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Effect of Statins Alone Versus Statins Plus Ezetimibe on Carotid Atherosclerosis in Type 2 Diabetes

The SANDS (Stop Atherosclerosis in Native Diabetics Study) Trial

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Objectives This secondary analysis from the SANDS (Stop Atherosclerosis in Native Diabetics Study) trial examines the effects of lowering low-density lipoprotein cholesterol (LDL-C) with statins alone versus statins plus ezetimibe on common carotid artery intima-media thickness (CIMT) in patients with type 2 diabetes and no prior cardiovascular event.

Background It is unknown whether the addition of ezetimibe to statin therapy affects subclinical atherosclerosis.

Methods Within an aggressive group (target LDL-C ≤70 mg/dl; non–high-density lipoprotein cholesterol ≤100 mg/dl; systolic blood pressure ≤115 mm Hg), change in CIMT over 36 months was compared in diabetic individuals >40 years of age receiving statins plus ezetimibe versus statins alone. The CIMT changes in both aggressive subgroups were compared with changes in the standard subgroups (target LDL-C ≤100 mg/dl; non–high-density lipoprotein cholesterol ≤130 mg/dl; systolic blood pressure ≤130 mm Hg).

Results Mean (95% confidence intervals) LDL-C was reduced by 31 (23 to 37) mg/dl and 32 (27 to 38) mg/dl in the aggressive group receiving statins plus ezetimibe and statins alone, respectively, compared with changes of 1 (−3 to 6) mg/dl in the standard group ($p < 0.0001$) versus both aggressive subgroups. Within the aggressive group, mean CIMT at 36 months regressed from baseline similarly in the ezetimibe (−0.025 [−0.05 to 0.003] mm) and nonezetimibe subgroups (−0.012 [−0.03 to 0.008] mm) but progressed in the standard treatment arm (0.039 [0.02 to 0.06] mm), intergroup $p < 0.0001$.

Conclusions Reducing LDL-C to aggressive targets resulted in similar regression of CIMT in patients who attained equivalent LDL-C reductions from a statin alone or statin plus ezetimibe. Common carotid artery IMT increased in those achieving standard targets. (Stop Atherosclerosis in Native Diabetics Study [SANDS]; NCT00047424) (J Am Coll Cardiol 2008;52:2198–205) © 2008 by the American College of Cardiology Foundation

Ezetimibe diminishes intestinal cholesterol absorption by inhibiting the Niemann-Pick–like 1 enterocyte receptor, thereby up-regulating low-density lipoprotein cholesterol (LDL-C) receptors and lowering serum levels of LDL-C and non–high-density lipoprotein cholesterol (HDL-C) (1). Since its approval for clinical use, it has become a major adjunct to statins in lowering LDL-C (2). Implicit in the use of ezetimibe to lower LDL-C is the belief that the

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resultant lowering will translate into a reduction in clinical atherosclerotic cardiovascular (CV) events, similar to that observed with statins. This hypothesis, however, remains unproven.

No data are available on the influence of ezetimibe on atherosclerosis except for findings from the ENHANCE (Effect of Combination Ezetimibe and High-Dose Simvastatin Versus Simvastatin Alone on the Atherosclerotic Process in Subjects With Heterozygous Familial Hypercholesterolemia) trial (3). Despite an additional 17% reduction in LDL-C in the group receiving ezetimibe plus simvastatin compared with LDL-C levels in the statin alone group, the average increase in common carotid artery intima-media thickness (CIMT) over 2 years in the group receiving combination therapy did not differ significantly from that in the statin-only group (3).

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The SANDS (Stop Atherosclerosis in Native Diabetics Study) trial was a randomized, open-label, blinded to outcomes, 3-year trial that examined the effects of aggressive goals for LDL-C (≤70 mg/dl), non–HDL-C (≤100 mg/dl), and blood pressure (BP) (≤115/75 mm Hg) reduction versus standard goals of ≤100 mg/dl, ≤130 mg/dl, and ≤130/80 mm Hg, respectively, in 499 individuals with type 2 diabetes (4). The primary outcome was change in CIMT after 36 months of treatment. Substantial epidemiological data document strong relationships among LDL-C, non–HDL-C, BP, and CV events in American Indians, a population with high rates of diabetes and diabetes-related CV disease (5,6). Among patients randomized to the aggressive treatment goals (n = 252), ezetimibe was used in about one-third as an adjunct to statin therapy. This secondary analysis from SANDS examines the effect of aggressive lowering of LDL-C and non–HDL-C with statins alone versus statins plus ezetimibe on CIMT and other measures of carotid atherosclerosis. Individuals randomized to standard LDL-C, non–HDL-C, and systolic blood pressure (SBP) targets served as a reference group.

Methods

Recruitment and intervention. Details of the design and main results of SANDS have been published (4,7). In total, 499 American Indian men and women ≥40 years of age with type 2 diabetes, LDL-C >100 mg/dl, SBP >130 mm Hg, and no prior CV events were enrolled between May 2003 and July 2004 at 4 clinical centers and randomized to aggressive (n = 252) or standard treatment groups (n = 247), stratified by center and gender (Fig. 1). All participants provided informed written consent. The study was approved by all participating institutional review boards, the National Institutes of Health, and all participating American Indian communities.

Abbreviations and Acronyms

BP = blood pressure
CIMT = common carotid artery intima-media thickness
CV = cardiovascular
HDL-C = high-density lipoprotein cholesterol
LDL-C = low-density lipoprotein cholesterol
SBP = systolic blood pressure

The standard group was treated to conventional goals for LDL-C (100 mg/dl), non–HDL-C (130 mg/dl), and SBP (130 mm Hg), and the aggressive group to goals of 70 mg/dl, 100 mg/dl, and 115 mm Hg, respectively. The algorithm for attaining lipid goals was based on recommendations of the National Cholesterol Education Program–Adult Treatment Panel III (8). If lifestyle modification was unsuccessful in lowering LDL-C to the prescribed goals within 3 months, a statin was started. If the LDL-C goal was not reached with a statin alone, ezetimibe was added. Non–HDL-C goals were addressed using fish oil, fenofibrate, or niacin. Details of the intervention procedures and targets have been published (4,7). The baseline visit included collection of demographic data, health history, and current medication use plus a physical exam, electrocardiogram, carotid artery ultrasound, and echocardiogram. Height, weight, waist circumference, and seated BP were measured; fasting blood samples were collected to measure chemistry panel, lipoprotein profile, glucose, hemoglobin A1c, C-reactive protein, and creatinine; and urine samples were obtained for urinary albumin and creatinine as described previously (4,7). Participants were followed from date of entry until death, loss to follow-up, request for no further contact, or completion of the study, regardless of adherence to the medication intervention. Follow-up visits occurred in both groups after 1 month and then every 3 months through 36 months, and a lipid profile was obtained using a Cholestech LDX apparatus (Cholestech Corporation, Hayward, California) standardized against the laboratory assay (9,10). At 36 months, fasting blood and urine samples were obtained to repeat all baseline measurements; additionally, fasting blood samples for complete lipoprotein profile and urine samples for albumin and creatinine were obtained at 6, 12, 18, 24, and 30 months (4,7).

Outcomes ascertainment. At baseline and 18- and 36-month visits, carotid ultrasound studies were performed following standardized protocols (11) by centrally trained sonographers and interpreted at a core reading center by a single experienced cardiologist reader blinded to treatment assignment (12). For these studies, B-mode imaging from multiple angles was performed to determine the presence and location of plaque (focal protrusion into the vessel lumen ≥50% greater than the surrounding wall), as well as arterial wall dimensions. Plaque score (0 to 8) was determined as the number of arterial segments (left and right common carotid, bulb, internal and external carotid arteries) containing plaque; a participant with plaque was anyone with a score ≥1. End-diastolic B-mode images of the distal right and left common carotid artery were acquired in real time, and a 1-cm segment of each far wall was measured using an automated system employing an edge detection algorithm

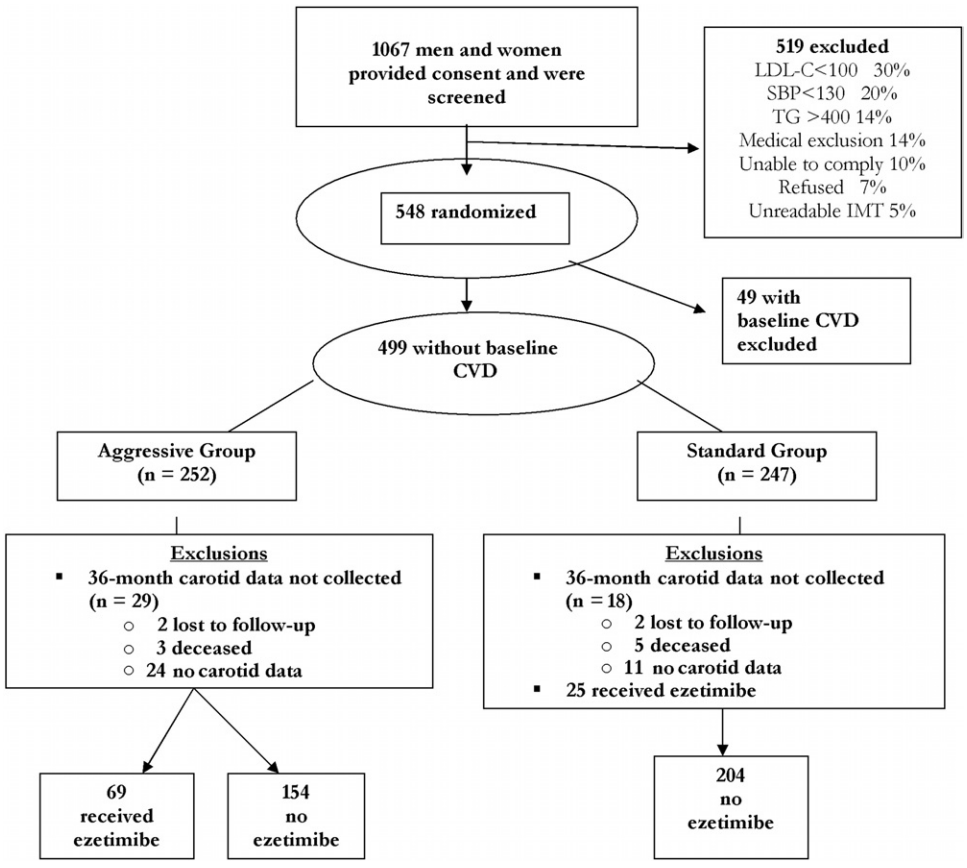

Figure 1 The SANDS Trial Participant Flow Diagram

The flow chart shows how participants were chosen and assigned to groups in the SANDS trial.
CVD = cardiovascular disease; IMT = intima-media thickness; LDL-C = low-density lipoprotein cholesterol; SBP = systolic blood pressure; TG = triglyceride.

with manual override capacity. One hundred separate dimensional measurements were obtained from the 1-cm segment and averaged to obtain mean CIMT and lumen diameter.

Data analysis. This non–pre-specified secondary analysis compared CIMT changes in those receiving: 1) aggressive lipid therapy with statin monotherapy; 2) aggressive therapy with statin plus ezetimibe; or 3) standard statin monotherapy. Of 499 participants, 47 individuals in whom CIMT measurements were not available after 36 months of treatment were excluded (Fig. 1). In addition, the 25 individuals in the standard group who received ezetimibe were excluded because their different lipid goals when compared with those of the aggressive group confounded the analysis. However, their inclusion did not significantly affect any of the comparisons shown. Including these individuals, change in CIMT in the standard group at 36 months was 0.041 mm (vs. 0.039 mm excluding them); change in LDL-C was 1.5 mg/dl (vs. 0.9 mg/dl excluding them). For all analyses, the aggressive group was divided into 2 subgroups: 1 group composed of patients receiving ezetimibe and 1 group composed of patients who were not receiving ezetimibe. Variables of interest at baseline and 36 months in each aggressive subgroup were compared with the standard group as well as with each other. The changes in these variables during the study period were tested using 2-sided F and chi-square tests. A Bonferroni adjustment was applied for multiple comparisons. To assess the effect of treatment, the changes in the carotid measures (CIMT mean and plaque score) were computed for each group and the differences in changes at 36 months across groups were compared using Bonferroni adjusted F tests. Change in CIMT was categorized into 2 possible outcomes (decreased/no change vs. increased), and logistic regression analyses adjusting for relevant variables were conducted to test for differences between the ezetimibe and nonezetimibe aggressive subgroups and between the aggressive subgroups and the standard treatment group.

Results

Altogether, 427 SANDS participants fulfilled the inclusion criteria for the secondary analysis, 204 in the standard treatment group and 223 in the aggressive group (154 who received statin alone and 69 who received statin plus

Table 1 Baseline Characteristics of the SANDS Participants

	Standard Group (n = 204)	Aggressive Group (n = 223)		p Value
		Ezetimibe (n = 69)	No Ezetimibe (n = 154)	
Age, yrs	57 (56–58)	55 (53–57)	57 (55–58)	0.20
Women	138 (68)	41 (59)	106 (69)	0.36
Diabetes therapy				
Lifestyle	23 (12)	3 (4)	13 (9)	
Oral hypoglycemic	117 (64)	40 (59)	100 (66)	0.20
Insulin	13 (7)	10 (15)	11 (7)	
Insulin plus oral	31 (17)	15 (22)	27 (18)	
Lipid medications				
Statins*	75 (37)	30 (44)	44 (29)	0.07
Fibrates*	10 (5)	5 (7)	6 (4)	0.54
Niacin*	2 (1)	0	0	0.66
Fish oil*	2 (1)	0	2 (1)	1.00
eGFR, n (S: 199, E+: 68; E−: 150)	87.7 (84–91)	93.4 (88–99)	89.5 (86–93)	0.25
Smoker	37 (18)	14 (20)	32 (21)	0.81
Aspirin (≥80 mg)	154 (68)	49 (71)	111 (72)	0.78

Values are n (%) or mean (95% confidence interval) unless otherwise indicated. Chi-square test was used for categorical variables and analysis of variance F test was used for continuous variables. The sample size for the baseline characteristics was determined by the available data on 36-month IMT mean measurement. The standard group excluded 25 patients who were on ezetimibe. *Before randomization.

CI = confidence interval; eGFR = estimated glomerular filtration rate; E+ = ezetimibe subgroup; E− = no-ezetimibe subgroup; IMT = intima-media thickness; S = standard group; SANDS = Stop Atherosclerosis in Native Diabetics Study.

ezetimibe). Median duration of ezetimibe therapy was 21 months. Baseline characteristics of these subgroups are compared in Tables 1 and 2. In Table 2, significant subgroup differences in the mean change values are indicated by superscripts in the standard-group column. The subgroups were comparable with regard to age, gender mix, diabetes therapy, aspirin use, smoking status, and renal function (Table 1). Similar infrequent use of fibrates, fish oil, and niacin was seen among all of the subgroups. The vast majority in all 3 subgroups were receiving oral hypoglycemic medication (Table 1). The ezetimibe subgroup, however, had significantly lower SBP (vs. no ezetimibe, $p = 0.007$; vs. standard, $p = 0.0004$) and diastolic BP (vs. no ezetimibe, $p = 0.02$; vs. standard, $p = 0.004$) at baseline than the other 2 subgroups.

Intervention. During the 36-month follow-up, no significant changes in body mass index or A1c levels were observed in any subgroup (Table 2). As anticipated, total cholesterol, LDL-C, and non–HDL-C were reduced substantially and to a nearly identical extent in both aggressive subgroups but not in the standard subgroup. Both LDL-C and non–HDL-C, however, averaged 10 mg/dl higher at follow-up in the aggressive subgroup using ezetimibe than in the aggressive subgroup using statin alone ($p = 0.02$), primarily reflecting higher baseline values. As designed, both LDL-C and non–HDL-C were significantly lower at 36 months in both aggressive subgroups than in the standard subgroup. Similar small increases in HDL-C occurred in all 3 subgroups, and there were greater decreases in triglycerides in the 2 aggressive subgroups. Serum C-reactive protein decreased similarly (24% to 26%) in the aggressive groups but increased by 11% in the standard subgroup ($p < 0.05$). As anticipated, BP was reduced more in both aggressive subgroups than in the standard subgroup; within the aggressive group, SBP reduction was slightly greater in the nonezetimibe than the ezetimibe subgroup. Adverse events thought to be related to lipid lowering drugs occurred in similar modest proportions (14% to 18%) in all 3 subgroups.

CIMT. Baseline and 36-month values for CIMT and plaque score, as well as changes from baseline, are detailed in Table 3. We found that CIMT progressed in the standard group and regressed in both aggressive subgroups; at 36 months, the aggressive subgroups significantly differed from the standard subgroup ($p < 0.001$). Plaque score was similar at baseline, with similar modest increases at 36 months in all 3 subgroups. Figure 2 compares the proportion of patients in the 3 subgroups who experienced an increase in CIMT >0.01 mm from baseline to 36 months versus no change or a decline in CIMT. Nearly identical proportions in the 2 aggressive subgroups (62% ezetimibe vs. 61% no ezetimibe) demonstrated no change or a decrease in CIMT during follow-up, compared with 39% in the standard subgroup ($p < 0.0001$). We found that CV events occurred in 16 individuals, 3.5%, 5.8%, and 3.3% of persons in the standard, aggressive with ezetimibe, and aggressive without ezetimibe subgroups, respectively ($p = 0.62$).

In a logistic regression analysis of the categorical change in CIMT mean over 36 months (decrease or same vs. increase) that included indicator variables for the ezetimibe and nonezetimibe subgroups—baseline age; CIMT; body mass index; and change in LDL-C, HDL-C, and SBP—the ezetimibe and nonezetimibe subgroups did not differ and were both more likely to experience a decrease in

Table 2 Baseline and 36-Month Changes in BP, Lipids, and Other Relevant Variables

	Baseline			36 Months			Mean Change at 36 Months			
	Standard Group (S)	Ezetimibe Group (E+)	No Ezetimibe Group (E−)	Standard Group (S)	Ezetimibe Group (E+)	No Ezetimibe Group (E−)	Standard Group (S)	Ezetimibe Group (E+)	No Ezetimibe Group (E−)	p Value (Mean Change)
Weight, kg	89* (86 to 91)	95 (90 to 100)	89 (86 to 92)	91 (88 to 94)	95 (90 to 99)	90 (87 to 94)	1.6 (−0.2 to 3.1)	−0.7 (−2.6 to 1.3)	1.3 (−0.8 to 3.4)	0.32
BMI, kg/m^2	33 (32 to 34)	35 (33 to 37)	33 (32 to 34)	34 (33 to 35)	35 (33 to 36)	34 (33 to 35)	0.7 (−0.1 to 1.2)	−0.2 (−0.1 to 0.5)	0.5 (−0.3 to 1.3)	0.33
Systolic BP, mm Hg	131* (129 to 133)	124 (121 to 127)	130 (127 to 132)	129*† (128 to 130)	115 (113 to 117)	117 (115 to 119)	−2.4*† (−5 to 0)	−9 (−12 to −6)	−13 (−15 to −10)	0.0001
Diastolic BP, mm Hg	75* (74 to 77)	71 (69 to 74)	75 (73 to 76)	73*† (72 to 74)	66 (64 to 68)	67 (66 to 69)	−2† (−3 to −1)	−5 (−7 to 3)	−7 (−9 to −6)	0.0001
Total C, mg/dl	183 (178 to 187)	187 (179 to 195)	181 (176 to 187)	185*† (181 to 188)	156‡ (148 to 163)	146 (142 to 151)	2*† (−3 to 7.1)	−31 (−40 to −22)	−34 (−40 to −28)	0.0001
LDL-C, mg/dl	102 (98 to 106)	108 (101 to 116)	101 (97 to 106)	103*† (100 to 105)	78‡ (72 to 84)	68 (65 to 72)	0.9*† (−3.6 to 5.4)	−31.1 (−36.7 to −23)	−32.3 (−38 to −26.6)	0.0001
HDL-C, mg/dl	46 (44 to 48)	46 (42 to 49)	46 (44 to 48)	49 (47 to 50)	48 (46 to 51)	49 (46 to 51)	2.7 (1.3 to 4.2)	2.7 (0.7 to 4.7)	2.5 (1 to 4.1)	0.987
Total C/HDL-C, mg/dl	4.2 (4.0 to 4.3)	4.4 (4.1 to 4.7)	4.2 (4 to 4.3)	4.0*† (3.9 to 4.1)	3.4 (3.1 to 3.6)	3.2 (3.0 to 3.4)	−0.2*† (−0.3 to −0.0.1)	−1.0 (−1.3 to −0.7)	−0.9 (−1.1 to −0.7)	0.0001
Non-HDL-C, mg/dl	137 (133 to 141)	141 (133 to 150)	135 (130 to 140)	136*† (133 to 139)	107 (100 to 115)	98 (93 to 102)	−0.7*† (−5.7 to 4.3)	−34.0 (−43 to −25)	−36.6 (−43 to −30)	0.0001
Triglycerides mg/dl	164 (140 to 171)	154 (139 to 171)	159 (148 to 171)	157*† (150 to 165)	136 (123 to 150)	138 (130 to 150)	−6% (−11 to −0.0)	−12% (−20 to −3)	−15% (−21 to −8%)	0.11
A1c, %	7.9 (7.6 to 8.2)	8.3 (7.8 to 8.8)	8.1 (7.8 to 8.4)	8.0* (7.7 to 8.2)	8.7 (8.2 to 9.3)	8.1 (7.7 to 8.4)	0.4 (−0.3 to 4)	0.4 (−0.1 to 0.9)	−0.04 (−0.4 to 0.3)	0.38
CRP, mg/dl	2.80 (2.4 to 3.3)	3.25 (2.5 to 4.3)	2.58 (2.1 to 3.2)	3.3† (2.8 to 3.9)	2.96 (2.1 to 4.2)	1.99 (1.6 to 2.5)	+11%† (−5 to 26)	−24% (−47 to −1%)	−26% (−47 to −4%)	0.008

Values are mean (95% confidence interval). The p values were determined using the ANOVA F test. Triglycerides and CRP were log-transformed. The means presented are exponential (mean) of the logarithmic variables. The differences of the 2 logarithmic variables indicate mean (%) changes at 36 months for each group. Sample size for baseline and 36 months may not be equal. Therefore, the mean changes apply to the sample where both measures exist. *Significant difference between S and E+. †Significant difference between S and E− (based on logarithm of CRP). ‡Significant difference between E+ and E−. 36-month lipid variables are based on the average of 24-, 30-, and 36-month observations. p values are based on the analysis of variance of the mean change measures comparing the standard group to E+ and E− groups. A Bonferroni adjustment was made to the significantly different pairs.

BMI = body mass index; BP = blood pressure; C = cholesterol; CRP = C-reactive protein; HDL = high-density lipoprotein; LDL = low-density lipoprotein; other abbreviations as in Table 1.

Table 3 Baseline and Follow-Up Carotid Measures

	Standard Group (n = 204)	Aggressive Group (n = 223)			Bonferroni Adjusted		
	Mean (95% CI)	Ezetimibe Group (E+) Mean (95% CI)	No Ezetimibe Group (E−) Mean (95% CI)	F Test (p Value)	Group Difference (p Value) E+ vs. E−	Group Difference (p Value) E+ vs. S	Group Difference (p Value) E− vs. S
CIMT, mm							
Baseline	0.794 (0.77 to 0.82)	0.819 (0.77 to 0.86)	0.813 (0.78 to 0.84)	0.46			
18 months	0.803 (0.78 to 0.82)	0.815 (0.78 to 0.86)	0.810 (0.78 to 0.84)	0.84			
36 months	0.833 (0.81 to 0.86)	0.794 (0.75 to 0.84)	0.801 (0.77 to 0.83)	0.17			
Mean change, 18 months	0.009 (−0.01 to 0.03)	−0.006 (−0.03 to 0.02)	−0.005 (0.02 to 0.014)	0.48			
Mean change, 36 months	0.039 (0.02 to 0.06)	−0.025 (−0.05 to 0.003)	−0.012 (0.03 to 0.008)	0.0001	0.01 (0.999)	0.06 (0.001)	0.05 (0.001)
Plaque score							
Baseline	1.83 (1.6 to 2.1)	1.93 (1.5 to 2.3)	1.88 (1.6 to 2.1)	0.89			
18 months	2.02 (1.8 to 2.2)	2.10 (1.7 to 2.5)	2.11 (1.9 to 2.4)	0.84			
36 months	2.33 (2.1 to 2.6)	2.35 (1.9 to 2.8)	2.49 (2.2 to 2.8)	0.65			
Mean change, 18 months	0.18 (0.04 to 0.3)	0.17 (−0.04 to 0.4)	0.21 (0.06 to 0.4)	0.94			
Mean change, 36 months	0.51 (0.4 to 0.7)	0.42 (0.1 to 0.7)	0.61 (0.4 to 0.8)	0.50			

CIMT = carotid artery intima-media thickness; other abbreviations as in Table 1.

CIMT than the standard subgroup (ezetimibe vs. standard, odds ratio [OR]: 2.30, p = 0.009; no ezetimibe vs. standard, OR: 2.07, p = 0.003). In this model, higher baseline CIMT (p < 0.0001) and changes in LDL-C (p = 0.06) were correlated with a greater reduction in CIMT. Baseline SBP and change in SBP did not correlate with change in CIMT.

Discussion

In the SANDS cohort, which was composed of persons with type 2 diabetes with baseline LDL-C ≥100 mg/dl, approximately one-third of those targeted to an aggressive LDL-C goal of ≤70 mg/dl and non–HDL-C ≤100 mg/dl required ezetimibe in addition to statins to reach these goals. Similar reductions in LDL-C and non–HDL-C were accompanied by a similar regression in CIMT over 36 months in the aggressive target subgroups (−0.025 mm in ezetimibe plus statin vs. −0.012 mm in nonezetimibe), whereas CIMT increased (+0.039 mm) in the group randomized to standard targets. In a multivariate model, greater reduction in LDL-C and non–HDL-C, higher baseline CIMT, and younger age correlated with a greater decrease in CIMT, whereas treatment with ezetimibe versus without ezetimibe made no independent contribution. Thus, comparable LDL-C and non–HDL-C lowering accomplished with statins plus ezetimibe versus statins alone resulted in similar benefit on CIMT. There were no serious adverse events related to lipid drugs in the trial. There were 5 cases of cancer: 3 in the nonezetimibe subgroup and 2 in the standard group.

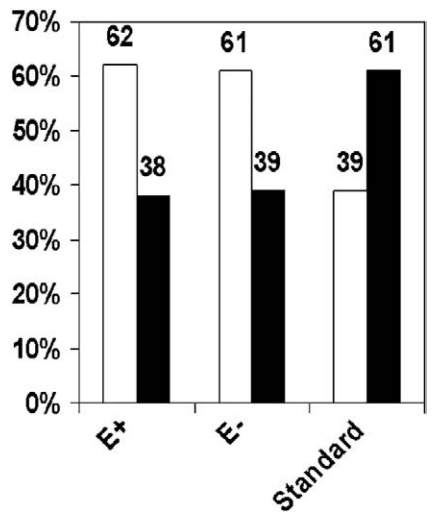

Figure 2 Categorical Change in CIMT in SANDS Subgroups

Numbers represent percentages of participants who experienced a decrease or no change **(open bars)** in common carotid artery intima-media thickness (CIMT) >0.01 mm versus an increase **(solid bars)**. The majority of both aggressive subgroups experienced a decline or no change in IMT, whereas the majority of the standard group showed an increase (p < 0.0001). E+ = statin plus ezetimibe; E− = statin alone.

Since its introduction into clinical practice in 2002, ezetimibe has become the primary adjunct to statins in reducing elevated LDL-C (1,2). Similar to other LDL-C lowering drugs, its approval by the U.S. Food and Drug Administration was based upon its ability to reduce LDL-C (1). Only 1 completed clinical trial (the SEAS [Simvastatin and Ezetimibe in Aortic Stenosis] trial) (13) has examined the ability of ezetimibe combined with statins to reduce CV events; it showed a 22% reduction compared with placebo treatment.

In the ENHANCE trial (3), of 720 patients with familial hypercholesterolemia, no statistically significant difference in the primary end point of mean increase in CIMT over 24 months was seen between the statin alone and the statin plus ezetimibe arms (p = 0.29), despite a 58% versus 41% reduction in LDL-C with combination therapy versus statin monotherapy. Despite recognized methodologic limita-

tions, including the high baseline LDL-C levels of participants, high prevalence of prior statin therapy, lower than expected baseline CIMT, short follow-up, and lack of statistically significant primary or secondary outcomes, the ENHANCE study has stimulated controversy and concern regarding the clinical utility of ezetimibe (3). In addition, the report of increased CV morbidity and mortality in patients receiving the cholesterol ester transport protein inhibitor torcetrapib plus high-dose statin compared with CV morbidity and mortality of those receiving statin alone, despite marked increases in HDL-C in the former group, has raised concern that achieving apparently beneficial changes in serum lipid levels may not necessarily improve clinical outcomes (14). The ENHANCE findings have further fueled this controversy.

In contrast to the ENHANCE trial, the findings in the current secondary analysis of the SANDS trial suggest that the combination of ezetimibe plus statin, despite higher final level of LDL-C, has essentially an identical beneficial effect on CIMT as statin alone, for a similar change in LDL-C and non–HDL-C. Although the SANDS trial was not a randomized comparison of these therapies, several strengths of the present analysis should be noted. As contrasted with the markedly elevated baseline LDL-C levels of 319 mg/dl in ENHANCE participants, the mild baseline elevation of LDL-C levels in the SANDS trial are more representative of the majority of patients requiring LDL-C lowering drugs. Additionally, the mean baseline CIMT of 0.81 mm in SANDS participants was substantially greater than the value of 0.69 mm in ENHANCE participants, providing perhaps more opportunity to detect regression in CIMT. The CASHMERE (Carotid Atorvastatin Study In Hyperlipidemic Post-Menopausal Women: A Randomized Evaluation of Atorvastatin, Versus Placebo) study (15), another study where baseline CIMTs were low, also showed no effect of statin on CIMT. Another difference from the ENHANCE trial is our sequential use of ezetimibe after high-dose statin therapy failed to adequately reduce LDL-C or was limited by side effects. Indeed, the LDL-C reductions in the aggressive subgroups with or without ezetimibe were nearly identical, as were the declines in CIMT. Mean LDL-C and non–HDL-C were slightly higher at both baseline and follow-up in the ezetimibe subgroup, although the change in LDL-C was nearly identical to the subgroup receiving statin alone. The higher baseline LDL-C and non–HDL-C levels in the subgroup requiring ezetimibe, although not statistically significant, might be anticipated; nevertheless, similar improvements in CIMT were observed in the 2 aggressive subgroups.

Study limitations. Certain limitations of the present analysis must be recognized. Our sample size was modest and was not powered to detect a difference in clinical events between treatment groups. Thus, the primary outcome was CIMT, an index of atherosclerotic progression that has been used in multiple modest sized trials of lipid-altering agents (16,17). Second, this was not a randomized comparison of statin plus ezetimibe versus statin alone; thus, there were differences in characteristics between these subgroups. We found that SBP averaged 6 mm Hg lower in the ezetimibe subgroup at baseline, and the decline in SBP at 36 months was 4 mm Hg less in this group than in the aggressive subgroup not receiving this drug; similar trends were observed for diastolic BP. Although this difference may have biased the outcomes against the ezetimibe subgroup, SBP change did not significantly influence CIMT in the main SANDS trial or in our multivariate analysis. Finally, the SANDS trial was limited to American Indians with diabetes; similar data in more diverse populations are needed.

Conclusions

The findings from this secondary analysis of the SANDS trial suggest that for a similar extent of LDL-C and non–HDL-C lowering to respective targets of ≤70 and ≤100 mg/dl, a nearly identical regression in carotid IMT occurs in patients with type 2 diabetes who achieve similar reductions in these lipid levels from a statin alone versus statin plus ezetimibe; in contrast, CIMT increased in patients titrated to a conventional LDL-C target of ≤100 mg/dl. Whether addition of ezetimibe to aggressive statin therapy will translate into lower CV event rates in populations without prior CV events must await the results of ongoing trials. In the interim, ezetimibe remains a viable therapeutic option for patients who fail to reach their LDL-C target on a statin alone.

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