

## EDITORIALS



## Niacin and HDL Cholesterol — Time to Face Facts

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For the past four decades, the concentration of cholesterol contained in high-density lipoprotein (HDL) particles has been a major focus of research and a target for potential prevention opportunities. Data from observational epidemiologic studies have consistently shown a strong inverse association between HDL cholesterol concentration and the risk of coronary heart disease that is linear and graded, at least through the majority of the HDL cholesterol distribution encountered in the general population.<sup>1</sup> But clinical trials have yet to show a causal role for HDL cholesterol or to deliver the longed-for outcome of reducing the risk of coronary heart disease and the broader cardiovascular risk by raising HDL cholesterol levels specifically.

Niacin, or nicotinic acid (also known as vitamin B<sub>3</sub>), is an essential human nutrient that increases HDL cholesterol concentrations by means of a variety of mechanisms affecting apolipoprotein A1, cholesterol ester transfer protein, and ATP-binding cassette transporter A1, all of which appear to enhance reverse cholesterol transport. Other effects of niacin also lead to modest reductions in low-density lipoprotein (LDL) cholesterol concentrations and more substantial reductions in triglyceride levels, all of which might be expected to have salutary effects on the risk of coronary heart disease. The earliest trial to test immediate-release niacin, the Coronary Drug Project, suggested that this might be the case among middle-aged men with coronary heart disease and marked hypercholesterolemia.<sup>2</sup>

In this issue of the *Journal*, the Heart Protection Study 2—Treatment of HDL to Reduce the Incidence of Vascular Events (HPS2-THRIVE) investigators present data from the latest and

largest trial to examine a strategy of raising the HDL cholesterol level to reduce cardiovascular risk.<sup>3</sup> This rigorously performed randomized, controlled trial enrolled 25,673 adults, 50 to 80 years of age, with clinically manifest cardiovascular disease and addressed the clinically relevant question of whether extended-release niacin combined with laropiprant, a new agent that helps prevent flushing, could reduce major vascular events, as compared with placebo. Background statin-based therapy was standardized before randomization, resulting in a mean LDL cholesterol level of 63 mg per deciliter (1.63 mmol per liter) before study-drug treatment. During the trial, participants receiving niacin–laropiprant on average had an HDL cholesterol level that was 6 mg per deciliter (0.16 mmol per liter) higher, an LDL cholesterol level that was 10 mg per deciliter (0.26 mmol per liter) lower, and a triglyceride level that was 33 mg per deciliter (0.37 mmol per liter) lower than levels in those receiving placebo. Despite these favorable responses, over a median follow-up of nearly 4 years there was no significant reduction in the primary end point of major vascular events associated with niacin–laropiprant, with a rate ratio of 0.96 (95% confidence interval, 0.90 to 1.03). The lack of efficacy was uniform, with no substantive differences in response to therapy noted across the major prespecified subgroups.

Given this lack of efficacy, the most important and worrisome findings of HPS2-THRIVE were the adverse events associated with niacin–laropiprant. In addition to the expected skin-related adverse effects, there were significant and excess adverse events related to gastrointestinal, musculoskeletal, infectious, and bleeding complications, as well as substantial excess ad-

verse events related to loss of glycemic control among persons with diabetes and new-onset diabetes among persons without diabetes at baseline. Of great concern was a 9% increase in the risk of death (number needed to harm, 200) associated with niacin-laropiprant that was of borderline statistical significance ( $P=0.08$ ).

Also in this issue of the *Journal*, further data are provided by Anderson et al.<sup>4</sup> regarding adverse events in the Atherothrombosis Intervention in Metabolic Syndrome with Low HDL/High Triglycerides: Impact on Global Health Outcomes (AIM-HIGH) trial,<sup>5</sup> which had examined the addition of extended-release niacin versus placebo to statin therapy in 3414 patients with stable atherosclerotic disease and a low HDL cholesterol level. The AIM-HIGH investigators had found no benefit in terms of a reduction in cardiovascular risk with niacin, but they also had observed excess adverse events including skin-related, gastrointestinal, glycemic, and other complications typically associated with niacin use.<sup>5</sup> The new data from the study by Anderson et al. suggest a significantly higher rate of infections and infestations among patients receiving niacin than among those receiving placebo, as well as a nonsignificantly higher rate of serious bleeding, in the AIM-HIGH trial, which was much smaller than HPS2-THRIVE.

It should be noted that the exhaustive systematic review of the literature performed by the recent American College of Cardiology–American Heart Association (ACC–AHA) cholesterol guideline panel identified many of these same niacin-related adverse events (in addition to excess atrial fibrillation). This assessment led to very limited and cautious recommendations regarding the use of niacin and extensive discussion of safety concerns in those guidelines.<sup>6</sup> Whereas some debate about the role of laropiprant in the excess adverse events observed in HPS2-THRIVE is warranted, the larger size of HPS2-THRIVE and 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. As suggested in the recent ACC–AHA

guidelines,<sup>6</sup> niacin may still have a role in patients at very high risk for cardiovascular events who truly have contraindications for taking statins (and other less-toxic drugs, such as bile-acid sequestrants) and who have a high LDL cholesterol level. Likewise, it might be considered as a fourth-line agent (after intensive lifestyle modification and use of fibric-acid derivatives and pharmaceutical-grade fish-oil preparations) for patients with severe hypertriglyceridemia, in whom we are trying to prevent pancreatitis.

The consistent findings of a lack of benefit of raising the HDL cholesterol level with the use of niacin when added to effective LDL cholesterol-lowering therapy with statins seriously undermine the hypothesis that HDL cholesterol is a causal risk factor. The failure (to date) of cholesteryl ester transfer protein inhibitors, such as torcetrapib and dalcetrapib, to show any reduction in cardiovascular risk despite the marked increases in the HDL cholesterol level associated with these drugs<sup>7,8</sup> lends further credence to the notion that HDL cholesterol is unlikely to be causal. Finally, compelling data from a large mendelian randomization study<sup>9</sup> also argue that the HDL cholesterol level has a role solely as a risk marker and not a risk factor that merits intervention to reduce cardiovascular events. Although higher HDL cholesterol levels are associated with better outcomes, it is time to face the fact that increasing the HDL cholesterol level in isolation seems unlikely to offer the same benefit.

Disclosure forms provided by the author are available with the full text of this article at NEJM.org.

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## Changes in the Treatment Landscape for Chronic Lymphoid Leukemia

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After decades during which the treatment of patients with chronic lymphoid leukemia (CLL) was based on chemotherapy and more recently on chemoimmunotherapy, we are witnessing a new mechanism-driven era with the development of compounds capable of targeting the B-cell receptor signaling pathway. In this issue of the *Journal*, after an earlier phase 2 study,<sup>1</sup> Byrd et al.<sup>2</sup> present the results of the first randomized trial comparing the effect of ibrutinib, an inhibitor of Bruton's tyrosine kinase, with that of the anti-CD20 antibody ofatumumab, both used alone, for patients with relapsed or refractory CLL or small lymphocytic lymphoma. The results indicate that ibrutinib significantly improved both progression-free survival and overall survival, as compared with ofatumumab. Similar effects were observed in patients carrying the unfavorable genetic marker, a 17p deletion. Overall, the toxic effects associated with treatment were those that were expected on the basis of earlier studies and were manageable.

These results, coupled with those obtained with idelalisib,<sup>3</sup> an inhibitor of phosphatidylinositol 3-kinase  $\delta$  (PI3K $\delta$ ), open new possibilities in the treatment of patients with CLL. No other drugs used alone have ever shown similar activity in relapsed or refractory CLL. The oral formulation of these B-cell receptor antagonists is clearly an added value. The overall response rate with ibrutinib was high, with a partial response in 43% of patients and a partial response with lymphocytosis in another 20%. As already observed, compounds targeting the B-cell receptor pathway are associated with good control of the leukemic clone — even at the nodal level — but with low rates of complete remission. This finding implies that with a single-agent approach, patients may need to be treated indefinitely.

Will control of the disease be sufficient for patients with poor prognostic markers (i.e., with a 17p deletion or p53 mutations)? This question is particularly relevant, since a p53 disruption is found in 25 to 35% of patients with relapsed or refractory disease, and this proportion may actually be higher, since minor p53 mutant subclones have also been associated with a poor prognosis.<sup>4</sup> In the study by Byrd et al., 32.5% of patients carried a 17p deletion. At a median follow-up of 9.4 months, these patients seemed to respond as well as those without the deletion. In the previous phase 2 study<sup>1</sup> with a longer follow-up, progression-free and overall survival were lower for patients with a 17p deletion. In view of the very poor prognosis of such patients, the long-term effect of these new targeted drugs on this CLL subgroup still needs to be clarified. At present, for such patients, an approach that is aimed at disease eradication — including allogeneic stem-cell transplantation — is offered when possible. Controlling the disease over time may not be the most effective strategy. The results of the ongoing combination studies with chemoimmunotherapy will be important in defining whether the depth of response can be improved.

For most patients with CLL who do not have unfavorable prognostic markers, an oral treatment that is capable of controlling the disease may be a valuable approach. This is even more important, since most patients with CLL are over the age of 70 years, have multiple coexisting medical conditions, and are often ineligible for chemoimmunotherapy regimens. In this respect, a recent phase 1b–2 trial has shown the effectiveness of ibrutinib as initial therapy for elderly patients with CLL.<sup>5</sup>

Although the short-term toxic effects of ibrutinib seem to be manageable, side effects and