

Effects of Niacin on LDL Particle Number

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Abstract and Niacin Overview

Abstract

Niacin has long been used as an effective lipid-altering therapy, particularly for raising HDL-C and lowering triglyceride levels. In addition, niacin modestly lowers LDL-C levels. LDL-C circulates in the blood as a heterogeneous population of various sized particles, with smaller LDL particles widely considered to be more closely associated with atherosclerosis and coronary heart disease. Recent evidence suggests that it is the total number of circulating LDL-C particles of various sizes that most closely predicts atherosclerosis risk. This review focuses on the growing body of literature suggesting that niacin favorably alters the number of circulating LDL particles of various sizes.

Niacin Overview

It was initially reported in 1955 that nicotinic acid (niacin) lowered cholesterol levels in normal subjects as well as in patients with hypercholesterolemia.^[1] There have been many subsequent studies that have supported niacin as a broad-spectrum lipid-regulating medication.^[2] Niacin reduces total cholesterol, triglycerides, VLDL-C, LDL-C and lipoprotein (a) (Lp[a]) levels, in addition to increasing HDL-C levels.^[3]

In its present clinical use, niacin is available in a number of formulations. Extended-release niacin (ERN) is the most widely used prescription niacin and has a better side-effect profile than the other available preparations, including dietary supplement versions of niacin. Dietary supplement niacin comes in many forms, including immediate-release or crystalline, sustained- or time-released and no-flush or flush-free formulations. Immediate-release niacin is effective and safe, even at relatively high doses (up to 12 g/day), but it has the highest incidence of flushing. Sustained-release niacin causes flushing less frequently, but it is associated with increased hepatotoxicity. Flush-free niacin is safe and well tolerated, but it has low efficacy because of limited bioavailability.^[4] In an analysis of the US FDA adverse event reporting (AER) database, Alsheikh-Ali *et al.* described that the rate of serious AERs associated with dietary supplement formulations of niacin was 6.2-fold higher and the rate of liver toxicity was 6.7-fold higher when compared with ERN.^[5] Of note, in this database, there was no distinction amongst the three types of dietary supplement niacin.

It should also be mentioned that previously, diabetes mellitus was a relative contraindication to niacin use; however, recent data suggest that niacin has modest and transient effects on hemoglobin A1C levels in patients with diabetes, which are amenable to adjustments in antidiabetic regimens. However, these same studies recommend that on an individual patient basis, glucose control should be monitored on initiating or increasing the dose of niacin in patients with diabetes or the metabolic syndrome.^[6]

One of the main uses of niacin is its ability to increase circulating levels of HDL-C and its major apolipoprotein, ApoA-I.^[7] Niacin inhibits the uptake and removal of HDL-C and ApoA-I, but does not inhibit the scavenger receptor class B type 1, thereby augmenting plasma levels without interfering with function.^[7-9] However, it should be noted that in a recent study from the Schaefer laboratory, niacin, in its extended-release formulation, is noted to have a slightly varied mechanism of action. This study supports that niacin increases ApoA-I but does so by increased production, and not by decreased removal, while having no effect on ApoA-II.

In addition to raising HDL-C, niacin also lowers circulating levels of ApoB-containing particles (VLDL-C, LDL-C and Lp[a]). This may be due to several different mechanisms. The first is by modulation of triglyceride synthesis and secretion of ApoB-containing compounds from the liver.^[7] Work from the Kayshap laboratory has shown that niacin inhibits the activity of diacylglycerol acyltransferase-2, an enzyme that is necessary for the synthesis of triglycerides. Moreover, this retards VLDL-C assembly, eventually resulting in ApoB degradation, thereby lowering circulating VLDL-C and LDL-C levels. The second mechanism by which niacin regulates circulating triglyceride levels is by inhibiting lipolysis in adipocytes, resulting in

lower plasma levels.^[10] Recently, it has also been shown that niacin significantly lowers ApoB-100 and ApoB-48, mainly owing to increased clearance.^[11]

In addition to the beneficial effects on lipid levels, niacin has been shown to have potentially beneficial cardiovascular effects via other mechanisms.^[12] Niacin therapy improves peripheral vascular endothelial function and increases endothelial nitric oxide synthase protein expression.^[13] In addition, niacin decreases inflammatory markers, namely levels of lipoprotein-associated phospholipase A2 and C-reactive protein (CRP).^[14] Furthermore, in an *in vitro* system, niacin has been shown to have antioxidant and anti-inflammatory properties. This is mediated by increases in NADP, reductions in glutathione levels and inhibition of the following: angiotensin II-induced reactive oxygen species production; LDL-C oxidation; TNF- α -induced redox-sensitive vascular cell adhesion molecule-1 and monocyte chemoattractant protein-1 messenger ribonucleic acid expression; and, TNF- α -induced and oxidized LDL-induced monocyte adhesion to endothelial cells.^[7] Finally, niacin favorably alters the distribution of LDL-C particles (LDL-Ps).^[15–18]

Niacin Therapy: Data from Clinical Trials

Several clinical trials support that niacin can improve certain defined cardiovascular end points. These studies include the Coronary Drug Project, the Familial Atherosclerosis Treatment Study (FATS), the HDL-Atherosclerosis Treatment Study (HATS), the Arterial Biology for the Investigation of the Treatment Effects of Reducing Cholesterol (ARBITER) 2 and ARBITER 3. The key features of each are listed in .^[19–23] In each of these studies, niacin therapy favorably altered the standard lipid profile, primarily by increasing HDL-C, and may have favorably affected these outcomes via the other mechanisms outlined above. We will now consider whether these improvements in outcomes may also be related to niacin's effect on circulating numbers of LDL-Ps.

Table 1. Niacin therapy: data from clinical trials.

Study	Year	Niacin type	Primary end point	Patient population	Main outcome	Ref.
CDP	1975	IRN	ACM	Men with a history of MI	Niacin decreased nonfatal MI (8.9% vs 12.2% in placebo-treated patients). 11% reduction in ACM when compared with placebo (p = 0.0004).	[19]
FATS	1990	IRN	Change in stenosis in 1 out of 9 proximal coronary artery segments	Men less than 62 years of age, with elevated ApoB levels, coronary atherosclerosis and a family history of CHD	Progression of atherosclerosis less frequent in niacin-colestipol group when compared with conventional therapy (25% vs 46%). Plaque regression more common in niacin-colestipol group when compared with placebo (p < 0.005). Clinical events (death, MI, revascularization) occurred in 2 out of 48 subjects as compared with 10 out of 52 subjects in conventional therapy group (RR: 0.27; 95% CI: 0.1–0.77).	[20]

HATS	2001	IRN and SRN	<p>Mean percent change per patient of stenosis in each of the nine proximal coronary artery segments</p> <p>Primary clinical end point was the time to first of the following events: death from coronary causes, nonfatal MI, stroke or revascularization for worsening ischemia</p>	<p>Men and women with clinical coronary disease and at least three stenoses of at least 30% of the luminal diameter or one stenosis of at least 50%</p>	<p>Mean percent coronary artery stenosis progressed by 0.7% for simvastatin–niacin plus antioxidant group, whereas by 3.9% and 1.8% for the placebo and antioxidant groups alone, respectively ($p = 0.004$).</p> <p>Plaque regressed by 0.4% for the simvastatin–niacin group ($p < 0.001$).</p> <p>Frequency of clinical end points highest for placebo group (24%) and lowest for simvastatin–niacin group (3%).</p> <p>Benefits of statin–niacin attenuated in patients receiving antioxidants.</p>	[21]
ARBITER 2	2004	ERN	<p>Mean change from baseline in CIMT after 1 year as detected by high-resolution ultrasound</p>	<p>Men and women over 30 years of age with known coronary vascular disease and who were on background statin therapy</p>	<p>Patients randomized to placebo had a significant increase in mean CIMT (0.044 ± 0.100 mm; $p < 0.001$).</p> <p>Patients on ERN had no change in CIMT (0.014 ± 0.104 mm; $p < 0.23$).</p> <p>Subanalysis of patients with insulin resistance showed that ERN reduced rate of CIMT progression when compared with placebo ($p = 0.026$).</p> <p>Also, when compared with placebo, therapy with ERN resulted in a 60% nonsignificant reduction in clinical events ($p = 0.20$).</p>	[22]
ARBITER 3	2006	ERN	<p>Time-dependent change in mean CIMT in patients treated with ERN for 12 versus 24 months.</p>	<p>Subjects who successfully completed the 12-month CIMT assessment of ARBITER 2</p>	<p>HDL-C increased in the ERN group by 23% ($p < 0.001$)</p> <p>Patients treated with ERN for 12 months had a net regression of CIMT of -0.027 ± 0.011 mm ($p < 0.001$) versus placebo.</p> <p>Patients treated with ERN for 24 months had an additional</p>	[23]

					<p>significant regression of CIMT of -0.041 ± 0.021 mm ($p = 0.001$) versus placebo.</p> <p>There was no significant difference between the 12 and 24 month ERN-treated patients for change in CIMT.</p> <p>After controlling for LDL-C and triglycerides, only changes in HDL-C were associated with regression in CIMT ($p = 0.001$).</p>
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ACM: All-cause mortality; ARBITER: Arterial Biology for the Investigation of the Treatment Effects of Reducing Cholesterol; CDP: Coronary drug project; CHD: Coronary heart disease; CIMT: Carotid-intima media thickness; ERN: Extended-release niacin; FATS: Familial atherosclerosis treatment study; HATS: HDL-atherosclerosis treatment study; IRN: Immediate-release niacin; MI: Myocardial infarction; RR: Relative risk; SRN: Sustained-release niacin.

LDL-P & Outcomes

The importance of LDL-P as a marker of atherosclerotic risk is increasingly being recognized. Recent consensus guidelines from the American College of Cardiology (ACC) and the American Diabetes Association (ADA) suggest that, in addition to LDL-C and non-HDL-C, LDL-P may be a valuable target of therapy to better assess cardiovascular risk.^[24] Of note, there are multiple methods to measure LDL subclasses and particle number, including NMR, gradient gel electrophoresis, ultracentrifugation-vertical auto profile and tube gel electrophoresis. Given that there is considerable variation amongst these methods and there is no adequate data to choose one or another method as the standard, we have decided to focus this review on studies utilizing NMR methodology as the ACC/ADA guidelines on lipoprotein management rely extensively on these studies.^[24–26]

Initially, it was believed that the number of small and total LDL-P were the more important subtypes related to cardiovascular outcomes. In a nested, case–control analysis of the Cardiovascular Health Study, Kuller *et al.* showed that in females, with mean age greater than 70 years, total LDL-P as well as small LDL-P showed a greater association with the risk of angina or myocardial infarction (MI) than did LDL-C.^[27] This correlation was no longer present when men were analyzed in this study. In a *post hoc* analysis of the Pravastatin Limitation of Atherosclerosis in Coronary arteries (PLAC-I) trial, Rosenson *et al.* demonstrated that high levels of LDL-C and small LDL-P were associated with greater rates of coronary artery luminal narrowing ($p < 0.05$ and $p < 0.01$, respectively^[28]). Of note, at baseline, large LDL-P were not associated with coronary artery disease (CAD) progression. Furthermore, within treatment groups, CAD progression was strongly associated with total LDL-P, after adjusting for other lipid levels, and a small LDL-P level of over 30 mg/dl was associated with a ninefold increased risk in CAD progression ($p < 0.01$).

In another prospective nested case–control study among healthy middle-aged women, Blake *et al.* assessed the relation between LDL-P size and concentration as risk factors for future MI, stroke or death from CAD. In this study, women who subsequently had a cardiovascular event had a higher number of total LDL-P ($p = 0.0001$), and a greater concentration of small LDL-P ($p = 0.046$). Although, the predictive value of these parameters for CAD was lower than the ratio of total cholesterol to HDL-C and of CRP, they remained significant predictors of future risk.^[29] El Harchaoui *et al.*, in a nested case–control study, analyzed the European Prospective Investigation into Cancer and Nutrition (EPIC)-Norfolk study and the relationship between LDL-P number and size with risk of future CAD. Univariate analysis of this study revealed that the total number of LDL-P (OR: 2.00; 95% CI: 1.58–2.59), as well as non-HDL-C, was more closely associated with CAD than was the level of total LDL-C.^[30] Of note, this relationship was no longer present after controlling for HDL-C and triglycerides. Additionally, the authors of this study suggest that other approaches, such as measuring multiple lipid components or ApoB, may be equal to or superior to LDL-P in the primary prevention setting.

In addition to total and small LDL-P, large LDL-P is also predictive of risk. In the Multi-Ethnic Study of Atherosclerosis (MESA) study, both large and small LDL-P were associated with subclinical atherosclerosis as evidenced by carotid-intima media thickness ($p < 0.001$ for both). Mora *et al.* concluded that this relationship was not appreciated before because previous studies did not adequately control for the inverse correlation between small and large LDL-P concentrations.^[31] In the Veterans Affairs High-Density Lipoprotein Intervention Trial (VA-HIT), Otvos *et al.* demonstrated that both baseline and on-trial values (with gemfibrozil) of large and small LDL-P were predictors of coronary heart disease events ($p < 0.005$ for all^[32]).

Although the importance of LDL-P and its relation to CAD risk is still being evaluated, there appears overall to be a strong relationship between LDL-P and future cardiac events.

Niacin & LDL-P

The ability of niacin to influence LDL-P is under active investigation and it appears that the beneficial effects of niacin extend beyond the traditional evaluation of the 'lipid profile.'

McKenney *et al.* compared the effect of once-daily low-dose atorvastatin with niacin (1 g three times daily) on LDL-P in patients with atherogenic dyslipidemia, defined by elevated triglycerides, reduced HDL-C and elevated small LDL-P.^[15] This was a multicenter, randomized, open-label parallel-design study. Treatment with either atorvastatin or niacin followed a 6-week lead-in period on a National Cholesterol Education Program (NCEP) step-one diet. The study enrolled 108 patients with total cholesterol values greater than 200 mg/dl, triglyceride levels 200–800 mg/dl, and ApoB levels greater than 110 mg/dl. During the 12-week study period, on average, both niacin and atorvastatin significantly decreased the number of small LDL-P (35.1 and 44.3%, respectively; $p < 0.05$ for both). Immediate-release niacin increased large LDL-P by 74% ($p < 0.05$), while atorvastatin had little effect on large LDL-P, with a nonsignificant decrease of 9.8%. It is unclear from this brief study, however, the ramifications of these alterations in LDL-P.

Superko *et al.* studied the effect of the immediate-release and extended-release formulations of niacin on LDL-P compared with placebo.^[16] They recruited 180 men and women, aged 21–75 years, with a history of CAD or greater than two CAD risk factors and LDL-C levels of 160–190 mg/dl, or no history of CAD and LDL-C of greater than 190 mg/dl. All subjects underwent 6 weeks of a NCEP step-one diet, followed by randomization to placebo ($n = 61$), immediate-release niacin (3 g/day; $n = 59$) or ERN (1.5 g/day; $n = 60$) for a total of 14 weeks. LDL subparticles were defined as LDL I through LDL IVb, with LDL I being the largest of the LDL-p and LDL IVb the smallest. When compared with placebo, both ERN and immediate-release niacin influenced LDL-P. Therapy with ERN resulted in a nonsignificant 10% increase ($p = 0.12$) for the larger LDL I particles, whereas immediate-release niacin resulted in a significant increase of 24% ($p < 0.0002$). ERN therapy resulted in a significant 10% decrease ($p < 0.02$) for the smaller LDL IVb particles and therapy with immediate-release niacin resulted in a significant 12% decrease ($p < 0.01$). Of note, total LDL-P is not reported in this study. Interestingly, when these data are compared with those from the previous study by McKenney *et al.*, immediate-release niacin significantly decreases small LDL-P, but with a potentially off-setting significant increase in large LDL-P. However, when examining ERN, there is only a significant decrease in small LDL-P, with no change in large LDL-P.^[16]

Further examining ERN's effect on LDL-P, Morgan *et al.* compared ERN at 1 and 2 g/day with placebo ($n = 21$, 20 and 19, respectively^[17]). This study was a multicenter, double-blinded, placebo-controlled trial where patients with CAD or greater than two CAD risk factors and an LDL-C level of 160–190 mg/dl or with LDL level greater than 190 mg/dl, were randomized to ERN 1 g/day, ERN 2 g/day or placebo for a total of 12 weeks. Patients who were randomized to ERN 1g/day and 2 g/day both had nonsignificant decreases in small LDL-P and nonsignificant increases in large LDL-P when compared with placebo. However, there was a significant 15 and 23% decrease in total LDL-P in the ERN 1 g/day and 2 g/day groups, respectively ($p = 0.002$ for both groups).^[17]

Finally, our group has shown that the addition of ERN to existing statin therapy has favorable effects on LDL-P in patients with established CAD and well-controlled LDL-C levels (< 100 mg/dl) at baseline.^[18] We enrolled 54 patients with a history of CAD into a randomized, placebo-controlled trial of ERN 1 g or active placebo added to the patient's baseline lipid-lowering therapy, over a 3-month period. At the end of the study, there was no significant change in total, large or small LDL-P in those randomized to placebo. However, those receiving ERN had a 9% decrease in total LDL-P and a 14% decrease in small LDL-P when compared from baseline to follow-up ($p < 0.05$ for both). Additionally, when compared with placebo at

follow-up, there were 18% fewer total LDL-P in patients randomized to ERN, and 26% fewer small LDL-P in patients randomized to ERN ($p < 0.05$ for both). Of note, there was no significant change in large LDL-P from baseline to follow-up for patients who received ERN, or in comparison to placebo at follow-up. In light of the previously published data, this study adds further evidence that ERN favorably alters LDL-P.^[18]

Taken together, these data support that ERN may have cardiovascular benefits that extend beyond the routine lipid profile. However, the trials to date have been too small and too short to suggest a definitive influence of ERN on LDL-P-mediated improvements in cardiovascular disease. Furthermore, there were no clinical events reported in any of these lipid-end point studies.^[15–18]

Future Perspective

It is clear that niacin is a broad-spectrum lipid-altering medication with substantial cardiovascular benefit. Multiple randomized, placebo-controlled trials have demonstrated niacin's ability to positively influence both angiographic and clinical outcomes.^[19–22] In addition to its lipid profile effects, ERN has beneficial effects on endothelial function as well as on inflammatory markers.^[13,14] Furthermore, it is clear that there is an association between LDL-P (total, large and small) and cardiovascular outcomes.^[27–32] Guidelines from the ACC and the ADA suggest that measurement of LDL-P may be a more accurate way to assess cardiovascular risk in addition to the standard lipid profile.^[24] Newer research with niacin, and more specifically ERN, indicates that therapy with ERN favorably alters these particle numbers, thereby potentially reducing cardiovascular risk.^[15–18] Of note, however, the additional value of LDL-P is still under debate and although potentially interesting and insightful, it is not generally recommended for routine analysis at this time.

Given this information, there remains a key question: will ERN's ability to change LDL-P result in a measurably favorable change in cardiovascular outcomes? The ongoing Atherothrombosis Intervention in Metabolic Syndrome with Low HDL/High Triglycerides and Impact on Global Health Outcomes (AIM-HIGH) study should assist in answering this important question. This study is planned to randomize approximately 3300 people to either simvastatin or simvastatin–niacin over the course of 5–6 years.^[101] The premise of the study is that, even with statin therapy and well-controlled LDL-C levels, there remains an unacceptably high risk of cardiovascular events. This residual risk may be attributable to multiple factors, including low levels of HDL-C and high numbers of small, or total LDL-Ps. This analysis will be an essential step to addressing ERN's ability to affect outcomes via its changes in LDL-P.

Sidebar

Executive Summary

Niacin overview

- Niacin, also known as nicotinic acid, is a broad-spectrum, lipid-altering drug, shown to increase HDL and decrease total cholesterol, triglycerides, VLDL, LDL-C and lipoprotein (a).
- In addition to effects on lipids, niacin has favorable effects on endothelial function and inflammatory markers.
- Extended-release niacin is the most commonly used prescription form of niacin and has the best side-effect profile.

Niacin therapy: data from clinical trials

- Niacin has been shown in multiple randomized controlled trials to have benefit both on angiographic outcomes and on clinical outcomes.

LDL-C particles & outcomes

- There is a strong correlation between total and small LDL-C particles (LDL-Ps) and cardiovascular outcomes.
- Current understanding on particle numbers indicates that in addition to small and total LDL-Ps, a greater number of large LDL-Ps is also a risk factor for cardiovascular disease.

Niacin & LDL-P

- Immediate-release niacin has been shown to significantly increase large LDL-Ps and significantly decrease small LDL-P.
- Extended-release niacin does not alter large LDL-Ps, but reduces small LDL-Ps in patients with coronary artery disease (CAD) or CAD risk factors. Similar to immediate-release niacin, extended-release niacin also decreases total LDL-Ps.
- In patients with CAD and well-controlled LDL levels, extended-release niacin favorably alters LDL-Ps by reducing the number of small and total particles.

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Papers of special note have been highlighted as:

of interest

of considerable interest

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