

Safety and efficacy of laropiprant and extended-release niacin combination in the management of mixed dyslipidemias and primary hypercholesterolemia

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Abstract: Statins form the cornerstone of pharmaceutical cardiovascular disease prevention. However, despite very effective statin intervention, the majority of events remain unpreventable. In some cases statin therapy alone is insufficient to achieve adequate lipid levels whereas other patients are unable to tolerate statins. This calls for additional treatment options. Niacin has a long history of success in reducing low-density lipoprotein cholesterol and triglycerides, and increasing high-density lipoprotein cholesterol. It was the first lipid-lowering drug to demonstrate a reduction in cardiovascular events, and remains the only one that has consistently shown benefits on surrogate outcomes when added to background therapies of other lipid-lowering drugs, including statins. Niacin's uptake in clinical practice has been less successful due to its side-effect profile, most notable being flushing. The uncovering of the mechanism by which flushing is induced, together with the development of a prostaglandin D₂ receptor inhibitor (laropiprant) which reduces this downstream flushing effect of niacin, has sparked new promise in therapeutic lipid management. It provides an additional treatment option into managing lipid abnormalities. The uptake in clinical practice of the niacin-laropiprant combination will depend on the relative improvements experienced by the patient in the side-effect profile compared to other treatment options, as well as on the the keenly-awaited outcome studies currently underway. Until these data become available guidelines and recommendations are unlikely to change and niacin's position in therapeutic cardiovascular risk prevention will be determined by clinician opinion and experience, and patient preferences.

Keywords: niacin, laropiprant, lipid abnormalities

Introduction

Cardiovascular disease (CVD) is the leading cause of illness and death in the world and this statistic is not projected to change in the next decade.^{1,2} It manifests most frequently as ischemic heart disease and cerebrovascular disease, and atherosclerosis is the primary cause of this.³ Research into understanding the underlying mechanisms of disease together with the formulation of compounds that are able address the underlying pathology has now spanned numerous decades. The fact that atherosclerotic plaque is largely made up of cholesterol has been known since the middle of the 19th century and, since then, abundant data link hypercholesterolemia to atherogenesis.⁴ The most extensively researched of the pharmaceutically modifiable

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risk factors is cholesterol; in particular, the lowering of low-density lipoprotein cholesterol (LDL-C) forms the primary target of focus in CVD risk prevention.^{5,6} Statins form the cornerstone of pharmaceutical CVD prevention, and their efficacy in reducing mortality in both primary and secondary prevention settings is beyond dispute.^{7,8} Over the past decade these drugs have been particularly successful in the market, growing in excess of \$25 billion.⁹ However despite very effective statin intervention the majority of events remain unpreventable. Around 20% of patients in the statin arm of the Heart Protection Study suffered from major cardiovascular events in 5 years, and it is reckoned that only 40%–50% of potential events may be prevented by statin therapy.^{10,11} Furthermore, statin therapy suffers from several limitations.⁴ These include both lack of sufficient efficacy and clinical side-effects related to their use. The treatment of 1000 patients is likely to prevent 37 events at the cost of five discontinuations due to side effects.¹² The main disadvantage of statins is their shallow dose efficacy profile in that doubling the dose only results in a 5%–7% extra reduction in LDL-C,^{13,14} but this occurs with an exponential effect in increasing side effects.¹⁵ This provides the drive in the search for additional benefits beyond statin treatment.

Low-density lipoprotein cholesterol and statins

LDL is the main atherogenic lipoprotein particle and remains the primary target for lipid-lowering therapy.^{5,6} Early epidemiological studies incriminated high levels of LDL-C as being atherogenic with the serum total cholesterol (TC) as a good correlate for LDL-C levels.⁵ This was followed by unequivocally demonstrating the clinical benefit of LDL-C lowering. The most notable evidence comes from the clinical trials of statins.^{7,8} Their primary effect on the lipid parameters is their ability to lower LDL-C. Statins act by inhibiting the enzyme 3-hydroxy-3-methylglutaryl coenzyme A (HMG CoA) reductase, which catalyzes the rate-limiting step in cholesterol synthesis. Inhibition of HMG CoA reductase leads to increased expression of LDL receptors on hepatocytes with increased LDL-C uptake from the circulation. Despite being prescribed for their cholesterol-lowering effect, statins have several other advantageous pleiotropic effects counteracting atherosclerosis. The pleiotropic effects of statins include improvement of endothelial dysfunction, increased nitric oxide bioavailability, antioxidant properties, inhibition of inflammatory responses, and stabilization of atherosclerotic plaques.¹⁰

Despite their success and the substantial benefits attributable to statins a significant preventable gap remains. There is also increasing demand for LDL-C reductions of more than 50%, and approaching 90% in some cases of familial hypercholesterolemia, and as LDL-C targets are progressively reduced in patients with established coronary heart disease. Statins also show wide variation in dose response,¹⁵ variations in bioavailability, and no clear pharmacogenetic basis to efficacy or safety.^{16,17}

Apart from the benefits shown following statin treatment, lowering of LDL-C seems beneficial irrespective of the method employed.¹⁸ A meta-analysis of five diet, three bile acid sequestrant, one surgery, and 10 statin trials, with 81,859 participants, showed a relationship between LDL-C lowering and reduction in cardiovascular events.¹⁹ Professional guidelines therefore focus primarily on LDL-C.^{5,6,20} However, demonstration of a mortality benefit is still awaited for most other therapies which lower LDL-C concentrations.

Owing to the disease burden and the substantial residual risk which remains despite statin treatment, the need exists for additional therapies. This may in part be due to the success of statin treatment, where newer agents have to show equivalent efficacy or additional benefit on the background of statin treatment, which is proving very costly in the clinical trial setting.²¹

Niacin

Vitamin B₃ is essential to all living cells. There are two forms of vitamin B₃: nicotinic acid (or niacin) and nicotinamide. Both the acid and the amide are precursors to the coenzyme, nicotinamide adenine dinucleotide (NAD⁺) and its phosphorylated form NADP, which are key factors in dehydrogenation reactions.²² These molecules are also essential components of numerous biosynthetic pathways, cell protection, and signaling mechanisms.^{23,24} Vitamin B₃ was initially best known for its clinical manifestation as a deficiency. Deficiency of vitamin B₃ was referred to as the disease with the four 'D's': namely: dermatitis, diarrhea, dementia and death.²⁵ Two centuries after pellagra was first described in 1735, its etiology was elucidated. It was shown that nicotinic acid could cure black tongue in dogs, which was an early animal model for pellagra.²⁶

It was a further two decades later, in the early 1950s that the lipid-lowering effects of niacin were described by the pathologist Rudolf Altschul.²⁷ He reported his initial findings following experiments in rabbits and then in a landmark study of its effects in humans.²⁸ Niacin was the first medication to show notable lipid-lowering effects in

humans. Merely a year after Altschul's report it was shown by another group that 3 g of nicotinic acid per day was able to reduce plasma cholesterol by 16% on average in a group of patients with familial hypercholesterolemia.²⁹ Importantly, this study showed that the reduction in cholesterol was due to a decrease in β -lipoproteins, ie, LDL-C. Furthermore, it was also shown that the ratio of β to α 1-cholesterol [ie, LDL-C to high-density lipoprotein cholesterol (HDL-C)] decreased from 9.0 to 5.6.

Clinical studies with niacin

These initial findings formed the basis for investigating the effect of lipid lowering to reduce cardiovascular events. Table 1 depicts the most notable clinical trials involving niacin. Niacin was the first lipid-lowering agent shown to significantly reduce cardiovascular events, although not in-trial mortality, in the Coronary Drug Project (CDP) which randomized 3908 men with previous myocardial infarction (MI) to either nicotinic acid or placebo.³⁰ Major coronary heart disease (CHD) events, nonfatal MI, and cerebrovascular events were reduced by 22% but there was no effect on overall mortality.

However in the 15-year post-trial follow-up, nearly 9 years after termination of the trial, mortality from all causes was 11% lower in the nicotinic acid group.³¹ The other arms of the CDP using clofibrate, d-thyroxine, and estrogen showed no effect or were terminated early.

Several long-term clinical studies with nicotinic acid have demonstrated a reduction in surrogate outcomes, CHD events, and mortality, when used in combination with other lipid-modifying drugs which include colestipol (a bile acid sequestrant),³² clofibrate³³ and statins.^{34,35} The Cholesterol-Lowering Atherosclerosis Study (CLAS)³² was a randomized, placebo-controlled, angiographic trial testing combined colestipol hydrochloride and niacin therapy in 162 men aged 40 to 59 years with previous coronary bypass surgery. Atherosclerosis regression, as indicated by perceptible improvement in overall coronary status, occurred in 16.2% of colestipol–niacin treated men vs 2.4% placebo treated ($P=0.002$). In the underpowered Stockholm Ischemic Heart Disease Secondary Prevention Study, 555 patients received either clofibrate and nicotinic acid, or standard treatment.³³ Total mortality was 82 cases in the control group and 61

Table 1 Notable trials including niacin^{30,32–36,39,40}

Study	Year reported	Interventions	Number patients	Outcome measures	Note
CDP	1975	Niacin Clofibrate Thyroxine Estrogen	8341	Decreased nonfatal MI for Niacin arm	1119 patients received niacin; all other arms had no effect or were terminated early
CLAS	1987	Niacin and colestipol	162	Coronary angiography	Decreased atherosclerosis
S-IHD		Niacin and clofibrate vs standard care	555	Overall mortality	Not blinded No placebo control Underpowered
HATS	2001	Niacin and simvastatin vs Antioxidants vs niacin and Simvastatin and antioxidants vs Placebo	160	Coronary angiography and MACE	Reduction in MACE on niacin and simvastatin arm
ARBITER 2	2004	Niacin vs placebo Added to statin	160	cIMT	cIMT progression between groups was not statistically significant
ARBITER 6	2009	Niacin vs ezetimibe Added to statin	208	cIMT	Superior efficacy of Niacin over ezetimibe
AIM HIGH	Due to report in 1–2 years	Niacin vs placebo Added to statin	~3300	MACE	
HPS2 – THRIVE	Due to report in 4–5 years	Niacin and laropiprant vs placebo Added to simvastatin $\pm$ ezetimibe	~28 000	MACE	

Abbreviations: CDP, Coronary Drug Project; CLAS, Cholesterol-Lowering Atherosclerosis Study; S-IHD, Stockholm Ischemic Heart Disease Secondary Prevention Study; HATS, HDL-Atherosclerosis Treatment Study; ARBITER, Arterial Biology for the Investigation of the Treatment Effects of Reducing Cholesterol; AIM-HIGH, HPS2 – THRIVE, Heart Protection Study 2-Treatment of HDL to Reduce the Incidence of Vascular Events; cIMT, carotid intima media thickness; MACE, major adverse cardiovascular event.

in the treatment group, a 26% reduction ($P < 0.05$). The main limitation of this study is that it was not blinded and was without a placebo control. The Arterial Biology for the Investigation of the Treatment Effects of Reducing Cholesterol (ARBITER) 2 study investigated the effect of niacin added to background statin treatment in patients with known CHD.³⁴ This was a double-blind randomized placebo-controlled study involving 167 patients, and the primary endpoint was the change in common carotid intima-media thickness (cIMT) after 1 year. The overall difference in cIMT progression between the niacin and placebo groups was not statistically significant ($P = 0.08$). The HDL-Atherosclerosis Treatment Study (HATS) enrolled 160 patients who were randomly assigned to receive one of four regimens: simvastatin plus niacin, antioxidants, simvastatin-niacin plus antioxidants, or placebos. The primary end point was arteriographic evidence of a change in luminal coronary stenosis and the secondary occurrence of a first cardiovascular event.³⁵ The study showed no effect of antioxidants but proved that patients receiving simvastatin in combination with niacin had a significant reduction in cardiovascular events but a lesser increment in HDL-C. The recently-reported ARBITER 6 study compared niacin to ezetimibe in patients who were receiving baseline statin treatment.³⁶ The primary endpoint was the between-group difference in the change from baseline in the mean cIMT after 14 months. The trial was terminated early, on the basis of efficacy, according to a prespecified analysis conducted after 208 patients had completed the trial. As compared with ezetimibe, niacin had greater efficacy regarding the change in mean cIMT over 14 months ($P = 0.003$).

These studies either did not test the additional benefit of niacin over statin treatment or when this was attempted, such as in the ARBITER studies, the surrogate marker of cIMT was employed. Furthermore, the limitations of employing surrogate markers need to be appreciated.³⁷ The use of the cIMTs as a surrogate marker for coronary atherosclerosis remains controversial. Although in observational studies the cIMT has been shown to predict future cardiovascular events, it is sometimes less clear what the changes in measurements under certain circumstances truly imply.³⁷ There are therapies other than niacin that retard the progression of cIMT (ie, estrogen and thiazolidinediones) but do not reduce the incidence of cardiovascular events.^{37,38}

These uncertainties call for outcome studies which will unequivocally demonstrate the benefit of niacin in addition to statin treatment. Fortunately, such studies are currently underway. The first is the Heart Protection Study

2-Treatment of HDL to Reduce the Incidence of Vascular Events (HPS2-THRIVE) which will evaluate niacin plus laropirant compared to placebo in patients with established cardiovascular disease on a background of simvastatin 40 milligrams (mg) with or without ezetimibe.³⁹ This study is currently still recruiting patients and aims to include around 28,000 individuals with a prespecified subgroup of 6000 patients with diabetes. The findings are expected to be reported in 4–5 years' time. The other outcome study underway is the Atherothrombosis Intervention in Metabolic syndrome with low HDL-C/high triglyceride and Impact on Global Health outcomes (AIM-HIGH) which compares a modified-release niacin in patients with established coronary heart disease allied with dyslipidemia to placebo in patients already receiving simvastatin.⁴⁰ This study is to include around 3300 patients and it is hoped that it will be reported in the next year. These studies will also help in casting more light on the other lipid parameters (other than LDL-C) on which niacin also has an effect.

Effect of niacin and position in treatment of lipid abnormalities

Whereas the vitamin activity of niacin, which involves cellular processes, is apparent in milligram doses, the lipid-modifying effects are seen in doses a thousand-fold greater. Owing to its favorable effects not only on LDL-C but also on HDL-C and triglycerides (TG), niacin has been referred to as the 'broad-spectrum' lipid drug.⁴¹ The magnitude of these effects can be broadly summarized by the 'rule of 20', namely a 20% reduction in LDL-C and TG, and a 20% increase in HDL-C, at a dose of more than 1.5 g/day.^{41,42}

Lipoproteins are complex particles and can be referred to as being heterogeneous and polydisperse.⁴³ Heterogeneity refers to the presence of several different subparticle classes within the lipoproteins. For example, depending on the analytical technique used, as many as 14 subfractions of high-density lipoprotein (HDL) can be distinguished. The term polydisperse indicates that each of the subclasses includes varying proportions of lipids and proteins. Around 60 protein types are associated with HDL and about 12 with LDL.^{44,45}

Low density lipoprotein

Niacin is a potential treatment option to lower LDL-C. This could include patients on existing statin therapy where additional reduction is desired, such as patients with familial hypercholesterolemia, or in patients' intolerant to statin treatment. Not only does niacin lower LDL-C but it also has a potential further beneficial effect on LDL. Like fibrates,

it shifts the subtype distribution by reducing the number of smaller and denser particles to ones which contain more cholesterol.⁴⁶ Large numbers of studies including the Quebec Cardiovascular study have confirmed the association of small dense LDL with cardiovascular disease, which reported that men with small dense LDL particles had an increased risk of CAD compared with men with normal-sized LDL particles, independent of LDL-C, triglyceride, and the total cholesterol: HDL-C ratio.^{47,48} The beneficial effects of niacin may be underestimated if LDL-C is the only parameter being assessed. This potential beneficial effect of niacin is tantalizing, as no prospective studies have specifically examined whether altering particle size profiles results in benefits on cardiovascular events, though analysis of the Veterans Affairs High-Density Lipoprotein Intervention Trial (VA-HIT) study does suggest some role for this mechanism, admittedly without including non-HDL-C or apolipoprotein B in the model.⁴⁹

High-density lipoprotein

Analogous to LDL, the HDL class also comprises a heterogeneous population of particles. The inverse relationship between HDL-C levels and atherosclerotic CVD provides the epidemiological basis for the widely accepted hypothesis that HDL-C is atheroprotective.^{50,51} Experimental studies, which include limited work on humans, have shown that HDL has several distinct but potentially overlapping atheroprotective functions. These include the well-known reverse cholesterol transport⁵² as well as reductions in oxidative stress and innate immune inflammation.⁵³ More HDL-associated proteins are involved in immune/inflammatory functions than in lipid transport and metabolism, suggesting the fundamental role for HDL in innate immunity.⁴⁴ Niacin is the most powerful drug currently available to raise HDL-C. Following the epidemiological evidence on HDL-C it would be intuitively reasonable to attempt to raise HDL-C with the expectation of reducing cardiovascular events. However, as opposed to LDL-C lowering, therapies to intervene in order to raise HDL-C have proven to be ‘not that simple’. Some HDL therapies may reduce CVD without actually changing HDL-C concentrations.⁵⁴ The intravascular ultrasound study (IVUS) of the effects of five weekly infusions of a hyper-functional apolipoprotein A-1-Milano (apoA-1)^{Milano}, produced significant regression of coronary atherosclerosis after three months. In contrast in the Investigation of Lipid Level Management to Understand Its Impact in Atherosclerotic Events (ILLUMINATE) trial which investigated the cholesterol ester transfer protein (CETP) inhibitor, torcetrapib in 15,000 patients, HDL-C increased by 72% and

LDL-C decreased by 25%, but this trial was terminated early because the treatment arm had an increase of major cardiovascular events by 25%, and death from cardiovascular causes by 40%.⁵⁵ The outcome studies with niacin that are currently underway will also help answer the question on raising HDL. Analogous to the apparent improvement in the LDL profile, niacin also causes a shift in the HDL profile leading to more HDL₂ (larger, cholesterol-rich particles) than HDL₃ (small, lipid-poor particles).⁴¹ Whether this shift is beneficial, as is sometimes advocated, is not clear. In general, controversy still exists in regard to whether the anti-atherogenic effect of HDL can be attributed to one or both HDL subfractions, and what is the relative importance of HDL₂ and HDL₃ cholesterol.⁵⁶ In the Kuopio Study⁵⁷ and Quebec City Suburbs Study,⁵⁸ HDL₂ was inversely associated with CHD, whereas HDL₃ had a stronger inverse association with CHD in the Physician’s Health Study⁵⁹ and the 9-year follow-up of the Caerphilly study.^{56,60} These differences in the results of various studies may be attributable to the different assay methods used, to ethnic variations, or to the probable heterogeneity of the subfractions with different physiological functions.⁵⁶

Triglycerides

Niacin generally reduces triglyceride levels by 15% to 25% in a dose-dependent manner, with the triglyceride-reduction effects seeming to parallel its action in raising HDL-C.^{41,61,62} It is well-established that elevated serum TG levels are associated with increased risk for atherosclerotic events.⁶³ However to prove its causality is more difficult, and directly targeting TG in curbing cardiovascular disease is more controversial.^{62,64} As high serum TG levels tend to ‘keep bad company’, being associated with abnormal lipoprotein metabolism, as well as with other cardiovascular risk factors including obesity, insulin resistance, diabetes mellitus, and lowered levels of HDL-C, it becomes more difficult to distinguish between cause and effect. Some causes of hypertriglyceridemia have no apparent effect on atherosclerotic vascular disease, making it difficult to prove that elevated TGs are a risk factor, as opposed to being an innocent bystander.^{62,65} Despite no clear consensus on the benefits of directly targeting hypertriglyceridemia to reduce CVD, it is generally recommended to reduce significantly-elevated triglyceride concentrations in order to reduce the risk of pancreatitis.^{66,67}

Lp(a) lipoprotein

Lp(a) lipoprotein is a lipoprotein of unknown physiologic function that is composed of apolipoprotein B-100 to which apolipoprotein(a) is covalently bound.⁶⁸ Elevated plasma

Lp(a) lipoprotein concentrations are associated with CHD.⁶⁹ A key unresolved question is whether an elevated plasma level is the cause or the consequence of CAD, but recent epidemiological and genetic data suggest the hypothesis that lowering the plasma Lp(a) lipoprotein concentration by pharmacological means may lower the risk of CAD.^{70–72} These recent findings have generated renewed interest in this molecule as a potential therapeutic target. The only currently approved agent to effectively lower Lp(a) lipoprotein levels is niacin. Other drugs in development (including anacetrapib—a CETP inhibitor, mipomersen – an antisense oligonucleotide directed against apolipoprotein B-100 and thyroid analogues) are also able to significantly reduce Lp(a) lipoprotein levels.

Position of niacin in treating hypercholesterolemia

From this it is clear that niacin has an advantageous effect on most lipid parameters. As statins form the mainstay of CVD risk prevention, other treatment options are generally only considered as add-on treatment to statins. Only in cases where patients are either intolerant to statins, or when statins are contraindicated, or in cases where the primary abnormality is that of hypertriglyceridemia, nonstatin treatments are considered as first line treatments.^{5,73} In cases where statins are not considered as the front line treatment, there is no clear guidance which drug is the best alternative, nor is there clear guidance on which treatment should follow statin treatment. Currently the only other treatment options include: fibrates, bile acid sequestrants and ezetimibe. As is the case with niacin, none of these therapies have outcome data when combined with statins.^{5,6}

Mechanism of action

The mechanism by which niacin affects plasma lipids is not completely understood.^{73,74} The basic mechanism for the lipid-modifying effects of nicotinic acid has previously been attributed to its inhibition of lipolysis in adipose tissue.⁷⁵ The reduction in free fatty acids liberated from adipose tissue results in a reduction of hepatic triglycerides available for very low density lipoprotein and LDL synthesis. More than 40 years ago Carlson described how nicotinic acid is rapidly taken up and preferentially accumulates in the adipose tissue.⁷⁶ This mechanism was supported by the discovery of a specific high-affinity receptor on the membranes of adipocytes.⁷⁷ This is a G-protein coupled receptor known as GPR109A but later specific GPR109A agonist showed no effects on lipids. This is only one of the potential

mechanisms by which nicotinic acid may affect lipids, and it is now believed that physiologically and clinically, this pathway may be only a minor factor in explaining the lipid effects of niacin.⁷⁸ New findings indicate that niacin directly and noncompetitively inhibits hepatocyte diacylglycerol acyltransferase-2 (DGAT-2), a key enzyme for TG synthesis. The inhibition of TG synthesis by niacin results in accelerated intracellular hepatic apolipoprotein B degradation and the decreased secretion of VLDL and LDL particles.⁷⁸ Niacin also retards the hepatic catabolism of apolipoprotein A-I which explains the increases in HDL half-life and concentrations of lipoprotein A-I HDL subfractions, which augment reverse cholesterol transport.⁷⁸

Safety and side effects of niacin

Despite its ability to significantly improve all these lipid parameters, relatively few clinicians resort to niacin as a treatment option. Apart from lacking evidence in demonstrating a benefit on all cause mortality its use is also hampered by its side-effect profile. One in depth report on the discontinuation of lipid-modifying drugs in clinical practice gauged the one-year adjusted cumulative incidence of discontinuation for extended-release (ER) niacin to be 55.4%.⁷⁹ This may not sound that encouraging, but the same study also found the adjusted cumulative incidence of discontinuation was 28.9% in statin users. The most notable side-effect leading to discontinuation of niacin is flushing. This side effect, although harmless, strongly affects patient compliance. Nicotinic acid was initially used as plain nicotinic acid, in crystalline immediate release form. In an attempt to minimize flushing, various release formulations were developed. Initially, a sustained release formulation was developed but this was associated with hepatotoxicity and its clinical use was abandoned. A prolonged release formulation, known as ER niacin (marketed as Niaspan) was developed. This compound has absorption rates between plain nicotinic acid and sustained release forms, while having equivalent efficacy to alter lipid parameters.^{80,42} As the overall safety profile of this formulation is significantly better compared to other nicotinic acid formulations, it is the form that is now being evaluated in the ongoing outcome studies. In particular, the ER form does not raise particular concerns related to hepatotoxicity. In a 59-week-study which evaluated once-daily dosing ER niacin, only two subjects out of 723 had aspartate aminotransferase (AST) levels >3 times the upper limit of normal (ULN) and no subjects with alanine aminotransferase (ALT) >3 times ULN.⁸¹ Trials involving the combination of ER niacin and a

statin show neither evidence of hepatotoxicity nor signs of potentiating statin-induced myopathies.^{82–84}

The other notable potential harmful effect of niacin is that it induces elevations of glucose in a dose-dependent manner. The mechanism by which this occurs is also not well understood, but it is thought to be related to its action on free fatty acids. In a study which investigated the efficacy, safety, and tolerability of once-daily ER niacin for the treatment of dyslipidemia associated with type 2 diabetes it was found that at week 16 the HbA1c did show an increase. This change wasn't statistically significant in the 1 g group, but the increase from 7.2% to 7.5% in the 1.5 g group was statistically and possibly clinically significant.⁸⁵ Analysis of data from the CDP showed that regardless of how patients were grouped, niacin appeared as effective in lowering cardiovascular outcomes in patients with hyperglycemia as it is in patients with normoglycemia.⁸⁶ The current Position Statement from the American Diabetes Association suggests the use of nicotinic acid as an option in treating lipoprotein fractions other than LDL-C. It reports that

only modest changes in glucose occur and that these are generally amenable to adjustment of diabetes therapy.⁸⁷ A previous statement⁸⁸ discouraged its routine use, as do the recent UK-based National Institute of Health and Clinical Excellence guidelines for management of diabetes.⁸⁹

Despite its having a better side-effect profile compared to the other forms of niacin, the discontinuation rate of the ER niacin still remains significant. The uncovering of the mechanism by which flushing is induced has sparked new promise into therapeutic lipid management.^{84,90} In general, flushing symptoms can occur following vasodilatation of small capillaries under the skin, a response that can be mediated via histamine/bradykinin or prostaglandins (PGs). This side-effect is not unique to niacin but is also seen with other drugs such as selective serotonin reuptake inhibitors.⁸⁴ The flushing of niacin is not believed to be via histamine/bradykinin pathways, but rather via PGs. The G-protein-coupled receptor GRP109A, seen in adipocytes, also exists on dermal dendritic cells. Activation of the receptor on these cells induces the mobilization of

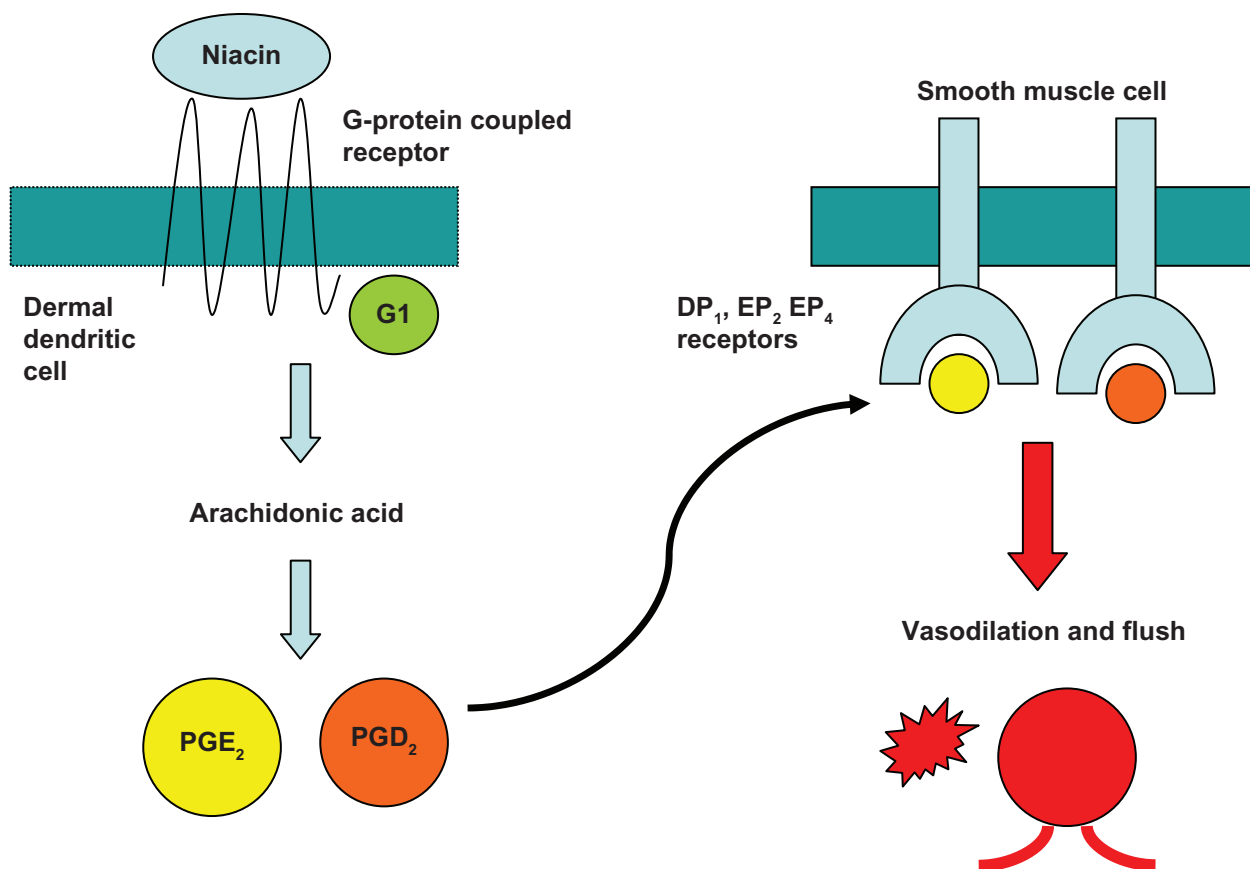


Figure 1 Schematic illustration of the mechanism by which niacin induces flushing.
Abbreviation: PG, prostaglandin.

arachidonic acid which leads to its conversion to, amongst other effects, the production of vasodilatory PGs, specifically forms D₂ and E₂. These PGs cause their effects by acting in particular through the DP₁, EP₂, and EP₄ receptors.^{84,90} Figure 1 illustrates schematically the mechanism by which niacin induces flushing. Considering the advantageous effects of niacin, strategies to improve patient compliance by reducing flushing are important. This can be managed by various approaches namely: dose titration, patient education and additional pharmacological therapies.⁸⁴ Nonsteroidal anti-inflammatory drugs are a logical treatment option as they are able to decrease the production of multiple prostaglandins by inhibiting cyclooxygenase and endoperoxidase (also referred to as COX).^{84,91}

Laropiprant

Mitigation of the downstream flushing effect of niacin by blockade of the PG receptors is another potential treatment option. The discovery of a selective DP₁ antagonist, MK-0542 (also known as laropiprant), was recently described, and combination of laropiprant with ER niacin has gained approval in Europe.⁹² Interestingly laropiprant was initially investigated as a treatment option for allergic rhinitis.^{92,93} Laropiprant is primarily metabolized by liver glucuronidation.⁹⁴ Laropiprant has detectable off-target antagonist effects at the thromboxane A receptor, but no clinically significant effect on collagen-induced platelet aggregation, or bleeding times,

with multiple doses up to 200 mg which is five times lower than the current dose regimen.⁹⁵ Table 2 depicts the notable clinical trials of niacin/laropiprant combination in patients with mixed dyslipidemias and primary hypercholesterolemia. Laropiprant does not seem to alter the lipid-modifying effect of niacin or statins.^{96,97} In a randomized controlled trial which consisted of three arms: placebo, ER niacin, and the combination of ER niacin with laropiprant, the combination lowered LDL-C by 18%, triglycerides by 25% and increased HDL-C by 20%, which was similar to ER niacin only.⁹⁶ This trial, along with several others,^{98,99} clearly demonstrated the attenuation of flushing with laropiprant. In this 24-week study the discontinuation due to flushing was 10% in the combination group versus 22% in the ER niacin group without laropiprant, compared to 0.7% in the placebo group.⁹⁶

In April 2008, the Food and Drug Administration (FDA) rejected the licensing application of the laropiprant/niacin combination which has lead to much speculation.¹⁰⁰ The FDA has however approved combinations of ER niacin with both simvastatin and lovastatin. Therefore the hesitancy to license this new combination may be related to laropiprant. Laropiprant is a first-in-class compound. Recently there has been increased skepticism and debate about surrogate markers in the field of lipids and diabetes which may have tipped the scales towards conservatism and a demand for outcome data.³⁷ Most would regard the FDA review process as highly

Table 2 Notable studies with niacin/laropiprant combination in patients with mixed dyslipidemias and primary hypercholesterolemia^{96–98}

Study	Year reported reference	Interventions	Number of patients study duration	Outcome measures	Note
Efficacy and tolerability of ER niacin/laropiprant	2008 Reference 96	• ER niacin • ER niacin and Laropiprant • Placebo	n = 1613 6 months	• Lipid parameters • Flushing	Discontinuation due to flushing: • ER niacin = 22% • ER niacin and Laropiprant = 10% • Placebo = 1%
ER niacin/laropiprant and simvastatin versus ER niacin/laropiprant or simvastatin	2009 Reference 97	• ER niacin and Laropiprant plus simvastatin • ER niacin and Laropiprant • Simvastatin	n = 1398 3 months	• Lipid parameters	% Reduction LDL-C • ER niacin and Laropiprant plus simvastatin = 47% • ER niacin and Laropiprant = 17% • Simvastatin = 37%
Flushing profile of ER niacin/laropiprant versus gradually titrated niacin ER	2009 Reference 98	• ER niacin • ER niacin and Laropiprant	n = 1455 4 months	• Safety and tolerability • Flushing	Discontinuation due to flushing: • ER niacin = 12% • ER niacin and Laropiprant = 7%

Abbreviations: ER, extended release; LDL-C, low density lipoprotein cholesterol.

successful, however it is not without its limitations of gaps, tensions and conflicts.¹⁰¹

Conclusion

Niacin has a long history of success in reducing LDL-C and TGs and increasing HDL-C. It was the first lipid-lowering drug to demonstrate a reduction in CVD events, and remains the only one that has consistently shown benefits on surrogate outcomes when added to background therapies of other lipid-lowering drugs including statins. Despite its ability to significantly improve all these lipid parameters, relatively few clinicians resort to niacin as a treatment option. Apart from lacking evidence in demonstrating a benefit on all cause mortality and on CVD events on the background of statin therapy, its use has been hampered by its side-effect profile. The most notable side-effect of niacin is flushing. This is significant enough to cause discontinuation in up to 50%. More modern formulations of intermediate-release niacin show reduced side-effects but are still limited by relatively high discontinuation rates. The recent formulation of intermediate-release niacin with a prostaglandin D₂ receptor inhibitor (laropiprant) has become available, and provides a definite improvement on the side-effect profile, as well as patient compliance to treatment. Whether this reduced rate of side-effects is acceptable today is uncertain, as patients complain about statins which have side-effect rates which are still lower. The other lipid-modifying properties of niacin are probably advantageous; however controversy remains as to the direct benefits of raising HDL-C and lowering TGs. Given these considerations, guidelines are unlikely to change until the niacin-statin endpoint trials are completed. The question as to the height of the bar for drug licensing sparks a lot of debate and there has been a shift which demands longer studies, more data and better-quality data prior to licensing.¹⁰² The balance between causing harm, and potentially denying a patient useful treatment is delicate. The evaluation remains complex, and this requires clinical acumen.

Declaration of interest

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