

'If Not Dead, Not Healthy': Niacin Full Results in HPS2-THRIVE Aired at ACC

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Drug & Reference Information

Primary and Secondary Prevention of Coronary Artery Disease

SAN FRANCISCO, California — Full results of the [Heart Protection Study 2-Treatment of HDL to Reduce the Incidence of Vascular Events \(HPS2-THRIVE\)](#) study, a large randomized trial testing the use of extended-release **niacin** and the antilflushing agent **laropiprant** for the reduction of major vascular events, kicked off the [American College of Cardiology \(ACC\) 2013 Scientific Sessions](#) here today, with investigators presenting the negative trial to attendees and the media.

As reported previously by [heartwire](#) , the combination of niacin and laropiprant in addition to statin therapy did not significantly reduce the risk of major vascular events in patients with well-controlled LDL-cholesterol levels. The failure of niacin in the 25 673-patient HPS2-THRIVE study was first announced in late December by Merck, with the company stating it no longer had any plans to take the drug before the US **Food and Drug Administration** (FDA) to gain approval.

Regarding the primary end point, the combination of coronary death, nonfatal MI, stroke, or coronary revascularization occurred in 15.0% of patients in the control arm and 14.5% of patients in the niacin/laropiprant arm, a difference that was not statistically significant. Regarding the individual components of the primary end point, there was a 10% reduction in the risk of coronary revascularization with niacin and laropiprant that just reached statistical significance. There was no significant effect of niacin/laropiprant on any of the other components of the primary end point.

Equally important, the researchers also documented a significantly increased risk of adverse events with niacin/laropiprant, with approximately 30 adverse events per 1000 treated patients. In the niacin arm, there was a significant 3.7% absolute excess risk of diabetic complications and a significant 1.8% excess risk of new-onset diabetes. In addition, treatment with niacin resulted in an excess 1.4% higher risk of infection and a 0.7% higher risk of bleeding, including an increased risk of hemorrhagic stroke.

Speaking to the media during a morning press conference announcing the results, lead investigator **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." She added that a negative study, even a large and expensive study such as HPS2-THRIVE, is beneficial, as it's just as important to find out whether a drug doesn't work.

Dr Rory Collins (Oxford University, UK), the chair of the HPS2-THRIVE study, addressed the ever-popular "Is niacin dead?" question, telling the media if the drug isn't yet dead it certainly isn't healthy. The negative result from this major study follows the disappointing results of the **National Heart, Lung, and Blood Institute (NHLBI)**–sponsored **Atherothrombosis Intervention in Metabolic Syndrome with Low HDL Cholesterol/High Triglyceride and Impact on Global Health Outcomes (AIM-HIGH)** study, a trial that was halted early after showing no benefit of niacin when given in addition to statin therapy.

Given the side effects of niacin and the risk of serious adverse events, including a 25% increased risk of new-onset diabetes and the difficulties in controlling glucose level when patients are on the drug, Collins said the evidence clearly suggests no benefit of niacin therapy given the risks. Physicians need to question whether or not there is a good reason to be using the treatment in any particular patient when there are alternative ways of lowering LDL cholesterol and there is no hard evidence suggesting that raising HDL cholesterol has any clinical benefit.

Patients Well Controlled, Different From Real World

Not everybody was completely sold on the results of HPS2-THRIVE, however. **Dr Steven Nissen** (Cleveland Clinic, OH) told **heartwire** that he would like to review the published paper before making firm conclusions. Nissen said he does not currently start new patients on niacin but he hasn't taken any patients off the drug, either.

"I have a patient who had her first MI when she was 30 years old," said Nissen. "She had bypass surgery and nobody had been able to control her LDL cholesterol. I put her on high-dose **rosuvastatin** and her LDL was still too high. Then I added **ezetimibe**, and her LDL went down some more. And then I added niacin and **colesevelam**, and I got her LDL cholesterol down below 100. She hasn't had an event, and that was six years ago. Now, am I going to take her off niacin?"

In HPS2-THRIVE, the patient population experienced only a 6-mg/dL increase in HDL-cholesterol levels, or approximately a 14% increase from the 44-mg/dL baseline level. This increase might not have been sufficient to reduce clinical events, especially when the baseline LDL-cholesterol level was an impressively low at 63 mg/dL, said Nissen. Moreover, the baseline HDL cholesterol is high enough that almost no clinician would start a patient on the drug, but for many that do, HDL increases of 25% to 30% are not uncommon, he added.

Why Aren't LDL-Cholesterol Levels Controlled?

To **heartwire**, Collins said that while there are some patients who benefit from the extra downward push in LDL-cholesterol levels, the vast majority of patients can be controlled with intensive statin therapy. He stressed that niacin is a notoriously difficult drug to take, with side effects like flushing that "make people glow in the dark," and the serious adverse events are another matter entirely. These serious adverse events that led to the hospitalization are on top of the side effects.

"For the patient without well-controlled LDL cholesterol, my first thought is, why isn't the LDL-C well controlled, given that we have statins available to us?" asked Collins. "There is a lot of anxiety generated about side effects about statins that aren't seen in the randomized clinical trials. So I think there is a tendency to encourage

people not to use statins, even though we have very good tolerability data."

Instead of thinking about niacin, physicians should be titrating patients to higher and higher doses of statins in order to achieve low levels of LDL cholesterol. "I think ensuring that people take statins, reassuring them with the evidence showing very good tolerability, and only then considering other ways of lowering LDL cholesterol with drugs that are well tolerated and have a good side-effect profile, such as ezetimibe or the [bile-acid] resins."

Regarding the trial design, Nissen told the media he believes the Oxford investigators made some critical mistakes when designing the trial, particularly with regard to the patient population studied.

"They enrolled 10 000 patients in China, but if you talk to any clinician they will tell you that Asiatic patients tend not to tolerate either niacin or high-dose statin therapy," said Nissen. "And of course that's exactly what they saw. This was a mistake. This is not the target population the drug was being developed for, but it saved money and it allowed for a larger enrollment." In addition, Nissen said the revascularization end point was statistically significant, even though it is difficult to interpret the significance of this reduction, given that clinical events were not adjudicated by a central committee (clinical events were adjudicated by the investigating sites).