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Scientific Update™

# Comprehensive Solutions for the Treatment of Atherosclerosis beyond Low-Density Lipoprotein Cholesterol

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## A Review of a Satellite Symposium presented at the European Society of Cardiology Congress 2007

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By DAVID FITCHETT, MD

**Statin therapy reduces cardiovascular (CV) mortality, nonfatal myocardial infarction (MI), and stroke due to benefits related to both the degree of low-density lipoprotein cholesterol (LDL-C) lowering and the level of LDL-C achieved. Recent clinical trials have demonstrated that CV event rates can be lowered further by reducing LDL-C to even lower levels. Yet, despite treatment with higher doses of powerful statins and the achievement of LDL-C levels that are <2.0 mmol/L, a high residual risk remains, with 65%-70% of events not prevented in patients receiving statin therapy. Consequently, other therapeutic targets need to be identified to reduce this residual disease burden; this is the subject of this issue of *Cardiology Scientific Update*.**

## Lipid risk variables beyond LDL-cholesterol

Beyond an elevated LDL-C level, the atherogenic lipid profile includes a reduced high-density lipoprotein cholesterol (HDL-C) and increased lipoprotein(a) [Lp(a)], triglycerides (especially nonfasting), and remnant lipoprotein levels (especially those derived from very low-density lipoprotein [VLDL] and chylomicrons). Each of these atherogenic lipids is a potential target for modification to reduce the large residual risk burden of atherosclerotic vascular disease.

In prospective population studies, such as the Framingham Heart study,[1] the Prospective Cardiovascular Munster Study (PROCAM),[2] and the Multiple Risk Factor Intervention trial (MRFIT),[3] low HDL-C was the most powerful lipid indicator for future CV events, independent of LDL-C levels, plasma triglycerides (TGs), body weight, and the presence of diabetes. In the PROCAM study,[2] men with HDL-C levels <0.91 mmol/L had a 4-fold increased risk of coronary heart disease (CHD) compared with those with an HDL-C of >0.91 mmol/L. The relationship between HDL-C and CHD may be stronger in men than in women. Furthermore, HDL-C remains of prognostic value in elderly patients aged ≥85 years.

The inverse relationship between HDL-C and CV events appears to be even steeper than the positive relationship between LDL-C and events (Figure 1). A meta-analysis[4] demonstrated that for every 1 mg/dL (0.026 mmol/L) increase in HDL, there was a 2%-3% decrease in the risk of CHD, independent of LDL-C. An analysis of 23 randomized clinical trials[5] indicated that the CV event rate is independently reduced by 1% for each 1% reduction in LDL-C and for each 1% elevation in HDL-C. It was estimated that a 30% increase in HDL-C and a 40% decrease in LDL-C would result in a 70% reduction in CHD risk.

In patients on contemporary lipid-lowering regimens, HDL-C remains predictive for CV events. For patients on statins, despite LDL-C reductions, subsequent CV event rates relate to baseline HDL-C levels.[6] A recent study[7] investigated the impact of HDL-C on the outcomes of patients receiving drug-eluting stents for acute coronary syndromes, comparing those with low HDL-C (HDL-C <1.03 mmol/L in men and <1.15 mmol/L in women, mean 0.82±0.2 mmol/L) with those with higher HDL-C levels (HDL-C >1.03 mmol/L in men and >1.15 mmol/L in women, mean 1.41±0.2 mmol/L). Almost all



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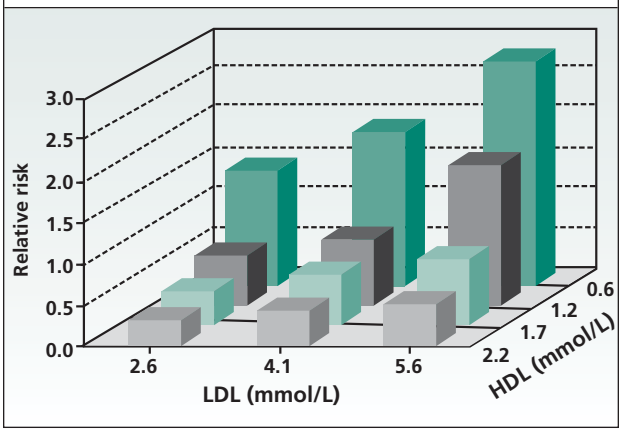
**Figure 1: Relationship between LDL-C and HDL-C levels and the relative risk of CHD from the Framingham study**




(98%) were receiving statins, and LDL-C levels were similar in the low and high HDL-C groups (approximately 2.62 mmol/L). Despite excellent contemporary treatment, adverse outcomes were more frequent in the low HDL-C group at 30 days and at 1 year. At 1 year, more deaths occurred in the low HDL-C group (12.5% vs. 5%, p<0.001, hazard ratio [HR] 3.33, 95% confidence interval [CI], 1.15-10) Thus, regardless of LDL-C levels and statin therapy, HDL-C levels at baseline remain predictive of outcomes.

Low HDL-C as a risk factor for CHD is a common finding. Individuals with metabolic syndrome and type II diabetes usually have a lipid profile characterized by low HDL-C, increased TGs, and mildly elevated LDL-C. It is estimated that 20%-30% of the North American population aged >50 years have criteria for metabolic syndrome and many of these individuals have low HDL-C.

Other lipid targets may provide opportunities to reduce CHD risk. Recently, nonfasting TG levels were shown to be related to adverse outcomes, whereas fasting levels had no predictive value.[8] This study suggested the importance of VLDL and chylomicron remnants as atherogenic lipid particles and the need to consider treatment to reduce their levels. Lp(a) has proatherothrombotic properties, such as attenuating fibrinolysis and promoting coagulation, as a carrier of proinflammatory lipids, and as a monocyte chemoattractant.[9] Increased circulating levels are associated with increased cardiovascular risk.[10]

## All HDL-C is not the same

High-density cholesterol particles are the smallest and densest of the lipoprotein fractions. HDL-C plays an important role in cholesterol efflux and reverse cholesterol transport by removing surplus cholesterol from cells and transporting it to the liver. It also has antiinflammatory, antioxidant, and antithrombotic roles. HDL-C protects against atherosclerosis via several potential mechanisms, including the removal of cholesterol from foam cells, the inhibition of the oxidative modification of LDL-C, and the inhibition of vascular inflammation and thrombosis. HDL-C is formed around the apolipoproteins A-1 (apo-A1), A-2 (apo-A2), and other apolipoproteins, and HDL-C levels are regulated by changes in synthesis and catabolism. Synthesis of HDL-C is largely controlled by apo-A1 and apo-A2 production by the liver. Uptake of HDL-C by the liver is achieved directly by the scavenger class B1 (SR-B1) receptor that recognizes apo-A1 as a ligand.

HDL-C is heterogeneous, with several discrete subpopulations that have different properties. Consequently, the level of HDL-C does not predict its functionality. HDL-C subpopulations can be classified according to their shape (discoidal or spherical), apolipoprotein composition, particle size, and electrophoretic mobility. HDL-C contains proteins that play a role in HDL-C remodeling, including cholesteryl ester transfer protein (CETP, which mediates exchange of cholesterol esters to LDL-C and VLDL-C in exchange for TG); lecithin:cholesterol acyl transferase (LCAT); phospholipid transfer protein (PLTP), and an important antioxidant, para-oxonase (PON). Although it has been reported that larger and more buoyant HDL-C is more vasculoprotective than smaller HDL-C, there is no consistent evidence that links protection against atherosclerotic vascular disease to specific HDL-C subpopulations.

Modification of HDL-C by factors associated with acute or chronic inflammation, such as changes in apo-A1 induced by leukocyte myeloperoxidase, can adversely alter the normally-protective HDL-C, making it dysfunctional, with proinflammatory and atherogenic properties. It has been reported that 75% of patients with CV disease or equivalents have increased levels of proinflammatory HDL-C despite statin treatment.[11] A further understanding of the complex interactions and responses of HDL-C subpopulations to therapeutic modification may explain the varied outcomes when total HDL-C is increased.

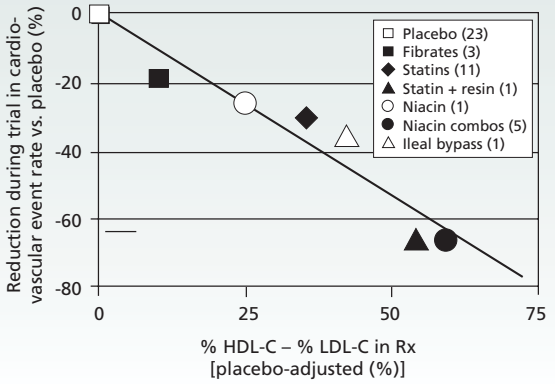
## Is increasing HDL-C beneficial?

Despite evidence indicating that better outcomes are associated with higher HDL-C levels, the therapeutic benefit of increasing HDL-C is not as clear. Administration of HDL-C (as apo A-1-phospholipid liposomes) results in net cholesterol excretion, and infusion of apo A1-Milano in patients with acute coronary syndromes resulted in a regression of atherosclerosis, as assessed by intracoronary ultrasound.[12]

Pharmacological agents modify most of the components of the lipid profile by varying degrees, and no currently available agent modifies HDL-C alone. Agents that increase HDL-C can be classified according to whether they:

- increase or modify levels of the HDL components such as apo-A1 and phospholipids (eg, niacin and statins), or

**Figure 2: Effect of various drug classes on the combined improvement in lipid profile (% increase in HDL-C minus % decrease in LDL-C)[5]**




- upregulate reverse cholesterol transport and macrophage cholesterol efflux (eg, fibrates).[13]

Statins increase HDL-C by 5%-15% and a greater benefit of statins is observed in patients with lower HDL-C levels, independent of LDL-C levels.[6] A recent post hoc analysis[14] of 4 trials showed that statin therapy is associated with coronary atherosclerosis regression when LDL-C is substantially reduced and HDL-C is increased by at least 7.5%.

Fibrates are agonists of peroxisome proliferator-activated receptors (PPARs); they enhance reverse cholesterol transport and macrophage cholesterol efflux and can reduce LDL-C by 10%-15%, increase HDL-C by up to 10%-20%, and reduce TGs by 40%-50%. However, in clinical trials, fibrates did not achieve this expected rise in HDL-C. In the VA-HIT trial,[15] the reduction of coronary events (22%) with gemfibrozil was attributed to a 6% increase in HDL-C.

An analysis of lipid trials indicates the benefit of the modification of both HDL-C and LDL-C, with the magnitude of the benefit on reducing CV outcomes related to the effect of the combined decrease in LDL-C and increase in HDL-C levels (Figure 2).

Novel treatments that modify lipid profiles increase HDL-C and may impact CV outcomes include CETP inhibitors, cannabinoid-1-receptor antagonists, PPAR agonists, and apo-A1-derived treatments. The CETP inhibitor, torcetrapib, increased HDL-C by 60%; yet, in the Investigation of Lipid Level Management to Understand Its Impact in Atherosclerotic Events (ILLUMINATE) trial, treatment with torcetrapib and atorvastatin was associated with a 61% increase in all-cause mortality, compared to the group receiving atorvastatin alone. Furthermore, there was no regression of carotid atherosclerosis in patients receiving torcetrapib. The cause of this surprising outcome is unknown, but is probably not due to the 3-4 mm Hg rise in mean blood pressure and likely represents a specific problem related to torcetrapib and not to CETP inhibition, in general.[16]

## Niacin and coronary heart disease

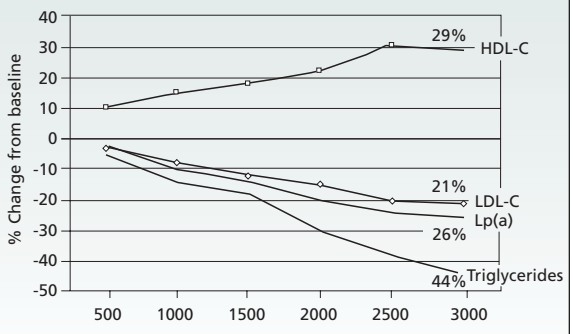
Nicotinic acid is a vitamin that is active at milligram doses. Over 50 years ago, a Canadian pathologist named Robert Altschul demonstrated that nicotinic acid reduced plasma cholesterol in rabbits and inhibited lipid deposits in cholesterol-fed rabbits.[17,18] Nicotinic acid (or niacin) at gram doses, is a broad-spectrum, lipid-modifying agent that increases HDL-C by up to 30% and reduces LDL-C by 20% and TGs by 40% (Figure 3).[19] Lp(a) is reduced by up to 26% and niacin is the only agent known to reduce Lp(a).

In the Coronary Drug Project,[20-21] MI patients were treated with niacin 3 g/day (1,119 patients) or placebo (2,789 patients) for 6.5 years. A recent analysis of the 6.2 year follow-up reveals an important reduction in the principal endpoints with niacin treatment compared to placebo (nonfatal MI/CV death -16%, $p < 0.05$; nonfatal MI -28%, $p < 0.005$; stroke/transient ischemic attack (TIA) -21%, $p < 0.05$, new angina -21%, $p < 0.005$, and need for CV surgery -54%, $p < 0.005$).[22] The Stockholm Ischemic Heart Disease Secondary Prevention study investigated the value of the combination of niacin 3 g/day with clofibrate in patients with MI; patients receiving the combination had a 26% reduction in total mortality and a 36% reduction in CV mortality over 5 years, compared to those receiving placebo.[23]

The incremental benefit of adding niacin to background statin therapy was studied in the Arterial Biology for the Investigation of the Treatment Effects of reducing cholesterol (ARBITER)2.[24] When HDL-C was increased 21% with extended-release niacin added to a statin, carotid intimal medial thickness (IMT) did not change over the first year of treatment yet, in patients receiving only statin treatment, IMT increased significantly.[24]

The combination of simvastatin and niacin was studied in the HDL Atherosclerosis Treatment Study (HATS).[25] LDL-C was reduced by 42%, from 3.4 to 2.1 mmol/L, VLDL decreased by 40%, and HDL-C increased by 29%, with a 61% increase in the buoyant large particle $HDL_2$. C-reactive protein (CRP) levels were reduced by 22% after 1 year of treatment and by 42% after 2 years. The primary endpoint was angiographically-determined coronary artery stenosis progression. With the simvastatin/niacin combination, average coronary stenosis regressed 0.6%, whereas there was a 3.9% progression in the placebo-treated group ($p<0.001$). Although not adequately powered to show changes in clinical outcomes, niacin and simvastatin appeared to reduce the risk of the primary composite endpoint (CV death, MI, stroke, or revascularization for worsening angina) by 90%. In HATS, only 3% of the niacin and simvastatin participants vs 24% of the placebo group experienced one of the composite endpoints ($p<0.03$). Unfortunately, no treatment group receiving only simvastatin was

**Figure 3: Changes in the lipid profile related to the dose of extended-release niacin[19]**




included. Hence, the incremental benefit of adding niacin to optimal statin therapy is unknown.

## Mechanisms of action in niacin

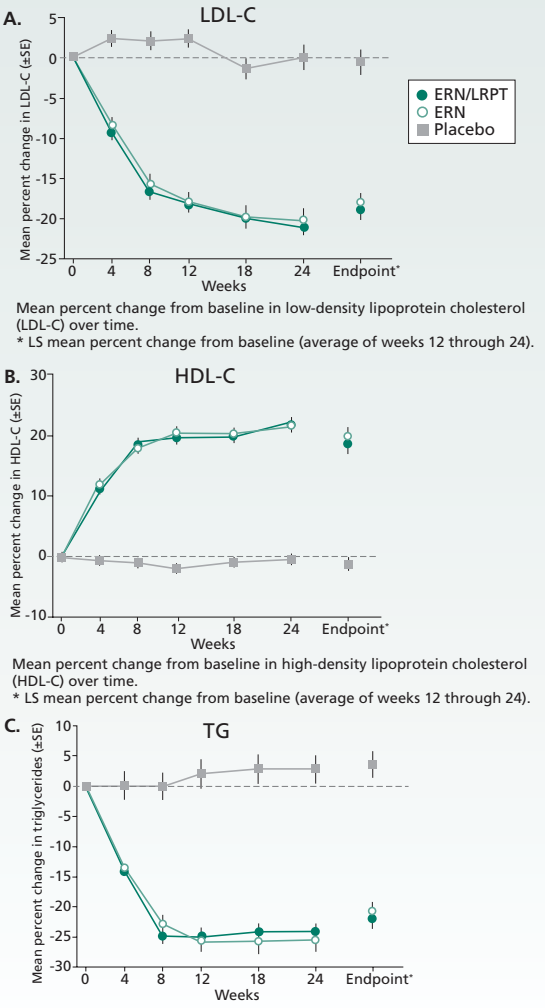
Niacin inhibits the mobilization of free fatty acids (FFAs) from adipose tissue by a receptor-dependent G-coupled protein inhibition of hormone-sensitive triglyceride lipase. Consequently, plasma FFAs are reduced, leading to reduced VLDL-C synthesis. The mechanism by which niacin increases HDL-C is not entirely clear.[26] HDL-C levels are usually lower when TG levels are elevated. This is due to transfer of TG from VDL to HDL by CETP. Subsequently TG in HDL is hydrolyzed by lipases, resulting in a smaller and denser HDL particle that is more readily excreted by the kidney. Niacin has a greater impact on increasing HDL-C when VLDL levels are decreased.[27]

Niacin is rapidly bound to a high-affinity membrane domain receptor GPR 109A that is highly expressed in adipose tissue.[28] Yet, despite an abundance of the receptor, its physiological role is unknown. FFA mobilization is reduced in knockout mice not expressing the niacin receptor.[28] However, the LDL-C and HDL-C effects of niacin might be GPR 109A receptor independent.[29] Yet, recent studies indicate that the antiatherosclerotic effects of niacin in a murine model are dependent on the niacin receptor. Flushing, due to peripheral vasodilatation, is the major side effect of niacin. A mouse ear model has been used to demonstrate that the niacin dose-dependent increase in skin blood flow is dependent on the niacin receptor.

## Niacin reborn

Although early studies indicated a benefit from niacin, the adverse effect of flushing limited its wide applicability. The standard niacin preparation results in troublesome flushing in approximately 90% of patients. An extended-release preparation reduces the frequency of flushing to approximately 50%.[30] The co-administration of aspirin

**Figure 4: Changes in the lipid profile with extended-release niacin (ERN), with ERN administered with laropiprant (ERN/LRPT) and with placebo[32]**



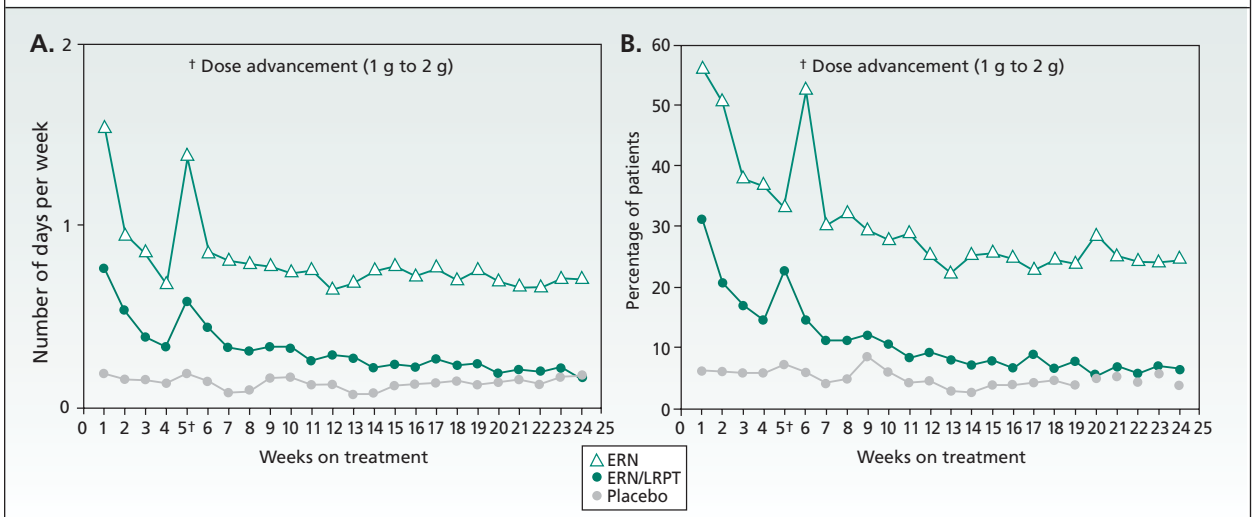

Mean percent change from baseline in low-density lipoprotein cholesterol (LDL-C) over time.
* LS mean percent change from baseline (average of weeks 12 through 24).

Mean percent change from baseline in high-density lipoprotein cholesterol (HDL-C) over time.
* LS mean percent change from baseline (average of weeks 12 through 24).

Mean percent change from baseline in triglycerides (TG) over time.
*Median percent change from baseline (average of weeks 12 through 24).

diminishes flushing and can reduce discontinuation rates to as low as 8%.[31] However, flushing bouts persisted and were unpredictable, even after many months of treatment. The benefits of niacin are dependent on the dose: increasing the dose from 1 to 2 g/day provides twice the LDL-C reduction, twice the HDL-C elevation, and a several-fold additional reduction in TGs.[19] However, the achievement produced by a 2 g/day dose is only possible after a slow 12-week titration, and fewer than 10% of patients reach this target. A better understanding of the mechanism of niacin-induced adverse effects has led to the development of an effective agent to significantly reduce the severity and frequency of flushing episodes, improve tolerance of the drug, and achieve target doses more frequently and faster.

**Figure 5: Reduction in flushing by the co-administration of laropiprant with extended-release niacin as recorded by:**
**A) Number of days per week with flushing episodes and**
**B) Percentage of patients with "moderate or severe" flushing between weeks 1 to 24**




Niacin stimulates the release of prostaglandin D2 ($PGD_2$) from immune lineage Langerhans cells in the skin. $PGD_2$ is metabolized to $PGJ_2$ and other metabolites that also cause vasodilatation through stimulation of DP1 receptors. This adverse effect of niacin is unrelated to its beneficial effects on plasma lipids. Laropiprant is a well-tolerated, potent, and highly-specific DP1 receptor antagonist. When it is administered with niacin, it reduces the frequency and severity of flushing and allows rapid titration to effective doses of niacin. DP1 receptors are found in the bronchi, blood vessels, platelets, retina, immune cells, and the central nervous system. However, DP1 inhibition does not have any known adverse effects and, in DP1 knockout mice, the receptor is not necessary for normal development. Furthermore, antagonism of the DP1 receptor does not produce a noticeable increase in levels of prostaglandins.

Recent trials have investigated the efficacy and tolerability of lipid-modification by extended-release niacin (ERN) co-administered with laropiprant in patients with dyslipidemia. In a double-blind, randomized, multicentre trial that included patients with either primary hypercholesterolemia or mixed dyslipidemia, patients were randomized to placebo, ERN, or ERN (co-administered with laropiprant; ERN/LRPT).[32] The starting dose of ERN was 1 g daily, that was increased to 2 g daily after 4 weeks. The lipid-altering efficacies of ERN/LRPT and ERN were identical (Figure 4), with a placebo-corrected reduction in LDL-C of 18.4% and in TGs of 25.8%, and a placebo-corrected increase in HDL-C of 20%. Similar effects were achieved, whether or not ERN/LRPT was administered with or without a statin. Patients receiving ERN/LRPT had significantly less flushing episodes compared to those receiving ERN, as measured by the severity of flushing occurring during the first week of treatment, the number of days/week that flushing was experienced, and the proportion of patients with moderate or severe flushing (Figure 5). The ERN/LRPT combination was well-tolerated, with a safety profile similar to ERN. Liver function abnormalities with alanine aminotransferase (ALT) or aspartate aminotransferase (AST) elevations that were >3 times the upper limit of normal occurred in 1% of the ERN/LRPT- and ERN-treated patients. Muscular symptoms were more frequent in the placebo group than in either of the ERN groups. Fasting plasma glucose increased by 0.2 mmol/L in both the ERN/LRPT and ERN groups, with A1Cs increasing 0.2% in the ERN/LRPT and 0.1% in the ERN group. In the small group of patients with diabetes, worsening of glycemic control occurred in 16.8% of the ERN/LRPT and 24% of the ERN groups. New-onset diabetes was observed in 0.8% of the ERN/LRPT group, 0.4% of the ERN group, and 0% of the placebo group. Serum uric acid was increased by 0.042 mmol/L in both the ERN and ERN/LRPT groups compared to 0.12 mmol/L in those receiving placebo, although gout was very infrequent (0.5% ERN vs 0% placebo). Overall adverse effects were more frequent in patients receiving niacin (ERN 63%, ERN/LRPT 62%), compared to placebo (53%). Discontinuation of medication due to treatment-related adverse events was slightly less in the ERN/LRPT, than in the ERN group (13% vs 14%).

This study showed that niacin 2 gm daily, in combination with laropiprant 40 mg daily, resulted in a sustained and important improvement in the lipid profile.

Furthermore, laropiprant did not interfere with the lipid-altering efficacy of niacin. The combination was well tolerated and associated with an important reduction in niacin-induced flushing compared to ERN and ASA, both during initiation and the maintenance phase of treatment.

## Conclusions

Reduction of CV risk by an LDL-C-centric approach with statins has historically improved outcomes. However, a large residual risk of 65%-70% remains. Wider spectrum lipid optimization by reducing LDL-C, increasing HDL-C, and decreasing TGs is predicted to have much greater benefits and may reduce the residual risk. Niacin has been shown to improve surrogate and clinical outcomes in high-risk patients. However, treatment with niacin has been limited by the high incidence of flushing, even when the drug is administered as an extended-release preparation with ASA. The development of a specific DP1 receptor antagonist that reduces niacin-induced flushing will allow more patients to reach and maintain the 2 g therapeutic dose. Further trials, such as the intimal medial thickness progression study, ACHIEVE, and the clinical endpoint study, Treatment of High-density lipoprotein to Reduce the Incidence of Vascular Events (HPS2-THRIVE), will show whether this translates into improved clinical outcomes.

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