Niacin in Cardiovascular Disease: Recent Preclinical and Clinical Developments

Janet E. Digby, Neil Ruparelia, Robin P. Choudhury

Abstract—Niacin has been used for more than 50 years in the treatment of cardiovascular disease, although its use has largely been superseded by better-tolerated lipid-modulating interventions. There has been a renewed interest in the HDL-cholesterol raising properties of niacin, with the appreciation that substantial cardiovascular risk remains despite effective treatment of LDL-cholesterol. This coincides with increasing evidence that the complex functional properties of HDL are not well reflected by measurement of HDL-cholesterol alone. In addition to favorable actions on lipoproteins, it is becoming apparent that niacin may also possess lipoprotein independent or pleiotropic effects including the inhibition of inflammatory pathways mediated by its receptor GPR109A, which is expressed by adipocytes and some leukocytes. In this article we consider emerging and prior clinical trial data relating to niacin. We review recent data in respect of mechanisms of action on lipoproteins, which remain complex and incompletely understood. We discuss the recent reports of anti-inflammatory effects of niacin in adipocytes and through bone marrow derived cells and vascular endothelium. These novel observations come at an interesting time, with current imaging and outcome studies leaving outstanding questions on niacin efficacy in statin-treated patients. (Arterioscler Thromb Vasc Biol. 2012;32:582-588.)

Key Words: atherosclerosis ■ cholesterol-lowering drugs ■ G proteins ■ lipids

Niacin (nicotinic acid) has been used to treat cardiovascular disease for over 50 years1 and was the first drug to show a reduction in cardiovascular events and mortality in patients with prior myocardial infarction.2,3 The focus of niacin treatment has been on its favorable actions in increasing HDL-cholesterol (HDL-c)4 and reducing LDL-cholesterol (LDL-c),5 very LDL-c [VLDL-c]) and lipoprotein(a).4 In spite of being the most effective available therapy at raising HDL-c,6 its widespread use has been curtailed by its principal side effect of cutaneous flushing7 and niacin has been superseded by better-tolerated statins in the treatment of dyslipidemia. The potential for benefit associated with raising absolute levels of HDL-c and improving the functional characteristics of HDL8 has renewed interest in the use of niacin in the treatment of cardiovascular disease.

Although treatment with statins achieves substantial LDL-c reduction, significant cardiovascular risk remains.9–11 There is strong epidemiological evidence of an inverse relationship between HDL-c level and coronary heart disease risk, regardless of the LDL-c level,12,13 which persists in patients who are treated with statins.10 Thus, HDL-c elevation presents a next rational target for lipid intervention. Surprisingly, there is very little evidence for the use of niacin (or any other adjunctive lipoprotein-modifying therapy) in patients treated with statins. Small imaging studies14,15 have suggested effects on atherosclerosis regression but the key to a clearer role of niacin treatment will lie with outcome studies. The AIM-HIGH trial16 (Atherothrombosis Intervention in Metabolic syndrome With Low HDL/High Triglycerides: Impact on Global Health Outcomes) has cast doubt in respect of niacin treatment, because this trial appears to show absence of treatment benefits with the addition of modified-release niacin, (1.5–2 g per day), in patients with low baseline HDL-c and intensively treated LDL-c. However, the power and design of that study was not optimal for definitive evaluation of the role of niacin in the treatment of cardiovascular disease.

The much larger HPS2-THRIVE17 (Heart Protection Study 2 Treatment on HDL to Reduce the Incidence of Vascular Events) trial should provide much needed clarity. The trials landscape is further complicated by the development of additional pharmacological agents, designed to raise HDL-c (notably cholesteryl ester transfer protein [CETP] inhibitors) and anacetrapib are awaited with interest.19,20

Recently, a number of laboratories have reported nonlipoprotein mediated effects of niacin that may have a bearing on atherosclerosis progression and risk.21 In addition to the potentially favorable lipoprotein modulating effects of niacin, study of the pharmacology and mechanisms of action of...
Niacin have revealed anti-inflammatory effects in monocytes/macrophages, adipocytes, and vascular endothelium. These effects raise interesting questions on mechanisms of action of niacin in cardiovascular diseases’ indications for use and clinical trial design.

**Niacin in Clinical Practice**

Niacin has been used in clinical practice for over half a century and, prior to the advent of statins, demonstrated favorable outcomes in patients with prior myocardial infarction. The major clinical trials to date concerning the use of niacin are summarized in the Table.

The principal limiting factor to the widespread usage of niacin has been its adverse side effect profile (in particular cutaneous flushing that can affect up to 90% patients). Although flushing is still a significant problem, modern formulations are better tolerated, because of the development of modified-release niacin and the coadministration of niacin with laropiprant (which reduces cutaneous flushing by inhibiting prostaglandin D2 mediated vasodilation through DP1 receptor antagonism). Niacin treatment has also been associated with insulin resistance. The underlying mechanisms remain unclear; however, acute niacin administration in humans results in a rapid decrease in the plasma free fatty acids level, followed by a rebound and subsequent overshoot to above that of preflushin levels. Such elevations in circulating free fatty acids are linked with insulin resistance and have multiple effects on gene expression that may be indirectly altered by niacin. These observations highlight the complexities of niacin treatment and alterations in insulin sensitivity.

Therapy to lower LDL-c improves clinical outcome with lower attained LDL-c levels conferring greater benefits. Because statins are firmly established in the treatment of atherosclerosis, current interest in niacin necessarily focuses on the potential benefit of its addition to statin therapy; but, surprisingly, this question is currently unanswered. The HATS trial (without a statin-only arm) demonstrated regression of atherosclerotic lesions, measured using invasive quantitative coronary angiography, with niacin therapy in patients in April 2010 and is due to report its findings in 2013. In addition, lipoprotein(a) has been shown to be an independent risk factor for coronary artery disease, and it has been reported that niacin treatment significantly reduces lipoprotein(a) levels in patients with atherosclerosis. This observation may also confer additional outcome benefits, although in vivo data specifically addressing this are lacking. Drug interactions with niacin treatment and resultant end-organ toxicity are rare.

**Niacin: Mechanisms of Action**

**Lipoprotein-Mediated Actions**

The effects of niacin on plasma lipoproteins are potentially complex and currently not clearly understood. The identification of a G-protein–coupled receptor GPR109A, also recently named hydroxyl-carboxylic acid receptor 2, that binds nicotinic acid with high affinity has led to a better understanding of possible mechanisms of action of niacin. This receptor is expressed in a range of immune cells and is also highly expressed on adipocytes. Activation of GPR109A in adipocytes results in a G2-mediated reduction in adenylate cyclase, limiting CAMP accumulation. This leads to reduced protein kinase A activity and decreased phosphorylation of hormone-sensitive lipase. The resultant reduction in triglyceride hydrolysis and release of free fatty acids reduces flux to the liver, which is believed to limit substrate availability for hepatic triglyceride and VLDL-c synthesis. It has been proposed that there is an accompanying decrease in CETP mediated exchange of triglyceride for cholesteryl
esters between VLDL and HDL particles, leading to a net rise in HDL-c. This interpretation is supported by evidence from apoE*3 Leiden mice transgenic for expression of human CETP, in which niacin significantly increased HDL-c and decreased total cholesterol and triglycerides. However HDL-c elevation was dependent on the presence of CETP, without which there was no HDL-c effect, suggesting a crucial role for CETP in mediating the effect of raising HDL-c by niacin.48

Table. Major Clinical Trials to Date Concerning the Use of Niacin

<table>
<thead>
<tr>
<th>Trial Name</th>
<th>Investigating</th>
<th>No. of Patients</th>
<th>Endpoints</th>
<th>Outcome</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Coronary Drug Project</td>
<td>Efficacy and safety of niacin in patients with previous myocardial infarction</td>
<td>8341</td>
<td>Death</td>
<td>After a mean follow-up of 5 y, no mortality benefit in comparison to placebo.</td>
<td>2</td>
</tr>
<tr>
<td>Coronary Drug Project</td>
<td>Efficacy and safety of niacin in patients with previous myocardial infarction</td>
<td>8341</td>
<td>Death</td>
<td>After a mean follow-up of 15 years, mortality in the niacin group was 11% lower than placebo (P&lt;0.0004).</td>
<td>3</td>
</tr>
<tr>
<td>Familial Atherosclerosis Treatment Study (FATS)</td>
<td>Niacin and colestipol in comparison to lovastatin alone or colestipol alone or placebo in patients with documented coronary artery disease</td>
<td>120</td>
<td>Average change between pre and post angiogram appearance of the worst stenosis</td>
<td>2.5 y follow-up. HDL-c in the niacin-colestipol group increased by 43% and was associated with angiographic atherosclerotic regression in 39%. There was also an associated significant outcome benefit with a 73% reduction in clinical events (death, myocardial infarction or revascularization for worsening symptoms).</td>
<td>72</td>
</tr>
<tr>
<td>The Cholesterol-Lowering Atherosclerosis Study (CLAS)</td>
<td>Niacin and colestipol in comparison to placebo in patients with documented coronary artery disease</td>
<td>162</td>
<td>Angiographic atherosclerosis appearance</td>
<td>At 4 y follow significantly more drug-treated subjects demonstrated non-progression (52% drug vs 15% placebo-treated) and regression (18% drug vs 6% placebo treated) in native coronary artery lesions.</td>
<td>73</td>
</tr>
<tr>
<td>Stockholm Ischaemic Heart Disease Secondary Prevention Study</td>
<td>Niacin and clofibrate in comparison to placebo in patients surviving myocardial infarction</td>
<td>555</td>
<td>Death</td>
<td>At 5 y follow up treatment with niacin and clofibrate was associated with 26% reduction in all-cause mortality and a 36% reduction in coronary heart disease mortality.</td>
<td>74</td>
</tr>
<tr>
<td>HDL-Atherosclerosis Treatment Study (HATS)</td>
<td>Niacin-simvastatin alone or together with anti-oxidant vitamin therapy or placebo in patients with coronary artery disease</td>
<td>160</td>
<td>Angiographic evidence of change in coronary stenosis or the occurrence of the first cardiovascular event</td>
<td>At 3 y follow up niacin-simvastatin was associated with significant regression of coronary stenosis and a combined 90% reduction in major clinical events (including death from coronary causes, nonfatal myocardial infarction, stroke or revascularization for worsening angina).</td>
<td>41</td>
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<tr>
<td>Arterial Biology for the Investigation of Treatment Effects of Reducing Cholesterol (ARBITER) 2</td>
<td>Once daily extended-release niacin with and without statin therapy in patients with coronary artery disease</td>
<td>167</td>
<td>The change in common carotid intima-thickness (CIMT) at 1 y</td>
<td>At 1 y, mean CIMT increased significantly in the statin alone group and was unchanged in the niacin-statin group.</td>
<td>75, 76</td>
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<tr>
<td>ARBITER 6</td>
<td>Extended release niacin-statin vs ezetemibe-statin in patients with coronary artery disease or a coronary heart disease risk equivalent</td>
<td>315</td>
<td>The between-group difference in the change from baseline in the mean CIMT</td>
<td>The trial was prematurely stopped after it was observed that the niacin-statin group had greater efficacy regarding the change in CIMT over 14 mo in comparison to statin-ezetimibe.</td>
<td>14, 77</td>
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<tr>
<td>Oxford Niaspan Study</td>
<td>Modified release niacin in comparison to placebo in statin-treated patients with low HDL-c and either type 2 diabetes mellitus or carotid/peripheral atherosclerosis</td>
<td>71</td>
<td>Change in carotid artery wall area as measured by magnetic resonance imaging (MRI)</td>
<td>At 1 y follow up the niacin group had a reduced mean carotid artery wall area in comparison to the statin alone group.</td>
<td>15</td>
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Niacin also has direct nonreceptor-mediated actions on the liver, which is involved in both the production and degradation of apolipoprotein B. In a human hepatocyte cell line (Hep G2 cells), niacin increased apolipoprotein B intracellular degradation and decreased secretion of apolipoprotein B into the culture media. It has also been shown to inhibit cell surface expression of the ATP synthase β-chains, which undergo endocytosis in the process of whole particle HDL-c uptake in HepG2 cells. In vitro, niacin noncompetitively inhibits hepatocyte microsomal diacylglycerol acyltransferase-2 activity, which catalyzes the final reaction in triglyceride synthesis, although at high niacin concentrations, so the significance of this mechanism in vivo is in doubt.

Adipose tissue is the body’s largest cholesterol reservoir and abundantly expresses ATP binding cassette transporter A1, a key cholesterol transporter for HDL biogenesis. A potentially important recent study has provided evidence that ATP binding cassette transporter A1-dependent cholesterol efflux in adipose tissue directly contributes to HDL biogenesis. It has previously been reported that niacin promotes cholesterol efflux from adipocytes to apoA-I via activation of the PPARγ-LXRα–ATP binding cassette transporter A1 pathway. Taken together these observations suggest another important mechanism by which niacin may alter systemic HDL-c levels.

In summary, there are several possible mechanisms through which niacin may affect plasma lipoproteins (both receptor-mediated and independent). Although not mutually exclusive, the relative contributions of each remain uncertain.

Nonlipoprotein Mediated Actions

There is a growing body of evidence demonstrating nonlipoprotein-mediated effects of niacin on a range of tissues and cells. If reproduced in the clinical setting, these “pleiotropic” effects may confer additional benefits. In patients with cardiovascular disease, niacin treatment has systemic anti-inflammatory effects manifest as reduced levels of C-reactive protein and lipoprotein-associated phospholipase A2. Adiponectin, which is increased by niacin (through mechanisms likely to be GPR109A-mediated), is inversely associated with risk of myocardial infarction in men and risk of coronary heart disease in male diabetic patients. GPR109A, is highly expressed in adipocytes, as well as neutrophils, macrophages, and Langerhans cells. In adipocytes, niacin inhibits tumor necrosis factor-α-stimulated expression and secretion of inflammatory cytokines, monocyte chemotactic protein-1, regulated on activation, normal T cell expressed and secreted, and fractalkine. Under conditions of inflammation associated with cardiovascular disease, increased secretion of proatherogenic, proinflammatory cytokines and chemokines contribute significantly to the recruitment of inflammatory T-cells and macrophages into atherosclerotic lesions. Adipose tissue has the potential to contribute to processes involved in both systemic and local (perivascular) inflammation in the context of atherosclerosis, both of which may be influenced by the actions of niacin.

Lukasova et al, using LDL-receptor knockout mice, showed that nicotinic acid reduced the progression of atherosclerosis. Importantly, this was lipoprotein independent as there were no changes to LDL-c, VLDL-c, and HDL-c levels. Moreover, these beneficial effects were abrogated in Ldr−/− and GPR109A−/− double knockout mice. Through bone marrow transplantation, mediation of anti-atherosclerotic mechanisms was shown to be via GPR109A in marrow-derived cells, which was further supported by the inhibition of monocyte chemotactic protein-1 induced recruitment of macrophages into the peritoneal cavity and impaired macrophage recruitment to atherosclerotic plaques. This study also reported a reduction in the expression of adhesion molecules in atherosclerotic vessels of nicotinic acid-treated Ldr−/− mice. These data suggest novel GPR109A receptor-mediated antiatherosclerotic effects of niacin, which are not dependent on alterations in lipoproteins.

There is also evidence that niacin exerts non-GPR109A–mediated anti-inflammatory and antioxidative effects in endothelial cells in vitro, in addition to inhibiting cytokine-induced expression of adhesion molecules and chemokines in response to inflammatory stimuli. In vivo, niacin supplementation (0.6% and 1.2%) in the diet of New Zealand White rabbits for 2 weeks was associated with significantly improved endothelial function independent of changes in plasma lipids. At 24 hours following peri-arterial carotid collar implantation, endothelial expression of vascular cell adhesion molecule-1, intercellular adhesion molecule-1, and monocyte chemotactic protein-1 were reduced in comparison to controls.

Niacin-induced cutaneous flushing mediated by GPR109A is a common side-effect and represents a major cause for lack of adherence to treatment. This response involves the biphasic release of prostaglandin D2 (PGD2) and E2 from GPR109A-expressing Langerhans cells (early phase), and prostaglandin E2 alone from keratinocytes (late phase). An approach to overcome this problem has been to co-administer larpiprant (a selective PGD2 receptor antagonist), however, because this is not the only prostanoid-mediated flushing pathway, the potential to fully counteract this side effect is hampered. A theoretical concern is that inhibition of PGD2 may affect these newly identified anti-inflammatory effects of niacin. For instance, PGD2 release in the skin can inhibit the mobilization of antigen-presenting dendritic cells in response to an inflammatory insult. A recent study in mice has shown that short-term niacin treatment impairs dendritic cell accumulation into draining skin lymph nodes, though this was not reversed by prostaglandin synthesis inhibition using the cyclooxygenase inhibitor, naproxen. Furthermore, recent work from our laboratory confirms that the anti-inflammatory effects of niacin treatment in human monocytes in vitro, measured by release of inflammatory mediators such as tumor necrosis factor-α, monocyte chemotactic protein-1, and IL6 persist despite inhibition of PGD2.

In summary, niacin exerts pleiotropic potentially beneficial actions, which are lipoprotein independent, through direct anti-inflammatory effects on cell types involved in the progression of atherosclerosis. These actions could contribute to the clinical benefits seen with niacin treatment.
Conclusions
Even with optimal LDL-c lowering, patients with coronary artery disease retain significant cardiovascular risk. Based on epidemiology and animal studies, increasing HDL-c has become a rational next target. With CETP inhibitors under evaluation in Phase III trials, niacin is currently the most effective available drug in this regard; however, the main limitation remains tolerability. Increasing understanding of the pharmacology of niacin and a variety of mechanisms of action suggest that some of the beneficial effects may lie beyond lipoprotein modulation, with demonstration of direct effects on endothelial cells, immune cells, and adipocytes, potentially changing indications for its use. In the future, new agents may be able to develop pleiotropic anti-inflammatory effects and avoid the intrusive side effects that have hampered the routine use of niacin in clinical practice. The major unanswered question remains: Can the addition of niacin to the range of currently used agents result in further benefit in clinical outcome?

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