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Niacin: another look at an underutilized lipid-lowering medication

Julia C. Creider, Robert A. Hegele and Tisha R. Joy

Abstract | Niacin, or water-soluble vitamin B_3, when given at pharmacologic doses, is a powerful lipid-altering agent. This drug, which lowers the levels of atherogenic, apolipoprotein-B-containing lipoproteins, is one of few medications that can raise the levels of atheroprotective HDL cholesterol. Niacin also has beneficial effects on other cardiovascular risk factors, including lipoprotein(a), C-reactive protein, platelet-activating factor acetylhydrolase, plasminogen activator inhibitor 1 and fibrinogen. Many clinical trials have confirmed the lipid effects of niacin treatment; however, its effects on cardiovascular outcomes have been called into question owing to the AIM-HIGH trial, which showed no benefit of niacin therapy on cardiovascular endpoints. Furthermore, use of niacin has historically been limited by tolerability issues. In addition to flushing, worsened hyperglycaemia among patients with diabetes mellitus has also been a concern with niacin therapy. This article reviews the utility of niacin including its mechanism of action, clinical trial data regarding cardiovascular outcomes, adverse effect profile and strategies to address these effects and improve compliance.

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Introduction

Low levels of HDL cholesterol—defined as values <1.1 mmol/l in men and <1.3 mmol/l in women[1]—are an independent risk factor for cardiovascular disease.[2,3] According to epidemiologic data, for every 0.03 mmol/l drop in HDL cholesterol levels, the risk of cardiovascular disease increases by 2–3%.[2] The prevalence of low HDL cholesterol ranges from 20% to 60% in patients with established cardiovascular disease.[4–8] Furthermore, low HDL cholesterol levels form part of the criteria for the metabolic syndrome and are highly prevalent among patients with diabetes mellitus, affecting more than 50% of men and 66% of women with this condition.[1,9]

The relationship between HDL and diabetes mellitus goes beyond merely low HDL cholesterol levels. Patients with this disorder have increased numbers of compositionally abnormal HDL particles, which are associated with increased cardiovascular disease risk. Although HDL is thought to mediate its anti-atherogenic effects primarily through reverse cholesterol transport, it may also have antithrombotic, anti-inflammatory, antioxidant and endovascular properties, particularly via its primary apolipoprotein (apo) A-I or associated enzymes, such as serum paraoxonase/arylesterase 1 (PON1). Poor glycaemic control in patients with diabetes mellitus can lead to glycation of apoA-I, which in turn impairs the ability of apoA-I to promote reverse cholesterol transport and inhibit inflammation.[10,11] Furthermore, dysfunction or loss of HDL-associated enzymes such as PON1 can be evident in inflammatory states, type 2 diabetes mellitus and the metabolic syndrome.[12] HDL itself has been suggested to influence glycaemic control. In particular, HDL inhibits apoptosis of β cells, increases insulin synthesis and secretion as well as glucose uptake in skeletal muscle.[13–15] Thus, the relationship between HDL cholesterol, cardiovascular disease risk and diabetes mellitus is more complex than initially presumed.

In clinical practice, the only currently marketed medication that significantly and consistently raises HDL cholesterol levels is water-soluble vitamin B_3, which is also known as niacin. This agent exerts several beneficial, lipid-altering effects—it lowers the levels of all atherogenic particles that contain apoB, including LDL, VLDL, IDL and lipoprotein(a) (Lp(a))—as well as non-lipid, pleiotropic effects.[16] Moreover, niacin has demonstrated beneficial effects on cardiovascular outcomes in several clinical trials.[17–23] Aside from being an attractive option for patients with low HDL cholesterol levels, niacin may be particularly helpful in the treatment of patients with diabetes mellitus or the metabolic syndrome. However, the use of niacin in these populations has been constrained due to concerns over worsened hyperglycaemia.[24,25] Furthermore, the results of the AIM-HIGH (Atherothrombosis Intervention in Metabolic Syndrome with Low HDL/High Triglyceride and Impact on Global Health Outcomes) trial have called into question the utility of raising HDL cholesterol levels in general and in particular with niacin therapy.[26] This Review discusses the mechanisms of action of niacin

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Key points

- Niacin exerts several beneficial lipid-altering effects, including lowering the levels of all atherogenic particles that contain apolipoprotein B, such as LDL, VLDL, IDL and lipoprotein(a), and raising HDL cholesterol levels
- Niacin should be used in the immediate-release or extended-release forms only, as the sustained-release preparations have been associated with hepatotoxicity
- Compliance with niacin can be hindered by flushing, gastrointestinal and metabolic effects; of these, flushing is the most common reason for discontinuation of niacin therapy
- Symptoms of flushing can be alleviated if the possibility of flushing is discussed in advance and advice is given to take a low-fat snack and a nonsteroidal anti-inflammatory drug and to avoid hot or spicy foods at the time of niacin ingestion
- Use of niacin in patients with diabetes mellitus is often constrained by concern over provoking hyperglycaemia, but evidence would suggest that increases in plasma glucose levels are modest and transient
- Despite the disappointing results of the AIM-HIGH trial, the relation between niacin therapy and cardiovascular disease endpoints remains yet to be fully defined by larger and more definitive clinical trials

as well as its lipid-altering and pleiotropic effects. This article also provides a practical outline for initiating patients on niacin therapy and addressing adverse effects of treatment.

Niacin—formulations and mode of action

Formulations

Niacin refers to both nicotinic acid and nicotinamide; however, importantly, only nicotinic acid, not nicotinamide, has lipid-altering effects.[27] Three formulations of niacin exist to date: immediate release (IR), sustained release (SR) and extended release (ER).

Niacin is metabolized by two pathways: firstly, the conjugative pathway, in which niacin is conjugated with glycine to form nicotinuric acid; and secondly, the nonconjugative pathway, in which niacin undergoes several redox reactions resulting in the production of nicotinamide and pyrimidine products.[28] These metabolic pathways are important for understanding two of the main adverse effects of niacin therapy—flushing and hepatotoxicity. The onset of flushing is closely related to a rapid increase in plasma levels of nicotinic acid.[29] The conjugative pathway is a low-affinity, high-capacity pathway that is activated only when the nonconjugative pathway has been saturated. IR-niacin quickly saturates the nonconjugative pathway and is then metabolized by the conjugative pathway, leading to substantial flushing.[28] SR-niacin, on the other hand, is mainly metabolized by the nonconjugative pathway owing to its slow dissolution rate, which leads to a higher incidence of hepatotoxicity compared with IR-niacin preparations.[30–32] Hence, SR-niacin is rarely used.

ER-niacin is functionally intermediate between the two other formulations in terms of its dissolution rate. This formulation has not been significantly associated with hepatotoxicity and displays a lower incidence of flushing than IR-niacin.[33–35] Thus, ER-niacin has become the most commonly prescribed form of niacin; a dose of 2 g can lower LDL cholesterol and triglyceride levels by 16% and 32%, respectively, whereas HDL cholesterol levels are increased by 24%.[36] ER-niacin and IR-niacin are both available on prescription in Europe and North America. SR-niacin is not currently available by prescription in North America, although it is found 'over the counter' across numerous jurisdictions and a range of preparations. Nevertheless, given the hepatotoxicity associated with SR-niacin, physicians should prescribe only the ER or IR formulations.

Of note, 'no-flush niacin'—another over-the-counter formulation—often contains inositol hexaniacinate, a complex of six nicotinic acid molecules esterified to inositol. Although this product technically contains niacin, it does not seem to have sufficient free or bioavailable niacin to impart lipid-lowering effects, and the few studies done with this preparation have revealed disappointing results.[37–39]

Effects on lipoproteins

The effects of niacin on lipoprotein parameters are varied (Figure 1). The receptor implicated in some of the effects of niacin has been identified as the G-protein-coupled hydroxycarboxylic acid receptor 2 (HCAR2; also termed GPR109A).[40–42] Niacin is thought to lower triglyceride levels by reducing hepatic VLDL synthesis through the activation of HCAR2, thereby limiting the activity of cholesteryl ester transfer protein (CETP), which exchanges triglycerides in VLDL and LDL particles for cholesteryl esters in HDL particles.[43,44] Niacin can decrease triglyceride levels by 20–50% and apoB levels by 40–65% through direct and noncompetitive inhibition of diacylglycerol O-acyltransferase 2 (DGAT2).[45] Inhibiting DGAT2 decreases triglyceride synthesis and thus its availability for VLDL assembly, resulting in a reduced production of VLDL and its catabolic product, LDL. Furthermore, niacin increases apoB catabolism, thereby further impairing synthesis of apoB-containing lipoproteins, including VLDL, LDL and Lp(a).[46]

Niacin increases HDL levels through a number of different mechanisms (Figure 1). In the liver, niacin selectively inhibits the surface expression of the ATP synthase β-chain, the putative hepatocyte HDL catabolism receptor, without inhibiting the function of SCARB1 (scavenger receptor class B member 1), a key player in the late stages of the reverse cholesterol transport.[47] Decreasing the fractional catabolic rate, in turn, increases the half-life of HDL, allowing for HDL to accumulate more cholesterol and form the larger HDL particles, which are considered to be more atheroprotective than other subspecies.[48,49] Although several studies have suggested no change in *de novo* synthesis of apoA-I or HDL particle concentration with niacin therapy,[49–52] data by Lamon-Fava *et al.* have suggested that niacin can increase the production rate of apoA-I.[53] Niacin also decreases hepatic *CETP* expression by 88% and CETP activity by 52%.[54] As plasma HDL cholesterol levels are inversely associated with plasma triglyceride levels, the reduction in triglyceride levels by niacin and the effects on CETP would also, thereby, indirectly raise HDL cholesterol levels. Thus, niacin can both directly and indirectly raise HDL cholesterol levels (Figure 1).

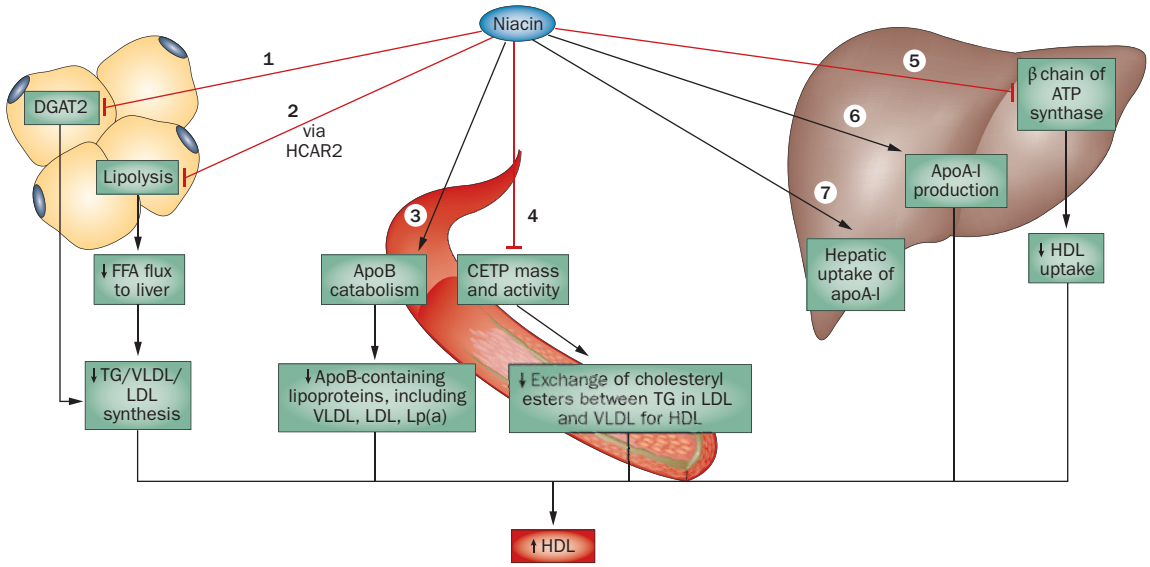

Figure 1 | Mechanisms of action of niacin on lipoprotein parameters. Niacin can decrease the synthesis of apoB-containing lipoproteins—VLDL, LDL, IDL and Lp(a)—via several mechanisms: (1) direct inhibition of DGAT2, a key enzyme for triglyceride synthesis; (2) binding to the receptor HCAR2 (also called GPR109A), thereby decreasing lipolysis and FFA flux to the liver for triglyceride synthesis; and (3) increased apoB catabolism. Meanwhile, HDL cholesterol levels are increased by niacin through direct and indirect pathways. (4) Niacin decreases CETP mass and activity, and this effect, together with the decrease in triglyceride levels, can indirectly raise HDL cholesterol levels. Direct effects on the β chain of ATP synthase (5) and on production (6) and hepatic uptake (7) of apoA-I also increase HDL cholesterol levels. Abbreviations: apo, apolipoprotein; CETP, cholesteryl ester transfer protein; DGAT2, diacylglycerol acyltransferase 2; FFA, free fatty acids; HCAR2, hydroxycarboxylic acid receptor 2; Lp(a), lipoprotein(a); TG, triglycerides.

In addition to its effects on HDL cholesterol, niacin can also mediate favourable effects on reverse cholesterol transport. Mice treated with niacin *in vitro* demonstrated increased expression of peroxisome proliferator-activated receptor γ (PPARγ), platelet glycoprotein 4 (CD36) and ABC transporter A family member 1 (ABCA1), the last being a key protein involved in cholesterol efflux early in the reverse cholesterol transport.[55]

Pleiotropic effects

Several pleiotropic effects of niacin, including antioxidant and anti-inflammatory effects, might contribute to its clinical benefit, although to precisely separate such contributory roles from the well-known effects on lipids is difficult. In particular, niacin has been demonstrated to have beneficial effects on a number of nontraditional cardiovascular disease markers. In a 1-year trial of niacin treatment in humans, C-reactive protein (CRP) levels were reduced by 20%, which correlated with a reduction in carotid intima-media thickness (cIMT), a surrogate marker and intermediate phenotype for cardiovascular endpoints.[56] Niacin has further been shown to be the only currently marketed medication to significantly lower Lp(a) levels via increased apoB catabolism.[57–59] Niacin can lower Lp(a) levels by 25% at doses of 2 g daily and has been postulated to attenuate the proinflammatory properties of Lp(a).[36]

Moreover, platelet-activating factor acetylhydrolase (PAFAH), which is also known as LDL-associated phospholipase A2, can modify LDL and HDL in a proinflammatory manner.[60] Niacin is known to decrease PAFAH levels by 20% in patients with cardiovascular disease treated for 3 months.[61] Whether the reduction in PAFAH concentration is independent of niacin's effects on apoB and/or whether PAFAH activity is also affected remains to be investigated.

Other independent risk factors for cardiovascular disease are fibrinogen and plasminogen activator inhibitor 1 (PAI-1), which are both involved in thrombogenesis.[62–64] Niacin is known to stimulate fibrinolysis and decrease plasma fibrinogen and PAI-1 levels.[65,66] Niacin also inhibits thrombosis through effects on coagulation factor VII activity, tissue factor and prothrombin activation peptide fragment 1.2.[67] Indirectly, through its effects on lipoproteins, niacin decreases platelet aggregation and reduces blood viscosity.[67] Niacin also increases plasma levels of adiponectin,[68] an adipokine with insulin-sensitizing, antiatherogenic and anti-inflammatory properties.[69,70] Furthermore, *in vitro* studies have shown that niacin inhibits the production of reactive oxygen species, LDL oxidation, vascular cell adhesion molecule-1 (VCAM-1) expression and monocyte chemotactic protein-1 (MCP-1) secretion.[71] This reduction in oxidation and expression of VCAM-1 and MCP-1 results in decreased monocyte and macrophage adhesion and accumulation, which are key events in early atherogenesis.[71]

Clinical trials of niacin therapy

Niacin trials in the 'pre-statin era'

The first clinical trial investigating niacin was the CDP (Coronary Drug Project) in 1975.[17] This large and

complex trial examined five potential lipid-lowering therapies in 8,341 men aged 30–64 years with prior myocardial infarction. Three arms (two examining oestrogen and one dextrothyroxine) were prematurely terminated owing to adverse events. No benefit was evident in the fourth arm, which examined clofibrate. After 6.5 years of follow-up, 3 g daily of niacin decreased the risk of stroke, myocardial infarction and coronary revascularization by 24%, 26%, and 67%, respectively, compared with placebo, without showing an effect on mortality.[17] After the CDP ended, mortality was examined in a post-hoc analysis, and individuals who had initially been randomly allocated to niacin demonstrated a decrease in total mortality of 11% at 15 years of follow-up.[72]

CDP was the largest clinical trial to examine the effects of niacin monotherapy on cardiovascular disease endpoints. However, even though individuals randomly allocated to niacin demonstrated a reduction in certain cardiovascular endpoints, they also experienced a higher incidence of atrial fibrillation as well as other metabolic effects, such as increased plasma uric acid and glucose levels, compared with control individuals. As such, the use of niacin was only cautiously supported. Moreover, this trial was conducted in the 'pre-statin era' and, thus, the benefits of niacin on concurrent statin therapy remained to be fully evaluated.

Importantly, since CDP, several clinical trials have evaluated various aspects of the clinical efficacy of niacin. For example, the Stockholm Ischaemic Heart Disease Secondary Prevention Study was the first trial to use niacin as part of combination therapy. 3 g per day of niacin together with 2 g daily of clofibrate were administered in an open-label fashion to patients with myocardial infarction for 5 years. This regimen was shown to reduce total and ischaemic heart disease mortality by 26% ($P<0.05$) and 36% ($P<0.01$), respectively, compared with the control group.[19]

The CDP and the Stockholm Study were the only two trials in the pre-statin era that assessed hard cardiovascular disease endpoints as primary outcomes.[17,19] Furthermore, the majority of trials evaluated niacin only as part of combination therapy. The CLAS (Cholesterol-Lowering Atherosclerosis Studies) I and II were first to demonstrate significant atherosclerotic lesion regression by coronary angiography in 162 patients who had received niacin in combination with colestipol, a bile acid sequestrant, after a coronary artery bypass graft.[20,73] Furthermore, at 4 years of follow-up, more treated than untreated patients demonstrated nonprogression (52% in the niacin plus colestipol group versus 15% in the placebo group, $P<0.0001$).[73] These results of coronary lesion regression with niacin in combination therapy were replicated in the UCSF-SCOR (University of California San Francisco Specialized Center of Research) study,[74] the FATS (Familial Atherosclerosis Treatment Study)[21] and the AFREGS (Armed Forces Regression Study).[75] AFREGS also demonstrated a 50% decrease in the composite clinical cardiovascular disease outcome.[75]

Niacin trials in the 'statin era'

HATS and ARBITER

The HDL Atherosclerosis Treatment Study (HATS) was the first randomized trial to examine niacin in combination with statin therapy.[18] HATS studied the effects of niacin plus simvastatin in patients with coronary heart disease (CHD), low HDL cholesterol and normal LDL cholesterol levels.[18] Major clinical events (death, myocardial infarction, stroke or revascularization) were significantly reduced by 90% ($P=0.03$).[18] Unfortunately, this study did not have a statin-only arm to compare the added effects of niacin on cardiovascular disease outcomes. To overcome this limitation, the ARBITER (Arterial Biology for the Investigation of the Treatment Effects of Reducing Cholesterol) trials 2,[22] 3[23] and 6[76] evaluated the effect of adding ER-niacin to pre-existing statin therapy on cIMT. In ARBITER-2, 167 patients with known CHD and HDL cholesterol levels <1.17 mmol/l were randomly allocated to ER-niacin 1 g daily or placebo. At 12 months, those receiving placebo demonstrated cIMT progression, whereas no progression was observed in those receiving ER-niacin.[22] In the open-label extension (ARBITER-3), those continuing on ER-niacin demonstrated significant regression of cIMT after an additional 12 months of therapy.[23]

The latest ARBITER trial examining niacin was ARBITER-6–HALTS (HDL and LDL Treatment Strategies), in which patients with CHD receiving statin therapy were randomly allocated to either ER-niacin (target dose 2 g daily) or ezetimibe 10 mg daily.[76] The trial was stopped early due to adjudicated beneficial effects among those receiving ER-niacin. Only 208 patients completed the trial at the time of analysis. Compared with those receiving ezetimibe, those receiving niacin demonstrated a significant decrease in cIMT and a reduced incidence of cardiovascular disease events, although the clinical event rate was quite low. ARBITER-6 was one of 11 randomized controlled trials included in a meta-analysis, which demonstrated a significant 25% reduction in major coronary events among individuals receiving niacin.[77]

AIM-HIGH

The AIM-HIGH trial[26] was prematurely terminated after a mean follow-up of 3 years owing to a lack of benefit in patients receiving niacin.[78] The AIM-HIGH investigators enrolled 3,414 individuals with established cardiovascular disease and an atherogenic lipid profile consisting of low HDL cholesterol and high triglycerides levels.[26] LDL cholesterol levels were optimally controlled at 1.04–2.07 mmol/l with the use of simvastatin with or without ezetimibe. Patients were randomly allocated to receive ER-niacin, with the dose titrated to 1,500 mg or 2,000 mg per day, or placebo. The placebo contained a small dose (50 mg) of IR-niacin in each 500 mg or 1,000 mg tablet to ensure blinding was maintained. Baseline mean LDL cholesterol, HDL cholesterol and median triglyceride levels were 1.97 mmol/l, 0.90 mmol/l and 1.83 mmol/l, respectively. 85% of study participants were men, 81% had been diagnosed as

having the metabolic syndrome, and 34% had diabetes mellitus. Individuals receiving ER-niacin demonstrated a 25% increase in HDL cholesterol, 31% reduction in triglyceride and 14% reduction in LDL cholesterol levels at 3 years. Despite these favourable changes, no significant reduction in the primary endpoint of major adverse cardiovascular events was observed. In addition, a small but unexplained increase in stroke rates was reported in the ER-niacin arm, affecting 1.7% versus 1.1% in the placebo arm ($P = 0.09$). Eight of the 30 strokes in the niacin group occurred in individuals who had discontinued the drug for at least 2 months.

Although raising HDL cholesterol levels would intuitively seem a useful strategy for cardiovascular disease reduction, the results of AIM-HIGH have called this approach into question. Nonetheless, a few limitations to the interpretation of the AIM-HIGH results exist. Firstly, patients in the placebo arm were actually receiving small amounts of IR-niacin, with evidence of a modest 12% increase in HDL cholesterol levels, signifying only a 13% net change in HDL cholesterol levels in the ER-niacin arm compared with placebo. However, most of the niacin-based trials that demonstrated benfits in surrogate or cardiovascular outcomes were accompanied by net changes of HDL cholesterol levels of at least 20% (Table 1). Secondly, the results of AIM-HIGH are limited in their generalization, given the high enrolment of men (85%) and white individuals (92%). Thirdly, and probably most importantly, in AIM-HIGH, mean baseline LDL cholesterol levels were at an optimal level (1.97 mmol/l) due to pre-existing statin therapy.

Thus, the results of AIM-HIGH suggest that raising HDL cholesterol levels once LDL cholesterol levels are at an optimal target does not result in additional reduction in cardiovascular events. The importance of HDL cholesterol in determining cardiovascular disease risk appears to be minimized in these circumstances, as supported by post-hoc analysis of the JUPITER (Justification for the Use of Statins in Primary Prevention: An Intervention Trial Evaluating Rosuvastatin) trial, in which HDL cholesterol levels were not predictive of residual cardiovascular disease risk after attainment of very low LDL cholesterol levels (1.40 mmol/l).[79] Another possibility could be that statins and HDL both upregulate SCARB1.[80] If SCARB1 is already maximally upregulated by statin therapy, addition of niacin might not have a substantial effect on reverse cholesterol transport, despite raising HDL cholesterol levels.

The trend towards an increase in stroke rates among study participants receiving ER-niacin is out of keeping with prior trials that have demonstrated benefits of niacin therapy. In particular, the CDP demonstrated a 24% reduction in strokes in the niacin arm.[17] Similarly, the ARBITER-6–HALTS trial demonstrated a significant improvement in the surrogate endpoint of cIMT in patients randomly allocated to receive ER-niacin as add-on therapy to statin treatment.[76] Thus, this trend in stroke risk is likely due to chance rather than a pathophysiological process.

HPS2-THRIVE

Importantly, another large, randomized, clinical trial examining cardiovascular disease outcomes with niacin therapy, namely the HPS2-THRIVE (Heart Protection Study 2: Treatment of HDL to Reduce the Incidence of Vascular Events),[81] was not terminated despite the disappointing results of AIM-HIGH and will provide valuable insight into the utility of niacin. HPS2-THRIVE is a randomized, placebo-controlled trial evaluating the effects of ER-niacin (with laropiprant) on cardiovascular endpoints in approximately 25,000 patients with a history of cardiovascular disease. The investigators plan to examine whether an increase in HDL cholesterol levels by 20–25% with ER-niacin 2 g daily translates into clinical benefit. Patients are being recruited from several European countries, as well as from China. The trial is scheduled to be completed in January 2013.[81] The results of HPS2-THRIVE will be more generalizable than those of AIM-HIGH because the trial will report on almost seven times as many patients and does not follow some of the very constraining inclusion criteria or 'clamping' of LDL cholesterol that AIM-HIGH did. Lastly, HPS2-THRIVE has a much more diverse study population with respect to demographic criteria than AIM-HIGH.

Niacin in clinical practice

Patient selection

Despite the disappointing results of AIM-HIGH and a need to clarify the benefits of HDL-cholesterol-raising therapy in general, niacin can still be useful to treat some individuals. Although statins are the primary choice for reducing LDL cholesterol levels, statin monotherapy is often insufficient to attain lipid targets. Furthermore, approximately 5–10% of individuals experience statin myopathy.[82,83] Hence, niacin is a useful alternative to statin therapy in patients with significant intolerance to statins or as a second-line or third-line addition to statin therapy in those unable to attain LDL cholesterol goals, as the LDL cholesterol reduction observed with niacin is approximately 15–18% with a daily 2 g dose.[84] The maximal reduction in LDL cholesterol levels achievable with niacin is similar to that achievable with ezetimibe, bile acid sequestrants or with fibrates.[84,85]

Niacin is well-suited for the treatment of patients with mixed dyslipidaemias, given its multiple, lipid-modifying effects—decreases in triglyceride levels of up to 40% and in LDL cholesterol levels of up to 18%, as well as increases in HDL cholesterol levels of up to 30%.[84–86] Although fibrates demonstrate reductions in triglyceride levels that are greater or comparable to those of niacin, the increase in HDL cholesterol levels induced by these agents is less. Omega-3 fatty acids induce primarily significant reductions in triglyceride levels and exhibit minimal effects on LDL or HDL cholesterol levels.[84,86,87] Thus, niacin remains a useful agent for the management of dyslipidaemias. Niacin might also be a useful therapeutic option for patients requesting 'natural' therapies, as niacin is technically a vitamin.

Although Lp(a) levels are modestly associated with an increased risk of cardiovascular disease outcomes,

Table 1 | Cardiovascular disease outcomes of randomized controlled trials on niacin

Study	*n*	Duration (years)	Treatment	Lipid changes	Cardiovascular effects of niacin
Coronary Drug Project (CDP)[17]	8,341 men aged 30–64 years with prior MI	6.0	Niacin or clofibrate vs placebo	9.9% reduction in TC; 26.1% reduction in TG	No difference in total mortality; 27% lower incidence of nonfatal MI; 24% lower incidence of all cerebrovascular events
Follow-up to CDP[72]	NA	15.0	NA	NA	11% lower mortality
Stockholm IHD Study[19]	555 patients with prior MI	5.0	Niacin plus clofibrate vs no treatment	13% reduction in TC; 19% reduction in TG	26% reduction in total mortality (P<0.05); 28% reduction in mortality in patients aged >60 years (P<0.05); 36% reduction in IHD mortality (P<0.01)
CLAS-I[20]	162 patients post CABG	2.0	Niacin plus colestipol vs placebo	TC, LDL-C and TG reduced by 26%, 43% and 22% respectively; 37% increase in HDL-C	Atherosclerosis regression in 16.2% vs 2.4% of controls
CLAS-II[73]	103 patients post CABG	4.0	Niacin plus colestipol vs placebo	Lipid changes from CLAS I were maintained	Atherosclerosis regression in 18% vs 6% in controls; nonprogression in 52% vs 15% in controls
FATS[21]	146 men with CHD aged <62 years with apoB levels ≥1.25 g/l	2.5	Group A: colestipol plus niacin Group B: colestipol plus lovastatin Group C: placebo	32% reduction in LDL-C and 43% increase in HDL-C in group A	Group A: coronary lesion progression and regression in 25% and 39%, respectively (vs 46% and 11% in placebo group)
UCSF-SCOR[74]	72 patients with heterozygous FH and CHD aged 19–72 years	2.0	Niacin plus colestipol with or without lovastatin vs diet alone	38% reduction in LDL-C; 19% reduction in TG; 28% increase in HDL-C	Significant coronary lesion regression (P=0.039)
HATS[18]	160 patients with CHD and low HDL-C (<0.90 mmol/l in men; <1.04 mmol/l in women)	3.0	Group A: niacin plus simvastatin Group B: antioxidants Group C: niacin plus simvastatin plus antioxidants Group D: placebo	Group A: 42% reduction in LDL-C; 26% increase in HDL-C	Group A: coronary lesion regression by 0.4% (P<0.0001); 88% decrease in composite primary endpoint* (P=0.03)
AFREGS[75]	143 military retirees aged <76 years with established or suspected CHD and low HDL-C (<1.04 mmol/l)	2.5	Gemfibrozil plus niacin plus cholestyramine vs placebo	At 50 weeks: 17%, 22% and 46% reduction in TC, LDL-C and TG respectively; 38% increase in HDL-C (similar results at 2.5 years)	Angiographic regression (P=0.04); lower incidence of primary cardiovascular events (26% vs 13%, P=0.04)
Thoenes *et al.*[56]	50 patients with the metabolic syndrome	1.0	ER-niacin 1 g daily vs placebo	17% reduction in LDL-C, 21% reduction in TG, 24% increase in HDL-C	More patients on niacin had cIMT regression (66.7% vs 13.3%, P=0.006); endothelial function increased by 22%
Lee *et al.*[120]	71 patients with low HDL-C (<1.04 mmol/l) and CA or PVD or T2DM with CHD	1.0	ER-niacin 2 g daily vs placebo	19% reduction in LDL-C; 23% increase in HDL-C	Significant reduction in mean carotid wall area (P=0.03)
ARBITER-2[22]	167 patients with CHD and low HDL-C (<1.17 mmol/l)	1.0	ER-niacin 1 g daily vs placebo (plus stable statin therapy)	21% increase in HDL-C	Decreased rate of cIMT progression in niacin group without insulin resistance
ARBITER-3[23]	130 patients from ARBITER-2	1.0	Patients were either continued on or crossed over (from placebo) to ER-niacin 1 g daily	LDL-C and TG decreased by 0.23 mmol/l and 0.37 mmol/l, respectively; HDL-C increased by 0.24 mmol/l	Net regression of cIMT after 1 year More significant regression after 2 years therapy
ARBITER-6[76]	208 patients aged ≥30 years with CHD or CHD risk equivalent Trial terminated prematurely; analysis of 180 patients (60% of planned sample size)	1.2	ER-niacin vs ezetimibe (on pre-existing statin therapy)	Reduction in LDL-C greater with ezetimibe than with niacin (20% vs 12%, P=0.01); increase in HDL-C greater with niacin than with ezetimibe (18% vs –7%, P<0.001)	Significant regression in cIMT (P=0.003); decreased incidence of major cardiovascular disease events (1% vs 5%, P=0.04)
AIM-HIGH[26]	3,414 patients aged ≥45 years with established cardiovascular disease Trial terminated prematurely owing to lack of efficacy	3.0	ER-niacin (1.5–2.0 g daily) vs placebo (on pre-existing statin with or without ezetimibe therapy)	Greater reduction in LDL-C and TG (14% vs 8% and 31% vs 10%, respectively) and higher increase in HDL-C (25% vs 12%) with ER-niacin	No significant difference in primary endpoint of cardiovascular disease events

*Death from coronary causes, MI, stroke or revascularization. Abbreviations: apoB, apolipoprotein B; CA, carotid atherosclerosis; CABG, coronary artery bypass graft; CHD, coronary heart disease; cIMT, carotid intima-media thickness; ER-niacin, extended release niacin; FH, familial hypercholesterolaemia; HDL-C, HDL cholesterol; IHD, ischaemic heart disease; LDL-C, LDL cholesterol; MI, myocardial infarction; NA, not applicable; PVD, peripheral vascular disease; TC, total cholesterol; TG, triglycerides; T2DM, type 2 diabetes mellitus.

the use of niacin to lower Lp(a) levels remains of uncertain benefit and has yet to be consistently advocated by guideline committees.[84,88–91]

Adverse effects

Although compliance to niacin therapy can improve with appropriate patient selection, diminishing and monitoring adverse effects is essential in the long term (Figure 2). Niacin tends to be underutilized owing to its adverse effect profile, which includes flushing, gastrointestinal and metabolic adverse effects.

Flushing

Perhaps the central aspect in ensuring compliance with niacin therapy involves addressing the adverse effect of flushing, as it is cited as the major reason for discontinuation of therapy, with rates as high as 25–40%.[92,93] A thorough description of flushing can help alleviate the patient's fear or panic that can occur with an episode. Cutaneous flushing typically involves the face and upper body and is described as a 'prickly heat' sensation. The flush starts in the face, usually within 1 h of taking niacin and is deep red in colour, with an intense feeling of warmth and itching. It can spread to the arms and chest and occasionally down to the legs and feet. The flush typically lasts <1 h and is not associated with a significant fall in blood pressure.[94]

Patients who are prescribed niacin should be advised to anticipate flushing and be reassured that it is a time-limited event and not an allergic reaction. Tachyphylaxis to the flushing often develops after as little as 1 week of regular dosing,[95] making patient education about consistent dosing and proper up-titration critical to maximize long-term compliance.

Flushing occurs most frequently with IR-niacin, with 10–50% of patients discontinuing therapy as a result.[96] In a meta-analysis of HDL-cholesterol-raising therapies, flushing occurred in up to 85% of individuals receiving IR-niacin, 66% of those receiving ER-niacin and <26% of those receiving SR-niacin.[97] However, in the ADMIT (Arterial Disease Multiple Intervention Trial), which examined the safety of niacin in 468 patients with peripheral vascular disease over 1 year, discontinuation rates for IR-niacin were 18% compared with 13% in individuals receiving placebo.[98] Given the decreased frequency of flushing with ER-niacin compared with IR-niacin,[34,35] the ER formulation might be preferable, although some patients favour the shorter duration of flushing associated with IR-niacin (generally <15 min, whereas ER-niacin-related flushing often lasts ≥30 min).[93] As mentioned previously, over-the-counter 'no-flush niacin' should be avoided owing to its lack of proven efficacy.

The expression of HCAR2 receptors in macrophages with resultant production of vasodilatory prostanoids has been shown to be involved in the production of a flush.[99,100] Epidermal Langerhans cells respond to niacin by activating the arachidonic acid pathway, which leads to the production and release of vasodilatory prostaglandins E_2 and D_2 (PGE_2 and PGD_2).[99] Via the PGD_2 receptor, PGD_2 interacts in a paracrine manner with local capillary smooth muscle cells, resulting in cutaneous capillary vasodilation.[101] Inhibiting prostaglandin release and/or interfering with the PGD_2 receptor are, therefore, potential strategies to reduce flushing.

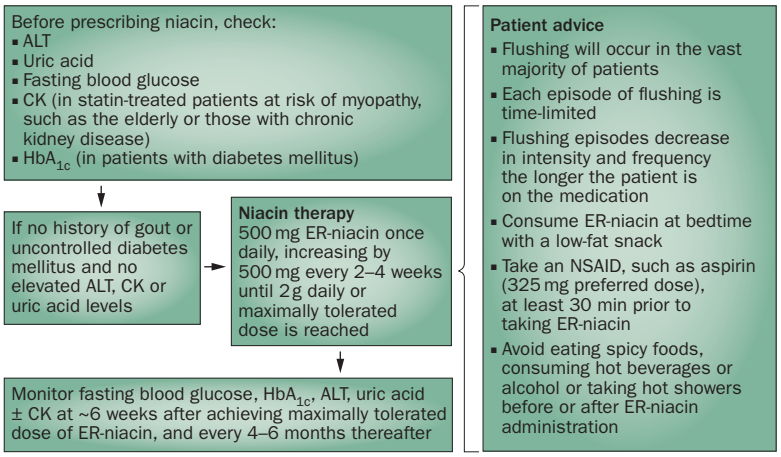

Figure 2 | Approach to initiating and monitoring niacin therapy. Niacin can be helpful as add-on therapy for further reducing LDL cholesterol levels in patients already on maximal doses of statin or as a therapeutic agent in patients with statin intolerance. Baseline and follow-up investigations, as well as strategies for optimizing compliance are outlined here. Abbreviations: ALT, alanine aminotransferase; CK, creatine kinase, ER, extended release; NSAID, non-steroidal anti-inflammatory drug.

Nonsteroidal anti-inflammatory drugs (NSAIDs), including aspirin, are cyclo-oxygenase inhibitors that can decrease prostaglandin release. Consequently, NSAIDs have been examined for their effect on decreasing niacin-associated flushing. In a randomized, placebo-controlled trial of 22 individuals receiving 500 mg crystalline niacin, that is IR-niacin, combined with either ibuprofen (200 mg) or uncoated aspirin (165 mg or 325 mg), individuals with the worst symptoms receiving any one of the three active treatments had statistically significant reductions in flushing.[102] Of the three treatments, high-dose aspirin was most effective in decreasing flushing.[102] Non-enteric coated aspirin, given 30 min before a niacin dose, significantly reduced the incidence of flushing by 42%.[102–107] Higher doses of aspirin (325 mg) have been demonstrated to be more effective than lower doses (80–160 mg).[108]

Also, coadministration of the PGD_2-receptor-selective inhibitor laropiprant decreases ER-niacin-induced flushing by 50% compared with ER-niacin alone.[101,109] Laropiprant combined with niacin has been demonstrated in early clinical trials to significantly decrease niacin-induced vasodilation.[101] However, this combination is currently available only in some European countries, such as the UK and Germany, and not yet approved for use in North America pending safety and efficacy data, which are expected from the ongoing HPS2-THRIVE trial.[81]

Given that the onset of a flush is linked to a rapid increase in peak plasma concentrations,[29] methods to slow the release of niacin, such as taking the drug with food or using the ER preparation, have been employed

to ameliorate flushing. Bedtime is the preferred time for ER-niacin administration, so flushing occurs when the patient is asleep. Thus, ER-niacin can be started at a dose of 500 mg once daily at bedtime with a low-fat snack and titrated by 500 mg every 2–4 weeks, depending on tolerability, until a maximum dose of 2 g daily is achieved (Figure 2). If only 1 g ER-niacin daily is tolerated, niacin therapy should not be abandoned, as favourable lipid changes are still seen at this dose. If IR-niacin is used, it should be administered in divided doses, starting at 50–100 mg twice daily at meal time (during or immediately after meals) and titrated by doubling the dose each week until 1.5–2.0 g per day is reached. Uncoated aspirin or ibuprofen 200 mg can be administered 30 min prior to either niacin formulation to decrease the risk of flushing. Conditions that predispose to vasodilation, such as hot showers, alcohol intake or consumption of hot liquids or spicy foods, should be avoided at the time of niacin administration.

Gastrointestinal adverse effects

Increases in liver enzyme levels can occur with any formulation of niacin, although hepatotoxicity was primarily seen with SR formulations.[93] Based on the FDA's Adverse Event Reporting System (AERS), Alsheikh-Ali and Karas demonstrated a 6.7-fold lower reported frequency of liver enzyme elevations for ER-niacin compared with other formulations.[33] In a randomized, placebo-controlled trial of 131 patients, other gastrointestinal adverse effects included a twofold and fivefold increased frequency of nausea and vomiting, respectively, with ER-niacin compared with placebo.[36] Although nicotinic acid has previously been shown to increase gastric acid production,[110] the frequency of dyspepsia was not significantly different between placebo-treated and ER-niacin-treated individuals.[36]

Liver enzyme values should be checked before niacin treatment to rule out a pre-existing liver condition. No formal guidelines exist to advise on the timing or requirement of repeat liver enzyme evaluations. In our practice, we recheck serum transaminase levels 4–8 weeks following achievement of the maximally tolerated niacin dose and only periodically every 4–6 months thereafter, as these patients are often prescribed other lipid-lowering agents. Ensuring the patient has a snack when administering niacin can alleviate nausea and dyspepsia. However, dyspepsia can be clinically significant enough to warrant discontinuation of niacin therapy.

Metabolic adverse effects

Increased insulin resistance has been reported in some patients taking niacin and could lead to an increased frequency of new-onset diabetes mellitus. Reports of substantial deterioration of glycaemic control in patients with diabetes mellitus were found in studies that used niacin doses as high as 4.5 g per day, doses commonly used in the pre-statin era to treat hypercholesterolaemia.[111] Importantly, however, the CDP trial showed no significant differences between niacin-treated and placebo-treated individuals in new prescriptions for insulin or oral hypoglycaemic drugs, or in dipstick-positive glycosuria.[17]

Moreover, examination of a subsample of patients with diabetes mellitus ($n = 25$) in the HATS trial revealed only a slight deterioration of glycaemic control due to niacin during the first 8 months of treatment, but a return to pretreatment levels for the remainder of the study.[112] Among 124 patients without diabetes mellitus or impaired fasting glucose (IFG) at baseline, 12 individuals developed IFG and three developed diabetes mellitus. Although the incidences of diabetes mellitus and IFG were higher in the group receiving niacin, the results were not statistically significant.[112] Among 50 patients with the metabolic syndrome who were randomly allocated to receive ER-niacin or placebo for 52 weeks, no significant changes in fasting glucose or HbA_{1c} levels were demonstrated in those receiving ER-niacin.[56] However, a paucity of data remains regarding the effect of niacin on the progression of patients with the metabolic syndrome or IFG to diabetes mellitus.

The safety of niacin use in diabetes mellitus was further demonstrated in ADMIT, which examined the effects of niacin (3 g daily) in patients with peripheral vascular disease over 1 year. Of 468 patients, 125 individuals had diabetes mellitus. The average blood glucose of both diabetic and nondiabetic patients increased marginally but was not of clinical significance (0.43 mmol/l and 0.3 mmol/l, respectively), whereas HbA_{1c} levels were unaffected.[98] Furthermore, no significant differences in niacin discontinuation, dosage or hypoglycaemic therapy were noted in patients with diabetes mellitus compared with the placebo group.[98] Similar results were evident in the ADVENT (Assessment of Diabetes Control and Evaluation of the Efficacy of Niaspan) trial, in which 148 patients with type 2 diabetes mellitus were randomly allocated to receive placebo or ER-niacin 1,000 mg or 1,500 mg daily.[113] At the end of this 16-week, double-blinded trial, HbA_{1c} levels were significantly increased only in the 1,500 mg ER-niacin arm (7.2% at baseline and 7.5% at completion, $P = 0.048$), although the difference was not clinically relevant.[113]

Analysis of an administrative claims database revealed no significant increase in antihyperglycaemic agent use among patients with type 2 diabetes mellitus treated with ER-niacin ($n = 392$) and those treated with another lipid-lowering agent ($n = 3,407$).[114] Furthermore, a systematic review of the effects of niacin on glycaemic control showed the increase in fasting glucose and HbA_{1c} levels to be modest (approximately 4–5% for fasting glucose and ≤0.3% for HbA_{1c}), transient or reversible and easily modifiable with adjustments in diabetic treatment regimens.[115] Whether similar modest and transient elevations in glucose values secondary to niacin therapy were evident in the AIM-HIGH trial remains to be reported. But, thus far, fear of possibly increasing insulin resistance should not deter clinicians from prescribing niacin to patients with diabetes mellitus, as its efficacy has been shown in those with stable, controlled disease. Nevertheless, as niacin can result in modest and transient

increases in glucose levels, fasting glucose levels should be monitored regularly in all patients, but especially in patients with diabetes mellitus.[17,18,98,115] Given the natural history of diabetes mellitus, changes in medical therapy for diabetes mellitus are often warranted regardless of niacin use. However, we instruct patients to notify us of any rapid deterioration after starting niacin, and we closely monitor glucose and HbA_{1c} levels to ensure that a sudden deterioration is not missed. To date, in our practice, we have not needed to discontinue niacin therapy in patients with diabetes mellitus or the metabolic syndrome as a result of a significant deterioration in glycaemic control.

Another possible adverse effect of niacin therapy is an elevation in plasma uric acid levels, particularly with long-term treatment, that can lead to a manifestation of gout. The mechanism has been proposed to be secondary to competitive inhibition of tubular secretion of uric acid by niacin.[116] Although the increase in serum uric acid is moderate in patients with normal pretreatment levels, it can be clinically relevant in patients with pre-existing gout and/or high levels of uric acid (>1.5 times the upper limit of normal) before treatment. In these patients, niacin therapy should be avoided. However, in patients with normal or slightly raised pretreatment levels of uric acid (<1.5 times upper limit of normal), niacin can be cautiously administered. Uric acid levels should be measured at baseline and throughout treatment with niacin.[93] With any increase in serum uric acid of clinical significance, treatment with allopurinol at doses of 100–300 mg per day has been advocated.[93]

Other adverse effects

Other adverse effects with niacin therapy include dry skin (albeit rarely severe), acanthosis nigricans and a few cases of retinal oedema, the latter of which dissipates immediately when treatment is stopped. Importantly, adverse effects in muscle, including significant creatine kinase elevations, have not been associated with niacin monotherapy. The presence of myalgias that are different from the patient's usual muscle symptoms should be determined at each visit. Baseline and follow-up creatine kinase values can be helpful, particularly in individuals already on statin therapy. Although no consistent guidelines exist on the requirement for baseline or periodic creatine kinase evaluations in patients on niacin monotherapy, the National Lipid Association has suggested monitoring creatine kinase levels when niacin is added to established statin therapy in those patients who might be at risk of statin-induced myopathy.[93] In our practice, we often recheck creatine kinase levels 4-8 weeks following achievement of a maximally tolerated niacin dose and only periodically thereafter.

In 2000–2004, based on the FDA AERS, the incidence of rhabdomyolysis was low, at one case per million prescriptions of ER-niacin.[33] Similarly, although an increased incidence of myopathy and rhabdomyolysis is an often cited concern with niacin–statin combination therapy, this effect is unlikely; *in vitro* experiments have demonstrated that niacin does not have inhibitory effects on cytochrome P450 (CYP) 3A4 (responsible for metabolism of atorvastatin, simvastatin and lovastatin) or on CYP2C9 (responsible for metabolism of rosuvastatin and fluvastatin).[117–119] In fact, an increased incidence of rhabdomyolysis with niacin–statin combination therapy has not yet been supported by clinical trial data[23,112] or in postmarketing surveillance studies.[33]

Conclusions

The body of evidence suggests that the majority of the clinically relevant benefit of niacin is related to its lipid-altering effects. Before the introduction of statins, niacin, as monotherapy[17] or in combination with other treatments,[18–21,73] exhibited relatively large effects on lipids, and its relationship with improved cardiovascular outcomes was more clearly observed. By contrast, most patients at high risk of cardiovascular events are nowadays well-treated with statins, so the opportunity to observe an incremental benefit from the addition of a second agent, whether niacin or another, is reduced. This hypothesis is perhaps most evident in the AIM-HIGH study,[26] in which the lipid-altering effects of niacin were greatly attenuated compared with expectations, and the accompanying effect on cardiovascular outcomes was essentially neutral.

Although most of the focus has been on raising HDL cholesterol levels, the disappointing results of the AIM-HIGH trial have called this approach and the utility of niacin for cardiovascular disease protection (in the presence of optimal LDL cholesterol levels) into question. Nonetheless, the AIM-HIGH results thus far do not warrant casting away niacin from the lipid-treatment armamentarium. Niacin-based therapies still have a role in selected patients as a second-line agent, to be added to maximally tolerated statin therapy when the LDL cholesterol level is highly increased above target. In our practice, niacin is also sometimes considered as a second-line or third-line agent when plasma triglyceride levels are elevated (for example, >4.0–5.0 mmol/l) and/or HDL cholesterol levels are low in the setting of an elevated total cholesterol:HDL cholesterol ratio. Also, niacin therapy is a reasonable consideration for patients at risk of cardiovascular disease who experience severe statin intolerance. However, niacin remains underutilized, primarily owing to concerns over adverse effects. Choosing the appropriate patient and knowing strategies to improve tolerability of niacin during initiation and continued treatment can help reduce noncompliance. Moreover, further research for the development of related molecules that can deliver the positive effects of niacin without any adverse effects is warranted.

Review criteria

A search of full-text articles in the English language published between 1950 and 2011 was performed in PubMed using the keywords "niacin", "nicotinic acid", "lipids", "cholesterol", "LDL", "HDL" and "cardiovascular disease". Reference lists in selected articles were used to further expand the search.

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Author contributions

J. C. Creider and T. R. Joy researched the data for the article. All authors provided a substantial contribution to discussions of the content, contributed equally to writing the article and reviewed and/or edited the manuscript before submission.