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ACHIEVING LIPID TARGETS IN ADULTS WITH TYPE 2 DIABETES--THE SANDS STUDY

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Abstract

Background—Although lipid management in diabetes is standard practice, goals often are neither met nor maintained. Strategies for achieving lower targets have not been explored. The Stop Atherosclerosis in Native Diabetics Study (SANDS) randomized patients with diabetes to standard versus aggressive lipid and blood pressure goals for 36 months.

Objective—To report strategies used to achieve and maintain lipid goals and to report adverse events (AEs).

Methods—Adults with type 2 diabetes and no history of cardiovascular disease (N=499) were randomized to standard (low-density lipoprotein cholesterol [LDL-C] ≤100 mg/dL, non-high-density lipoprotein cholesterol [non-HDL-C] ≤130 mg/dL) or aggressive (LDL-C ≤70 mg/dL, non-HDL-C ≤100 mg/dL) targets. An algorithm started with statin monotherapy, adding intestinally acting agents as required to reach LDL-C targets. Triglyceride [TG]-lowering agents were next used to reach non-HDL-C goals. Lipid management was performed by mid-level practitioners, with physician consultation, using point-of-care lipid determinations.

Results—On average, both groups achieved the LDL-C and non-HDL-C goals within 12 months and maintained them throughout the study. At 36 months, mean (SD) LDL-C and non-HDL-C were 72 (24) and 102 (29) mg/dL in the aggressive group (AGG) and 104 (20) and 138 (26) mg/dL, respectively, in the standard group (STD); systolic blood pressure targets were 115 and 130

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mmHg, respectively. 68% of participants reached target LDL-C for >50% of the visits and 46% for >75% of visits. At 36 months, the AGG averaged 1.5 lipid lowering medications and the STD 1.2. Statins were used in 91% and 68% of the AGG and STD; ezetimibe by 31% and 10%; fibrates by 8% and 18%. No serious adverse events (SAEs) were observed; AEs occurred in 18% of the AGG and 14% of the STD.

Conclusion—Standard and aggressive lipid targets can be safely maintained in diabetic patients. Standardized algorithms, point-of-care lipid testing, and non-physician providers facilitate care delivery.

Keywords

lipids; blood pressure; carotid artery intima media thickness; cardiovascular disease; American Indians

INTRODUCTION

Individuals with diabetes are at increased risk for developing cardiovascular disease (CVD), and coronary heart disease (CHD) is the leading cause of death in adults with type 2 diabetes.^{1, 2, 3} The increased diabetes-associated CVD risk is due in part to the prevalence of other major CVD risk factors, such as dyslipidemia and hypertension.^{4, 5} Individuals with diabetes have a characteristic dyslipidemia consisting of high triglyceride (TG) levels, low high-density lipoprotein cholesterol (HDL-C), and increased non-HDL-C signifying an increase in the number of atherogenic lipoprotein particles. Despite the lack of randomized trials evaluating specific targets, consensus panels (Adult Treatment Panel III [ATPIII], American Diabetes Association [ADA], and ADA/American College of Cardiology [ACC] consensus conference on cardio-metabolic risk⁶ have recommended LDL-C targets and associated TG and non-HDL-C targets for diabetic patients. Thus, there is a need for lipid-lowering therapy in many diabetic patients.

Studies have shown that although patients are prescribed lipid-lowering agents, many do not achieve an acceptable LDL-C level and non-HDL-C is usually ignored. Failure to achieve recommended targets may result from patient-related factors, such as adherence and affordability of medications, or from health-care provider factors, such as not following guidelines, lack of understanding of guidelines, difficulty with follow-up laboratory evaluation, inadequate drug titration, and disagreement with guidelines.⁶

The Stop Atherosclerosis in Native Diabetics Study (SANDS) was conducted to evaluate the feasibility and efficacy of more aggressive versus standard targets for lipids and blood pressure in patients with type 2 diabetes and no history of a prior CVD event. The primary outcome was the change in carotid artery intima media thickness (CIMT) after 36 months of intervention.⁷ The aggressive group achieved significant regression of CIMT while the standard group showed progression of CIMT, but at a lesser rate than predicted. In this article, the strategies for achieving and maintaining lipid goals throughout the 3-year intervention, occurrence of adverse events (AEs), and approaches used to maintain adherence are summarized.

METHODS

Participants

Four hundred and ninety-nine men and women $\geq$ age 40 with type 2 diabetes and no history of a CVD event were randomly assigned to an aggressive (n=252) or standard intervention group (n=247). All participants were American Indian, as defined by Indian Health Service

(IHS) criteria, had type 2 diabetes as defined by 1997 ADA criteria, LDL-C ≥ 100 mg/dL, and systolic blood pressure >130 mmHg within the previous 12 months. All participants provided written informed consent and the study was approved by the Institutional Review Boards of the participating institutions and IHS as well as by the sponsor, the National Institutes of Health, an independent Data and Safety Monitoring Board, and all participating American Indian communities. Details of the SANDS study design and methods have been published.⁸

Interventions

Study personnel performed lipid and blood pressure management for both groups. All other medical care, including diabetes management, was performed by the participants' IHS providers. For lipid management (Figure 1), if lifestyle modification was unsuccessful, statin monotherapy was initiated. If the LDL-C goal was not reached with the maximal tolerable statin dosage, combination therapy with ezetimibe, bile acid resin, or a fiber supplement was used. The non-HDL-C goal was then addressed using fish oil, fenofibrate, or niacin (Figure 1).⁸ Statins did not exceed mid-maximal dosages when used in combination with a fibrate. Lipid management was performed by trained mid-level practitioners, including nurse practitioners and physician assistants, with input from field physicians and an expert lipidologist. Systolic blood pressure was treated to goals of 115 mmHg and 130 mmHg in the aggressive and standard groups, respectively.⁹

Baseline and follow-up visits

All procedures followed standardized methods and were performed by trained, certified personnel. The baseline visit included a physical exam, collection of demographic data, health history, and medication use. Height, weight, waist circumference, and seated blood pressure were measured. Food frequency, physical activity, and quality of life questionnaires were administered, and fasting blood and urine samples collected for measures of lipid profile, complete metabolic profile, apolipoproteins B and A1, glucose, insulin, hemoglobin A1c, and C-reactive protein.

Based on the intent-to-treat criteria, the participants were followed from the date of randomization until trial completion, death, loss to follow up, or request for no further contact regardless of their adherence to the medication intervention. All participants were scheduled for a visit at 1 month, with follow-up visits scheduled every 3 months until 36 months. At each follow-up visit, a lipid profile was measured using a Cholestech LDX device (Cholestech Corporation, Hayward, CA) standardized against the laboratory assay. Medications were adjusted to meet treatment goals, side effects were assessed, and information on health outcomes was obtained. Liver function studies were conducted at baseline, 1, 3, and 6 months, and every 6 months thereafter, according to the IHS protocol for initiating or changing statin therapy dosage. In addition to the regular visits, interim visits were added as necessary for medication adjustment and/or side effect management. At each visit, participants were encouraged to take an active role in their treatment. Participants and field staff worked closely to achieve the treatment goal with minimal effect on quality of life. Participants suffering from myalgias caused by statins were switched to a different statin. Creatine kinase (CK) levels were obtained on any participant with a myalgia significant enough to warrant a change in medication.

Fasting blood and urine samples were obtained at 18 and 36 months and forwarded to the core laboratory for repeat of all measures obtained at baseline. In addition, at 6, 12, 24, and 30 months, a fasting blood sample was obtained for a complete laboratory lipoprotein profile.

Adverse Event Data Assessment

At each visit after randomization, information was collected on AEs. These were defined as being possibly, probably, or definitely related to pharmacotherapy. Serious adverse events (SAEs) were defined as those requiring medical attention. All AEs and SAEs were reviewed by the Morbidity and Mortality Committee and the Data Safety and Monitoring Board. The AEs were presented blinded to treatment arm for the Morbidity and Mortality Committee and unblinded for the Data Safety and Monitoring Board.

Lipid Measurement

Field staff at each study site were certified in performance of the Cholestech LDX device. A field service technical representative retrained the field staff every 8 months to ensure proper technique and accurate results. Cholestech LDX measurements were obtained quarterly, and serum was collected biannually for repeat lipid analysis at the core laboratory. Measures between the Cholestech LDX and the central laboratory for LDL-C were well correlated (Figure 2).

Data Analysis

Baseline characteristics of the SANDS participants were compared between the standard and aggressive treatment groups using the t-test for continuous variables and the chi-square test for categorical variables. The continuous variables that did not follow the normal distribution were log-transformed or described using geometric means and corresponding 95% confidence intervals. All two-sided significance tests were based on a significance level of .05.

Mean changes in LDL-C, HDL-C, triglycerides, and non-HDL-C, along with other CVD risk factors between baseline and 36 months, were compared between the treatment groups, and significant changes were determined using two-sided t-tests. Unpaired t-tests were used to compare groups. The mean or median of the 24-, 30-, and 36-month values was used as the end-of-study measurement for all lipids.

The proportion of participants who used each type of hypolipidemic drug (statins, ezetimibe, niacin, fibrate, and fish oil) was compared between the treatment groups using the chi-square test. The mean number of hypolipidemic drugs used by the participants was computed for the aggressive and standard groups and compared using a nonparametric test. Agreement between the point-of-care (Cholestech) LDL-C and the LDL-C measured in a central laboratory was evaluated using an ordinary least squares regression.

The proportion of participants with at least one AE and the number of AEs per group were compared using the chi-square test and t-tests, respectively. The most frequently occurring AEs were also compared between treatment groups.

RESULTS

Mean age was 56 years, 66% were women, average body mass index (BMI) was 33, and 21% were current smokers (Table 1). At randomization, 38% of participants were taking lipid-lowering medication. Statins were the most commonly used lipid-lowering agents (34%) at baseline, while fibrates were used by 5%. Ezetimibe became available to our communities in 2003, after randomization was complete. Baseline LDL-C averaged 104 mg/dL and non-HDL-C averaged 139 mg/dL. Mean duration of diabetes was 8.7 years in the standard group and 9.2 years in the aggressive group. The majority of participants took some form of hypoglycemic therapy; hemoglobin A1c averaged 8.1%.

Study retention was excellent, with a 94% overall follow-up rate that did not differ by treatment group. On average, individuals in the aggressive group achieved the LDL-C goal of ≤ 70 mg/dL within 12 months of randomization and the non-HDL-C goal of ≤ 100 mg/dL within 18 months. The average goals for the aggressive group were maintained consistently throughout the 36-month follow-up (Table 2 and Figure 3). LDL-C and non-HDL-C goals were also maintained in the standard group, with LDL-C ≤ 100 mg/dL and non-HDL-C ≤ 130 mg/dL during follow up. In the aggressive group, 68% of the participants reached the target LDL-C (defined as ≤ 73 mg/dL) for $>50\%$ of the visits and 46% for $>75\%$ of visits. During the last 12 months, the difference in LDL-C between the groups was maintained at 32 mg/dL. The average number of clinic visits per participant was 19.2 in the standard group and 17.7 in the aggressive group. Comparable goal achievement was observed in non-HDL-C (Figure 3b). Mean weight, average BMI, waist circumference, and fasting glucose also remained unchanged in both groups (Table 2). CIMT regressed in the aggressive group and progressed in the standard group (-0.012 mm vs. 0.038 mm, $p<.001$); however, the observed progression was less than predicted when compared to a concomitant case control group (Table 2). Carotid arterial cross-sectional area also regressed (-0.02 mm² vs. 1.05 mm², $p<.0001$), and there was greater decrease in left ventricular mass index (-2.4 g/m^{2.7} vs. -1.2 g/m^{2.7}, $p=.026$) in the aggressive versus the standard group.⁷

At 36 months, the aggressive group on average was taking 1.5 lipid-lowering medications and the standard group 1.2 (Table 3). A statin was used in 91% and 68% of the aggressive and standard groups, respectively (Table 4). Ezetimibe was used in 31% and 10% ($p<0.001$) of the aggressive and standard groups, respectively. To obtain an indication of dose response to statin, we analyzed 88 participants who took no lipid medication at baseline, had an average LDL-C of 115 mg/dL, and were placed on atorvastatin 10 mg daily. At 1 month, LDL-C had decreased 34% to an average of 76 mg/dL, non HDL-C decreased by 28%, and TG decreased by 16%; there was a 2% increase in HDL-C. No SAEs were due to lipid lowering medication, and rates of AEs were 18% and 14% in the aggressive and standard groups, respectively (Table 5). The most commonly reported AE was myalgia; none had associated CK elevation.

DISCUSSION

SANDS demonstrates that both standard and aggressive lipid targets can be reached and maintained safely in diabetic patients without prevalent CVD. Aggressive therapy required an average of 1.5 medications and standard therapy an average of 1.2 to reach the target, with 68% of participants maintaining target for 3 years. It has been observed in national surveys that only 30% of patients with type 2 diabetes achieve these recommended levels.¹⁰ Lipid therapy was based on evidence-based algorithms and was administered by consistent mid-level practitioners, with available consultation with a lipid specialist. Participants were seen at 3-month intervals with additional visits as needed. Goal setting, education, and support for self-management were promoted at each visit. Statins were the most frequently used drugs in both groups and were readily available. The success of this population in reaching and maintaining targets probably was multifactorial and related to visit frequency, consistency of study staff, availability of medications, patient education, and engagement in the study.

In 2001, the Institute of Medicine described three main problems with delivery of ambulatory care: delivery of care is not safe or effective, patients are not engaged in their care, and care is not provided in a timely manner.¹¹ SANDS was able to demonstrate that both LDL-C and non-HDL-C targets can be reached safely and effectively. Participants were encouraged to engage in self-management and were an active part of their care team. Participants were seen on a regular and timely basis. SANDS exemplifies how care can be

delivered in a safe, efficacious, timely, and patient-centered manner. The use of registered nurses and mid-level practitioners, detailed treatment algorithms, and available expert physician consultation were key elements in achieving patient treatment targets. This format created a care team for the patient that consisted of multiple levels of expertise and resulted in increased efficiency. The increased availability of a registered nurse or mid-level practitioner as opposed to a physician led to the development of trusting relationships between the patients and providers.

Lipid targets were achieved in both groups with no SAEs and low rates of AEs, although AEs were slightly more common in the aggressive group. SANDS provides the first data on the effects of hypolipidemic drugs in an American Indian population. Ten mg of atorvastatin resulted in 34% reductions in LDL-C. There was little effect of atorvastatin on HDL-C, but meaningful decreases occurred in non-HDL-C (28%) and TG (16%). Despite the relatively low baseline lipid values, these data establish the efficacy of statins in this population. Baseline liver functions tests were within normal limits in both the aggressive and standard groups and did not change significantly during the study. A minimal number of participants developed myalgia or liver enzyme elevations.

The optimal lipid targets for individuals with diabetes and no clinical CVD remain unclear. In the Collaborative Atorvastatin Diabetes Study (CARDS), atorvastatin 10 mg reduced LDL-C to ~80mg/dL and reduced CVD events by 37% versus placebo.¹² However, the Atorvastatin Study for Prevention of Coronary Heart Disease Endpoints (ASPEN) trial¹³ was unable to demonstrate cardiovascular protection with 10 mg atorvastatin despite reducing LDL-C from 114 to 80 mg/dL in a similar population. Neither study was designed to test specific LDL-C goals, but rather to examine the impact of statin therapy in diabetic individuals with normal LDL-C and no history of CVD. In both the large Action to Control Cardiovascular Risk in Diabetes (ACCORD)¹⁴ and the Fenofibrate Intervention and Event Lowering in Diabetes (FIELD)¹⁵ trials, fenofibrate failed to reduce coronary events, although total CVD events were reduced a modest 11% in FIELD.

Based on the limited evidence available, a consensus statement from the ADA and the ACC⁶ recommends statins in addition to lifestyle therapy for most patients with diabetes. This consensus statement lists the primary LDL-C treatment goal as < 100 mg/dL (2.6 mmol/l) for diabetic individuals without overt CVD and < 70 mg/dL (1.8 mmol/l) for diabetic patients with overt CVD or with one major risk factor.¹⁶ In addition, the American Heart Association/ACC statement recommends statin therapy to achieve an LDL-C reduction of >50% in those unable to achieve the above targets,¹⁷ regardless of baseline LDL-C.

The strengths of this study lie in the careful training of the personnel performing the lipid management and the use of algorithms for delivery of care. Point-of-care lipid testing allowed for immediate adjustment of medication and feedback to the patient. A quality-control program with standardization, training, and practice will need to be in place in clinical practice settings using point-of-care testing. Adverse events were monitored and recorded. This study was limited by the homogeneity of the participants. None of the patients had severe hyperlipidemia, which would have required higher dosages and more lipid lowering agents and the possibility of additional side effects. Further, although this study was administered in a clinic setting, study personnel probably had more time than generally is available for ensuring that patients attended visits and for counseling patients in adhering to the study regimen. Risk factor profiles should be considered in determining lipid targets for persons with diabetes.¹⁸

CONCLUSION

In summary, the results of this study reinforce the feasibility and safety of achieving both standard and aggressive lipid targets in diabetic patients and suggest that standard algorithms and point-of-care lipid testing should be more widely available. Additional controlled trials need to be conducted to determine whether more aggressive LDL-C targets achieve reduction in clinical cardiovascular endpoints.

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ABBREVIATIONS

AE	adverse event
SAE	serious adverse event requiring medical intervention
CHD	coronary heart disease
CRP	C-reactive protein
CVD	cardiovascular disease
HDL-C	high-density lipoprotein cholesterol
CIMT	carotid intima media thickness
LDL-C	low-density lipoprotein cholesterol
Non-HDL-C	non-high-density lipoprotein cholesterol
SANDS	Stop Atherosclerosis in Native Diabetics Study
TG	triglyceride

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Figure 1.
Algorithm for Lipid Management
LDL-C therapy: aggressive target <70 mg/dL; standard target <100 mg/dL

Figure 2.
Comparison of Point-of-Care LDL Cholesterol with Central Laboratory Measures

Figure 3. Lipid Goal Achievement

a. Mean (SD) of LDL Cholesterol by Treatment Group

b. Mean (SD) of Non-HDL Cholesterol by Treatment Group

Table 1

Baseline Characteristics of the SANDS Participants (N = 499)

	Aggressive (N = 252)	Standard (N = 247)	P-value
	N (%)	N (%)	
Age (years)	55 (9)	57 (9)	.06
Gender, women N, %)	167 (66)	160 (65)	.73
Body mass index (BMI), kg/m ²	33.5 (6.6)	33.2 (6.2)	.57
Waist (cm)	110.2 (15.4)	110.1 (14.0)	.90
Cholesterol (mg/dL)			
Total	184 (33)	185 (33)	.56
LDL	104 (30)	104 (29)	.95
HDL	46 (13)	46 (12)	.90
Non-HDL	138 (32)	140 (32)	.50
Triglycerides (mg/dL) **	158 (149–167)	168 (159–177)	.10 *
Systolic blood pressure (mm Hg)	128 (15)	133 (17)	.002
Diastolic blood pressure (mm Hg)	74 (10)	76 (10)	.04
A1c	8.2 (1.8)	7.9 (1.8)	.10
Diabetes Therapy			
Lifestyle	27 (11.0)	34 (13.9)	.33
Oral hypoglycemic medication	206 (82)	180 (73)	.02
Insulin	70 (28.6)	53 (22.0)	.10
Insulin plus oral	247 (98)	227 (92)	.002
eGFR	91 (24)	88 (23)	.21
Smoking	243	244	
Never	109 (45)	123 (51)	.20
Current	54 (22)	48 (20)	.58
Former	80 (33)	73 (30)	.60
Aspirin use (≥ 80 mg)			
Yes	177 (70)	168 (69)	.74
CRP (mg/dL) **	2.7 (2.3–3.1)	2.8 (2.4–3.3)	.56 *
Carotid			
IMT (mm)	.810 (.19)	.797 (.17)	.48 *
Arterial area (mm ²)	17.4 (5.0)	17.3 (4.6)	.85
Plaque score (1–8)	1.85 (1.6)	1.83 (1.7)	.89 *
Plaque (N, %)	188 (75)	188 (76)	.64
Cardiac			
LV mass	156.7 (38.3)	156.1 (38.3)	.56 *
LV mass index (g/m ^{2.7})	41.2 (9.5)	40.6 (8.5)	.87 *

	Aggressive (N = 252)	Standard (N = 247)	P-value
	N (%)	N (%)	
LV ejection fraction	60.5 (5.7)	59.8 (5.8)	.26*

Abbreviations: CRP = C-reactive protein; eGFR = estimated glomerular filtration rate; HDL = high-density lipoprotein; IMT = intimal medial thickness; LDL = low-density lipoprotein; LV = left ventricular.

* Two-sample comparison t-tests were calculated based on log-transformed variables.

** Geometric mean with 95% confidence interval in parenthesis.

Table 2
Differences in Mean Changes from Baseline to 36 Months, Aggressive vs. Standard Group

	Baseline		36 months		Mean Change at 36 months		
	Aggressive	Standard	Aggressive	Standard	Aggressive	Standard	Difference
	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	p-value
Weight, kg	90 (20)	90 (19)	91 (21)	91 (21)	1 (12)	1 (10)	.83
BMI, kg/m ²	33.5 (6.6)	33.2 (6.2)	33.8 (6.9)	33.6 (7.0)	.3 (4.5)	.4 (3.8)	.77
Waist, cm	110 (15)	110 (14)	110 (16)	110 (15)	.2 (11)	.6 (10)	.66
Systolic BP, mm Hg	128 (15)	133 (17)	117 (11)	129 (10)	-11 (15)	-3 (15)	.000
Diastolic BP, mm Hg	74 (10)	76 (10)	67 (8)	73 (8)	-7 (8)	-3 (9)	.000
Total cholesterol, mg/dL	184 (33)	185 (33)	150 (29)	187 (27)	-32(39)	3 (36)	.000
LDL-C, mg/dL	104 (30)	104 (29)	72 (24)	104 (20)	-31(35)	1(32)	.000
HDL-C, mg/dL	46 (13)	46 (12)	48 (13)	48 (13)	3(9)	3(11)	.94
Total cholesterol/HDL-C	4.2 (1.1)	4.2 (1.1)	3.3 (1.0)	4.0 (1.0)	-1(1.0)	-.1(1.1)	.000
Non-HDL-C, mg/dL	138 (32)	140 (32)	102 (29)	138 (26)	-35 (38)	.2(36)	.000
Triglycerides, mg/dL (geo mean and 95% CI)	158(149–167)	168 (159–177)	137(130–144)	160 (153–168)	-26(78)*	-12(84)*	.06*
CRP mg/dL (geo mean and 95% CI)	2.7 (2.3–3.1)	2.8 (2.4–3.3)	2.2 (1.9–2.7)	3.3 (2.8–3.8)	-.7(11)*	.9(9)*	.12*
Glucose, mg/dL	159 (69)	156 (72)	169(78)	169(80)	11 (88)	14(97)	.68
A1c	8.2 (1.8)	7.9 (1.8)	8.3 (2.2)	8.2 (2.3)	.1(2.0)	.3(2.4)	.45

Note: N for the 36-month lipid variables was 458, and the means were based on the average of the 24-, 30[–] and 36-month observations.

* Based on arithmetic mean.

Abbreviations: BMI = body mass index; BP = blood pressure; CRP = C-reactive protein; HDL = high-density lipoprotein; LDL = low-density lipoprotein.

Table 3

Numbers of Hypolipidemic Drugs by Treatment Group

Number of Drugs	Aggressive Group N=252	Standard Group N=247
0	14 (6%)	38 (16%)
1	128 (51%)	139 (57%)
2	92 (37%)	58 (24%)
3	16 (6%)	8 (3%)
4	1 (.4%)	1 (.4%)
5	1 (.4%)	0
Mean (S.D.)	1.5 (.75)	1.2 (.73)

Values are from last half of the intervention period.

Table 4

Hypolipidemic Drug Dosage Differences Across the SANDS Treatment Groups

Lipid Drugs	Aggressive Group	Standard Group	P
	Avg mg (SD) N	Avg mg (SD) N	
Atorvastatin	46 (28) 189	15 (14) 88	<.001
Simvastatin	41 (27) 8	13 (15) 35	<.001
Ezetimibe	10 (1) 75	9 (2) 21	.008
Niacin ^a	857 (244) 7	720 (409) 5	.48
Fenofibrate	126 (43) 5	113 (41) 16	.55

Values are for the second half of the intervention period. A t-test was used to compare the dosage by treatment groups for participants on a given lipid drug.

^a Niaspan or Niacin.

Table 5

Adverse events related to lipid lowering medications

	Aggressive Group (N=252)	Standard Group (N=247)	P-value
Participants with 1 or more AEs (N, %)	46 (18%)	35 (14%)	0.271
Number of AEs	86	56	0.037
Most Common AEs			
Muscle cramps, muscle aches, muscle pain, or myalgia	39 (15%)	19 (7.7%)	0.010
Nausea	8 (3.1%)	6 (2.4%)	NS
Pruritis	5 (2.0%)	5 (2.0 %)	NS
Increased liver enzymes	6 (2.4%)	3 (1.2%)	NS

NS = nonsignificant.