

EXCERPT FROM...

## **Preventive Cardiology: A Practical Approach**

By Nathan D. Wong, Henry R. Black, Julius M. Gardin

### **Niacin**

Among lipid-regulating agents, niacin is unique in that it is the only agent that favorably affects all major lipoprotein subfractions, resulting in a 15 to 25% reduction in LDL-C, 15 to 30% increases in HDL-C, and even greater reductions in triglycerides (20-50%). It also lowers Lp(a) by as much as 30 to 40%, and may convert individuals from the "small, dense" LDL-C pattern B to a larger, more buoyant pattern A.<sup>49</sup>

Recent studies indicate that niacin also increases lipoprotein A-I (LpA-I), a sub fraction of HDL that is considered to be antiatherogenic, versus lipoprotein A-II which is not.<sup>21</sup> Older studies indicated that niacin decreases free fatty acid mobilization by inhibition of adipose tissue lipolysis<sup>116</sup>; however, more recent research indicates that it raises HDL-C and ApoA-I by decreasing the hepatic catabolism of ApoA-I. It decreases hepatic uptake of ApoA-I without affecting cholesterol uptake from the HDL-C. Thus, the half-life of HDL-C is prolonged, but its ability to deliver cholesterol to the liver remains intact, augmenting reverse cholesterol transport.<sup>17</sup>

In addition, new information indicates that niacin reduces plasma triglycerides (TGs) and VLDL-C by inhibiting VLDL TG synthetic rate through the inhibition of both fatty acid synthesis and fatty acid esterification to form TGs.<sup>18</sup>

A very recent report indicates that niacin noncompetitively, directly, and selectively inhibits diacylglycerol acyltransferase (DGAT2 but not DGAT1), thereby defining a specific target of this agent<sup>119</sup>. DGAT2 is the specific key enzyme involved in VLDL TG synthesis, whereas DGAT1 is involved in nonlipoprotein TG synthesis. Both these enzymes are distinct in their structure and have recently been cloned.<sup>1\*0</sup> Decreased TG synthesis results in poorer lipidation of hepatocellular ApoB, which renders it more susceptible to degradation by proteases.

This results in lower secretion of ApoB and smaller TG-poor VLDL-C particles by the liver. Because the larger VLDL-C particles are a precursor of small, dense LDL-C particles, the reduction in VLDL-C size caused by niacin has been proposed as the mechanism by which small, dense LDL-C particles are reduced in concentration and rendered larger (and more buoyant).

Decreased VLDL-C concentrations lead to decreased LDL-C concentrations, as VLDL-C is converted into intermediate-density lipoprotein (IDL) cholesterol and then to LDL-C<sup>121</sup>

In the past, niacin preparations were difficult to tolerate. With the immediate-release niacin preparation, multiple-dosing regimens and intolerable flushing frequently led to noncompliance. A newer formulation, extended-release (ER) niacin,<sup>122</sup> minimizes flushing and hepatotoxicity without eliminating its effectiveness in modifying the lipid levels, and also provides a convenient once-daily regimen. It should be distinguished from other over-the-counter time-release preparations (designated as "sustained-release," "controlled-release"), which have variable efficacy and toxicity. Other side effects include dry skin, itching, gastritis, hepatitis, increased uric acid levels, and hyperglycemia.

Tips for improving tolerability include starting at a low dosage and gradually increasing the dosage over several weeks to a maximum in the range of 1 to 3 g per day, as necessary and tolerated. Enteric-coated aspirin minimizes flushing and can be given one-half to one hour before administration. Liver enzyme elevations may accompany use of higher dosages. Enzyme levels should be monitored and niacin dosage reduced or withdrawn if they exceed three times the upper limit of normal.

Niacin is contraindicated in patients with a history of gout or active peptic ulcer disease and hepatic dysfunction. It has been traditionally taught that niacin is also a relative contraindication for patients with diabetes.

However, recent studies have shown that niacin does not significantly worsen hyperglycemia in patients with impaired glucose tolerance/glycemic control.<sup>123,124</sup>

The ADMIT study, which looked at the effects of niacin in diabetic patients, concluded that immediate-release niacin was equally effective in modifying lipid and lipoprotein levels in people with or without diabetes.<sup>123</sup>

The study showed that plasma glucose levels were increased in people with and without diabetes, but the effects after 60 weeks of follow-up did not significantly increase niacin discontinuation rates or change glycemic therapy. In addition to ADMIT, Grundy and co-workers examined the use of niacin in diabetics and showed that extended-release niacin had a significant effect on triglyceride as well as HDL-C levels (ADVENT).<sup>124</sup>

The changes in HbA1C levels were small in all treatment groups. Increases in fasting blood glucose occurred between weeks 4 and 8 in the niacin-treated groups; levels returned to baseline by week 16. ADVENT demonstrated that extended-release niacin at the doses tested was effective and well tolerated in diabetics. The recommendation is that high niacin doses (>1500-2000 mg/d) not be used.