

Safety and Tolerability of *Simvastatin Plus Niacin* in Patients With Coronary Artery Disease and Low High-Density Lipoprotein Cholesterol (The HDL Atherosclerosis Treatment Study)

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The high-density lipoprotein (HDL)-Atherosclerosis Treatment Study showed that simvastatin plus niacin (mean daily dose 13 mg and 2.4 g, respectively) halt angiographic atherosclerosis progression and reduce major clinical events by 60% in patients with coronary artery disease (CAD) who have low HDL, in comparison with placebos, over 3 years. How safe and well-tolerated is this combination? One hundred sixty patients with CAD, including 25 with diabetes mellitus, with mean low-density lipoprotein cholesterol of 128 mg/dl, HDL cholesterol of ≤ 35 mg/dl (mean 31), and mean triglycerides of 217 mg/dl were randomized to 4 factorial combinations of antioxidant vitamins or their placebos and simvastatin plus niacin or their placebos. Patients were examined monthly or bimonthly for 38 months; side effects (gastrointestinal upset, nausea, anorexia, vision, skin, and energy problems, or muscle aches) were directly queried and recorded. Aspartate aminotransferase, creatine phosphokinase (CPK), uric acid, homocysteine, and fasting glucose levels were regularly monitored. A safety monitor reviewed all side effects

and adjusted drug dosages accordingly. Patients who received simvastatin plus niacin and those on placebo had similar frequencies of clinical or laboratory side effects: any degree of flushing (30% vs 23%, $p = \text{NS}$), symptoms of fatigue, nausea, and/or muscle aches (9% vs 5%, $p = \text{NS}$), aspartate aminotransferase (SGOT) ≥ 3 times upper limit of normal (3% vs 1%, $p = \text{NS}$), CPK ≥ 2 times upper limit of normal (3% vs 4%, $p = \text{NS}$), CPK ≥ 5 times upper limit of normal, new onset of uric acid ≥ 7.5 mg/dl (18% vs 15%, $p = \text{NS}$), and homocysteine ≥ 15 $\mu\text{mol/L}$ (9% vs 4%, $p = \text{NS}$). Glycemic control among diabetics declined mildly in the simvastatin-niacin group but returned to pretreatment levels at 8 months and remained stable for rest of the study. This combination regimen was repeatedly described by 91% of treated patients and 86% of placebo subjects as "very easy" or "fairly easy" to take. Thus, the simvastatin plus niacin regimen is effective, safe, and well tolerated in patients with or without diabetes mellitus. ©2004 by Excerpta Medica, Inc.

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We recently reported that simvastatin plus niacin provided marked clinical and angiographic benefits in patients with coronary artery disease (CAD), average low-density lipoprotein (LDL) cholesterol, and low-high-density lipoprotein (HDL) cholesterol in the HDL-Atherosclerosis Treatment Study (HATS).¹ In patients who received simvastatin plus niacin, the rate of progressive coronary obstruc-

tion was reduced by 93% and major coronary events by 60% compared with placebos; LDL cholesterol decreased by 42%, whereas HDL cholesterol increased by 26%. In this study, we examined the safety and tolerability of this therapy combination among the patients in HATS trial, focusing on clinical side effects, hepatic and skeletal muscle toxicity, and on glycemic control for those with diabetes.²

METHODS

Patients: Between January 1995 and January 1997, we enrolled 160 patients who met the clinical and angiographic criteria for coronary disease and who had low HDL cholesterol (21 women, 139 men; mean age 53 years). Diabetic patients were included if fasting glucose was ≤ 180 mg/dl. Mean HDL cholesterol was 31 mg/dl and mean LDL cholesterol was 125 mg/dl. Baseline characteristics are described in detail; risk characteristics among the 4 treatment groups were well balanced during randomization.¹ Fourteen patients did not complete the study; 2 died and 12 withdrew (2 due to niacin intolerance) after a mean of

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14 ± 11 months. Available safety data from all 160 patients are reported.

Study design and treatments: HATS¹ was a 3-year, placebo-controlled, double-blind, factorial design trial evaluating the angiographic and clinical benefits of simvastatin plus niacin, antioxidant vitamins, or their combination in patients with CAD and low HDL cholesterol. All 160 patients were counseled with regard to diet, exercise training, and smoking cessation.¹

Eighty patients were randomized to simvastatin + niacin (S + N). The simvastatin (Zocor, Merck, West Point, Pennsylvania) starting dose was 10 mg/day for patients with LDL cholesterol ≤110 mg/dl and 20 mg for those with higher LDL cholesterol. Dosage was adjusted in 10 mg/day increments to maintain LDL cholesterol levels between 40 and 90 mg/dl. The dose of slow-release niacin (Slo-Niacin, Upsher-Smith, Minneapolis, Minnesota) was increased linearly from 250 mg twice daily to 1,000 mg twice daily at 4 weeks. Patients who did not reach the preset HDL cholesterol targets on this dose at 3 months (+5 mg/dl from baseline), at 8 months (+8 mg/dl), or at 12 months (+10 mg/dl) were switched to crystalline niacin (Niacor, Upsher-Smith, Minneapolis, Minnesota), which was gradually increased to 3 to 4 g/day to attain target HDL cholesterol levels. Forty-two patients in the S + N group also received twice-daily antioxidants (800 IU vitamin C, 1,000 mg vitamin E, 25-mg natural beta carotene, 100-μg selenium); 38 patients on S + N received an antioxidant placebo. The mean daily dose in the S + N group over the course of the study was 13 ± 6 mg simvastatin and 2.4 ± 2.0 g niacin. Overall pill count compliance with the study regimens was 81% for niacin (vs 83% for niacin active placebo) and 91% for simvastatin (vs 89% for simvastatin placebo).

The other half of the study group (n = 80) received matching simvastatin and niacin; these patients comprised the placebo group. The niacin placebo dose actually contained 50 mg twice daily of crystalline niacin, previously determined to provoke flushing in most patients, without significantly affecting lipid levels.^{3,4} The placebo group were given simvastatin 10 mg if LDL cholesterol was ever >140 mg/dl (n = 24).

Safety monitoring: All patients were seen monthly for 4 months and then bimonthly for the remaining 32 months. At each visit, in addition to compliance checks and lifestyle counseling, a directed interview was completed and vital signs were monitored. Patients were directly queried about side effects, such as gastrointestinal upset, nausea, anorexia, vision problems, skin problems, lack of energy, or muscle aches. Patients were also asked at each visit to answer the following question: "Overall, how difficult is it to take the study medication?" The choice of answers was: (1) very easy, (2) fairly easy, (3) not too hard, (4) very hard, or (5) impossible. Responses to all direct queries were recorded.

Routine lipid studies were performed every 4 months, with more detailed lipid analyses performed at baseline, at 1 and 2 years, and 2 months after therapy termination. At regular intervals (every 2 to 12 months), laboratory measurements of uric acid,

homocysteine, aspartate aminotransferase, creatine phosphokinase (CPK), fasting glucose, and insulin levels were performed. An unblinded safety monitor tracked all laboratory results and spoke with patients in the event of side effects requiring adjustment of simvastatin or niacin dosages (see the following). In addition, home glucometer results in patients with diabetes were reviewed on a monthly or bimonthly basis by a nurse experienced in the management of diabetes, with diet/exercise recommendations made as indicated; adjustment of diabetes medication was made by their attending physician.

Medication dosage adjustment: A physician safety monitor reviewed all symptomatic and laboratory side effects, and adjusted simvastatin and/or niacin dosages in both S + N and placebo groups to reduce problems and to maintain patient and investigator blinding. For side effects due to study medication, dosages were reduced by half or discontinued until side effects disappeared, then restarted at an appropriately reduced dosage. In some cases for patients with diabetes, changes in glycemic medication were instituted based on glucose monitoring results. Changes in study medication dosage were also considered, based on lipid monitoring to maintain target levels. If LDL cholesterol levels decreased to <60 mg/dl, the patient was asked on the telephone about specific symptoms related to low cholesterol. If LDL cholesterol decreased to <40 mg/dl, simvastatin and/or niacin were reduced or discontinued temporarily, and, after LDL cholesterol increased about 40 mg/dl, lipid therapy was restarted at an appropriately reduced dosage.

Statistical analysis: This study focuses on the safety and tolerability in all patients given active S + N (with or without antioxidants) compared with the placebo group (with or without antioxidants).

Differences between the 2 groups in clinical and laboratory side effects, the number of patients who required adjustment of study or diabetes medication dosages, and the overall tolerability evaluation were compared by chi-square test or Fisher's exact test. A 2-tailed p value of <0.05 was considered statistically significant. There were no side effects attributable to the antioxidant regimen.

RESULTS

Baseline characteristics: The mean age of the 160 patients was 53 years; the body mass index was 29; 55% had a previous myocardial infarction; 49% had been diagnosed with hypertension; 15% had diabetes; and 24% were current smokers. Mean total cholesterol was 197 mg/dl; triglycerides averaged 217 mg/dl; LDL cholesterol and HDL cholesterol were 128 and 31 mg/dl, respectively. The average fasting glucose and insulin levels were 103 mg/dl and 24 μU/dl. High-sensitivity C-reactive protein was 4.6 mg/L. The mean severity of proximal stenosis was 34.9%. These variables, plus others in Table 1, did not distribute significantly differently between patients treated with and without the S + N combination.

Clinical side effects: Table 2 presents the number of patients reporting, on ≥2 different occasions, clinical

TABLE 1 Comparison of Baseline Characteristics Between Patients Treated With and Without Simvastatin-Niacin (S + N) combination

Variable	S + N		p Value
	+	-	
	(n = 80)	(n = 80)	
Age (yrs)	53.7	53.0	0.54
Body mass index (kg/m ²)	29.2	28.7	0.44
History of myocardial infarction	42 (52.5%)	46 (57.5%)	0.53
Systemic hypertension	34 (42.5%)	44 (55.0%)	0.11
Diabetes mellitus	12 (15%)	12 (15%)	1.0
Smokers	18 (22.5%)	21 (26.3%)	0.58
Total cholesterol (mg/dl)	199	195	0.45
Very-low-density lipoprotein (mg/dl)	41.2	40.2	0.75
Intermediate-density lipoprotein (mg/dl)	14.3	13.7	0.57
Low-density lipoprotein (mg/dl)	125.4	122.0	0.46
High-density lipoprotein (mg/dl)	30.6	31.9	0.08
High-density lipoprotein 2 (mg/dl)	3.8	3.9	0.60
Triglycerides (mg/dl)	225.2	209.4	0.34
Apolipoprotein B (mg/dl)	117.7	113.6	0.24
Apolipoprotein A1 (mg/dl)	107.4	110.3	0.21
Apolipoprotein E (mg/dl)	4.9	5.0	0.68
Fasting glucose (mg/dl)	103.0	102.0	0.83
Insulin level (μU/dl)	25.9	22.8	0.14
Hs-C-reactive protein (mg/dl)	0.49	0.42	0.48
Mean coronary disease severity (%S)*	36.3	33.5	0.10

*The mean percent stenosis caused by the most severe lesion in each of the 9 proximal coronary segments.

symptoms, including gastrointestinal upset, nausea, vision problems, skin problems, lack of energy, muscle aches, or flushing, which were possibly related to simvastatin and/or niacin. Symptoms were graded as mild, moderate, or severe. Overall, the clinical side effects were usually described as mild or moderate; severe side effects were rare (0% to 5%). There were no statistically significant differences between S + N and placebo in terms of frequency of patients with any of these side effects. Flushing of any severity was seen in 30% of patients in the S + N group and in 23% of the placebo group (p = 0.35); severe flushing was 5% versus 0%, respectively. Flu-like symptoms (fatigue, nausea, muscle ache) were reported in 9% of those in the S + N group and in 5% of the placebo group (p = 0.35).

Laboratory measures: As shown in Table 3, compared with the placebo group, S + N did not significantly increase the number of patients with elevated aspartate aminotransferase (SGOT), CPK, uric acid, or homocysteine. None of patients had persistent (≥2 measurements) SGOT of ≥3 times the upper limit of normal because elevated SGOT levels were normalized by temporally reducing or halting the medication(s). CPK ≥5 times the upper limit of normal never occurred. The S + N combination powerfully lowered LDL cholesterol; during the 3-year study, LDL cholesterol levels <40 mg/dl were seen on ≥1 occasion in 22 of the S + N patients (28%) and none of the placebo group (p <0.001).

Glycemic control and insulin levels: Figure 1 shows the fasting glucose and insulin levels during the study

TABLE 2 Clinical Side Effects Reported by Patients at ≥2 Times

Symptoms (severity)	S + N		p Value*
	-	+	
	(n = 80)	(n = 80)	
Heartburn			
Mild	7 (9%)	6 (8%)	0.518
Moderate	9 (11%)	4 (5%)	
Severe	1 (1%)	1 (1%)	
Increased intestinal gas			
Mild	12 (15%)	8 (10%)	0.582
Moderate	16 (20%)	15 (19%)	
Severe	1 (1%)	3 (4%)	
Nausea			
Mild	3 (4%)	5 (6%)	0.703
Moderate	3 (4%)	4 (5%)	
Severe	0	0	
Vision impairment			
Mild	5 (6%)	2 (3%)	0.315
Moderate	0	1 (1%)	
Severe	0	0	
Skin (itchy, rash or dry)			
Mild	15 (19%)	17 (21%)	0.196
Moderate	3 (4%)	4 (5%)	
Severe	0	4 (5%)	
Fatigue			
Mild	27 (34%)	28 (35%)	0.960
Moderate	11 (14%)	13 (16%)	
Severe	1 (1%)	1 (1%)	
Muscle ache			
Mild	14 (18%)	17 (21%)	0.359
Moderate	9 (11%)	4 (5%)	
Severe	0	1 (1%)	
Flu-like symptoms (fatigue + nausea + muscle ache)			
Any	4 (5%)	7 (9%)	0.349
Flushing			
Severe	0	4 (5%)	0.060
Any	18 (23%)	24 (30%)	0.280

*By chi-square comparison.

TABLE 3 Frequency of Patients With Laboratory Side Effects

	S + N		p Value
	-	+	
	(n = 80)	(n = 80)	
Any SGOT ≥3 times ULN	1 (1%)	2 (3%)	0.560
≥2 SGOT ≥3 times ULN	0	0	—
Any CPK ≥2 times ULN	3 (4%)	2 (3%)	0.650
Any CPK ≥5 times ULN	0	0	—
Any uric acid ≥7.5 mg/dl	19 (24%)	20 (25%)	0.854
Any new uric Acid ≥7.5 mg/dl	12 (15%)	14 (18%)	0.67
Any homocysteine ≥15 μmol/L	3 (4%)	7 (9%)	0.191
Any LDL <40 mg/dl	0	22 (28%)	<0.0001

SGOT = aspartate aminotransferase; ULN = upper limit of normal.

for patients with and without diabetes. As expected, diabetic subjects had significantly higher fasting glucose and insulin levels at baseline. Overall fluctuations in the mean levels of fasting glucose were more noticeable in diabetic subjects, particularly in those who received S + N. Glycemic control was more variable and slightly worse in the S + N group during the first few months of treatment, but by 8 months had returned to the pretreatment levels and remained sta-

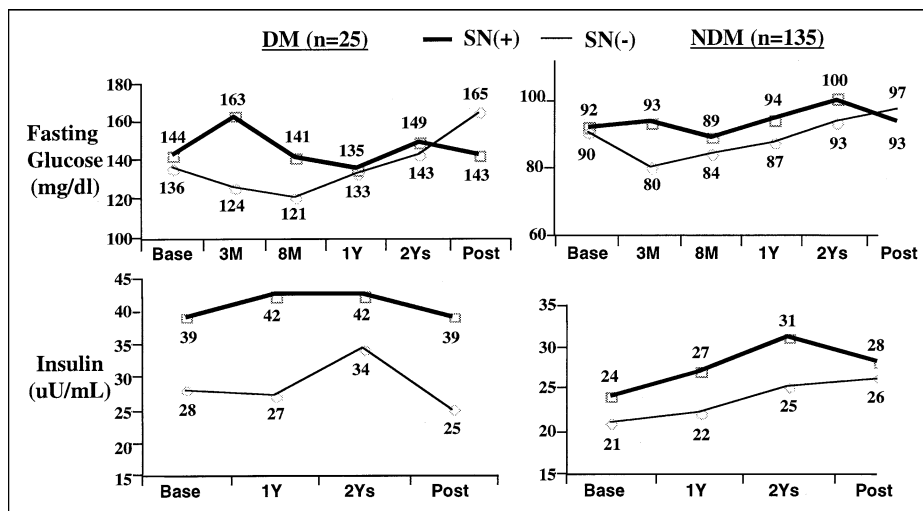


FIGURE 1. The fasting glucose and insulin levels during the study for patients with (DM) and without diabetes (NDM). The diabetic subjects had significantly higher fasting glucose and insulin levels at baseline. Glycemic control for diabetic patients was more variable and slightly worse in the S + N group during the first few months of treatment, but by 8 months had returned to the pretreatment levels and remained stable for the rest of the study. Insulin levels were persistently mildly elevated among diabetic subjects receiving S + N throughout the study.

TABLE 4 Study Medication Adjustment Due to Clinical or Laboratory Side Effects

	Temporarily Reduced/Discontinued* S + N			
	- (n = 80)	+ (n = 80)	- (n = 80)	+ (n = 80)
Flushing	1	3	0	2
Flu-like symptoms	1	5	0	1
SGOT ≥ 3 times ULN	1	3	0	0
CPK ≥ 2 times ULN	1	2	0	0
Fasting glucose ≥ 180 mg/dl	3	6	2	2 [†]
Uric acid ≥ 7.5 mg/dl	5	3	0	0
Homocysteine ≥ 15 μ mol/L	0	0	0	0
LDL < 40 mg/dl	0	18	0	0

*Study medication was reduced to half dose or discontinued until symptoms and/or blood test normalized; then an appropriate dose was restored.
[†]Patients quit niacin only, continued in study.
 Abbreviations as in Table 3.

4% of patients on S + N and 1% of those on placebo considered the study regimen “very hard” to take (p = NS).

DISCUSSION

The main concerns in combining statins with niacin are the heightened potential for muscle and liver toxicity.⁵ Several case reports⁵⁻⁷ have suggested that muscle and liver toxicity can occur when high doses of both statins and niacin are combined; muscle toxicity with the combination is principally due to statin side effects. When this combination is studied, in the moderate dose range, toxic effects are rare. Guyton and Capuzzi⁸ analyzed data from 9 studies

in 263 subjects taking a combination of statin and niacin and showed that no cases of myopathy occurred and no patient discontinued treatment due to hepatic toxicity. Furthermore, in a 1-year prospective open-label study of lovastatin (≤ 40 mg) plus extended-release niacin (≤ 2 g/day) in 814 patients with dyslipidemia, no drug-induced myopathy was noted, and the incidence of elevated liver enzymes (≥ 3 times the upper limit of normal) was 0.5%.⁸ In our prospective, placebo-controlled study, reported moderate or greater muscle pain during 3 years was less frequent among the 80 patients taking the S + N combination compared with those taking placebos (6% vs 11%); the incidence of CPK elevation ≥ 2 times the upper limit normal was similar between 2 groups (3% vs 4%). No cases of CPK elevation ≥ 5 times the upper limit of normal occurred. Liver enzyme elevation (≥ 3 times the upper limit of normal) was seen in 2 patients (3%) on the active S + N combination and in 1% of those on placebos. After discontinuing or reducing the study medication(s), liver enzymes returned to the normal range; at restarting therapy, these 2 patients did not have recurrent elevation. These findings are consistent with other reports that suggest that the S + N com-

ble for the rest of the study. Insulin levels were persistently mildly elevated among diabetic subjects who received S + N throughout the study. Among 124 subjects without diabetes or impaired fasting glucose (IFG) at baseline, 3 (2.4%) developed diabetes and 12 (9.7%) developed IFG. Both new diabetes and new IFG occurred more frequently in S + N group than in the placebo group, but the differences between the groups were not statistically significant.

Need for medication adjustments: Study medication dose adjustment (reduced or discontinued) because of clinical or laboratory side effects did not differ between the S + N and placebo groups (Table 4). However, temporary reductions in niacin or simvastatin dose were required in 18 of 80 patients (23%) who received S + N, but were not required in the placebo group (p < 0.01) due to LDL cholesterol of < 40 mg/dl. Overall, 5 patients who received S + N discontinued niacin due to flushing (3 temporarily and 2 permanently).

Tolerability evaluation: The S + N regimen was repeatedly described by 91% of patients as “very,” or “fairly easy” to take compared with 86% of the placebo group (p = NS) (Figure 2). In direct questioning,

ies in 263 subjects taking a combination of statin and niacin and showed that no cases of myopathy occurred and no patient discontinued treatment due to hepatic toxicity. Furthermore, in a 1-year prospective open-label study of lovastatin (≤ 40 mg) plus extended-release niacin (≤ 2 g/day) in 814 patients with dyslipidemia, no drug-induced myopathy was noted, and the incidence of elevated liver enzymes (≥ 3 times the upper limit of normal) was 0.5%.⁸ In our prospective, placebo-controlled study, reported moderate or greater muscle pain during 3 years was less frequent among the 80 patients taking the S + N combination compared with those taking placebos (6% vs 11%); the incidence of CPK elevation ≥ 2 times the upper limit normal was similar between 2 groups (3% vs 4%). No cases of CPK elevation ≥ 5 times the upper limit of normal occurred. Liver enzyme elevation (≥ 3 times the upper limit of normal) was seen in 2 patients (3%) on the active S + N combination and in 1% of those on placebos. After discontinuing or reducing the study medication(s), liver enzymes returned to the normal range; at restarting therapy, these 2 patients did not have recurrent elevation. These findings are consistent with other reports that suggest that the S + N com-

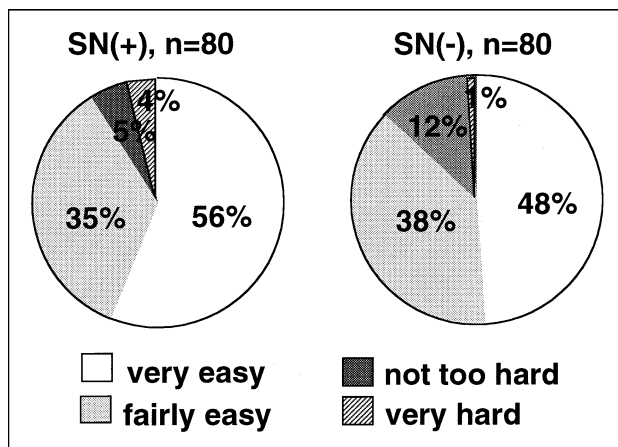


FIGURE 2. The tolerability evaluation of S + N. Over 3 years, 91% of patients taking S + N and 86% on placebo repeatedly described S + N as “very easy,” or “fairly easy” to take; 4% of patients treated with S + N and 1% receiving placebo considered the study regimen as “very hard” to take.

combination appears to have minimal adverse effects on muscles and the liver.

The well-known flushing effects of niacin have limited physician and patient acceptance.^{10,11} Early experience^{12,13} with immediate-release niacin showed that the vasodilatory side effects of flushing, tingling, and itching occurred in up to 100% of patients. In clinical trials, about 25% of patients had to discontinue niacin use because of these symptoms.^{13,15} Development of the new formulations of niacin (sustained- and extended-release niacin), plus accumulated experience on how to use niacin (e.g., gradually increasing niacin dose) preceded by aspirin, have reduced the incidence of vasodilatory side effects to <50% and the discontinuation rate from 10% to 15%.^{9,15,16} For example, 9% of hyperlipidemic subjects discontinued Niaspan (Kos Pharmaceuticals, Weston, Florida) (extended-release niacin) at <2,000 mg once daily at bedtime because of flushing.¹⁶ However, these “slow-release” formulations at high doses (>2,000 mg/day) may actually increase the potential for hepatotoxicity.^{17–20} In our study, in which we used extended-release niacin up to 2,000 mg/day, with immediate release >2,000 mg/day, with gradual dose escalation, taken with meals and with aspirin, flushing of any degree was reported by 30% of patients on S + N; severe flushing was reported by 5% of patients who were taking active S + N. Overall, discontinuation due to flushing was 6% (temporary in 4% and permanent in 2%). Thus, flushing is an infrequent problem with the above niacin and statin regimen in properly educated patients, 95% of whom tolerate and continue doses in the 2,000- to 4,000-mg range.

Diabetes mellitus is now considered to be a coronary heart disease risk-equivalent by the National Cholesterol Education Program Adult Treatment Panel III²¹ and the American Heart Association.²² Diabetes is characterized by high triglyceride levels, low HDL cholesterol levels, and small, dense LDL particles. Thus, niacin, which substantially improves

these abnormalities, appears to be ideal in combination with a statin for this type of dyslipidemia. However, the use of niacin in patients with diabetes has been discouraged because high doses have been reported to worsen glycemic control. The Arterial Disease Multiple Intervention Trial (ADMIT) investigators²³ reported the effect of niacin on glucose and glycosylated hemoglobin (HbA1c) levels. In this trial, 468 patients (125 with diabetes) with peripheral arterial disease received crystalline niacin (average dose was 2.5 g/day) or placebo. Niacin modestly increased glucose levels in patients with and without diabetes (8.7 and 6.3 mg/dl, $p < 0.05$). Levels of HbA1c were unchanged from baseline to follow-up in patients with diabetes who were treated with niacin, but these levels decreased by 0.3% ($p = 0.04$) in the placebo group. The recent Assessment of Diabetes Control and Evaluation of the Efficacy Niaspan Trial (ADVENT) report²⁴ showed that after a 16-week treatment period among 148 diabetic patients with type II diabetes, HbA1c levels were decreased 0.02% (from 7.13% at baseline) among the placebo group, increased 0.07% (from 7.28% at baseline) among the 1,000-mg Niaspan group ($p = 0.16$ vs placebo), and increased 0.3% (from 7.2% at baseline) among the 1,500-mg Niaspan group ($p = 0.048$ vs placebo). Thus, ADMIT, ADVENT, and the present study, using niacin at average 2,400 mg/day, convincingly showed that changes in glycemic control were minimal transient and could be successfully managed by adjusting antidiabetic medications. The accumulating evidence support the current recommendations from the American Diabetes Association of using <2 g nicotinic acid per day and frequent glucose monitoring in patients with diabetes.²

Another concern is that niacin may convert a non-diabetic subject to diabetes. We saw nonstatistically significant higher frequencies of new diabetes and IFG in the S + N-treated group compared with placebos (3.2% vs 1.6% for new diabetes and 12.9% vs 6.5% for new IFG). These findings need to be confirmed by large and prospective clinical studies and require consideration of the risks versus the benefits derived from the combination therapy. However, our study demonstrated that the primary event rate was reduced by 48% and the rate of CAD progression was 77% lower for those who received S + N compared with placebo-treated diabetic or IFG subjects.²⁵ This is in consistent with the recent report on the Coronary Drug Project.²⁶ In balance, the benefits of niacin with statins in diabetic patients appear to outweigh the adverse consequences of an increase in glucose levels.

Taking all the side effects into account, the combination of S + N was very well tolerated in this study. More than 90% of patients on active S + N reported this combination regimen as very or fairly easy to take; only 4% of patients considered it to be very hard, a rate that was not significantly different from that in the placebo group (2%). These data suggest that the S + N combination is a practical approach for the treatment of dyslipidemia.

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