

Efficacy, Safety, and Tolerability of Once-Daily Niacin for the Treatment of Dyslipidemia Associated With Type 2 Diabetes

Results of the Assessment of Diabetes Control and Evaluation of the Efficacy of Niaspan Trial

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Background: Diabetic dyslipidemia is characterized by high triglyceride levels; low high-density lipoprotein cholesterol levels; small, dense low-density lipoprotein particles; and high free fatty acid levels. Niacin reduces concentrations of triglyceride-rich and small low-density lipoprotein particles while increasing high-density lipoprotein cholesterol levels. It also lowers levels of free fatty acids and lipoprotein(a). However, the use of niacin in patients with diabetes has been discouraged because high doses can worsen glycemic control. We evaluated the efficacy and safety of once-daily extended-release (ER) niacin in patients with diabetic dyslipidemia.

Methods: During a 16-week, double-blind, placebo-controlled trial, 148 patients were randomized to placebo (n=49) or 1000 (n=45) or 1500 mg/d (n=52) of ER niacin. Sixty-nine patients (47%) were also receiving concomitant therapy with statins.

Results: Dose-dependent increases in high-density lipoprotein cholesterol levels (+19% to +24% [$P<.05$] vs

placebo for both niacin dosages) and reductions in triglyceride levels (−13% to −28% [$P<.05$] vs placebo for the 1500-mg ER niacin) were observed. Baseline and week 16 values for glycosylated hemoglobin levels were 7.13% and 7.11%, respectively, in the placebo group; 7.28% and 7.35%, respectively, in the 1000-mg ER niacin group ($P=.16$ vs placebo); and 7.2% and 7.5%, respectively, in the 1500-mg ER niacin group ($P=.048$ vs placebo). Four patients discontinued participation because of inadequate glucose control. Rates of adverse event rates other than flushing were similar for the niacin and placebo groups. Four patients discontinued participation owing to flushing (including 1 receiving placebo). No hepatotoxic effects or myopathy were observed.

Conclusion: Low doses of ER niacin (1000 or 1500 mg/d) are a treatment option for dyslipidemia in patients with type 2 diabetes.

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ALTERATIONS in lipid metabolism are recognized concomitant symptoms of diabetes mellitus. It is believed that even before the development of overt diabetes, insulin resistance and a prediabetic state impair the mechanism that suppresses fatty acid release from adipose tissue after food intake.¹ The resultant excess of free fatty acids leads to increased concentrations of triglyceride (TG)-rich particles (very low-density lipoproteins and chylomicrons) and TG enrichment of high- and low-density lipoprotein (HDL and LDL), affecting virtually every lipid and lipoprotein variable.² The end result is a dyslipidemia that is characterized by elevated TG levels, the

generation of small, dense LDL particles, and reduced HDL cholesterol (HDL-C) concentrations. This combination of features is known by many designations, including *atherogenic dyslipidemia*, *dyslipidemia of insulin resistance*, or the *atherogenic lipoprotein phenotype*. It contributes to the 2- to 4-fold excess risk for cardiovascular disease observed in patients with type 2 diabetes mellitus compared with nondiabetic individuals.³ It is also increasingly recognized that the presence of diabetes places most patients at the same near-term risk for a coronary event as that of a patient with existing coronary heart disease (CHD). In this respect, diabetes is now considered to be a CHD risk equivalent by the National Cholesterol Education Program Adult

PATIENTS AND METHODS

The study was performed at 19 sites throughout the United States. The protocol and consent forms were approved by the institutional review board of each clinical center. Written informed consent was obtained from all participants before enrollment into the study.

PATIENT POPULATION

ADVENT enrolled subjects 21 years or older with stable type 2 diabetes, defined as an FBG level of no greater than 200 mg/dL (≤ 11.1 mmol/L) and an HbA_{1c} level of no greater than 9%, on 2 separate measures. Eligible patients had a history of diabetes controlled by diet, oral hypoglycemic agents (sulfonylureas, metformin, and/or acarbose; thiazolidinediones were excluded), or insulin. Lipid level variables for inclusion were based on treatment status. Patients currently being treated with an HMG-CoA reductase inhibitor were required to have an LDL cholesterol (LDL-C) level of at least 130 mg/dL (≥ 3.36 mmol/L), an HDL-C level of no greater than 40 mg/dL (≤ 1.03 mmol/L), or a TG level of at least 200 mg/dL (≥ 2.2 mmol/L). Those not receiving HMG-CoA reductase inhibitors were required to have an LDL-C level of no greater than 130 mg/dL (≤ 3.36 mmol/L) (because of the possibility of receiving placebo) but could qualify if they had an HDL-C level of no greater than 40 mg/dL (≤ 1.03 mmol/L) or a TG level of at least 200 mg/dL (≥ 2.2 mmol/L). Thus, all of the patients had 1 or more of the following lipid characteristics: an LDL-C level of at least 130 mg/dL (≥ 3.36 mmol/L); an HDL-C level of no greater than 40 mg/dL (≤ 1.03 mmol/L); or a TG level of at least 200 mg/dL (≥ 2.2 mmol/L). Baseline aspartate aminotransferase and alanine aminotransferase levels had to be no greater than 1.3 times the upper limit of the reference range.

All participants were willing to continue treatment for the study duration, and women were not breastfeeding or planning to become pregnant. Patients with chronic stable conditions such as hypertension or previous myocardial infarction

or stroke (>6 months before randomization) were eligible, unless treated with medication that might affect lipid levels. Patients with a clinically significant history of psychiatric illness, substance abuse, liver disease, gout, peptic ulcer disease, or other conditions that might be adversely affected by participation in the study were excluded. Fibrates, bile-acid sequestrants, or any product (such as a multivitamin supplement) containing at least 30 mg/d of niacin were not permitted during the trial. All concomitant hypoglycemic medications were allowed except troglitazone (the only member of the thiazolidinedione class available in the United States at the time the study was initiated), which was specifically excluded. Patients were also allowed to receive insulin. The investigators could adjust the dosage of any concomitant antidiabetic pharmacotherapy during the trial as needed to maintain glycemic control, based on the standard of practice at each center.

TREATMENT REGIMEN

Patients who were not documented to be following a recommended diabetes dietary program were formally instructed in medical nutrition therapy, as described by the American Diabetes Association.¹⁶ A minimum of 4 weeks with an appropriate diet, as recorded in a diet log, was required for qualification. In addition, a minimum 4-week drug washout phase, in which all lipid-lowering medications other than HMG-CoA reductase inhibitors were discontinued before laboratory assessment, was required for study entry.

On qualification for enrollment, patients were randomized to 1 of the following 3 treatment groups: placebo or ER niacin at a dosage of 1000 or 1500 mg/d. For the first 4 weeks of treatment, the dosage of ER niacin was escalated as follows. During week 1, patients received 375 mg/d of ER niacin (or matching placebo) at bedtime; during week 2, 500 mg/d of ER niacin (or matching placebo); during week 3, 750 mg/d of ER niacin (or matching placebo); and during week 4, 1000 mg/d of ER niacin as two 500-mg

Continued on next page

Treatment Panel III⁴ and the American Heart Association.⁵ At present, most patients with diabetes die of CHD.

Diabetes incidence is increasing rapidly in the general population, drawing attention to the role of atherogenic dyslipidemia in the evolution of CHD among these patients. Attempts to correlate CHD incidence among patients with diabetes with the classic coronary risk factors (age, increased plasma cholesterol levels, increased blood pressure, obesity, cigarette smoking, and electrocardiographic abnormalities) showed that these risk factors account for only 25% to 30% of the excess risk for CHD.⁶ The degree to which hyperglycemia makes up the difference in risk observed in the diabetic compared with the nondiabetic population is unresolved. Aggressive glycemic control substantially reduces the incidence of microvascular complications of diabetes, such as retinopathy and nephropathy; however, benefits in terms of macrovascular complications, including CHD, have been more difficult to document. In the United Kingdom Prospective Diabetes Study,⁷ for example, a 0.9% reduction in hemoglobin A_{1c} (HbA_{1c}) levels significantly decreased the risk for microvascular complications, but not

macrovascular disease such as myocardial infarction and stroke.

Lowering LDL-C levels with 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors significantly reduces the risk for major coronary events in patients with diabetes.⁵ Additional benefit may also be derived from therapeutic modification of diabetic dyslipidemia in these patients. Treatment of diabetic dyslipidemia with niacin is a logical choice, because the drug directly affects the main lipoprotein and lipid disorders observed in diabetes. Niacin blocks fatty acid flux from adipose tissue. It also suppresses hepatic assembly and release of very low-density lipoprotein; this latter effect reduces TG levels and decreases the number of small, dense LDL particles. Niacin may also block a putative HDL holoparticle catabolic receptor responsible for intrahepatic degradation of HDL, thereby increasing the effective half-life of HDL and raising HDL-C concentrations.⁸ Niacin is the most potent drug currently available to raise HDL-C levels.

Despite this rationale, use of high doses of niacin has been discouraged in patients with diabetes because

tablets (or matching placebo). Thereafter, subjects randomized to the 1000-mg/d group received two 500-mg tablets once a day at bedtime through week 16. Subjects randomized to receive 1500 mg/d received two 750-mg tablets once a day at bedtime through week 16. Those assigned to placebo continued to receive placebo matching the ER niacin. Use of aspirin, 325 mg, up to one half hour before study medication to relieve flushing, was permitted.

FOLLOW-UP

Patient visits were scheduled every 4 weeks during the course of the study. Visits at weeks 4, 8, 12, and 16 included measurement of vital signs (blood pressure, pulse, and weight) and blood samples for complete lipid profile, serum chemistry, and HbA_{1c} assessments. Glycemic control was evaluated at each visit, and adjustments in anti-diabetic medications, including changes in the dose of an existing medication or the initiation of a new drug therapy, were recorded. All unused study medication was collected. At week 12 only, a 3-day diet log was dispensed with instructions to complete and return it at the week 16 visit.

The primary safety end point variable was the change from baseline to week 16 in HbA_{1c} level. Other safety measures included FBG levels, serum transaminase concentrations, and self-reported adverse events. Patients were dispensed flushing diaries to document the occurrence and intensity of flushing during the trial. The primary efficacy end point variables were the changes from baseline to week 16 in HDL-C and TG levels. Other variables included total cholesterol and LDL-C levels, ratio of total cholesterol to HDL-C, and lipoprotein(a) (Lp[a]) levels, high-sensitivity C-reactive protein (hsCRP) levels, and LDL particle size.

LABORATORY EVALUATION

Enzymatic methods were used to determine the concentrations of total cholesterol, HDL-C, and TG (LabCorp, Raritan, NJ). Serum LDL-C levels were calculated using the

Friedewald equation. If the TG level was higher than 400 mg/dL (>4.4 mmol/L), the LDL-C level was measured directly (Roche Reagent for LDL Cholesterol Direct; Roche Diagnostics Corporation, Indianapolis, Ind). We used immunoturbidimetric assays to measure levels of Lp(a) (Wako Chemicals USA, Inc, Richmond, Va) and hsCRP (K-assay; Kamiya Biochemical Company, Seattle, Wash). Both assays were performed at the Laboratory for Clinical Studies, Washington University, St Louis, Mo. Low-density lipoprotein particle size was determined using a nongradient polyacrylamide gel tube electrophoresis system (Lipo-print LDL System; Quantimetrix Corp, Redondo Beach, Calif). The reference range for HbA_{1c} levels measured in the core laboratory was 4.2% to 5.9%.

STATISTICAL METHODS

All tests were 2-tailed, with an α level of .05. Baseline characteristics were summarized for the intent-to-treat population. Continuous variables were summarized using mean (SE), median, minimum, and maximum. Categorical variables were summarized using frequency and percentage. Categorical variables were compared using Mantel-Haenszel procedures, and continuous variables were tested using a 2-way analysis of variance. A repeated-measures analysis was used to compare the mean levels across visits for primary efficacy (HDL-C and TG) and safety (HbA_{1c}) variables. A multiple-comparison test was conducted to compare the mean baseline level with the mean postbaseline level at every postbaseline visit. For secondary variables, results of continuous laboratory tests (eg, LDL-C, aspartate aminotransferase, and alanine aminotransferase levels) were analyzed within and between treatments as performed for the primary efficacy and safety variables. Results of TG tests are summarized for the median change from baseline because of a non-normal distribution. Treatment-emergent adverse events were compared across treatment groups using the Fisher exact test. Distinctions were made among all events, regardless of cause, and those possibly or probably related to study treatment.

of reports of increased fasting blood glucose (FBG) levels during therapy.⁹ Therefore, selection of niacin for treatment of diabetic dyslipidemia requires consideration of the risks vs the benefits derived from this therapy. The benefits of niacin for cardiovascular risk reduction may outweigh any adverse consequences of a rise in FBG levels. For example, niacin has been shown to significantly reduce the risk for nonfatal myocardial infarction and stroke in the Coronary Drug Project, in which approximately 40% of patients had evidence of abnormal glucose tolerance (FBG level, ≥ 100 mg/dL [≥ 5.6 mmol/L] and/or plasma 1-hour glucose level, ≥ 180 mg/dL [≥ 10.0 mmol/L]) at baseline.¹⁰

Niacin is available in a variety of formulations that can be distinguished by their release rates. Immediate-release (IR) niacin requires extensive patient education and involvement of clinical staff to maintain therapy, and its use is limited by patient intolerance to flushing. Over-the-counter, slow-release (SR) preparations reduce the frequency of flushing but have been associated with an increased risk for hepatotoxic effects and reduced efficacy for HDL-C.^{11,12} Extended-release (ER)

niacin (Niaspan; Kos Pharmaceuticals, Miami, Fla) is a new prescription formulation for once-daily administration that was designed to circumvent the problems associated with IR and SR formulations. Previous clinical studies of this agent have demonstrated that it provides lipid-modifying efficacy equivalent to that of IR niacin, but with less flushing, while avoiding the hepatotoxicity of other long-acting niacins.¹³⁻¹⁵ This preparation of niacin appears to be well tolerated and safe for long-term administration. The Assessment of Diabetes Control and Evaluation of the Efficacy of Niaspan Trial (ADVENT) was therefore conducted to evaluate the safety and efficacy of low doses of this ER niacin formulation for the treatment of dyslipidemia in patients with type 2 diabetes. Patients who had been receiving HMG-CoA reductase inhibitors (statins) before the study continued to receive these agents concomitantly with ER niacin during the trial. A major aim of this study was to determine whether increases in FBG levels would occur, and whether such increases could be adequately controlled by adjusting the concomitant antidiabetic pharmacotherapy.

Table 1. Baseline Patient Demographics by Treatment Group*

	Treatment Group		
	Placebo (n = 49)	1000-mg ER Niacin (n = 45)	1500-mg ER Niacin (n = 52)
Age, y	61 (1.4)	57 (1.4)	63 (1.6)
Sex, M/F	29/20	25/20	32/20
Weight, kg†	93 (2.8)	99 (3.8)	89 (2.3)
BMI†‡	33 (1.0)	34 (1.0)	31 (0.8)
Lipid levels, mg/dL			
HDL-C†§	42 (1.5)	39 (1.2)	41 (1.3)
TG§	268 (17.4)	278 (22.5)	259 (16.0)
LDL-C§	97 (3.8)	105 (3.9)	106 (4.2)
HbA _{1c} levels, %	7.13 (0.12)	7.23 (0.14)	7.21 (0.11)
Glucose levels, mg/dL§			
Mean	134 (4.2)	142 (4.6)	137 (4.7)
Median	127	140	142

*Two patients randomized to the 1000-mg ER niacin group never received study drug and therefore were not included. Unless otherwise indicated, data are given as mean (SE). ER indicates extended release; BMI, body mass index; HbA_{1c}, glycosylated hemoglobin; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; and TG, triglycerides.

†Significantly different between treatment groups at $P < .001$.

‡Determined by dividing the weight in kilograms by the square of height in meters.

§To convert to millimoles per liter, multiply by 0.0259 for HDL-C and LDL-C, by 0.0113 for TG, and by 0.0555 for glucose.

RESULTS

A total of 148 patients were enrolled in the study. Forty-nine patients were randomized to treatment with placebo; 47, ER niacin, 1000 mg/d; and 52, ER niacin, 1500 mg/d. Two patients assigned to the 1000-mg ER niacin group did not receive study medication and were excluded from the analysis, for a total of 146 patients in the intent-to-treat population.

PATIENT DEMOGRAPHICS

Baseline demographic characteristics of the study population are given in **Table 1**. The groups were generally well balanced. However, significant differences in weight, body mass index (determined by dividing the weight in kilograms by the square of the height in meters), and HDL-C levels were found among treatment groups ($P < .001$), with patients in the 1000-mg ER niacin group having higher baseline weight and body mass index and lower baseline HDL-C levels. These patients also tended to have higher baseline TG and FBG levels. As is common among patients with diabetes, average body mass index was substantially elevated.

Concomitant medications for diabetes were common, with 81% using drugs for diabetes control. The most frequently used antidiabetic medications were metformin (54.8%) and sulfonylureas (47.9%), which were equally common across treatment groups. Insulin was used by approximately 15% of patients. Other common drugs included angiotensin-converting enzyme inhibitors, α -blockers, and aspirin. Overall, 69 patients (47.3%) concomitantly received HMG-CoA reductase inhibitors on the

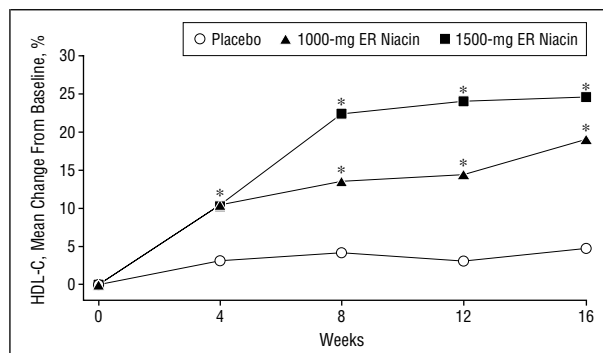


Figure 1. Effect of extended-release (ER) niacin, 1000 and 1500 mg/d, on the primary end point, high-density lipoprotein cholesterol (HDL-C) level, in patients with type 2 diabetes. Dose-related increases in HDL-C levels were evident in patients receiving ER niacin compared with placebo ($P < .05$ [asterisk]).

basis of previous use of these agents, ie, 29 (59%) in the placebo group, 19 (42%) in the 1000-mg ER niacin group, and 21 (40%) in the 1500-mg ER niacin group. Atorvastatin calcium was the most frequently used HMG-CoA reductase inhibitor (23% of patients), followed by simvastatin (14%) and pravastatin sodium (12%).

PATIENT DISPOSITION

Twenty-five patients were discontinued from the study prematurely, 7 (14%) in the placebo group, 8 (18%) in the 1000-mg ER niacin group, and 10 (19%) in the 1500-mg ER niacin group. Four patients dropped out because of inadequate glucose control (1 in the 1000-mg ER niacin group and 3 in the 1500-mg ER niacin group). Adverse events were responsible for 5 (10%), 3 (7%), and 7 (13%) patients discontinuing in the placebo and 1000- and 1500-mg ER niacin groups, respectively. Four patients discontinued participation in the study because of flushing, including 1 in the placebo group.

EFFICACY END POINTS

The mean duration of treatment was 15.0 weeks for patients in the 1000- and 1500-mg ER niacin groups and 15.5 weeks for those in the placebo group. More than 90% compliance with study medication was maintained in all groups throughout the study. No significant differences in body weight between baseline and termination of study were found for any of the groups.

For the primary efficacy end points, HDL-C and TG levels, ER niacin had a significant effect. The HDL-C level increased from baseline in a dose-dependent manner at all study visits, and the increases were significantly greater at all time points ($P < .05$) for both ER niacin groups compared with the placebo group (**Figure 1**). In the placebo group, very little change occurred in HDL-C levels. In the 1000-mg ER niacin group, mean increases in HDL-C levels ranged from 13% (2.2%) to 19% (2.7%). In the 1500-mg ER niacin group, mean increases in HDL-C levels ranged from 22% (3.0%) to 24% (3.4%). At week 16, the mean absolute increases in HDL-C levels were 1.6 mg/dL (0.04 mmol/L), 7.6 mg/dL (0.20 mmol/L), and 11.0 mg/dL (0.28 mmol/L) in the placebo and 1000- and 1500-mg ER niacin groups, respectively.

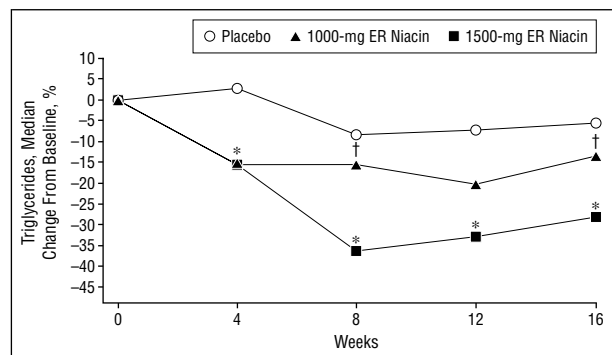


Figure 2. Effect of extended-release (ER) niacin, 1000 and 1500 mg/d, on the primary end point, triglyceride (TG) level, in patients with type 2 diabetes. Dose-related reductions in TG levels were evident in patients receiving ER niacin compared with placebo ($P < .05$ [asterisk]) and with patients receiving 1000 compared with 1500 mg/d of ER niacin ($P < .05$ [dagger]).

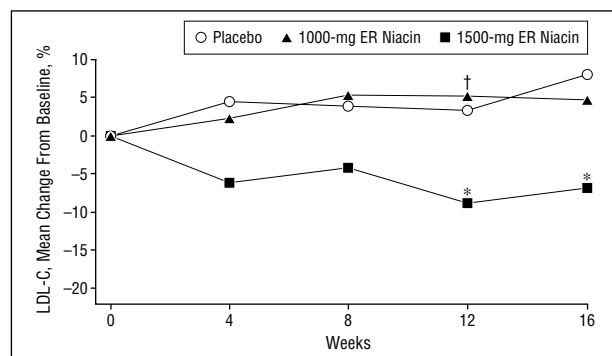


Figure 3. Effect of extended-release (ER) niacin, 1000 and 1500 mg/d, on the secondary end point, low-density lipoprotein cholesterol (LDL-C) level, in patients with type 2 diabetes. A reduction in LDL-C levels was observed only in patients receiving the 1500-mg/d dosage of ER niacin in this population with low LDL-C levels at baseline ($P < .05$ compared with patients receiving placebo [asterisk] and those receiving 1000-mg/d ER niacin [dagger]).

We also found a dose-related reduction in TG levels in the ER niacin groups. The median percentage of changes from baseline in the placebo group were small, ranging from -5% to -8% . In the 1000-mg ER niacin group, the median percentage of change ranged from -15% to -20% ; these changes were not significantly different from those in the placebo group. In the 1500-mg ER niacin group, the median percentage of change ranged from -28% to -36% ; all changes in this group were significantly different ($P < .05$) compared with those in the placebo group (**Figure 2**).

Mean LDL-C levels were slightly elevated at all visits in the placebo and 1000-mg ER niacin groups, but these changes from baseline were not statistically significant. In the 1500-mg ER niacin group, LDL-C levels decreased at all time points, and the difference compared with the placebo group was statistically significant at weeks 12 and 16 ($P < .05$) (**Figure 3**). The mean changes from baseline at 16 weeks were $+9\%$ (3.6%), $+5\%$ (4.7%), and -7% (3.2%) in the placebo and 1000- and 1500-mg ER niacin groups, respectively. This same trend was observed for total cholesterol measures, in which mean increases of $+4\%$ (2.0%) and $+4\%$ (2.7%) occurred in the placebo and 1000-mg ER niacin groups, respectively, but we found a decrease of -6% (2.1%) in the 1500-mg ER niacin group. Results for the total cholesterol-HDL-C ra-

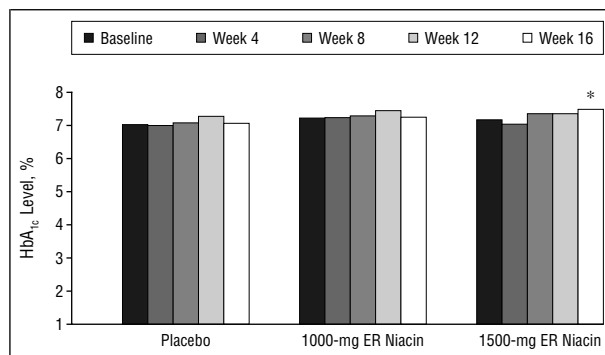


Figure 4. The effect of extended-release (ER) niacin, 1000 and 1500 mg/d, on the primary safety variable, hemoglobin (HbA_{1c}) level (as a measure of glycemic control), in patients with type 2 diabetes. Minimal changes are observed among patients treated with ER niacin ($P = .048$ [asterisk] compared with placebo).

tio favored both dosages of ER niacin, with mean changes at week 16 in the 1000- and 1500-mg ER niacin groups of -12% (2.8%) and -22% (2.7%), respectively, which were significantly different from those of the placebo group ($P < .01$).

Additional analyses were performed retrospectively from stored frozen samples for Lp(a) and hsCRP levels and LDL phenotype (for 42, 37, and 41 patients in the placebo and 1000- and 1500-mg ER niacin groups, respectively). For Lp(a), we found a trend in favor of ER niacin, with changes of $+3\%$ (5.4%), -10% (6.2%), and -12% (4.1%) in the placebo and 1000- and 1500-mg ER niacin groups, respectively ($P = .21$). Likewise, the median changes from baseline for hsCRP suggested a dose-related, although not significant, trend of -2% , -11% , and -20% for the respective groups. At baseline, average LDL particle diameter was 26.4 nm (0.07 nm), 26.3 nm (0.10 nm), and 26.2 nm (0.08 nm) for the respective groups. At week 16, average LDL particle diameter increased in a dose-related but nonsignificant manner, by 0.01, 0.05, and 1.17 nm for the respective groups.

SAFETY END POINTS

The primary safety variable was the effect of treatment on mean HbA_{1c} level. Changes in HbA_{1c} level from baseline were small in all treatment groups. At week 16, mean HbA_{1c} values were 7.1% (0.13%), 7.4% (0.19%), and 7.5% (0.14%) in the placebo and 1000- and 1500-mg ER niacin groups, respectively, representing respective changes of -0.02% , $+0.07\%$, and $+0.29\%$. The HbA_{1c} values associated with administration of 1000 mg of ER niacin were in the same range as, and not significantly different from, those noted during placebo administration. In the group receiving 1500 mg of ER niacin, the change from baseline to week 16 of 0.29% was marginally significantly different from that of the placebo group ($P = .048$). The time course of the changes in HbA_{1c} levels during the 16-week study are shown in **Figure 4**. **Figure 5** shows the changes over time in FBG levels. In both ER niacin groups, we found an initial rise in FBG levels between weeks 4 and 8; this value, however, returned to the baseline level by week 16. At week 16, no statistically significant difference

was found between the active treatment groups for the change in FBG levels. These findings suggest that adjustments in concomitant antidiabetic therapies were being made to control FBG levels in some patients. This is also evident from inspection of the results given in **Table 2** and **Table 3**, which provide investigator-subjective assessments of diabetes control and medication use by treatment group at baseline and study end point. The data suggest that 1000 mg/d of ER niacin produces little to no alteration in diabetes control, whereas a small but greater proportion of patients receiving 1500 mg/d of ER niacin needed adjustments in their antidiabetic pharmacotherapy.

Few clinical or laboratory adverse effects were reported in the study population, and no statistically significant difference was found in the rates of adverse events across treatment groups. The total number of patients reporting any treatment-emergent adverse event was not significantly different among treatment groups, ie, 36 (73%) in the placebo group, 31 (69%) in the 1000-mg ER niacin group, and 40 (77%) in the 1500-mg ER niacin group. Adverse events considered even remotely related to the study drug occurred in 19 (39%), 20 (44%), and 23 (44%) patients of the 3 groups, respectively. We found no statistically significant differences among the 3 treatment groups in the incidence of any individual adverse event, except for flushing. Flushing was reported at some time during the trial by two thirds of patients receiving ER niacin and by approximately 10% of pa-

tients receiving placebo. Flushing was a reason for study discontinuation in only 4 patients; however, 1 of these was receiving placebo. Serious adverse events (events that are life-threatening or that result in hospitalization, prolongation of hospitalization, death, or disability) affected 7 patients, ie, 4 in the placebo group (asthma, hernia repair, carotid stent placement, and urinary tract infection with sepsis); 1 in the 1000-mg ER niacin group (cholecystitis); and 2 in the 1500-mg ER niacin group (ventricular tachycardia and cholecystitis). Of particular note, no patient in the study experienced elevation of liver enzyme levels of greater than 3 times the upper limit of the reference range. No significant differences in uric acid levels were found at any time point across groups. No patient was reported to have the syndrome of drug-induced myopathy (myalgia and elevated creatine kinase level of >10 times the upper limit of the reference range). Overall, the study drug was well tolerated, with few differences between the ER niacin and placebo groups. Safety and tolerability were not compromised for patients receiving ER niacin and HMG-CoA reductase inhibitors concomitantly.

COMMENT

ADVENT demonstrates that ER niacin at dosages of 1000 and 1500 mg/d is effective and well tolerated for the treatment of atherogenic dyslipidemia in type 2 diabetes, whether given alone or with an HMG-CoA reductase inhibitor. Both doses produced significantly greater increases than placebo in plasma levels of HDL-C. Consistently greater decreases in plasma TG levels were also observed with both doses of ER niacin compared with placebo. These changes were consistent with those previously reported with ER niacin in nondiabetic patients¹³⁻¹⁵; however, the result was statistically significant only for the 1500-mg ER niacin group. By chance, baseline body mass index and levels of HbA_{1c} and FBG were higher in the 1000-mg ER niacin group compared with the other groups; these differences could have dampened the TG-lowering effect in the 1000-mg ER niacin group. Treatment with 1500 mg/d of ER niacin reduced LDL-C levels from baseline, in contrast to 1000 mg/d of ER niacin and placebo, each of which increased LDL-C levels slightly compared with baseline. These results reflect the normal LDL-C levels at baseline and are consistent with results from another study of ER

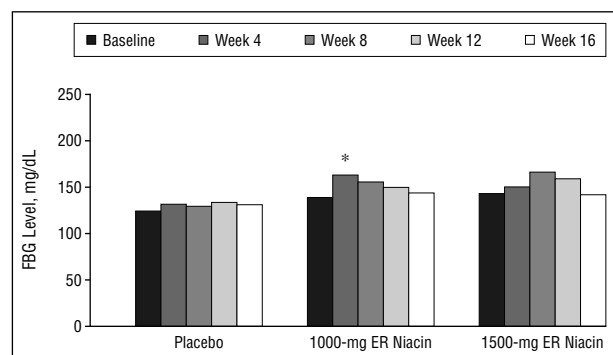


Figure 5. Effect of extended-release (ER) niacin, 1000 and 1500 mg/d, on median fasting blood glucose (FBG) levels in patients with type 2 diabetes. Initial small increases in FBG levels in both ER niacin groups returned to baseline levels by week 16. To convert FBG levels to millimoles per liter, multiply by 0.0555. Asterisk indicates $P < .05$ compared with baseline.

Table 2. Investigator Assessments and Medication Changes by Treatment Group*

	Treatment Group, No. (%) of Patients			P Value
	Placebo (n = 49)	1000-mg ER Niacin (n = 45)	1500-mg ER Niacin (n = 52)	
Patients completing the study	42 (86)	39 (87)	42 (81)	.80
Global assessment of glycemic control†				
Improved/same	43 (88)	36 (80)	37 (71)	.60
Worse	6 (12)	8 (18)	15 (29)	
Missing	0	1 (2)	0	
Added new drug/increased dose‡	8 (16)	11 (24)	15 (29)	.32

*ER indicates extended release.

†Judged by individual investigators according to usual standards at each site.

‡Added new hypoglycemic medication or increased dose of an existing one.

Table 3. Antidiabetic Medication Use During the Trial*

	Treatment Group					
	Placebo		1000-mg ER Niacin		1500-mg ER Niacin	
	BL	End Point	BL	End Point	BL	End Point
Diet only	5 (10)	5 (10)	4 (9)	5 (11)	11 (21)	11 (21)
Oral monotherapy	25 (51)	24 (49)	17 (38)	16 (36)	19 (37)	15 (29)
Oral combination	9 (18)	9 (18)	14 (31)	14 (31)	12 (23)	14 (27)
Insulin alone	4 (8)	4 (8)	6 (13)	6 (13)	7 (13)	8 (15)
U/d for 3 previous days, mean (SE)	106 (8.6)	110 (15)	42 (9.6)	43 (10.1)	78 (11.6)	88 (22.7)
Insulin plus oral therapy	6 (12)	6 (12)	4 (9)	4 (9)	3 (6)	4 (8)
U/d for 3 previous days, mean (SE)	48 (14.8)	54 (12.5)	90 (15.7)	93 (19.8)	32 (10.3)	33 (7.3)

*Unless otherwise indicated, data are given as number (%) of patients. End point is week 16 or last study visit. ER indicates extended release; BL, baseline.

niacin in a similar patient population with low HDL-C levels in whom baseline LDL-C levels were also quite low.¹⁷ We also found trends in dose-related decreases in Lp(a) and hsCRP levels and in the proportion of patients with LDL phenotypic pattern B. However, none of these changes were statistically significant between treatment groups.

Treatment with ER niacin was well tolerated. More than 80% of patients in all 3 treatment groups remained in the study. Only 4 patients discontinued owing to inadequate glucose control; 3 of these were receiving the highest dose of ER niacin. Three patients receiving ER niacin and 1 receiving placebo discontinued owing to flushing. Flushing was reported at least once during the study by most patients receiving ER niacin and by approximately 10% of patients receiving placebo. No statistically significant differences were found among the groups in the incidence or type of any other adverse events.

With respect to HbA_{1c} levels and glycemic control, by chance, patients randomized to receive placebo had lower baseline FBG and HbA_{1c} levels than the patients receiving any dose of ER niacin. Nevertheless, the changes in HbA_{1c} levels in the 1000-mg ER niacin group appeared to be almost indistinguishable from those of the placebo group. The change in the 1500-mg ER niacin group, from 7.21% to 7.50% at week 16, although small, was significantly different from that of the placebo group ($P=.048$). Any increased risk for microvascular complications associated with a 0.29% increase in HbA_{1c} level would be expected to be offset by the decreased risk for macrovascular disease consequent to the improvements in the lipoprotein profile. Also, the thiazolidinedione class of drugs was excluded from the trial. Future studies are needed to evaluate whether their use may eliminate even this very small increase in HbA_{1c} level observed in the 1500-mg ER niacin group. The protocol was also not designed to force investigators to maintain FBG or HbA_{1c} level within a certain range, but rather allowed each clinic to follow their usual standard of care. Overall, then, niacin therapy was effective, safe, and well tolerated.

A strong argument can be made for treating atherogenic dyslipidemia in patients with type 2 diabetes mellitus in addition to lowering of the LDL-C levels. Although, to our knowledge, no large, prospective studies specifically on the effects of lipid modification on clinical coronary events have been reported to date in patients with diabetes, such trials are in progress. Until the

results of these trials have been reported, clinical decisions about therapy must be made on indirect evidence, eg, subgroup analyses of other trials and/or favorable changes in lipoprotein levels. For example, subanalyses from several major intervention trials have addressed the effect of statin therapy in patients with diabetes. For example, evaluation in 202 diabetic patients enrolled in the Scandinavian Simvastatin Survival Study showed that HMG-CoA reductase inhibitor therapy reduced serum TG and LDL-C levels by 27% and 36%, respectively, and increased HDL-C levels by 7% in patients with diabetes, equivalent to the changes observed in nondiabetic individuals.¹⁸ This degree of lipid-modifying activity was associated with reductions in rates of deaths due to CHD of 17.5% and deaths due to any cause of 24.7%. Similar subanalysis results from the Cholesterol and Recurrent Events trial showed that beneficial lipid alterations in 586 diabetic patients treated with pravastatin led to a 25% reduction in CHD events (CHD death, confirmed nonfatal myocardial infarction, bypass grafting, or coronary angioplasty [$P=.05$]).¹⁹

Treatment with fibrates has also been shown to be of benefit in slowing the progression of coronary atherosclerosis and reducing the risk for clinical cardiac events in patients with diabetes. In a 3-year placebo-controlled study of 731 men and women with type 2 diabetes, treatment with fenofibrate raised HDL-C levels by approximately 7% and decreased TG and LDL-C levels by approximately 27% and 7%, respectively. These changes were associated with a significant reduction in the secondary angiographic end points of minimum lumen diameter and percentage of diameter of stenosis. The HbA_{1c} level increased by 0.47% in the fenofibrate group compared with 0.24% in the placebo group.²⁰ In the Veterans Affairs High-Density Lipoprotein Intervention Trial, a secondary prevention study, treatment with gemfibrozil that raised HDL-C levels by a mean of 6% and lowered TG levels by a mean of 31% without affecting LDL-C levels was associated with a reduction in coronary and cerebrovascular events in patients with low levels of both HDL-C and LDL-C at baseline.²¹ Recent subanalyses from that study suggest that the benefit was confined to the subset of patients with diabetes and/or insulin resistance,²² and that the HDL-C level was the only major lipid variable to predict a significant reduction in CHD.²³ In

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this regard, the patients in the ADVENT are in some ways similar to those enrolled in the Veterans Affairs High-Density Lipoprotein Intervention Trial, with low levels of LDL-C and HDL-C at baseline.

As more is known about the nature of diabetic dyslipidemia and its impact on CHD risk in patients with diabetes, optimal therapy should target all of the abnormalities associated with diabetes, including lowering LDL-C and TG levels and raising HDL-C levels. This targeted approach may represent the best treatment strategy for achieving substantial reductions in the high and growing incidence of CHD among patients with diabetes and is consistent with the 2001 National Cholesterol Education Program Adult Treatment Panel III guidelines.⁴ With this awareness has come increased interest in the action of niacin and, in particular, its safety in terms of glycemic control in the diabetic population.

The Arterial Disease Multiple Intervention Trial investigators²⁴ reported results of a study designed to evaluate the effect of lipid-modifying doses of niacin on blood glucose, HbA_{1c}, alanine aminotransferase, and uric acid levels. In this trial, 468 patients (125 with diabetes) with peripheral arterial disease received crystalline niacin (average dose was approximately 2.5 g) or placebo. Niacin significantly increased HDL-C levels (29% and 29% in dia-

betic and nondiabetic subjects, respectively), decreased TG levels (23% and 28%, respectively), and reduced LDL-C levels (8% and 9%, respectively). Niacin modestly increased glucose levels (8.7 mg/dL [0.5 mmol/L] and 6.3 mg/dL [0.3 mmol/L]; $P < .05$ vs placebo) in patients with and without diabetes, respectively. Levels of HbA_{1c} were unchanged from baseline to follow-up in patients with diabetes treated with niacin, but declined 0.3% ($P = .04$) in the placebo group. Thus, results of the Arterial Disease Multiple Intervention Trial are consistent with those of the present study and add to the accumulating evidence that low doses of niacin can be safely administered to diabetic individuals without risking loss of glycemic control.

The availability of the once-daily formulation used in the present study has simplified the therapeutic use of niacin. Use of IR niacin is complicated by the requirement of high doses to attain desirable treatment levels of lipoproteins. Furthermore, long-term compliance is difficult because of persistent problems with flushing and pruritus. During early experience with SR formulations of niacin (which had been developed to control drug blood levels and to minimize vasodilatory effects), several reports were made of elevated liver enzyme levels or hepatotoxic effects and diminished efficacy in raising HDL-C levels.^{11,12,25} The new ER niacin, however, has been reported to be relatively safe and effective in the treatment of dyslipidemias, with reduced incidence of flushing and pruritus, a once-daily administration schedule, no loss in efficacy, and no evidence of the hepatotoxicity of earlier SR formulations.^{11-13,15} In another recent report,²⁶ a longitudinal analysis was presented of 20 patients treated with either IR niacin or the new ER niacin; both niacin preparations effected positive changes across all lipid variables without affecting HbA_{1c} levels.²⁶ The investigators noted that the improvements were somewhat greater with ER niacin, with the advantage of once-daily dosing.

CONCLUSIONS

Low doses of ER niacin were effective and safe in the management of dyslipidemia associated with type 2 diabetes. Changes in glycemic control were minimal, were more associated with the higher dose, and where evident were successfully managed by adjusting the antidiabetic pharmacotherapy. Most patients were able to maintain ER niacin therapy for the duration of the study. The formulation described herein produces activity equivalent to that of crystalline niacin with an improved once-daily treatment schedule, reduced flushing, and no significant hepatotoxicity to date. Even when given concomitantly with HMG-CoA reductase inhibitors, ER niacin was safe and well tolerated. No cases of myopathy were observed. Extended-release niacin may be considered as therapy in combination with statins, or in some cases, without statins, in the management of dyslipidemia associated with type 2 diabetes. Further long-term studies will help to define the full potential of combined statin and ER niacin in patients with diabetes.

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