Niacin: From Mechanisms of Action to Therapeutic Uses

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Abstract: Niacin has broad spectrum lipid modifying and anti-atherosclerotic properties. It is the most effective medication available for raising raise high density lipoprotein (HDL) levels. Despite statin therapy there remains a considerable residual cardiovascular risk attributed to low HDL levels. Currently, statins decrease cardiovascular events and death by about 25-40%. Trials with surrogate endpoints have shown a decrease in endpoints by 60-90% when a combination of statin and niacin has been used. There is a growing interest in niacin in combination therapy to fill the treatment gap by modifying lipid parameters other than low density lipoprotein cholesterol. This review addresses the role of niacin in comprehensive lipid management with an emphasis on its mechanism of action, formulations, side effects, evidence from clinical trials and also focuses on practical issues related to niacin therapy.

Keywords: Niacin, nicotinic acid, mechanism of action, receptors, GPR109A, high density lipoprotein, side effects, clinical trials.

INTRODUCTION

Niacin is a broad spectrum lipid modifying drug that was first used for the management of dyslipidemia in the 1950s [1]. It is notable for its favorable effects on serum triglyceride, HDL-C and lipoprotein(a) levels (Lp(a)), despite moderate efficacy in lowering low density lipoprotein cholesterol (LDL-C). The importance of raising HDL has helped to renew interest in niacin, especially when it is used with other lipid modifying medications.

The side effect profile of niacin has limited widespread adoption; this is an important focus of new research. The discovery of niacin receptors has improved our understanding of its mechanism of action and may provide solutions to its side effects and create opportunities for better tolerated synthetic alternatives.

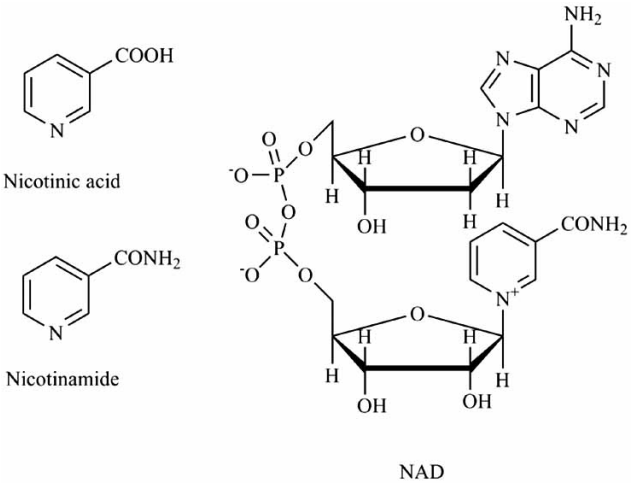

Fig. (1). The chemical structure of nicotinic acid, nicotinamide and nicotinamide adenine dinucleotide (NAD). Adapted from [2].

NIACIN

Niacin (vitamin B3) refers to both nicotinic acid and nicotinamide, an essential vitamin for all living cells. It is biosynthetically converted to nicotinamide adenine dinucleotide (NAD), "Fig. (**1**)" a versatile acceptor of hydride equivalents to form the reduced dinucleotide, NADH. The phosphorylated forms of the nicotinamide dinucleotides (NADP/NADPH) perform similar chemical functions within cells and enter in cellular biosynthetic pathways, energy metabolism and cell protection mechanisms against reactive oxygen species. The lipid lowering effect of niacin is not related to NADP/NADPH production but is a result of direct binding to specific cell receptors. It is unique to nicotinic acid and not observed with nicotinamide [2]. For the purpose

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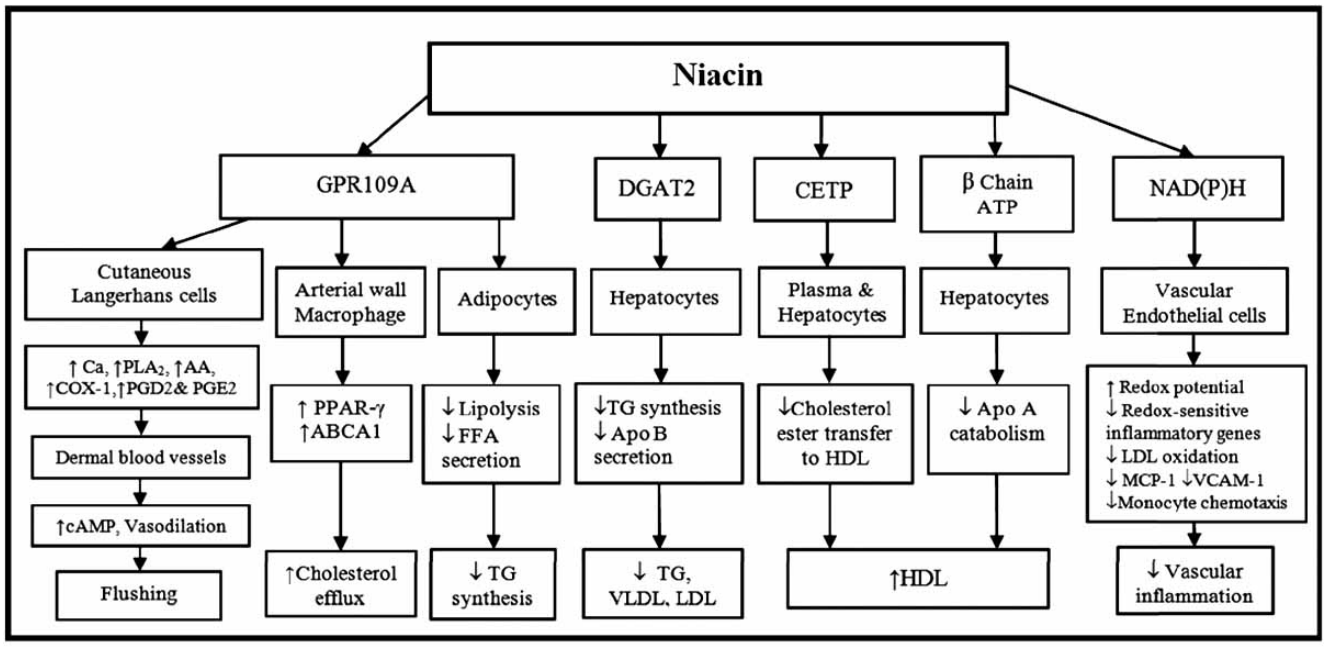

Fig. (2). Niacin receptors and target tissue enzymes. AA = arachidonic acid; ABCA1 = ATP-binding cassette transporter A1; Apo = apolipoprotein; ATP = adenosine triphosphate; CETP= Cholesteryl ester transfer protein; COX-1= cyclooxygenase-1; DGAT2 = diacylglycerol acyltransferase 2; FFA = free fatty acid; GPR109A = G protein-coupled receptor 109A (= HM74a); GPR109B = G protein-coupled receptor 109B (=HM74); HDL = high density lipoprotein; LDL = low density lipoprotein; MCP-1 = monocyte chemotactic protein-1; NAD(P)H = reduced nicotinamide adenine dinucleotide phosphate; PGD2 = prostaglandin D2; PGE2 = prostaglandin E2; PLA2 = phospholipase A2; PPAR-γ = peroxisome proliferator activated receptor-gamma; TG = triglyceride; VCAM-1 = vascular cell adhesion molecule-1; VLDL = very-low density lipoprotein; ↑= increased; ↓= decreased.

Adapted from [3,10,12,23].

of this review, the term niacin will be used to refer only to nicotinic acid.

THE NICOTINIC ACID RECEPTOR

Niacin acts through several receptors "Fig. (**2**)" [3,4]. The high affinity G-protein coupled receptor GPR109A (GPR109A, HM74A, PUMA-G in mouse) mediates most of the niacin effects and is responsible for skin flushing [5-8]. Niacin also activates the β-chain of ATP synthetase in liver cells [9]. The other niacin effects are related to its effect on NADPH and direct enzymatic inhibition [10,11].

In 2003, the receptor for nicotinic acid was identified [5-7]. GPR109A is expressed in brown and white adipose tissue and various immune cells including monocytes, macrophages, dendritic cells and neutrophils. The closest homologue of the human GPR109A is GPR109B, which is absent in rodents and represents the result of a relatively recent gene duplication. Nicotinic acid and related drugs with comparable pharmacological effects bind to GPR109A but not to GPR109B. The exception is the furan carboxylic acid acifran, which is able to activate both receptors. Several heterocyclic small molecules have been shown to act as selective agonists of GPR109A "Fig. (**3**)", but their potency when compared to nicotinic acid is much lower. The half maximal effective concentration (EC_{50}) for nicotinic acid is 0.1 μM, whereas those for acipimox, 3-hydroxybutyrate, 1-isopropyl-benzotriazole-5 carboxylic acid (1-IPBT-5-CA), acifran and acetoacetate are, 5.1, 750, >1000, 1.2 and >25,000 μM respectively. Nicotinamide on the other hand does not activate GPR109A or GPR109B [12].

Under physiological conditions, nicotinic acid concentrations in the plasma are relatively low and therefore nicotinic acid is unlikely to be the endogenous ligand for GPR109A. The endogenous ketone body β-hydroxybutyrate has been shown to selectively activate GPR109A and despite its relatively low potency within its physiological concentrations in the plasma, during periods of starvation, it is thought that high concentrations of the molecule (6–8mM) through stimulation of the GPR109A receptor mediate a negative feedback mechanism that may contribute to metabolic homoeostasis during starvation [12].

Agonists of the nicotinic acid receptor GPR109A are relatively small molecules that contain a carboxylic acid moiety "Fig. (**3**)". The molecules bind to a pocket in the receptor that is formed by transmembrane helices 2, 3 and 7. An arginine residue (Arg111) in the transmembrane helix 3 forms the anchor point for the carboxylic acid group of nicotinic acid and other receptor agonists. Other important contacts of the pyridine ring of nicotinic acid with the receptor appear to be localized at the extracellular junction of transmembrane helix 2, the extracellular loop 1 and the transmembrane helix 7. A serine residue (Ser178) in the extracellular loop 2 is essential for the binding of nicotinic acid to the receptor and may mediate the interaction with the nitrogen of the pyridine ring [12].

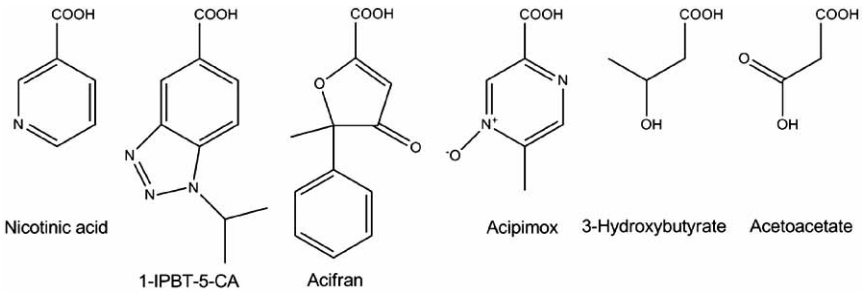

Fig. (3). Structures of various GPR109A ligands. 1-IPBT-5-CA =1-isopropyl-benzotriazole-5 carboxylic acid Adapted from [12].

MECHANISM OF ACTION

In adipose tissue niacin activates GPR109A which inhibits adenylyl cyclase (AC) activity within adipocytes. The resulting decrease in intracellular cyclic adenosine monophosphate (cAMP) leads to lower protein kinase A (PKA) levels and a reduction in lipolysis [13,14]. Consequently, levels of free fatty acids (FFA), the substrate for hepatic triglycerides (TG) and very low density lipoprotein (VLDL) synthesis, are reduced "Fig. (**4**)". This results in lower plasma TG and VLDL levels [5,15].

Niacin further modulates TG and VLDL/LDL secretion in hepatocytes by directly and noncompetitively inhibiting the activity of hepatocyte microsomal diacylglycerol acyltransferase 2 (DGAT2), an enzyme involved in TG synthesis [16]. It also increases apo-B catabolism, which further impairs VLDL and TG synthesis and secretion [17]. Niacin is transferred into human liver cells by an acidic, pH-dependent, high-affinity, specific carrier-mediated system that appears to be regulated by an intracellular Ca^{2+}/ calmodulin-mediated pathway [18].

While the effect of niacin administration on lipolysis is transient, there is a persistent decrease in VLDL-TG production which continues for about 6 hours after niacin administration. It has been suggested that the suppressive effects of niacin on lipolysis and FFA delivery to the liver may exert a long-lasting inhibitory effect on VLDL-TG secretion and assembly. Alternatively, the effects on VLDL synthesis may be a direct pharmacological effect of niacin, independent of FFA metabolism [15]. Both mechanisms are complementary to each other.

Niacin increases HDL levels both directly and indirectly. In the liver niacin inhibits the ectopic β chain of ATP synthase, a protein complex of the mitochondrial inner membrane that, when expressed on the hepatocyte surface, serves as a high-affinity receptor for apoA-I. Binding of apoA-I to the β chain of ATP synthase triggers the endocytosis of holo-HDL particles (protein plus lipid) by an adenosine diphosphate (ADP) dependent mechanism. This process is followed by a series of steps, culminating in HDL catabolism [9]. Niacin decreases the surface expression of the β-chain of ATP synthetase in the liver by 27%, leading to a 35% decrease in HDL uptake [19]. It also selectively reduces the hepatic uptake of HDL-apoA-I, but not HDL cholesterol esters, without affecting the de novo synthesis of apo-A-I in Hep G2 cells [17]. This results in higher levels of HDL [20].

By decreasing triglyceride levels in apoB-containing lipoproteins (LDL and VLDL) niacin also increases HDL-C concentrations indirectly; as the lower LDL and VLDL levels result in less exchange of cholesterol esters between HDL and LDL/VLDL, leading to increased HDL levels [21]. Plasma triglyceride concentrations are known to correlate negatively with HDL-C levels [22]. Niacin also increases HDL by reducing cholesteryl ester transfer protein (CETP) concentration and activity. In APOE*3Leiden CETP mice, Niacin significantly decreased the hepatic expression of CETP by up to 88%, plasma CETP mass by 45% and CETP activity by 52% [10].

Niacin promotes cholesterol efflux from arterial wall macrophages, probably through activation of the GPR109A and GPR109B (HM74, and HM74a) receptors. The secreted cholesterol is then taken up by HDL particles "Fig. (**4**)" [23].

At therapeutic doses, niacin increases plasma HDL-C by 20 to 35% and reduces TC by 15%, LDL-C by 20%, TG by 40%, Lp(a) by 25% and TG/HDL-C ratio by 30% [12,24,25]. Niacin also modifies lipoprotein particle size and subclass distribution into less atherogenic entities [26].

In subjects with CAD, the HDL particle sizes are smaller [27]. Furthermore, HDL3, the dense subfraction of HDL, contains a different composition of proteins that is selectively enriched in apolipoprotein E [28]. Niacin increases the large HDL-C particles (H5 and H4, corresponding to the HDL2ab fraction) without affecting small HDL-C particles (H3, H2, and H1, corresponding to the HDL3abc fraction) and in combination with a statin, it has been shown to decrease apolipoprotein E in HDL3 while increasing other macrophage proteins implicated in reverse cholesterol transport [26,29].

Niacin also decreases the proportion of smaller, denser LDL-C particles and increases the larger more buoyant LDL-C subclass [26]. This favorable redistribution of lipoprotein particle sizes is seen even in patients with already well-controlled LDL-C levels [30].

In addition to its effect on lipids, niacin also has antioxidant and vascular anti-inflammatory effects [31]. In one study, niacin decreased plasma lipoprotein-associated phospholipase A2 and C-reactive protein levels by 20% and 15%, respectively [30]. In cultured human aortic endothelial cells, niacin inhibited LDL oxidation by 60%, angiotensin II-induced reactive oxygen species production by 24–86%, tumor necrosis factor α (TNF-α)-induced NF- κ B activation

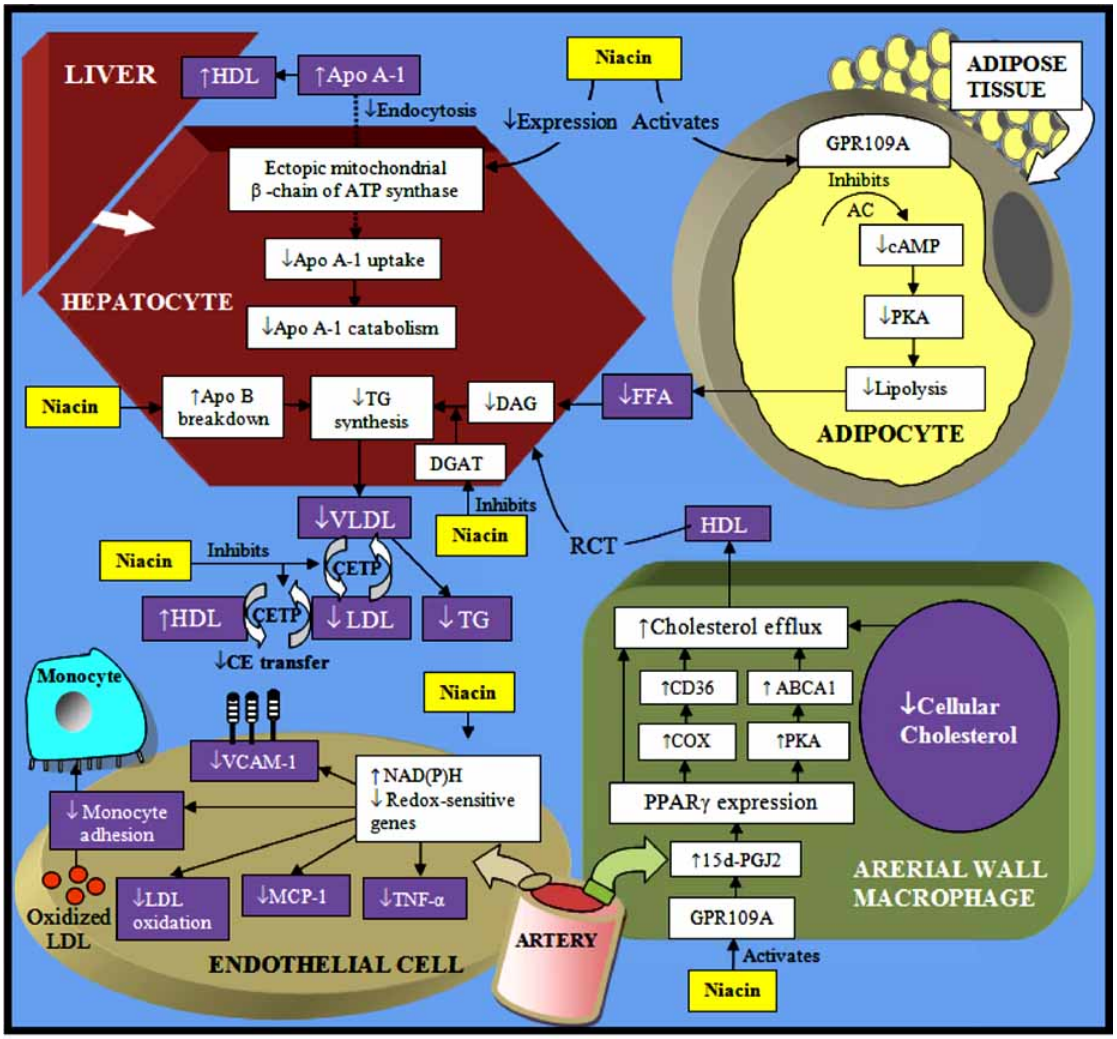

Fig. (4). Mechanism of action of niacin in various organ tissues resulting in serum lipoprotein modification and reduction in vascular inflammation and atherosclerosis; ABCA1 = ATP-binding cassette transporter 1; AC = adenylate cyclase; Apo = apolipoprotein; cAMP = cyclic adenosine monophosphate; CE = cholesteryl ester; CD36 = CD36 molecule (Cluster of Differentiation 36, thrombospondin receptor); COX = Cyclooxygenase; DAG = diacylglycerol; DGAT2 = diacylglycerol acyltransferase 2; 15d-PGJ2 = 15-Deoxy-Delta-12,14-prostaglandin J2; FFA = free fatty acid; GPR109A = G protein-coupled receptor 109A (=HM74a) ; GPR109B = G protein-coupled receptor 109B (=HM74); HDL = high density lipoprotein; LDL = low density lipoprotein; MCP-1 = monocyte chemotactic protein-1; NAD(P)H = reduced nicotinamide adenine dinucleotide phosphate; PKA = protein kinase A; PPARγ = peroxisome proliferator activated receptor-gamma; RCT = reverse cholesterol transport; TG = triglyceride; TNF-α = tumor necrosis factor-alpha; VCAM-1 = vascular cell adhesion molecule-1; VLDL = very-low density lipoprotein; ↑= increased; ↓= decreased.

Adapted from [10,23,26,97].

Table 1. Pharmacokinetics of Niacin Formulations and their Currently Recommended Uses

Formulation	Absorption rate	Absorption time	Dosing frequency	Metabolism		Therapeutic uses
				Amidation pathway	Conjugative pathway	
Immediate release (IR)	500 mg/hr	1-2 hr	2-3 times a day. Target: 1500-2000 mg/day.	8%	92%	FDA approved for the treatment of dyslipidemia Niacor, several over the counter agents
Extended release (ER)	100 mg/hr	8-12 hr	Once daily. Target: 1500-2000 mg/day.	40%	60%	FDA approved for the treatment of dyslipidemia Niaspan
Slow release (SR)	50 mg/hr	>20 hr	Once daily	80%	20%	Not FDA approved for the treatment of dyslipidemia. Available as over the counter nutritional supplement

Adapted from [33-35]

by 46%, vascular cell adhesion molecule-1 (VCAM-1) by 77–93%, monocyte chemotactic protein-1 (MCP-1) secretion by 34–124% and TNF- α -induced monocyte adhesion to HAEC by 41–54%. Niacin also increased NADPH levels by 54% and reduced glutathione by 98% [11]. Niacin may exert anti-inflammatory effects in non-vascular tissues as well like the spleen and lens, as demonstrated in a rat model [32].

In summary, niacin reduces the progression of atherosclerosis by reducing circulating LDL-C and triglyceride (TG) levels, induces regression of the atherosclerotic burden by increasing HDL-C levels and augmenting the process of reverse cholesterol transport. It also has pleiotropic effects including antioxidant and vascular anti-inflammatory actions [3].

FORMULATIONS AND DOSAGE

Three formulations of niacin are currently available (Table **1**) [33-35]. Only immediate release (IR) and extended release (ER) niacin are food and drug administration (FDA) approved for the treatment of dyslipidemia. Slow release (SR) niacin is associated with a high rate of hepatotoxicity and is currently available only as a nutritional supplement [34]. IR and SR niacin preparations are available without prescription, whereas ER niacin is available only by prescription [36].

Niacin is metabolized by two hepatic pathways: 1) the conjugative pathway in which it is conjugated with glycine to form nicotinuric acid and 2) the amidation pathway which involves several general oxidation-reduction reactions that produce nicotinamide and a series of related products. The conjugative pathway is a low-affinity, high-capacity pathway that generates metabolites associated with flushing. The second pathway is a high-affinity, low-capacity pathway whose metabolites are hepatotoxic [33].

Due to its fast dissolution rate, IR niacin saturates the amidation pathway rapidly and most drug metabolism is shifted to the conjugative pathway, leading to a high incidence of flushing. SR niacin, on the other hand, is mainly metabolized by the amidation pathway as it saturates it at a slower rate. Therefore, it is associated with a higher incidence of hepatotoxicity and less flushing. ER niacin, which allows drug absorption over 8 to 12 hours, is intermediate between the two [33].

Knopp *et. al.* compared the lipid modifying effects of IR niacin and SR niacin using a dose of 3000 mg/day in 77 patients with dyslipidemia. IR niacin was significantly superior to SR niacin in favorably modifying all the measured lipid parameters. In that study, LDL cholesterol was reduced by 21% with IR niacin versus 13% for SR niacin, TG were reduced by 27% and 8% and HDL was increased by 26% and 9%, respectively [37]. Studies on the ER niacin, Niaspan, have shown that it is comparable to IR niacin [38].

The daily dose of niacin ranges from a starting dose of 375-500mg once daily (in the European Union and North America respectively). The dose is increased gradually by ≤500mg increments every 4 weeks (according to the patient's response) to a recommended maintenance dose of 1000–2000mg. Although in clinical trials, doses up to 3000 mg daily have been used, it is advisable not to exceed 2000mg daily [39,40]. The maximum benefits on triglyceride and HDL-C are seen at this dose. Although a linear reduction is observed in the case of LDL-C, persistent elevations in LDL-C, however, can be managed with addition of modest doses of a statin in combination [40]. IR niacin should be taken with meals in three divided doses whereas ER niacin can be taken once daily. The highest tolerated dose, producing the fewest side effects, should be maintained.

"No-flush niacin" and "flush-free niacin" are two terms conventionally used for inositol hexanicotinate, a compound in which 6 molecules of nicotinic acid (niacin) are covalently attached to inositol by ester bonds. There is no evidence that niacin in this formulation is bioavailable as there are no published studies demonstrating that inositol hexanicotinate releases free niacin or leads to demonstrable increases in circulating niacin. There is also no evidence that it alters plasma lipid levels [41].

MK-0524A is an ER niacin/laropiprant combination designed to reduce flushing. Laropiprant is a selective prostaglandin D2 receptor 1 antagonist (DP_1) [42]. Preliminary data suggests good tolerability and minimal side effects [8,42,43]. Co-administration of laropiprant and ER niacin lowered flushing symptom scores by more than 50% and attenuated the increased malar skin blood flow measured by laser Doppler perfusion imaging [44]. A recent study showed that the laropiprant/niacin combination was associated with less flushing compared to niacin alone and its efficacy as a lipid modifying agent was unaltered [45]. MK-0524A is not yet FDA approved for the treatment of dyslipidemia.

INDICATIONS, IMPORTANCE OF COMPREHENSIVE LIPID MANAGEMENT

Niacin is effective in patients with most types of dyslipidemias as monotherapy or in combination with other lipid modifying drugs (Table **2**) [24,46-59]. Niacin is effective in patients with high LDL-C, isolated low HDL-C, elevated Lp(a), and hypertriglyceridemia [35,60-64]. It is also effective for the mixed dyslipidemia associated with the metabolic syndrome and diabetes [65-68].

The commonest and most prevalent lipid disorder associated with CAD is familial combined hyperlipidemia (or mixed hyperlipidemia) a condition also associated with PVD and stroke. This condition is characterized by increased hepatic secretion of apolipoprotein B–containing VLDL with conversion to LDL-C, and is associated with elevated triglycerides, low HDL-C, and small dense LDL particles [69,70]. Similar clustering of multiple lipid abnormalities is frequently encountered in subjects with the mixed dyslipidemia associated with metabolic syndrome or type 2 diabetes, where high triglycerides, low levels of HDL-C and a preponderance of small, dense LDL particles are also common [71]. In these patients, lipid abnormalities and CAD risk may persist despite statin treatment, including elevations in lipoprotein (a) level, and low HDL-C which are independent predictors of CAD [72-74].

Table 2. Clinical Trials Involving Niacin

Study	Year of publi-cation	Design	Population	Treatment	Primary endpoint	Results	Follow-up	P-value
CDP, 15 yr follow up [48]	1986	Randomized placebo controlled trial	8,341 men, 30-64 yr, 3 mo post MI	Niacin 3 g/d vs. placebo	All cause mortality	Niacin vs. placebo: 52% vs. 58.2%. (RRR= 11%)	15 yr	P=0.0004
Stockholm IHD [49]	1988	Randomized, open label, placebo controlled study	555 post MI patients <70 yr of age.	Niacin + clofibrate vs placebo	Total mortality and IHD mortality	1)Total mortality ↓ by 26% 2) IHD mortality ↓ by 36% with niacin + clofibrate therapy	5 yr	1)P< 0.05 2)P< 0.01
CLAS [50]	1987	Randomized, double blind placebo-controlled, angiographic study	162 men non-smokers, aged 40-59 with previous CABG.	Combined colestipol-niacin vs. placebo	Angiographic changes	Drug combination vs. placebo: 1)Number of lesions/subject that progressed 1 vs. 1.4 2)% Subjects with new lesions in graft vessels 18% vs. 30% 3)% Subjects with new lesions in native vessels 10% vs. 22%	2 yr	1)P=0.03 2)P=0.04 3)P=0.03
CLAS-II [51]	1990	Randomized placebo controlled, angiographic study	103 men, 40-59 yr, post CABG, TC: 4.79 - 9.07	Combined colestipol-niacin vs. placebo	Angiographic changes	Angiographic non-progression 52% in drug versus 15% in placebo	4 yr	P<0.001
UCSFSCOR [52]	1990	Randomized controlled, angiographic study	72 patients with heterozygous familial hypercholesterolemia	Niacin, colestipol, lovastatin	Within-patient mean change in percent area stenosis	Mean change in % area stenosis among controls +0.80 vs. -1.53 in the treatment group	26 months	P = 0.039
FATS [53]	1990	Randomized, double blind angiographic study	146 men, ≤62 yr, with familial atherosclerosis (Apo B≥ 125 mg/dl & CAD & FH of vascular disease)	Combined: niacin 4 g/d + colestipol 30 g/d vs lovastatin 40 mg /d + colestipol 30 g/d vs. conventional treatment (43% received colestipol and 57% placebo)	Change in percent stenosis	Mean change in stenosis in all lesions: -1.1% , -0.3% and +2% in the three treatment groups respectively	2 ½ yr	P=0.0009
HARP [54]	1994	Randomized, placebo controlled angiographic study	79 men and women, average age 58 yr with normal cholesterol and CAD	Stepwise therapy to achieve TC≤ 4.1 mmol/L and LDL/HDL < 2. Parvastatin 40 mg OD with add on niacin 1.5-3 g/d, cholestyramine, and gemfibrozil as needed.	Change in percent stenosis	Active treatment vs. placebo: 2.1% vs. 2.4%	2.5 yr	P=NS

(Table 2) Cont…..

Study	Year of publi-cation	Design	Population	Treatment	Primary endpoint	Results	Follow-up	P-value
HATS [55]	2001	Randomized, double blind, with clinical and angiographic endpoints.	160 men and women, average age 53 yr, with CAD & coronary stenosis & low HDL	Combined simvastatin + SR niacin 2 g/d or IR (crystalline) niacin 4 g/d	1) Death from cardiovascular causes, nonfatal MI, revascularization or hospitalization for confirmed ischemia 2) Change in coronary stenosis	1) 3% in simvastatin + SR niacin vs. 32% in placebo 2)Stenosis regressed 0.4% with simvastatin + SR niacin and progressed 3.9% with placebo	3 yr	1)P=0.003 2)P<0.001
ARBITER 2 [56]	2004	Randomized, double blind placebo controlled	167 patients 67±10 yr, 91% men Known CAD and low HDL.	Combined: ERN 1 g/d vs. placebo added to background statin therapy	Change in mean common CIMT after 1 year	Overall no significant difference in common CIMT progression between the niacin and placebo	1 yr	*P*=0.08
AFREGS [57]	2005	Randomized, double-blind, placebo-controlled trial	143 men and women, <76 yr with stable CAD, angiographic stenosis and HDL-C < 40 mg/dl, LDL≤160 mg/dl)	Combined: IR Niacin up to 3g OD, gemfibrozil 600 mg BID, and cholestyramine up to 16 g OD versus Placebo	1) Change in coronary stenosis. 2) Composite end point: hospitalization for angina, MI, TIA, CVA, Revascularization procedure and death	1) Stenosis increased 1.4% with placebo but decreased by 0.8% in the combination therapy group 2) composite cardiovascular event end point occurred in 26% in the placebo group and 13% in the drug group	30 months	1) P=0.04 2) P=0.04
ARBITER 3 [58]	2006	Open label study.	130 patients (88% of the 149 patients who completed ARBITER2, 61 patients from the placebo group and 69 patients from the ERN group)	Combined: ERN 1g added to background statin therapy (ERN group had a total of 24 months and placebo group received ERN for 12 months)	Within-group change in CIMT and HDL-C	1) 125 participants treated with ERN for 12 months (subjects from ERN arm during ARBITER 2 (*n* = 78) and those crossed over to ERN from placebo after ARBITER 2 (*n*=47 completed ARBITER3), there was a net regression of CIMT of –0.027 ±0.011 mm 2) 57 in ERN arm completed the study. There was additional regression of CIMT of –0.041 ± 0.021 mm).	1yr 2yr	1) P< 0.001 vs. placebo. 2)P = 0.001 vs. placebo
ARBITER 6-HALTS [59]	2009	Randomized, parallel-group, open-label study. Blinded evaluation of end points	383 patients with CAD or CAD risk equivalent, LDL< 2.6 mmol/L HDL< (1.3 or 1.4 mmol/L for men and women respectively	ERN target dose 2 gm OD vs ezetimibe 10 mg OD added to background statin therapy.	The between group difference in the change from baseline in the mean common CIMT after 14 months.	Ezetimibe vs ERN: mean CIMT change from baseline (mm) −0.0007±0.0035 −0.0142±0.0041 (P value for within group change from baseline for ezetimibe P =0.84 and for ERN P=0.001). Study terminated early after enrolling 208 patients.	14 months	P =0.01

Table (2) Clinical studies in which niacin has been used solely or in combination with other lipid modifying agents. AFREGS = Armed Forces Regression Study; ARBITER = Arterial Biology for the Investigation of the Treatment Effects of Reducing cholesterol trial; Apo = apolipoprotein; CABG: coronary artery bypass graft surgery; CAD = coronary artery disease; CDP = Coronary Drug Project; CIMT = carotid intima-media thickness; CLAS = Cholesterol-Lowering Atherosclerosis Study; ERN = extended –release niacin; FATS = Familial Atherosclerosis Treatment Study; FH = family history; g/d = grams per day; HARP = Harvard Atherosclerosis Reversibility Project; HATS = HDL-Atherosclerosis Treatment Study; HDL = high density lipoprotein; IMT = intima-media thickness; IR = immediate release; LDL = low density lipoprotein; MI = myocardial infarction; NS = not significant; OD = once daily; RRR = relative risk reduction; SR = slow release; TC = total cholesterol. UCSF-SCOR = University of California, San Francisco, Atherosclerosis Specialized Center of Research Intervention Trial.

Niacin helps control lipids and lipoproteins independently associated with CAD and can be used alone or in combination with a variety of lipid modifying agents [75,76]. Niacin modifies all lipoprotein parameters in a dose dependent manner [25].

When combined with an LDL lowering agent, niacin provides additional lowering of LDL-C levels and favorably modifies HDL-C, TG and Lp (a). In the OCEANS study (Open-label evaluation of the safety and efficacy of a Combination of niacin ER and simvAstatin in patieNts with dySlipidemia), the addition of niacin to patients already receiving simvastatin provided an additional reduction in LDL-C of 25.0%, triglycerides of 35.9% and an increase in HDL-C of 23.9%, compared to simvastatin alone ($p < 0.0001$). The combination was well tolerated over a 12-week time period with 20% discontinuation rate due to treatment related side effects [76].

In the HATS study (HDL-Atherosclerosis Treatment Study), the combination of niacin and simvastatin in a mean dose of 2.4 g/d and 13 mg/d respectively resulted in a significant 42 % reduction in LDL-C, 37% reduction in TG, 15% reduction in Lp(a) and 26 % increase in HDL-C when compared to placebo. Only 4 out of 80 treated patients (5%) discontinued niacin due to side effects. There were minor changes in AST and CK levels with treatment (absolute increases of 6 U/L and 18 U/L respectively) [55].

Similarly, in the COMPELL study (COMParative Effects on Lipid Levels of Niaspan and a Statin versus Other Lipid-Modifying Therapies) the combination of niacin ER and small doses of either atorvastatin or rosuvastatin in patients at high risk for cardiovascular events resulted in lowering of LDL-C to target levels without the need for high doses of either atorvastatin or rosuvastatin. In addition, the niacin plus statin combinations had greater benefits for HDL cholesterol, HDL2, triglycerides, and Lp(a) than either statin alone [60].

Post hoc analysis of two large statin trials have shown that even when low density lipoprotein cholesterol (LDL-C) levels are decreased below 1.81 mmol/L, low levels of high density lipoprotein cholesterol (HDL-C) were associated with increased risk for major cardiovascular events [77,78]. A more recent analysis from the BIP trial (Bezafibrate Infarction Prevention Trial) demonstrated that patients with low baseline LDL cholesterol may derive greater benefit from increasing HDL-C compared to patients with high LDL-C levels [79].

Niacin raises HDL-C in plasma by up to 35% compared to 10-15% with statins, and 6-10% with fibrates, making it the most effective medication currently available for raising HDL-C levels [80-83]. Several studies have demonstrated that raising HDL-C, using a variety of therapeutic agents, decreases cardiovascular events and CAD progression [48,50-58]. On average, an increase of 0.03 mmol/L in HDL-C is associated with a 2-3% decrease in CAD risk [84].

Niacin is one of the few medications that lowers Lp(a) levels [35,61]. The magnitude of reduction varies according to the type of lipid abnormality associated with Lp(a), the dose of niacin (whether IR or ER niacin is used), and the length of observation [85]. Statin treatment on the other hand does not affect serum Lp(a) levels [86,87]. The presence of a high Lp(a) level has been shown to significantly aggravate the CAD risk associated with high LDL-C level. In subjects with LDL-C >4.22 mmol/L, a Lp(a) level > 0.85 mmol/L carries a 3.95 fold risk of coronary events compared to 2.5 fold with a Lp(a) level of < 0.85 mmol/L [88]. Therefore, niacin-statin combination may be beneficial in patients with high levels of this lipoprotein especially if high levels of LDL-C are also present.

Niacin has also been used in combination with gemfibrozil with or without cholestyramine. In the AFREGS study (Armed Forces Regression Study), this combination resulted in a 21.8% reduction in LDL-C, 45.6% in TG, and 37.9% increase in HDL-C. The treatment group had higher incidence of gastrointestinal symptoms and flushing was almost universal. Only 7% of the patients, however, withdrew from the study due to flushing, and no increase in ALT levels was observed [57].

In the FATS study (Familial Atherosclerosis Treatment Study), the niacin-colestipol combination (1 gm four times daily and 10 gm three times daily respectively) resulted in 32% reduction in LDL-C, and 43% increase in HDL-C levels compared to baseline levels. This combination was associated with constipation, hemorrhoids, acanthosis negricans, pruritic skin rash, minor elevations in AST levels (<3X normal) and elevations in alkaline phosphatase. 2 patients developed gout and 2 patients required the addition of antidiabetic regimen [53]. A triple therapy of niacin, statin (lovastatin) and colestipol has also been used as well as a quadruple therapy of nicotinic acid, cholestyramine, pravastatin and gemfibrozil [52,54].

CLINICAL TRIALS INVOLVING NIACIN

The Coronary Drug Project (CDP) was the largest clinical trial that investigated the effect of niacin therapy on clinical outcomes. Most other clinical studies either included smaller numbers of patients, used niacin in combination with other agents or used surrogate end-points (Table **2**). Two ongoing large multicenter trials of combination therapy, directed to both lowering LDL-C and raising HDL-C, address the limitations of previous studies [89,90].

The CDP was one of the oldest placebo-controlled clinical trials of lipid lowering therapy. In this study 8341 hypercholesterolemic men with prior history of myocardial infarction were randomized into six treatment groups: niacin, placebo, clofibrate, dextrothyroxine, low dose and high dose estrogen. 2789 patients were allocated to placebo and 1119 patients were allocated to niacin with a target dose of 3 g/d and an average dose of 2 gm/d. At mean follow up of six years, niacin reduced nonfatal MI by 27% (10.1% *vs*. 13.9% P= 0.0015) and cerebrovascular events by 26% (8.4% *vs*. 11.3% P= 0.0074) compared to placebo [91]. No mortality benefit was observed in the original CDP trial, however, fifteen year follow up showed 11% relative risk reduction in all-cause mortality in the niacin group compared to placebo (Niacin vs. placebo: 52% vs. 58.2%. P=0.0004) and 13% reduction in death due to CAD (36.5% *vs*. 41.3% P=0.0051) [48].

The Stockholm IHD study was an open label placebo controlled study that investigated the effect of niacin in combination with clofibrate on overall mortality and IHD

mortality. The study involved 555 MI survivors less than 70 years of age that were followed up over a 5 year period. The results showed 26% reduction in overall mortality ($p < 0.05$) and 36% reduction in IHD mortality ($p < 0.01$) in the treatment group compared to placebo [49].

AIM-HIGH (Atherothrombosis Intervention in Metabolic Syndrome with Low HDL/High Triglycerides and Impact on Global Health Outcomes) is a multicenter, randomized, double-blind, parallel-group, active comparator trial designed to evaluate how increasing low HDL-C and lowering elevated TG and LDL-C can reduce cardiovascular endpoints in 3,300 high risk (presence of cardiovascular disease with low HDL-C and high TG) men and women ≥ 45 years old. Patients are randomized to simvastatin alone or to the combination of ER niacin plus simvastatin. The primary end point assesses the comparative efficacy and safety of statin monotherapy versus combination therapy, at comparable levels of on-treatment LDL-C (<2.1 mmol/L), in reducing the risk for clinical events (CAD death, nonfatal MI, ischemic stroke, or hospitalization for high-risk non-ST elevation acute coronary syndrome) [89].

HPS2-THRIVE (Heart Protection Study 2-Treatment of HDL to Reduce the Incidence of Vascular Events) is a randomized, double-blind, placebo controlled multicenter trial involving 20,000 patients aged 50-80 years with either a history of MI, cerebrovascular atherosclerotic disease, peripheral arterial disease, or diabetes plus either one of the previous conditions or CAD. Patients will have their LDL-C optimized with statin based therapy and then randomized to MK-0524A (ER niacin/laropiprant combination) versus a matching placebo, with a follow up period of 4 years [90].

ADVERSE EFFECTS

Use of niacin is associated with side effects which fall into three main categories: 1) cutaneous (e.g., flushing, pruritus, rash, acanthosis nigricans); 2) gastrointestinal (e.g., nausea, vomiting, diarrhea, anorexia); and 3) metabolic (e.g., increases in glucose, uric acid and hepatic enzymes) [92].

Niacin-induced flushing is the commonest side effect, often leading to patient non-adherence and discontinuation [45]. It occurs with all niacin formulations but is seen to a lesser extent with the once daily ER formulation.

Niacin-induced flushing is described as redness, warmth, itching and tingling that usually involves the upper half of the body and face and lasts 1-2 hours after oral administration. Flushing is caused by cutaneous vasodilation mediated by prostaglandin D_2 (PGD_2) and E_2 (PGE_2) *via* activation of DP_1 and EP_2/EP_4 receptors [42,43]. Niacin stimulates the GPR109A receptor in cutaneous langerhans cells leading to G-protein activation and transient increase in cytoplasmic calcium, leading to the activation of phospholipase A2 and subsequent formation of arachidonic acid. Metabolism of arachidonic acid leads to the production of PDG_2 and PGE_2 responsible for the flushing [43].

Liver enzyme elevations can occur with all niacin formulations. Mild elevations are seen with IR and ER niacin, these are usually less than twice the upper limit of normal range and are reversible. In contrast, elevations of up to 4 times normal and even liver necrosis have been reported with SR niacin [92]. Chemical hepatitis has also been described with IR niacin in doses ≥ 3g/day [41].

Another side effect of niacin therapy is minor elevation in blood glucose. This is attributed to insulin resistance with no change in insulin secretory responsiveness. ER niacin in doses of 2-2.25 gm/d has been associated with an increase of 5% in fasting glucose levels and a mean increase of 0.3% in HbA1c [41].

These elevations in blood glucose are modest, and are either transient or reversible. They are typically amenable to adjustments in oral hypoglycemic regimens without discontinuing niacin [93]. The ADMIT trial (The Arterial Disease Muliple Intervention Trial) found no significant differences in niacin discontinuation rate, dosage or hypoglycemic therapy in diabetic patients receiving niacin versus those on placebo [67]. Increases in hypoglycemic therapy for blood sugar control may be required however in some niacin treated patients [68].

The potential of this minor, treatable hyperglycemia in causing worsened cardiovascular outcomes is probably not significant and must be weighed against the improved outcomes with niacin therapy [41]. Studies have shown important clinical benefits of niacin or niacin-statin regimens despite the modest observed effects on glucose control [93].

A recent subgroup analysis of the HATS study has shown that the niacin-simvastatin combination reduced coronary stenosis progression among patients with metabolic syndrome despite a modest increase in insulin resistance. In the group of patients with dysglycemia, stenosis progression was slower compared to the patients treated with placebo [94].

The reduction in cardiovascular events in dyslipidemic diabetics treated with niacin likely outweights the mild effects on glycemic control. However, monitoring glycemic control after initiating niacin treatment or increasing its dosage is recommend [93].

The use of niacin in individuals with impaired fasting glucose is controversial but not contraindicated. There is a continuum of risk between pre-diabetes and diabetes. It may be reasonable to delay using niacin in patients with impaired fasting glucose or impaired glucose tolerance until blood sugar control is optimized with lifestyle and dietary measures or to implement these measures when niacin is first introduced [41]. A post-hoc analysis of the CDP has shown that patients with decreased glucose tolerance derive similar benefits from niacin compared to patients with normal glucose tolerance [66].

Gastrointestinal side effects such as dyspepsia, diarrhea and nausea are experienced by 10-20% of patients [65]. Increases in plasma uric acid levels are sometimes seen and clinical gout has been reported [21,65]. Other less common side effects include rashes, conjunctivitis and nasal stuffiness [41]. Niacin is not associated with myopathy when used as monotherapy and clinical trials in which niacin has been used in combination with fluvastatin, pravastatin, or simvastatin also did not report an increased risk of myopathy, but, the number of patients in these trials was small. There are, however, case reports of rhabdomyolysis when niacin was used in combination with lovastatin,

pravastatin, and simvastatin, but not with atorvastatin or fluvastatin [95].

SAFETY

The incidence of niacin related adverse effects varies according to the formulation used (Table **3**). A recent analysis on the safety of niacin in the US Food and Drug Administration adverse event reporting database suggested a significantly more favourable safety profile for ER niacin compared with other niacin preparations. The rate of serious adverse effects (deemed life threatening by the reporters or resulting in hospitalization or death) associated with other niacin formulations was 6.2 fold higher than with ER niacin ($p < 0.001$). Liver toxicity was also more common with other niacin formulations being 6.7 fold higher than ER niacin ($p < 0.001$) [36].

Table 3. Percent Patients Experiencing Side Effects with Niacin Formulations

	Immediate Release Niacin	Slow Release Niacin	Extended Release Niacin
Flushing	100%	82%	75%
Nausea or vomiting	8%	19%	15%
Rash/welts	3%	3%	7%
Abdominal pain/ dyspepsia	9%	21%	14%
Itching	8%	3%	8%
Diarrhea	22%	45%	13%

Adapted from [35,37]. Data does not reflect direct comparison of the three formulations.

When compared to other lipid-altering agents namely simvastatin, pravastatin, atorvastatin, gemfibrozil, fenofibrate, the rates of serious adverse events and reports of liver toxicity associated with ER niacin were significantly lower than what has been observed with other commonly used lipid-altering drugs.

PRACTICAL ISSUES IN NIACIN THERAPY, MANAGING "THE FLUSH"

The use of niacin in clinical practice has been suboptimal due to its side effects, principally flushing. Patient education, preparation and instruction can help to minimize the adverse effects and lead to improved adherence [92].

It is important to describe the flush to the patient before first use. Flushing can be described as an uncomfortable, prickly heat feeling that usually involves the head, neck, and shoulders. It is limited to the skin, non-allergic and does not lead to permanent harm. Flushing usually occurs 15–30 minutes after the ingestion of immediate release (IR) niacin and 30–120 minutes after the ingestion of extended release (ER) niacin. The episodes typically last 5–60 minutes [41].

Measures to avoid this side effect include starting with a low dose (e.g., 100 mg 3 times per day IR niacin or 500 mg once daily of ER niacin and increasing the dose gradually on a weekly basis to 600, 750, 1500, 2000 mg/day. Flushing occurs at a threshold dose between 250–1,000 mg. Flushing does not occur after every dose of niacin. The median number of flushing episodes is about 5 in the first 8 weeks after initiation of ER niacin. Flushing frequency diminishes by the fourth week with repeated and consistent dosing and disappears by 1 year in most patients. Failure of flushing rates to diminish, or its reappearance, may be due to inconsistent dosing. Re-titration is necessary if treatment is interrupted for greater than 3 days [41].

Aspirin 325 mg, ibuprofen 200 mg, or another non-steroidal anti-inflammatory drug taken 30–60 minutes before niacin ingestion can reduce the frequency and intensity of flushing. Chewing aspirin may help with prolonged episodes through buccal absorption. Aspirin 81 mg may not be as effective. Flushing is also minimized by taking IR niacin in the middle of the meal and ER niacin at bedtime and with a snack. Alcohol, spicy foods, hot beverages and hot baths shortly before or after niacin dose should be avoided [41].

Despite these measures, however, discontinuation rates up to 55% have been reported, a rate almost double the discontinuation rate of statins [96]. In our experience, adherence rates up to 80% can be achieved if patients are counseled prior to initiating therapy and educated on the side effects of niacin and how to minimize them. The following are helpful recommendations for healthcare professionals regarding the use of niacin.

Recommendations to Healthcare Professionals on the Use and Safety of Niacin

- Expect that 5%–10% of patients will not tolerate niacin because of flushing.
- Extended release (ER) niacin is better tolerated than immediate release (IR) niacin.
- Skin rashes associated with niacin are due to prostaglandin release and are not allergic. They may respond to moisturizing or steroid creams, but niacin withdrawal or dose reduction may be necessary.
- Serious hepatic toxicity can occur with niacin therapy. However it is almost entirely seen with slow release (SR) formulations. SR niacin should not be used for dyslipidemia management.
- Mild liver toxicity from SR niacin might lead to decreased hepatic clearance of statins and serious myopathy.
- Hepatic transaminase levels should be monitored every 6–12 weeks during the first 6–12 months of treatment and periodically thereafter. Withdrawal of niacin or dosage reduction should be undertaken if persistent and substantial transaminase increases are found, especially if 1) they are 3 times the upper limit of normal, 2) accompanied by elevated bilirubin or prothrombin time (PT), or 3) accompanied with nausea, malaise, or fever.
- Unexplained increases in PT with minor transaminase increases may rarely be a niacin side effect. Nevertheless, because of the rarity of this effect and the lack of a drug interaction with

warfarin, niacin can be safely used in patients anticoagulated with warfarin.

- Niacin is useful for the treatment of the dyslipidemia in patients with diabetes mellitus, minor increases in glucose levels are often clinically insignificant or treatable. Monitor blood sugar levels following initiation of niacin or dosage increase.
- In patients with impaired fasting glucose (IFG) or impaired glucose tolerance (IGT), especially with fasting glucose levels of 6.1-7.0 mmol/L, it is reasonable to defer niacin therapy while attempting to improve glycemic status. Alternatively, niacin may be administered with careful monitoring as lifestyle and dietary measures are instituted.In patients with familial or ethnic predisposition for type 2diabetes, but who do not have IFG or IGT, no increase in the risk for new-onset diabetes or hyperglycemia has been shown to date.
- Consider niacin withdrawal or dosage reduction if a patient develops type 2 diabetes (multiple fasting glucose levels >7.0 mmol/L) or postprandial glucose levels >11.1 mmol/L, as niacin-associated insulin resistance is reversible. In a few cases where cardiovascular benefits might be judged to outweigh the role of niacin in inducing diabetes or if diabetes persists and requires treatment after niacin withdrawal, the reinitiation of niacin should be considered.
- Co-administration of niacin with a statin has rarely been associated with increased risk of statin-related myopathy (see text for details).
- Myopathic reactions or myalgia are rarely reported with niacin-statin therapy, and other contributors to myopathy such as drugs, hypothyroidism, excessive alcohol ingestion and polymyositis should be sought.
- In patients predisposed to statin-induced myopathy such as the elderly, patients with chronic kidney disease or those engaging in extreme physical activity, consider obtaining pretreatment CK levels before the addition of niacin.
- Ocular effects like cystoid macular edema are dose-related side effects seen with niacin and rarely occur with doses <3,000 mg/day. They require niacin withdrawal and perhaps retitration to a lower dose.
- Niacin should be avoided in the presence of active peptic ulcer disease (PUD). Remote history of PUD and gastroesophageal reflux disease are generally not affected by niacin.
- Nausea and vomiting have occurred in association with higher doses of niacin but are very uncommon at doses up to 2,000 mg/day.
- Palpitations and tachycardia are potential side effects with niacin. Niacin may be relatively contraindicated in patients with paroxysmal atrial fibrillation (AF). Niacin is not contraindicated in postoperative AF or established AF.
- Active gout is a relative contraindication to niacin usage.
- Reductions in platelet levels and serum phosphorus may occur with niacin therapy and generally do not require monitoring or dosage adjustment.

Adapted from [41,95].

CONCLUSION

It is important to adopt a comprehensive approach to the management of dyslipidemia. Niacin is an underutilized lipid modifying agent with a broad spectrum of effects that are particularly useful in patients with mixed dyslipidemia.

Niacin is the oldest studied drug in secondary prevention of CAD, and the first lipid modifying drug to show a clinical benefit. Large ongoing trials will provide further insights on its clinical effects in different patient populations. Studies on combination with prostaglandin antagonists are also promising.

Advances in our understanding of the side effects and their management will likely increase the use of niacin in clinical practice.

CONFLICT OF INTEREST

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