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# NIACIN AND NIACIN / LAROPIPRANT COMBINATION: OPENING NEW HOPES FOR DYSLIPIDEMIA AND CARDIOVASCULAR DISEASES WITH FEW NOVEL ACTIONS

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## ABSTRACT

Niacin (nicotinic acid- NA), B – complex vitamin, one of the oldest lipid modulating drugs used almost over 50 years, is the most effective option for raising HDL-C, lowering LDL-C and TG that carries the risk for cardiovacsular diseases like MI, but is largely underutilized due to flushing and hepatotoxicity discouraging its use in patients. Alternative strategies for regular niacin available are extended release niacin (ERN) with or without Laropiprant (DP1 antagonist, a prostanoid receptor) that decrease flushing, less/no hepatotoxicity, decrease BP, safe in diabetics and increase in patient compliance. Additional insights for niacin induced flushing and role in atherosclerosis, hypolipidemic actions revealed are discussed in detail. Novel actions of niacin in immune system improves peripheral mononuclear cells cell viability, decrease in genotoxic stress, drug for hyperphosphatemia, improvement in symptoms of Parkinsonism and psoriasis. If FDA clears the legal issues on the combination strategy of ERN with Laropiprant, it may further succeed in doing a comeback after a long time and will enable to fully exploit the therapeutic potential of niacin. The pharmacodynamics of Laropiprant and the combination of ERN and Laropiprant in reducing overall risk of cardiovascular diseases is discussed in detail.

**KEY WORDS: Niacin , extended release niacin, Laropiprant, cardiovascular disease, HDL-C, LDL-C, TG, GPR109A**

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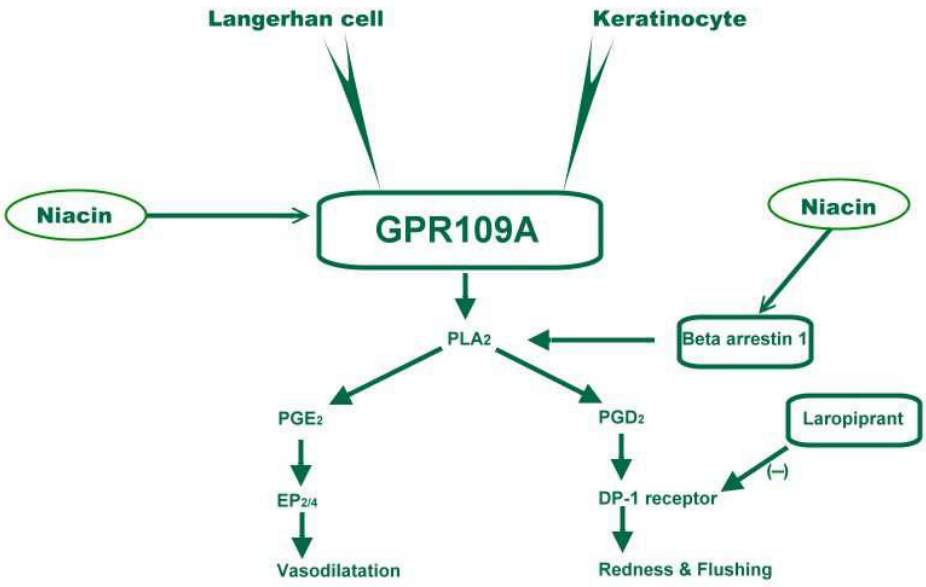
# INTRODUCTION

Niacin (nicotinic acid- NA), is a water soluble B – complex vitamin, one of the oldest drugs used as a lipid modulating drug since the 1950s, almost over 50 years.[1,2] Niacin has been described as the Roman God Janus, having two faces - one is the vitamin, the other being the broad-spectrum lipid drug.[3,4] Currently, it is the most effective available option for raising high-density lipoprotein cholesterol (HDL-C),[5,6,7] modestly lowers low-density lipoprotein cholesterol (LDL-C) and triglycerides (TG)[8] which carries the risk for cardiovascular (CV) diseases.[9,10,11] Thus, increasing HDL is an attractive strategy for decreasing the risks of CV disease, [12,13,14] other therapeutic options being statins, fibrates.[15] Niacin, has shown to reduce coronary death and nonfatal myocardial infarction (MI) in 15 years follow-up.[16] Unfortunately, Niacin is underutilized now-a-days due to flushing in 90% patients causing discomfort,[17,18,19] negatively affecting patient compliance.[20,21] Flushing, mediated by prostaglandin[22] via GPR109A (G protein coupled receptor for niacin),[23] contributes frequently to drug discontinuation and inhibition of lipolysis is by other mechanisms (Figure 1).[24] Thus, non-steroidal anti-inflammatory agents (NSAIDS), such as aspirin, indomethacin[24,25] are able to reduce the incidence of flushing [19,25 ,26,27,28,29] without affecting its free fatty acid (FFA) lowering effect.[24] However, flushing increases with increase in dose, but decreases when dose is constant. [30] Flushing is rapid and transient (~ 1 hr) [26] with rapid tolerance in 1 week due to reduced mediator ( PGD2).[31]

**Figure 1**




Flow Diagram to Depict Mechanism of Flushing by Niacin
And Role of Laropiprant in Reducing Flushing

**Legend 1**

***Diagram showing role of GPR109A in niacin induced flushing and suppression of flushing by Laropiprant, a DP1 antagonist. The cells expressing GPR109A receptors are also shown. (Refer text for details)***

The importance of raising HDL with niacin will be emphasized in this article, with emphasis on its co-administration along with Laropiprant to decrease flushing, which is approved in Europe but not in U.S.[7] Further strategies may include niacin extended release (ERN) or

ERN/ Laropiprant combination alone and/ or combination with statin, resins. ERN can raise HDL-C upto 30% and decrease TG to about 50%.[32,33] Apolipoproteins constitutes approximately 70% of the protein in HDL and 35% of total HDL mass. A novel strategy acting via HDL may be a promising strategy in atherosclerosclerosis prevention.[34] These are ApoA-1 mimetic peptides, AImilano[35] (ApoA-1 Milano- naturally occurring mutant of ApoA-I, MDCO-216) and oral D-4F.[36,37] The suggested mechanisms are HDL mediated reverse cholesterol transport (RCT) from macrophages via ATP-binding cassette(ABC) transporter A1 ( ABCA1),[38] HDL mediated anti-inflammatory action due to selective increase in lipid hydroperoxidases[36] i.e. paraoxonase activity[39] reducing formation of oxidised LDL[40] due to changes to conversion of HDL to prebeta HDL, a fraction known for its efflux efficacy.[39] Experimental studies confirm the effect on D-4F addition to drinking water, emhasizing that D-4F therapy induced a qualitative rather than a quantitative effect on HDL.[39] Human studies also support increase in the anti-inflammatory index without effect on lipids and lipoproteins.[39] Niacin is widely available as over-the-counter (OTC) drug. A study questioned the safety of (immediate release) IR niacin 0.5gm single dose, since it caused severe gastrointestinal side effects apart from flushing.[41] It cannot be trusted that patients receive information about these side effects or their prevention (with aspirin) from the OTC packet insert.[41] A recent modality, Laropiprant, a selective PGD2 antagonist, in combination with niacin, reduces flushing and improves tolerability of niacin.[19]

## *AVAILABLE PREPARATIONS OF NIACIN*

Niacin preparations include regular (or IR /crystalline niacin), sustained release (SR) niacin, no-flush niacin (costliest, with no free niacin)[42], extended release niacin (ERN). All vary markedly in side effects, safety and efficacy. [43] SR niacin preparations and no-flush niacin (available in health food stores), are not approved, while ERN (Niaspan) is US FDA approved for use in dyslipidaemia.[43] IR is hepatotoxic with 100% flushing incidence, should not be approved as OTC medication,[21, 41,44,45,46] and to be used under careful monitoring.[47] Different formulations, timely release and IR niacin are being developed to overcome flushing.[48] IR and *high dose* SR has increased flushing and hepatotoxicity respectively.[49,50] The Niacin SR cause less flushing, lower LDL (- 24%), TG (-33%), HDL (+6%), but is generally discontinued due to adverse drug reaction (ADR) of hepatotoxicity or fulminant hepatitis within 13months.[43] The main advantage of niacin-ER over niacin-IR are less flushing, lesser rise in uric acid levels, no hepatotoxicity and its convenient one nighttime dose. So, Niaspan is better alternative than plain niacin[51] with less flushing in comparison to older ER formulation. [52] Earlier literature documents use of inositol hexaniacinate (inositol nicotinate or “no-flush niacin”), consisting of 6 nicotinic acid molecules crossed-linked together with an inositol molecule, having lipid-lowering action, vasodilatory and fibrinolytic action,[53] gone in disuse due to “no cholesterol lowering action”.[54]

## *NIACIN (N)*

Previous studies demonstrate long term niacin therapy significantly reduces the risk of CV events[55] even in high risk subject,[9] attributing this to its additional anti-inflammatory properties.[56] Extent of response to therapy depends on severity and type of underlying lipid abnormality.[57] Niacin 4 g/day for six week reduce Lp-a (38%), raise HDL.[55] Low dose niacin (1.5gm) is better tolerated alone/combined drug therapy, and can alone raise
HDL-C .[58]

## *EXTENDED RELEASE NIACIN (ERN)*

ERN 1.5gm (absorbed in 8-12 hours[59]) monotherapy show dramatic decrease in LDL-C and TG while IR cause greater increases in HDL-C,[16] with less flushing (than IR) and minimal changes in glycemia/antidiabetic adjustments, so is a good option in hyperlipidemia[60] with diabetes, [61,62] metabolic syndrome, insulin resistance.[63] ERN has acceptable safety of hepatic profile[64,26] and good tolerability[65] especially when used once daily,[64] without increase in myopathy with statins.[50] The maximum 2g dose of ER also

has less flushing, decrease LDL (- 16%), TG (-32%), HDL (+24%, 2 fold greater than gemfibrozil) [66], Lp-a (-15%), with least hepatotoxicity.[67,68] However, gradual dose titration over about 1 ½ months is required to achieve its full efficacy at a target of 2gm dose.[65]

### *SAFETY, TOLERABILITY OF NIACIN*

### *SAFETY OF NIACIN & EXTENDED RELEASE NIACIN*

European Consensus Panel recommends the ERN/statin combination with lifestyle modification, to lower CV risks.[69] The US FDA Adverse Event Reporting System database of analyses, demonstrated significantly better safety profile of ERN as compared with other niacin formulations. FDC of ERN/simvastatin may be a cost effective strategy for CV diseases than high-dose simvastatin monotherapy.[70] FDC of ERN/ Lovastatin is a safe combination, safety comparable with the safety of individual drugs.[5] Once daily dose of low doses ERN(1000 or 1500 mg/d)[64] is safe treatment option for dyslipidemia in patients with type 2 diabetes (DT2M) with acceptable safety and tolerability profile, insignificantly affecting glycemic control.[71,72]

### *ADVERSE DRUG EFFECTS*

Niacin (500–2000 mg per day) causes facial flushes, where PGD2 acts as vasodilator via DP1 receptors, increasing cutaneous blood flow that results in non-adherence to drug therapy on a large scale.[5,73] But these symptoms partly decrease on its own in 1-2 weeks or with the use of NSAIDs given 30 min prior to niacin. Apart from flushing, causes palpitations and toxicity like worsening of diabetes control, exacerbation of peptic ulcer disease, gout, hepatitis that warrants close monitoring.[16,74] Niacin increase glucose levels, temporarily[60] and insignificantly,[62] liver enzymes, uric acid levels[6] and associated with insulin resistance.[50] Hepatotoxicity, a serious side effect of high dose niacin also compromises its utility, is lesser with ERN,[64] that is associated with metabolites of the nicotinamide pathway.[75] Marked lowering of LDL-C during niacin therapy may be a warning of hepatotoxicity.[76] However, coadministration of betaine, may be a cost effective measure to reduce this and probably other adverse effect[77] in future.

### *NIACIN AND FLUSHING - the underlying mechanism*

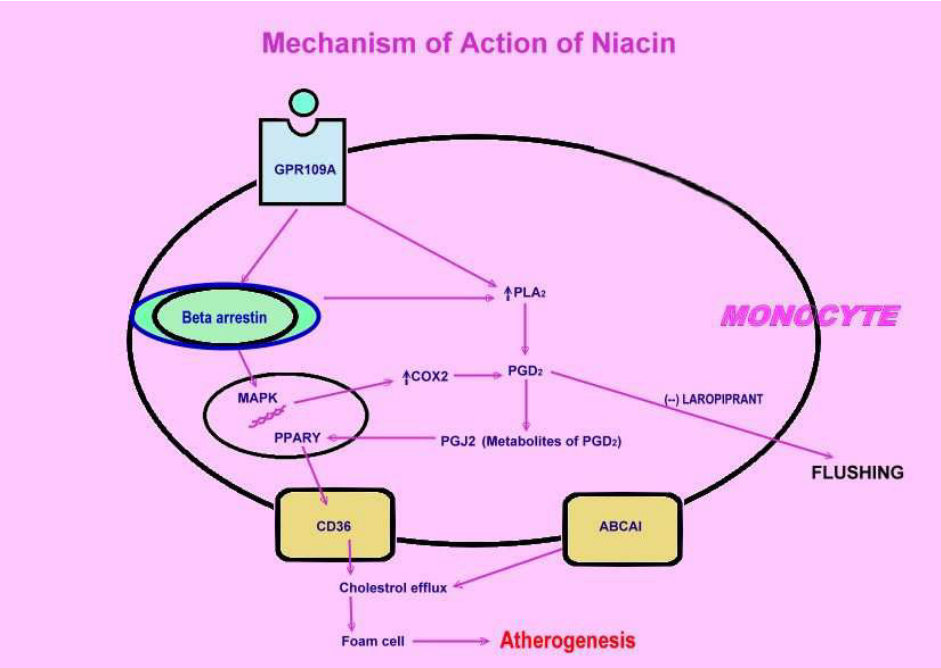
Flushing is the most common reason for dropout rate in practice and clinical trials (CT) for non-adherence and discontinuation of niacin therapy.[78] The molecular knowledge for this has been revolutionized today with the identification of GPR109A receptor,[79,80,81] highly expressed in a variety of cells, notably Langerhans cells, neutrophils, adipocytes, keratinocytes, and monocytes[82] with evidence suggesting these receptors to initiate a cascade of events that cause rubor.[83,84] GPR109A stimulation promotes phospholipase A activation and generation of prostaglandins(PG), PGD2 and PDE2 that activates DP1 {also called chemoattractant receptor homologous-molecule expressed on T helper type 2 (CRTH2)} and EP2/4 receptors respectively[26] (primarily on Langerhans cells, [26 , 50 ,82 ,85, 86] may include macrophages,[87] mast cells,[88] platelets[88]) causing cutaneous vasodilation and rubor. [83] PGD2 secretion is found to be a concentration dependent effect of niacin and the time of exposure.[87] A DP1 antagonist Laropiprant, substantially but not totally,[89] reduce rubor and calor objectively in reports of a clinical trial,[90] indicating the toxicity of niacin to be multifactorial, which needs to be further elucidated. This theory is also supported by animal studies.[105] So strategies need to be discussed to extend its benefits to prevent MI on a larger scale.

### *ADDITIONAL INSIGHTS IN MECHANISMS FOR FLUSHING*

Animal studies suggest that niacin stimulation leads to pertussis toxin-sensitive G-protein mediated lowering of cAMP, and release of $Ca^{+2}$ and bradykinin leading to $PLA_2$ activation and subsequent increase in PGD2.[91] Also recruitment of beta-arrestins (adapter proteins) to the cell membrane induces conformational changes in beta-arrestin, and beta-arrestin-dependent signaling to ERK MAPK. Further, niacin facilitated binding of beta-arrestin 1 to activated phospholipase $A_2$ ($PLA_2$) and release of arachidonate ,a

precursor of $PGD_2$ is responsible for flushing (Figure 2). [92,88] Flushing is found to be associated with the formation of nicotinuric acid by the conjugation pathway.[75] Earlier studies suggested that flushing is not mediated by mast cells since topical and oral niacin administration of niacin was not associated with increases in blood levels of either histamine/bradykinin, [93,94] but recent data suggest role of serotonin in flushing and thus use of cyproheptadine to reduce flushing in rats that calls for further evaluation.[88]

**Figure 2**




**Legend 2**

***Stimulation of GPR109A by niacin on monocytes promotes activation of PLA2 leading to formation of PGD2 and flushing. Formation of PGJ2, a metabolite of PGD2, is a potent endogenous activator of PPAR gamma that increases cell surface expression of CD36 leading to cholesterol efflux and cAMP/PKA pathway increasing ABCA1 expression. (for details refer text)***

### *REDUCING INCIDENCE OF FLUSHING*

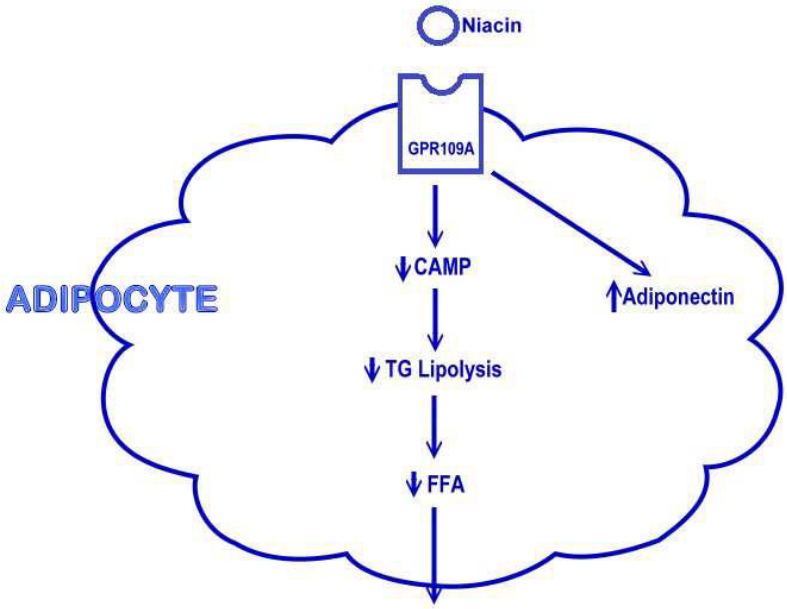
Starting with a lower dose ERN 0.5-1gm reduces the severity of flushing. In addition, aspirin [14,45,97,] indomethacin (100mg), naproxen [26] or ibuprofen [26] given 30 minutes before reduced the severity of flushing episodes/patient/week,[95] and improves adherability and compliance to therapy. [96] Aspirin 650mg reduced flushing in 90% patients[97] but increased risk of gastrointestinal bleeding. [98] Thus, ERN is equally efficacious as IR niacin with less flushing [51,99,100] and hepatotoxicity, thus improving the adherence to regimen.[100] Another way of reducing flushing may be by adding a natural flavonoid containing formulation quercetin with niacin, that reduces flushing in humans and also reduce methylnicotinate-induced human mast cell PGD2 release.[101] Recent approach is coadministration of Laropiprant with ERN, that reduces flushing symptoms and decreases skin perfusion in mice and humans.[102] The combination significantly reduces flushing versus ERN used alone, and allows fast titration to 2g therapeutic dose of niacin.[17,103] Thus the combination of ERN/LRPT may enable us to exploit full potential of niacin,[89] that is well tolerated in Asians showing less flushing experience and flushing-related discontinuations, [17] with significant decrease in Global Flushing Severity Score (GFSS). [17,104]

### *PHARMACODYNAMICS OF NIACIN*
### *NIACIN AND HYPOLIPIDEMIC ACTION*

Niacin acts on human orphan receptors GPR109A (its mouse analog PUMA-G)[105,106] and GPR109B [107] (HM74A and HM74, respectively) expressed on adipocytes and

immune cells.[56] Recent advances reveals cellular and molecular mechanisms, that decrease in TG and Apo-B containing lipoproteins (e.g. VLDL and LDL) are mainly through decreased FFA mobilization from adipose tissue TG stores, via GPR109A. This mechanism is doubtful in humans, since transient decrease in plasma FFA is followed by rebound increase in FFA levels, [56,108] and may be the basis of development of insulin resistance.[109] Experimental studies confirm FFA rebound after initial lowering but the underlying mechanism suggested, is not downregulation of niacin's action, since plasma FFA levels rapidly rise significantly (twofold) with discontinuation of niacin infusion, indicating increased basal lipolysis and this appears to be due to altered gene expression in adipocytes as shown by microarray analysis.[109] ERN showing minimal changes in insulin sensitivity, is not associated with FFA rebound.[63] GPR109A action, stimulates Gi –adenylyl cyclase pathway in adipocytes, inhibiting cyclic AMP production and decreasing TG lipolysis and FFA release (Figure 3).[110] In addition, inhibition of hepatocyte surface expression of beta-chain ATP synthase (a newly described HDL/apolipoprotein A receptor for HDL endocytosis in HepG2 cells),[111] leading to removal of HDL-apo A-I [112] implicates potential cellular target for niacin to raise HDL.[56] Niacin inhibits a key enzyme in TG synthesis, hepatocyte diacylglycerol acyltransferase (DGAT2) directly and non-competitively decrease TG.[56] [,112,113] This, leads to controversy whether GPR109A stimulation in adipocytes or DGAT2 inhibition in liver by niacin best explains reduction in VLDL and LDL in dyslipidemia (Figure 4).[56] Experimental studies report macrophage GPR109A mediated anti-inflammatory effect to be useful in atherosclerosis regression.[114]

**Figure 3**

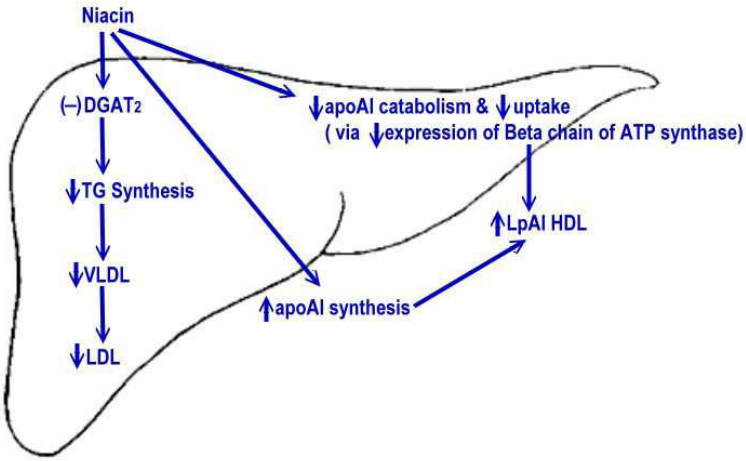



Schematic Diagram Representing Lipid Lowering Mechanism of Niacin in Adipocyte

**Legend 3**

***GPR109A stimulation in adipocytes by niacin inhibits cAMP formation in adipocytes thereby decreasing triglyceride lipolysis and decreased free fatty acid (FFA) release. Stimulation of adiponectin secretion from adipocytes confers additional atheroprotection.***

**Figure 4**




Schematic Diagram Representing Lipid Lowering Mechanism & HDL Modulation by Niacin

**Legend 4**

***Niacin inhibits diacylglycerol tranferase 2 (DGAT-2), a key enzyme in triglyceride synthesis, thus decreasing apo B containing lipoproteins like VLDL and LDL. Increased synthesis and decreased catabolism of apo A1 contributes to increased plasma levels of LpA1 – a cardioprotective subfraction of HDL (HDL – apo A1).***

Niacin selectively increases plasma levels of Lp-AI [35,115] (HDL subfraction without apo AII) through increased apoAI synthesis (also by statins, fibrates) and decreased apoAI catabolism,[35] a cardioprotective subfraction of HDL, thus suggesting an additional mechanism for its antiatherogenic properties.[116] This augments reverse cholesterol transport by increasing half life of HDL.[112, 117] Update using human hepatocytes (Hep G2 cells) supports selective inhibition of uptake/removal of HDL-apo AI but not HDL-cholesterol esters by hepatocytes, thus increasing the capacity of retained HDL-apo AI to augment cholesterol efflux through reverse cholesterol transport.[112,117,118, 119] Niacin induced GPR109A mediated decrease in lipolysis and increased adiponectin secretion,[120] the later may confer additional atheroprotection.[121, 122] So, the mechanisms of HDL that helps to reduce atherosclerosis are cholesterol efflux (Figure 2),[12] as an antiinflammatory lipoprotein,[123] decreasing oxidized LDL-C , as a plasma transport lipoprotein for biologically important proteins, and as an antithrombotic agent. [124] Since niacin is one of the few available medicines that raise HDL levels[8] and decrease TG, G protein coupled receptors(GPCR) like HM74A(GPR109A) and HM74 (GPR109B) involved in molecular mechanism of niacin may be promising targets for future pharmacotherapy.[23, 79]

## *EVIDENCE OF LAROPIPRANT/NIACIN IN HYPERCHOLERSTEROLEMIA/ DYSLIPIDEMIA*

Adding statins, like simvastatin[70,125]/atorvastatin/lovastatin[126] to ERN, demonstrated more significant elevation of HDL-C, LDL-C, attenuation of vascular inflammation[127] compared to monotherapy, and well tolerated safety profile.[8,128,129,] Trials also show triple drug combination simvastatin/ERN/laropiprant to be a more comprehensive treatment for patients with mixed dyslipidemia with decreased flushing.[9] Statin/ERN combination are beneficial regimens[14] increasing HDL-C, HDL2, lowered TG and Lp-a significantly, without drug-related myopathy[50] or hepatotoxicity.[130] Moreover, study show low to moderate dose combination therapy with a statin and ERN provide broad control of lipids and lipoproteins independently

associated with CHD.[130] Except for some flushing, ezitimibe-statin(E/S) plus ERN proved to be superior to E/S. [131,132,133] Statin/niacin combination is useful in patients with Familial Combined Hyperlipidemia, without a higher frequency of myopathy. Niacin induced flushing can be managed partly with aspirin and ER forms , but in the scenario of niacin induced increase plasma glucose and uric acid levels complete evaluation of risk of therapy to patient needs to be done before initiation of therapy.[134] In OCEANS study (Open-label evaluation of the safety and efficacy of a Combination of ER niacin and simvAstatin in patieNts with dySlipidemia), ERN/Simvastatin combination, titrated to maximum dose of 2gm/40mg/day, of established good tolerability, efficacyβ, long term safety with significant and favourable changes in all three lipid targets LDL-C, HDL-C, TG.[135, 136] So, niacin (low dose alone increase HDL-C)[58] or niacin/statins are one of the treatment options in metabolic syndrome, diabetes[69] to decrease overall CV risks.[12,129,135] Moreover, long term studies show ERN/ezitimibe/statin combination well tolerated, even in diabetics without deterioration.[132] ERN/lovastatin is more effective than atorvastatin or simvastatin monotherapies in reducing LDL-C at relative starting doses, and was more effective in increasing HDL, cardioprotective 2b subclass[35,115,137] at all doses.[138,139]

### *NIACIN AND DIABETES MELLITUS*

Next to flushing, other major concern of niacin therapy is hyperglycemia (reversible)[140], insulin resistance and disturbed glycemic control in diabetics. Insulin resistance doesnot cause hyperglycemia in the presence of normal B cell function.[141] Low serum phosphate levels may increase insulin resistance.[57] Use of niacin in diabetes causes reversal of low levels of HDL, reduces LDL,[142] reduces TG (higher doses)[143] and Lp-a, but use is discouraged due to hyperglycemia in diabetes[144] and non-diabetics [60, 145] (ADMIT study- Arterial Disease Multiple Intervention Trial).[145] So, consensus guidelines recommend monitoring glycemic control after initiating niacin treatment or increasing its dosage.[146] But recent findings suggest transient, reversible changes in FBG and HbA1c, that doesnot need discontinuation of niacin therapy, [146] encouraging its use in future.

### *STUDIES IN DIABETES MELLITUS*

Study in DT2M with once-daily ERN 1gm/1.5gm/d, proved safe in patients with diabetic dyslipidemia, reducing levels of HbA1c, a primary safety variable in diabetes, in comparison to placebo,[71] and hence risk of microvascular complications but not macrovascular disease(MI, stroke).[147] Another study supports little[64,174,148]/no[65] baseline changes in HbA1c level, in diabetics but not in non diabetics, while in niacin 1.5gm group the differences were only marginally significant. An initial rise in FBG levels was found between 4 to 8 wks returning back to normal by 16th wk.[71] So, data suggestive of little or no alteration in diabetes control.[71,145] Niacin is found to improve endothelial dysfunction and tolerability in DT2M.[149] Long term study with simvastatin-niacin combination in DT2M show mild decline in glycemic control returning to pretreatment levels[132] within 8 months in diabetics, proving safe, effective and well tolerated regimen in diabetics/nondiabetics.[150] Lipid modifying doses of niacin that are safe in diabetes (ADMIT study), can be therapeutically used as an alternative to statin/fibrates, if later are not tolerated.[145, 151] Hypertriglyceridemia ( > 150 mg/dl), necessitate niacin-statin combination therapy in metabolic syndrome.[152] To conclude, ERN, low dose strategy [115] doesnot worsen glycemic control in diabetes (with temporary rise in glucose levels) and is safe in DT2M [72, 150, 32]and nondiabetics. Ongoing CT in high risk patients (a 4 year follow up study, AIM-HIGH Study - "Atherothrombosis Intervention in Metabolic syndrome with low HDL/high TG and Impact on Global Health outcomes"), to test whether patients with atherosclerotic cardiovascular (CV) disease optimally treated on a statin but with residual atherogenic dyslipidemia (lowLDL , HDL-C and high TG) will benefit from addition of niacin with fewer CV events compared with placebo,[153] with documentation of baseline characteristics of study participants is terminated.[154]

## *NIACIN AND ATHEROSCLEROSIS*

Atherosclerotic CV disease is a major cause of morbidity and mortality. Inflammation contributes to atherosclerotic plaque initiation and progression, and niacin contributes to antiatherogenic effect by anti-inflammatory action on advanced atherosclerotic plaques that are independent of its lipid-modifying actions, reducing CV complications and mortality.[123] The cell adhesion molecules (CAM) mediate adhesion, recruitment and migration of white blood cells through vascular surfaces, an essential process in atherogenesis and intercellular CAM (ICAM-1) is a significant predictor of future coronary events. [155] Factors involved in atherogenesis are lowered like fibrinogen (significantly), plasminogen activator inhibitor-1 and platelet endothelium cell adhesion molecule (PECAM).[155] In vitro studies show niacin to reduce CAM (ICAM- 66-89% [155] & PECAM) and monocyte adhesion to endothelial cells by reducing NF- kappaB, thus reducing atherosclerosis. [156]

## *ADDITIONAL INSIGHTS INTO NIACIN MEDIATED REGRESSION OF ATHEROSCLEROSIS*

The proposed underlying mechanism is niacin induced cholesterol mobilisation from macrophages,[157] thereby providing a potential link between atherosclerosis regression and niacin.[158] Studies suggest leucocyte ABCA1 (member 1 of human transporter sub-family ABCA, also known as the cholesterol efflux regulatory protein (CERP) in humans[159]) to play a critical role in protection against atherosclerosis, by controlling recruitment of inflammatory cells.[160] Niacin, at molecular level interferes with cyclic AMP (cAMP)/protein kinase A (PKA) pathway, stimulating massive PGD2 formation causing flushing and it is of great interest to note, that the major metabolite of PGD2, 15-deoxy-Delta(12,14)-prostaglandin J2 (15d-PGJ2), has been identified as the most potent endogenous PPAR $\gamma$ activator,[161] that leads to PPAR $\gamma$ and cAMP-dependent expression of receptors promoting reverse cholesterol transport (RCT) in monocytes by HM74 and HM74A and PG synthesis. [162] Thus niacin enhanced HDL-mediated cholesterol efflux reduces the cellular cholesterol content of macrophages i.e. via RCT.[157, 114] Further, PPAR $\gamma$ activation (via MAPK-dependent COX-2 pathway) in macrophages, leading to increases CD36 expression on macrophages[163] that contributes positively to cholesterol efflux (Figure 2).[164] Thus niacin results in reduced cellular cholesterol content, [157] and its effect on CD36 (but not ABCA1) is prevented by cyclooxygenase inhibition.[157] Both cholesterol efflux and transcription of efflux receptors, namely CD36 and ABCA1 are increased by niacin.[106]

Interestingly, EP 80317, a selective ligand of CD36 (derived from the growth hormone (GH)-releasing peptide family, devoid of any GH releasing activity), exerts an antiatherosclerotic effect and possess anti-inflammatory actions.[165] This novel ligand exerts reduction in LDL-C and up-regulate genes involved in cholesterol efflux, PPAR$\gamma$, liver X receptor alpha (LXRalpha), transporters ABCA1 and ABCG1 mediating cholesterol efflux, reduces VCAM( 52%), reduces monocyte accumulation in vessel wall and reduction in lesion area.[165] Further, ABCA1 is highly regulated in macrophages increasing HDL formation and reducing the foam cell formation and atherosclerosis.[166] The liver ABCA1 initiates formation of HDL particles, while macrophage ABCA1 protects arteries from developing atherosclerotic lesions (arterial macrophages).[167,168] ABC transporters, modulate lipids, ABCA1, ABCG1 export excess cellular cholesterol into the HDL pathway (RCT) while ABCG5 and ABCG8 limit dietary cholesterol absorption(intestine) and promote cholesterol elimination from the body through hepatobiliary secretion. [169] ABCA1 behaves both as a lipid exporter and a signaling receptor.[170] Effect of niacin on hepatic ABCA1, can be summarised as reduction in HDL-C due to suppression of ABCA1, but increasing RCT.[171] Data support GPR109A activation leads to reduced hepatic ABCA1 expression and HDL-C levels, reduced hepatic cholesterol efflux to apoA-I and HDL, so its role in HDL metabolism is not clear.[172]

### *STUDIES ON ATHEROSCLEROSIS*

Recently, two studies ARBITER 6-HALTS study (Arterial Biology for the Investigation of the Treatment Effects of Reducing Cholesterol 6-HDL and LDL Treatment Strategies) study and the Oxford Niacin Study published, document significantly diminished carotid atherosclerosis as measured by ultrasound carotid intima-media thickness or magnetic resonance imaging with ERN/statin combination.[173] In the Familial Atherosclerosis Treatment Study and the HDL Atherosclerosis Treatment Study (HATS), niacin/statin or resin combination therapy resulted in significant reduction in CV events.[174]

### *BLOOD PRESSURE LOWERING EFFECTS OF NIACIN*

A worldwide study, a post hoc analysis of 24-weeks, multicentric, double-blinded, randomized, placebo-controlled, parallel, Phase III, based on previously published study of dyslipidemic patients, showed significant reduction in systolic blood pressure (SBP) and diastolic blood pressure(DBP) from baseline observed in both situations i.e. ERN alone, or in combination with LRPT at the end of 24 wks period.[175] Thus, niacin may be beneficial in hypertension to lower BP. [8] Normalization of lipid components, particularly HDL, is important for management of hypertension with metabolic syndrome or diabetes, since HDL is inversely proportional to the incidence of hypertension.[8]

### *MECHANISMS OF NIACIN EFFECT ON BLOOD PRESSURE*

The package insert of a prescription, ERN includes acute hypotension due to acute vasodilatory effects of niacin, rare cases of acute syncope, hypotension, and postural hypotension, especially when co-administered with ganglionic-blocking and vasoactive medications.[176,177] Coronary Drug Project, suggest chronic, dose-dependent, BP-lowering effect of niacin. [178] Laropiprant could not attenuate niacin's BP-lowering effects, hence other mechanisms may contribute to BP lowering and DP1 receptor activation is unlikely the cause of vasodilatation.[178] The chronotropic effects of niacin was found similar to normotensives and hypertensives, but the acute increases in HR did not affect CO in normotensives, which may be due to significant decrease in SV, the proposed mechanism for this divergent effects on BP in normotensives compared with those with hypertension is differential effects upon large-artery compliance. [178]

### *STUDIES ON BLOOD PRESSURE*

Study on evaluation of blood pressure on intravenous niacin infusion show no significant effects on BP in normotensive individual,[179] while in contrast acute niacin administration may lower BP in patients with hypertension with significant decrease in systolic BP (SBP), diastolic BP (DBP), mean arterial pressure (MAP), SVR(systemic vascular resistance) and SV(stroke volume) from baseline, till 60 min after the onset of niacin infusion.[179] Another study found ERN/statin together exerts beneficical effects on lipid profile in addition to lowering BP in patients with dyslipidemia and hypertension. [8] Hence it may be concluded that hypotension is a side effect with niacin therapy, acting as two faceted drug in patients of dyslipidemia and hypertension.

### *NIACIN AND IMMUNE SYSTEM*

There is much concern about atherosclerosis now-a-days, and interleukin-1 receptor-associated kinase (IRAK-1) signaling is said to be a key to innate immunity, associated with an increased risk of atherosclerosis in humans and mice. The lipid modifying action and regression in atherosclerosis of niacin is mediated via activation of GPR109A on immune cells.[114] Further, there might be a novel connection between innate immunity signaling process and ABCA1 expression regulation in macrophages, in addition to be a future target for treating atherosclerosis.[180] However, future research may prove/disprove whether niacin has any effect on immunity and status of IRAK-1/ABCA1 as a drug target.

### *IMPROVED VIABILITY OF PERIPHERAL MONONUCLEAR CELLS BY NIACIN*

Ex vivo supplementation of human peripheral blood mononuclear cells with niacin increases cellular NAD(+) levels, boosts the cellular poly(ADP-ribosyl)ation response against genotoxic stress, thus protecting DNA-

damage-induced cell death as assessed by poly ADP-ribose (PAR) accumulation (parameter of genotoxic stress) by a novel, sensitive flow-cytometric method for the rapid analysis of poly(ADP-ribose) accumulation (RAPARA). [181]

### *LAROPIPRANT INTRODUCTION*

Laropiprant (LRPT) is a potent, highly selective prostanoid DP(1) receptor antagonist[19] that decreases the incidence and intensity of niacin-induced flushing without affecting its beneficial lipid effects,[182] suggesting that lipid-lowering and flushing are mediated by two independent pathways,[183] that was initially introduced as antiallergic agent.[184] Niacin cause flushing through production of PGE2 and PGD2 via DP1, so LRPT used in conjunction with niacin may improve the tolerability and improve compliance. [1,19] LRPT reduces facial flushes significantly, in mice and humans, [185] more compared to pretreatment with aspirin,[59] but has no cholesterol lowering effect by itself.[186] Antagonism at DP1 antagonism with LRPT, reduces flushing associated with niacin, with improved patient tolerability. [18, 103,186] This has been correlated with reduction in skin vasodilation in Doppler perfusion imaging.[187] Niacin, when given as a combination of ERN/LRPT (1g niacin & 20mg LRPT – a PGD2 receptor antagonist) decreased flushing significantly in comparison to ERN alone. [102,188] The safety, tolerability of ERN/LRPT was similar to ERN group in dyslipidemia patients, except for more flushing in ERN group,[17] without affecting its hypolipidemic effects. [188] Thus leads to the conclusion that LRPT reduced flushing without affecting lipid lowering action. In addition, DP2 receptor blockade inhibits inflammation induced by cigarette smoke, mucus cell metaplasia and epithelial hyperplasia,[189] but donot reduce symptoms of either asthma or allergic rhinitis.[190] In vitro studies suggest that DP2 receptor antagonism may represent a novel therapy for COPD or other conditions characterized by neutrophil influx, mucus hypersecretion, and airway remodelling.[189] PGD2 acts via DP1 and DP2 receptor, the latter is predominantly expressed on eosinophils, Th2 cells, basophils, on monocytes, mast cells, and epithelial cells. Interaction of PGD 2 and metabolites results in cellular chemotaxis, degranulation, up-regulation of adhesion molecules, cytokine production, that reduced inflammation in experimental studies.[189]

### *LAROPIPRANT AND NIACIN COMBINATION*

A combination of niacin and Laropiprant (LRPT) is used in combination for hyperlipidemia under trade name Cordaptive (extended release niacin / laropiprant) and Tredaptive (contains 1 gm of niacin and 20 mg of laropiprant in each tablet).[191] But on April 28, 2008, the U.S. Food and Drug Administration (FDA) issued a "not approved" letter for Cordaptive.[192] Tredaptive was approved by the European Medicines Agency (EMA) on July 3, 2008.[193] Laropiprant have no effect on lipids or other side effects of niacin (ie, gastro-intestinal problems, glucose elevation). The combination, therefore may enable use of niacin at higher doses and therefore exploit full potential of the drug.[89]

### *REGULATORY STATUS OF NIACIN/LAROPIPRANT COMBINATION*

Niacin 1 g / laropiprant 20 mg has been approved by the European Commission for marketing (marketed as Tredaptive™) throughout 27 countries of the European Union, Iceland, and Norway. Tredaptive™ is indicated for treatment of mixed dyslipidemia, particularly in patients with combined mixed dyslipidemia (elevated levels of LDL-C, TG and low HDL-C) and in patients with primary hypercholesterolemia (heterozygous familial and nonfamilial). Niacin- statin combination is used, when the cholesterol-lowering effect of statin monotherapy is inadequate; and can be monotherapy in patients in whom statins are considered inappropriate or not tolerated.[194] In July 2008, Merck announced receipt of a Not Approvable action letter from the US FDA in response to its New Drug Application (NDA) for ER niacin/laropiprant. [195] FDA had asked for additional efficacy and safety data and suggested that the company should wait for the results of the HPS2-THRIVE study. In addition, Merck is seeking further approvals

for the fixed combination outside the United States in addition to Europe. REF

### *PHARMACOKINETICS*

Laropiprant, chemically (3R)-4-(4-Chlorobenzyl)-7-fluoro-5-(methylsulfonyl)-1,2,3,4-tetrahydrocyclopenta[b]indol-3-yl acetic acid, previously called as MK-0524, is absorbed rapidly, with plasma C(max) achieved 1 to 1.5 h after dose administration[196] mainly metabolised by glucoronidation, the major in vitro and in vivo metabolite is the acyl glucuronic acid conjugate of the parent compound M2, with minor amounts of M1, M3, M4, and their corresponding glucuronides. [197] The minor pathway consists of Phase I oxidation reaction by CYP3A4, with a minor contribution from CYP2C9. The major route of excretion is into bile and eventually via feces, with 68% of the administered dose recovered in feces and 22% in urinary excretion, for a total excretion recovery of approximately 90%. Within 96 h of dosing, majority of drug is excreted, while parent compound was the primary circulating component M2 in plasma.[196]

### *EFFICACY, SAFETY AND TOLERABILITY OF ERN/LRPT COMBINATION*

Concerns about safety and efficacy has been raised by FDA, the final conclusion will be done after completion of two major ongoing studies, HSP2-THRIVE study (Heart Protection Study 2 - Treatment of HDL to Reduce the Incidence of Vascular Events) [198] and AIM-HIGH (Atherothrombosis Intervention in Metabolic syndrome with low HDL/high TG and Impact on Global Health outcomes).[183] Combination of ERN/LRPT (1g ERN & 20mg LRPT), decreased the incidence of flushing in comparison to ERN alone, the safety and tolerability was similar to ERN/LRPT and ERN alone group in dyslipidemia.[17] The results of HSP2-THRIVE study completed in 2013 suggested that the most common medical reasons for stopping ERN/LRPT were related to skin, gastrointestinal, diabetes, and musculoskeletal side effects. Statins increased risk of myopathy The risk of myopathy was increased by adding ERN/LRPT to simvastatin 40 mg daily (with or without ezetimibe), particularly in Chinese patients whose myopathy rates on simvastatin were higher. To add further, the patients who tolerated ERN/LRPT therapy for 1 month, majority of them continued the therapy for approximately 4 years inspite of of the side effects of ERN/LRPT.[199] A study undertaken to assess the safety, tolerability of LRPT in patients of renal insufficiency conclude it to be well tolerated and neither the maximum plasma concentration (Cmax) nor the time to Cmax (Tmax) was significantly affected.[199] Hence, LRPT pharmacokinetics is not affected in renal insufficiency, but caution is to be taken while using the combination, since niacin and its metabolites are excreted through kidneys.[199]

### *NIACIN AND ERN/ LRPT FOR DYSLIPIDEMIAS IN DIABETES*

The ERN/ LRPT, show good tolerability, decreased incidence and intensity of flushing compared with ERN alone in RCT, with significant reduction in LDL-C.[186] Study reported 18.4% reduction in LDL which was statistically significant with ERN/ LRPT (2gm /40mg) once daily (after an initial 4-week lower-dose regimen) or in combination with statin compared with placebo in adults with primary/mixed dyslipidemia.[186] In T2DM significant reduction lipids/ lipoproteins at end of 12 wks of therapy in T2DM with ERN/LRPT with tolerable adverse effect profile.[200] Combination therapy with ERN, as in mixed hyperlipidemia reduce flushing and facilitate a more comprehensive treatment with the triple combination of simvastatin/ ERN / laropiprant. [9,201] ERN2g /LRPT 40 mg combination plus simvastatin caused larger reductions in LDL-C and reduced flushing as compared with ERN/ LRPT or simvastatin alone.[202] Combination proved superior to doubling statin dose, and adverse effects were similar to niacin.[203]

### *DYSLIPIDEMIA WITH METABOLIC SYNDROME*

The combination ERN/LRPT improves TG levels more in patients with metabolic syndrome (MetS) {where there is increased baseline TG levels} versus those without MetS and decrease CVD risk.[204] Another ongoing study, in China HPS2-THRIVE study (Heart Protection Study 2 - Treatment of HDL

to Reduce the Incidence of Vascular Events), a large multicentric trial, had recruited 25,000 patients, from age 50 to 80 years, a history of MI, cerebrovascular atherosclerotic disease, peripheral arterial disease, or diabetes mellitus with any of the above or other evidence of symptomatic CHD, to study CV outcomes. Patients are randomized to receive ERN 2gm/LRPT 40 mg or ERN 2gm with simvastatin 40 mg and ezetimibe 10 mg/ placebo with simvastatin 40 mg and ezetimibe 10 mg. This is a 4-year trial whose primary objective is to assess major CV events. The expected completion date is in 2012. Study outcome will be analysed further, for safety and efficacy.[183]

### *NIACIN AND ERN/LRPT IN CARDIOVASCULAR DISEASES*

Trials with niacin alone, as found by Coronary Drug Project (between 1966 & 1975), demonstrated 27% and 15% reduction in non-fatal myocardial infarction (MI); and MI and death taken together as combined end point.[205] Niacin should be used in full therapeutic doses for its lipid modifying action for its benefits in CVD,[182] and this combination helps for full exploitation of this potential drug,[206] this notion is supported by other CT too.[207,208,209,210] In DT2M patients, monocytes show reduced adhesion to endothelial cells that also decreases the overall CV risks.[122] Statins are beneficial individually, and thus niacin/statin combination significantly reduce atherosclerotic coronary artery events.[12,129]

### *OTHER PHARMACODYNAMIC EFFECTS OF LAROPIPRANT*

### *EFFECT ON PLATELET AGGREGATION*

Since PGD2 inhibits platelet aggregation in vitro, it has been speculated that Laropiprant, an antagonist of DP1 may enhance platelet reactivity.[211] But clinical studies demonstrate that laropiprant does not enhance in vivo platelet reactivity, either alone or in combination with niacin [211,212,213] thus not altering the bleeding time and no alteration of urine 11-dehydrothromboxane B2 (marker of in vivo platelet function).[211]

### *GPR109A AS FUTURE DRUG TARGETS*

GPR109A, mediates niacin-induced inhibition of lipolysis, while in epidermal Langerhans cells mediates flushing, an unwanted side effect of niacin therapy. Theoretically, development of niacin receptor agonists would result in increased flushing and adipocyte TG accumulation (and clinical adiposity) that may compromise their therapeutic use.[56] Further research can answer whether these agonists will be able to exert all beneficial properties of niacin on atherosclerosis with/without significant adverse effects.[56]

### *GPR109A AGONISTS IN CLINICAL TRIAL*

In 2009 several tricyclic analogues (various tricyclic anthranilide and cycloalkene carboxylic acid) identified as GPR109A agonists have shown excellent in vitro activity and good therapeutic index regarding FFA reduction with minimal flushing, [214] are been evaluated in clinical trials. These drugs may prove valuable,[215] to treat dyslipidemia, atherosclerosis, metabolic syndromes and diabetes in future,[216] but their clinical properties are not clear till now.[48] But it may be a promising pharmacological target in future [23, 79, ,217,218] especially for dyslipidemia since it is the only drug found to raise HDL. Further it may be exploited for its potential antipsoriatic effects of GPR109A agonists in the skin.[84]

**Box 1**
***Novel actions of Niacin***

**Niacin improved rigidity and bradykinesia in a Parkinson's disease**
(an accidental finding) *Ref 1*
**Niacin for protection against DNA damage induced by ionising radiations** (showed inverse association between chromosome translocation frequency and high dietary intake of niacin in airline pilots) *Ref 2*
**Niacin: potential for psoriasis**
Niacin & monomethylfumarate { active metabolite of psoriasis drug Fumaderm } activates GPR109A, on neutrophils and epidermal keratinocytes in human psoriatic lesions. Thus, GPR109A is a target for the drug Fumaderm and that niacin should be investigated as future drug for treat psoriasis. *Ref 3*
**Niacin/Laropiprant: Can be a treatment strategy for hyperphosphetemia?**
ERN cause statistically significant, transient, dose related decrease in phosphorous levels and probably with niacin induced diabetes worsening. A recent randomized controlled trial over 36 weeks in diabetics type2, supported lowering effects of single daily dose ERN/LRPT on phosphorous level, in patients with end-stage renal disease, which may have therapeutic implication in hyperphophatemia and possibly prevention of renal dysfunction in DT2M. **Error! Bookmark not defined.** Thus, niacin may be a future drug for hyperphosphatemia. *Ref 4 & 5*

*References for the Box for Novel actions*
*Ref 1 Alisky JM. Niacin improved rigidity and bradykinesia in a Parkinson's disease patient but also caused unacceptable nightmares and skin rash--a case report. Nutr Neurosci. 2005; 8(5-6): 327-9.*
*Ref 2 Yong LC, Petersen MR. High dietary niacin intake is associated with decreased chromosome translocation frequency in airline pilots. Br J Nutr. 2011; 105(4): 496-505. Epub 2010 Oct 8.*
*Ref 3 Tang H, Lu JY, Zheng X, Yang Y, Reagan JD. The psoriasis drug monomethylfumarate is a potent nicotinic acid receptor agonist. Biochem Biophys Res Commun. 2008; 375(4): 562-5. Epub 2008 Aug 21.*
*Ref 4 Al-Shaer MH, AbuSabha HS. Are the effects of nicotinic acid on insulin resistance precipitated by abnormal phosphorous metabolism? Lipids Health Dis. 2004; 28(3): 23.*
*Ref 5 Haglin L. Hypophosphataemia: cause of the disturbed metabolism in the metabolic syndrome. Med Hypotheses. 2001; 56(6): 657-63.*
*Ref 6 Bostom AG et al. Extended-release niacin/laropiprant lowers serum phosphorus concentrations in patients with type 2 diabetes. J Clin Lipidol. 2011; 5(4): 281-7. Epub 2011 May 13.*

# CONCLUSION

Niacin, as such is not popular for dyslipidemia , but the efficacy, safety and tolerability of niacin ER 1000mg and 1500mg use is justified for decrease in LDL, increase in HDL, ability of HDL to promote net cholesterol efflux.with the safety been proved in diabetes in clinical trials with 80% patients remaining in study[54] as well as in metabolic syndrome.[204] Combination of ERN/ Laropiprant improves tolerability to niacin while retaining its efficacy, hence giving maximum benefits in CV diseases as well as in dyslipidemia. Further it can be stated that more benefits are exerted in combination with statins than monotherapy. The new actions of niacin on reverse cholesterol transport, in monocytes provide a rational to expect regression of atherosclerosis and thus the combination of niacin with statins have an overadditive clinical benefit. So, niacin, “an old drug with promising future” may be an

upcoming drug in dyslipidemia with combination with LRPT to emerge as new modality to reduce risk of CV events and decrease mortality and morbidity. Fortunately, LRPT doesnot effect the hypolidemic effect of niacin. GPR109A agonists are being evaluated in clinical trials for the advantage of robust FFA reduction and minimal flushing, which may prove excellent in dyslipidemia. The ABCA1 pathway can be therefore an important new therapeutic target for treating cardiovascular disease (CVD). New and ongoing trials will definitively prove in the long term whether this drug combination significantly reduces the severity of flushing and the incidence of CV events. Niacin is the most effective agent for raising HDL-C levels, and pharmacoeconomic modeling suggests that niacin ER/statin combination therapy may promote the cost-effective achievement of optimum lipid values (OLVs) in several at-risk patient populations.[70] Recently developed understanding of the mechanisms, efficacy, and safety of niacin, along with progress in reducing the chief side effect of flushing, should enhance the use of this valuable agent for CV risk prevention. These analyses should encourage the use of niacin-ER in patients at high risk for CV disease, as recommended by current national guidelines for cardiovascular prevention.[5] Overall the adverse effects in AIM-HIGH trial of Niaspan are consistent and in accordance with the results reported from the recent HPS2-THRIVE trial of ER Niacin plus Laropiprant. Further analysis and more formalised future clinical trials specifically designed to explore other pros and cons of niacin therapy are required in future.

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