

Niacin's effect on cardiovascular risk: Have we finally learned our lesson?

RANDOMIZED CONTROLLED TRIALS have unequivocally shown that lowering levels of low-density lipoprotein cholesterol (LDL-C) with statins reduces the rate of cardiovascular events.¹⁻³ Yet many patients still have heart attacks even though they are on statins, so the search continues for other agents to lower cardiovascular risk.⁴

Niacin has been used for its lipid-modifying effects for more than 50 years. In addition to being the most potent agent for raising the level of high-density lipoprotein cholesterol (HDL-C), niacin decreases the atherogenic lipids triglyceride, LDL-C, and lipoprotein (a)⁵ and can be very effective in treating mixed dyslipidemias such as hypertriglyceridemia and low HDL-C. This is particularly important for the challenging patients seen in preventive cardiology clinics.

In 1986, before statins were available, the Coronary Drug Project⁶ showed that immediate-release forms of niacin lowered the rates of nonfatal myocardial infarction and long-term mortality. Later, imaging studies demonstrated that niacin slows progression of carotid intima-medial thickness and coronary atherosclerosis.⁷⁻⁹ Furthermore, meta-analyses of these studies suggest cardiovascular benefit for patients at high vascular risk.¹⁰

However, niacin is difficult to use in clinical practice. The near-ubiquitous experience of flushing has limited our ability to give doses

high enough to modify plasma lipid levels and rates of clinical events.

To try to mitigate this side effect, investigators developed extended-release formulations and agents such as laropiprant, a chemical antagonist of the interaction between niacin and epidermal prostanoid receptors implicated as the mechanism behind flushing. Although these innovations do not eliminate flushing, they reduce it, and thus have prompted hopes of using niacin more widely in statin-treated patients. However, whether widespread use of niacin on a background of statin therapy would have an impact on cardiovascular events remained to be established.

■ WHAT WE HAVE LEARNED LATELY ABOUT NIACIN?

More-tolerable formulations of niacin prompted interest in its potential to lower the residual cardiovascular risk observed in statin-treated patients. Two large clinical trials attempted to determine its impact on cardiovascular events in the contemporary era.

The AIM-HIGH study

In the Atherothrombosis Intervention in Metabolic Syndrome With Low HDL/High Triglycerides: Impact on Global Health Outcomes (AIM-HIGH) study,¹¹ 3,414 patients at high vascular risk with low HDL-C were treated with niacin or placebo. The trial was stopped early because of no evidence of clinical benefit with niacin and because of concern about an increased risk of stroke, a finding ultimately not observed on a complete review of the data.

I reviewed the limitations of this study earlier in this journal.¹² The study was small, use

Flushing limits our ability to give doses of niacin high enough to modify lipid levels and rates of clinical events

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of low-dose niacin was allowed in the placebo group, and physicians could treat high LDL-C as they saw fit during the study, so that more patients in the placebo group received high-dose statin therapy and ezetimibe. All of this likely limited the study's ability to measure the clinical impact of niacin. As a result, this study was not a pure evaluation of the benefits of niacin vs placebo in addition to standard medical therapy. Hope remained that a much larger study with greater statistical power and a simpler design would provide a definitive answer.

HPS2-THRIVE

The Heart Protection Study 2—Treatment of HDL to Reduce the Incidence of Vascular Events (HPS2-THRIVE), with more than 40,000 patients, was the largest cardiovascular outcomes trial of lipid-modifying therapy to date.¹³ Its purpose was to determine whether extended-release niacin plus the prostanoid receptor antagonist laropiprant would reduce the rate of cardiovascular events in patients with clinically established vascular disease.

Patients age 50 to 80 with a history of myocardial infarction, ischemic stroke, transient ischemic attack, peripheral arterial disease, or diabetes with other forms of coronary heart disease received a standardized LDL-C-lowering regimen with simvastatin 40 mg daily, with or without ezetimibe 10 mg daily, to achieve a total cholesterol target of 135 mg/dL or below. All were treated with extended-release niacin 2 g daily plus laropiprant 40 mg daily for 1 month to assess compliance. They were then randomized to treatment with extended-release niacin 2 g plus laropiprant 40 mg or placebo daily. At baseline, the mean lipid values were LDL-C 63 mg/dL, HDL-C 44 mg/dL, and triglyceride 125 mg/dL.

Before the end of the trial, the investigators reported a high rate of myopathy-related adverse events in the niacin group, particularly in Chinese patients.¹³ This contributed to a high dropout rate in the niacin group, in which one quarter of patients stopped taking the study drug.

During the study, niacin lowered the LDL-C level by a mean of 10 mg/dL, lowered triglycerides by 33 mg/dL, and raised HDL-C by 6 mg/dL. On the basis of previous observational studies and randomized clinical trials,

the authors calculated that such lipid changes should translate to a 10% to 15% reduction in vascular events. However, no reduction was observed in the primary end point of major vascular events, which included nonfatal myocardial infarction, coronary death, any nonfatal or fatal stroke, and any arterial revascularization, including amputation. The rates were 15% in the placebo group vs 14.5% in the niacin group ($P = .96$).

A statistically significant 10% reduction in the rate of arterial revascularization was observed in the niacin group, perhaps consistent with earlier observations of an antiatherosclerotic effect.

Subgroup analyses, while always to be interpreted with caution, also provide some interesting findings for consideration. A significant interaction was observed between treatment and baseline LDL-C, with those in the highest LDL-C tertile (> 77 mg/dL) demonstrating a potential reduction in the primary end point with niacin treatment. In addition, a trend toward potential benefit with niacin in patients in Europe, but not in China, was also observed; however, this just failed to meet statistical significance.

HPS2-THRIVE provided important information about the safety of extended-release niacin in combination with laropiprant. The niacin group experienced higher rates not only of myopathy but also of diabetic complications, new diagnosis of diabetes, serious infections, and bleeding. Whether these observations were related to niacin or to laropiprant is unknown. In fact, recent reports suggest laropiprant has adverse effects that may have substantially reduced the potential benefits of niacin.

The overall conclusion of HPS2-THRIVE was that there was no widespread clinical benefit from the combination of niacin and laropiprant in statin-treated patients with vascular disease, and that there was a potential increase in adverse events. Accordingly, the combination treatment will not be integrated into clinical practice.

■ WHERE DO WE GO FROM HERE?

Despite their limitations, these two large trials suggest that niacin does not reduce cardiovascular risk in patients already receiving a statin.

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Might some subgroups be more likely to benefit from niacin? The finding of potential benefit in patients with higher baseline LDL-C suggests this may be true. At baseline, the HPS2-THRIVE patients had very good LDL-C control and had HDL-C levels within the normal range, not necessarily reflecting the patients we see in daily practice, who require more effective reductions in vascular risk. Furthermore, failure of both fibrates and niacin to reduce risk may have reflected the attempt to study these agents in broad patient populations as opposed to focusing on specific cohorts, such as patients with mixed dyslipidemia, for which there is suggestion of benefit.¹⁴ It seems unlikely that such a study will be performed in a clinical setting in which niacin may be of greater utility. The experience of adverse events would appear to make that a certainty.

For now, niacin will remain useful in lipid

clinics for managing refractory dyslipidemia. Specifically, its ability to lower triglyceride and lipoprotein (a) and to raise HDL-C will continue to be of interest in the clinical management of patients and in the formulation of treatment guidelines. Another reason to use it is to lower LDL-C in patients who cannot tolerate statins. However, there is currently no evidence from randomized controlled trials to support its broader use.

While registry information could provide some sense of real-world effects of niacin's use, this is a suboptimal way to evaluate the potential efficacy of a therapy—randomized controlled trials are the gold standard. The major flaws of both of the large trials of niacin point out the need for thoughtful study design to avoid incorrectly dismissing potentially useful therapies. But for now, the renaissance of niacin as a means of lowering cardiovascular risk is only wishful thinking. ■

REFERENCES

1. Randomised trial of cholesterol lowering in 4444 patients with coronary heart disease: the Scandinavian Simvastatin Survival Study (4S). *Lancet* 1994; 344:1383–1389.
2. **Heart Protection Study Collaborative Group.** MRC/BHF Heart Protection Study of cholesterol lowering with simvastatin in 20,536 high-risk individuals: a randomised placebo-controlled trial. *Lancet* 2002; 360:7–22.
3. **Ridker PM, Danielson E, Fonseca FA, et al; JUPITER Study Group.** Rosuvastatin to prevent vascular events in men and women with elevated C-reactive protein. *N Engl J Med* 2008; 359:2195–2207.
4. **Libby P.** The forgotten majority: unfinished business in cardiovascular risk reduction. *J Am Coll Cardiol* 2005; 46:1225–1228.
5. **deLemos AS, Wolfe ML, Long CJ, Sivapackianathan R, Rader DJ.** Identification of genetic variants in endothelial lipase in persons with elevated high-density lipoprotein cholesterol. *Circulation* 2002; 106:1321–1326.
6. **Canner PL, Berge KG, Wenger NK, et al.** Fifteen year mortality in Coronary Drug Project patients: long-term benefit with niacin. *J Am Coll Cardiol* 1986; 8:1245–1255.
7. **Taylor AJ, Sullenberger LE, Lee HJ, Lee JK, Grace KA.** Arterial Biology for the Investigation of the Treatment Effects of Reducing Cholesterol (ARBITER) 2: a double-blind, placebo-controlled study of extended-release niacin on atherosclerosis progression in secondary prevention patients treated with statins. *Circulation* 2004; 110:3512–3517.
8. **Taylor AJ, Lee HJ, Sullenberger LE.** The effect of 24 months of combination statin and extended-release niacin on carotid intima-media thickness: ARBITER 3. *Curr Med Res Opin* 2006; 22:2243–2250.
9. **Brown BG, Zhao XQ, Chait A, et al.** Simvastatin and niacin, antioxidant vitamins, or the combination for the prevention of coronary disease. *N Engl J Med* 2001; 345:1583–1592.
10. **Lavigne PM, Karas RH.** The current state of niacin in cardiovascular disease prevention: a systematic review and meta-regression. *J Am Coll Cardiol* 2013; 61:440–446.
11. **AIM-HIGH Investigators; Boden WE, Probstfield JL, Anderson T, et al.** Niacin in patients with low HDL cholesterol levels receiving intensive statin therapy. *N Engl J Med* 2011; 365:2255–2267.
12. **Nicholls SJ.** Is niacin ineffective? Or did AIM-HIGH miss its target? *Cleve Clin J Med* 2012; 79:38–43.
13. **HPS2-THRIVE Collaborative Group.** HPS2-THRIVE randomized placebo-controlled trial in 25 673 high-risk patients of ER niacin/laropiprant: trial design, pre-specified muscle and liver outcomes, and reasons for stopping study treatment. *Eur Heart J* 2013; 34:1279–1291.
14. **Jun M, Foote C, Lv J, et al.** Effects of fibrates on cardiovascular outcomes: a systematic review and meta-analysis. *Lancet* 2010; 375:1875–1884.

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