Editorial

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Raising High-Density Lipoprotein Levels: Out with the New, In with the Old?

Recent years have witnessed a tremendous interest in pharmacologic strategies to increase high-density lipoprotein (HDL) cholesterol levels. The hope has been that the well known antiatherosclerotic benefits associated with lowering low-density lipoprotein (LDL) cholesterol levels could be enhanced significantly by medications designed to elevate levels of HDL.

This past fall, however, advocates of this strategy suffered a major setback when Pfizer (New York, NY) pulled its promising candidate drug, torcetrapib, from further development. This action was prompted by results from the Investigation of Lipid Level Management to Understand its Impact in Atherosclerotic Events (ILLUMINATE) trial, which showed an increased number of deaths in the group of patients randomly assigned to receive a combination of torcetrapib and atorvastatin compared with those assigned to atorvastatin alone.[1,2]

Data on torcetrapib from several studies also has shown a consistent, though modest, increase in blood pressure with this drug.[3] Even slight blood pressure elevations can translate—across large patient populations—into significant associated increases in cardiovascular morbidity and mortality.[4] Could it be that torcetrapib's potential effects on HDL levels, which occur through inhibition of the enzyme cholesteryl ester transfer protein (CETP), were "swamped out" by this compound's unfortunate proclivity to increase blood pressure? The connection does not seem implausible.

Given this disappointment, a pessimist hardly could be blamed for concluding that strategies for raising HDL levels might not be all they were cracked up to be. But a closer examination of the situation reveals a few rays of hope. For instance, data on several other candidate CETP inhibitors under development by rival drug companies seem, thus far, to show comparable elevations in HDL levels without any associated effects on blood pressure. These data, though preliminary, suggest that the blood pressure problem might be specific to torcetrapib.[5]

Furthermore, in our quest for the latest pharmaceutical blockbuster, we may have neglected a tried and true remedy that, since the 1950s, has been known to produce quite reliable and robust HDL elevations. I am speaking, of course, of niacin, or nicotinic acid. Niacin has long suffered from its "lowly" status as a generic medication, with very limited appeal to the pharmaceutical industry as a source of revenue and profit. But despite the lack of promotion, it's a highly effective medication with a good safety profile when prescribed by a knowledgeable provider.

Let's review what niacin can do for lipids. First and foremost, its ability to cause robust elevations in HDL levels—up to 40%—renders it in a class by itself in terms of efficacy. By contrast, statins typically raise HDL levels in the range of 5% to 10%. Fibrates (including fenofibrate and gemfibrozil) may do a little better, sometimes in the range of 10% to 15%. It's true that thiazolidinediones (also known as glitazones) may raise HDL levels by as much as 20%, but their use is strictly confined to patients with diabetes. Diabetic patients certainly are at high risk for atherosclerotic events, but they represent a relatively modest fraction of all patients with low HDL levels.

And the lipid benefits of niacin don't stop there. It turns out that niacin is also fairly potent at lowering both LDL and triglyceride levels, either alone or in combination with other medications (such as statins). Additionally, it's the only agent other than estrogens that has been shown to lower lipoprotein(a) levels. High lipoprotein(a) levels may be an independent risk factor for coronary artery disease in certain patients.

Given these substantial benefits, why aren't we using niacin much more widely? The answer, of course, is that the drug has acquired a reputation for being difficult, a situation that isn't helped by the reluctance of major drug companies to speak on its behalf. But is niacin really that problematic? I would submit that the answer is no—if both the patient and the provider show a modest amount of patience and persistence.

The main concern with niacin is the adverse effect of flushing, which occurs almost universally—though the number of flushing episodes may be fewer with a newer, proprietary, extended-release formulation, Niaspan (Kos Pharmaceuticals, Cranbury, NJ).[6] Flushing usually abates after several days in all but the most fairly complexioned individuals. Although flushing does no serious or lasting damage to the body, it's amazing how dismayed patients and providers can become over this phenomenon. It may help to provide patients with some tips for managing flushing (such as avoiding ingestion of alcohol or hot drinks around the time they take the drug)—and to suggest to them that this nuisance can be a reminder that the medication is hard at work increas-

ing their good cholesterol and lowering their bad cholesterol.

Another persistent hindrance to the widespread use of niacin is the idea that it shouldn't be used in diabetic patients due to a detrimental effect on blood glucose control. Two large studies, the Arterial Disease Multiple Intervention Trial (ADMIT) on crystalline niacin and the Assessment of Diabetes Control and Evaluation of the Efficacy of Niaspan Trial (ADVENT), showed that the effects on blood glucose levels are generally very small and easily managed with a minor tweaking of the antiglycemic regimen.[7,8] Indeed, diabetic patients are high risk individuals who typically have subpar levels of HDL and, therefore, are strong candidates for niacin therapy.

The other adverse effects of niacin are relatively infrequent. Mild gastrointestinal distress is seen occasionally, and an acute episode of gout can sometimes be precipitated by niacin therapy. The disastrous complication of fulminant hepatic necrosis essentially is seen only with the long-acting, timed-release preparations. There is little need to fear this outcome if one sticks to the crystalline or extended-release formulations.

It is disappointing to have lost the promise of torcetrapib from the therapeutic armamentarium. But the silver lining in this dark cloud is in the opportunity to rediscover an old friend—niacin. Niacin has been highly effective at improving lipids for half a century and undoubtedly will remain an important lipid lowering medication 50 years from now. ●

Author disclosures

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