



Niacin and Statin Combination Therapy: Regression of Coronary Atherosclerosis in Patients with Cardiovascular Disease

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Expert Commentary

Provided by

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Statin-induced reductions in low-density lipoprotein (LDL)-cholesterol form the cornerstone of treatment of hyperlipidemia to reduce cardiovascular morbidity and mortality. Despite the substantial reductions in cardiovascular morbidity and mortality that have been achieved with statins,¹⁻⁶ these same data indicate that approximately two-thirds of all adverse cardiovascular events are not prevented with statin therapy. In addition, more aggressive dosing of statin monotherapy has resulted in incremental, but limited benefit, of lowering of LDL-cholesterol for further reductions in cardiovascular events.⁷⁻¹⁰ Collectively, these data suggest that patients may benefit from additional therapies aimed at normalizing other lipid abnormalities such as low high-density lipoprotein (HDL)-cholesterol or elevated triglyceride levels.

A body of epidemiological evidence reveals a consistent association between low HDL-cholesterol levels, extent of atherosclerosis,¹¹⁻¹⁴ and incident coronary heart disease.¹⁵ Furthermore, epidemiological studies indicate that an approximate 1mg/dL increase in HDL-cholesterol is associated with a 2% to 4% reduction in coronary heart disease outcomes.¹⁶ Thus, the National Cholesterol Education Program Adult Treatment Panel III (ATP III)¹⁷ and the American Diabetes Association/American Heart Association (ADA/AHA)¹⁸ recognize low HDL-cholesterol (<40 mg/dL) as a risk factor for cardiovascular disease and support efforts to raise low HDL-cholesterol in patients with, or at high risk, for cardiovascular disease.

Because statin therapy does not adequately control the cardiovascular risk associated with low-HDL-cholesterol,^{6,19} combination therapy that includes a focus on raising HDL-cholesterol should be considered as an adjunctive approach to further reduce cardiovascular risk. Indeed, studies have shown an additional relative risk reduction of 30–60% in incident coronary heart disease event rates may be achievable through treatment of multiple components of the dyslipidemic profile.²⁰⁻²²

While fibrate agents (eg, fenofibrate, gemfibrozil) may be used to increase low HDL-cholesterol levels,^{23,24} the ADA/AHA guidelines suggest that niacin is the most effective agent for raising HDL-cholesterol.¹⁸

Furthermore, ATP III guidelines report that among lipid-lowering agents, niacin appears to be the most effective for favorably modifying all of the lipoprotein abnormalities associated with atherogenic dyslipidemia.¹⁷

These recommendations are underscored by an expanding understanding of the biologic role of HDL-cholesterol in atherogenesis. HDL particles remove esterified cholesterol via the liver in the process known as reverse cholesterol transport. This removal occurs primarily through the interaction of apoA1 (the principal apoprotein of HDL) with the membrane cholesterol transporters, such as ABCA1^{25,26} and ABCG1.²⁷ While experimental studies have revealed that HDL and apoA1 are anti-atherogenic,²⁸ exogenously administered phospholipids-apoA1 particles in human studies have shown short-term effects on the regression of coronary atherosclerosis.²⁹ Thus, it is biologically plausible that niacin, which leads to dose-dependent increases in both HDL-cholesterol and apoA1 levels via interaction with the nicotinic acid receptor³⁰ and delayed clearance of apoA1, may stimulate atherosclerosis regression.

Although niacin has been in clinical use for over 4 decades, limited data exist that have assessed its incremental effect on atherosclerosis and cardiovascular outcomes. In the Coronary Drug Project,³¹ niacin monotherapy demonstrated a significant reduction in the combined outcome of coronary heart disease death and nonfatal myocardial infarction (15% reduction, $P < .05$) and in the outcome of nonfatal myocardial infarction (26% reduction, $P < .05$) compared with placebo in patients with a history of coronary heart disease. In a 15-year follow-up study,³² total mortality was significantly reduced (11% reduction, $P = .0004$) and coronary mortality was significantly decreased (12% reduction, $P < .05$) in patients who received niacin therapy.

More recent data reveals that the addition of niacin to statin therapy results in regression of atherosclerosis and reduction in adverse cardiovascular events.²¹ The High-density Lipoprotein-Atherosclerosis Treatment Study (HATS) showed marked clinical and angiographically measurable benefits of the addition of niacin to simvastatin therapy in patients with low HDL-cholesterol and a history of coronary heart disease. The addition of niacin to simvastatin therapy resulted in a -0.4% regression of stenosis compared with a 3.9% progression of stenosis with placebo ($P < .001$). Furthermore, the combination of niacin and simvastatin resulted in a significant 90% reduction ($P = .03$) in the composite clinical end point of cardiovascular events (death from coronary causes, confirmed myocardial infarction or stroke, or revascularization).²¹

Different forms of niacin therapy have been available for clinical use. Older niacin preparations have been associated with a high incidence of

adverse reactions such as flushing, liver transaminase elevations more than 3 times the upper limit of normal, and development of hepatotoxic effects.^{33,34} However, extended-release niacin has been associated with a significant reduction in the incidence, intensity, and duration of flushing.³⁵ Moreover, safety data from therapy with extended-release niacin plus lovastatin shows no excess in the rate of liver toxicity or rhabdomyolysis over statin monotherapy.³⁶

This *Cardiology Express Report*™ reviews the results of 2 clinical trials (Arterial Biology for the Investigation of the Treatment Effects of Reducing Cholesterol [ARBITER] 2 and ARBITER 3) that evaluated the benefit of extended-release niacin therapy when added to statin monotherapy on the regression of atherosclerosis in patients with low HDL-cholesterol and a history of cardiovascular disease.^{37,38}

Slowing the Progression of Atherosclerosis with Extended-release Niacin

ARBITER 2 was a single-center, double-blind, randomized, placebo-controlled study of once-daily extended-release niacin in 167 patients (mean age, 67 years) with low levels of HDL-cholesterol (<45 mg/dL) and known coronary vascular disease being treated with statin therapy for 12 months.³⁷ Patients were randomized to receive either extended-release niacin (n = 87) or placebo (statin monotherapy; n = 80). Extended-release niacin was initiated at a daily dose of 500 mg for 30 days, then increased to 1000 mg for the remainder of the 12-month study period. Patients were advised to take their daily dose at night with their usual daily dose of aspirin. Baseline patient characteristics, lipid concentrations, and carotid intima-media thickness were similar between treatment groups.

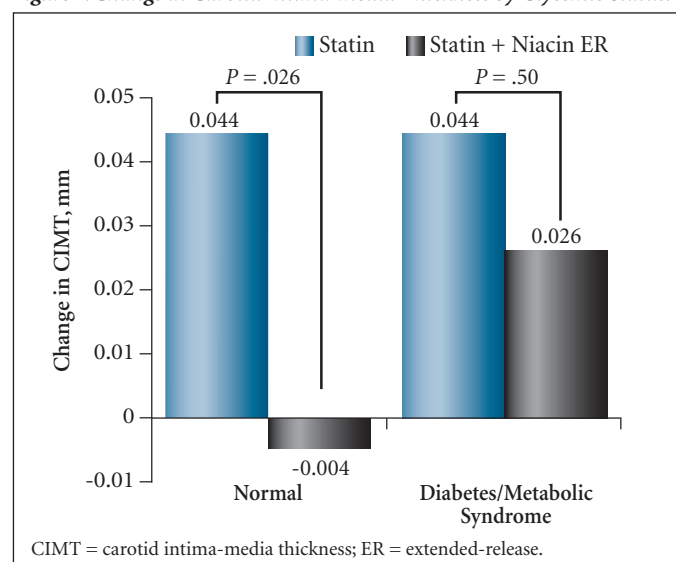
The predefined primary end point of this study was the change in mean common carotid intima-media thickness, a validated surrogate cardiovascular end point,³⁹ after 1 year of treatment. Secondary end points included changes in serum lipid concentrations, adverse events including liver-associated enzyme elevations, and a composite of clinical cardiovascular events including any hospitalization for acute coronary syndrome (unstable angina, myocardial infarction), stroke, an arterial revascularization procedure (percutaneous coronary revascularization, coronary bypass surgery, or peripheral vascular revascularization), or sudden cardiac death.

After 12 months of treatment, the increase in carotid intima-media thickness in patients treated with extended-release niacin (n = 78) was 0.014 mm compared with 0.044 mm in patients treated with placebo (n = 71). Thus, carotid intima-media thickness progression was 68% lower with in patients treated with extended-release niacin than in patients treated with placebo. On paired analysis, the increase in carotid intima-media thickness progression with extended-release niacin from baseline to 12 months (0.893 ±0.259 mm to 0.907 ±0.235 mm) was not statistically significant (P = .23). However, the increase in carotid intima-media thickness with placebo from baseline to 12 months (0.868 ±0.207 mm to 0.912 ±0.202 mm) was statistically significant (P<.001). Stabilized or regression of carotid intima-media thickness was found in 38.5% of patients treated with extended-release niacin compared with 25.4% of patients treated with placebo (P = .087).

The progression of carotid intima-media thickness during treatment was related to the presence of both diabetes and metabolic syndrome. In a non-prespecified subgroup analysis in 88 patients with insulin resistance (diabetes or the metabolic

syndrome), the lowest progression rate was observed in patients with normal glycemic status (Figure 1). A significant difference was observed in carotid intima-media thickness progression between treatment with extended-release niacin (-0.004 mm) and placebo (0.044 mm) in patients with normal glycemic status (P = .026). Patients treated with placebo had the greatest carotid intima-media thickness progression, regardless of insulin-resistance status. No significant difference was observed in patients with insulin resistance treated with extended-release niacin (0.026 mm) and placebo (0.044 mm).

Figure 1. Change in Carotid Intima-media Thickness by Glycemic Status.³⁷



After 12 months of treatment, HDL-cholesterol significantly increased by 21% in patients treated with extended-release niacin (baseline 39 mg/dL to 47 mg/dL; P = .003) (Table 1). HDL-cholesterol was unchanged in patients treated with placebo. Triglyceride levels also decreased significantly with extended-release niacin (baseline 154 mg/dL to 134 mg/dL; P = .03); triglyceride levels in patients treated with placebo did not change significantly (baseline 172 mg/dL to 164 mg/dL).

Patients treated with extended-release niacin realized a 60% decrease in cardiovascular clinical events (secondary end points) compared with placebo, although this was not a statistically significant difference (P = .20). Figure 2 illustrates the secondary end points.

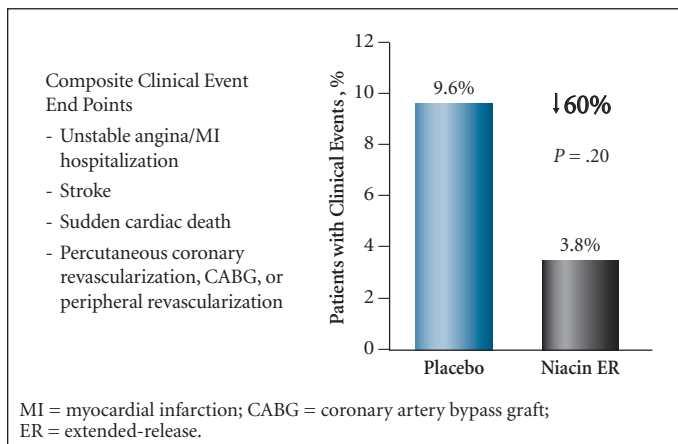
Skin flushing occurred significantly more often (P<.001) in patients treated with extended-release niacin (54/78, 69.2%) compared with placebo (9/71, 12.7%). However, there was no significant difference in

Table 1. Comparison of Baseline and 12-month Serologic Results for Selected Lipid Parameters.^[adapted from 37]

| | Placebo (n = 71) | Baseline Extended-release Niacin (n = 78) | P-value | 12 Months Placebo (n = 71) | 12 Months Extended-release Niacin (n = 78) | P-value |
|----------------|------------------|---|---------|----------------------------|--|---------|
| LDL-C, (mg/dL) | 91 | 87 | .19 | 86 | 85 | .61 |
| HDL-C (mg/dL) | 40 | 39 | .52 | 40 | 47 | .003 |
| TG (mg/dL) | 172 | 154 | .25 | 164 | 134 | .03 |

LDL-C = low-density lipoprotein cholesterol; HDL-C = high-density lipoprotein cholesterol; TG = triglycerides.

Figure 2. Secondary End Points for Placebo and Extended-release Niacin. [adapted from 37]



study withdrawal due to concern about adverse drug effects between extended-release niacin and placebo. No patient in the study experienced significant (3 times the upper limit of normal) elevations of liver-associated enzymes or developed myositis.

Sustained Effect on Progression of Atherosclerosis

ARBITER 3 was a prespecified extension study of ARBITER 2 in which patients completing the blinded 12-month carotid intima-media thickness end point assessment were followed for an additional 12 months on open-label extended-release niacin.³⁸ Patients previously on extended-release niacin 1000 mg (n = 69) continued their treatment, while patients previously on placebo (n = 61) received extended-release niacin 500 mg once daily for 30 days, then increasing to 1000 mg once daily.

The predefined primary end point of ARBITER 3 was the time-dependent change in mean carotid intima-media thickness in patients treated with extended-release niacin for up to 24 months compared with treatment with placebo for 12 months during ARBITER 2. Thus, extended-release niacin therapy was examined at 2 time-points: 12 and 24 months.

At 24 months, continued treatment with extended-release niacin (n = 57) was associated with significant regression (-0.041 mm; *P* = .001 vs placebo phase) of carotid intima-media thickness (Figure 3). Pooling the 12-month effects of extended-release niacin indicated a net regression of carotid intima-media thickness of -0.027 mm (n = 125, *P* < .001 vs placebo phase).

For patients with diabetes or metabolic syndrome, 12 to 24 months of extended-release niacin resulted in a significant regression of carotid intima-media thickness (-0.046 mm; *P* < .001 vs placebo phase) (Figure 3).

Patients converting from placebo to extended-release niacin experienced a significant regression of carotid intima-media thickness of -0.095 mm (*P* < .001 vs placebo phase). In these patients, the regression in carotid intima-media thickness was quantitatively greater than that observed with 12 months of extended-release niacin in the original ARBITER 2 study.

After 24 months of treatment with extended-release niacin, LDL-cholesterol decreased by a mean of 8.8 mg/dL (-10%), HDL-cholesterol increased by 9.1 mg/dL (+23%), and triglyceride levels decreased by 33 mg/dL (-20%) (Figure 4).

Extended-release niacin therapy was generally well tolerated; only 5 patients (3.8%) withdrew due to flushing associated with treatment.

Figure 3. Changes in Carotid Intima-media Thickness from Placebo and Extended-release Niacin. [adapted from 38]

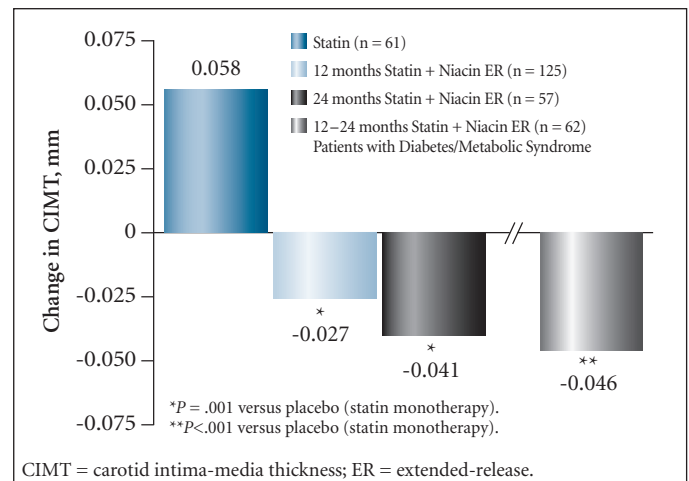
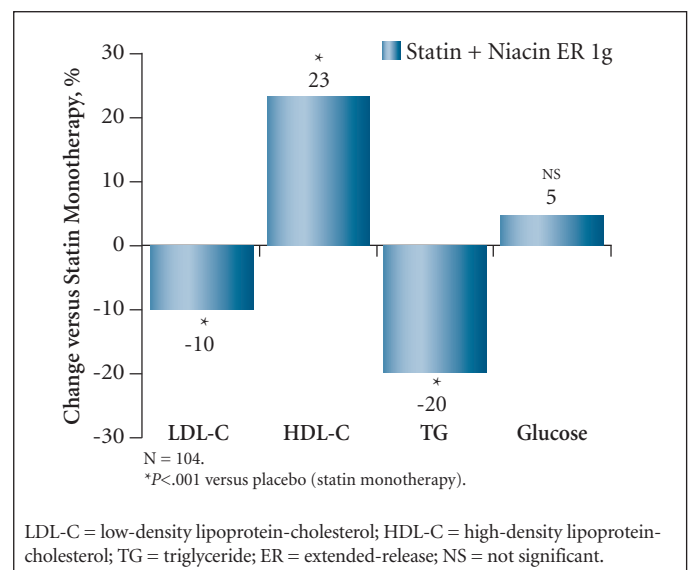


Figure 4. Change from Baseline to 24 Months from Extended-release Niacin Compared with Placebo on Lipid Parameters. [adapted from 38]



Importantly, no significant (>3x above upper limit of normal) changes in liver-associated enzymes or myopathy was observed.

Conclusion

The findings of ARBITER 2 and ARBITER 3 are notable and relevant to current clinical management of hyperlipidemia. When added to statin therapy, extended-release niacin significantly increases HDL-cholesterol and induces atherosclerosis regression as measured by carotid intima-media thickness in patients with low HDL-cholesterol and established coronary heart disease. The link between atherosclerosis stabilization and regression and protection from cardiovascular events is well documented from angiographic,⁴⁰ coronary intravascular ultrasound,⁴¹ and carotid intima-media thickness studies.³⁹ However, further studies are warranted to more fully assess the beneficial effects of extended-release niacin therapy in reducing residual cardiovascular risk and improving cardiovascular outcomes.

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Upon completing this multimedia CME activity, you should be able to:

1. Identify pharmacologic agents used to increase low HDL-cholesterol levels.
2. Discuss the effects of niacin and statin combination therapy on carotid intima-media thickness.
3. Discuss the effects of niacin and statin combination therapy in patients with low HDL-cholesterol and cardiovascular disease.

Instructions

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Upon successfully completing this program as designed and achieving a passing score of 70% or higher on the Activity Self-assessment Test, participants will receive a continuing education credit letter awarding the appropriate credit and the Activity Self-assessment Test answers four to six weeks after the receipt of the registration and evaluation materials.

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This multimedia CME activity was reviewed for relevance, accuracy of content, balance of presentation, and time required for participation by Mark A. Gendreau, MD, MS; Nicole Weinreb, MD; and Abigail Zavod, MD.

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