

Effect of Lower Targets for Blood Pressure and LDL Cholesterol on Atherosclerosis in Diabetes

The SANDS Randomized Trial

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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 diabetes.¹⁻³ The increased diabetes-associated CVD risk is due in large part to higher prevalences of other major CVD risk factors, such as dyslipidemia and hypertension.^{4,5} Prevention of CVD and control of its associated risk factors in individuals with diabetes have be-

For editorial comment see p 1718.

Context Individuals with diabetes are at increased risk for cardiovascular disease (CVD), but more aggressive targets for risk factor control have not been tested.

Objective To compare progression of subclinical atherosclerosis in adults with type 2 diabetes treated to reach aggressive targets of low-density lipoprotein cholesterol (LDL-C) of 70 mg/dL or lower and systolic blood pressure (SBP) of 115 mm Hg or lower vs standard targets of LDL-C of 100 mg/dL or lower and SBP of 130 mm Hg or lower.

Design, Setting, and Participants A randomized, open-label, blinded-to-end point, 3-year trial from April 2003-July 2007 at 4 clinical centers in Oklahoma, Arizona, and South Dakota. Participants were 499 American Indian men and women aged 40 years or older with type 2 diabetes and no prior CVD events.

Interventions Participants were randomized to aggressive (n=252) vs standard (n=247) treatment groups with stepped treatment algorithms defined for both.

Main Outcome Measures Primary end point was progression of atherosclerosis measured by common carotid artery intimal medial thickness (IMT). Secondary end points were other carotid and cardiac ultrasonographic measures and clinical events.

Results Mean target LDL-C and SBP levels for both groups were reached and maintained. Mean (95% confidence interval) levels for LDL-C in the last 12 months were 72 (69-75) and 104 (101-106) mg/dL and SBP levels were 117 (115-118) and 129 (128-130) mm Hg in the aggressive vs standard groups, respectively. Compared with baseline, IMT regressed in the aggressive group and progressed in the standard group (-0.012 mm vs 0.038 mm; $P < .001$); carotid arterial cross-sectional area also regressed (-0.02 mm² vs 1.05 mm²; $P < .001$); and there was greater decrease in left ventricular mass index (-2.4 g/m^{2.7} vs -1.2 g/m^{2.7}; $P = .03$) in the aggressive group. Rates of adverse events (38.5% and 26.7%; $P = .005$) and serious adverse events (n=4 vs 1; $P = .18$) related to blood pressure medications were higher in the aggressive group. Clinical CVD events (1.6/100 and 1.5/100 person-years; $P = .87$) did not differ significantly between groups.

Conclusions Reducing LDL-C and SBP to lower targets resulted in regression of carotid IMT and greater decrease in left ventricular mass in individuals with type 2 diabetes. Clinical events were lower than expected and did not differ significantly between groups. Further follow-up is needed to determine whether these improvements will result in lower long-term CVD event rates and costs and favorable risk-benefit outcomes.

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come a priority.¹⁻⁵ Expert panels have defined targets for low-density lipoprotein cholesterol (LDL-C)⁶ and blood pressure (BP)⁷ in patients with diabetes based on epidemiological and clinical trial data. However, a number of secondary prevention studies in high-risk patients have suggested that LDL-C lowering beneath the current target, generally to lower than 70 mg/dL, may be associated with improved outcomes in individuals with diabetes.⁸⁻¹⁸ (To convert cholesterol values to mmol/L, multiply by 0.0259). Several studies using statin therapy in high-risk patients with diabetes also have suggested that further reduction in CVD events may be achieved in individuals who are at or below current LDL-C targets.¹⁸⁻²⁵ In addition, antihypertensive treatment to levels below recommended goals (systolic blood pressure [SBP] < 130 mm Hg) may delay progression of microalbuminuria to clinical proteinuria in diabetes,²⁶ but the utility of this target in preventing CVD has not been assessed. Because no studies have specifically evaluated the benefits and risks of aggressive treatment targets for both LDL-C and BP in individuals with diabetes, the optimal treatment targets remain elusive.

A large body of epidemiologic data in American Indians, a population with high prevalence of diabetes and diabetes-related CVD, documents strong relations between LDL-C and BP levels and CVD events.^{27,28} These data suggest that lowering LDL-C and BP beyond current targets could help slow or reverse CVD progression in patients with diabetes. Thus, the present study (Stop Atherosclerosis in Native Diabetics Study [SANDS]), was undertaken to compare progression of subclinical atherosclerotic disease, as evaluated by carotid ultrasound, in American Indians with type 2 diabetes, aged 40 years or older, randomly assigned to either aggressive targets of LDL-C of 70 mg/dL or lower plus SBP of 115 mm Hg or lower or current standard targets of LDL-C of 100 mg/dL or lower and SBP of 130 mm Hg or lower. Impact on cardiac structure and function was also evaluated.

METHODS

Details of this study design and methods have been previously published.²⁹ All participants provided written informed consent and the study was approved by all participating institutional review boards, the National Institutes of Health, and all participating American Indian communities.

Recruitment

Participants were 548 men and women with type 2 diabetes, aged 40 years or older, enrolled between May 2003 and July 2004 at 4 clinical centers in the United States: southwestern Oklahoma; Phoenix, Arizona; northeastern Arizona; and South Dakota. All participants were American Indians as defined by Indian Health Service criteria.³⁰

The participants were randomized to the aggressive (n=276) or standard treatment group (n=272) using the urn method stratified by clinical center and sex.

Eligibility criteria included documented type 2 diabetes,^{31,32} plus LDL-C of at least 100 mg/dL and SBP greater than 130 mm Hg within the previous 12 months.

Major exclusion criteria were characteristics that might preclude trial completion or confound the outcomes. These included New York Heart Association class III or IV heart failure, SBP greater than 180 mm Hg, liver transaminase levels more than twice the upper limit of normal, or diagnosis of primary hyperlipidemia or hypercholesterolemia due to hyperthyroidism or nephrotic syndrome.

Lipid and BP Interventions

Study personnel performed BP and lipid management for both groups, with equal frequency of clinic visits. Indian Health Service clinicians provided all other medical care, including diabetes management, dietary, exercise, and smoking cessation counseling, and were not involved in the study. Targets for each participant's SBP and LDL-C were entered into the medical record to deter changes in lipid and BP medications.

The algorithm for hypertension management was based on the Sixth Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure.⁷ The goals of therapy were SBP of 115 mm Hg or lower and 130 mm Hg or lower in the aggressive and standard groups, respectively. Secondary goals were diastolic BP (DBP) of 75 mm Hg or lower and 85 mm Hg or lower, respectively. Step 1 drugs were angiotensin-converting enzyme (ACE) inhibitors or angiotensin II receptor blockers (ARB), in case of intolerance to ACE inhibitors. Step 2 was use of hydrochlorothiazide. Steps 3 to 5 added calcium channel blockers, β -blockers, and then α -blockers and other vasodilators. Treatment for DBP was at the physician's discretion once SBP target was reached.

The algorithm for achieving lipid goals was based on recommendations of the National Cholesterol Education Program Adult Treatment Panel III.^{6,33} Goals for LDL-C were 70 mg/dL or lower and 100 mg/dL or lower and non-high-density lipoprotein cholesterol (non-HDL-C) goals were 100 mg/dL or lower and 130 mg/dL or lower in the aggressive and standard groups, respectively. If lifestyle modification was unsuccessful, use of a statin drug was initiated. If the LDL-C goal was not reached with statin use, combination therapy with ezetimibe was initiated. In addition, the non-HDL-C goals were addressed using fish oil, fenofibrate, or niacin. The field clinicians used the algorithms for both interventions as guides to assist in achievement of targets, but changes were made at physician discretion in the context of the participant's prior medication experiences or concurrent medical condition. Details of the intervention procedures and targets have been published.²⁹

Baseline and Follow-up Visits

All procedures followed standardized methods performed by trained, certified clinicians. Field clinicians who delivered the intervention were not blinded; however, research assistants, ultrasound technicians and readers, and

all core laboratory personnel were blinded to study assignment. The baseline visit included a physical examination, electrocardiogram, carotid artery ultrasound, echocardiogram, and collection of demographic data, health history, and current medication use. Height, weight, waist circumference, and seated BP were measured, and fasting blood samples were collected to measure chemistry panel, lipoprotein profile, glucose, hemoglobin A_{1c}, C-reactive protein (CRP), and creatinine, and urine samples were analyzed for urinary albumin and creatinine.²⁹

Participants were observed 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. At follow-up visits in both groups after 1 month, and every 3 months until 36 months, seated and standing BP levels were determined and a lipid profile was obtained from capillary blood using a lipid profile analyzer (Cholestech Corp, Hayward, California).³⁴ Recorded BP levels were the mean of the second and third of 3 consecutive readings taken after 5 minutes of rest. Orthostatic hypotension was defined as an SBP decline of greater than 20 mm Hg after 2 minutes of standing and with symptoms lasting longer than 1 minute. Medications were adjusted to meet treatment goals, adverse effects were assessed, and information on health outcomes was obtained. Fasting blood and urine samples were obtained at 36 months 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.

Outcomes Ascertainment

At the baseline, 18-, and 36-month visits, carotid and cardiac ultrasound studies were performed following standardized protocols³⁵ by centrally trained sonographers, and interpreted at a core reading center by physician readers blinded to treatment assignment. For carotid ultrasound studies, B-mode

imaging from multiple angles was performed to determine the presence and location of plaque (focal protrusion of the vessel $\geq 50\%$ greater than the surrounding wall), as well as arterial wall dimensions. Plaque score (0-8) 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 of at least 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 with an automated system using an edge detection algorithm with manual override capacity. One hundred separate dimensional measurements were obtained from the 1-cm segment and averaged to obtain mean intimal medial thickness (IMT) and lumen diameter. Carotid arterial cross-sectional area was calculated as $3.1416 \left(\left[\frac{\text{diameter}}{2} + \text{IMT} \right]^2 - \left[\frac{\text{diameter}}{2} \right]^2 \right)$ using end-diastolic IMT and lumen diameter measurements.³⁶

Echocardiographic measures included assessment of left ventricular (LV) structure and function.^{37,38} Methods for ascertaining and classifying clinical outcomes have been previously described.²⁹ Medical records for all hospitalizations and outpatient coronary revascularization procedures were reviewed centrally by a panel of 6 physician adjudicators blinded to treatment assignment. The composite CVD end point included fatal and nonfatal CVD events, defined as fatal CHD or stroke, nonfatal myocardial infarction (MI) or stroke, unstable angina, coronary revascularization, and carotid arterial revascularization.

Data Analysis

Specific details on sample size and power calculations are published elsewhere.²⁹ In brief, the planned total sample size was 498. With this sample size, there was 80% power to detect a difference of 0.05 mm between the 2 groups in the change from baseline to 36 months in common carotid artery

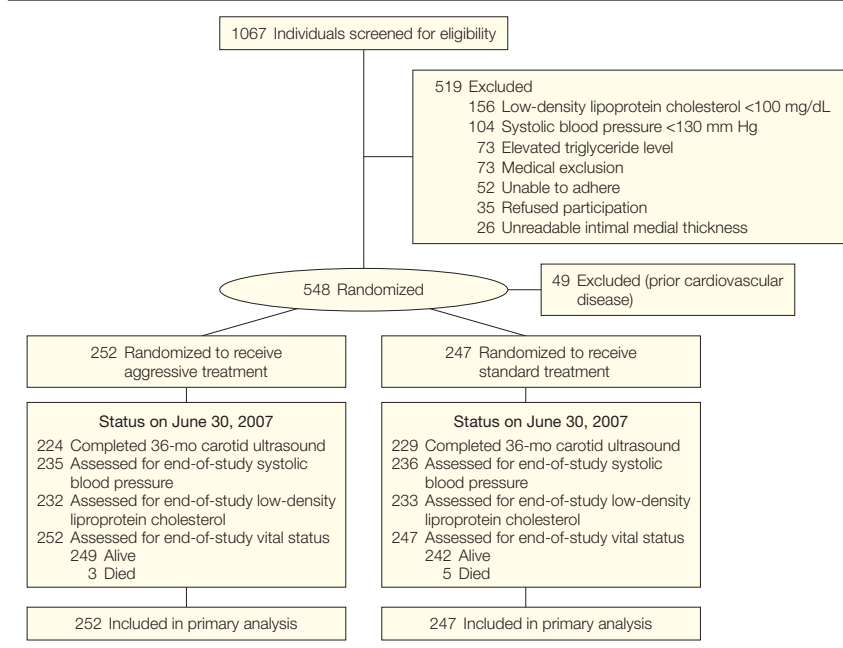
IMT using a 2-sided *t* test and with a type I error of .05. The mean group difference of 0.05 mm was considered clinically significant based on previous trial publications.³⁹ The sample size calculations incorporated a 10% dropout rate and a 15% healthy volunteer effect. Given this sample size, there is 80% power to detect a difference of 1.36 mm² in carotid arterial cross-sectional area and 2.33/m^{2.7} in left ventricular mass index (LVMI) between the 2 groups. Given the expected rates of CVD events,²⁷ this study was not intended to compare incidence of clinical events between groups.

The primary end point that determined the sample size was the change in common carotid artery IMT. All major treatment comparisons between the 2 randomized groups in this trial were performed according to the principle of intention-to-treat, that is, regardless of compliance with assigned treatment. The primary hypothesis was that compared with standard goals, achieving lower targets for LDL-C and SBP will retard progression of atherosclerosis, as measured by change in carotid IMT. Changes in other carotid and echocardiographic measures and clinical events were defined as secondary end points. However, in developing an analysis plan at the beginning of the trial, the worst-rank score method of Wei and Lachin⁴⁰ was proposed to account for CVD events that might be informative and not occurring at random. With this method, the ranked scores of the IMT change are used for participants with no CVD events and interpreted scores are created for participants who had an informative event. Participants with a CVD event were assigned a worse rank score than participants without an event; fatal events were ranked worse than nonfatal ones, and the earlier an event, the worse the rank. In the presence of informatively missing observations, as in this study, the worst-score analysis provides an unbiased test against a restricted alternative. However, because CVD events were few and did not statistically differ between the 2 groups, the ranked method yielded identical conclusions to the analyses using

only IMT as the primary outcome. Therefore, for clarity we present changes in IMT as a continuous variable. Results for ranked analyses of IMT and arterial cross-sectional area are shown in the Table 4 footnote. All multivariate models were adjusted for baseline measure, clinical center, and baseline SBP. Predefined secondary end points included carotid arterial cross-sectional area, plaque score, LVMI, ejection fraction, and CRP; and safety measures were also examined. For participants missing the 36-month carotid measures ($n=45$), changes were imputed conservatively from the 18-month or baseline value using the mean change in the standard group. For the echocardiographic measures, 46 participants missed the 36-month measure because of an equipment failure; these were considered missing completely at random and were eliminated from the analyses. For the other participants ($n=44$), data were imputed using the mean change in the standard group. All tests performed were 2-sided, and a P value of less than .05 was considered significant. To control for type 1 error in multiple comparisons, the Bonferroni-adjusted significance level was used to assess statistical significances between the 2 groups for the 7 ultrasound outcomes. Additional intention-to-treat analyses compared changes in IMT and LVMI between the treatment groups, stratified by predefined baseline characteristics, including age, sex, body mass index (BMI, calculated as weight in kilograms divided by height in meters squared), SBP, LDL-C, non-HDL-C, CRP, and hemoglobin A_{1c}, and tests for interactions between baseline characteristics and treatment were performed.

Secondary analyses explored the time of treatment effect on change in IMT or LVMI using linear regression models that included proportion of months at SBP or LDL-C target as independent variables; reaching target was defined as SBP from 124 to 136 mm Hg and LDL-C from 94 to 106 mg/dL for the standard group and lower than 117 mm Hg and lower than 73mg/dL for the aggressive group; these ranges were based on known measurement variances and val-

Figure 1. Participant Flow in SANDS



ues that would have triggered medication adjustment. Sensitivity analyses were performed to compare participants in the aggressive group who maintained either the SBP goal of 117 mm Hg or lower or the LDL-C goal of lower than 73 mg/dL during the last 12 months of follow-up with participants in the standard group, and to compare participants in the aggressive group who maintained goal levels to participants in the upper quartile with SBP of 121 mm Hg or greater and LDL-C of 90 mg/dL or greater at the end of the study. Finally, change in IMT and LVMI variables were categorized into 3 groups in terms of the type of change in the outcome measure, and ordered logit analyses were conducted to test the effect of LDL-C and SBP changes on the probability of observing no change (defined as no change within the variance of the measurement), a decrease, or an increase, by controlling for baseline characteristics (ie, IMT, LVMI, age, BMI, sex, and clinical center). All analyses were performed using Intercooled Stata 9.2 (StataCorp LP, College Station, Texas), or SAS version 9.1 (SAS Institute, Inc, Cary, North Carolina).

RESULTS

Recruitment and Baseline Characteristics

Between April 2003 and July 2004, 548 men and women aged 40 years and older with type 2 diabetes, were randomized (FIGURE 1). Four months after initiation of recruitment, the steering committee voted (with concurrence of the data and safety monitoring board) to change the LDL-C goal to 70 mg/dL or lower for participants with baseline CVD ($n=49$) who had been already randomized into the study to comply with the newly released Adult Treatment Panel III recommendations.³³ Recruitment was limited thereafter to individuals who had not experienced a prior CVD event, and recruitment continued until the prespecified sample size was reached. Thus, 499 participants without baseline CVD were included in the analyses (Figure 1). After 36 months, 8 participants died. Physical examination, and lipid and blood measurements were obtained on 94%, and carotid ultrasound data were collected on 91% of those alive. Only 4 were lost to follow-up, but vital status and CVD events were known for all of these participants.

Baseline characteristics of the participants are shown in TABLE 1 and TABLE 2.²⁹ Mean age was 56 years, 66% were women, mean BMI was 33, and 21% were current smokers. Upon entry, 38% of participants were taking lipid-lowering medication and 73% were undergoing antihypertensive therapy. Mean baseline LDL-C and SBP were 104 mg/dL and 131 mm Hg;

upon entry, 8 participants had an LDL-C level of 70 mg/dL or lower and 23 had SBP level of 115 mm Hg or lower. The majority were taking some form of hypoglycemic therapy; mean hemoglobin A_{1c} was 8.1%, and mean duration of diabetes was 8.7 years in the standard group and 9.2 years in the aggressive treatment group.

The 2 treatment groups were well matched with no meaningful differences in baseline characteristics except that mean clinic SBP was 5 mm Hg lower in the group randomized to aggressive therapy. No statistically significant differences were observed in any carotid ultrasound or echocardiographic parameter.

Intervention

The aggressive treatment group achieved the mean LDL-C goal of 70 mg/dL or lower and the mean SBP goal of 115 mm Hg or lower, and the group means were main-

Table 1. Baseline Characteristics of the SANDS Participants (N = 499)^a

	No. (Mean) [95% Confidence Interval]		P Value
	Aggressive (n = 252)	Standard (n = 247)	
Age, mean (range), y	55 (54-57)	57 (56-58)	.05
Women, %	167 (66) [60-72]	160 (65) [59-71]	.73
Diabetes therapy, %			
Lifestyle ^{b,c}	27 (11) [7-15]	34 (14) [10-18]	.33
Oral hypoglycemics	206 (82) [77-87]	180 (73) [67-78]	.02
Insulin ^c	70 (29) [23-34]	53 (22) [17-27]	.10
Insulin plus hypoglycemics	230 (91) [88-95]	196 (79) [74-84]	.002
Estimated glomerular filtration rate, mL/min ^c	246 (91) [88-94]	242 (88) [85-91]	.21
Smoker, %	54 (22) [16-27]	48 (20) [15-24]	.58
Aspirin use ≥80 mg/d, %	177 (70) [65-76]	168 (69) [63-75]	.74

^aTwenty-three baseline variables are compared and presented in Tables 1 and 2.

^bReceived counseling for lifestyle but not receiving medication.

^cBecause of missing cases in the aggressive and standard treatment groups: n=245 and 244 for lifestyle; n=245 and 241 for insulin; and n=246 and 242 for estimated glomerular filtration rate, respectively.

Table 2. Differences in Mean Changes From Baseline to 36 Months, Aggressive vs Standard Groups^a

	Mean (95% Confidence Interval)							P Value for Difference
	Baseline		36 mo ^b		Change at 36 mo			
	Aggressive	Standard	Aggressive	Standard	Aggressive	Standard	Difference	
Weight, kg	90 (88 to 93)	90 (88 to 92)	91 (89 to 94)	91 (88 to 93)	1.0 (-0.8 to 2.2)	1.0 (-0.3 to 2.3)	0.3 (-1.7 to 2.3)	.83
BMI ^c	34 (33 to 34)	33 (32 to 34)	34 (33 to 35)	34 (33 to 34.4)	0.3 (-0.3 to 0.9)	0.4 (-0.1 to 0.9)	0.1 (-0.6 to 0.9)	.77
Waist, cm	110 (108 to 112)	110 (108 to 112)	111 (109 to 113)	110 (108 to 112)	0.2 (-1.0 to 1.6)	0.6 (-0.7 to 2.0)	0.4 (-1.5 to 2.3)	.66
CRP mg/L ^d	2.7 (2.3 to 3.1)	2.8 (2.4 to 3.3)	2.2 (1.9 to 2.7)	3.3 (2.8 to 3.8)	-0.7 (11) ^e	0.9 (9) ^e	1.6 (-0.4 to 3.6) ^e	.12 ^e
DBP, mm Hg	74 (73 to 76)	76 (75 to 78)	67 (66 to 68)	73 (72 to 74)	-7 (-8 to -6)	-3 (-4 to -1)	4.0 (2.5 to 5.5) ^f	<.001
SBP, mm Hg	128 (126 to 130) ^g	133 (131 to 135) ^g	117 (115 to 118)	129 (128 to 130)	-11 (-13 to -9)	-3 (-5 to -1)	8 (6 to 12) ^f	<.001
Glucose, mg/dL	159 (151 to 168)	156 (147 to 166)	169 (158 to 179)	169 (158 to 180)	11 (1 to 23)	14 (1 to 28)	4 (-14 to 22)	.68
HDL-C, mg/dL	46 (44 to 48)	46 (44 to 47)	48 (47 to 50)	48 (47 to 50)	3.0 (1.4 to 3.8)	3.0 (1.2 to 3.9)	0.1 (-1.9 to 1.8)	.94
LDL-C, mg/dL	104 (100 to 108)	104 (100 to 108)	72 (69 to 75)	104 (101 to 106)	-31 (-35 to -26)	1 (-3 to 6)	32 (26 to 38) ^f	<.001
Non-HDL-C, mg/dL	138 (134 to 142)	140 (136 to 144)	102 (98 to 106)	138 (135 to 141)	-35 (-40 to -30)	0.2 (-4.4 to 4.9)	35 (28 to -42) ^f	<.001
TC, mg/dL	184 (180 to 188)	185 (181 to 190)	150 (146 to 154)	187 (183 to 190)	-32 (-37 to -27)	3 (-2 to 8)	35 (27 to 42) ^f	<.001
TC/HDL-C, mg/dL	4.2 (4.1 to 4.4)	4.2 (4.1 to 4.4)	3.3 (3.1 to 3.4)	4.0 (3.9 to 4.2)	-1.0 (-1.1 to -0.8)	-0.1 (-0.3 to 0.0)	0.8 (0.6 to 1.0) ^f	<.001
Triglycerides, mg/dL ^d	158 (149 to 167)	168 (159 to 177)	137 (130 to 144)	160 (153 to 168)	-26 (78) ^e	-12 (84) ^e	14 (-3 to 29) ^{ef}	.06 ^e
Hemoglobin A _{1c}	8.2 (7.9 to 8.4)	7.9 (7.6 to 8.1)	8.3 (8.0 to 8.6)	8.2 (7.8 to 8.5)	0.1 (-0.2 to 0.4)	0.3 (-0.1 to 0.6)	0.2 (-0.3 to 0.6)	.45

Abbreviations: BMI, body mass index; CRP, C-reactive protein; DBP, diastolic blood pressure; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; SBP, systolic blood pressure; TC, total cholesterol.

SI conversions: for CRP to nmol/L, multiply by 9.524; for glucose to mmol/L, multiply by 0.0555; for HDL-C, LDL-C, and TC to mmol/L multiply by 0.0259; for hemoglobin A_{1c} to proportion of total hemoglobin, multiply by 0.01; and for triglycerides to mmol/L, multiply by 0.0113.

^aTwenty-three baseline variables are compared and presented in Tables 1 and 2.

^bN for the 36-mo lipids variables was 458 and the mean values were based on the average of 24-, 30- and 36-month observations.

^cBMI is calculated as weight in kilograms divided by height in meters squared.

^dGeometric mean (95% confidence interval).

^eP value is based on arithmetic mean.

^fSignificant mean difference at 36 mo: DBP, LDL-C, non-HDL-C, SBP, TC, TC/LDL-C, and triglycerides (P < .001).

^gSignificant differences at baseline for SBP, P = .003.

tained until the end of the study (FIGURE 2). Sixty-eight percent of the participants reached the target LDL-C (defined as ≤ 73 mg/dL for $> 50\%$ of the visits, and 46% of participants for $> 75\%$ of visits). For SBP, 67% and 43% achieved target of 117 mm Hg at more than 50% and more than 75% of the visits. Comparable mean decreases were observed in non-HDL-C and DBP in the aggressive treatment group (Table 2) at the end of the study. Group means for LDL-C and SBP (100 mg/dL and 130 mm Hg) were also maintained in the standard treatment group (Figure 2). During the last 12 months, the difference in LDL-C between the groups was 32 mg/dL and for SBP was 13 mm Hg (Table 2). Mean weight, BMI, waist circumference, and fasting glucose level remained unchanged in both groups. C-reactive protein decreased in the aggressive treatment group and increased in the standard treatment group, but the difference was not statistically significant (Table 2).

To achieve the treatment goals in both groups, the mean (SD) numbers of lipid-lowering and antihypertensive drugs used in the aggressive and standard treatment groups were 1.5 (0.75) vs 1.2 (0.73) and 2.3 (1.3) vs 1.6 (1.2), respectively. There were no serious adverse events related to lipid drugs, and no difference was ob-

served between groups in adverse events related to lipid-lowering drugs ($P = .22$; TABLE 3). More adverse events related to BP drugs occurred in the aggressive group (27% vs 15%; $P = .002$). Orthostatic hypotension occurred in 2 participants in each group. One serious adverse event judged to be possibly related to the BP interventions occurred in the standard group (hypotension) and 4 in the aggressive group (2 hypotension and 2 hyperkalemia). All recovered after reduction or withdrawal of medication.

Outcomes

Mean carotid IMT progressed slightly in the standard treatment group and regressed in the aggressive group (TABLE 4). At 36 months, there was a significant difference between the standard vs aggressive treatment groups ($P < .001$). There were also significant differences in carotid arterial cross-sectional area ($P < .001$). Plaque score increased slightly in both groups at 36 months, with no intergroup difference. Similarly, the percentage of individuals with at least 1 discrete plaque increased slightly in both groups at 36 months without significant intergroup difference.

For echocardiographic measures (Table 4), LV mass and LVMI decreased in both groups at 36 months, but to a

greater degree in the aggressive treatment group ($P > .02$ and $< .03$, respectively).

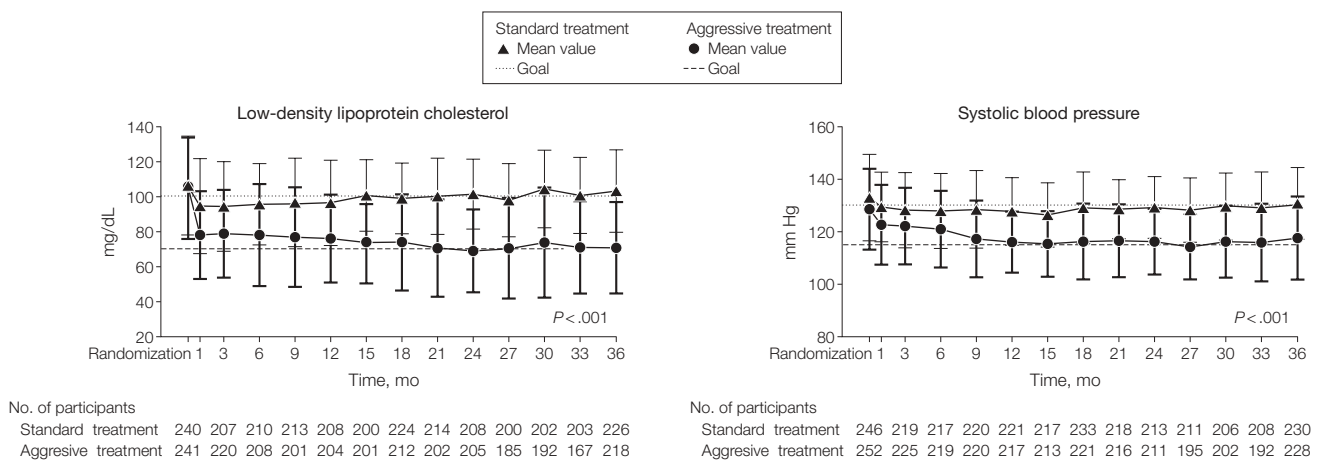
When both treatment groups were divided into those individuals whose measures decreased (improved), remained the same (± 0.01 mm for IMT or ± 0.5 gm/m^{2.7} for LVMI), or worsened over the treatment period (FIGURE 3), participants in the aggressive group were more likely to have a decrease in IMT ($P < .001$) but the likelihood of a decrease in LVMI was not significant ($P = .17$).

Primary CVD events occurred in 11 and 8 participants in the aggressive and standard treatment groups, respectively ($P = .51$; Table 3). Other CV events and non-CVD death occurred in 1 vs 3 and 2 vs 4 participants in the 2 groups, respectively. The total number of CVD end points, either primary or secondary, did not differ significantly between treatment groups. When outcomes were included with carotid IMT or arterial cross-sectional area in a ranked analysis, the significance of the differences did not change (Table 4).

Secondary Analyses

Intention-to-treat analyses compared groups stratified by prespecified characteristics, including age, BMI, baseline LDL-C, non-HDL-C, baseline SBP,

Figure 2. LDL Cholesterol and Systolic Blood Pressure Levels for SANDS Participants



Mean levels for low-density lipoprotein cholesterol (LDL-C) and systolic blood pressure by treatment group at 3-month intervals throughout the study. Error bars denote SD. P values denote the significance between treatment groups during months 18 through 36. LDL-C values were obtained from capillary blood. For 2292 samples having both laboratory and capillary measures, mean (SD) values were 89.2 (31.2) and 87.9 (29.1) mg/dL, respectively. To convert cholesterol values to mmol/L multiply by 0.0259.

Table 3. Cardiovascular Disease Events and Adverse Events by Study Group

	Aggressive (n = 252)	Standard (n = 247)	P Value ^a
No. (Rate per 100 person-years) [95% Confidence Interval]			
Cardiovascular disease events			
Primary	11 (1.5) [0.6 to 2.3] ^b	8 (1.1) [0.3 to 1.9] ^c	.51
Other	1 (0.1) [-0.1 to 0.4] ^d	3 (0.4) [-0.1 to 0.9] ^e	.31
Total	12 (1.6) [0.7 to 2.5]	11 (1.5) [0.6 to 2.3]	.87
Non-cardiovascular disease deaths	2 (0.3) [-0.1 to 0.6]	4 (0.5) [0 to 1.0]	.40
No. (%) [95% Confidence Interval]			
Adverse events			
Participants with adverse events ^f	97 (38.5) [32 to 45]	66 (26.7) [21 to 32]	.005
Related to lipid drugs	46 (18.3) [14 to 23]	35 (14.2) [10 to 19]	.22
Related to blood pressure drugs	67 (26.6) [21 to 32]	38 (15.4) [11 to 20]	.002
Participants with serious adverse events ^f	74 (29.4) [24 to 35]	55 (22.3) [17 to 28]	.07
Related to blood pressure drugs	4 (0.2) [0 to 3]	1 (0.004) [-0.004 to 0.1]	.18

^aP values are based on 2-sample tests of proportions.

^b2 Myocardial infarctions, 4 coronary artery bypass graft/percutaneous transluminal coronary angioplasty procedures, 2 unstable anginas, 1 definite stroke, and 1 congenital heart disease death.

^c2 Myocardial infarctions, 4 coronary artery bypass graft/percutaneous transluminal coronary angioplasty procedures, 1 definite stroke, 1 congenital heart disease death.

^d1 Transient ischemic attack.

^e2 Possible nonfatal strokes and 1 supraventricular tachycardia.

^fNo serious adverse events were related to lipid drugs.

sex, hemoglobin A_{1c}, smoking, CRP, and estimated glomerular filtration rate. No significant interactions were observed between treatment and any of the variables (*P* values for interactions were all > .20). When these prespecified variables were included in the multivariate models that analyzed the primary and secondary end points, they did not significantly influence the results.

A post hoc sensitivity analysis was performed by evaluating IMT, arterial cross-sectional area, and LVMI changes in individuals in the aggressive treatment group who achieved either LDL-C of 73 mg/dL or lower (n=145) or SBP of 117 mm Hg or lower (n=146) consistently during the last 12 months of the intervention compared with those in the standard treatment group. For IMT and arterial cross-sectional area, there was a bigger improvement in the group that achieved the LDL-C goal of 73 mg/dL or lower (changes of -0.022 mm² and -0.30 mm², respectively; both *P* < .001 compared with the standard group). For differences in LVMI, there was also a greater decrease (-2.7 g/m^{2.7})

in the group that achieved the LDL-C goal. Participants achieving the aggressive SBP target (≤117 mm Hg) had greater mean decreases in LVMI (-3.0 g/m^{2.7}; *P* < .001) compared with the standard treatment group.

Ordered logit analyses were performed on the combined cohort to explore relation of IMT and LVMI changes to changes in LDL-C and SBP. The probability of a decrease in IMT was significantly related to decrease in LDL-C (*P* < .005) but not significantly related to a decrease in SBP when the 2 factors were present in a combined model. Conversely, probability of decreases in LVMI were significantly related to decreases in SBP (*P* = .002) but not to LDL-C decreases. In these models, age was a significant positive predictor of IMT increase and BMI was a significant positive predictor of LVMI increase. To explore the time dependence of the treatment effects on changes in IMT and LVMI, regression models were run for each group, with IMT or LVMI changes as dependent variables, including all significant covariates (*P* < .05) plus the propor-

tion of months the treatment goal was maintained for LDL-C, SBP, or both. The proportion of months at LDL-C goal or at both LDL-C and SBP goals in the aggressive treatment group was a significant determinant of IMT changes (*P* < .04 and *P* > .02, respectively) after adjustment for all significant covariates. However, proportion of months at BP or at both LDL-C and BP goals were not significantly related to change in LVMI.

COMMENT

This randomized trial in American Indian men and women with type 2 diabetes compared groups treated aggressively to target levels of LDL-C of 70 mg/dL or lower and SBP of 115 mm Hg or lower with a group treated to current LDL-C and SBP targets. The group treated to lower targets had an improvement (decrease) in IMT and thus a regression of atherosclerosis, whereas the standard treatment group had a worsening (increase) in IMT. There was also a greater decrease in LVMI in the aggressive group. Few CVD events occurred overall, with no intergroup statistical difference.

This trial, the first to compare predefined treatment targets for both LDL-C and SBP, answered several questions. First, it showed that lower targets for LDL-C and BP can be achieved in a large proportion of patients. Adverse events related to BP (but not lipid) agents were significantly higher in the group that received aggressive treatment but these rates were within the range of adverse events reported in previous trials of BP-lowering agents.⁴¹⁻⁴³ Previous trials of LDL-C levels lowering⁸⁻²⁵ when fixed doses of statins were used, showed reduced CVD events in participants achieving targets lower than the standard goals, but in none of these trials were lower targets prespecified; thus participants who achieved lower targets may have had lower LDL-C at baseline or may have been more adherent or responsive to the regimen. One previous trial that targeted DBP below standard goals achieved fewer CVD events in the aggressive treatment group⁴⁴; others focused only on microvascular complica-

tions.^{45,46} In our trial, both LDL-C and BP were treated to aggressive targets, low-dose aspirin therapy was maintained in the majority of both groups, and only 20% were smokers.

We used surrogate end points for this trial because of a number of practical constraints, including the trial cost, rapidly evolving evidence in this field, and concern about the feasibility of conducting

a long-term intervention in a vulnerable population. Carotid ultrasound measures of IMT have been validated against pathologic specimens, and the carotid and echocardiographic measures used

Table 4. Baseline and Follow-up Carotid and Cardiac Measures

	Mean (95% Confidence Interval)		Difference	P Value
	Aggressive	Standard		
Carotid (N = 499)				
Intimal medial thickness, mm				
Baseline	0.808 (0.78 to 0.83)	0.797 (0.78 to 0.82)		
18 mo	0.802 (0.78 to 0.82)	0.804 (0.78 to 0.83)		
36 mo	0.796 (0.77 to 0.82)	0.837 (0.81 to 0.86)		
Mean change, 18 mo	-0.006 (-0.02 to 0.008)	0.007 (-0.01 to 0.02)		
Mean change, 36 mo	-0.012 (-0.03 to 0.003) ^a	0.038 (0.02 to 0.06) ^{a,b}	0.05	< .001 ^c
Arterial cross-sectional area, mm ²				
Baseline	17.36 (16.7 to 18.0)	17.33 (16.8 to 17.9)		
18 mo	17.22 (16.6 to 17.8)	17.53 (17.0 to 18.1)		
36 mo	17.53 (17.0 to 18.1)	18.39 (17.8 to 19.0)		
Mean change, 18 mo	-0.13 (-0.42 to 0.15)	0.20 (-0.13 to 0.53)		
Mean change, 36 mo	-0.02 (-0.33 to 0.30) ^a	1.05 (0.73 to 1.38) ^{a,b}	1.07	< .001 ^d
Plaque score (0-8)				
Baseline	1.85 (1.64 to 2.05)	1.84 (1.64 to 2.03)		
18 mo	2.02 (1.82 to 2.23)	2.02 (1.82 to 2.22)		
36 mo	2.38 (2.17 to 2.59)	2.34 (2.13 to 2.55)		
Mean change, 18 mo	0.18 (0.07 to 0.29)	0.18 (0.05 to 0.32)		
Mean change, 36 mo	0.54 (0.39 to 0.68) ^b	0.50 (0.36 to 0.65) ^b	0.03	.75
Plaque, %				
Baseline	74.6 (69 to 80)	76.5 (71 to 82)		
18 mo	81.0 (76 to 86)	81.4 (77 to 86)		
36 mo	86.5 (82 to 91)	84.2 (80 to 89)		
Point change, 18 mo	6.3 (1 to 13.5)	4.9 (-2 to 12)		
Point change, 36 mo	11.9 (5 to 19) ^b	7.7 (1 to 15) ^e		
Cardiac (n = 453)				
Left ventricular mass, g				
Baseline	156.7 (152 to 162)	156.1 (151 to 161)		
18 mo	143.2 (139 to 148)	148.3 (143 to 154)		
36 mo	149.3 (145 to 154)	152.5 (147 to 157)		
Mean change, 18 mo	-14.0 (-17 to -11.)	-7.1 (-10.6 to -3.6)		
Mean change, 36 mo	-8.0 (-10.9 to -5.1) ^b	-3.3 (-6.2 to -0.35) ^e	4.8	.02
Left ventricular mass index, g/m ^{2.7}				
Baseline	41.2 (40 to 42)	40.5 (40 to 42)		
18 mo	37.6 (37 to 39)	38.8 (38 to 40)		
36 mo	38.9 (37.8 to 40.1)	39.4 (38.2 to 40.6)		
Mean change, 18 mo	-3.7 (-4.4 to -2.9)	-1.7 (-2.7 to -0.8)		
Mean change, 36 mo	-2.4 (-3.2 to -1.6) ^b	-1.2 (-1.9 to -0.4) ^b	1.3	.03
Ejection fraction, %				
Baseline	60.5 (60 to 61)	59.8 (59 to 61)		
18 mo	60 (59 to 60.4)	58.7 (58 to 60)		
36 mo	59.7 (59 to 60.3)	59.1 (58 to 60)		
Mean change, 18 mo	-0.9 (-1.5 to -0.2)	-1.2 (-2 to -0.5)		
Mean change, 36 mo	-0.7 (-1.4 to 0)	-0.74 (-1.5 to 0)	0.03	.95

^aThe changes at 36 mo in intimal medial thickness and in arterial cross-sectional area remained significantly different between the 2 groups under the Bonferroni-adjusted significant level. 007 (= .05/7).

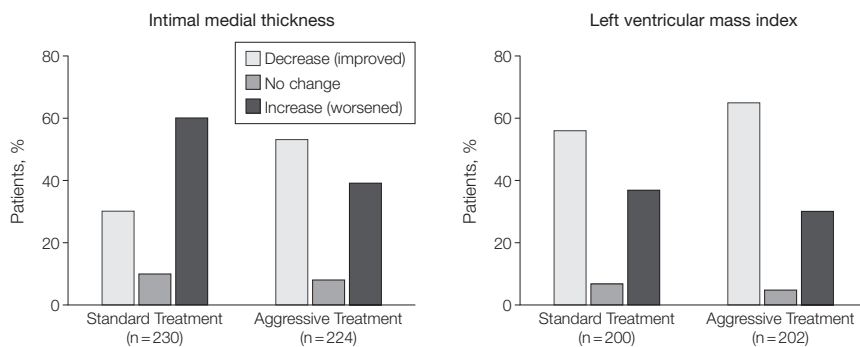
^bSignificant within-group change (P value < .01).

^cP values from the worst-rank analyses for intimal medial thickness were .691 at 18 mo and <.0001 at 36 mo.

^dP values from the worst-rank analyses for arterial cross-sectional area were .194 at 18 mo and <.0001 at 36 mo.

^eSignificant within-group change (P value < .05).

Figure 3. Categorical Changes in Left Ventricular Mass Index and Intimal Medial Thickness by Treatment Group



For intimal medial thickness, n=454; P value < .001. For left ventricular mass index, n=402; P value = .17. The "no change" category was defined as ± 0.01 mm for intimal medial thickness or ± 0.05 gm/m^{2.7} for left ventricular mass index. P is for trend by each treatment group for intimal medial thickness and left ventricular mass index.

have been demonstrated to be potent predictors of CVD outcomes in the Strong Heart Study population of American Indians, which closely resembles the current cohort. At least 12 lipid lowering trials⁴⁷⁻⁵⁸ have used carotid ultrasound measures as end points and showed improvement in carotid measures corresponding to reductions in CVD events. However, the reliability of surrogate outcomes remains to be established.

Although carotid IMT progressed in the standard treatment group, IMT decreased in the aggressive treatment group. This trial is one of the few to show regression of IMT.^{52,58,59} More commonly, clinical trials have observed less IMT progression in the treatment vs control group.^{49,50,58,60-64} This may suggest that intensive control of both lipids and BP may be necessary to reverse the atherosclerotic process. In contrast to IMT, plaque score and percentage of individuals with plaque did not differ between the 2 groups in the current study. These end points reflect established atherosclerotic lesions, and thus a longer period of therapy or control of risk factors at younger ages may be needed to affect the development of advanced lesions. Furthermore, because atherosclerotic plaques are complex 3-dimensional structures with wide variations in composition, improvement may have occurred (plaque stabilization) that could not be detected by ultrasound.

Left ventricular hypertrophy, greater LVMI, or both have been shown to predict CVD outcomes in both observational studies⁶⁵ and clinical trials.^{66,67} Echocardiographic measures have not been used as commonly as surrogate end points in trials of risk factor reduction. However, lower echocardiographic LV mass and ECG estimates of such mass during antihypertensive treatment have recently been shown to predict, independently of changes in BP and other covariates, lower rates of major CVD events,^{66,67} as well as of incident heart failure,⁶⁸ sudden death,⁶⁹ and atrial fibrillation.⁷⁰ Although LV mass measures declined in both groups, there was a significantly greater reduction in the aggressively treated group.

Because we targeted both BP and lipid goals, the trial was not designed to distinguish which intervention was responsible for the improved measures of atherosclerosis and cardiac structure. Sensitivity analyses exploring the changes in participants who met or exceeded LDL-C and SBP goals confirm the results of the intention-to-treat analyses, suggesting that the observed changes in end points could be attributable to the interventions on LDL-C and BP. Secondary analyses with the combined group across a range of LDL-C and SBP changes suggested that the IMT changes correlated more closely with the extent of lipid lower-

ing. However, BP lowering also correlated with IMT changes, and it is difficult in secondary analyses to rule out confounding by compliance. The changes in LVMI appeared more closely related to changes in SBP, although this analysis has the same limitation. Additional posthoc analyses suggested that length of time at LDL-C and SBP targets in the group that received aggressive treatment were determinants of IMT changes. Stratified analyses suggested that the effects were broadly applicable, regardless of age, obesity, sex, and baseline CVD risk factors.

An important finding was that few CVD events occurred in either treatment group. The rate of events in the combined sample was approximately 1.5 per 100 person-years, compared to 2.2 to 3.6 per 100 person-years in diabetic participants of comparable ages in a population-based study of American Indians.^{27,71} In addition, progression of IMT in the standard treatment group in this trial was 3-fold lower than in a meta-analysis of control groups for trials using carotid IMT as an end point.⁷² Our lower rates may be the result of achieving defined targets in both groups at or better than current levels, a "healthy volunteer effect," and the education on CVD prevention provided to both groups. In previous primary prevention studies that suggested major improvements in CVD rates at lower LDL-C targets, BP was not controlled, aspirin use was low, and smoking was often more common. To our knowledge, no prior trials have had a SBP target of 115 mm Hg or lower. In the Hypertension Optimal Treatment Trial,⁴⁴ the group in which DBP target was lower than 80 mm Hg had the lowest incidence of major CVD events among participants with diabetes, although lipid levels were not targeted.

Our study suggests the possibility of incremental CV benefit of achieving lower LDL-C and BP targets. Our data show significant retardation of atherosclerosis progression and regression of LV hypertrophy through more intensive therapy, suggesting that if these targets were achieved and sustained longer,

incidence of CVD events would be reduced. Conversely, adverse events attributable to the BP agents were significantly higher in the aggressive group; therefore long-term data are needed to determine overall risks and benefits.

The strength of this study includes it being the first trial to test specific targets for both LDL-C and BP in individuals with type 2 diabetes. These targets were reached in each group, and adherence and follow-up were excellent. Subclinical ultrasound measures of atherosclerosis and cardiac function were assessed with standardized protocols. Observational data obtained using these methods are available from a comparable population-based sample of American Indians with diabetes,^{27,71} allowing comparison of progression rates as well as disease outcomes.

A reason to be cautious in interpreting this study is that only a single ethnic population was studied, American Indians. Although this group has high rates of CVD, their LDL-C and BP levels are slightly lower than in other US populations; other treat-to-target studies are needed to assess the safety and feasibility of achieving aggressive targets for LDL-C and BP in groups with higher initial levels. A second limitation is that surrogate end points were used. As the effectiveness of therapy improves and new treatment strategies are widely applied, it is becoming more difficult to conduct a trial in which adequate numbers of clinical end points are achievable in a reasonable length of time for individuals without CVD at baseline. Thus, it may become increasingly important in the future to rely upon surrogate end points. We are planning an extended follow-up of these individuals to determine whether the improvements in subclinical atherosclerosis and cardiac structure are maintained in the aggressive group and whether they are reflected in fewer clinical CVD outcomes. The recent report from the STENO-2 extension showing reduction in CVD events 7.8 years after intense risk-factor management ceased suggests that improvement in CVD outcomes will be found.⁷³

In conclusion, in this first trial to evaluate lower targets for both LDL-C and BP compared with standard targets in adults with type 2 diabetes, regression of IMT and greater decrease in LV mass were observed in the aggressive treatment group. Although there were no differences in clinical CVD outcomes, event rates were low in both groups, and progression of subclinical disease in the standard treatment group was lower than expected. The data suggest that targeted treatment of LDL-C and SBP improved surrogate measures of CVD, with greater benefits being attributable to the lower target levels. Conversely, the lack of difference in occurrence of events and the increase in adverse events and SAEs attributable to the BP lowering raise the possibility that there may not be favorable long-term outcomes. Whether the strategy of more aggressive targets for either LDL-C or BP will result in lower long-term CVD event rates or economic benefit remains to be determined.

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