Editorial

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Niacin: Not Dead Yet, But On Life Support

Let me begin by confirming unequivocally that I've long been one of the strongest and loudest advocates of using niacin in the treatment of dyslipidemia. I've been taking large doses of immediate-release niacin for more than 20 years, to the current tune of a whopping 5 grams a day. It's been nearly 2 decades since I penned a muscular editorial for the *Archives of Family Practice* entitled, "Why Aren't We Using More Niacin?" I've written similarly-haranguing editorials in this very journal you hold in your hands, aggressively advocating more widespread use of this seemingly-miraculous lipid-lowering therapy.

Why have I been so enthusiastic in my support of niacin? For starters, niacin does absolutely everything you could possibly ask of a lipid-lowering medication. It's clearly the most potent agent by far for raising high-density lipoprotein-cholesterol (HDL-C) levels, with typical increases routinely in the 20% to 35% range. Niacin also lowers triglycerides (TGs), although perhaps a bit less effectively than fibric acid derivatives (fibrates). Niacin also reduces elevated levels of low-density lipoprotein-cholesterol (LDL-C), although again the effect is quantitatively smaller than that of the statins, which are firmly established as the agents of choice to lower LDL-C levels. As an added benefit, niacin is the only lipid-lowering agent known to reduce levels of Lp(a), pronounced L-p little-a, an independent cardiovascular (CV) risk factor in some individuals—that is, assuming you don't count estrogen as a lipid-lowering agent.

The appeal of niacin was always more than just these favorable lipid effects. A credible body of evidence showed that niacin was more than just a pretty face; that it could actually improve the CV outcomes we all strive for. Niacin emerged as a front-runner in the first-ever randomized prospective trial of lipid-lowering therapy with the 10 year Coronary Drug Project, which began in 1965. Niacin and clofibrate were 2 of the original 5 contenders to even make it across the finish line in this primary prevention trial. Early on, d-thyroxine and 2 different estrogen doses were dropped because of significant toxicity. The original study identified reductions of roughly 25% for both strokes and myocardial infarctions (MIs) in the subjects prescribed niacin; niacin did not demonstrate a mortality benefit at that stage. Then a subsequent analysis done 9 years after the end of the original trial showed a legacy reduction in mortality of 11% for those who had been in the niacin wing of the study.

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In the 1980s and 1990s, similarly-encouraging effects of combination statin and niacin therapy were reported using surrogate endpoints such as carotid intima-medial thickness. Then in 2001, the **H**DL-**A**therosclerosis **T**reatment **S**tudy (HATS) suggested a phenomenal 90% reduction in CV events in subjects treated with a combination of niacin and a statin, compared with placebo, although the sample size was quantitatively small, because the focus of the trial was again on plaque burden.

Nonetheless, the HATS results were so impressive that an NIH-sponsored study called **A**therothrombosis **I**ntervention in **M**etabolic Syndrome With Low HDL/**H**igh Triglycerides: **I**mpact on **G**lobal **H**ealth Outcomes study (AIM-HIGH) was organized to compare niacin, plus simvastatin therapy, with simvastatin alone in a high-risk population with low HDL-C levels. I was one of a large number of principal investigators who were recruited across the country to conduct this trial. All the subjects received enough simvastatin to drive their LDL-C levels down to the range of 40 mg/dL to 80 mg/dL, and then either a therapeutic dose of niacin in the range of 1,500 g to 2,000 g a day as tolerated or a tiny nontherapeutic niacin dose of 50 mg to 100 mg a day. The reason for randomizing half the subjects to the tiny dose was to ensure that all subjects would flush (flushing isn't really dose related), so that neither the subjects nor the investigators would know which group a given subject had been randomized to.

The plan was to follow the subjects for an average of 5 years to determine whether there was a difference in the rate of CV events between the 2 groups. As with most such studies, before the trial began criteria were developed for stopping the study early if one wing performed significantly better than the other, or for so-called futility, if it became statistically unlikely that one wing would eventually prove superior to the other. Like many investigators, I'm sure, I struggled to main-

tain equipoise, a fancy term meaning that the investigators should remain completely open-minded that any of the possible outcomes might indeed occur. If there was no equipoise, and we all thought that we actually knew beforehand which wing would prove superior, such a study would be unethical to conduct; we should simply place all patients on the better treatment.

In spite of my struggle to maintain equipoise, I was truly shocked and dismayed when the AIM-HIGH trial was stopped in early spring 2011 with more than 1 year to go. The primary reason for stopping was futility, although there was also a small increase in the number of cerebrovascular events in those on the niacin, plus statin therapy. Because it was likely to simply be a reflection of the play of chance, the latter finding didn't bother me much. However, the futility bit really floored me: Does niacin really add NOTHING on top of statin therapy?

So I began the frustrating mental exercise of trying to explain away these findings that seemed to indict my old favorite so convincingly. I took small comfort in noting that at the time the study was stopped the final difference in HDL-C levels between the 2 groups was only a little more than 4 mg/dL. This happened because the HDL-C levels rose in both groups from baseline, probably because of a phenomenon known as regression to the mean. This means the low baseline levels at the beginning of the trial probably reflected the very low end of the range in which they normally fluctuated and, hence, were likely to increase regardless of the assigned therapy. So maybe the subjects in the therapeutic wing really didn't take as much niacin as they were supposed to, which would be easy to believe because of the flushing issue. Against this theory was the significant difference in TG levels between the 2 groups, which suggests that there really was a meaningful difference in the level of niacin exposure. One unhappy but plausible way to look at the data overall is to conclude that statin therapy is so effective at reducing CV events that there is simply no room or any need for an additional lipid-lowering intervention, even one as seemingly promising as niacin.

The HPS2-THRIVE study compares a statin alone with a statin, plus a combination drug containing both niacin and laropiprant, an investigational drug that uses laropiprant, a prostaglandin inhibitor, to blunt the niacin-induced flushing.

This conclusion would, indeed, be a very bitter pill for me to swallow, no pun intended. However, hope springs eternal, and I have reason to hope. A much larger trial than AIM-HIGH is already well underway, testing a very similar hypothesis. The **T**reatment of **H**DL to **R**educe the **I**ncidence of **V**ascular **E**vents (HPS2-THRIVE) study is being conducted by the University of Oxford under the auspices of the British government, which sponsored the original **H**eart **P**rotection **S**tudy (HPS) over a decade go, a trial that established the efficacy of statins in high-risk subjects regardless of the starting LDL-C level. The HPS2-THRIVE study compares a statin alone with a statin, plus a combination drug containing both niacin and laropiprant, an investigational drug that uses laropiprant, a prostaglandin inhibitor, to blunt the niacin-induced flushing.

This trial began in 2007 and will conclude in 2013, assuming that it is not stopped early like AIM-HIGH. More than 25,000 subjects have been enrolled compared with just 3,400 subjects in AIM-HIGH. So this trial really is the big enchilada that will make or break niacin once and for all. The bottom line is that niacin is not quite dead yet as a lipid-lowering agent, and there is still room for diehard fans like me to keep hoping for a turnaround in its fortunes. However, the reality is that niacin is currently on life support as a lipid-lowering agent, at least in patients who can tolerate a statin, with 1 remaining opportunity to be saved by our able colleagues across the pond. ●

Author disclosure

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