

## Niacin: Throwing the baby out with the bathwater?

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Headlines March 15, 2013:

**HPS2-THRIVE: Randomized placebo-controlled trial of ER niacin and laropiprant.**

**American College Cardiology:  
“HPS2-THRIVE May Signal the End for Niacin”**

**HPS2-THRIVE study chairman, Dr. Rory Collins, responded to a question in the press conference:  
“To the question is niacin dead? Well, it’s not healthy!”**

**Dr Jane Armitage (Oxford University, UK) said the results of the study are clear, and “in light of these findings the role of extended-release niacin for the prevention of cardiovascular disease should be reconsidered.”**

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HPS2-THRIVE: 25,673 high risk patients were randomized to either placebo or Tredaptive (extended-release niacin plus laropiprant -an anti-flushing agent) in addition to background therapy with simvastatin or simvastatin/ezetimibe (Vytorin). Baseline demographics – 83% men, mean age 64.9 years, 78% with coronary disease (CAD), 32% with cerebrovascular disease (CVD), 13% with peripheral arterial disease (PAD), and 32% with diabetes (DM). This was a 4 year trial.

Importantly, the baseline (prior to treatment) lipids were optimal in both arms – TC/HDL was 2.9 mg/dL. In the treatment arm (ER Niacin/Laropiprant – ERN/LRPT) LDL was reduced on

average 10mg/dL, HDL increased 6 mg/dL at one year and 4 years and Triglycerides were reduced on average of 33mg/dL. The typical, slow steady rise of HDL (“niacin creep”) historically noted with ER Niacin was not observed in this trial. The lipid improvement observed would have taken the TC/HDL from 2.9 to ~2.5. We would not anticipate any significant CV risk reduction when that ratio goes from ‘optimal’ to ‘optimal’. Interestingly, coronary revascularization was significantly reduced in the ERN/LRPT arm [0.89 (0.80-0.99) p=0.04]. This raises the possibility that the ERN/LRPT arm may have respectfully improved the reverse cholesterol transport pathway. We anticipate more information on this when the HPS2-THRIVE is published.

We must reflect upon the high residual risk in BOTH study arms. At the end of the four year follow-up, 15% of the statin patients suffered CV events while 14.5% of the ERN/LRPT patients suffered CV events, leaving substantial risk of a CV event in each group (certainly, a percentage of risk which would qualify as “high risk”). Because cholesterol was optimally controlled in both arms according to the most predictive measurement TC/HDL, the persistent high risk for a CV event is compatible with inflammation as causal as opposed to cholesterol. There are numerous potential drivers of arterial inflammation that include oral health issues, auto-immune issues, insulin resistance, psychosocial issues, sleep disturbances, nicotine use, lifestyle issues with physical activity and diet, and genetically driven risk. At this point in time, we have no details from the study

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elucidating these pathologies.

This is a trial of a new drug called Laropiprant, not a trial testing Niacin ER. It is important to examine the historical perspective of Laropiprant and its potential role in mitigating the most valuable effects of Niacin ER. Due to Niacin's clinical challenge of tolerability, Merck developed an anti-flushing product to combine with ER-Niacin to improve tolerability in 2007. We (Bale/Doneen) questioned this approach on 3/7/2008 with a public statement challenging the concept that the 'new' Merck investigational product which was a prostaglandin D2 (PD2) receptor antagonist designed to reduce flushing by blocking the DP1 receptor. We recognized that ER-Niacin (in its true form) increases levels of PD2 and that one of its metabolites is 15-deoxyprostaglandin J2 which is one of the most potent endogenous ligands of PPAR-gamma. Benefits of stimulating PPAR-gamma are numerous and very favorable for reducing CV risk. Some of these benefits include: reduction of arterial inflammation, improvement of endothelial function, decreasing the prothrombotic state, enhancement of the quality of HDL, reduction in BP, reducing insulin resistance and improvement in glycemic control. We were pleased that the FDA shared our concern about blocking one of the main receptors for PD2. The FDA failed to approve Merck's 'new' anti-flushing product due to safety reasons.

To understand the full disclosure of this trial, we must articulate the mechanisms of Laropiprant and how it can block health driven endogenous pathways. Laropiprant blocks the DP-1 receptor in order to enhance the tolerability of niacin by blocking the skin flush caused by Niacin (Vit. B3). Unfortunately, the dermal response caused by Niacin is more complex than this single pathway and involves mechanisms of macrophages and platelets. Therefore, we would not expect this drug to mitigate all the dermal issues from niacin.

Knowing that Laropiprant blocks the DP-1 pathway, it is important to appreciate the value of stimulating this pathway as it relates to vascular wellness and inflammation. We can then appreciate the side-effects witnessed in this trial which were unique to Laropiprant and have not been demonstrated with ER-Niacin trials. There are numerous health benefits as a consequence of stimulating DP-1. Stimulation

of DP-1 provides anti-inflammatory effects in asthma, dilatory effects for the bronchial tree and penis, enhancement of sleep, neuroprotection for the brain and potential enhancement of insulin sensitivity. All of the forementioned benefits would, of course, be lost with the administration of Laropiprant.

In addition to blocking DP1, it is logical to assume Laropiprant via blocking one of the main receptors for PGD2 would increase the plasma levels of PGD2. This consequence could have several adverse effects. PGD2 has immunosuppressive effects in viral infections. In mice PGD2 caused diminished viral T-cell response in lung tissue. In addition, one would assume greater interaction with the other known receptor for PGD2 which is the DP-2 receptor. Stimulation of DP-2 appears to cause pro-inflammatory effects! It is unknown how increased levels of PGD2 and the blockage of DP-1 along with greater stimulation of DP-2 might affect the levels of various metabolites. In particular, the known ligand for PPAR gamma 15 deoxyPGJ2. It is conceivable that the production and or mechanism by which 15 deoxyPGJ2 stimulates PPAR gamma could be adversely affected. Also, the drug Laropiprant has been shown to antagonize (block) the TP receptor which mediates the activation of thromboxane A2 which plays a key role in platelet activation. It would be anticipated that its use would increase hemorrhagic issues.

As discussed in the earlier paragraph, Niacin's ability to turn on PPAR-gamma provides much of its anti-inflammatory benefits. It is of great concern that Laropiprant may affect levels of 15 deoxy-PGJ2 which in turn would limit the PPAR-gamma expression necessary to deliver Niacin's vascular benefits such as the reverse cholesterol benefit of HDL, endothelial protection, and reducing the escape of albumin through the endothelium. Lastly, PPAR-gamma is critical in insulin sensitivity and, if blocked, we would expect problems with insulin resistance and glucose elevations.

Taking all of the potential interactions into account with laropiprant which include defects in virus-specific T-cell responses, decreases bronchial dilatation, increased inflammation, inhibition of platelet aggregation, increased stimulation of DP2 receptor which leads to heightened inflammation and reduced the stimulation of PPAR gamma, we

should not be surprised by the side effects noted in this trial. Diabetic complications increased 3.7%, new onset diabetes increased 1.8%, infections (mainly lower respiratory) by 1.4%, gastrointestinal 1% increase, heart failure 0.4%, bleeding 0.7% and skin 0.3%. It is important to point out that major hyperglycemic problems were increased 3 fold and any diabetic complications were up by 55% leading to the halting of this trial at 3.9 years. Comparatively and importantly, the AIM-HIGH trial (similar in demographics and time) did not show ANY increase in new onset Diabetes with ER-Niacin. Also – the Diabetes Prevention Project demonstrated that patients with hyperglycemia received more benefit with ER-Niacin than their non-hyperglycemic counterparts.

The HPS2-Thrive was halted due to serious adverse events (SAEs) which should have been expected with the use of this experimental drug intended to improve the tolerability of niacin when, in fact, laropiprant likely removed the ability of niacin to perform its most valuable effects of vascular impact and exposed pathways that led to the negative side-effects observed in this trial. Unfortunately, ER-Niacin is taking the blame

for something that is beyond its control. The investigators noted that the significant excesses of serious adverse events in the ERN/LP arm were due to known and unrecognized side-effects of niacin. The known side-effects would have been only the increased hepatic and myopathy events. The SAEs involving diabetic complications, new onset diabetes, infection and GI bleeding could very well have been the result of Laropiprant. It is amazing there was even one significant benefit in the ERN/LP arm; namely reduced need for revascularization which many patients would find very appealing. Conclusions about ER-Niacin CAN NOT be derived from this trial. Rather, discerning that blocking the DP1 pathway in order to prevent the flushing from ER-Niacin is not a good idea.

This was a very expensive trial to reiterate the fact that the flushing from Niacin probably isn't a bad thing and that blocking it with an experimental product can mitigate the very reason why ER-Niacin is necessary. The HSP2-Thrive DOES NOT deter our use of ER-Niacin in patients who are statin intolerant, are not at TC/HDL goal of <3.0, have lipo(a), have insulin resistant dyslipidemia or have persistent arterial inflammation.



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References available on website [www.baldoneen.com](http://www.baldoneen.com)*

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