation ex vivo in healthy subjects and in patients with dyslipidemia.13 Stimulation of the prostaglandin D receptors as well metabolites of prostaglandin D2 to prostaglandin J 2 must be considered as part of the beneficial effects of niacin and the propensity for flushing which may be beneficial.14-27

In a recent meta-analysis of niacin-CHD studies, definitive benefit from niacin was demonstrated for CVD and CHD.28 This included eleven trials of 9,959 patients showing a reduction in composite endpoints 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 CVD outcomes; thus, niacin's reduction in CVD events may occur through a mechanism not reflected by changes in HDL or other lipid parameters.29-33 Niacin use over three years increased glucose levels by 5 mg % compared to placebo. There was no increased DM risk.34 Niacin significantly reduced CHD progression and stenosis
and other major CV events in 407 subjects in other major clinical trials, including FATS, HATS, AFREGS and CPC clinical trials. Also, analysis of the AIM HIGH trial by Guyton et al indicated a CV benefit by niacin in patients with baseline HDL < 32 mg/dl and triglyceride > 200 mg/dl (American Heart Association 2012 Scientific Sessions. November 3-7, 2012; Los Angeles, California). The data from HPS 2 THRIVE does not support harm resulting from the addition of ERNL alone. The data from previous studies as well as the improvement in revascularization procedures in HPS2-THRIVE support CV benefit of ERNL as monotherapy and as additive therapy with statins and other lipid-lowering agents.

**Conclusion & Summary of Major Points**

1. Niacin remains an efficacious agent for the treatment of dyslipidemia and prevention of CVD as single therapy, and with statins and other lipid-lowering agents with a relatively low side effect profile. Neither the HPS2-THRIVE nor the AIM HIGH studies provide any convincing evidence against the use of niacin in the appropriate clinical situation.

2. The vast majority of clinical trials with niacin alone or niacin with other anti-lipid agents show significant reductions in CVD, CHD and carotid atherosclerosis.

3. In patients not taking statins or those with high LDL levels at baseline (over about 85 mg/dl), high TG over 200 mg/dl and HDL-C < 32 mg/dl, HPS2-THRIVE study results are not likely to be applicable.

4. The addition of laropiprant may well have caused harm in the treatment arm, and the conclusions relating to both safety and efficacy cannot be attributed to niacin alone.

5. The available evidence strongly suggests that individuals who are not adequately treated on a statin medication alone can safely benefit from niacin’s additive effect on LDL reduction, LDL particle number reduction, increase in LDL size, increase in HDL, HDL 2b, HDL particle number, HDL function, reverse cholesterol transport and triglyceride reduction.

6. Patients with CVD and dyslipidemia with HDL < 32 mg/dl and triglyceride > 200 mg/dl may benefit from extended-release niacin added to intensive statin based LDL-C lowering therapy.

7. Niacin may have non-lipoprotein actions that are clinically important to prevent and treat CVD and CHD.


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Citations to literature:


Otvos JD. The surprising AIM-HIGH results are not surprising when viewed through a particle lens. *J Clin Lipidol.* 2011;5(5):368-70


34. Phan BA, Muñoz L, Shadzi P, Isquith D, Triller M, Brown BG, Zhao XQ Effects of niacin on glucose levels, coronary stenosis progression, and clinical events in subjects with normal baseline glucose levels (<100 mg/dl): a combined analysis of the Familial Atherosclerosis Treatment Study (FATS), HDL-Atherosclerosis Treatment Study (HATS), Armed Forces Regression Study (AFREGS), and Carotid Plaque Composition by MRI during lipid-lowering (CPC) study. *Am J Cardiol.* 2013;111(3):352-5