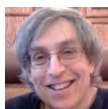


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New Evidence Fuels Concerns About The Safety Of Niacin

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The string of failures— for HDL therapies in general and for niacin in particular— continues unabated.

The publication of the main results of the HPS2-THRIVE trial, along with new information from the AIM-HIGH trial, provide no evidence of a beneficial effect for niacin but do fuel concerns that it may cause serious adverse effects.

In HPS2-THRIVE, published in the *New England Journal of Medicine* (<http://www.nejm.org/doi/full/10.1056/NEJMoa1300955>), the combination of extended-release niacin and laropiprant (Tredaptive, Merck) was compared to placebo in more than

25,000 high risk patients already receiving statin therapy. Patients in the treatment group had significant reductions in LDL cholesterol (10 mg/dL), significant increases in HDL (6 mg/dL), and significant reductions in triglycerides (33 mg/dL). But there was no difference in the rate of major vascular events (13.2% for niacin-laropiprant versus 13.7% for placebo, RR 0.96, CI 0.90 – 1.03, p=0.29). There was also no significant difference in an exploratory analysis of patients with low HDL and high triglyceride levels who might be expected to benefit the most from niacin therapy.

There were signs of harm associated with niacin-laropiprant. Serious adverse events occurred more often in the combination group (55.6% versus 52.7%, p < 0.001). Diabetes complications were especially concerning. Among patients who had diabetes at the start of the trial, serious complications related to diabetes occurred in 11.1% of patients in the treatment group versus 7.5% of patients in the control group, a 55% increase. Among patients who did not have diabetes at the start of the trial, there was a 32% increase in the diagnosis of diabetes in the treatment group (5.7% versus 4.3%).

Niacin therapy was also associated with significant increases in infections (8% versus 6.6%, p < .001) and bleeding (2.5% versus 1.9%, p < 0.001). These

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findings came as a surprise to the investigators. There were also significant increases in other, previously known adverse effects of niacin, including gastrointestinal, musculoskeletal, and skin-related adverse events.

The troubling findings of HPS2-THRIVE were not contradicted, and were at least partially confirmed, by a new analysis from the AIM-HIGH trial published in the correspondence section of *NEJM* (<http://www.nejm.org/doi/full/10.1056/NEJMe1406410>). The trial randomized more than 3,400 patients with stable coronary artery disease to extended-release niacin (Niaspan, AbbVie) or placebo **in addition to simvastatin and, if needed, ezetimibe**. The trial was stopped early for lack of efficacy.



In their new analysis the AIM-HIGH investigators report a significant increase in serious infections (8.1% versus 5.8%, $p=0.008$) and a nonsignificant increase in serious bleeding events (3.4% versus 2.9%, $p=0.36$). But there was also a significant increase in all bleeding events in AIM-HIGH (10.1% versus 8.1%, $p=0.04$).

The AIM-HIGH authors were reluctant to conclude that the new adverse effects seen in HPS2-THRIVE were also a genuine problem in AIM-HIGH. The findings, they wrote, “should be considered to be provisional and exploratory.” But the HPS2-THRIVE authors were more certain:

“ In light of the consistency of the results with those from previous trials of niacin alone, we believe that the findings from HPS2-THRIVE are likely to be generalizable to all high-dose niacin formulations. Although niacin might still be relevant for particular patient groups (e.g., patients at high risk for vascular events who have high levels of LDL cholesterol), any potential benefits should be considered in the context of the observed hazards.

Much of the initial discussion about HPS2-THRIVE revolved around the relative importance of the niacin and laropiprant components of the drug. In an accompanying editorial (<http://www.nejm.org/doi/full/10.1056/NEJMe1406410>), Donald-Lloyd Jones writes that “the consistency of the overall findings with earlier trials of niacin alone suggest that niacin is the major problem.”

“ What now should we make of niacin and the HDL cholesterol causation hypothesis? On the basis of the weight of available evidence showing net clinical harm, niacin must be considered to have an unacceptable toxicity profile for the majority of patients, and it should not be used routinely.

The failure of the niacin trials, as well as other HDL-related trials, “lends further credence to the notion that HDL cholesterol is unlikely to be causal.”

Sanjay Kaul said that because the results of these trials have been known the lack of efficacy “is not surprising.” The safety findings, however, are “noteworthy.”

“ The increase in adverse events, including infections and bleeding, observed in HPS2-THRIVE likely represents an underestimate given that only about 50% of those screened were enrolled in the trial (one-third withdrawals on active drug). I do not agree with the AIM-HIGH investigators assertion that the significantly increased risk of infection and numerical excess in serious bleeding should be considered provisional and exploratory. AIM-HIGH, like most other lipid lowering trials, was powered for efficacy and not safety assessments. Lack of a significant difference in safety outcomes in inadequately powered studies should not be viewed as reassuring. Instead, safety should be assessed by examining the 95% CI and ruling out unacceptable harm. The difference in serious bleeding of 3.4% vs 2.9% results in a risk ratio of 1.19 (0.82, 1.73). In absence of any efficacy outcome benefit, I would argue that not being able to rule out a 73% increase in serious bleeding is unacceptable and points to an unfavorable benefit-risk balance. One has to also take into consideration that an absolute difference in the serious bleeding rate of 0.55% was observed in about 1/8th the number of patients enrolled in HPS2-THRIVE (difference in bleeding risk was 0.7%). Had AIM-HIGH enrolled as many patients as were enrolled in HPS2-THRIVE, this difference would have been statistically significant. If one were to count bleeding events of any severity in AIM-HIGH, the increase in risk would be statistically significant: 174 vs 137, risk ratio 1.25 (1.01, 1.55), p=0.04.

Bottom line, given the undesirable benefit-risk balance of extended release niacin, it is hard to make a case for it as frontline therapy in patients evaluated in these trials.

Another interesting observation is lack of efficacy in patients with mixed dyslipidemia (elevated TG and low HDL) in HPS2-THRIVE. In contrast, a beneficial effect was observed in AIM-HIGH. This could be related to different cutoffs for elevated TG or low HDL used in the 2 studies. Alternatively, the positive finding in AIM-HIGH might be spurious (false positive) given the overall null result!

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