

The Resurgence of Niacin: From Nicotinic Acid to Niaspan/Laropirant

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ABSTRACT: Hypercholesterolemia is one of the main factors in the development of atherosclerotic cardiovascular disease. The advent of statins led to huge progress in the treatment of hypercholesterolemia, yet the proportion of patients with prohibitive lipid values and the high incidence of cardiovascular events despite treatment are still very high. Niacin, one of the older drugs used to treat hyperlipidemia, was shown to reduce low-density lipoprotein-cholesterol (LDL-C) and triglycerides and to markedly increase high-density lipoprotein-cholesterol (HDL-C) levels. This drug came into disuse owing to frequent side effects, mainly flushing, but in recent years a reemergence of its application has occurred, and multiple clinical trials have shown its effectiveness in the treatment of hyperlipidemia and in the reduction of cardiovascular events. New formulations such as extended-release niacin (ERN) have been developed with the purpose of reducing side effects. Lately, a new compound, laropirant, which selectively antagonizes the prostaglandin 2 (PGD2) receptor responsible for flushing, has been developed. Laropirant, when combined with ERN, significantly reduces the incidence of flushing. 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 cardiovascular events.

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Hypercholesterolemia is one of the main risk factors in the development of atherosclerosis. During the last 20 years, concurrent with the arrival and development of statins, considerable advances were made in the treatment of hypercholesterolemia. Statins were shown to reduce the incidence of cardiovascular events by 25–40% [1], although this reduction may be considered insufficient and many patients may need additional therapy to reach

Although statins have improved the treatment of hypercholesterolemia, most patients with hyperlipidemia still do not reach recommended lipid levels

more optimal lipid levels and prevent cardiovascular events. Furthermore, dyslipidemia in general, and hypercholesterolemia in particular, remain underdiagnosed and undertreated in many patients with coronary artery disease [2].

Regarding triglycerides, fibrates continue to be the most effective drugs today for the treatment of hypertriglyceridemia; however, despite the regular administration of these drugs a high proportion of patients, mainly those with type V hyperlipidemia, continue to have triglyceride values well above recommended levels. Although the role of triglycerides in the pathogenesis of atherosclerosis is still controversial [3], some studies such as the Copenhagen Hale Study [4] showed that elevated fasting triglyceride levels were a strong risk factor for ischemic heart disease, independent of other known risk factors for atherosclerosis.

Not only are cholesterol and triglycerides the target of lipid treatment, but increasing high-density lipoprotein-cholesterol has become one of the main objectives in the treatment of hyperlipidemia. There is considerable evidence that a minor improvement in HDL-C levels may significantly reduce CV risk [5,6]. As previously reported, an increase of 1 mg/dl in HDL-C levels results in a parallel reduction in coronary artery disease risk by 2% in men and 3% in women [5,6]. Furthermore, HDL-C has a cardinal role in the transport of cholesterol from peripheral tissues to the liver and, in addition, has potential anti-inflammatory, anti-thrombotic and anti-oxidant effects [7].

The search for a drug that is effective in increasing HDL-C levels has been frustrating. Although there is evidence supporting the notion that inhibition of cholesteryl ester transfer protein raises HDL-C levels in humans and inhibits the development of atherosclerosis in animals, a recent study with torcetrapib, an inhibitor of CETP, has been disappointing [8]. Torcetrapib therapy in humans resulted in an increased risk of mortality and morbidity of unknown mechanism [8]. Although an increase of 72.1% in HDL-C and a decrease of 24.9% in low-density lipoprotein-cholesterol were confirmed, there was also an elevated

ERN = extended release niacin

HDL-C = high-density lipoprotein-cholesterol
CETP = cholesteryl ester transfer protein

incidence of cardiovascular events and an increased risk of death in patients treated with torcetrapib [8]. This resulted in abandoning the use of this drug, and the quest for a "perfect" drug to treat hyperlipidemia remains unsettled.

Nicotinic acid and nicotinamide (collectively termed niacin) serve as precursors of co-enzymes nicotinamide adenine dinucleotide and nicotinamide adenine dinucleotide phosphate (NAD⁺ and NADP⁺) and are water-soluble vitamins of the vitamin B complex. Niacin was one of the first drugs used to treat hyperlipidemia that proved effective in reducing the levels of cholesterol and LDL-C and in increasing HDL levels. More than five decades ago, niacin was shown to lower plasma cholesterol in normal as well as hypercholesterolemic individuals [9]. In addition, this drug reduces triglyceride levels and lipoprotein (a), a known atherogenic lipoprotein [10,11].

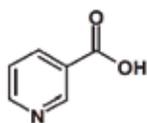
Niacin is the most effective lipid-regulating agent for increasing HDL levels [12]. Structurally, niacin consists of a pyridine ring with a carboxylic acid group in the 3-position [Figure 1]. This acid group is particularly important for activity: substitutions are generally poorly tolerated, as exemplified by nicotinamide which has an amide group at the 3-position and is almost inactive at the receptor. Niacin selectively increases apolipoprotein A-I-containing HDL particles, a cardioprotective subfraction and efficient mediator of the reverse cholesterol transport pathway [13].

Several clinical trials have demonstrated that the administration of niacin, either alone or combined with other lipid-lowering agents, significantly reduces total mortality and coronary events, retards progression, and induces regression of coronary atherosclerosis. Nicotinic acid, in fact, was the first drug shown to have an effect on total mortality in the long-term treatment of coronary heart disease. In one of the earlier studies, the Coronary Drug Project, a large-scale placebo-controlled trial conducted between 1966 and 1975, niacin combined with clofibrate reduced non-fatal myocardial infarction by 27% and the combined end-point, namely non-fatal MI and death, by 15%. In the Coronary Drug Project (1966–1975), monotherapy with nicotinic acid at doses of 3 g/day was shown to improve secondary prevention of myocardial infarction [14]. An extension of the previous study to a longer 15-year follow-up showed that patients in the niacin group had an 11% reduction in total mortality compared with those in the placebo group [15].

Similarly, in other studies, co-administration of niacin with colestipol, a bile acid sequestrant, halted progression or even resulted in regression of the atherosclerotic plaque [16-18]. Lastly, administration of slow-release niacin together with simvastatin resulted in significant regression of coronary stenosis and reduction in cardiovascular events [19].

LDL-C = low density lipoprotein cholesterol
MI = myocardial infarction

Figure 1. Niacin



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The way that niacin exerts its lipid reduction effects is not entirely clear. Enormous progress has been made in our understanding of its mechanism of effect, particularly the recent discovery of niacin receptors. Two niacin receptors have been identified in humans: HM74 (GPR109b) and HM74A (GPR109a) [20]. HM74A is thought to be responsible for most of the clinical effects of niacin, especially the effects on plasma lipids [20]. Both HM74 and HM74A are G-protein-coupled receptors.

Following administration, niacin rapidly inhibits adipocyte lipolysis apparently by inhibiting hepatic diacylglycerol acyltransferase 2, resulting in inhibition of triglyceride synthesis and a decrease in apolipoprotein B-containing lipoproteins; this is accompanied by a similarly rapid drop in plasma levels of free fatty acids [12,20,21]. Nicotinic acid anti-lipolytic effects seem to be related to its inhibition of cyclic adenosine monophosphate accumulation in adipocytes via the inhibition of adenylyl cyclase activity; nicotinic acid might act via the Gi-coupled receptor to inhibit adenylyl cyclase activity and lower cAMP levels [21]. It is hypothesized that this results in a reduced substrate supply for synthesis of very low-density lipoproteins by the liver, and that the consequent attenuation of VLDL production limits the CETP-mediated exchange of: a) cholesterol from HDL to VLDL, b) triglycerides from VLDL to HDL, and c) cholesterol between HDL and LDL [1,21]. The net effect is reduced catabolism of HDL and decreased accumulation of cholesterol esters in LDL particles [Table 1]. It has also been suggested that niacin may directly inhibit the uptake and catabolism of apolipoprotein A1-containing HDL particles, thus acting to further increase plasma levels of HDL [20].

Another important effect of niacin is related to the generation of nicotinamide and nicotinamide adenine dinucleotide. NAD⁺ activity (as an acceptor of hydride equivalents) is essential for all living cells, and high doses of niacin or nicotinamide thus increase cellular NAD⁺ pools. Although thought to be unrelated to its effects on lipid profiles, there is evidence that increased intracellular NAD⁺ may be beneficial with regard to cardiovascular disease in a number of ways.

cAMP = cyclic adenosine monophosphate
VLDL = very low-density lipoprotein
NAD⁺ = nicotinamide adenine dinucleotide

Table 1. Effects of nicotinic acid (> 1.5 g day) on plasma concentrations of lipids and lipoproteins

VLDL	Decreased	25–40%
LDL-cholesterol	Decreased	6–22%
Total cholesterol	Decreased	4–16%
HDL-cholesterol	Increased	18–35%
Triglycerides	Decreased	21–44%
Lipoprotein a	Decreased	16–36%

For example, niacin has been shown to inhibit reactive oxygen species production in endothelial cells, with subsequent down-regulation of a number of cytokines and adhesion molecules that are known to be involved in the development and progression of atherosclerosis, such as C-reactive protein, vascular cell adhesion molecule-1 and monocyte chemoattractant protein-1, as well as enzymes involved in the oxidation of LDL. By inhibiting ROS production and LDL oxidation in this manner, niacin-induced increases in NAD⁺ may directly interfere with the cellular and molecular processes underlying atherosclerosis [22]. There is also evidence to suggest that maintaining high concentrations of NAD⁺ may offer protection against damage caused by ischemia/reperfusion following myocardial infarction.

The main problem with the use of niacin is its side effects. Administration of pharmacological doses of niacin is accompanied by unwanted effects, primarily a cutaneous reaction called flushing, which occurs in up to 90% of patients. These undesirable effects and the introduction of statins resulted in less interest in the therapeutic effects of nicotinic acid in the

years following the arrival of statins. Niacin-induced flushing is mediated primarily by the production of prostaglandins D₂ and E₂ by dermal/epidermal immune cells, leading to vasodilation of blood vessels and resulting in the symptoms of redness, warmth, tingling, and itching [20,23]. This confirms previous knowledge that niacin-induced flushing can be

attenuated by co-administration with cyclo-oxygenase inhibitors such as acetylsalicylic acid [20], although some investigators have recently suggested [24] that serotonin released from platelets also contributes to the flushing response and that blocking of both pathways may be required for symptom relief. Flushing occurs in numerous patients treated with this drug and consequently results in many patients discontinuing this medication and physicians being reluctant to prescribe this drug.

Recently, several niacin receptor agonists were recognized and studied. These include B-hydroxybutyrate, acipimox, acifran and anthranilic acid derivatives. Although they are able to bind and activate the HM74A (GPR109A) receptor in plasma and induce changes on lipids similar to those of niacin, they are not without adverse clinical effects, including flushing. So far, their clinical properties have not been fully described and it is unclear whether they can accomplish the beneficial effects of nicotinic acid on atherosclerosis without significant adverse results [20,25].

ROS = reactive oxygen species

Neither has it been entirely clarified if the beneficial lipid effects of nicotinic acid are exclusively due to activation of HM74a. Recent studies have identified MK-0354, a partial HM74A agonist that retains full activity at the adipocyte level while profiling as a partial agonist in cAMP and guanosine-5'-triphosphate gamma assays. A recent MK-0354 phase II study demonstrated that despite a significant decrease in free fatty acid levels with absence of flushing events, no effects on LDL-C, triglycerides or HDL-C occurred. This brings into question the validity of HM74a as the unique target of nicotinic acid, and it may well be that partial agonists have a different downstream signaling pathway [26].

Since niacin has a short duration of action, frequent dosing is required. In addition, the drug is usually completely absorbed within 1–2 hours. The advantages of this immediate-release preparation are stronger effects on lipid metabolism and decreased hepatotoxicity; the disadvantage is increased flushing. Different formulations have tried to overcome this effect. Sustained-release preparations are absorbed over 12 hours, resulting in decreased flushing but also in reduced effects on

lipids. In addition, this drug modality has been shown to have increased hepatotoxicity and therefore has not been approved for clinical use [20].

A different formulation, extended-release niacin (ERN-NiaspanTM), has an absorption time of 8 and 12 hours after ingestion. The ERN, introduced 10 years ago, has a more balanced metabolism, resulting

in less flushing and a reduced risk of hepatotoxic effects compared with the other formulations [12]. Very recently, a newly reformulated ERN of 1000 mg was introduced to the market (Niaspan film-coated). In a study by Cefali et al. [27], patients reported 9% less flushing, a 42% reduction in median flushing intensity, and a 43% reduction in median flushing duration with this preparation. Additionally, the same authors demonstrated that in patients who took this compound, pretreatment with aspirin (650 mg) resulted in an additional 31% reduction in flushing incidence. Aspirin also significantly reduced intensity and duration of flushing (by 43%–45%) compared with no aspirin [28]. However, for this drug to be effective, a dose of 2000 mg has to be reached. Therefore, to ameliorate flushing, some authors recommend gradual titration over 3 months to arrive at the efficacious dose [29].

The development of new niacin formulations has sparked renewed interest in the use of this drug. Several recent studies have shown the efficacy of niacin in potentiating the effect of statins on lipid metabolism [19,30–32] [Table 2]. These studies showed that the addition of niacin to statins led to a significant

Table 2. Combination of niacin and statins for hyperlipidemia

Trial [ref]	Study population	Treatment (mean dose)	No. of patients (on niacin)	Change of lipid levels in treatment group (%)					Findings
				TC	TG	LDL-C	HDL-C	Non-HDL-C	
HATS [19]	Men & women with CHD & low HDL-C	Simvastatin 13 ± 6/day Niacin 2.4 ± 2.0 g/day	33	-31	-37	-42	26+	NR	Significant angiographic regression and marked decrease in clinical events
ARBITER 2 [31]	90% of patients were men	Niacin 1000 mg	87	UC	-13	UC	+20	-7	CIMT progression stopped
COMPELL [30] First arm	Men and women with high LDL-C	Atorvastatin 40 mg/day Niacin 2000 mg/day	60	NR	-47	-56	+22	-55	Significant decrease in LDL-C and TG and increase in HDL-C
COMPELL [30] Second arm	Men and women with high LDL-C	Rosuvastatin 20 mg/day Niacin 1000 mg/day	65	NR	-40	-51	+24	-49	Significant decrease in LDL-C and TG and increase in HDL-C
HALTS [32]	Men 78%, with ASCVD, on statins	Niacin 2000 mg/day ezetimibe 10 mg/day	97	-5	-15	-10	+7.5	NR	Significant regression of CIMT

HATS = HDL-C-Atherosclerosis Treatment Study [19], ARBITER 2 = Arterial Biology for the Investigation of the Treatment Effects of Reducing cholesterol [31], COMPELL = Comparative Effects on Lipid Levels of combination therapy with a statin and extended-release niacin or ezetimibe versus a statin alone [30], HALTS = HDL and LDL

Treatment Strategies [32]
CHD = coronary artery disease, ASCVD = atherosclerotic cardiovascular disease, HDL-C = high-density lipoprotein, LDL-C = low-density lipoprotein, TC = total cholesterol, TG = triglycerides, NR = not reported, UC = unchanged, CIMT = carotid intima media thickness

decrease in LDL-C levels and an increase in HDL-C and tricyclerides [19,30]. Furthermore, in niacin-treated patients the progression of atherosclerosis was slower and there was even a significant regression of arterial stenosis [19,31,32]. A recent study, the ARBITER 6 HALTS study (Arterial Biology for the Investigation of the Treatment Effects of Reducing Cholesterol 6-HDL and LDL Treatment Strategies) [32], compared the efficacy of niacin or ezetimibe when added to a statin. The study demonstrated that the use of extended-release niacin caused a significant regression of carotid intima media thickness when combined with a statin and that the incidence of major cardiovascular events was lower in the niacin group than in the ezetimibe group. The trial was terminated early, on the basis of efficacy, after showing that niacin was clearly superior to ezetimibe.

Despite these encouraging results, the administration of nicotinic acid at a full dose on a daily basis outside of research trials is still problematic.

For niacin to be effective, a minimal dose of 1 g/day is required. The optimal therapeutic dose is twice higher. However, administration of the drug results in frequent and bothersome flushing episodes that seriously limit patients' acceptance and frequently leads to discontinuation of the drug [29,33-35]. One study showed that after the first year of therapy with ERN (Niaspan®) only 14.6% of the original group of patients was still receiving the drug. Furthermore, only 5.8% of the original cohort received 1000 mg, and only 2.2% received more than 1500 mg/day [33].

Two other studies demonstrated that flushing was the main reason for discontinuation of the drug [34,35]. In one of the trials, 54% of the patients experienced severe or extreme flush-

ing [34]. In the other study, at 6 months follow-up, 53% of the patients still received 500 mg of ERN, 37% received 1 g, and only 2% received 2 g [35]. The use of aspirin to reduce flushing was suboptimal with regard to both the proportion of patients using aspirin and the dosage being used. Others found a much higher long-term compliance, 85% with doses higher than 1500 mg/day, underscoring the importance of patient education for maintenance of compliance [5]. The conclusion from these trials is that if niacin is to be used in clinical practice, more has to be done to reduce its side effects. As previously mentioned, niacin-induced flushing is mediated by activation of prostaglandin-2 subtype receptor-1 (DP1 receptors) in vascular smooth-muscle cells of dermal arterioles, resulting in dilation,

increased blood flow and subsequently flushing. Niacin appears to activate this cascade of events by stimulation of PGD2 release from Langerhans cells.

As a result, a new compound, laropiprant (LRPT), which selectively antagonizes the PGD2 receptor, was developed. LRPT is a highly selective DP1-receptor antagonist that was initially introduced as an anti-allergy agent and has rapid absorption and elimination properties. In early trials the drug reduced niacin-induced flushing without affecting its therapeutic effects, suggesting that lipid lowering and flushing are mediated by two independent pathways [5]. Interest in combining LRPT with ERN led to early clinical trials in which the co-administration of both drugs significantly reduced flushing. Subsequently, a combination pill with LRPT and ERN (Tredaptive-MSD®, USA-Israel) was developed, aiming to improve lipid profiles with the

PGD2 = prostaglandin 2
LRPT = laropiprant

Several new trials have shown that the combination of niacin-laropiprant significantly reduced the incidence of side effects without affecting its efficacy. Hopefully, ongoing long-term studies will show the effectiveness of this drug combination in preventing cardiovascular events without causing serious undesirable results

same efficacy of ERN while reducing side effects by using LRPT. As shown in earlier short-term studies, LRPT does not affect the lipid-modifying properties of niacin and has few side effects of its own. In an early phase II study, co-administration of LRPT with ERN significantly reduced niacin-induced flushing without affecting the niacin effects on lipid parameters [36] [Table 3]. Doses of 20 mg or 40 mg LRPT provide maximum protection against flushing when combined with niacin at doses of 1000 mg and 2000 mg respectively [29]. A tablet containing 1000 mg of niacin and 20 mg of LRPT was developed (Tredaptive®), and a two-step escalation of the dose from 1000 mg/20 mg to 2000 mg/40 mg was adapted.

Several phase III studies showed that ERN/LRPT (40 mg of LRPT/2000 mg of niacin), when added to a statin, or as monotherapy, significantly improved lipid parameters compared to placebo, and resulted in significant reductions of LDL-C and triglycerides and non-HDL-C and a significant increase in HDL-C [23,29,37-39] [Table 3]. In a recent study, the addition of ERN/LRPT to ongoing statin treatment resulted in significantly improved lipid-modifying benefits for LDL-C, HDL-C and triglycerides and all other lipid parameters, compared with doubling the statin dose, in patients with primary hypercholesterolemia or mixed dyslipidemia [39].

In a different study, ERN/LRPT was compared to ERN or placebo. LRPT did not interfere with the efficacy of ERN, and similar effects on lipid profiles were observed in the ERN/LRPT and ERN groups. Furthermore, patients receiving ERN/LRPT during the first week experienced a decrease in

moderate and severe flushing symptoms compared to those receiving ERN alone: 31% vs. 56%, respectively, of those with moderate symptoms and 14% vs. 33%, respectively, of the patients with severe symptoms [38]. At week 6, the symptoms in the ERN/LRPT group were similar to those in the placebo group, but patients in the ERN group continued to have symptoms [38]. These findings persisted until the completion of the trial (24 weeks), with overall reduction of moderate to severe duration of symptoms to 1 day per month in the LRPT group compared to 1 day per week in the ERN group [5].

In another phase III trial, patients on niacin could take aspirin or non-steroidal anti-inflammatory drugs under a new two-step dose escalation regimen of ERN/LRPT [23]. The addition of LRPT resulted in reduction of the flushing with ERN 1000 mg to a lower level than that experienced with ERN at a dose of 500 mg. Symptoms in the LRPT group decreased after week 5 but persisted in the ERN group. The differences between the groups were even larger with time. Remarkably, therapeutic doses of 2000 mg were reached by week 8 in the ERN/LRPT group, with only a few patients experiencing severe symptoms. More patients in the ERN group used aspirin or NSAIDs, suggesting that LRPT provided a strong protection against flushing [23].

These findings suggest superiority but do not necessarily reflect a real-life situation. In contrast to regular-day experience, patients in clinical trials are under close follow-up and are more motivated, prepared and educated through the

NSAIDs = non-steroidal anti-inflammatory drugs

Table 3. Laropiprant/niacin combination trials

Trial [ref]	Study population	Final dose	Duration	Flushing severity	Other findings
Factorial study Gleim et al. [37], 2007	Compare treatment with ERN/LRP, simvastatin or ERN/LRP + simvastatin	ERN 2.0 g/day LRP 40 mg/day Simvastatin 20–40 mg/day	12 wks	ERN/LRP+simvastatin was well tolerated	ERN/LRP+simvastatin significantly improved all lipid parameters
LRPT Paolini et al. [36], 2008	Dyslipidemic men and women aged 18–75 years	ERN 2.0 g/day LRPT 18.75, 37.5, 75, or 150 mg	4 wks (Part B of the study)	Patients treated with LRPT plus ERN experienced significantly less flushing than those treated with ERN alone	A phase II study. LRPT did not alter the beneficial lipid effects of ERN. LRPT plus ERN were well tolerated
Maccubbin et al. [38], 2008	Men and women with primary FH or mixed dyslipidemia	ERN/LRPT (Niacin 2 g)	24 wks	ERN/LRPT led to less flushing than ERN during initiation (wk 1) and maintenance (wks 2–24) ERN/LRPT had a safety/tolerability profile comparable with ERN CV risk	Significant decrease in LDL-C (18.4%), non-HDL-C (19.8%), TG (25.8%), Apo B (18.8%), and significant increase in HDL-C (20.0%)
Paolini et al. [29], 2008 pool of trials	Dyslipidemic and non-dyslipidemic patients	ERN 2.0 g/day LRPT 18.75 to 150 mg/day	12–52 wks	Clear advantage of ER niacin/laropiprant on flushing-related adverse events and discontinuations	Similar incidence of CV events, hepatitis, myopathy, and increases in fasting blood glucose levels with ERN or LRPT/ERN
PN054 Maccubbin et al. [23], 2009	Patients with or without CAD, and/or DM	ERN 2.0 g/day	16 wks	More than twice as many patients had no episodes of moderate, severe, or extreme flushing with ERN/LRPT than with ERN (47.0% vs. 22.0%)	The safety and tolerability profile of ERN/LRPT was similar to that of ERN
Shah et al. [39], 2010	Compare ERN/LRPT + statin vs. doubling the dose of statin	Simvastatin 10-20 mg to 20-40 mg; atorvastatin 10 mg to 20 mg; ERN/LRPT (niacin 2 g)	12 wks	Flushing and gastrointestinal symptoms were more frequent with ERN/LRPT than with statin alone	Significantly improved lipid-modifying benefits with ERN/LRPT (+statin) compared with doubling the statin dose

LRPT = laropiprant, CAD = coronary artery disease, DM = diabetes mellitus, FH = familial hypercholesterolemia, ERN = extended-release niacin, CV = cardiovascular, LDL-C = low-density lipoprotein-cholesterol, HDL-C = high-density lipoprotein-cholesterol, TG = triglycerides

enrollment procedure and the informed consent process [36]. In addition, patients showing a particular tendency to flushing are commonly excluded and the duration of the trial is usually shorter than in real life.

Despite the fact that laropiprant has been shown to be effective, some patients continue to have flushing, even when higher doses of this drug are given or aspirin is administered. It has been postulated that other mediators, such as PGE2 or serotonin and their pathways, could be involved [36].

Regarding safety, the addition of laropiprant to niacin did not increase adverse side effects. An analysis of several studies comparing ERN to ERN/LRPT showed that a mild increase of liver enzymes could occur with either preparation, and that severe hepatic toxicity was uncommon. Similarly, both formulations may increase glucose levels by 4 mg/dl and are rarely related to new-onset diabetes [33]. Other side effects reported are mild increases in uric acid, hypotension, and precipitation of angina in patients on vasodilators.

CONCLUSIONS

The addition of laropiprant to niacin is an important adjunct in the treatment of hyperlipidemia. We have to await the results of two ongoing trials before reaching definitive conclusions. For the first trial, "Atherothrombosis Intervention in Metabolic syndrome with low HDL/high TG and Impact on Global Health outcomes" (AIM-HIGH), a large study comparing simvastatin plus ERN to simvastatin alone, the completion date is expected to be in late 2012. The other major ongoing niacin trial is the "Heart Protection Study – Treatment of HDL-C to Reduce the Incidence of Vascular Events" (HPS2-THRIVE) that recruited 25,000 patients randomized to laropiprant 40 mg and ERN 2000 mg with simvastatin 40 mg and ezetimibe 10 mg or to placebo with simvastatin 40 mg and ezetimibe 10 mg. This is a 4-year trial whose primary objective is to assess major cardiovascular events. The expected completion date is in 2012.

If the incidence and severity of flushing in these trials would be reduced significantly in the long term and a reduction in cardiovascular events demonstrated, niacin could reemerge as one of the most complete and promising lipid-reducing drug of the future.

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